Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Engineering
Department of Structural Engineering

Jakob Svane

A Minimal Haemodynamic System Model for Varying Exercise Intensity

Master's thesis in Mechanical Engineering
Supervisor: Leif Rune Hellevik
Co-supervisor: Jacob T. Sturdy
June 2021

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A Minimal Haemodynamic System Model for Varying Exercise Intensity

En Minimal Hemodynamisk System-modell for Varierende Treningsintensitet

BY:

Jakob Svane

SUMMARY:

A mathematical model of the cardiovascular response to exercise during steady state is presented, with the objective of creating a personalizable, simple, computationally low-cost model that yields results in accordance with experimental data. The model includes dynamic responses in the systemic resistance, ventricular elastance, aortic elastance, systolic period and a venous muscle pump. Exercise intensity is defined as a function of heart rate, and six main cardiovascular properties are evaluated at varying intensity: mean arterial pressure, systolic pressure, diastolic pressure, cardiac output, active muscle flow and systemic vascular conductance. In addition, a sensitivity analysis is carried out on the model to determine the influence of the regulatory mechanisms on the model. The model corresponds well with available data for the cardiovascular response to exercise, with a good potential for individualization. In particular, the model shows the importance of the systemic resistance, including how the value at resting conditions may influence the cardiovascular response to exercise.

RESPONSIBLE TEACHER:
Leif Rune Hellevik, NTNU

SUPERVISOR(S):
Leif Rune Hellevik, NTNU.
Jacob T. Sturdy, NTNU

CARRIED OUT AT:
Department of Structural Engineering, NTNU

Abstract

A mathematical model of the cardiovascular response to exercise during steady state is presented, with the objective of creating a personalizable, simple, computationally low-cost model that yields results in accordance with experimental data. The model includes dynamic responses in the systemic resistance, ventricular elastance, aortic elastance, systolic period and a venous muscle pump. Exercise intensity is defined as a function of heart rate, and six main cardiovascular properties are evaluated at varying intensity: mean arterial pressure, systolic pressure, diastolic pressure, cardiac output, active muscle flow and systemic vascular conductance. In addition, a sensitivity analysis is carried out on the model to determine the influence of the regulatory mechanisms on the model. The model corresponds well with available data for the cardiovascular response to exercise, with a good potential for individualization. In particular, the model shows the importance of the systemic resistance, including how the value at resting conditions may influence the cardiovascular response to exercise.

Sammendrag

En matematisk modell av kardiovaskulær respons til trening under steady state presenteres, med sikte på å lage en tilpassbar, enkel, beregningsmessig billig modell som gir resultater i samsvar med eksperimentelle data. Modellen inkluderer dynamiske responser i systemisk resistans, ventrikulær elastanse, aortaelastanse, systolisk periode og en venøs muskelpumpe. Treningsintensitet er definert som en funksjon av hjertefrekvens, og seks hoved-kardiovaskulære egenskaper evalueres for varierende intensitet: gjennomsnittlig arterielt trykk, systolisk trykk, diastolisk trykk, minuttvolum, aktiv muskelstrøm og vaskulær konduktivitet. I tillegg gjennomføres en sensitivitetsanalyse på modellen for å undersøke påvirkningen av reguleringsmekanismene på modellen. Modellen samsvarer godt med tilgjengelige data for kardiovaskulær respons på trening, med et anselig potensial for individualisering. Spesielt viser modellen viktigheten av systemisk resistans, inkludert hvordan verdien for hvileforhold kan påvirke den kardiovaskulære responsen til trening.

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Chapter 1

Introduction

Cardiovascular diseases are the leading cause of death globally, and more than a billion people worldwide suffer from hypertension. It is called "the silent killer", because more often than not, the symptoms go undetected. Usually, hypertension is divided into two groups, primary and secondary hypertension. Primary hypertension has no obvious cause, and accounts for around 95% of all cases of hypertension [1]. To diagnose hypertension, a medical professional will measure the patient's blood pressure. Since additional physiological data is both unreliable and not necessarily available, this means that the diagnosis is usually based on only intuition and experience. Specific treatment is normally based on trial and error until the blood pressure is reduced, which often leads to inefficient treatment [2].

1.1 Haemodynamic Modelling

Physical activity is commonly recommended as a treatment and a prevention method for hypertension [3]. However, the effect of exercise on blood pressure for different individuals is difficult to predict, and invasive measurements of cardiovascular properties during exercise are both challenging and laborious, and in many cases unavailable. It is therefore useful to develop computational models that can simulate the effect exercise will have on the patient. Specifically, if the model can input patient specific parameters and output personalized results, the model would be of great use. Hose *et al.* [4] state that one of the primary benefits of cardiovascular modelling is its predictive capacity. Using computer models, it is possible to predict how a state evolves with respect to various interventions. Long-term effects are usually harder to predict than short-term effects, due to biological remodelling that occurs over a longer time span and the intrinsic variability of the biological system [4]. Furthermore, even determining the concept of resting blood pressure proves challenging, since blood pressure may vary significantly over the course of a day [5]. Short-term response to exercise, as analyzed in this thesis, may therefore be used to better understand and predict the long term response.

1.2 Related Work

Examples of haemodynamic models that work for varying exercise intensities can be found in Magosso and Ursino [6] and Fresiello *et al.* [7]. These models include transient regulatory mechanisms - mechanisms that take into account a continuous change in exercise intensity - and are highly complex, requiring a substantial amount of computational power and numerical parameters. In this paper we seek out to create a minimal model that neglects these transient effects, with a small amount of components, yielding similar results at steady state but at a lower cost.

1.3 Thesis

This thesis is inspired by the My Medical Digital Twin project at NTNU, Trondheim, of which the goal is to create a digital twin that can monitor important health factors related to hypertension. The project combines exercise physiology, computational modelling, statistics and sensor technology to create the best possible model [8].

1.3.1 Previous Work

In the fall of 2020, I began the work that would eventually conclude in this master's thesis. The work done during the fall was presented in the project thesis (Svane, 2020), which will occasionally be referred to in this paper. The project thesis serves as both an introduction and a guideline for this master's thesis. In the project thesis, it was attempted to create a model predicting the cardiovascular response to exercise by implementing a simple exercise-dependent systemic resistance and ventricular elastance. The model predicted a vastly different response compared to available data from Magosso and Ursino [6] and Pawelczyk *et al.* [9]. Although the results from the project thesis were unsatisfactory, it gave valuable insight regarding haemodynamic modelling and methods to improve the model.

1.3.2 Objective

The main objective of this thesis is to create a computational haemodynamic system model that produces realistic results for cardiovascular values during exercise at steady state, at a low computational cost. It is also desirable that the model has a potential for personalization. By using the minimal haemodynamic model created by Smith *et al.* [10] as a starting point, a model is developed by combining mechanisms from the models by Magosso and Ursino [6] and Smith, in addition to adding mechanisms based on population data. Two models will be created. First, a model with a curve-fitted systemic resistance. This will be referred to as the "curve-fit model". Then, a model with a physiologically reasoned systemic resistance will be made. This model will be referred to as the "physiological model".

Following the creation of these two models, a sensitivity analysis on the physiological model will be carried out. This is to evaluate how the model responds to different changes with respect to variance in input parameters and exercise response. Ultimately, the goal is to create a model that can input patient specific parameters and output personalized results. The sensitivity analysis aids in assessing this particular functionality of the model.

1.3.3 Outline

The thesis is divided into five chapters, with the current chapter being the first. Chapter 2 covers the fundamental theory that is applied in both the development of the models and the interpretation of the results. In Chapter 3, the development of the models with the implementation of the mechanisms is presented. Chapter 4 contains all the relevant results and comparisons with both experimental data and other models in the literature. Finally, in Chapter 5, a discussion based on the results is carried out, in which the performance of the model is evaluated.

Chapter 2

Theory

In this chapter, a brief introduction to the circulatory system will be given, followed by basic theory on fluid mechanics and arterial blood flow. Next, some of the most important cardiovascular responses to exercise will be explained. The chapter will conclude with a short description of how computational physiology may be carried out by analogy to electrical circuit theory. The goal of this chapter is to introduce and explain every mechanism and aspect of the computational model that will be introduced in Chapter 3. This chapter will also give the necessary theory for understanding the results and discussion presented in Chapter 4 and Chapter 5.

2.1 The Circulatory System

The circulatory system - or cardiovascular system - is the system of organs and blood vessels in which the blood is circulated and transported inside the body. The term encompasses both the systemic and pulmonary circulation, in addition to the heart. It can be thought of as any part of the body that contains or carries blood.

2.1.1 The Heart

The heart acts as a pump that moves the blood through the body. The pumping of the heart generates a pressure gradient that drives the blood into circulation, to the muscles and organs, and back again to the heart. Functionally, it can be viewed as a set of two pumps. As the blood enters the right atrium and subsequently passes the tricuspid valve to the right ventricle, it is pumped through the pulmonary valve and into the pulmonary circulation by contraction of the heart. Here the blood moves to the lungs, exchanges carbon dioxide for oxygen, and then moves to the left atrium. When the left ventricle relaxes, the pressure in the left atrium surpasses that of the ventricle, causing the mitral valve to open and the blood to enter the left ventricle. At the end of the relaxation phase of the ventricle, the atrium contracts to give a final push for filling. Again the heart contracts and ejects

the blood through the aortic valve into the aorta and the systemic circulation. A schematic of the circulatory system can be seen in Figure 2.1. When the heart is in its contracting phase it is said to be in *systole*, and maximum contraction is called end-systole. Equally, its relaxing phase is called *diastole*, with maximum relaxation called end-diastole.

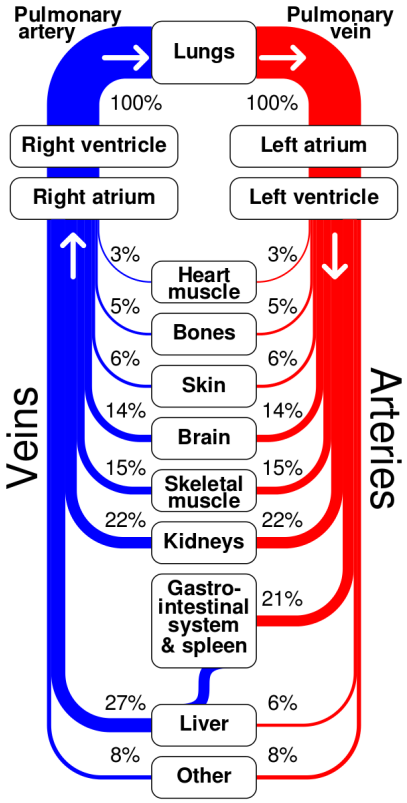


Figure 2.1: A conceptual division of the circulatory system. The numbers represent the approximate relative percentages of cardiac output delivered to major organ systems. "Creative Commons Sankey diagram human circulatory system" by cmglee is licensed under CC BY-SA 3.0.

2.1.2 The Systemic Circulation

The aorta is the largest blood vessel, leaving the left ventricle of the heart. It quickly branches to smaller vessels, which again branch to even smaller vessels. Conventionally, the blood vessels branching off the aorta are called arteries, which then branch to arterioles and finally to capillaries. The capillaries carry the blood to muscles and organs, after which the blood enters the venules and begins its way back to the heart. From the venules the blood drains into larger veins, finally entering the vena cava, from where the blood enters the right atrium of the heart and the blood cycle repeats. Typical sizes of the different blood vessels are

Table 2.1: Size of different types of blood vessels in the systemic circulation. Adapted from [11].

Vessel type	Diameter [mm]
Aorta	25
Large arteries	$1.0-4.0$
Small arteries	$0.2-1.0$
Arterioles	$0.01-0.20$
Capillaries	$0.006-0.010$
Venules	$0.01-0.20$
Veins	$0.2-5.0$
Vena cava	35

presented in Table 2.1.

2.2 Fluid Mechanics

By analyzing blood flow, a better understanding of the behaviour of the blood in the arterial circulation can be achieved. Although usually derived for ideal conditions, theory on fluid flow mechanics can aid in determining which simplifications can be made when building a model.

2.2.1 Resistance

The resistance exerted on a fluid inside a vessel is the opposing force the fluid must overcome to create flow. Using an analogy to electric circuit theory and Ohm's law, the resistance can be calculated as the ratio between driving pressure and flow rate,

$$R = \frac{\Delta P}{Q}, \tag{2.1}$$

where R is the resistance, ΔP is the pressure drop over a given distance and Q is the flow rate. Assuming a rigid, uniform pipe with steady, fully developed flow, Poiseuille calculated the relationship between flow rate and pressure drop for a newtonian fluid as

$$Q = \frac{\Delta P \pi r_i^4}{8\mu l}, \tag{2.2}$$

where r_i is the inner radius of the tube, μ is the dynamic viscosity of the fluid and l is the length of the tube [12]. Combining Equations (2.1) and (2.2) the expression for resistance becomes

$$R = \frac{8\mu l}{\pi r_i^4}. \tag{2.3}$$

Unfortunately, to apply Equation (2.3) to blood vessels, the vessel needs to be uniform and the radius of the vessel has to be accurately determined. Furthermore, the law of Poiseuille assumes constant viscosity, which is not necessarily the case in smaller blood vessels [12]. Therefore, Equation (2.3) is better used to approximate the ratio of resistance between vessels of different radius and length, seeing as the resistance is dependent on radius to the fourth power, and only linearly on length.

2.2.2 Conductance

Conductance, G, is a measure of the vessel's ability to transport fluid and is simply defined as

$$G = \frac{1}{R}. \tag{2.4}$$

Conductance and resistance are just the inverse of each other, but conductance is generally used when focusing on the flow generated by a given pressure. This is a useful physiological concept, as the cardiovascular system regulates the blood pressure at the heart. The blood flow to the organs can then be analyzed effectively by considering the amount of flow generated for a given pressure.

2.2.3 Inertance

Inertance is a property that relates the pressure drop and the rate of change of the flow rate with time in a fluid. The inertance can be derived starting with Newton's second law

$$F = ma = m\frac{dv}{dt}, \tag{2.5}$$

which relates the force, F, to mass, m, and the rate of change in velocity v, or acceleration, a. In a uniform tube this force is $F = \Delta PA$, with A being the cross-sectional area of the tube. The mass in Equation (2.5) can be written as ρAl, where ρ is density and l is the length of the tube. Using the fact that velocity can be written as the flow rate divided by area, $v = Q/A$, and assuming constant area in time, Equation (2.5) becomes

$$\Delta PA = \rho Al\frac{(dQ/A)}{dt},$$

which yields

$$\Delta P = \frac{\rho l}{A}\frac{dQ}{dt}. \tag{2.6}$$

Equation (2.6) relates the pressure drop to the rate of change of the flow rate with time, and gives the definition of inertance, L,

$$L = \frac{\rho l}{A}. \tag{2.7}$$

Recalling from Equation (2.3) that resistance is inversely proportional to r^4, while inertance is inversely proportional to r^2 (since $A \sim r^2$), one can deduce that in large vessels inertance will be more significant than resistance, while the opposite will be true in smaller vessels. Also, where there are significant temporal variations in flow velocity - such as in valves or at the beginning of the cardiac cycle - the inertial effects will be significant.

2.3 Arterial Blood Flow

Since arteries are not rigid tubes, a measure of their elasticity needs to be defined. This measure is commonly called the compliance, and will be explained in the following. Additionally, cardiac output and pulse pressure will be presented to give a better foundation for interpreting the results in Chapter 4.

2.3.1 Compliance and Elastance

Compliance is the ratio of change in volume to change in pressure in a given blood vessel,

$$C = \frac{\Delta V}{\Delta P}, \tag{2.8}$$

where C is the compliance, and ΔV denotes the change in volume. When the pressure difference across the vessel wall - the *transmural* pressure - increases, the vessel will expand in the radial direction, causing the volume to increase as well. The compliance is related to Laplace's law for tension in a cylinder. Laplace's law states that the pressure within a cylinder is inversely proportional to the radius of the cylinder, and that the tension in the wall will balance the pressure difference across the wall. A compliant vessel under negative transmural pressure will therefore constrict as a result of the external pressure, until the internal pressure matches the external pressure and the transmural pressure reaches zero.

The inverse of the compliance is called elastance, defined by

$$E = \frac{1}{C} = \frac{\Delta P}{\Delta V}, \tag{2.9}$$

with E being the elastance. Elastance is used as a measure of a vessel's or organ's tendency to recoil to its original dimensions when removing a compressing or distending force.

2.3.2 Cardiac Output

Cardiac output is defined as

$$CO = HR \cdot SV, \tag{2.10}$$

where HR is heart rate and SV is the stroke volume. Stroke volume is given by the difference in end-systolic and end-diastolic left ventricle volume for one heartbeat, V_{lv}^{es} and V_{lv}^{ed} respectively, yielding

$$SV = V_{lv}^{es} - V_{lv}^{ed}. \tag{2.11}$$

2.3.3 Pulse Pressure

The arterial pulse pressure, PP, is the difference in systolic and diastolic pressure over one heartbeat,

$$PP = P_{ao}^{s} - P_{ao}^{d}, \tag{2.12}$$

where P_{ao} is the aortic pressure, and the superscripts s and d denote systolic and diastolic pressure, respectively.

2.4 Cardiovascular Response During Exercise

The blood flow is driven by the pressure generated by the heart as it pumps blood into the vasculature. During exercise the metabolic activity of the active skeletal muscles increases, which increases not only the muscles' demand of oxygen and nutrient supply, but also the removal of metabolic byproducts. By dilating the blood vessels within and around the active muscle, the resistance is decreased and the blood flow to the muscle is increased. For the blood flow to increase, it is necessary to maintain the arterial blood pressure. This is done by increasing the cardiac output and by constricting blood vessels in other parts of the body.

2.4.1 Frank-Starling Mechanism

Equation (2.10) shows there are two ways to increase cardiac output: by increasing heart rate and by increasing the stroke volume. During exercise, limb movement will enhance the venous return to the heart. With increased venous return, more blood will enter the heart - the *preload* increases. As more blood enters the heart, the heart expands, effectively stretching the muscle fibers in the heart. Since the tension in the fibers is proportional to the fiber length, the heart will contract with more force, increasing the stroke volume. This effect is commonly called the Frank-Starling mechanism [13].

2.4.2 Regulatory Mechanisms

Using several regulatory mechanisms, the body adjusts to the increased demand from the muscles. This is typically done by constricting or dilating blood vessels, or by increasing heart rate. Receptors that sense pressure changes are located inside the aortic arch and the carotid sinus. These *baroreceptors* respond to changes in tension in the arterial wall, and send signals to the brain for regulating heart rate and blood pressure. *Chemoreceptors* detect decreased oxygen concentration or increased carbon dioxide concentration in the blood, and transmit that information to the central nervous system. *Pulmonary stretch receptors* are located in the lungs, detecting the expansion of the lungs during inspiration and thereby regulating the respiratory cycle. For the baroreceptors, chemoreceptors and pulmonary stretch receptors, the associated responses are called baroreflex, chemoreflex and pulmonary stretch reflex, respectively. Through the hormonal and nervous systems, metabolic regulation is achieved. The metabolic regulation controls the energy supply in the body, consequently affecting blood flow and resistance as well [14].

2.4.3 Sympathetic Activity

The sympathetic nervous system is a division of the nervous system that controls the reflex adjustment of the cardiovascular system. Sympathetic activation is the driver behind the well-known "flight-or-fight" response. When the body exercises, sympathetic activation - or increase in *sympathetic tone* - leads to increased heart rate, skeletal muscle vasodilation and non-active vasoconstriction, among other things [15]. Typically, the bodily tissue or organ that reacts to the signal from the sympathetic tone is referred to as an *effector*. For example, when heart rate increases, cardiac muscle is seen as the effector for the sympathetic activity.

2.4.4 Central Command

Central command is a hypothesis which suggests that impulses from the brain, specifically the cerebral cortex, also regulate cardiovascular control. This hypothesis proposes there is a nervous signal that, at the onset of exercise, sets the basic pattern of the effector activity. There are still questions as to how central command works, and whether or not it works directly on neural pathways or indirectly through other reflex systems such as the baroreflex. Nevertheless, the experimental evidence for the central command hypothesis is quite strong [16–18].

2.4.5 Skeletal Muscle Pump

The skeletal muscle pump - or the venous muscle pump - is an important mechanism for increasing venous return. Since a lot of veins are located within large muscle groups, the veins are compressed as the muscles contract. This causes the venous blood flow of the veins to increase, which in turn increases venous return and consequently the preload of the heart. Veins directly in contact with the

Table 2.2: The hydraulic-electric analogies. The law in each row in the hydraulic column is analogous to the law in the corresponding row of the electric column.

Electric	Hydraulic
Kirchhoff's law (current balance)	Continuity equation (mass conservation)
Ohm's law (voltage-current relation steady state)	Poiseuille's law (momentum balance steady state)
Transmission line equation (voltage-current relation high frequency)	1D Navier Stokes in a compliant tube (momentum balance unsteady state)
Voltage gradient	Pressure gradient
Resistance	Frictional loss (resistance)
Capacitance	Compliance
Inductance	Inertance

contracting muscles have one-way valves that prevent backflow, thus preventing retrograde flow back into the arteries [19]. Since the veins expand when the muscles relax, it can be argued that the muscle pump also aids in muscle perfusion. This effect is more unclear however, and is discussed more in detail in Sheriff [20].

2.5 Computational Physiology

The governing laws of haemodynamics may be shown to, under appropriate assumptions, be equivalent to those of electrical circuit theory. The pressure gradient in the blood vessels is akin to the voltage gradient in an electrical circuit, both being the driving force. The hydraulic impedance experienced by the blood flow can be compared to the electrical impedance, with frictional loss being electrical resistance, compliance being capacitance, and inertance being inductance. Furthermore, the governing laws of blood flow dynamics are analogous to those of electric currents, meaning the cardiovascular system can be represented as an electrical circuit, using the well-established methods of electrical circuit theory [21]. Table 2.2 displays the hydraulic-electric analogies.

By setting up a system of equations from the equations listed in Table 2.2, numerical methods can be used to simulate physiological systems. Values for physiological parameters such as compliance and resistance can be estimated based on experimental data, along with initial conditions for differential equations. Regula-

tory reflexes can be modelled through differential and algebraic equations, serving as the efferents for the cardiovascular effectors.

Chapter 3

Methodology

The following model is based on the minimal haemodynamic model by Smith *et al.* [10] for resting conditions, and largely inspired by the model by Magosso and Ursino [6] for varying exercise intensity. A similar model was created in the project thesis, from which the results serve as a guidance for further necessary additions and assumptions. Insight retrieved from the project thesis will be explicitly specified as such.

3.1 Outline

First, the most important cardiovascular regulatory mechanisms will be added to the model by Smith. Some of these mechanisms will either be implemented as in Magosso and Ursino [6], or they will be fitted to have the same effect as those of Magosso, while some of them will be based on population data. The curve-fit to Magosso's results is done to easily build a model that produces reasonable results, which can then be analyzed to aid in a physiologically reasoned implementation. The goal of such an implementation is not only the desired macro-scale output from the model, but also to have a useful description of how the physiological reflexes at the micro-scale initiate and subsequently affect the macro-scale parameters. In effect: start with the desired results, then work backwards to figure out how to get there.

The implementation of these mechanisms is explained in Section 3.2. When a model with realistic results is reached, a physiological reasoned implementation will be attempted. Finally, by the use of this model, a sensitivity analysis will be carried out to assess the influence of the different cardiovascular mechanisms on the main properties evaluated. This is explained in Section 3.5.

3.2 A Minimal Haemodynamic Model For Varying Exercise Intensity

The project thesis gave insight into which regulatory mechanisms were most necessary, and which cardiovascular properties need correction. Smith's model is the basis of the model, to which the various regulating mechanisms are added. Most mechanisms will be implemented based on physiology, except for two (ventricular and aortic elastance), which are based on population data. Neglecting the effects of gravity, the current model can be used to simulate exercise in supine position only. A supine ergometer cycle where exercise intensity is regulated by adjusting ergometer-resistance is preferable, as will be explained in Section 3.2.5.

As in the project thesis, exercise intensity will be modelled as a function of heart rate, and a continuous heartbeat period is implemented to ensure the simulation reaches steady state. Left and right ventricular elastance will be made to increase for increasing exercise intensity. Further, a systemic venous muscle pump will be added. To begin with, a first model with the systemic resistance curve-fitted to Magosso's resistance function will be implemented. This is based on the results from the project thesis, which proved it difficult to implement a realistic resistance. However, in Section 3.3, a second model with the systemic resistance implemented on a physiological basis will be implemented. For simplicity, the two models will be referred to as the "curve-fit model" and the "physiological model", respectively. Although the pulmonary resistance tends to decrease during exercise, it is neglected in this model, based on results from Wolsk *et al.* [22] which show a negligible decrease in pulmonary resistance compared to systemic resistance during exercise. The relation between systolic and diastolic pressure will be mediated by adding an intensity dependent aortic elastance, which is based on population data from Bal-Theoleyre *et al.* [23]. The elastance driver function will also be modified to account for changes in systolic period during exercise.

3.2.1 Exercise Intensity

To account for the influence of exercise on the cardiovascular system, a way to define the exercise intensity is needed. A conventional way of describing the exercise intensity is to normalize the oxygen consumption rate, VO_2, by its maximum value, or by calculating intensity based on power output in watt. However, in this simplified model it is desirable to describe the exercise intensity as a function of a more easily measured and personalizable parameter. Thus, the exercise intensity, I, is defined as a function of heart rate, HR,

$$I = \frac{HR - HR_{rest}}{HR_{max} - HR_{rest}}, \tag{3.1}$$

where the subscripts *rest* and *max* correspond to resting heart rate and maximum heart rate, respectively. In this way, exercise intensity is normalized, and ranges between values of $0-1$. A linear relation between heart rate, VO_2 and power out-

put is supported by Pawelczyk *et al.* [9] and Bogaard *et al.* [24]. In this model the resting heart rate is set to 70 beats/min based on population data from Nauman *et al.* [25]. Max heart rate is estimated to 200 beats/min by the commonly used equation for max heart rate $HR_{max} = 220 - \text{age}$. Hence, the simulations in this paper are in theory done on a 20-year old human subject. Nevertheless, the model can assume any range of maximum and minimum heart rates.

3.2.2 Heartbeat Period

The amount of time it takes for the heart to beat once - a complete cycle from diastole to systole and back to diastole - is called the period of the heartbeat. To ensure the model reaches steady state, it is desirable to design a continuous heartbeat period function that allows for simulation of an arbitrary length. The chosen period function, τ, is defined as

$$\tau = \frac{\text{mod}(\text{time}, (1/\text{HR}))}{1/\text{HR}}. \tag{3.2}$$

In the above equation, mod is the modulus operator - it divides the time by $1/\text{HR}$ and returns the remainder. In this equation, $1/\text{HR}$ is the period of one heartbeat. By defining the period function in this way, τ will output the current fraction of the heartbeat period, meaning τ will vary between 0 and 1.

3.2.3 Ventricular Elastance

A change to the end-systolic elastance in the right and left ventricular compartment is made to account for the change in the contractility of the ventricles during exercise. The data in Chantler *et al.* [26] displays a nearly linear relation between the left ventricular end-systolic elastance and exercise intensity. By assuming a similar relation in the right ventricle, a linear equation can be implemented for the elastances

$$\begin{aligned} E_{lv} &= (1 + 2I)E_{lv}^{rest}, \\ E_{rv} &= (1 + 2I)E_{rv}^{rest}, \end{aligned} \tag{3.3}$$

where the proportionality constant is determined from data in Chantler *et al.* [26]. The elastances E_{lv} and E_{rv} are the end-systolic elastances in the left and right ventricle during exercise, respectively, and the superscript *rest* denotes the end-systolic elastance at rest. The values for resting elastances are equal to those used in Smith's model, and can be found in Table 3.1.

3.2.4 Removing Septum Wall

In the model used by Smith, the septum pressure is defined as the difference in left and right ventricular pressure. However, when applying Equation (3.3) in the

model, the difference in left and right ventricle pressure becomes too large to yield a realistic septum pressure value, and the model fails to run. The pressure interaction between the ventricles (the septum wall) is therefore removed. This is supported by the results from both the project thesis and Pettersen *et al.* [27], which show a negligible effect from the septum wall, in addition to an increased computational cost when including the septum wall.

3.2.5 Venous Muscle Pump

The systemic venous muscle pump is implemented by applying a time-varying intramuscular pressure. It is this intramuscular pressure that exerts an external force on the blood vessels, as alluded to in Section 3.2.5. The intramuscular pressure varies in a half-sine pattern as the active muscles contract and relax. In reality, the venous muscle pump works in the active muscle veins, with the effects propagating through the vena cava and to the heart. In this simplified model there are no active muscle veins, thus the effect of the muscle pump is applied directly to the vena cava.

Without the muscle pump, the equation for the systemic venous pressure is given by

$$P_{vc} = E_{vc} \cdot (V_{vc} - V_{vc,d}). \tag{3.4}$$

The subscript *vc* denotes the vena cava and the subscript *d* denotes the unstressed volume. The unstressed volume is simply the volume inside a vessel at near zero transmural pressure. When including the muscle pump, the expression becomes

$$P_{vc} = \begin{cases} E_{vc} \cdot (V_{vc} - V_{vc,d}) + P_{im}, & V_{vc} > V_{vc,d} \\ P_{im}, & \text{otherwise,} \end{cases} \tag{3.5}$$

with P_{im} being the intramuscular pressure caused by the muscle pump, given by

$$P_{im} = \begin{cases} A_{mp} \cdot \psi, & I > 0 \\ 0, & I = 0. \end{cases} \tag{3.6}$$

This way, if we assume a completely stationary resting condition, the muscle pump works only during movement. The amplitude, A_{mp}, is a constant factor, and ψ is the half sine function

$$\psi = \begin{cases} \sin(\pi \cdot \frac{T_{im}}{T_c} \cdot \alpha), & 0 \leq \alpha \leq \frac{T_c}{T_{im}} \\ 0, & \frac{T_c}{T_{im}} \leq \alpha \leq 1. \end{cases} \tag{3.7}$$

Here T_c is the time period of the contraction phase of the muscle pump, T_{im} is the time period of the entire contraction-relaxation cycle, and α is a function that represents the fraction of the overall cycle, defined as

$$\alpha = \frac{\text{mod}(\text{time}, T_{im})}{T_{im}}, \tag{3.8}$$

where mod is the modulus operator. The values of A_{mp}, T_{im} and T_c are given in Table 3.1, and are based on the values from Magosso and Ursino [6].

It is important to note that the way the muscle pump is implemented here, neither the frequency nor the amplitude of the muscle pump change with increasing intensity. Since the model assumes ergometer cycling in a supine position, the exercise intensity can be regulated by adjusting resistance. This way, the frequency of the contraction-relaxation cycle of the muscles will remain the same, and the muscle pump can be assumed to work equally for all intensities.

3.2.6 Systemic Resistance

As mentioned earlier, it proved challenging in the project thesis to achieve a realistic physiological systemic resistance. Therefore, the systemic conductance is approximated as a polynomial by using Lagrange interpolation on the conductance given in Magosso and Ursino [6]. The systemic resistance is then the inverse of the conductance,

$$\begin{aligned} R_{sys} = \quad & 1/(0.918 + 2.4125 \cdot I - 0.453951 \cdot I^2 - 2.07615 \cdot I^3 \\ & + 1.21517 \cdot I^4 - 0.0141739 \cdot I^5)\,\mathrm{mmHg\,s\,mL^{-1}}. \end{aligned} \tag{3.9}$$

3.2.7 Aortic Elastance

Arterial elastance is implemented as aortic elastance in this model, since it is desirable to reduce the number of compartments in the model. The aortic elastance is an important factor for the magnitude of systolic and diastolic pressure. This is explained by the Windkessel model [28], and will be explained in Section 5.1.2. Since diastolic pressure does not increase as much as systolic pressure for increasing intensity, it is necessary to regulate the aortic elastance for varying exercise intensity [29, 30]. The relative increase in aortic elastance from resting conditions to during exercise is based on results from Bal-Theoleyre *et al.* [23]. The aortic elastance function is defined as

$$E_{ao} = 0.6913 + \frac{0.3087}{1 + e^{5-10 \cdot I}}\,\mathrm{mmHg\,mL^{-1}}. \tag{3.10}$$

At rest ($I = 0$), this quantity becomes the same as the aortic elastance in the original Smith model.

3.2.8 Elastance Driver Function

A new elastance driver function is also implemented in the model, based on insight from Stergiopulos *et al.* [31]. This is partly to apply a more realistic driver function shape, as argued by Stergiopulos *et al.* [31], but mostly to use a driver function that can differ in shape for varying exercise intensities. Results from both Cheng *et al.* [32] and Mertens *et al.* [33] show that the relative duration of systole to

heartbeat period increases significantly for increasing exercise intensity. The new driver function is defined as

$$e_t = \beta \left(\frac{\left(\frac{\tau}{\beta_1 \cdot t_{peak}}\right)^{n_1}}{1+\left(\frac{\tau}{\beta_1 \cdot t_{peak}}\right)^{n_1}} \right) \times \left(\frac{1}{1+\left(\frac{\tau}{\beta_2 \cdot t_{peak}}\right)^{n_2}} \right), \tag{3.11}$$

where β, β_1, β_2, n_1 and n_2 are constants whose values are given in Table 3.1, all retrieved from Stergiopulos *et al.* [31]. The variable τ is the heartbeat period function and t_{peak} is a variable that controls where in the heart period the peak of the driver function (end-systole) occurs. Thus, t_{peak} is a function of heart period T. By making it dependent on exercise intensity it also accounts for the change in the fraction of systole to total heart period that takes place for increasing intensity. Assuming, based on results from Mertens *et al.* [33], a systolic fraction of 0.3 during rest and 0.5 at $I = 1$, with a linear increase between the two extremities, the expression for t_{peak} becomes

$$t_{peak} = (0.3 + 0.2I)\, T. \tag{3.12}$$

T is the heartbeat period, simply given as $1/HR$.

3.3 Physiological Implementation

In this section, the systemic resistance will be implemented on a physiological basis. To get an accurate model, several regulatory mechanisms are included. The following implementation, as well as most parameter values, are based on the implementation in Magosso and Ursino [6] and Ursino and Magosso [34]. Parameter values from other sources will be explicitly stated.

3.3.1 Systemic Resistance

A parallel configuration of resistances between the aorta and vena cava yields an expression for the systemic resistance,

$$\frac{1}{R_{sys}} = \frac{1}{R_{am}} + \frac{1}{R_b}, \tag{3.13}$$

where R_{am} is the resistance in the active muscles and R_b is the resistance in the non-active parts of the systemic circulation. The active muscle resistance is then modelled similarly to that in Magasso's model,

$$R_{am} = \frac{R_{am,n}}{1 + x_{am,O2} + x_{met}}. \tag{3.14}$$

Here, and in the following, the subscript n denotes the basal value (value at resting conditions) of the given parameter. The state variable x_{met} represents the effect

of various metabolic byproducts that need to be removed, thus stimulating a vasodilatory response. The dimensionless variable $x_{am,O2}$ describes the amount of oxygen in the muscle tissue. Note that, although a baseline value, $R_{am,n}$ is not a constant value as it depends on sympathetic activity to maintain homeostasis [35]. In this model, however, the sympathetic activity is constant for $I = 0$.

The dynamics of x_{met} is given as a first order differential equation,

$$\frac{dx_{met}}{dt} = \frac{1}{\tau_{met}} \cdot (-x_{met} + \phi_{met}), \tag{3.15}$$

with τ_{met} being a time constant, and ϕ_{met} a static sigmoidal characteristic

$$\phi_{met} = \frac{\phi_{min} + \phi_{max} \cdot exp\left(\frac{I - I_{0,met}}{k_{met}}\right)}{1 + exp\left(\frac{I - I_{0,met}}{k_{met}}\right)}. \tag{3.16}$$

The subscripts min and max denote lower and upper saturation level, and k_{met} and $I_{0,met}$ are constants related to the slope of the sigmoidal.

The dynamics of $x_{am,O2}$ are also described by a first order dynamic equation

$$\frac{dx_{am,O2}}{dt} = \frac{1}{\tau_{O2}} \cdot (-x_{am,O2} - g_{am,O2} \cdot (C_{vam,O2} - C_{vam,O2n})), \tag{3.17}$$

with $g_{am,O2}$ being a constant gain factor, τ_{O2} a constant time factor, and $C_{vam,O2}$ being the oxygen concentration in the venous blood leaving the active muscles. By applying a mass balance of oxygen before and after the active muscles,

$$Q_{am} \cdot C_{a,O2} = Q_{am} \cdot C_{vam,O2} + \dot{M}_{am},$$

an expression for the venous oxygen concentration is achieved

$$C_{vam,O2} = C_{a,O2} - \frac{\dot{M}_{am}}{Q_{am}}. \tag{3.18}$$

Here $C_{a,O2}$ is the oxygen concentration in the arterial blood, Q_{am} is the blood flow to the active muscles, and $\dot{M}_{am}$ is the metabolic oxygen consumption rate in the active muscles. The basal value of $\dot{M}_{am,n}$ is chosen so that the arteriovenous oxygen concentration difference matches that of Bogaard *et al.* [24]. To calculate the blood flow to the active muscles, Equation (2.1) is applied. As the resistance over the active muscles is in parallel with the non-active resistance, the pressure drop is the same over both resistances. Hence, solving for Q_{am} yields

$$Q_{am} = \frac{\Delta P}{R_{am}} = \frac{P_{ao} - P_{vc}}{R_{am}}, \tag{3.19}$$

where P_{ao} is the pressure in the aorta, and P_{vc} is the pressure in the vena cava.

Again using insight from Magasso's model, an expression for the metabolic oxygen consumption rate is given

$$\dot{M}_{am} = \dot{M}_{am,n} \cdot (1 + x_M), \tag{3.20}$$

with x_M being a dimensionless variable defined by the first order differential equation

$$\frac{dx_M}{dt} = \frac{1}{\tau_M} \cdot (-x_M + g_M \cdot I), \tag{3.21}$$

where g_M and τ_M are constant gain and time factors, respectively, and I is the exercise intensity.

Effectors Driven by Sympathetic Activity

Non-active resistance, R_b, and baseline active muscle resistance, $R_{am,n}$, are driven by sympathetic tone. These quantities are defined as the sum of a constant basal value and an intensity-dependent value

$$\theta = \theta_0 + \Delta\theta, \tag{3.22}$$

where θ represents the generic controlled parameter (R_b, $R_{am,n}$), θ_0 is the basal constant, and $\Delta\theta$ is the intensity-dependent term of θ. Both $R_{am,n,0}$ and $R_{b,0}$ are chosen in order to match the resting active muscle resistance of Magosso and Ursino [6] and the resting systemic resistance of Smith *et al.* [10].

The following equations defining $\Delta\theta$ are retrieved from Magosso and Ursino [6] and Ursino and Magosso [34].

The expression for the intensity dependent effectors are given by a first-order dynamic equation

$$\frac{\mathrm{d}\Delta\theta}{\mathrm{d}t} = \frac{1}{\tau_\theta} \cdot (-\Delta\theta + \sigma_\theta), \tag{3.23}$$

where τ_θ is a time constant and σ_θ is a logarithmic function given by

$$\sigma_\theta = \begin{cases} G_\theta \cdot \ln\left(f_{es} - f_{es,min} + 1\right), & f_{es} \geq f_{es,min}, \\ 0, & f_{es} < f_{es,min}. \end{cases} \tag{3.24}$$

Here G_θ is a gain constant, ln is the natural logarithm, f_{es} is the sympathetic activity controlling the generic parameter, and the subscript min denotes the minimal value of the sympathetic activity. The logarithmic function usually includes a latency constant, but since this model is only for steady state, this delay is neglected.

Further, f_{es} is defined as

$$f_{es} = \begin{cases} f_{es,\infty} + \left(f_{es,0} - f_{es,\infty}\right) \cdot exp\left[k_{es} \cdot \left(W_{sb} \cdot f_{ab} + W_{sp} \cdot f_{ap} - \omega\right)\right] + \gamma, & f_{es} < f_{es,max} \\ f_{es,max}, & f_{es} \geq f_{es,max} \end{cases}, \tag{3.25}$$

where k_{es}, ω, $f_{es,0}$, $f_{es,\infty}$ and $f_{es,max}$ are constants, with $f_{es,max}$ being the upper saturation level for the sympathetic activity. The parameters f_{ab} and f_{ap} are afferent activities from baroreceptors and lung-stretch receptors, while W_{sb} and W_{sp} are corresponding synaptic weights. The variable γ is the term representing the effect of the central command, described in the following.

According to Rowell *et al.* [16] and Coote [36], central command has an excitatory effect on the sympathetic system. This is included in Equation (3.25). Central command is made as an intensity-dependent sigmoidal function starting at zero, increasing for increasing intensity, reaching an upper saturation at higher intensities. This way, the equation for γ becomes

$$\gamma = \frac{\gamma_{min} + \gamma_{max} \cdot exp\left(\frac{I-I_0}{k_{cc}}\right)}{1 + exp\left(\frac{I-I_0}{k_{cc}}\right)}. \tag{3.26}$$

The subscripts max and min denote the upper and lower saturation level of the central command, and I_0 and k_{cc} are constants related to the slope of the sigmoidal function.

The afferent activity from the baroreceptors, f_{ab}, is assumed constant, meanwhile f_{ap} is defined as a first-order dynamic

$$\frac{df_{ap}}{dt} = \frac{1}{\tau_{ap}} \cdot \left(-f_{ap} + \phi_{ap}\right), \tag{3.27}$$

where ϕ_{ap} is an expression dependent on tidal volume V_T,

$$\phi_{ap} = G_{ap} \cdot V_T. \tag{3.28}$$

Here G_{ap} is a gain factor, and V_T is assumed to increase linearly based on results from Magosso and Ursino [6], as

$$V_T = V_{T,n} \cdot (1 + 2.74 \cdot I). \tag{3.29}$$

The basal value for tidal value is retrieved from Mines [37]. All constants can be found in Table 3.1.

3.3.2 Full Model

The full model with all compartments is seen in Figure 3.1. In addition, the diagram in Figure 3.2 shows the block diagram of the control mechanisms, and how each effector is regulated by exercise intensity.

3.4 Analysis

The results from the model will be compared to simulation results from Magosso and Ursino [6] and Smith *et al.* [10], as well as to experimental data from Pawel-

Table 3.1: Values for all constants used in the model. Does not include values already reported in Smith *et al.* [10].

	Ventricular Elastance	
$E_{lv}^{rest} = 2.8798\,\mathrm{mmHg\,mL^{-1}}$	$E_{lv}^{rest} = 0.585\,\mathrm{mmHg\,mL^{-1}}$	
	Muscle Pump	
$A_{mp} = 3.5\,\mathrm{mmHg}$	$T_{im} = 1\,\mathrm{s}$	$T_c = 0.75\,\mathrm{s}$
	Elastance Driver Function	
$\beta = 1.672$	$\beta_1 = 0.708$	$\beta_2 = 1.187$
$n_1 = 1.32$	$n_2 = 21.9$	
	x_{met}	
$\tau_{met} = 10\,\mathrm{s}$	$\phi_{max} = 20$	$I_{0,met} = 0.427$
	$\phi_{min} = -1.87$	$k_{met} = 0.18$
	$x_{am,O2}$	
$\tau_{O2} = 10\,\mathrm{s}$	$g_{am,O2} = 30$	$C_{vam,O2n} = 0.152$
$\tau_M = 40\,\mathrm{s}$	$g_M = 40$	$C_{a,O2} = 0.2$
		$\dot{M}_{am,n} = 1.0\,\mathrm{mL\,s^{-1}}$
	Sympathetic Tone	
$R_{b,0} = 0.6\,\mathrm{mmHg\,s\,mL^{-1}}$	$G_{R_b} = 0.69$	$f_{es,min} = 2.66\,\mathrm{s^{-1}}$
$R_{am,n,0} = 13\,\mathrm{mmHg\,s\,mL^{-1}}$	$G_{R_{am}} = 2.47$	$f_{es,0} = 16.11\,\mathrm{s^{-1}}$
$k_{es} = 0.0675\,\mathrm{s}$	$W_{sb} = -1$	$f_{es,\infty} = 2.10\,\mathrm{s^{-1}}$
$\tau_{R_b} = 6\,\mathrm{s}$	$W_{sp} = -0.34$	$f_{es,max} = 60\,\mathrm{s^{-1}}$
$\tau_{R_{am}} = 6\,\mathrm{s}$	$\omega = -4.6\mathrm{s^{-1}}$	$f_{ab} = 25.15\,\mathrm{s^{-1}}$
	f_{ap}	
$\tau_{ap} = 2\,\mathrm{s}$	$G_{ap} = 23.29\mathrm{l^{-1}}$	$V_{T,n} = 0.5831\,\mathrm{s^{-1}}$
	Central Command	
$\gamma_{min} = -0.037\,\mathrm{s^{-1}}$	$\gamma_{max} = 5.5\,\mathrm{s^{-1}}$	$I_0 = 0.65$
		$k_{cc} = 0.13$

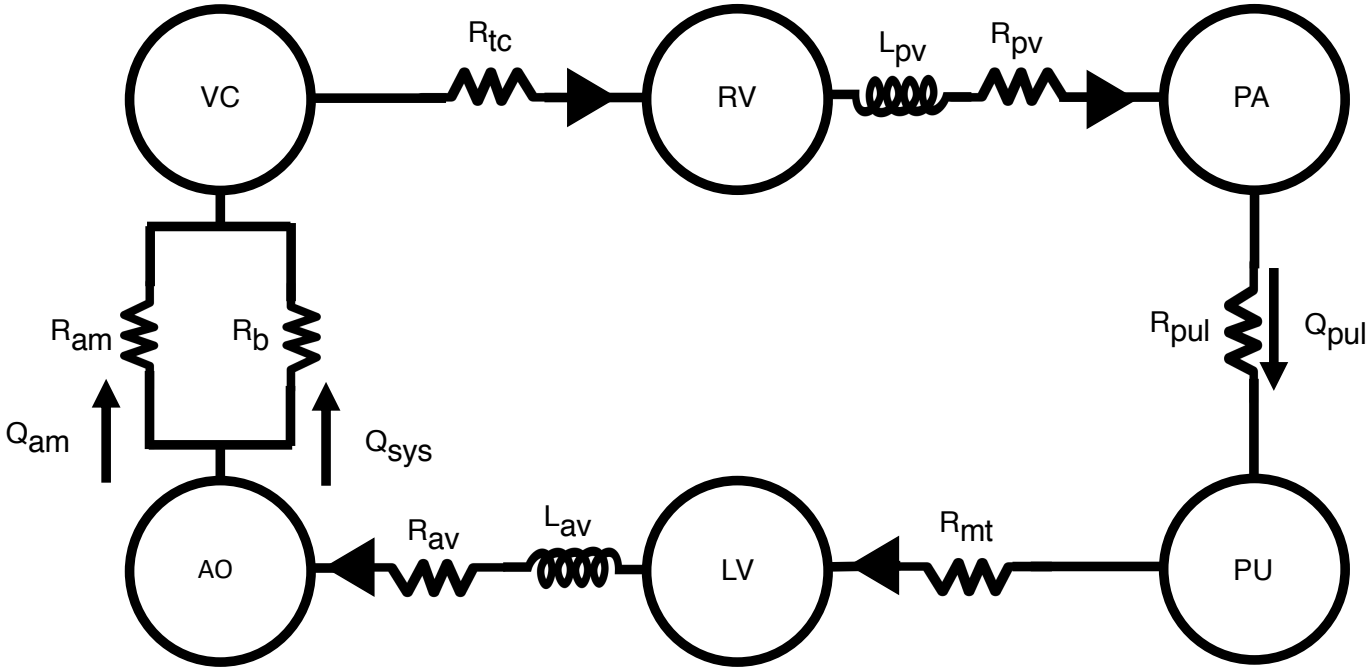


Figure 3.1: A circuit drawing of the model. R is resistance, L inertance and Q flow rate, ► and ◄ represent valves. am = active muscles, AO = aorta, av = aortic valve, b = baseline, LV = left ventricle, mt = mitral valve, PA = pulmonary arteries, PU = lungs, pul = pulmonary, pv = pulmonary valve, RV = right ventricle, sys = systemic, tc = tricuspid valve, VC = vena cava.

czyk *et al.* [9]. The current model does not account for transient effects, therefore these will naturally not be evaluated.

3.4.1 Properties Evaluated

Six cardiovascular properties will be the main focus of the analysis: mean arterial pressure, cardiac output, systolic arterial pressure, diastolic arterial pressure, systemic conductance and active muscle flow. These are the main cardiovascular quantities reported in Magosso and Ursino [6] for steady state conditions, and will therefore also be emphasized in this paper. The systemic conductance is just the inverse of the systemic resistance, but will be used when compared to Magosso and Ursino [6] and Pawelczyk *et al.* [9], since they both report conductance, not resistance. The results are extracted by using the period function τ from Equation (3.2) to determine the last heartbeat of the simulation, which then may readily be

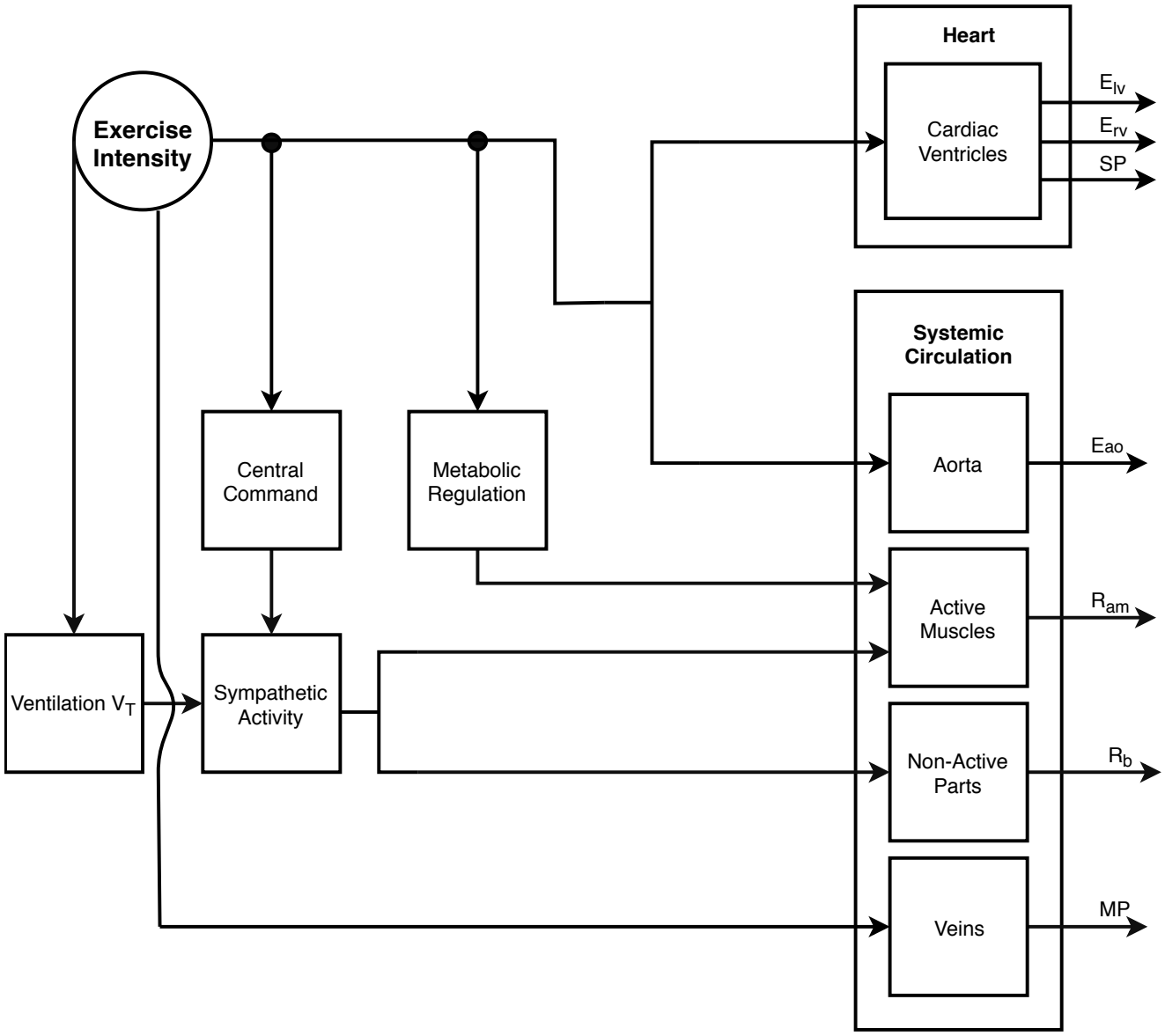


Figure 3.2: Block diagram of how exercise intensity and the control system modulate the cardiovascular mechanisms. SP = systolic period, MP = muscle pump.

analyzed. Since the period function τ varies between 0 and 1, the start of every heartbeat will be found where $\tau = 0$. The last heartbeat will begin at the second to last instance where $\tau = 0$, and end at the last instance.

Main Cardiovascular Properties

The mean arterial pressure is approximated as the time average of the aortic pressure over the last heartbeat. The cardiac output is calculated simply by Equation (2.10) and Equation (2.11), with end-systolic and end-diastolic left ventricular volume being maximum and minimum values of the left ventricular volume of the last heartbeat. The active muscle flow is calculated as the time average of Q_{am} over the last heartbeat, while the systemic vascular conductance is calculated by Equation (2.4) with $R = R_{sys}$. Here, R_{sys} is the resistance at the last heartbeat, which is constant when steady state has been reached.

Systolic and diastolic pressure will also be evaluated to give a clearer picture of the pressure development. These are extracted as the maximum and minimum values of the aortic pressure over the last heartbeat.

3.5 Sensitivity Analysis

To evaluate the influence of the cardiovascular regulatory mechanisms, a simple local sensitivity analysis from Saltelli *et al.* [38] is carried out on the added mechanisms of the physiological model. The results of increasing and decreasing systemic resistance, aortic elastance, venous muscle pump amplitude, systolic period fraction and ventricular elastance are analyzed. The sensitivity analysis of these mechanisms will be referred to as the "mechanical" sensitivity analysis. In addition, the results of changing resting and max heart rate, sympathetic tone, central command, resting metabolism and arterial oxygen concentration will be plotted. These will be referred to as the "physiological reflex" sensitivity analysis. Max heart rate, resting heart rate, resting metabolism and arterial oxygen concentration are parameters that can be measured and personalized, while central command and sympathetic activity are the main driving mechanisms of the systemic resistance response to exercise in this model. This is the main reason these components will be focused on in the reflex sensitivity analysis.

The most important changes that occur when increasing and decreasing the various mechanisms will be plotted. In addition to plots, tables displaying the accumulated difference between the nominal value and the altered value will be presented. To get this difference, the sensitivity for a given intensity, S_i, is calculated by

$$S_i = \frac{\partial y_i}{\partial x_i} \cdot \frac{x_{nom}}{y_{nom,i}}, \tag{3.30}$$

where y_i represents the relative increase from rest for the property being evaluated (i.e. aortic pressure, diastolic pressure, etc.), while x_i represents the mech-

anism that is altered (i.e. systemic resistance, muscle pump amplitude, etc.). The subscript i denotes the exercise intensity. The subscript nom denotes the nominal values for the respective properties and mechanisms, included to non-dimensionalize and normalize the sensitivity. By normalizing the sensitivities, the sensitivity of different properties can be compared, since they are all normalized by their own nominal value. Alternatively, if the nominal value is close to zero, yielding an excessive normalized sensitivity, the unnormalized sensitivity may be presented as

$$U_i = \frac{\partial y_i}{\partial x_i} \cdot x_{nom}. \tag{3.31}$$

It will be explicitly specified if Equation (3.31) is used for calculating the sensitivity. The difference between Equations (3.30) and (3.31) is that the former calculates how sensitive the relative increase in the property is compared to the nominal value, while the latter calculates the actual relative change when augmenting the effect of a mechanism.

Finally, the root mean square, RMS, of the sensitivity for all intensities is calculated simply by

$$RMS = \frac{\text{avg}}{|\text{avg}|}\sqrt{\frac{1}{N}\sum S_i^2}, \tag{3.32}$$

where N is the total amount of intensities the sensitivity was calculated for, and avg is the average of the sensitivity for all intensities. The first factor in the expression is added to include a negative sign for mechanisms that have a negative effect. The value of RMS is the value of the accumulated sensitivity for each property.

Local linearity is assumed, and each mechanism is increased by 10% for the sensitivity analysis. Conceptually, the sensitivity analysis is calculated by a finite difference computation, but in practice 10% may be more robust, as it averages out the curvature and reduces potential limitations in numerical accuracy for very small changes in the parameters.

In addition to the aforementioned sensitivity analysis, a "strength" sensitivity analysis on the curve-fitted/population data mechanisms will be carried out. That is, the curve-fitted resistance and the population data based aortic and ventricular elastance are written on the form

$$\Omega(I) = \theta(0) + [\theta(I) - \theta(0)] \cdot b. \tag{3.33}$$

The mechanism being evaluated is $\Omega(I)$, and the reference value for the same mechanism is $\theta(I)$, both being functions of exercise intensity. For example, if $\theta(I)$ is the systemic resistance from the curve-fit model, $\Omega(I)$ is the new systemic resistance in this sensitivity analysis. The constant b is the strength of the property evaluated. The population data gives a typical change in mechanisms at a given intensity, but it can be hypothesized that the exact total change of the mechanisms for increasing intensities may vary. Therefore, it is useful to investigate the effect a strengthened response may have. To model differences in relative change from

rest, Equation (3.33) is introduced, which can be applied on Equations (3.30) and (3.32). In this case, b is x, and is increased by 10%.

The difference between the mechanical sensitivity analysis and the strength sensitivity analysis is that in the mechanical analysis the resting value of the property is altered, but the relative response remains the same. A practical example would be a hypertensive patient with a normal response to exercise. In the strength analysis on the other hand, the resting value remains the same, but the response is augmented. This could for example be a normotensive patient with a "defect" response to exercise.

3.6 Simulation

To complete the model, the modifications in Section 3.2, and subsequently Section 3.3, are applied to Smith's model. The model can now be solved numerically. In this project the open-source modelling system JSim [39] is used for solving the system of equations. The full JSim code can be found in Appendix A.

3.6.1 Numerical Method

In JSim, solver settings for the ordinary differential equation (ODE) solver and the non-linear zero finder can be set. In this model, the DOPRI5 (Dormand-Prince method) is used as the ODE-solver, with both relative and absolute tolerance set to $1 \cdot 10^{-7}$. The Simplex-method is used as the zero-finder, with an error tolerance of $1 \cdot 10^{-6}$. These are all default settings in JSim.

3.6.2 Time Interval

To ensure steady state is reached, a sufficiently large time interval is needed. It was found that a time interval of $[0\text{s}, 200\text{s}]$ with timesteps $\Delta t = 0.005\,\text{s}$ was acceptable to yield a steady state solution.

3.6.3 Initial Conditions

Since differential equations make up a big part of the computational model, initial conditions are needed. However, this model is made for steady state exercise only, meaning the initial conditions have no effect on the outcome of the simulation, as long as stability is ensured. With all initial conditions set to 0, the current model runs as desired.

Chapter 4

Results

To begin, the effect of adding each mechanism is evaluated and plotted to see how the different mechanisms affect the model. Then, the results from the physiological model will be presented. Finally, a local sensitivity analysis is carried out to assess the influence of increasing or decreasing the various mechanisms and parameters.

The focus will be on the mechanical cardiovascular properties, in addition to sub-properties that may explain or elaborate on particular responses. These sub-properties are parameters that are included in the equations for the bigger cardiovascular properties, e.g. evaluating arterial oxygen concentration to properly understand the response of systemic resistance. In particular, the cardiovascular properties evaluated will be mean arterial pressure, systolic pressure, diastolic pressure, cardiac output, systemic conductance and active muscle flow. Mainly, the response of the properties relative to their resting conditions will be assessed, since this most easily shows the impact of exercise. In some cases it will be expedient to consider the actual values as well.

4.1 Adding Mechanisms

First, Smith's model is plotted for increasing intensities. Next, the full curve-fit model is plotted. Then the curve-fit model is plotted with one mechanism removed - for every mechanism - to show the effect each mechanism has on the model. In addition, Magosso's results are also plotted, as a basis for comparison.

Mean Arterial Pressure

Figure 4.1a shows how the arterial pressure changes when removing each mechanism regulating the exercise haemodynamics in the model. Evidently, the arterial pressure increases excessively for Smith's model. Smith's model was designed only for resting conditions, and is not expected to work well when increasing the heart rate. The reason for this increase in arterial pressure is due to the increased cardiac output, as seen from Equation 2.1. The increase in cardiac output is explained in

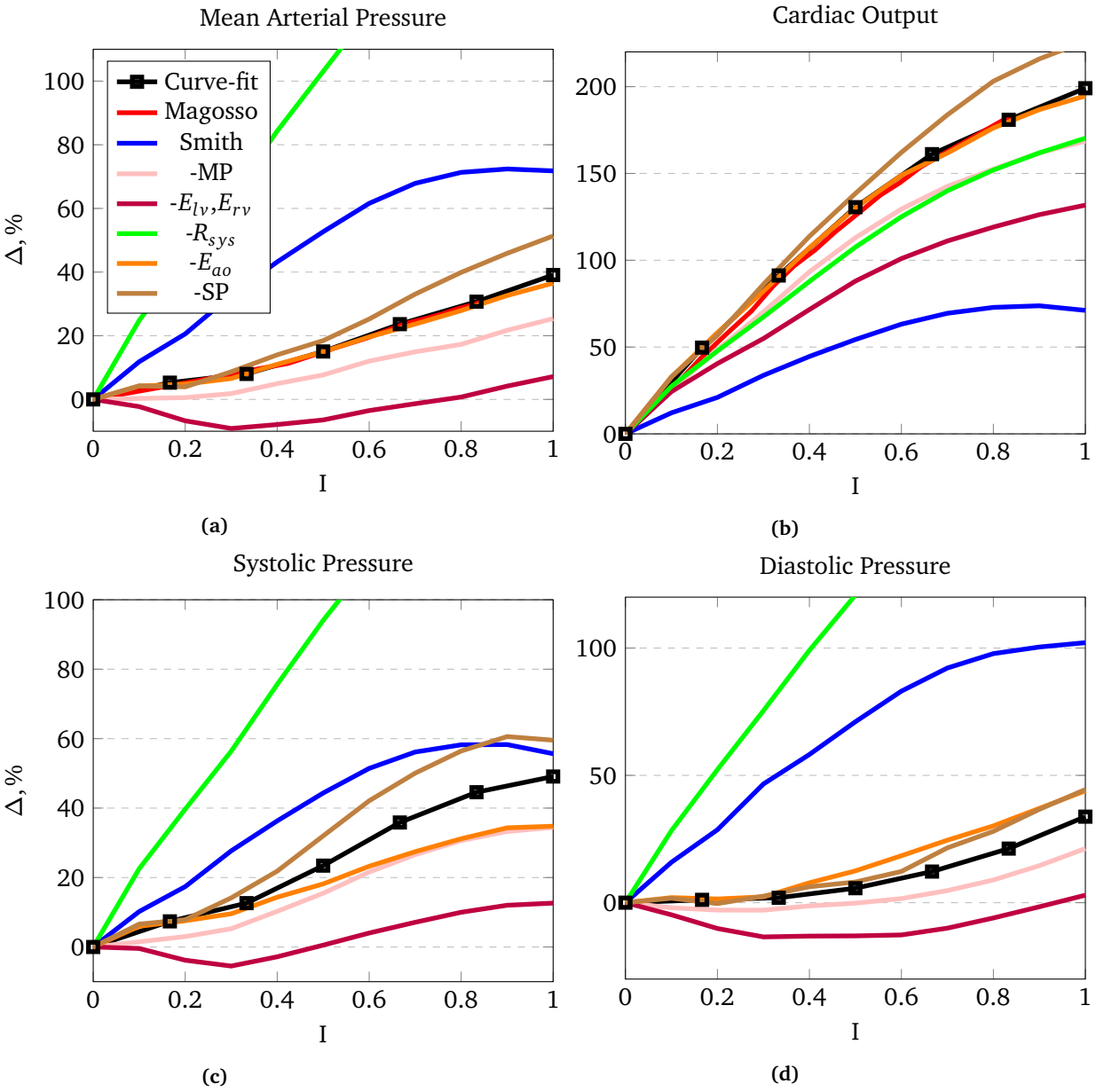


Figure 4.1: Relative change in mean arterial pressure, cardiac output, systolic pressure and diastolic pressure for the curve-fit model - but with leaving one mechanism out at a time - plotted against exercise intensity. The legend shows which mechanism is left out. Magosso's model is only included for mean arterial pressure and cardiac output, since they present no data for systolic and diastolic pressure. In addition, Smith's model is plotted with no added mechanisms. MP = muscle pump, SP = systolic period.

the next paragraph. Adding the dynamic systemic resistance decreases mean arterial pressure significantly. Aortic elastance has negligible influence, while the muscle pump has a slight increasing effect and the intensity-dependent systolic period a slight decreasing effect. The intensity-dependent ventricular elastance increases the pressure substantially. In fact, when not including the intensity-dependent ventricular elastance, the mean arterial pressure becomes less than at resting conditions for $I = 0$ to $I = 0.8$.

Cardiac Output

In Figure 4.1b, cardiac output is plotted for when leaving out one regulating mechanism at a time. Smith's model shows an increase in cardiac output for increasing exercise intensity, owing to the increased heart rate. In addition, the stroke volume is decreased as a result of the shortened diastolic filling time for increasing heart rates. Considering these two effects, the increase in cardiac output is explained by Equation (2.10). Both the muscle pump and the intensity-dependent ventricular elastance increase the cardiac output, with ventricular elastance having the biggest effect. The intensity-dependent systemic resistance increases cardiac output about as much as the muscle pump, while aortic elastance has a negligible effect. A decrease in cardiac output occurs when the intensity-dependent systolic period is added.

Diastolic and Systolic Pressure

Figure 4.1d displays the diastolic pressure, while Figure 4.1c shows how the systolic pressure changes. Smith's model yields a larger increase in diastolic pressure than systolic pressure, but the shape is similar. Adding the muscle pump and the intensity-dependent ventricular elastance increases both pressures, with ventricular elastance having the biggest influence. The intensity-dependent systemic resistance and systolic period decrease both pressures, although the systemic resistance has a much bigger effect. Including the aortic elastance has an opposite effect on diastolic and systolic pressure, increasing systolic pressure and decreasing diastolic pressure.

4.2 Physiological Implementation

In this section, the results from the physiological implementation of the systemic resistance are presented. The results will be compared to the curve-fit model, Magosso's results, and experimental data from Pawelczyk *et al.* [9].

Arterial Pressure

In Figure 4.2a, the mean arterial pressure increase is plotted for increasing intensities. Included in the plot are also the results from the curve-fit model, Magosso's results and experimental data from Pawelczyk *et al.* [9]. In the physiological model,

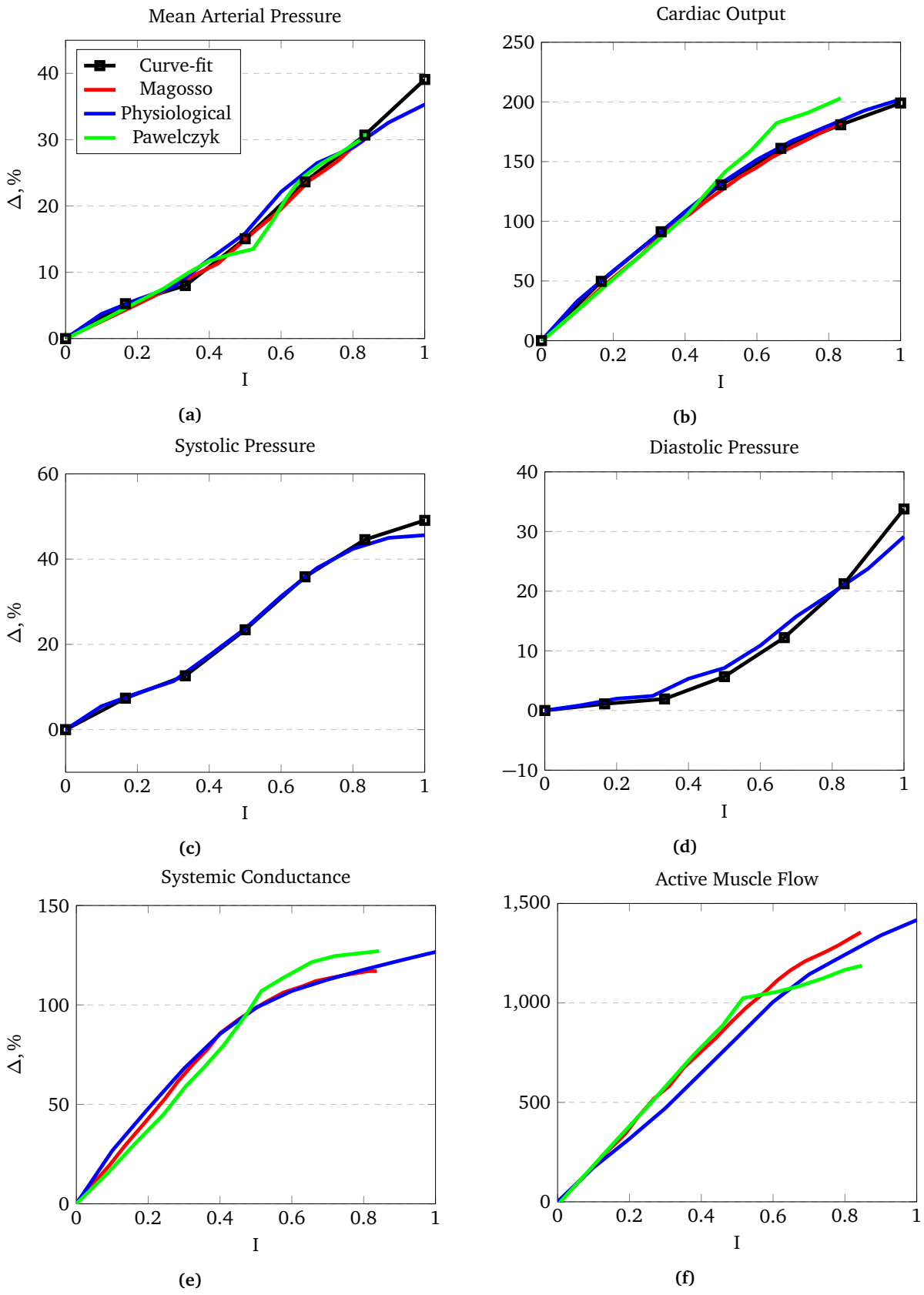


Figure 4.2: Relative change in mean arterial pressure, cardiac output, systolic pressure, diastolic pressure, systemic conductance and active muscle flow for the physiological model and reference values plotted against exercise intensity.

the mean arterial pressure increases slightly less than in the curve-fit model. This decrease is also seen in the diastolic pressure and the systolic pressure in Figures 4.2d and 4.2c. Table 4.1 shows the systolic, diastolic and pulse pressures for the current model and Magosso's model for $I = 0$ and $I = 0.5$. These are, unfortunately, the only intensities systolic and diastolic pressure are reported for in Magosso and Ursino [6].

Table 4.1: Systolic, diastolic and pulse pressures during rest ($I = 0$) and at $I = 0.5$ for the physiological model and Magosso's model.

		Physiological	Magosso
$I = 0$	Systolic	119 mmHg	132 mmHg
	Diastolic	80 mmHg	88 mmHg
	Pulse	39 mmHg	44 mmHg
$I = 0.5$	Systolic	147 mmHg	155 mmHg
	Diastolic	85 mmHg	93 mmHg
	Pulse	62 mmHg	62 mmHg

Systemic Conductance

Figure 4.2e shows that the conductance for the physiological model is almost exactly the same as in Magosso. At $I = 0.5$, the data from Pawelczyk increases marginally more than the physiological model. Magosso and Pawelczyk only have data up to $I = 0.8$, which makes it hard to evaluate the performance of the physiological model between $I = 0.8$ to $I = 1$.

Cardiac Output

The cardiac output for the physiological model is plotted in Figure 4.2b. As can be seen, the cardiac output is almost exactly the same as that of Magosso and the curve-fitted model. There is, however, a slight discrepancy between the current model and the data from Pawelczyk, which arises around $I = 0.5$. The biggest difference between the two occurs at $I = 0.64$, where the difference is 16%.

Active Muscle Flow

The active muscle flow in the physiological model is slightly less than in Magosso and Pawelczyk for low intensities, as seen in 4.2f. Nevertheless, as intensity increases above $I = 0.6$, the physiological model increases above the data from Pawelczyk. At $I = 0$, the active muscle flow is 12.5mL/s, which is 14.6% of the total cardiac output at rest. At $I = 1$, the percentage is 73.3%.

Arteriovenous Oxygen Concentration Difference

Since the conductance depends on the difference in oxygen concentration between arteries and veins, the arteriovenous oxygen concentration difference has been calculated and plotted in Figure 4.3. Included in the figure is experimental data from Bogaard *et al.* [24]. The data is interpolated for intermediate values, and since exercise intensity is given as load (in units of Watt), it is assumed a linear relation between heart rate and load. This is supported by the results in Bogaard *et al.* [24].

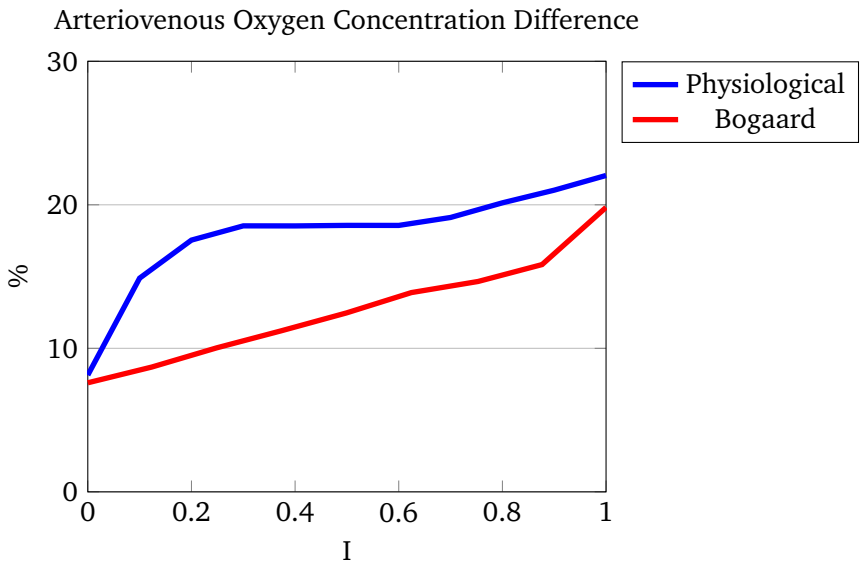


Figure 4.3: The difference in oxygen concentration between the arteries and veins for the physiological model and for data from Bogaard *et al.* [24].

Although not plotted in Magosso and Ursino [6], the arteriovenous oxygen difference is given for $I = 0$ and $I = 0.84$ as $C_{a,O2} - C_{vam,O2} = 4.5\%$ and $C_{a,O2} - C_{vam,O2} = 10\%$. In the current model the difference for $I = 0$ is $C_{a,O2} - C_{vam,O2} = 8.1\%$, and for $I = 0.84$ it is $C_{a,O2} - C_{vam,O2} = 22.0\%$. As it turns out, the venous oxygen concentration becomes negative for $I > 0.8$ in the current model, which is unphysical since concentration cannot be negative.

Metabolic Oxygen Consumption Rate

The resting metabolic oxygen consumption rate, $\dot{M}_{am,n}$, is important for both active muscle flow and arteriovenous oxygen concentration. In the physiological model, $\dot{M}_{am,n} = 1.0\,\mathrm{mL\,s^{-1}}$ is used. By using the same resting metabolic oxygen consumption rate as Magosso, $\dot{M}_{am,n} = 0.516$, the arteriovenous oxygen concentration difference becomes $C_{a,O2} - C_{vam,O2} = 5.9\%$ for $I = 0$ and $C_{a,O2} - C_{vam,O2} = 11.0\%$ for $I = 0.84$. These values are closer to what Magosso reports, but further away from the values in Bogaard *et al.* [24].

Table 4.2: Accumulated mechanical sensitivity, RMS, of properties (top row) to mechanisms (far-left column). MAP = mean arterial pressure, P_d = diastolic pressure, P_s = systolic pressure, CO = Cardiac output, Q_{am} = active muscle flow.

	MAP	P_d	P_s	CO	Q_{am}
R_{sys}	2.16	8.2	0.86	0.26	0.73
MP	0.56	1.38	0.42	0.14	0.06
E_{ao}	0.10	-1.17	0.31	0.03	0.01
E_{lv}, E_{rv}	-0.60	-1.40	-0.40	-0.15	-0.02
Systolic period	-1.71	-3.67	-1.25	-0.46	-0.26

4.3 Sensitivity Analysis

The sensitivity analysis is split in three parts. First, in Section 4.3.1, the results of the mechanical sensitivity analysis are presented. Then, in Section 4.3.2, follow the results of the physiological reflex sensitivity analysis. Finally, in Section 4.3.3 are the results of the strength analysis on the exercise response. The plots are mainly calculated by Equation (3.30). In these plots, the values on the y-axis mark the increase in the property for a 100% increase in the mechanism (i.e. a value of 0 means zero change, a value of 1 a 100% increase, and so on).

4.3.1 Mechanical Sensitivity

Recall from Section 3.5 that the mechanical sensitivity is the sensitivity each property has to changing the resting value of the different mechanisms. Table 4.2 gives the accumulated local sensitivity to each mechanism on each property, with a negative sign indicating a decreasing effect on the property.

Pressure

The large values in the diastolic pressure column of Table 4.2 are conspicuous. The reason for this is simply due to the shape of the diastolic pressure in Figure 4.2d. For low intensities, the increase in diastolic pressure is very small, causing the nominal value in the denominator of Equation (3.30) to become very small, thus yielding very large values for the sensitivity. For this reason, the unnormalized sensitivity of diastolic pressure is plotted in Figure 4.4. In practice, this means applying Equation (3.31). As seen in Figure 4.4, systemic resistance and systolic period change the pressures the most. Although not plotted, the effect is very similar for mean arterial pressure and systolic pressure, with the change in relative pressure for augmented systemic resistance increasing for increasing intensity, and for augmented systolic period decreasing for increasing intensity.

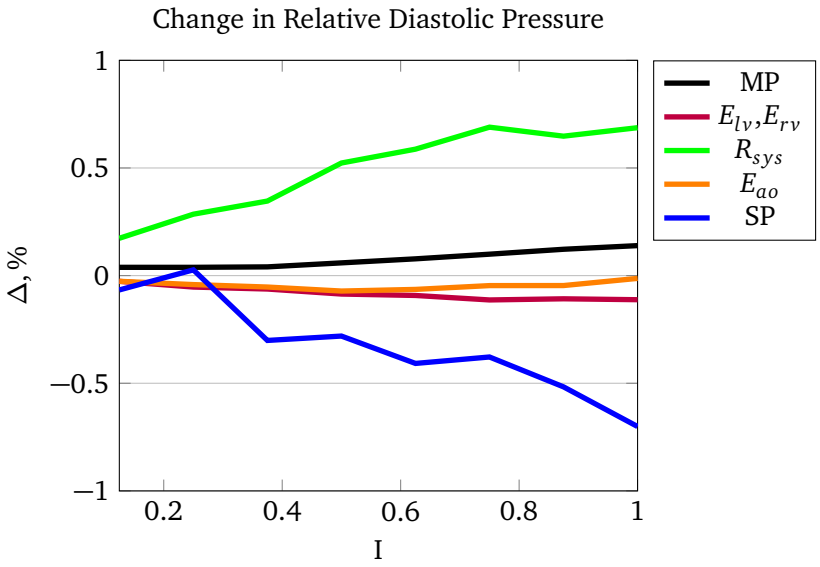


Figure 4.4: Change in relative diastolic pressure for a 10% increase in the mechanisms for all intensities. Notice that the y-axis is change in the relative diastolic pressure, not sensitivity. Calculated by Equation (3.31).

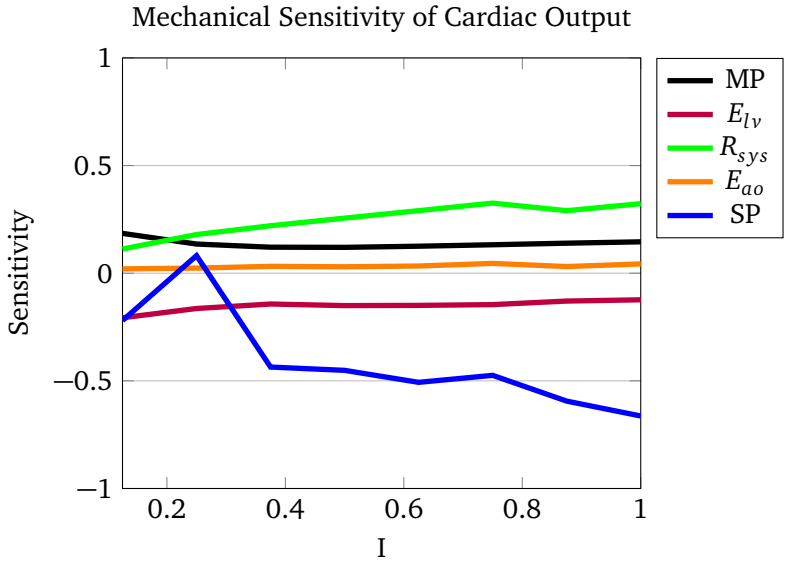


Figure 4.5: Sensitivity of cardiac output to an increase in mechanisms for all intensities.

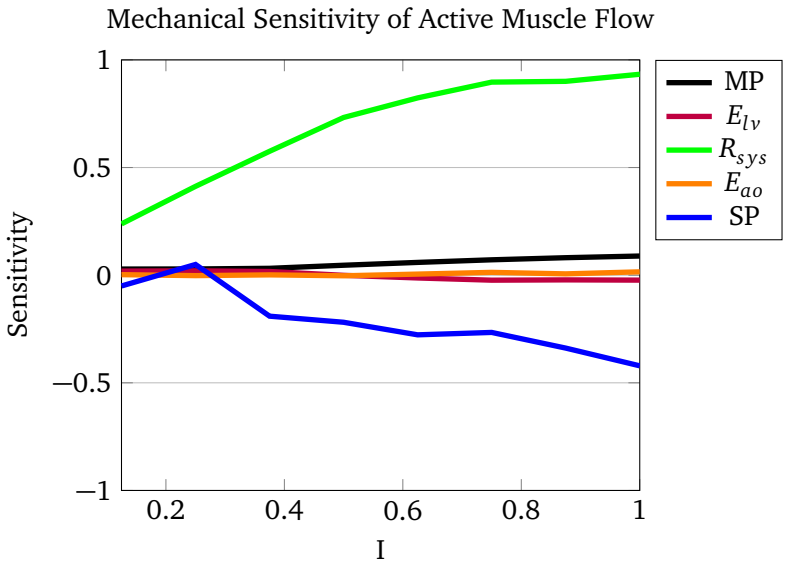


Figure 4.6: Sensitivity of active muscle flow to an increase in mechanisms for all intensities.

Cardiac Output

Figure 4.5 shows the sensitivity of cardiac output to the different mechanisms. The sensitivity is close to constant across all exercise intensities for all mechanisms, except for systolic period, to which the sensitivity decreases gradually from −0.20 to −0.6. The sharp spike at $I = 0.25$ is caused by a marginally slower increase in cardiac output for the nominal value, which is magnified when dividing by the nominal values.

Active Muscle Flow

Active muscle flow is most affected by changes in systemic resistance, as seen in Figure 4.6. For $I = 0.13$, the sensitivity to systemic resistance is 0.25, but from there it grows to 1 at $I = 1$. Active muscle flow is therefore more sensitive to changes in systemic resistance at higher intensities. Note that this is only the sensitivity to the total systemic resistance, and not to the active muscle resistance. Also systolic period affects the active muscle flow, with a decreasing effect for increasing intensities. Like for the cardiac output, there is a small spike at $I = 0.25$ for the sensitivity to systolic period.

4.3.2 Physiological Reflex Sensitivity

The physiological reflex sensitivity is the sensitivity of each property to increasing the value of a selection of the physiological constants, in addition to the sympathetic tone and central command. Table 4.3 shows the accumulated sensitivity of

Table 4.3: Accumulated physiological reflex sensitivity, RMS, of properties (top row) to parameters (far-left column). G = systemic conductance.

	MAP	P_d	P_s	CO	Q_{am}	G
HR_{max}	4.47	15.84	2.68	0.79	0.43	-0.17
HR_{rest}	-3.41	-9.1	-2.01	-0.75	-0.22	0.07
Symp	-0.72	-1.43	-0.53	0.12	-0.04	0.41
CC	0.00	0.00	0.00	0.00	0.00	0.00
$M_{am,n}$	-0.90	-3.58	-0.48	0.02	-0.38	0.21
$C_{a,o2}$	0.19	0.97	0.09	0.03	1.34	0.04

each property to each mechanism.

Pressure

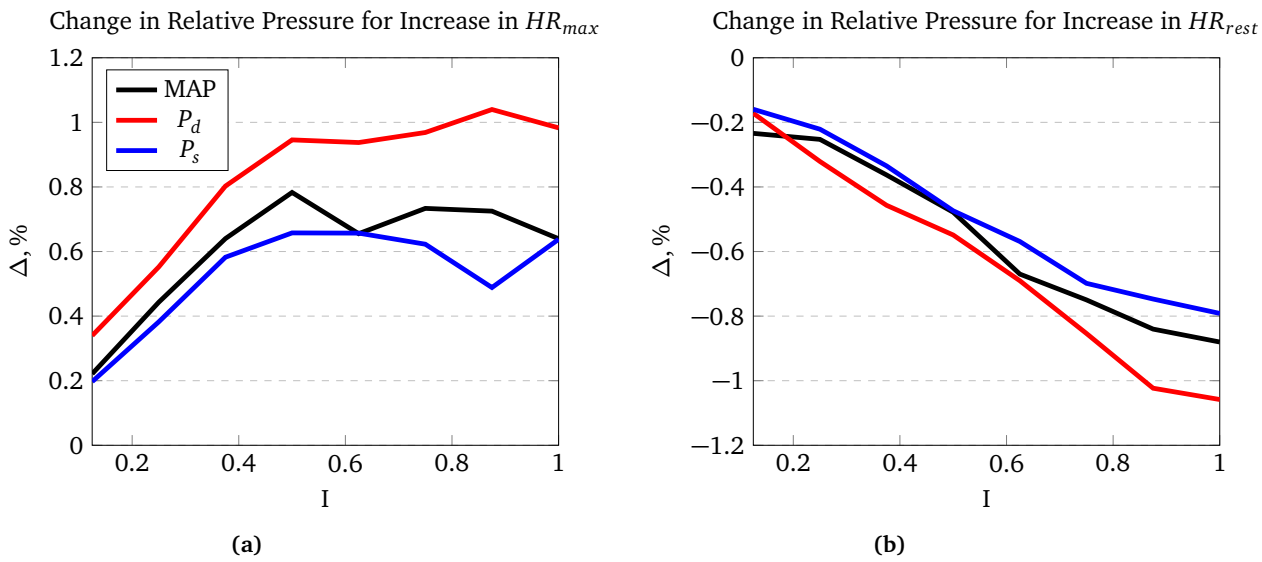
The sensitivity to max and resting heart rate is by far the largest for all three pressures. The diastolic pressure sensitivity is obviously again affected by the low values of the diastolic pressure increase. To compare between the three pressures, the unnormalized change in relative pressure (i.e. by Equation (3.31)) is plotted in Figure 4.7. The effect of increasing max heart rate is opposite to that of increasing resting heart rate. With increased max heart rate, the increase in pressures start at low values, and then grows for growing intensities. The change in both relative mean and systolic pressure drops suddenly at $I = 0.63$ and $I = 0.88$, respectively, before increasing again. When redoing the sensitivity analysis with a 15% increase, or a 10% decrease, instead, the drop in systolic pressure at $I = 0.83$ still occurs, but the increase in pressure from $I = 0.83$ to $I = 1$ does not. Rather, the change in the relative systolic pressure drops to 0.3% at $I = 1$.

For increased resting heart rate, the pressures decrease gradually as the intensity increases.

In addition to the heart rate sensitivity, resting metabolic oxygen consumption rate has a noticeable effect on the pressures. Applying Equation (3.31), the effect is constant for all intensities, reducing the relative increase in pressures by around 2% in all three cases.

Cardiac Output

For cardiac output, the heart rate is the biggest factor. The sensitivity of cardiac output to resting and max heart rate is shown in Figure 4.8. Increasing the resting heart rate attenuates the increase in cardiac output, whereas increasing the maximum heart rate augments the increase in cardiac output. The sensitivity reaches a maximum at $I = 0.38$, but, when calculated by Equation (3.31), the change in relative increase in cardiac output increases almost linearly. The stroke volume decreases when increasing the max heart rate, in particular for higher intensities. At $I = 0.13$ the stroke volume (the actual value) falls by 1%, while for $I = 1$ it



(a) **(b)**

Figure 4.7: Change in relative mean, diastolic and systolic pressure for a 10% increase in max and resting heart rate. Notice that the y-axis is change in the relative pressures, not sensitivity. Calculated by Equation (3.31).

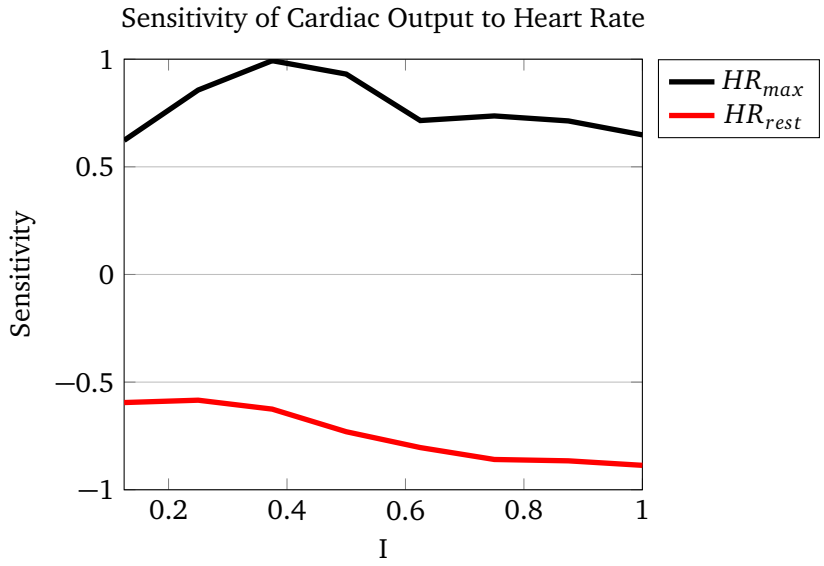


Figure 4.8: Sensitivity of cardiac output to an increase in max and resting heart rate.

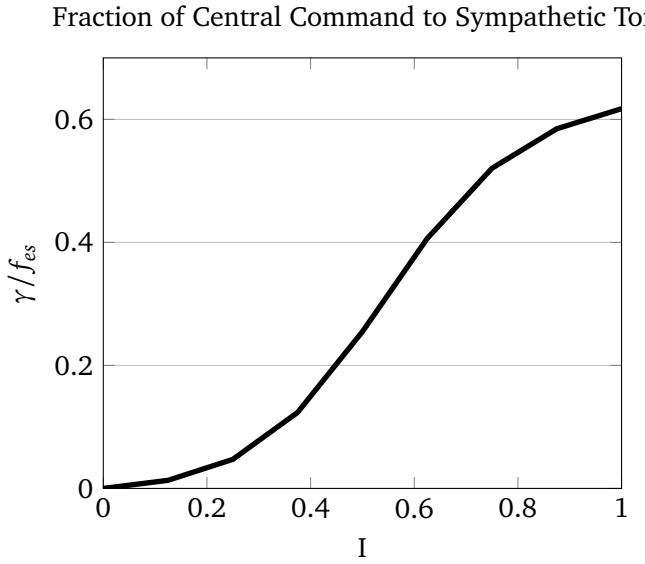


Figure 4.9: The fraction of central command to sympathetic tone for all intensities.

falls by 5%. When increasing the resting heart rate, the stroke volume falls 2.5% and 0%, for $I = 0.13$ and $I = 1$, respectively.

Table 4.3 shows there is almost no sensitivity to any of the other parameters.

Active Muscle Flow

For active muscle flow the sensitivity is both small and constant for all physiological parameters, except $C_{a,o2}$. Increasing the arterial oxygen concentration has a constant augmenting effect on the relative increase in active muscle flow for all intensities $I > 0$, at around 1.3. This strong positive sensitivity is due to a reduced value of active muscle flow at $I = 0$.

Conductance

Conductance is mainly affected by sympathetic tone, while the other parameters have little influence. Nevertheless, sympathetic tone has relatively little influence as well, reaching only 0.5 at its maximum, and being nearly constant for all intensities.

Central Command

As seen in Table 4.3, central command has zero accumulated sensitivity on all properties. The reason for this is due to the x_{nom} in Equation (3.30), which for central command is very small.

Table 4.4: Accumulated reflex strength sensitivity, RMS, of properties (top row) to mechanisms (far-left column).

	MAP	P_d	P_s	CO
R_{sys}	-6.48	-73.09	-3.32	0.17
E_{ao}	-0.52	-1.18	0.22	0.01
E_{lv}	0.97	9.30	0.70	0.17

To assess the sensitivity to central command, the fraction γ/f_{es} is plotted in Figure 4.9.

4.3.3 Reflex Strength

The strength sensitivity analysis shows the sensitivity of the four main cardiovascular properties of the curve-fit model when increasing the magnitude of the response of the curve-fitted/population based mechanisms. Table 4.4 shows the accumulated sensitivity of each property.

Pressures

The strength sensitivity of mean arterial pressure, diastolic pressure and systolic pressure is presented in Figure 4.10. The diastolic pressure sensitivity is calculated by Equation (3.31). Both ventricular and aortic elastance have very little influence on the pressures, while the systemic resistance has a larger negative effect. The spikes at $I = 0.25$ in the mean and systolic pressures seem curious, but are only a result of the slow increase in mean and systolic pressure for low intensities in the physiological model. If plotted by Equation (3.31), the relative change for all three pressures would look similar in shape for a strengthened systemic resistance response.

Cardiac Output

The sensitivity of cardiac output to systemic resistance and ventricular elastance is almost identical, with both being almost constant for all intensities at a value of 0.17. The aortic elastance has virtually no effect.

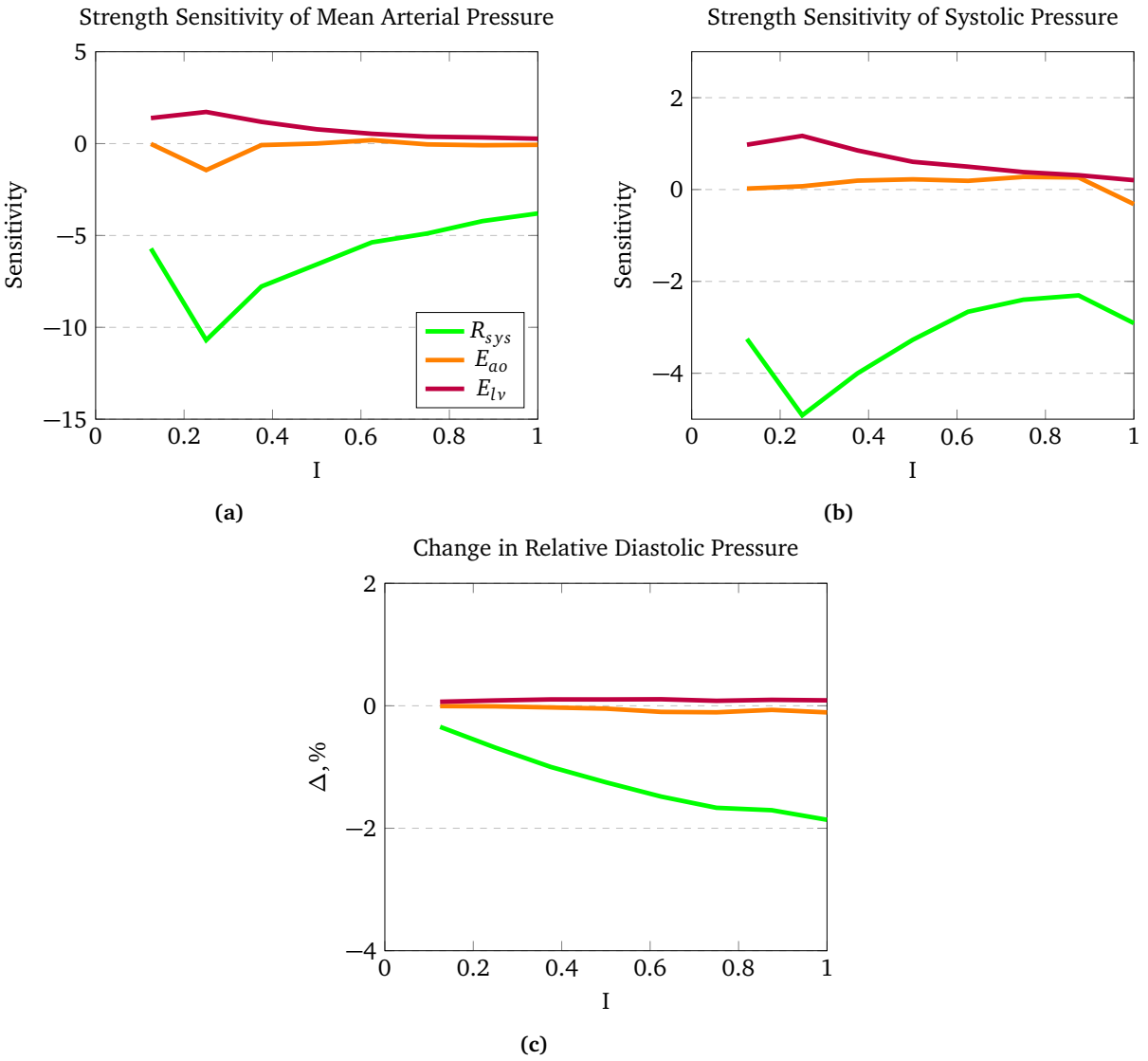


Figure 4.10: (a) Sensitivity of mean arterial pressure to a strengthened response of the mechanisms. (b) Sensitivity of systolic pressure to a strengthened response of the mechanisms. (c) Change in relative diastolic pressure for a strengthened response in the mechanisms. Notice that the y-axis in (c) is change in the relative diastolic pressure, not sensitivity. (c) is calculated by Equation (3.31).

Chapter 5

Discussion

As stated in the introduction, the objective of this master's thesis is to create a haemodynamic model that corresponds well with experimental data and results from other models in the literature, at a low computational cost, as well as not having an excessive amount of parameters needed to personalize the model. In the project thesis this was done by using Smith's model as a starting point and then adding mechanisms from Magosso. This did not yield satisfactory results, and a somewhat different approach was applied in this master's thesis. By implementing some of the mechanisms by curve-fit, it was possible to work in the reverse direction, from the desired results to the necessary mechanisms. The necessary mechanisms could then be implemented and the model evaluated based on this implementation. In this chapter, the curve-fit model will be discussed in Section 5.1, followed by a discussion of the physiological model in Section 5.2. In Section 5.3, the sensitivity analysis carried out on the physiological model will be discussed. Finally, in Section 5.4, a conclusion based on the preceding discussion will close this chapter.

5.1 Curve-fit Model

Instead of implementing the systemic resistance as either a set of dynamic equations or fitting it to population data, the curve-fit model applies a curve-fit to the systemic resistance reported in Magosso. This was done to assess the influence of the various mechanisms and to assess the model output, without needing to implement a large system of equations for the systemic resistance.

5.1.1 Mean Arterial Pressure and Cardiac Output

Even without adding any mechanisms, Smith's model yields an increase in mean arterial pressure for increasing intensity. This is simply due to the increased heart rate, which increases the cardiac output, which increases pressure. Figure 4.1a shows how the dynamic systemic resistance is by far the most important mechanism to attenuate the increase in pressure for increasing intensity.

Ventricular elastance and systolic period are qualities related to the heart, which affect the pressure by changing the cardiac output. With an increasing systolic period relative to the heart beat period for increasing exercise intensities, the diastolic period relative to the heart beat period shortens, allowing for less filling time of the heart, and consequently a lower cardiac output. This is seen in Figure 4.1b, where the cardiac output is seen to be higher when not including the increasing systolic period. Ventricular elastance determines the force of each pump of the heart. Therefore, it is also important for cardiac output. Again, as can be seen by comparing Figures 4.1a and 4.1b, the decrease in pressure from excluding the intensity-dependent ventricular elastance can be explained by the decrease in cardiac output. Similarly, as explained in Section 2.4.5, the muscle pump enhances venous return and preload, thereby increasing the stroke volume and cardiac output from the heart by the Frank-Starling mechanism.

The aortic elastance is a mechanical property of the aortic wall, and has very little effect on cardiac output. It has opposite effect on diastolic and systolic pressure, which results in very little change in mean arterial pressure. This is expanded on in the next paragraph.

5.1.2 Systolic and Diastolic Pressure

For both systolic and diastolic pressure, most of the mechanisms have the same effect as on the mean arterial pressure. However, the aortic elastance has the opposite effect on the two pressures. An intensity-dependent aortic elastance increases the systolic pressure, but decreases the diastolic pressure. This may be explained by the Windkessel effect [28]. During systole the blood enters the aorta, which expands as the blood enters. The higher the elastance of the aorta, the stiffer the walls are. An augmented elastance will allow less expansion, making the blood pressure build up faster inside the vessel. Meanwhile, during diastole, no blood enters the aorta, except for the blood stored in the expanded aorta. With a stiffer aorta, less blood will be stored, and consequently there will be a lower diastolic blood pressure.

5.1.3 Summary

Both the mean arterial pressure and cardiac output in the curve-fit model correspond very well with the results from Magosso. The systemic resistance seems to be the most important mechanism for mean, systolic and diastolic pressure. In the curve-fit model, the systemic resistance is curve-fitted to Magosso's results, which is mainly done to test if, with a correct resistance, the other mechanisms are enough to yield realistic results. This seems to be the case.

Ventricular and aortic elastance are also curve-fitted, although not to the desired outcome, but rather to population data. It would be favorable to implement them as physiologically based equations, to allow for more individualization and personalization of the model, but it could also be possible to adjust the resting values to individual values and assume a "populational" response to exercise.

5.2 Physiological Model

In the physiological model, the curve-fitted systemic resistance is replaced with a systemic resistance driven by sympathetic tone and local metabolic regulation. All other mechanisms remain the same. In Section 5.1, the importance of the mechanisms was assessed. In this section, the correctness of a physiologically based systemic resistance will be discussed, in addition to a brief discussion of the pressures and active muscle flow. The cardiac output is the same as in the curve-fit model, since the only difference is the systemic resistance, which has very little influence on the cardiac output.

5.2.1 Systemic Conductance

The systemic conductance is the inverse of the systemic resistance, as explained in Section 2.2.2. The systemic conductance and systemic resistance will both be discussed in the following chapter, although they represent the same property. The conductance will mainly be used when comparing to other data from the literature, since it is reported as conductance in Magosso and Ursino [6] and Pawelczyk *et al.* [9].

Figure 4.2e shows how the physiological systemic conductance overestimates the data from Pawelczyk for intensities below $I = 0.5$, but coincides with Magosso's results. Both baseline resting values for non-active resistance and active muscle resistance in this model were assigned considering the resting values used for resistance in Smith's original model. In addition, the resting oxygen consumption rate in the active muscles, $\dot{M}_{am,n}$, is higher in the current model. Since arterial oxygen concentration is more or less constant at $C_{a,O2} = 0.2$ for a given individual [37, 40], Figure 4.3 shows that the venous oxygen concentration drops below zero for $I > 0.8$. By inspection of Equation (3.18), this might imply that $\dot{M}_{am}$ and $\dot{M}_{am,n}$ are too large in the current model. On the other hand, for $I = 0$ and $I = 1$, the arteriovenous oxygen concentration difference is very close to data from Bogaard *et al.* [24], which may imply correctness for $\dot{M}_{am,n}$ and $\dot{M}_{am}$. Nevertheless, the shape of the oxygen difference for increasing intensity is different from that of Bogaard, with a strong increase at low intensities. As seen from Equation (3.18), this is due to the shape of $\dot{M}_{am}$ and Q_{am} for increasing intensities. However, both of these properties are almost identical in shape to those of both Magosso and Pawelczyk, supporting the arteriovenous oxygen difference in the current model. It is also worth noting that the arteriovenous oxygen difference from Bogaard *et al.* [24] in Figure 4.3 is extrapolated from fewer datapoints than what is seen in the figure, possibly invalidating the shape of the graph.

Although the resistance in non-active parts of the cardiovascular system increases during exercise, the decrease in active muscles resistance causes the total systemic conductance to increase significantly, which reduces the pressure. This can be seen by rearranging Equation (2.1).

5.2.2 Pressures

The mean arterial pressure, systolic pressure and diastolic pressure are all very close to the curve-fit model, with only a slight reduction at $I = 1$. For low intensities, the diastolic pressure increases very little. It is recognized that diastolic pressure increases marginally during exercise, or may even drop in value [30, 41]. Table 4.1 also indicates a possible correctness in the pressures, as the increase in both systolic and diastolic pressure is very similar for the physiological model and Magosso's results, although the values are lower in the physiological model compared to those of Magosso. The discrepancy is due to the lower resting values in the physiological model, but they correspond very well with the values given in Smith *et al.* [10]. The pulse pressure at $I = 0.5$ is the same for the physiological model and Magosso's model, which suggests a reasonable relation between systolic and diastolic pressure.

5.2.3 Active Muscle Flow

Although the relative increase in active muscle flow is less than in Magosso and Pawelczyk at intensities below $I = 0.6$, it exceeds the data from Pawelczyk at intensities above $I = 0.6$, as seen in Figure 4.2f. The change in steepness of Pawelczyk's data at $I = 0.5$ is curious however, since it suggests the sudden onset of some mechanism at $I = 0.5$. A possible explanation could be that either the raw data, or the interpolation of the data, is insufficient at this point. Another possible explanation is simply a lack of data points, which, if added, would smooth out the curve. Either way, at intensities above $I = 0.6$, the physiological model lies between Magosso's and Pawelczyk's.

The active muscle flow at rest is 14.6% of the total cardiac output. Klabunde [42] states that skeletal muscle accounts for about 20% of total cardiac output at rest, and Radegran and Saltin [43] reports that around 13% of the cardiac output enters the skeletal muscles in the legs during rest. For $I = 1$, the percentage in the physiological model is 73.3%, which is close to the 80% reported in Klabunde [42] for strenuous exercise.

5.2.4 Summary

The physiological model predicts a marginally lower mean, diastolic and systolic pressure than the curve-fit model. The mean arterial pressure is very close to the one predicted by Magosso and that reported by Pawelczyk, and the increase in systolic and diastolic pressure matches very well with that reported in Magosso from $I = 0$ to $I = 0.5$. Conductance and active muscle flow are very close to Pawelczyk's data, meanwhile cardiac output remains the same as in the curve-fit model and Magosso's model. For higher intensities, both conductance and active muscle flow intersect the data from Pawelczyk. It seems that, despite not perfect correspondence between the physiological model and Pawelczyk's data, the systemic resistance and the other mechanisms included in this model are enough to

yield realistic results for the cardiovascular response to exercise. While the data reported by Pawelczyk only cover up to $I = 0.8$, the difference between models at $I > 0.8$ is worth exploring. Linearly extrapolating the data from Pawelczyk indicates that the physiological model predicts a relative increase in active muscle flow slightly closer to Pawelczyk's data at $I = 1$ than what Magosso's model does. It is worth noting that measuring cardiovascular properties at $I = 1$ is challenging, since this means sustaining max heart rate for a significant period of time. Thus most data is only available for $I < 1$, making it difficult to test model performance at very high exercise intensities.

5.3 Sensitivity Analysis

The sensitivity analysis was threefold. First, the mechanical sensitivity: an analysis on the influence of the added mechanisms, where the mechanisms were increased by 10%. This means that both the resting value and values at $I > 0$ were increased by 10%. Second, the physiological reflex sensitivity: the most "personalizable" and individual parameters were increased by 10%. Third, the strength sensitivity: the magnitude of the response of the three curve-fitted mechanisms (curve-fitted resistance and population based ventricular and aortic elastance) was analyzed, without changing the resting values. For the mechanical and physiological reflex sensitivity analyses, the percent change in the mechanisms and parameters is the same for a given intensity, while for the latter strength analysis, the percent change is different.

5.3.1 Mechanical Sensitivity

In the mechanical sensitivity analysis, the effects of increasing systemic resistance, muscle pump amplitude, aortic elastance, ventricular elastance and systolic period were presented, and will presently be discussed.

Pressures

Like mentioned earlier, the sensitivity of the diastolic pressure in Table 4.2 is offset by the low values for the increase in diastolic pressure at low intensities. Figure 4.4 shows the change in the relative diastolic pressure, with both mean and systolic pressure having a very similar shape. The muscle pump and ventricular and aortic elastance have little influence, while the systemic resistance and systolic period have effects of similar magnitude, but of opposite sign. It is important to note that the value in Figure 4.4 is the actual increase in the relative pressure, not the sensitivity of the relative increase in pressure from resting pressure. In fact, although the change in relative pressure grows for increased systemic resistance, the sensitivity of the relative increase in pressure is nearly constant across all intensities.

Both systemic resistance and systolic period have direct impact on blood pressure. Increasing the systemic resistance increases all three pressures directly from Equation (2.1), and increasing the systolic period decreases the preload of the heart due to a shortened filling time, decreasing cardiac output - as seen in Table 4.2 - consequently decreasing the pressure. An increase in the muscle pump amplitude has little effect on both cardiac output and pressure. Interestingly, increasing ventricular elastance has a negative effect on the increase of both pressure and cardiac output. The reason for this is due to a larger increase in mean arterial pressure and cardiac output at resting conditions, than for during exercise. That is, by increasing ventricular elastance, the effect is bigger at resting conditions, meaning that the relative increase is smaller.

Cardiac Output

Systolic period has the biggest effect on the cardiac output. It reduces the increase in cardiac output. By increasing the systolic period, the diastolic period is correspondingly shortened, which allows for less filling time and a smaller stroke volume for a given heart rate, and thus a smaller value for cardiac output.

Active Muscle Flow

Active muscle flow is most sensitive to systemic resistance. The sensitivity analysis was carried out by increasing the systemic resistance, but not the active muscle resistance. So the systemic resistance is increased, therefore arterial pressure is increased. Thus, by Equation (3.19), active muscle flow has to increase as well. Obviously, the systemic resistance cannot increase without one of its components increasing, but this shows that, in this model, an increase in non-active resistance will also increase active muscle flow. This makes sense intuitively as well, since less blood to non-active parts leaves more blood for active parts.

The sensitivity of active muscle flow to systolic period follows directly from the sensitivity of the cardiac output. Essentially, less total blood flow, less blood flow to the active muscles.

Table 4.2 shows that the sensitivity of active muscle flow to the muscle pump is very small. Therefore, this model supports the claim in the counterpoint in Sheriff [20] that the muscle pump has little effect on muscle perfusion.

Summary

Not surprisingly, the sensitivity to systemic resistance is one of the biggest for all pressures. Systolic period also has a big influence, not only on the pressures, but on cardiac output as well. With regards to filling time and preload of the heart, this makes sense. It is conspicuous that ventricular elastance has a negative effect on all properties, but as mentioned above, this is related to the relative increase between resting conditions and during exercise. In conclusion, abnormalities and pathologies related to blood vessel resistance are very important when assessing

possible hypertensive patients, and atypical resting values should be considered carefully, as they may alter the expected cardiovascular response to exercise.

5.3.2 Physiological Reflex Sensitivity

In the physiological reflex sensitivity analysis, the parameters considered were max heart rate, resting heart rate, resting metabolic oxygen consumption and arterial oxygen concentration, in addition to sympathetic tone and central command.

Pressure

For the mean, systolic and diastolic pressures, the resting and max heart rate are by far the most important parameters. Increasing the max heart rate obviously has zero effect at $I = 0$, since the resting heart rate still remains the same. Figure 4.7 shows that, as the intensity increases, so does the increase in pressure, until the mean pressure increase flattens out at around $I = 0.5$. This shape is related to how the cardiac output changes, which can be seen in Figure 4.8. Equation (2.1), with $Q = CO$ and $\Delta P = MAP$, shows the relation between cardiac output and mean pressure. The sudden drop in systolic pressure at $I = 0.83$ is curious. When redoing the sensitivity analysis with a 15% increase, or a 10% decrease, the increase in relative systolic pressure at $I = 1$ is 0.3%. This implies a numerical error for the sensitivity to max heart rate with a 10% increase. It is reasonable that the change in relative systolic pressure should be 0.3% at $I = 1$, since the change in mean arterial pressure then will be close to the generally applied formula for mean pressure, $MAP = (2 \cdot P_d + P_s)/3$ [44, 45].

The pressure drop for increased resting heart rate in Figure 4.7b is also related to the sensitivity of the cardiac output in Figure 4.8. The sensitivity to cardiac output is explained in the next paragraph.

Increasing resting metabolic oxygen consumption reduces all three relative pressures by around 2%. This is probably due to an increase in conductance for increased $\dot{M}_{am,n}$, which is what Table 4.3 shows as well.

Cardiac Output

The sensitivity of the cardiac output to max and resting heart rate is seen in Figure 4.8. A higher max heart rate will augment the increase in cardiac output, and a higher resting heart rate will attenuate the increase in cardiac output. This will be explained in the following. When increasing the max heart rate, the x-axis is effectively distorted, meaning that for low exercise intensities, the heart rate will be higher. For example, at $I = 0.2$ with $HR_{max} = 200$, the heart rate will be $HR = 96$, whereas for $HR_{max} = 220$, it would be $HR = 100$. Since the stroke volume falls only slightly for low intensities with a higher max heart rate, the increase in heart rate means that the increase in cardiac output also grows, by definition of Equation (2.10). At higher intensities the stroke volume decreases

more, but the increase in heart rate is also bigger. For $I = 1$ with $HR_{max} = 200$ and $HR_{max} = 220$, the respective heart rates will be $HR = 200$ and $HR = 220$. These two effects counteract each other, which leads to an almost constant sensitivity at higher intensities. The stroke volume falls because the heart rate is higher, leading to a shorter diastolic period and less filling.

The principle is the same for when increasing resting heart rate, but opposite. At low intensities the difference in heart rate is bigger, but so is the drop in stroke volume. As the drop in stroke volume lessens, the difference in heart rate lessens as well, until at $I = 0$, where the difference is zero.

Active Muscle Flow

Only arterial oxygen concentration has a significant effect on the active muscle flow. By increasing the arterial oxygen concentration, the value (in $\mathrm{mL\,s^{-1}}$) of active muscle flow is decreased equally for all intensities. Since the active muscle flow is higher for higher intensities, the relative decrease is lower for higher intensities. That means that arterial oxygen concentration is a more important factor for active muscle flow during rest than during exercise. Physically this makes sense as well, as one can imagine the active muscles needing a certain amount of oxygen, which is supplied through the active muscle flow. In fact, this need is defined as the metabolism. The oxygen delivered to the muscles is calculated by multiplying the arterial oxygen concentration with the amount of blood flow to the active muscles, i.e. $C_{a,O2} \cdot Q_{am}$. If the concentration of oxygen in the blood is higher, and all else equal, less blood is needed to supply the oxygen.

Systemic Conductance

The systemic conductance is mainly influenced by sympathetic tone, where an increase in sympathetic tone increases the conductance. This means that by increasing sympathetic tone, the active muscle resistance is reduced more than the non-active resistance is increased. In the physiological model, sympathetic activity is only an efferent for active muscle resistance and non-active resistance, and not for the heart, lungs or other organs that in reality are modulated by sympathetic activity [15]. Since the active and non-active resistances counteract each other during exercise, the sympathetic activity may seem to influence the variables of interest less than would be expected if it were connected to other mechanisms in the physiological model. This is a possible explanation for the low sensitivity to sympathetic activity in this model.

Central Command and Sympathetic Activity

Although Table 4.3 shows that the local sensitivity to central command is zero for all properties, the influence from central command is not necessarily zero. Figure 4.9 shows that for low intensities, sympathetic tone is essentially independent of central command. As the intensity increases, central command becomes more

important, until at $I = 1$, where it accounts for more than 60% of the sympathetic activity. This means that properties sensitive to sympathetic tone at low intensities will barely be sensitive to central command. Properties sensitive to sympathetic tone at higher intensities will indirectly be sensitive to central command as well.

Summary

Overall, the sensitivity to max and resting heart rate is the largest for all three pressures and cardiac output. The reason for this is the effect it has on cardiac output, which in turn affects the pressures. The effect is influenced by both change in heart rate and a reduction in stroke volume. It is also evident that resting values for arterial oxygen concentration and metabolic oxygen consumption rate affect not only the cardiovascular properties during rest, but also the cardiovascular response to exercise. This indicates that measuring resting and max heart rate, arterial oxygen concentration and resting metabolic oxygen consumption rate may help in determining how a patient will respond to exercise. Sympathetic activity has little influence in this model, which is probably a result of few effectors connected to the sympathetic efferent pathways. As a consequence of little sympathetic influence, the central command has little effect as well.

5.3.3 Reflex Strength Sensitivity

In the reflex strength sensitivity analysis, the resting values of the mechanisms remain the same, but the proportional change of the effector is amplified. The only mechanisms considered are the curve-fitted, since they can be applied to Equation (3.33). These are systemic resistance, ventricular elastance and aortic elastance. The sensitivity analysis will in this case obviously be carried out with reference to the curve-fitted model.

Pressure

Amplifying the response of the systemic resistance reduces the increase in mean, diastolic and systolic pressure. Figure 4.10 shows the sensitivities of all three pressures. The spike at $I = 0.25$ for mean and systolic pressure is related to the slow increase in mean and systolic pressure in the physiological model at low intensities. If plotted as change in relative pressure, not sensitivity of the relative pressure, all three pressures look similar to the diastolic pressure sensitivity in Figure 4.10c. The figure shows that at low intensities, the decrease in pressure is almost zero, with an increasing effect for increasing intensities. However, looking at Figures 4.10a and 4.10b, the relative sensitivity is actually greater at lower intensities. This means that a stronger response in systemic resistance is actually more significant at low intensities than at higher intensities (note that, since the resistance falls for increasing intensities, a strengthened response of the systemic resistance actually means a reduction in resistance). In other words, according to this model,

a normotensive person with an augmented systemic resistance response to exercise, will see bigger relative changes in blood pressure for low intensities than for high intensities.

Compared to the systemic resistance, the influence of an amplified response in ventricular and aortic elastance is negligible.

Cardiac Output

For cardiac output, a strengthened response in systemic resistance and ventricular elastance leads to a constant increase of the relative cardiac output for all intensities. That is, a stronger response has the same effect for all intensities. A strengthened response of the ventricular elastance yields a stronger contraction of the heart, which gives more force to counteract the afterload during systole. The increase in cardiac output follows directly from Equation 2.1, since the resistance decreases more for a strengthened response (again, since the resistance falls for increasing intensities, a strengthened response of the systemic resistance actually means a reduction in resistance).

Summary

The reflex strength sensitivity shows that the response of the systemic resistance is very important for the relative increase in blood pressure. Also, the effect is bigger at low intensities than at higher intensities. Meanwhile, the effect on cardiac output is equal for all intensities for a strengthened response in both systemic resistance and ventricular elastance.

5.4 Conclusion

Both the curve-fit model and the physiological model in this thesis predict a response to exercise that corresponds very well with results and data from Magosso and Ursino [6] and Pawelczyk *et al.* [9]. In the physiological model, the implemented systemic resistance is very similar to that of the curve-fit model and Magosso's model. The physiological model can be used to predict a response to exercise at max heart rate, which might be a useful feature, since measurements at max heart rate are difficult to carry out. The responses of ventricular and aortic elastance are both implemented based on population data, and not through sympathetic activity or other efferent activities. Because of this, these two mechanisms are less personalizable than for example the systemic resistance. However, as mentioned in Section 5.1.3, it could be possible to use an individualized resting value and then use population data to predict the relative response of these mechanisms. It could also be possible to implement the full reflex model from Magosso and Ursino [6] into the current model, and from there try to identify the most important parameters in the reflexes. This would of course increase the complexity of the model, but might serve a useful purpose regarding personalization.

The sensitivity analysis showed that the response to exercise depends strongly on the systemic resistance. Atypical resting values for the systemic resistance may alter the response to exercise for all intensities, and should be considered carefully. An interesting perspective is that an abnormal response to exercise could be used to help diagnose diseases that narrow the blood vessels, such as stenosis or edema in the larger arteries [46, 47]. In fact, exercise tests are sometimes used to assess coronary stenosis [48]. Further, the sensitivity analysis indicated that a stronger systemic resistance response to exercise will increase the blood pressure more for low intensities than for high intensities. This could also be useful for a medical professional when diagnosing a hypertensive patient, regarding what kind of exercise or medicine should be prescribed. Lastly, the physiological reflex proved the importance of knowing the resting and max heart rate when determining the exercise response, in addition to the dependency on arterial oxygen concentration and metabolic oxygen concentration. The strong sensitivity to heart rate is partly due to the fact that the exercise intensity is defined as a function of resting and max heart rate. To reduce the strong dependence on heart rate, it could be advantageous to define the exercise intensity by $VO2$ or power output.

In conclusion, the physiological model in this thesis, with exercise intensity-dependent systemic resistance, ventricular elastance, aortic elastance, systolic period and venous muscle pump as the regulatory mechanisms of the cardiovascular system, is a low-computational-cost haemodynamic model that may aid in understanding cardiovascular adjustments that occur during exercise.

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Appendix A

JSim Code for Physiological Model

```
import nsrunit;
unit conversion on;
unit kPa=1E3 kilogram^1*meter^(-1)*second^(-2);
unit mL=1E-6 meter^3;
unit per_mL=1E6 meter^(-3);
unit kPa_per_mL=1E9 kilogram^1*meter^(-4)*second^(-2);
unit kPa_second_per_mL=1E9 kilogram^1*meter^(-4)*second^(-1);
unit mL_per_second=1E-6 meter^3*second^(-1);
unit mL_per_second2=1E-6 meter^3*second^(-2);
unit per_second2=1 second^(-2);
unit kPa_second2_per_mL=1E9 kilogram^1*meter^(-4);
unit Beats = dimensionless;
unit Beats_per_min = Beats*min^(-1);
unit per_second=1 second^(-1);
property cellMLNames=string;

math main {

 realDomain time second;
 time.min=0;
 extern time.max;
 extern time.delta;

 real HR Beats_per_min;
 real HR_rest Beats_per_min;
 real HR_max Beats_per_min;
 HR=70;
 HR_rest = 70;
 HR_max = 200;
 real I dimensionless;
 I = (HR-HR_rest)/(HR_max-HR_rest);


 //Declare for muscle pump
 real P_im(time) kPa;
 real A_mp kPa;
 real psi(time) dimensionless;
 real T_im second;
```

```
real T_c second;
real alpha_mp(time);
real P_0_mp kPa;



//Declare new driver function shapefunctions
real shapeFunction1(time) dimensionless;
real shapeFunction2(time) dimensionless;
real T second;
T=1/HR;
 real t_peak second;
t_peak = (0.3 + I*0.2)*T;
  real alpha dimensionless;
  alpha = 1.672;
  real n1 dimensionless;
  n1 = 1.32;
  real n2 dimensionless;
  n2 = 21.9;
  real a dimensionless;
  a = 0.708;
  real a2Factor dimensionless;
  a2Factor = 1.677;
real a1 dimensionless;
a1 = a*t_peak/T;
real a2 dimensionless;
  a2 = a2Factor*a1;


//Declare resistance parameters
//Declare tabulated values
real g_M dimensionless;
real g_am_o2 dimensionless;
real M_am_n mL_per_second ;
real C_a_o2 dimensionless;
real C_vam_o2_n dimensionless;
real tau_o2 second;
real tau_M second;

//Declare x02 equation
real x_M(time) dimensionless;
when(time=time.min) x_M=0;
real M_am(time) mL_per_second;
real Q_am(time) mL_per_second;
real C_vam_o2(time) dimensionless;
real x_am_o2(time) dimensionless;
when(time=time.min) x_am_o2=0;

//Declare X_met equation
real x_met(time) dimensionless;
real tau_met second;
real phi_met dimensionless;
real phi_max dimensionless;
real phi_min dimensionless;
real I_met dimensionless;
real k_met dimensionless;

//Declare resistance in active muscles
real R_amp(time) kPa_second_per_mL;
```

```
//Declare baseline resistance
real sigma_r(time) kPa_second_per_mL;
real R_b(time) kPa_second_per_mL;
real delta_Rb(time) kPa_second_per_mL;
real tau_r second;
real G_r kPa_second_per_mL;
real R_b_n kPa_second_per_mL;
real f_es_min per_second;
real gamma per_second; //central command
real gamma_max per_second; //max value for cc
real gamma_min per_second; //min value for cc
real kcc dimensionless; //slope parameter
real I_0 dimensionless; //intensity const in symp activity
real symp per_second; //sympathetic (symp) activity
real symp_const per_second; //constant term in symp expression
real symp_max per_second; //max value of symp
real fes_inf dimensionless; //Constant in symp expression
real fes_0 dimensionless; //Constant in symp expression
real kes dimensionless; //Constant in symp expression
real Wb dimensionless; //Constant in symp expression
real fab dimensionless; //Constant in symp expression
real Wp dimensionless; //Constant in symp expression
real theta dimensionless; //Constant in symp expression

real f_ap dimensionless; //Expression in symp
real phi_ap dimensionless; //To get fap
real G_ap dimensionless; //Constant in phi_ap
real V_t dimensionless; //Tidal volume in simple phi_ap
real V_t_n dimensionless; //Basal Tidal volume in phi_ap
real tau_p second; //Time constant


//R_amp_n
real R_amp_n(time) kPa_second_per_mL;
real R_amp_n0 kPa_second_per_mL;
real delta_ram(time) kPa_second_per_mL;
real G_ram kPa_second_per_mL;
real sigma_ram kPa_second_per_mL;
real tau_ram second;



real R_mt kPa_second_per_mL;
R_mt.cellMLNames="heart_parameters.R_mt;left_ventricle.R_mt;pulmonary_vein.R_mt;
    flow.R_mt";
R_mt=0.0158;
real R_av kPa_second_per_mL;
R_av.cellMLNames="heart_parameters.R_av;left_ventricle.R_av;aorta.R_av;flow.R_av";
R_av=0.0180;
real R_tc kPa_second_per_mL;
R_tc.cellMLNames="heart_parameters.R_tc;right_ventricle.R_tc;vena_cava.R_tc;flow.
    R_tc";
R_tc=0.0237;
real R_pv kPa_second_per_mL;
R_pv.cellMLNames="heart_parameters.R_pv;right_ventricle.R_pv;pulmonary_artery.R_pv
    ;flow.R_pv";
R_pv=0.0055;
real R_pul kPa_second_per_mL;
R_pul.cellMLNames="heart_parameters.R_pul;pulmonary_artery.R_pul;pulmonary_vein.
    R_pul;flow.R_pul";
```

```
R_pul=0.1552;


real R_sys(time) kPa_second_per_mL;
R_sys.cellMLNames="heart_parameters.R_sys;aorta.R_sys;vena_cava.R_sys;flow.R_sys";

real L_tc kPa_second2_per_mL;
L_tc.cellMLNames="heart_parameters.L_tc;flow.L_tc";
L_tc=8.0093e-5;
real L_pv kPa_second2_per_mL;
L_pv.cellMLNames="heart_parameters.L_pv;flow.L_pv";
L_pv=1.4868e-4;
real L_mt kPa_second2_per_mL;
L_mt.cellMLNames="heart_parameters.L_mt;flow.L_mt";
L_mt=7.6968e-5;
real L_av kPa_second2_per_mL;
L_av.cellMLNames="heart_parameters.L_av;flow.L_av";
L_av=1.2189e-4;
real V_tot mL;
V_tot.cellMLNames="heart_parameters.V_tot";
V_tot=5.5;
real P_th kPa;
P_th.cellMLNames="heart_parameters.P_th;pulmonary_artery.P_th;pulmonary_vein.P_th;
    pericardium.P_th";
P_th=-4;
real e_t(time) dimensionless;
e_t.cellMLNames="driver_function.e_t;left_ventricle.e_t;right_ventricle.e_t;septum
    .e_t";
real A dimensionless;
A.cellMLNames="driver_function.A";
A=1;
real B per_second2;
B.cellMLNames="driver_function.B";
B=80;
real C second;
C.cellMLNames="driver_function.C";
C=0.375;
real tau(time) second;
tau.cellMLNames="driver_function.tau";
real period second;
period.cellMLNames="driver_function.period";
period=0.75;
real V_pcd(time) mL;
V_pcd.cellMLNames="pericardium.V_pcd";
real P_pcd(time) kPa;
P_pcd.cellMLNames="pericardium.P_pcd";
real P_peri(time) kPa;
P_peri.cellMLNames="pericardium.P_peri;left_ventricle.P_peri;right_ventricle.
    P_peri";
real V_lv(time) mL;
V_lv.cellMLNames="pericardium.V_lv;left_ventricle.V_lv;septum.V_lv";
when(time=time.min) V_lv=94.6812;
real V_rv(time) mL;
V_rv.cellMLNames="pericardium.V_rv;right_ventricle.V_rv;septum.V_rv";
when(time=time.min) V_rv=90.7302;
real P_0_pcd kPa;
P_0_pcd.cellMLNames="pericardium.P_0_pcd";
P_0_pcd=0.5003;
real V_0_pcd mL;
V_0_pcd.cellMLNames="pericardium.V_0_pcd";
```

```
V_0_pcd=200;
real lambda_pcd per_mL;
lambda_pcd.cellMLNames="pericardium.lambda_pcd";
lambda_pcd=0.03;
real V_lvf(time) mL;
V_lvf.cellMLNames="left_ventricle.V_lvf;lvf_calculator.V_lvf";
real P_lvf(time) kPa;
P_lvf.cellMLNames="left_ventricle.P_lvf";
real P_lv(time) kPa;
P_lv.cellMLNames="left_ventricle.P_lv;septum.P_lv;pulmonary_vein.P_lv;aorta.P_lv;
    flow.P_lv";
real P_es_lvf(time) kPa;
P_es_lvf.cellMLNames="left_ventricle.P_es_lvf;lvf_calculator.P_es_lvf";
real P_ed_lvf(time) kPa;
P_ed_lvf.cellMLNames="left_ventricle.P_ed_lvf;lvf_calculator.P_ed_lvf";
real P_pu(time) kPa;
P_pu.cellMLNames="left_ventricle.P_pu;pulmonary_vein.P_pu;pulmonary_artery.P_pu;
    flow.P_pu";
real P_ao(time) kPa;
P_ao.cellMLNames="left_ventricle.P_ao;aorta.P_ao;vena_cava.P_ao;flow.P_ao";



//Adding my model for the LV elastance
real E_es_lvf kPa_per_mL;
real E_es_lvf_rest kPa_per_mL;
E_es_lvf.cellMLNames="left_ventricle.E_es_lvf;septum.E_es_lvf;lvf_calculator.
    E_es_lvf";
E_es_lvf_rest = 2.8798;
E_es_lvf = (2*I*E_es_lvf_rest + E_es_lvf_rest); //ADD THIS



real lambda_lvf per_mL;
lambda_lvf.cellMLNames="left_ventricle.lambda_lvf;septum.lambda_lvf;lvf_calculator
    .lambda_lvf";
lambda_lvf=0.033;
real P_0_lvf kPa;
P_0_lvf.cellMLNames="left_ventricle.P_0_lvf;septum.P_0_lvf;lvf_calculator.P_0_lvf
    ";
P_0_lvf=0.1203;
real Q_mt(time) mL_per_second;
Q_mt.cellMLNames="left_ventricle.Q_mt;flow.Q_mt;pulmonary_vein.Q_mt";
when(time=time.min) Q_mt=245.5813;
real Q_av(time) mL_per_second;
Q_av.cellMLNames="left_ventricle.Q_av;flow.Q_av;aorta.Q_av";
when(time=time.min) Q_av=0;
real V_d_lvf mL;
V_d_lvf.cellMLNames="lvf_calculator.V_d_lvf";
V_d_lvf=0;
real V_0_lvf mL;
V_0_lvf.cellMLNames="lvf_calculator.V_0_lvf";
V_0_lvf=0;
real V_rvf(time) mL;
V_rvf.cellMLNames="right_ventricle.V_rvf;rvf_calculator.V_rvf";
real P_rvf(time) kPa;
P_rvf.cellMLNames="right_ventricle.P_rvf";
real P_rv(time) kPa;
P_rv.cellMLNames="right_ventricle.P_rv;septum.P_rv;pulmonary_artery.P_rv;vena_cava
```

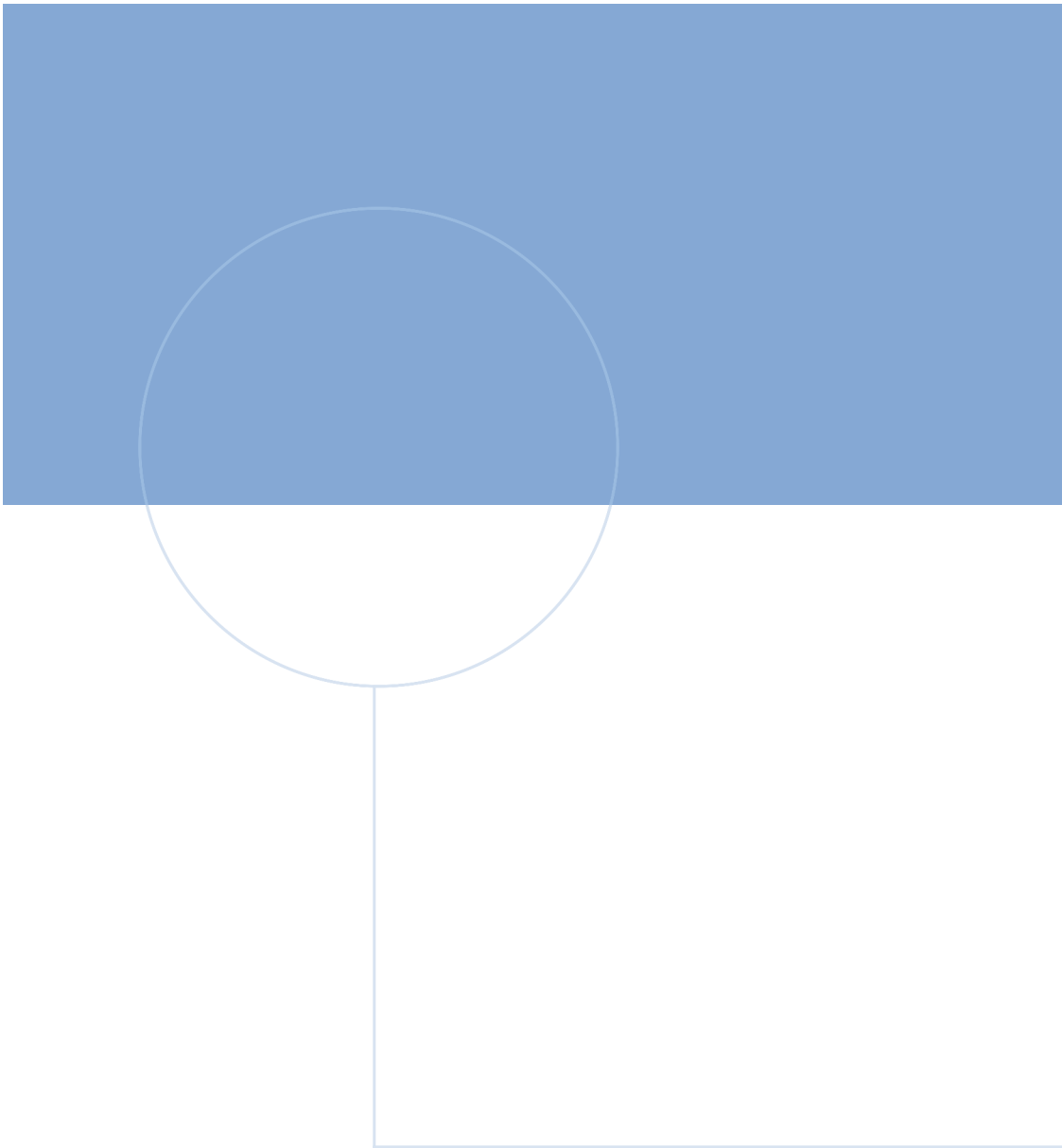
```
    .P_rv;flow.P_rv";
real P_es_rvf(time) kPa;
P_es_rvf.cellMLNames="right_ventricle.P_es_rvf;rvf_calculator.P_es_rvf";
real P_ed_rvf(time) kPa;
P_ed_rvf.cellMLNames="right_ventricle.P_ed_rvf;rvf_calculator.P_ed_rvf";
real P_pa(time) kPa;
P_pa.cellMLNames="right_ventricle.P_pa;pulmonary_artery.P_pa;pulmonary_vein.P_pa;
    flow.P_pa";
real P_vc(time) kPa;
P_vc.cellMLNames="right_ventricle.P_vc;vena_cava.P_vc;aorta.P_vc;flow.P_vc";


//Adding my model for rv elastance
real E_es_rvf kPa_per_mL;
real E_es_rvf_rest kPa_per_mL;
E_es_rvf.cellMLNames="right_ventricle.E_es_rvf;septum.E_es_rvf;rvf_calculator.
    E_es_rvf";
E_es_rvf_rest=0.585;
E_es_rvf = (2*I*E_es_rvf_rest + E_es_rvf_rest); //ADD THIS


real lambda_rvf per_mL;
lambda_rvf.cellMLNames="right_ventricle.lambda_rvf;septum.lambda_rvf;
    rvf_calculator.lambda_rvf";
lambda_rvf=0.023;
real P_0_rvf kPa;
P_0_rvf.cellMLNames="right_ventricle.P_0_rvf;septum.P_0_rvf;rvf_calculator.P_0_rvf
    ";
P_0_rvf=0.2157;
real Q_tc(time) mL_per_second;
Q_tc.cellMLNames="right_ventricle.Q_tc;flow.Q_tc;vena_cava.Q_tc";
when(time=time.min) Q_tc=190.0661;
real Q_pv(time) mL_per_second;
Q_pv.cellMLNames="right_ventricle.Q_pv;flow.Q_pv;pulmonary_artery.Q_pv";
when(time=time.min) Q_pv=0;
real V_d_rvf mL;
V_d_rvf.cellMLNames="rvf_calculator.V_d_rvf";
V_d_rvf=0;
real V_0_rvf mL;
V_0_rvf.cellMLNames="rvf_calculator.V_0_rvf";
V_0_rvf=0;
real one dimensionless;
one.cellMLNames="septum.one";
one=1;
real E_es_pa kPa_per_mL;
E_es_pa.cellMLNames="pulmonary_artery.E_es_pa";
E_es_pa=0.369;
real V_pa(time) mL;
V_pa.cellMLNames="pulmonary_artery.V_pa";
when(time=time.min) V_pa=43.0123;
real V_d_pa mL;
V_d_pa.cellMLNames="pulmonary_artery.V_d_pa";
V_d_pa=0;
real Q_pul(time) mL_per_second;
Q_pul.cellMLNames="pulmonary_artery.Q_pul;flow.Q_pul;pulmonary_vein.Q_pul";
real E_es_pu kPa_per_mL;
E_es_pu.cellMLNames="pulmonary_vein.E_es_pu";
E_es_pu=0.0073;
real V_pu(time) mL;
V_pu.cellMLNames="pulmonary_vein.V_pu";
```

```
when(time=time.min) V_pu=808.4579;
real V_d_pu mL;
V_d_pu.cellMLNames="pulmonary_vein.V_d_pu";
V_d_pu=0;


//Old model for E_es_ao
real E_es_ao kPa_per_mL;
E_es_ao.cellMLNames="aorta.E_es_ao";


real V_ao(time) mL;
V_ao.cellMLNames="aorta.V_ao";
when(time=time.min) V_ao=133.3381;
real V_d_ao mL;
V_d_ao.cellMLNames="aorta.V_d_ao";
V_d_ao=0;
real Q_sys(time) mL_per_second;
Q_sys.cellMLNames="aorta.Q_sys;flow.Q_sys;vena_cava.Q_sys";
real E_es_vc kPa_per_mL;
E_es_vc.cellMLNames="vena_cava.E_es_vc";
E_es_vc=0.0059;
real V_vc(time) mL;
V_vc.cellMLNames="vena_cava.V_vc";
when(time=time.min) V_vc=329.7803;
real V_d_vc mL;
V_d_vc.cellMLNames="vena_cava.V_d_vc";
V_d_vc=0;

// <component name="environment">

// <component name="heart_parameters">


//Add new driver function
shapeFunction1(time) = ((tau/(a1*T))^n1)/(1.0+(tau/(a1*T))^n1);
shapeFunction2(time) = (1.0+(tau/(a2*T))^n2);
e_t = alpha*shapeFunction1/shapeFunction2;



// <component name="pericardium">
V_pcd=(V_lv+V_rv);
P_pcd=(P_0_pcd*(exp(lambda_pcd*(V_pcd-V_0_pcd))-1));
P_peri=(P_pcd+P_th);

// <component name="left_ventricle">
V_lvf=V_lv;
P_lvf=(e_t*P_es_lvf+(1-e_t)*P_ed_lvf);
P_lv=(P_lvf+P_peri);
V_lv:time=(if ((Q_mt<(0 mL_per_second)) and (Q_av<(0 mL_per_second))) (0
    mL_per_second) else if (Q_mt<(0 mL_per_second)) (-1)*Q_av else if (Q_av<(0
    mL_per_second)) Q_mt else Q_mt-Q_av);

// <component name="lvf_calculator">
P_es_lvf=(E_es_lvf*(V_lvf-V_d_lvf));
P_ed_lvf=(P_0_lvf*(exp(lambda_lvf*(V_lvf-V_0_lvf))-1));

// <component name="right_ventricle">
V_rvf=V_rv;
```

```
P_rvf=(e_t*P_es_rvf+(1-e_t)*P_ed_rvf);
P_rv=(P_rvf+P_peri);
V_rv:time=(if ((Q_tc<(0 mL_per_second)) and (Q_pv<(0 mL_per_second))) (0
    mL_per_second) else if (Q_tc<(0 mL_per_second)) (-1)*Q_pv else if (Q_pv<(0
    mL_per_second)) Q_tc else Q_tc-Q_pv);

// <component name="rvf_calculator">
P_es_rvf=(E_es_rvf*(V_rvf-V_d_rvf));
P_ed_rvf=(P_0_rvf*(exp(lambda_rvf*(V_rvf-V_0_rvf))-1));


// <component name="pulmonary_artery">
P_pa=(E_es_pa*(V_pa-V_d_pa)+P_th);
V_pa:time=(if (Q_pv<(0 mL_per_second)) (-1)*Q_pul else Q_pv-Q_pul);

// <component name="pulmonary_vein">
P_pu=(E_es_pu*(V_pu-V_d_pu)+P_th);
V_pu:time=(if (Q_mt<(0 mL_per_second)) Q_pul else Q_pul-Q_mt);

// <component name="aorta">
P_ao=(E_es_ao*(V_ao-V_d_ao));
V_ao:time=(if (Q_av<(0 mL_per_second)) (-1)*Q_sys else Q_av-Q_sys);

// <component name="vena_cava">
//ADD MUSCLE PUMP
P_vc=(if ((V_vc-V_d_vc)>(0 mL)) (E_es_vc*(V_vc-V_d_vc)+P_im) else (P_im));
V_vc:time=(if (Q_tc<(0 mL_per_second)) Q_sys else Q_sys-Q_tc);

// <component name="flow">
Q_sys=((P_ao-P_vc)/R_sys);
Q_pul=((P_pa-P_pu)/R_pul);
Q_mt:time=(if (((P_pu-P_lv)<(0 kPa)) and (Q_mt<(0 mL_per_second))) (0
    mL_per_second2) else (P_pu-P_lv-Q_mt*R_mt)/L_mt);
Q_av:time=(if (((P_lv-P_ao)<(0 kPa)) and (Q_av<(0 mL_per_second))) (0
    mL_per_second2) else (P_lv-P_ao-Q_av*R_av)/L_av);
Q_tc:time=(if (((P_vc-P_rv)<(0 kPa)) and (Q_tc<(0 mL_per_second))) (0
    mL_per_second2) else (P_vc-P_rv-Q_tc*R_tc)/L_tc);
Q_pv:time=(if (((P_rv-P_pa)<(0 kPa)) and (Q_pv<(0 mL_per_second))) (0
    mL_per_second2) else (P_rv-P_pa-Q_pv*R_pv)/L_pv);



//Venous muscle pump

A_mp = 3.5; //ADD THIS
T_im = 1;
T_c = 0.75;
alpha_mp = (rem(time,T_im))/(T_im);
psi = (if (((alpha_mp)<=(T_c/T_im)) and (alpha_mp>=(0))) (sin(alpha_mp*PI*T_im/T_c
    )) else 0);
P_im = (if (I>0) (A_mp*psi) else 0);
P_0_mp = 10;


//Simple linear model for systemic resistance
real R_sys_rest kPa_second_per_mL;
R_sys_rest = 1.0889;
   kPa_second_per_mL); //ADD THIS
```

```
//Testing physiological Rsys
//Add tabulated values
g_M = 40;
g_am_o2 = 30;
M_am_n = 1.5; //0.516;
C_a_o2 = 0.2;
C_vam_o2_n = 0.15156;
tau_o2 = 10;
tau_M = 40;

//X02 equation
x_M:time = 1/tau_M*(-x_M+g_M*I);
M_am = M_am_n*(1+x_M);
Q_am = (P_ao-P_vc)/R_amp;
C_vam_o2 = C_a_o2 - M_am/Q_am;
x_am_o2:time =1/tau_o2*(-x_am_o2 - g_am_o2*(C_vam_o2-C_vam_o2_n));

//X_met equation
phi_met = (phi_min + phi_max*exp((I-I_met)/k_met))/(1 + exp((I-I_met)/k_met));
phi_min = -1.87;
phi_max = 20; //Magosso value
I_met = 0.4266;
k_met = 0.18;
tau_met = 10;
x_met:time = 1/tau_met*(-x_met+phi_met);
when(time=time.min) x_met=0;

//Baseline resistance
R_b_n=0.6; //1.275 for Baseline
sigma_r = (if (symp>=f_es_min) (G_r*ln((symp-f_es_min+1)*(1 second))) else 0);
delta_Rb:time = 1/tau_r*(-delta_Rb+ sigma_r); //Effector equation (differential eq
    )
when(time=time.min) delta_Rb = 1.2;
tau_r = 6;
G_r = 0.69;
symp = (if (symp<=symp_max) (symp_const + gamma) else symp_max); //Sympathetic
    acitivity
symp_const = (fes_inf + (fes_0-fes_inf)*exp(kes*(Wb*fab+Wp*f_ap-theta)))*(1
    per_second); //Constant in symp activ
symp_max = 60;
f_es_min = 2.66;
fes_inf = 2.10;
fes_0 = 16.11;
kes = 0.0675;
Wb = -1;
fab = 25.15;
Wp = -0.34;
theta = -4.6;
gamma = (gamma_min + gamma_max*exp((I-I_0)/kcc))/(1+exp((I-I_0)/kcc)); //Central
    command
gamma_max = 5.5;
gamma_min = -0.037;
kcc = 0.13;
I_0 = 0.65;
R_b = R_b_n + delta_Rb;

f_ap:time = (1/tau_p)*(-f_ap + phi_ap); //Activity from lung stretch receptors
tau_p = 2;
phi_ap = G_ap*V_t;
G_ap = 23.29;
```

```
V_t_n = 0.583; //Basal tidal volume
V_t = V_t_n*(1 + 2.74*I);  //Tidal volume

//Expression for baseeline active muscle resistance
sigma_ram = (if (symp>=f_es_min) (G_ram*ln((symp-f_es_min+1)*(1 second))) else 0);
delta_ram:time = 1/tau_ram*(-delta_ram + sigma_ram); //Effector equation (
    differential eq)
when(time=time.min) delta_ram = 4.5;
R_amp_n = R_amp_n0 + delta_ram;
tau_ram = 6; //From ursino_sympathetic tau_rmp
G_ram = 2.47; //From ursino_sympathetic G_rmp
R_amp_n0 = 13; //3.2; if R_amp=7.46









//Define resistances
R_amp = R_amp_n/(1+x_am_o2+x_met);
R_sys=(1/R_amp + 1/R_b)^(-1);



//Simple linear model for aortic elastance
E_es_ao = (0.6913 + 0.3087/(1+exp(5-10*I)))*(1 kPa_per_mL);




}
```



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