

# **Simulation of Cardiovascular System Diseases by Including the Autonomic Nervous System into a Minimal Model**

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## **ABSTRACT**

Diagnosing cardiovascular system (CVS) diseases from clinically measured data is difficult, due to the complexity of the hemodynamic and autonomic nervous system (ANS) interactions. Physiological models could describe these interactions to enable simulation of a variety of diseases, and could be combined with parameter estimation algorithms to help clinicians diagnose CVS dysfunctions. This paper presents modifications to an existing CVS model to include a minimal physiological model of ANS activation. A minimal model is used so as to minimise the number of parameters required to specify ANS activation, enabling the effects of each parameter on hemodynamics to be easily understood. The combined CVS and ANS model is verified by simulating a variety of CVS diseases, and comparing simulation results with common physiological understanding of ANS function and the characteristic hemodynamics seen in these diseases. The model of ANS activation is required to simulate hemodynamic effects such as increased cardiac output in septic shock, elevated pulmonary artery pressure in left ventricular infarction, and elevated filling pressures in pericardial tamponade. This is the first known example of a minimal CVS model that includes a generic model of ANS activation and is shown to simulate diseases from throughout the CVS.

**Keywords:** Hemodynamics, modelling, autonomic nervous system, cardiovascular system

# 1 Introduction

Diagnosing cardiovascular system (CVS) diseases requires medical staff to interpret a range of clinical data and measurements of patient CVS function. Measurements seen by the clinician such as pressures (eg. mean arterial, pulmonary artery, central venous), volumes (eg. ventricle volumes measured by echocardiography) and cardiac output (CO) can be influenced by a variety of hydraulic effects, underlying diseases, autonomic nervous system (ANS) responses, and the interactions between these mechanisms. This confusing array of effects makes the process of diagnosing CVS diseases difficult.

Physiological models could be built that describe these interactions and enable simulation of a variety of diseases. These models could then be fitted to clinical data for specific patients by adjusting model parameters using parameter estimation algorithms [1]. The resulting model parameters may then provide useful insight into the underlying disorder and assist the clinician in selecting a suitable treatment strategy. Such models need to be simple enough such that their parameters can be identified given the available clinical data, whilst retaining enough complexity to capture the fundamental dynamics.

There are many examples of physiological models in the literature that simulate the hemodynamics of the heart and circulatory system to varying degrees of complexity [2,3,4,5,6,7]. However, most are only shown to simulate specific types of dysfunctions in certain areas of the CVS, and very few include consideration of ANS function [8,9]. Those that do simulate ANS function focus on specific diseases, and whilst showing the usefulness of the modelling approach, have not been shown to be able to simulate the

necessary range of CVS diseases seen in clinical practice [8,9]. Detailed models of the circulatory system including short and long term regulatory function have been created, such as that proposed by Guyton et al. [10], however the complexity of these models limits their potential applicability for patient specific simulations [11].

This research investigates modifications to a previously presented model of CVS function to include a model of ANS response [6,7]. The aim is to develop a model of the CVS including ANS response which can simulate a variety of relevant disease scenarios commonly seen in critically ill patients, including examples of the 4 fundamental types of shock. Whilst no formal identifiability analysis will be performed in this paper, the models presented here are formulated so as to have minimal complexity. This is intended to both enable understanding of the individual contributions of the model parameters to the overall hemodynamics, and increase the possibility of identifying model parameters from clinical data.

This paper will present an overview of the CVS model and a description of the ANS model. The CVS model and the combined CVS and ANS model are used to investigate the effects of the individual mechanisms of ANS response on arterial blood pressure and cardiac output, and to simulate a variety of different diseases. In each case the simulated results are examined to see if the model can reproduce common physiological understanding and clinical observations.

## 2 Model specification

### 2.1 Cardiovascular system model

The minimal CVS model used in this study is shown schematically in Figure 1 including the governing equations. The model structure and method of implementation is outlined in detail in Smith et al. [6], and is summarised only briefly here. The two central heart chambers represent the left and right ventricles (lv and rv). Resistances at the inlet and exit of the right ventricle simulate pressure drops of blood flow entering through the tricuspid valve ( $R_{tc}$ ) and exiting through the pulmonary valve ( $R_{pv}$ ). For the left ventricle, resistances affect blood flow entering through the mitral valve ( $R_{mt}$ ) and exiting through the aortic valve ( $R_{av}$ ). Ventricular interaction due to the septum (spt) and pericardium (peri) is also accounted for in the model. The effects of the thoracic cavity ( $P_{pl}$ ) pressure on the ventricles and pulmonary circulation chambers are also included to account for the influence of respiration.

The systemic circulation is made up of two chambers representing the pressures (P) and volumes (V) in the vena-cava (vc) and the aorta (ao) connected by a resistor to simulate the systemic resistance ( $R_{sys}$ ). Similarly, the pulmonary circulation is simulated as the pulmonary artery (pa) connected to the pulmonary vein (pu) by the pulmonary vascular resistance ( $R_{pul}$ ). Both ventricles are driven by time varying elastances which cycle between a maximum defined by the end-systolic pressure-volume relationship (ESPVR), and a minimum end-diastolic pressure-volume relationship (EDPVR). This enables simulation of pulsatile blood flow which results in ventricular pressures varying between

systolic and diastolic values. A cardiac driver function (Equation C4 in Figure 1) is defined that controls the variation in ventricular elastance between diastolic and systolic levels over the cardiac cycle for a specified heart rate (HR). Figure 2 illustrates the ESPVR and EDPVR on a pressure-volume (PV) diagram of the cardiac cycle. The contractility ( $E_{es}$ ) of the left ventricle wall (lvf), right ventricle wall (rvf) and septum (spt) are adjusted by using the parameters  $E_{es,lvf}$ ,  $E_{es,rvf}$  and  $E_{es,spt}$  respectively. Similarly, the ventricular end-diastolic elastances ( $P_0$ ) are adjusted by varying the parameters  $P_{0,lvf}$ ,  $P_{0,rvf}$  and  $P_{0,spt}$ , the non-linearity in this elastance ( $\lambda$ ) being adjusted using the parameters  $\lambda_{lvf}$ ,  $\lambda_{rvf}$  and  $\lambda_{spt}$ .

This model contains 6 state variables representing the compartmental volumes ( $V_{pa}$ ,  $V_{pu}$ ,  $V_{lv}$ ,  $V_{ao}$ ,  $V_{vc}$  and  $V_{rv}$ ), and uses 38 parameters in the governing equations shown in Figure 1. Reference values for these parameters can be found in numerous literature sources and are listed in Tables 1 and 2 [4,6,8,9]. Simulations performed using the model have been previously shown to reproduce normal values and characteristic trends in volumes and pressures in the heart and circulatory system that are comparable to a normal human [6,7]. The model is designed to contain a minimal number of parameters in order to improve identifiability, whilst preserving parameters that are necessary to simulate a variety of relevant diseases, as will be illustrated.

## **2.2 Autonomic nervous system activation model**

Changes in arterial blood pressure are detected through baroreceptors located in the walls of the large systemic arteries, and transmitted to the central nervous system. A drop in arterial blood pressure causes simultaneous stimulation of the sympathetic nervous

system and inhibition of the parasympathetic vagal activity. The primary effects of this autonomic nervous system response are: constriction of the arterioles which increases peripheral resistance; constriction of the venous system which pushes more blood into the circulation; and improved cardiac function through increased heart rate and contractility. These changes occur rapidly, where typically the ANS is capable of activating these compensatory mechanisms and causing large change in blood pressure within 5-40 seconds [12].

The model of ANS activation presented here includes all of the four, above mentioned, mechanisms for autonomic regulation, i.e.: vaso-constriction; venous constriction; increased heart rate and increased ventricular contractility [8]. ANS activation is assumed to respond to changes in systemic arterial blood pressure ( $\Delta P_{ao}$ ), the effects of which are modelled as proportional changes in the following CVS parameters: systemic resistance ( $R_{sys}$ ); venous dead-space ( $V_{d,vc}$ ); heart rate (HR) and ventricular contractilities ( $E_{es,lvf}$  and  $E_{es,rvf}$ ) [12,13]. This section describes the mathematical model formulation of these relationships along with their physiological justification and estimation of the model's parameter values.

Equations 1-5 describe the relationship between changes in  $P_{ao}$  and the resulting changes in the selected CVS model parameters. The ANS parameters ( $S_{R_{sys}}$ ,  $S_{V_{d,vc}}$ ,  $S_{HR}$  and  $S_{E_{es}}$ ) define the sensitivity of the CVS parameters to changes in  $P_{ao}$ , where  $R_{sys}(100)$ ,  $V_{d,vc}(100)$ ,  $HR(100)$ ,  $E_{es,lvf}(100)$  and  $E_{es,rvf}(100)$  define the values of the CVS parameters when  $P_{ao}$  is 100mmHg.

$$\Delta R_{\text{sys}} = S_{R_{\text{sys}}} \cdot \Delta P_{\text{ao}} \cdot R_{\text{sys}}(100) \quad (1)$$

$$\Delta V_{\text{d,vc}} = S_{V_{\text{dvc}}} \cdot \Delta P_{\text{ao}} \cdot V_{\text{d,vc}}(100) \quad (2)$$

$$\Delta \text{HR} = S_{\text{HR}} \cdot \Delta P_{\text{ao}} \cdot \text{HR}(100) \quad (3)$$

$$\Delta E_{\text{es,lvf}} = S_{E_{\text{es}}} \cdot \Delta P_{\text{ao}} \cdot E_{\text{es,lvf}}(100) \quad (4)$$

$$\Delta E_{\text{es,rvf}} = S_{E_{\text{es}}} \cdot \Delta P_{\text{ao}} \cdot E_{\text{es,rvf}}(100) \quad (5)$$

This linear model can be seen as a very simple representation of the ANS. However, it will be shown that even a simple representation such as this can be used to simulate the major characteristics of clinical diseases. The relationships described in Equations 1-5 will now be discussed individually, in order to provide physiological justification of the relationships in terms of major ANS responses (i.e. vaso-constriction, venous constriction, heart rate and contractility) and to provide estimation of the sensitivity parameters listed in Table 3.

Vaso-constriction responds to a decrease in  $P_{\text{ao}}$  by constricting the arterioles to increase  $R_{\text{sys}}$ , the resulting feedback acting so as to reduce the changes in  $P_{\text{ao}}$ . This mechanism is simulated in the ANS model by increasing  $R_{\text{sys}}$  on changes in  $P_{\text{ao}}$  (Equation 1). Using the systemic resistance sensitivity ( $S_{R_{\text{sys}}}$ ) listed in Table 3, means that the vaso-constriction response to a drop in average  $P_{\text{ao}}$  from 100mmHg to 80mmHg will be to increase  $R_{\text{sys}}$  by 35%.

Venous constriction responds to changes in  $P_{\text{ao}}$  by increasing the elastance of the larger peripheral blood vessels, which contain most of the blood volume in the body. This constriction increases the stressed blood volume [8,12,14]. The total blood volume ( $V_{\text{tot}}$ )



in the model is made up of the sum of the stressed blood volume and the unstressed blood volume, where the unstressed blood volume is equal to the sum of all the dead-space volumes (e.g.,  $V_{d,vc}$ ,  $V_{d,ao}$ ,  $V_{d,pa}$  and  $V_{d,pu}$ ) [9]. Venous constriction is simulated by reducing the venous dead-space in the model ( $V_{d,vc}$ ), on changes in  $P_{ao}$  (Equation 2), which has the effect of pushing blood from the unstressed blood volume into the stressed blood volume. Using the venous dead-space sensitivity ( $S_{V_{dvc}}$ ) listed in Table 3, means that the venous-constriction response to a drop in average  $P_{ao}$  from 100mmHg to 80mmHg will be to decrease  $V_{d,vc}$  by 35% from the base value.

The pumping ability of the heart responds to changes in  $P_{ao}$  by increasing heart rate and contractility [8,14]. These mechanisms are simulated in the ANS model by increasing HR,  $E_{es,lvf}$  and  $E_{es,rvf}$  on changes in  $P_{ao}$  (Equations 3-5). Using the heart rate sensitivity ( $S_{HR}$ ) and contractility sensitivity ( $S_{Ees}$ ) values listed in Table 3, means that a drop in average  $P_{ao}$  from 100mmHg to 80mmHg results in increased HR by 50% and increased left and right ventricular contractilities ( $E_{es,lvf}$  and  $E_{es,rvf}$ ) by 35% respectively.

### 3 Simulation results

#### 3.1 *Using the model to simulate autonomic nervous system activation*

This section investigates whether changes in the CVS parameters selected to represent ANS function, reasonably represent the physiological changes seen due to the ANS. Simulations are performed using the CVS model to investigate the independent effects of changes in CVS parameter values ( $R_{sys}$ ,  $V_{d,vc}$ , HR,  $E_{es,lvf}$  and  $E_{es,rvf}$ ) on average arterial blood pressure (Avg  $P_{ao}$ ) and cardiac output (CO). Each of the CVS parameters is varied independently over a range from 0.1 to 2 times their base values, shown in Tables 1 and

2. Values of other parameters are held constant and the model is run to a steady state solution to find Avg  $P_{ao}$  and CO. In this way the independent effects of each ANS response on blood pressure and cardiac output are found.

Figure 3 shows the results of these simulations. Several important conclusions can be drawn from these in relation to common physiological and clinical understanding, illustrating the power of these simple models to capture well known changes in hemodynamics. The simulated effect of changes in venous dead space ( $V_{d,vc}$ ) are nonlinearly related to  $P_{ao}$  and CO, meaning that at low values of  $V_{d,vc}$ ,  $P_{ao}$  and CO are only changed minimally. Reducing dead-space can be seen as equivalent to increasing blood volume. Therefore, this simulation is consistent with the clinical observation that while increases in blood volume in hypovolemic patients will cause increases in blood pressure and CO, these values tend to remain stable when blood volume is increased in adequately volume loaded patients [12]. The effect of changes in both contractility ( $E_{es}$ ) and heart rate (HR) on  $P_{ao}$  and CO are also non-linear, where  $P_{ao}$  and CO are significantly affected at low values of  $E_{es}$  and HR, but to a lesser degree at high values. This flattening of the  $P_{ao}$  and CO curves as  $E_{es}$  and HR are increased is indicative of the increasing dependence of the heart on ventricular preload [12]. Systemic vascular resistance ( $R_{sys}$ ) is almost linearly related to average  $P_{ao}$  and CO, where an increase in  $R_{sys}$  causes an increase in blood pressure and a decrease in cardiac output. This response is consistent with the clinically observed response to vaso-constrictor treatment [12].

### ***3.2 Using the model to simulate CVS diseases***

This section investigates the use of the combined CVS and ANS model to simulate the effect of severe acute cardiovascular diseases on hemodynamic variables. Five different cases of severe acute cardiovascular diseases are simulated, representing dysfunctions commonly seen in the intensive care unit, i.e.: hypovolemic shock; cardiogenic shock; septic shock; pericardial tamponade and pulmonary embolism. Each disease is simulated by adjusting model parameters from the base values given in Tables 1 and 2. In each case the model is run to steady state conditions. The resulting simulated CVS hemodynamics are compared with trends reported in medical literature.

In order to investigate the effects of the model of ANS activation on hemodynamics, simulation results are given for each disease using the CVS model only (Table 4, values in brackets) and using the combined CVS and ANS model (Table 4, values without brackets). The variables shown in Table 4 are selected to characterise the hemodynamic response, i.e.: The average pressures in the peripheral chambers ( $P_{ao}$ ,  $P_{vc}$ ,  $P_{pa}$  and  $P_{pu}$ ) which give the filling pressures and the afterload of each ventricle; The cardiac output (CO), showing how effectively the heart and circulatory system are working together to transport blood; The end-diastolic left and right ventricular volumes (LVEDV and RVEDV), indicating the preload in each ventricle, which is dependent on the venous return [12]; The average deflection of the septum ( $V_{spt}$ ) and the average pressure in the pericardium ( $P_{peri}$ ), quantifying the level of ventricular interaction.

To enable comparison between model simulations, the severity of the diseases simulated in all cases except pulmonary embolism are adjusted so that the average  $P_{ao}$  will reduce to

80mmHg when ANS activation is included. Moderate pulmonary embolism typically does not cause such a large drop in blood pressure, so in this case the severity of illness is modified until  $P_{ao}$  is reduced to 98 mmHg, resulting in a proportionally smaller ANS activation. Simulation of each of the disease states is now considered in turn.

### **3.2.1 Hypovolemic shock**

Hypovolemic shock is caused by a severe drop in total blood volume, due to dehydration, hemorrhage or other fluid loss. Reduced blood volume is clinically characterised by a drop in ventricular filling pressures, cardiac output and mean arterial pressure [13,14]. Hypovolemic shock is simulated using the model by reducing total blood volume ( $V_{tot}$ ) by 3.1 litres. This example simulates a patient with acute hypovolemic shock due to external hemorrhage.

Simulations without ANS activation (Table 4) result in significant decreases in all hemodynamic pressures to levels inadequate to maintain life, and no steady state solution was reached. In simulations using the combined CVS and ANS model, Table 4 shows that ANS activation partially compensates for the drop in arterial blood pressure due to the blood loss by activating mechanisms to increase blood pressure. These compensatory mechanisms cause simulated pressures and flows to stabilise at values that are adequate to maintain life. Average  $P_{ao}$  stabilises at 80mmHg, but all pressures are low relative to base values along with end-diastolic ventricular volumes and cardiac output. The model response described matches commonly seen trends during hypovolemic shock [14].

### 3.2.2 Septic shock

Septic shock is a common type of distributive shock that is often characterised by a drop in systemic vascular resistance and venous elastance [15,16]. This dilation in the systemic circulatory system is thought to occur due to a drop in vascular auto-regulatory control [14]. Acute septic shock prior to fluid resuscitation is usually clinically characterised by a drop in blood pressures throughout the circulatory system, particularly in the aorta ( $P_{ao}$ ) whilst cardiac output increases markedly [17]. Septic shock is simulated using the model by reducing systemic resistance ( $R_{sys}$ ) by 50% and increasing venous dead-space by 1.7 litres. This example simulates a patient suffering from acute septic shock, perhaps as a result of a bacterial infection. Values of  $S_{Rsys}$  and  $S_{Vdvc}$  were not changed in this simulation, in order to maintain consistency with the other disease simulations, although these values could also be affected in septic shock due to impaired auto-regulatory function.

Simulations without ANS activation (Table 4) result in values of hemodynamic pressures and cardiac output below those necessary to maintain life. In simulations with the combined CVS and ANS model, Table 4 shows that the pressure drops are much less significant, with Avg  $P_{ao}$  stabilising at 80 mmHg and pulmonary artery pressure ( $P_{pa}$ ) almost recovering to its base value. The left and right ventricular volumes also decrease, but the cardiac output increases from a normal value of 5.6l/min to 6.8l/min. The characteristic rise in cardiac output commonly seen in septic shock is only present in simulations that include ANS activation.

### 3.2.3 Cardiogenic shock

Cardiogenic shock is often caused when the heart is unable to pump enough blood to maintain adequate perfusion of oxygen to the tissues including the myocardium [14,18]. The lack of oxygen supply to the myocardium causes even further depression of cardiac function by decreasing the ventricular contractility and increasing diastolic elastance [19]. Cardiogenic shock is characterised hemodynamically by decreased mean arterial pressure below 90mmHg, decreased cardiac output, hypotension and an elevated pulmonary capillary occlusion pressure to greater than 15 mmHg [14,18,19,20]. Cardiogenic shock is simulated using the model by reducing the left ventricular contractility ( $E_{es,lvf}$ ) by 28%, and increasing diastolic elastance ( $P_{o,lvf}$ ) by 350%. This example simulates a patient suffering from left ventricular infarction due to a blocked coronary artery where the left ventricular function is severely compromised due to ischemia. The value of  $S_{Ees,lvf}$  was not altered for these simulations, although the ability of the heart to increase contractility due to ANS activation could also be impaired in cardiac shock.

Simulations without ANS activation (Table 4) result in significant reductions in systemic circulatory pressures ( $P_{ao}$  and  $P_{vc}$ ) and CO, while  $P_{pa}$  reduces slightly and  $P_{pu}$  increases. In simulations with the combined CVS and ANS model, Table 4 shows that the systemic pressures and CO reduce to a lesser degree,  $P_{pa}$  increases significantly above the base value, and  $P_{pu}$  is increased to a greater degree. These increased pulmonary pressures are the main contributing factor to pulmonary edema commonly seen in patients with left ventricular dysfunction [14]. The results show that  $P_{pu}$  increases even without ANS activation, and is most likely caused by the increase in left ventricular end-diastolic

elastance which increases the filling pressure necessary for the left ventricle to continue pumping. The increase in  $P_{pa}$  after the inclusion of ANS activation is probably predominantly caused by the decrease in venous dead-space, as discussed by Burkhoff and Tyberg [8].

### 3.2.4 Pericardial tamponade

Pericardial tamponade is caused by an excessive build-up of fluid in the pericardium which limits the expansion of the ventricles. It can occur due to a variety of causes including trauma resulting from injury, or complications as a result of surgery [14]. In the long term the pericardium can slowly stretch, but in the acute stages the pericardium can have a high stiffness causing significant pericardial pressure increases [14]. In most cases, pericardial tamponade will cause a rise in filling pressures along with a reduction in cardiac output and mean arterial pressure [14,21]. Pericardial tamponade is simulated using the model by reducing the pericardium dead-space volume ( $V_{o,pcd}$ ) by 194 ml, to achieve steady state  $P_{ao}$  of 80 mmHg. This example simulates a patient following cardiac surgery where fluid has rapidly built up in the pericardium.

Simulations without ANS activation (Table 4) result in significantly reduced after-load pressures ( $P_{ao}$  and  $P_{pa}$ ), while filling pressures ( $P_{vc}$  and  $P_{pu}$ ) remain relatively constant. In simulations using the combined CVS and ANS model, Table 4 shows that the arterial pressures reduce to a lesser degree, and filling pressures increase. The simulations show that the commonly seen increase in filling pressures is only simulated with inclusion of the ANS model. The pressure in the pericardium ( $P_{peri}$ ) increases considerably in both

simulations due to the stretching the pericardium, and this in turn causes the reduction in ventricular preload volumes below half the base values.

### 3.2.5 Pulmonary embolism

Pulmonary embolism occurs due to blockage of a large fraction of the pulmonary circulation [22,23]. Diagnosis can be difficult, with patients appearing to be hemodynamically stable, with normal mean arterial pressure and cardiac output [14,23]. However, the pressure in the pulmonary artery pressure ( $P_{pa}$ ) can rise to 40mmHg, increasing right ventricular after-load and causing significant right ventricular dilation. In previously healthy patients, more than 50% of the pulmonary vasculature must be obstructed before pulmonary artery pressures will increase significantly [14]. Pulmonary embolism is simulated using the model by increasing pulmonary vascular resistance ( $R_{pul}$ ) by 240%.

Simulations without ANS activation (Table 4) result in increases in right heart preload and afterload pressures ( $P_{vc}$  and  $P_{pa}$ ), while left heart preload and after-load pressures ( $P_{pu}$  and  $P_{ao}$ ) reduce. In simulations with the combined CVS and ANS model, Table 4 shows that the same trends are seen with a greater increase in  $P_{vc}$  and  $P_{pa}$ , and a lesser decrease in  $P_{pu}$  and  $P_{ao}$ . The simulation shows the typical clinical picture of apparent hemodynamic stability ( $P_{ao} = 98$  mmHg and  $CO = 5.2$  l/min), but with an elevated pulmonary artery pressure ( $P_{pa} = 32.3$  mmHg). The simulated increased right ventricular after-load causes the right ventricle to expand, compressing the left ventricle. This effect is simulated in the reduced value of left ventricular volume and the average septal deflection, which becomes negative ( $V_{spt} = -0.7$  ml) compared to the base value of 4.6 ml. A positive value



for  $V_{\text{spt}}$  means the septum is deflecting into the right ventricle as normal, but a negative value means the septum is deflecting into the left ventricle. This interaction occurs even without ANS activation and is caused by the increased  $R_{\text{pul}}$ , causing a damming of blood in the right heart.

## 4 Discussion and Conclusions

This study has shown how a minimal CVS model can be modified to include the effects of ANS activation in order to simulate a variety of different CVS diseases. Four main ANS mechanisms have been identified that respond to blood pressure changes. The effect of each of these mechanisms on simulated hemodynamics is first investigated separately, before combining them in the model to simulate their combined effects in disease states. This is the first known example of a minimal CVS model that includes a generic model of ANS activation that is verified by simulating hemodynamic trends reported in medical literature for a variety of CVS diseases.

The necessity for the ANS model is illustrated in this paper through physiologically realistic disease conditions which can only be simulated using the combined CVS and ANS model. ANS activation is required to simulate pressure changes in hypovolemic and septic shock, without which simulated hemodynamic pressure levels are inadequate to maintain life. ANS activation is required to simulate the characteristic rise in CO during septic shock and the increased pulmonary artery pressure during cardiogenic shock due to left ventricular infarction. In pericardial tamponade, ANS activation is required to simulate the increased filling pressures and in pulmonary embolism ANS activation is also required to simulate the typical clinical picture of apparent hemodynamic stability

with significantly increased pulmonary artery pressure. In addition to these effects, the model captures ventricular interaction during pulmonary embolism. It is possible that the model could also be used to simulate impairments in ANS function such as in cardiovascular autonomic neuropathy [24].

The ANS model presented here uses only linear equations relating changes in CVS parameters to changes in arterial pressure, meaning that only 4 additional parameters are necessary, these representing ANS sensitivity. The same combined CVS and simple ANS model was used for all disease simulations. Despite the simplicity of the ANS model, it is possible to simulate the characteristic hemodynamic responses of CVS diseases seen in clinical practice.

All the simulated diseases are in their acute stage, which means that only the rapid reflex responses are simulated. It is assumed that slower acting mechanisms such as renal fluid retention do not affect hemodynamics significantly during the acute stage, or over short periods of time.

Simulation of the range of diseases shown here is the first step in verifying the model for use as a tool for aiding the clinician in diagnosing CVS diseases. Previous publications have presented identifiability analysis of the CVS model, excluding the ANS [25]. No formal analysis of the identifiability of the combined CVS and ANS model has been presented here, however, the simplicity of the linear equations included in the ANS model mean that only 4 additional parameters are necessary. Future work is required to

develop parameter identification methods, such as those described by Hann et al. [1], to enable patient specific diagnosis for the combined CVS and ANS model. If shown to be identifiable, then studies are required to investigate whether the model parameters fitted from individual patient data accurately reflect the disease state of that patient. For example, if the model is fitted to data from a patient with left ventricular myocardial infarction, will the fitted parameters show a reduction in left ventricular contractility? In this way the model could be used as decision support to identify CVS disease states in critically ill patients.

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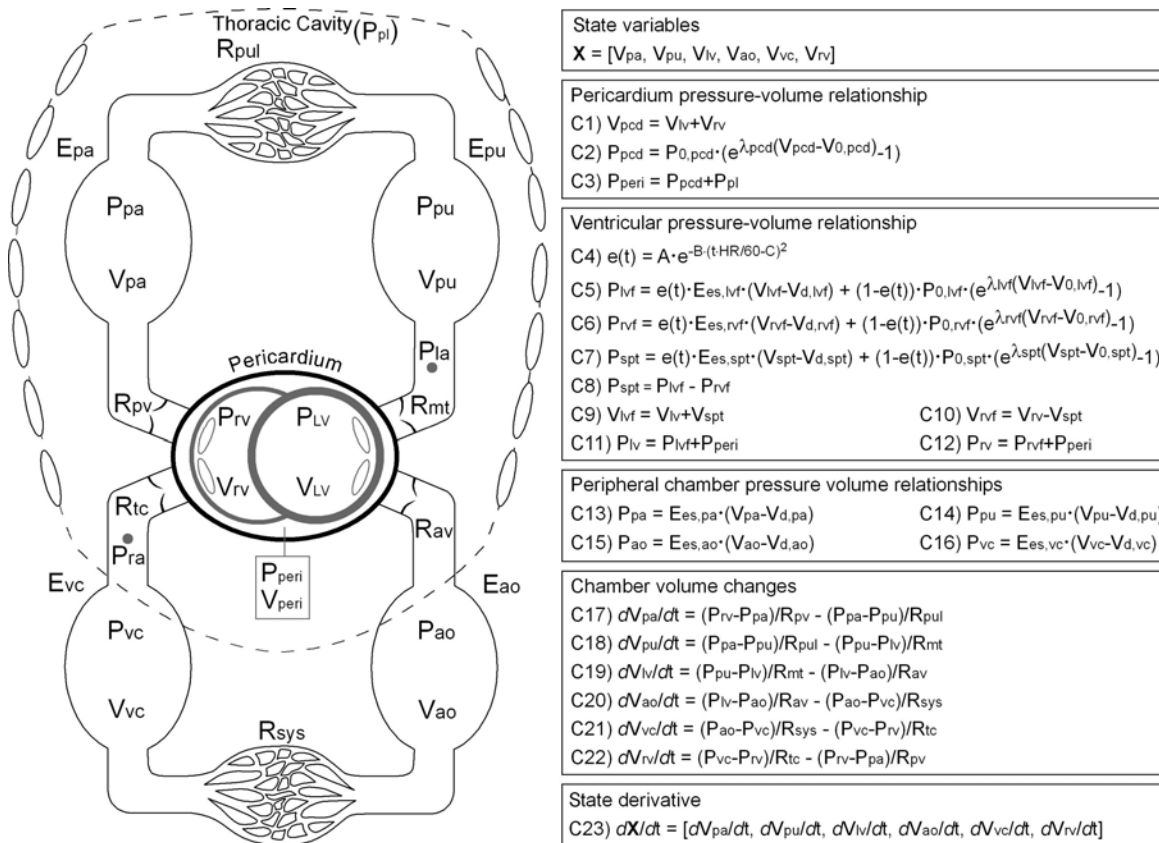


Figure 1, SmithAndreasen - CMPB-D-06-00222

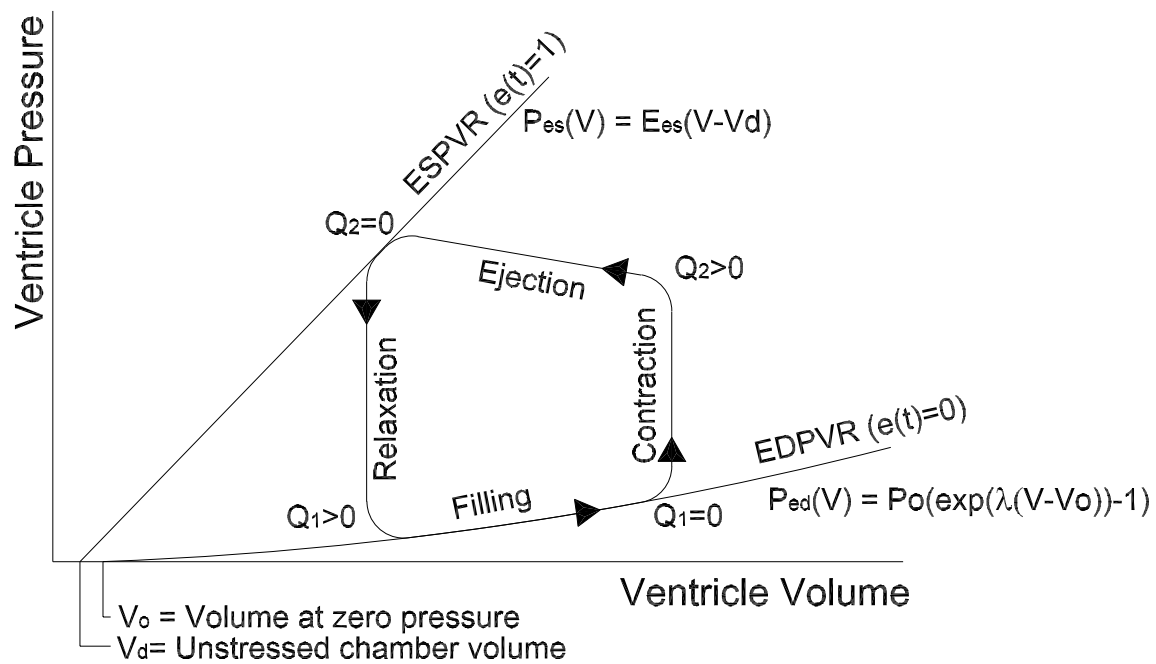


Figure 2, SmithAndreasen - CMPB-D-06-00222

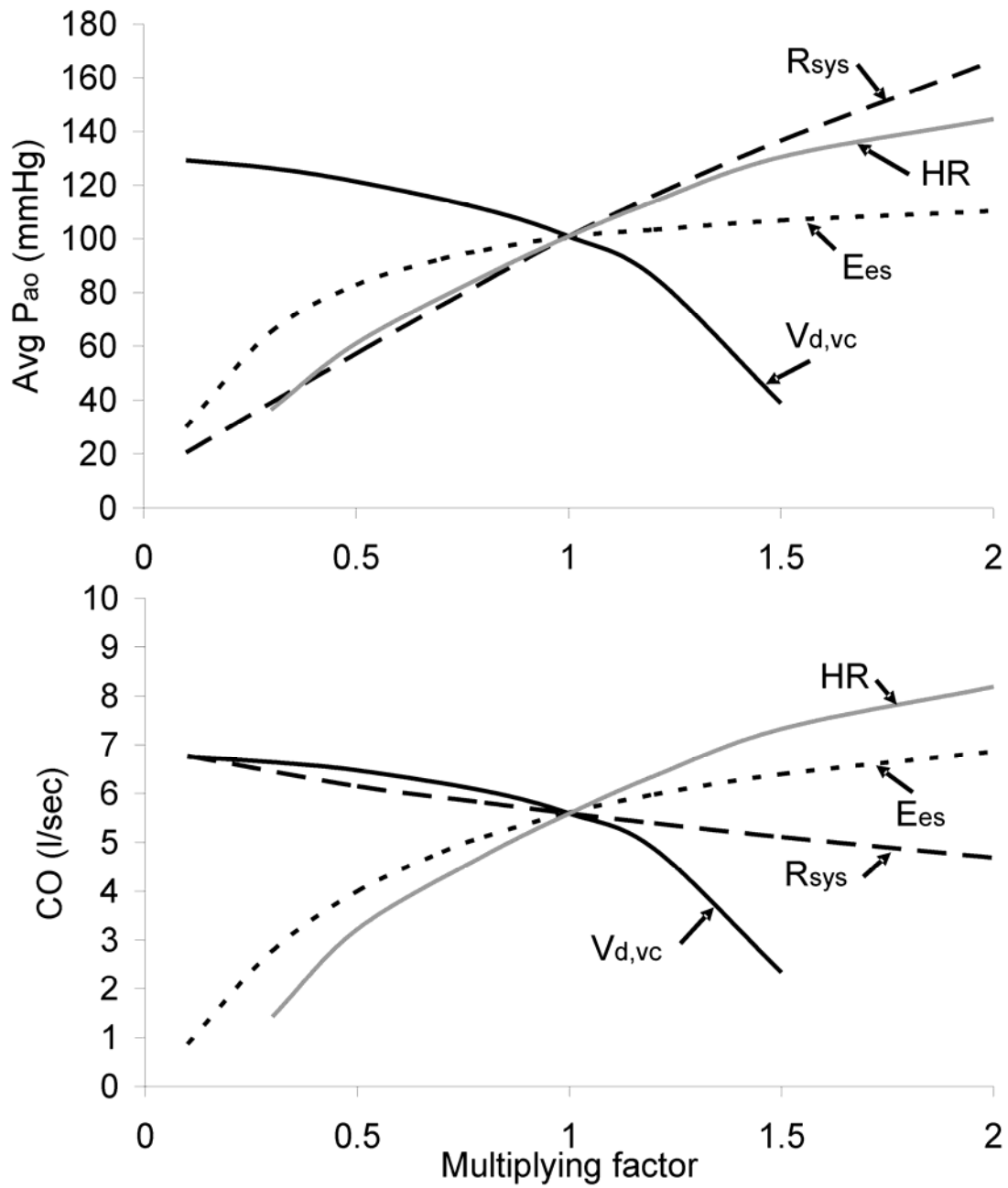


Figure 3, SmithAndreassen - CMPB-D-06-00222

**Table 1, SmithAndreassen - CMPB-D-06-00222**

<b>Parameter</b>	$E_{es}$	$V_d$	$V_o$	$\lambda$	$P_o$
<b>Units</b>	kPa/l	l	l	1/l	kPa
Left ventricle free wall (lvf)	454	0.005	0.005	15	0.17
Right ventricle free wall (rvf)	87	0.005	0.005	15	0.16
Septum free wall (spt)	6500	0.002	0.002	435	0.148
Pericardium (pcd)	-	-	0.2	30	0.0667
Vena-cava (vc)	1.5	2.83	-	-	-
Pulmonary artery (pa)	45	0.16	-	-	-
Pulmonary vein (pu)	0.8	0.2	-	-	-
Aorta (ao)	94	0.8	-	-	-

**Table 2, SmithAndreassen - CMPB-D-06-00222**

<b>Parameter</b>	<b>Value</b>
Mitral Valve ( $R_{mt}$ )	0.06 kPa.s/l
Aortic Valve ( $R_{av}$ )	1.4 kPa.s/l
Tricuspid Valve ( $R_{tc}$ )	0.18 kPa.s/l
Pulmonary Valve ( $R_{pv}$ )	0.48 kPa.s/l
Pulmonary Circulation ( $R_{pul}$ )	19 kPa.s/l
Systemic Circulation ( $R_{sys}$ )	140 kPa.s/l
Heart Rate (HR)	80 bpm
Total blood volume ( $V_{tot}$ )	5.5 l
Thoracic cavity pressure ( $P_{pl}$ )	-4 mmHg

**Table 3, SmithAndreassen - CMPB-D-06-00222**

<b>Parameter</b>	<b>Value</b>	
$S_{R_{sys}}$	$-0.0175 \text{ mmHg}^{-1}$	$(-0.131 \text{ kPa}^{-1})$
$S_{V_{dvc}}$	$0.0175 \text{ mmHg}^{-1}$	$(0.131 \text{ kPa}^{-1})$
$S_{HR}$	$-0.025 \text{ mmHg}^{-1}$	$(-0.188 \text{ kPa}^{-1})$
$S_{Ees}$	$-0.0175 \text{ mmHg}^{-1}$	$(-0.131 \text{ kPa}^{-1})$

Table 4, SmithAndreassen - CMPB-D-06-00222

	Base	Hypovol	Septic	LV Infarct	Peri Tamp	Pul Emb
<b><u>Ventricular filling pressures</u></b>						
Avg Pvc (mmHg)	(2) 2	(NA) -2.7	(-3.6) -0.6	(-2.2) -1.9	(2.0) 4.6	(2.6) 2.9
Avg Ppu (mmHg)	(2) 2	(NA) -2.3	(-3.6) -0.7	(5.3) 10.6	(3.2) 7.4	(1.4) 1.7
<b><u>Ventricular afterload pressures</u></b>						
Avg Pao (mmHg)	(100) 100	(NA) 80	(5) 80	(37) 80	(36) 80	(89) 98
Avg Ppa (mmHg)	(16.5) 16.5	(NA) 6.3	(-1.2) 16.0	(11) 19.2	(8.2) 15.4	(30.2) 32.3
<b><u>Perfusion</u></b>						
CO (l/min)	(5.6) 5.6	(NA) 3.5	(0.9) 6.8	(2.2) 3.4	(1.9) 3.2	(4.9) 5.2
<b><u>Ventricular preload volumes</u></b>						
LVEDV (ml)	(115) 115	(NA) 58	(22) 86	(87) 110	(45) 55	(101) 104
RVEDV (ml)	(115) 115	(NA) 46	(21) 88	(58) 61	(47) 52	(128) 130
<b><u>Ventricular interaction</u></b>						
Avg Vspt (ml)	(4.6) 4.6	(NA) 4.2	(2.3) 4.5	(4.7) 5.6	(2.8) 3.8	(0.5) -0.7
Avg Pperi (mmHg)	(-3.6) -3.6	(NA) -4	(-4) -4	(-4) -4	(3.7) 4.2	(0.4) -1.3