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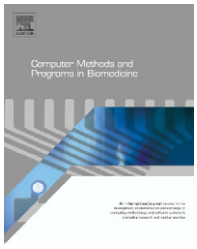

Simulation of cardiovascular system diseases by including the autonomic nervous system into a minimal model

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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.

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 (e.g. mean arterial, pulmonary artery, central venous), volumes (e.g. 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

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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 [2–7]. 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].

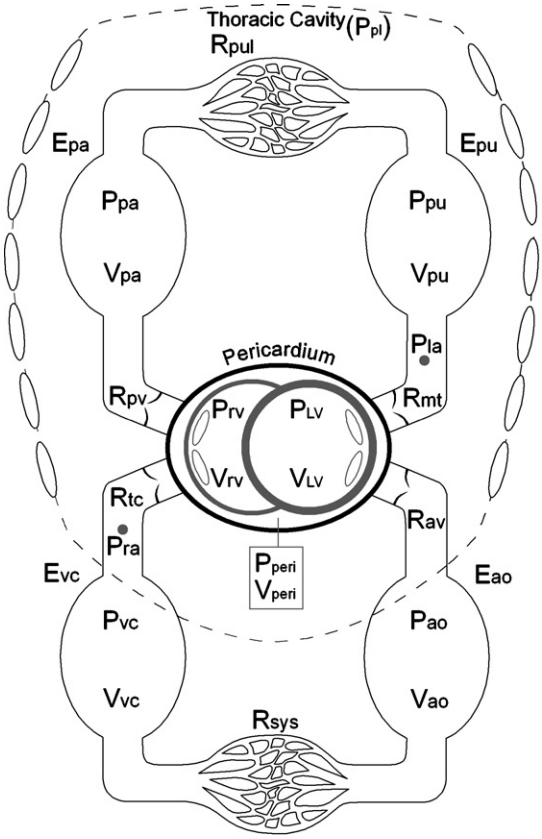
This research investigates modifications to a previously presented model of CVS function to include a model of ANS response [6,7]. The aim is to develop a model of the CVS including ANS response which can simulate a variety of relevant disease scenarios commonly seen in critically ill patients, including examples of the four 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 Fig. 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



State variables

$\mathbf{X} = [V_{pa}, V_{pu}, V_{lv}, V_{ao}, V_{vc}, V_{rv}]$

Pericardium pressure-volume relationship

C1) $V_{pcd} = V_{lv}+V_{rv}$

C2) $P_{pcd} = P_{0,pcd}\cdot(e^{\lambda pcd(V_{pcd}-V_{0,pcd})}-1)$

C3) $P_{peri} = P_{pcd}+P_{pl}$

Ventricular pressure-volume relationship

C4) $e(t) = A\cdot e^{-B\cdot(t\cdot HR/60-C)^2}$

C5) $P_{lvf} = e(t)\cdot E_{es,lvf}\cdot(V_{lvf}-V_{d,lvf}) + (1-e(t))\cdot P_{0,lvf}\cdot(e^{\lambda lvf(V_{lvf}-V_{0,lvf})}-1)$

C6) $P_{rvf} = e(t)\cdot E_{es,rvf}\cdot(V_{rvf}-V_{d,rvf}) + (1-e(t))\cdot P_{0,rvf}\cdot(e^{\lambda rvf(V_{rvf}-V_{0,rvf})}-1)$

C7) $P_{spt} = e(t)\cdot E_{es,spt}\cdot(V_{spt}-V_{d,spt}) + (1-e(t))\cdot P_{0,spt}\cdot(e^{\lambda spt(V_{spt}-V_{0,spt})}-1)$

C8) $P_{spt} = P_{lvf} - P_{rvf}$

C9) $V_{lvf} = V_{lv}+V_{spt}$ C10) $V_{rvf} = V_{rv}-V_{spt}$

C11) $P_{lv} = P_{lvf}+P_{peri}$ C12) $P_{rv} = P_{rvf}+P_{peri}$

Peripheral chamber pressure volume relationships

C13) $P_{pa} = E_{es,pa}\cdot(V_{pa}-V_{d,pa})$ C14) $P_{pu} = E_{es,pu}\cdot(V_{pu}-V_{d,pu})$

C15) $P_{ao} = E_{es,ao}\cdot(V_{ao}-V_{d,ao})$ C16) $P_{vc} = E_{es,vc}\cdot(V_{vc}-V_{d,vc})$

Chamber volume changes

C17) $dV_{pa}/dt = (P_{rv}-P_{pa})/R_{pv} - (P_{pa}-P_{pu})/R_{pul}$

C18) $dV_{pu}/dt = (P_{pa}-P_{pu})/R_{pul} - (P_{pu}-P_{lv})/R_{mt}$

C19) $dV_{lv}/dt = (P_{pu}-P_{lv})/R_{mt} - (P_{lv}-P_{ao})/R_{av}$

C20) $dV_{ao}/dt = (P_{lv}-P_{ao})/R_{av} - (P_{ao}-P_{vc})/R_{sys}$

C21) $dV_{vc}/dt = (P_{ao}-P_{vc})/R_{sys} - (P_{vc}-P_{rv})/R_{tc}$

C22) $dV_{rv}/dt = (P_{vc}-P_{rv})/R_{tc} - (P_{rv}-P_{pa})/R_{pv}$

State derivative

C23) $d\mathbf{X}/dt = [dV_{pa}/dt, dV_{pu}/dt, dV_{lv}/dt, dV_{ao}/dt, dV_{vc}/dt, dV_{rv}/dt]$

Fig. 1 – The minimal closed loop model of the cardiovascular system showing the heart (V_{lv} and V_{rv}) and pulmonary circulation (V_{pa} and V_{pu}) inside the thoracic cavity (P_{pl}), and the systemic circulation (V_{ao} and V_{vc}) outside.