Modelling the cardiovascular system

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ABSTRACT

Cardiovascular disease claims more lives than any other disease in westernised countries, affecting millions. Pinpointing cardiovascular system dysfunction is often difficult because the clinical signs, or the availability and interpretation of physiological measurements, are unreliable. Often patient-specific information is incomplete or confusing, as it comes from a diverse range of sources, such as invasive and non-invasive pressure measurements, flow rates and electrocardiogram signals. Health professionals therefore rely on intuition and experience to make a "clinical" diagnosis and decide treatment. Sometimes this approach results in multiple therapies being applied until a suitable treatment is found. Poor outcomes result from failure to quickly and correctly diagnose and treat the underlying condition.

We introduce the concept of using full circulatory and cardiovascular models to aggregate the large number of diverse signals facing clinicians into a clear physiological picture of haemodynamic status. We briefly review the field, still in its infancy, of such models, focusing primarily on the basic approaches taken in the literature. Finally, we present one of the more advanced and best validated models, including initial results of animal validation studies. The overall approach is shown to have significant potential to provide clear, measured insight to replace often misled intuition in the monitoring, diagnosis and treatment of circulatory dysfunction in critical care. In the future, models and modern sensors will increasingly "invade" the critical care environment, and will provide the opportunity for better, more consistent care at the bedside in real time.

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How well do clinicians understand cardiovascular dysfunction?

All doctors have some notional understanding of why fluids might be useful to resuscitate patients with low blood pressure, poor peripheral perfusion or poor urine output. However, beyond giving fluids to support patients with circulatory failure, our physiological understanding of the complex cardiovascular responses in shocked states is poor. In particular, there is a paucity of evidence for any specific therapeutic intervention used in cardiovascular support.

Where evidence does exist regarding supportive therapy, it is usually about interventions that are not effective, such as dopamine for renal protection.[1] The best evidence for a positive result is for the early goal-directed therapy care bundle promulgated by Rivers et al.[2] However, their study is criticised for its high mortality in the control group and lack of generalisability, having not been validated to date in any but a single centre.[3]

A disadvantage of seeking answers in randomised controlled trials (RCTs) is that the resulting empirical evidence does not improve our understanding of the complex physiology and reflex actions involved. The level of complexity involved in the haemodynamics of critically ill patients is significant, even for mathematicians and engineers trained to model and manipulate such complex systems. Hence, empirically driven strategies derived from clinical observations often fail to meet the highly variable, highly dynamic needs of broad cohorts of critically ill patients. It is thus not surprising that, while there has been great reliance on RCTs to provide the answers, the results have been — to say the least — disappointing.

For example, studies using the pulmonary artery catheter to guide fluid or inotrope choice and dose have not shown specific benefits.[4-7] Studies of even the simplest decision — the choice of fluid — have shown no benefit for either crystalloids or colloids in critically ill patients.[8] This is not to say that these approaches are wrong, but that perhaps they are not right for all patients.

Where are we going wrong?

When treatment strategies for highly complex pathophysiological disturbances are based on incomplete or wrong paradigms of care, then the chance of finding an effective one-size-fits-all therapeutic intervention is almost zero. One-size-fits-all paradigms are particularly prone to failing when the patient's demands are variable, and necessitate modulation in response to changes in condition. Therefore, is it wise to keep pumping money and resources into clinical trials, seeking serendipitous "fortunes" lacking in scientific foundation or explanation?

Consider today's state-of-the-art haemodynamic monitoring and interventions. There is no evidence that static

pressure measurements of preload and central venous and pulmonary artery occlusion pressures are useful in predicting fluid responsiveness.[9] This problem arises because preload is not the same as preload-responsiveness.[9] Dynamic tests of preload, such as arterial pulse pressure or systolic pressure variations in ventilated patients, or central venous pressure falls in spontaneously breathing patients, can predict fluid responsiveness.[9] However, this does not inform the clinician how much fluid to give, or how, in combination with fluid, to start or to titrate vasoactive drugs. In addition, this information is not particularly useful diagnostically. So, in the end, patients are subjected to therapies using guesswork — the so-called "art" of medicine.

Hundreds of scientific papers and dozens of text books have been written about the "science" of resuscitation. However, this knowledge is essentially based on small observational or experimental studies that explored only specific aspects of cardiovascular responses in isolation. None of these limited studies or outcomes explores the fact that haemodynamics are a combination of several complex responses, linked by a wide variety of sometimes redundant, and sometimes destabilising, reflex actions. That is, none of them truly touches on the reality of the intensive care clinician looking at a specific patient.

What is missing?

First, there has been no attempt to integrate these disparate packages of knowledge into a robust cardiovascular model to improve monitoring, diagnosis and prediction. Hence, we are left with incomplete paradigms that have resulted in potentially poor therapeutic choices for some patients, without knowing beforehand which patients are receiving the poor choice. A robust cardiovascular model that would provide the tools needed by clinicians — both expert and non-expert — to deliver appropriate and consistent, patient-specific care is long overdue.

The past 20 years have seen a revolution in the computational power of computers. However, the high computational speeds required to develop models of the cardiovascular system have only recently become available to researchers. With an appropriate model, medical staff could gain a better understanding of cardiovascular function, by varying parameters to simulate a variety of dysfunctions, such as stiff heart walls or pump failure. In particular, a model whose parameters have been identified to match a specific patient could be used to assist diagnosis and treatment, through comparing model outputs simulating various cardiovascular dysfunctions and therapies to make the best choice. By measuring physiological parameters such as blood pressure, heart rate, stroke volume and ventricular pressures, the governing elastances, resistances and pressure–volume relationships for a given patient's haemodynamics can be determined. Hence, the performance of the patient's circulation can be rapidly identified, enabling comment on any irregularities found, and simulated testing of potential therapies.

We suggest that any such model needs to fulfil the following criteria to ensure that it is practical and effective as a diagnostic aid:

- Model parameters should be relatively easily identified for a specific patient.
- Although quantitatively exact results are not necessary, accurate prediction of trends with changes in parameters or therapy is needed.

Current approaches

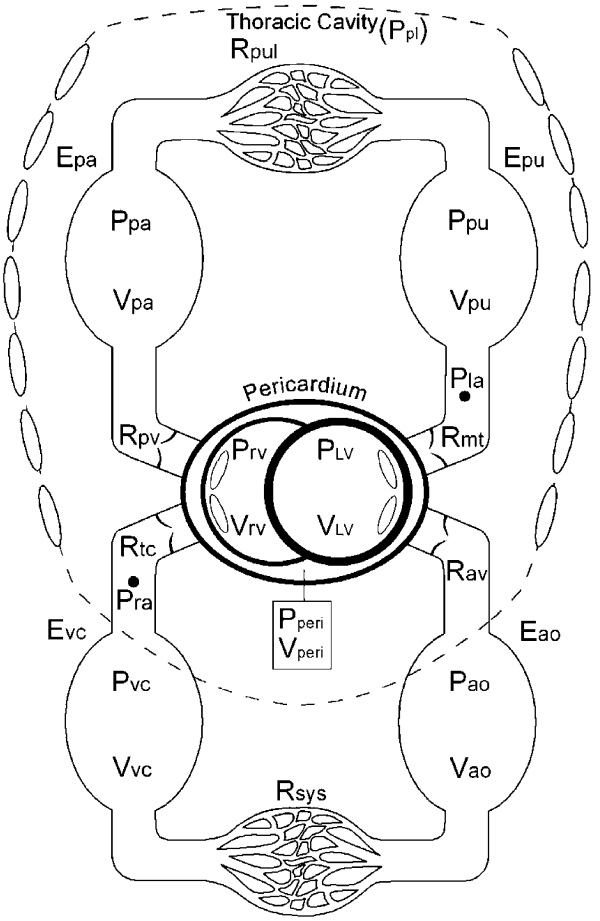
Most current approaches to modelling the human circulation can be grouped into either the "finite element" or the "pressure volume" approach. Finite element techniques offer accurate results but require immensely detailed inputs, such as muscle fibre orientations, structures and mechanical properties.[10,11] Limitations on the availability of detailed in-vitro patient-specific data and computational power mean that finite element methods are not well suited as rapid diagnostic tools.

In contrast, pressure–volume methods divide the circulation into a series of elastic chambers separated by resistances, with inductors simulating inertial effects where required. Each elastic chamber models a section, such as the ventricles, the atria or the aorta, each with its own pressure–volume relationship. A minimal number of parameters, such as chamber elastances and arterial resistances, are required to create such a model. These models can be solved on modern, commonly available desktop computers in very reasonable times, suitable for immediate clinical feedback.

The minimal cardiovascular system model

An example of a pressure–volume model of the cardiovascular system is the minimal closed loop model, which is shown schematically in Figure 1, along with the governing equations.[12] The model structure and method of implementation are outlined in detail by Smith et al,[13] and are 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

Figure 1. The minimal closed loop model of the cardiovascular system



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

The model shows 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.

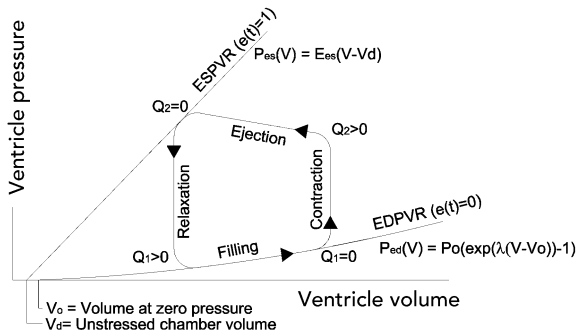
the aortic valve (R_{av}). Ventricular interaction due to the septum (spt) and pericardium (peri) is also accounted for in the model. The effects of the thoracic cavity (P_{pl}) pressure on the ventricles and pulmonary circulation chambers are also included to account for the influence of respiration.

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 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 (λ) being adjusted using the parameters λ_{lvf}, λ_{rvf} and λ_{spt}.

Overall, this model contains six 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 Table 1 and Table 2.[13-15] Simulations performed using the model have been previously shown to reproduce

Figure 2. Pressure–volume diagram of the cardiac cycle



The pressure–volume diagram shows the variations in end-diastolic (EDPVR) and end-systolic (ESPVR) pressure–volume relationships for the ventricular and septal walls (V_{lvf}, V_{rvf} and V_{spt}).

normal values and characteristic trends in volumes and pressures in the heart and circulatory system comparable to those in the healthy human.[13,16] The model is designed to minimise the number of parameters needed to identify disease states. However it is important not to oversimplify the model and risk failing to identify important disease-specific characteristics.[12]

Model validation

This model has been validated for a wide variety of clinical data and trends, including five disease states, and circulatory and septal interaction.[17,18] More recently, we used this model to identify the effect of pulmonary embolism in animal studies — the first validation of model-based diagnostics for circulatory haemodynamics in an animal.[19]

This validation of model-based diagnosis of cardiac dysfunction used data from pulmonary embolism induced in pigs.[20] Briefly, pulmonary emboli were injected every 2 hours, inducing increasing levels of pulmonary hypertension. The model was able to accurately identify this behaviour at each interval, and the changes in model parameters to match it were physiologically justified. This task was accomplished using only measurements available in critical care units utilising modern monitoring systems such as the PiCCO (pulse contour cardiac output) system (Pulsion Medical Systems AG, Munich, Germany).

In particular, the identification method required measurements of only the pressures in the aorta and pulmonary artery, and the volumes in each ventricle. This is a very limited set of data. The ideal model goal was to identify an increasing level of pulmonary resistance (Rpul) while seeing all or most other model parameters remain constant, thus physiologically identifying the pulmonary hypertension.

Figure 3 show the PV loops for both ventricles in one pig, and the trend in pulmonary resistance value (model parameter) for all six pigs studied. In the upper panel, it is evident that the measured clinical PV loop data and the identified model results match within 10%, an extremely accurate fit given the noise on the measured data.[20] This good fit holds for both ventricles at 0, 120 and 180 minutes into the experiment. In the lower panel, it is clear that all six pigs had increasing pulmonary resistance with increasing pulmonary hypertension as greater numbers of emboli were injected. In addition, five of the six pigs had similar values for this parameter, showing a fairly general result for the model. The exception may have been due to sensor noise with those particular data.

Table 1. Base values of the pressure–volume relationship parameters used in the minimal cardiovascular system model

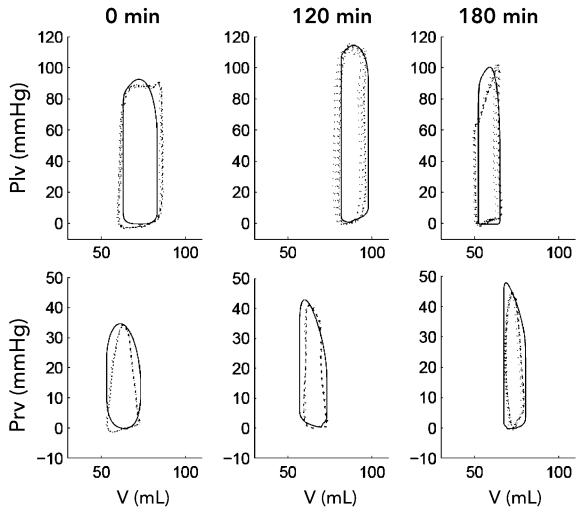
Parameter	E_{es} (kPa/L)	V_d (L)	V_o (L)	λ (1/L)	P_o (kPa)
Left ventricle free wall (lvf)	454	0.005	0.005	15	0.17
Right ventricle free wall (rvf)	87	0.005	0.005	15	0.16
Septum free wall (spt)	6500	0.002	0.002	435	0.148
Pericardium (pcd)	–	–	0.2	30	0.067
Vena cava (vc)	1.5	2.83	_	_	_
Pulmonary artery (pa)	45	0.16	_	_	_
Pulmonary vein (pu)	0.8	0.2	_	_	_
Aorta (ao)	94	0.8	_	_	_

E_{es} = contractility, end-systolic elastance. V_d = unstressed volume. V_o = volume at zero pressure. λ = parameter in the end-diastolic pressure–volume relationship (EDPVR). P_o = stiffness, end-diastolic elastance.

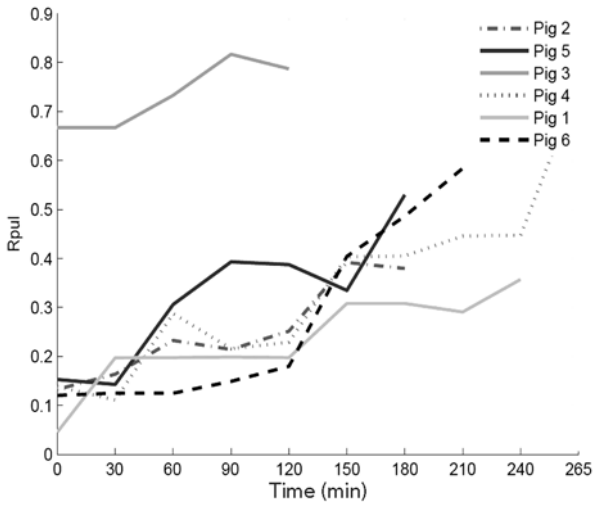
Table 2. Base values of the resistances and other parameters used in the minimal cardiovascular system model[12]

Parameter	Value
Mitral valve (R_{mt}) (kPa.s/L)	0.06
Aortic valve (R_{av}) (kPa.s/L)	1.4
Tricuspid valve (R_{tc}) (kPa.s/L)	0.18
Pulmonary valve (R_{pv}) (kPa.s/L)	0.48
Pulmonary circulation system (R_{pul}) (kPa.s/L)	19
Systemic circulation system (R_{sys}) (kPa.s/L)	140
Heart rate (HR) (beats per min)	80
Total blood volume (V_{tot}) (L)	5.5
Thoracic cavity pressure (P_{pl}) (mmHg)	–4

Figure 3. Clinical results in pulmonary embolism studies in six pigs[20]



A. Pressure–volume loops for the left and right ventricles (lv and rv) at 0, 120 and 180 minutes after injection of pumonary emboli in Pig 2. (Dashed line represents clinical data, and solid line represents values predicted by the model.)



B. Identified pulmonary vascular resistance (Rpul) for all six pigs during the experiment.

Summary

We have briefly described the need for modelling or other methods of aggregating diverse amounts of data into coherent pictures of the haemodynamic state of the highly dynamic circulation in critical illness. We have introduced the concept of modelling, a method that is very much in its infancy with regard to whole-body circulatory models of haemodynamics. Finally, we present a model that has been developed, validated on clinical data and used in first-of-their-kind animal studies, with moderate success in identifying physiologically meaningful changes in model parameters. Overall, this discussion is less about what has been achieved, but more a glimpse of what is needed and what, in the near future, we hope can be achieved.

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