MODELLING THE CARDIOVASCULAR SYSTEM

Geoffrey M. Shaw[1], J. Geoffrey Chase[2], Christina Starfinger[2], Bram W. Smith[3]. Christopher E. Hann[2]. T. Desaive[4] and A. Ghuysen[5]

[1] Department of Medicine, University of Otago, Christchurch, New Zealand
[2] Centre of Bioengineering, Dept of Mechanical Eng, Univ of Canterbury, Christchurch, New Zealand
[3] Centre for Model-Based Medical Decision Support, Aalborg University, Aalborg, Denmark
[4] Institute of Physics, University of Liege, Belgium
[5] Hemodynamics Research Laboratory, University of Liege, Belgium

ABSTRACT

Cardiovascular disease claims more lives than any other disease in westernised countries, affecting millions. Pin-pointing CVS dysfunction is often difficult because the clinical signs, or the availability and interpretation of physiological measurements are unreliable. Often patient specific information is incomplete and/or confusing as it comes from a diverse range of sources such as invasive and non-invasive pressure measurements, flow rates and ECG signals. Health professionals therefore rely on intuition and experience to make a 'clinical' diagnosis and treatment decisions. 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.

This monograph introduces 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. A brief review of the field, still in its infancy, of such models is presented focusing primarily on the basic approaches taken in the literature. Finally, one of the more advanced and best validated models is presented including initial animal validation study results. 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, and in real time.

Even an orthopaedic surgeon has 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 of fluids to support circulatory failure, our physiological understanding of the complex cardiovascular responses in shocked states is very poor. In particular, there is 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 don't work, such as dopamine for renal protection[1]. The best evidence for a positive result pointing clinicians towards what they should do is the Early Goal-Directed (EGT) therapy care bundle promulgated by Rivers et al[2]. However, this study is criticised for its high control mortality and lack of generalisability, having not been validated outside of a single centre to date[3].

One of the disadvantages of looking for answers in randomised controlled trials (RCTs) is that the empiric evidence does not help imperfect understanding of the complex physiology and reflex actions involved. The level of complexity involved in the haemodynamics of the critically ill is significant, even for those 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. Therefore, it is not surprising that while there has been a great reliance on RCTs to provide the answers, the results have been, to say the least, very disappointing.

For example, studies using the pulmonary artery catheter to guide fluid or inotrope choice/dose have not shown specific benefits[4,5,6,7]. Even the simplest decision, the choice of fluid, has not shown any benefit for either crystalloids or colloids in critically patients[8]. This is not to say that these approaches are wrong, but that perhaps they are also 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 chances of finding a one-size-fits-all therapeutic intervention that works is almost zero. In particular, one size fits all paradigms are prone to failing whenever the patient's demands are variable and require adaptive modulation in response to changes in condition. Therefore, is it wise to keep pumping money and resources into clinical trials, looking for serendipitous 'fortunes' lacking in scientific foundation or explanation?

Consider the state-of-the art haemodynamic monitoring and interventions today. There is no evidence that static pressure measurements of preload, 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, thus providing only a partial answer. In addition, this information tells nothing about how, in combination with fluid therapies, to start, or titrate, vaso-active drugs. Finally this information is not particularly useful diagnostically. So, in the end, patients are subjected to therapies using guesswork- the so called 'art' of medicine.

Overall, hundreds of scientific papers, and dozens of text books, have been written about the 'science' of resuscitation. However, the foundations of this knowledge are essentially all based on small observational or experimental studies that have, in isolation, only explored specific aspects of cardiovascular responses. 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 destabilizing reflex actions. I.e. 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, diagnostics and prediction. Hence, we are left with incomplete paradigms that have resulted in potentially poor therapeutic choices for some patients, without knowing which patients are receiving the poor choice before making the clinical decision. A robust cardiovascular model would allow expert, and non-expert clinicians alike access to the tools required delivering appropriate and consistent, patient-specific care is long overdue.

The last twenty years has seen a revolution in the computational power of computers. However, access to the high computational speeds required to set about developing models of the cardiovascular system have only been made available to researchers in very recent times. With an appropriate model, medical staff can 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 by comparing model outputs simulating various cardiovascular dysfunctions and therapies to make a best choice. Thus, by measuring various 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 a patient's circulation can be rapidly identified, enabling comment on any irregularities found, and the simulated testing of several potential therapies.

It is suggested that any such model fulfil the following aims 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 are required.

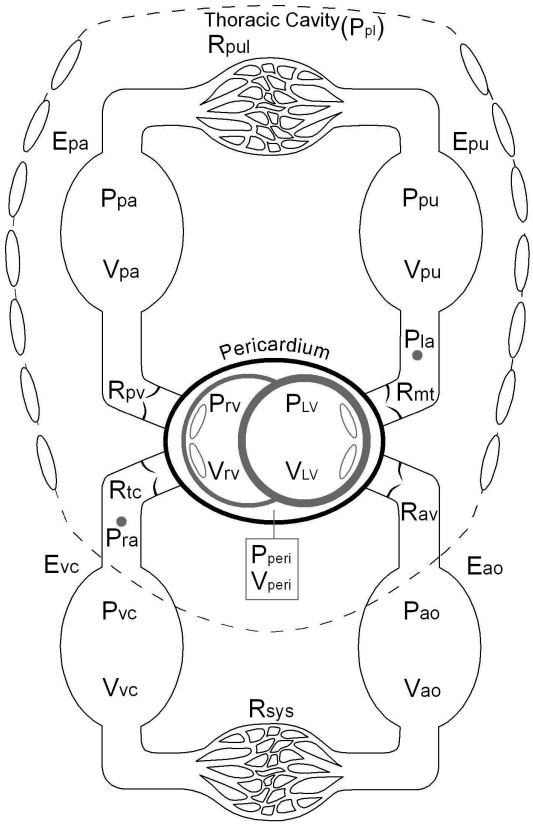
Most current approaches to modelling the human circulation can be grouped into either Finite Element (FE) or Pressure Volume (PV) approaches. FE techniques offer accurate results, but require immensely detailed inputs such as muscle fibre orientations, structures and mechanical properties[10,11]. Limitations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

In contrast, PV methods divide the circulation into a series of elastic chambers separated by resistances, and inductors simulating inertial effects where required. Each elastic chamber models a section such as the ventricles, the atria, or the aorta, each with their own pressure-volume relationship. Only 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 (CVS) model used in this study is shown schematically in Figure 1, including the governing equations[12]. The model structure and method of implementation is outlined in detail in Smith et al[13] 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 (λ) being adjusted using the parameters λ_{lvf}, λ_{rvf} and λ_{spt}.



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

Figure 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. [12]

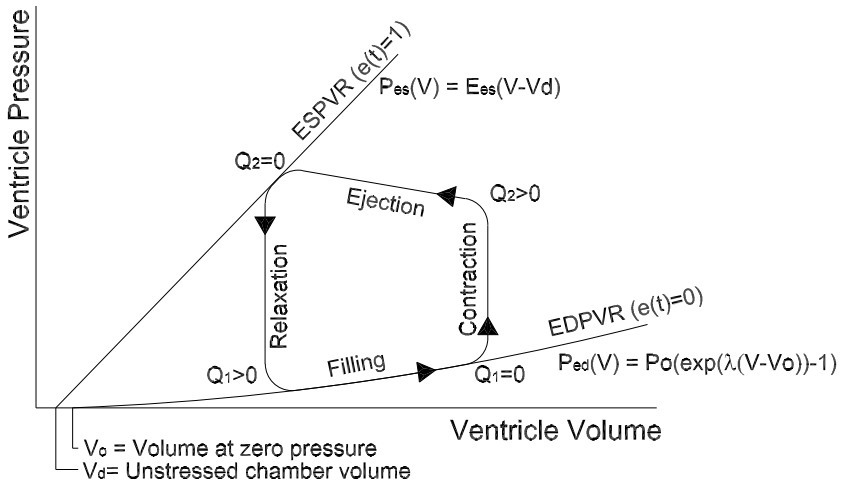


Figure 2, Pressure-volume diagram of the cardiac cycle and the variations in end-diastolic (EDPVR) and end-systolic (ESPVR) pressure-volume relationships for the ventricular and septal walls (V_{lvf}, V_{rvf} and V_{spt}).

Overall, 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.[13,14,15] 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[13,16]. The model is designed to contain a minimal number of parameters in order to improve identifiably, whilst preserving parameters that are necessary to simulate a variety of relevant diseases, as will be illustrated[12].

Table 1, Base values of the PV relationship parameters used in the CVS model[12]

Parameter	E_{es}	V_d	V_o	λ	P_o
Units	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, Base values of the resistances and other parameters in the CVS model[12]

Parameter	Value
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 System (R_{pul})	19 kPa.s/l
Systemic Circulation System (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

This model has been validated for a wide variety of clinical data and trends, including 5 disease states, and circulatory and septal interaction[17,18]. More recently, it has been utilised to identify the effect of pulmonary embolism in animal studies using pigs, the first validation of model-based diagnostics for circulatory haemodynamics in an animal[19].

This first validation of model-based diagnosis of cardiac dysfunction utilised data from pulmonary embolism induced in pigs[20]. Details can be found in the reference, however 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 like the PiCCO™ system.

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 6 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 6 pigs saw

increasing pulmonary resistance with increasing pulmonary hypertension as greater numbers of emboli were injected. In addition, all 8 pigs have similar values for this parameter, showing a fairly general result for the model, with one exception that may be due to sensor noise issues with that particular data.

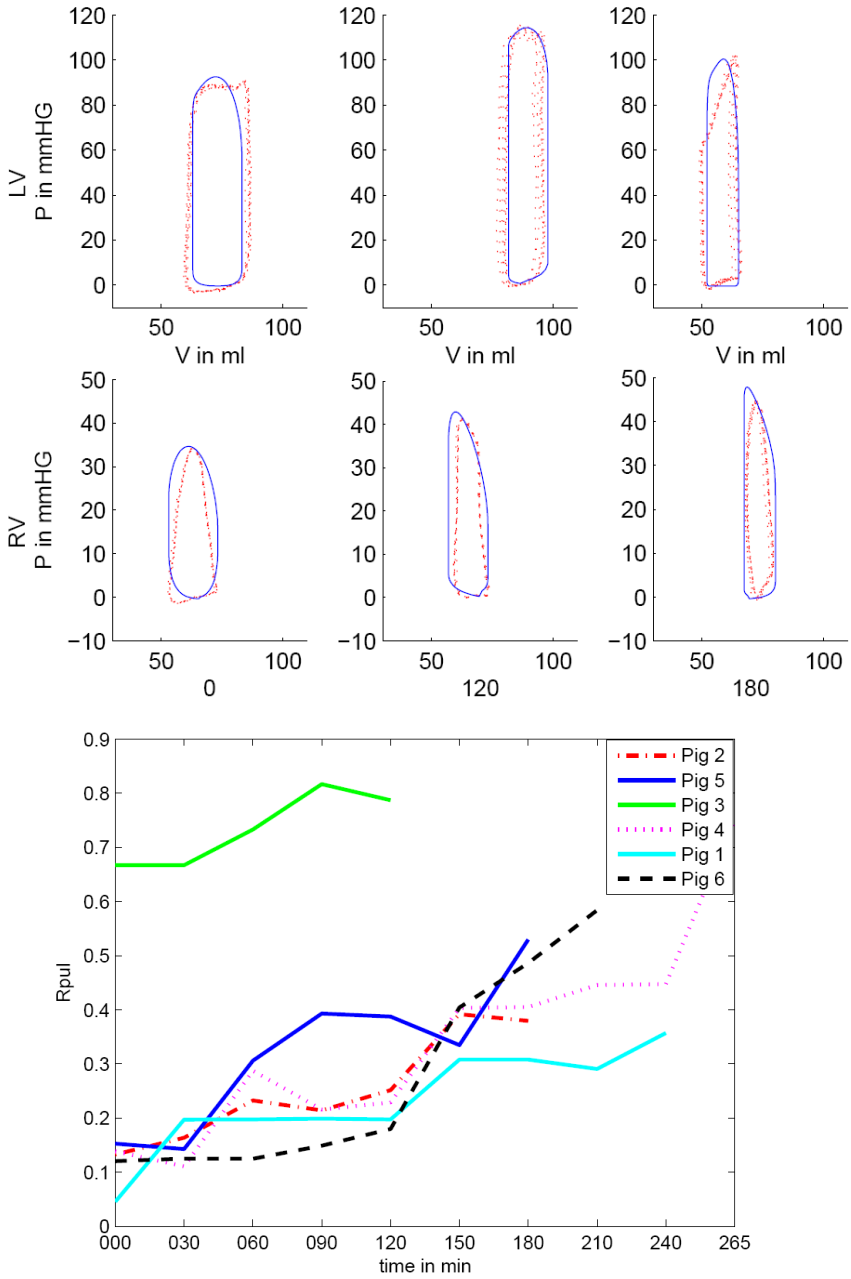


Figure 3, Clinical results in pulmonary embolism studies in 6 pigs[20]

Top: P-V Loops for left and right ventricle at 30, 120 and 180 mins in pig 2 (Dashed is clinical data and solid is identified model)

Bottom: Pulmonary vascular resistance (R_{pul}) for all 6 pigs during the experiment

SUMMARY

This paper has 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 critically ill circulation. The idea of modelling has been introduced, a method that is very much in its infancy with regard to whole body circulatory models of haemodynamics. Finally, a model is presented that has been developed, validated on clinical data and used in first of its kind animal studies with some moderate success in identifying physiologically meaningful model parameter changes. Overall, this discussion is not about what has been done but an attempt to provide a glimpse at what is needed and what, in hopefully the nearer future, can be done.

REFERENCES

[1] Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet. 2000 Dec 23-30;356(9248):2139-43.

[2] Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001, 345:1368-1377.

[3] Ho BC, Bellomo R, McGain F, Jones D, Naka T, Wan L, Braitberg G. The incidence and outcome of septic shock patients in the absence of early-goal directed therapy. Crit Care. 2006;10(3):R80. Epub 2006 May 16.

[4] Connors AF, Speroff TS, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA* 1996; 276: 889–97.

[5] W, Williams D, Young D, Rowan K; PAC-Man study collaboration. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet. 2005 Aug 6-12;366(9484):472-7.

[6] Gore JM, Goldberg RJ, Spodick DH, Alpert JS, Dalen JE. A community-wide assessment of the use of pulmonary artery catheters in patients with acute myocardial infarction. *Chest* 1987; 92: 721–27.

[7] Zion MM, Balkin J, Rosenmann D, et al. Use of pulmonary artery catheters in patients with acute myocardial infarction. *Chest* 1990;98: 1331–35.

[8] Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004 May 27;350(22):2247-56.

[9] Pinsky MR, Hemodynamic monitoring in the intensive care unit. Clin Chest Med 2003; 24:549–560

[10] Peskin CS. and McQueen DM. Cardiac fluid dynamics. *Crit Rev Biomed Eng* 1992;20(5-6):451-9.

[11] Legrice IJ., Hunter PJ. Smaill BH. Laminar structure of the heart: a mathematical model. *Am J Physiol* 1997;272, H2466-76.

[12] Smith, BW, Andreassen, S, Shaw, GM, Jensen, PL, Rees, SE and Chase, JG. Simulation of Cardiovascular System Diseases by Including the Autonomic Nervous System into a Minimal Model. Computer Methods and Programs in Biomedicine, accepted 12/06– to appear.

[13] Smith BW, Chase JG, Nokes RI, Shaw GM, Wake G, Minimal haemodynamic system model including ventricular interaction and valve dynamics. Medical Engineering and Physics 2004; 26(2):131-139.

[14] Burkhoff D, Tyberg JV, Why does pulmonary venous pressure rise after onset of LV dysfunction: A theoretical analysis, in Am. J. Physiol 1993;265:H1819-H1828.

[15] Ursino M. A mathematical model of the carotid baroregulation in pulsating conditions. IEEE Trans Biomed Eng 1999;46(4):82-92

[16] Smith BW, Chase JG, Shaw GM, Nokes RI. Experimentally verified minimal cardiovascular system model for rapid diagnostic assistance. Control Engineering Practice. 2005:13(9):1183-1193.

[17] Smith BW Minimal Haemodynamic Modelling of the Heart & Circulation for Clinical Application. Thesis presented for the degree of Doctor of Philosophy in Mechanical Engineering at the University of Canterbury, Christchurch, New Zealand, 26 September 2003

[18] Smith BW, Chase JG, Shaw GM, Nokes RI. Simulating transient ventricular interaction using a minimal cardiovascular system model. Physiol Meas. 2006; Feb 27(2):165-79. Epub 2006 Jan 4.

[19] Hann, CE, Andreassen, S, Smith, BW, Shaw, GM, Chase, JG Identification of Time-Varying Cardiac Disease State Using a Minimal Cardiac Model with Reflex Actions. Proc of 14th IFAC Symposium on System Identification (SYSID 2006), Newcastle, Australia, Mar 29-31:475-480

[20] Starfinger, C, Hann, CE, Chase, JG, Desaive, T, Ghuysen, A Shaw, GM. Clinical Cardiac Parameter Identification in a Porcine Model of Pulmonary Embolism, Computer Methods and Programs in Biomedicine, accepted 12/06 – to appear