A Hybrid Hierarchical Decision Support System for Cardiac Surgical Intensive Care Patients: Part I - Physiological Modelling and Decision Support System Design

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Summary

**Objective:** To develop a Clinical Decision Support System (CDSS) that models the different levels of the clinician’s decision-making strategies when controlling post cardiac surgery patients weaned from cardio pulmonary bypass.

**Methods:** A clinical trial was conducted to define and elucidate an expert anesthetists’ decision pathway utilized in controlling this patient population. This data and derived knowledge were used to elicit a decision-making model. The structural framework of the decision-making model is hierarchical, clearly defined, and dynamic. The decision levels are linked to five important components of the cardiovascular physiology in turn, i.e. the systolic blood pressure (SBP), central venous pressure (CVP), systemic vascular resistance (SVR), cardiac output (CO), and heart rate (HR). Progress down the hierarchy is dependent upon the normalization of each physiological parameter to a value pre-selected by the clinician via fluid, chronotropes or inotropes. Since interventions at each and every level cause changes and disturbances in the other components, the proposed decision support model continuously refers back decision outcomes back to the SBP which is considered to be the overriding supervisory safety component in this hierarchical decision structure. The decision model was then translated into a computerized decision support system prototype and comprehensively tested on a physiological model of the human cardiovascular system. This model was able to reproduce conditions experienced by post-operative cardiac surgery patients including hypertension, hypovolemia, vasodilation and the Systemic Inflammatory Response Syndrome.

**Results:** In all the simulated patients scenarios considered the CDSS was able to initiate similar therapeutic interventions to that of the expert, and as a result, was also able to control the hemodynamic parameters to the prescribed target values.
Key Words
Cardiac ICU, cardiovascular system model, hemodynamics, cardiovascular drugs, clinical decision support system, fuzzy control, genetic algorithms.

1. Introduction
Cardiac surgery on Cardio-Pulmonary Bypass (CBP) is associated with various physiological changes that profoundly alter a patient’s hemodynamic status. They can include hypotension (low blood pressure) arising from hypovolemia, blood loss, dysrhythmias, arterial vasodilation, and pump failure from myocardial dysfunction [1,2]. These can present themselves clinically in isolation, arise together, develop sequentially, or even consequent upon another pathophysiological process. For example, hypovolemia causing arterial hypotension will reduce myocardial perfusion resulting in a poorer cardiac contractility. This would manifest as sequential and possible exponentially worsening drop in blood pressure which may not be fully reversed by restoration of the depleted circulating fluid volumes. Conversely, hypertension (elevated arterial blood pressures) may arise from a re-vascularised and therefore better-perfused heart which pumps more vigorously, from a stress response arising from pain, from insufficient sedation, or from poorly controlled pre-existing hypertension. A patient, with hypotension immediately after an operation secondary to myocardial stunning from CPB, may recover within hours and develop hypertension during weaning from ventilatory support. Therefore, a successful CDSS must be flexible in its implementation of advisory support, and be robust enough to interpret apparently contradictory responses to its outputs, and take into account the potential changes arising extraneously in the target system.

One approach to controlling this complex environment is to reduce the cardiovascular system to a set of physiological components which are maintained at prescribed targets, and any deviations from the desired set-points are corrected promptly by drug administration and
fluid therapy. The authors selected the systolic blood pressure (SBP), central venous pressure (CVP), systemic vascular resistance (SVR), cardiac output (CO) and heart rate (HR) as such physiological components. The decision model based on these interacting hemodynamic components of the cardiovascular system is well-defined, hierarchically structured and can be prioritized in different sequences, if required, to adapt to a wide range of intensive care patients. In our population we maintained the prioritization in the above order for all cases.

Many cardiac surgery units prioritize systolic blood pressure (rather than the Mean Arterial Pressure (MAP)) as the over-riding clinically relevant parameter as systemic hypotension leads to poorer myocardial perfusion, poorer myocardial function and low cardiac output, and can precipitate the failure (by vasospasm) of arterial grafts used in the coronary artery bypass grafting surgery. This can be life-threatening. Also, hypertension can disrupt suture lines or cause delicate tissues in the heart and aorta to fail.

Postoperatively, these high-risk patients require close monitoring and judicious therapeutic decisions to avert complications which may have repercussions upon the length of patient hospital stay, costs, and the quality of life.

The complexity of this decision-making task poses a significant challenge to healthcare personnel who need to interpret many data-streams of real-time information generated from a proliferation of bedside monitoring devices, make rapid decisions and intervene promptly to reestablish the optimum function of the patient’s vital organs. This control environment constitutes an appealing field for a computerized CDSS application as a systematic means to overcome the stark disjunctions in clinicians’ choices of therapies.

There has been substantial evidence of the effectiveness of CDSS in improving the quality, safety and efficiency of healthcare delivery and many CDSSs are now in routine use in clinical care settings, clinical laboratories, incorporated in electronic medical record systems and in educational institutions [3-5]. CDSSs have been shown to be particularly useful in
prescribing medication by providing alerts and reminders to possible drug interaction or incorrect drug dosage, in diagnostic assistance and in therapy critiquing and planning [6,7]. In the critical care arena, CDSS research activities have focussed mainly on diagnosis [8-11] and therapy advice [12,13]. The implementation approaches range from simple decision trees, truth tables and rule-based systems to more complex paradigms such as those associated with neural networks, fuzzy reasoning, Bayesian statistics and machine learning theories which have the ability to model the inherently uncertain medical domain knowledge and learn from observed data. A comprehensive taxonomic description of the technical and contextual characteristics of CDSSs is presented in [14].

For this study a fuzzy logic-based decision support system has been chosen as the main overarching theme. The principal components of this CDSS are: the input module which performs the classification of the numerical data into linguistic terms; a diagnosis module which uses expert decision rules to designate the appropriate therapeutic actions; and a multiple-drug fuzzy control system for adjusting the fluid/drug infusion rates to maintain the hemodynamic variables at the specified target bands.

As an intermediate step to clinical validation, the CDSS is tested on a physiological model of the human cardiovascular system. This combines a pulsatile pressure-flow physiological model with a pharmacological model and defines the relationships between the drug dose and its effects on the simulated body compartments of the physiological model [15]. The resulting hybrid physiological/pharmacological model reproduces hemodynamic abnormalities observed in post-surgical intensive care patients and successfully predicts the response to different therapeutic interventions such as fluid, inotropic drugs, vasoconstrictor and vasodilators.

The rest of the paper is organized as follows. Section 2 focuses on the hierarchical structure of the expert’s decision model developed in this research. Section 3 deals
specifically with the description and implementation aspects of the CDSS. In Section 4 a simulation study to evaluate the CDSS under different model scenarios replicating common cardiovascular manifestations observed in post cardiac surgical patients is presented. Finally, a discussion and concluding remarks are summarised in Sections 5 and 6 of the paper.

2. The Expert’s Decision-Making Model in Cardiac Intensive Care Unit

For the purpose of this study a conceptual model of the customary clinical decision support pathway that a senior anesthetist with substantial experience uses to formulate physiological hypothesis and determine treatment options in post cardiac surgery intensive care patients emerging from CPB has been investigated. The decision-making model is assumed to be already ‘validated’ in a sense that it is successfully used by several experienced anesthetists to treat Cardiac Intensive Care Unit (CICU) patients in their daily practice. To generate the conceptual model, it was necessary to setup a clinical trial to gain an understanding of the reasoning strategies employed by the experienced anesthetist in the monitoring and treatment of these high-risk patients. The clinical study was approved by the NHS ethics committee and conducted at the Cardio-Thoracic Surgical Unit and CICU, Northern General Hospital (NGH), Sheffield (UK). The clinical study involved seven patients (see Table 1) with impaired cardiac function (less than 50% ejection fraction) undergoing elective cardiac surgery utilising CPB who all gave informed written consent prior to the operation. The patients underwent routine induction and maintenance of anaesthesia by the consultant anaesthetist designated for the case, and the operation performed. The patients were weaned from CPB with the preferred inotrope treatment selected. After chest closure, and transfer to the CICU, the patients’ care was transferred to the study anaesthetist, and the study commenced.

The primary phase of the study involved data collection and interrogation of the study anaesthetist’s therapeutic interventions with the consequent patient hemodynamic responses.
In the secondary phase, this data was analysed and commented upon during several interviews with the anaesthetist and finally transcribed into a systematic decision-making model suitable for computer implementation.

The LiDCCOplus® (Lithium Dilution Cardiac Output) monitor was chosen for its ability to measure and display cardiac output, systemic blood pressures and derived CVS variables in real time. For each case the device was calibrated utilising 0.3mmol of Lithium Chloride injected intravenously and detected at a sensor downstream of the patient’s radial artery. This procedure allowed the calibration of the area under the curve of the displayed patient radial arterial trace, thus deriving the CO. The following data (and its indexed value to the Body Surface Area (BSA)) is recorded by the monitor for off-line analysis: Systolic and Diastolic Blood Pressure (SPB/DPB), Mean Arterial Blood Pressure (MAP), Cardiac Output (CO/CI), Systemic Vascular Resistance (SVR/SVRI), Stroke Volume (SV/SVI) and Heart Rate (HR). For each case the patient’s CVS was stabilised and controlled at the clinically appropriate SBP requested by the treating (non-study) anesthetist. Table 2 displays the beat-to-beat hemodynamic parameters with their respective mean and standard deviation (SD) for an average recording time of 1h 30min.

The study anaesthetist was asked to identify the clinical signs and trends which prompted his clinical decisions on fluid and drug therapy. These identifiers included the times of such therapy decisions, when they were started, the dose regimes, the anticipated effect on patient hemodynamics, the observed effect and explanation for any discrepancy, and the factors which may have influenced changes in the infusion rates of the drugs being administered. Therapeutic interventions include cardiac filling with fluid administration to restore the intravascular volume in hypovolemic or vasodilated patients; vasoconstrictors administration to reverse hypotensive vasodilation; vasodilators in the treatment of hypertension and heart failure and positive inotropic drugs to improve the contractility of the heart and the cardiac
output. These interventions were event-marked on the LiDCOplus® monitor and contemporaneously recorded in written linguistic descriptive terms on the study documentation. The study anesthetist’s customary clinical decisions in the care pathway were implemented, commencing with the absolute and primary requirement for precise control of a desired SBP. When control of the SBP to the target value was achieved, the CVP, as a surrogate marker for cardiac filling, is then optimized. Under-filling causes a decline in contractility according to Starling’s law whereas over-filling causes sometimes a precipitate drop in contractility. Thirdly, after stabilizing the systolic blood pressure and then the central venous pressure, the indexed systemic vascular resistance is monitored and normalized, with vasodilators or vasoconstrictors as required. After stabilising these parameters the cardiac output is optimized/ normalized accordingly. The last variable to be optimized is the heart rate, at between 60 and 95 beats per minutes. Bradycardias were treated with single-dose drugs such as atropine and glycopyrrolate, or epicardial temporary pacing wires. There were no tachycardias requiring treatment with antiarrythmics.

The decision tasks performed by the anaesthetist were thoroughly analysed off-line at interviews to elicit his definitive cognitive model used to control a CICU patient. After examining each event and matching the hemodynamic decisions and analysing the physiological responses, the decision model was finally constructed, in these five components of the CVS, with SBP parameter of overriding importance in the decision-making process. The decision levels associated with these hemodynamic parameters have been prioritized, typically for patients weaned from cardiopulmonary bypass as shown in Fig. 1. However, they could be re-ordered to support the CVS in unstable situations arising from other causes [16].
3. Design Methodology of the CDSS

The structure adopted for the implementation of the CDSS includes three basic building blocks: a Hemodynamic Classifier, a Therapy Adviser and a Multiple-Drug Fuzzy Control System which are described in the following sections:

3.1. The Haemodynamic Classifier

The key to a successful CDSS tool is precision monitoring coupled with an effective and robust methodology for the automatic detection of physiologic events of clinical significance in the patient's haemodynamic parameters and their translation into a machine-useable form. The transition from the quantitative (numeric) to qualitative (symbolic) information is termed data abstraction or symbolisation. This can either define the state (low, normal, high, etc.) associated with the absolute value of the given haemodynamic variable such as systolic blood pressure, or the trend (increasing, steady, decreasing, transient, etc.) related to a time-series extracted from the data stream of the monitored signal.

The Hemodynamic Classifier receives the pre-processed hemodynamic numerical and performs its classification into states such as 'low', 'normal' or 'high'. Data classification and abstraction is implemented using a simple data-driven finite state machine as shown in Fig. 2. The reference intervals are defined by \([L_{\text{min}} L_{\text{max}}]\) for low, \([N_{\text{min}} N_{\text{max}}]\) for normal and \([H_{\text{min}} H_{\text{max}}]\) for high respectively. The transitions between the above states are triggered by an adjustable crossing threshold value (\(\Delta\)). The reference intervals are patient-specific because a parameter value deemed 'normal' for one patient (e.g., CVP = 3 mmHg) might be insufficient (low) for another. The 'normal' ranges of the given parameters are defined by the operating medical staff and these are then used as the target values by the study anaesthetist. In the real-time version of the CDSS, these target ranges are adjusted by the clinician at the beginning of the trial relative to the underlying patient conditions.
3.2. The Therapy Adviser

This block performs the diagnosis and outputs the therapeutic recommendations based on the patient’s haemodynamic status, using the expert's reasoning protocol described in Fig. 1.

The Therapy Advisor is a simple production system with a main rule-base which includes all the appropriate expert’s knowledge encoded into a set of IF-THEN decision rules associated with each haemodynamic component; a working memory containing the haemodynamic and therapy status; and an interpreter which cycles through the rule-base, and activates any rule whose condition is satisfied based on the working memory, performs conflict resolution and fires the candidates rules.

3.3. The Multiple-Drug Fuzzy Control System

The Multiple Fuzzy Control System is evoked by the Therapy Advisor which decides, based on the hemodynamic status, which type of therapy should be started/stopped. For example, fluid administration is started when the CVP (Central Venous Pressure) is Low. The fuzzy controller then calculates the infusion rate based on the CVP error (CVPe) and error change (CVPde).

The overall control system integrates a set of fuzzy logic controllers to adjust the infusion rates of fluid and drugs based on the error (difference between the target and the current value of the variable) and the rate of change of the error of the controlled hemodynamic parameters. There are three main steps in the fuzzy inference process:

1) Fuzzification converts numerical (crisp) value of an input parameter to a fuzzy or linguistic value (Low, High, etc.) using the associated input membership functions.

2) Inference mechanism computes the degree of membership of the output variable for each rule and combines (using Min-Max operation) all the results into a single fuzzy value.
3) *Defuzzification* converts the output fuzzy value back to a crisp value (using the centre of gravity method).

The error and error change variables were divided into seven fuzzy sets labelled as ‘Negative Large’, ‘Negative Medium’, ‘Negative Small’, ‘Zero’, ‘Positive Small’, ‘Positive Medium’, and ‘Positive Large’. These fuzzy membership functions for the error and error change were directly estimated from the membership functions associated with the corresponding absolute values which have been constructed by asking the expert to grade a typical numerical scale of ranges for the relevant hemodynamic parameter.

In general, a robust fuzzy system is not sensitive to the shape of the membership function whether it is ‘triangular’, ‘trapezoidal’ or ‘Gaussian’. The ‘trapezoidal’ has been chosen as it is a good approximation of the much favoured ‘Gaussian’ and is not computationally taxing. Fig. 3 shows the fuzzy membership functions for the error and its rate of change related to SBP, MAP, CVP and CO.

The membership functions for the fluid infusion rate shown in Fig. 4 have been labelled as ‘Very Low’, ‘Low’, ‘Moderate’, ‘High’ and ‘Very High’. The translation of these terms into changes in fluid infusion rates in ml/h was decided with advice from the expert and then tuned off-line to achieve reasonable infusion rates for specific CVP ‘error’ and ‘error-change’ values.

The fuzzy rule-base for adjusting the fluid infusion rate consists of 49 rules. A fuzzy rule has an ‘IF-THEN’ structure with the following format:

**IF** CVPe is PS AND CVPde is NS **THEN** FLUID is M.

The rule-base is designed to avoid overshoot (i.e. avoiding fluid overload).

The drug infusion rates were updated with \( D(t) = K_f(t) \cdot D(t-1) \), \( D(t-1) \) being the infusion rate at the previous sample period, \( K_f(t) \) represents the fuzzy infusion rate factor (i.e. the factor by which the infusion rate is changed) which is defined by seven fuzzy sets labelled as

Fig. 5 shows the fuzzy membership functions for the drug infusion rate factor where a higher discrimination is defined at lower infusion rates corresponding to the ‘Maintenance Range’ where $K_f$ assumes a value close to 1. For the purposes of the simulations, MAP will be used as the controlled blood pressure instead of the SBP.

4. Evaluation of the System via a Patient Physiological Model

A lumped-parameters time-varying electrical circuit analog model was employed to represent the human cardiovascular system (CVS) with a detailed compartmental description of the heart, regional vascular circulations and baroreflex controls. The heart model was based on the varying elastance idea. The CVS is combined with a pharmacological model describing the uptake, distribution and the haemodynamic response of various cardiovascular drugs. Cardiovascular drugs induce changes to the rate (chronotropic) and force (positive inotropic) of contraction of the heart and/or the tone of blood vessels (vasoconstrictor or vasodilator) by acting directly on the cardiac and smooth muscles respectively.

The relationships between the drug dose and its effect on the various cardiovascular model parameters (resistances, compliances and elastances) have been derived from published quantitative and clinical data [17,18] and rescaled to approximate human dose-response to inotropic and vasoactive drugs.

A detailed description of the model components is presented in the Appendix. All the hemodynamic variables of interest are derived from the circulation based on averaged pressures and flows over a cardiac cycle.

Simulated patient scenarios were developed in collaboration with the expert/ study anesthetist (3rd author) to reproduce a range of pathophysiological conditions resembling those observed in post-cardiac surgery patients. The quantitative description of the patients’
models considered in this study are summarised in Table 3 where the terms ‘mild’, ‘moderate’ and ‘severe’ represent simulated intensities of the underlying complications.

The authors validated the CVS model off-line using recorded data from several patients emerging from cardiopulmonary bypass and treated in the CICU. A simple genetic algorithm (GA) [19] was implemented with selection, recombination, and mutation operators and used to optimise the CVS model parameters to match the patient’s data.

The basic principle of operation of GA can be described as follows: At the beginning of the computation a population is created with a group of randomly initialized individuals. The objective, or fitness function, is then evaluated for these individuals. The first generation is produced. If the optimisation criteria are not met the creation of a new generation starts. Individuals are selected according to their fitness for the production of offspring. Parents are recombined to produce offspring. All offspring will be mutated with a certain probability. The fitness of the offspring is then computed. The offspring are inserted into the population replacing the parents, producing a new generation. This cycle is repeated until the optimization criteria are reached. The approach used to adjust the model parameters to bring the model initially into the best agreement with the patient’s haemodynamic status was based on the adaptive tuning of the percentage of change of the most effective parameters in the cardiovascular function: the SVR, the left and right ventricles maximum elastances $E_{\text{max}}$, the HR and the Total Blood Volume (TBV). The schematic diagram of inference procedure is outlined in Fig. 6.

The comparison of the model outputs with the actual patient data generates the following total output error as the fitness (objective) function to be minimised by the GA procedure.

$$E = E_{\text{CO}}^2 + E_{\text{MAP}}^2 + E_{\text{SVR}}^2 + E_{\text{SV}}^2 + E_{\text{HR}}^2$$

(1)
Where $E_j$, $j$ = CO, SVR, SV, MAP and HR are the errors between the patient’s hemodynamic data and those predicted by the model, $\hat{p} = [\Delta E_{\text{max}}, \Delta SVR, \Delta HR, \Delta TBV]$ are the estimated percentage of changes in the optimised parameters.

The hypothesis was that a realistic and reliable model tuned on real patient data would behave in a similar fashion and that the model’s reactions to the same therapeutic interventions made by the expert on the real patient would be similar. The optimised model was able to track closely the haemodynamic variability in trend and magnitude when subjected to the same therapeutic manoeuvres as those made by the clinician when controlling the real patients in the absences of external influences such as the patient coughing against the ventilator, shivering, etc, which appear as transient changes in the patient haemodynamic waveforms).

This model-validation process is described in detail on Patient 6’s data, the clinical course following aortic valve repair and closure of atrial septal defect. Patient 6’s ventricle was hypertrophied, with a reduced cavity size and was therefore dependent upon a 'higher than normal' perfusion pressure, which is reflected by the SBP (though the authors acknowledge perfusion pressure is consequent on the MAP). Myocardial contractility was poor secondary to myocardial hypertrophy and subsequent ischemic damage. The clinician decided to start milrinone (inodilator) to improve cardiac contractility and also dilate the peripheral arterial beds, reducing resistance to flow and improving CO. The resulting drop in SBP is treated with supplementary noradrenaline infusion. This vasodilation also required fluid administration to improve the intravascular depletion. This patient was weaned from the ventilator and subsequently made a successful recovery from surgery.

The GA optimisation algorithm produced the following values: $\Delta SVR = 0.55$, $\Delta E_{\text{max}} = 1.3009$, $\Delta TBV = 0.9068$ and $\Delta HR = 1.42$. When adapting the model parameters to these optimised values the following hemodynamics values were obtained:
MAP = 47.42 mmHg, CO = 4.44 l.min\(^{-1}\), SV = 44.68 ml, CVP = 4.95 mmHg, SVR = 854.2 dynes.sec.cm\(^{-5}\) and HR = 99.4 beats.min\(^{-1}\) which were deemed to represent a reasonable approximation of the patient’s hemodynamic status at the commencement of the clinical study.

Fig. 7 shows the patient’s hemodynamic waveforms as displayed by the LiDCOplus\(^{®}\) monitor.

The model was initially loaded with 250 ml of fluid given over 5 minutes resulting in a marked increase in blood pressure which remained stable thereafter. Noradrenaline was started next at a rate of 0.04 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) because SVR was considered to be too low. Another 250 ml was administered over 5 minutes in an attempt to normalise the CVP. These interventions resulted in a good control of the patient. Noradrenaline was later on stepped down to 0.03 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) which produced a minimal change in the current patient’s status.

The infusion rate of milrinone was increased to 0.4 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) resulting in a small increase in CO and a decrease in CVP and SVR as a consequence of its vasodilating effects. Fig. 8 shows the hemodynamic waveforms and the simulated interventions which reasonably replicate those of the real patient in trend and magnitude.

The CDSS is tested on the simulated post cardiac surgery patient’s models scenarios presented in Table 3 and on the model tuned with real patient data. In the simulation study presented in this paper, the CDSS is operated in closed-loop, in other words, the clinician is excluded from the loop and therefore the status of the therapy recommendations are directly input to the Multiple Drug Fuzzy control system.

### 4.1. Post Operative Hypovolemia

Intravascular volume deficits or hypovolemia often occur as a result of surgical bleeding and/or vasodilation. The consequences are a reduced circulating blood volume, a low cardiac preload and a decreased perfusion pressure. This results in underperfusion of some vital
organs like the kidney and the possible development of multiorgan dysfunction. To restore the lost intravascular volume, the patient is transfused with fluids. However, there is no available guideline for estimating the patient's fluid level and the fluid delivery rate. The medical decision is based on the patient's physiological conditions and the clinician's judgements. The clinician uses his experience, knowledge of the patient and visualisation of the heart function correlated to the CVP and thereby determines an optimum circulating fluid volume.

The CDSS integrates a fuzzy rule-base to control the fluid infusion rates based on the CVP error and error change. The controller rule-based was tuned to minimise CVP overshoots to ensure optimal fluid loading. With reference to Table 3, hypovolemia has been simulated as a drop in blood volume. The urine output rate (see the Appendix) has been set to an average value of 45 ml/hr. Target CVP is 7 mmHg. The simulation results for the three cases of hypovolemia are shown in Fig. 9. The controller rule-base was tuned to minimise CVP overshoots to ensure optimal fluid loading. TBV was restored to its nominal value in all simulated hypovolemia scenarios.

4.2. Post Operative Hypertension

In the immediate period after open heart surgery, the patient’s MAP should be kept in the range of 60-80 mmHg avoiding arterial hypertension. Vasodilator therapy is required to relax the vascular smooth muscle allowing peripheral arteries and veins to dilate. Glyceryl Trinitrate (GTN) is a venodilator at low, and an arterial dilator at higher infusion rates. In the model, the vasodilation effects of GTN have been simulated as a decrease in the arteriolar resistance and an increase in the compliances of systemic, renal, muscular and splanchnic beds.
Since the reference intervals need to be readjusted for these patients requiring a target MAP in the range of 60-80 mmHg, the CDSS recommended the administration of GTN and as a result activated the fuzzy rule based controller to adjust the drug infusion rate. The MAP responses and GTN infusion rates for the three hypertensive cases are shown in Fig. 10. The results demonstrate good transient and steady-state performances of the fuzzy rule-based controller for the range of hypertension considered.

4.3. Post Operative Vasodilation

Peripheral vasodilation associated with a low SVR is a common complication in cardiopulmonary bypass patients as a result of an acute inflammatory response following the exposure of blood to exogenous factors like the cardiopulmonary bypass pump circuitry. Occasionally, patients develop a postoperative hypotension referred to as vasodilatory shock when there is a persistent and severe fall in SVR. Treatment with vasoconstrictor drugs is therefore required to restore and maintain adequate perfusion pressure. However, care should be taken during administration of these drugs as under certain circumstances vasoconstriction can cause a redistribution of blood flow which may compromise other organs such as the kidney. One suitable vasoconstrictor is noradrenaline which, in the model, induces an increase in the ventricles’ contractilities, heart rate and peripheral resistances, and a decrease in the compliances of the muscle and splanchnic beds.

Noradrenaline half-life has been set to 90 sec and a time-delay of 30 sec is assumed between the commencement of infusion and the onset of action, based on clinical experience. NA was chosen to restore the perfusion pressure to normal. The MAP target has been set to 90 mmHg and stepped up to 100 mmHg for the patient’s model with mild vasodilation. The results for these three hypothetical models simulating post surgical vasodilation are shown in
Fig. 11. The controller demonstrates good transient response characteristics and the MAP was controlled to the prescribed target values with minor overshoots for all the simulated subjects.

4.4. Systemic Inflammatory Response Syndrome (SIRS)

Some patients can develop a syndrome post CPB similar to septic shock termed SIRS [20]. These patients are characterized by severe physiologic abnormalities including (1) peripheral arteriolar vasodilation which results in low systemic vascular resistance causing hypotension (2) widespread dysfunction of the microvasculature causing fluid loss from the intravascular space and hypovolemia (3) myocardial depression with impaired systolic and diastolic function, noncompliant, dilated and poorly contractile ventricles and (4) tachycardia (increased heart rate). These patients require fluid, inotropic and vasoconstrictor treatment simultaneously. Inotropic drug administration is often required in post cardiac surgery patients to improve the cardiac performance. The most useful inotrope/vasopressor drugs in septic shock are dopamine, dobutamine or milrinone, noradrenaline and adrenaline. Dobutamine predominantly increases the contractility and heart rate and hence the cardiac output. It also causes a mild vasodilation and thus decreases the afterload. Noradrenaline, on the other hand, is very effective in raising arterial blood pressure through its potential vasoconstriction. Clinical studies demonstrate phosphodiesterases like milrinone [21, 22] used in conjunction with noradrenaline improves the contractility of the stunned myocardium.

The physiological model has been parameterised to describe the three classes of increasing severity of SIRS presented in Table 3. In the simulation result of Fig. 12, where a subject with moderate SIRS has been considered, the MAP target was set to 80 mmHg initially and then stepped to 100 mmHg while CVP target was stepped from 6 mmHg to 7 mmHg. The Multi-Drug Fuzzy Controller produced good transient responses and target tracking with acceptable
overshoots in the MAP. Again, as shown in Fig. 13, the other hemodynamic parameters reached reasonable final values.

4.5. Model Tuned on a Real Patient Data

The simulated patient model was thus controlled with fluid to adjust the CVP to a target value of 7 mmHg. Milrinone administration was started and followed by noradrenaline infusion to control the CO at 5 l/min and the MAP to an average value of 70 mmHg. The results in Fig. 14 demonstrate a good performance of the multiple-drug fuzzy controllers in maintaining a stable hemodynamic profile.

5. Discussions

Preliminary simulation studies show good feasibility for the application of CDSS for controlling the patients’ cardiovascular system following surgery. This patient population features the following properties: there is a marked individual variation between subjects; the control environment within individuals is non-linear with differing responses expected and seen with differing CVS parameters. Thus, the response to an inotrope may be more vigorous at higher blood pressures, or the heart may begin to fail if over-transfused. The cardiovascular system can be ‘self-tuning’ or ‘self-improving’ after cardiac surgery as myocardial stunning wears off and the myocardium can fail as persistent hypotension reduces vital coronary perfusion.

Control of the systolic blood pressure was prioritised as this is the routine and over-riding parameter in our post-operative care pathway. At lower perfusion pressures, the myocardium becomes ischemic, and contractility declines even if there are no other perturbations in the system. It declines in a non-linear and patient-specific way. At higher blood pressures the shearing forces on the aorta can cause suture lines to leak, or anastomoses to break down with potentially catastrophic results. Our unit is primarily geared to observing the systolic blood
pressure for this phenomenon, as there are significant numbers of patients treated who have systolic hypertension due to poorly compliant arterial vasculature. Thus, they may have a ‘normal’ mean arterial pressure, but in the presence of pathologically elevated systolic blood pressure, sufficiently high to cause undesirable stresses in the post-operative patient’s vascular tree. There are many reasons why prioritisation of the SBP control is of paramount importance in this patient population. Indeed, not only does the heart work better when well perfused (a blood pressure-linked phenomenon), but it can also fail when generating very high pressures. At lower perfusion pressures the myocardium becomes ischaemic, pumps less well, and its function starts to spiral downwards. At high pressures the operative suture lines may rupture, causing bleeding, and threatening death.

Although the CDSS appears to be based on one expert’s clinical practice it is nevertheless the recognised technique of the experts working in a cohesive medical unit to control the CVS, and is taught as such to trainees learning cardiac surgery and anaesthesia. Thus, the technique concentrating on controlling the cardiovascular system has been developed and tested over hundreds of patients over many years.

A simple but a robust and flexible approach was adopted to design the CDSS to manage post-cardiac surgery patients in ICU because of the lack of uniformity in the patients, the magnitudes of response to drug therapy; the age-range, the multiple causes of CVS disturbance and the likelihood of two or more causes being present in the same patient. However, simplicity does not necessarily always lead to sub-optimal treatment but rather as argued here leads to a transparent (interpretable) set of rules that can easily be interpreted and therefore modulated over time by the medical staff.

Due to the obvious constraint of insufficient time to gather and analyse all the data before a clinical decision can be taken, the authors and the experts prioritised a single parameter (the
systolic blood pressure), considered to be among the most hazardous factors leading to control instability, as the fundamental value to base the CDSS upon.

Cardiac surgery patients represent an ideal group for a study such as those included in this paper as they represent elective cases, and as such they may be recruited to a trial readily; they are susceptible to major perturbations of the CVS, and target values for control are readily identifiable. In addition, the extra information elicited by direct visualisation of the heart responding to inputs, either with the chest open, or by trans-oesophageal echocardiography, means that there is a rare degree of certainty in determining the effect of treatment pathways. These are better defined than in patients in a General Intensive Care setting.

Fuzzy systems excel as controllers in rapidly changing, and data-poor environments. Clinicians consider them reasonably ‘open’ in their computations/reasoning, at least ‘grey box’ rather than ‘black box’. They are accessible to tune the sets to clinically relevant values and can be self-learning as well as self-organising.

An interim clinical study was therefore performed to gather data and determine the robustness of the hypothesised CVS model with the interwoven CVS pharmacology, physiology and drug transport features. This should build confidence in the methodology for the development of CDSS as being sound and above all realistic. The CDSS should be tested on a reliable model reflecting true physiological behaviour.

The final stage of this research study is to test the CDSS in a clinical environment. The authors propose to run the CDSS in an advisory mode alongside an expert who should have the option to override the system by inputting the desired infusion rates if he disagrees with CDSS output.
6. Conclusions

Cardiac surgery patients are susceptible to major hemodynamic instabilities in the immediate post-operative phase because of transient, multiple physiological disturbances associated with cardiopulmonary bypass and the surgery itself. The control environment of those vital interacting hemodynamic components is well-defined and hierarchical which makes it suitable for a computerized implementation. The authors have elaborated, in collaboration with an expert anaesthetist, a conceptual format for these clinical reasoning strategies and developed a hybrid hierarchical Clinical Decision Support System (CDSS) for the management of Cardiac Intensive Care Unit (CICU) patients.

The CDSS has been tested on a physiological model of the cardiovascular hemodynamics under a wide range of simulated pathological conditions characterizing post surgical CICU patients. For each situation, three scenarios have been considered to assess the performance of the control system with respect to inter-patient variability. In all the simulated patients scenarios the CDSS was able to initiate the right therapeutic action and control the hemodynamic parameters to the prescribed target values.

The proposed CDSS has been designed with a sufficient degree of flexibility to allow future extensions to be made gradually to enhance its functionality and performance. Because of its modular structure, the CDSS can be easily configured to accommodate a larger number of monitored variables. The CDSS can also be extended to accommodate different parameter hierarchies in the decision model to adhere with the clinician’s workflow and/or preference in the management of post-cardiopulmonary bypass patients. Subsequent rounds of system enhancement will involve the inclusion of incremental learning within the fuzzy decision making architecture and a knowledge fusion framework that permits the system to amalgamate various types of information (discrete variables, linguistic statements, physical models, etc.).
Part II of the paper describes the final stage of the project, testing the CDSS in a clinical trial on a series of patients. It demonstrates the CDSS in ‘Advisory Mode’ advising therapeutic interventions in parallel with the clinician to evaluate the variance between the advice provided and the actual decision implemented. Any discrepancy is used to tune the computer advisor, learning from the expert so as to harmonise decisions with the clinical practice in following next trials.

**Appendix**

1) **Model of the human cardiovascular physiology**

The model is conceptually formulated in terms of an electric analog circuit comprising fourteen compartments including the right and left ventricles, the systemic, pulmonary, coronary and cerebral circulations [15,23].

The relationships between pressure (P), flow (Q) and volume (V) in a compartment are given by

\[
\begin{align*}
P_i &= (V_i - V_{i0}) / C_i \\
Q_i &= (P_i - P_{i+1}) / R_i \\
dV_i / dt &= Q_i - Q_{i+1}
\end{align*}
\]

Where \( V_0 \) denotes the unstressed volume of the relevant compartment.

Initial compartment volumes have been calculated for each compartment as the sum of the unstressed volume and the volume given by the integration procedure (i.e. the stressed volume). In order to impose the conservation of the initially assumed total blood volume (TBV) in the circulation, the pressure in the splanchnic compartment is calculated as follows

\[
V_{\text{splanchnic}} = 5600 - V_{\text{stressed}} + V_{\text{unstressed}}
\]

Where \( V_{\text{stressed}} \) is the total stressed volume and \( V_{\text{unstressed}} \) is the total unstressed volume in all the rest of the compartments.
The parameters settings of the CVS model are listed in Table A.1 and correspond to a human subject of 75 Kg with a total blood volume of 5.6 litres and a heart rate of 75 bpm.

The pumping action of the left and right ventricles are modeled by Equation (A.3) where the first bracket accounts for the ascending part of E(t) or systolic phase and the second descending part of E(t) or diastolic phase [24].

\[
E(t) = E_{\text{min}} + \left[ \frac{\left( \frac{t}{a_1T} \right)^{n_1}}{1 + \left( \frac{t}{a_1T} \right)^{n_1}} \right] \frac{1}{\left[ 1 + \left( \frac{t}{a_2T} \right)^{n_2} \right]^{\frac{b_2}{b_1}}} E_{\text{max}}
\]

where \(t = t_c / (a+bT)\) and \(T = 60/\text{HR}\). \(E_{\text{min}}\) and \(E_{\text{max}}\) denote the minimum and maximum elastance respectively. \(E_{\text{min}}\) characterizes the end-diastolic volume and \(E_{\text{max}}\) is a measure of the inotropic state or contractility of the heart. \(T\) denotes the heart period and \(t\) is the time within a cardiac cycle. The parameters \(n_1\), \(n_2\), \(a_1\) and \(a_2\) define the shapes of the two Hill functions in (A.3) and are obtained from fitting the model to experimentally observed elastance curves. Table A.2 gives the numerical values of the heart model parameters defined above.

The heart valves are modeled as ideal diodes to constrain unidirectional flow to and from the ventricles.

The mathematical model of the baroreflex has been adapted from [25]. The model includes the afferent carotid baroreflex pathway, the sympathetic and the vagal efferent activities. The effector sites of these nerve stimulations are the left and right ventricular cardiac contractilities, the heart period, the different peripheral arterial resistances and the unstressed volume.

2) Pharmacological model

The drug uptake and distribution model consists of the same number of compartments as the CVS and is used to calculate drug concentrations in the relevant body compartments using
inter-compartmental blood flows and mass balance principles. A single compartment is shown in Fig. A.2.

Drug mass in each compartment is governed by the following equation:

\[
\frac{dM_{i+1}}{dt} = Q_i \cdot [X_i] - Q_{i+1} \cdot [X_{i+1}] - M_{i+1,0}
\]  
(A.4)

\[
M_{i+1,0} = M_{i+1} \frac{\ln 2}{\tau} \quad \tau = \text{drug half-life}
\]  
(A.5)

Where \(M_{i+1}\) is the mass of drug in compartment \((i+1)\), \(X_i\) and \(X_{i+1}\) represent the inflow and outflow concentrations, \(Q_i\) and \(Q_{i+1}\) are the inward (leaving the previous compartment) and outward blood flows respectively. \(M_{i+1,0}\) denotes the mass of drug removed from that compartment. Drug elimination from the body is assumed to occur within each compartment.

The instantaneous drug concentration in the \(i^{th}\) compartment is calculated as follows:

\[
[X_i] = \frac{M_i}{V_i}
\]  
(A.6)

Where \(V_i\) denotes the total blood volume (stressed and unstressed) available in that compartment.

Once the drug concentration at the effector’s site is calculated, the pharmacodynamic model is used to quantify its effect. The effect of the \(j^{th}\) drug on the circulatory parameters values (resistances, compliances, cardiac contractilities and heart rate) is described by the following equations:

\[
R_j = (1 + f_{R_j}([X_i])) R_{base}
\]
\[
C_j = (1 + f_{C_j}([X_i])) C_{base}
\]
\[
HR_j = (1 + f_{HR_j}([X_i])) HR_{base}
\]
\[
E_{max,j} = (1 + f_{E_{max,j}}([X_i])) E_{max,base}
\]  
(A.7)

Where \(f_{R_j}([X_i]) = a(1 - e^{b[X_i]}) + c\), \(a\), \(b\) and \(c\) are calculated using the nonlinear least-squares optimisation method based on dose-response quantitative data of the simulated drugs. The
model allows for multiple-drug administration and the compound effect of two drugs j and k is calculated as

\[ R_k = (1 + f_{R_k} ([X_j]))R_j \]
\[ = (1 + f_{R_k} ([X_j])) (1 + f_{R_j} ([X_j])) R_{base} \]  
(A.8)

The physiological model is extended with an additional compartment which describes fluid balance in the circulation. The following equation is used

\[ \frac{d(TBV)}{dt} = FIR - UOR \]  
(A.9)

Where TBV is the total blood volume, FIR is the fluid infusion rate (directly added to total blood volume) and UOR is the urine output rate (directly retrieved from total blood volume). Here, UOR has been assumed constant; however a model of human renal system could easily incorporated in the physiological model.

The model can also be extended with an interstitial compartment model with describes the dynamics of fluid exchange between the circulation and the extravascular space to illustrate the physiological features of capillary leak and edema [26].

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The authors would like to thank the anonymous reviewers for their comments on the earlier drafts of the paper.

**References**


Table 1  Demographic and clinical data of the patient’s population.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>Co-morbidities</th>
<th>Type of surgery</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>60</td>
<td>83</td>
<td>MR secondary to failed MV repair</td>
<td>MVR</td>
<td>fluid, morphine, propofol, NA</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>50</td>
<td>62</td>
<td>LVH</td>
<td>AVR</td>
<td>Fluid, GTN</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>58</td>
<td>60</td>
<td>None</td>
<td>Fluid</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>88</td>
<td>69</td>
<td>PAPM, MI, HT,</td>
<td>fluid, GTN</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>48</td>
<td>108</td>
<td>Obesity,</td>
<td>fluid, NA</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>74</td>
<td>109</td>
<td>NIDDM, HT</td>
<td>fluid, milrinone, NA, propofol, insulin</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>71</td>
<td>74</td>
<td>HT, CRF</td>
<td>CABG</td>
<td>fluid, GTN</td>
</tr>
</tbody>
</table>

PAPM: permanent atrial pacemaker; LVH: left ventricular hypertrophy; pAVS previous aortic valve surgery; AVR: aortic valve repair; ASD: Atrial Septal Defect; NIDDM: non-insulin dependent diabetes mellitus; MVR mitral valve replacement; MI: myocardial infarction; HT: Hypertension; CRF: Chronic Renal Failure; GTN: Glyceryl Tri Nitrate; NA: Noradrenaline
Table 2 Hemodynamic data of the studied patients (Mean ± SD).

<table>
<thead>
<tr>
<th>Patient</th>
<th>SBP/DBP (mmHg)</th>
<th>MAP (mmHg)</th>
<th>CVP (mmHg)</th>
<th>CO/CI (l.min⁻¹)</th>
<th>SVR/SVRI (dyn.sec.cm⁻⁵)</th>
<th>SV/SVI (ml)</th>
<th>HR (beat.min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>129.3±13.5</td>
<td>77.2±10.2</td>
<td>10</td>
<td>4.7±0.3</td>
<td>1060.2±529.8</td>
<td>55.5±3.9</td>
<td>85.4±4.5</td>
</tr>
<tr>
<td></td>
<td>46.6±6.5</td>
<td></td>
<td></td>
<td>3.2±0.2</td>
<td>1581.6±782.6</td>
<td>37.2±2.6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>108.1±11.6</td>
<td>67.0±6.6</td>
<td>8</td>
<td>6.5±0.8</td>
<td>853.89±107.0</td>
<td>91.0±12.1</td>
<td>72.4±9.6</td>
</tr>
<tr>
<td></td>
<td>48.6±3.1</td>
<td></td>
<td></td>
<td>3.4±0.4</td>
<td>1636.5±205.2</td>
<td>47.5±6.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>102.9±7.8</td>
<td>77.0±5.6</td>
<td>5</td>
<td>3.5±0.9</td>
<td>1585.0±280.2</td>
<td>49.5±13.6</td>
<td>72.3±2.6</td>
</tr>
<tr>
<td></td>
<td>55.4±4.6</td>
<td></td>
<td></td>
<td>2.2±0.5</td>
<td>2607.0±460.9</td>
<td>30.1±8.2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>106.7±8.4</td>
<td>71.5±7.7</td>
<td>6</td>
<td>4.0±1.4</td>
<td>881.5±131.4</td>
<td>49.2±16.1</td>
<td>81.8±5.6</td>
</tr>
<tr>
<td></td>
<td>53.0±7.4</td>
<td></td>
<td></td>
<td>2.4±0.8</td>
<td>1473.0±219.6</td>
<td>29.4±9.6</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>108.8±8.5</td>
<td>71.7±4.3</td>
<td>5</td>
<td>7.1±0.6</td>
<td>755.7±48.2</td>
<td>95.3±11.4</td>
<td>75.2±6.9</td>
</tr>
<tr>
<td></td>
<td>51.7±3.4</td>
<td></td>
<td></td>
<td>4.1±0.3</td>
<td>1300.9±83.1</td>
<td>55.3±6.6</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>95.5±6.9</td>
<td>58.7±3.8</td>
<td>4</td>
<td>5.3±0.3</td>
<td>780.0±55.4</td>
<td>530±3.3</td>
<td>100.4±2.0</td>
</tr>
<tr>
<td></td>
<td>45.0±3.2</td>
<td></td>
<td></td>
<td>2.3±0.1</td>
<td>1790.5±127.2</td>
<td>23.0±1.4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>137.4±8.4</td>
<td>74.8±5.6</td>
<td>8</td>
<td>5.6±0.2</td>
<td>1008.2±80.5</td>
<td>64.3±2.2</td>
<td>87.5±3.2</td>
</tr>
<tr>
<td></td>
<td>47.4±3.6</td>
<td></td>
<td></td>
<td>3.0±0.1</td>
<td>1881.4±150.3</td>
<td>34.4±1.4</td>
<td></td>
</tr>
</tbody>
</table>
Table 3 Scenarios of simulated post cardiac surgery patient’s models.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Degree</th>
<th>TBV</th>
<th>SVR</th>
<th>E_{max}</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemia</td>
<td>Mild</td>
<td>↓ 10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>↓ 15%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>↓ 20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Mild</td>
<td>↑ 20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>↑ 30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>↑ 50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilation</td>
<td>Mild</td>
<td>↓ 20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>↓ 35%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>↓ 50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIRS</td>
<td>Mild</td>
<td>↓ 5%</td>
<td>↓ 20%</td>
<td>normal</td>
<td>60 ∼ 80</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>↓ 10%</td>
<td>↓ 25%</td>
<td>↓ 20%</td>
<td>81 ∼ 100</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>↓ 15%</td>
<td>↓ 30%</td>
<td>↓ 30%</td>
<td>&gt; 100</td>
</tr>
</tbody>
</table>
Table A.1 Parameters values in the electric analog circuit of the CVS model.

<table>
<thead>
<tr>
<th>Resistance values (mmHg/s/ml)</th>
<th>Inertance (mmHg.ml/s²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_0 = 0.01$</td>
<td>$R_{5a} = 0.707$</td>
</tr>
<tr>
<td>$R_1 = 0.0026$</td>
<td>$L_{0} = 0.0225$</td>
</tr>
<tr>
<td>$R_2 = 0.098$</td>
<td>$R_{6a} = 12.105$</td>
</tr>
<tr>
<td>$R_3 = 0.019$</td>
<td>$R_{10a} = 2.421$</td>
</tr>
<tr>
<td>$R_4 = 0.0075$</td>
<td>$R_{10b} = 2.65$</td>
</tr>
<tr>
<td>$R_5 = 0.0075$</td>
<td>$R_{10b} = 0.53$</td>
</tr>
<tr>
<td>$R_6 = 17.481$</td>
<td>$R_{11a} = 3.158$</td>
</tr>
<tr>
<td>$R_7 = 3.534$</td>
<td>$R_{11b} = 0.632$</td>
</tr>
<tr>
<td>$R_8 = 3.534$</td>
<td>$R_{12a} = 6.015$</td>
</tr>
<tr>
<td>$R_9 = 3.534$</td>
<td>$R_{12b} = 1.203$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compliance values (ml/mmHg)</th>
<th>Unstressed volumes (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_r$, variable</td>
<td></td>
</tr>
<tr>
<td>$C_1 = 3.99$</td>
<td>$C_8 = 8.91$</td>
</tr>
<tr>
<td>$C_2 = 2.66$</td>
<td>$C_9 = 2.71$</td>
</tr>
<tr>
<td>$C_3 = 13.3$</td>
<td>$C_{10} = 8.38$</td>
</tr>
<tr>
<td>$E_l$, variable</td>
<td></td>
</tr>
<tr>
<td>$C_{11} = 9.98$</td>
<td>$C_{12} = 5.0$</td>
</tr>
<tr>
<td>$C_5 = 0.91$</td>
<td>$C_{13} = 13.3$</td>
</tr>
<tr>
<td>$C_6 = 0.38$</td>
<td>$C_{14} = 13.3$</td>
</tr>
<tr>
<td>$C_7 = 1.46$</td>
<td>$C_{15} = 1.46$</td>
</tr>
<tr>
<td>$C_{16} = 1.46$</td>
<td>$C_{17} = 1.46$</td>
</tr>
<tr>
<td>$U_{v_0} = 20$</td>
<td>$U_{v_1} = 200$</td>
</tr>
<tr>
<td>$U_{v_2} = 150$</td>
<td>$U_{v_3} = 490$</td>
</tr>
<tr>
<td>$U_{v_4} = 20$</td>
<td>$U_{v_5} = 264$</td>
</tr>
<tr>
<td>$U_{v_6} = 124$</td>
<td>$U_{v_7} = 111$</td>
</tr>
<tr>
<td>$U_{v_8} = 657$</td>
<td>$U_{v_9} = 200$</td>
</tr>
<tr>
<td>$U_{v_{10}} = 608$</td>
<td>$U_{v_{11}} = 732$</td>
</tr>
<tr>
<td>$U_{v_{12}} = 240$</td>
<td>$U_{v_{13}} = 353$</td>
</tr>
</tbody>
</table>
Table A.2 Parameters in the heart model

<table>
<thead>
<tr>
<th></th>
<th>$E_{lv}$</th>
<th>$E_{rv}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{min}$</td>
<td>0.1</td>
<td>0.05</td>
</tr>
<tr>
<td>$E_{max}$</td>
<td>2.0</td>
<td>0.45</td>
</tr>
<tr>
<td>$n_1$</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>$\alpha_1 T$</td>
<td>0.7</td>
<td>1.17</td>
</tr>
<tr>
<td>$a$</td>
<td>0.2</td>
<td>0.15</td>
</tr>
</tbody>
</table>
Fig. 1 Synopsis of the decision-making model.

Fig. 2 Classification of SBP state into low, normal and high. L = Low, N = Normal, H = High, Δ = Threshold.
Fig. 3 Fuzzy membership functions for SBP, MAP, CVP and CO.

Fig. 4 Fuzzy membership functions for fluid infusion rate.
Fig. 5 Fuzzy membership functions for drugs infusion rate.

Fig. 6 Optimised tuning of the CVS model with Genetic Algorithm.
**Fig. 7** LiDCOplus® snapshot showing the recorded patient’s hemodynamic data.

**Fig. 8** Hemodynamic waveforms of the patient model under the same therapeutic interventions as the real patient.
Fig. 9 Simulated patient CVP response and fluid infusion rate for the three cases of hypovolemia. Top to bottom panels mild, moderate and severe hypovolemia. CVP (solid-line), target (dotted-line).

Fig. 10 Simulated patient MAP response and Glyceril Trinitrates (GTN) infusion rate for the three classes of hypertension. Mild (solid), moderate (dashed) and severe (dotted).
Fig. 11 Simulated patient MAP response and noradrenaline (NORAD) infusion rate for the three classes of vasodilation. Top to bottom panels mild, moderate and severe vasodilation. MAP (solid-line), target (dotted-line).

Fig. 12 Simulated moderate SIRS patient with control of MAP and CVP under noradrenaline (NORAD) and fluid respectively. MAP and CVP (solid-line), targets (dotted-line).
Fig. 13 CO, SVR and HR related to Fig. 12.

Fig. 14 Simulated real patient with control of MAP, CVP and CO under noradrenaline (Norad), fluid and milrinone (Milrin) respectively. MAP, CVP, CO (solid-line), targets (dotted-line).
Fig. A.1 The cardiovascular system model structure [23].

Fig. A.2 Drug transport model compartment.