ABSTRACT

DEVELOPMENT AND TESTING OF A SIMULATED CLOSED LOOP DRUG DELIVERY SYSTEM FOR CHF PATIENTS UNDER MILRINONE ADMINISTRATION

by
Runa Shah

The purpose of this thesis project is the development and testing of a simulated closed loop drug delivery (CLDD) system that consists of a pharmacokinetic, physiological, and feedback-controlling model. The focus of this study is on the control of milrinone infusion to maintain cardiac output at desired setpoint range for patients suffering from congestive heart failure (CHF). The simulated CLDD system is written in VisSim dynamic simulation language for an IBM-compatible PC.

Milrinone pharmacokinetics are represented by a three compartment model. The physiological model consists of the cardiovascular system model linked to the pharmacodynamic submodel of milrinone. The feedback-controlling model consists of a cascade controlling mechanism incorporating a PID controller.

Validation of system dynamics was performed by comparison of simulated results of the loop model (pharmacokinetic and physiological model) to available experimental data. Pharmacokinetic and hemodynamic responses showed that the behavior of the simulated open loop model was similar to that of CHF patients under milrinone administration.

The addition of the feedback-controlling model to the open loop model resulted in the development of the CLDD system. Performance of the cascade controller was optimized with tuning of PID controller. A two-hour control performance was monitored as the CLDD system underwent the following situations: (1) target CO was modified

(transient response), (2) perturbation was incorporated as circulatory vessel resistances were changed, and (3) randomization of system parameter was achieved by varying the elimination rate constant. Onset delay, time taken for controller to bring CO within set boundaries, and percentage overshoot of cardiac output from target were the underlining results analyzed in understanding the performance of the controller.

Aside from some minor refinements, the overall performance of the controller showed it to be robust in responding to the changes in the system by adjusting milrinone infusion so that cardiac output could track to the setpoint. The simulated CLDD system as a whole was observed to correctly represent clinical automated drug delivery. The results of the simulated controller also lead into the possibility of developing an automated control milrinone infusion system for maintaining cardiac output for CHF patients.

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DEVELOPMENT AND TESTING OF A SIMULATED CLOSED LOOP DRUG DELIVERY SYSTEM FOR CONGESTIVE HEART FAILURE PATIENTS UNDER MILRINONE ADMINISTRATION

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To my parents
Mohammad D. Shah and Bakht J. Shah

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CHAPTER 1

INTRODUCTON AND BACKGROUND

As the society moves into the next millennium, the use of computers in daily activities has advanced. Many responsibilities formerly performed by humans are now in the command of computers. The use of computers reduces problems caused by human error. The focus of this thesis is the administration of drugs by the use of computers in the field of medicine.

1.1 Introduction

Traditionally delivery of drugs has been empirically regulated by the clinicians based on the known physiological effects and observed efficacy and toxicity. Now with the advances in closed loop technology, the computer control can be used to administer drug in order to maintain a physiological response. The use of closed loop systems provides two main advantages: (1) clinical personnel are relieved of some of the mundane and repetitive monitoring and infusion adjustment tasks that are done automatically by the closed loop system and (2) this system provides tighter regulation of a physiological variable at a desired level than can be accomplished with manual methods.[1] Since this task is now the responsibility of the computer, the clinician can better concentrate on other duties. This can be considered as a third non-direct advantage for the use of closed loop drug delivery (CLDD) systems.

This research concentrates on the design and evaluation of a simulated closed loop drug delivery system for the infusion of milrinone. Milrinone is a second generation drug used to increase cardiac contractility in congestive heart failure patients in order to

increase cardiac output during surgery. The physiological response that is monitored is cardiac output. The primary focus is the design of a CLDD system for congestive heart failure patients. Thus a closed loop feedback system is designed to control the infusion of milrinone in order to maintain the cardiac output at a desired target for patients suffering from congestive heart failure.

The following sections document available research studies done on drug delivery control system, proposes a closed loop system for monitoring and administering drug, and presents results of computer simulation of the closed loop response. It also explains VisSim, the simulation language used in this research. Additional discussion focuses on the appropriateness of the use of milrinone for congestive heart failure patients.

1.2 Control Systems

Much of the work with closed loop system control has focused on arterial pressure control in cardiac surgery patients. Systems using a variety of drugs for both hypertension and hypotension have been reported to rapidly and faithfully control arterial pressure under research conditions. Martin [2] designed a multiple-model adaptive

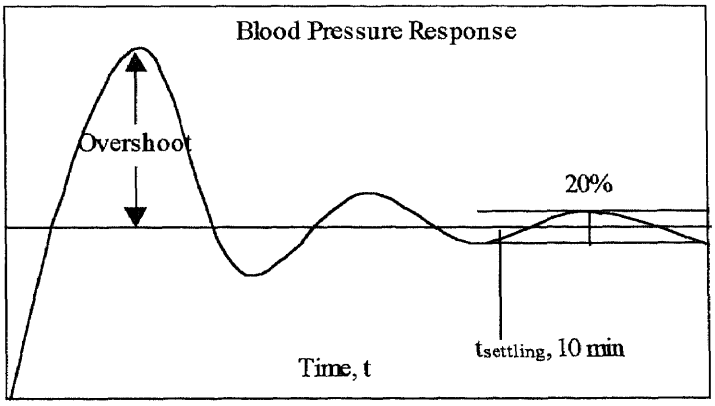

Figure 1.1 Diagram representation of desired blood pressure response using MMAC control

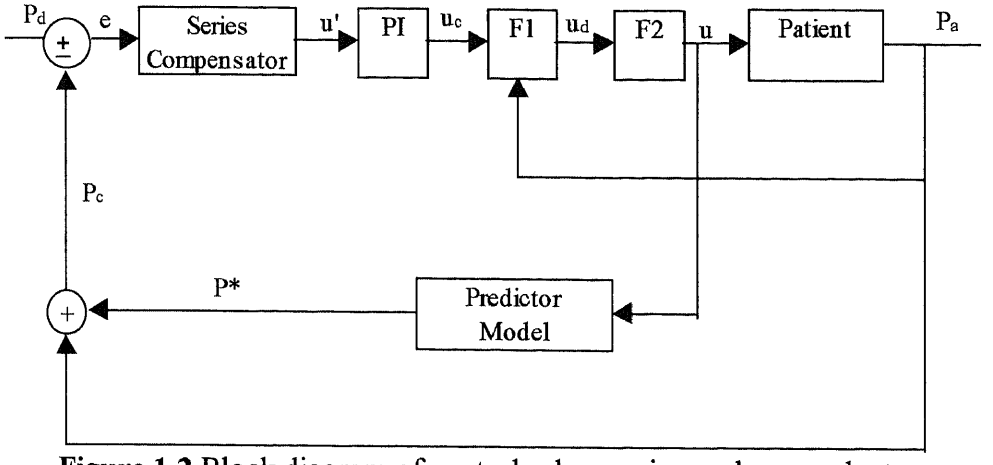

Figure 1.2 Block diagram of control scheme given a known plant

controller (MMAC) for the control of blood pressure using sodium nitroprusside (SNP). MMAC is a control strategy that can identify and then adapt to changing characteristics. Lainiotis [2] introduced the concept of multiple model adaptive control. MMAC uses a finite range of models, assumed in this case to be reasonable representations of possible patients, from which to identify the patient. An automated drug infusion system for blood pressure should have certain performance characteristics. These include, a 20 percent settling time of less than 10 min, a maximum overshoot of less than 10 mmHg, and a steady-state error within ± 5 mmHg, Figure 1.1. Along with these performance characteristics, the controller also has clinical constraints, as well. The first of the clinical constraints is the maximum allowable infusion rate. The basic controller is shown in figure 1.2. The concept of the controller is that a given a transfer function or known plant, the desired closed-loop responses can be achieved via pole-placement and state-variable feedback. The series compensator in Figure 1.2 was obtained using this method. The proportional plus integral (PI) unit was used to achieve a steady state error of ± 5 mmHg with no dc offset. To remove the effects of infusion delay a predictor model

was used. A low-pass filter was included to minimize the effects of noise. To help maximize patient safety, two nonlinear units were built into the system. The first, F_1, is used to turn off the infusion of SNP if patient's blood pressure drops too low. The other nonlinearity, F_2, limits the actual infusion rate according to the maximum allowable infusion rate. Numerous tests, including variation of the gains, time constants, and infusion delays were performed to demonstrate the robustness of the controller. The results showed that the controller controlled wide ranges of patient characteristics. In all cases, the desired performance characteristics or better (20 percent settling time < 10 min, overshoot < 10 mmHg, and steady-state error within $\pm$ 5 mmHg) were achieved. In 35 cases, the average settling time was 2.6 min and the average overshoot was 2.4 mmHg. Furthermore, steady-state error of blood pressure was within the boundaries specified. Patient safety was also maintained in all cases. In conclusion, the controller satisfied the desired performance characteristics while maintaining patient safety.[2]

Additional studies on closed loop drug delivery focus on the simultaneous control of blood pressure and cardiac output. Yu [3] has applied the MMAC concept to design a controller to simultaneously regulate MAP and cardiac output in congestive heart failure (CHF) subjects by adjusting the infusion rates of sodium nitroprusside (SNP), a vasodilator, and dopamine, a positive inotropic agent, respectively. Instead of the conventional PI and PID controllers utilized in previous single-input, single-output MMAC designs, a model predictive controller (MPC) was used for each model subspace. The MPC is comparatively simpler to tune than the PI and PID controllers in a multivariable environment. The controller was evaluated on laboratory animals that were either surgically or pharmacologically altered to exhibit symptoms of CHF. Although the

design called for the regulation of both outputs, a tighter regulation of MAP was sought (±10 mmHg). The transient response should have a settling time of less than 10 min for MAP and 20-25 min for CO. A total of 16 runs were performed for each test. Before the start of each run, baseline values for each output were obtained. Each trial started with a step command for both outputs and continued for 80 minutes. The initial step always asked for an increase in CO while MAP could either be increased or decreased. Controller performance to the initial step commands is summarized in Table 1.1. The response time is the time needed for the output to come within 5 mmHg of the steady state setpoints for MAP and the time taken to climb within 5 ml/min/kg of the steady state setpoint flow for CO. The response time of the outputs were within the settling times specified in the design. The mean MAP undershoots less than 10 mmHg.

Table 1.1 Summarizes the performance of the MMAC design using MPC controller in maintaining MAP and CO, n = # of patients

	MAP	CO
Step down in MAP (n=13)		
Step size Range	-21.15 ± 4.45 -9.7 to -24.80 mmHg	41.05 ± 13.83mL/min/kg 21.3 to 69.8 mL/min/kg
Undershoot/Overshoot Range	5.92 ± 3.54 mmHg 0 to 12 mmHg	16.64 ± 11.85 mL/min/kg 4.5 to 43.0 mL/min/kg
Response Time Range	5.81 ± 1.98 min 3 to 10.5 min	15.31 ± 5.36 min 3.5 to 22 min
Step up in MAP (n=3)		
Step size Range	7.50 ± 1.43 mmHg 5.5 to 8.75 mmHg	22.57 ± 8.77 mL/min/kg 14.32 to 34.7 mL/min/kg
Overshoot Range	2.67 ± 0.47 mmHg 2 to 3 mmHg	18.35 ± 10.53 mL/min/kg 4.5 to 30.0 mL/min/kg
Response Time Range	5.5 ± 0.41 min 5 to 6 min	9.17 ± 5.33 min 4.0 to 16.5 min
Regulation after step (n=16)		
Standard deviation Range	4.00 ± 1.35 mmHg 1.95 to 6.59 mmHg	10.36 ± 7.99 mL/min/kg 3.28 to 29.67 mL/min/kg

Large overshoots were sometimes observed with step command increases in CO, but there was no design constraint on this value. As shown in the table the magnitude of the step up in pressure is significantly smaller than that of the step down because considerable increase in pressure could augment the load on the heart. The results outlined in Table 1.1 show that the controller is robust in regulating both physiological outputs at the desired levels.

Another point of interest in CLDD systems are the studies done to compare closed loop control with nurse or anesthesiologist control. Most of the studies report superior performance by closed loop control systems.[4] Stern performed a study that compared the human performance with that of a controller in the control of arterial pressure by adjusting the infusion of SNP. The automated system used a computer-controlled Watson-Marlow infusion pump to infuse SNP, while the anesthesiologist administered the drug through an IVAC 530 infusion pump. The anesthesiologist had more than ten years experience, which included the management of patients during open-heart surgery. The protocol consisted of requiring the computer and the physician to perform identical control tasks. Only those control tasks that were part of the comparison were included in the analysis. A comparison pair consisted of one automated control and one manual control performed under identical conditions in the same animal. The target MAP was generally achieved within the required 5 min by both controllers. The mean steady-state error was below 5 mmHg, standard deviation of the steady-state pressure was less than 2 and 3 mmHg for the computer and physician, respectively. The mean SNP infusion rate for the two controllers was below the recommended maximum infusion rate of 3mg/kg/h. The controller proved to perform as well, if not better, than the physician. Note that the

control task performed by the anesthesiologist in this work is by no means typical of the clinical use of SNP. The anesthesiologist devoted his full concentration to controlling blood pressure as accurately as possible, knowing that his performance was monitored. In clinical situations, many other tasks would also compete for the physician's attention, leading to a likely degradation of his performance as a controller of blood pressure. Some of the anesthesiologist's functions are as follows: (1) control ventilation, (2) monitor vital signs such as ECG, pulse, and temperature, (3) continue administering anesthetics and drugs to maintain homeostasis, (4) give blood or other blood products, (5) titrate anesthetics to the level of surgical stimulation, (6) reverse muscle relaxation in the end of surgery, (7) and finally extubate the patient. Thus the performance on the closed loop control would be superior. Sheppard and Kouchoukos reported that closed loop regulation of arterial pressure has contributed to a 50% reduction in the length of stay in the postcardiac surgery ICU with some associated cost savings.[1]

1.3 Simulation Studies on Control Systems

Development of a clinically useful closed loop drug delivery system is both time consuming and expensive. Thus making simulation studies an attractive alternative in the development of a closed loop drug delivery system. Through the use of simulation studies both time and cost can be reduced. This approach allows for the evaluation of the controller's performance over a complete spectrum of patient population. Another advantage of simulation studies is repeatability. Woodruff [5] designed a simulator for closed loop cardiovascular therapy. The simulator contains mathematical models that relate the infusion rates of specific drugs to dynamic changes in physiological

parameters. The simulator consists of four different types of models, a nonlinear pulsatile-flow cardiovascular model, a physiological regulatory model of baroreceptors, a pharmacokinetic model, and a pharmacodynamic model for each drug. Its control mechanism is multiple model based. The nonlinear, pulsatile-flow model of the cardiovascular system consists of five compartments, left ventricle, systemic arteries, capillaries, systemic veins, and a low-pressure compartment. The regulatory model attempts to maintain a homeostatic pressure by adjusting arterial resistance, venous tone, ventricle contractility, and HR. The pharmacokinetic and pharmacodynamic models were developed from experimental tests of the drug. To validate that this simulator was an appropriate representation of clinical situations that patients undergo, a series of verification studies were performed. These studies included comparisons of simulator results to published data (both animal and clinical). The multiple-model simulator was further validated with a series of dynamic simulation studies. The study included evaluating the ability of anesthesiologists, ranging from first year resident to full professor, to manually control the drug using the simulator. All participants in the study concluded that the simulator responded similarly to drug administration, as a patient would have. Additional study on the simulator included using it to compare the relative abilities of the closed-loop drug delivery device and clinicians to induce and maintain deliberate hypotension. The results were that there was no statistical difference between the experienced clinician and the closed-loop device in inducing and maintaining deliberate hypotension. This simulator has been used in the design and validation of both MMAC and multiple-input-multiple-output control advance moving-average controller (CAMAC). It is the use of simulation studies that allows for the development of the

closed loop system. The simulation language used in the design and testing of the CLDD system in this paper is VisSim.

1.4 VisSim Simulation Language

VisSim or visual simulation is appropriate software for this research. VisSim is a simulation package for developing continuous, discrete, multi-rate and hybrid system models and running dynamic simulations on IBM PCs and compatibles. VisSim incorporates a graphics user interface that is used to create diagrams of the systems being simulated. Each model consists of a collection of components or blocks connected by flexwires. These blocks can perform many kinds of activities such as evaluating a mathematical function, generating a random value, performing an arithmetic or logical test, and producing different forms of animation. There are two types of blocks within VisSim: (1) standard blocks, and (2) compound blocks. Standard blocks include (1) Arithmetic blocks, (2) Integration blocks, (3) Time Delay blocks, (4) Boolean blocks, (5) Linear System blocks, etc. A compound block, on the other hand, is a combination of one or more standard blocks. The purpose of a compound block is to make the block diagram more organized, less confusing, and more presentable. Other simulation studies involving CLDD systems have used Mathlab, C, or C++, but this research looks into the power of VisSim to regulate cardiac output via the infusion of milrinone for CHF patients.

1.5 Congestive Heart Failure

Congestive heart failure (CHF) is a condition characterized by the loss of contractile force by the cardiac muscle fibers leading to an inability of the heart to maintain cardiac output sufficiently in order to meet the requirements of the metabolizing tissues.[6] Therefore there is a transudation of fluid into the tissues giving rise to congestion and oedema at various sites. It is the weakening of the heart muscle that prevents the heart from pumping blood effectively. Depending on the degree failure, the patient has limited exercise tolerance, fatigue or effort dyspnoea. CHF usually occurs as a late manifest of most forms of heart disease. Other causes include low flow, ishemia, defective valve, pulmonary embolism, infection, anemia, arrhythmia, hypertension, and physical, dietary, environmental and emotional excesses. Because the heart is not strong enough to pump blood sufficiently, agents with positive inotropic activity are indicated in the treatment of CHF.

The main final pathway for control of cardiac output is via a group of receptors linked to a G protein-adenylate cyclase (RGC) complex at the sarcolemma. This complex has two distinct effects: it directly opens slow calcium channels in the plasma membrane, and it activates the production of the intracellular second messenger, cyclic adenosine monophosphate (cAMP), from adenosine triphosphate (ATP). The results of these effects include (1) more force development and (2) increased velocity of shortening.[7] In the chronically failing heart there are possible defects in some of the receptors. High energy phosphates are also reduced, therefore increasing the dependence on inotropic support from the neurohumoral system to maintain cardiac output. Phosphodiesterase (PDE) inhibitors offer a rational therapy for CHF patients and thus

promote an increase in cAMP and so increase cardiac output.[8] The PDE inhibitors are a class of bipyridine compounds that increase the inward calcium flux during the action potential (mode of action opposite to that of the calcium blockers), effect the intracellular movements of calcium, and have been shown to inhibit phosphodiesterase. Phosphodiesterase is the intracellular regulator of cAMP and cGMP by degrading these second messengers to 5 'AMP 5 'GMP, respectively. Milrinone is a PDE III inhibitor that produces positive inotropic and vasodilator effects.

1.6 Milrinone

Milrinone and amrinone are the two selective PDE inhibitors approved for clinical use in the United States The chemical structures of the two PDE inhibitors are shown in Figure 1.3. Both bipyridine compounds inhibit phosphodiesterase enzyme resulting in an increase of cAMP and increased Ca to the myocardium. Milrinone is the derivative of amrinone, with approximately 10 to 75 times greater positive inotropic potency, and separate direct vasodilatory properties. Also, milrinone produces the same hemodynamic changes without causing the noncardiac adverse effects, such as thrombocytopenic effects, fever and gastrointestinal effects as observed with amrinone.[6] Additional studies conclude similar findings. Hasegawa [9] made the following conclusions from his study of the drug: (i) Patients receiving milrinone have tolerated the drug well.
(ii) Milrinone therapy has not been complicated by the noncardiac side effects. (iii) In fact, one patient who had developed fever and thrombocytopenia while taking amrinone tolerated milrinone therapy without recurrence of these complications.

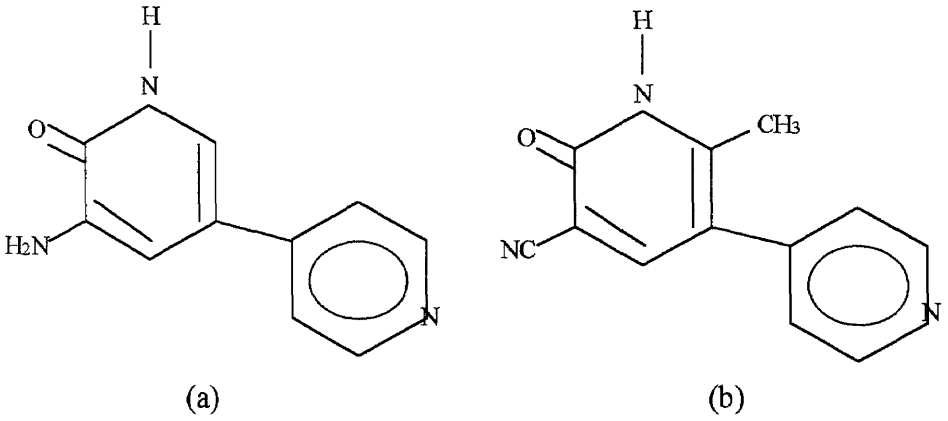

Figure 1.3 Chemical structure of (a) amrinone and (b) milrinone, the 2-methyl, 5-carbonitrile derivative

In addition to these advantages this drug increases myocardial contractility in CHF patients without increasing myocardial oxygen consumption.[10] Aside from milrinone's comparative studies with amrinone, milrinone has also been evaluated with other inotropic and vasodilator agents including dobutamine, nitroprusside, and captopril.[6] When dobutamine infusion was compared with milrinone, both drugs produced similar sustained improvement in cardiac index. But dobutamine infusion resulted in an increase in heart rate to a greater extent than did milrinone, thereby increasing myocardial oxygen demand that was not evident with milrinone. When compared with nitroprusside, milrinone increased cardiac output to much greater extent than did nitroprusside infusions. In a comparative study with captopril, it was observed that milrinone increases cardiac index to a greater extent than captopril. Young [6] concluded that milrinone shows evidence of producing more sustained and significant improvements in hemodynamic measurements. Therefore, milrinone is the selected drug used in this research.

CHAPTER 2

CLOSED LOOP MODEL

VisSim simulation study of the CLDD system consists of three main interfacing models, milrinone pharmacokinetic (PK) model, physiological model, and feedback-controlling model. The purpose of this research includes the development of the PK model for milrinone and feedback-controlling model as well as testing of the CLDD system (consisting of all three models).

2.1 Physiological Model

The physiological model, designed in previous research, is the mathematical representation of the physiological response of the body to the drug infusion. The physiological model consists of the cardiovascular system model linked to the pharmacodynamic submodel of milrinone.[11]

The cardiovascular system [12] is composed of twenty compartments which includes the left and right ventricles, the systemic and pulmonary circulation as shown in Figure 2.1. In this model the arterial system is represented by one or more interconnected elastic reservoirs, the Windkessel approach. A Windkessel compartment is described by a single ordinary differential equation. A two-element Windkessel model, which consists of a resistance (R) and compliance (C) represents each compartment. The relationship between the blood flow and blood pressure in a compartment is represented by Equation 2.1.

$$F_i = (P_i - P_{i+1}) / R_{i+1} \qquad (2.1)$$

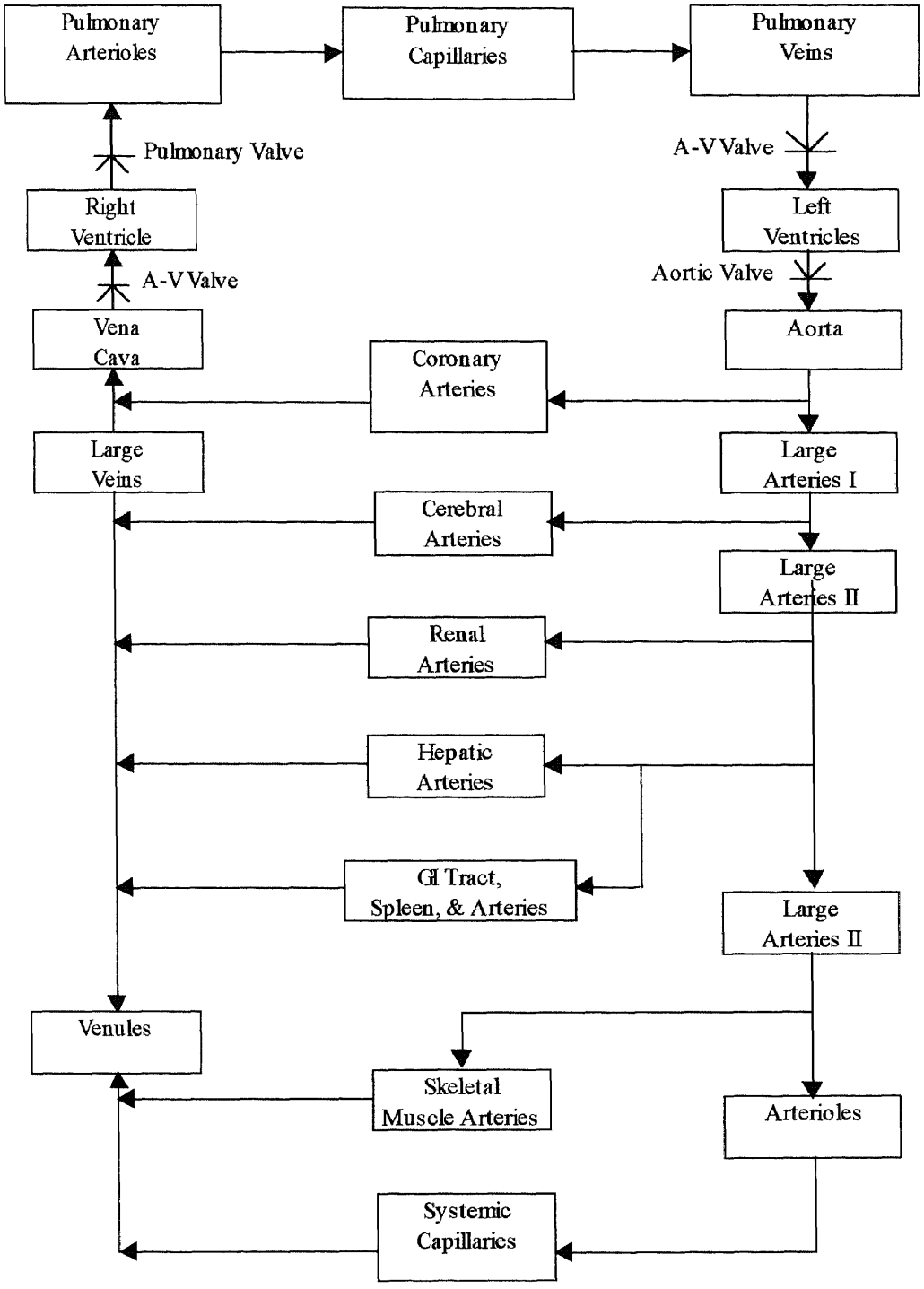

Figure 2.1 Schematic diagram of the cardiovascular system used in this work

where:

F_i = blood flow out of compartment i

P_i = blood pressure in compartment i

P_{i+1} = blood pressure in compartment i+1

R_{i+1} = vessel resistance of compartment i+1

The pressure P in a compartment is related to the compartment's volume V by a compliance term. Equation 2.2

$$C = (dV/dt) / (dC/dt) \tag{2.2}$$

Finally the change of volume (dV/dt) is represented as the difference of the inflow (F_{in}) and outflow (F_{out}) by Equation 2.3. According to the law of conservation of mass, this equation describes the variation of blood flow.

$$dV/dt = F_{in} - F_{out} \tag{2.3}$$

The model also accounts for autoregulation of blood flow and baroreceptor reflex regulation of arterial pressure. Autoregulation is the changing of local resistance to blood flow through metabolic and myogenic mechanisms, which causes a match between oxygen supply and demand for any tissue or organ. To maintain the equilibrium between supply and demand of oxygen, blood flow is adjusted. Baroreceptors are located at the carotid sinuses and aortic arch. Of the two locations, the carotid receptors are more

sensitive to pressure than are the aortic arch receptors. Therefore the carotid sinus receptors are considered in the physiological model. Baroreceptors act through neural pathways to alter heart rate, contractility and peripheral resistance to return sudden changes in blood pressure to normal "set point".[12] Congestive heart failure was simulated by reducing ventricular maximum systolic elastance to 40% of normal.[11] An in depth study of this model can be found in Gu.

The pharmacodynamic (PD) model for milrinone was represented by changes in vascular resistance, cardiac contractility, and heart rate. The experimental data and corresponding equations used in the PD submodel were obtained from www.amwtech.com/cardiac. Approximate drug concentration-heart rate relationships were obtained through the use of linear relationships.[11]

The physiological model, linking of the cardiovascular model to milrinone PD model, is used to predict hemodynamic responses and ischemic potential of milrinone therapy in simulated patients with CHF. The input of the physiological model is the milrinone plasma concentration (ng/ml) and the output that is the focus is the cardiac output (CO).

2.2 Pharmacokinetic Model

The PK or pharmacokinetic model describes the uptake, distribution, and elimination of the drug (in this case milrinone) as defined by Hull [13]. Pharmacokinetics is what the body does to the drug. The essentials of pharmacokinetic theory include compartmental approaches, which consists of the use of compartments.

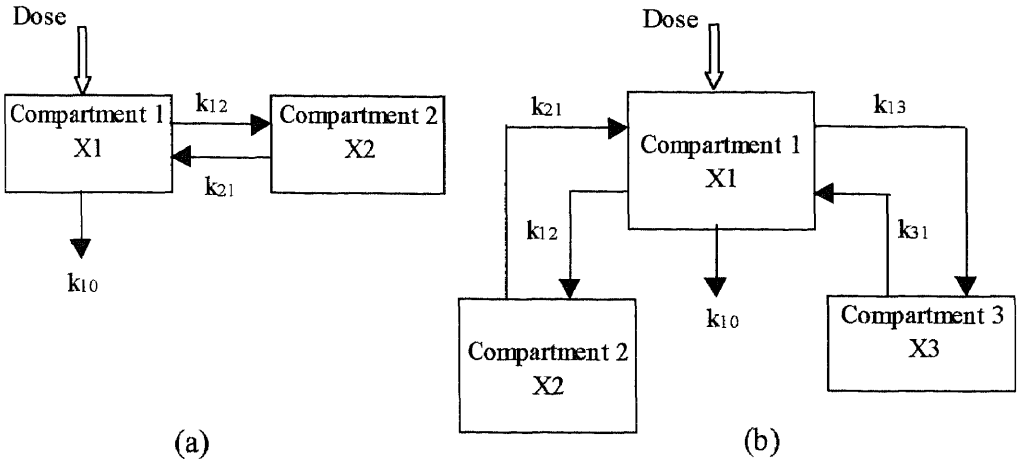

Figure 2.2 Pharmacokinetic compartment models for milrinone.(a) 2-compartment (b) 3-compartment.

A compartment is defined as an apparent volume of distribution that behaves as a single physical and mathematical entity. When placed in the compartment, any quantity of drug is assumed to be completely and instantaneously distributed throughout the apparent space.[13] Milrinone has been described both as a two compartment PK model and as a three compartment PK model.(Figure 2.2) Butterworth [14] and Bailey [15] independently performed a study that compared two compartment analysis to a three compartment analysis for PK model of milrinone. Both studies worked with cardiac patients. The two studies concluded that a three-compartment model was found to be a better description of the data for majority of patients than the two-compartment model. Therefore a three compartment PK model for milrinone is used here. The first or central compartment represents the blood, and is used to provide drug concentration in the plasma. The remaining two compartments represent the shallow peripheral compartment (1) and deep peripheral compartment (2).[13] The two compartments are basically storage areas of fat, tissue, etc. The three compartment model is written in terms of rate constants (Figure 2.2b), which represent the rate of drug distribution from one

compartment to the other. The rate constants were calculated from the known volumes and clearances obtained from Butterworth's study.

$$k_{10} = Cl_1/V_1 \tag{2.4}$$

$$k_{12} = Cl_2/V_1 \tag{2.5}$$

$$k_{13} = Cl_3/V_1 \tag{2.6}$$

$$k_{21} = Cl_2/V_2 \tag{2.7}$$

$$k_{31} = Cl_3/V_3 \tag{2.8}$$

where:

Cl_n = clearance of compartment n

V_n = volume of compartment n

k_{nm} = the rate of drug elimination from compartment n to compartment m

The concept of clearance is a measure of the eliminational efficiency, and is defined as the rate of drug flow per unit concentration. Hull [13] explains the relationship between volume and clearance using a bucket of water analogue. Hulls analogue is as follows. Clearance of water from the bucket is a way of describing the size of the outflow pipe; the wider the pipe, the greater the clearance. Clearance from this system can be defined as the flow rate per unit water level. Since any volume in the bucket can be re-stated as the product of cross-sectional area and difference in water level, the flow rate term can be restated as the product of the cross-sectional area and the rate of decline of water level at some stated time. Rewriting the expression for clearance (Cl), Equation 2.9 is obtained.

$$Cl = \text{Area} (\text{Rate of fall/Water level}) \tag{2.9}$$

The rate constant k of any exponential change can be defined as the ratio of rate of change at any time to the magnitude of the variable at that time; in this case the rate of fall divided by the water level. Furthermore, one observes that the cross-sectional area of the bucket represents the apparent volume of distribution Vd. Therefore Equation 2.10 is obtained.

$$Cl = Vd*k \tag{2.10}$$

With the rate constants being known, a differential equation approach was used to describe the three compartment PK model.[16] This notation describes the rate of change of drug concentration following drug administration.

$$dx_1(t)/dt = k_{21}x_2(t) + k_{31}x_3(t) - (k_{10} + k_{12} + k_{13})x_1(t) + i(t) \tag{2.11}$$

$$dx_2(t)/dt = k_{12}x_1(t) - k_{21}x_2(t) \tag{2.12}$$

$$dx_3(t)/dt = k_{13}x_1(t) - k_{31}x_3(t) \tag{2.13}$$

where:

$x_n(t)$ = concentration of drug in compartment n at time t

$dx_n(t)/dt$ = rate of change of drug in compartment n at time t

k_{ab} = rate constant for drug transfer from compartment a to compartment b

k_{10} = elimination rate constant from compartment 1

i(t) = the dosage of drug into compartment 1 at time t

Each of the three differential equations simply sets out a pattern of drug flows; inputs are positive and outflows are negative. The rate of drug movement in or out of the compartment 1 is simply the resultant of the two processes. Observing Equation 2.11: concentration x_1 in central compartment is emptying into compartments 1 and 2 according to the rate constants k_{12} and k_{13}, respectively. While concentration x_2 and x_3 are emptying back into the central compartment according to rate constants k_{21} and k_{31} respectively. Finally the third term is simply the elimination route, with drug leaving the model according to the concentration of the drug in compartment 1, x_1, and rate constant k_{10}. Equation 2.12 and 2.13 sees the same process of inflow minus outflow.

Transferring these equations into VisSim block diagram was very simple. The availability of the integrator block allowed the writing of the differential equations. The integrator block performs numerical integration on the input signal using the integration algorithm. The equations were completed in VisSim format by the use of arithmetic blocks. The block diagram of the PK model can be seen in Figure 2.3. This figure shows three summation blocks. The first summation block produces $dx_n(t)/dt$, which is the resultant of the two process, inflow and outflow of drug. This is then fed into the integrator block, thus producing x_n, drug concentration in compartment n. The input into the PK model is the milrinone dose and the output that is of concern is the drug concentration (ng/ml) in the first or central compartment, x_1.

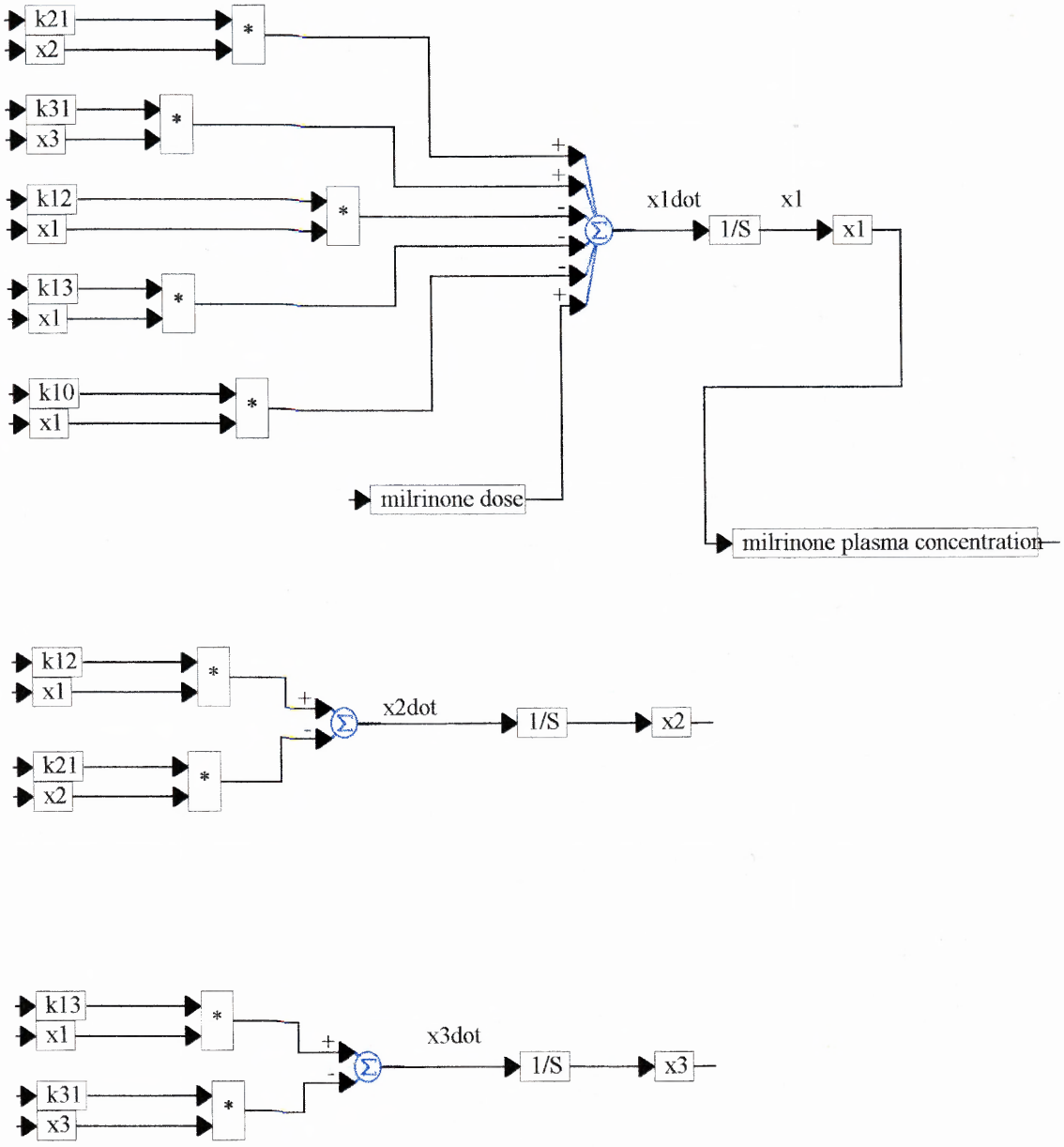

Figure 2.3 VisSim block diagram of three compartment pharmacokinetic model for milrinone

2.3 Feedback Controlling Model

The third model of the closed loop system is the feedback-controlling model. This is the brain of the CLDD system that decides on the milrinone dose so that desired set points are met for the cardiac output The feedback-controlling model consists mainly of a cascade controller. The cascade controller contains two controllers, the output of the first controller is input into the second controller before it is feed back into the rest of the system. The first controller is a PID controller. The second controller contains commands and conditions of how PID output is feed back into the milrinone PK model. The rest of the feedback-controlling model contains additional commands of when the PID controller is implemented. The importance of the second controller will be made obvious in later chapters.

PID, short for Proportional-Integral-Derivative, controllers are known as the "bread and butter of control engineering", the most common control algorithm.[17] PID controllers are used in all kinds of control systems. This controller has several important functions, (1) provides feedback, (2) has the ability to eliminate steady-state offsets through the integral action, (3) anticipate the future through the derivative action, (4) and can cope with actuator saturation. There have been many systems designed to control physiological variables automatically, but the majority use some form of PID control.[4] PID controllers often work well and are simple to implement. In fact Hao Ying, Ph.D. of the University of Texas-Medical Branch and control professor states that PID is very appropriate controller for closed loop drug delivery because (1) 90% of controllers used are PID or some form, (2) PID controllers are very simple to use, and (3), it is effective. Dr. Ying's [18] study with fuzzy control of mean arterial pressure in postsurgical patients

with sodium nitroprusside infusion uses a nonlinear PI controller. Fuzzy controllers are linguistic if-then-rule based and can be designed using control operators' knowledge and experienced about processes. A fuzzy controller can thus be regarded as an expert system employing fuzzy logic for its reasoning. Fuzzy controllers, being generally nonlinear, provide an alternative means to solve time-delay, nonlinear and time-variant control problems whether mathematical models of processes involved are available. Biological systems such as the human body involve time-delay, nonlinearity and time-variance. Results of Dr. Ying's research with this controller revealed that the performance of the fuzzy control SNP delivery was clinically acceptable and it will perform well for most patients. Therefore making the selection and use of PID control algorithm appropriate for this research.

The textbook version of the PID algorithm [17] has the following form:

$$u(t) = K[\, e(t) + 1/T_i \{ e(s)ds + T_d * de(t)/dt] \qquad (2.14)$$

where u is the control variable (milrinone dose) and e is the control error ($e = r - y$), which is the difference between set point r (target cardiac output) and measured value y (true cardiac output). The dosage is the sum of the three terms: the P-term (which is proportional to the error), the I-term (which is proportional to the integral of the error), and the D-term (which is proportional to the derivative of the error). K is the gain or proportional gain of the controller, T_i the integration time, and T_d the derivative time. The proportional action is simply proportional to the control error, e. The main function

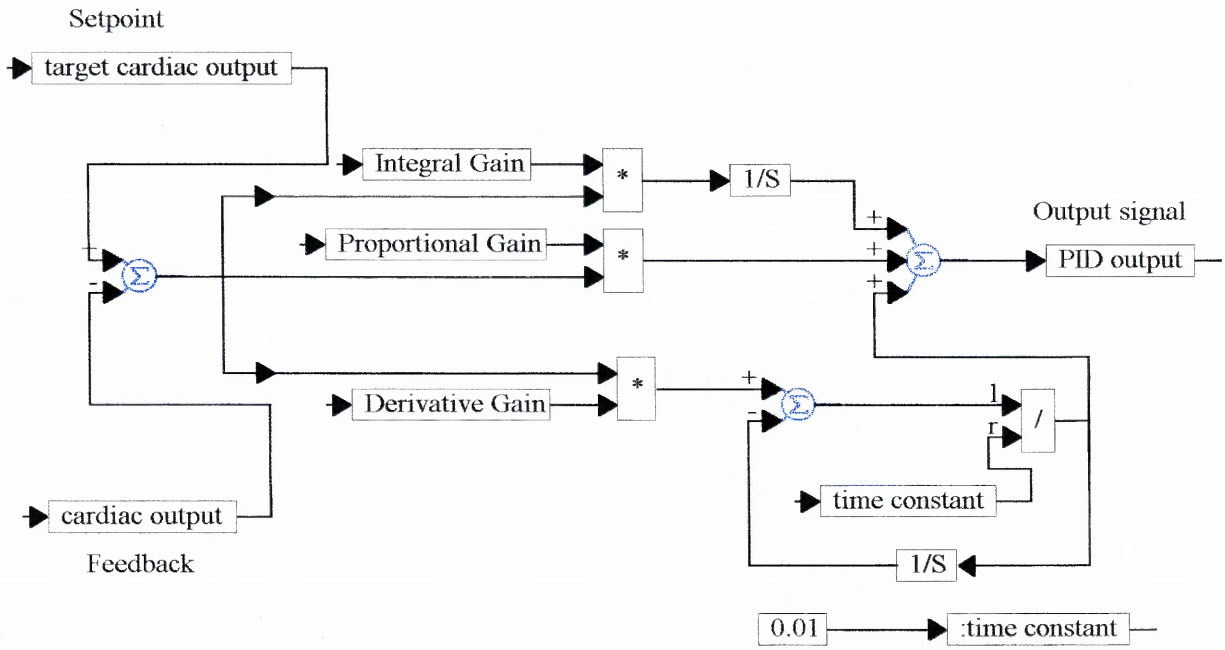

Figure 2.4 VisSim block diagram of PID controller

of the integral action is to make sure that the process output agrees with the set point in steady state. The purpose of the derivative action is to improve the closed loop stability

Transferring the textbook version of the PID algorithm to VisSim block diagram was very simple. In the VisSim toolbox folder there are available block diagrams of several controllers, one of them being PID control. The VisSim block diagram of the PID controller is obtained by use of integrator blocks and simple arithmetic blocks as shown in Figure 2.4. From the figure, target cardiac output and the cardiac output are the setpoint and feedback inputs into the PID controller, respectively. The difference of these two signals, the error, becomes part of the proportional, integral, and, derivative term. The PID output is the summation of the proportional of the error, integral of the error, and derivative of the error terms as seen in the block diagram. The PID controller is used to control both steady state accuracy (using the integral and proportional terms) and transient response (using the derivative and proportional terms). The limitations of

this controller are (1) time constant > 0 and (2) simulation stepsize must be greater than the time constant for stability.

In addition to the PID controller, the feedback-controlling model also contains block diagram that controls when PID is implemented into the rest of the system. To understand how this is done, lets first discuss at the compound block called hysteresis.[19]

The hysteresis block provides ON/OFF output depending on some input signal and its set limits. In other words the hysteresis block is a switch for the PID controller. The input signal, upper limit, and lower limit are set to the error of the cardiac output, 5% of target cardiac output, and 2.5% of target cardiac output respectfully. Given these set limits, the function of the block is as follows. Block output is ON (1) when the error is above the upper limit. The compound block continues to output ON until the error reaches the lower limit from above. Once lower limit is exceeded from above the output is switched to OFF(0). The output is OFF until the upper limit is exceeded from below. The detailed block diagram of the hysteresis compound block is shown in the appendix, Figure A1.

The input into hysteresis is the error, the output is either 1 (ON) or 0 (OFF). This output is feed into two distinct merge blocks. The VisSim merge block is an equivalent of the if-then-else algorithm of text based languages.

$$y = x_2 \text{ if } |x_1| \geq 1 \text{ or } y = x_3 \text{ if } |x_1| < 1 \qquad (2.15)$$

The merge block examines x_1, Boolean signal, to determine the output signal y. If the Boolean signal is true ($|x_1| \geq 1$) than $y = x_2$, but if the Boolean signal if false ($|x_1| < 1$),

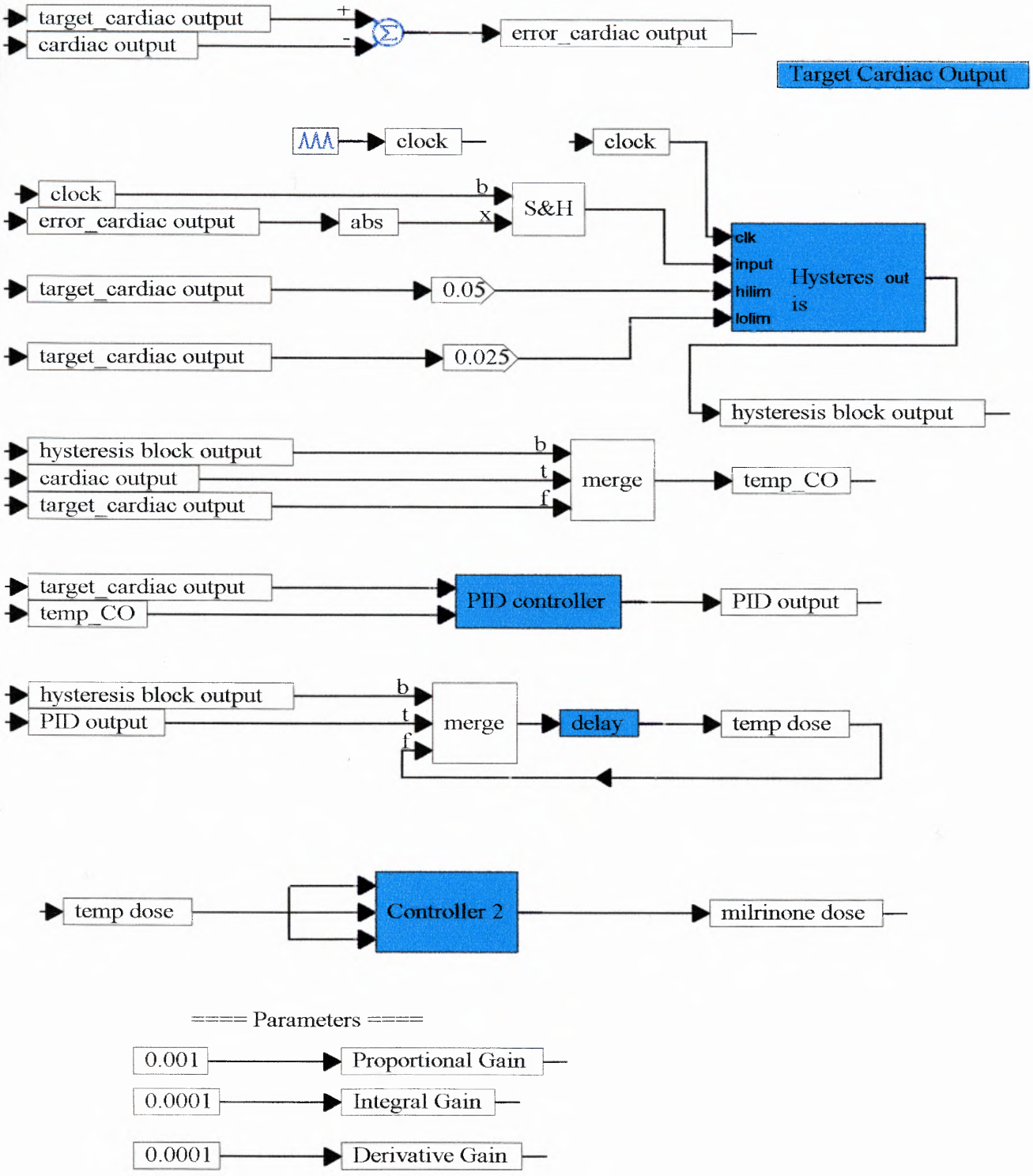

Figure 2.5 VisSim block diagram of the feedback-controlling model. The blue VisSim blocks represent compound blocks. A compound block is a combination of one or more standard VisSim blocks.

than $y = x_3$ as seen in equation 2.15. The first merge block decides whether to enable or disable the PID controller. Looking at Figure 2.5 that shows VisSim block diagram of the feedback-controlling model, the following can be observed. The first merge block either assigns the cardiac output or target cardiac output value to the temp CO variable block depending on the hysteresis block output. The temp CO value is feedback into the PID controller. The PID controller is enabled when temp CO = cardiac output. But the controller is disabled when temp CO = target cardiac output because zero error is forced on the PID controller therefore providing zero output. The second merge block functions as follows. Again the hysteresis output is the Boolean signal. Here a new variable block is introduced, temp dose. Temp dose is assigned the new PID output if a value of 1 is feed into Boolean signal; temp dose is assigned the previous PID output if Boolean output is 0. The delay block is attached to the output of second merge block because temp dose is continually assigned a new value each simulation step size. VisSim updates or increments variables by use of delay blocks. The two merge blocks work together either to enable the PID controller therefore assigning temp dose the new PID output value (incrementing dose), or to disable the PID controller therefore assigning temp dose the previous PID output value. The value of temp dose is then feed into the second controller.

The second controller plays a very vital role in performance of the cascade controller as a whole. A detailed description of the second controller is as follows. The value of temp dose that is fed into this controller can take one of the two available paths before entering the PK model as milrinone dose. The first path interprets this input as a bolus dose. The second path interprets the value of temp dose as an infusion rate. Given

the case that a bolus is implemented, than it can either be a large bolus or a small bolus. The large bolus has upper limit of 50 μg/kg given the condition that the error is above 10% of target cardiac output (Error > 10% target CO). Target cardiac output is given as a 50% increase in baseline CO, therefore target CO is 4587 ml/min. The small bolus has an upper limit of 10 μg/kg given that the error falls above 5% of target CO and below 10% of target CO (5% target CO < Error < 10% target CO). The second path which interprets the value of temp dose an infusion rate, has an upper limit of 4 μg/kg/min given that the error is below 5% of target CO (Error < 5% target CO).

The VisSim block diagram of the second controller can be seen on Figure 2.6. When the error is above 5% of target CO than a pulse is generated holding the magnitude for 30 seconds. The magnitude of the pulse is dependent on the criteria outlined above. If after 30 second from the start of the pulse, the error continues to be above 5% target CO, than another pulse is called (the magnitude is updated). If anytime during a pulse the error drops below the 5% target CO, than after 30 seconds from beginning of the pulse an infusion rate starts. The incrementing of the infusion rate stops either when the error has gone below 2.5% of target CO or if it has risen above 5% target CO (pulse generated again). These distinct paths and limitations makes it easy to see how PID output is controlled and adjusted before administration as a drug dose.

Another interesting observation with the PID controller is that it outputs negative numbers as well. This occurs when an overshoot is observed in the CO response. This is not practical for drug delivery systems. Therefore the dose is given a lower limit of zero for both bolus and infusion rate administrations to block the negative PID output. It is this second controller that prevents dramatic output responses from occurring due to

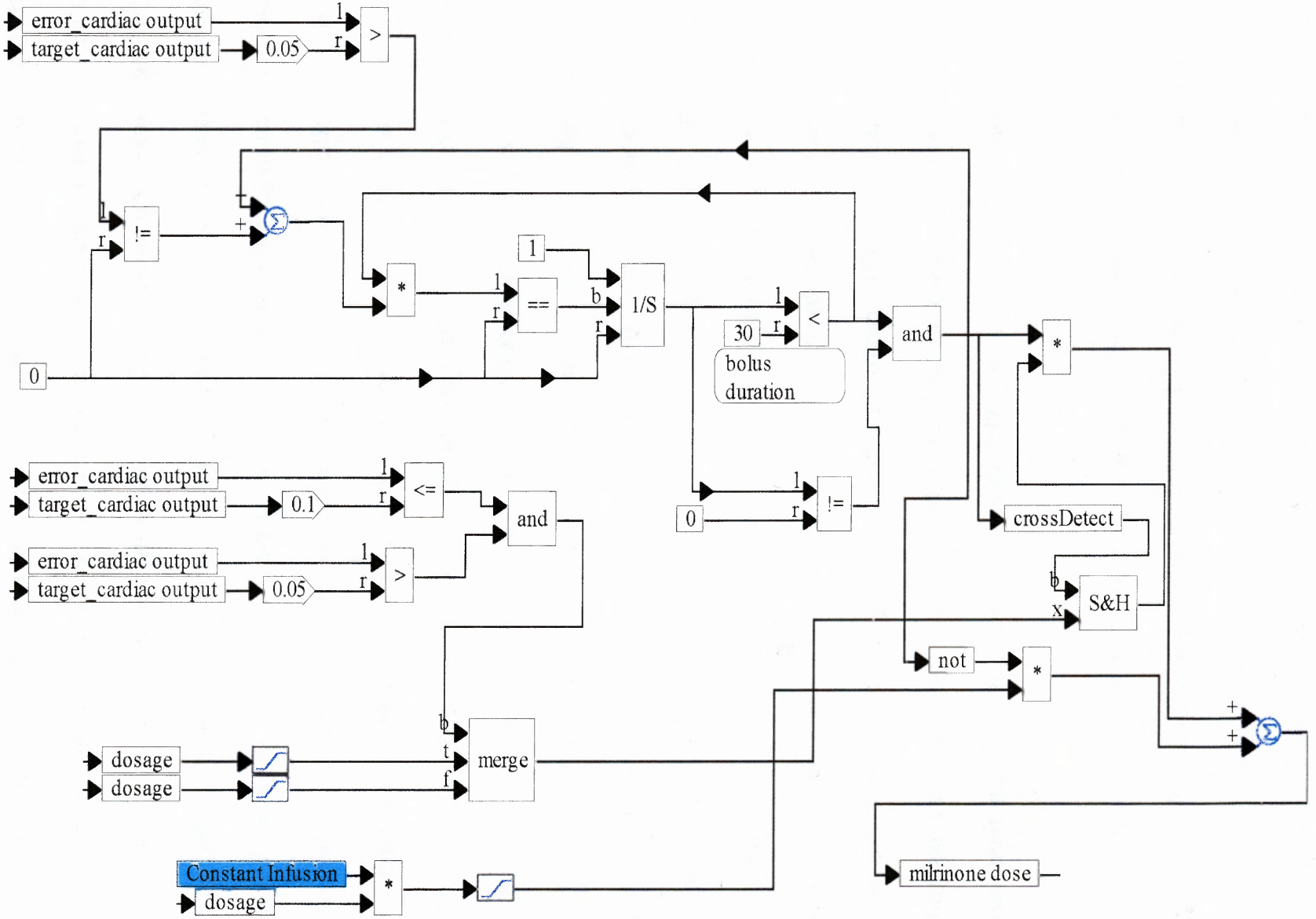

Figure 2.6 VisSim block diagram of second controller in cascade controlling mechanism

overdosing. The importance of the second controller will be made obvious as a comparison is done between cascade controller output and PID output in the chapter 4.

2.4 Interfacing Three Models

All three models now discussed, the focus of the section is how their input and output interface to give the closed loop drug delivery system. Since the focus here is on CHF patients, the cardiac output is expected to be much below target with no drug present in the body. Therefore as the simulation starts, the cardiac output is below the upper limit set for the hysteresis, thus allowing the cascade-controlling system to administer milrinone to the body. PID controller is enabled and its output (via the temp dose variable block) is fed into the second controller thus providing the drug dose. Milrinone dose is both the output of the feedback controlling model and the input into the PK model. Once milrinone dose is feed into the PK model, the milrinone plasma concentration is obtained. This PK output is input into the physiological model. The physiological model takes this drug concentration and calculates the response, the output. The response that is of concern, the cardiac output, is needed for the input (error cardiac output) back into the feedback controlling model, and thus making the closed loop drug delivery controlling system. (Figure 2.7)

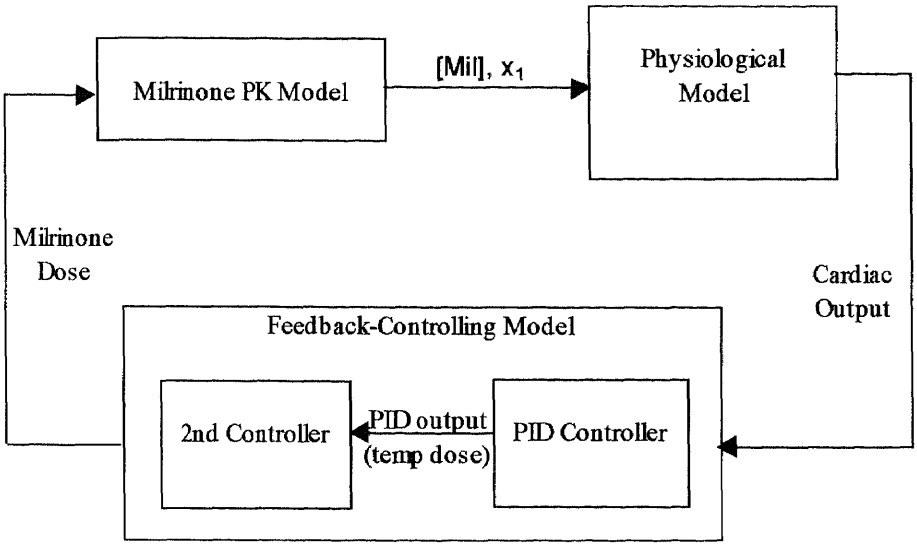

Figure 2.7 Block diagram representation of the closed loop drug delivery system. All three models are accounted for: milrinone PK model, physiological model, and feedback controlling model

CHAPTER 3

UNDERSTANDING DYNAMICS

This chapter concentrates on understanding and comparing the pharmacokinetic and hemodynamic responses of a single intravenous (IV) bolus administration of milrinone of a simulated CHF patient to a simulated normal patient. On the same note the results obtained from the simulated models are compared to studies done on human patients to confirm that the simulated models behave as the patient would under milrinone administration. The physiological model of the normal patient was obtained from the research done by Gu [12]. To do this study the feedback controlling model was disabled, leaving the milrinone PK model attached to the physiological model. Therefore these two interfacing parts can be referred to as an open loop dynamic model.(Figure 3.1)

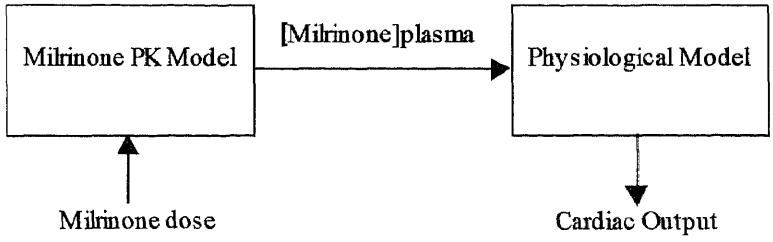

Figure 3.1 Block diagram of open loop dynamic model used to test the dynamics of the system

In understanding the dynamics of the system, CHF patient model responses are compared to normal patient model responses. Prior to simulating these results, it is essential to develop a pharmacokinetic model for a normal patient. There is a small amount of research available focusing on the pharmacokinetic behavior of milrinone on

normal patients. Of the research available, a two compartment PK model for milrinone is used to fit the pharmacokinetic data for the normal human patients.

Therefore when comparing the dynamics of a CHF patient model to a normal patient model, our results would not be valid because a three compartment PK model is used in one case (CHF patient) while a two compartment PK model is used in the other (normal patient). Two compartment and three compartment PK models do not provide the same dynamic output. This can be seen in the two-three compartment comparisons for CHF patient model for a 50 and 75 μg/kg doses.(Table 3.1)

Table 3.1 Comparison of a two and three compartment milrinone pharmacokinetic model for CHF patient model using a 50 and 75 μg/kg bolus dose administration

	50 μg/kg		75μg/kg	
Properties	2-compartment	3-compartment	2-compartment	3-compartment
[mil]max ng/ml	343	336	514	506
Context sensitive t1/2 (min)	8.5	5.9	8.4	6.3
Efficacy(100ng/ml) time (min)	19.8	13.2	40.7	29.6
%elimination [mil] in 5hrs	98.4	93.3	98.4	93.3
%CO increase	58.2	58.2	79.5	77.4
% CO from baseline in 5hrs	0.8	3.4	1.2	5.1

The solution here is to switch to a two compartment PK model for CHF patient model thereby allowing a valid comparison to the normal patient model dynamics. Only in this chapter is milrinone pharmacokinetics defined by a two compartment model. This is done primarily due to the lack of available research on milrinone pharmacokinetics for normal patients. The rest of the work uses the three compartment milrinone PK model for CHF patients as discussed in chapter 2.

A two compartment PK model for CHF patient model was obtained using Butterworth's [14] research done on the pharmacokinetic evaluation of milrinone in CHF patients. The rate constants were calculated from known volumes and clearances as discussed in Sec 2.2. A two compartment milrinone PK model for simulated normal patient was obtained through research done by Stroshane.[20] Stroshane provided the true coefficients (A,B) and exponents (α, β) for various doses. The rate constants were calculated using a pharmacokinetic conversion file available through *pkpd.icon.palo-alto.med.va.gov*.[21] The relationship between the model parameters that make it possible to calculate the rate constants is outlined in the following equations.[13]

$$k_{21} = (A\beta + b\alpha) / (A + B) \tag{3.1}$$

$$k_{10} = (\alpha\beta) / k_{21} \tag{3.2}$$

$$k_{12} = \alpha + \beta - k_{10} - k_{21} \tag{3.3}$$

The mean of the resulting rate constants was used to obtain the two compartment milrinone PK model for healthy patients as shown in the appendix, Figure A2

After baseline hemodynamics were obtained (CO and MAP), the IV bolus doses were administered to the patient models. Four different IV bolus doses were given to both simulated models (CHF and normal) and responses were recorded. A 25μg/kg, 50μg/kg, 75μg/kg, and 100μg/kg IV bolus doses were administered to both models. Milrinone plasma concentration, cardiac output (CO) and mean arterial pressure (MAP) were recorded over a period of five and half hours after drug administration. There was a

delay of 60 seconds before the drug was administered and the bolus was given over a period of 60 seconds as seen in Figure 3.2.

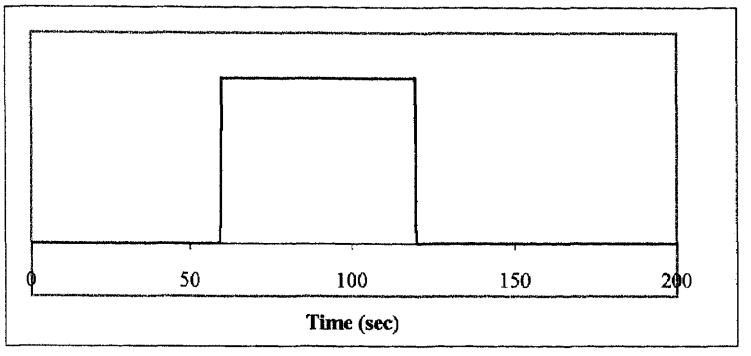

Figure 3.2 Bolus administration of milrinone that is used for the dynamic study

3.1 Phamacokinetic Analysis

The pharmacokinetics of milrinone was studied following a single IV bolus administration. Figure 3.3 and Figure 3.4 is a display of plasma milrinone concentration after the IV bolus administration as a function of time. Figure 3.3 is of the normal patient model. Figure 3.4 is of the CHF patient model. Bolus administration of milrinone rapidly increases milrinone plasma concentration. Maximum milrinone concentrations differed significantly among the four bolus doses for both normal and CHF patient models. Maximum milrinone concentrations for normal patient model are 170, 340, 511, and 675 ng/ml for the 25, 50, 75, and 100 μg/kg doses, respectively. Maximum milrinone concentrations for CHF patient model are 171, 343, 514, and 686 ng/ml for the 25, 50, 75, and 100 μg/kg doses, respectfully. These results correlate with previous studies on human patients. Benolti [22] reports peak plasma concentrations of 88 to 454 ng/ml for IV bolus doses of 12.5 to 75 μg/ kg for CHF patients and Stroshane

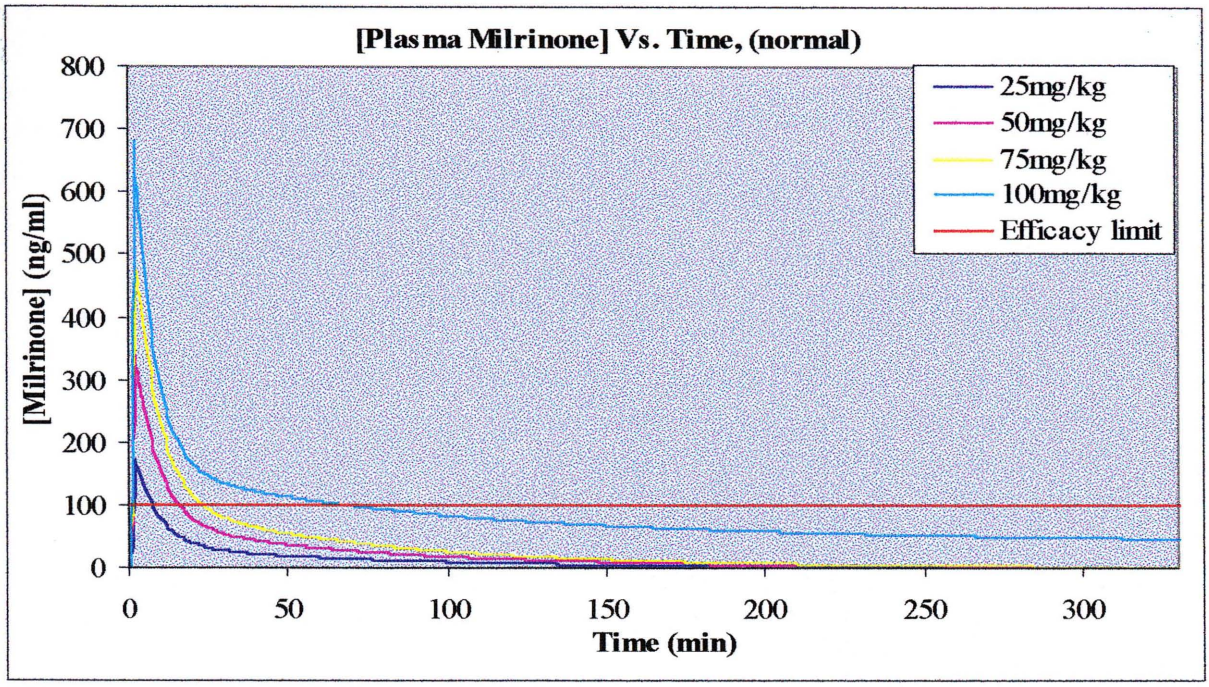

Figure 3.3 Plasma concentrations of milrinone as a function of time after intravenous bolus administration of 25, 50, 75, and 100 μg/kg doses for simulated normal patient

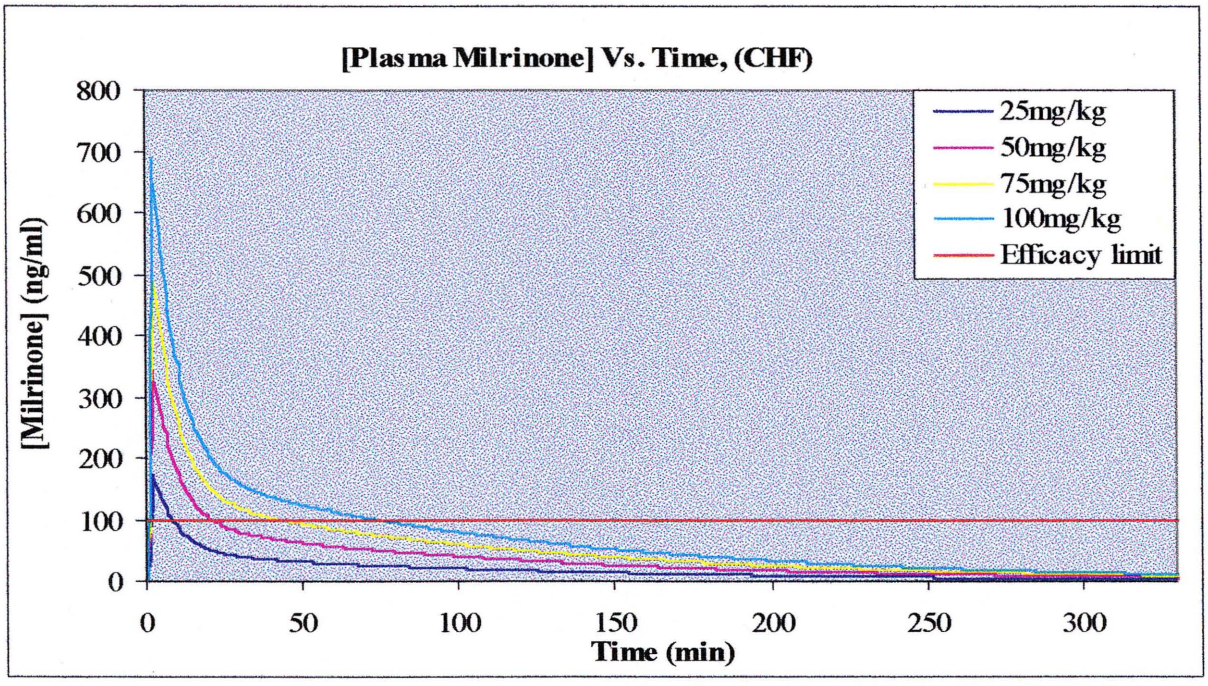

Figure 3.4 Plasma concentrations of milrinone as a function of time after intravenous bolus administration of 25, 50, 75, and 100 μg/kg doses for simulated CHF patient

[20] reports 63-640 ng/ml after bolus doses of 10 to 125 μg/kg in healthy volunteers. Peak plasma concentrations increased with the magnitude of the loading dose and occurred at the end of the dose in both models. Peak plasma concentrations were observed at around 117 seconds. Given a delay of 60 seconds before drug administration and an IV bolus over a 60 second period, 117 seconds is the end of the dose. However plasma concentrations dissipate rapidly after the loading dose for both patient models.

Milrinone is reported to have clinical efficacy at a threshold concentration of 100ng/ml.[14,23] Clinical efficacy for normal patient model was 6.3, 14.6, 21.9, and 66.8 min and CHF patient model was 7.5, 19.8, 40.7, and 72.7 min for the 25, 50, 75, and 100 μg/kg dose, respectively. CHF patient results show a slower rate of milrinone elimination in plasma; therefore the drug maintains efficacy for a longer period of time.[6] Efficacy data suggests that the 75μg/kg dose is most effective because there is a two-fold difference in efficacy time between normal patient and CHF patient model.

Elimination half-life is the time required by the body, tissue, or organ to metabolize or inactivate half of the amount of the substance taken in.[24] Elimination half lives often fail to adequately describe the rate of drug disposition of multicompartment models at clinically relevant drug concentrations.[14] Hughes coined the term "context-sensitive half time" as a measure of the time needed for the concentration of the central compartment to decrease in drug concentration by half after one or more infusions of the drug. Young [6] and Shafer [25] further demonstrated the usefulness of "context-sensitive" drug disposition and expanded the measure to included times to concentration reductions greater than 50%. The context-sensitive elimination times for milrinone are of a greater use to the clinician than the terminal elimination half-

life.[14] Therefore, milrinone context-sensitive elimination times are calculated for both patient models. The milrinone two compartment PK model for the normal and CHF patient models gave context-sensitive elimination times that agreed with previous research done on human patients. A 1 minute bolus infusion gave mean context-sensitive elimination times of 6.7, 22.0, and 74.5 min for 50%, 80%, and 90% drug elimination, respectively, for simulated normal patient. A 1 minute bolus infusion gave mean context-sensitive elimination times of 8.9, 37.8, and 114.9 min for 50%, 80%, and 90% drug elimination, respectively, for simulated CHF patient. The CHF statistics agreed with Butterworth's [14] pharmacokinetic analysis, elimination times of 6.7, 41, and 107 min for 50%, 80%, and 90% drug elimination were observed. Due to the lack of available literature on milrinone administration on healthy volunteers, context-sensitive elimination times were not compared to previous research. But the results confirm that milrinone is eliminated at a quicker rate in healthy subjects than in CHF subjects. These results correlate with studies done on the elimination half-life of milrinone in healthy and CHF patients. Following IV administration of milrinone to 21 healthy subjects, a mean elimination half-life of 0.8 hours was recorded.[20] In another study that concentrated on CHF patients, the elimination half-life of milrinone after IV bolus doses of 12.5 to 75 μg/kg was 2.3 hours.[6] These studies emphasize that milrinone is maintained in the blood for a longer duration of time in patients suffering from a failing heart rather than in healthy, normal volunteers

Another measurement that was recorded was the percentage of plasma milrinone elimination five and half hours after drug administration. The overall results again confirmed that milrinone plasma elimination occurred at a slower rate for CHF patient.

Table 3.2 Pharmacokinetic response of intravenous bolus administration of milrinone for simulated normal and CHF patient

Patient	Dose (μg/kg)	[milrinone] max (ng/ml)	Context-sensitive elimination time (min)			% [mil]elimination at 5.5 hrs	Efficacy Time(min)
			50%	80%	90%		
Normal	25	170.4	6.9	20.2	50.9	99.8	6.3
CHF		171.5	10.2	37.8	114.2	98.4	7.5
Normal	50	340.8	7	20.2	50.9	99.8	14.6
CHF		343.1	8.5	37.8	114.2	98.4	19.8
Normal	75	511.2	6.9	20.2	50.9	99.8	21.9
CHF		514.6	8.4	37.8	114.2	98.4	40.7
Normal	100	675.9	6.2	27.4	145.4	93.3	66.8
CHF		686.2	8.5	37.8	114.2	98.4	72.7

than for normal patient. The overall % elimination of milrinone five and half hours after bolus administration was 99.8% and 98.4% for normal and CHF patient models, respectively. Milrinone pharmacokinetic analysis is summarized in Table 3.2. But the 100 μg/kg statistics for normal patient do not behave as the other doses. Graphical representation (Figure 3.3) as well as analysis (Table 3.2) shows that after 50% elimination it takes longer for the 100 μg/kg dose to be eliminated from the body when compared to CHF results.

3.2 Hemodynamic Analysis

Cardiac output and mean arterial pressure were monitored five and half hour after drug administration. Figure 3.5, Figure 3.6, Figure 3.7, and Figure 3.8 are plots of CO and MAP as a function of time for the different IV bolus for simulated normal and CHF patients.

Intravenous administration of milrinone has shown to improve cardiac output for both normal and CHF patients.[6] This is also evident in this simulated study. For both

cases there is a dose dependant hemodynamic response as outlined by Young.[6] As the dose is increased, the maximum cardiac output relative to baseline is increased. Maximum cardiac output increases to 16.4%, 25.5%, 31.4%, and 34.7% relative to normal patient model baseline for the 25, 50, 75, and 100μg/kg doses, respectively. Maximum cardiac output increases to 31.1%, 58.2%, 79.5%, and 91.6% relative to CHF patient model baseline for the 25, 50, 75, 100 μg/kg doses. This simulated hemodynamic data agrees with Young's dose dependant hemodynamic response relationship.

Another thing to note is that maximum cardiac output increases to a higher percentage relative to baseline for the CHF patient model more so than in the normal patient model for all four doses. In all four doses the CHF maximum percentage change of CO relative to baseline is about double of the change in the normal patient model. In fact, studies done using animal models of experimental heart failure show that there is a greater cardiac output increase relative to baseline in dogs with induced heart failure than in normal healthy dogs when similar doses of milrinone were administered. Maximum percentage change of CO relative to baseline for induced heart failure patient is about twice that of the normal patient.[6] Both simulated and experimental data show milrinone to be more effective, in terms of increasing CO relative to baseline, for CHF comparison to normal patients. The correlation of these simulated results to the available experimental results, again confirm that both models respond to milrinone administration in the same manner as reported by previous research.

Effect of milrinone administration on MAP as a function of time for normal and simulated patients is shown in Figure 3.7 and Figure 3.8, respectively. A drop or

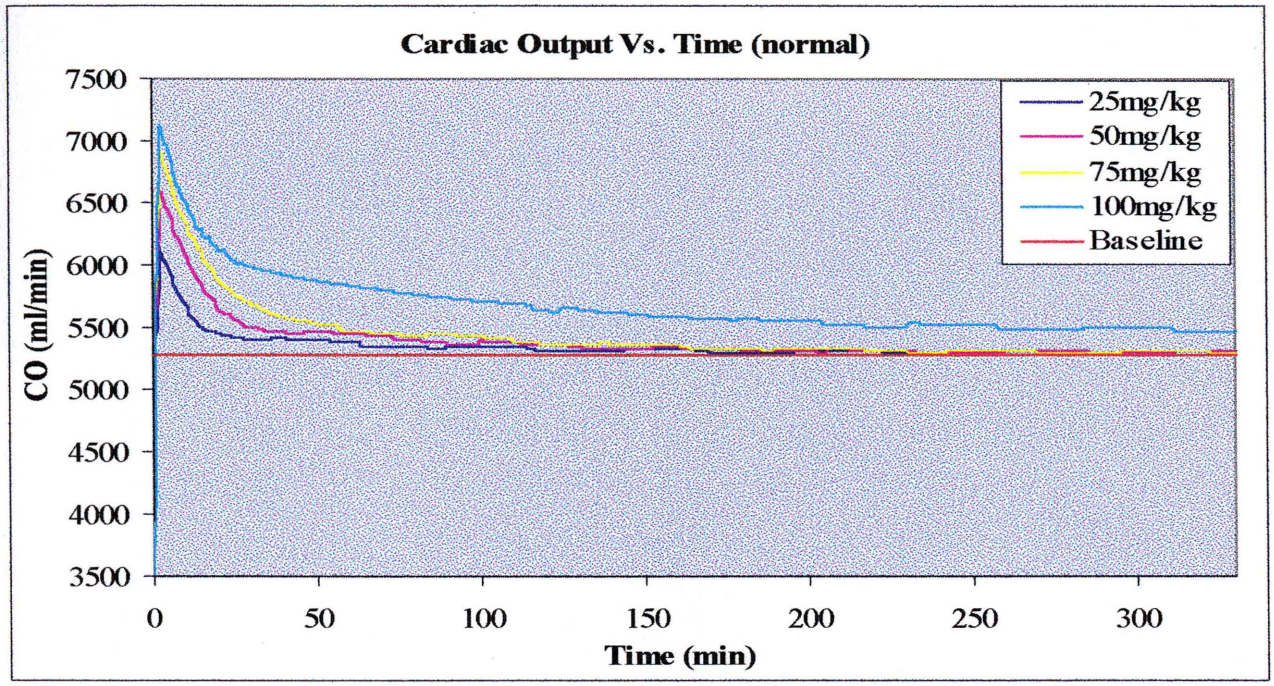

Figure 3.5 Cardiac output as a function of time after milrinone IV bolus administration of 25, 50, 75, and 100 μg/kg dose for simulated normal patient

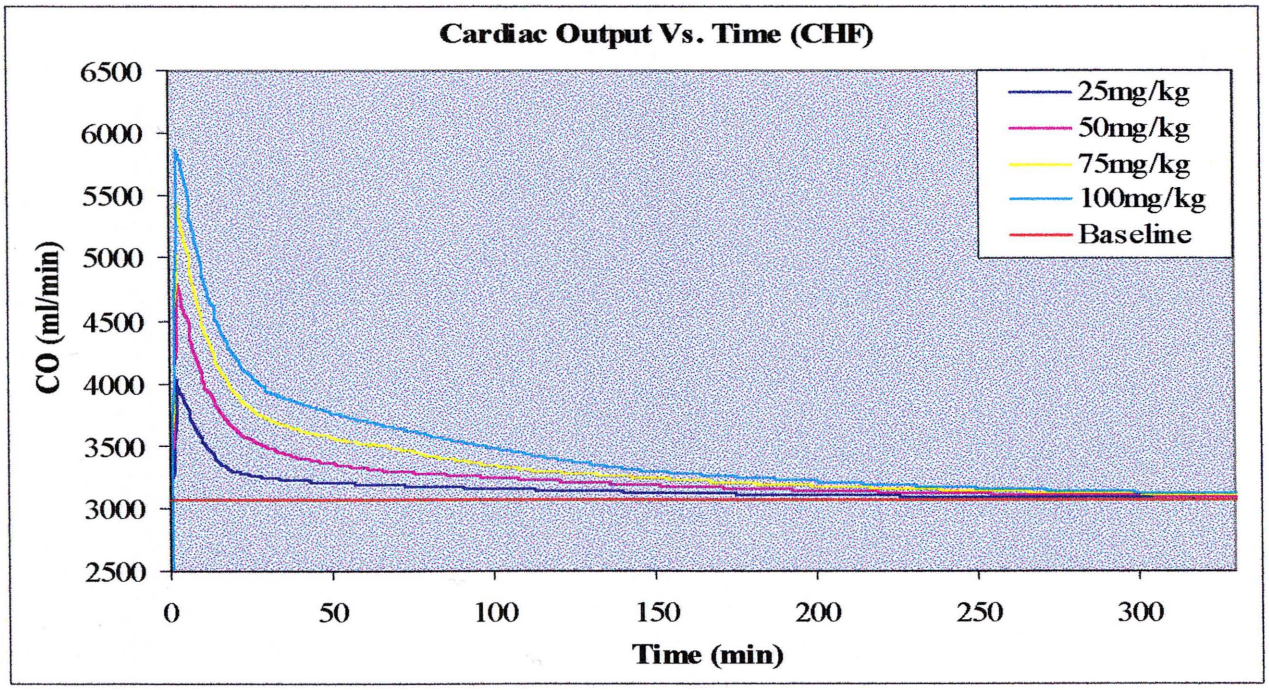

Figure 3.6 Cardiac output as a function of time after milrinone IV bolus administration of 25, 50, 75, and 100 μg/kg doses for simulated CHF patient patients

decrease in MAP is shown for both patient models in the graphical representation. But data analysis gives an increase in MAP relative to baseline for CHF patient model for the 25 and 50 μg/kg doses, while a decline is observed in the two larger doses. The percentage change in MAP relative to baseline for the first 3 minutes for simulated CHF patients is +11.6, +2.4, -11.6, -19.8 for the 25, 50, 75, and 100 μg/kg doses, respectively. The same statistics for the normal patient model are –14.9, -26.2, -36.0, and –44.2. The effect of milrinone on MAP (first 3 min recording) for normal patients appears to have more of a pattern than that of the CHF patient dynamics. MAP is further decreased as dose is increased for simulated normal patient, but MAP is increased and then decreased for simulated CHF patients. Benotti [6] administered milrinone intravenously, 12.5, 25.5, 50.0, and 75 μg/kg bolus doses, to nine CHF patients, maximum MAP percentage change from baseline was +4, +8, -5, and –6. Here again there is a rise in MAP followed by a decline as dose is increased for CHF dynamics. Therefore the simulated dynamic results for MAP behave the same when compared to studies done on human patients with CHF. As for the results for the normal patient model, milrinone is expected to decrease MAP. The decrease in MAP is more prominent in the larger doses, 75 and 100μg/kg. Under clinical conditions it is normal or "safe' to decrease MAP to 70mmHg. Any dose that drops MAP below this threshold, should not be administered. For CHF model, the 100μg/kg dose exceeds this limit, for normal model both the 75 and the 100μg/kg dose exceed the limit. In fact, investigators suggest that there is a plateau response to intravenous bolus milrinone administration and that doses above 50 and 75μg/kg tend to increase cardiac rate or produce significant decline in arterial pressure.[6]

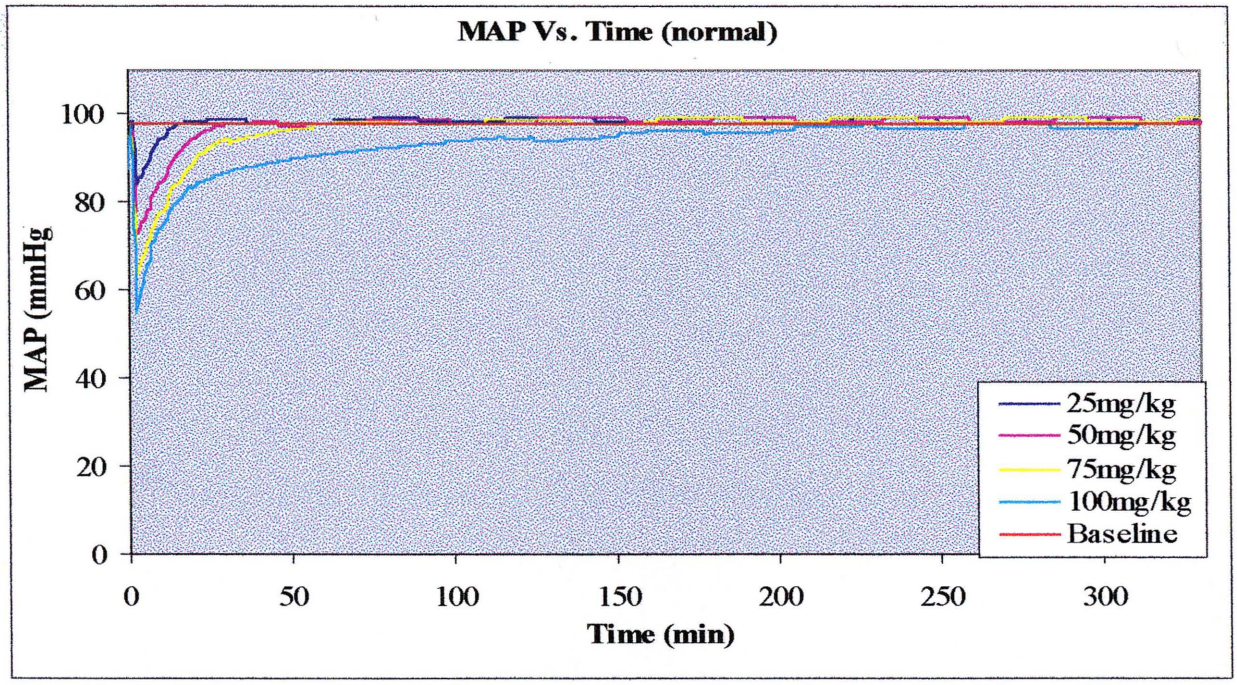

Figure 3.7 Mean arterial pressure as a function of time after milrinone IV bolu administration of 25, 50, 75, and 100 μg/kg dose for simulated normal patient

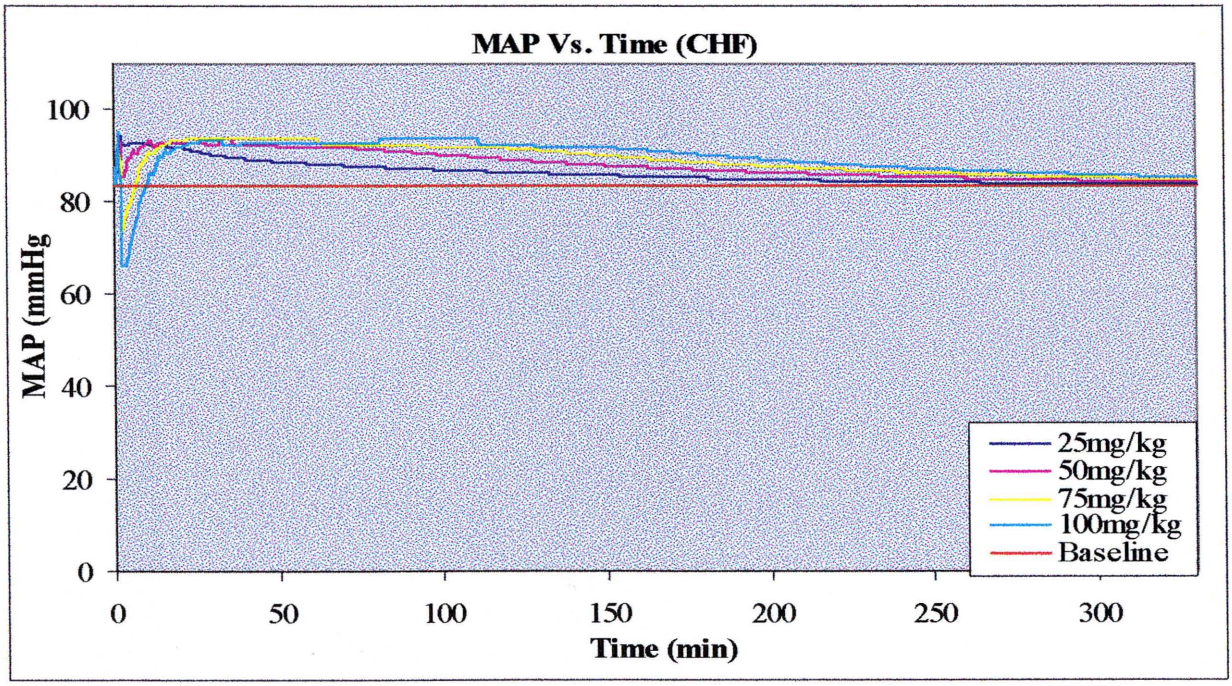

Figure 3.8 Mean arterial pressure as a function of time after milrinone IV bol administration of 25, 50, 75, and 100 μg/kg dose for simulated CHF patient

Another interesting observation made from the plots of MAP vs. time is the behavior of it after the initial decline (or increase). Both model plots show that after the initial change MAP quickly begins to stabilize and there is no oscillation evident. In fact at a certain point in time there is no distinction between the MAP relative to baseline for all four doses. Specifically, the plot for the normal patient shows a quick decline in pressure followed by steadying of MAP to baseline. The amount of time it takes MAP to stabilize for simulated normal patient is 16.9, 29.4, 59.4, and 204.8 min for the 25, 50, 75, and 100 μg/kg dose, respectively. Stabilization time for the 100 μg/kg dose is more than the other three times together. In fact as the dose is increased the time of stabilization becomes twice of the previous dose. The MAP for CHF model also behaves in similar manner, but here MAP stabilizes while slowly decreasing to baseline. The amount of time for stabilization is 6.5, 10.4, 16.3 and 20.8 min for the 25, 50, 75, and 100μg/kg dose, respectively. Here there is not a drastic jump between time of stabilization of the doses. Instead, MAP of later three doses appears the same relative to baseline in about 20 minutes. The 25 μg/kg dose seems to be too small of a bolus administration to have a distinct effect on MAP. In Butterworth's [14] pharmacokinetic study of milrinone, he

Table 3.3 Hemodynamic response of intravenous bolus administration of milrinone for simulated normal and CHF patient

Patient	Dose(□g/kg)	%CO Increase(max)	%CO from Baseline at 5.5hrs	% MAP from Baseline	stable MAP time (min)
Normal	25	16.4	0.1	(-)14.9	16.9
CHF		31.1	0.4	(+) 11.6	6.5
Normal	50	25.5	0.5	(-)26.2	29.4
CHF		58.2	0.8	(+)2.4	10.4
Normal	75	31.4	0.1	(-)36.04	59.4
CHF		79.5	1.2	(-)11.6	16.3
Normal	100	34.7	3.6	(-)44.2	204.8
CHF		91.6	1.7	(-)19.8	20.8

concluded that there are no other significant changes in MAP relative to baseline at any time in any of the doses studies after several minutes of drug administration.

Likewise, there were no significant differences between the dose groups at any time after the initial change. The correlation between Butterworth's observation to the simulated results further make the CHF physiological model an appropriate mathematical representation of the human response. The simulation results show that hemodynamic changes are expected to return to baseline at the end of six hours. These results are summarized in Table 3.3.

These simulated results have characterized the magnitude and time course of the optimal first dose response to a bolus milrinone in patients with congestive heart failure. There is a clear dose-dependent response relation, with each successive dose producing incremental plasma milrinone concentration and hemodynamic effect. Among the four doses, the 100μg/kg dose resulted in an unwanted decline in MAP without any wanted response, therefore this would not be an appropriate loading dose. The 25 μg/kg dose was to small of a dose to maintain responses for an adequate amount of time. What is left is the 50 and 75 μg/kg doses. Among these two doses both result positive hemodynamic response without dropping MAP below 70mmHg. Given a target CO as an increase of 50% of baseline (target CO=4587 ml/min), the 50μg/kg dose is more appropriate for our purposes. This dose achieves target CO without unnecessary overshoot. Therefore, bolus administration for the CLDD model will be limited to 50μg/kg. Also researchers performing IV dose range studies have concluded that a 50 μg/kg bolus dose of milrinone is effective for CHF condition. They further conclude that this dose achieves adequate hemodynamic efficacy with minimal side effects.

CHAPTER 4

OPTIMIZATION OF PID CONTROLLER

As stated in section 3.3, PID controller is short for proportional, integral, and derivative controller. These three parameter gains (P, I, and D) dictate the performance of the controller. Each term opts to maintain minimum error so that the control of CO is stable. Therefore selection or optimization of the P, I, and D parameter gains is necessary for stable performance of the controller. This chapter concentrates on selecting the parameter gain that optimizes the controller. Each parameter gain is changed individually, keeping the other two constant at values of 0.001, 0.0001, and 0.0001 for the P, I, and D gains, respectively. The error, cardiac output, and milrinone dose are monitored for a two-hour control period. The error is given as the difference between the target cardiac output and the true or observed cardiac output. The aim is to minimize error thus giving a more stable CO response. Comparisons of the results provide the information necessary in the selection of the optimal parameter gain in each case. This is referred to as tuning of the PID controller.

An important reminder is that PID parameters are selected while observing the outputs due to the cascade controller as a whole. Therefore what is observed is not the direct results of the PID tuning mechanism, but the responses after the second controller has adjusted the PID output. The second controller acts to stabilize the output of the PID controller, preventing overshoot or undershoot of response. What happens is that PID controller outputs a number to be translated into milrinone dose by the second controller. Then that dose is fed into the milrinone PK model, therefore providing the responses of CO due to the drug administration.

4.1 PID Output

The importance of this section is to show why there is a need for a second controller that adjusts the PID output before it can be implemented as the next dose. This section also shows how changing individual parameter gains influences the PID output to a greater extent than the output of the two controllers together. The proportional parameter gain is increased by a factor of ten, P = 0.00001, 0.0001, 0.001, 0.01, 0.1 ,and 1. For each modification, the PID output is recorded while the controller administers milrinone for a two hour period. The objective is to observe the changes to the PID controller, thus the PID output as the P gain is increased and to confirm that the second controller is an essential part of the controlling mechanism.

Figure 4.1 shows the PID output as a function of time for each proportional gain modification. The variation of the PID output as the P gain is increased is obvious in the plots. The PID output for the plots with P = 0.00001 and P = 0.0001 have very slight noticeable changes, both output range from –4 to +10. As P in increased further to 0.001, the change of the output becomes more obvious. The PID output is still within the previous range but the controlling mechanism of the PID controller appears to change as seen by the initial response to the error. Instead of the constant response of 8.4 for the first 23 minutes (as seen in the two previous simulations), here ones observes a rapid increase to 7.6 followed by a decline to 0.3 in 10 minutes. For the remainder of time the controller's output behavior is similar to the previous runs (P = 0.00001, 0.0001) in the magnitude of the response, but differ in time of the response as seen in Figure 4.1. Further increases in the P gain shows to have drastic changes on the PID output. A tenfold change in the P gain produces a tenfold change in the PID output.

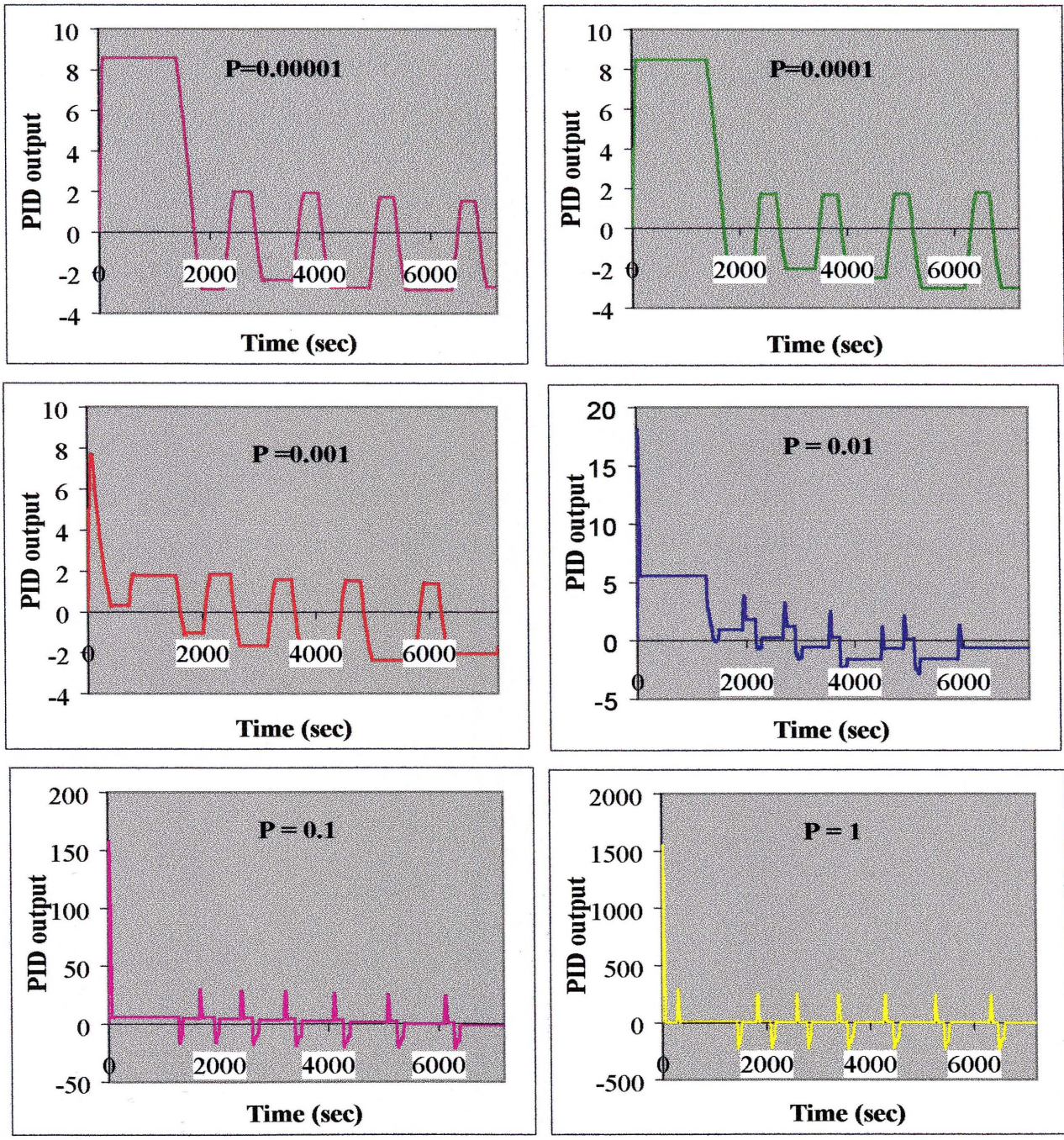

Figure 4.1 Plots of PID output as a function of time when the proportional gain increased. These plots show how the behavior of the PID controller changes as P gain changed as well as the important of the second controller in the cascade control mechanism

The PID output ranges from -5 to + 20, -50 to + 200, and –500 to + 2000 for the proportional gain of 0.01, 0.1, and 1, respectively. One can easily see how the parameter gains affect the performance of the PID controller and thus understand the importance of tuning the controller. Given the situation where this PID controller would be implemented (drug delivery) there must a control on the output, especially since PID outputs negative values, as well. A negative output is not practical for drug delivery purposes. Also the large overshoots in PID output will have potential harmful effects in the clinical situation. In the case of simulation studies, as is done in this thesis, the system will crash. Therefore a second controller is necessary to administer the milrinone as bolus and infusion rate without possibility of overdosing. In the same note this controller minimizes the degree of change of the cascade controller output, milrinone dose, as the PID parameter gains are modified. Nevertheless the optimization of the PID controller is performed for each parameter gain. Six different simulation runs were performed for each parameter gain while keeping the remaining two parameter gains constant. A seventh additional run was performed for the derivative gain because of the lack of change in CO response as the gain was modified. The mean of the errors is shown for all simulation runs in Table 4.1. The three minimum error results for each parameter were observed in detail in deciding the final parameter gains.

Table 4.1 Lists the mean of the error as parameter gains are changed

P-Gain	Mean	I-Gain	Mean	D-Gain	Mean
0.00001	139.4639	0.00001	150.0731	0.00001	151.5218
0.0001	136.7297	0.0001	151.4502	0.0001	151.4502
0.001	131.0645	0.001	158.9349	0.001	151.6583
0.01	112.3074	0.01	157.3521	0.01	151.3409
0.1	127.7208	0.1	157.3519	0.1	151.9548
1	117.3849	1	157.3518	1	151.3915
				10	165.4081

4.2 Proportional Gain

From the results given in Table 4.1, P values of 0.01, 0.1, and 1 are observed to have the minimum mean error from the six simulation trials. To better understand and therefore select the optimal proportional gain, plots of CO and milrinone dosage as a function of time were used. Figure 4.2 and Figure 4.3 describe system output responses when P is changed for milrinone dose and CO, respectively.

Looking at the two plots simultaneously, the following observations can be made. Milrinone administration differs for each choice of the P gain. Initially a bolus of 50μg/kg is administered in all three cases. But after that initial bolus, drug administration changes. For P= 0.01 and 0.1 an infusion rate follows the bolus dose. The infusion rate is continued until CO has exceeded its overshot boundary. This is evident in the CO plot. There is an immediate rise in CO due to the initial bolus, but CO begins to decline after the bolus. The effect of the infusion rate is seen as the CO begins to rise again even when it is above target. This is not seen for P = 1, because drug administration is stopped after the initial bolus, only to begin when CO has fallen below the given boundaries. The effect of this second bolus is observed as the CO quickly begins to rise afterwards. In this case an infusion rate follows the second bolus which maintains the CO above target. The behavior of the controller due to the different P gain is hereafter similar in that each P gain causes an administration of a bolus followed by an infusion rate, but is different because the drug is administered at a different time. Thus causing the maximums for the CO to occur at different times within the two hour control period. But towards the last thirty minutes of the control period, the P = 0.01 gain shows a stabilization of the CO. For this P gain, the controller better understands what it is monitoring, because it appears

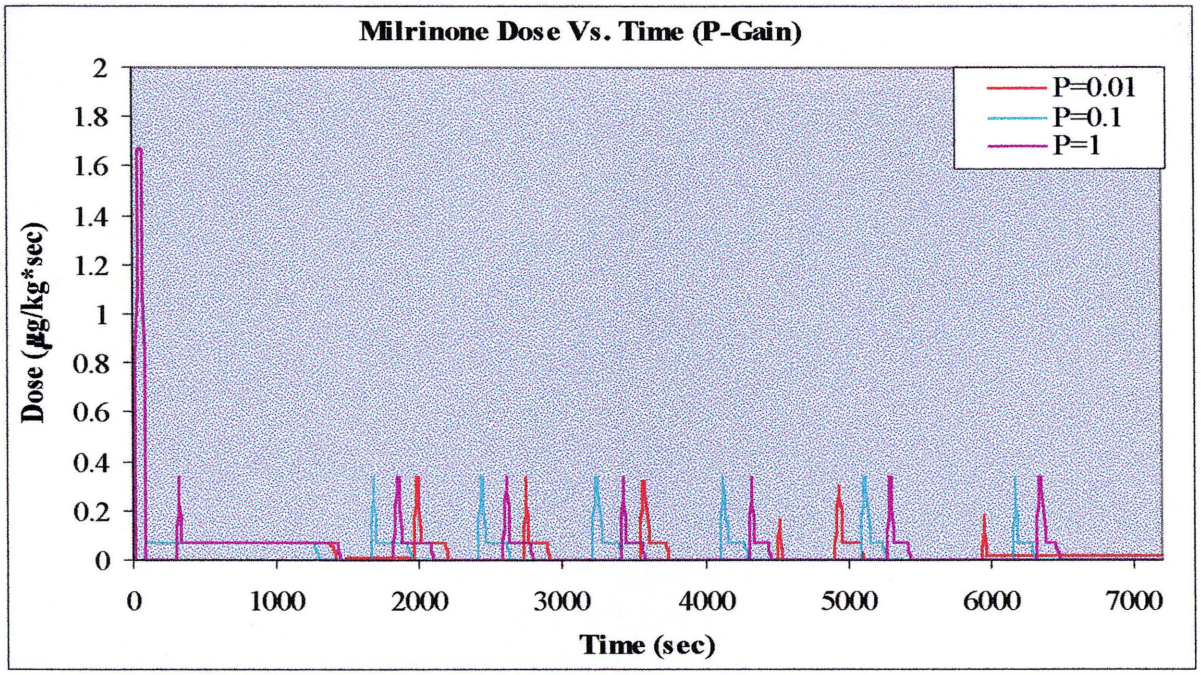

Figure 4.2 Infusion rate of milrinone for the three proportional gains with minimun mean error. The peaks are the bolus doses. The magnitude of the bolus dose i calculated by multiplying the dose by 30 sec., because each bolus is administered over a 30 sec. period

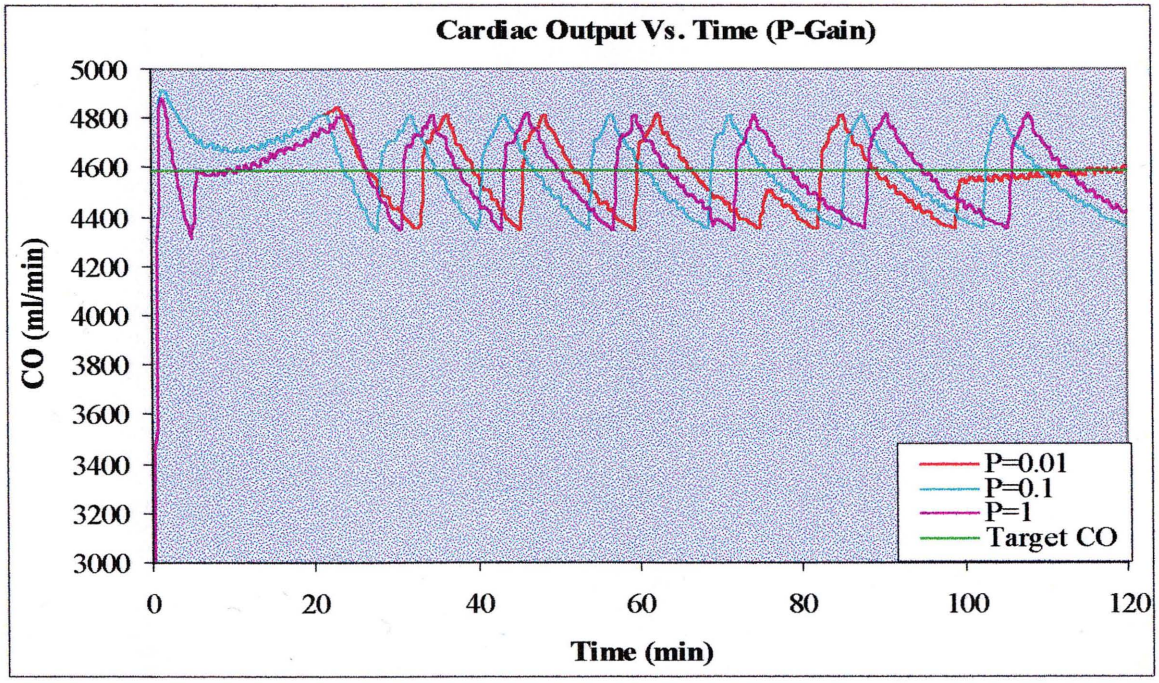

Figure 4.3 CO as a function of time for the three proportional gains with minimum mea errors.

to have learned with time how to adjust its output while maintaining CO at the desired set points. The controller has learned that in decreasing the bolus and following it with an infusion rate, CO can be maintained within limits. Thus P = 0.01 is the choice for optimal proportional gain.

4.3 Integral Gain

The integral parameter gain was narrowed to I = 0.00001, 0.0001, and .01. These choices for the integral gain gave the minimum mean error of the six simulation trials. In deciding upon the optimal integral parameter gain, the CO and the dose are plotted for the two-hours control period.(Figure 4.4, Figure 4.5) Analysis of these plots helps to better understand the controlling mechanism of the system and therefore selection of the optimal I gain can be done.

Unlike the case for the P parameter gain, there is more variation in the dosage scheme between the three different I gains which then produces different curves of CO in the two-control period. For I = 0.00001, the controller maintains CO by administering milrinone mainly as an infusion rate. Instead of constantly stopping and starting drug administration, here one observes milrinone being given as a small infusion rate. This also prevents the CO from oscillating between maximums and minimums, instead the CO is more stable. The initial overshoot of CO is greater than the other two simulations, but the undershoot is also less and there are a lot less maximums and minimums observed in the two-hour control period. The only setback is that CO reaches target 15 minutes after control has begun.

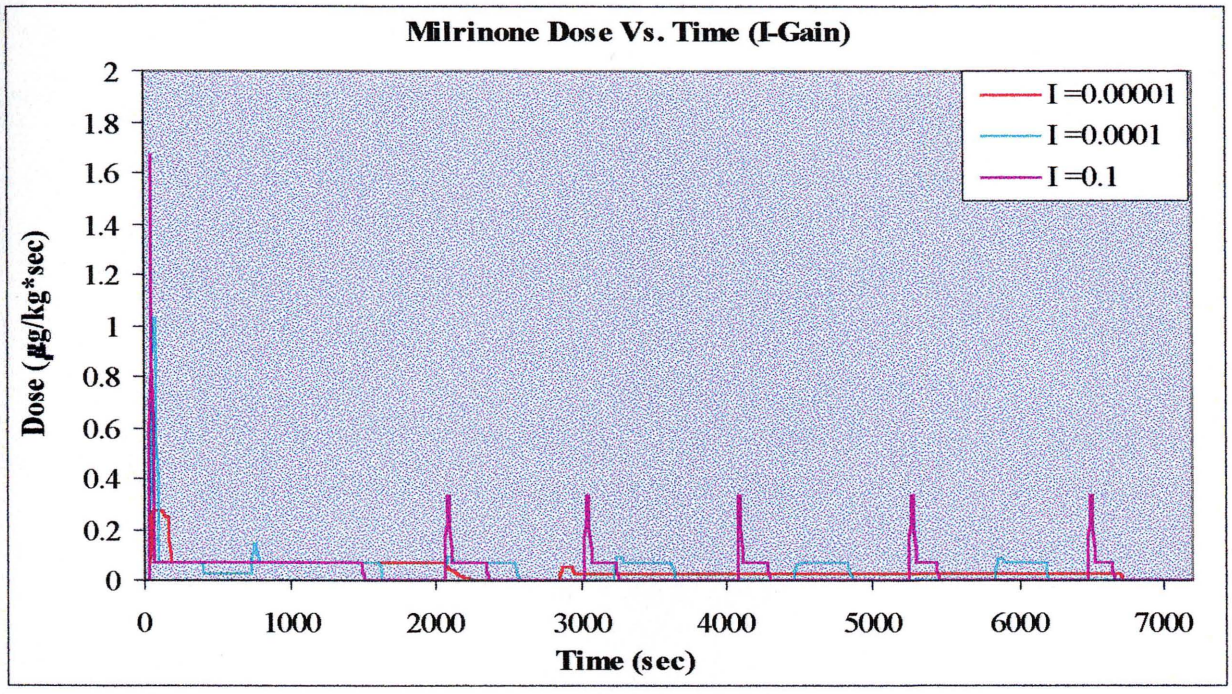

Figure 4.4 Infusion rate of milrinone for the three integral gains with minimum mea
error. The peaks are the bolus doses. The magnitude of the bolus dose is calculated b
multiplying the dose by 30 sec, because each bolus is administered over a 30 sec. period

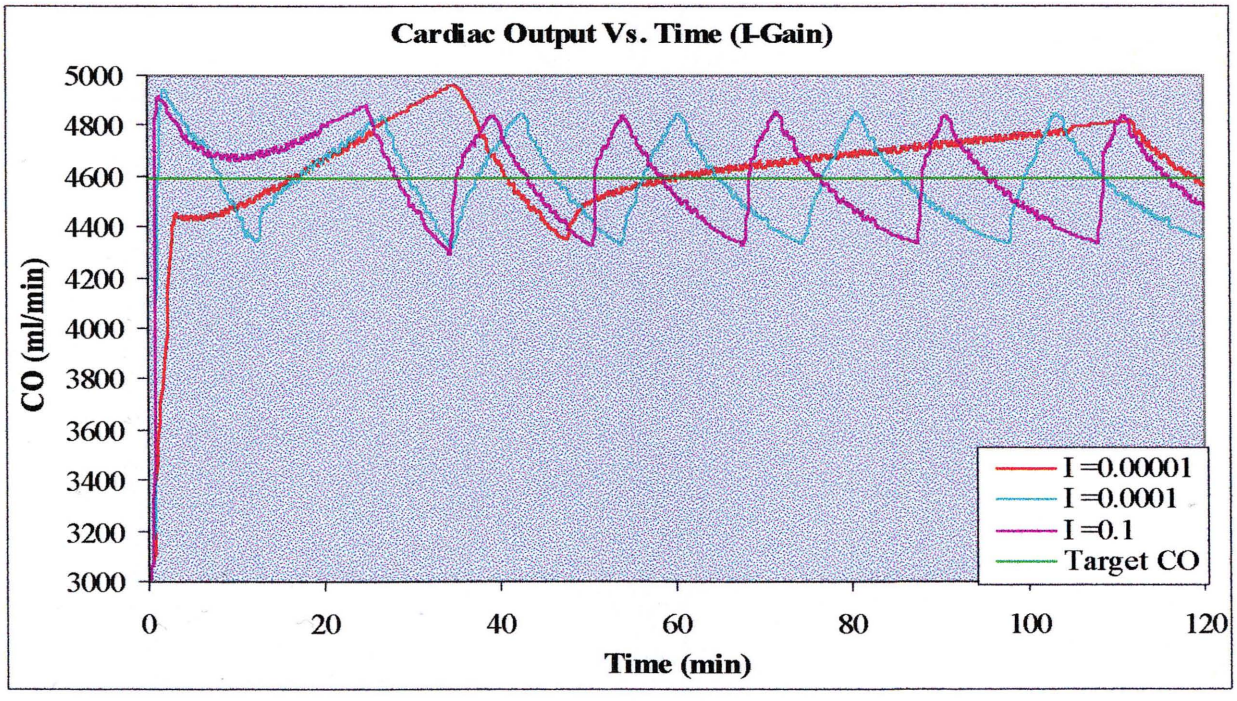

Figure 4.5 CO as a function of time for the three integral gains with minimum mea
error

The behavior of I = 0.0001 simulation is similar to I = 0.00001 in that drug is administered mainly as an infusion rate, only two bolus doses are observed. But the difference is in the magnitude of the infusion rate. For I = 0.0001, drug is given at a higher infusion rate when compared to I = 0.00001. This also produces more frequent stops and starts of milrinone administration. The effect of this can be seen as the CO moves between maximums and minimums. There are six maximums for CO observed within the two-hour control period.

The controller's behavior is observed to change to administrations of bolus followed by infusion rates for I gain at 0.1. The initial bolus is at a greater magnitude, 50μg/kg and it is immediately followed by an infusion rate. This prevents CO from getting below target after the initial overshoot. The administration of drug is mainly characterized by a bolus followed by an infusion rate. Again there are frequent stops and starts of drug administration causing oscillations in the CO. There are seven maximums observed for CO within the control period.

Although stabilization of CO is more evident for I = 0.00001 parameter gain selection, this gain can not be considered in practical terms. The feedback controlling models should bring CO to target within five minutes of control time. I = 0.0001 and I = 0.1 satisfies this criteria. But between the two choices, I = 0.0001 parameter gain maintains CO while producing less maximums and minimums for CO. Therefore I = 0.0001 is selected as the optimal integral parameter gain for the control model.

4.4 Derivative Gain

The three derivative gains with the minimum mean error were D = 0.001, 0.01, and 1. As was the case in the P and I gain, the dosage and CO plots were analyzed in deciding upon the optimal derivative gain. Figure 4.6 and Figure 4.7 are plots of dosage and CO as a function of time for the two-hour control period. For all three cases, similar magnitudes of milrinone doses are administered. Milrinone is given as an infusion rate rather than a bolus dose. There are slight differences observed in milrinone administration for the three cases in the control period. These differences do not appear to have a major influence in the CO response. CO is observed to respond in the same manner to the three doses from D gain of 0.0001, 0.01, 1. There are six maximums observed for CO in all three cases. The magnitude of the maximums for CO is observed to be similar as well. The CO minimums or the undershoot of CO also occur at the same magnitude as well. After the first hour of control there is difference evident in time that the controller begins and stops to administer milrinone for the three simulations. The effect of this is also observed in the CO response because it increases and decreases at different times. For D=1, drug is given about one and half to two minutes before the simulations using D gain of 0.001 and .01. This also delays the rise of CO for these simulations with respect to the simulation using D = 1.

But when the control mechanism of the three different D gains are compared so that a selection can be made, one concludes that the modification of the D gain does not produce vital changes within the milrinone dose output. Table 4.1 listing the mean error of the CO using seven different modifications to the derivative gain also confirms this observation. The CO errors for the seven simulations are very close.

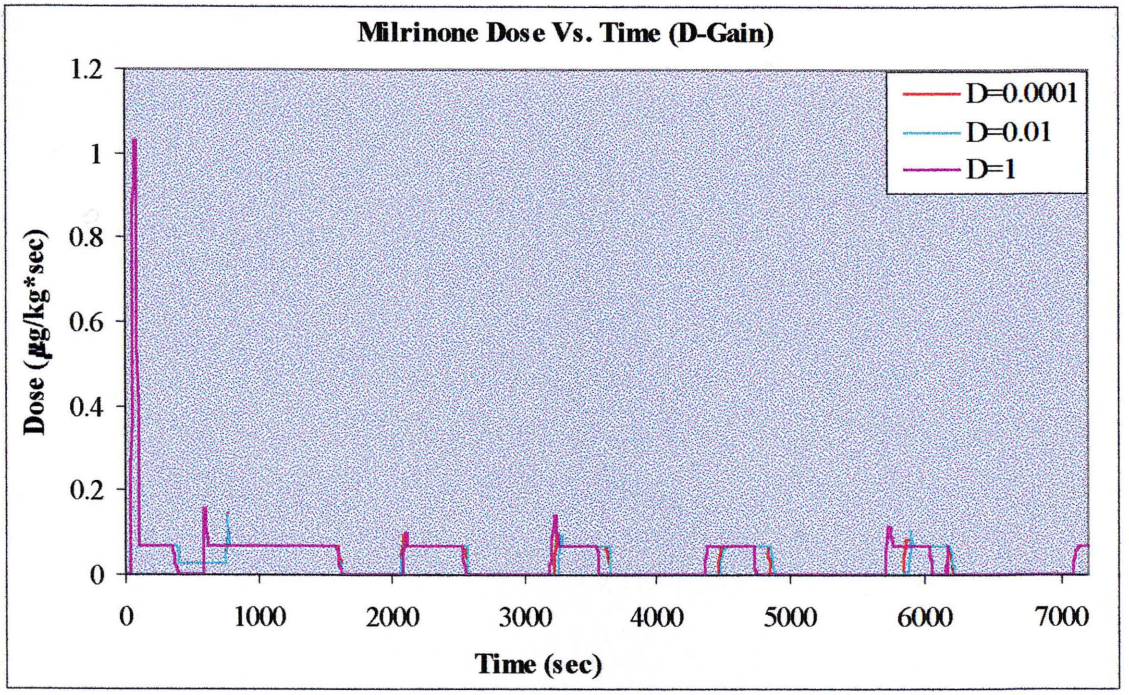

Figure 4.6 Infusion rate of milrinone for the three derivative gains with minimum mean error. The peaks are the bolus doses. The magnitude of the bolus dose is calculated by multiplying the dose by 30 sec, because each bolus is administered over a 30 sec. period.

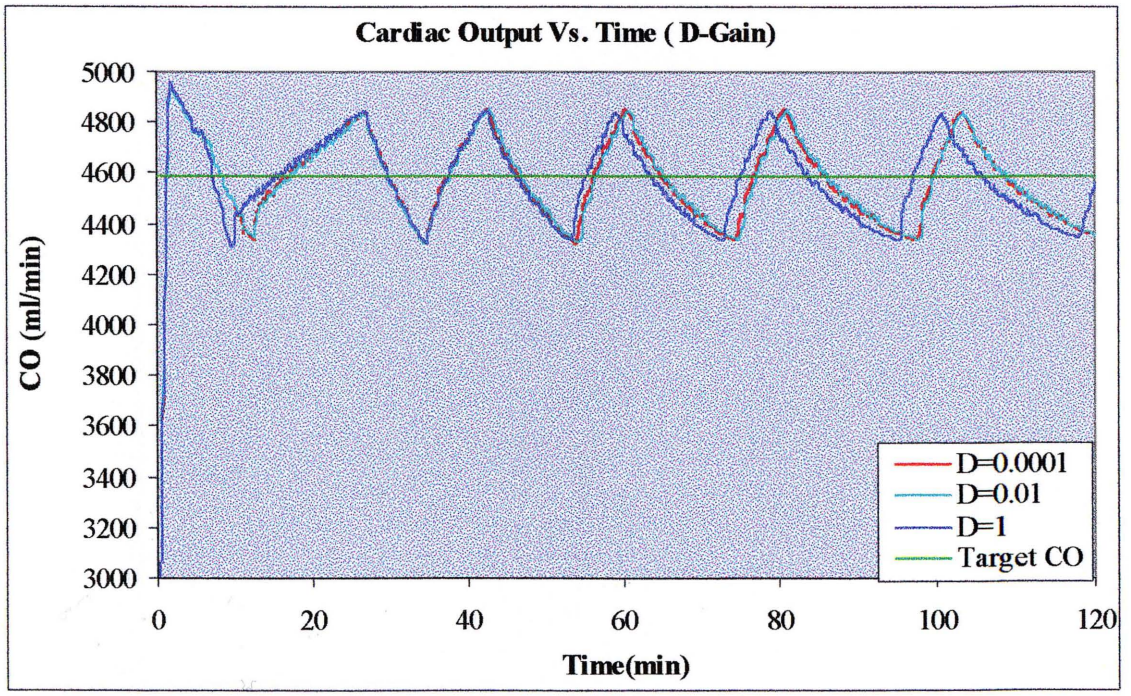

Figure 4.7 CO as a function of time for the three derivative gains with minimum mean error.

In other words, the D gain does not influence the performance of the controller. The controller's behavior is outlined more so by the proportional and integral gain. This is an indication that a PI controller would be appropriate for milrinone delivery purposes. But the decision is to keep the PID controller. Even though the derivative of the error factor does not contribute to the performance of the controller, it does not deteriorate the performance either. To confirm this conclusion, the CLDD system was simulated using a PI controller while keeping the P and I parameter gains the same. Figure 4.8 and Figure 4.9 plot the dose and CO during the two hour PI control period. Both plots are observed to behave similar to plots of dose and CO from Figure 4.6 and Figure 4.7, respectively. But the decision is to keep the first controller as a PID controller, using D = 0.01 for optimal derivative gain.

The performance of the controller was observed to be optimal using parameter gains of 0.01, 0.0001, and 0.01 for the proportional, integral, and derivative gains, respectively. Further testing of the CLDD system will be simulated using these PID parameter gains.

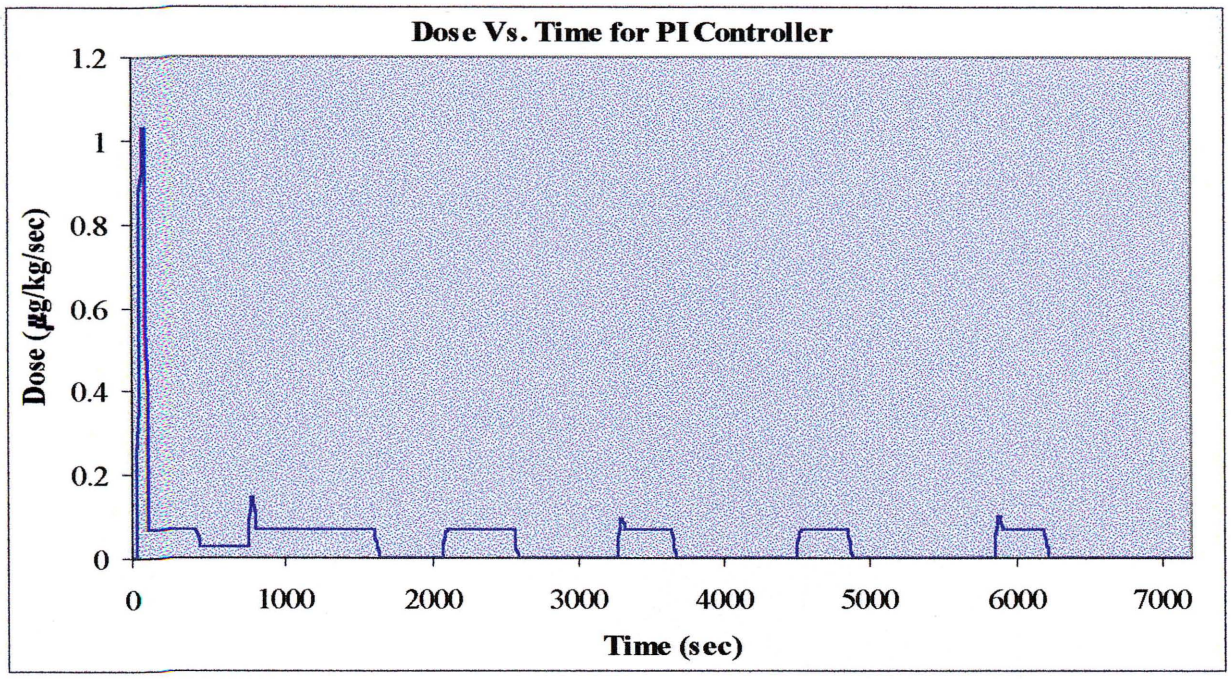

Figure 4.8 Infusion rate of milrinone using PI control. The peaks are the bolus doses. The magnitude of the bolus is calculated by multiplying the dose by 30 sec., because ea bolus is administered over a 30 sec period.

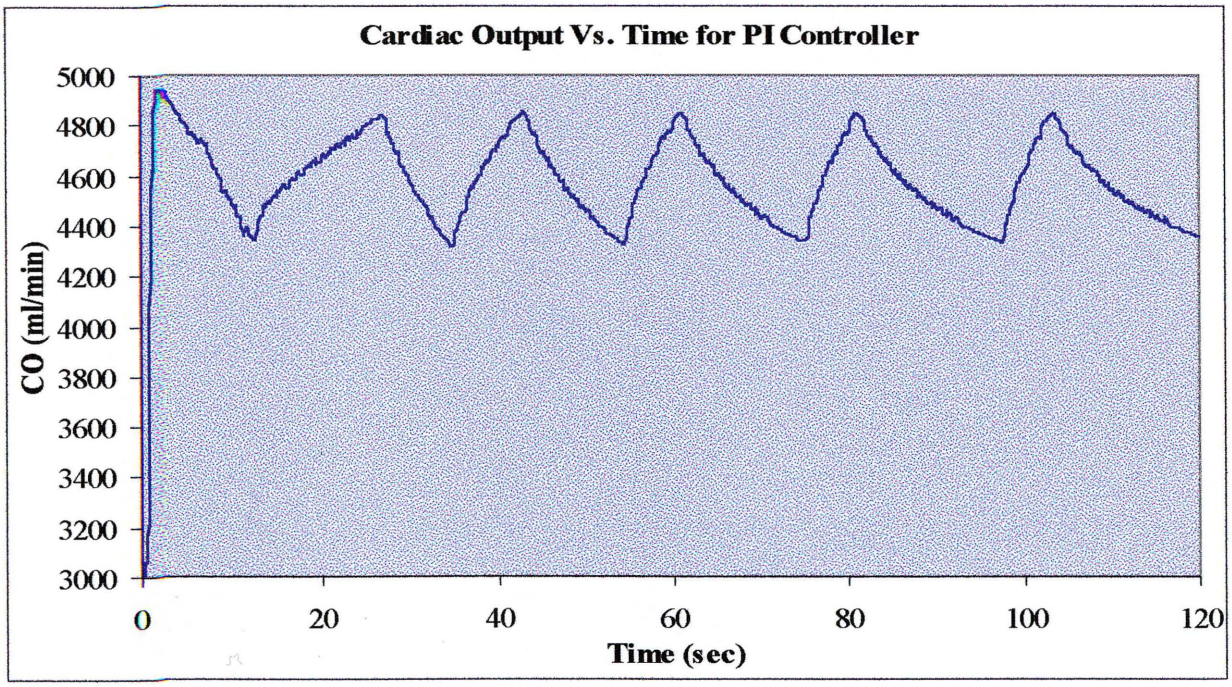

Figure 4.9 CO as a function of time using PI control

CHAPTER 5

TESTING OF THE CLOSED LOOP DRUG DELIVERY SYSTEM

Chapter 3 concentrates on validating the performance of the milrinone PK model and physiological model together. Four different bolus doses were administered to the CHF patient model, recording the pharmacokinetic and hemodynamic responses. The results validate that the behavior is similar to available human studies performed using milrinone administration. With the validation of the PK and physiological model, as well as, the optimization of the PID controller, the next step is to test the performance of the controller under varying situations.

The controller must be able to respond to changes within the system by adjusting the milrinone dose of the drug. In the previous simulations, CHF model parameters were kept constant. This is not practical in real situations. In fact a patient's characteristics can change during the course of drug administration. Also certain patient characteristics can vary as much as 36 fold from one patient to the next.[26] Therefore the controller must be able to handle a wide variety of patient types; adjusting the milrinone dose to meet these changes does this.

The robustness of the cascade controller used in this research was tested under three different situations. The first test observed the transient response of the cascade controlling mechanism as the target or setpoint CO was changed. In the second test, the controller responses were observed as perturbation was achieved by changing the vessel resistance parameters in the circulatory system in the physiological model. The third test incorporated randomization into the model, using the elimination rate constant, k_{10}, as the randomizing factor in the system. All three tests were performed to better understand

controller performance in a more realistic situation. Not only does one patient characteristics differ from the next, but also the characteristics within the same patient can change during the course of drug administration. Prior to simulating these test results, it is essential to simulate the controller responses using the three PID parameter gains that were chosen to optimize the performance of the cascade controller.

5.1 Controller Output with Optimized PID Gains

The values for the P, I, and D parameter gains that were observed to optimize the performance of the cascade controller are 0.01, 0.0001, and 0.01, respectively. Simulation of a two hour control period was performed using these gains. Figure 5.1 and Figure 5.2 are plots of milrinone dose and cardiac output as a function of time. There is an initial bolus observed immediately followed by an infusion rate. The effect of this dose is observed in the CO response: an overshoot is seen initially, then a decline is evident, finally before decreasing to setpoint, CO makes a U-turn and begins to increase again. Drug is administered in similar manner within the two-hour period because there is a bolus followed by an infusion rate given each time drug administration begins. During the second half of the control period, the controller responds by decreasing the magnitude of the bolus dose, while increasing the duration of the infusion rate. This achieves more stability in maintaining CO as observed in Figure 5.2. The CO plot begins to smooth out during the second half of the control period. In comparison to the individual simulations for each optimized parameter gain (found in chapter 4), there are fewer maximums and minimums observed in the CO plot using all three optimized gains, Figure 5.2.

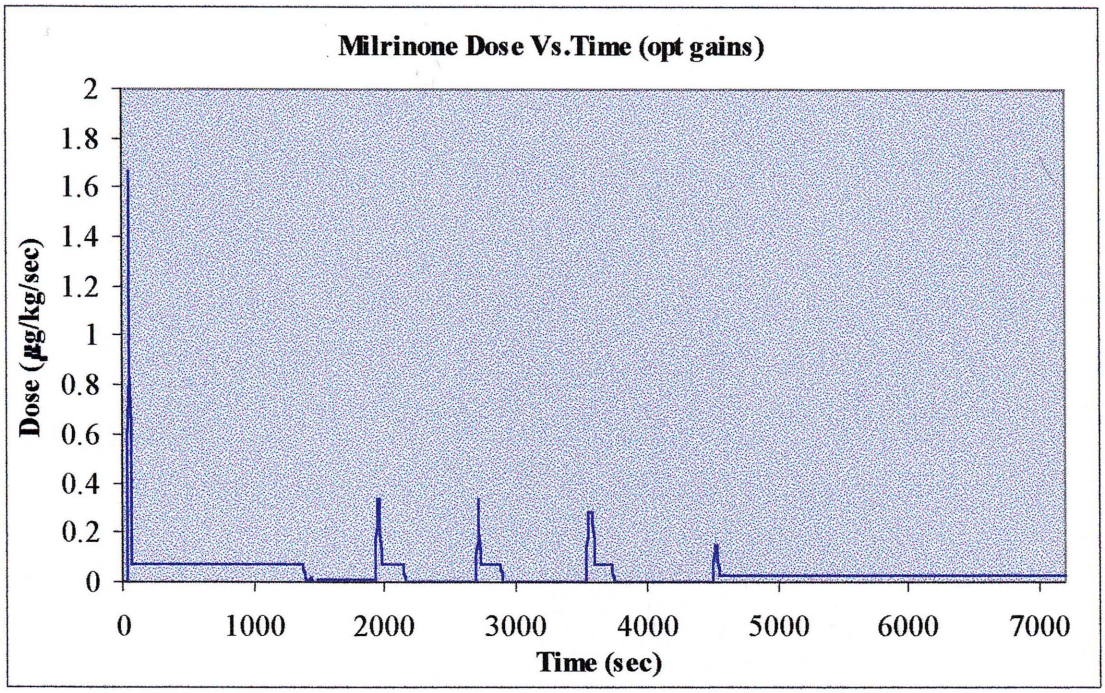

Figure 5.1 Infusion rate of milrinone using the PID gains that optimizes the performance of the cascade controller. The peaks are the bolus doses. The magnitude of the bolus dose is calculated by multiplying the dose by 30 sec, because each bolus is administered over a 30 sec period.

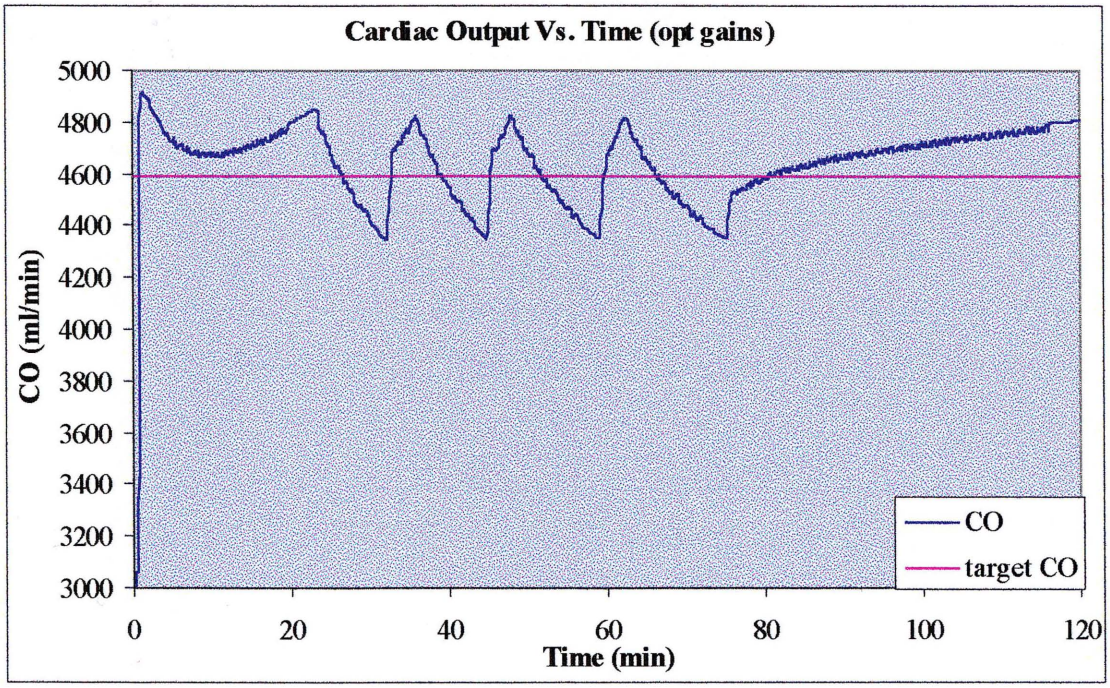

Figure 5.2 CO as a function of time using the PID gains that optimizes the performance

Table 5.1 Summarizes controller performance using PID optimized parameter gains

Dose Start	Controller response time (sec)	System response time (sec)	Onset delay (sec)	Error between ±2.5% T_CO(sec), Time taken(sec)	% Overshoot from T_CO
1	28	30	2	50, 22	7.15%
2	2695	2698	3	2715, 20	5.01%
3	3538	3550	12	3560, 22	5.01%
4	4508	4510	2	4545, 37	4.64%

In analyzing the performance of the controller, onset delay, time CO error reached 2.5% target CO, and overshoot from target CO was monitored each time drug administration was begun during the two hour control period. Table 5.1 summarizes these results each time drug administration was started, T_CO is target cardiac output. Onset delay is the "deadtime" between drug infusion and system response.[4] Figure 5.1 shows four distinct times milrinone was given. The longest onset delay for that two-hour period is 12 seconds. The overall results from Table 5.1 shows an increase in onset delay as control time progresses. With time the controller understands how to maintain CO and thus better to stabilize it by decreasing the amount drug given at one time (bolus) and increasing the duration of drug administration (infusion rate). It is this decrease in drug magnitude that causes an increase in onset delay with time because there is less drug available in compartment 1 at one time therefore delaying system response.

The desired range that the controller is trying to maintain the CO error is within ±2.5% of target CO. Each time drug administration was begun during the two-hour period, the time it took CO error to reach 2.5% of target CO was recorded. The results were 22, 20, 22, and 37 sec. for the four times drug administration was given. It takes an average of 25 sec for the controller to bring the error to the desired range. This shows a

very responsive controller system, because it takes less than half a minute to bring the output to the desired error range.

In addition the percentage of overshoot from target CO was recording each time the drug was begun during the two-hour period. The results are 7.15, 5.01, 5.01, and 4.64% overshoot. The controller responds with an overall overshoot of less than 10% target CO. Throughout the controller period it is observed that the percentage overshoot decreases with time, as well. This shows that the controller has learned how to maintain and better stabilize CO error each time it begins to administer drug as is shown in Figure 5.2. The results from this simulation trial, summarized in Table 5.1, will be used as reference in analyzing and understanding the performance of the controller during the three simulation tests.

5.2 Transient Response

The transient response of the controller is observed as the setpoint or target for cardiac output is changed during the simulation. This section will demonstrate the ability of the cascade controller to change milrinone dose such that the cardiac output tracks to the new setpoint. The transient response is observed using step setpoint and ramp setpoint changes.

The simulation testing for step setpoint changes begins using the original target CO (50% increase in baseline CO) as the setpoint. Then the target CO or setpoint is changed in a stepwise manner as shown in Figure 5.4. The setpoint is increased three times after original setpoint. Each setpoint is held for 30 minutes. The setpoint was incremented by 55, 65, and 85% of baseline each step increase.

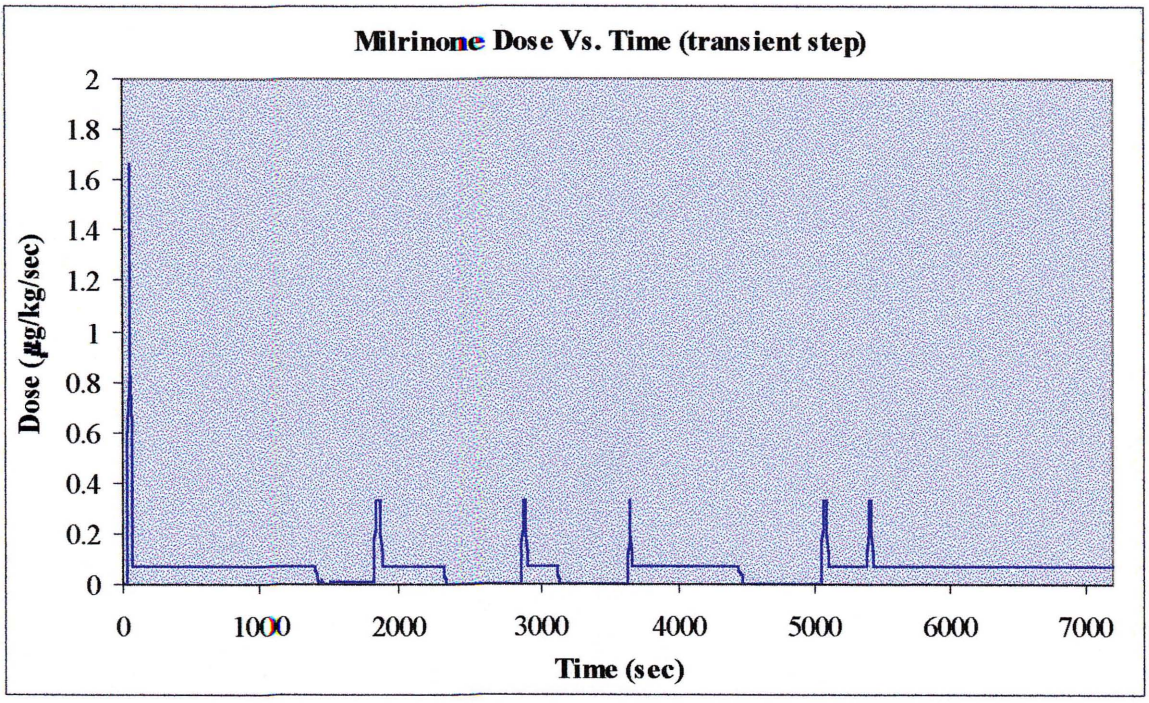

Figure 5.3 Infusion rate of milrinone as three step transient response is observed. The peaks are the bolus doses. The magnitude of the bolus is calculated by multiplying the dose by 30 sec, because each bolus is administered over a 30 sec. period.

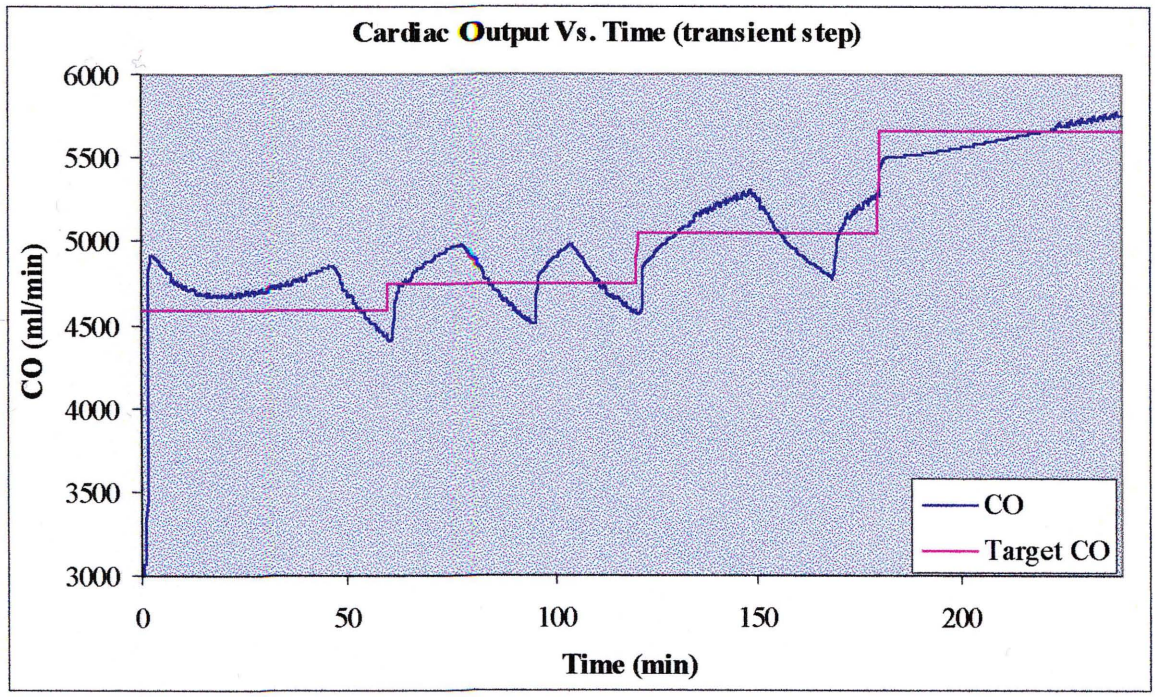

Figure 5.4 CO as a function of time as three step transient response is observed.

Therefore there is a 3.33, 6.45, 12.12% increase in setpoint from the previous setpoint each step increment. Figure 5.3 and Figure 5.4 are plots of the milrinone dose and cardiac output in the control period. The onset delay for the 55, 65, and 85% of baseline CO is 5, 15, and 15 sec, respectively. The "deadtime" of the control system increases between with the first two step changes, but remains the same with the final step change. Overall the onset delay is less than half a minute, which shows the cascade controlling mechanism to react quickly to changes in the model. Also the CO error reaches desired range within 60, 139, and 315 sec after the target CO has been changed. As the difference between the new setpoint and previous setpoint increases, time to reach 2.5 % of target CO increase as well. But the percentage of overshoot from target CO decreases with the three step changes. The overshoot is observed to be 5.00, 3.67, and 2.10% of target CO for the step changes of 55, 65, and 85% of baseline CO. Although the time it takes CO error to reach desired range increases with time, the percent overshoot decreases with time. From the these results it is observed that as the magnitude of the step change from the previous step change increases; it takes longer for the controller to reach desired range, but the controller is less likely to overdose as well. The controller becomes less quick to react to the changes because (1) it takes longer for CO error to reach 2.5% of target CO, and (2) the overshoot decreases as well. To better understand these results, a second transient step simulation was performed.

The second transient step simulation involved changing the target CO from original target (50% of baseline) to 85% baseline CO in one step increment. The purpose of this simulation was to better investigate if indeed the controller's response deteriorated as the difference between previous and new target CO increased. Figure 5.5 and Figure

5.6 are plots of milrinone dose and CO as a function of time. The control was simulated for one hour; the step change was done half-hour after control was begun. The onset delay, time for CO error to be within 2.5% of target CO, and the percent overshoot are 1 sec, 61 sec, and 1.47% respectively. These observations counteract the previous conclusion that as the change between previous and new target CO increases, the feedback-controlling model becomes less responsive. An onset delay of 1 sec shows that the physiological model responds quickly to controller input of drug. From Figure 5.5 a large (50μg/kg) bolus administration is observed to track CO to the new setpoint. Give the magnitude of a bolus administration, there is more drug available within that 30 sec period for the physiological system to respond. In the case where target CO was incremented from 50 to 85% of baseline in three step increments, an increase in onset delay is observed as step changes occur because controller administers smaller bolus doses (less drug available within the 30 sec bolus administration period). This causes a delay in system response relative to the case where setpoint is incremented from 50 to 85% of baseline in one step increment. The controller chooses between a bolus and an infusion rate, and furthermore the magnitude of the bolus after the error has been analyzed; this is explained in detail in section 2.3. Therefore it is observed that the choice of the magnitude of the bolus dose affects the onset delay.

Also CO error reaches 2.5 % target CO in about one minute. Unlike the previous three-step increment to 85% baseline CO, it takes 1/5 of time for CO error to reach desired range in this one step increment. This also is attributed to the magnitude of the bolus dose administration. The larger bolus brings CO error within desired boundaries quickly relative to the small bolus administration. The percentage overshoot of CO from

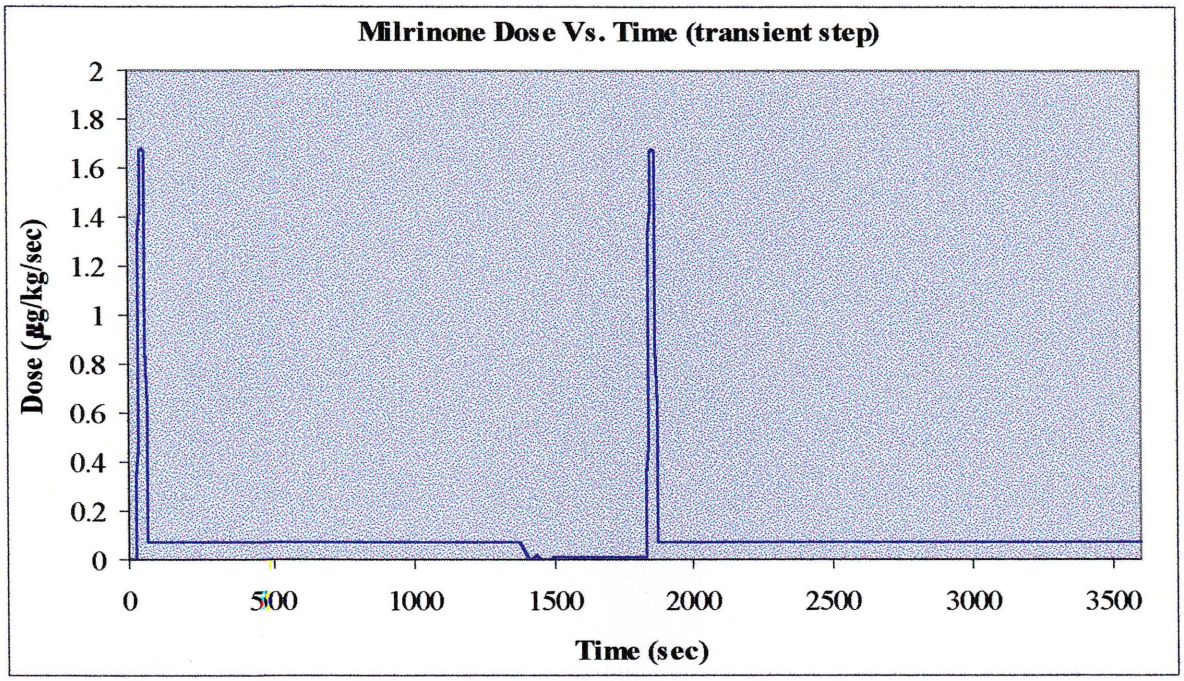

Figure 5.5 Infusion rate of milrinone as one step transient response is observed. The peaks are the bolus doses. The magnitude of the bolus is calculated by multiplying the dose by 30 sec, because each bolus is administered over a 30 sec period.

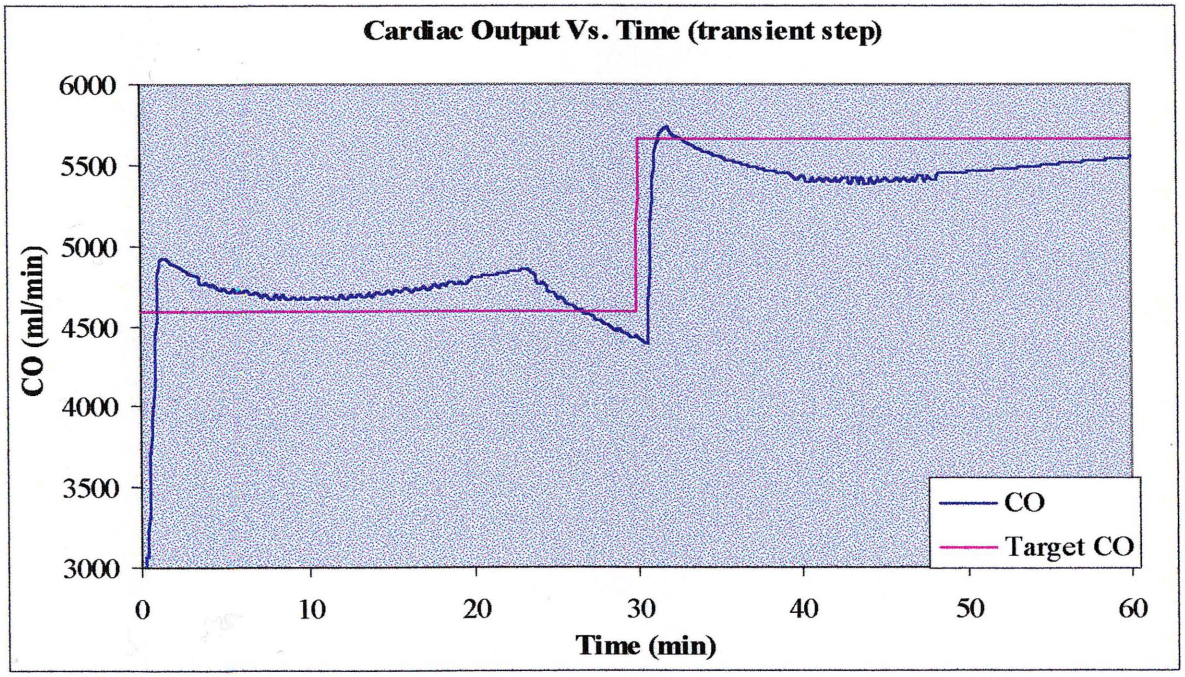

Figure 5.6 CO as a function of time as one step transient response is observed.

target is also less, it is observed to be 1.47%. In Figure 5.6 the controller shows to quickly maintain CO to the new setpoint by adjusting milrinone dose without causing excessive overshoot.

In both transient step changes from 50 to 85% of baseline CO (3-step increment, 1 step increment), the controller is observed to adjust to new target by responding with a change in milrinone dose. Depending on how much of a transient step change has occurred, the controller responds accordingly. On an average the controller begins to administer drug 22 sec after the change for setpoint has been made. Also when comparing the onset delay of the transient response to the onset delay with no change to the system, Table 5.1, the controller maintains transient step control. In addition, the percentage overshoot is observed to decrease each time transient step change occurred within the two-hour control period for the three transient step simulation test.

Transient control showed the controller to be robust in maintaining CO at the new setpoint when incrementing in stepwise manner. An additional transient control simulation was performed where the target was ramped from r_o to a constant value over a period of 7 min, r_o is given 50% of baseline and the constant value is given as 85% of baseline. VisSim ramp block was used to increment the setpoint using a slope of 2.5. The ramp block creates a unit ramp signal based on simulation time. The ramp block is expressed as $y = slope^* (t-t_{delay})$. The setpoint was limited to constant value by the use of VisSim limit block. The VisSim block diagram representation can be seen is Figure 5.7. Figure 5.8 and Figure 5.9 are plots of milrinone dose and cardiac output during the one hour control period. The setpoint is ramped after 30 min of control as seen in Figure 5.9. An onset delay of 4 sec is recorded prior to the initial response of the system.

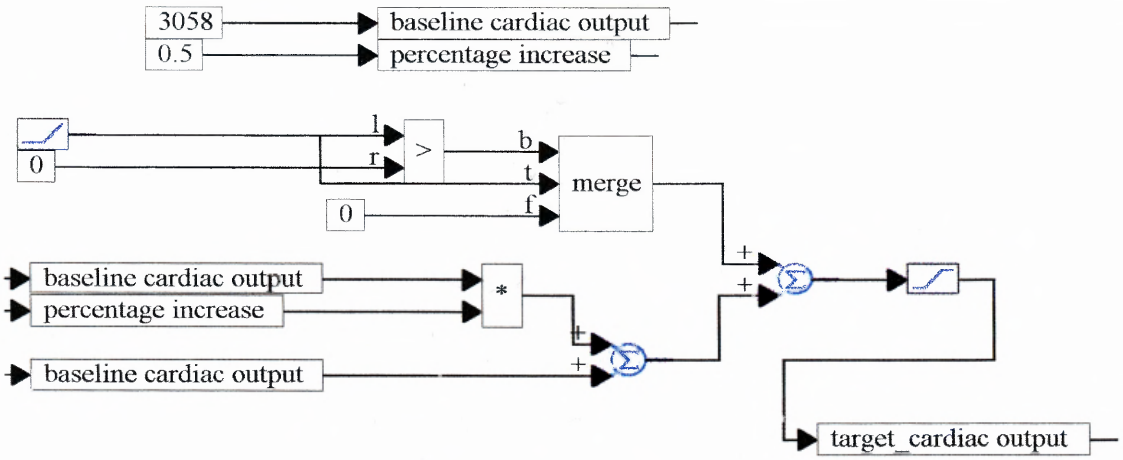

Figure 5.7 VisSim block diagram representation of ramped target CO transient response

To maintain CO to the changing setpoint the controller continuously administers small bolus followed by an infusion rate as shown in Figure 5.8. The drug administration is not stopped as target is ramped. The administration of the small bolus dose and infusion rates is evident in Figure 5.9, because there are peaks observed in CO as it is increased with the ramped target CO. The controller begins to administer milrinone 46 sec after the initial target CO change. In comparison to the step change, 22 sec, it takes longer for the controller to respond to the ramped change. Also, from Figure 5.9, it is observed that CO does not overshoot. But after the seven minutes of ramped signal, when target CO has reached the constant value, it takes 116 sec for CO error to be within the 2.5% target CO range. The results of the step and ramped transient control are summarized in Table 5.2. From both the plots and the result table the controller proves to respond to changes in the CO target by adjusting the infusion of milrinone. The CO is observed to be maintained within set boundaries without an oscillatory behavior. Therefore this test shows the controller to be robust in monitoring and controlling CO by milrinone infusion.

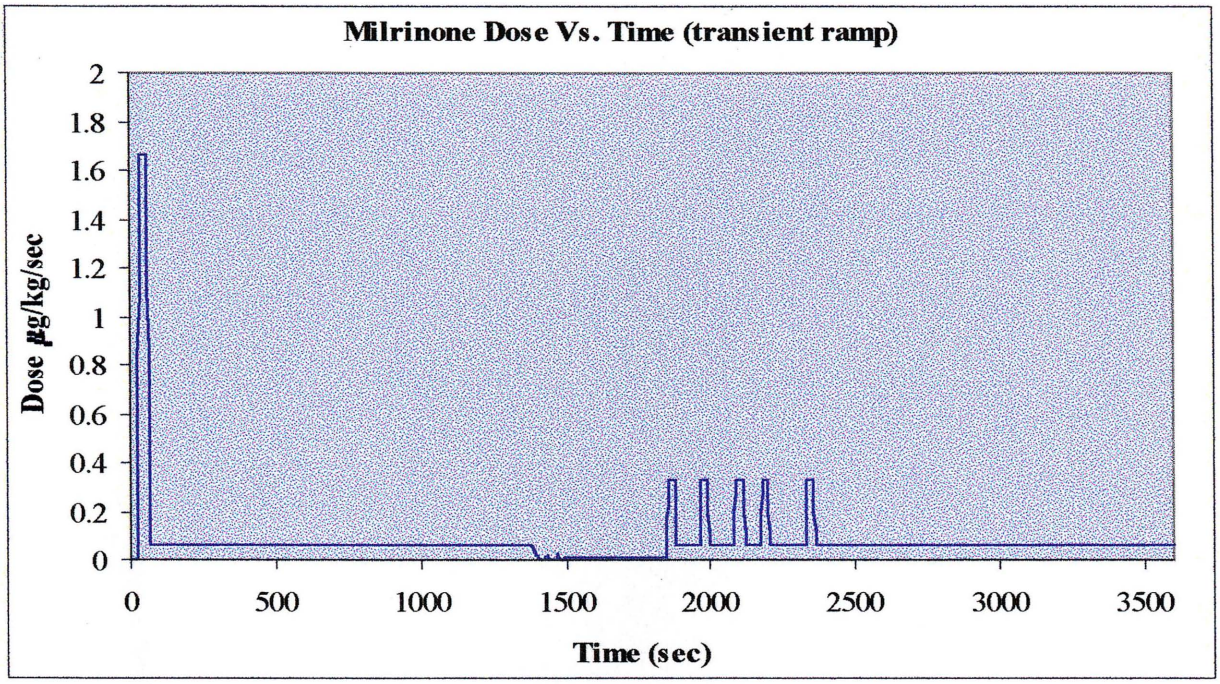

Figure 5.8 Infusion rate of milrinone as ramped transient response is observed. Th peaks are the bolus doses. The magnitude of the bolus is calculated by multiplying th dose by 30 sec, because each bolus is administered over a 30 sec. period.

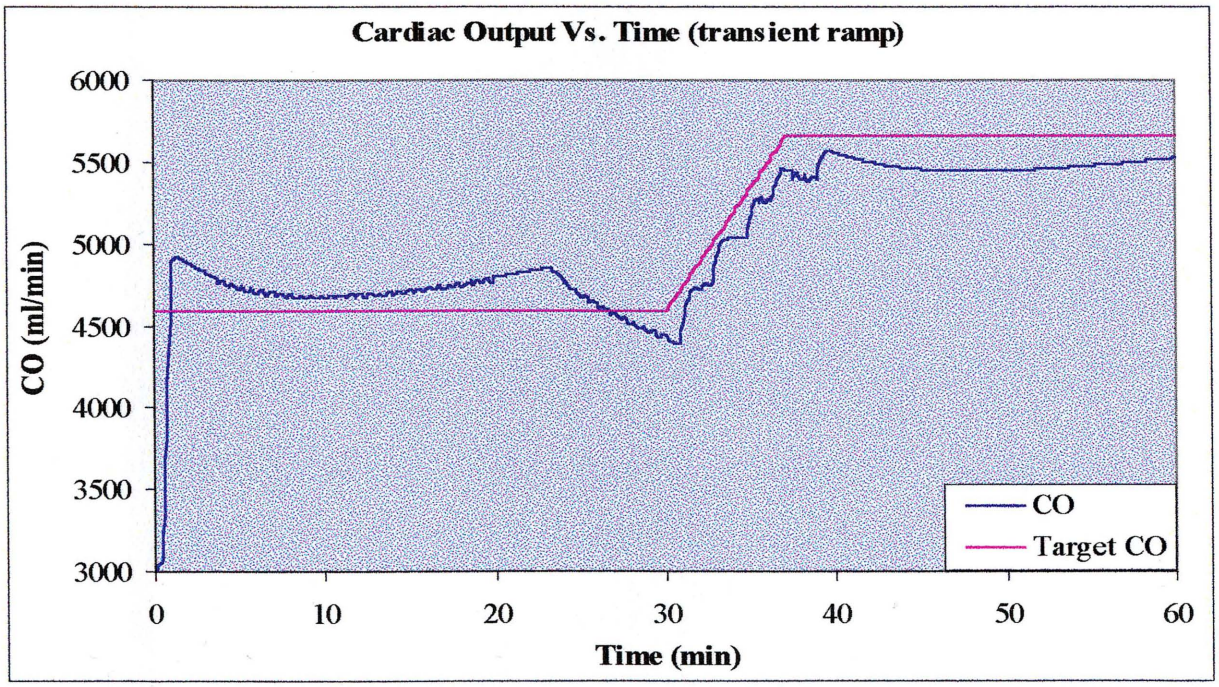

Figure 5.9 CO as a function of time as ramped transient response is observed.

Table 5.2 Summarizes the transient response of the cascade controller as target CO (T_CO) is changed

TRANSIENT RESPONSE					
Properties	Step				Ramp
T_CO % increase From baseline	55%	65%	85%	85%	in 7 min 50-85%
T_CO % increase from previous T_CO	153ml/min 3.33%	305ml/min 6.45%	611ml/min 12.12%	1070ml/min 23.33%	increases, slope= 2.5
T_CO change (sec)	1798	3595	5390	1797	1800
Controller response (sec)	1825	3622	5391	1832	1846
System response (sec)	1830	3637	5406	1833	1850
Onset delay (sec)	5	15	15	1	4
Time error between ± 2.5%T_CO Time taken (sec)	1858 60	3734 139	5705 315	1858 61	N/A
% Overshoot from T_CO	5.00%	3.67%	2.10%	1.47%	none

5.3 Perturbation

This second simulation test observes the effects caused as perturbation or a disturbance is achieved by changing the resistance parameters in the circulatory system in the physiological model. The resistances of the following are changed: systemic capillaries, venules, vena cava, pulmonary capillaries, and pulmonary venules. All resistance parameters are changed by the same factor. A two-hour simulation test was performed to test the effect of resistance disturbance. Changes to the simulation were as follows. In the first half-hour the system ran with no change (disturbance). In the second half-hour all resistance parameters were reduced to half of the original values. In the third half hour parameters were set back to their original values. In the final half hour the resistance parameters were increased to twice the original value. Figure 5.10 and Figure

5.11 are plots of milrinone dose and cardiac output during the changes of the resistance parameters.

The first half-hour the system was simulated using the original values for the resistances in the circulatory system, hence there was no change in the system. Change or perturbation was introduced to the system the second half-hour, the resistances were reduced by half. With a reduction in the resistance of the circulatory system, the blood is able to circulate through the body easier using the same or weaker contractile force from the heart. There is less strain on the heart because it does not have to work as hard. Producing an increase in cardiac output and therefore there is less, if any, need for drug administration. This is evident between 30 and 60 minutes of control as shown in Figures 5.10 and 5.11. When reduction in circulatory resistance is made CO immediately rises above target CO. Since CO is above target CO, cascade controller stops milrinone administration. Figure 5.11 There is no drug administration during this half hour therefore obtaining values for onset delay and time CO error reached set range were not applicable during this period. An overshoot of 14.23% percent was observed. This overshoot is not a direct cause of the controller response after the disturbance because no drug was given at this period. Instead it is caused by the drug that was available in the body before the disturbance and more importantly the CO increase that occurred due to the lowering of circulatory resistances. .

At the start of the second hour resistances are set back to their original values. This returns CO below target. Controller begins milrinone administration in response to the change. The onset delay and the time taken for CO error to reach 2.5% of target CO are 15, and 50 sec.

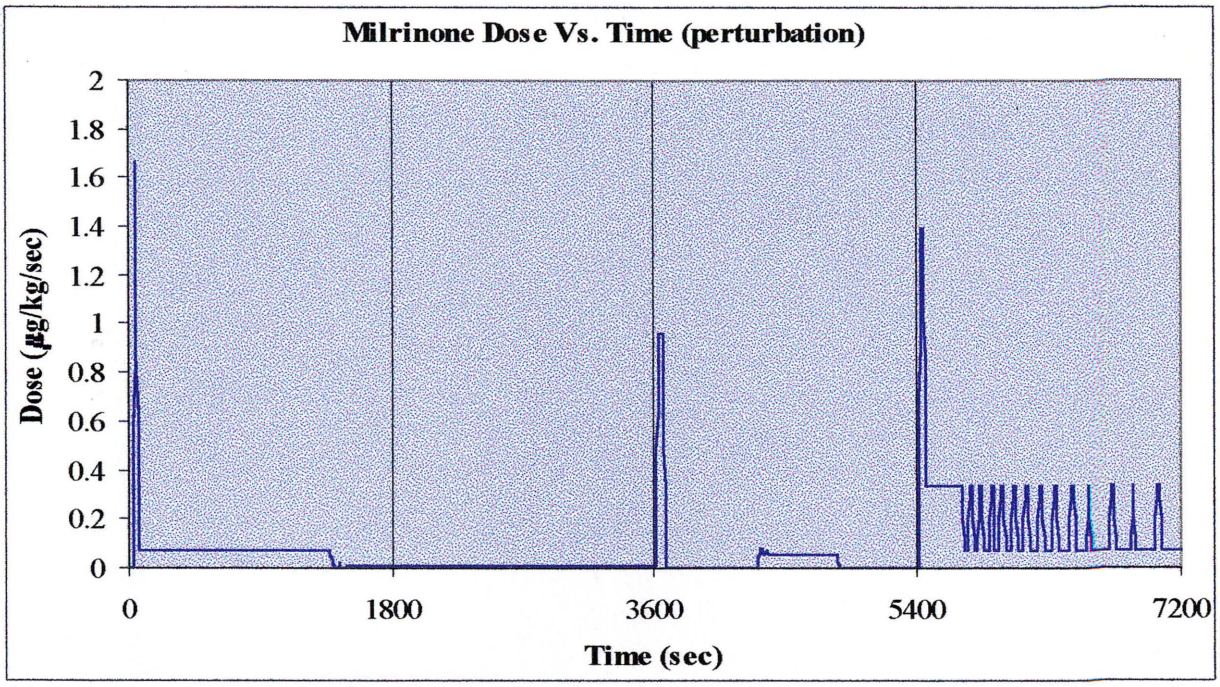

Figure 5.10 Infusion rate of milrinone as perturbation is achieved by changing the vesse resistances of the circulatory system. The peaks are the bolus doses. The magnitude o the bolus is calculated by multiplying the dose by 30 sec, because each bolus i administered over a 30 sec. period.

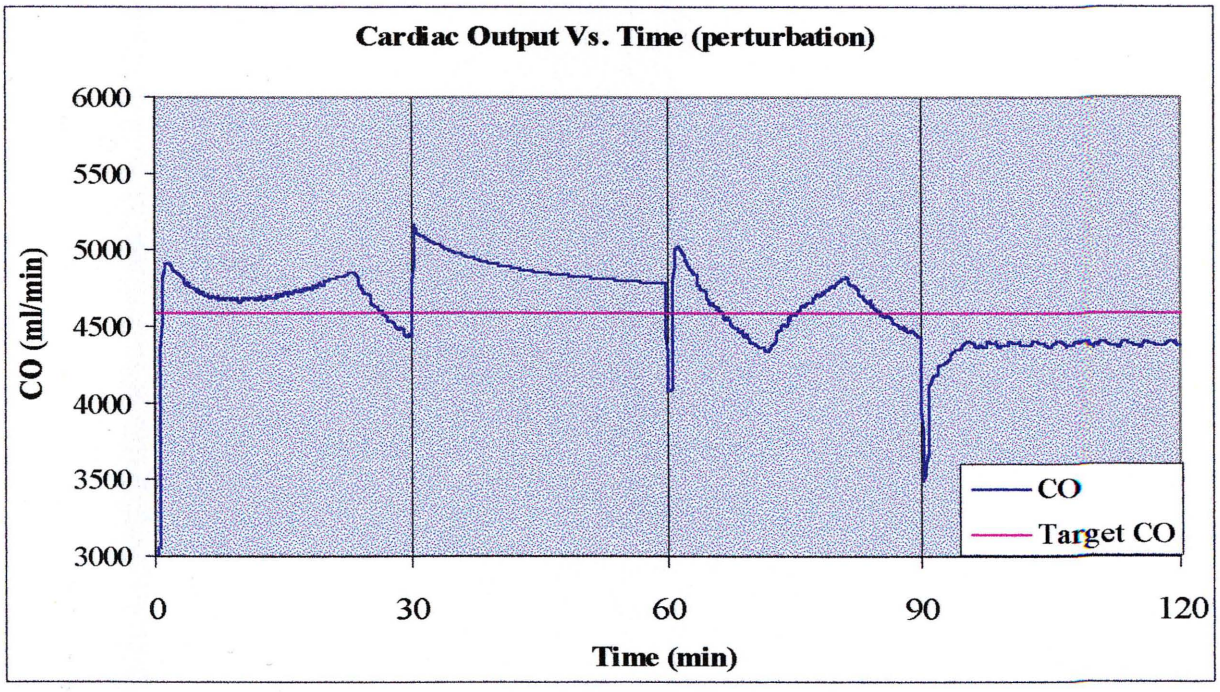

Figure 5.11 CO as a function of time as perturbation is achieved by changing the vesse resistances of the circulatory system.

The onset delay agrees with previous simulation test results in Table 5.1. The time for error to reach the 2.5% boundary again shows the controller to quickly adjust drug infusion to changes in the system.

The fourth and final half-hour, perturbation is again achieved by increasing circulatory resistances by twice the original value. With an increase of these resistances, blood is expected to circulate using a stronger contractile force from the heart. Cardiac output decreases. More strain on the heart exists causing an increase in demand of drug administration as seen in Figures 5.10 and 5.11. The results of the perturbation test simulations are seen in Table 5.3. An increase in the resistance immediately drops CO below target, the controller responds by adjusting milrinone dose. The onset delay of the system after the disturbance has been introduced is 13 sec. The controller begins drug administration with an initial bolus dose of 50 μg/kg. This bolus dose brings the CO error within 5 to 10% of target CO. The controller continues to administer drug at maximum small bolus doses (10μg/kg). Milrinone is administered as continuous bolus doses, in fact it appears to be a better representation of an infusion rate. The magnitude of the small bolus dose appears to be insufficient in bringing error CO within 2.5% of target CO during the half-hour, although the controller is maintaining CO in a stable, smooth curve. The controller is administering drug at the maximum magnitude (10μg/kg) but it appears that this dose (given when 5% target CO $<$ CO error $<$ 10% target CO) fails to bring CO error within 2.5% of target CO. Indeed as the resistances are doubled, the performance of the controller drastically degrades because the controller fails to bring CO within set boundaries, if not target CO. The controller is working at its

Tables 5.3 Summarizes controller performance as circulatory vessel resistances (perturbation) are changed. T_CO is target CO

PERTURBATION RESPONSE				
Properties	1st half hour	2nd half hour	3rd half hour	final half hour
	Original	Reduce by 1/2	Original	Increase by 2
Disturbance time (sec)	Original at 0	1797	original at 3595	5390
Controller response (sec)	28	no drug given	3623	5420
System response (sec)	30	N/A	3638	5433
Onset delay (sec)	2	N/A	15	13
Time error between ± 2.5%T_CO Time taken (sec)	50 22	N/A	3645 50	Doesn't reach range in Simulated time
% Overshoot from T_CO	7.15%	14.23%	9.44%	N/A

full potential as is seen in Figure 5.10. Given that the CO error falls between 5 and 10% of target CO the controller can administer small bolus dose with maximum magnitude of 10 μg/kg. From the milrinone plot it us observed that the controller continuously administers maximum bolus doses so that CO reaches the desired setpoint. Although the controller is successful in both increasing and stabilizes CO, the CO increase does not reach the desired target range. This reduction in the performance of the controller is due to the magnitude of the limit for the small bolus dose rather than the cascade controlling mechanism itself. The cascade controller is successful in responding to the disturbance by increasing the administration of drug as well as maintaining a stabile or smooth CO response. It is the limit of 10 μg/kg bolus dose that prevents the CO from rising to target in reasonable amount of time (5 minutes). In addition the limit set for the infusion rate might also prevent CO from rising to target CO in necessary time.

5.4 Randomization

Randomization is the third change in the system that is done in understanding the performance of the controller in realistic situations. The third test is performed by randomizing the elimination rate constant, k_{10}, as a two hour control period is simulated. This simulation test can represent the situation where a patient characteristics change during the administration of the drug. Four simulation runs are performed. The rate of drug elimination is changed every one minute and five minutes under set standard deviation (25% and 50% of original value) and mean (original value).

Randomization of k10 is achieved with the use of VisSim gaussian random generator block. The gaussian block creates a normally distributed random signal. The original vale of k_{10} was chosen as the mean and the value was randomized using standard deviation (1) 25% and (2) 50% of the original value. Each value was held for one minute and five minutes before a next guess was made. Minimum of one-minute samples was chosen because anything smaller would cause the value to change too quickly for any effect to be noticed. In the case where the values are randomized and held for less than a minute, the change would be too quick to effect the system. Because the value of k_{10} would change to rapidly for the system to notice the change and thus be effected by the change. Since k_{10} would oscillate some standard deviation from the original value, the change would be so quick that the system would be effected by the mean of the changed values: that value being approximately the original k_{10}. The k10 guess was sampled and held with the use of VisSim sampleHold block. The VisSim pulseTrain block was input

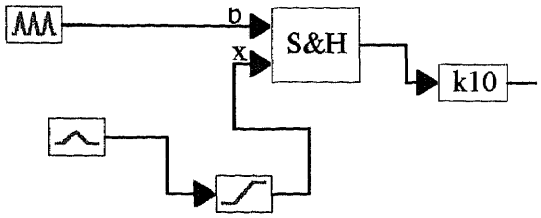

Figure 5.12 VisSim block diagram of randomizing elimination rate constant,k_{10}

into the sampleHold block that determines how long the signal is held. The pulseTrain block produces a sequence of unit amplitude pulses separated by zeros.[27] The signal, the other input into sampleHold block, is the random guess for k_{10}. The VisSim block diagram representation can be seen in Figure 5.12.

Four randomization tests were simulated; (1) standard deviation (STD) = 25% of original value of k_{10}, 1 minute hold, (2) standard deviation (STD) = 25% of original value of k_{10}, 5 minute hold, (3) standard deviation = 50% of original value of k_{10}, 1 minute hold, and (4) standard deviation = 50% of original value of k_{10}, 5 minute hold. The onset delay, time CO error reached 2.5% of target CO, and percentage overshoot of CO from target were recorded each time the controller began milrinone administration during the

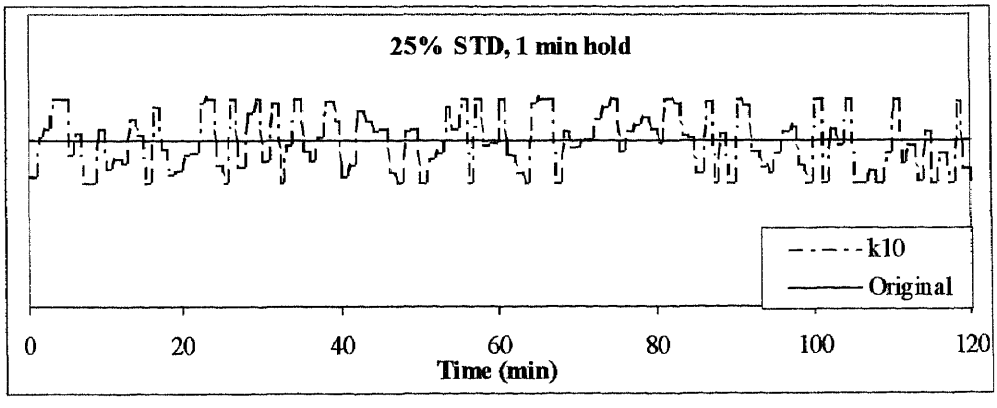

Figure 5.13 plots the randomization of k10 using a standard deviation of 25% of original value and guess is held for one minute before next guess is made

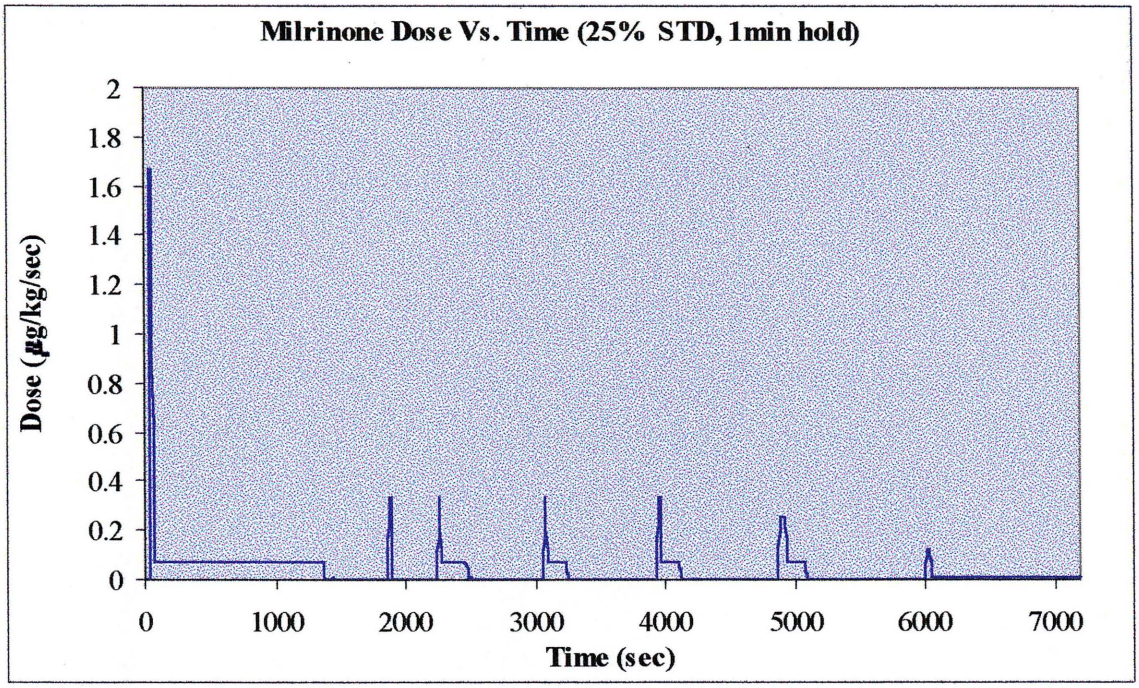

Figure 5.14 Infusion rate of milrinone as k_{10} is held for 1 min with a standard deviation of 25% of original value. The peaks are the bolus doses. The magnitude of the bolus is calculated by multiplying the dose by 30 sec, because each bolus is administered over a 30 sec period.

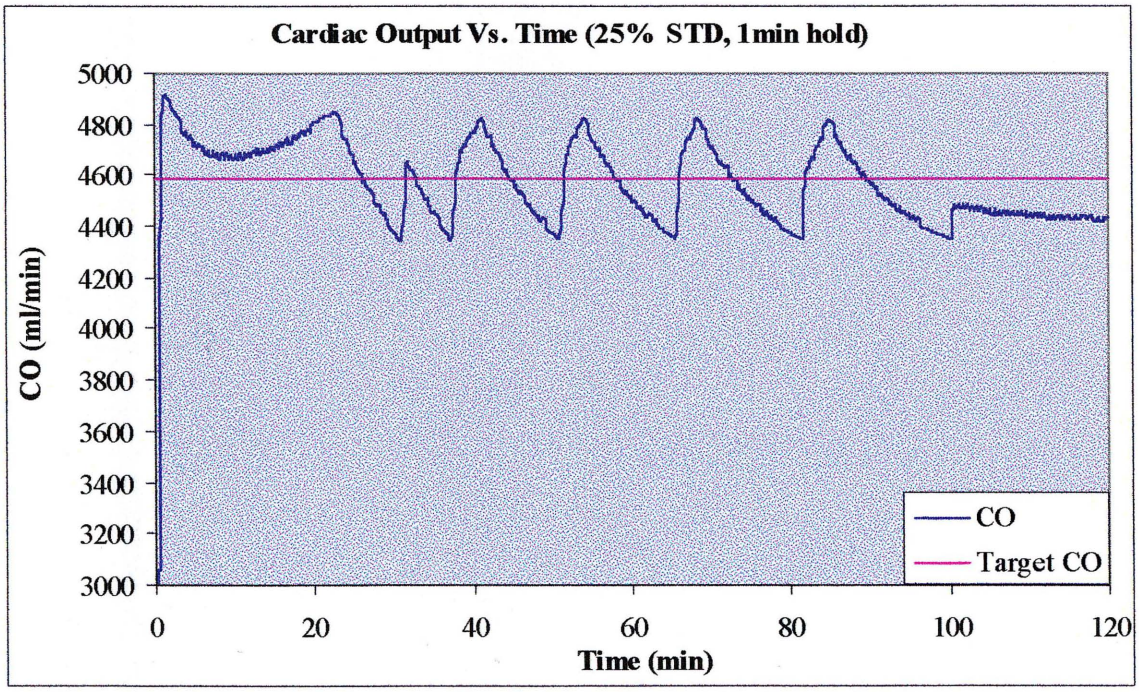

Figure 5.15 CO as a function of time as k_{10} is held for 1 min with a standard deviation o 25% of original value

two hour control period for each simulation trial. The plot that shows how k_{10} is randomized using a 25% of original value as STD and holding the guess for 1 minute is shown Figure 5.13. This plot shows how indeed randomly the next guess for k_{10} is made, there is no set pattern. In other words there is no mechanism for the controller to prepare for the next guess, therefore the controller has to continually adjust to the change. This is a good representation of how patient response to drug can vary within the drug administration. Figure 5.14 and 5.15 are plots of milrinone dose and CO in the controlling period as k_{10} is randomized. Table 5.4 summarizes the observations from this simulation. The onset delay each time drug was given is within 2-12 sec range that was observed when simulating the system under no changes using optimized gains, Table 5.1. The average time it takes for the CO error to reach within the 2.5% target CO range is 22 minutes. The average for this simulation, 22 sec, not only agrees with the reference average value of 25 sec, but is less as well. Also the percentage overshoot is observed to decrease each time drug administration is begun during the control period. It is observed to be 7.15, 5.16, 5.18, 5.07, and 5.03% for the six distinct times milrinone was given. There is an overall decrease in CO overshoot.

Table 5.4 Summarizes controller performance as k_{10} is held for 1 min with a standard deviation of 25% of original value. T_CO is target CO

k10, 25% Standard Deviation, 1 minute hold					
Milrinone Administration	Controller response time (sec)	System response time (sec)	Onset Delay (sec)	Error between ±2.5% T_CO(sec), Time taken(sec)	% Overshoot from T_CO
1	28	30	2	50, 22	7.15%
2	2246	2250	4	2268, 22	5.16%
3	3061	3062	1	3083, 22	5.18%
4	3932	3944	12	3946, 14	5.07%
5	4886	4890	4	4902, 16	5.03%
6	6010	6020	10	6050, 40	None

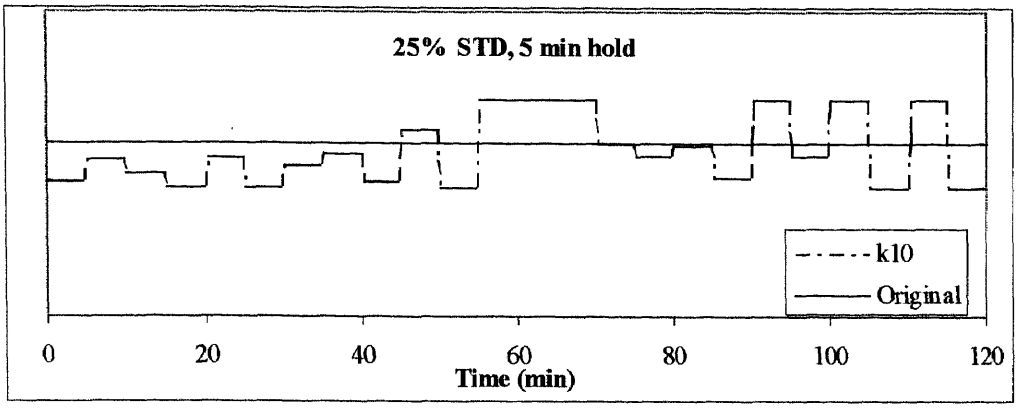

Figure 5.16 Plots the randomization of k_{10} using a standard deviation of 25% of original value and guess is held five minute before next guess is made

The pattern agrees with percentage overshoot observation outlined in Table 5.1. The elimination rate constant is again randomized with a STD of 25% of original value but here the guess is held for five minutes before the next guess is made, Figure 5.16. The plots for milrinone dose and CO during the control period for this simulation test as shown in Figure 5.17 and 5.18, respectively. Table 5.5 outlines the analysis made from these plots. The onset delay ranges from 2-15 sec. The average time taken for CO error to reach 2.5% of target CO is 24 min. The percentage overshoot of CO from target for the six distinct times of drug administration is 7.15, 5.01, 5.03, none, 5.14, and 4.02%. The results for the onset delay, time taken to reach desired setpoint, and percentage overshoot corresponds to results observed in Table 5.1. The randomization of k10 using a STD of 25% of original value for both the one and five minute value hold shows that the controller's performance does not deteriorate as randomization is incorporated into the system.

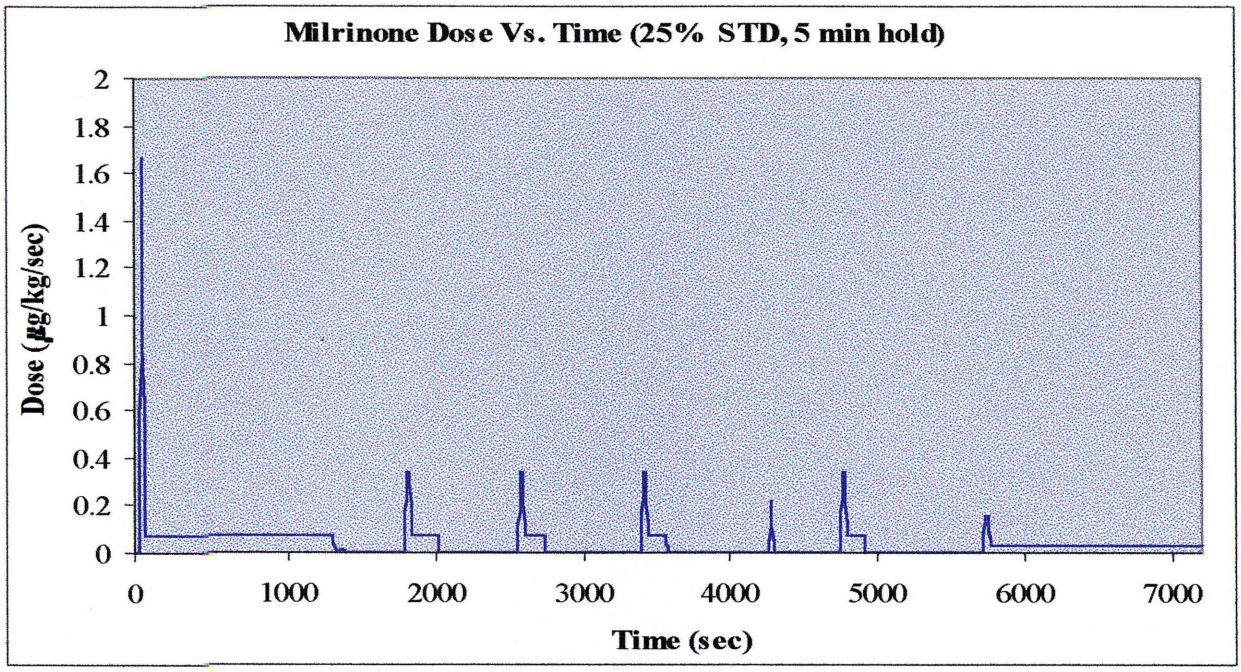

Figure 5.17 Infusion rate of milrinone as k_{10} is held for 5 min with a standard deviati of 25% of original value. The peaks are the bolus doses. The magnitude of the bolus calculated by multiplying the dose by 30 sec., because each bolus is administered over 30 sec period

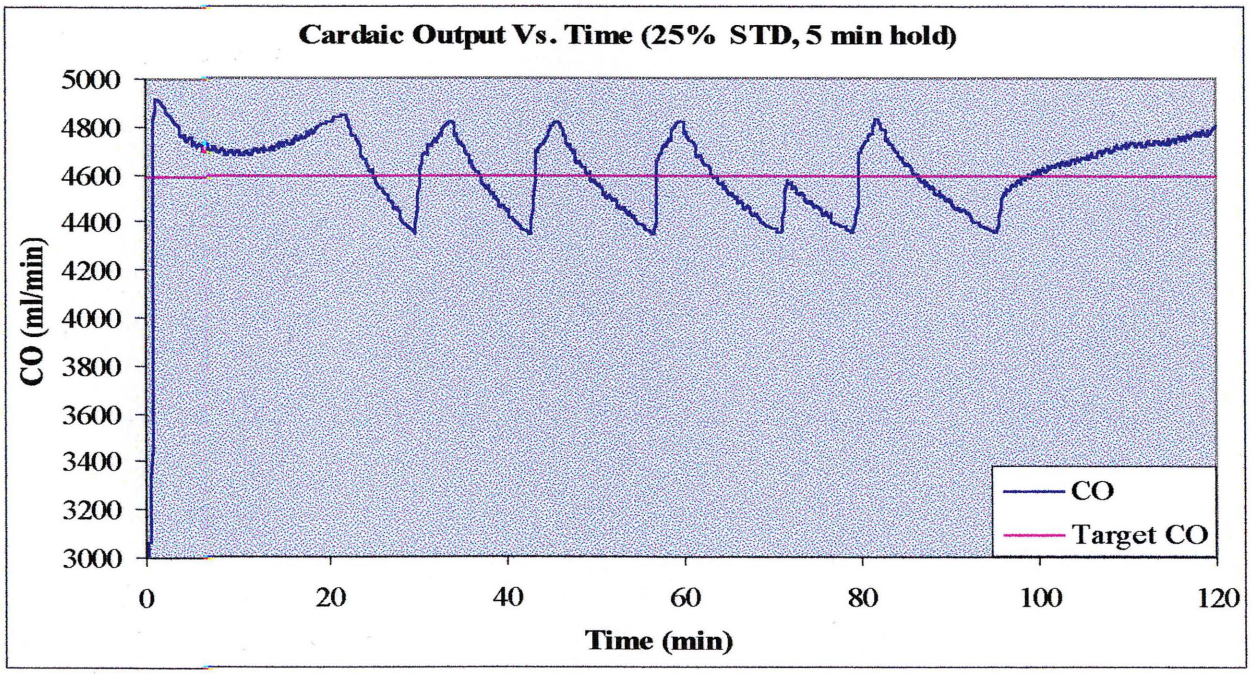

Figure 5.18 CO as a function of time as k_{10} is held for 5 min with a standard deviation 25% of original value

Table 5.5 Summarizes controller performance as k_{10} is held for 5 min with a standard deviation of 25% of original value. T_CO is target CO

k10, 25% Standard Deviation, 5 minute hold					
Milrinone Administration	Controller Response time (sec)	System response time (sec)	Onset delay (sec)	Error between ±2.5% T_CO(sec), Time taken(sec)	% Overshoot From T_CO
1	28	30	2	50, 22	7.15%
2	2555	2560	5	2578, 23	5.01%
3	3398	3400	2	3405, 7	5.03%
4	4255	4268	13	4290, 35	None
5	4746	4760	14	4770, 24	5.14%
6	5715	5730	15	5750, 35	4.20%

A third simulation test was performed using a STD of 50% of the original value and the guess was held for one minute. Figure 5.19 is a plot of k10 as it is randomized during the simulation. The plots of milrinone dose and CO during the control period are shown in figure 5.20 and 5.21, respectively. Table 5.6 is a summary of the observations from the simulation. The onset delay ranges from 2-16 sec for the five times milrinone administration was given. It takes an average 28.4 sec for the CO error to reach the desired setpoint. The percentage overshoot is observed as 6.82, 5.08, 5.03, 5.01, and 4.64% for the five times drug is begun.

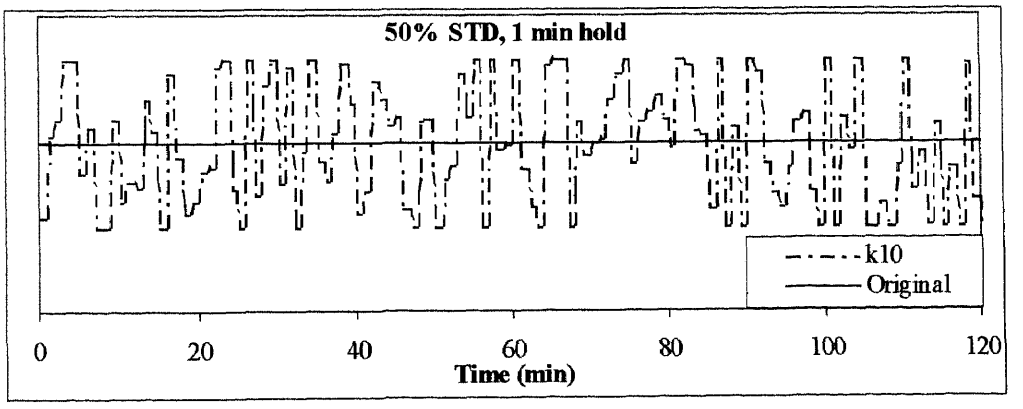

Figure 5.19 Plots the randomization of k_{10} using a standard deviation of 50% of original value and guess is held one minute before next guess is made

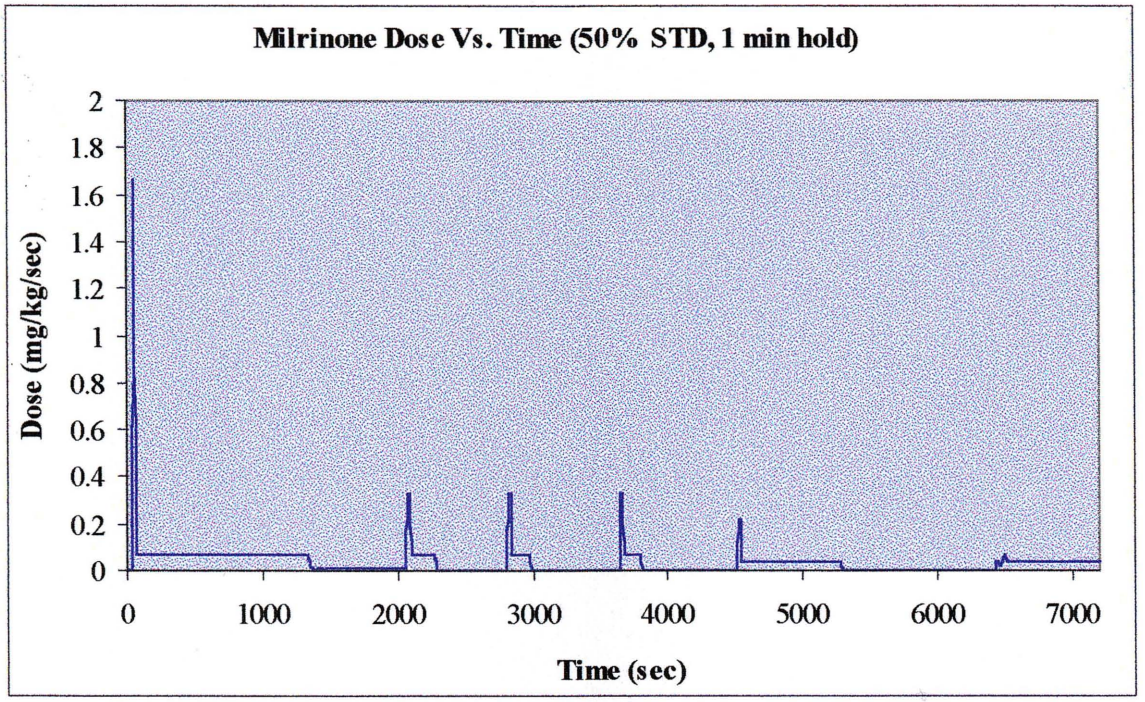

Figure 5.20 Infusion rate of milrinone as k_{10} is held for 1 min with a standard deviation of 50% of original value. The peaks are the bolus doses. The magnitude of the bolus is calculated by multiplying the dose by 30 sec, because each bolus is administered over a 30 sec period

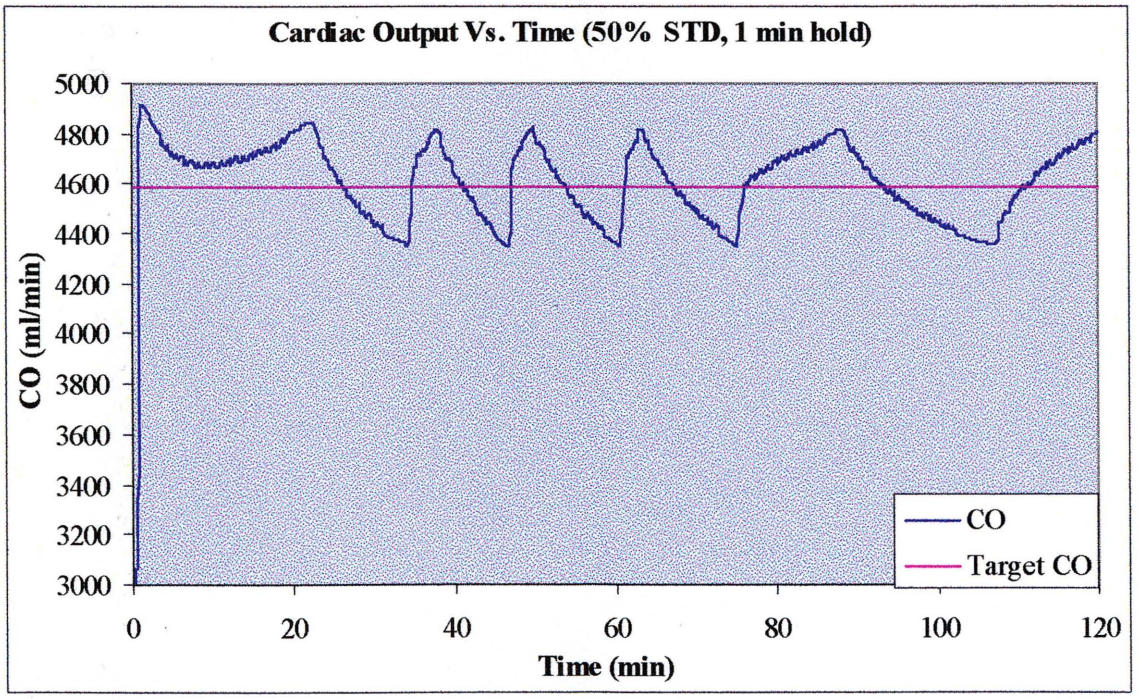

Figure 5.21 CO as a function of time as k_{10} is held for 1 min with a standard deviation of 50% of original value

Table 5.6 Summarizes controller performance as k_{10} is held for 1 min with a standard deviation of 50% of original value. T_CO is target CO

k10, 50% Standard Deviation, 1 minute hold					
Milrinone Administration	Controller response time (sec)	System response time (sec)	Onset delay (sec)	Error between ±2.5% T_CO(sec), Time taken(sec)	% Overshoot from T_CO
1	28	30	2	48, 20	6.82%
2	2794	2810	16	2815, 21	5.08%
3	3637	3640	3	3650, 13	5.03%
4	4507	4510	3	4530, 23	5.01%
5	6430	6445	15	6495, 65	4.64%

Analysis of these results again confirm that randomization does not degrade the performance of the controller. Comparison of these results to results obtained when simulating model without incorporating a change, Table 5.1, proves this.

The final simulation was performed again using a STD of 50% of original value while the guess was held for five minutes before next guess was made, Figure 5.22. Figure 5.23 and 5.24 are plot of milrinone dose and CO during the control period as the elimination rate constant is randomized. Table 5.7 summarizes the results of the simulation trail. Unlike the previous simulations, milrinone administration was begun two times in the two hours. The onset delay for the both administrations was 2 sec.

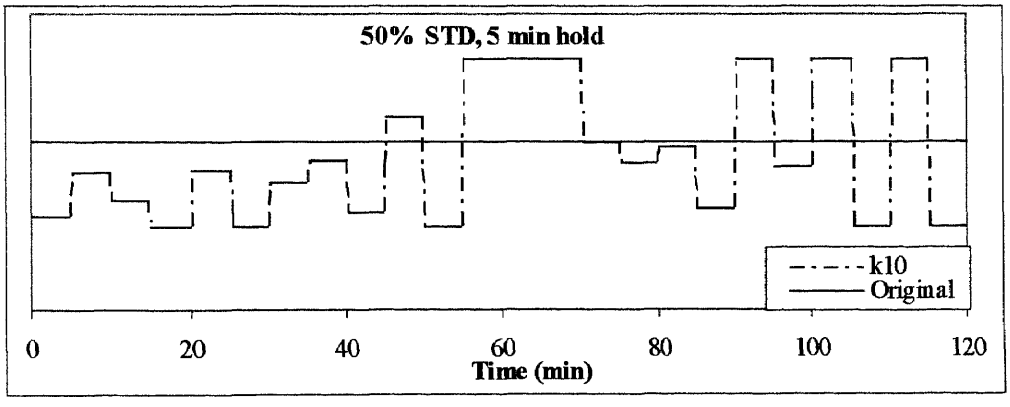

Figure 5.22 Plots the randomization of k_{10} using a standard deviation of 50% of original value and guess is held five minute before next guess is made

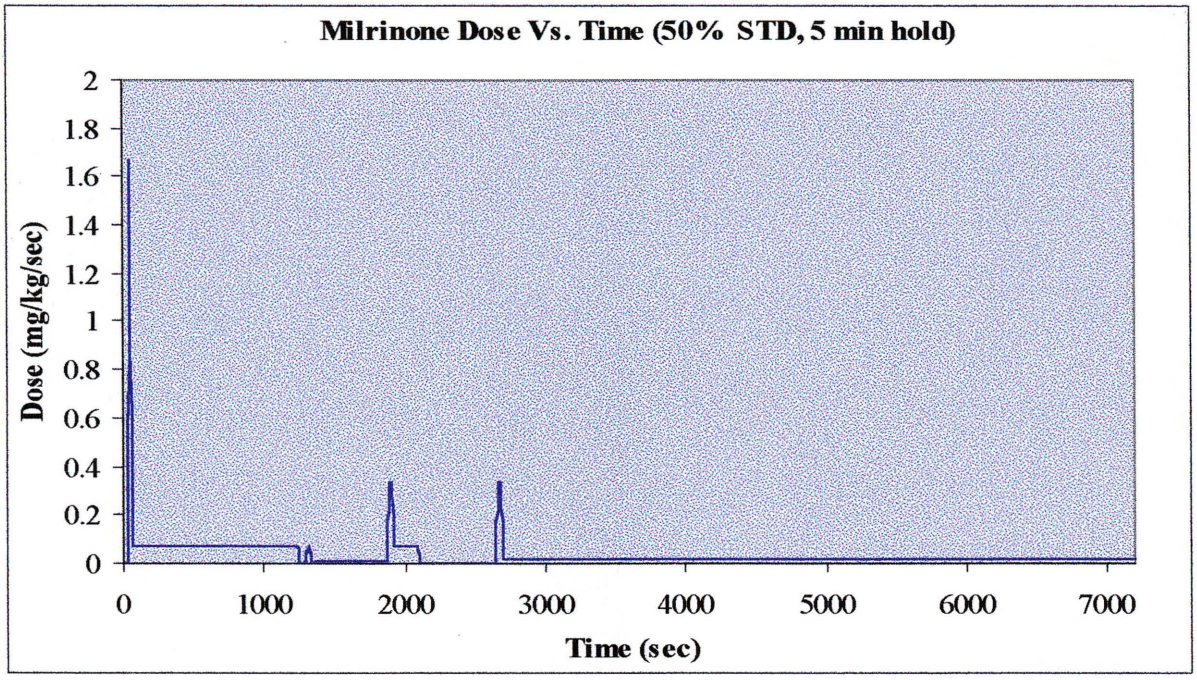

Figure 5.23 Infusion rate of milrinone as k_{10} is held for 5 min with a standard deviation of 50% of original value. The peaks are the bolus doses. The magnitude of the bolus is calculated by multiplying the dose by 30 sec., because each bolus is administered over a 30 sec period

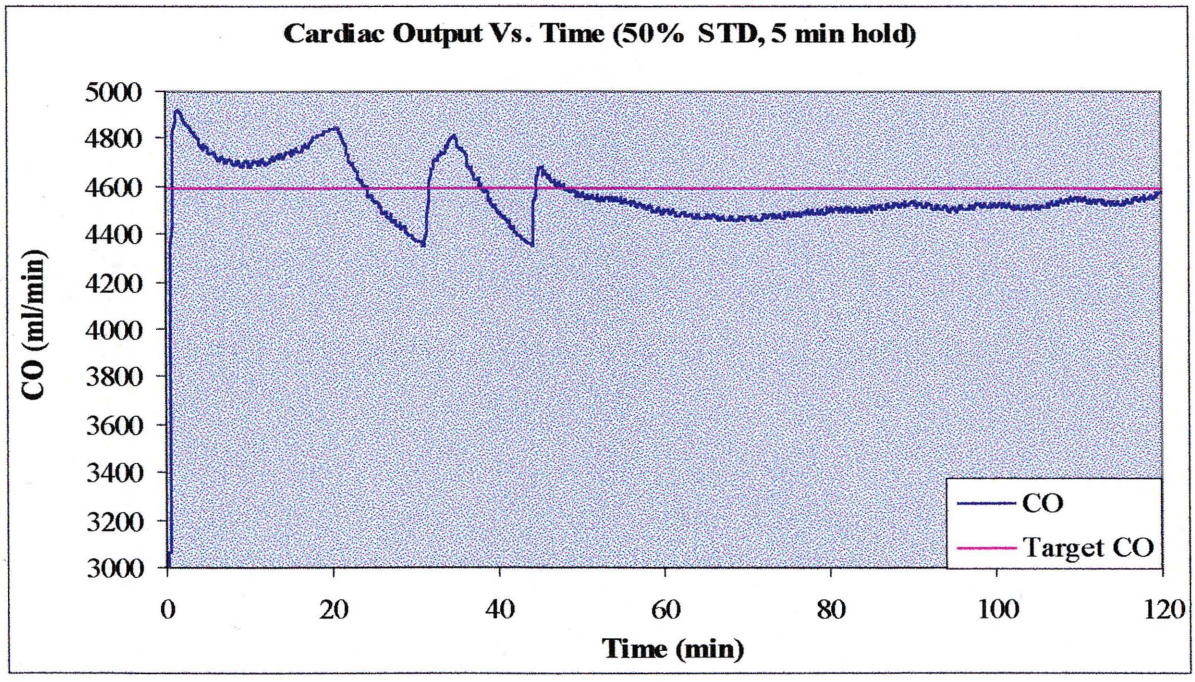

Figure 5.24 CO as a function of time as k_{10} is held for 1 min with a standard deviation o 50% of original value

It took an average of 16.5 sec for CO error to reach set boundary. Milrinone administration results in a CO overshoot of 7.21 and 1.91%. The CO plot, Figure 5.24, is a visible representation of the how the controller maintains a smooth and stable CO response toward the second half of the control period. The onset delay results again confirm with Table 5.1 listing onset delay time between 2 and 12 sec. The average time taken for CO error to be within range is less than 25 sec reference value. And finally the percentage overshoot behaves similar to previous results; it is observed to decrease with time.

Table 5.7 Summarizes controller performance as k_{10} is held for 5 min with a standard deviation of 50% of original value. T_CO is target CO

k10, 50% Standard Deviation, 5 minute hold					
Milrinone administration	Controller Response Time (sec)	System response time (sec)	Onset delay (sec)	Error between ±2.5% T_CO(sec), Time taken(sec)	% Overshoot from T_CO
1	28	30	2	51, 23	7.21%
2	2653	2655	2	2663, 10	1.91%

The findings from the randomization simulation studies performed using the rate constant k10 as the randomizing factor prove that the controller can maintain CO response to set boundaries by adjusting drug infusion when a parameter in the system is continuously varied during the control period. The results for each simulation were compared to simulation results obtained in sec 5.1, the case where system was simulated when no change had occurred. The behavior of randomization of the elimination rate constant models the patient varying pharmacokinetic response of eliminating the drug from the blood. These simulations monitor the cascade controller performance given a simulated condition of how a patient response or characteristics can vary within the drug

administration. All simulation results confirm that the controller can adjust milrinone infusion to maintain CO response within setpoint limits as a parameter is varied with time. In fact, in the four simulation studies, the controller was observed to bring CO error to setpoint range in less than half a minute. This result shows a very responsive and quick controlling mechanism. In addition there was a decreasing pattern observed for the percentage overshoot of CO in all simulations. Here it is observed that the controller goes through a learning process in the controlling period because it can better maintain a smooth and stable CO response with time.

The three simulation tests, transient response, perturbation, and randomization, helped to better understand the performance of the cascade controlling mechanism using to monitor cardiac output of congestive heart failure patients by milrinone infusion. On the same note, the results convey the robustness of the controller as well as the necessary refinements.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

The objective in this thesis was the design and testing of a simulated closed loop drug delivery system. The focus was the administration of milrinone used to maintain cardiac output for congestive heart failure patients. The CLDD system consists of a pharmacokinetic model, physiological model, and feedback-controlling model.

Prior to simulating the controller's performance in maintaining CO, system dynamics were observed. An analysis of system dynamics was observed to see if an open loop CHF patient model responded to milrinone administration in the same manner as available experimental data. The open loop dynamic model (milrinone PK, and physiological model) was simulated as four different bolus doses were given. In addition to comparing CHF open loop dynamic model results to available experimental data, an open loop dynamic model was simulated for a normal patient as well. Simulation results of "context- sensitive" elimination times, efficacy time, CO response, and MAP response confirm that the behavior of the open loop dynamic model is similar to experimental research available for CHF patients under milrinone administration. Therefore the open loop dynamic model of the CHF patient is an accurate representation of clinical situation. This open loop model can be further used to understand the responses of varying dose regimens of milrinone. In addition to understanding the appropriate bolus administration in achieving a certain response, research can be done on effects of different infusion rates of milrinone as well. In fact this model can be used to describe the best combination of bolus and infusion rate of milrinone in obtaining a desired response. The focus in the dynamic study was on milrinone plasma concentration, CO response, and MAP response.

The focus can also be extended to include the effect of milrinone on heart rate, systolic arterial pressure, diastolic arterial pressure, contractile force, etc. With additional responses monitored, one gets a better picture of the effects of milrinone administration on the CHF patient. Since the simulated observations from milrinone plasma concentration, CO response, and MAP response agree with previous clinical studies, there is more room available for further simulated analysis of milrinone administration for CHF patients.

After the validation of the open loop dynamic model, optimization of PID parameter gains was performed. The optimized gains were chosen as 0.01, 0.0001, and 0.01 for the P, I, D gain, respectively. The variation of the parameter gains did not show drastic differences in maintaining CO because the second controller adjusted the PID output and fed it into the PK model as a milrinone dose. Instead there were obvious changes observed in the PID controller output, rather than the cascade controller output. But the analysis was done to obtain minimum CO error as PID parameters were modified. Therefore the means of choosing the optimized PID parameter gains were sufficient.

Dynamic analysis and optimization of the PID controller led into the testing of the simulated CLDD system. The CLDD system underwent three tests, observing the controller performance in maintaining CO for each test. The results were compared to the simulation test of the CLDD system using optimized parameter gains; these results are referred to as the reference simulation test.

The most successful of the three tests was the randomization of the elimination rate constant during the two hour controlled drug administration. Success was measured

primary by how long it took controller to bring CO error to within 2.5% of target CO and what the percentage overshoot of CO was each time drug administration was begun during the control period. During randomization of k10, the controller brought the CO error within set boundaries in less than half a minute and a decreasing pattern was evident for the percent overshoot. Both of these observations confirm with the results of the reference simulation. Therefore the controller maintained its performance as a drug elimination rate was varied throughout the control. Its controlling mechanism did not deteriorate due to the incorporation of a randomizing factor. To further validate these findings, additional rate constants can be randomized as responses are recorded. Also randomization should be further implemented into parameters of the physiological model. This simulation test looked into the controller's response as a pharmacokinetic parameter was continuously modified. The results confirm the cascade controller's ability to continuously adjust to the changing PK model and therefore an expansion can be made to the parameters that can be randomized, leading into further understanding of the controller and of the CLDD system as a whole.

The observations of the remaining two tests show the controller to be robust in maintaining CO by adjusting milrinone infusion. The results of the transient response and perturbation tests are in common in the sense that the controller's performance degrades at certain times within the controller period. The controller's performance is not deteriorated by the fact that it can not adjust to the change in the system. But the performance is deteriorated by how quickly the controller can bring CO error within the set range. From the plots in sec 5.2 and 5.3 it is observed that although the controller fails to bring CO to set boundaries, it is administering drug at the maximum magnitude

(controller is working at its full potential). This shows that the controller is aware of the difference between the target CO and the true CO, and thus is continuously administrating milrinone at the maximum magnitude specified by the second controller given how far the error is from target. Therefore it is realized that the deterioration of controlling mechanism is not to blame on the cascade controller, but its decay lies in the magnitude limits set for the drug administration. Specifically, the limit of the small bolus doses (10μg/kg) given when CO error is between 5- 10% of target CO contributes to the performance degradation. A solution would be to increase the magnitude of the small bolus, but this would also introduce an increase in CO overshoot when the error lies in the lower portion of the range. A better solution would be to increase the available paths that the PID output can take before being fed into the PK model as milrinone dose. In other words refinement of the second controller is necessary. Presently, the second controller takes the PID output and implements it either as a larger bolus with a limit of 50 μg/kg, a small bolus with a limit of 50μg/kg, or an infusion rate with a limit of 4μg/kg/min. The distinction between what path the PID output will take depends on how far the CO error is from the target CO. Further system dynamic study is necessary in understanding exactly what magnitudes of bolus and infusion rate administration are necessary to bring the CO to the required setpoint range. Then the second controller can better understand what magnitude of drug administration is necessary in quickly maintaining CO response to the target. Therefore there would be more appropriate paths for the PID output to take before fed in as a milrinone dose. This refinement in the system will also improve the overall response of the controller, not just when it fails to bring CO to the setpoint in the necessary amount of time (5 minutes). Aside from this

weakness in the CLDD system, the controller performance matched the performance of the reference simulation test.

The CLDD system model was tested under three varying conditions. The overall performance of the controller maintains the output response to the setpoint by adjusting the infusion of the drug. But along the way limitations of the system were observed and thus refinement was necessary. In this thesis, as is the case in many other theses, what is important is not that the student's research has brought about a sufficient solution to what he/she has tried to develop or understand, but that the student grasps an understanding of the limitations and thus realizes the necessary refinement to his/her thesis. In doing so the end result is not only developing the simulated CLDD system, but also understanding how it can be improved to better meet the performance requirements. Therefore this thesis involves the development, testing, and room for improvement of a simulated closed loop drug delivery system used to control the infusion of milrinone for congestive heart failure patients. In addition it leads to the possibility of the development of an automated milrinone infusion system used to maintain CO for patients suffering from CHF.

APPENDIX

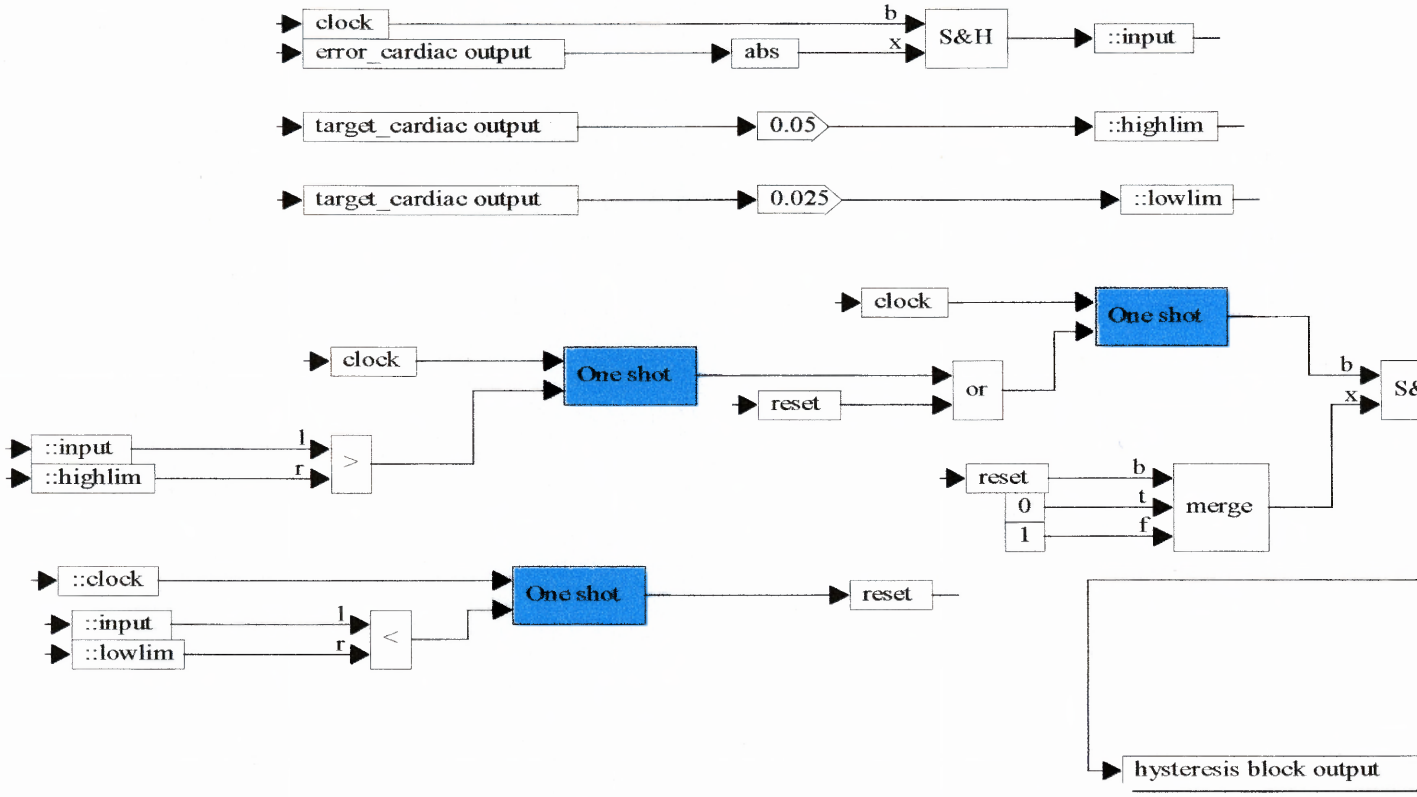

Figure A1 VisSim block diagram of hysteresis compound block

Table A2 Intravenous milrinone pharmacokinetic data for healthy patients

Patient	Dosage(mg/kg)	k10	k12	k21
1	10	0.065	0.0944	0.0491
2	10	0.068	0.1512	0.1025
3	10	0.041	0.0681	0.0535
1	30	0.077	0.0939	0.0471
2	30	0.059	0.0807	0.0508
3	30	0.053	0.0833	0.0471
1	45	0.068	0.0721	0.0353
2	45	0.056	0.0554	0.036
3	45	0.057	0.067	0.0426
1	60	0.067	0.0821	0.039
2	60	0.063	0.0806	0.0425
3	60	0.071	0.0749	0.0417
1	75	0.03	0.0171	0.019
2	75	0.073	0.0888	0.0406
3	75	0.057	0.0669	0.0366
1	100	0.032	0.012	0.0086
2	100	0.047	0.0452	0.0269
3	100	0.029	0.0145	0.0171
1	125	0.047	0.073	0.0467
2	125	0.034	0.0144	0.0121
3	125	0.024	0.0115	0.023
	MEAN	0.053238095	0.064147619	0.038942857

REFERENCES

1. M. Jastremski, C. Jastremski, M. Shepherd, V. Friedman, D. Porembka, R. Smith, and E. Gonzales, "A model for technology assessment as applied to closed lop infusion systems," *Critical Care Medicine*, vol. 23, no. 10, pp. 1745-1754, 1995.

1. J. F. Martin, A. M. Schneider, and N. TY. Smith, "Multiple-model adaptive control of blood pressure using sodium nitroprusside," *IEEE Trans. Biomed. Eng.*, vol. BME-34, no. 8, pp. 603-611, 1987.

2. C. Yu, R. Roy, H. Kaufman, and B. W. Baquette, "Multiple-model adaptive predictive control of mean arterial pressure and cardiac output," *IEEE Trans. Biomed. Eng.*, vol. BME-39, no. 8, pp. 765-777, 1992.

3. K. S. Stern, H. J. Chizeck, B. K. Walker P. S. Krishnaprasad, P. J. Dauchot, and P. G. Katona, "The self-tuning controller: Comparison with human performance in the control of arterial pressure," *Ann. Biomed. Eng.*, vol. 13, pp. 341-357, 1985.

4. E. A. Woodruff, J. F. Martin, and M. Omens, "A model for the design and evaluation of algorithms for closed-loop cardiovascular therapy," *IEEE Trans. Biomed. Eng.*, vol. BME-44, no. 8, pp. 694-704, 1997.

5. R. Young and A. Ward, "Milrinone: A preliminary review of its pharmacological properties and therapeutic use," *Drugs*, vol. 36, pp. 158-192, 1988.

6. A. J. Vander J. H. Sherman, and D. S. Luciano, *Human Physiology: The mechanisms of body functions*. New York, NY: McGraw-Hill, Inc., 1994.

7. K. M. Sherry, and T. J. Locke, "Use of milrinone in cardiac surgical patients," *Cardiovascular Drugs and Therapy*, vol. 7, pp. 671-675, 1993.

8. G. R. Hasegawa, "Milrinone, a new agent for the treatment of congestive heart failure," *Clinical Pharmacy*, vol. 5, pp. 201-205, 1986.

9. D. M. Watson, K. M. Sherry, and G. A. Weston, "Milrinone, a bridge to heart transplantation," *Anaesthesia*, vol. 46, pp. 285-287, 1991.

11. A. Y. Bekker, S. Wolk, A. B. Ritter, J. Rim, and H. Turndorf, "Comparison of cardiotropic rug effects on hemodynamic and myocardial energetics in patients with congestive heart failure. A computer simulation," *1998 Annual meeting of the Society for Technology in Anesthesia*. San Diego, CA, 1999

12. J. Gu, "Mathematical modeling of cardiovascular system for simulation of baroreceptor and local autoregulation responses," Masters thesis, New Jersey Institute of Technology, Newark, NJ, 1996.

13. C. J. Hull, *Pharmacokinetics for Anaesthesia*. Jordan Hill, Oxford: Butterworth-Heinemann Ltd, 1991.

14. J. F. Butterworth, R. L. Hines, R. L. Royster, and R. L. James, "A pharmacokinetics and pharmacodynamic evaluation of milrinone in adults undergoing cardiac surgery," *Anesh. Analg.*, vol. 81, pp. 783-792, 1995.

15. J. M. Bailey, J. H. Levy, M. Kikura, F. Szlam, and C. C. Hug, "Pharmacokinetics of intravenous milrinone in patients undergoing cardiac surgery," *Anesthesiol.*, vol. 81, no. 3, pp. 616-622, 1994.

16. R. H. Epstein, *The Pharmacokinetic Simulator-User Manual*. Jenkintown, PA: Specialized Data Systems, 1997, pp. 51.

17. K. J. Astrom and T. Hagglund, *Automatic Tuning of PID Controllers*. Research Triangle Park, NC: Instrument Society of America, 1988.

18. H. Ying, M. McEachern , D. W. Eddleman, and L. C. Sheppard, "Fuzzy control of mean arterial pressure in post surgical patients with sodium nitroprusside infusion," *IEEE Tran. Biomed. Eng.*, vol. BME-39, no. 10, pp. 1060-1070, 1992.

19. M. Borrello, www.ixpres.com/maborrello

20. R. M. Stroshane, R. F. Koss, C. E. Biddlecome, C. Luczkowec, and J. Edelson, "Oral and intravenous pharmacokinetics of milrinone in human volunteers," *J. Pharmaceutical Sciences*, vol. 73, no. 10, pp. 1438-1441, 1984.

21. S. Shafer, pkpd.icon.palo-alto.med.va.gov/

22. J. R. Benotti, L. J. Lesko, J. E. McCue, and J. S. Alpert, "Pharmacokinetics and pharmacodynamics of milrinone in chronic heart failure," *Am J. Cardiol.*, vol. 56, pp. 685-689, 1985.

23. R. C. Prielipp, D. A. MacGregor, J. F. Butterworth, J. W. Meredith, J. H. Levy, K. E. Wood, and D. B. Coursin, "Pharmacodynamics and pharmacokinetics of milrinone administration to increase oxygen in critically ill patients," *Chest*, vol. 109, no. 5, pp. 1291-1301, 1996.

24. *Taber's Encyclopedic Medical Dictionary,* Philedilphia, PA: F. A. Davis Company, 1997.

25. S. L. Shafer, L. C. Siegel, J. E. Cooke, and J. C. Scoot, "Testing computer-controlled infusion pumps by simulation," *Anesthesiol.*, vol. 68, no. 2, pp. 261-266, 1988.

26. G. I. Voss, P. G. Katona, and H. J. Chizeck, "Adaptive multivariable drug delivery: Control of arterial pressure and cardiac output in anesthetized dogs," *IEEE Trans. Biomed. Eng.*, vol. BME-34, no. 8, pp. 617-623, 1987.

27. *VisSim User's Guide-Version*. Visual Simulations Inc., Westford, MA, 1998