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A mathematical model of cardiovascular system with feedback control

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ABSTRACT

A MATHEMATICAL MODEL OF CARDIOVASCULAR SYSTEM WITH FEEDBACK CONTROL

by
Jiayu Gu

A mathematical model of human cardiovascular system is presented in this study. The closed-loop model is composed of twenty compartments which includes the left and right ventricles, and the systemic and pulmonary circulations. Two physiologic feedback control mechanisms, autoregulation of blood flow and baroreceptor reflex regulation of arterial pressure, are incorporated in the model. Autoregulation acts by changing local resistance to blood flow through metabolic and myogenic mechanisms, thereby insuring a match between oxygen supply and demand for any tissue or organ. Baroreceptors act through neural pathways to alter heart rate, contractility and peripheral resistance in order to return sudden changes in blood pressure to a normal "set point". Pressure and volume waves in a simulated normal human at rest throughout the systemic circulation were generated. Parameters of the model were set to simulate heart failure in two stages. The effects of autoregulation on the coronary circulation with the changes in ventricular contractility, heart rate and peripheral resistance were studied. The results suggest that the oxygen consumption rate of the coronary circulation is mainly affected by afterload. Maximizing ventricular contractility and peripheral resistance, and minimizing heart rate were shown to improve ventricular coronary vascular reserve.

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by
Jiayu Gu

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APPROVAL PAGE

A MATHEMATICAL MODEL OF CARDIOVASCULAR SYSTEM WITH FEEDBACK CONTROL

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This thesis is dedicated to
my parents and my wife

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CHAPTER 1

INTRODUCTION

1.1 Objective

Many aspects of the structure and function of the cardiovascular system can be described and analyzed in mathematical terms. The anatomy of the cardiovascular system and the hydraulic principles that govern the movement of blood within the system are relatively well understood. Important variables, such as pressures and flows, are well suited to a quantitative description. In analyzing the cardiovascular system, one of the most useful tools is mathematical modeling, which leads to a greater understanding of its function and provides reliable indicators of cardiovascular performance. Mathematical modeling can extrapolate from known states to those projected states that cannot be measured directly and to approximate those variables that are inaccessible to experiment. Furthermore, mathematical modeling is a flexible tool allowing change of parameters and control of variables while reducing the need for animal and human experimentation.

In the present study, a mathematical model of the closed-loop cardiovascular system was devised. Local regulation (autoregulation) and baroreceptor reflex control of blood pressure were incorporated into the model. The model was used to study heart failure, and the response of local autoregulatory mechanisms and baroreceptor reflex to parameter changes in the closed-loop circulation.

1.2 Physiology of Cardiovascular Circulation

The cardiovascular system is made up of a pump (the heart), a series of distributing and collecting tubes (the large arteries), and an extensive system of thin vessels that permit rapid exchange of substances between the tissues and the vascular channels (the capillaries) (Fig. 1.1). The heart consists of two pumps in series, the right and left ventricles. The right ventricle propels blood through the lungs. The left ventricle propels blood to all other tissues. Unidirectional flow through the heart is achieved by the appropriate arrangement of effective flap valves. Blood moves rapidly through the aorta and arteries. From the aorta to the arterioles, frictional resistance to blood flow is relatively small, and the pressure drop is also relatively small (Fig. 1.2). The arterioles are the principal points of resistance to blood flow in the circulatory system. The large resistance offered by the arterioles is reflected by the considerable fall in pressure from arterioles to capillaries. In addition to a sharp reduction in pressure, the flow changes from pulsatile to steady. The total cross-sectional area of capillaries is very large. Therefore, the velocity of blood flow in capillaries is low. On its return to the heart from the capillaries, blood passes through venules and then through veins of increasing size. The velocity of blood flow increases. Most of the blood in the systemic circulation is located in the venous vessels. Blood entering the right ventricle is pumped through the pulmonary arterial system at a mean pressure about one-seventh that in

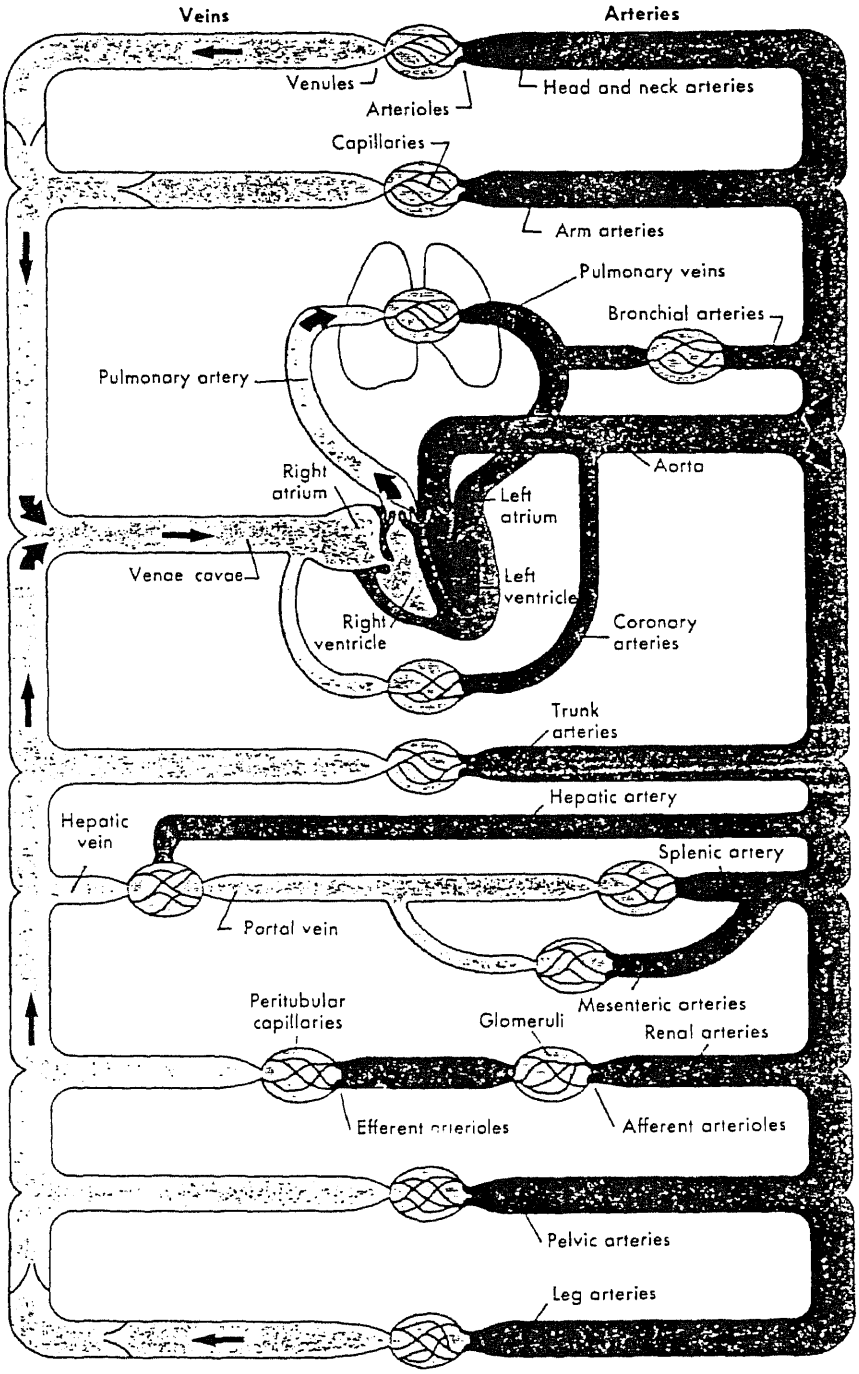

Figure 1.1 Schematic disgram of the parallel and series arrangement of the vessels composing the circulation system.

the systemic arteries. The blood then passes through the pulmonary capillaries and pulmonary venules and returns to the left ventricle. The blood in the pulmonary system is about equally divided among the arterial, capillary and venous vessels.

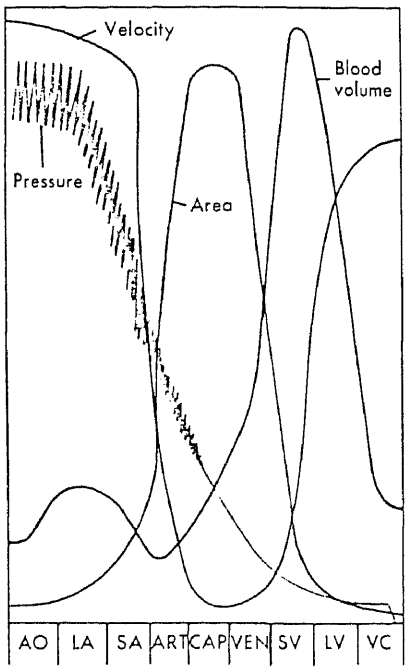

Figure 1.2 Pressure, velocity of flow, cross-sectional area and capacity of the blood vessels of systemic circulation

The peripheral circulation is essentially under dual control: centrally by the nervous system, and locally in the tissues by the conditions in the immediate vicinity of the blood vessels. The relative importance of these two control mechanisms is not the same in all tissues. In some areas of the body,

such as the skin and the splanchnic regions, neural regulation of blood flow predominates, whereas in others, such as the heart and brain, local factors are dominant. In certain tissues such as skeletal muscle and heart, the blood flow is adjusted to the existing metabolic activity of the tissue. Furthermore, at constant levels of tissue metabolism, imposed changes in the perfusion pressure are met with vascular resistance changes that maintain a constant blood flow (Fig. 1.3). This mechanism is commonly referred to as "autoregulation of blood flow". Any intervention that results in an oxygen supply that is inadequate for the tissue requirements releases vasodilator metabolites from the tissue and dilates the resistance vessels. An increase in concentration of vasodilator will increases the vessel resistance and a decrease in concentration of vasodilator will decreases the vessel resistance. If perfusion pressure is constant, a decrease in the metabolic activity will decrease the concentration of vasodilator in the tissue and an increase in the metabolic activity will increase the concentration of vasodilator in the tissue. Similarly, if metabolic activity is constant, an increase in perfusion pressure will decrease the tissue concentration of vasodilator (by increasing local blood flow) and a decrease in perfusion pressure will increase the tissue concentration of vasodilator. Autoregulation is only effective over a certain range of perfusion pressures.

When relative abrupt changes in blood volume, cardiac output or peripheral resistance (as in exercise) occur, the baroreceptors play a key role in

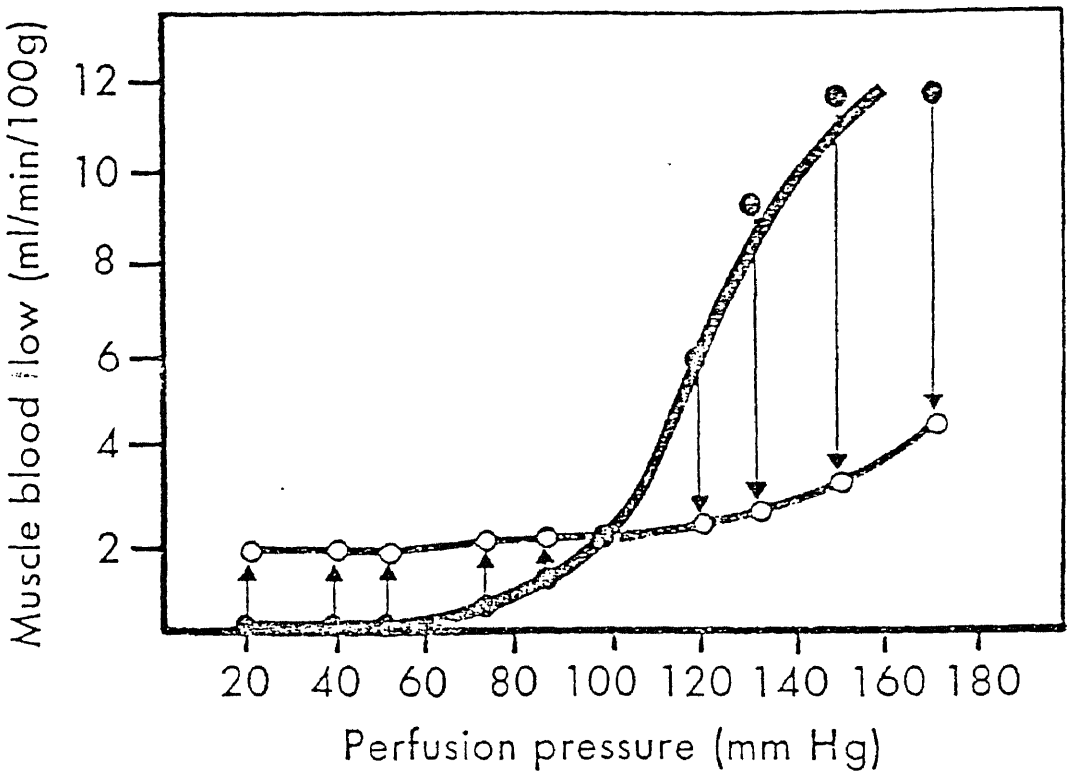

Figure 1.3 Pressure-flow relationship in a certain vascualr bed of the dog. The dot represents the flows obtained immediately after abrupt change in perfusion pressure changes from the control level (point where lines cross). The circle represents the steady-state flows obtained at new perfusion pressure.

short term adjustments of blood pressure. The baroreceptors are located in the carotid sinuses and in the aortic arch. The baroreceptor nerve terminals in the walls of the carotid sinus and aortic arch respond to the stretch and deformation of the vessel induced by the arterial pressure. The frequency of firing of baroreceptors is enhanced by an increase in blood pressure and diminished by a reduction in blood pressure. An increase in impulse frequency caused by increased blood pressure which cause a decrease in peripheral resistance, heart rate and myocardial contractility, which then results in a lowering of blood

pressure. A decrease in impulse frequency caused by decreased blood pressure, causes an increase in peripheral resistance, heart rate and myocardial contractility, which then results in an increased blood pressure. The baroreceptor reflex is also only effective among a limited range of arterial pressure.

1.3 History of Mathematical Model of Cardiovascular System

Early work in the modeling of the cardiovascular system focused mainly on hemodynamics in the major arteries. There were two major themes: one represented the arterial system as a long elastic tube and the other represented it as one or more interconnected elastic reservoirs, i.e., Windkessels. A Windkessel compartment is described by a single ordinary first-order differential equation. The pressure P in the compartment is related to the compartment's volume V by a compliance term C ($P = V/C$). The change of volume is equal to the difference of inflow F_I and outflow F_O ($dV/dt = F_I - F_O$). The ventricle was thought of as a Windkessel with time-varying compliance and valves. The compliance is a scale factor which translates any given ventricular volume into a ventricular pressure. The compliance is large during diastole and small during systole.

In 1959, Grodins [1] published one of the first mathematical models of the complete or closed circulatory system. Six compartments were defined corresponding to those shown in Fig. 1.4. The heart used a Frank-Starling

mechanism wherein stroke volume was a variable fraction of diastolic volume. For the most part, solutions demonstrated the basic properties of the system.

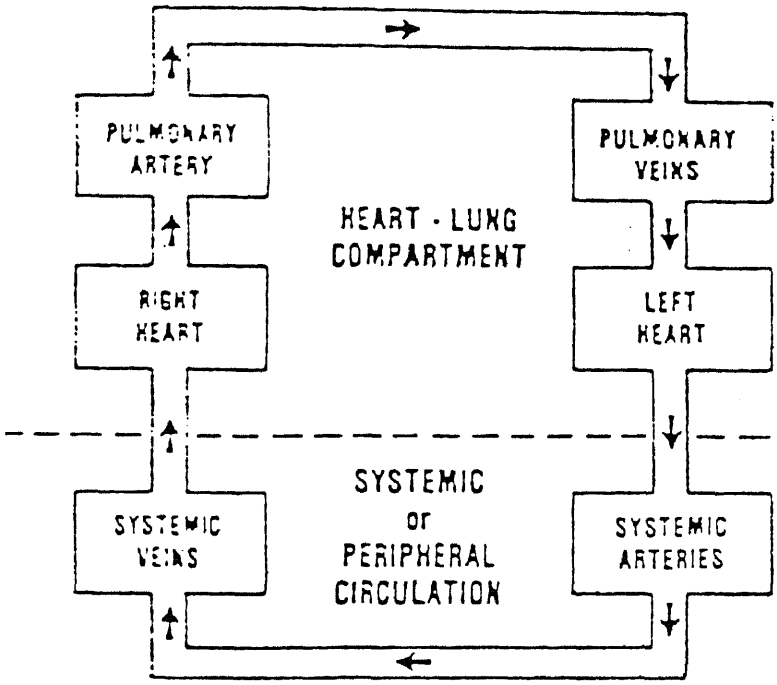

Figure 1.4 A six-compartment model of the closed model

In 1967, Guyton and Coleman [2] presented a model of the circulation which included cardiovascular control mechanisms. Cardiac output was determined by the strength of the heart, vascular resistance and blood volume. Vascular resistance was determined by autoregulation of blood flow with above-normal cardiac output causing vasoconstriction and below-normal cardiac output causing vasodilatation, the baroreflexes were included but they had only a short-term effect on the circulation.

In 1979, Coleman [3] described a model, called HUMAN, which combined detailed cardiovascular function with many interacting physiological processes including the lungs and control of respiration, transport and exchange of blood gases, fluid shifts, kidney function, baroreflexes, acid-base balance skeletal muscle mechanics.

At the present time there are many published models of the cardiovascular system which range from simple to complex. Different models are used in different research projects.

CHAPTER 2

A MODEL OF THE SYSTEMIC CIRCULATION

2.1 Overall Model Concept

The model of the cardiovascular system which is used in this work is composed of twenty compartments (Fig. 2.1). It includes compartments of the left ventricle, aorta, large arteries(I, II, III), arterioles, systemic capillaries, venules, large veins, vena cava, right ventricle, pulmonary arterioles, pulmonary capillaries, pulmonary venueles, coronary artery, cerebral arteries, renal arteries, hepatic arteries, spleen and GI tract arteries and skeletal muscle arteries. Each compartment is represented by a two-element Windkessel model, which consists of a resistance (R) and a compliance (C). For the last five compartments, capillaries are omitted and their venules are lumped into the large vein compartment. Because the blood volume of arteries in these compartments is much smaller than the blood volume of the venules, the blood volume is neglected and these compartments are represented by a resistance only.

The relationship of blood flow and blood pressure in a compartment is given by Equation (1).

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

where F_i is the blood flow out of compartment i and into compartment i+1. R_{i+1} is the vessel resistance of compartment i+1. P_i and P_{i+1} are blood pressures in

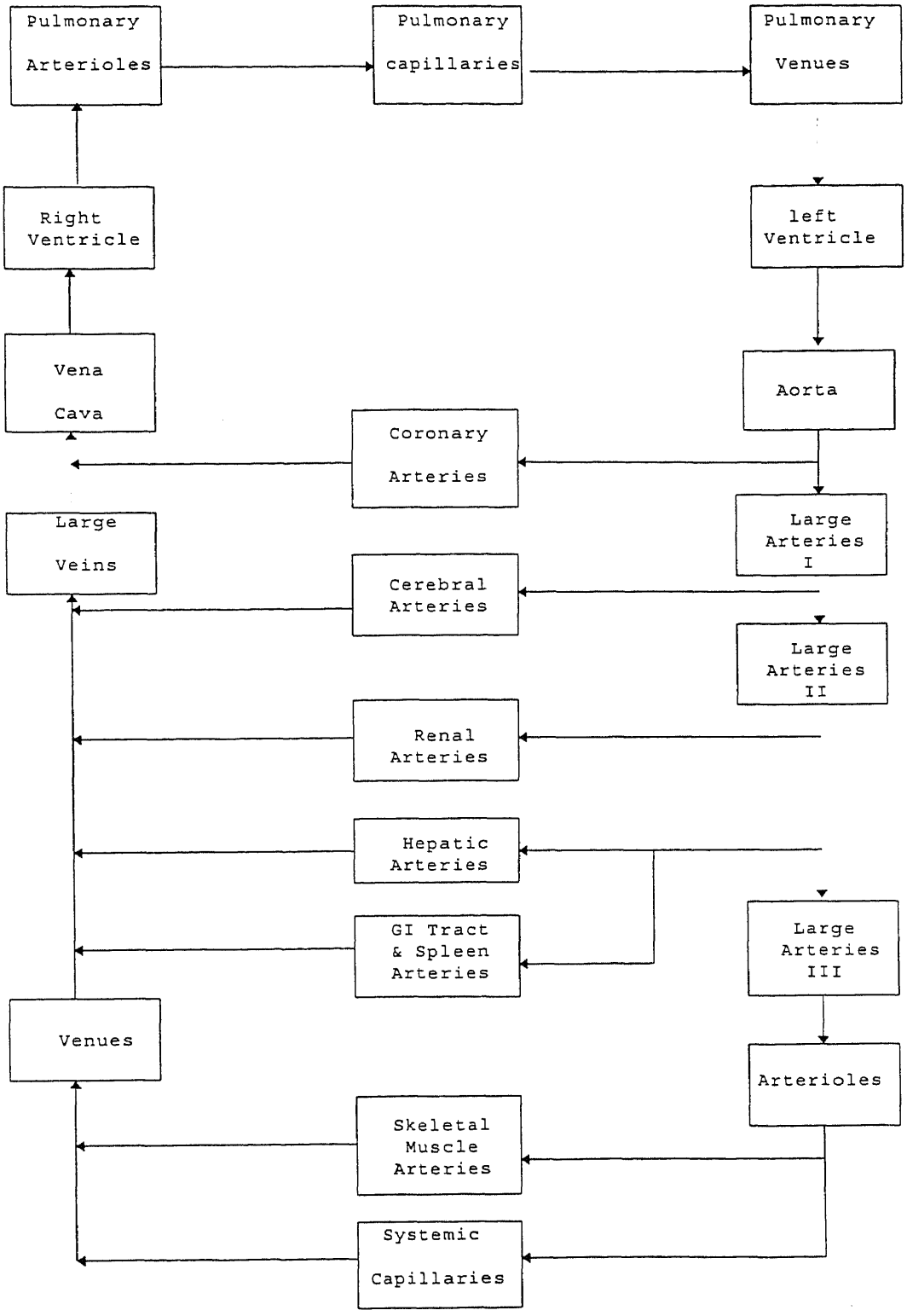

Figure 2.1 Schematic diagram of the closed loop model of cardiovascular system used in this work

compartment i and i+1. compartment i is upstream of compartment i+1. The relationship between blood volume and pressure is described by Equation (2).

$$P_i = (V_i - V_{0i}) / C_i \; ; \text{ for } V_i < V_{0i}; \quad P_i = 0 \qquad (2)$$

where C_i is the compliance of compartment i. V_i is the blood volume of compartment i. V_{0i} is the unstressed volume which is the maximum achievable volume with an internal pressure of zero in compartment i. Unstressed volume is particularly important on the venous side of the circulation where over one-half of a vein's normal volume is unstressed volume.

According to Equation (2); the relationship of dynamic volume and pressure is described by Equation (3):

$$dP_i / dt = (dV_i / dt) / C_i \qquad (3)$$

According to the law of conservation of mass, Equation (4) describes the variation of blood volume in compartment i.

$$dV_i / dt = F_{in} - F_{out} \qquad (4)$$

where F_{in} is the flow into compartment i and F_{out} is the flow out of compartment i.

The ventricles have a time-varying compliance. In the present model each ventricle is analyzed separately in systole and in diastole. A Suga-Sagawa [4] "varying elastance" model is chosen to represent the left ventricle in systole. In Suga's study they used the time-varying ratio of pressure to volume at any instant to represent the pressure-volume relationship of left ventricle in the dog. The ratio was defined as the elastance of a ventricle E(t) (where E(t)=

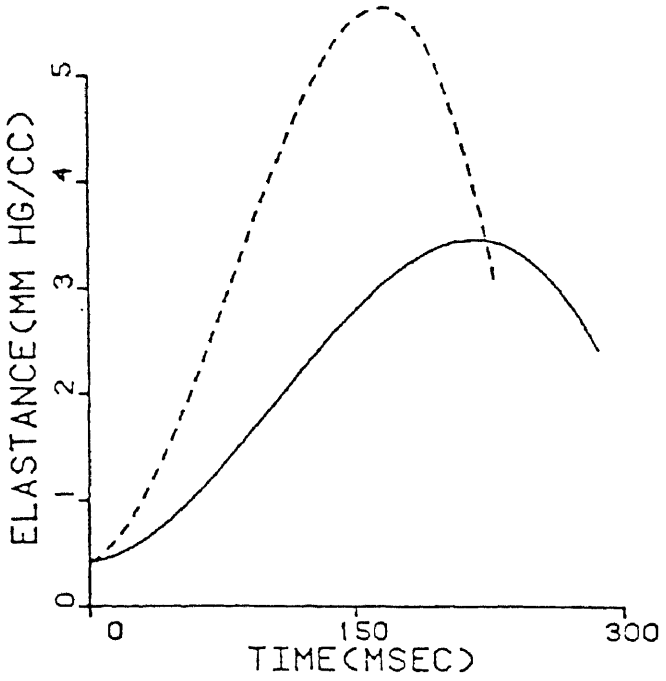

Figure 2.2 Time-varying pressure-volume ratio, E(t), with different contractility state (stolid line, control; dash line, enhanced).

P(t)/V(t)). E(t) (Fig. 2.2) can be characterized by E_{max} (the peak value of the pressure-volume curve) and T_{max} (the time to E_{max} from the onset of systole). Their results show that E_{max} and T_{max} are not affected by changes in the loading of the ventricles, but E_{max} was increased and T_{max} was decreased when ventricular contractility was enhanced by a infusion of norepinephrine. The normalized E(t) curve was similar in shape under different loading conditions.

The results of their study demonstrated that E(t) adequately represents the instantaneous pressure-volume relationship of the left ventricle in systole. The load-independence and the similarity of the basic shape of E(t) curve seems to be a fundamental feature of ventricular contraction. The contractility of the ventricle can be fully represented by two parameters, E_{max} and T_{max}. Therefore, the pressure-volume relationship of the left ventricle in the present model is represented as follows:

$$P_{lv}(t) = E_{lv}(t) [V_{lv}(t) - V_{lv0}] \quad (5)$$

where $E_{lv}(t)$ is the elastance of left ventricle. V_{lv0} is the volume axis intercept of the line connecting the maximum left ventricular elastance P/V points for different loaded beats and was confirmed experimentally to be a constant.

$E_{lv}(t)$ can be expressed as equation (6).

$$E_{lv}(t) = E_{lmax} E_n(t/ T_{max}) \quad (6)$$

where E_{lmax} is the maximum value of $E_{lv}(t)$. $E_n(t)$ is the normalized elastance. (i.e. the maximum of $E_n(t) = E_n(1) = 1$). $E_n(t)$ is represented by a third-order polynomial approximation as follows:

$$E_n(t) = a_1 t + a_2 t^2 + a_3 t^3 \quad (7)$$

where the coefficients a_1, a_2 and a_3 can be obtained by using the least square method. In the present model $E_n(t)$ is based on the normalized function used by Shroff et al. [5] and Barnea et al. [6]. The coefficients are given as follow:

$a_1 = 0.158;$ $a_2 = 2.685;$ $a_3 = -1.841$

T_{max} is the time at which the $E_{lv}(t)$ reaches the maximum value E_{max} from the onset of systole. It can be calculated as follows [6]:

$$T_{max} = (413 - 1.7 * HR) / 1000 ; \quad (8)$$

where HR is in beats per minute. T_{max} is in seconds.

The right ventricle model is similar to left ventricle, but has a different elastance $E_{rv}(t)$. In this study the same normalized elastance as the left ventricle is used. Therefore, the pressure-volume relationship is represented as follows:

$$E_{rv}(t) = E_{rmax} E_n(t/T_{max}) [V_{rv}(t) - V_{rv0}] \quad (9)$$

where E_{rmax} is the elastance of right ventricle and has a different value than the left ventricle. Generally, E_{rmax} is about one-fifth of E_{lmax}.V_{rv0} is the volume axis intercept of the line connecting the maximum right ventricular elastance P/V points for different loaded beats. Unlike the left ventricle, V_{rv0} varies continuously throughout the cardiac cycle. In this model. V_{rvo} is assumed to be constant.

In diastole, the compliance of the ventricles is assumed to be constant, but the left ventricle and right ventricle have the different values.

2.2 Hemodynamic Variables and Systemic Parameters

The cardiovascular system variables are classified into two categories:

(1) cardiovascular parameters, which characterize the mechanical properties of a particular part of the system, such as vascular resistance and capacitance and ventricular contractility.

(2) hemodynamic variables, which are determined wholly in the circulation as a function of cardiovascular parameters, such as cardiac output, blood pressure and volume in each compartment,

Computer simulation of the cardiovascular system poses two different problems.

(1) a forward problem which predicts the performance of the system for given parameter values under various conditions.

(2) an inverse problem which estimates the values of unknown parameters and variables from the measured hemodynamic variables.

Most of hemodynamic variables, such as cardiac output and blood pressure, can be measured directly. However, many of the independent parameters, such as vascular resistance and compliance and ventricular contractility, are difficult to measure directly. In model studies, the values of these independent parameters are usually determined by

(1) measuring experimentally if possible.

(2) estimating from measured data with appropriate assumptions.

(3) assuming a reasonable constant value.

In present study, most of the standard values of hemodynamic variables in a normal human at rest were chosen from published books and literature [7, 8, 9, 10, 11, 13]. Because cardiovascular parameters are difficult to measure experimentally, there is no standard set of values available. We tried to estimate cardiovascular parameters with as few assumptions as possible.

Table 2.1 Standard values of variables and parameters in a normal human at rest

	R (mm Hg/ml/sec)	C (ml/mm Hg)	V_0 (ml)
Left Ventricle	0.02		
Aorta	0.02	0.625	60
Large arteries I	0.0944	0.725	58
Large arteries II	0.1308	1	70
Large arteries III	0.17	1	75
Arterioles	0.85	1.6667	53
Systemic capillaries	0.85	15	171
Venules	0.0567	20.5	278
Large veins	0.0057	121.5	1587
Vena cava	0.0283	21.5	197
Right Ventricle	0.0069		
Pulmonary Arterioles	0.0333	5	88
Pulmonary capillary	0.025	4.44	68
Pulmonary venules	0.02	7.9	147

Heart rate (beat/ min)	75
E_{lmax} (mm Hg/ml)	2
E_{rmax} (mm Hg/ml)	0.45
V_{lv0} (ml)	0
V_{rv0} (ml)	10

where R is the resistance, C is the compliance and V0 is the unstressed volume

Some parameters, such as contractility of the left ventricle [8], were chosen from the literature. Some parameters, such as resistance which can be determined by mean blood pressure and blood flow and compliance which can be determined by the range of pulsatile blood pressure and blood volume, were estimated from hemodynamic variables. The value of parameters were adjusted to obtain the standard values of the hemodynamic variables in the simulation.

The parameters and some of the cardiovascular system variables in a normal human at rest which were used in the present model are listed in Table 2.1.

2.3 Model Equations

Using Equations (1), (2), (3) and (4), we can describe each compartment in the model. The parameters and variables for each compartment are given in Table 2.1. We use the following equations for the model.

(1) Left ventricle

$d(VLV)/dt = FVP - FLV$

$FVP = 50(PVP - PLV), \quad FVP = 0; \quad \text{for } PLV > PVP$

$FLV = 50(PLV - PAO), \quad FLV = 0; \quad \text{for } PAO > PLV$

$PLV = E_{lv}(t)^* VLV$

VLV is the volume of the left ventricle. FVP and FLV are the flows from pulmonary venules to the left ventricle and from the left ventricle to the aorta.

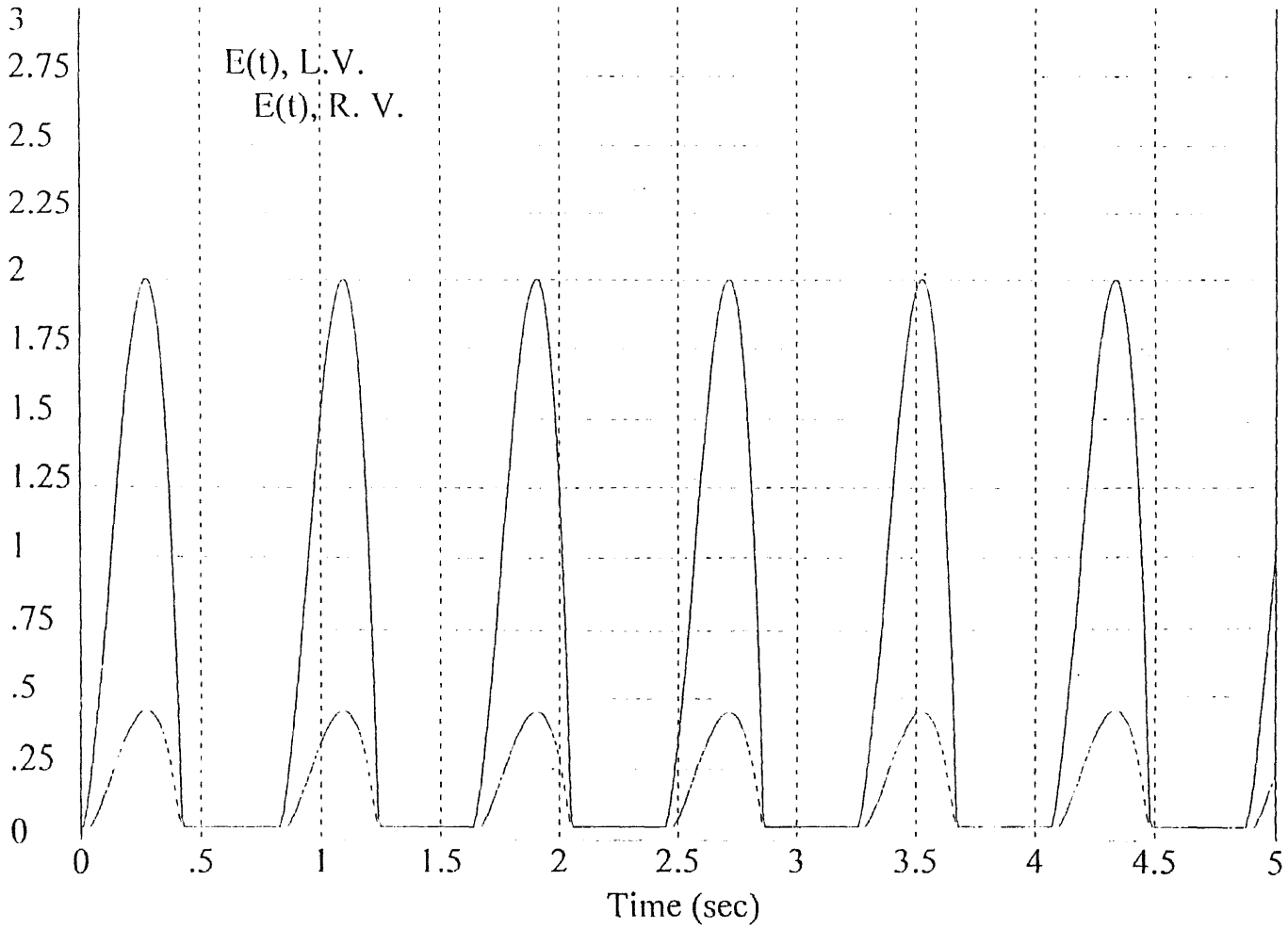

Figure 2.3 Elv(t) and Erv(t)

PVP, PLV and PAO are the pressures in the pulmonary venules, left ventricle and aorta. To represent the closing of the mitral valve, FVP is set to zero when PLV > PVP. To represent the closing of the aortic valve, FLV is set to zero when PAO > PLV. The curve of elastance of left ventricle $E_{lv}(t)$ used in the model is shown in Fig. 2.3. In systole $E_{lv}(t) = 2\ E_n(t)$. $E_n(t)$ is calculated by Equation 7 and 8. In diastole $E_{lv}(t) = 0.051$.

(2) Aorta

$d(VAO)/dt = FLV - FAO - FCOR$

$FAO = 10.5882(PAO - PLAI)$

$PAO = (VAO - 60) / 0.625$

VAO is the volume of the aorta. FAO and FCOR are the flows from the aorta to the large arteries I and from the aorta to the coronary artery. FCOR is controlled by autoregulation of the coronary artery. PLAI is the pressure in the large arteries I.

(3) Large arteries I

$d(VLAI)/dt = FAO - FCER- FLAI$

$FLAI = 7.6471(PLAI - PLAII)$

$PLAI = (VLAI - 58) / 0.725$

VLAI is the volume of the large arteries I. FLAI and FCER are the flows from the large arteries I to the large arteries II and from the large arteries I to the cerebral arteries. FCER is controlled by autoregulation of the cerebral artery. PLAII is the pressure in the large arteries II.

(4) Large arteries II

d(VLAII)/dt = FLAI - FREN - FSGI - FHEP - FLAII

FLAII = 5.8824(PLAII - PLAIII)

PLAII = (VLAII - 70) / 1

VLAII is the volume of the large arteries II. FLAII, FREN, FSGI and FHEP are the flows from the large arteries II to the large arteries III, from the large arteries II to the renal arteries, from the large arteries II to the spleen and the GI tract and from the large arteries II to the hepatic artery. FREN, FSGI and FHEP are controlled by autoregulation of the renal, spleen and GI tract and hepatic arteries. PLAIII is the pressure in the large arteries III.

(5) Large arteries III

d(VLAIII)/dt = FLAII - FLAIII

FLAIII = 1.1765(PLAIII - PAA)

PLAIII = (VLAIII - 75) / 1

VLAIII is the volume of the large arteries III. FLAIII is the flow from the large arteries III to the arterioles. PAA is the pressure in the arterioles.

(6) Arterioles

d(VAA)/dt = FLAIII - FSM - FAA

FAA = 1.1765(PAA - PSC)

PAA = (VAA - 53) / 1.6667

VAA is the volume of the arterioles. FAA and FSM are the flows from the arterioles to the systemic capillaries and flow from the arteriole to the skeletal

muscle. FSM is controlled by autoregulation of the skeletal muscle arteries. PSC is the pressure in the systemic capillaries.

(7) Systemic capillaries

$d(VSC)/dt = FAA - FSC$

$FSC = 17.647(PSC - PVU)$

$PSC = (VSC - 171) / 15$

VSC is the volume of the systemic capillaries. FSC is the flow from the systemic capillaries to the venules. PVU is the pressure in the venules.

(8) Venules

$d(VVU)/dt = FSC + FSM - FVU$

$FVU = 176.471(PVU - PLVE)$

$PVU = (VVU - 278) / 20.5$

VVU is the volume of the venules. FVU is the flow from the venules to the large veins. PLVE is the pressure in the large veins.

(9) Large veins

$d(VLVE)/dt = FVU + FCER + FREN + FSGI + FHEP - FLVE$

$FLVE = 135.294(PLVE - PVC)$

$PLVE = (VLVE - 1587) /121.5$

VLVE is the volume of the large veins. FLVE is the flow from the large veins to the vena cava. PVC is the pressure in the vena cava.

(10) Vena cava

$d(VVC)/dt = FLVE + FCOR - FVC$

FVC = 145(PVC - PRV)

PVC = (VVC - 197) / 21.5

VVC is the volume of the vena cava. FVC is the flow from the vena cava to the right ventricle. PRV is the pressure in the right ventricle.

(11) Right ventricle

d(VRV)/dt = FVC - FRV

FVC = 145(PVC - PRV), FVC = 0; for FRV > PVC

FRV = 30(PRV - PAP), FRV = 0; for PAP > PRV

$PRV = E_{rv}(t)^* VRV$

VRV is the volume of the right ventricle. FRV is the flow from the right ventricle to the pulmonary arteries. PAP is the pressures in the pulmonary arteries. To represent the closing of the tricuspid valve, FVC is set to zero when PRV > PVC. To represent the closing of the pulmonic valve, FRV is set to zero when PAP > PRV. The curve of elastance of right ventricle $E_{rv}(t)$ is shown in Fig. 2.3. In systole $E_{rv}(t) = 0.45E_n(t)$, and $E_{lv}(t) = 0.048$ in diastole.

(12) Pulmonary arteries

d(VAP)/dt = FRV - FAP

FAP = 40(PAP - PCP)

PAP = (VAP - 88) / 5

VAP is the volume of the pulmonary arteries. FAP is the flow from the pulmonary arteries to the pulmonary capillaries. PCP is the pressure in the pulmonary capillaries.

(13) Pulmonary capillaries

$d(VCP)/dt = FAP - FCP$

$FCP = 50(PCP - PVP)$

$PCP = (VAP - 68) / 4.44$

VCP is the volume of the pulmonary capillaries. FAP is the flow from the pulmonary capillaries to the pulmonary venules. PVP is the pressure in the pulmonary venules.

(14) Pulmonary venues

$d(VVP)/dt = FCP - FVP$

$FVP = 50(PVP - PLV)$

$PVP = (VAP - 147) / 7.9$

VVP is the volume of the pulmonary venules. FVP is the flow from the pulmonary venules to the left ventricle. PLV is the pressure in the left ventricle.

Thus completes the closed loop representing the pressures, volumes and flows in the systemic circulation.

CHAPTER 3

THE MODEL OF FEEDBACK CONTROL

3.1 The Overall Concept of a Model for Autoregulation

One of the mechanisms which is responsible for autoregulation of blood flow is that the rate of oxygen extraction from blood is equal to the rate of oxygen consumption by tissue. Therefore, the blood flow is adjusted to maintain this equilibrium. The rate of oxygen supply to tissue is calculated as follows:

$$M_s = F_t (O_{2a} - O_{2v}) \qquad (10)$$

where M_s is the rate of oxygen supply to tissue. F_t is the average blood flow in tissue. O_{2a} and O_{2v} are the oxygen concentrations in the arteries and veins. Ft is defined as Equation (11).

$$F_t = (P_u - P_d) / R_t \qquad (11)$$

where P_u and P_d are the blood pressures upstream and downstream of tissue or organ being autoregulated. R_t is the hemodynamic resistance between upstream and downstream points. From Equation (10) and (11), The resistance between the two points can be calculated as follows:

$$R_t = [(P_u - P_d) (O_{2a} - O_{2v})] / M_s \qquad (12)$$

We define M_c as the rate of oxygen consumption by the tissue or organ. Because there is a equilibrium between Mc and Ms, Equation (12) can be changed as follows:

$$R_t = [(P_u - P_d) (O_{2a} - O_{2v})] / M_c \qquad (13)$$

In the present model the complex relationship between coronary resistance and arteriovenous coronary oxygen difference (O_{2a}-O_{2v}) is not considered. (O_{2a}-O_{2v}) is assumed to be constant throughout the active range of autoregulation.

From Equation (13), we see that the resistance of the tissue or organ varies with the pressure and the rate of oxygen consumption. The direction of the change in resistance is determined experimentally.

3.2 A Model of Autoregulation in the Coronary Artery

There are many indexes such as tension-time index (TTI), tension-time or force-time integral (FTI), rate-pressure product (RPP), pressure-work index (PWI) and systolic pressure-volume area (PVA) which have been developed as predictors of myocardial oxygen consumption. In Takaoka's study [11], they assessed the relationship between these indexes and myocardial oxygen consumption per beat. Their results demonstrated that PVA is the best predictor of myocardial oxygen consumption among these indexes. Therefore, in the present model PVA is used as the index to calculate myocardial oxygen consumption.

PVA was defined by Suga [12] as the area in the pressure-volume plane that is enclosed by the diastolic curve, the systolic pressure-volume curve, and the tangent line-Emax as in Fig. 3.1. PVA is considered to be the

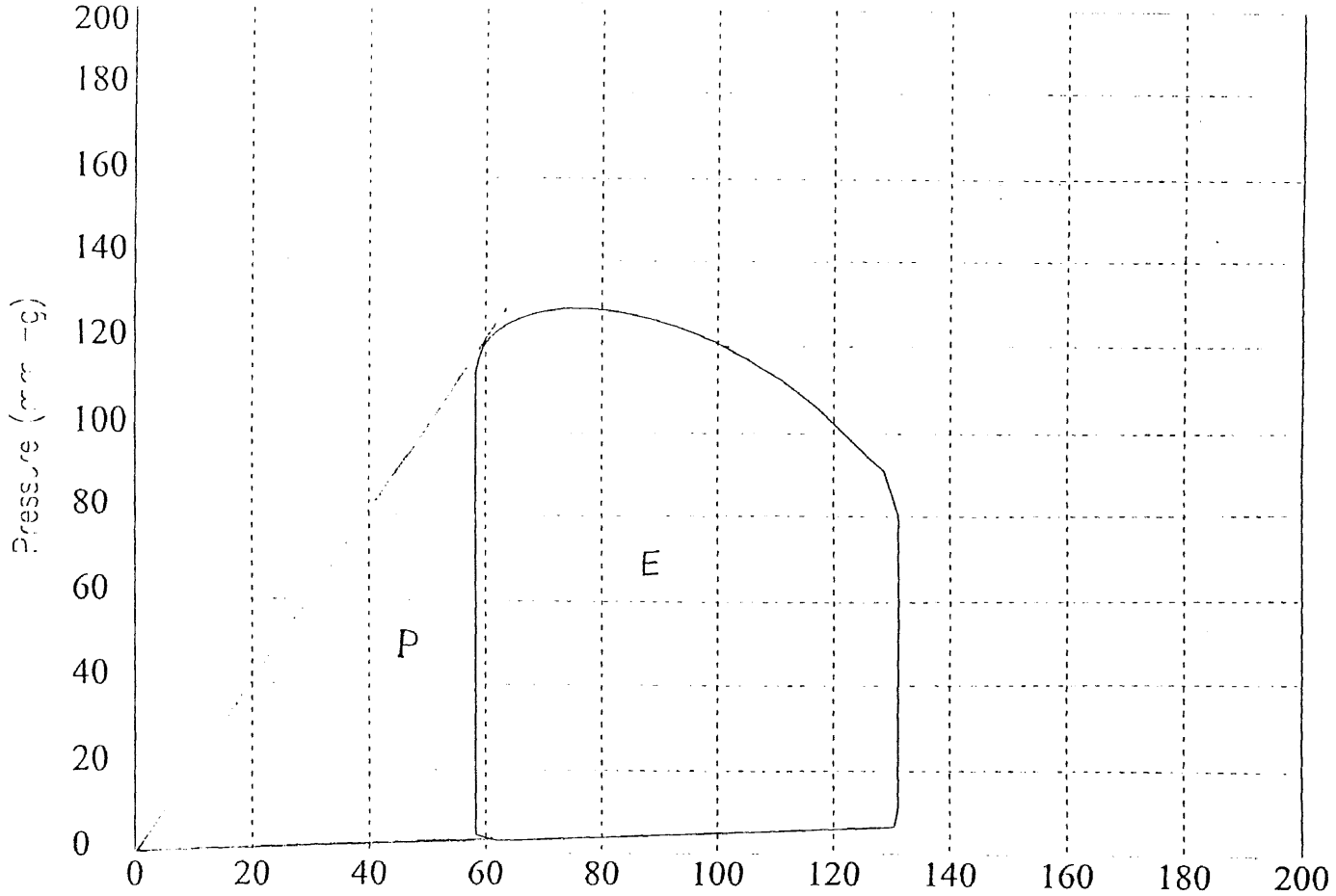

Figure 3.1 Pressure-volume plane of the left ventricle

driving energy of a ventricle per heart beat. PVA can be divided into external or pumping work (W_E) which is related to ejection contraction, and mechanical potential energy (W_P) which corresponds to isovolumic contraction. W_E is calculated by integrating the ventricular pressure in systole and diastole with respect to the volume as indicated by the area E in Fig. 3.1. W_P is calculated by the triangular area P in Fig. 3.1. Because blood flow in the right coronary artery is much less than in the left coronary artery, only the left coronary artery is incorporated into the model. According to Suga's study, the oxygen consumption rate of 100g left ventricle (M_{cor}) per beat is calculated as follows:

$$M_{cor} = A*PVA + B*E_{max} + C \qquad (14)$$

where PVA is calculated as the pressure-volume area per 100g of left ventricle and the coefficients A, B and C are as follows:

$A = 1.8 \times 10^{-5}$ mlO_2 / mmHg /(ml of ventricle)

$B = 2.4 \times 10^{-3}$ (mlO_2)*(ml of ventricle) / (beat mmHg 100g)

C = 0.014 mlO_2 / (beat 100g)

In the present model, the left ventricle is assumed to have a weight of 150g. To calculate the total oxygen consumption rate of left ventricle per beat, the coefficients of Equation (14) are adjusted for the actual heart weight as follows:

$A = 1.8 \times 10^{-5}$ mlO_2 / (mmHg ml of ventricle)

$B = 3.6 \times 10^{-3}$ (mlO_2)*(ml of ventricle) / (beat mmHg)

C = 0.021 mlO_2 / beat

and PVA is the total pressure-volume area previously defined.

The upstream pressure of the coronary artery is the pressure in the aorta (PAO). The downstream pressure of the coronary artery is the pressure in the coronary sinuses. For this model we approximate coronary sinus pressure as the pressure in vena cava (PVC). In addition to driving blood through the coronary vessels, the heart also influences its blood supply by the squeezing effect of the contracting myocardium on the blood vessels. This force is so great during early ventricular systole that blood flow in a large coronary artery supplying the left ventricle is briefly reversed. The pressure caused by squeezing of the heart muscle is calculated from ventricular pressure and is equal to $0.75P_{lv}$ [6]. Therefore, the resistance of the coronary arteries is calculated as follows:

$$R_{cor} = [\ (PAO - 0.75P_{lv} - PVC)^* (O_{2a}-O_{2v})\ ] / M_{cor} \qquad (15)$$

The arteriovenous oxygen difference $(O_{2a}-O_{2v})$ across the coronary arteries is assumed to be constant throughout the active range of autoregulation. $(O_{2a} -O_{2v})$ can be calculated as the product of $O_{2a} = 0.194$ (ml O_2/ ml blood) and the normal oxygen uptake ratio which is 0.647. We then have $(O_{2a} -O_{2v})$ = 0.1255 (ml O_2/ ml blood).

3.3 Models of Autoregulation in Other Organs and Tissues

We assume that the rate of metabolism in other organs is constant at rest, while arterial and venous oxygen concentrations of these organs are also constant. From equation (10) we know that the blood flow (F) should be constant to

constant metabolic rate. Therefore, the resistances of organs change to maintain a constant flow when perfusion pressure changes. The resistances of these organs are calculated as follows:

$$K = F(T) / F_0 \qquad (16)$$

$$R(T+1) = K * R(T) \qquad (17)$$

where K is a control factor. F_0 is a predetermined set point for flow (i.e. the flow in a certain organ or tissue is maintained at F_0 by autoregulation). F(T) is the average preregulated flow during a cardiac period T. R(T+1) and R(T) are the regulated and preregulated resistance. During a simulation, resistance is adjusted by beat-to-beat autoregulation. Because autoregulation is active only over a limited range of perfusion pressure, the resistance has upper and lower limits, which can be calculated using Equation (1), i.e. the upper and lower resistances can be calculated by dividing the upper and lower perfusion pressure by F_0.

The predetermined set points for flow (F_0, ml/sec), the active ranges of resistance (R, mmHg/ml/sec) and the active ranges of perfusion pressure (mmHg) are as follows [13]:

	F_0 (ml/sec)	Resistance (mmHg/ml/sec)	Pressure (mmHg)
Cerebral	12.5	4.8 - 12.8	60 - 160
Renal	18	3.33 - 8.89	60 - 160
Hepatic	3.1	19.35.5 - 51.61	60 - 160

Spleen and GI Tract	11.1	5.41 - 14.41	60 - 160
Skeletal muscle	20	1 - 6	20 - 120

3.4 A Model for Baroreceptor Reflex Regulation

Baroreceptors are located at the carotid sinuses and aortic arch. The carotid sinus receptors are more sensitive to pressure than are the aortic arch receptors. Therefore, only carotid sinus receptors are considered in this model. The carotid arteries are incorporated into the large arteries I compartment. Therefore, the blood pressure in the large arteries I compartment is taken as the regulated pressure. The mean pressure in the large arteries I compartment in a normal human at rest is the set point for baroreceptor reflex. When a sudden change of pressure in the large arteries I compartment occurs, the baroreceptor reflex regulates the pressure to the set point by changing ventricular contractility, heart rate, vascular resistance and capacitance. In the present model only heart rate and vascular resistance are controlled by the baroreceptor reflex. Since the baroreceptors are constantly responding to changes in blood pressure, the heart rate and peripheral resistance are assumed to be regulated continuously until the arterial pressure returns to the set point of reflex.

The effect of the baroreceptor reflex on heart rate is described by Equation (18) [14].

$$\Delta HR = -m(P_{pre} - P_s) \qquad (18)$$

where m is a control factor for heart rate, which is a constant. P_s is the set point for reflex. P_{pre} is the preregulated mean pressure in the large arteries I compartment. ΔHR is the change in heart rate caused by the baroreceptor reflex. Heart rate is updated every 0.4 seconds. Therefore, every 0.4 seconds the heart rate changes by ΔHR beat/min.

The effect of the baroreceptor reflex on peripheral resistance is described by Equation (19) [14].

$$\Delta R = -k(P_{pre} - P_s) \qquad (19)$$

where k is a control factor for resistance, which is a constant. The definitions of P_s and P_{pre} are the same as in equation (18). ΔR is the change in total peripheral resistance. Like heart rate, the resistance is updated by ΔR every 0.4s.

The distribution of change in total peripheral resistance is assumed to be across all compartments in the systemic circulation. The resistance of the pulmonary circulation is not affected by the baroreceptor reflex. For example, for a change of 10% increase in total peripheral resistance, the resistance of each compartment in the systemic circulation is increased by 10%.

The parameters and variables are given as follows:

P_s = 85 mm Hg

R = 0.9473 mm Hg/ml/sec

HR = 75 beat/min

m = 0.4

k = 0.004

where R is the total resistance of the systemic circulation in a normal human at rest. This value is calculated during the simulation and is used for the distribution of the change in total peripheral resistance. HR is the basal value in a normal human at rest. P_s is the set point for reflex. This value is calculated during the simulation of the circulation under normal physiology at rest.

CHAPTER 4

METHODS

The simulation was implemented on a MS-DOS microcomputer system. VisSim was chosen as the software. VisSim is a powerful computer-aided engineering program that provides a complete visual and graphical work space for designing, and plotting models of dynamic systems. The Eular method was chosen as the integration algorithm. Computation was performed with a simulated time step size of 0.01seccond.

Simulations in this study were divided into four parts.

(1) simulation of the circulation under normal physiological condition at rest to provide a baseline for comparison under other conditions.

(2) simulations of two stages of left heart failure.

(a) stage I: Left ventricular contractility was decreased to 52.5% of normal. Right ventricular contractility was decreased to 90.9% of normal. The total resistance in the circulation was increased 12% from normal. Heart rate was increased to 85 beats/min from 75 beats/min.

(b) stage II: Left ventricular contractility was decreased to 31.6% of normal. Right ventricular contractility was increased 17.6% from normal. The total resistance in the circulation was increased 75% from normal. Heart rate was increased to 85 beats/min from 75 beats/min.

(3) to investigate the effects of autoregulation on coronary artery flow and pressure, simulation of the circulation by changing left ventricular

contractility, heart rate and afterload. Four simulations were performed with the following changes of parameters. All other parameters were held constantly at their normal values.

(a) left ventricular contractility (mm Hg/ml) was set to 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 while simultaneously T_{max} was set to 85%, 90%, 95%, 100%, 105%, 110% of the value calculated by equation (8). The meaning of changing T_{max} will be discussed later.

(b) left ventricular contractility (mm Hg/ml) was set to 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0. T_{max} was held constant at its normal value.

(c) heart rate (beat/min) was set to 55, 65, 75, 100, and 120

(d) total peripheral resistance was set to the value of 50%, 75%, 100%, 125%, and 150% of normal.

(4) to investigate the effects of baroreceptor reflexes, the regulatory effects on sudden changes in blood pressure caused by sudden changes in left ventricular contractility or in peripheral resistance were simulated. Two simulations were done using the following conditions:

(a) left ventricular contractility was decreased 50%. After 60 seconds it was set to its normal value.

(b) peripheral resistance was increased 25%. After 60 seconds it was set to its normal value.

CHAPTER 5

RESULTS

Using the parameters given in table 2.1, the waves of pressures and volumes of each compartments in a normal human at rest were obtained in the first series of simulations. Fig 5.1 shows the pressure and volume in the left ventricle. Fig. 5.2 shows the waveform of the pressure in the left ventricle and aorta generated by the simulation. Stroke volume is 73.58 ml. Cardiac output is 5518.5 ml/min. Total blood volume is 5080 ml. The maximum and minimum values of pressure and volume are given in the table 5.1. The maximum pressure is approximated by the end systolic pressure. In following study we use the maximum pressure as the end systolic pressure. The minimum pressure is the end diastolic pressure. The maximum volume is the end diastolic volume and the minimum volume is the end systolic volume.

The normal mean values of the variables in the coronary artery compartment which is controlled by autoregulation are as follows:

M_{cor}(oxygen consumption rate of coronary artery) 0.2871 (ml O_2/sec)

R_{cor}(resistance of coronary artery) 22.17(mm Hg/ml/sec)

F_{cor}(flow of coronary artery) 2.285(ml/sec)

As shown in Table 5.1, the perfusion pressures in the renal, cerebral hepatic, skeletal muscle, and spleen and GI tract were in their active range of autoregulation. Therefore, their blood flows were maintained at the values

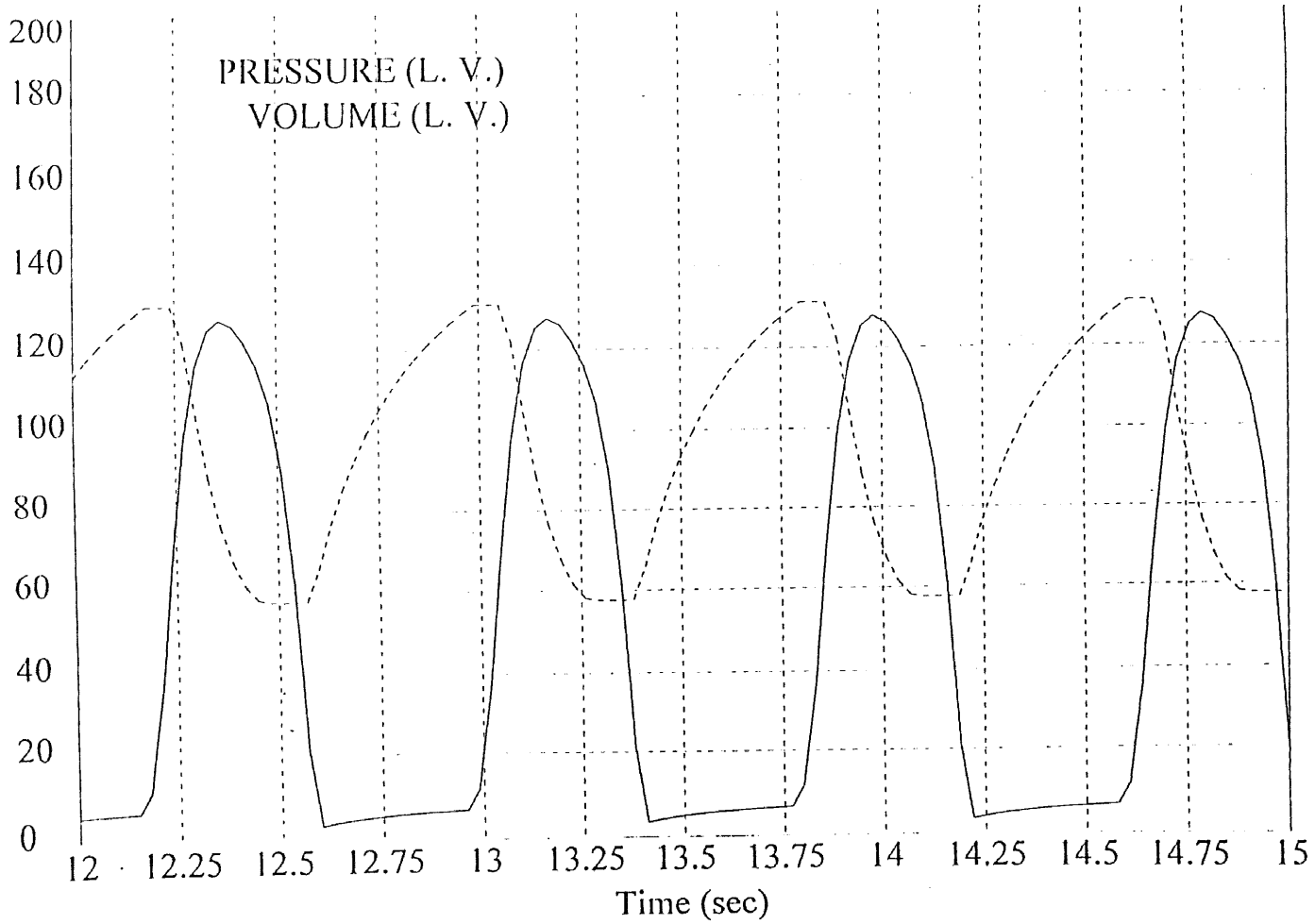

Figure 5.1 Blood pressure and volume of the left ventricle generated by the simulation

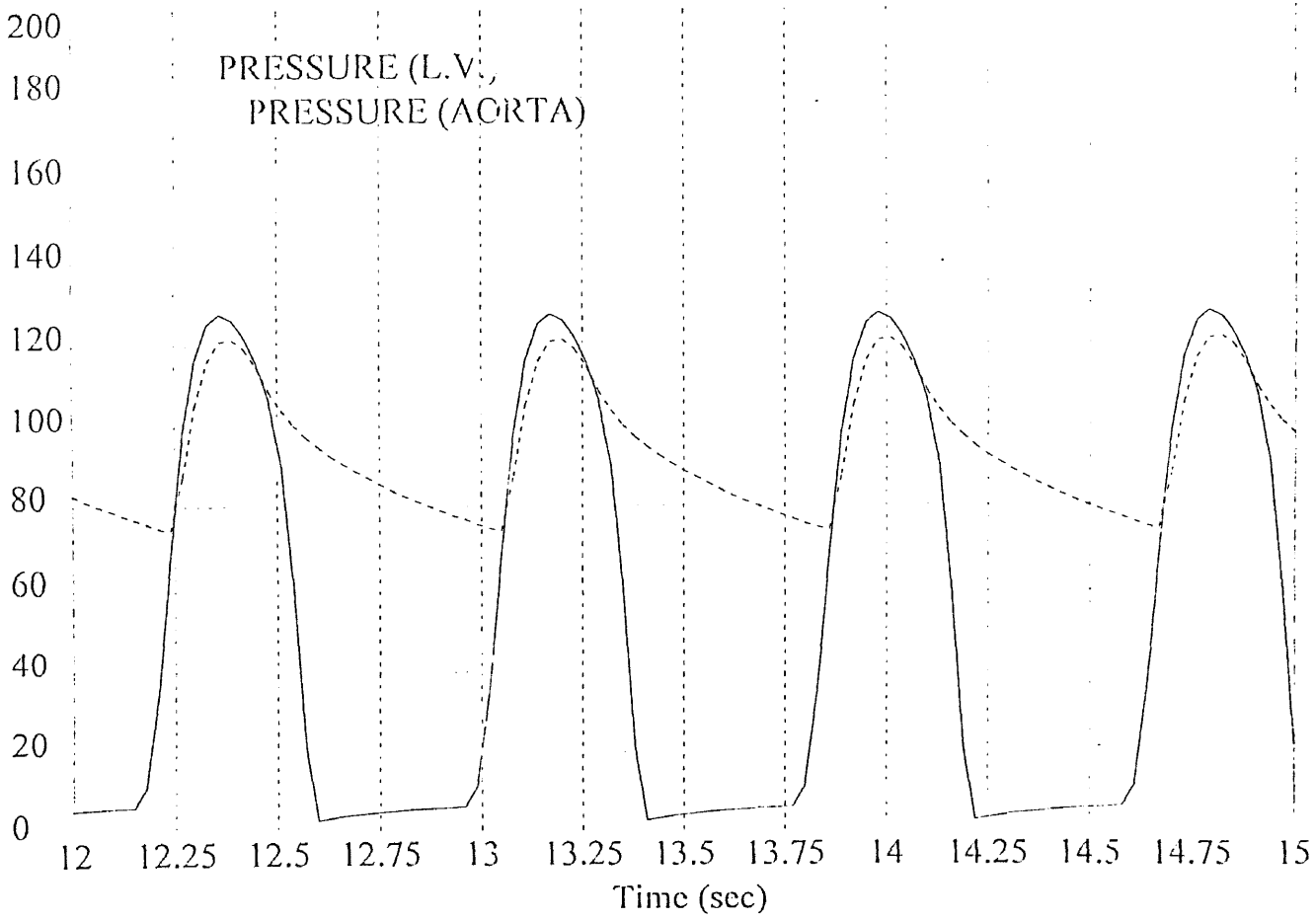

Figure 5.2 Blood pressure of the left ventricle and the aorta generated by the simulation

Table 5.1 The range of blood pressure and volume in the normal human at rest

	Pressure (mm Hg)	Volume (ml)
Left ventricle	127.50 - 6.64	131.20 - 57.62
Aorta	121.50 - 74.22	135.90 - 106.40
Large arteries I	99.83 - 72.22	130.50 - 110.50
Large arteries II	80.91 - 68.37	150.90 - 138.20
Large arteries III	70.46 - 63.84	145.60 - 138.90
Arterioles	30.69 - 30.13	104.10 - 103.10
Systemic capillaries	10.33 - 10.32	325.60 - 325.40
Venules	9.00 - 8.96	462.60 - 461.80
Large veins	8.77 - 8.71	2651.00- 2645.00
Vena cava	7.20 - 5.53	349.30 - 316.10
Right ventricle	29.00 - 5.61	128.40 - 54.85
Pulmonary arteries	17.30 - 9.85	173.50 - 136.90
Pulmonary capillaries	13.36 - 9.07	126.80 - 107.80
Pulmonary venules	11.86 - 8.47	240 - 210

described in section 3.3. The mean value of blood flows in these compartments generated by the simulation are as follows:

F_{ren}(flow of renal arteries) 17.97(ml/sec)

F_{cer}(flow of cerebral arteries) 12.48(ml/sec)

F_{hep}(flow of hepatic arteries)	3.135(ml/sec)
F_{SGI}(flow of spleen and GI tract)	11.21(ml/sec)
F_{sm}(flow of skeletal muscle arteries)	20(ml/sec)

Figure 5.3 shows the wave of blood flow for the left coronary artery. As stated in the previous chapter, the heart has a squeezing effect on the left coronary artery. During early ventricular systole blood flow in the left coronary arteries is reversed because of the large transmural pressure gradient caused by the contracting of left ventricle. During isovolumic relaxation of the left ventricle, coronary artery flow increases rapidly.

For heart failure in stage I, the simulation predicted a maximum left ventricular pressure of 118.6 mm Hg , the end systolic and end diastolic pressures in the aorta were 112.6 mm Hg and 74.2 mm Hg, and end diastolic and end systolic blood volume in the left ventricle were 167.6 ml and 109.6 ml, respectively. This results in a stroke volume of 58 ml and a cardiac output of 4930 ml/min, a decrease of 10.7% from normal. For the heart failure in stage II, the simulation predicted a maximum left ventricular pressure of 128.1 mm Hg, the end systolic and end diastolic pressures in the aorta were 125.8 mm Hg and 90.04 mm Hg, and the end diastolic and end systolic blood volumes in the left ventricle were 245.8 ml and 205.5 ml , respectively. This results in a stroke volume of 40.3 ml and a cardiac output of 3425.5 ml/min, a decrease of 37.9% from normal.

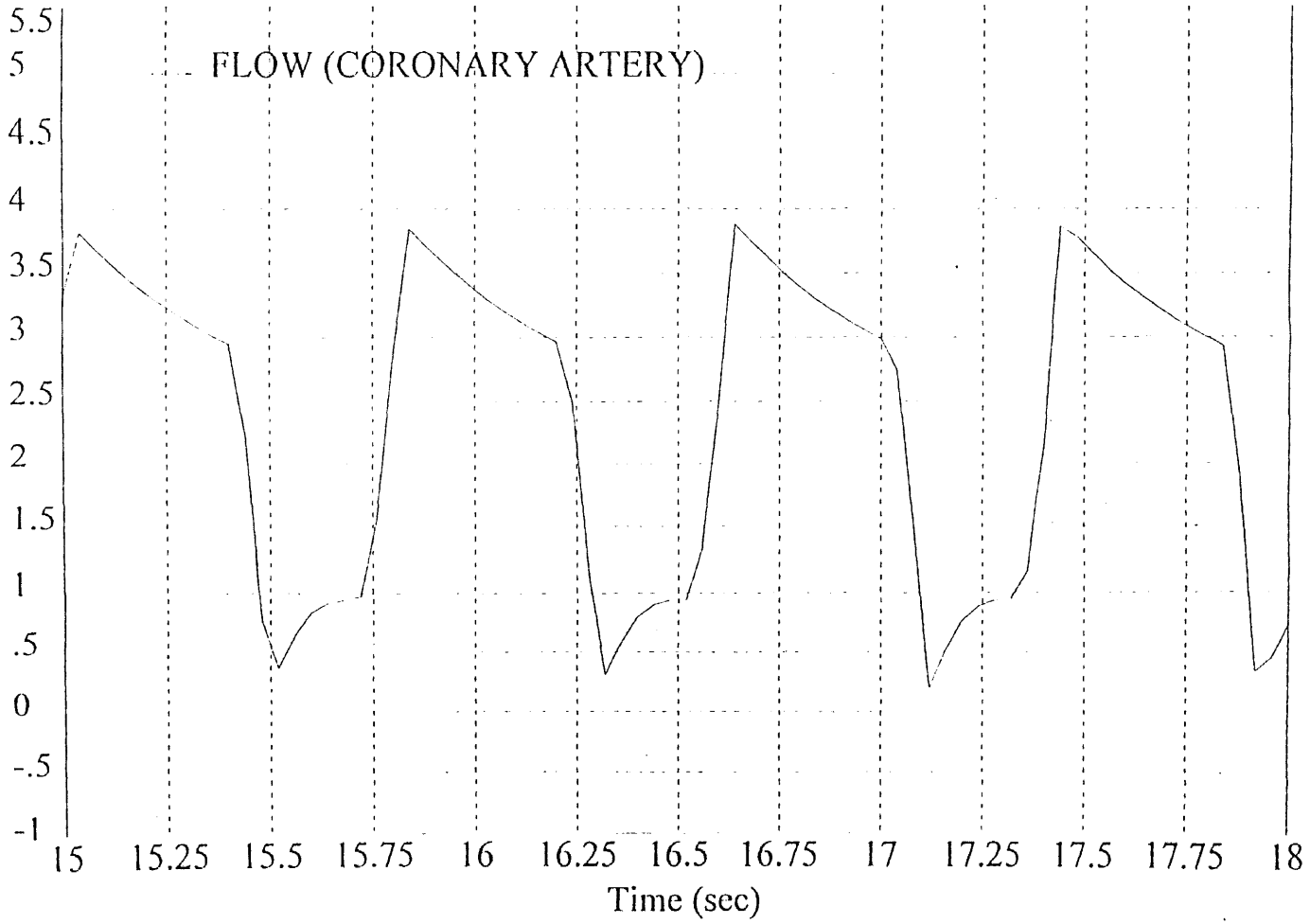

Figure 5.3 Blood flow of the coronary artery generated by the simulation

Table 5.2 The effects of autoregulation on coronary artery flow and pressure with changes in left ventricular contractility and T_{max}.

E_{lvmax} (mm Hg/ml)	0.5	1.0	1.5	2.0	2.5	3.0
T_{max} (% of base value)	130	120	110	100	90	80
M_{cor} (ml O_2/sec)	0.2598	0.2642	0.2753	0.2870	0.2941	0.2998
R_{COR} (mm Hg/ml/sec)	13.34	17.26	20.00	22.17	23.64	25.03
FCOR (ml/sec)	2.069	2.106	2.193	2.285	2.342	2.387
MPAO (mm Hg)	68.36	80.00	89.00	93.36	96.04	97.85
PLV (mm Hg)	90.7	110.0	121.2	127.5	130.5	138.6
EDVLV (ml)	230.4	166.8	141.5	131.2	118.7	112.2
ESVLV (ml)	171.40	98.80	68.99	57.62	41.16	33.28
SV (ml/beat)	59.00	68.00	72.51	73.58	77.54	78.92

T_{max} is the percentage of the value calculated by Equation 8 at the basal value of heart rate. FCOR and MPAO are the mean blood flow of coronary artery and the mean blood pressure in the aorta, respectively. PLV is the peak pressure in the left ventricle. EDVLV and ESVLV are the end diastolic and end systolic volumes of the left ventricle, respectively. SV is the stroke volume of the left ventricle. FCOR, MPAO, SV, EDVLV and ESVLV will have the same definitions in the following tables.

Table 5.2 shows the effects of autoregulation on coronary artery flow and pressure with changes in left ventricular contractility and T_{max}. As contractility increases with a corresponding change of T_{max}, the peak left ventricle pressure and the mean aortic pressure increases, stroke volume increased, and both the end diastolic and end systolic volumes in the left

ventricle decrease. That results in an increase in oxygen consumption, resistance and blood flow in the coronary artery.

Table 5.3 shows the effects of autoregulation on the coronary artery with changes in the left contractility but without change of T_{max}. In this simulation T_{max} was the value calculated by equation (8) and was not changed throughout the simulation. As contractility increased without change of T_{max}. PLV, MPAO and stroke volume increases, and EDVLV and ESVLV decrease. The resulting increase in R_{cor} and FCOR, and decrease in M_{cor} is different from that in Table 5.2.

Table 5.3 The effects of autoregulation on coronary artery flow and pressure with changes in left ventricular contractility but without change of T_{max}

E_{lvmax} (mm Hg/ml)	0.5	1	1.5	2	2.5	3
M_{cor} (ml O_2/sec)	0.3026	0.2936	0.2904	0.2871	0.2856	0.2857
R_{COR} (mm Hg/ml/sec)	14.60	18.84	20.86	22.17	23.02	23.41
FCOR (ml/sec)	2.411	2.338	2.313	2.285	2.275	2.278
MPAO (mm Hg)	70.21	82.76	89.26	93.36	111.60	126.20
PLV (mm Hg)	98.3	110.7	121.1	127.5	131.0	132.6
EDVLV (ml)	251.8	177.2	147.5	131.2	121.1	113.7
ESVLV (ml)	191.70	108.30	75.00	57.62	47.17	38.27
SV (ml/beat)	60.10	68.90	72.5	73.58	74.93	75.43

Table 5.4 shows the effects of autoregulation on the coronary artery with changes in heart rate. As heart rate increases, PLV, MPAO and ESVLV increase, and EDVLV and stroke volume decrease. This results in an increase in M_{cor} and FCOR, and a decrease in R_{cor}.

Table 5.4 The effects of autoregulation on the coronary artery flow and pressure with changes in heart rate

HR(beat/min)	55	65	75	100	120
M_{cor} (ml O_2/sec)	0.2174	0.2517	0.2871	0.3674	0.4295
M'_{cor} (ml O_2/beat)	0.2372	0.2323	0.2297	0.2204	0.2148
R_{COR} (mm Hg/ml/sec)	25.53	23.75	22.17	19.44	17.82
FCOR (ml/sec)	1.726	1.999	2.285	2.925	3.417
MPAO (mm Hg)	80.0	86.7	93.4	105.0	110.9
PLV (mm Hg)	119.5	123.5	127.5	134.8	139.0
EDVLV (ml)	142.1	136.7	131.2	121.1	116.2
ESVLV (ml)	52.34	54.98	57.62	61.91	64.94
SV (ml/beat)	89.76	81.72	73.58	59.19	51.26

M'_{cor} is the oxygen consumption of coronary artery per beat.

Table 5.5 shows the effects of autoregulation on coronary artery flow and pressure with changes in total peripheral resistance. As total peripheral resistance increases, PLV, MPAO, EDVLV and ESVLV increase, and stroke volume decreased. This results in increased Mcor, Rcor and FCOR

Table 5.5 The effects of autoregulation on coronary artery flow and pressure with changes in peripheral resistance

Kr (% of base value)	50	75	100	125	150
M_{cor} (ml O_2/sec)	0.2274	0.2563	0.2871	0.3167	0.3405
R_{COR} (mm Hg/ml/sec)	13.56	17.98	22.17	25.86	28.33
FCOR (ml/sec)	1.808	2.044	2.285	2.525	2.712
MPAO (mm Hg)	59.0	75.2	93.4	111.6	126.2
PLV (mm Hg)	93.1	110.0	127.5	144.3	158.3
EDVLV (ml)	130.2	130.5	131.2	133.1	133.8
ESVLV (ml)	37.40	46.97	57.62	67.58	75.20
SV (ml/beat)	92.80	83.53	73.58	65.52	58.60

where Kr is the percentage of normal value of total peripheral resistance

Fig 5.4 shows the effects of baroreceptor reflex on the sudden decrease in blood pressure caused by the sudden decrease in left ventricular contractility at 40s after the onset of simulation. After the regulation of baroreceptor reflex, the arterial pressure was back to set point. HR was increased to 89 beat/min. Total peripheral resistance was increased 8% of the normal value. At 100s after the onset of simulation, left ventricular contractility was increased to its normal value. This resulted in a sudden increase in blood pressure. After the regulation of baroreceptor reflex, the arterial pressure was back to set point. HR and total peripheral resistance were decreased to their normal value.

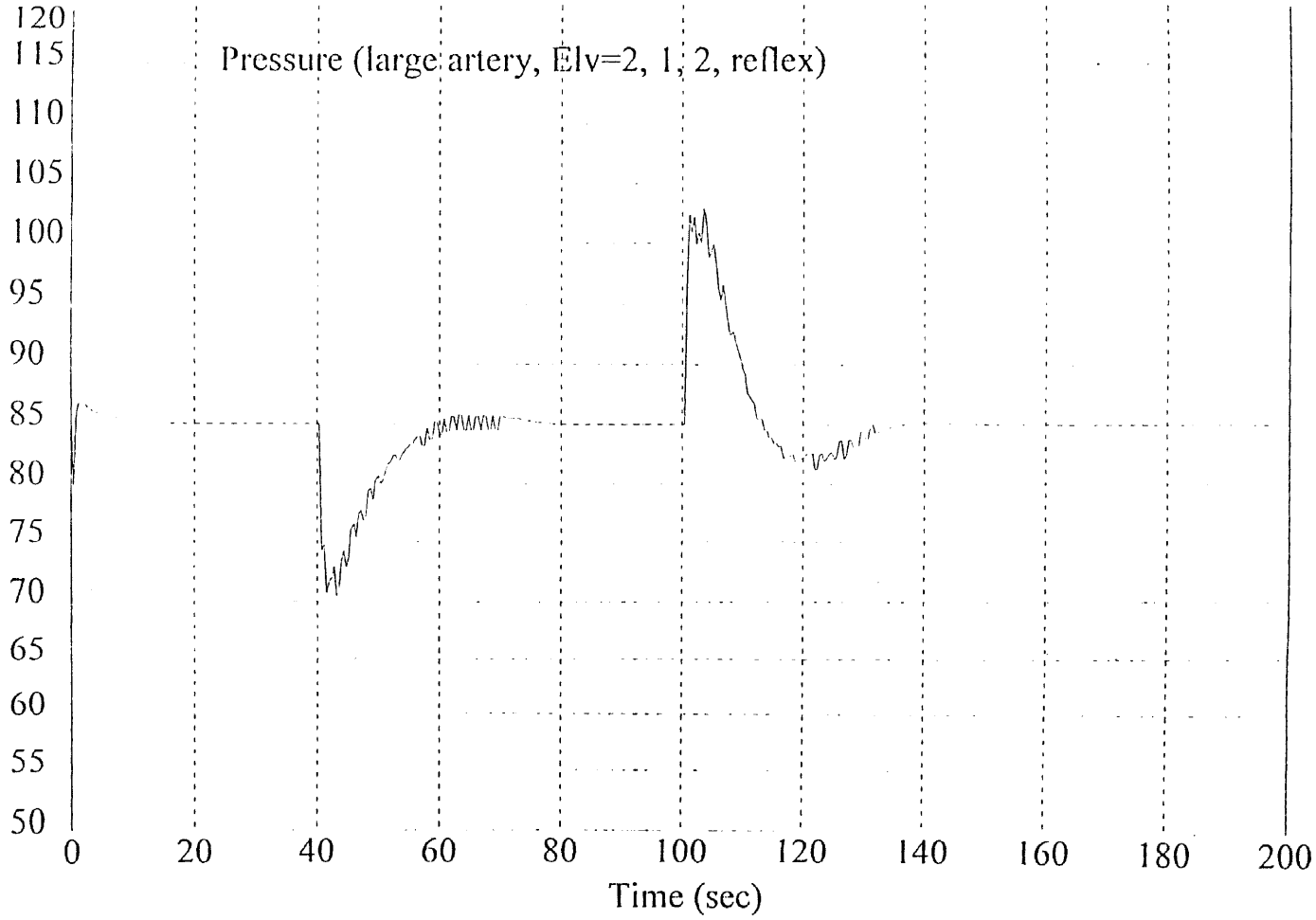

Figure 5.4 The effects of baroreceptor reflex on a sudden change of blood pressure caused by the sudden changes of left ventricular contractility, **(a)** pressure

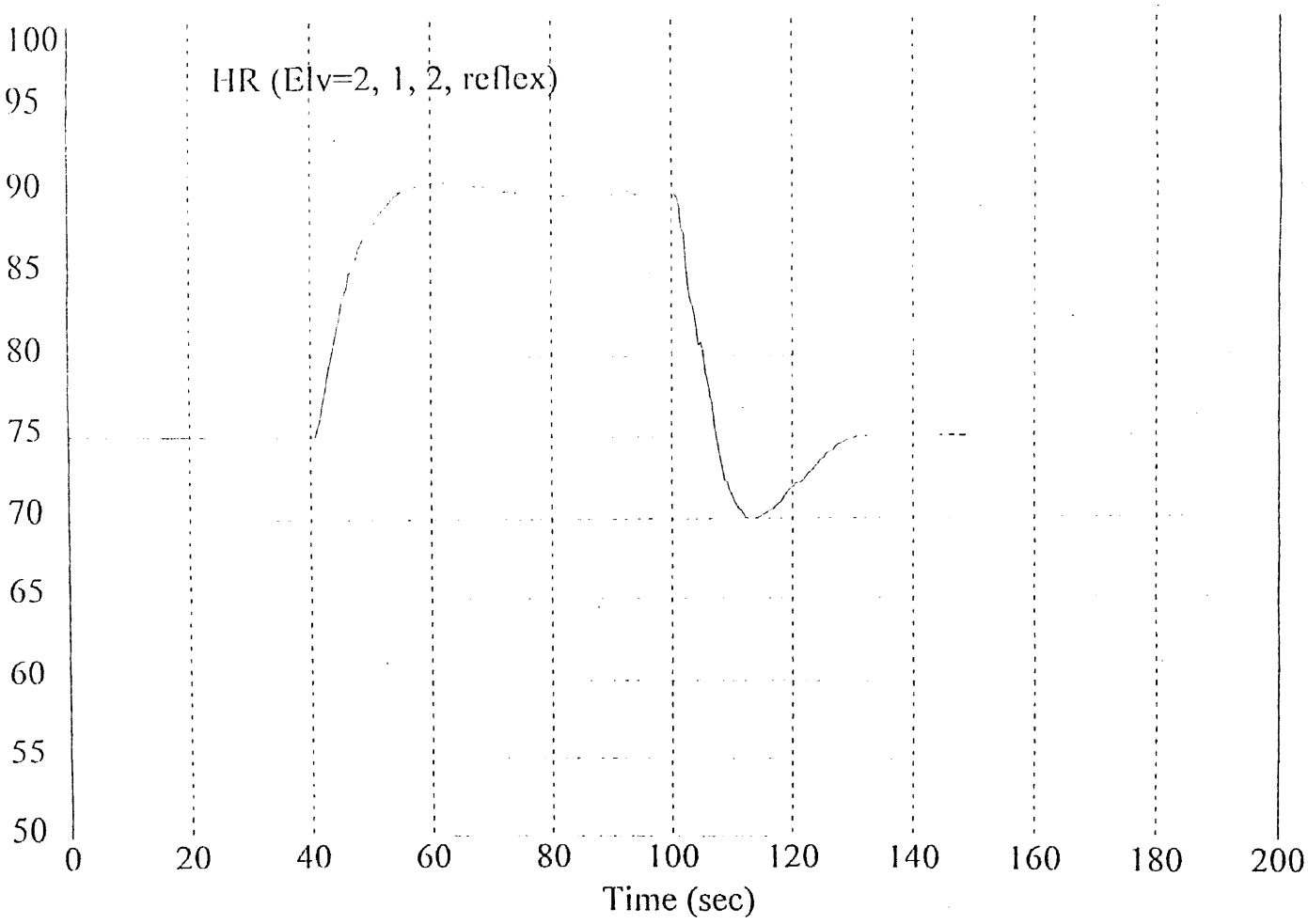

Figure 5.4 The effects of baroreceptor reflex on a sudden change of blood pressure caused by the sudden changes of left ventricular contractility, **(b)** HR

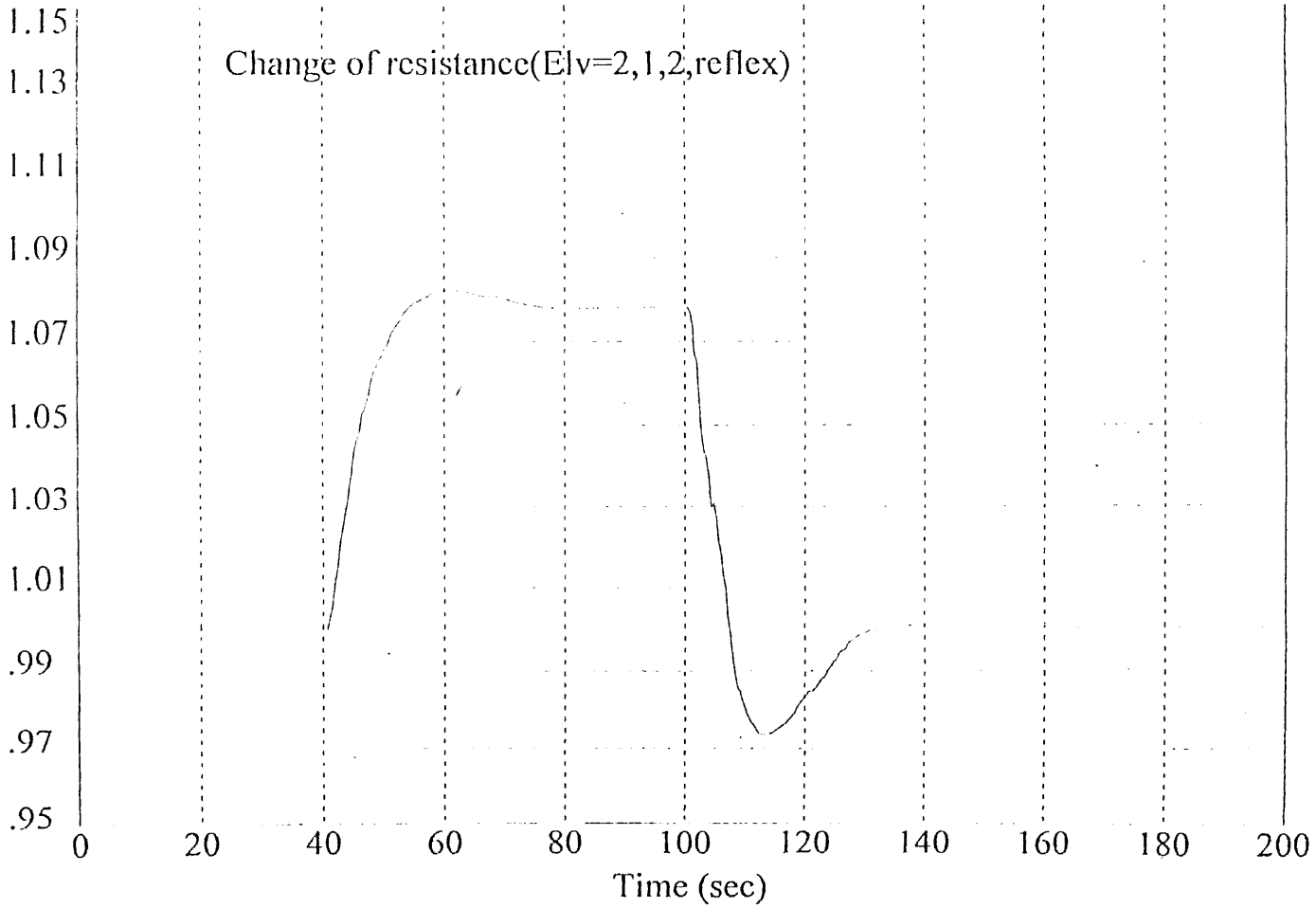

Figure 5.4 The effects of baroreceptor reflex on a sudden change of blood pressure caused by the sudden changes of left ventricular contractility, **(c)** (value of total peripheral resistance) / (normal value of total peripheral resistance).

Fig 5.5 shows the effects of baroreceptor reflex on the sudden increase in blood pressure caused by the sudden increase in total peripheral resistance by 25% of the normal value at 40s after the onset of simulation. After the regulation of baroreceptor reflex, the arterial pressure was back to set point. HR was decreased to 59 beat/min. Total peripheral resistance was decreased from 125% to 117% of the normal value. At 100s after the onset of simulation, Total peripheral resistance was decreased by 25% of the normal value. This resulted in a sudden decrease in blood pressure. HR and total peripheral resistance are back to the normal value. After the regulation of baroreceptor reflex, the arterial pressure was back to set point. HR and total peripheral resistance were increased to their normal value.

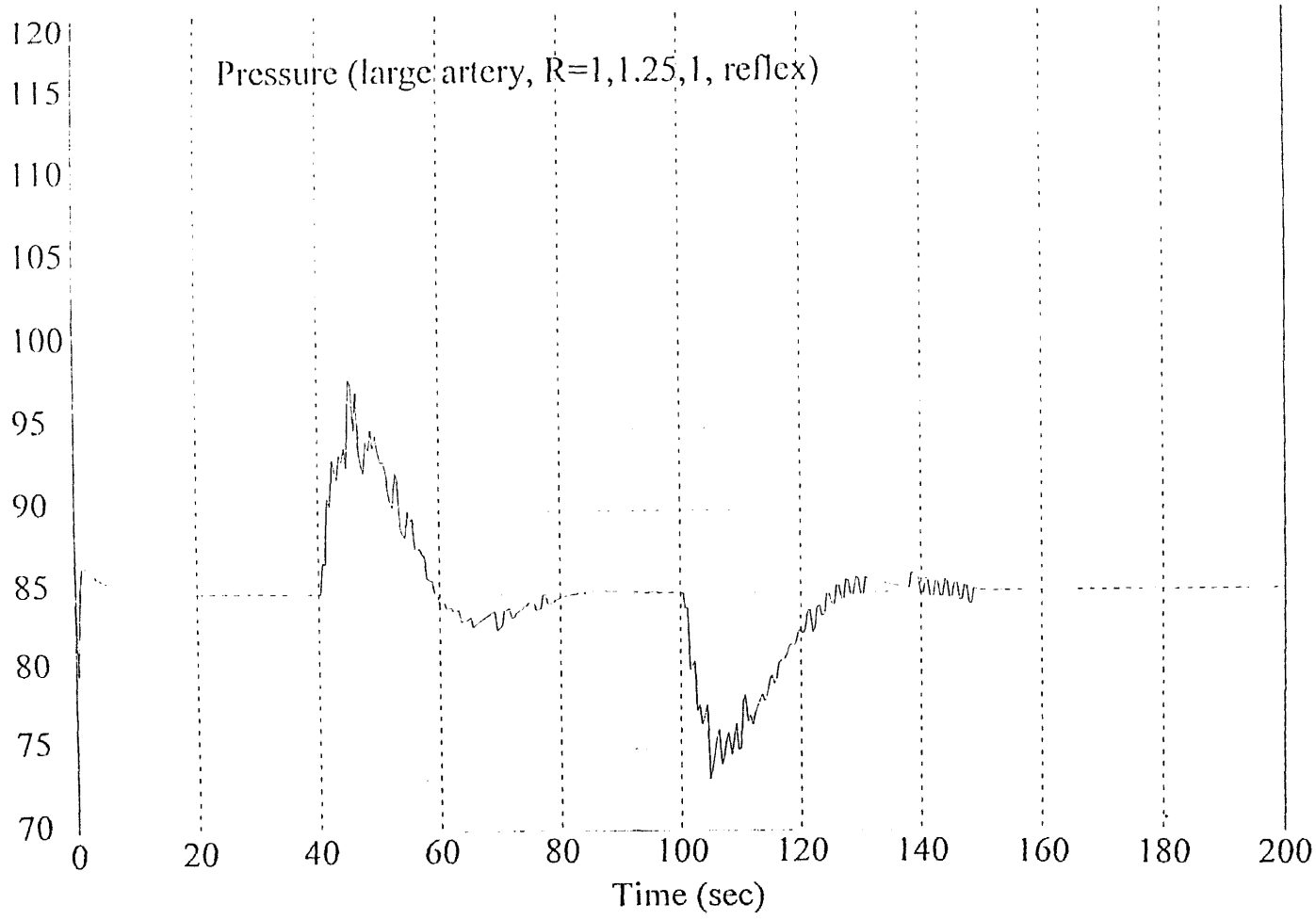

Figure 5.5 The effects of baroreceptor reflex on a sudden change of blood pressure caused by the sudden changes of peripheral resistance, **(a)** pressure

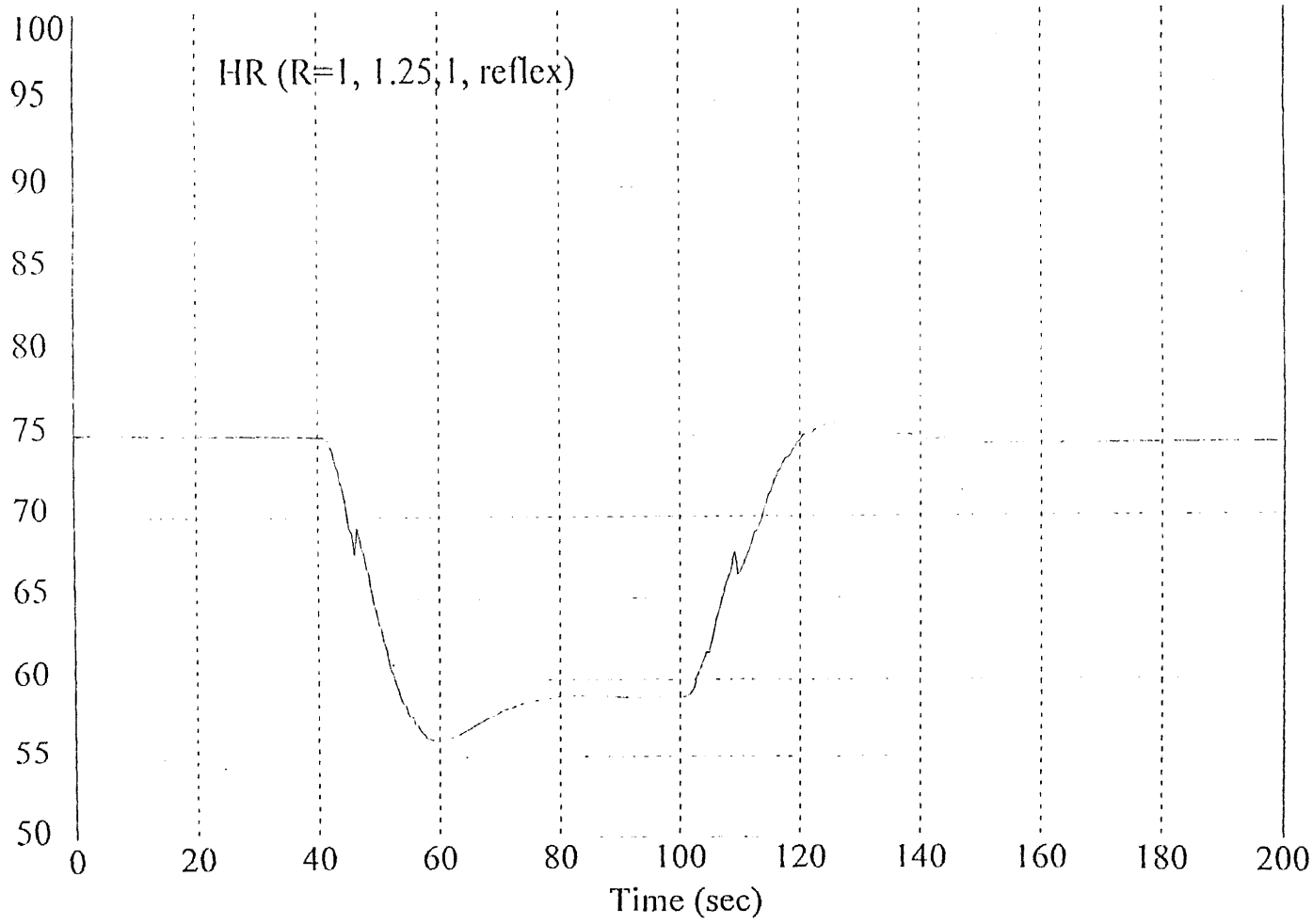

Figure 5.5 The effects of baroreceptor reflex on a sudden change of blood pressure caused by the sudden changes of peripheral resistance, **(b)** HR

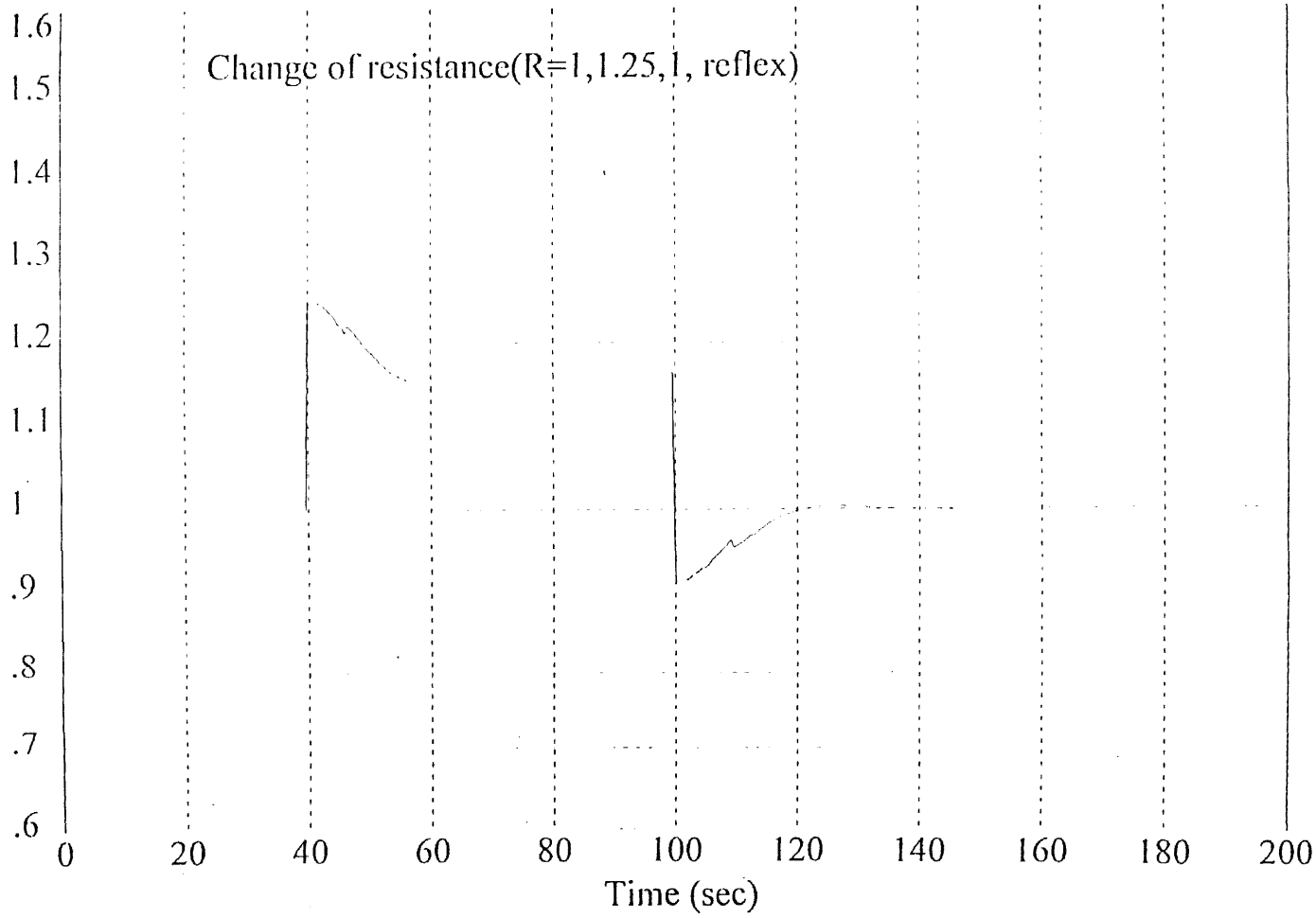

Figure 5.5 The effects of baroreceptor reflex on a sudden change of blood pressure caused by the sudden changes of peripheral resistance, **(c)** (value of total peripheral resistance) / (normal value of total peripheral resistance).

CHAPTER 6

DISCUSSION

6.1 Simulation of Heart Failure

A general procedure for mathematical modeling should follow a logical progression that optimizes the model for the particular application. The generation of an accurate model involves an iterative process of modifying existing model parameters and the reinterpretation of experimental data. Once the parameters are well defined and the equations are expressed, the model should be ready to be tested. In this study the model was tested by simulation the heart failure in two stages. The changes of parameters in the simulation of stage I and stage II heart failure are similar to stage A and stage D heart failure in Tsuruta's study [8]. Tsuruta used four different stages (A-D) of heart failure corresponding to the classification of various NYHA (New York Heart Association) Functional Classes. Among these four stages of heart failure, stage A heart failure the least serious one resulted in a decrease of 10.7% in cardiac output, and stage D heart failure the most serious one resulted in a decrease of 42.9% in cardiac output. Then he estimated the parameters for the four stages of heart failure by his model. The estimated parameters show good agreement with clinical and experimental data. In our simulation of heart failure stage I and stage II were corresponded to Stage A and stage D, respectively. Our model predicted that stage I heart failure resulted in a decrease of 10.7% in cardiac output and stage II heart failure resulted in a decrease of 37.9% in cardiac

output, the arterial pressure had no significant change, which agree with Tsuruta's results.

6.2 Simulation of Autoregulation of Coronary Arteries

Changes in arterial pressure can be generated by four key parameters: ventricle contractility (E_{max}), preload (end diastole volume of ventricle, EDV), afterload (peripheral resistance, R) and heart rate (HR). Any such change affects the rate of myocardial oxygen consumption and thereby alters the required rate of coronary blood flow. Coronary resistance must change so that coronary blood flow under the new pressure, will meet the new myocardial oxygen demand. The direction of this change in coronary resistance is not directly predictable. It may either increase or decrease depending on the change in myocardial oxygen consumption and the associated pressure change. In Barnea's study [6], a model of the left ventricle coupled to the arterial load was used to study autoregulation of the coronary circulation. The results show that an independent increase in one of the four parameters: E_{max}, end diastole volume, peripheral resistance and heart rate results in an increase in arterial blood pressure and myocardial oxygen consumption rate. EDV was the most sensitive among the four parameters. However, In a complete closed-loop circulation EDV is a hemodynamic variable and can not be changed independently of the parameters E_{max}, peripheral resistance and heart rate. Any change in Emax, peripheral resistance and heart rate can result in a change of EDV. Therefore in our model

the effect of autoregulation on an independent change in Emax, peripheral resistance and heart rate includes the effect of change in EDV.

First we discuss the effect of autoregulation on the coronary arterial circulation with changes in peripheral resistance. As shown in Table 6.5, when total peripheral resistance increases from 50% of base value to 150% of base value myocardial oxygen consumption rate (M_{cor})increases 49.7% and Mean aorta pressure (MPAO) increases 113.9%. Since the increase in Mcor is less significant than the increase in MPAO, the resistance of the coronary arterial circulation (R_{cor}) increases. A 108.9% increase in R_{cor} has less effect on blood flow than the increase in MPAO. Therefore, coronary blood flow (FCOR) increases to meet the new coronary metabolic rate requirement.

As heart rate (HR) increases from 55 beat/min to 120 beat/min. M_{cor} increases 97.6% and MPAO increases 38.6%. This results in a 30.2% decrease in R_{cor}. Here the increase of M_{cor} is more significant than that of MPAO. However, the FCOR increases due to the increase in MPAO and the decrease in R_{cor}. After M_{cor} is expressed as the oxygen consumption per beat(In the previous discussion M_{cor} is in ml O_2/sec), we find that there is no significant change in M_{cor}.

The results of changing E_{max} without changing T_{max} shows that increasing E_{max} from 0.5 to 3 results in a 5.5% decrease in M_{cor}. The results seem to disagree with Barnea's [6] results. However, in practice increasing E_{max} results in decreasing EDV that, in turn, leads to a decrease in M_{cor}. We have

discussed the pressure-volume area (PVA) which is a measure of the total work done by the ventricle per heart beat. PVA is the sum of external work (W_E) and mechanical potential energy (W_P). When E_{max} increases from 0.5 to 3, the peak pressure of the left ventricle increased 34.9%, and stroke volume increased 25.5%. This results in am increase in external work (W_E). Meanwhile the end systolic volume of the left ventricle decreases 80%. This results in a decrease in mechanical potential energy (W_P). Therefore, PVA decreases. Suga [4] and Shroff [5] report that T_{max} decreases with increased E_{max} when other conditions are held constant. We then changed T_{max} from 130% to 80 % of the value calculated by equation (8) corresponding to E_{max} changing from 0.5 to 3. The results show that M_{cor} increases as E_{max} increases with a decrease in T_{max}. The exact relationship between E_{max} and T_{max}. is complex. The simulation listed in table 6.2 do not correspond to any physiological processes since the degree to which T_{max} changes in vivo is unknown. However, in comparison to the results obtained without changing T_{max}, we believe that decreasing T_{max} results in increasing M_{cor}.

We compared the effects of autoregulation when peripheral resistance, HR and E_{max} were changed. We found that only peripheral resistance affected M_{cor} significantly. The simulations predict that M_{cor} is mainly affected by afterload. If afterload is not changed, changes in HR will not significant affect the oxygen consumption per beat, also changes in E_{max} will not significant

affect M_{cor}. The relationship of E_{max} and T_{max} might be important in this prediction.

The maximum coronary circulation resistance, which is a measure of coronary vascular reserve and higher efficiency of arterial pressure generation, is defined as an optimal condition. The model in this work shows that the resistance of the coronary circulation increases as contractility and peripheral resistance increases, and heart rate decreases. These observations suggest that maximizing contractility and peripheral resistance, and minimizing heart rate may improve ventricular coronary vascular reserve.

6.3 Some Limitations of the Model

(1) In present model, the compliance of the arterial compartment is constant throughtout the cardiac cycle. However, the compliance of arteries, especially in the aorta, is a time-varying paramenter.

(2) We assumed that the the oxygen consumption rate in all tissues except for myocardium is constant. Actually the oxygen consumption rate in all tissues are a function of their metabolic demands as in the myocardial circulatio.

(2) The baroreceptor reflex is actuated when a sudden change in arterial pressure occurs. In our model, the pressure is returned exactly to the set point by a negative feedback regulator. In practice, the arterial pressure will only be returned to within ±10% of the set point. There are low-frequency oscillations in arterial pressure and heart rate when the baroreceptor reflex is actuated.

These oscillations are caused by a time delay between the actuation of the reflex and the changes in HR, peripheral resistance and contractility necessary to implement the feedback controller

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