ABSTRACT

Modification, Reimplementation and Studies Using the Meisner Model of the Heart

by

Ari Zvi Zivotofsky

The study of left ventricular filling in both the normal and the pathological heart is of great importance. A computer model simulation of the heart with emphasis on mitral flow was designed by Meisner in 1986 and implemented in QuickBASIC. This paper discusses how the original program was altered to be able to perform "Parameter vs. Parameter" runs in which it can be observed how varying an input parameter affects output parameters. The output data is then formatted in such a way that it can be used by QUATTRO PRO, a standard spreadsheet package, to yield graphical outputs.

In addition, the original model was implemented in the circuit simulation package PSPICE. This, coupled with the graphics post-processor PROBE that accompanies PSPICE, enables the model to yield higher quality graphs, both P-V loops as well as parameters versus time. This also permits additional information to be gained from the model and offers potential for more easily expanding the model.

MODIFICATION, REIMPLEMENTATION AND STUDIES USING THE MEISNER MODEL OF THE HEART

by

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APPROVAL PAGE

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This thesis is the culmination of over a year of work. But without the help of many people I could not have accomplished even a small part of it. I came from NJIT to the Albert Einstein College of Medicine (AECOM), looking for a warm, active and intellectually stimulating lab in which to do research directed towards a masters thesis. What I happened upon was Dr. Ed Yellin's lab at AECOM. It was what I was looking for, and a whole lot more. He generously gave of his lab, his equipment, his expertise and, most importantly, of himself. There is no way to thank him, except to say that without him I would not have this thesis. He also offered one more source of assistance, but this he could not give of his own accord. This was the assistance of his former student, Dr. Jay Meisner. Jay was always ready and willing to make time, to explain anything and to assist with everything. What better way to learn the Meisner model than from Meisner! His assistance and friendship have been invaluable in the preparation of this thesis.

For assistance with equipment I am indebted to Essex County College (ECC) for loaning me their licensed copy of PSPICE.

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CHAPTER I

INTRODUCTION

An understanding of cardiac function is essential for proper diagnosis and treatment of many heart related maladies. One of the least understood and yet essential aspects of heart function is that of diastolic filling and mitral flow. Particularly nowadays, when mitral flow can easily be imaged noninvasively with echocardiography it is essential to understand the significance of various flow patterns. A useful tool for gaining further understanding of this process is through computer simulation and modeling. As part of his doctoral dissertation in the Sue Golding Graduate School of the Albert Einstein College of Medicine of Yeshiva University, Jay Meisner in 1986 developed a model of the heart with a particular emphasis on mitral flow. This model continues to be used as a research tool by Dr. Ed Yellin and the members of his lab, and continues to be regularly upgraded by Meisner. This model was implemented in compiled QUICKBASIC and is designed for single "control" or "control-intervention" runs. Significant modification of the model requires changes in the defining differential equations.

The goal of this thesis is two-fold. First, is to provide for an additional mode of operation of Meisner's original implementation, to be called "parameter vs. parameter" runs. this enables the program to perform multiple intervention runs, one right after the other, and format the data in such a way that it can be graphed using a spreadsheet package. The second goal is to present a totally new implementation of the existing model

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using the PSPICE circuit simulation package. This will then enable the model to be more flexible in terms of additions and modifications, as well as to possibly yield new information even without modification to the model. Both of these goals were accomplished. This thesis contains the background information, including the relevant physiology and modeling, the development of the Meisner model, the methods of accomplishing both goals and examples of the results.

CHAPTER II

ANATOMY and PHYSIOLOGY:

Introduction: Because the major focus of this paper is modeling the mechanical functioning of the heart, with a particular emphasis on transmitral blood flow, the anatomy and physiology required as background is primarily that of the heart. However, because the heart serves as the principal pump in the body's circulatory system, before discussing the heart it is necessary to briefly describe the overall functioning of the circulatory system.

Almost all physiological processes within the body involve the maintenance of the internal environment, or homeostasis. A number of different body systems, including the endocrine, nervous and circulatory systems, participate in this regulation. The circulatory system serves to transport and distribute essential substances to the tissues and to remove by-products of metabolism. It also shares in humoral communication, the immune response, and the homeostatic regulation of body temperature.

Circulatory system: The circulatory system consists of a pump, a series of distributing and collecting tubes and an extensive system of thin vessels (the capillaries) that permit the rapid exchange between the tissues and these vascular channels. In mammals this system is actually a double system, consisting of two pumps in series, the left and right hearts, and two corresponding distensible, closed vascular systems. These are the pulmonary circulation, originating from the right heart, propelling blood through the lungs for the exchange of oxygen and carbon dioxide, and the systemic circulation, flowing from the left heart, propelling blood to all

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other tissues of the body.(See figures 1 and 2.) Each system has a distribution manifold (the pulmonary artery and the aorta, respectively) which also acts as a capacitance (storage chamber), and a peripheral circulation which distributes, transports and controls flow, and is predominantly resistive (frictional).

Because the double heart and the lungs constitute a series branch that drives all the parallel connected branches of the entire circulatory system, one can start at any point in tracing the flow of blood. From the left heart, blood is pumped intermittently into the aorta, the largest artery in the body. Although this pumping is intermittent, flow to the periphery is continuous due to the distension of the aorta and its branches during flow out of the heart, which results in the storing of blood, followed by elastic recoil of the aorta and the large arteries while the heart is relaxing, releasing the stored blood and maintaining the continuous flow. The blood moves rapidly through the aorta and into the arteries which branch off from it. These arteries become progressively narrower and their walls become thinner and more muscular. From these the blood proceeds into still narrower, even more muscular and less elastic arterioles, which are characterized by a relatively large resistance to flow. Thus, both pressure and velocity drop significantly at this stage. Many exceedingly thin walled, narrow capillaries branch from each arteriole. Although the capillaries are very narrow, the extraordinary branching ensures that the capillary bed has a greater total cross-sectional area than the rest of the circulatory system and thus guarantees that almost all cells in the body are within a few cell diameters of at least one of these smallest branches of the circulatory system. The capillary walls are only one cell thick, and the blood flow rate at this point is slow --- conditions ideal for diffusion between

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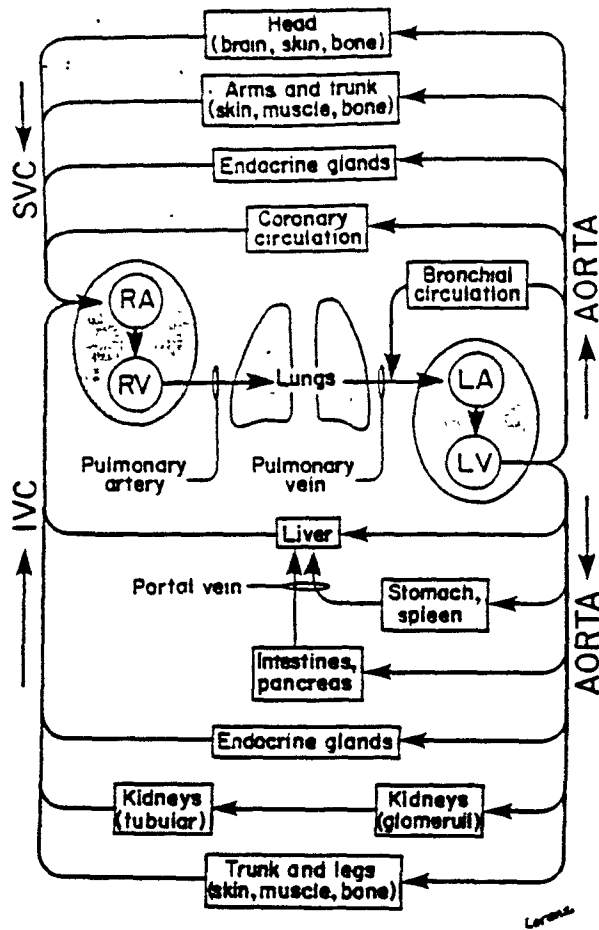
Schematic outline of the cardiovascular system. RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle, IVC = inferior vena cava, SVC = superior vena cava.

Fig. 1
Sparks, p.3
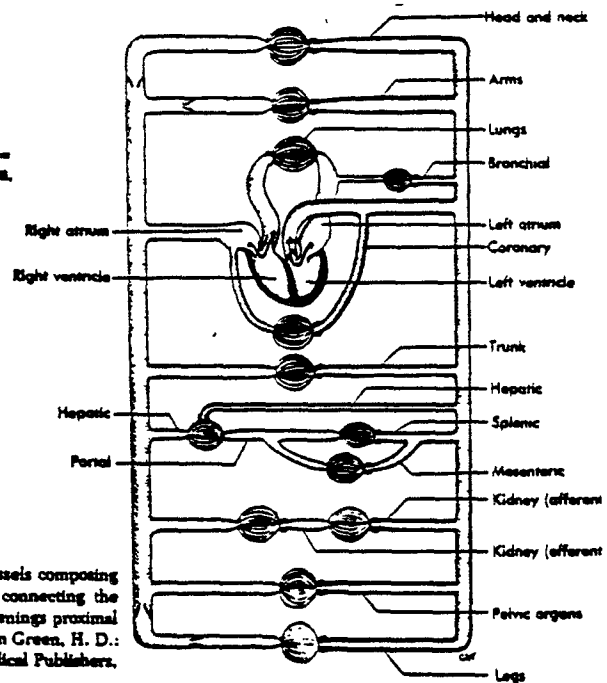
Fig. 2
Berne, 1977, p.4

Schematic diagram of the parallel and series arrangement of the vessels composing the circulatory system. The capillary beds are represented by thin lines connecting the arteries (on the right) with the veins (on the left). The crescent-shaped thickenings proximal to the capillary beds represent the arterioles (resistance vessels). (Redrawn from Green, H. D.: In Glasser, O., editor: Medical physics, vol. I, Chicago, 1944, Year Book Medical Publishers, Inc.)

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the blood and its surrounding tissue, enabling delivery of the needed products and removal of waste. As seen in figures 1 and 2, there are several exceptions to the usual pattern of circulation, most notably the liver and kidneys.

On the return trip to the heart the blood travels through the capillaries and is collected in venules of increasing diameter and cell wall thickness. It proceeds into the veins and eventually into the two largest veins, the superior and inferior vena cavae. This returning blood enters the right side of the heart from where it is pumped into the pulmonary arteries. Parallel to the systemic circulation, blood flows from the pulmonary arteries into arterioles and then into the pulmonary capillaries. These capillaries are all located around alveoli (tiny air-sacs) in the lungs, where the exchange of gases occurs. The blood then makes its way back through the pulmonary venules to the pulmonary veins and into the left heart.

All blood pumped out of the right heart is received by the lungs and then returned to the left heart. Thus, the lungs is the last organ that all blood pumped out of the left heart has passed through. In contrast, peripheral organs and tissues each receive only a small fraction of the blood pumped by the left heart. Accordingly, all blood returning to the right side has not been through any particular organ, for example the kidney or liver.

The circulatory system is a closed loop with a constant volume. Any acute increase in volume in one region must be compensated for by a corresponding decrease in an other. Pressure and velocity in the different parts of the circulatory system vary greatly and are determined by many variables, including overall flow rate and volume, vessel thickness, vessel contractibility and compliance. (See figure 3.)

Anatomy of the heart: The heart is a muscular organ that pumps blood through the circulatory system. It consists of a series of four separate chambers, two atria and two ventricles one of each in the right and in the left hearts, that have one-way valves to direct the flow of blood. (See figure 4.) The atria are thin walled, low pressure chambers that, while their pumping has significance, function more as large reservoir conduits of blood for their respective ventricles than as important pumps for the forward propulsion of blood. The ventricles serve as the main pumping chambers of the heart and are responsible for most of the propulsion of the blood. Located between the atrium and the ventricle in each side of the heart are AV (atrioventricular) valves which permit blood to flow from the atrium to the ventricle but not in the other direction. The AV valve in the right heart is called the tricuspid valve and the left AV valve is called the mitral valve. The tricuspid valve consists of three overlapping cusps and the mitral valve two overlapping cusps. The right ventricle pumps into the pulmonary artery with the opening regulated by the pulmonary valve, while the left ventricle leads into the aorta through the aortic valve. These valves both consist of three cuplike cusps and are known as semilunar valves. During contraction of the ventricles these valves permit blood to flow out of the ventricles into the arteries, and they prevent blood from moving in the opposite direction during ventricular relaxation. All four of these valves act primarily in a passive manner; their being open or closed depending primarily upon the pressure difference across them and the flow through them.

In contrast, the veins that lead into the atrium are not capped by valves. Thus at the entrance of the vena cavae into the right atrium and of the pulmonary veins into the left atrium there are no valves and the

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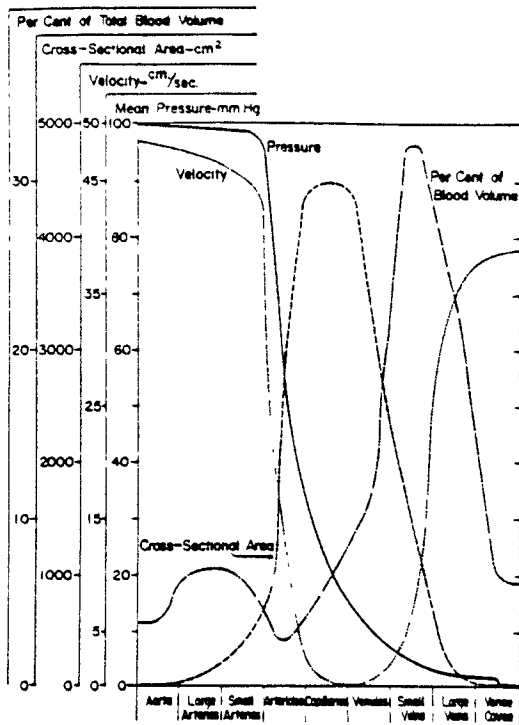
Pressure, velocity of flow, cross-sectional area, and capacity of the blood vessels of the systemic circulation. The important features are the inverse relationship between velocity and cross-sectional area, the major pressure drop across the arterioles, the maximal cross-sectional area and minimal flow rate in the capillaries, and the large capacity of the venous system.
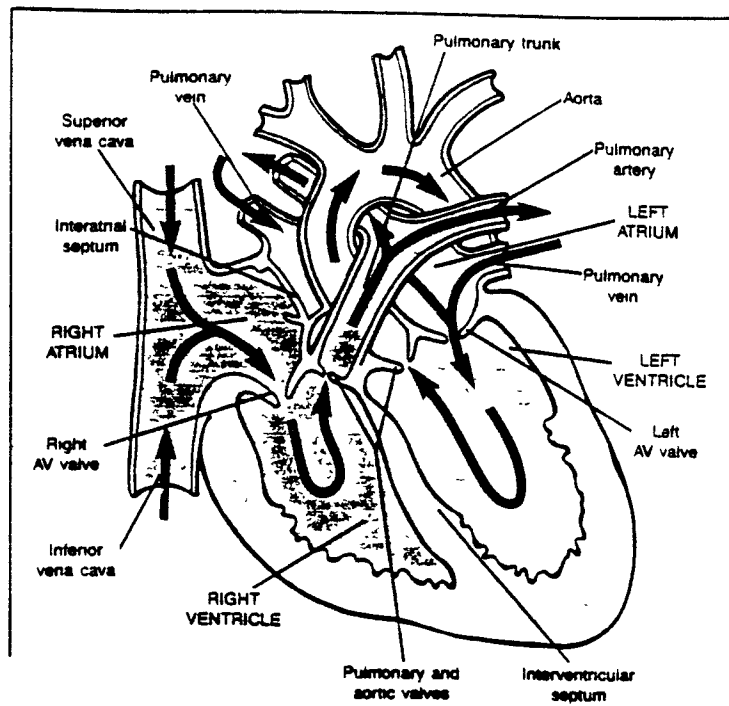
Diagrammatic section of the heart. The arrows indicate the direction of blood flow

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possibility of backflow exists. In actuality, however, during atrial contraction very little blood flows back into the veins. This is explained by three aspects of atrial contraction. First, the pressure generated by atrial contraction is not so large as to cause extensive backflow. Second, atrial contraction causes the veins at their site of entry into the atrium to become constricted, which increases the resistance to backflow; and third, the inertia of the inflowing blood tends to counter any backflow.

Cardiac Cycle:

Introduction: The orderly process of atrial and ventricular contraction and relaxation is controlled by precisely timed electrical signals generated by the cyclical depolarization and repolarization of the cardiac cells. The external recording of these signals produces the electrocardiogram (ECG). This orderly electrical process triggers an orderly mechanical process, known as the cardiac cycle, responsible for pumping the blood. This cycle of events occurs almost simultaneously in the left and right hearts, with higher pressures on the left side. It is therefore adequate to describe the process once, conventionally for the left side.

The cardiac cycle is divided into two major phases, both named for events taking place in the ventricle. Specific demarcation of each phase is difficult to define. Roughly, systole, comprising about one-third of the cycle, is when the ventricle is contracting and blood is ejected into the arteries; diastole, occupying the remaining two-thirds of the cycle, is the part of the cycle during which the ventricle relaxes and is filled with blood. Although the major concerns in this paper are mechanical, i.e. pressures, flows, stored volumes, etc., in describing the cardiac cycle the important electrical

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and auditory milestones will be pointed out as well. Figures 5 and 6 show the various events of the cardiac cycle.

Diastole: A significant portion of ventricular filling occurs immediately on the opening of the mitral valve when blood that had returned to and stored in the atrium during the prior ventricular systole is abruptly released into the relaxing ventricle. This period is known as the rapid filling phase and lasts about 100 msec. This phase is preceded by a decrease in ventricular pressure until it is below atrial pressure, allowing for the opening of the AV valve and the inrush of blood. During this phase of rapid filling there is a decrease in both atrial and ventricular pressures as well as a sharp increase in ventricular volume, followed by an increase in pressures causing the two chambers' pressures to equilibrate. This rapid ventricular filling is responsible for the faint third heart sound discernible on a phonocardiogram, and audible in certain physiologic conditions, such as in young people and in athletes with large stroke volumes, and in certain diseased states with large hearts. The flow then oscillates due to oscillations in the pressure gradient and thus, following rapid filling there is a slow filling phase known as diastasis, in which blood returning from the periphery uses the atrium as a conduit to slowly add volume to the ventricle. This phase is characterized by a gradual increase in atrial, ventricular and venous pressures and in ventricular volume. Its duration depends on heart rate, since with higher heart rates the diastolic period shortens more than the systolic.

Atrial systole, which occurs towards the end of the diastolic phase in the cycle, completes ventricular filling by "topping it off" with a final small volume of blood, about 10-15% of the total filling volume -- the "atrial kick". This is the actual pumping of blood by the atrium through the AV valves

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Fig. 5
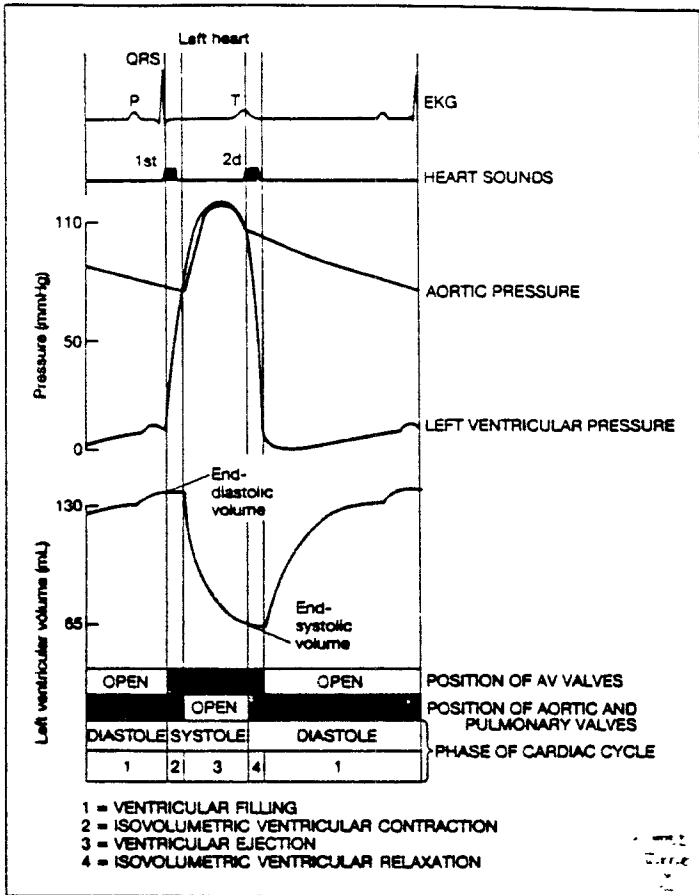
Vander, 1990, p.373

Summary of events in the left ventricle and aorta during the cardiac cycle.

Within Fig. 5:

- Left heart
- QRS, P, T — EKG
- 1st, 2d — HEART SOUNDS
- AORTIC PRESSURE
- LEFT VENTRICULAR PRESSURE
- End-diastolic volume
- End-systolic volume
- Pressure (mm Hg): 110, 50, 0
- Left ventricular volume (mL): 130, 65

OPEN		OPEN	POSITION OF AV VALVES
	OPEN		POSITION OF AORTIC AND PULMONARY VALVES
DIASTOLE	SYSTOLE	DIASTOLE	PHASE OF CARDIAC CYCLE
1	2	3	4	1	

1 = VENTRICULAR FILLING
2 = ISOVOLUMETRIC VENTRICULAR CONTRACTION
3 = VENTRICULAR EJECTION
4 = ISOVOLUMETRIC VENTRICULAR RELAXATION

Fig. 6

Berne, 1977, p.19

Left atrial, aortic, and left ventricular pressure pulses correlated in time with aortic flow ventricular volume, heart sounds, venous pulse, and electrocardiogram for a complete cardiac cycle in the dog.

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into the ventricle and is initiated by an electrical stimulus seen as the P-wave on the ECG. Atrial systole causes a further rise of atrial (known as the "a" wave), ventricular and venous pressures and in ventricular volume. The few small vibrations caused by atrial systole together with the concurrent changes in ventricular compliance account for the audible fourth or atrial heart sounds seen only on the phonocardiogram or heard in certain diseased states. Throughout this process of ventricular filling, atrial pressure is never more than only slightly higher than ventricular pressure. Though the pressure gradient across the AV valve is small (about 1-3 mm Hg), it is a large enough gradient to maintain the flow which in turn keeps the valves open.

The actual importance of atrial systole in ventricular filling is a subject of much controversy. Early studies (Harvey, 1628) felt that most of the ventricular filling volume was due to atrial pumping. The first modern investigation (Henderson, 1906) reached the opposite conclusion, suggesting that atrial systole contributed almost nothing. More recent clinical investigations have found a wide range of values for the atrial pump contribution to ventricular filling, all somewhere between these two extremes (Meisner, 1986). Its relative contribution and importance, however, certainly varies with the conditions. For instance, in a slow beating heart in which there is time in diastole to complete the entire rapid filling phase plus some diastasis, atrial systole is certainly less important than in tachycardia where rapid filling may not even have time to be completed, certainly no slow filling occurred. Additionally, in a normal heart in which the AV valves present little resistance, the contribution of atrial systole to ventricular filling should be different than in a case of mitral stenosis, where there is marked narrowing of the valves, allowing

for less, more difficult blood flow. Traditionally, it has been assumed that in mitral stenosis the contribution of atrial systole was of greater importance. However Meisner, et al. (1991) have recently demonstrated that atrial systole is in fact less significant in mitral stenosis that in a normal heart.

Systole: Atrial depolarization, the electrical signal originating at the SA node which initiated atrial contraction and is seen as the P wave on the ECG, is followed by an electrically quiet period during which the atrium contracts and the electrical signal, traveling to the ventricle, is delayed by the AV node. This interval, known as the PR interval, is approximately 0.1 seconds long. Upon reaching the ventricle, the electrical signal initiates ventricular contraction, or systole. This signal is seen as the R wave in the QRS complex on the ECG. The ventricular contraction causes a quick, sudden rise in ventricular pressure which, due to the very small pressure gradient that existed across the AV valves, causes an almost immediate change in the direction of the pressure gradient. In general, the healthier the heart the more rapid will be this rise in pressure; dP/dt is higher. Though the change in direction of the pressure gradient is almost immediate, it takes about 25 msec. to overcome the momentum of the inflowing blood and for the mitral valve to actually close (Laniado, 1973). Though this delay in mitral valve closure due to inertia is now well known and accepted, it is important to note that the graphs found in many standard texts, such as the one in figure 6, still do not take this into account, and show the mitral valve closing at the pressure cross-over. The closing of the mitral and the tricuspid valves produces the first audible heart sounds as well as the "c" wave. The mitral and tricuspid valves, though not closing simultaneously, do so so closely in time that in a healthy

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heart they are heard as one heart sound with the mitral valve closure contributing the louder portion. Although the precise definition of the end of diastole is open to debate, by many physiologic definitions it is at this point, the instant the the AV valves close. The quantity of blood in the ventricle at this time, which is the largest volume to be attained during the entire cycle, is therefore called the end diastolic volume (EDV). The pressure rise in the ventricle at the start of systole does not immediately increase the pressure above that of the aortic pressure and it is thus insufficient to force open the aortic valve. With both the mitral and aortic valves closed the volume of blood in the ventricle remains constant for a short period. Since blood, like water, is essentially incompressible, in response to ventricular contraction the ventricular walls develop tension but cannot shorten and the ventricular pressure continues to increase, in a phase known as isovolumetric contraction. The increased pressure within the sealed ventricle is also transmitted to a small degree across the closed aortic valve, resulting in a small increase in aortic pressure.

When ventricular pressure exceeds aortic pressure the aortic valve opens, allowing blood to flow from the ventricle to the aorta. This constitutes the ejection phase. The first, shorter part of the phase is known as the rapid ejection phase. It is characterized by a (continued) sharp rise in ventricular and aortic pressures, a sharp decrease in ventricular volume and a large aortic blood flow. At this time there is also a sudden sharp drop in atrial pressure, because the base of the heart descends allowing the atrium to stretch and reduce its pressure. However, throughout the remainder of ventricular systole, atrial pressure rises gradually because the mitral valve is closed and the atrium is stretching as new venous blood is continually returning to it. After approximately the

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first third of the ejection phase, aortic flow peaks as runoff of blood from the aorta to the periphery exceeds the ventricular output. Almost immediately thereafter ventricular pressure begins to decrease and rapidly falls below aortic pressure. During this phase of reduced ejection the aortic valve remains open and blood continues to flow even though aortic pressure is now above ventricular pressure. This continued flow is possible due to the forward inertia of the flowing blood. The amount of flow, however, gradually decreases as ventricular pressure falls well below aortic pressure until there is almost no flow and finally the aortic valve is forced closed.

The total volume ejected from the ventricle during systole is called the stroke volume (SV) and is normally about 60% of the EDV; that which remains in the left ventricle after systole, the smallest ventricular volume attained in the cycle, is termed residual volume or end systolic volume (ESV). Cardiac output, another important measure of heart function, is defined as the amount of blood ejected by the heart per unit time. It is therefore the product of heart rate and stroke volume and in an average adult human is about 5 - 6 Liters/minute.

The closing of the aortic and pulmonic valves produces the second audible heart sound. These two closures are physiologically split during inspiration producing a "split sound", and merge during expiration yielding a single second heart sound. Pulmonary venous return which has been flowing into the left atrium throughout systole continues to do so after the closing of the aortic and pulmonic valves. The small increase in atrial pressure that occurs throughout mid-late systole due to this venous return is called the "v" wave.

Ventricular repolarization, indicated by the T wave on the ECG, initiates ventricular relaxation. During the early part of ventricular relaxation the valves at both ends of the ventricle are closed. The ventricle thus relaxes with no change in volume, resulting in a precipitous fall in ventricular pressure. This phase is known as isovolumetric relaxation. The ventricular pressure continues to fall until just below atrial pressure, at which time the mitral valve opens and the rapid filling phase occurs again.

Starling's law : An important factor in establishing SV is the force, or pressure, with which blood is ejected when the heart contracts. It has been shown that, similar to skeletal muscle, longer initial length of the cardiac muscle results in an increased force development during contraction. It is possible in experimental conditions to stretch cardiac muscle so far as to begin reducing the developed force. It is rare for this to occur, however, in an intact, operational heart. This length-tension relationship in the heart, which can be viewed as a transfer function relating EDV to force developed in systole, is known as the Frank-Starling relationship or simply Starling's law of the heart. (See figures 7 and 8.)

Three factors which are important in determining stroke volume are preload, afterload and contractility. The load stretching a resting muscle is called the preload. This is what determines the force of contraction according to Starling's law. When the muscle contracts, the load, or impedance, that it then sees, which it did not see before the contraction, is called the afterload. In the heart the afterload is the aortic pressure which is felt only after contraction starts and the aortic valve opens. Figure 9 demonstrates the effect of increased afterload on ventricular pressure and

Cardiac output
Stroke volume
Stroke work

End diastolic fiber length
End diastolic volume
End diastolic pressure
Atrial pressure
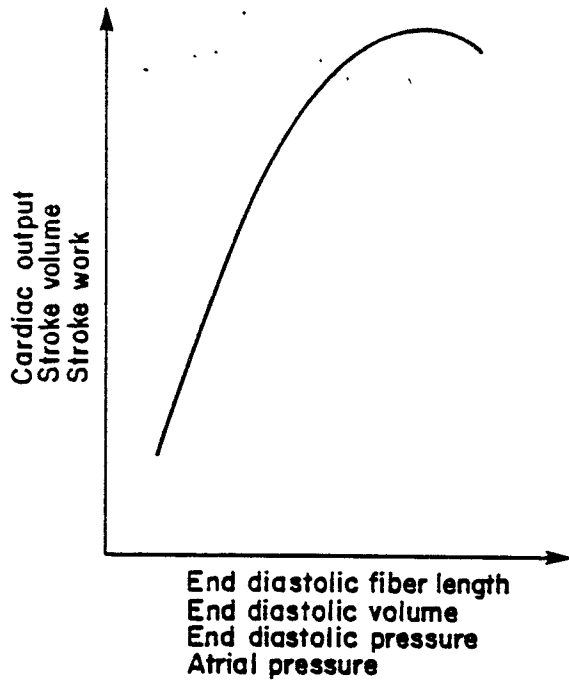
Ventricular function curve. Several combinations of variables can be used to plot the ventricular response curve.

Fig. 7
Sparks, p.61

Fig. 9
Sparks, p.69
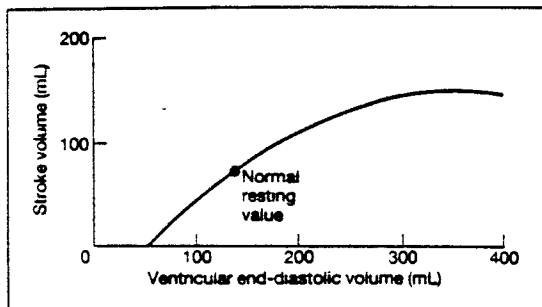
Relationship between ventricular end-diastolic volume and stroke volume (Starling's law of the heart). The data were obtained by progressively increasing ventricular filling pressure with a heart-lung preparation. The horizontal axis could have been labeled "sarcomere length," and the vertical "contractile force." In other words, this is a length-tension curve.

Fig. 8
Vander, 1990, p.378
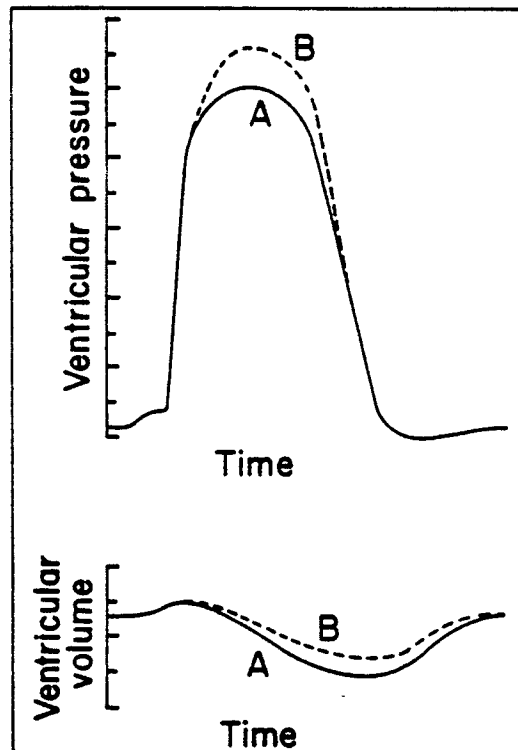
Effect of aortic pressure on ventricular function.

normal (A) and elevated (B) aortic pressure.

volume. One more factor in determining SV, contractility, is defined as the force of contraction at any given length, i.e., on which Starling curve is the heart functioning. Therefore, increased contractility translates into increased force at a given length. (See figure 10.)

Unlike the pressure developed in the ventricle during systole, which rises very steeply for small early changes in EDV, the pressure developed during diastole due to the ventricular filling is initially quite flat, indicating that large increases in volume can be accommodated with only a small increase in pressure (See figure 11). However, with greater filling the heart becomes much less distensible, as evidenced by the sharp rise of the diastolic curve at higher volumes. Another factor in determining the pressure in the ventricle is the shape of the ventricular chamber. A good approximation for the relationship between ventricular pressure and ventricular diameter is Laplace's law for the sphere in which stress developed is directly proportional to the radius.

Aortic Flow: Since the primary goal of the cardiac cycle is to efficiently pump blood throughout the body, and since all the blood that will circulate begins by being pumped out of the ventricle into the aorta, it is important to consider the graphs of aortic pressure and flow. As can be seen in Fig. 12, the aortic pressure climbs rapidly at the beginning of systole as the aortic valve opens and blood rushes from ventricle to aorta. This pressure rise and subsequent "cap" in the pressure curve follows the ventricular pressure curve, lagging slightly behind in time. As the left ventricular pressure drops and the aortic valve closes, the compliant and stretched aorta tries to send some blood back towards the ventricle. This attempted backflow, which is stopped by the closed valve, accounts for the notches in the aortic pressure wave at the end of systole. The aortic
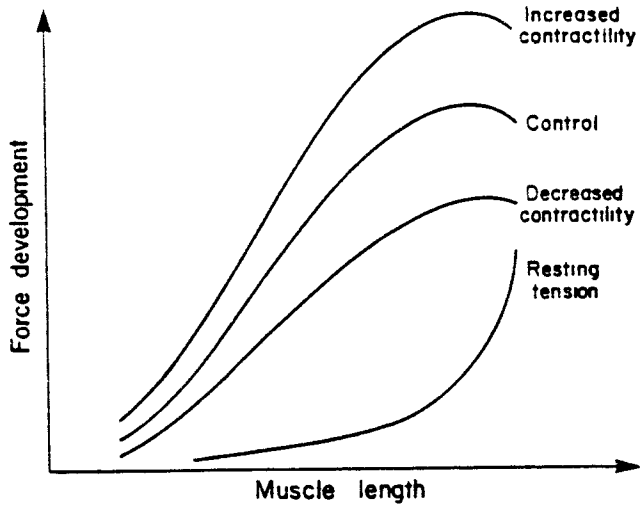
Fig. 10
Sparks, p.51
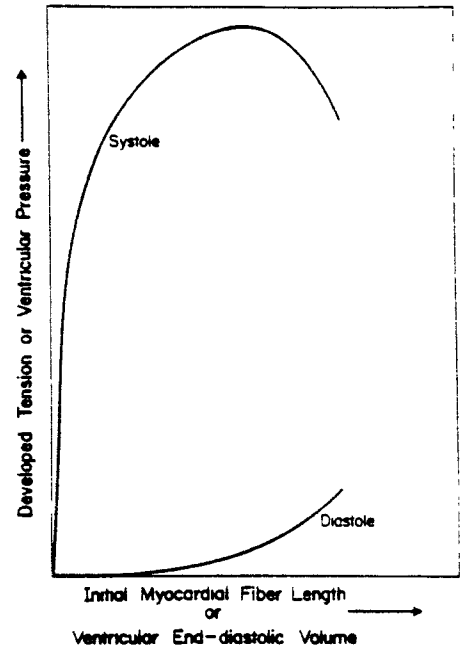
Fig. 11
Berne, 1977, p.76
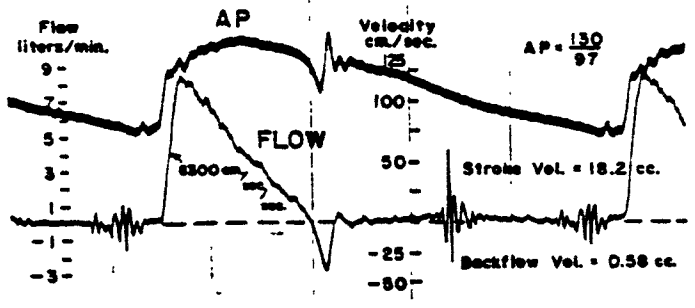
Fig. 12   Aortic Pressure (top) and Flow (bottom)

Little, 1989, p.102

pressure then begins to decay, usually from about 120 to 80 mm Hg, at which point the next pulse from the ventricle drives it back up. The aortic flow curve can thus be seen to rise rapidly upon the opening of the aortic valve, decay as the pressure difference decreases and then have a slight apparent negative flow at the end of systole.

Mitral Flow: Since it is obvious that an empty ventricle cannot eject, an understanding of left ventricular filling, and thus mitral flow, is of importance. As can be seen in the graphs of ventricular volume in Figures 5 and 6 and of mitral flow in Figure 39, immediately upon the opening of the mitral valve there is a tremendous inrush of blood into the ventricle. The system then behaves as an underdamped system, flow decreasing to near zero and then rising up again into another peak. As this flow rate decays for a second time the atrium kicks in producing yet a third peak, which then falls to zero when the mitral valve closes. The peak flow rate through the mitral valve during early filling and during atrial contraction are known, respectively, as the E and A waves. The L wave is the mid-diastolic rebound in flow. The flows through the mitral valve can be imaged and quantified by echocardiography and the echocardiographic E/A ratio is a widely used clinical index of the cardiac condition.

P-V Loops: In contrast to the above discussions in which all flows and pressures were plotted versus time, an alternate, and sometimes very useful, plot is that of left ventricular pressure vs. left ventricular volume (See figure 13). Isovolumetric contraction and relaxation cause changes in pressure at constant volumes and hence appear as vertical lines on the graph. As can be seen on the graph, after the mitral valve opens, although the ventricular volume begins to increase, the pressure initially continues to fall as the ventricle relaxes. Eventually the pressure increases due to the

increased volume, though only slightly as discussed above. After the aortic valve opens the ventricular pressure continues to rise for a time as the ventricle is contracting, but eventually it begins to fall, causing the aortic valve to close and isovolumetric relaxation to commence. The area within the closed loop on the p-v graph is the stroke work (SW) of the ventricle. SW is defined as stroke volume x mean atrial pressure (MAP). From some of the other graphs (see figure 14) it can be seen how the p-v loop can be useful in understanding the relation between afterload, preload and the pressures and volumes by comparing the various loops.

Fig. 13

Rubinstein, 1985, II:4,1

Pressure-volume loops depict the relative changes in left ventricular pressure and volume that develop during the cardiac cycle for a normal heart

During the normal cardiac cycle, as the mitral valve closes (MVC), isovolemic contraction (IVC) occurs and the pressure rises until the aortic valve opens (AVO). Left ventricular ejection (LVE) then ensues accompanied by a further increase in ventricular pressure as the left ventricular volume falls. After ejection, the ventricular pressure starts to fall and when the aortic valve closes (AVC), isovolemic relaxation (IVR) takes place with a marked drop in left ventricular pressure. When the mitral valve opens (MVO), diastolic filling (DF) occurs, and volume increases with little change in pressure. The end-diastolic volume and end-diastolic pressure occur just before systole and the closing of the mitral valve. The point at the end of diastole represents the end-diastolic pressure-volume relation, and the point of aortic valve closure represents the end-systolic pressure-volume relation.
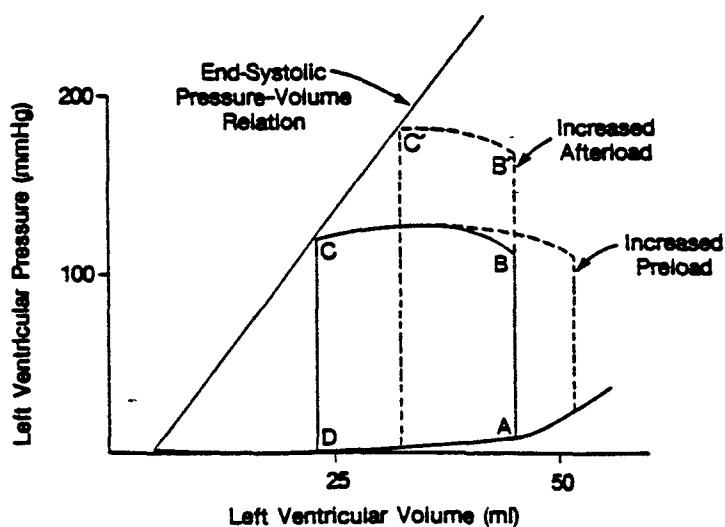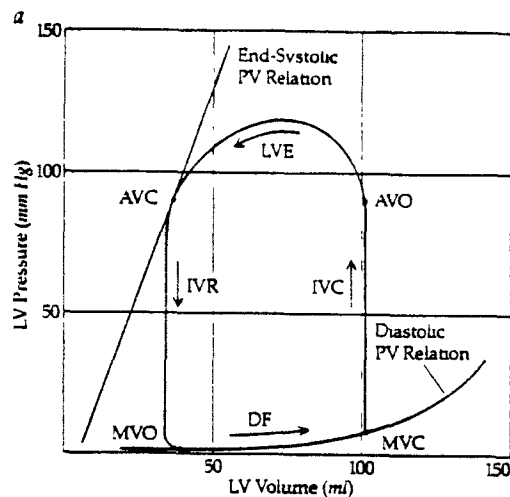
Fig. 14

Little, 1989, p.186

Effect of increased preload and increased afterload on the normal pressure-volume loop (ABCD)

CHAPTER III

MODELING:

Introduction: The concept of representing the mechanical activities of the heart through the medium of mathematical equations or electrical circuit analogs has been employed for many years, with varied reasons for developing such models. Two basic types of models have been employed -- the distributed parameter model and the lumped parameter model. These two varieties of models are the basic two categories universally used in modeling.

Transmission lines: In electrical engineering the distinctions between and the applications of these two models are well demonstrated in the study of transmission lines. In short transmission lines (less than about 50 miles) lumped parameter models are satisfactory. In medium length lines (between 50 and 200 miles), lumped parameter models may still be used but the system must then be broken down into multiple elements by using T or Π sections. For long lines (greater than 200 miles) lumped parameter models will yield erroneous results for the endpoints and will not provide any information regarding what is taking place along the line. For long lines, therefore, a distributed parameter model must be used. Since herein the concern is with cardiovascular models examples of such models will be used to further illustrate these two basic approaches.

Diastolic Filling Models:

Distributed parameter models: Distributed parameter models designed to study diastolic filling typically use continuum mechanics to

characterize various properties of the left ventricle, such as the pressure-volume relationship of the chamber. These models may be useful in understanding the particular relationship they describe, such as providing a choice of relations with which to model the properties of the chambers. However, they often provide little insight into the relation between the physical properties of the biological structure and the dynamics of the mechanical phenomenon occurring within the structure and being studied, such as filling dynamics. Distributed parameter models used in studying left ventricular filling have also used the tools of fluid dynamics. These models shed light on what is occurring throughout the entire interior of the chamber but are more limited in their contribution to the events at the orifices of the chamber. If desired, a model using the governing equations of fluid dynamics can be extended, for instance, by including compliance. This may require imposing additional limitations but may enable the model to provide certain information regarding the relationship between the physical properties of the biological structure and the dynamics of the phenomenon occurring within the structure being studied. One of the few useful distributed parameter models was designed by Peskin (1972) who was able to study the blood flow pattern around heart valves and thus shed light on the physiology of mitral valve closure. The common theme in all distributed parameter models is the consideration of what is taking place at different points, i.e., distributed within the chamber, rather than viewing the chamber as a single unit.

Lumped parameter models: Lumped parameter models are models in which the material properties of a structure are described, possibly by time-varying equations, such that each component of the system is considered to be located at a discrete, "lumped", point and for which values

of relevant parameters are calculated only for the terminals of the structure and possibly at one interior point of the whole component. Lumped parameter models are well suited for the study of a system such as the cardiovascular system where flows can be modeled as proceeding through "black box" elements which have properties of inertance and compliance (which are equivalent to elastance and storage respectively) and resistance. In such a case pressures and flows are calculated only at the ports. No spatial information regarding the processes taking place within the "black box" element is obtained, such as is gained from the distributed model. Thus, the lumped parameter model cannot be used to study spatial pressure gradients or flow streamlines within a structure, nor can it shed light on mechanisms of valve or regional chamber wall motion, unless these were the actual elements represented by the lumped parameter, in which case many more parameters would be needed. However, these drawbacks are more than compensated for by the advantages of the model when used to study the effect of varying the values of these parameters and to observe their effect on the terminal input and output of the various components. In addition, the solution to these models is readily attainable by solving ordinary differential equations using standard computational methods. This is true even if the model is not limited to classical resistive, inertial and capacitive elements, but also allows non-linear elements whose values are functions of one or more of the quantities within the model or are functions of time. Furthermore, although such models do not deal with the mechanisms of valve motion themselves, digital computer solutions of the models allow for complex sets of criteria for valve opening and closing. Lastly, the values of many of the parameters that would be required in a lumped parameter model are often readily available in the literature. One

of the most recently developed lumped parameter models is that of Thomas, (1991) who has been able to shed light on the roles of net atrioventricular compliance and mitral valve impedance on transmitral velocity.

Since the equations for lumped parameter models are often simpler to solve than those for distributed parameter models, it is sometimes easier to connect many small lumped parameter models together thus providing access to many data points as in a distributed parameter model while still maintaining solvability. An early example of such a model, used in the study of the human cardiovascular system, though not specifically with respect to the study of ventricular filling, was developed by Jager (1965). As part of his approach towards modeling the human "arterial tree" he treated each small section of the arterial tree as a transmission line with parameters unique to that region. He connected all of these transmission lines to form an extensive tree and then used the lumped parameter models already available for the study of transmission lines to study the entire human cardiovascular system.

In order to study ventricular filling itself, a lumped parameter model of the cardiovascular system with an emphasis on the left heart may be developed. The cardiovascular system lends itself to straightforward, mechanical/hydraulic to electrical conversions. In the conversion from hydraulic to electrical conventions all the standard equations and relations can be maintained. Thus, flow of charge, or current, corresponds to flow of fluid; a voltage difference or "drop" corresponds to a pressure gradient; resistance to current corresponds to resistance to flow; capacitance, or storage of charge corresponds to compliance/elastance or storage of fluid; inductance or "storage of flow" corresponds to inertance; and a diode corresponds to a mechanical valve. **Figure 15a** shows the

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electrical/hydraulic conventions used by Meisner, and Figure 15b shows the scaled hemodynamic/electrical analogs of Jager.
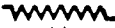
Cook and Simes Model: Using these analogs, and with the purpose being: "to illustrate biological system simulation to bioengineering students" (Cook), a model was designed by Cook and Simes (1972). (See figure 16 for the circuit schematic and component values.) For simplicity, they reduced the entire cardiovascular system to a three-chamber, two-valve model. The three chambers are: a left ventricle chamber, a chamber for the aorta, and a systemic chamber which includes everything else including the pulmonary system, the right heart, the left atrium and the peripheral circulation. Each chamber is represented by a storage element in the form of a capacitor. The systemic chamber also includes resistance to flow, and the left ventricular chamber is a time-varying, two-state capacitance to account for its varying storage capacity over the duration of the cardiac cycle. Two valves are included, the mitral valve and the aortic valve, each modeled by an ideal diode in series with a resistor. In addition, since the time-varying pumping nature of the right side was omitted, a dc voltage source was inserted between the systemic chamber and the left ventricle chamber (simulating the pressure rise between the vena cavae and the left atrium).

This model was implemented on an analog computer, which necessitated that its amplitudes be scaled to accommodate the expected values. (See figure 17 for the analog computer implementation and scaling.) The outputs (see figure 18) were recorded and compared to known physiological data, to which they bore a similarity. Thus, for the purpose for which this model was designed, to provide a reasonable simulation of the cardiovascular system for the purpose of demonstrating modeling, it

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Fig. 15-a

Meisner, 1986 (Einstein Quarterly), p.48

Lumped Parameter Electric/Hydraulic Conventions

Hydraulic Element	Electrical Analog	Symbol	Characterizing Equation
Resistance	Resistor, R	⌁	$\Delta P = Q \cdot R$
Compliance, C or Elastance, E	Capacitor, C = 1/E	⊣⊢	$\Delta P = E \cdot V$ or $d\Delta P/dt = E \cdot Q$
Inertance	Inductor, L	⧢	$\Delta P = L \cdot dQ/dt$
Valve	Diode	▸⊢	forward resistance = 0 reverse resistance = infinite

V = volume, Q = dV/dt = flow, ΔP = pressure gradient

Fig. 15-b

Jager, 1965, p.78

hemodynamic		electrical	
time:	1 sec	10^{-3} sec	

impedance: $\dfrac{1 \text{ dyne cm}^{-2}}{1 \text{ cm}^3 \text{ sec}^{-1}}$ = 1 volt coulomb^{-1} sec = 1 ohm

$= 1 \text{ g cm}^{-4} \text{sec}^{-1}$

Assuming that a pressure of P mm Hg is equivalent with a voltage of V volts, the equivalent units can be derived :

hemodynamic		electrical	
pressure	P mm Hg	voltage	V volts
flow	1 cm^3 sec^{-1}	current	$\frac{1}{1.33} \frac{V}{P} 10^{-3}$amps
volume	1 cm^3	charge	$\frac{1}{1.33} \frac{V}{P} 10^{-6}$coulombs
time	1 sec	time	10^{-3} sec
frequency	1 cps	frequency	1 kcps
resistance	1 g cm^{-4}sec^{-1}	resistance	1 ohm
inertia	1 g cm^{-4}	inductance	10^{-3} henry
distensibility	1 g^{-1}cm^{4}sec^2	capacitance	10^{-3} farad
leakage	1 g^{-1}cm^{5}sec	conductance	1 ohm^{-1}

Fig. 16
Cook and Simes, 1972, p.97
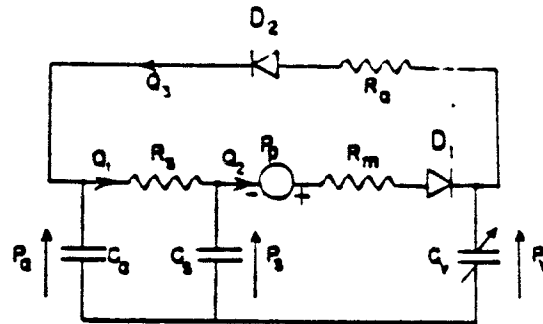
Electrical analog of cardiovascular system. D_2 and D_1 represent the aortic and mitral valve, respectively. Q represents flow; V, volume; P, pressure; C, capacitance; R, resistance. Subscripts: a represents aorta; s, systemic; v, left ventricle; 1, systemic; 2, mitral valve; 3, aortic valve.

RESISTANCE

Flow (ml/s)	Pressure (mmHg)	Resistance (mmHg·s/ml)
70	75	$R_s = 1.07$
100	5	$R_a = 0.05$
100	2	$R_m = 0.02$

CAPACITANCE

Volume (ml)	Pressure (mmHg)	Capacitance (ml/mmHg)
120	80	$C_a = 1.5$
4000	4	$C_s = 1000$
160	4	C_v (diastole) $= 40$
160	80	C_v (systole) $= 2$

Fig. 17
Cook and Simes, 1972, p.99

Analog computer diagram.
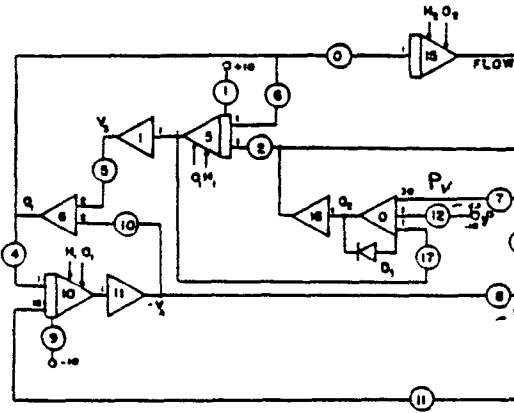
Variable	Maximum Expected Value	Ratio Scaled to Unscaled Variable
Q_1	70 ml/s	1/10
Q_2	200 ml/s	1/40
Q_3	600 ml/s	1/100
V_o	120 ml	1/20
V_s	4000 ml	1/500
V_4	160 ml	1/40
P_o	120 mmHg	1/12
P_s	4 mmHg	2/1
P_v (diastole)	4 mmHg	20/1
P_v (systole)	100 mmHg	20/1
P_p	Same as P_s	2/1

Fig. 18
Cook and Simes, 1972, p.100
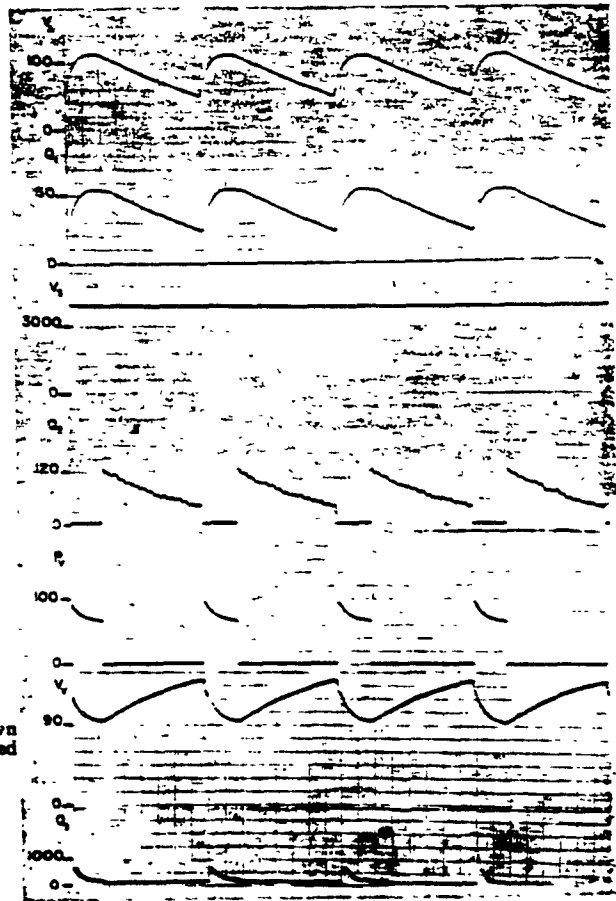
Typical output from computer simulation. All flows shown in ml/s, volumes in ml, and pressure in mmHg. Variables defined in Fig. 16

functioned satisfactorily. However, due to the numerous assumptions implicit in its design, the model serves little benefit in further understanding or studying the cardiovascular system. At the same time, though, it does lay the groundwork for future models which follow similar design schemes while taking into account some of the simplifications and assumptions. One of the areas of glaring simplification in the Cook and Simes model was the assumption that the left ventricle has only two states, that these two states jump discretely from one to the other in a discontinuous manner and that these two states always have the same fixed values irrespective of other events in the system.

Goldstein Model: An alternate approach in modeling the cardiovascular system is to choose one particular aspect of the system to model very accurately with the goal and hope that others will then use that model as part of an overall model which will have research benefit. The goal of Goldstein, et. al. (1990) in designing their model (shown in figure 19) was that it should accurately model the left ventricular pressure waveform, including the effect of the beat-to-beat venous return as explained by Starling's law and be constrained by the hemodynamic conditions that cause congestive heart failure (CHF). Their secondary goal was that others will be able to easily incorporate this model into other circuits allowing for sophisticated simulations of cardiovascular hemodynamics. Their model has advantages in its mode of implementation as well as in its avoidance of the over-simplifications of left ventricular function as is found in the Cook and Simes model.

An important advantage of the Goldstein model over the Cook model is its mode of implementation. Cook, et. al., who developed their model in the early nineteen-seventies, perhaps could have used a primitive, slow,

cumbersome early digital computer or, as they chose to do, implement it on less accurate, less flexible analog machines. Goldstein, et. al., having developed their model in the early nineteen-nineties, not only had a choice of much faster, more sophisticated digital computers, but also had available a selection of methods of how to implement the model on a computer. They chose to do so by using an electrical circuit simulation program, PSPICE, which provides a great deal of flexibility in using the model. Though PSPICE is not an interactive program, changes can easily be made in the program by commenting code in or out, something they took full advantage of. In addition, since PSPICE is a standard program, the model is easily transportable, thus realizing the goal of being able to incorporate their accurate representation of the left ventricle into more elaborate or useful models. Because of these and other advantages, I chose to implement the Meisner model in PSPICE as well, as is found in a later section.

An important over-simplification of Cook's model, that the ventricular compliance is a two-state system and changes from one state to the other instantaneously, is absent in the Goldstein model. Goldstein et. al. suggest that many of the various alternatives commonly used, such as a dc voltage simulating mean arterial pressure, a sinusoidal waveform, a square wave or combinations thereof, are inaccurate, and that even more sophisticated attempts at using rectified rectangular or sine waves are not sufficient. They therefore proposed their own function, and compared it to the actual left ventricular pressure as shown in figure 20. They used a computerized curve fitting program to generate a second order polynomial to represent systole over a .32 second interval and a dc waveform to represent the remaining .48 seconds of diastole. They then use the PSPICE Pulse waveform (shown in figure 21) to create this function by producing a
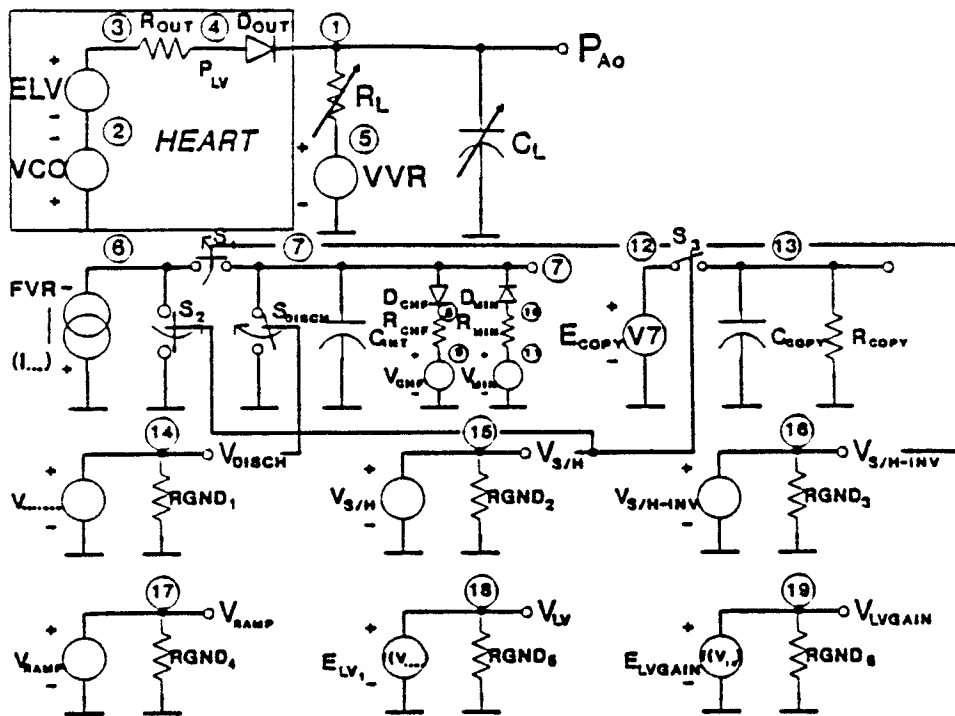
Schematic diagram of the heart model.

Fig. 19
Goldstein, 1990, p.28
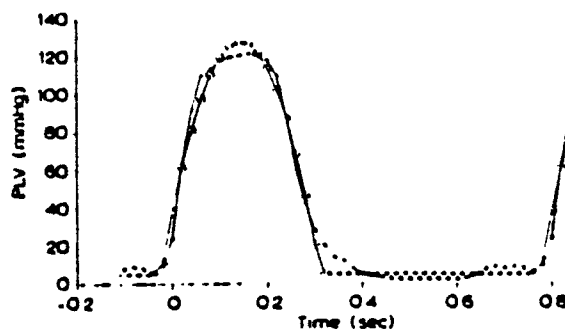
Fig. 20
Goldstein, 1990

Comparison of actual LVP vs. model. Empirical left
ventricular pressure (PLV) versus our second-order hybrid
model showing a correlation of $r^2 = 0.985$. (●) Actual; (○)
model.

repetitive ramp by assigning a V1 of 0 volts, V2 of .3489, TD of 0 and a rise time, TR, equal to V2, .3489 seconds. This produces a ramp of slope 1 starting at time zero and extending to .3489 as seen in the bottom of figure 22. In order to terminate the ramp they assign an insignificant .1 millisecond to TF and PW. To make it repetitive with a period of .8 seconds they simply set PER equal to .8. They then use this ramp in a second order polynomial to generate the left ventricular pressure function at the top of figure 22.

While implementing the Meisner model, an attempt was made to generate the function used in the Goldstein model in the hope that it could then be tried in the Meisner model and compared to the function used there. The ramp function behaved as expected, producing the graphs shown in figures 23 and 24. However, the attempt at generating the function consistently yielded the problematic results shown in figures 25 and 26, and it is not clear how Goldstein produced the clean function shown in his paper (figure 22).

In order to rectify a further problem, the assumption that the values used in one heartbeat are identical in every other beat, a scaling factor based on the Frank-Starling transfer function was introduced to scale the ventricular output as a function of venous return. An example of their output is shown in figure 27.

VOLTAGE

SPICE Pulse Waveform.
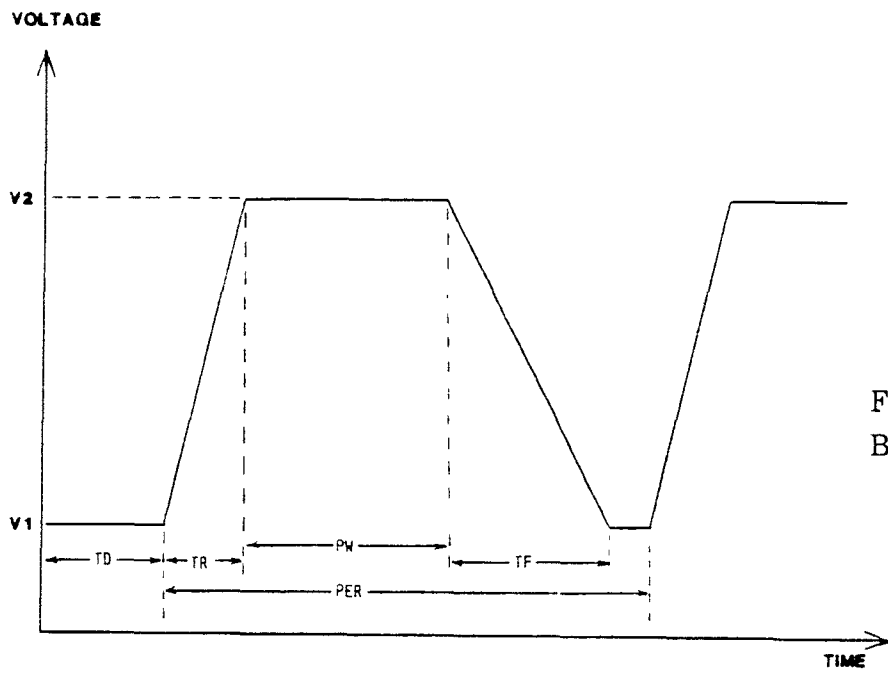
Fig. 21
Banzhaf, 1989, p.23
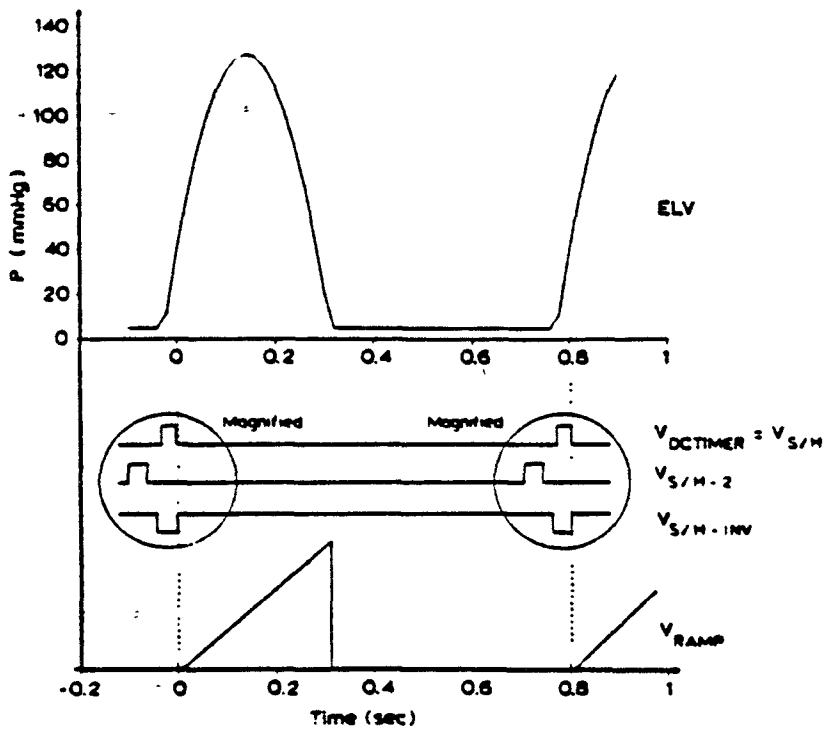
Fig. 22
Goldstein, 1990, p.28

Timing diagram of the signals used to generate the
hybrid waveform of left ventricular pressure in the model.
The three timing pulses were magnified for clarity.
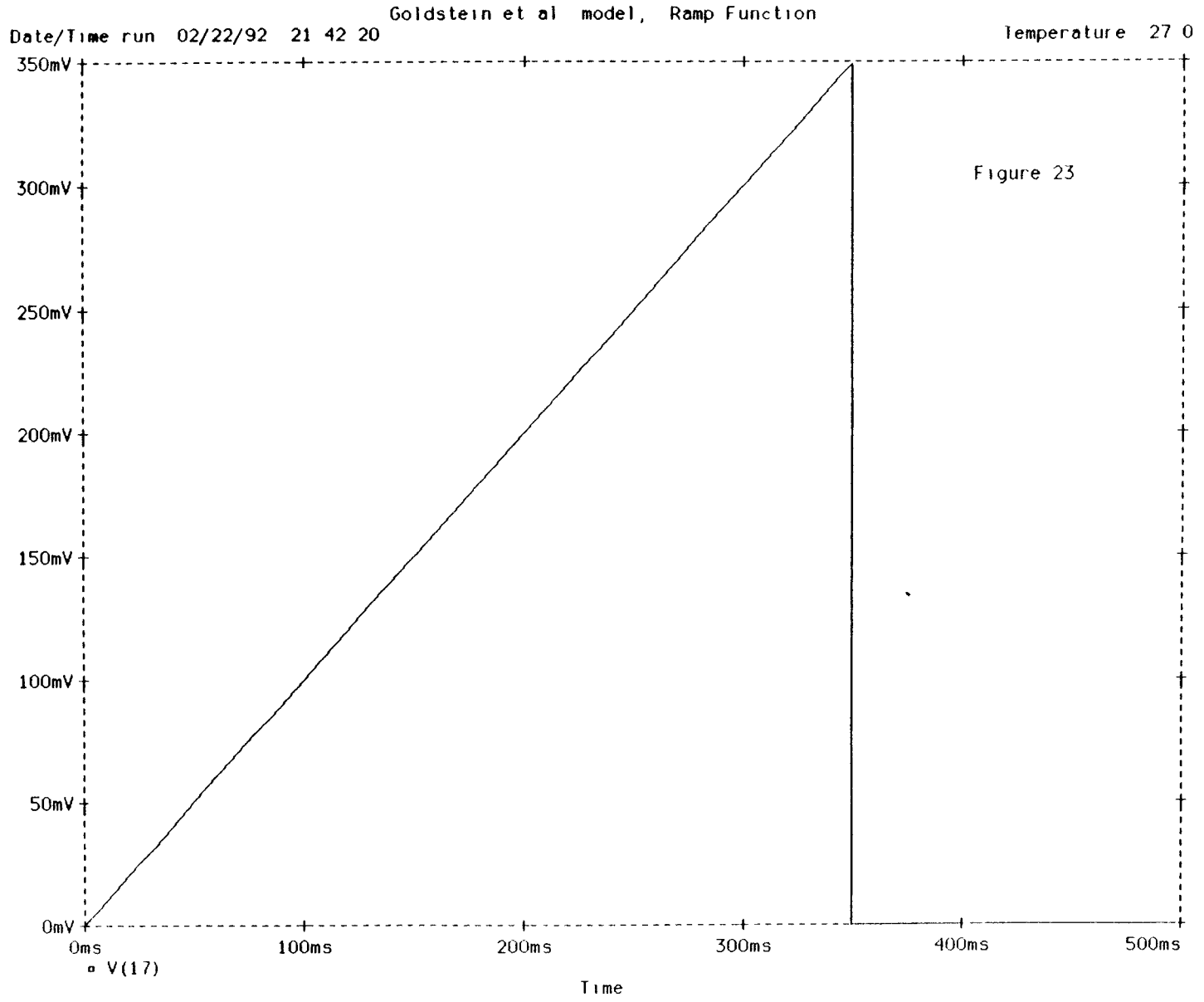
Goldstein et al model, Ramp Function

Date/Time run 02/22/92 21 42 20

Temperature 27 0

Figure 23

□ V(17)

Time

36

Goldstein et al model, Ramp Function

Date/Time run 02/22/92 21 42 20

Temperature 27 0

Figure 24

V(17)

Time

37
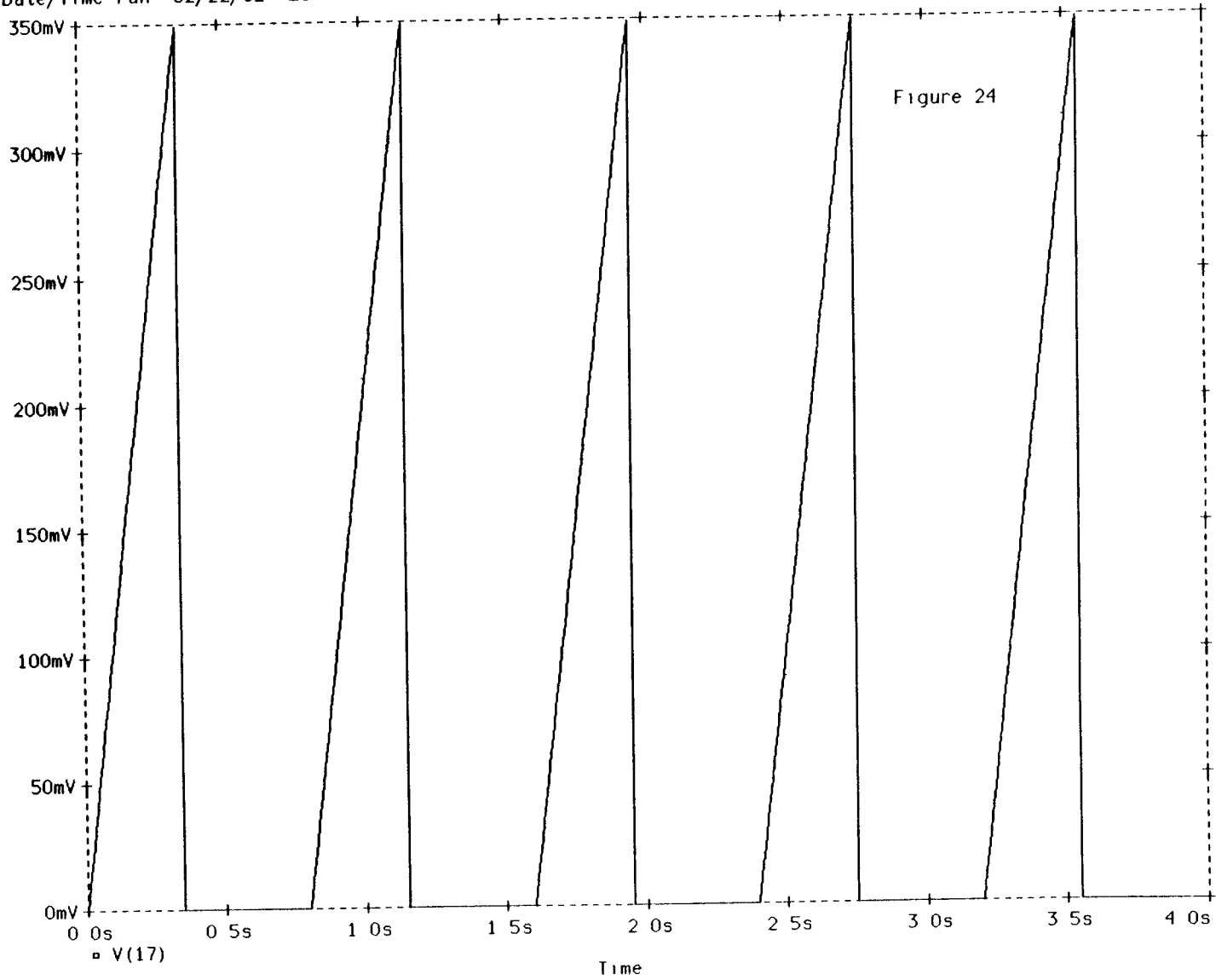
Goldstein et al model, Function used in the Goldstein model

Date/Time run 02/22/92 21 42 20   Temperature 27 0

Figure 25

o V(3)
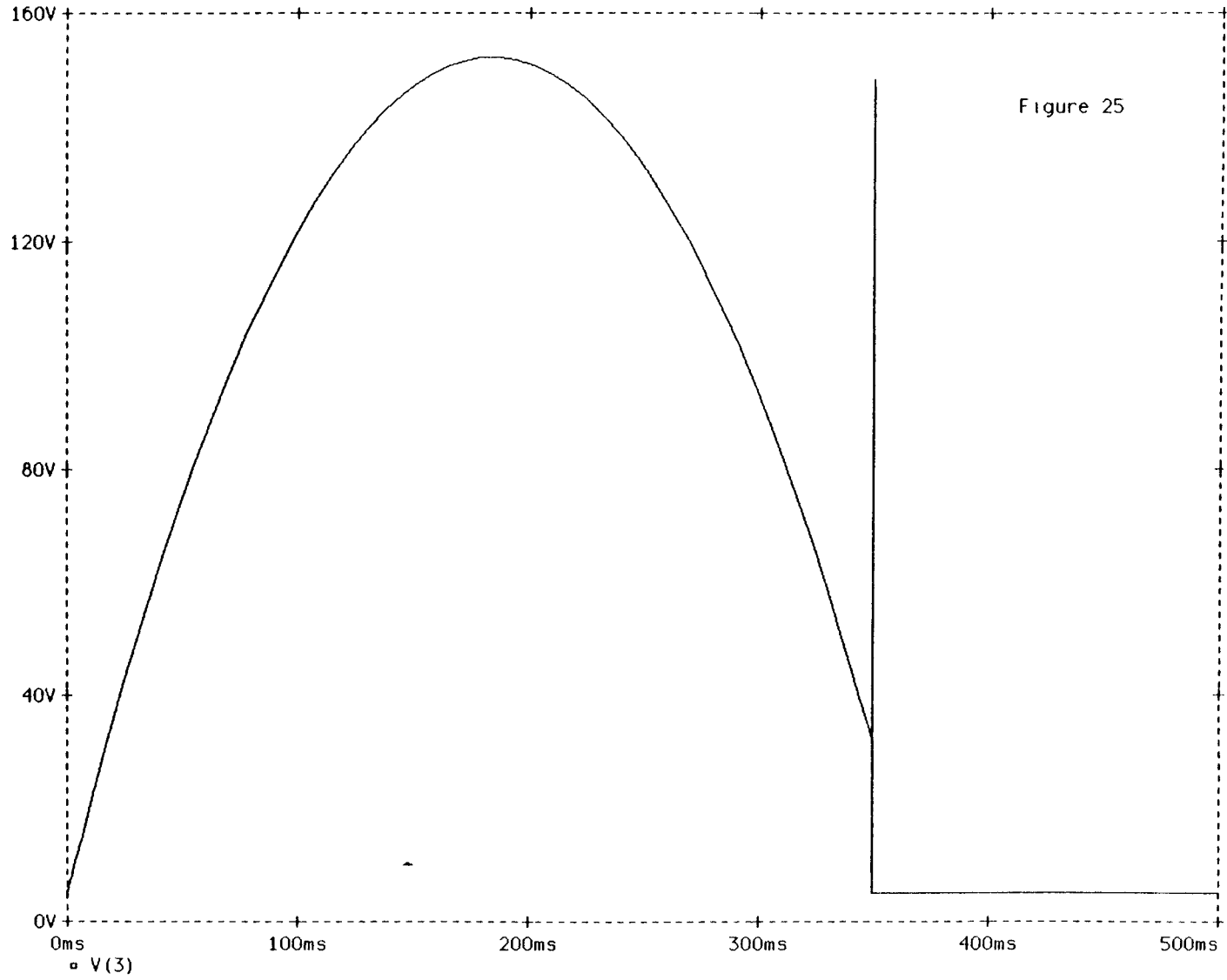
Time

Goldstein Model, Function used in the Goldstein model

Temperature 27 0

Figure 26

□ V(3)

Time
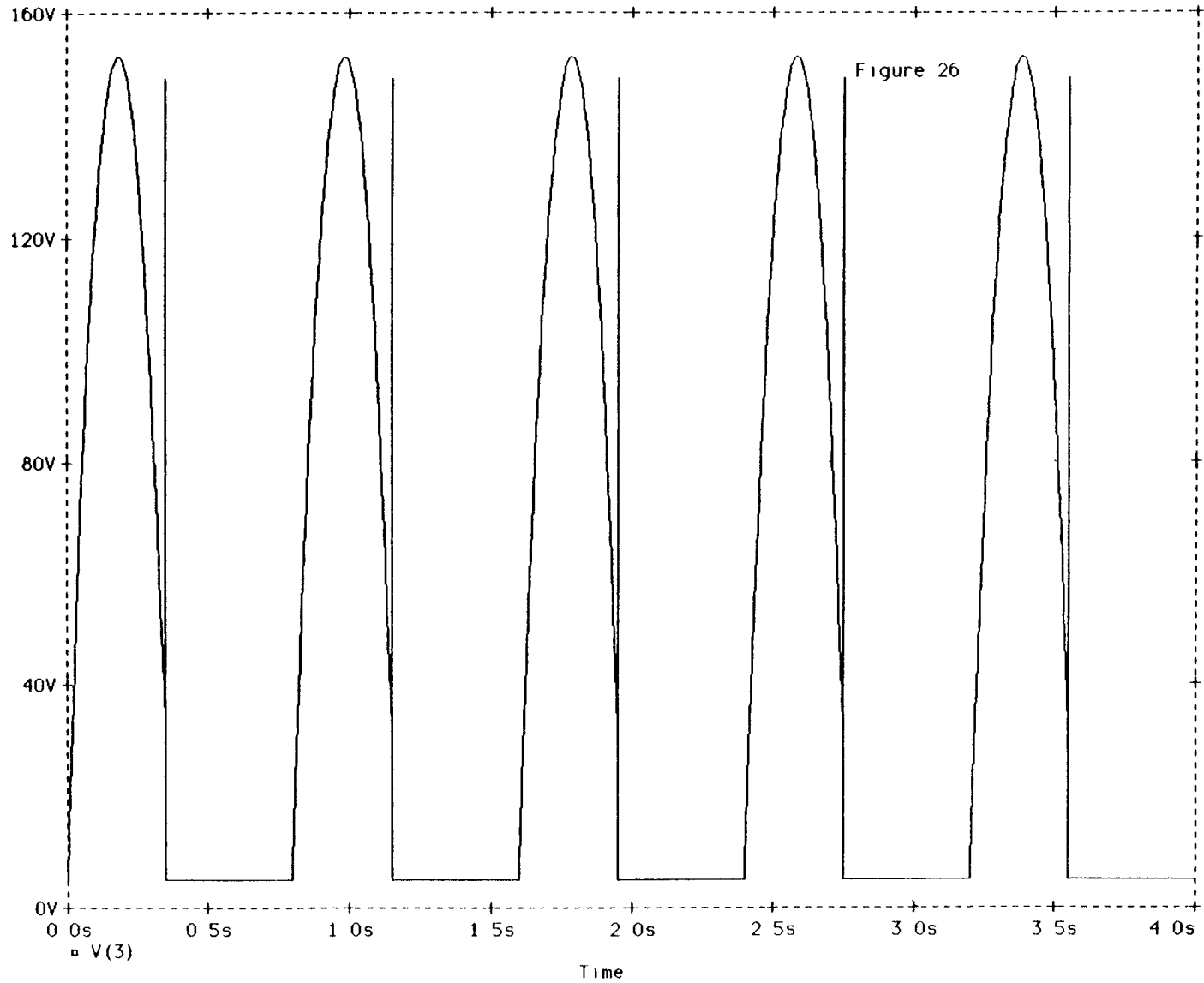
Fig. 27
Goldstein, 1990, p.30
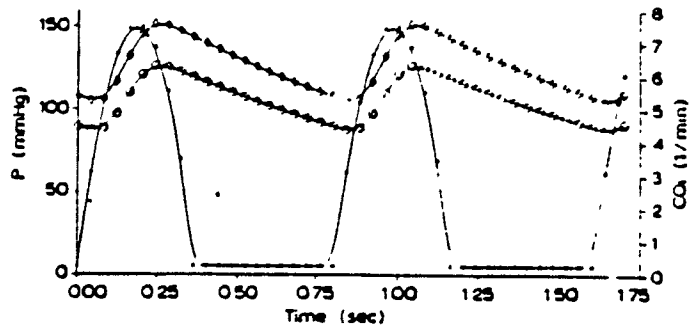
Heart model beating into a static load.

(●) ELV (hydromotive pressure) in mm Hg; (○) aortic
pressure (mm Hg); (◊) instantaneous cardiac output (COi) in
l/min.

CHAPTER IV

MEISNER MODEL:

Introduction: A more formidable goal than simply using the model to demonstrate modeling techniques (as in Cook) or showing that the model can achieve a ventricular output that has a correlation of greater than 97% with the true output (as in Goldstein) is to develop a model that is at least predictive, if not diagnostic. By predictive is meant the ability of the model to adequately predict the effect of a change in material property on cardiac function. For a model to have diagnostic properties means that, given a set of *in vivo* observations, the model can tell something about the material properties. To create a model with such properties for the entire cardiovascular system is obviously a formidable task which requires beginning with some subset of the whole. Since the proper ejection of the left ventricle is a principle function of the heart, and since proper ejection cannot take place without proper filling, clearly, the filling mechanism of the left ventricle is of vital importance. In normal circumstances, the only way for the left ventricle to fill is via the mitral valve. Transmitral blood flow is therefore one of the essential waveforms that needs to be represented in the model. Furthermore, "the waveform of transmitral blood flow is determined uniquely by the pressure difference between the atrium and ventricle, and by the impedance of the mitral apparatus. The atrioventricular pressure difference, in turn, is determined by the active and passive properties of both left heart chambers, the atrium as well as the ventricle. Transmitral flow patterns should thus provide information regarding the state of the heart." (Yellin, 1991)

4 1

Thus, if a model accurately relates the various properties of both left heart chambers as well as those of the mitral apparatus to the correct transmitral flow patterns, it would have many uses. As a research tool it could suggest new areas for investigation, help interpret existing data, determine values for parameters not directly measurable *in vivo* (e.g., pulmonary vein flow, absolute chamber volumes, local chamber pressures and flows), predict the effect of some interventions not easily performed *in vivo* (e.g., changes in the rate of left ventricular relaxation, changes in hydraulic parameters), and support and direct *in vivo*, studies thus minimizing the number of animal or human studies that need to be performed. Furthermore, it can serve as an educational tool both in its development as well as in its final form, in that it can assist, in an interactive way, in the understanding of how the various material properties, flows and pressures in the heart are related. It was with such a goal in mind that Meisner developed his model, the detailed development of which is explained next.

Design: The Meisner model was designed as a lumped parameter model using electrical/hydraulic symmetries and a general approach similar to Cook's. However, unlike the Cook model which models the complete cardiovascular system as a closed loop, the Meisner model simulates only from the pulmonic valve of the right heart through the periphery into which the left ventricle ejects, and does so as an open loop. This is because, unlike Cook's model, the Meisner model is designed to study something specific, mitral flow. The existence of a closed loop would have required additional detail in other parts of the circuit in which we are

not as interested. In order to present the total model in an understandable fashion, it will be broken down into six subunits, each of which will be explained individually in some detail (see Figure 32).

Right Ventricle: The input to the model is a right ventricular waveform. This pressure is generated actively, that is, it is an independent pressure, or voltage generator, that actively and independently produces the desired waveform. This is in contrast to most of the model, in which passive elements cause the desired waveform. The need for an active generator is due to the simulation being an open rather than a closed loop. Because charge is dissipated at the output of the model, an independent input voltage is required. The right ventricular waveform occurs once each "heartbeat", simultaneously with the left ventricular contraction. In the original model it was a sine function from 0 to Π radians of 300 ms duration (frequency = 3.333 Hz.) with a peak value, PmaxRV, which was variable, of approximately 25 mm Hg. It was recently modified to be a scaled version of the left ventricular excitation function (described below) with the scaling factor consisting of the same peak value as in the original divided by the peak value attained by the left ventricle, EmaxLV.

Pulmonary Circulation: The minimum required to model the pulmonary circulation is a compliance connected to the right and left hearts by two resistors, i.e. a simple T-network (see figure 28). This would account for the storage capability, predominantly in the pulmonary arteries, as well as the resistance to flow in the pulmonary network. However, such a model deviates considerably from the physiological and anatomical realities and would probably present less accurate input impedances than a more complex model. In addition, the experimental

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data necessary to assign values to the resistive and compliant elements in the more complex model does exist. Thus, the more detailed model (see figure 29) of a pi-network was chosen. This consists of three resistors separated by two compliances, along with two inertances -- one in the input and one in the output. The addition of inertances (inductors) into the model in no way affects steady-state, constant flow analysis or steady-state input impedances. It does, however, play a significant role in the impedance of time-varying flow. This is particularly important in pulmonary venous impedance as seen from the left atrium, in that it may play a major role in preventing a large retrograde flow back up the pulmonary veins when the left atrium contacts (as there is no valve between the pulmonary vein and the left atrium). This section of the total model is treated as a black-box model of the pulmonary circulation and, in general, values are not obtained from within this "box". However correspondence between specific elements in the pulmonary section of the model and true anatomical locations is possible.

Left Atrium: The left atrium is modeled by a time-varying lumped parameter elastance connected at the input to the pulmonary model and at the output to the model of the mitral orifice/valve. This elastance contains both passive and active components. In general, both the passive and active left atrial properties are assumed to be linear; that is the pressure (corresponding to voltage in the electrical analog) of the left atrium is:

$$P = E \, (V - V_d) \qquad\qquad [1]$$

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Minimum Model Required for Pulmonary Circulation

Fig. 28

PULMONARY MODEL
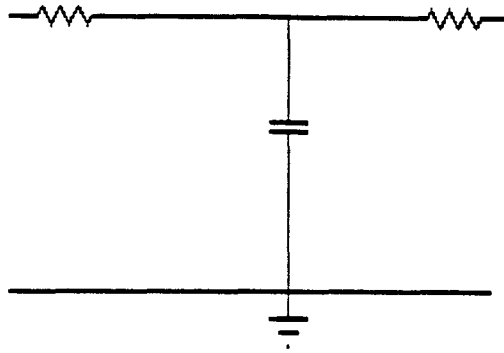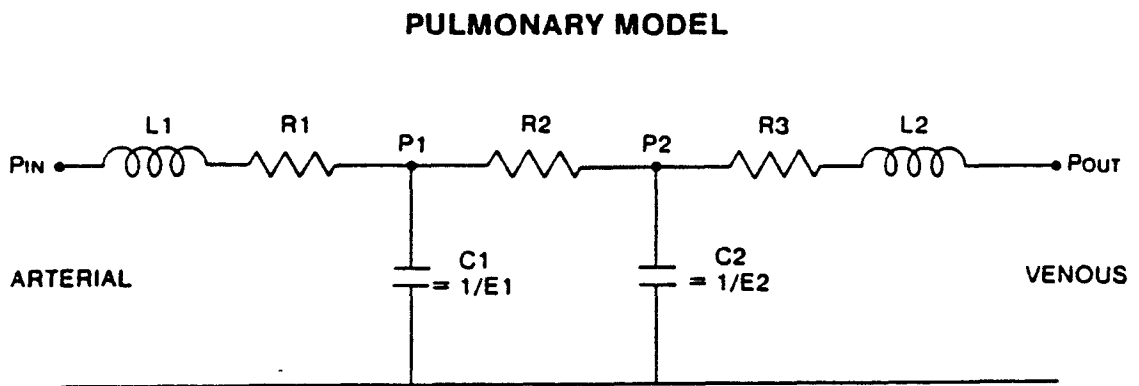
Fig. 29
Meisner, 1986 (Doctoral Thesis), p.101

where E is an activation/deactivation function, V is the instantaneous volume stored in the left atrium (charge on the capacitor), and V_d is an offset or dead volume. The differences between systole and diastole are that in systole E is a variable rather than a constant as in diastole and in diastole V_d is a variable rather than a constant. The change in V_d is minor. In systole it is a constant, called "VD10" in the program, and in diastole it is a sine wave decaying from "VD10" (approximately 20 ml.) to "VD10" - 2, and then rising back to "VD10", i.e. -sin(x) from 0 to Π, and lasting the duration of atrial contraction, 200 ms. The contribution of varying E is much more significant than that of varying V_d. In diastole E is a constant (approximately 1). In order to simulate atrial contraction the value of E is varied, thereby simulating a varying elastance. It is a sine wave from 0 to Π radians of 200 ms duration starting at the diastolic constant value with a peak of E_{maxLA} and occurring once at the beginning of each "heartbeat".

Mitral Orifice/Valve: Since the main thrust of the Meisner model is the study of blood flow across the mitral valve, it is to be expected that the Mitral Orifice/Valve should be modeled in great detail (see figure 30). Intuitively, it would be expected that the impedance of the mitral orifice should have both inertial and resistive components. In addition, there is also obviously going to be a diode (modeling the valve itself) which permits, with zero resistance, only forward blood flow, that is from the atrium to the ventricle, and which blocks, with infinite resistance, retrograde flow. The forward link between the atrium and ventricle therefore consists of the series connection of a diode, resistance and inertance.

MITRAL ORIFICE / VALVE
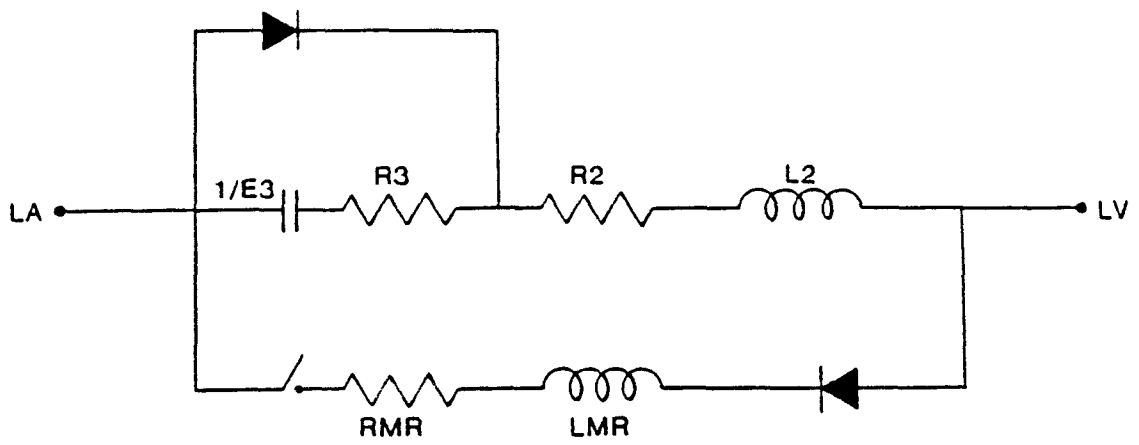
Fig. 30
Meisner, 1986 (Doctoral Thesis)

This forward resistance (R2) was chosen to be nonlinear. If the orifice were very wide, on the order of the diameter of the chambers themselves, then the resistance would be linear, that is the pressure drop is proportional to flow, as in Ohm's law. If the orifice is very narrow then the pressure drop is non-linear and proportional to the square of the flow, that is $V = I^2 R$. The normal mitral orifice falls somewhere between these extremes and the impedance can be reasonably modeled by either. However, since under conditions of mitral stenosis only the nonlinear square of flow approximation is valid, it was decided to always model the mitral forward resistance as a nonlinear square of flow pressure drop thus enabling the model to be used in studies of mitral stenosis as well. The total pressure-flow relationship across the mitral orifice in the forward direction is thus represented as:

$$\Delta P = [L]dQ/dt + [R]Q^2 \qquad [2]$$

where ΔP is the atrioventricular pressure difference, [L] (L2 in Fig. 30) and [R] (R2 in Fig. 30) are, respectively, inertial and resistive coefficients (assumed to be constant) and Q is the volume flow.

There is an additional path which links the atrium to the ventricle by by-passing the diode, consisting of an additional resistance (R3) and a compliance (1/E3). (This is how it appears in the schematic - in reality it is a more complex function). This simulates the storage of blood in the viscoelastic mitral valve leaflets as they bulge towards the left atrium when the atrioventricular pressure gradient is negative. It is significant that the retrograde mitral flow associated with this billowing does not represent any true ventriculoatrial blood transfer either *in vivo* or in the model. Rather,

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this blood is simply stored, in the leaflets *in vivo* and in the storage element in the model, and is recovered when the valve leaflets return to their neutral position immediately preceding their opening in early diastole. There is also potentially one additional path, a mitral regurgitant path (a diode, LMR and RMR). This was included in the model and used for a paper, but will not be further discussed here.

Left Ventricle: The left ventricle, like the left atrium, was modeled (see Fig. 32) by a time-varying lumped parameter elastance, albeit a more complex one, incorporating both the passive and active components. The passive left ventricle has an exponential pressure-volume relationship (see chap.1). However, when the filling rate is high, the viscous and inertial properties raise the pressure to a higher degree than that predicted from a simple exponential. This viscous component was assumed to be proportional to the rate of change of chamber volume (ie, to mitral flow). The total passive, instantaneous left ventricular pressure is thus given by:

$$P = Ae^{\alpha V} + B(dV/dt) + P_{inf} \qquad [3]$$

where A is the passive elastance coefficient, α is the passive elastance exponent, V is the instantaneous left ventricular volume, B is the viscous coefficient, dV/dt is the mitral flow, and P_{inf} is the left ventricular pressure asymptotic offset, that is, the left ventricular pressure when left ventricular volume is negative infinity and its derivative (mitral flow) is zero.

The active left ventricular pressure-volume relationship was modeled (similar to that of the left atrium) by:

$$P = E (V - V_d) \qquad [4]$$

where P is the active left ventricular pressure, V is the instantaneous left ventricular volume, V_d is a "dead volume" offset and E is an activation function. The activation function is a rising sine wave from $3\Pi/2$ to $5\Pi/2$, offset by EmaxLV so that it always starts at zero, lasting 150 ms and starting in each "heart beat" at one PR interval after the start of the beat. After reaching its peak, the activation function decays exponentially with a time constant, τ, which can be varied. The total left ventricular pressure is the sum of equations [3] and [4]. The B term (in equation [3]) can be thought of as a separate resistor and removed from the equation. This is because B is a linear constant of proportionality between the pressure and the change in volume, which is the same as relating pressure to flow or voltage to current, which is precisely what a resistance does.

Periphery: Since the primary concern in this model is ventricular filling, the aorta and the periphery were modeled as simply as possible. The aortic valve is modeled by an ideal diode and a resistor, representing **valve resistance.** The periphery follows immediately and is modeled by an elastance, to account for the storage capacity of the aorta and other large arteries, and a runoff resistance in parallel to it, as shown in Figure 31. Aortic inertance, which would be required in more detailed models of ventricular ejection, is omitted in this model. An additional link is possible from the aorta back to the ventricle, bypassing the ideal diode of the aortic

valve, as in Fig. 32 and including RAR. This would simulate aortic regurgitation, but is not used in the present model.

The complete Meisner model is presented in figure 32.

Implementation: The differential equations (which are shown in figure 33) for this model were solved using the Euler point-slope method at 1 ms. intervals. The program is written in compiled BASIC using Quick BASIC, on an IBM PC. The program is interactive and allows the user to select a set of control parameters (default or otherwise) and, if desired, a set of intervention parameters. The control parameters together with their default values are given in figure 34. The program solves for the control cycle twice, once with atrial systole and once without, thus enabling a comparison of the two, and then it similarly solves for the intervention cycle, also twice. There is a choice of outputs to represent the solutions. Two separate graphs are plotted on the monitor. One plots mitral flow versus time and the other includes both left atrial and left ventricular pressure together versus time. In addition, an entire sequence of graphs of parameters versus time can be plotted for both the control (as in figure 35) and the intervention runs (as in figure 36), either overlaid or side-by-side. Similarly, overlaid or side-by-side plots of the pressure/volume loops for the two runs can be plotted, as in figure 37. And finally, a numerical printout of selected results for both runs, as well as the differences between the runs for these parameters, is available. An example of this is shown in figure 34. Included next to the values on figure 38 are explanations of the various output parameters which are not standardly included in the printout. These parameters are illustrated in figure 39 which displays typical mitral

Model of Aorta and Periphery

Fig. 31
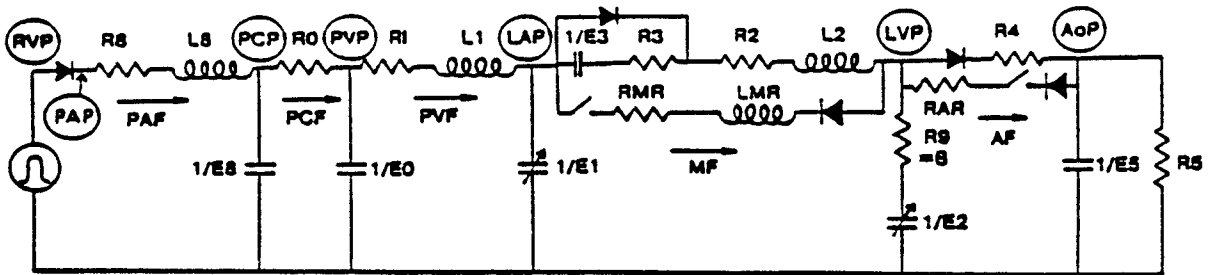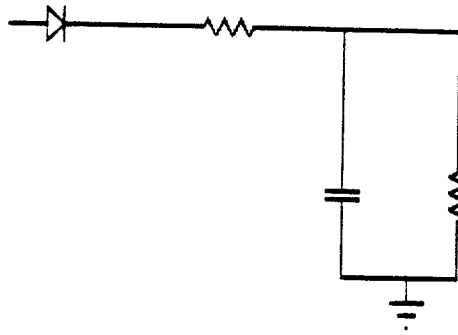
Fig. 32

Meisner, 1966 (Doctoral Thesis)

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$d(PAF)/dt = (RVP - PCP - R8*PAF)/L8$

$d(PCV)/dt = PAF - PCF$ (note: PCV = V8)

$PCP = E8*V8$

$d(PVV)/dt = PCF - PVF$ (note: PVV = V0)

$PVP = E0*V0$

$PCF = (PCP - PVP)/R0$

$d(PVF)/dt = (PVP - LAP - PVF*R1)/L1$

$d(LAV)/dt = PVF - MF$ (note: LAV = V1)

$d(MF)/dt = (LAP - LVP - R2*MF^2)/L2$ (valve open)

$d(LVV)/dt = MF - AoF$ (note: LVV = V2)

$AoF = (LVP - AoP)/R4$

$d(AoP)/dt = (E5)(AoF - AoP*R5^{-1})$

Fig. 33
Yellin, Modified from Meisner , 1991

1	0.00400	L8-PA inertance	19	0.00001	R9-LV viscous res.
2	0.02000	R8-PA resistance	20	0.05000	ALPHA-LV passive exp.
3	0.32000	E8-PA elastance	21	0.55000	A-LV passive coef.
4	0.18000	R0-Pcap resistance	22	2.00000	Emax-LA
5	0.48000	E0-Pcap elastance	23	0.00000	MR-Res. (0=no MR)
6	0.10000	R1-PV resistance	24	0.00200	MR-Inertance
7	0.00200	L1-PV inertance	25	0.00000	MR-LVV dependence
8	0.00010	R2-MV resistance	26	0.00000	AR-Res (0=no AR)
9	0.00200	L2-MV inertance	27	1.00000	MV 0=closed 1=open
10	1280.00000	E3-MV bulge elastance	28	130.00000	PR
11	8.00000	R3-MV bulge resistance	29	800.00000	RR
12	0.10000	R4-Ao resistance	30	8.00000	Emax-LV
13	2.40000	R5-periph resistance	31	25.00000	Pmax-RV
14	1.25000	E5-Ao elastance	32	25.00000	tau
15	1.00000	K10-LA passive elast.	33	10.00000	con. cycls
16	20.00000	VD10-LA unstressed vol.	34	8.00000	int. cycls
17	8.00000	VD2-LV unstressed vol.	35	0.00000	CO
18	-2.00000	Pinf - LVP asymptote			

The control values of the parameters are shown
most of the components are self explanatory. E1 and E2 are the time varying elastances of the atrium and ventricle, #22 and #30 in the listing. Listed, but not shown in the schematic are: #15, K10, the left atrial passive elastance (linear); #16, VD10, the left atrial equilibrium volume and elastance intercept #17, VD2, the left ventricular ESPVR intercept #18, Pinf, the asymptote of the passive left ventricular P-V relation (exponential); #20, ALPHA, the exponent of the left ventricular passive P-V relation; #21, A, the coefficient of the passive left ventricular P-V relation; #23-27, parameters related to mitral regurgitation; #31, Pmax-RV, the peak developed right ventricular pressure; #32, Tau, the time constant of the exponential decay in LV pressure; #34,#35, number of cycles to reach a steady state in the control and intervention runs.

Fig. 34
Yellin, Modified from Meisner , 1991

Central PF
PVF

PAP
PVP

LVV
LAV

AoP
AoF
LVP
LAP

− 100
(ml/s)

E
MITRAL FLOW
(ml/s)
A
L

0

ΔP
− 5
(mmHg)
0

LVP

LAP
− 10
(mmHg)

0

⊢— 800 ms —⊣
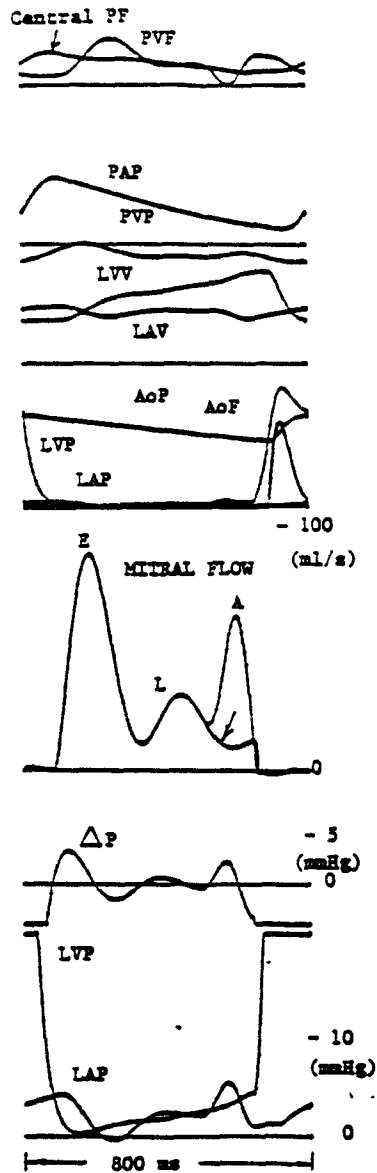
Fig. 35
Modified from Meisner

Fig. 36

Meisner, 1986 (Doctoral Thesis)

R-R = 1000 ms   R-R = 500 ms

PCF
PVF
(ml/s)
50
0

PVF   PCF   PVF   PCF
                        PVF

PVF

PAP
PVP
(mmHg)
20

0

LVV
LAV
(ml)
40

0

AoP
LVP
LAP
(mmHg)
80

0
AF

MF
(ml/s)
80

0
PRFR

(LAP-LVP)
(mmHg)
5
0

LAP/LVP
(mmHg)
10

0

54

Fig. 37

Meisner, 1986 (Doctoral Thesis)

P − V LOOPS

pressure−volume (P−V) plots for ventricle (upper) and atrium (lower) at heart rates of 60, 70, 80, 90, 100, 110, and 120. The end−systolic pressure−volume ratio (E) line is drawn in both plots. Note that the slope of the diastolic ventricular pressure−volume relationship increases with increasing ventricular volume and deviates slightly from an exponential during atrial systole (immediately preceding ventricular contraction) due to the ventricular viscous wall properties. At slow heart rates, the ventricular pressure−volume loop is short and wide. This is because filling is large and afterload is low pressure to fall to a low level − the mechanisms are complex and interrelated.

```
INTERVENTION parameter(s):
    K10-LA passive elast.    3.00000

Parameter              C              I        I-C      (I-C)/C

PCO                    4.0   mmHg     5.5       1.5      0.388  AV pressure crossover
LVPmin                 0.3            0.3       0.1      0.261  minimum LV pressure
LVEDP                  4.3            3.9      -0.4     -0.093  end diastolic LVP
LVEDV                 38.3   ml      37.2      -1.1     -0.029  end diastolic LV volume
EF                    53.3           52.8      -0.5     -0.010  ejection fraction
(LAP-LVP)max           3.3   mmHg     3.6       0.3      0.103  maximum AV pressure difference
PLVP                 100.0           95.8      -4.2     -0.042  peak LV pressure
M-(LA-LV)-diast        0.28           0.17     -0.11    -0.394  mean AV diastolic press. diff.
MLAP                   2.25           2.75      0.51     0.225  mean LA pressure
MLAP-diast             2.20           2.13     -0.07    -0.031  mean LA diastolic pressure
MLAP-syst              2.36           4.32      1.96     0.829  mean LA systolic pressure
LVP-a-min              2.6            2.7       0.1      0.048  LVP at minimum LA pressure
LAP-a-max              5.3            4.4      -0.9     -0.165  LAP at peak A-wave
LAV-a-min             22.13          20.90     -1.23    -0.056  LA volume prior to A-wave

PMF                   90.3   ml/s    70.8     -19.5     -0.216  peak mitral flow (E-wave)
MF-a-min              21.3           21.2      -0.1     -0.006  mitral flow prior to A-wave
MF-a-max              64.3           44.5     -19.8     -0.308  peak A-wave
MF-a-max/PMF           0.712          0.629    -0.083   -0.117  A/E ratio

FV                    20.4   ml      19.6      -0.8     -0.038  filling volume (=stroke vol)
FV-PMF                 4.6            2.5      -2.1     -0.458  filling volume prior to E-wave
FV-a-min              15.0           15.9       0.9      0.058  filling volume prior to A-wave
FVA (Yellin)           3.6            1.3      -2.3     -0.630  filling due to A-wave
FVA (clin)             5.4            3.7      -1.7     -0.310  filling during A-wave
FV-lost after MF=0     0.0            0.0       0.0      0.000  filling loss due to valve closure
FVA(Y)/FV              0.176          0.068    -0.109   -0.615  "true" atrial pump contribution
FVA(Y)-FVlost/FV       0.176          0.067    -0.109   -0.617  (ignore, not useful)
FV-PMF/FV              0.223          0.126    -0.097   -0.436  %filling prior to E-wave

t-LVPmin              68     ms      83        15       0.221  time to minimum LVP
t-(LAP-LVP)max        40             28       -12      -0.300  time to peak AV gradient
t-PMF                 94             67       -27      -0.287  time to E-wave
t-MF-a-min           396            405         9       0.023  time to start of A-wave
t-MF-a-max           484            461       -23      -0.048  time to A-wave
DFP-f                536            537         1       0.002  filling time based on flow
DFP-p                526            535         9       0.017  filling time based on pressure
DFP-f/RR               0.715          0.716     0.001    0.002  normalized by RR interval
                                                                (a questionable approach)
```

model analysis printout for intervention

The columns are

(from left to right): parameter names, control values, intervention
values, intervention values minus control values (change from
control to intervention), and intervention values minus control
values divided by control values (fractional change from control to
intervention).

Fig. 38

Yellin, Modified from Meisner , 1991

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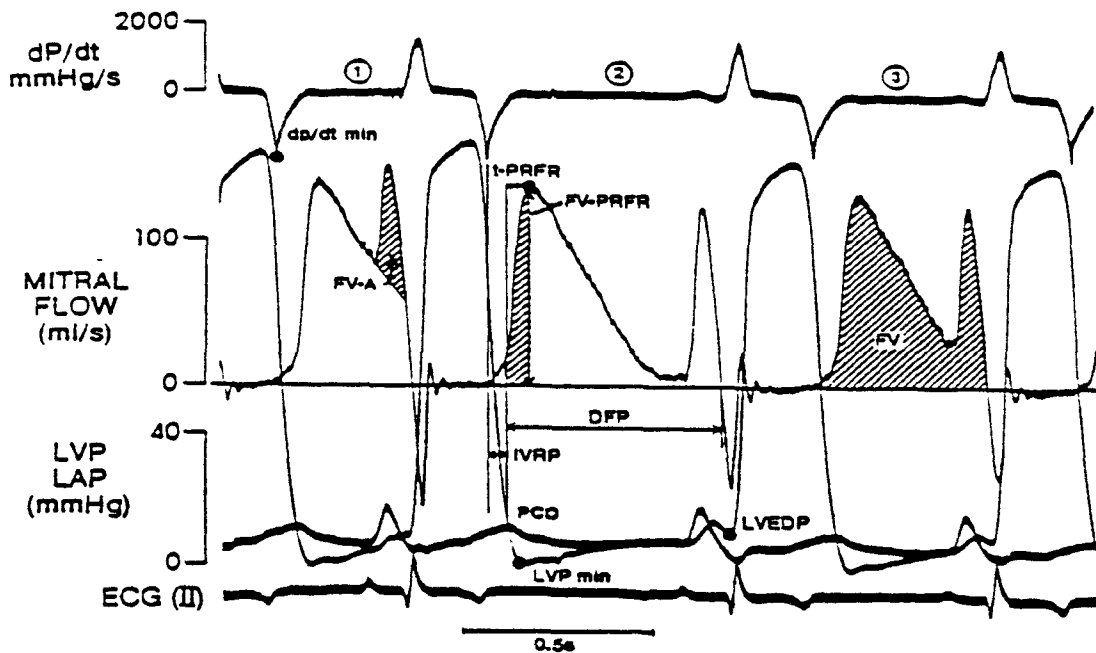
Oscillographic record from a conscious dog defining several indices of diastolic function. FV, filling volume; FV-A, filling volume due to atrial contraction; FV-PRFR, filling volume to peak rapid filling rate; t-PRFR, time from onset of flow to PRFR; IVRP, isovolumic relaxation period; DFP, diastolic filling period; PCO, first diastolic atrioventricular pressure crossover; LVPmin, minimum left ventricular pressure; LVEDP, left ventricular end diastolic pressure. (Unpublished observation, courtesy of Drs. Takako Tamura and Koichi Tamura.)

Fig. 39
Solomon

flow, LAP and LVP waveforms from a dog. The text below the graphs describes which parameters are illustrated so that this graph can assist in visualizing how they are related.

Verification: Before a model can be used as a research or teaching tool it must be validated by comparing its predictions with *in vivo* observations. By the very definition of the statement of purpose of the Meisner model, there are many measurements obtainable via the model which cannot be measured directly *in vivo*. Conversely, by definition of a lumped parameter model such as this, there are many data points which can be taken within a structure *in vivo* which are not available via the model. An example of this is demonstrated by Courtois, et. al. (1988), who measured left ventricular pressure at several locations within the left ventricular cavity, while the Meisner model gives only one value for left ventricular pressure. In addition, there are areas where the model will show more detail than can be seen in *in vivo* experiments and there are measurements which give much more precise readings than the model can accommodate. Thus, no authentication of a model can unequivocally attest to the "correctness" of the model and guarantee that it will be correct for all runs over a wide range of values. Nevertheless, it is important to verify, to whatever extent possible, that the model is performing as expected, and then, to actually use the model with an eye open for flaws. This was and is done with the Meisner model (Meisner, 1986, pp. 138-139). A thorough and detailed experiment was performed using the model and the results were compared with previously obtained in *in vivo* results. This extensive test, along with using the model as a research tool for a number

of years, verified the integrity of this model, and thus legitimized its further and expanded use.

CHAPTER V

Parameter vs. Parameter Runs:

Background: One important area in which the model can be useful is in varying the values of physical parameters and predicting their effects on the resulting flow and pressure patterns. In other words, one may want to vary one of the approximately thirty input parameters over a range in small steps and see how this affects one of the approximately thirty-five output parameters. In order to do this with the original program it was necessary to run the model with the desired input value changed, record the output values by hand or keep the output hardcopy, rerun the program with the value changed again, again either record by hand the values or keep the output hardcopy, and repeat this as many times as desired. This information could then all be transcribed in tabular form or plotted by hand (as was done by Meisner).

Implementation: It was decided that this type of study, which the model should be able to simulate so simply and straightforwardly, should be performed in a more direct manner. This necessitated two tasks. First, the interactive program which runs the model had to be modified, and second, there needed to be some program which could accept the output of the modified program and present it in tabular and graphical form.

Before changing the inner workings of the program it was necessary to provide for the background subroutines to enable the running of a "parameter vs. parameter" run. This included ascertaining early in the run the desire to perform the parameter vs. parameter run. Thus, this was inserted as an early option in the running of the program. If the response is

negative, which is the default response (if nothing is entered and the return key is struck) then the program runs as before with no changes; that is, it permits either just a control run, or a control and intervention, and still permits all the various output forms. If the response is affirmative, that is, a parameter vs. parameter run is desired, then all the other options are suppressed and the only type of run permitted is a parameter vs. parameter run. In such a case, all the other forms of output are then non-functional and only the thirty-five or so output variables will be available for each of the increments. No graphs will be plotted by the BASIC program. The program then requests information regarding which input parameter is to be varied, over what range (as specified by a starting and ending value) and in what increments. The increment given can be either positive or negative but it must agree with the direction of change from starting to ending value or the program will run only one intervention, the starting value. This sequence of prompts is shown in Figure 40.

The original program first solves the differential equations for the control run, stores the output variables and then resets itself to perform the intervention run. In a parameter vs. parameter run the program runs the normal routine for the control run but then opens an output file called "bigfile.dat" and stores the values there as well. Then, instead of arriving at the intervention value in the usual way it looks at the starting, ending and increment values that had been input. The first intervention run is always the starting value. It then stores the output values of that run in the same "bigfile.dat", returns to the beginning of the intervention section, resets itself, and, if the expression (current parameter value + increment < final value) is true, it increments the intervention parameter and then runs again. Thus, at the end it has always ended on or below the value input for

```
CONTROL Parameter Set-Up Routine        flashing=non-default

 1     0.00400 L8-PA inertance       19     0.00001 R9-LV viscous res.
 2     0.02000 R8-PA resistance      20     0.05000 ALPHA-LV passive exp.
 3     0.32000 E8-PA elastance       21     1.09000 A-LV passive coef.
 4     0.18000 R0-Pcap resistance    22     2.00000 Emax-LA
 5     0.48000 E0-Pcap elastance     23     0.00000 MR-Res. (0=no MR)
 6     0.10000 R1-PV resistance      24     0.00200 MR-Inertance
 7     0.00200 L1-PV inertance       25     0.00000 MR-LVV dependence
 8     0.00010 R2-MV resistance      26     0.00000 AR-Res  (0=no AR)
 9     0.00200 L2-MV inertance       27     1.00000 MV 0=closed 1=open
10  1280.00000 E3-MV bulge elastance 28   130.00000 PR
11     8.00000 R3-MV bulge resistance 29  750.00000 RR
12     0.10000 R4-Ao resistance      30     8.00000 Emax-LV
13     2.40000 R5-periph resistance  31    25.00000 Pmax-RV
14     1.25000 E5-Ao elastance       32    20.00000 tau
15     1.00000 K10-LA passive elast. 33    10.00000 con. cycls
16    13.00000 VD10-LA dead vol.     34    10.00000 int. cycls
17     8.00000 VD2-LV dead vol.      35     0.00000 CO
18    -4.00000 Pinf - LVP asymptote
```

Enter # to be changed or 36 to default all or <RETURN> to END?

    parameter vs parameter run ? (N)?

    what parameter do you want to vary ?

    what parameter do you want to vary ? 32
starting value? 10   end value? 100   step? 8

        Fig. 40

the final value. At the conclusion of all the runs, the value of the parameter being altered, along with all the output values, are stored for each incremental run in the one big file, "bigfile.dat". In that file are also stored some additional pieces of information which are useful when the file is uploaded into the package used to display the data. Once all of the needed information is stored in one file, QuickBASIC and the model simulation program are no longer needed and are exited. The complete modified QUICK BASIC program can be found in Appendix A.

Display of Results: The package chosen to display the data was QUATTRO PRO, a commercially available spreadsheet program designed to run on any IBM XT, AT, PS/2 or fully compatible computer which uses DOS 2.0 or a later version operating system, has at least 512K of RAM and a hard drive with at least 3MB of available space. In choosing to use a spreadsheet program it enables us to not only obtain quick, quality graphs, but it also has the ability to manipulate and analyze the data such as by performing regression analyses.

In order to access and graph the data which is stored in "bigfile.dat", QUATTRO PRO is run. Under the menu of options is the possibility of importing a stored file. The file that is desired is "bigfile.dat", which is in the subdirectory from which the BASIC program was run. The sequence of commands necessary to import the file is shown in Figure 41. When this file is loaded in, all the data appears readily usable. The row representing the changing parameter can be graphed versus any one or more of the output parameters, or all or part of the data can be printed out in tabular form.

```
 File  Edit  Style  Graph  Print  Database ‖Tools‖ Options  Window          ↑↓
A1:                                                                        │ ?
⌐        A        B         C         D     │Macro          Alt-F2 ►│        ↑
1                                           │Reformat                ·End
2                                           │                         ▲
3                                           │Import              ►│     ◄ ►
4                                   ┌────────────────────────────────┐   ▼
5                                   │ ASCII Text File                │
6                                   │ Comma & "" Delimited File      │Esc
7              ┌─────────────────────────────────────────────┐
8              │ Enter name of file to import:               │      ←⌐
9              │ C:\QB\BIGFILE.DAT                           │
10             │                                             │     Del
11             │                                             │
12             │        ┌───────┐        ┌─────┐             │      @
13             │        │ Enter │        │ Esc │             │
14             │        └───────┘        └─────┘             │      5
               └─────────────────────────────────────────────┘
```
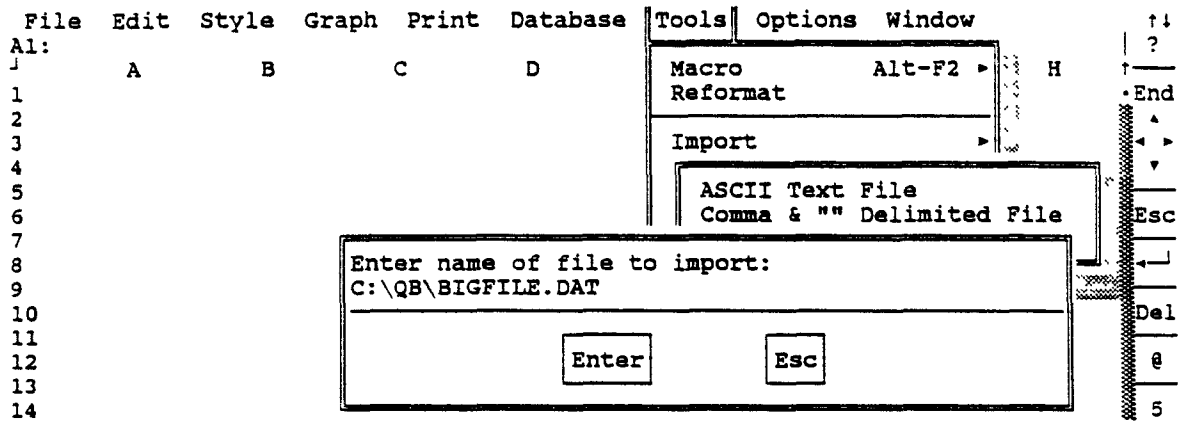
Fig. 41

At present, only one parameter can be varied at a time and then any output parameter can be plotted against this varied input. A future goal is to enable the BASIC program to vary two of the input parameters concurrently and plot, in a 3-D graph of the type QUATTRO PRO can handle, any output parameter vs. the two varied input parameters.

Results: In order to demonstrate that the new program was functioning correctly it was decided to redo the massive experiment that Meisner had originally done to verify his model and thus to show that the current results agree with his, which in turn had agreed with his *in vivo* results. The program was run with the PR interval varying from 1 to 402 ms. (the control is 130 ms.) in steps of 50 ms. The numerical output is presented in figure 42. Two of the graphs that Meisner plotted by hand in his thesis were of FV (filling volume) vs. PR interval, and DFP-f (filling time based on flow) vs. PR interval. He had shown that his model results for these two graphs agreed with his *in vivo* dog results. Figure 43 shows the results for FV (filling volume) vs. PR interval as generated by the new program (top) and as drawn by Meisner. Figure 44 shows a similar presentation for DFP-f (filling time based on flow) vs. PR interval. Following those, figures 45 and 46 show the new programs results for LVP-a-min (LVP at minimum LA pressure) vs. PR interval and PLVP (peak LV pressure) vs. PR interval, respectively.

Fig. 42

```
this run vaPR      from       1 to        402 in ste     50
output       control
               130      1     51    101    151    201    251    301    351    401
PCO          2.963  2.284  2.949   2.69  3.076  3.481  3.895  4.264  4.281  4.152
LVPmin       -1.65  -1.79   -1.7  -1.71  -1.65  -1.63  -1.59  -1.56  -1.57  -1.58
LVEDP        3.139  2.275  2.284   2.74   3.09  2.914  2.763  2.603  2.425   2.57
LVEDV        40.43  38.21  38.23  39.44  40.31  39.88  39.49  39.08  38.61     39
EF           53.57  53.23  54.57  54.57  53.46  53.39  53.25  53.12  51.15  46.73
(LAP-LVP)ma  4.122  4.438  4.412  4.006  4.186  4.452  4.758  4.997  5.017   4.95
PLVP         106.3  98.97  101.9  104.9  105.3  103.8  102.5  101.1  100.5  101.4
M-(LA-LV)-d   0.31  0.316  0.403  0.437  0.206  0.022  -0.07  -0.05   0.09  0.208
MLAP         0.996  1.943  1.531  0.937  1.041  1.246  1.457  1.669  1.723  1.682
MLAP-diast   0.819  0.853  0.895  0.792  0.772  0.765  0.828  0.958   1.05  1.081
MLAP-syst    1.468  4.804  3.233  1.331  1.761  2.542  3.176  3.628  3.576  3.335
LVP-a-min    1.467  2.269  1.892  1.474  1.364  1.046  0.666  0.469  0.335  -0.17
LAP-a-max    3.964  7.986  4.614  4.109  3.664   2.85  2.713  3.507  3.489  2.101
LAV-a-min    13.96  15.45  15.13  14.24  13.78  13.87  14.42  14.16  12.24  10.68
PMF          105.3  115.8  112.2    103  106.6    112  117.9  122.7  123.1  121.6
MF-a-min     15.51  15.45   10.4  10.53  21.68   35.1  31.22  11.39  14.99  65.99
MF-a-max     57.78      1  49.49  60.87  54.83  51.56  63.63  76.74   72.3  38.55
MF-a-max/PM  0.549  0.009  0.441  0.591  0.514   0.46   0.54  0.625  0.587  0.317
FV           21.66  20.34  20.87  21.52  21.55  21.29  21.03  20.76  19.75  18.22
FV-PMF       5.031  5.614  5.357  4.918  5.091  5.269  5.518  5.745  5.653  5.606
FV-a-min        17   20.1  18.74  17.21  16.81  15.97  14.81  14.26  13.83  11.76
FVA(Yellin)  2.982  0.014  1.218  2.915  2.928  2.806  2.417  2.277  2.302  2.088
FVA(clin)    4.656  0.242   2.13  4.307  4.743  5.319  6.216  6.496  5.923  6.466
FV-lost aft   0.01   0.01   0.01   0.01  0.137   0.78  1.237  1.873  2.981  4.179
FVA(Y)/FV    0.138  ******0.058  0.135  0.136  0.132  0.115   0.11  0.117  0.115
FVA(Y)-FVlo  0.137  0.000  0.058  0.135   0.13  0.095  0.056  0.019  -0.03  -0.11
FV-PMF/FV    0.232  0.276  0.257  0.229  0.236  0.248  0.262  0.277  0.286  0.308
t-LVPmin        59     58     59     60     60     60     61     61     61     61
t-(LAP-LVP)     36     40     37     37     36     36     36     36     35     36
t-PMF           88     91     88     89     88     87     87     86     85     86
t-MF-a-min     412    541    492    441    392    344    296    247    197    147
t-MF-a-max     501      1    553    528    481    427    370    328    291    173
DFP-f          553    567    570    563    536    488    438    392    353    322
DFP-p          542    542    543    542    543    545    547    548    548    548
DFP-f/RR     0.737  0.756   0.76  0.751  0.715  0.651  0.584  0.523  0.471  0.429
```

Fig 43

FV (filling volume) vs. PR interval
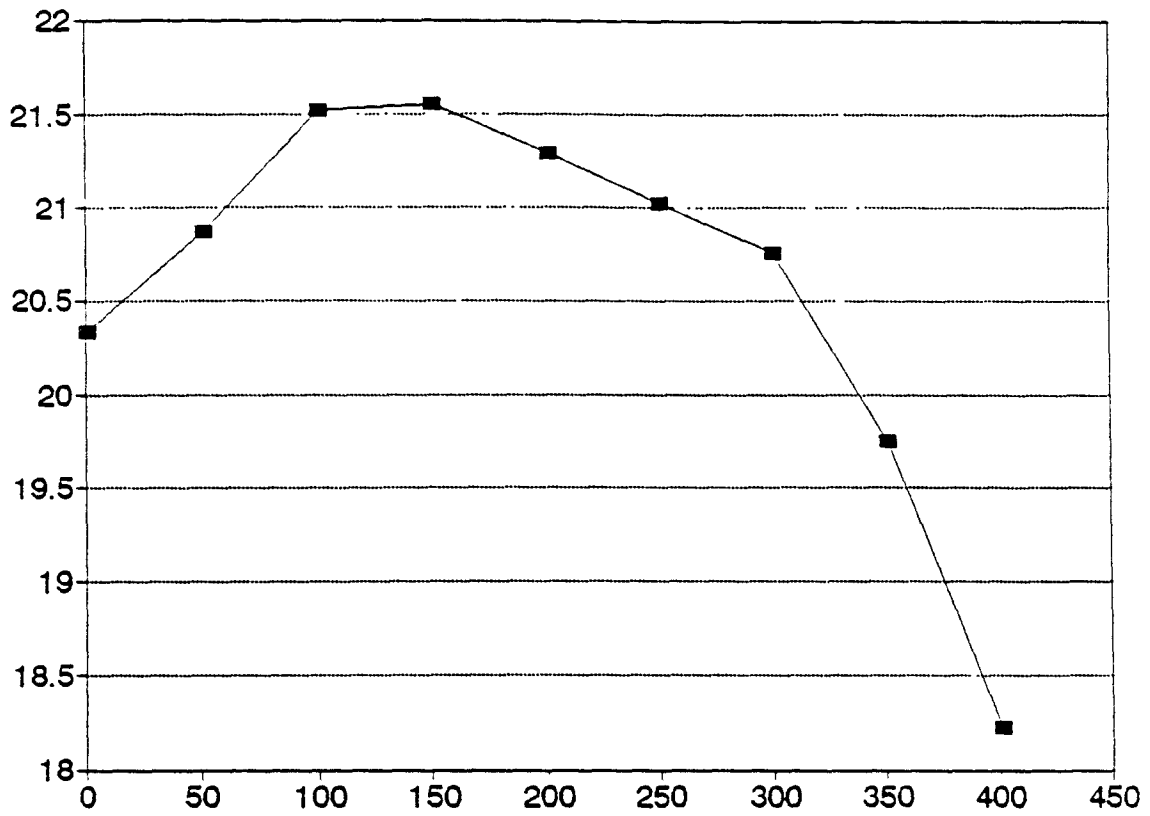
MODEL: NORMALIZED FV vs AV DELAY

Meisner, 1986 (Doctoral Thesis)

Fig. 44
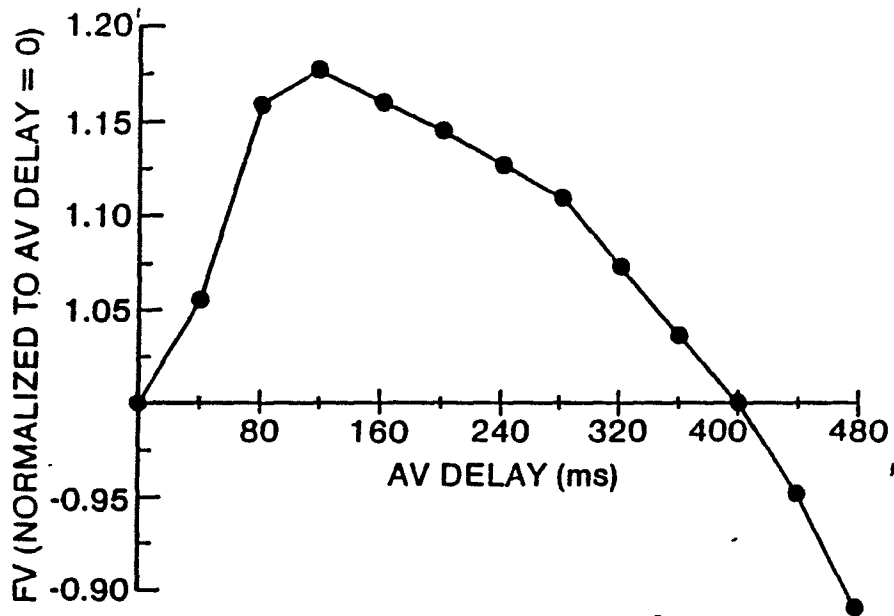
DFP-f (filling time based on flow) vs. PR interval

Meisner, 1986 (Doctoral Thesis)

Fig. 45
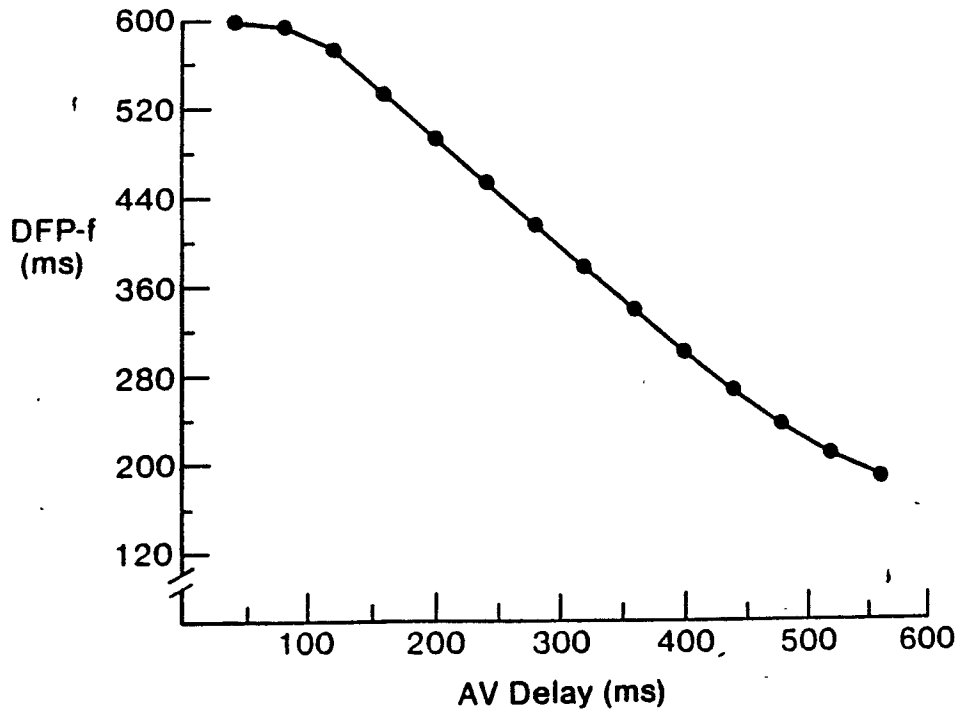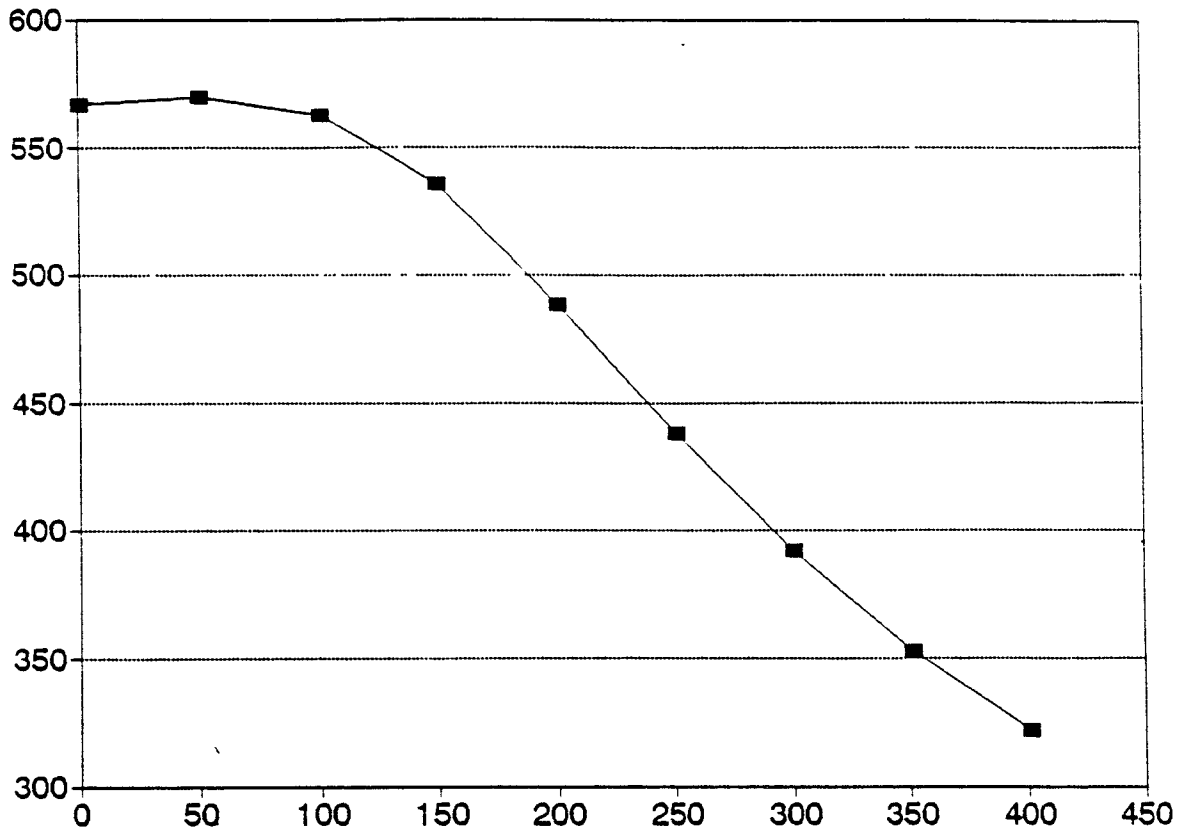
LVP-a-min (LVP at minimum LA pressure) vs. PR interval
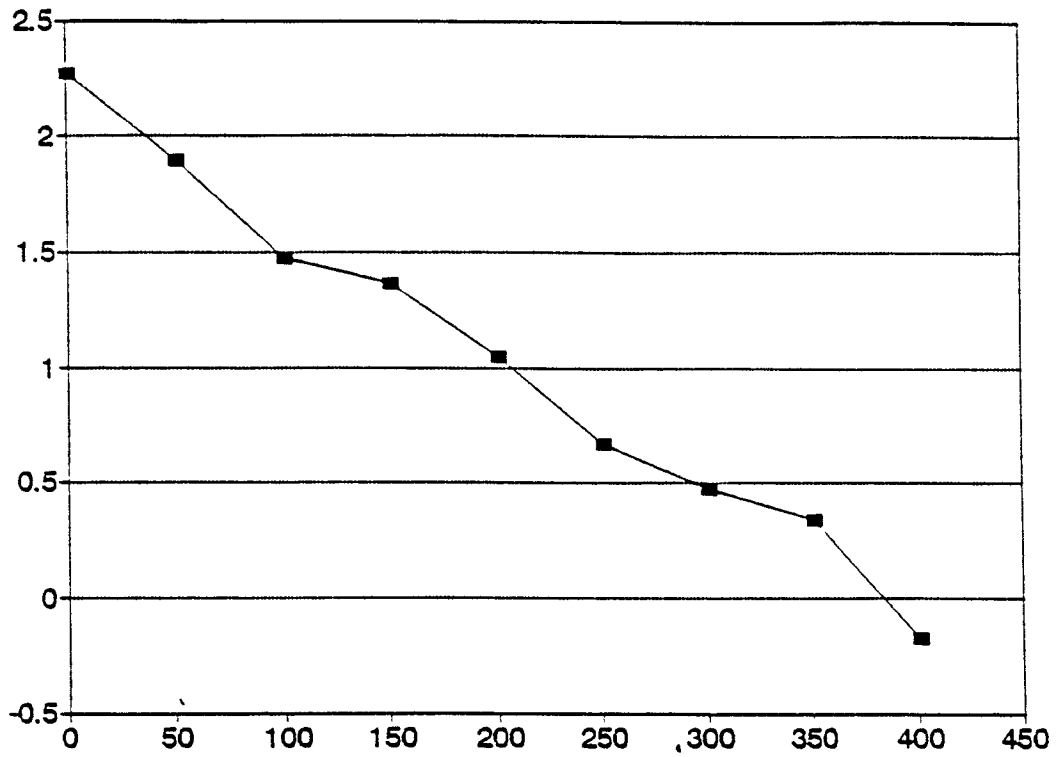
Fig. 46

PLVP (peak LV pressure) vs. PR interval
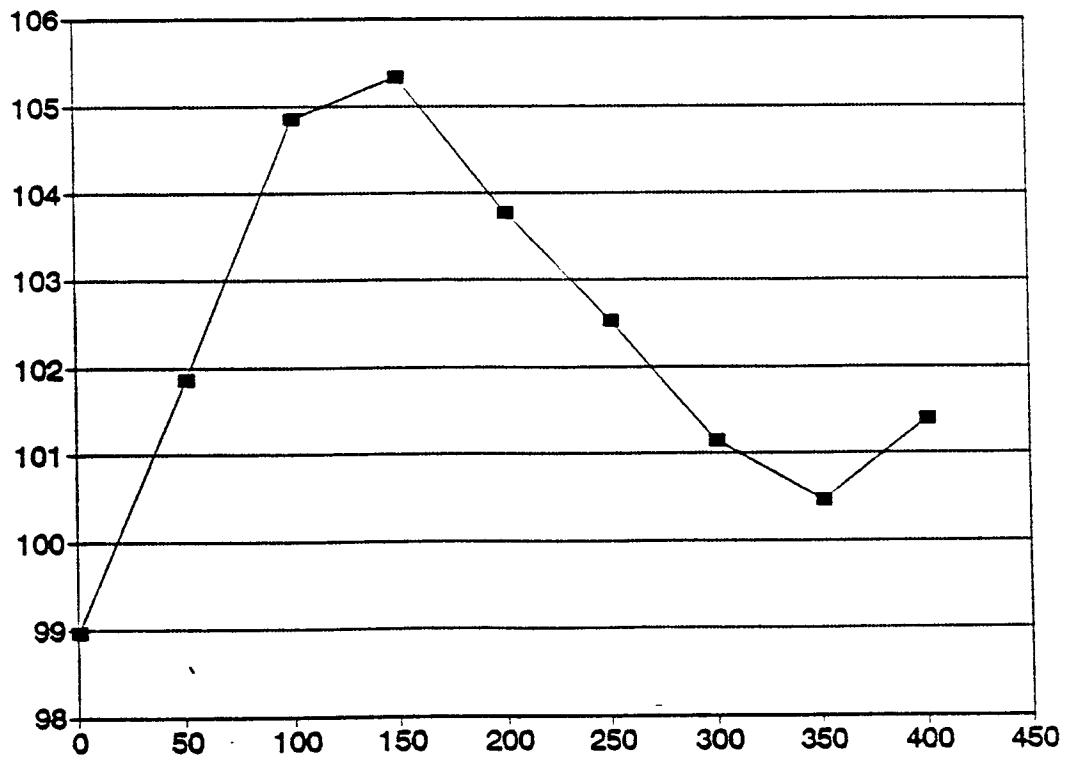
Vary Emax-LA: The next series of results were designed to do an experiment for which the results, though not presented in Meisner's work, should intuitively be clear enough to determine whether they are correct or not. Figure 47 presents the tabular results of varying Emax-LA, that is increasing the degree to which the LA contracts, from 1 to 3 (the control value is 2) in steps of .2. Following the numerical data, are four graphs showing MF-a-max (peak A-wave) vs. Emax-LA (figure 48), LAP-a-max (LAP at peak A-wave) vs. Emax-LA (figure 49), PMF (peak mitral flow - E wave) vs. Emax-LA (figure 50) and FVA (filling due to A-wave) vs. Emax-LA (figure 51). Since the strength of the atrial contraction is increasing it makes sense that the first three graphs should all be rising. And since the A-wave is increasing it follows the the fourth graph, PMF, should be decreasing.

this run vaEmax-from   1 to   3 in st 0.2
output   control

	control										
	2	1	1.2	1.4	1.6	1.8	2	2.2	2.4	2.6	2.8
PCO	2.96	3.33	3.15	3.03	2.97	2.96	2.91	2.93	2.89	2.97	2.9
LVPmin	-1.7	-1.6	-1.7	-1.7	-1.7	-1.7	-1.7	-1.7	-1.7	-1.7	-1.7
LVEDP	3.14	2.81	2.89	2.94	3.01	3.11	3.11	3.14	3.17	3.24	3.19
LVEDV	40.4	39.6	39.8	39.9	40.1	40.3	40.4	40.4	40.5	40.7	40.5
EF	53.6	53.8	53.9	53.8	53.8	53.9	53.7	53.7	53.7	53.8	53.7
(LAP-LVP)ma	4.12	4.38	4.28	4.18	4.16	4.15	4.09	4.11	4.07	4.14	4.09
PLVP	106	104	104	105	105	106	106	106	106	106	106
M-(LA-LV)-d	0.31	0.34	0.35	0.34	0.33	0.33	0.31	0.3	0.28	0.27	0.25
MLAP	1	1.24	1.14	1.06	1.02	1.01	0.97	0.96	0.95	0.98	0.94
MLAP-diast	0.82	0.9	0.86	0.82	0.82	0.82	0.79	0.78	0.77	0.79	0.75
MLAP-syst	1.47	2.17	1.89	1.69	1.56	1.53	1.46	1.44	1.45	1.49	1.47
LVP-a-min	1.47	1.59	1.53	1.47	1.46	1.47	1.44	1.44	1.43	1.47	1.43
LAP-a-max	3.96	2.9	3.13	3.33	3.54	3.78	3.93	4.11	4.28	4.51	4.59
LAV-a-min	14	14.1	14	14	14	14	13.9	13.9	13.9	14	13.9
PMF	105	110	108	106	106	106	105	105	104	106	105
MF-a-min	15.5	15	15.4	15.6	15.6	15.8	15.8	15.6	15.9	15.6	15.7
MF-a-max	57.8	36.9	42.9	47.5	51.3	55.2	57.9	60.3	62.8	65.2	66.7
MF-a-max/PM	0.55	0.33	0.4	0.45	0.48	0.52	0.55	0.57	0.6	0.62	0.64
FV	21.7	21.3	21.5	21.5	21.6	21.8	21.7	21.7	21.7	21.9	21.8
FV-PMF	5.03	5.21	5.12	5.08	5.09	5.08	5	5.03	4.97	5.06	4.99
FV-a-min	17	17.6	17.4	17.2	17.1	17.1	17	17	17	17.1	17
FVA(Yellin)	2.98	1.91	2.28	2.54	2.73	2.87	2.97	3.05	3.11	3.2	3.21
FVA(clin)	4.66	3.67	4.06	4.3	4.46	4.63	4.69	4.71	4.77	4.78	4.78
FV-lost aft	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
FVA(Y)/FV	0.14	0.09	0.11	0.12	0.13	0.13	0.14	0.14	0.14	0.15	0.15
FVA(Y)-FVlo	0.14	0.09	0.11	0.12	0.13	0.13	0.14	0.14	0.14	0.15	0.15
FV-PMF/FV	0.23	0.24	0.24	0.24	0.24	0.23	0.23	0.23	0.23	0.23	0.23
t-LVPmin	59	60	60	60	60	60	59	59	59	59	59
t-(LAP-LVP)	ˎ36	36	37	36	37	37	36	36	36	36	36
t-PMF	88	87	88	88	89	89	88	88	88	88	88
t-MF-a-min	412	414	414	413	413	413	412	412	412	412	412
t-MF-a-max	501	510	510	507	505	503	501	499	497	496	495
DFP-f	553	561	560	558	557	556	553	551	549	546	544
DFP-p	542	544	544	543	543	543	542	542	542	542	542
DFP-f/RR	0.74	0.75	0.75	0.74	0.74	0.74	0.74	0.73	0.73	0.73	0.73

Fig. 47

Fig. 48

MF-a-max (peak A-wave) vs. Emax-LA
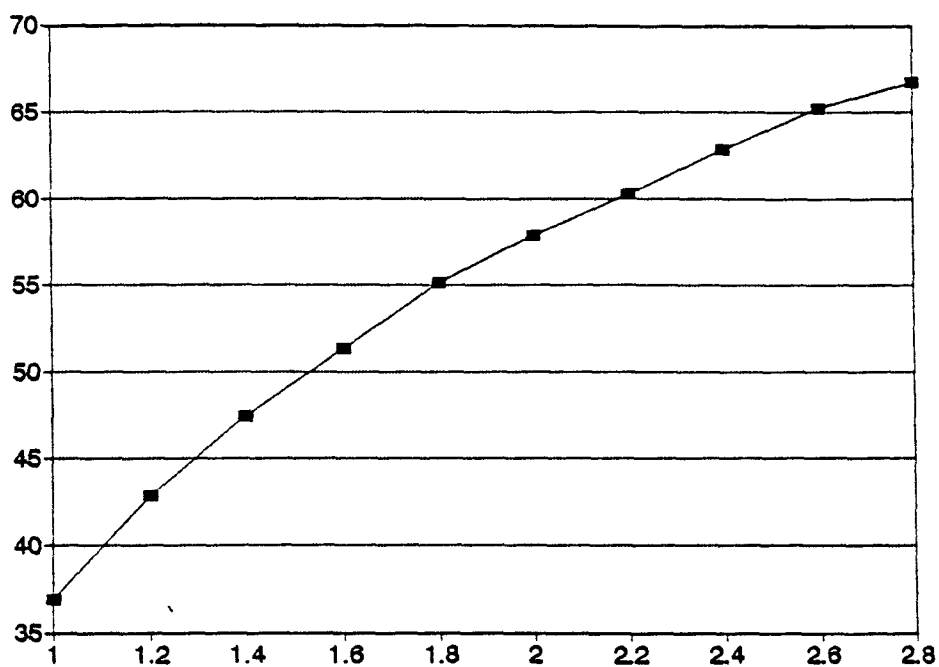
Fig. 49

LAP-a-max (LAP at peak A-wave) vs. Emax-LA
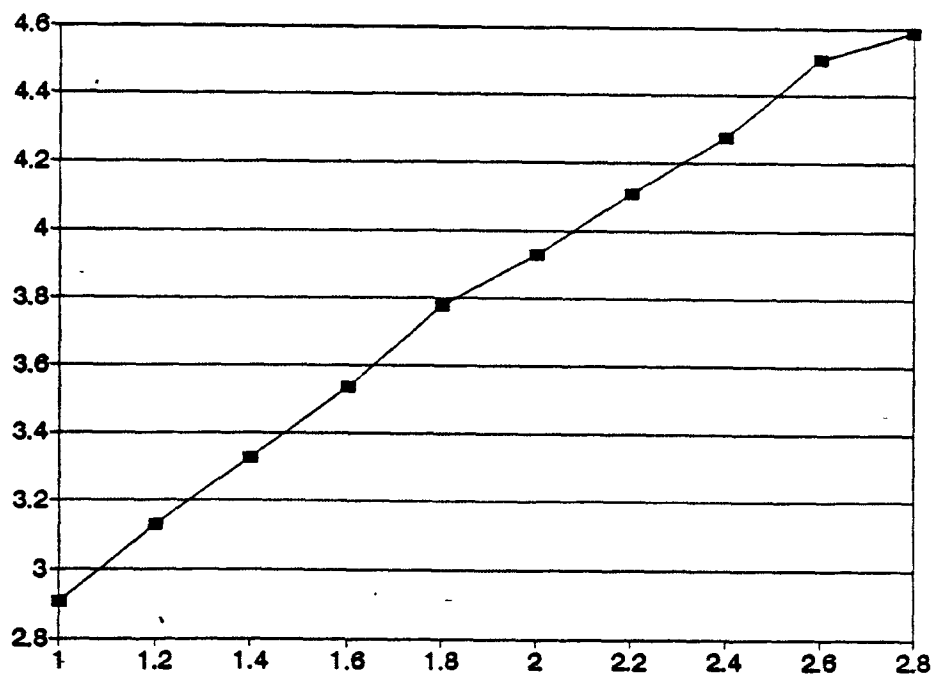
Fig. 50

PMF (peak mitral flow - E wave) vs. Emax-LA
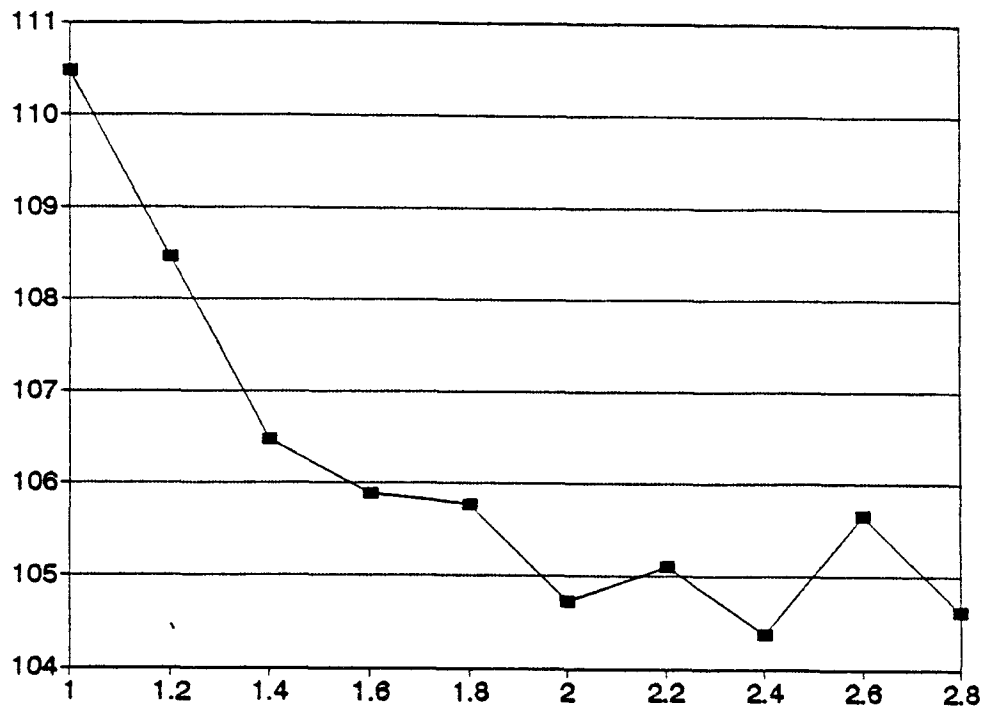
Fig. 51

FVA (filling due to A-wave) vs. Emax-LA
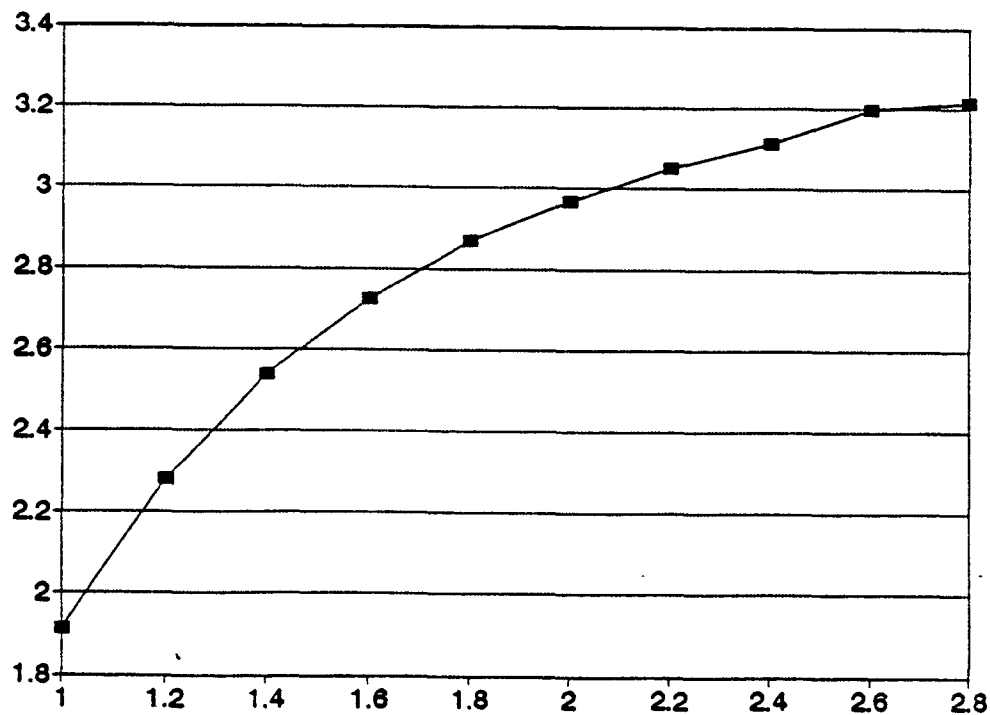
Vary Tau: A second experiment of the above genre was performed, this time varying tau (the time constant of relaxation of the LV following a contraction) from 10 to 100 ms (the control is 20 ms) in increments of 8 ms. The tabular results are presented in figure 52. Following that are the graphs of MF-a-max/PMF (A/E ratio) vs. tau (figure 53), MLAP (mean LA pressure) vs. tau (figure 54) and (LAP-LVP)max (maximum AV pressure difference) vs. tau (figure 55). Since the ventricle is relaxing much slower it makes sense that its pressure drop is slower and less precipitous, thus maintaining a raised MLAP. This also leads to a significant rise in the A/E ratio as well as a decrease in the maximum pressure difference.

```
this run vatau from 10 to    100 in s  8
output      control
```

	control 20	10	18	26	34	42	50	58	66	74	82	90	98
PCO	3	2.1	2.8	3.4	3.94	4.5	5	5.4	5.9	6.4	6.9	7.2	7.7
LVPmin	-2	-2	-2	-1	-0.8	-0	0.2	0.7	1.3	1.8	2.1	2.4	2.7
LVEDP	3.1	2.6	3	3.4	3.72	4	4.2	4.4	4.5	4.6	4.7	4.7	4.9
LVEDV	40	39	40	41	41.8	42	43	43	43	44	44	43	43
EF	54	53	54	54	54.2	54	54	55	55	55	55	55	55
(LAP-LVP)ma	4.1	4.2	4.1	4.1	3.96	3.9	3.8	3.7	3.5	3.5	3.4	3.3	3.2
PLVP	106	101	105	108	110	113	114	115	115	116	116	115	115
M-(LA-LV)-d	0.3	0.3	0.3	0.3	0.35	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.6
MLAP	1	0.5	0.9	1.3	1.66	2.1	2.4	2.7	3	3.4	3.8	4.1	4.6
MLAP-diast	0.8	0.3	0.7	1.1	1.38	1.7	2	2.3	2.6	3	3.5	3.8	4.3
MLAP-syst	1.5	0.8	1.3	1.8	2.25	2.7	3	3.3	3.6	3.9	4.2	4.5	4.8
LVP-a-min	1.5	1	1.4	1.6	1.76	1.9	1.9	1.9	1.9	2.1	2.2	2.4	2.7
LAP-a-max	4	3.5	3.9	4.1	4.08	4.2	4.3	4.5	4.6	4.8	5	5.2	5.6
LAV-a-min	14	14	14	14	14.3	15	15	15	15	15	15	16	16
PMF	105	97	104	108	109	110	109	107	105	103	101	98	95
MF-a-min	16	10	14	21	27.6	31	32	33	34	36	39	42	44
MF-a-max	58	58	58	57	56.2	59	63	67	71	76	81	86	92
MF-a-max/PM	0.5	0.6	0.6	0.5	0.51	0.5	0.6	0.6	0.7	0.7	0.8	0.9	1
FV	22	21	22	22	22.6	23	23	24	24	24	24	24	24
FV-PMF	5	4.4	4.9	5.3	5.65	5.8	5.8	5.8	5.8	5.8	5.7	5.5	5.3
FV-a-min	17	16	17	17	17.5	18	17	17	17	17	16	15	15
FVA(Yellin)	3	2.7	2.9	3.1	3.13	3.1	3.1	3.1	3	3.1	3	3	3
FVA(clin)	4.7	4.6	4.7	4.8	5.11	5.5	5.9	6.3	6.7	7.2	7.8	8.3	8.9
FV-lost aft	0.0	0.0	0.0	0.0	0.01	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
FVA(Y)/FV	0.1	0.1	0.1	0.1	0.14	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
FVA(Y)-FVlo	0.1	0.1	0.1	0.1	0.14	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
FV-PMF/FV	0.2	0.2	0.2	0.2	0.25	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
t-LVPmin	59	39	57	69	79	88	96	104	114	206	236	248	258
t-(LAP-LVP)	36	27	35	40	43	46	47	48	49	49	49	49	49
t-PMF	88	81	87	92	96	99	101	103	104	105	106	106	106
t-MF-a-min	412	439	418	397	377	359	340	323	306	290	276	261	249
t-MF-a-max	501	526	506	486	464	443	422	404	386	370	356	341	329
DFP-f	553	579	559	538	517	498	479	462	446	430	417	404	393
DFP-p	542	569	548	527	507	489	470	453	436	420	406	391	379
DFP-f/RR	0.7	0.8	0.7	0.7	0.69	0.7	0.6	0.6	0.6	0.6	0.6	0.5	0.5

Fig. 52

Fig. 53

MF-a-max/PMF (A/E ratio) vs. tau
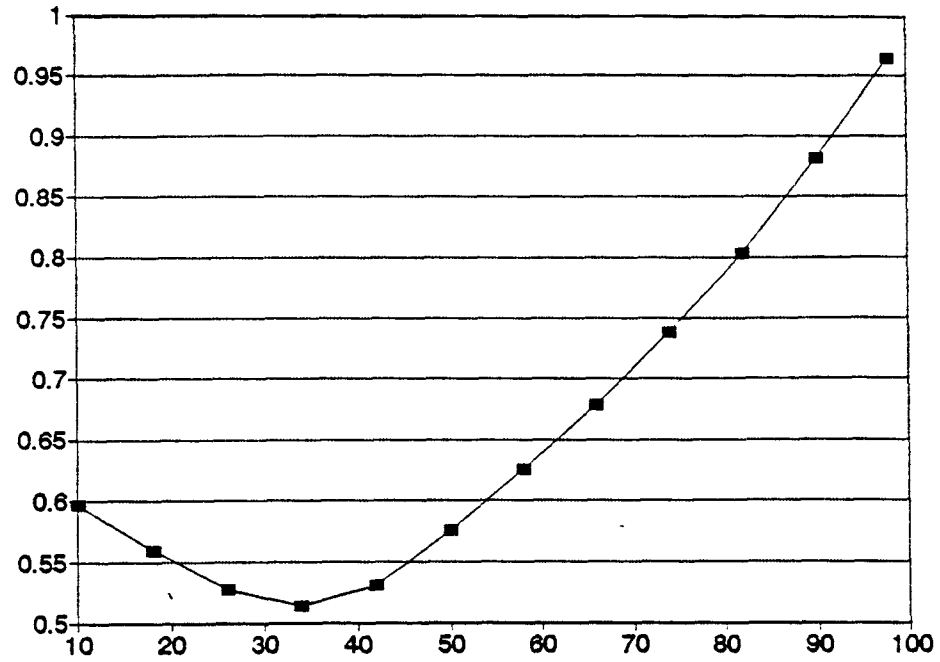
Fig. 54

MLAP (mean LA pressure) vs. tau
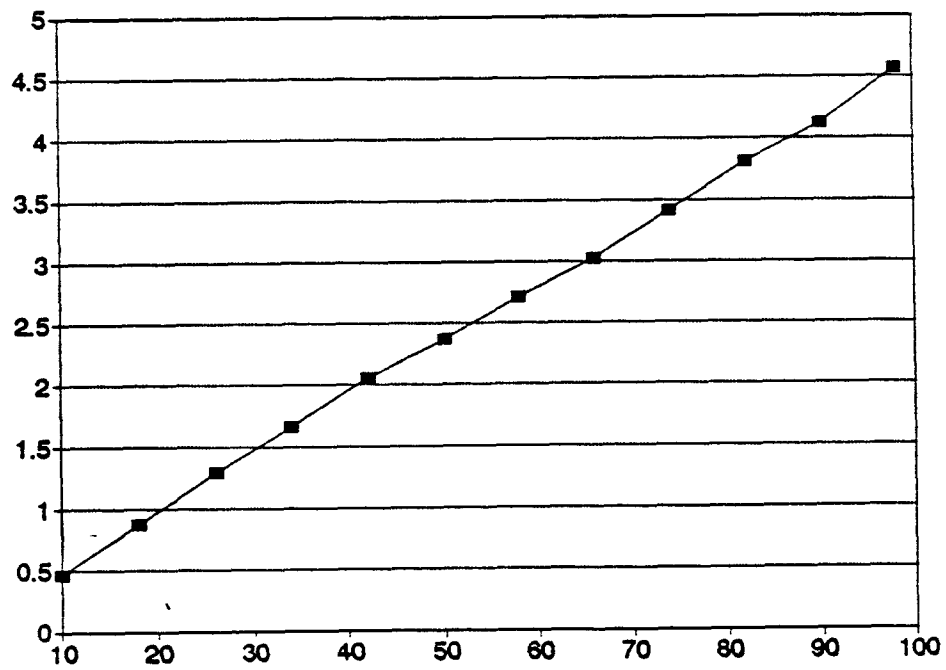
Fig. 55

(LAP-LVP)max (maximum AV pressure difference) vs. tau
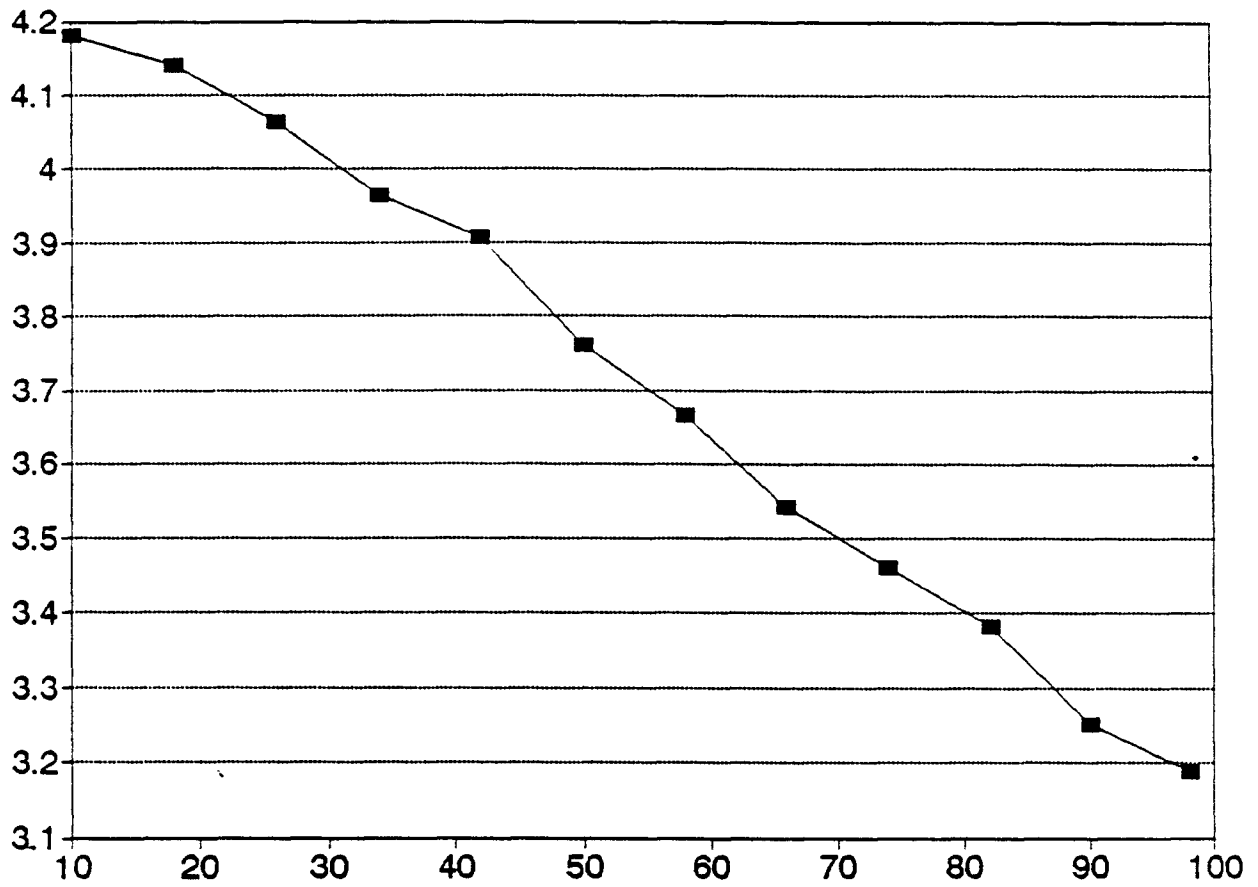
Affect of Tau on MLAP: The final series of experiments was designed to see how MLAP (Mean Left Atrial Pressure) is affected by tau under a variety of conditions. Thus, all the graphs presented below are of MLAP vs. tau. In addition to changing certain of the control parameters in each run a second variable was added. Under each set of conditions two runs were performed, one in which the CO was permitted to settle to whatever value it settled, and a second run in which cardiac output was maintained at a constant 1736 ml. Many such runs were performed, though only a few of these are presented below. The first two are the control conditions. Figures 56 and 57 present the tabular results of the control run for CO=0 and CO=1736 respectively. Figures 58 and 59 are the respective graphs for those two runs. The first intervention shown is that of changing P_{inf} from its control value of -4 to -1, thus shifting up the entire passive response curve of the LV. Figures 60 and 61 present the numerical results of this run and figures 62 and 63 contain the graphical results. In the next experiment Emax-LV was lowered to 4 (control = 8) thus causing the strength of ventricular contraction to decrease. The numerical results are shown in figures 64 and 65 and the graphical results are presented in figures 66 and 67.

```
this run vatau  from    20 to     100 in st  10
output        control
               20    20    30    40    50    60    70    80    90   100
PCO           2.96  2.91   3.6  4.36  4.97  5.64   6.1  6.73  7.22  7.82
LVPmin        -1.7  -1.7  -1.1  -0.5   0.2  0.91  1.53  2.05  2.39  2.81
LVEDP         3.14  3.11  3.53  3.93  4.26  4.48  4.53  4.71  4.76  4.94
LVEDV         40.4  40.4  41.4  42.3    43  43.4  43.4  43.6  43.3  42.9
EF            53.6  53.7  54.2  54.4  54.6  54.7  54.7  54.9  54.9  54.9
(LAP-LVP)ma   4.12  4.09  3.99  3.91  3.78  3.66   3.5   3.4  3.26  3.17
PLVP           106   106   109   112   114   116   116   116   115   115
M-(LA-LV)-d   0.31  0.31  0.34  0.37  0.39  0.42  0.46   0.5  0.55   0.6
MLAP             1  0.97  1.44  1.93  2.39  2.84   3.2  3.71  4.14  4.67
MLAP-diast    0.82  0.79  1.19  1.62  2.03  2.46  2.83  3.36  3.83  4.44
MLAP-syst     1.47  1.46  2.02  2.55  3.01  3.43  3.72  4.15  4.49  4.92
LVP-a-min     1.47  1.44  1.67  1.83  1.89  1.97  1.99  2.18  2.41  2.83
LAP-a-max     3.96  3.93  4.02  4.13  4.32  4.56  4.67  4.97  5.24  5.75
LAV-a-min       14  13.9  14.1  14.6  14.9  15.1  15.2  15.4  15.6  16.1
PMF            105   105   108   110   109   107   104   101  97.9  94.8
MF-a-min      15.5  15.8    25  30.4  32.4  32.9  34.8  38.3  41.9  44.9
MF-a-max      57.8  57.8  56.2  57.6  62.9  68.2  73.5  79.8  86.5  93.8
MF-a-max/PM   0.55  0.55  0.52  0.52  0.58  0.64  0.71  0.79  0.88  0.99
FV            21.7  21.7  22.4    23  23.5  23.8  23.8  23.9  23.8  23.6
FV-PMF        5.03     5  5.42  5.77  5.88  5.87  5.81  5.67  5.44  5.29
FV-a-min        17    17  17.4  17.6  17.5  17.4  16.8  16.3  15.4  14.5
FVA(Yellin)   2.98  2.97   3.1  3.07  3.12   3.1     3  3.04     3  3.02
FVA(clin)     4.66  4.69  4.97   5.4  5.96  6.41  6.94  7.61  8.34  9.09
FV-lost aft   0.01  0.01  0.01  0.01  0.01  0.01  0.01  0.01  0.01  0.01
FVA(Y)/FV     0.14  0.14  0.14  0.13  0.13  0.13  0.13  0.13  0.13  0.13
FVA(Y)-FVlo   0.14  0.14  0.14  0.13  0.13  0.13  0.13  0.13  0.13  0.13
FV-PMF/FV     0.23  0.23  0.24  0.25  0.25  0.25  0.24  0.24  0.23  0.22
t-LVPmin        59    59    74    86    97   106   122   232   248   259
t-(LAP-LVP)     36    36    42    45    48    48    49    50    49    50
t-PMF           88    88    94    98   102   103   105   106   105   106
t-MF-a-min     412   412   387   363   341   319   298   280   261   246

t-MF-a-max     501   501   475   448   423   400   378   360   341   326
DFP-f          553   553   528   503   480   458   438   421   404   390
DFP-p          542   542   517   493   471   449   428   410   391   376
DFP-f/RR      0.74  0.74   0.7  0.67  0.64  0.61  0.58  0.56  0.54  0.52
```

Control Parameters, CO = 0

Fig. 56

```
this run vatau     from       30 to        100 in ste     10
output      control
                20       30       40       50       60       70       80       90      100
PCO         3.383    3.529      3.9    4.283    4.689    5.138    5.632    6.194    6.817
LVPmin      -1.54    -1.16    -0.67    -0.15    0.383    0.913    1.225    1.585    2.016
LVEDP       3.508    3.162    3.136    3.134    3.133    3.153    3.222    3.377     3.65
LVEDV       41.31    40.48    40.42    40.41    40.39    40.34    40.28     40.2    40.11
EF          53.55    53.73    53.74    53.74    53.76     53.8    53.86    53.93    54.02
(LAP-LVP)ma 4.376    3.917    3.675    3.458    3.279    3.123    3.021    2.923    2.857
PLVP        109.7    106.2    105.9    105.8    105.8    105.7    105.6    105.5    105.3
M-(LA-LV)-d 0.325    0.326    0.336    0.349    0.371      0.4    0.439    0.484    0.535
MLAP        1.245    1.261     1.48    1.727    2.008    2.344    2.746    3.225    3.785
MLAP-diast  1.061    1.006    1.167    1.375    1.638     1.97    2.392    2.907    3.529
MLAP-syst   1.739     1.84    2.092    2.328    2.569    2.849    3.179     3.58     4.05
LVP-a-min   1.728     1.44    1.303    1.185    1.121    1.144    1.287    1.585    2.052
LAP-a-max   4.383    3.661    3.326    3.233    3.281    3.399    3.612    3.986    4.565
LAV-a-min   14.21    13.92    14.08    14.25    14.33    14.38    14.52     14.8    15.25
PMF         110.2    106.4    104.1      101    97.75    94.48    91.77    89.12    86.92
MF-a-min    14.58    24.28    29.62    30.51    30.58       32    34.76    38.03    41.03
MF-a-max    60.17    53.91    53.68    57.38    62.02    66.81    72.31    78.77    86.16
MF-a-max/PM 0.546    0.507    0.516    0.568    0.634    0.707    0.788    0.884    0.991
FV          22.12    21.75    21.72    21.72    21.71     21.7    21.69    21.68    21.67
FV-PMF      5.182    5.296     5.49    5.436    5.436    5.322    5.192    4.991    4.883
FV-a-min    17.37    16.96    16.57    16.16    15.75    15.27    14.68    13.99    13.23
FVA(Yellin) 3.113    3.002    2.899    2.787    2.715    2.668    2.649    2.643    2.696
FVA(clin)   4.748    4.794    5.147    5.554    5.961     6.43    7.013    7.696    8.441
FV-lost aft  0.01     0.01     0.01     0.01     0.01     0.01     0.01     0.01     0.01
FVA(Y)/FV   0.141    0.138    0.133    0.128    0.125    0.123    0.122    0.122    0.124
FVA(Y)-FVlo  0.14    0.138    0.133    0.128    0.125    0.122    0.122    0.121    0.124
FV-PMF/FV   0.234    0.243    0.253     0.25     0.25    0.245    0.239     0.23    0.225
t-LVPmin       59       74       87       99      112      210      244      258      262
t-(LAP-LVP)    36       41       45       47       48       49       49       49       49
t-PMF          87       93       99      102      105      106      107      106      106
t-MF-a-min    413      387      363      340      318      297      278      260      244
t-MF-a-max    502      475      447      421      398      377      358      340      325
DFP-f         553      528      503      480      458      438      420      404      389
DFP-p         543      517      493      470      448      427      408      390      374
DFP-f/RR    0.737    0.704    0.671     0.64    0.611    0.584     0.56    0.539    0.519
```

Control Parameters, CO = 1736

Fig. 57

Fig. 58

Control Parameters, CO = 0

MLAP vs. tau

Fig. 59

Control Parameters, CO = 1736

MLAP vs. tau

```
this run vatau      from       30 to        100 in ste    10
output        control
                20      30      40      50      60      70      80      90     100
```
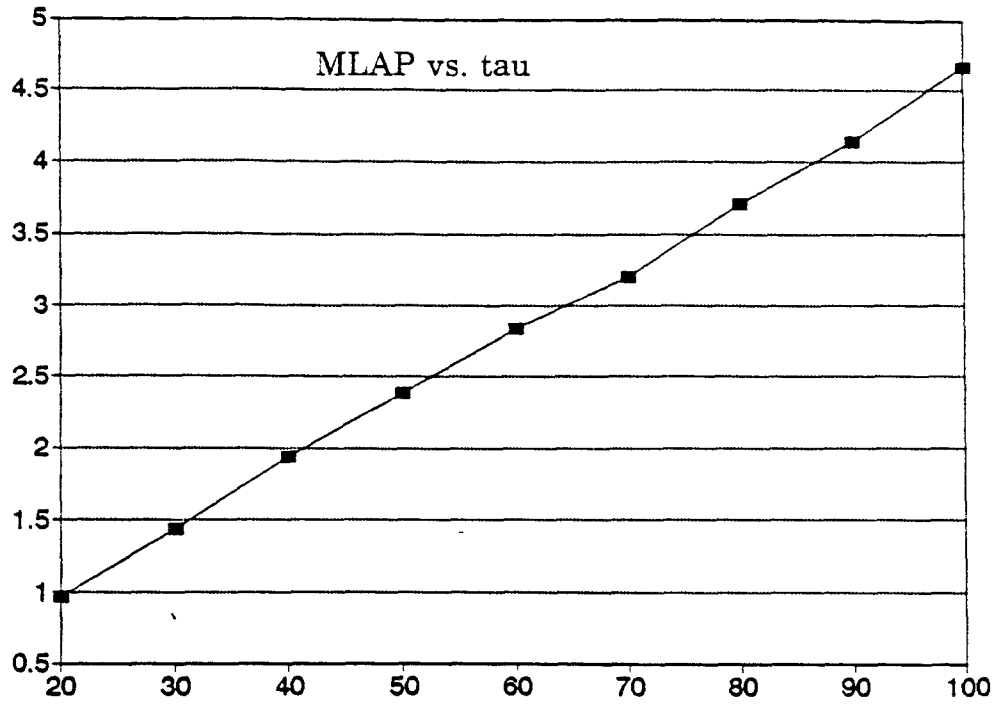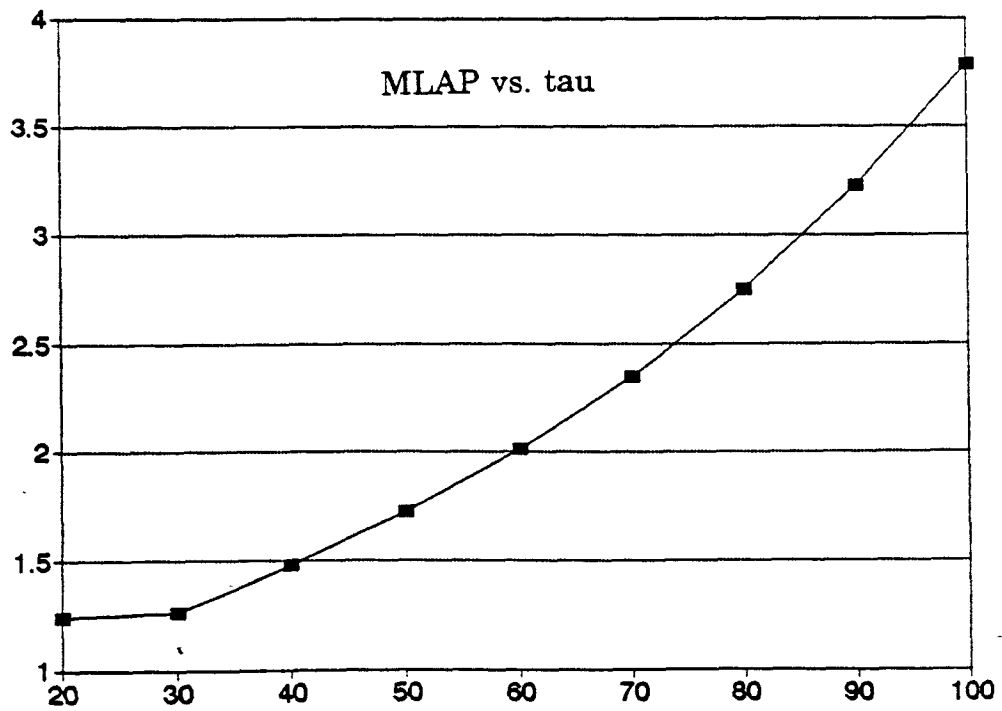
output	20	30	40	50	60	70	80	90	100
PCO	4.095	4.752	5.323	5.972	6.487	7.013	7.622	8.144	8.658
LVPmin	0.926	1.331	1.794	2.326	2.85	3.386	3.782	4.103	4.46
LVEDP	4.703	5.04	5.311	5.604	5.756	5.911	6.063	6.179	6.364
LVEDV	36.59	37.56	38.31	39.08	39.45	39.74	39.89	39.72	39.42
EF	52.83	53.47	53.58	53.98	54.11	54.3	54.41	54.3	54.41
(LAP-LVP)ma	2.948	2.978	2.962	2.959	2.881	2.808	2.767	2.685	2.619
PLVP	94.79	97.47	100.1	102.4	103.7	104.7	105.2	105.1	104.1
M-(LA-LV)-d	0.253	0.28	0.306	0.339	0.374	0.42	0.466	0.515	0.567
MLAP	2.639	3.01	3.364	3.767	4.116	4.505	4.954	5.381	5.85
MLAP-diast	2.708	3.025	3.34	3.713	4.057	4.447	4.927	5.401	5.943
MLAP-syst	2.475	2.992	3.422	3.868	4.213	4.591	4.998	5.374	5.773
LVP-a-min	3.085	3.258	3.339	3.44	3.494	3.605	3.82	4.105	4.511
LAP-a-max	6.025	6.068	6.132	6.406	6.649	6.921	7.223	7.569	8.041
LAV-a-min	15.67	15.9	16.27	16.6	16.75	16.86	17.02	17.24	17.59
PMF	79.94	85.38	87.64	89.24	88.33	86.94	85.81	83.54	81.34
MF-a-min	17.63	24.87	28.52	28.74	28.38	29.8	32.38	35.27	38.35
MF-a-max	69.41	68.82	71.25	76.3	81.4	86.77	91.75	97.19	103.2
MF-a-max/PM	0.868	0.806	0.813	0.855	0.922	0.998	1.069	1.163	1.268
FV	19.33	20.08	20.53	21.09	21.34	21.58	21.7	21.57	21.45
FV-PMF	4.013	4.439	4.745	4.888	4.983	4.923	4.862	4.777	4.666
FV-a-min	13.78	14.22	14.23	14.35	14.19	13.92	13.54	12.84	12.09
FVA(Yellin)	3.899	3.908	3.888	3.872	3.848	3.838	3.842	3.844	3.849
FVA(clin)	5.556	5.86	6.295	6.743	7.153	7.656	8.163	8.733	9.362
FV-lost aft	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
FVA(Y)/FV	0.202	0.195	0.189	0.184	0.18	0.178	0.177	0.178	0.179
FVA(Y)-FVlo	0.201	0.194	0.189	0.183	0.18	0.177	0.177	0.178	0.179
FV-PMF/FV	0.208	0.221	0.231	0.232	0.233	0.228	0.224	0.221	0.218
t-LVPmin	60	75	87	98	110	129	242	257	259
t-(LAP-LVP)	38	42	46	48	49	49	50	50	50
t-PMF	93	97	102	104	107	107	108	108	109
t-MF-a-min	408	381	356	333	311	289	271	252	237
t-MF-a-max	496	468	440	416	393	371	353	335	320
DFP-f	548	521	495	472	450	429	412	394	381
DFP-p	538	511	486	463	441	419	401	382	367
DFP-f/RR	0.731	0.695	0.66	0.629	0.6	0.572	0.549	0.525	0.508

Control Parameters except Pinf = -1, CO = 0

Fig. 60

```
this run vatau     from     30 to       100 in ste   10
output      control
              20      30      40      50      60      70      80      90     100
PCO          5.273   5.606    6.03   6.434   6.847     7.3   7.807   8.355   8.976
LVPmin       1.225   1.599   2.047   2.514   3.004   3.509   3.813   4.152   4.569
LVEDP        6.091   5.973   5.994   5.995   5.997   6.018   6.089   6.245    6.52
LVEDV        40.31   40.02   40.07   40.07   40.05   40.01   39.95   39.88    39.8
EF           54.16   54.25   54.23   54.23   54.25   54.29   54.34   54.41   54.49
(LAP-LVP)ma   3.69    3.44   3.274   3.123   2.983   2.872   2.779   2.717   2.671
PLVP         106.9   105.6   105.8   105.8   105.7   105.7   105.6   105.5   105.3
M-(LA-LV)-d0.308   0.319   0.333   0.354   0.381   0.417    0.46   0.511   0.567
MLAP         3.466   3.598   3.824   4.056   4.323   4.644   5.031   5.494   6.039
MLAP-diast   3.505   3.588   3.771   3.976   4.238   4.567   4.975   5.488   6.098
MLAP-syst    3.382   3.636    3.94     4.2    4.46   4.756   5.108   5.513   5.995
LVP-a-min    4.013   3.884   3.791   3.694   3.651   3.691   3.849   4.153    4.62
LAP-a-max    7.486   7.025   6.798   6.765   6.858   7.007   7.238   7.614   8.178
LAV-a-min    16.53   16.45   16.65   16.83    16.9   16.94   17.06   17.32   17.73
PMF          96.06   95.74   94.96   93.05   90.62   88.25   85.97   84.06   82.34
MF-a-min     16.78   25.16   29.37   29.44   28.87   29.82   32.27   35.39   38.48
MF-a-max     77.31   73.28   73.93   77.63   82.04   86.49   91.41   97.16   103.7
MF-a-max/PM0.805   0.765   0.778   0.834   0.905    0.98   1.063   1.156   1.259
FV           21.83   21.71   21.73   21.73   21.73   21.72   21.71    21.7   21.69
FV-PMF       4.631   4.908   5.011   5.048   5.057   4.955   4.858   4.766   4.689
FV-a-min     15.88   15.62   15.28    14.9   14.53   14.11   13.59   12.97    12.3
FVA(Yellin)4.253     4.2   4.093   3.995   3.916    3.87   3.848   3.858   3.902
FVA(clin)    5.959   6.094   6.454   6.834   7.197   7.611   8.122   8.728   9.391
FV-lost aft 0.01    0.01    0.01    0.01    0.01    0.01    0.01    0.01    0.01
FVA(Y)/FV    0.195   0.193   0.188   0.184    0.18   0.178   0.177   0.178    0.18
FVA(Y)-FVlo0.194   0.193   0.188   0.183    0.18   0.178   0.177   0.177   0.179
FV-PMF/FV    0.212   0.226   0.231   0.232   0.233   0.228   0.224    0.22   0.216
t-LVPmin        59      75      87      98     111     139     244     260     260
t-(LAP-LVP)     36      42      46      47      49      50      49      50      50
t-PMF           89      96     100     103     106     107     107     108     108
t-MF-a-min     410     384     359     335     313     292     272     255     239
t-MF-a-max     498     471     444     418     395     374     354     337     322
DFP-f          549     523     498     473     452     432     413     397     382
DFP-p          540     514     489     465     443     422     402     385     369
DFP-f/RR     0.732   0.697   0.664   0.631   0.603   0.576   0.551   0.529   0.509
```

Control Parameters except Pinf = -1, CO = 1736

Fig. 61

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Fig 62

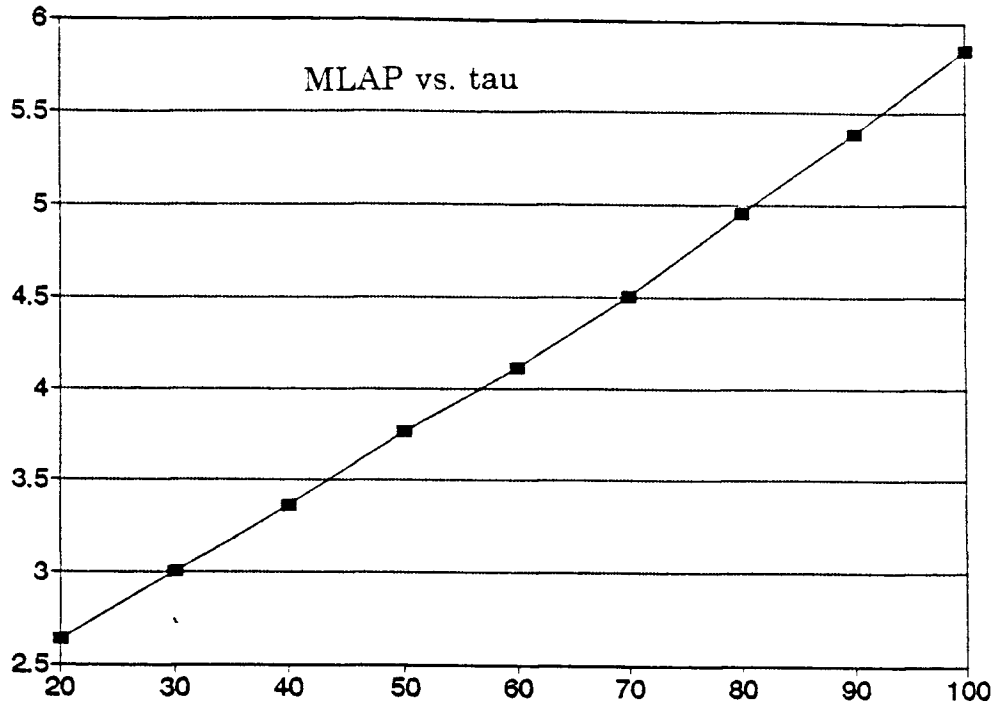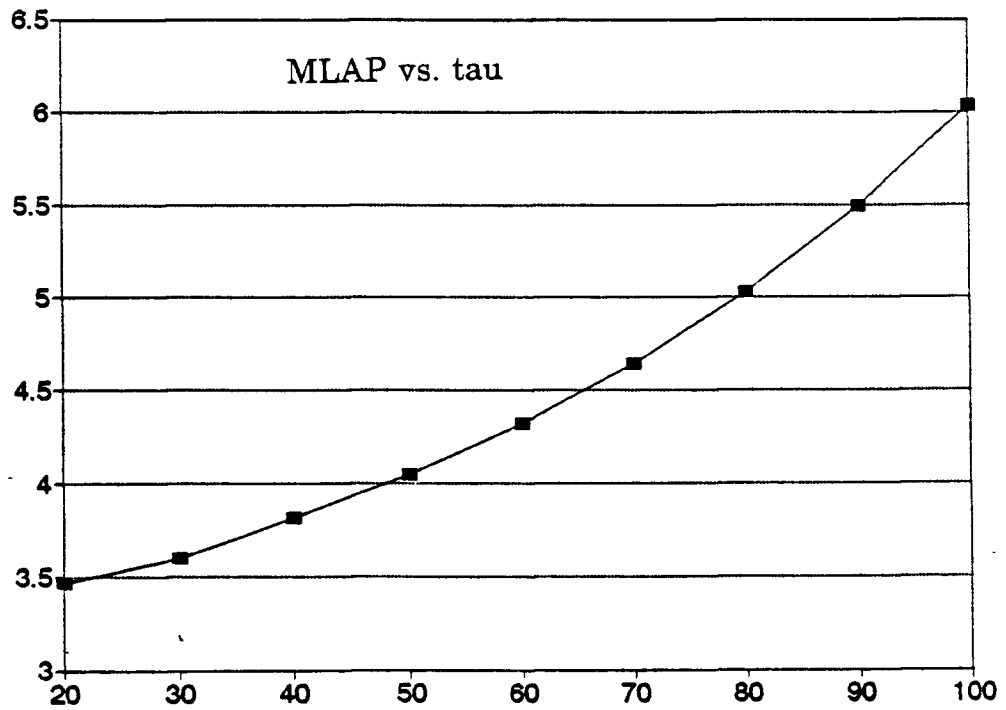Control Parameters except Pinf = -1, CO = 0

MLAP vs. tau

Fig. 63

Control Parameters except Pinf = -1, CO = 1736

MLAP vs. tau

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```
this run vatau    from      30 to       100 in ste    10
output        control
                  20      30      40      50      60      70      80      90     100
PCO            4.15   4.977   5.598   6.316   6.918   7.464    7.97   8.445   8.849
LVPmin        -0.05   0.578   1.227   1.923   2.581    3.21   3.805   4.377   4.891
LVEDP         5.851   6.456   6.906   7.442   7.775   8.063   8.252   8.414   8.446
LVEDV         46.13    47.2   47.97   48.84   49.35   49.76   49.95   50.01   49.76
EF            40.32   40.92   41.02   41.31   41.41   41.55   41.61   41.69   41.52
(LAP-LVP)ma3.827   3.814   3.666   3.594   3.484   3.366   3.247   3.139    3.03
PLVP          88.87   91.14   93.03      95   96.26   97.21   97.71   97.89   97.52
M-(LA-LV)-d0.232   0.265   0.274   0.285   0.296   0.318   0.349    0.39   0.434
MLAP          2.719   3.277   3.745   4.266    4.68   5.081   5.453   5.836   6.162
MLAP-diast 2.745   3.271   3.697   4.181   4.587   4.991   5.378   5.792   6.168
MLAP-syst  2.665   3.307   3.856   4.431    4.84   5.223   5.563   5.902   6.172
LVP-a-min  3.504   3.961   4.147   4.304   4.355   4.433   4.551   4.747   4.974
LAP-a-max  6.952    7.32   7.326   7.512    7.72   8.068   8.437    8.83   9.143
LAV-a-min  16.04    16.2   16.56   17.14   17.59   17.89   18.05   18.13   18.14
PMF           95.83   100.9   101.2   101.6   100.5   98.67   96.43   94.23   91.67
MF-a-min   6.249   15.18      25   29.51   29.15   26.96   24.86   24.33   25.12
MF-a-max   70.75   67.84   65.54   68.54   74.25   81.47   88.17   94.21    98.8
MF-a-max/PM0.738   0.672   0.648   0.674   0.739   0.826   0.914       1   1.078
FV            18.6   19.32   19.68   20.18   20.44   20.68   20.79   20.85   20.66
FV-PMF     4.362   4.865   5.098   5.179   5.297   5.197   5.179   5.087   5.015
FV-a-min   13.74   14.41   14.42   14.38   14.14    13.9   13.59   13.23   12.69
FVA(Yellin)3.786   4.034   4.103   4.109   4.052   4.014   3.998   3.997   4.017
FVA(clin)  4.863   4.905   5.252   5.798   6.292   6.778   7.201    7.62   7.973
FV-lost aft 0.01    0.01    0.01    0.01    0.01    0.01    0.01    0.01    0.01
FVA(Y)/FV  0.204   0.209   0.209   0.204   0.198   0.194   0.192   0.192   0.194
FVA(Y)-FVlo0.203   0.208   0.208   0.203   0.198   0.194   0.192   0.191   0.194
FV-PMF/FV  0.235   0.252   0.259   0.257   0.259   0.251   0.249   0.244   0.243
t-LVPmin      53      65      74      80      85      90      93      96      99
t-(LAP-LVP)   35      41      45      47      48      50      50      50      51
t-PMF         85      91      96      98     101     102     103     104     105
t-MF-a-min   413     389     366     344     323     303     283     265     247
t-MF-a-max   500     477     452     427     403     382     363     345     328
DFP-f        549     525     501     477     455     435     415     399     382
DFP-p        543     519     496     474     453     433     413     395     377
DFP-f/RR   0.732     0.7   0.668   0.636   0.607    0.58   0.553   0.532   0.509
```

Control Parameters except EmaxLV = 4, CO = 0

Fig. 64

```
this run vatau    from      30 to        100 in ste    10
output       control
                 20      30      40      50      60      70      80      90     100
PCO         6.402   6.963   7.506   7.938    8.31   8.672    9.06   9.508   9.994
LVPmin      0.807   1.497   2.191   2.822   3.411    3.97   4.529     5.1   5.697
LVEDP       9.184   9.375   9.525   9.572   9.582   9.583   9.606   9.676    9.82
LVEDV       51.45   51.71   51.92   51.98   51.98   51.95   51.89   51.81   51.72
EF           41.8    41.8    41.8   41.82   41.84   41.87   41.89   41.92   41.96
(LAP-LVP)ma5.065   4.704     4.4   4.133   3.885   3.688   3.509   3.369   3.267
PLVP        100.9   101.7   102.3   102.5   102.5   102.5   102.3   102.2     102
M-(LA-LV)-d0.264   0.297   0.321   0.318   0.318   0.332   0.357   0.394   0.439
MLAP        4.636    4.98    5.33   5.597    5.83    6.07    6.35   6.689   7.099
MLAP-diast  4.682   4.999   5.308   5.534   5.744   5.983   6.278   6.639   7.096
MLAP-syst   4.535   4.962   5.399   5.734   5.987   6.214   6.462   6.766    7.12
LVP-a-min   5.646   5.888    5.96   5.779   5.558   5.412   5.394   5.519   5.789
LAP-a-max   10.19   10.27   10.04   9.631   9.402   9.406   9.593     9.9   10.31
LAV-a-min   18.32    18.1    18.1   18.36   18.64   18.83   18.92   18.98   19.09
PMF           120     119   116.7   113.4   109.4   105.8   102.3   99.36   97.02
MF-a-min    2.691   10.52    22.2   29.84   31.19   29.29   26.91   25.74   26.28
MF-a-max    87.61    82.9   76.86      75   78.68   84.99   91.67   97.88   103.6
MF-a-max/PM  0.73   0.697   0.658   0.662   0.719   0.804   0.896   0.985   1.068
FV          21.51   21.61    21.7   21.74   21.75   21.75   21.74   21.72    21.7
FV-PMF      5.261    5.53   5.665   5.642   5.603   5.565   5.377   5.357   5.214
FV-a-min    15.81   16.09    16.1   15.72   15.24   14.76   14.31   13.88   13.43
FVA(Yellin)4.536   4.723   4.783   4.685   4.518   4.385   4.299   4.273     4.3
FVA(clin)     5.7   5.526   5.602   6.012   6.515   6.994   7.429   7.847   8.275
FV-lost aft 0.01    0.01    0.01    0.01   0.012   0.014    0.01    0.01    0.01
FVA(Y)/FV   0.211   0.218    0.22   0.216   0.208   0.202   0.198   0.197   0.198
FVA(Y)-FVlo 0.21   0.218    0.22   0.215   0.207   0.201   0.197   0.196   0.198
FV-PMF/FV   0.245   0.256   0.261    0.26   0.258   0.256   0.247   0.247    0.24
t-LVPmin       52      63      71      77      83      88      92      94      97
t-(LAP-LVP)    35      40      43      45      47      49      50      50      51
t-PMF          82      88      92      95      98     101     102     103     104
t-MF-a-min    417     393     370     348     327     307     288     269     253
t-MF-a-max    502     480     457     432     408     386     367     349     333
DFP-f         549     525     502     479     457     437     419     401     386
DFP-p         547     523     500     478     457     437     418     399     383
DFP-f/RR    0.732     0.7   0.669   0.639   0.609   0.583   0.559   0.535   0.515
```

Control Parameters except EmaxLV = 4, CO = 1736

Fig. 65

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Fig 66

Control Parameters except EmaxLV = 4, CO = 0
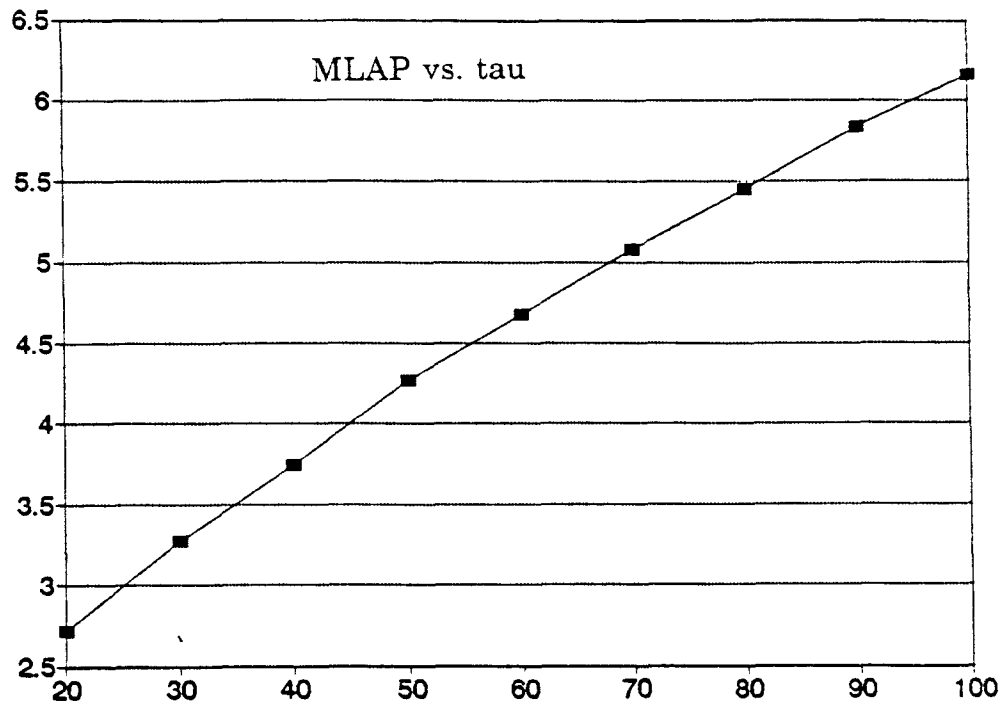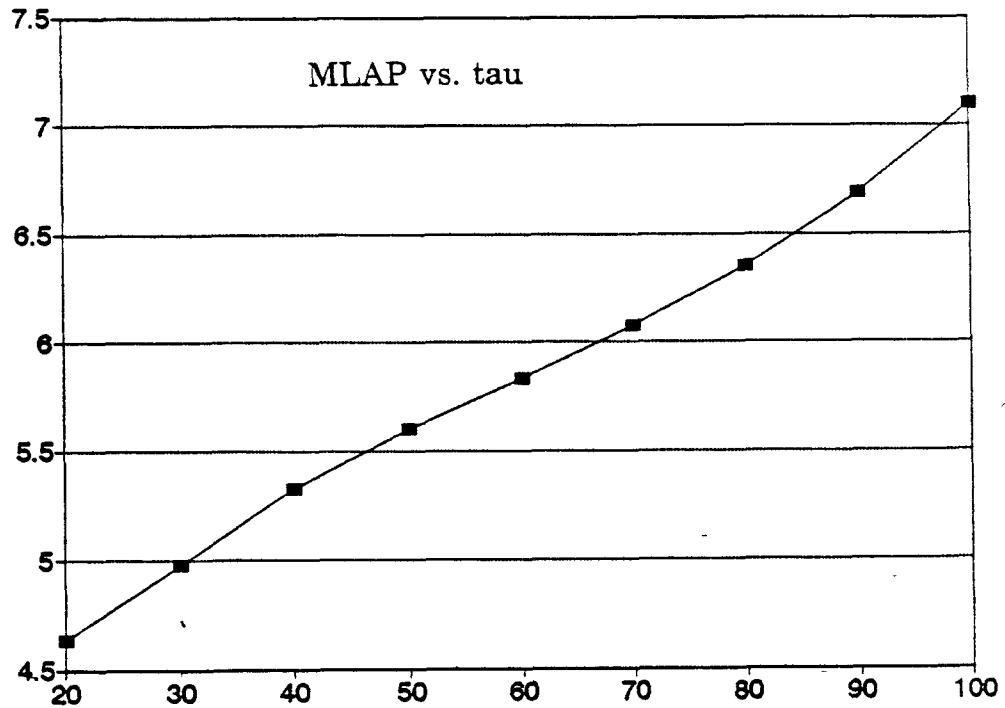

MLAP vs. tau

Fig. 67

Control Parameters except EmaxLV = 4, CO = 1736

MLAP vs. tau

CHAPTER VI

PSPICE Implementation:

Motivation: Up to this point, the method used to implement the Meisner model of the cardiovascular system was a general method of solving differential equations, equally applicable to an electric circuit or an hydraulic system. This approach, though using a schematic diagram of the type frequently used by electrical as opposed to mechanical engineers, did not specifically demonstrate that this was an electrical model of a mechanical system. An alternate approach to the implementation of this model is to treat it purely as an electrical circuit and to implement it using a circuit analysis program. Thus, the circulation was modeled and treated as an electrical circuit using the simulation program PSPICE, version 4.05 (MicroSim Incorporated, Irvine, CA). The program uses standard network theory to analyze electrical circuits and is available for IBM, IBM compatible and Macintosh microcomputers.

Use of PSPICE: To simulate a circuit using PSPICE, each node in the circuit diagram needs to be labeled with a number and the entire circuit needs to be described to PSPICE in an input file by describing which circuit element(s) (resistor, capacitor, inductor, voltage and/or current source, etc.) are located between the various nodes. In addition to the information which describes the circuit, PSPICE requires other information which is described on "control lines". These include the type of analysis to be performed, in this case transient, as well as other controlling information to be described below. PSPICE reads this input file and then uses Kirchhoff's Current Law to create a system of equations for the circuit,

where the voltages at each node are the unknowns and the admittances of each branch are the knowns. The resulting simultaneous equations are formed into an admittance matrix which is solved using the Newton-Raphson method. There is a student version of PSPICE available which performs many of the basic functions and analyses of the full version. However there were some functions and features needed for this implementation that could not be done on the student version but required the full version of PSPICE.

The file containing the circuit description and the control lines must be stored in a file called ****.cir. The circuit describing the Meisner model is called mod17a.cir. When this file is operated on by running PSPICE.BAT the output is stored in two files. One. called mod17a.out, is an output file which contains a copy of the input file as well as a numerical list of time versus any values requested in a ".PRINT" statement in that input file. The second output file, called PROBE.DAT, is a data file which is available to PROBE.EXE (Which is run automatically when the batch file is run.) and can be stored under a different name, thus making it available for later recall even after another run has taken place. When PROBE is run, it reads in this massive data file which contains all of the currents and voltages at every node in the circuit for all time increments through which the program was run and asked to store. It is an interactive routine which permits plots of all of the circuit voltages and currents to be graphed versus time. A voltage between node "X" and ground is represented by V(X), while the voltage between nodes "X" and "Y" is represented by V(X,Y). Thus, looking at the circuit diagram in figure 88, it can be seen that the left ventricular pressure corresponds to the voltage at node 110 and would be referred to as V(110) by PROBE, while the drop across the mitral resistance

90

would be called V(90,100). Current through the element Xi is similarly represented by I(Xi) and the mitral flow, which is the flow through R2, would be I(R2). In addition, PROBE permits the scales of the x and y axes to be manipulated enabling any part of the graphs that are of interest to be observed, as well as allowing the use of cursors to accurately measure values. Figure 68 shows how this can be used to calculate EDV, ESV and FV from the graph of LVV.

Implementation: If the circuit used to simulate the heart had contained only standard elements, then the above description of how to simulate a circuit in PSPICE is all that would have been required -- to very simply and straight forwardly describe the circuit by listing the various elements along with their corresponding nodes, as well as several control lines. In this circuit, those straightforward elements account for the majority of the components, but are actually an insignificant portion of the work and the PSPICE code. The elements that need to be handled in a more complex manner are presented below with a description of how they were implemented.

Right ventricle: The right ventricle, as discussed above, is likened to an independent input voltage source occurring once each "heartbeat". As discussed above in the Meisner model, the right ventricular waveform was originally a rectified sine. Thus, this is what is now described. However, it has since been changed to a scaled version of the left ventricle. (That is V(62) is now simply a scaled version of V(82) in the PSPICE implementation.) Generating a voltage source in the form of a sine wave is not difficult since PSPICE can generate five kinds of time-dependent functions for use in independent sources, one of them being a sinusoidal

Fig. 68
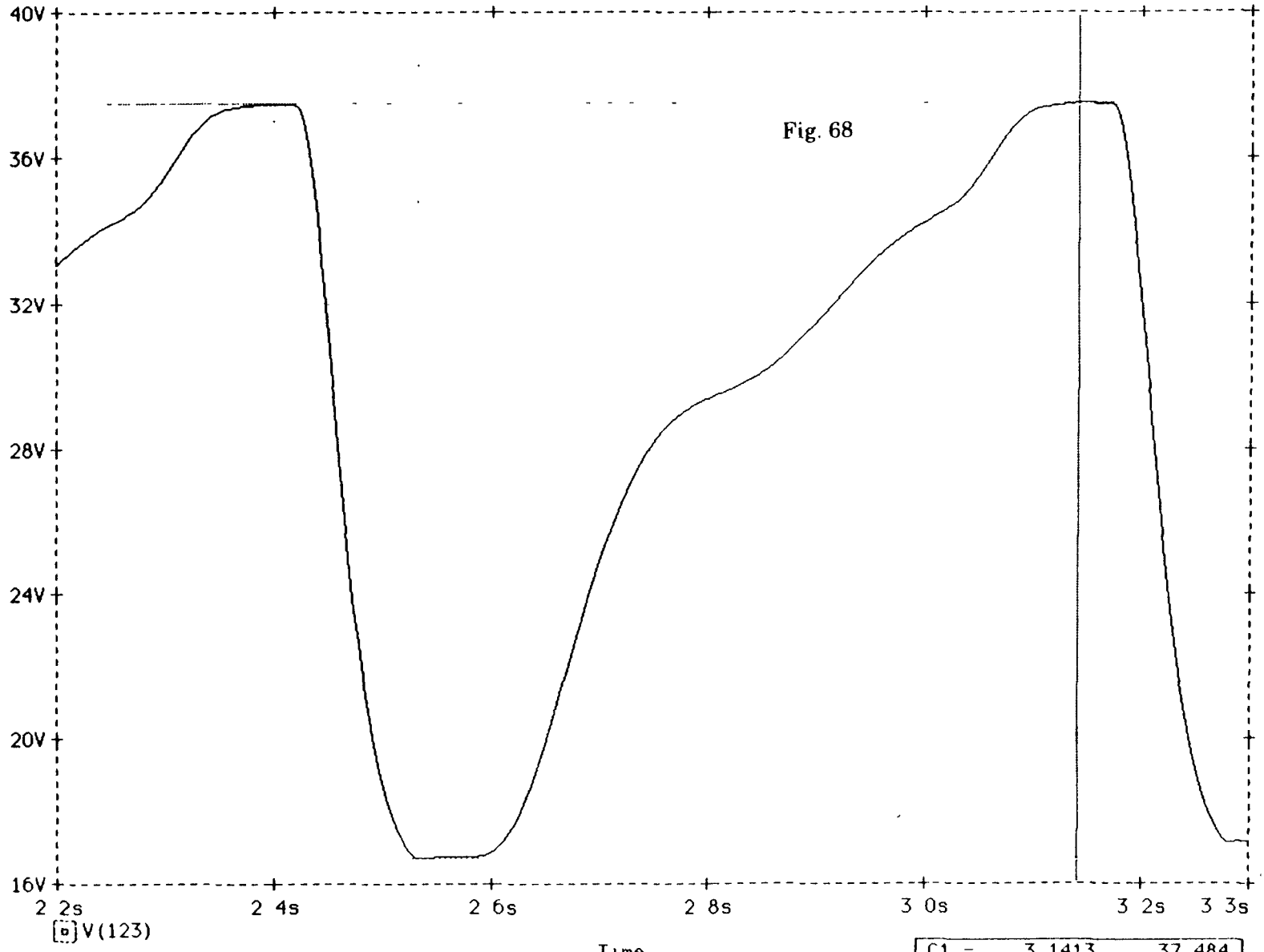
source. The problem is that once the frequency of a sine wave is specified, that obviously determines at what interval the wave repeats. For the right ventricle, the duration of 300 ms determines a frequency of 3.3333 Hz. However, once the 0 to Π radians section of the wave is complete the wave is not desired again until the next "heartbeat" which is an RR interval (about 750 ms) away.

It was thus necessary to start the pulse chain by generating just one pulse of the right ventricle waveform rather than a repetitive, continuous wave. This was accomplished by producing the required sine wave and multiplying it by a pulse that was zero everywhere except for the 300 ms duration of that first pulse, where it is one. Once this was created, as shown in figure 69, another problem (which was also faced in the left atrium and ventricle) needed to be overcome, namely how to create a pulse train, of the type shown in fig. 70, out of these pulses. Three methods were successfully attempted. At this point it is not yet certain which method has the fastest run time nor which is the most precise, though, as will be clear soon, it is obvious which is the easiest to implement.

The first method entailed simply generating another equivalent pulse later in time by the identical method used for the first: generating a sine wave, generating a pulse, and then multiplying the two, but this time starting everything integer-multiples of the RR interval later. This was repeated over and over and then all of these pulses were added together. This clearly entails an inordinate amount of programming and, since generating a pulse with a rapid rise time requires small-stepped, slow calculations, probably is slow in running as well. This method is illustrated in Figure 71. The left side shows the creation of four right ventricular

Fig. 69

* V(10)

Time

Fig. 70

* V(10)

Time
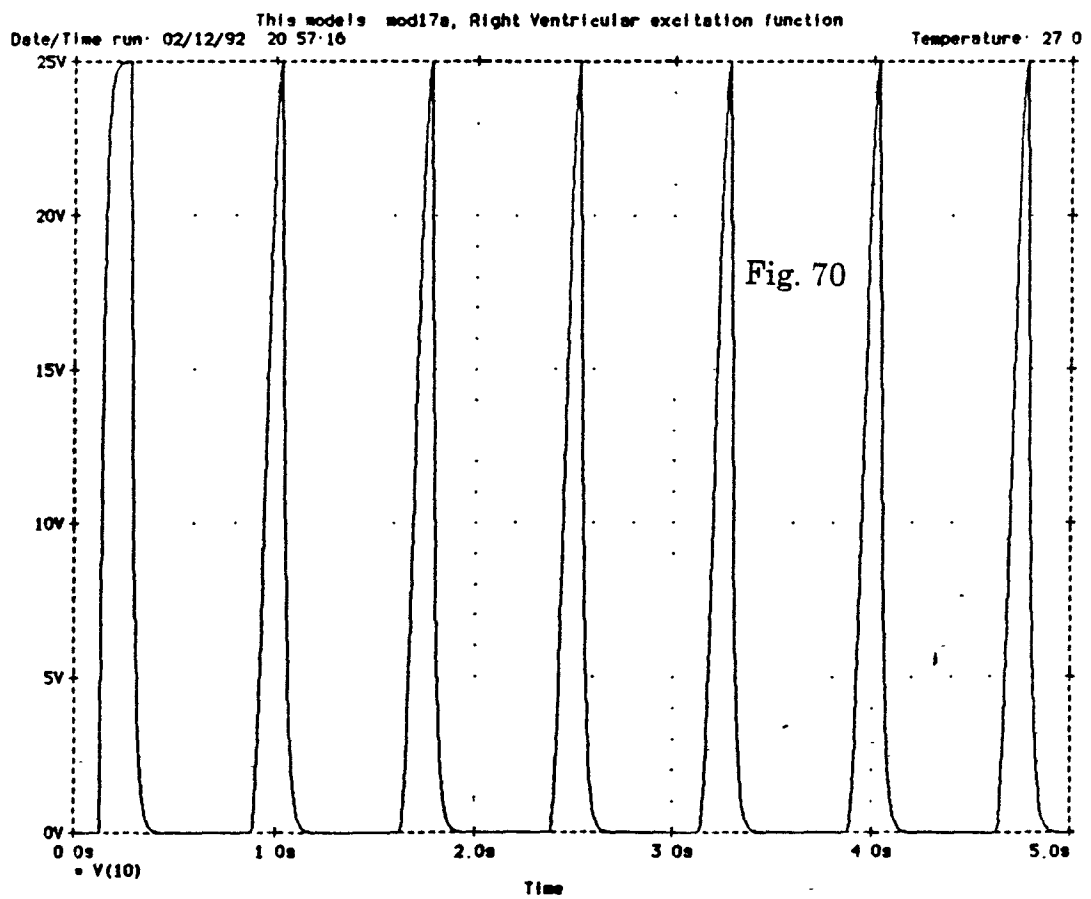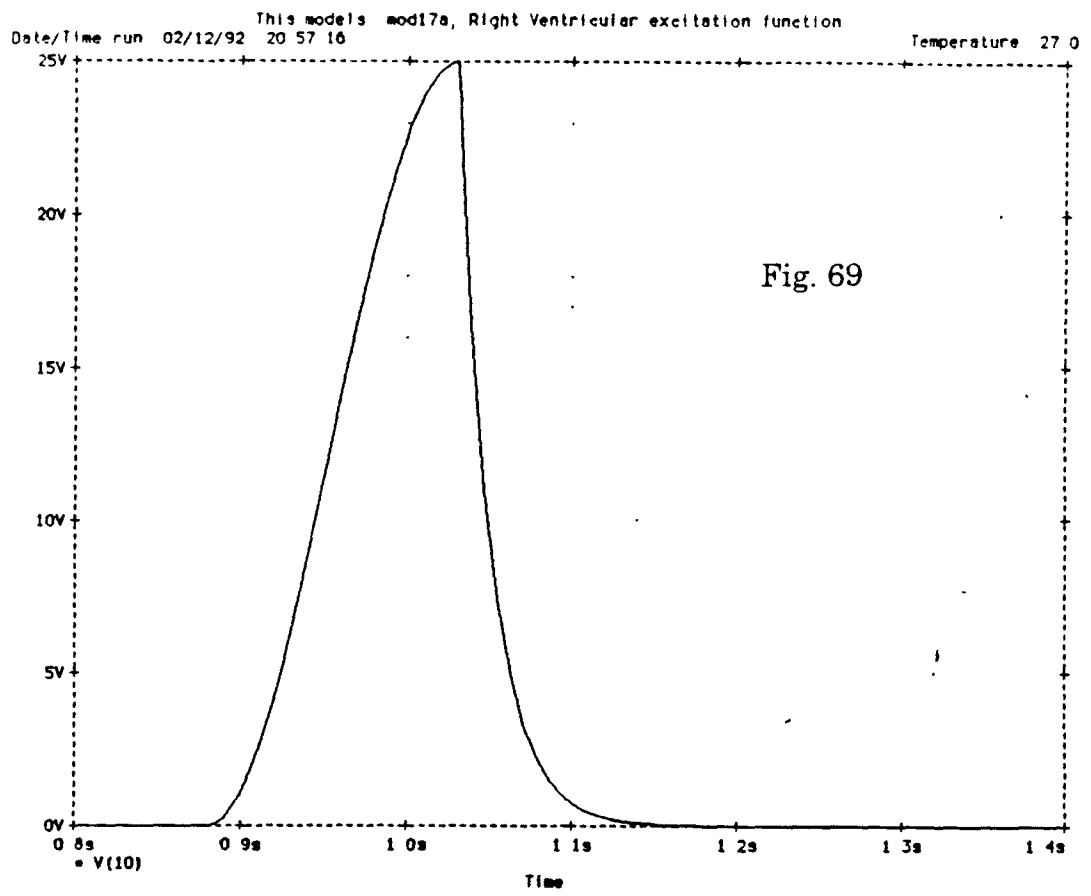
```
*Creates function used in the right ventricle
 SUBCKT RV 299 298 PARAMS: PMAXRV=25
VSIN1  201 0 SIN(0 (PMAXRV)  1.6666666667 (PR))
VCHOP1 202 0 PULSE(0 1 (PR) 1U 1U (2*PR) 40)
EPROD1 203 0 POLY(2) 201 0 202 0 0 0 0 0 1
R201   201 0 1G
R202   202 0 1G
R203   203 0 1G


VSIN2  211 0 SIN(0 (PMAXRV) 1.6666666667 (PR+RR))
VCHOP2 212 0 PULSE (0 1 (PR+RR) 1U 1U (2*PR) 40)
EPROD2 213 0 POLY(2) 211 0 212 0 0 0 0 0 1
ESUM2  219 0 POLY(2) 203 0 213 0 0 1 1
R211   211 0 1G
R212   212 0 1G
R213   213 0 1G
R219   219 0 1G


VSIN3  221 0 SIN(0 (PMAXRV) 1.6666666667 (PR+(2*RR))
VCHOP3 222 0 PULSE(0 1 (PR+(2*RR)) 1U 1U (2*PR) 40)
EPROD3 223 0 POLY(2) 221 0 222 0 0 0 0 0 1
ESUM3  229 0 POLY(2) 219 0 223 0 0 1 1
R221   221 0 1G
R222   222 0 1G
R223   223 0 1G
R229   229 0 1G


VSIN4  231 0 SIN(0 (PMAXRV) 1.6666666667 (PR+(3*RR))
VCHOP4 232 0 PULSE(0 1 (PR+(3*RR)) 1U 1U (2*PR) 40)
EPROD4 233 0 POLY(2) 231 0 232 0 0 0 0 0 1
ESUM4  239 0 POLY(2) 229 0 233 0 0 1 1
R231   231 0 100K
R232   232 0 100K
R233   233 0 100K
R239   239 0 100K


EOUT   299 298 VALUE=(V(239))
R299   299 0 10K
R298   298 0 10K
.ENDS
```

```
*CREATES function used in LEFT VENTRICLE
 SUBCKT LV 399 398 PARAMS: EMAXLV=8
VSIN1  201 0 SIN((EMAXLV/2) (EMAXLV/2) 3.3333333 (RR-(.5*PR)))
VCHOP1 202 0 PULSE(0 1 (RR+PR) 1U 1U (PR) 40)
EPROD1 203 0 POLY(2) 201 0 202 0 0 0 0 0 1
VEXP1  204 0 EXP(0 (EMAXLV) (RR+PR) 8M (RR+(2*PR)) (TAU))
VCOP1  205 0 PULSE(0 1 (RR+(2*PR)+ 000001) 1U 1U (RR-(2*PR)) 50)
EPOD1  206 0 POLY(2) 204 0 205 0 0 0 0 0 1
ESUM1  207 0 POLY(2) 203 0 206 0 0 1 1
R201   201 0 10K
R202   202 0 10K
R203   203 0 10K
R204   204 0 10K
R205   205 0 10K
R206   206 0 10K
R207   207 0 10K


VSIN2  211 0 SIN((EMAXLV/2) (EMAXLV/2) 3.33333333 ((2*RR)-(.5*PR)))
VCHOP2 212 0 PULSE(0 1 ((2*RR)+PR) 1U 1U (PR) 40)
EPROD  213 0 POLY(2) 211 0 212 0 0 0 0 0 1
VEXP2  214 0 EXP(0 (EMAXLV) ((2*RR)+PR) 8M ((2*RR)+(2*PR)) (TAU))
VCOP2  215 0 PULSE(0 1 ((2*RR)+(2*PR)+.000001) 1U 1U (RR-(2*PR)) 50)
EPOD2  216 0 POLY(2) 214 0 215 0 0 0 0 0 1

ESUM2  217 0 POLY(2) 213 0 216 0 0 1 1
ETOTAL 218 0 POLY(2) 217 0 207 0 0 1 1
R211   211 0 10K
R212   212 0 10K
R213   213 0 10K
R214   214 0 10K
R215   215 0 10K
R216   216 0 10K
R217   217 0 10K
R218   218 0 10K


EOUT   399 398 VALUE=(V(218)+.001)
R98    398 0 10K
R99    399 0 10K

.ENDS
```

Fig. 71

pulses. On the right side, taking as much code as the left side, the creation of only two left ventricular pulses is shown.

The other two methods involve the use of transmission lines, which in PSPICE can be lossless, ideal time delay elements. An important consideration when using transmission lines, particularly more than one originating from a common source, is the need to terminate them properly in order to avoid reflections which do occur in PSPICE and can seriously alter the originally intended signal. The second method involved using many transmission lines which all originated from the first voltage source, each delayed by one RR interval more than the previous one. This generated a whole series of pulses which were then added together to form the desired pulse train. This method required one transmission line for each heartbeat in the simulation, but only one summer, all the way at the end. This method is illustrated in Figure 72, where twenty right ventricle pulses are produced. Since the implementation of transmission lines is considered time consuming in PSPICE analysis, this is not, except for very small trains, the fastest method either.

The third method builds the pulse train in exponential form. First, one transmission line delays the original pulse one RR interval. These two pulses are added to form a train of two pulses. This whole new train is now delayed by two RR intervals yielding an identical train starting two RR delays after the first train. When these two trains are added together, the result is a train of four pulses. This whole train is now delayed four RR intervals, the new delayed train and the existing train are added producing a new train of eight pulses, etc. This method is illustrated in Figure 73 where sixty-four ventricular pulses are produced. Thus to produce a train n pulses long, just $\log_2(n)$ transmission lines and adders are required. This

```
*Creates function used in the right ventricle
.SUBCKT RV 299 298
VSIN1   201 0 SIN(0 {PMAXRV}  {1/(2*(RVDUR/1000))} {PR})
VCHOP1  202 0 PULSE(0 1 {PR} .1U .1U {2*PR} 40)
EPROD1  203 0 POLY(2) 201 0 202 0 0 0 0 0 1
R201    201 0 10K
R202    202 0 10K


R203  203 400 1.0K
T1     400 0 401 0 Z0=10K TD={RR}
T2     400 0 411 0 Z0=10K TD={2*RR}
T3     400 0 421 0 Z0=10K TD={3*RR}
T4     400 0 431 0 Z0=10K TD={4*RR}
T5     400 0 441 0 Z0=10K TD={5*RR}
T6     400 0 451 0 Z0=10K TD={6*RR}
T7     400 0 461 0 Z0=10K TD={7*RR}
T8     400 0 471 0 Z0=10K TD={8*RR}
T9     400 0 481 0 Z0=10K TD={9*RR}
T10    400 0 491 0 Z0=10K TD={10*RR}


R401 401 0 10K
R411 411 0 10K

R421 421 0 10K
R431 431 0 10K
R441 441 0 10K
R451 451 0 10K
R461 461 0 10K
R471 471 0 10K
R481 481 0 10K
R491 491 0 10K


E2 499 0 POLY(11) 203 0 401 0 411 0 421 0 431 0 441 0 451 0 461 0 471 0 481 0 491 0 0 1 2 2 2 2 2 2 2 2 2 2
R499 499 0 1K


ENEXT 600 0 VALUE={V(499)}
R600  600 601 10K
T20    601 0 610 0 Z0=10K TD={11*RR}
R610  610 0 10K


ESUM9 613 0 POLY(2) 601 0 610 0 0 2 2
R613  613 0 10K


EOUT    299 298 VALUE={V(613)}
R299    299 0 10K
R298    298 0 10K
.ENDS
```

Fig. 72

```
*Creates function used in the right ventricle
.SUBCKT RV 299 298
VSIN1  201 0 SIN(0 {PMAXRV}  {1/(2*(RVDUR/1000))} {PR})
VCHOP1 202 0 PULSE(0 1 {PR} 1U 1U {RVDUR/1000} 50)
EPROD1 203 0 POLY(2) 201 0 202 0 0 0 0 0 1
R201   201 0 10K
R202   202 0 10K


R203   203 400 10K


T11    400 0 301 0 Z0=10K TD={RR}
ES1    308 0 POLY(2) 203 0 301 0 0 1 2
R301   301 0 10K
R308   308 313 10K


T12    313 0 317 0 Z0=10K TD={2*RR}
ES2    318 0 POLY(2) 308 0 317 0 0 1 2
R317   317 0 10K
R318   318 323 10K


T13    323 0 327 0 Z0=10K TD={4*RR}
ES3    328 0 POLY(2) 318 0 327 0 0 1 2
R327   327 0 10K
R328   328 333 10K

T14    333 0 337 0 Z0=10K TD={8*RR}
ES4    338 0 POLY(2) 328 0 337 0 0 1 2
R337   337 0 10K
R338   338 343 10K


T15 343 0 347 0 Z0=10K TD={16*RR}
ES5 348 0 POLY(2) 338 0 347 0 0 1 2
R347 347 0 10K
R348 348 353 10K


T16 353 0 357 0 Z0=10K TD={32*RR}
ES6 358 0 POLY(2) 348 0 357 0 0 1 2
R357 357 0 10K
R358 358 0 10K


EOUT   299 298 VALUE={V(358)}
R299   299 0 10K
R298   298 0 10K
.ENDS
```
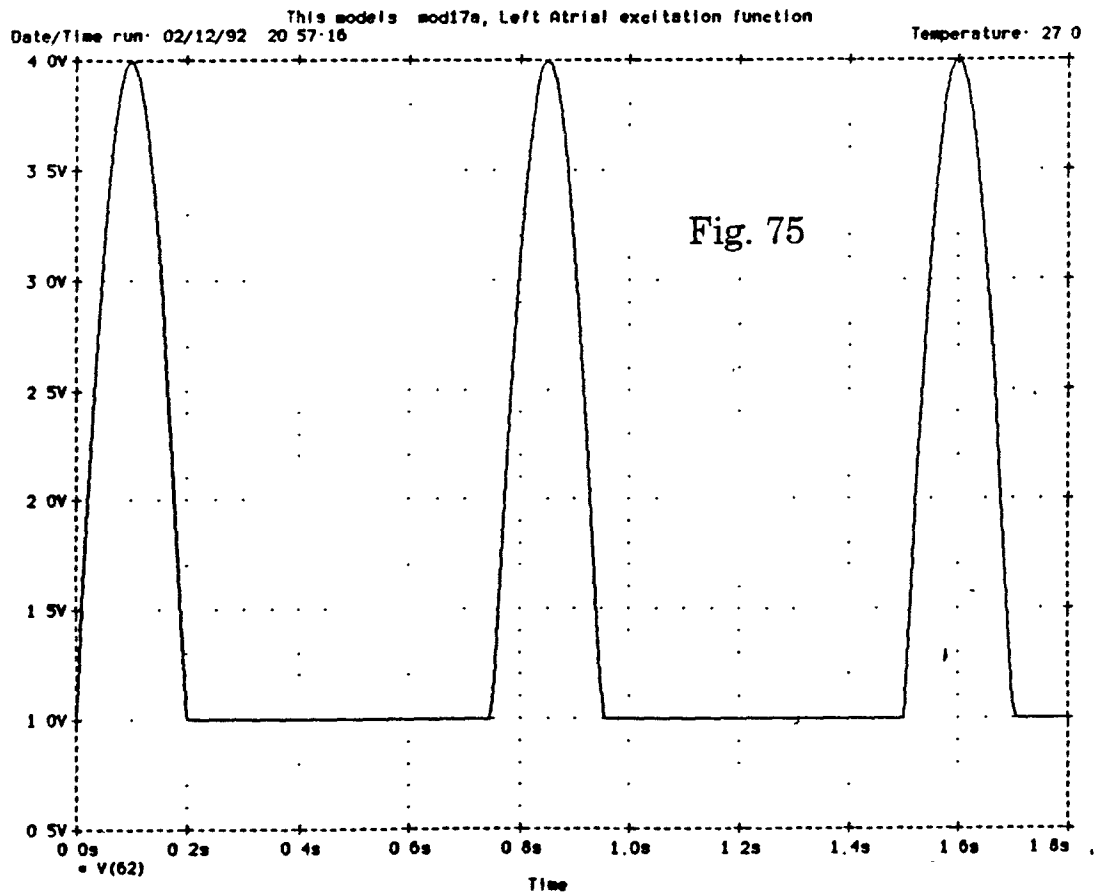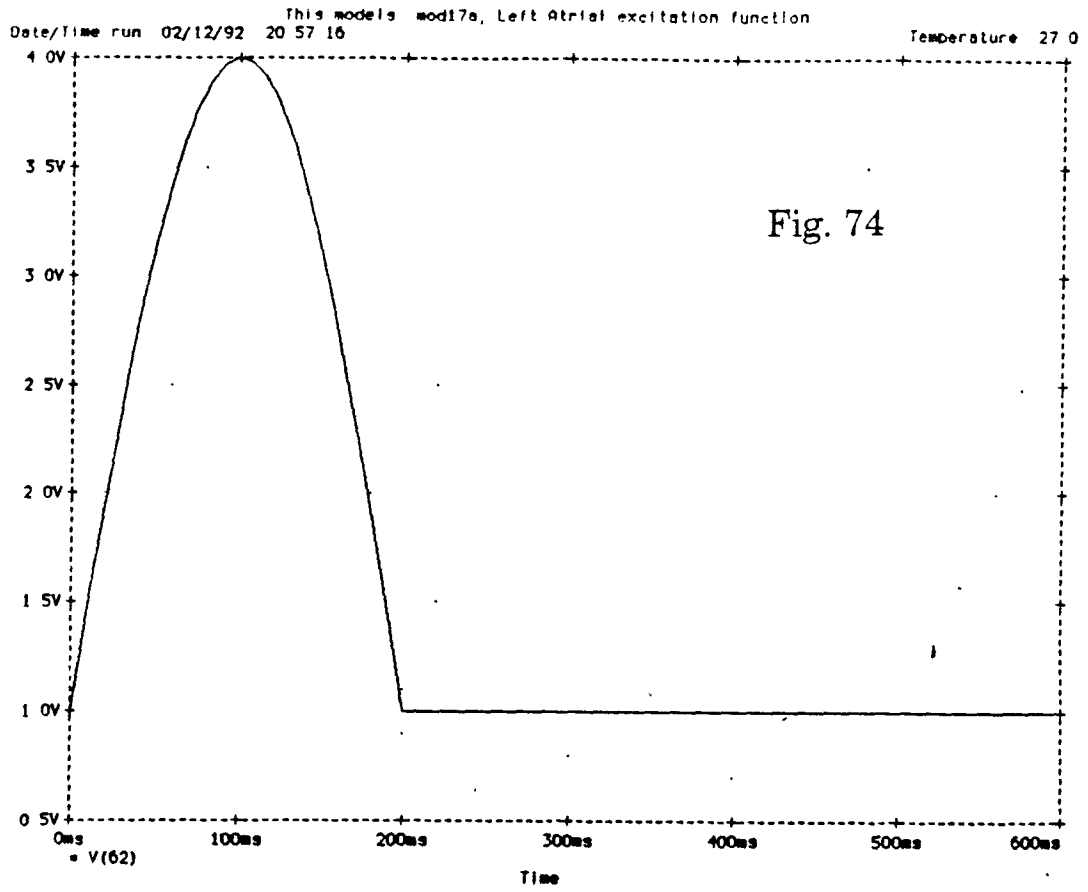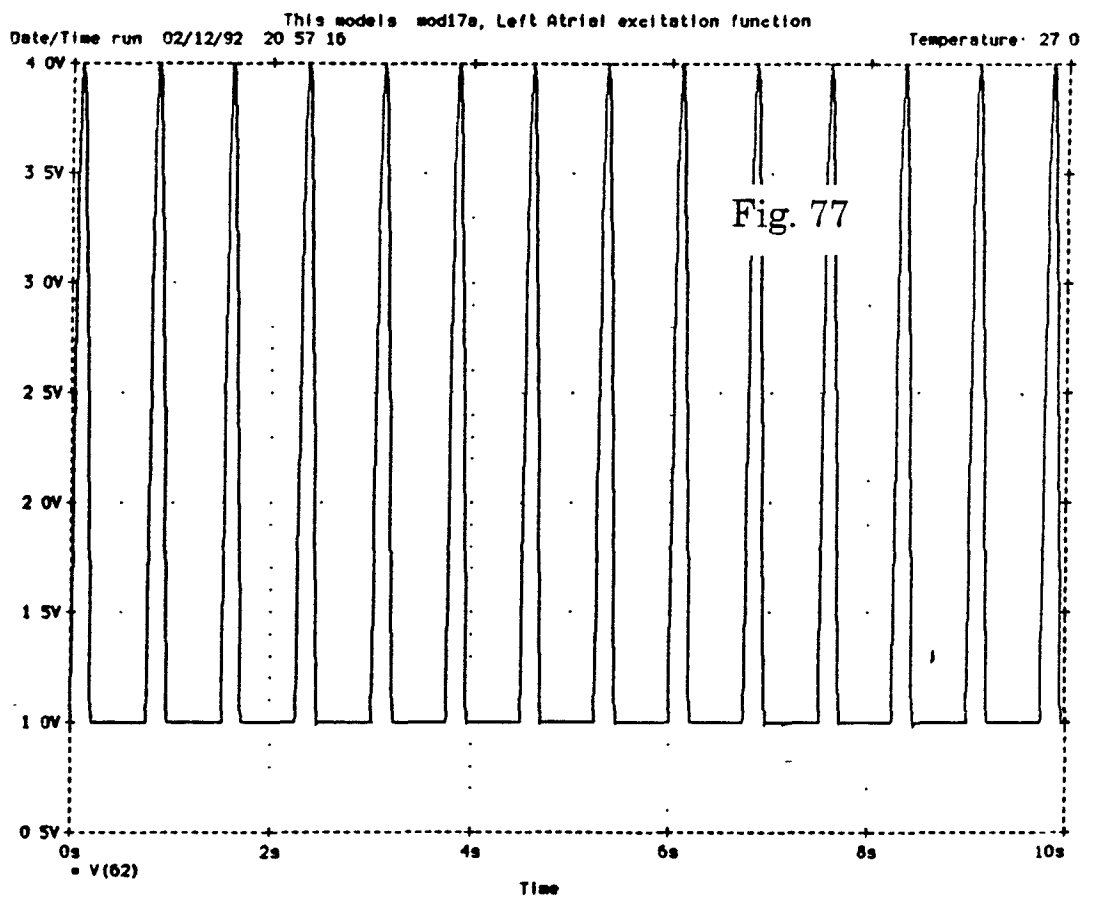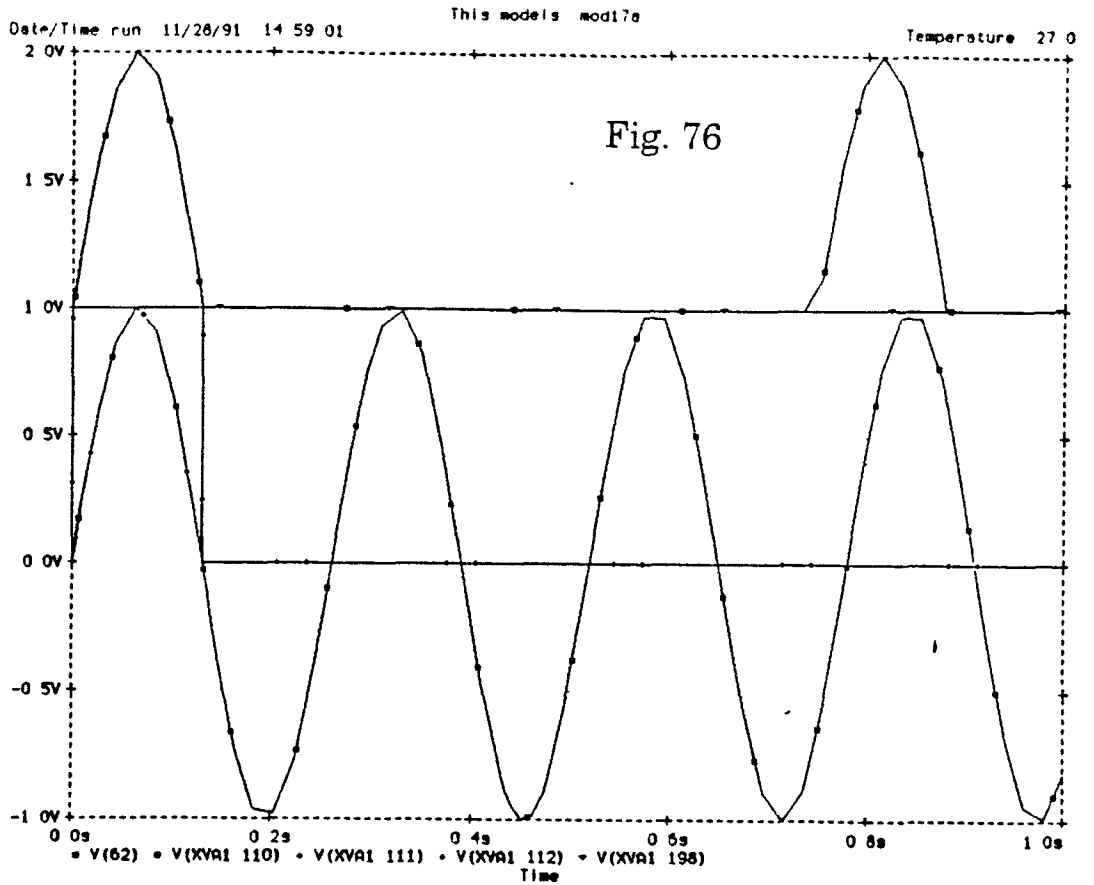
Fig. 73

method requires the least programming, especially as the trains get longer, and is, for any run other than for very small trains, the fastest of the methods. For the right ventricle each of these methods was attempted, each yielded the required pulse train and each could be used in a final version. However, all runs presented herein used the third method. The right ventricle pulse train is V(10) in all of the PSPICE implementations.

Left Atrium: The total voltage (pressure) in the left atrium is, as described above (in equation 1): $P = E (V - V_d)$ where E is an activation function, V is the instantaneous volume, and V_d is the "dead volume", which is a volume offset that differs from diastole to systole. In order to implement such a function in PSPICE it was expanded into two separate components: 1) $E * V$ and 2) $- (E * V_d)$.

Since the activation function E appears in both terms, it is generated first. A single pulse of it is shown in fig.74, and three identical pulses in fig.75. It is a rectified sine function from 0 to Π radians with a peak of EmaxLA, a duration of 200 ms and baseline of K10. In order to generate the first pulse, an almost identical method as that used for the right ventricle was used. In addition, for the pulse train the same three possible methods as described for the right ventricle were used. A sine pulse of amplitude (EmaxLA-K10) and duration 200 ms was generated and then multiplied by a pulse that was zero everywhere except during the 200 ms for which it was desired. This pulse was the pulse that was then recreated or delayed in time to create the pulse train. Finally, once this long train was created, a dc source of K10 amplitude was added to the entire function to yield the desired pulse train. The creation of the first pulse is illustrated in Figure

Fig. 74

● V(62)

Time

Fig. 75

● V(62)

Time

100

Date/Time run 11/26/91 14 59 01

Temperature 27 0

Fig. 76

2 0V

1 5V

1 0V

0 5V

0 0V

-0 5V

-1 0V

0 0s   0 2s   0 4s   0 6s   0 8s   1 0s

▫ V(62) ▪ V(XVA1 110) ◆ V(XVA1 111) ● V(XVA1 112) ▾ V(XVA1 198)

Time

This models mod17a, Left Atrial excitation function

Date/Time run 02/12/92 20 57 16

Temperature: 27 0

4 0V

3 5V

Fig. 77

3 0V

2 5V

2 0V

1 5V

1 0V

0 5V

0s   2s   4s   6s   8s   10s

▫ V(62)

Time

101

76. The final pulse train, always designated as V(62) in the model, is illustrated in Figure 77.

The second component of the left atrium, (- (E * V_d)), is an independent voltage source consisting of the pulse train E multiplied by V_d. However, since V_d in actuality varies very little it was decided to treat it as a constant, called LAV0 in the PSPICE code. This term is therefore just a voltage source which looks like an inverted and scaled version of E.

The first term, (E * V), is somewhat more complicated since it involves the instantaneous volume of the chamber. However, if the mechanical/electrical analogs are kept in mind it becomes much simpler. This term calls for the pressure (=voltage) to be a linear function of the volume (=stored charge). This is the exact relationship of a capacitor, where $Q = C * V$. Thus if $P = E * V$, all that is needed is to use a variable capacitor where the capacitance varies as 1/E, and then this relationship is automatically implemented. The complete left atrial branch is shown in Figure 78. Implementing a variable capacitance in PSPICE entails providing the controlling function, E in this case, and a reference value capacitance, chosen to be 1 Farad in this program, to a standard subroutine called "yx", which is provided by MicroSim (the producer of PSPICE). (This is not as straightforward and simple as it sounds.)

Mitral Orifice: In the mitral orifice/valve section of the model the only non-standard component is that of mitral resistance, which does not follow the usual V = IR relationship but rather, follows the non-linear V = I^2R. Therefore, instead of putting a resistor in that location in the PSPICE model, which would produce a linear pressure drop, the drop itself was inserted by using a current controlled voltage source. In such a source the

voltage across it is of the form $V(x,y) = a + b * I(z) + c * I(z)^2 + d * I(z)^3 +$ .... Therefore, in order to simulate the resistance of the mitral valve a "dead" voltage source was inserted immediately following the mitral valve in order to measure the mitral current. A current-controlled voltage source with $I(z)$ being the current through the "dead" voltage source and all the coefficients being zero except for c (which was the value of the resistance) was used in place of the resistor. This form has the added advantage that if it is later desired to simulate the resistance not solely as a function of the square of the flow but also with constant, linear or higher order terms it is as simple as changing the values of those zeros.

Left Ventricle: Simulating the left ventricle in PSPICE presented a number of problems due to the number and types of terms present in the total pressure equation. The total pressure of the left ventricle is represented, as described earlier, by the sum of equations 3 and 4 to yield:

$$P = Ae^{\alpha V} + B(dV/dt) + P_{inf} + E(V-V_d) \qquad [5]$$

where A is the passive elastance coefficient, α is the passive elastance exponent, V is the instantaneous left ventricular volume, B is the viscous coefficient and P_{inf} is the left ventricular pressure asymptotic offset, E is an activation function and V_d is a "dead volume" offset. The last term represents the active component while the first three terms represent the passive response. This passive response, as generated by PSPICE, is shown in fig. 79.

In order to describe this to PSPICE it was expanded and subdivided into 5 distinct terms which were each handled separately.

103

Fig. 78

Model of Left Atrium

Passive Pressure-Volume Response of the LV as Generated by PSPICE
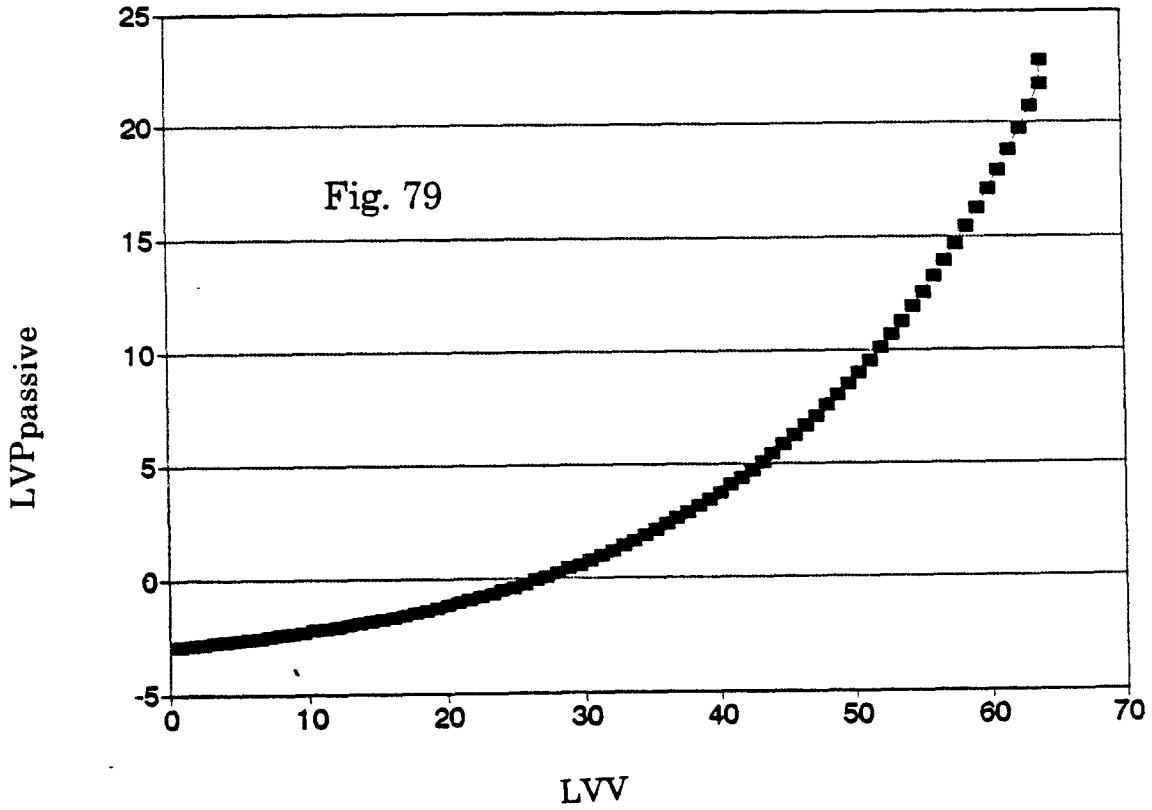

Fig. 79

1) The easiest term is the P_{inf} which is represented as a constant dc source, a battery, of value P_{inf}, which is changeable at the beginning of the program.
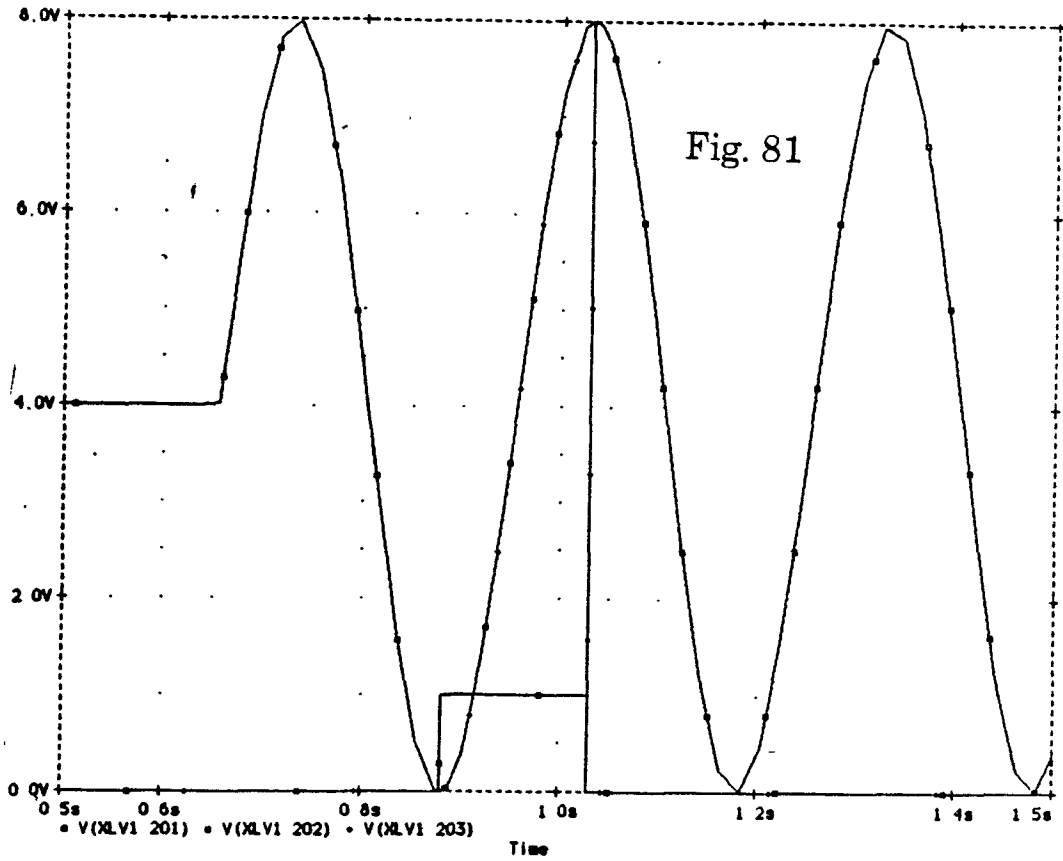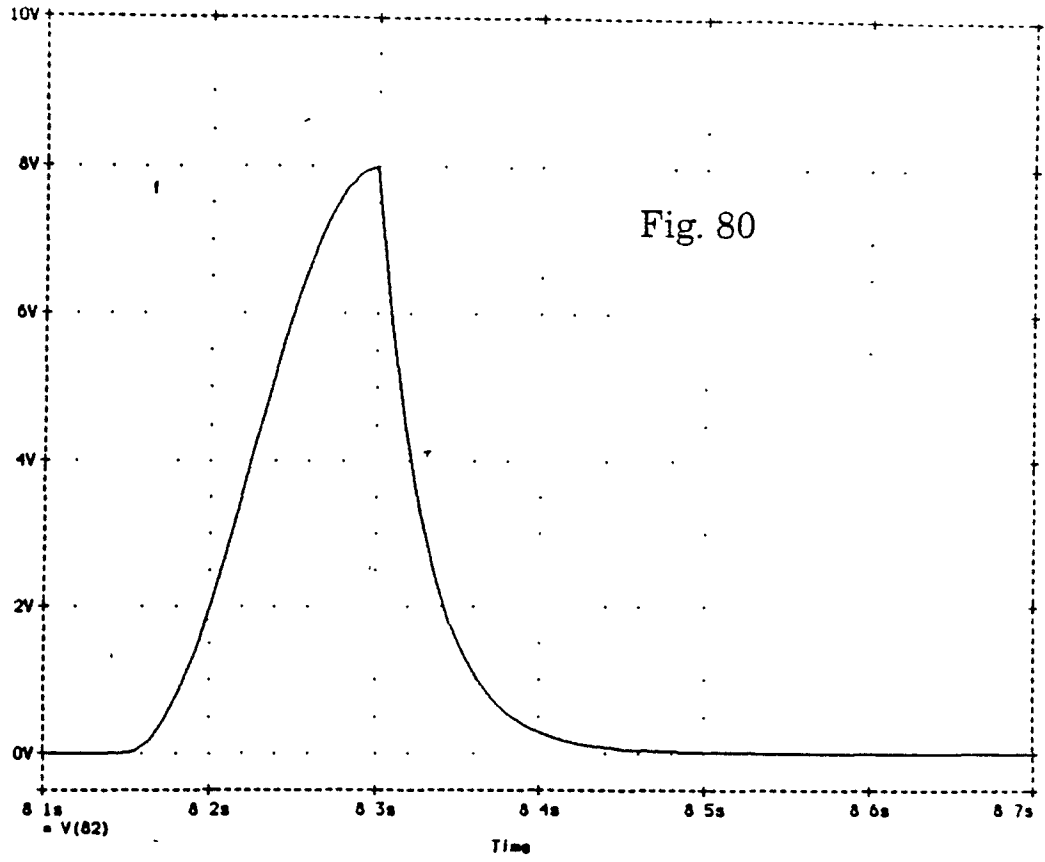
2) The B(dV/dt) term relates the rate of change of left ventricular volume to the pressure by a linear multiplier B. Since rate of change of volume is flow, this is the equivalent of V = IR where the value of the resistance is B. Thus a resistance was placed in series with the battery.

3&4) The $E(V-V_d)$ term was expanded into two terms:

3) $E * V$ and 4) $-(E * V_d)$. Since both terms contain the activation function E it was necessary to generate that first. The same three methods used for both the right ventricle and the left atrium were employed in creating the train of pulses for this function. However, creating the first one was much more difficult. The first problem involved the fact that the rising section of this function begins after 3/4's of a sine wave have elapsed. The sine wave has a frequency of 3.3333 Hz which means that the function picks it up 225 ms after it has begun. The first occurrence of this pulse is expected at one PR interval after the start of the program, about 130 ms. Since PSPICE cannot be "tricked" into thinking that a pulse has started at a negative time it is impossible to create the first pulse at the point in time where the first pulse should appear (using this particular activation function). The first occurrence of this pulse was therefore created at one PR interval after the start of the second "heartbeat", one RR interval after time zero. In order that there not be such a long interval before the first ventricular contraction, an alternate activation function, consisting of a rising as well as a decaying exponential, was inserted for the first pulse in the pulse train of E. Once the pulse train for E was complete, it was then possible to simulate the $E * V$ and $-(E * V_d)$ terms in the same way as was done in the

left atrium. This completed pulse train consisted of the first pulse being not quite correct, the second pulse, which was the first correct pulse, and many copies of the correct second pulse created using one of the three methods described above following these first two. An example of a completed correct pulse appears in Figure 80. The process of building the first half of the pulse, i.e., the rising sine, is illustrated in Figure 81, and the process of building the second half of the pulse is illustrated in Figure 82. The completed pulse train, referred to in the model as V(82), is shown in Figure 83. Thus, a variable capacitor and a variable voltage source were appended in series with the resistor and battery.

5) The $Ae^{\alpha V}$ term presented a new challenge in that, in order to implement the exponential term, it is required to know the instantaneous left ventricular volume (LVV), which is equivalent to the charge stored across the variable capacitor. That value is not accessible in PSPICE. In addition to being a significant quantity in terms of producing the final pressure term, the charge across the capacitor, representing LVV, is an important term in its own right in that one of the important parameters that should be looked at in any model of the heart is left ventricular volume, considering its time course and absolute values. It was therefore quite important, for two reasons, to be able to determine the left ventricular volume. The solution to this problem was to include another, very large, fixed value capacitor in series with the variable capacitor. Since when two capacitors are in series the total effective capacitance is the reciprocal of the sum of the reciprocals, if one of the two is many orders of magnitude greater than the other, the larger one will have a negligible effect on the effective overall capacitance. This is demonstrated in Figures 84 and 85, where the voltage across the large capacitor, V(114,115), is plotted on the same axis as the

Fig. 80

Fig. 81

107

This models mod17s

Fig. 82

• V(XLV1 204) • V(XLV1 205) • V(XLV1 206)

Time

This models mod17s

Fig. 83

• V(82)

Time

108

This models mod17a

Fig. 84

200V
160V
120V
80V
40V
0V
0s   2s   4s   6s   8s   10s   12s
▪ V(114,115) ▪ V(120,125)
Time

This models mod17a

Fig. 85

100mV
80mV
60mV
40mV
20mV
0mV
0s   2s   4s   6s   8s   10s   12s
▪ V(114,115) ▪ V(120,125)
Time

109
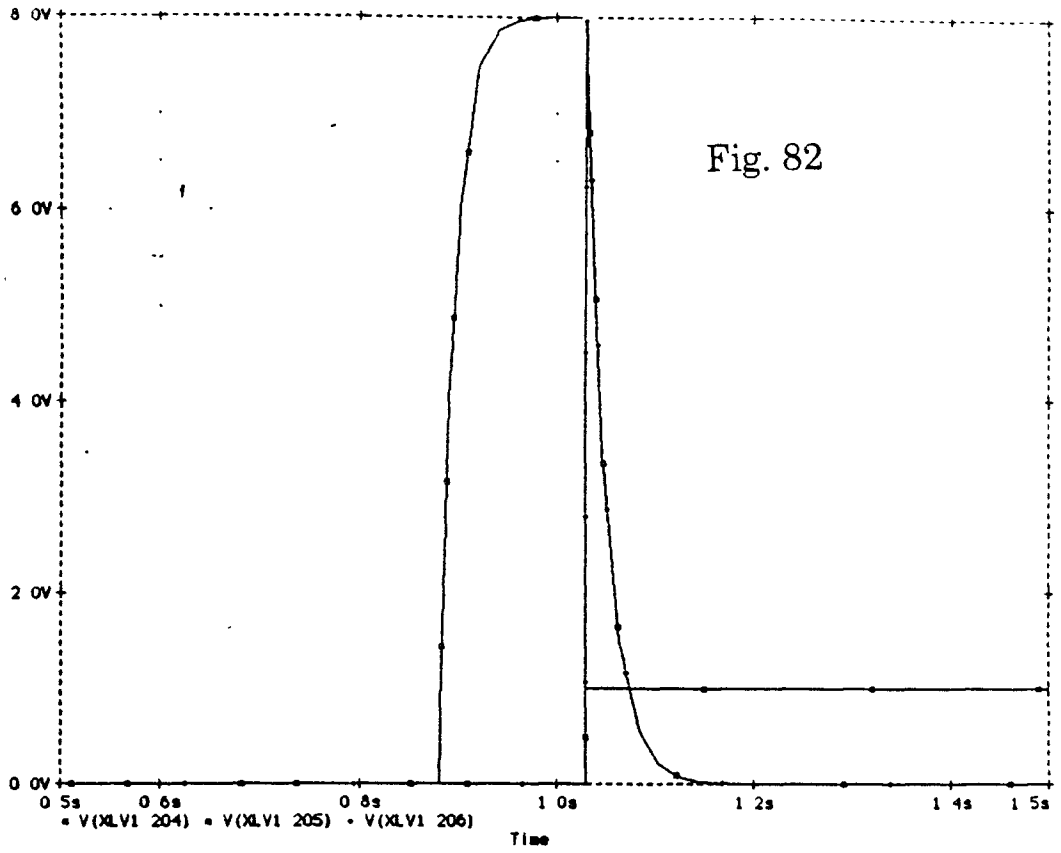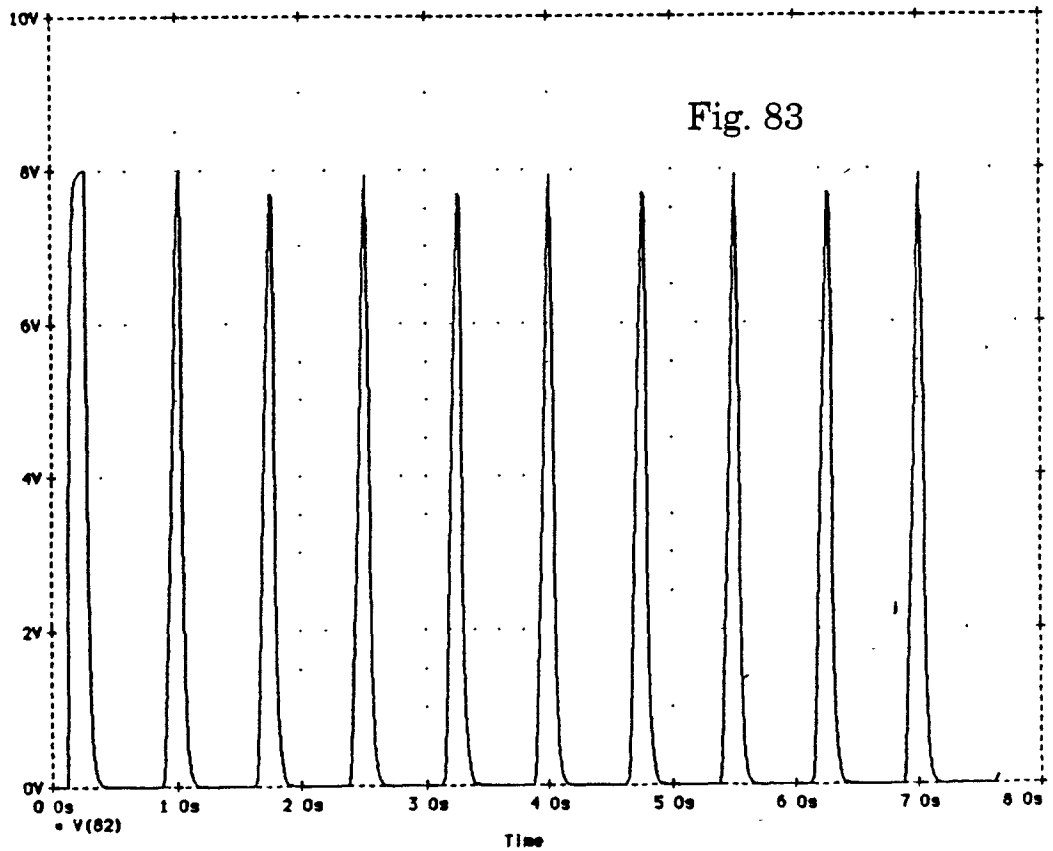
voltage across the variable capacitor, V(120,125). Figure 84 is scaled such that all of the voltage across the variable capacitor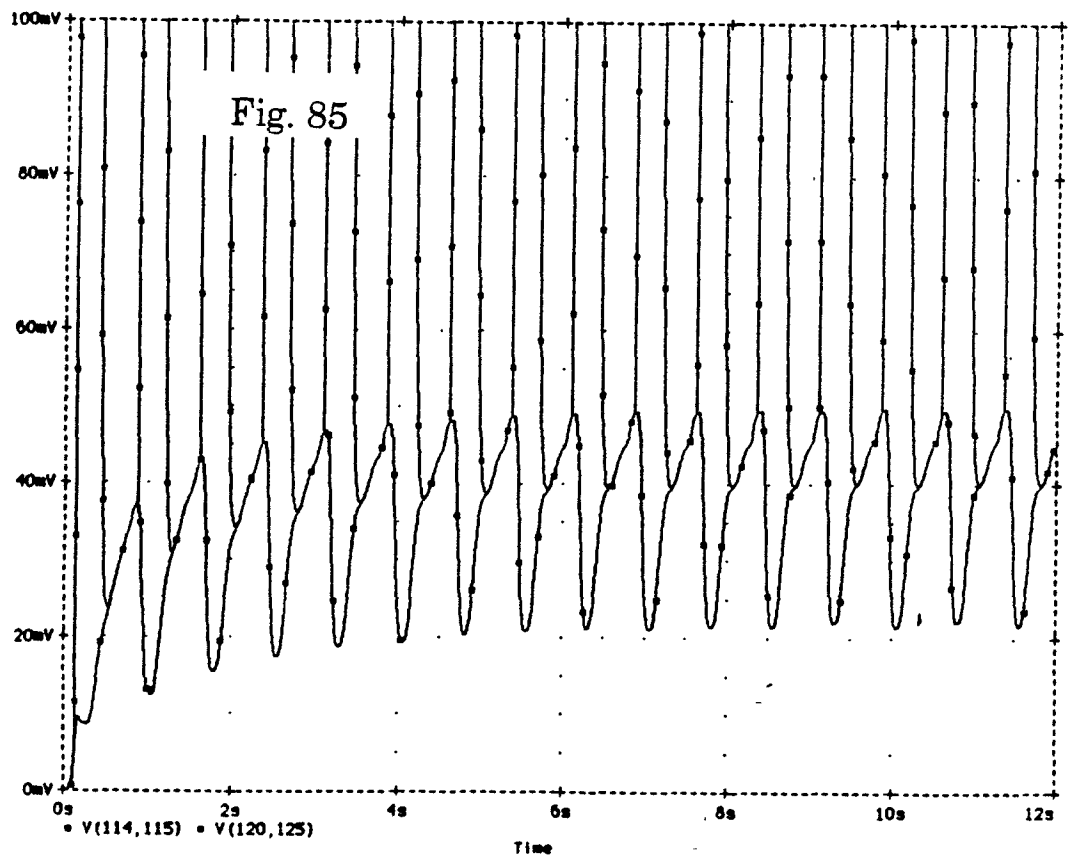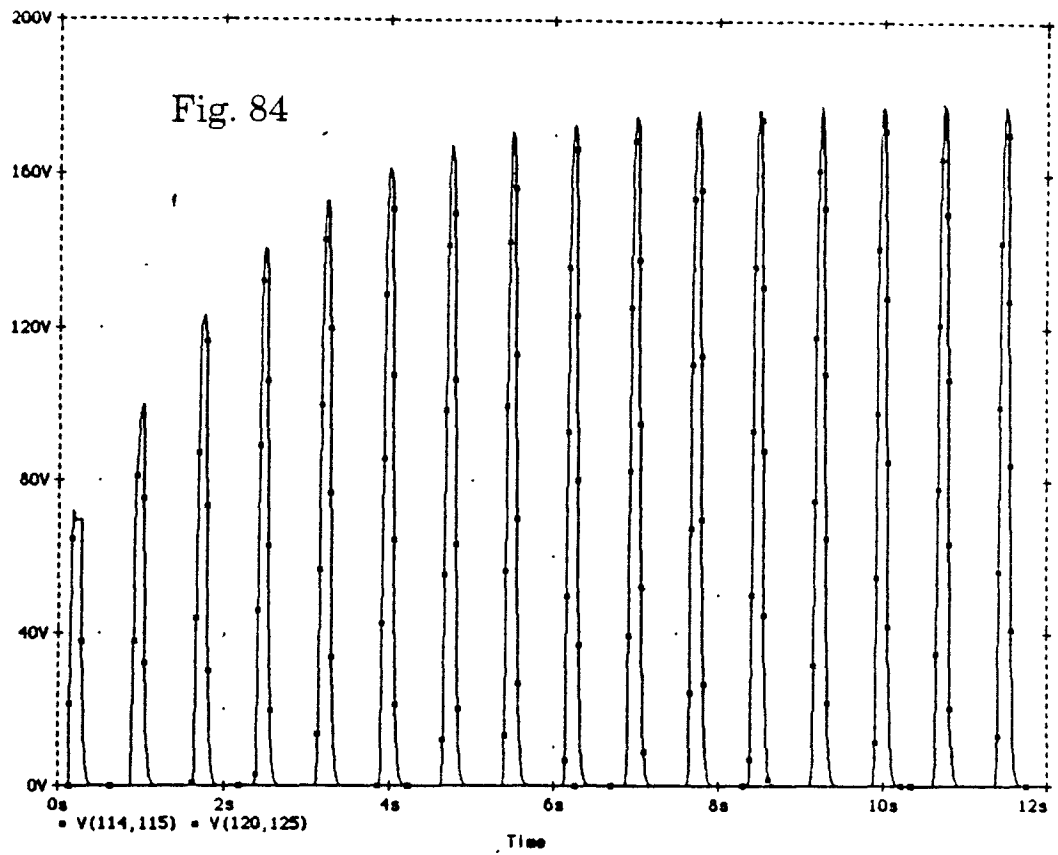 is visible, and it is seen that on this scale the large capacitor can not even be seen. Figure 85 is scaled appropriately for the large capacitor and it can be seen how truly negligible it is in comparison to the variable capacitor. In addition, when two capacitors are in series the charge stored on each of them is the same. Therefore this very large capacitor which was added will not affect the total capacitance, will have the same charge stored on it as the variable capacitor, that is charge equal to left ventricular volume, and the value of the charge is readily accessible. This is true because Q = C * V and C is a known fixed value and V across any component is readily accessible to PSPICE. The implementation of the term $(Ae^{\alpha V})$ consisted therefore of inserting a large capacitor in series with the variable capacitor and inserting a variable voltage source with output $Ae^{\alpha(\text{value of capacitor} * \text{voltage across capacitor})}$ in series with it all. In order to satisfy the PSPICE requirement that all nodes have a path to ground, which the nodes between the two capacitors do not have, a large resistor was placed from between the capacitors to ground. The total left ventricle branch is shown in Figure 86.

With all of the above details included in the PSPICE circuit, it was possible to run it. Upon running the program two outputs are generated. One is an output file which contains a numerical list of time versus any values requested in a ".PRINT" statement. The second output is a data file which is available to PROBE and is storable and thus available for later recall as well. When PROBE is run, it reads in this massive data file which contains all the currents and voltages at every node in the circuit for all time increments through which the program was run and asked to store. Any combination of currents and voltages can then be plotted on common

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axes, and the x and y scales can be manipulated to observe any part of the graphs that are of interest.

Most of the important variables in the circuit, for the most part the same ones that were available as interventions in the BASIC program, are easily changeable here as well. This is done by assigning them all "parameter" names in PSPICE and placing the entire list at the top of the program, as shown in Figure 87. To change any of the values, all that is needed is to change the value at the top of the program before running it. In addition it is not difficult to alter the various activation functions that were used throughout. This is because each pulse is only generated once (and then delayed many times) and therefore the elements of the function appear only once and are thus easily changed.

The complete circuit diagram for the PSPICE implementation of the Meisner model is shown in figure 88.

The complete PSPICE implementation is given in Appendix B.

Fig. 86

Model of Left Ventricle

This models mod17a

.PARAM RR8=.02
.PARAM RR0=.180
.PARAM RR1=.10
.PARAM RR2=.0001
.PARAM RR3=8.0
.PARAM RR4=.10
.PARAM RR5=2.4
.PARAM RR9B=.00001
.PARAM LL8=.004
.PARAM LL1=.002
.PARAM LL2=.002
.PARAM PR=.13
.PARAM RR=.75
.PARAM E8=.32
.PARAM E0=.48
.PARAM E3=1280
.PARAM E5=1.25
.PARAM LAV0=13 ;is same as VD10
.PARAM LVVD=8   ;is same as VD2
.PARAM PINF=-4
.PARAM AY=1.09
.PARAM ALPHA=.05
.PARAM TAU=.02
.PARAM K10=1.0
.PARAM PMAXRV=25
.PARAM RVDUR=300   ;duration of rv contraction in ms
.PARAM EMAXLA=2.0
.PARAM EMAXLV=8
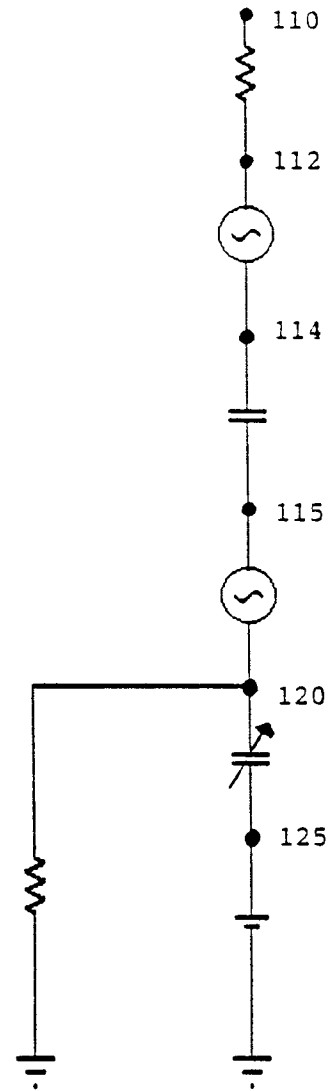
Fig. 87
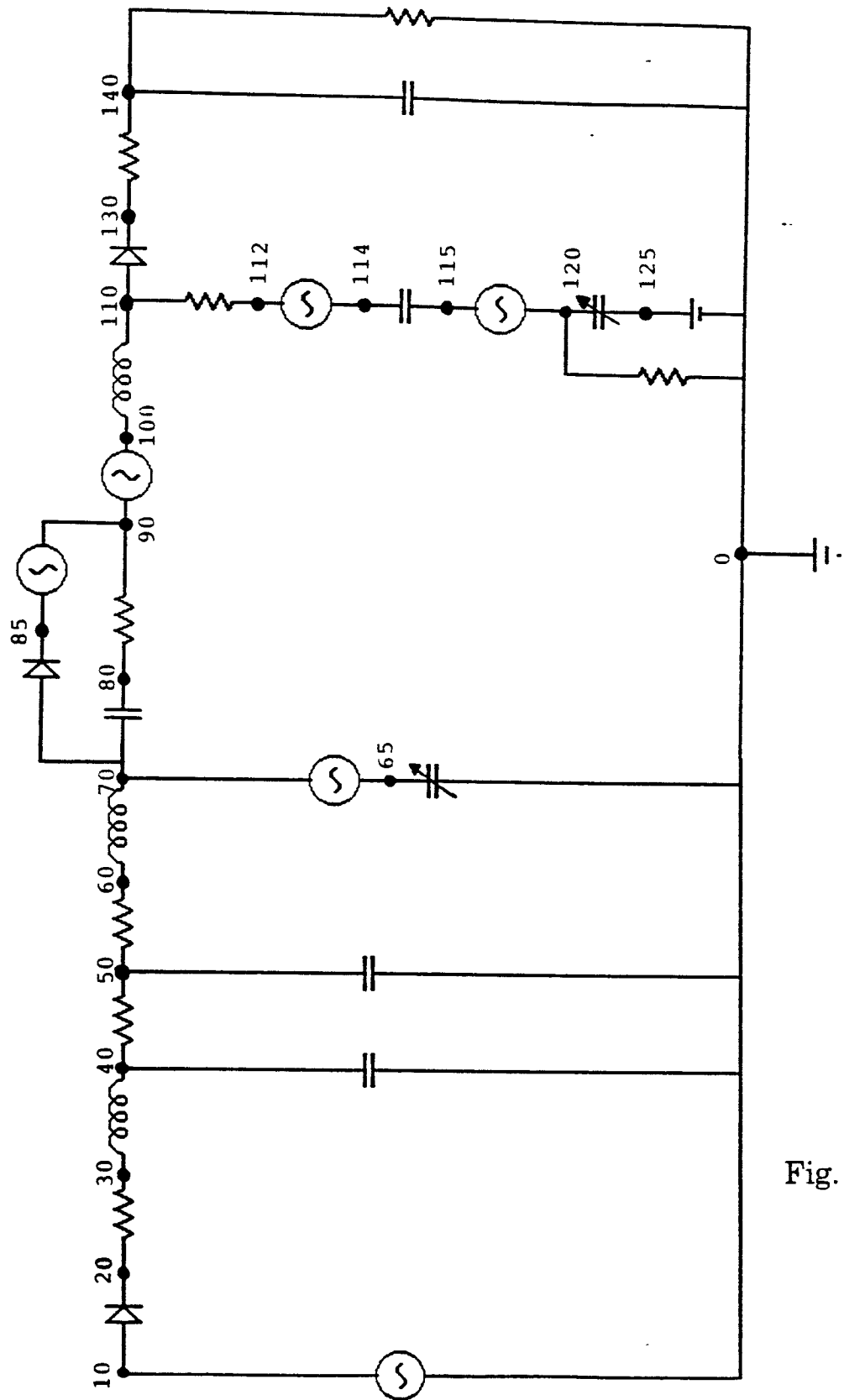
Complete PSPICE Model

Fig. 88

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CHAPTER VII

PSPICE RESULTS: Before the PSPICE implementation could be used it must be demonstrated that it is behaving as expected. Two important aspects of this behavior are the fact that the various results are converging to a steady state and that the placing of initial conditions of current (flow) through inductors and charge (volume) on capacitors will not affect the final values of the steady state. This since assumption is not at all obvious due to the presence of non-linear elements within the model. Many such tests were run, all confirming the desired and expected result. Figure 89 illustrates the left ventricular volume waveforms over time with initial conditions of zero, 42, and 55 volts across the LV variable capacitor. As can be seen, a final steady state condition is reached in all three cases, with no difference due to the initial condition. Figure 90 shows similar results for mitral flow, again starting with the above three initial conditions on left ventricular volume.

This models mod17a

No IC

Fig. 89

This models mod17a

IC=42V

This models mod17a

IC=55V

Fig. 90

No IC

IC=42V

IC=55V
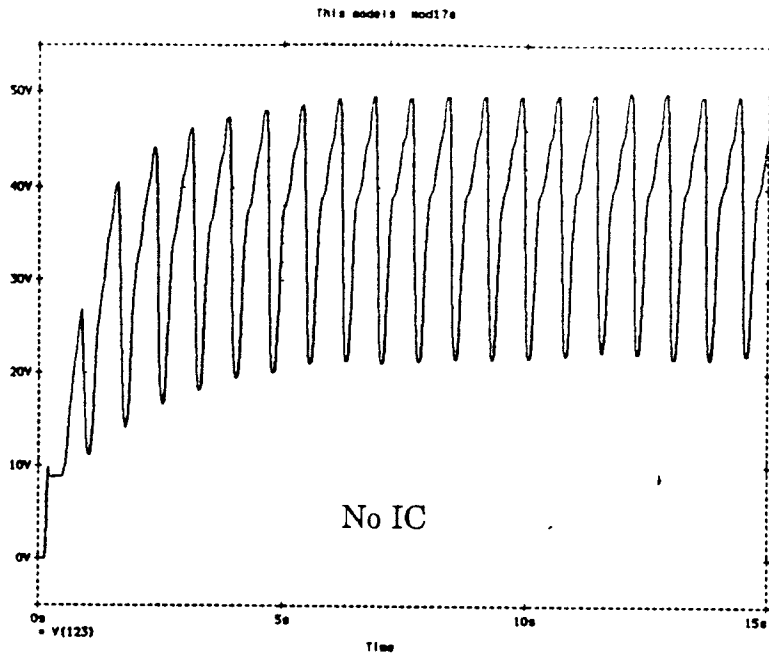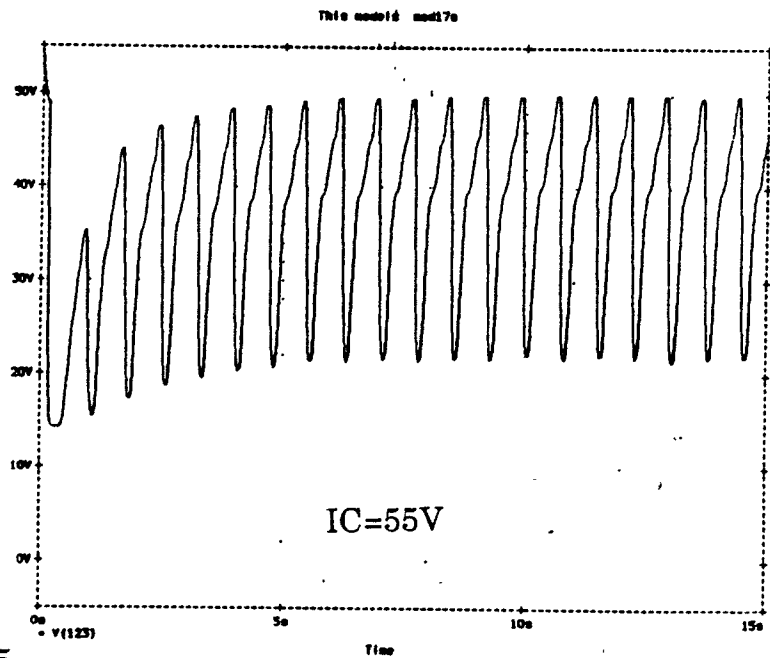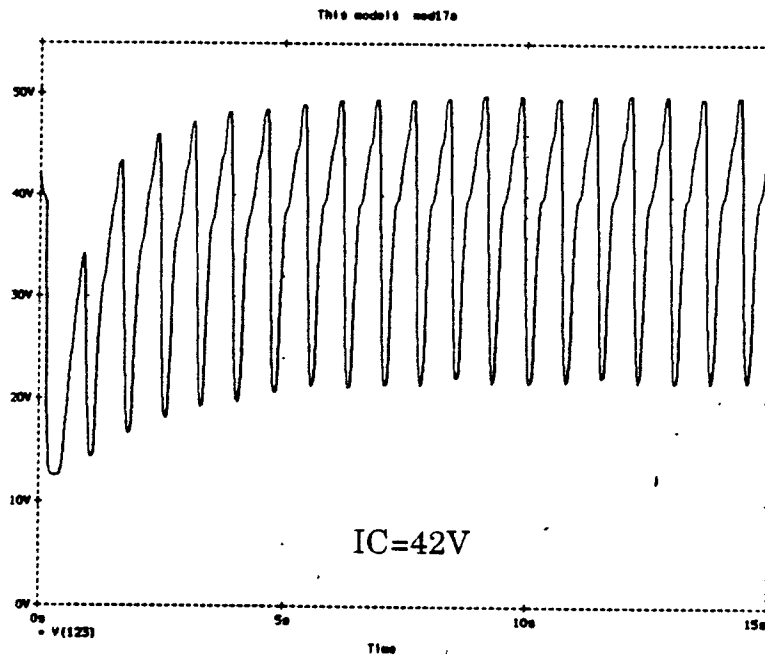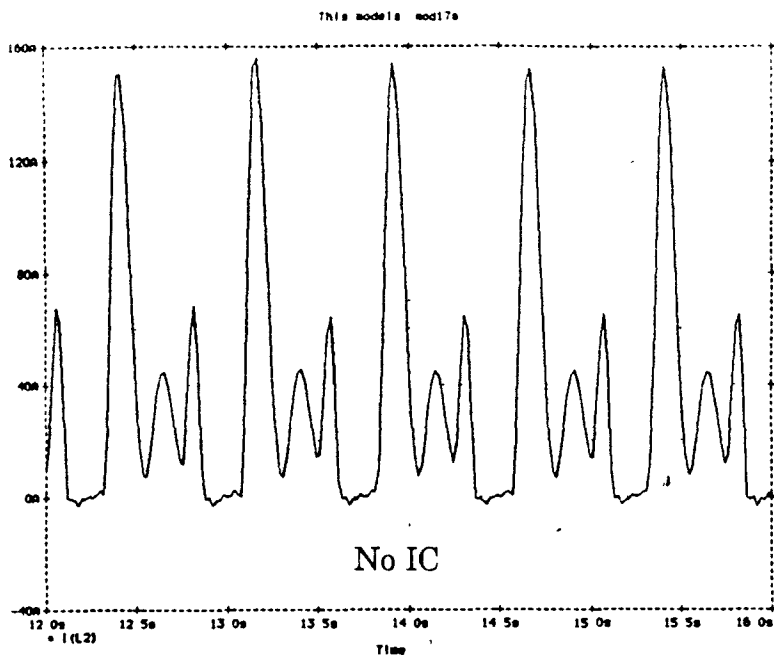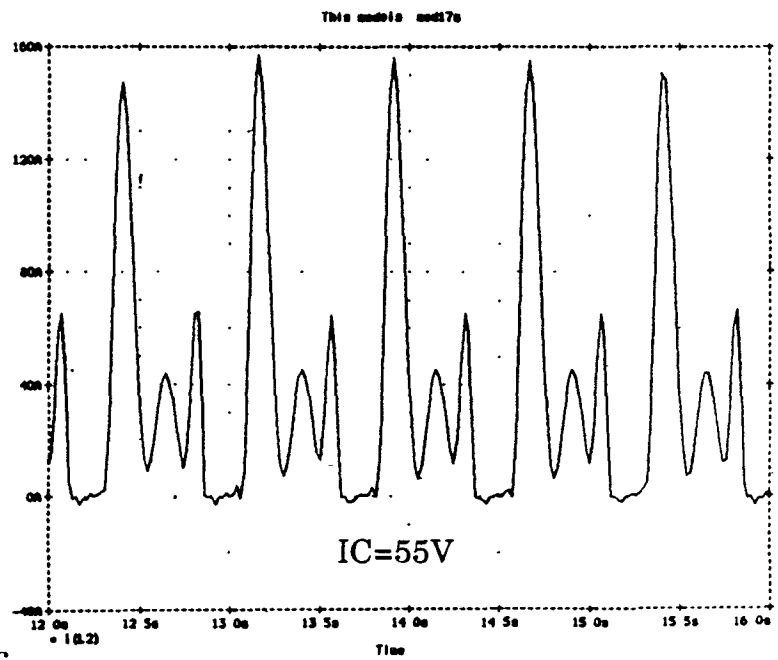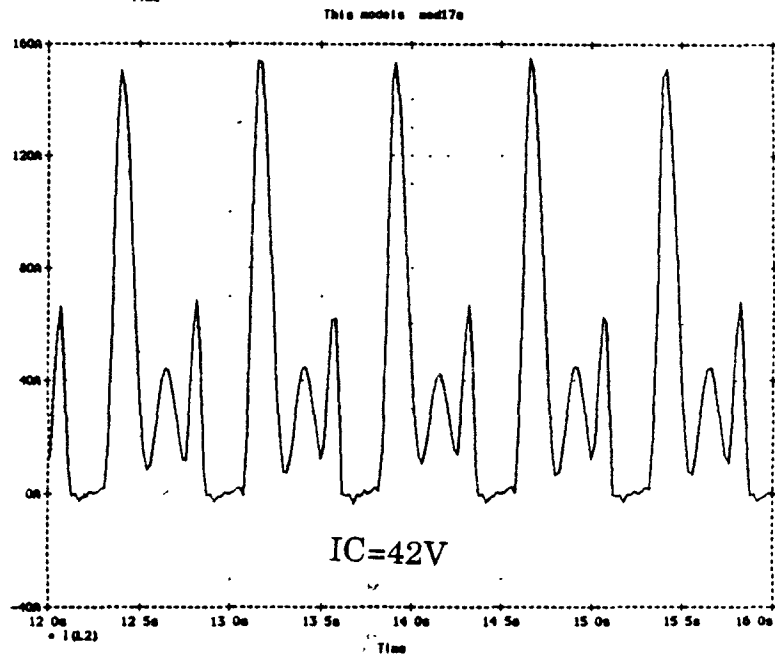
Varying the PR Interval: In order to verify that the model was functioning properly it was decided that along with running a control run, a number of runs varying the PR interval should be run, thus repeating the Meisner experiment that had already been done three times; once *in vivo*, once by Meisner in his thesis and once earlier in this thesis in the parameter vs. parameter section. Thus, presented below are the graphs of LVP & LAP, MF, LVV and LAV for PR intervals of 1 ms., 130 ms. (control), and 240 ms., as well as graphs of the atrial V(62) and ventricular V(82) excitation functions as the PR interval is varied. For each PR interval these five graphs are shown, with the first always demonstrating the PR interval by means of the excitation functions. Figures 91-95 are for PR=1 ms., fig. 96-100 are of PR=130 ms. and figure 101-105 show a PR of 240 ms.
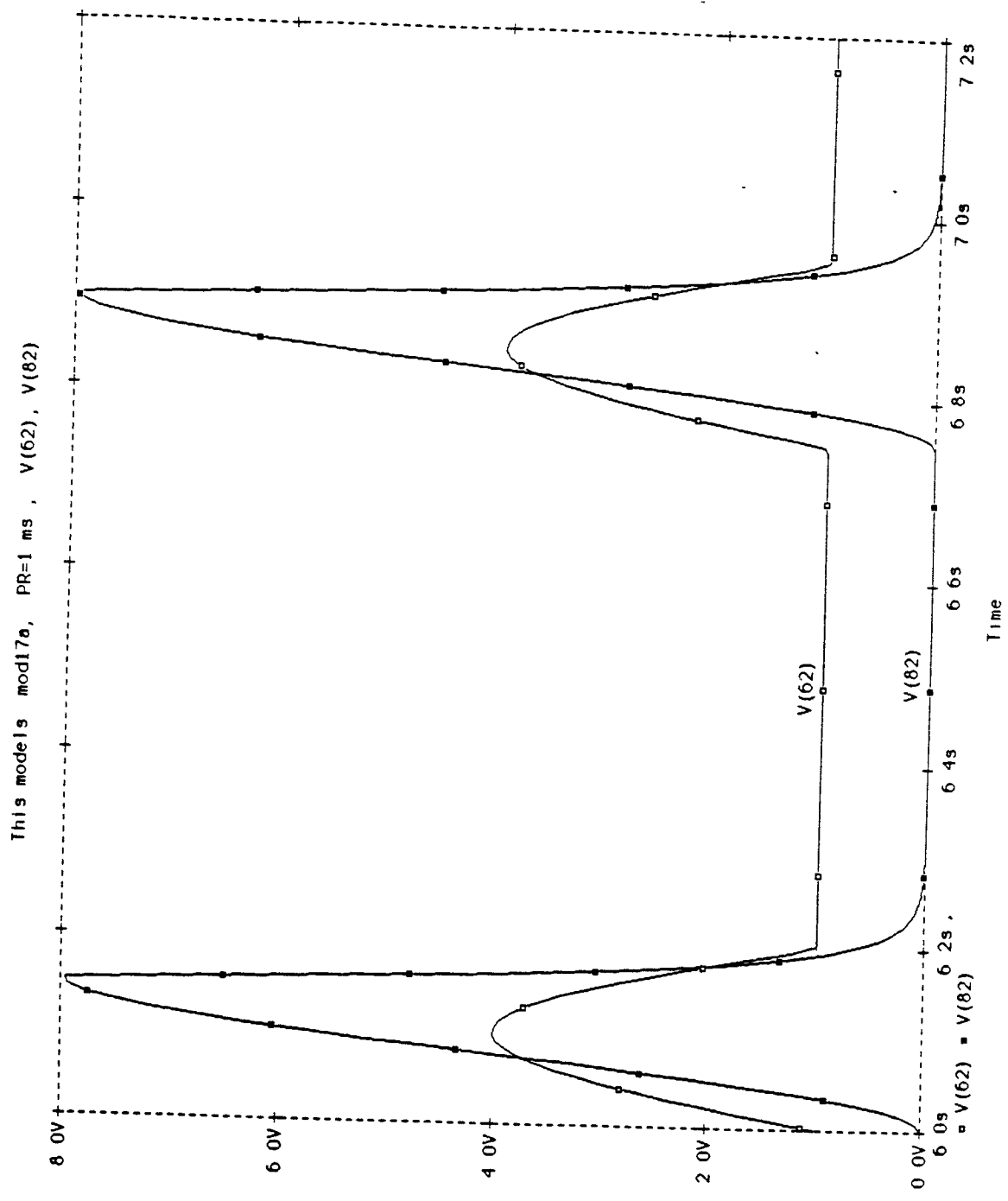
Fig. 91
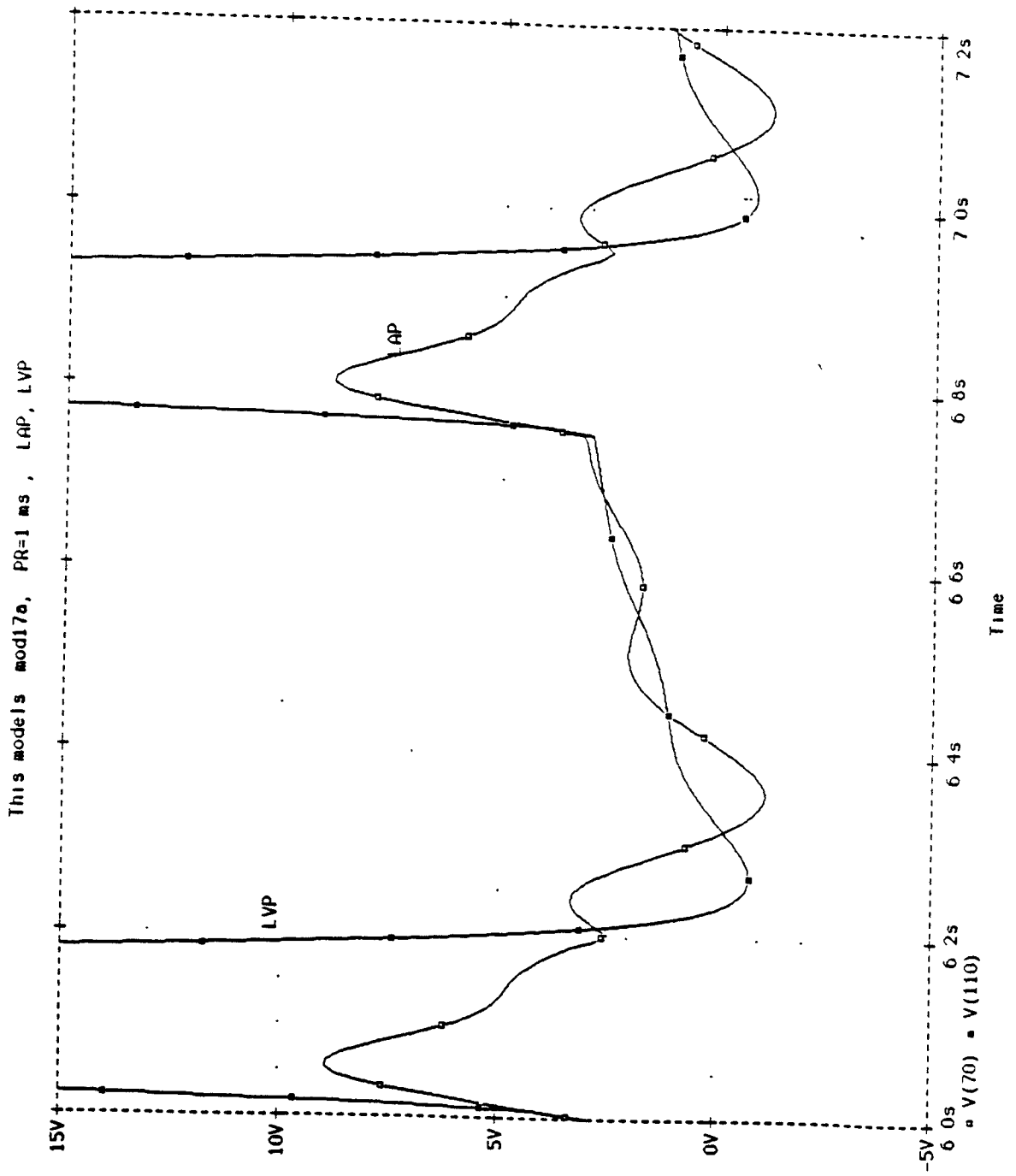
This models mod17a, PR=1 ms , LAP, LVP

Fig. 92

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This models mod17a, PR=1 ms , tlF

MF

I(L2)

Fig. 93

120

Fig. 94

121
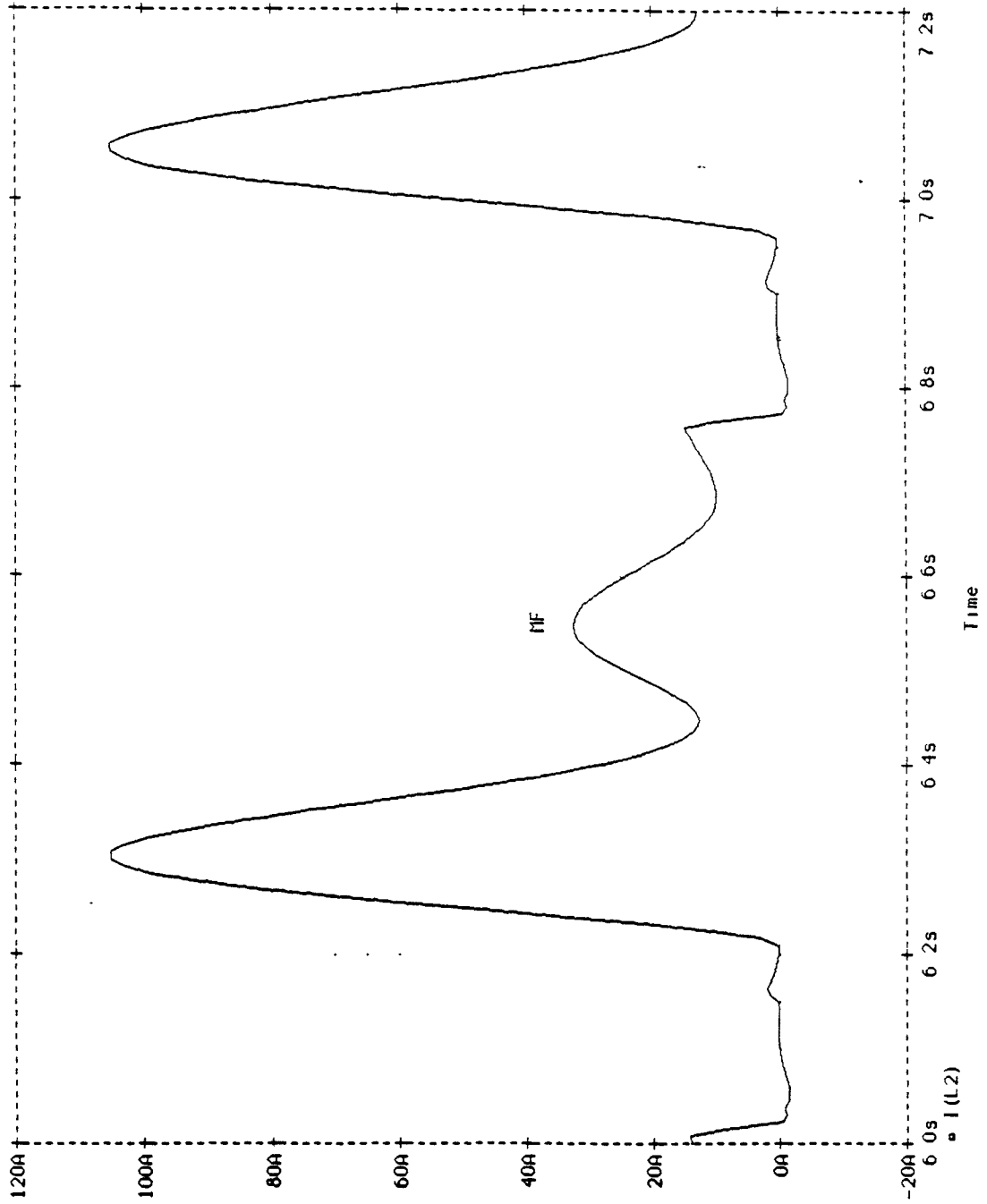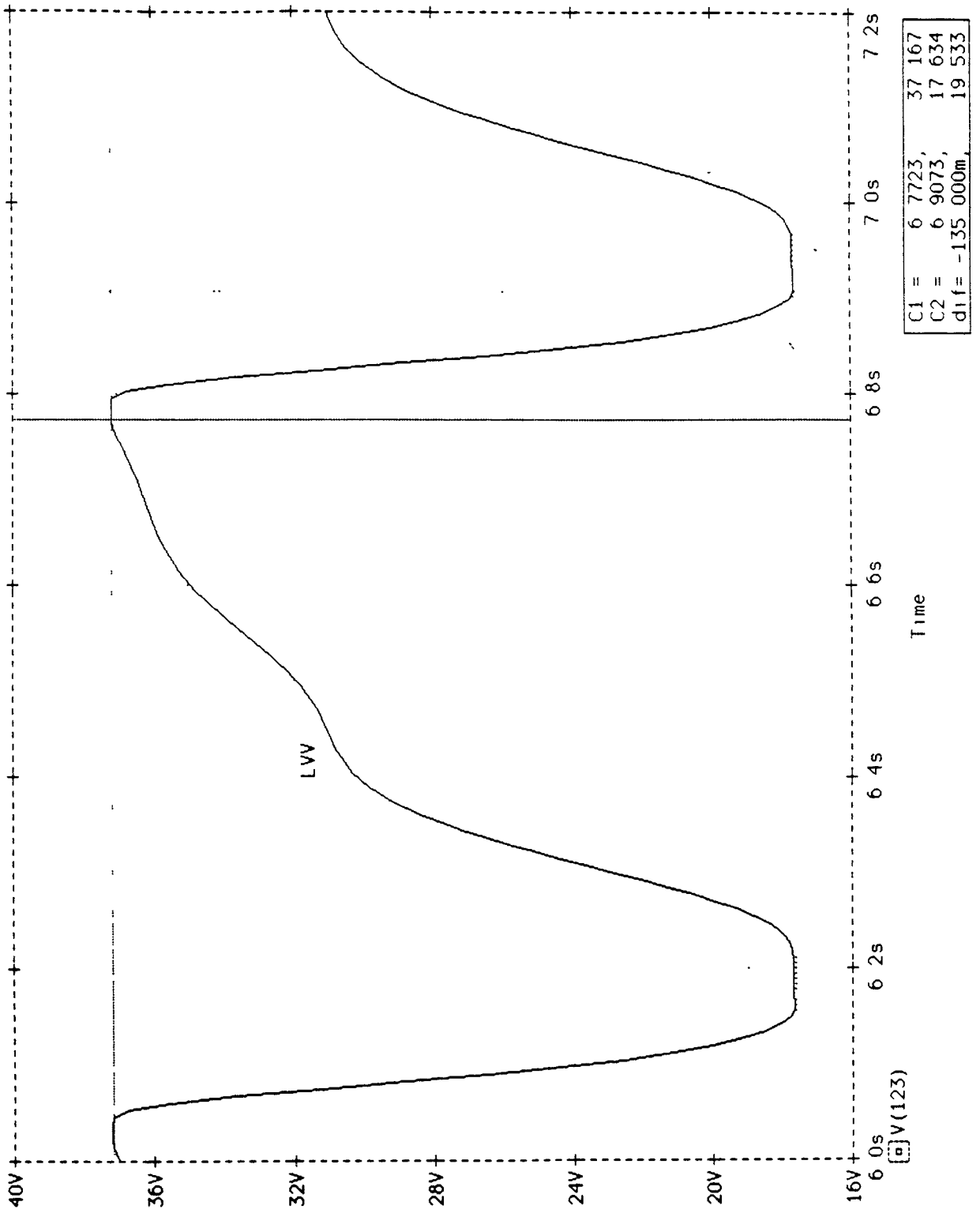
This models mod17a, PR=1 ms , LAV
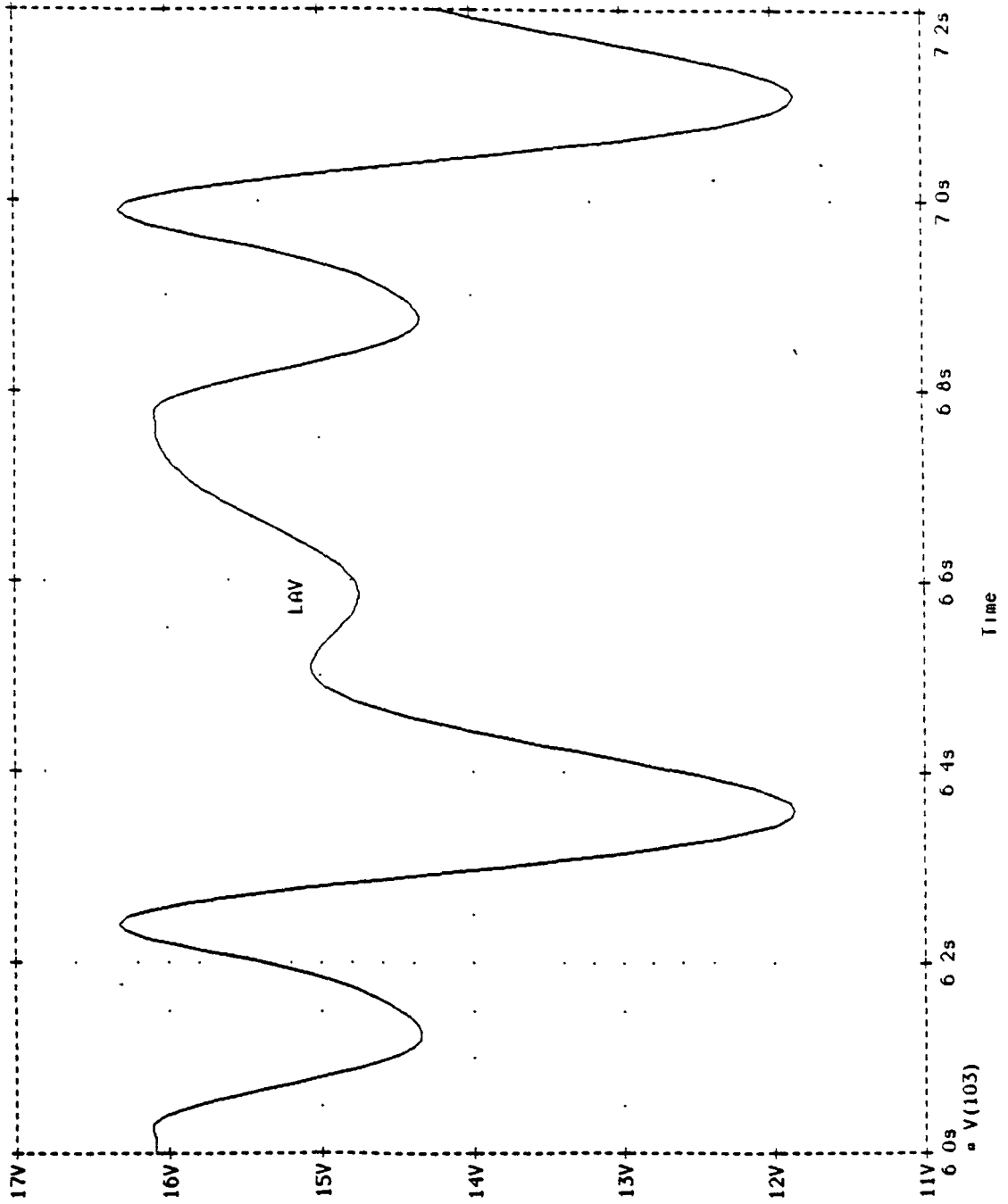
Fig. 95
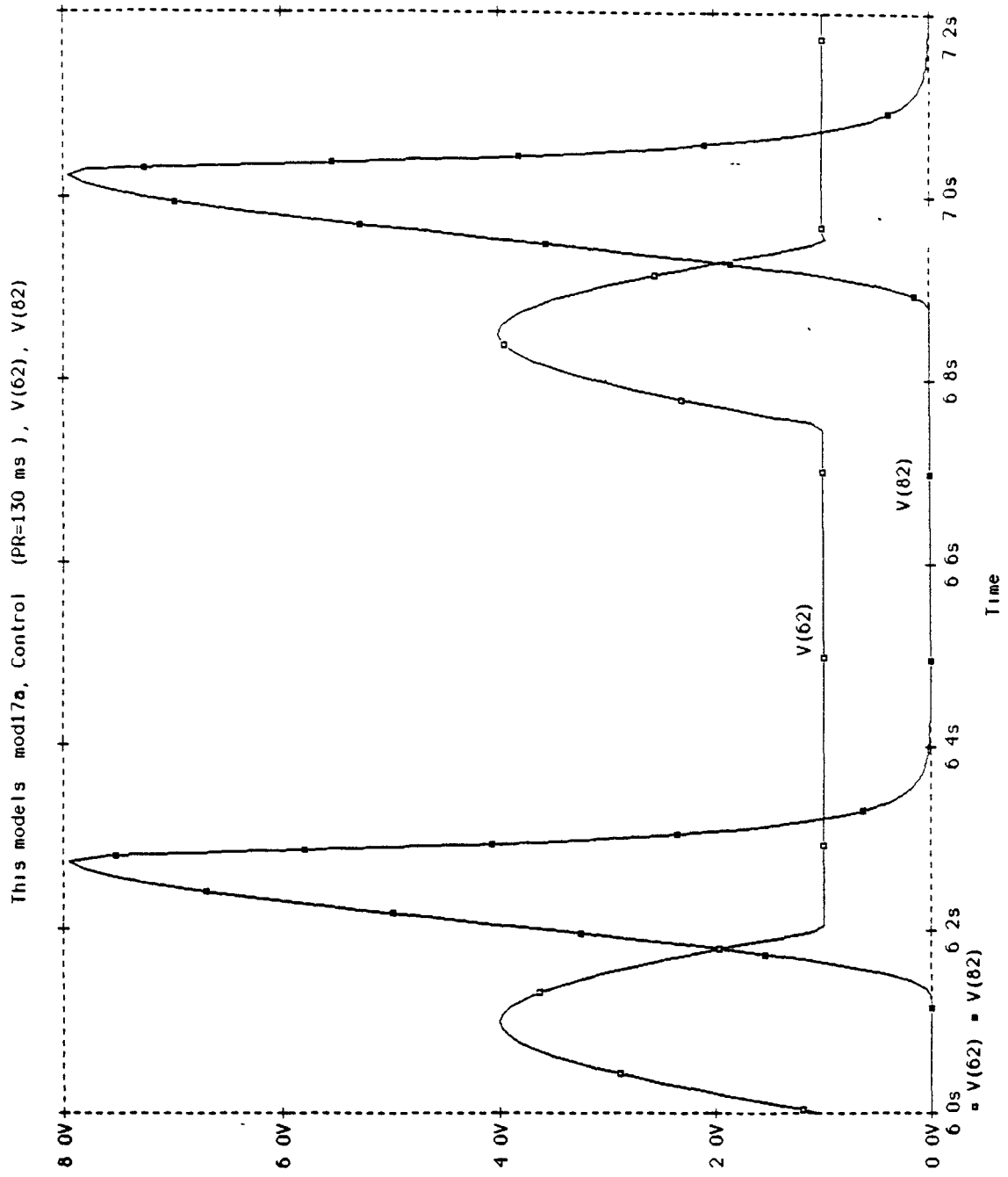
Fig. 96
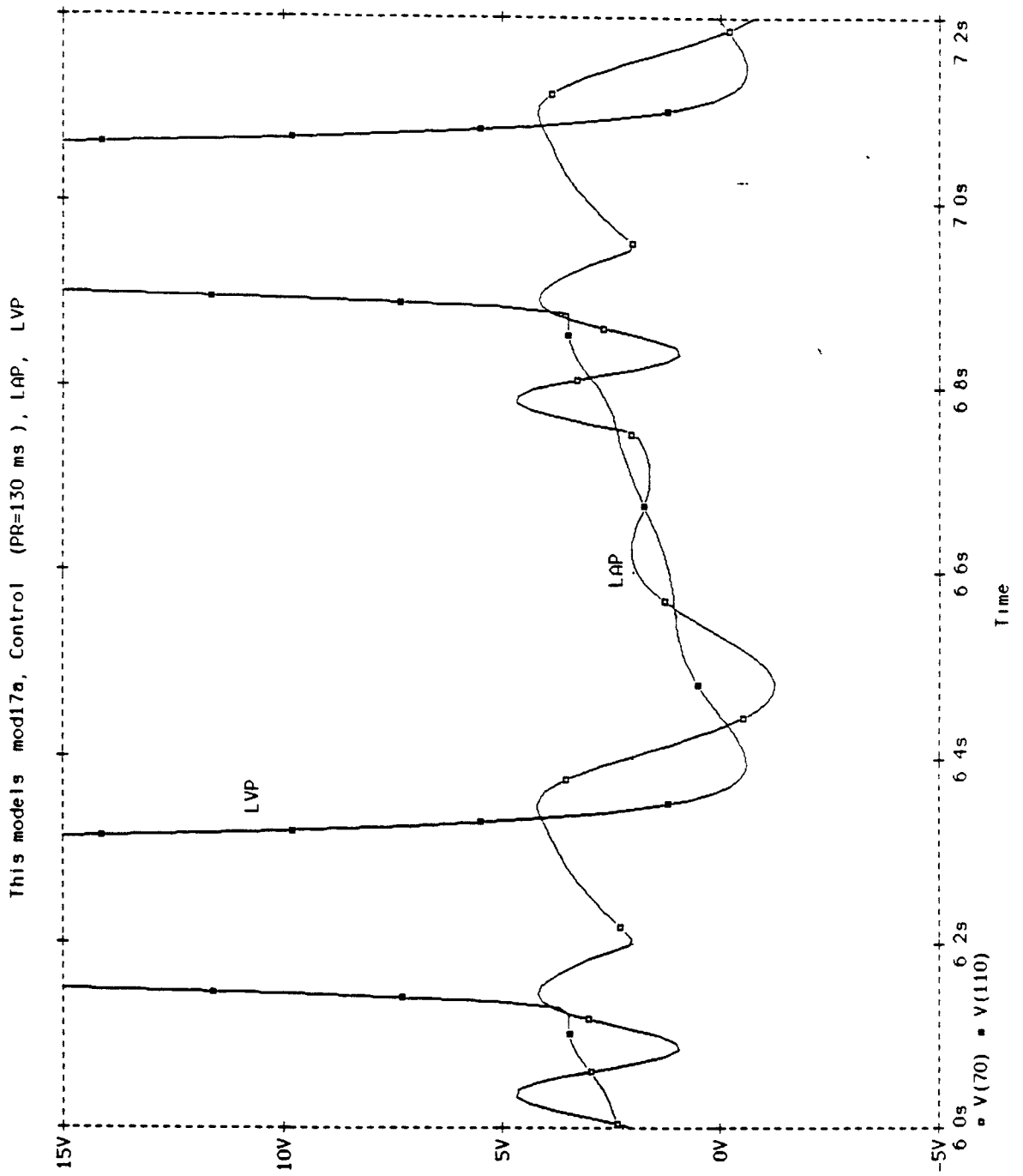
123

Fig. 97

124

This models mod17a, Control (PR=130 ms), MF

Fig. 98

125

This models mod17a, Control (PR=130 ms), LVV

LVV

C1 =   6 8881,   38 514
C2 =   7 0381,   18 111
dif = -150 000m,   20 403

[a] V(123)

40V⊤
36V⊤
32V⊤
28V⊤
24V⊤
20V⊤
16V⊤
6 0s   6 2s   6 4s   6 6s   6 8s   7 0s   7 2s

Time

Fig. 99

126
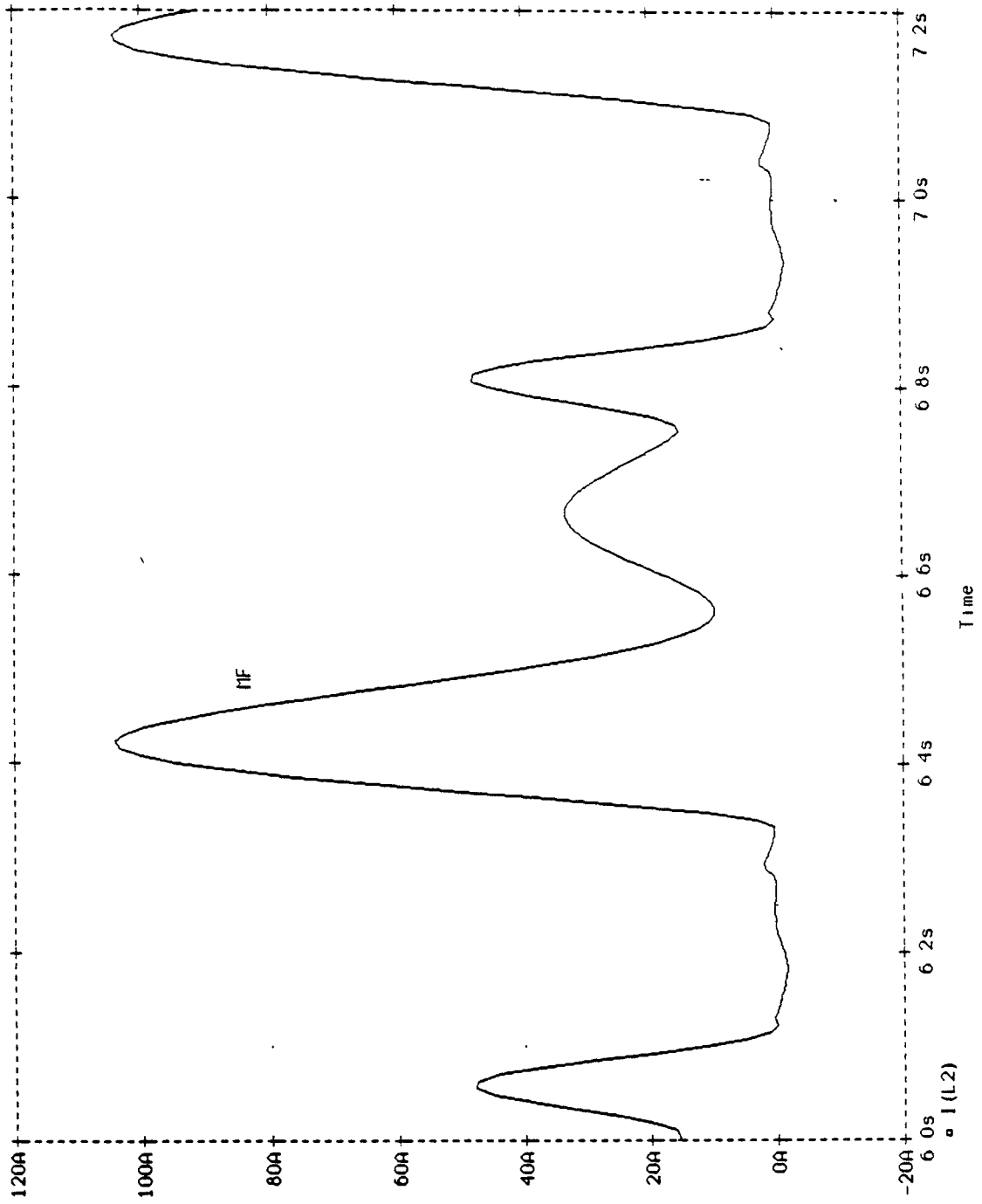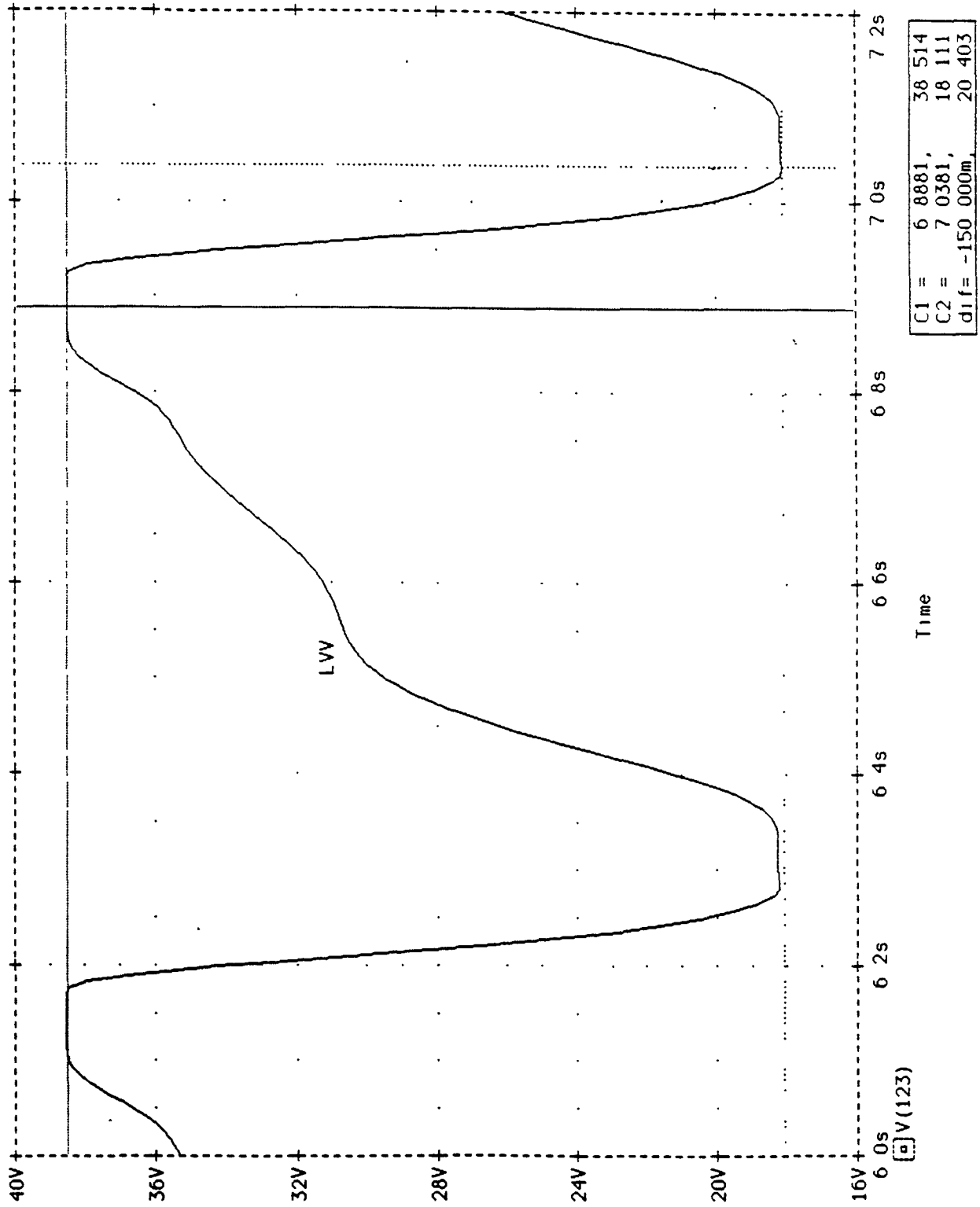
This models mod17a, Control (PR=130 ms.), LAV

LAV

18V   17V   16V   15V   14V   13V   12V   11V

6 0s   6 2s   6 4s   6 6s   6 8s   7 0s   7 2s

Time

□ V(103)

Figure 100

127
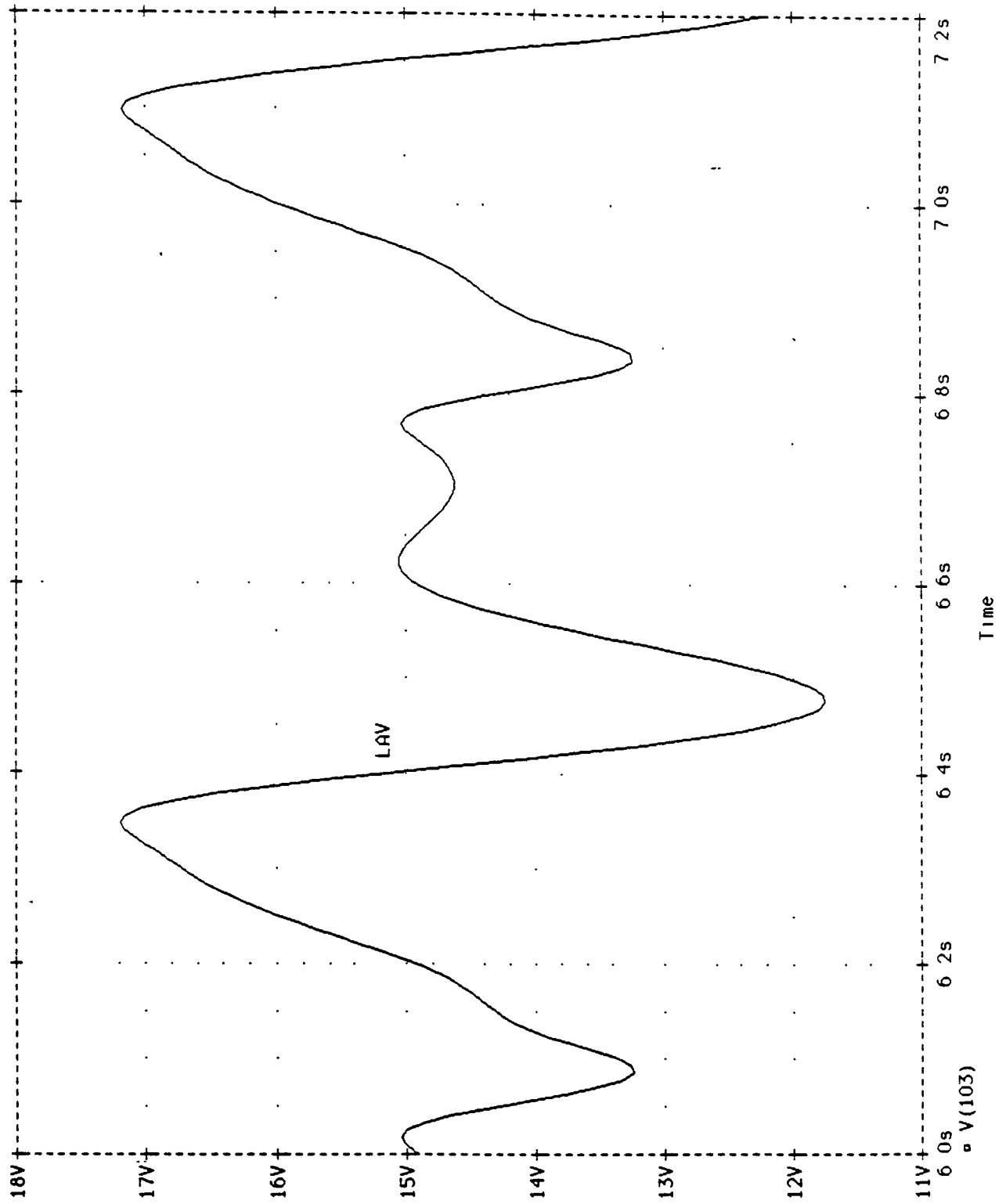
This models mod17a, PR=240ms , V(62) , V(82)

Figure 101

128

Figure 102

129
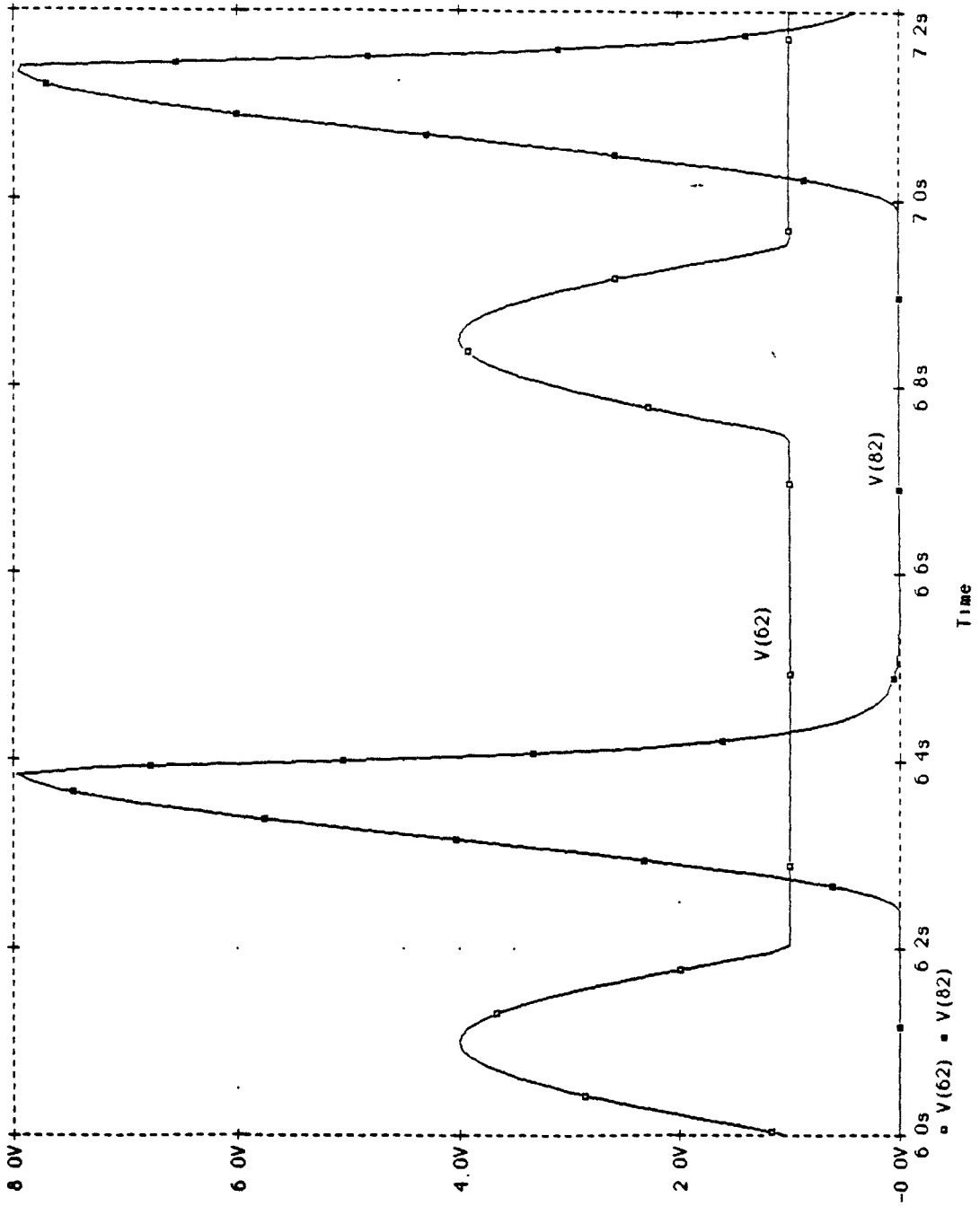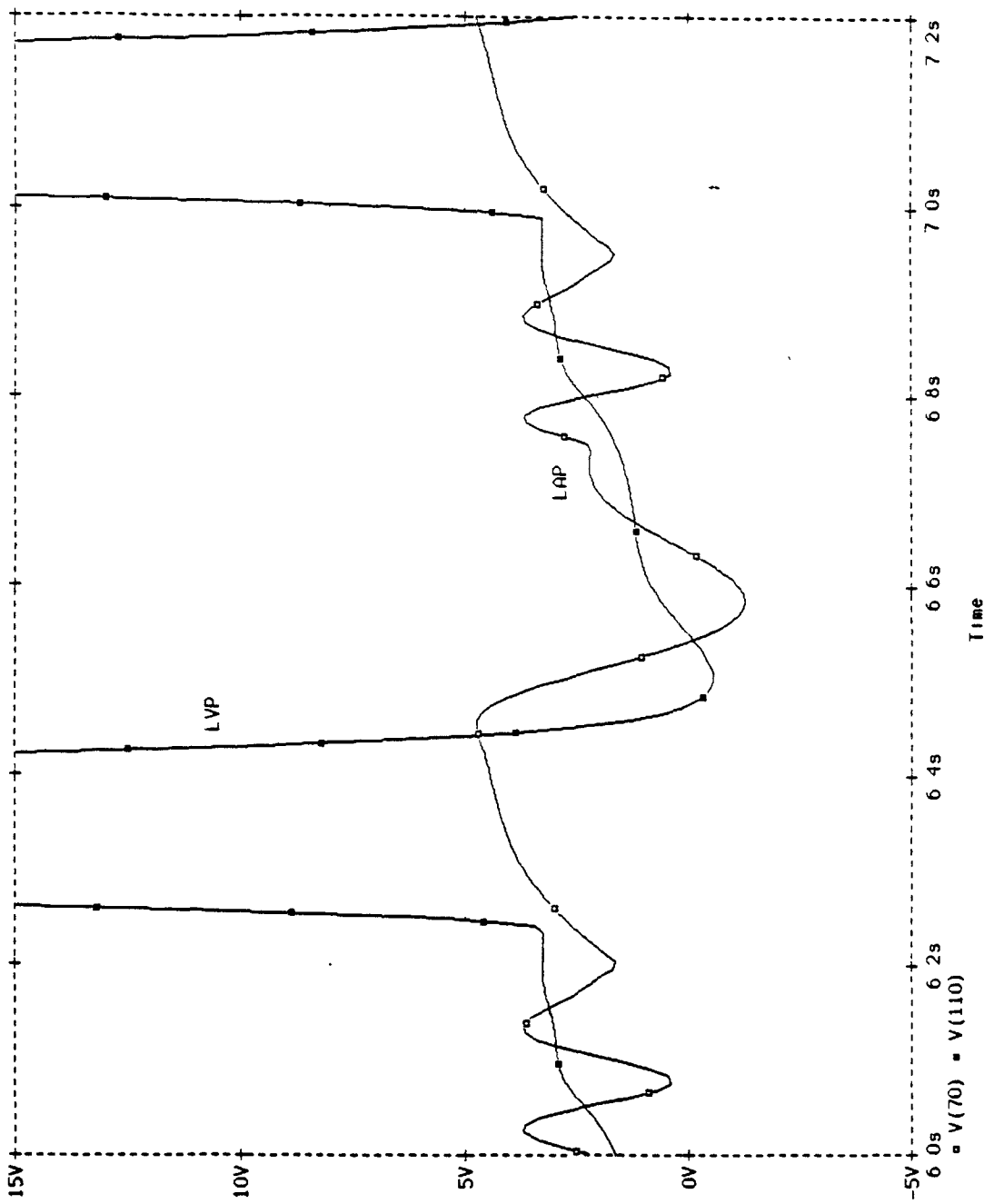
This models mod17a, PR=240ms , MF

Figure 103

130

Figure 104

Figure 105

132
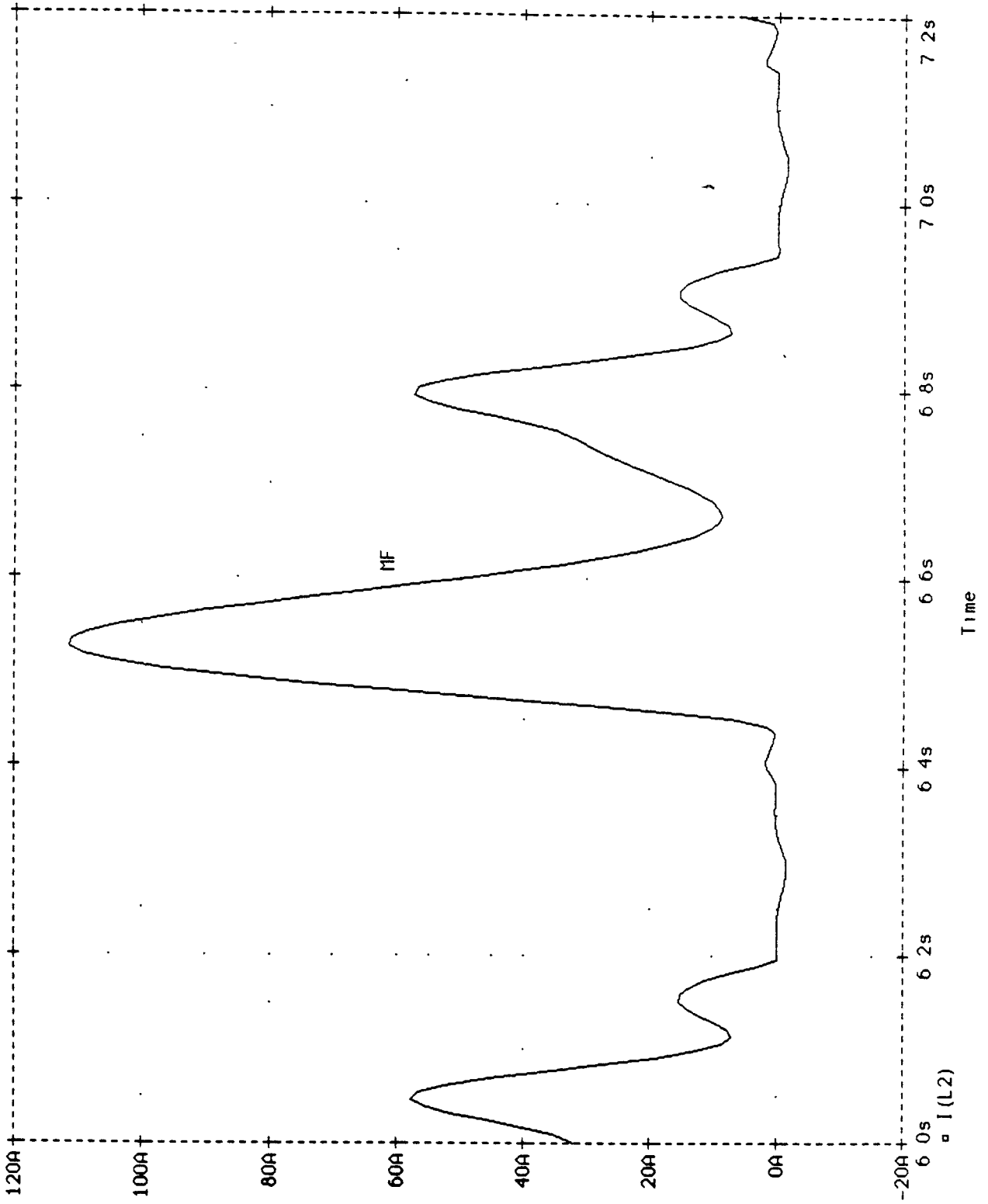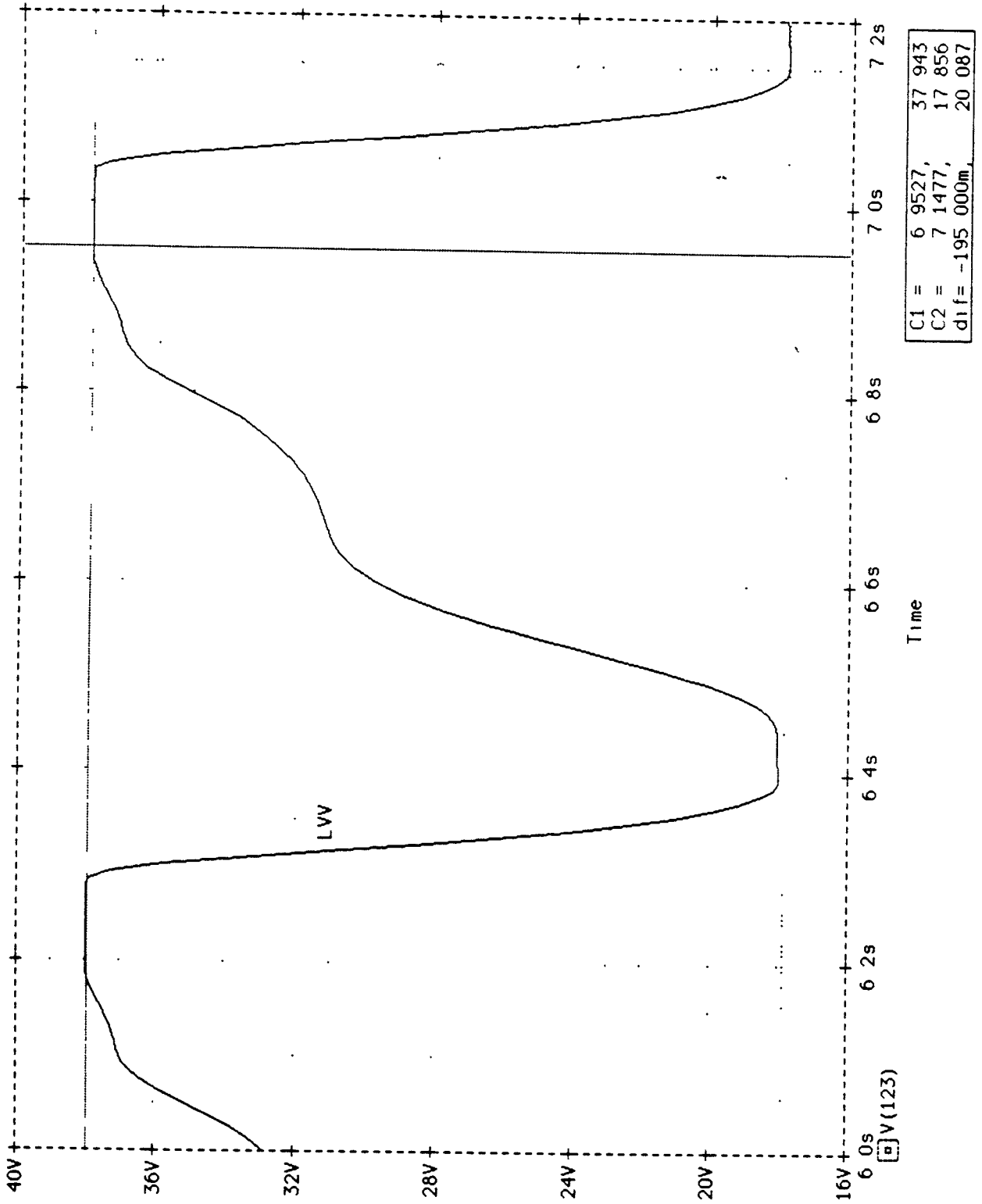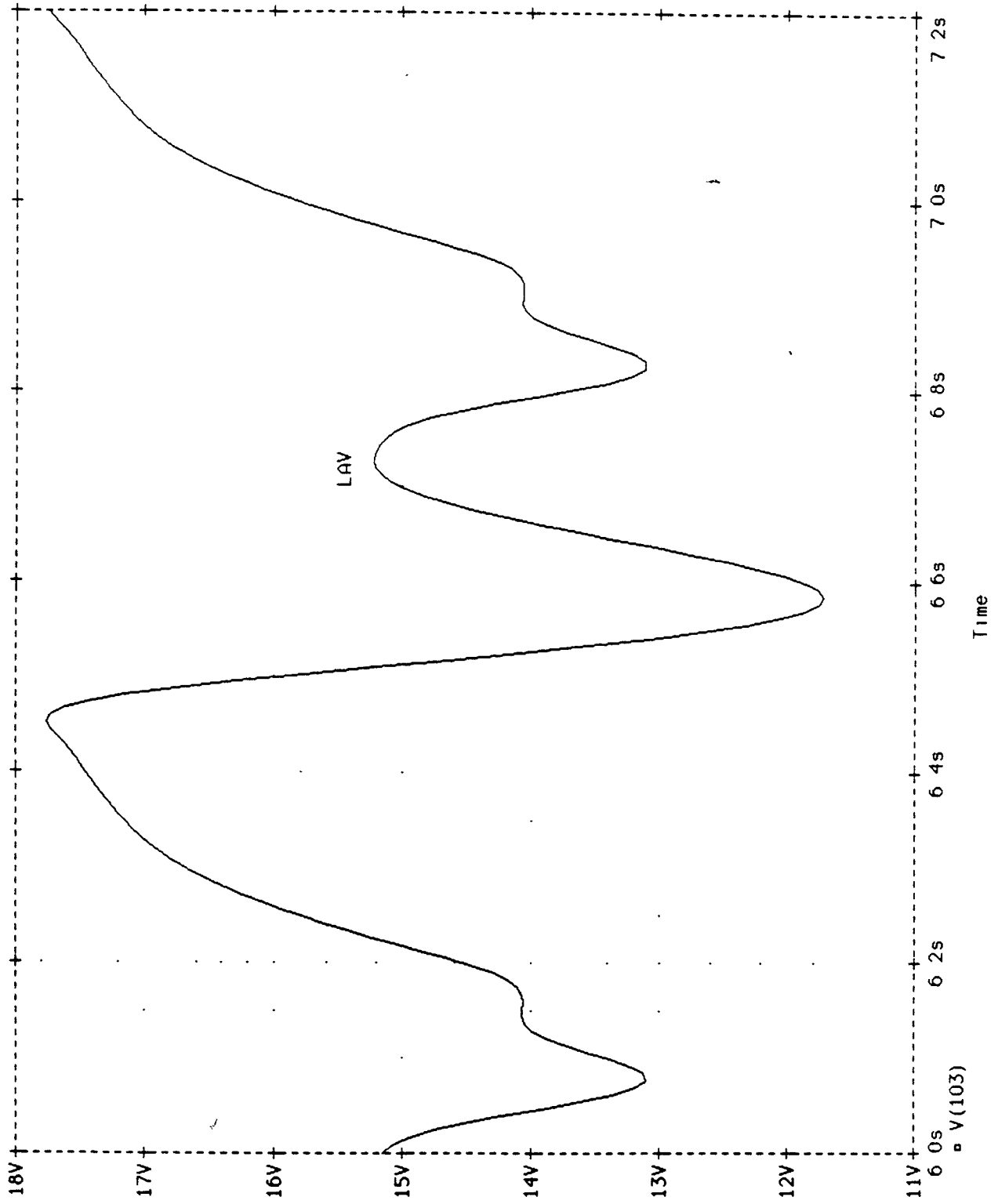
Mitral Stenosis and No Atrial Contraction: The following graphs present the results of two more experiments that were run on the PSPICE model. They include the graphs of LVP & LAP, MF, LVV and LAV for two non-control conditions. The first series of four graphs, figures 106-109, show a simulation of mitral stenosis which was accomplished by increasing the mitral resistance (R2) ten fold. The second group of four graphs, figures 110-113, show a simulation of no atrial contraction, which was done by setting Emax-LA equal to K10-LA (the passive elastance). In both scenarios the model behaves as would be expected, attesting to the validity of the model.

Figure 106

134
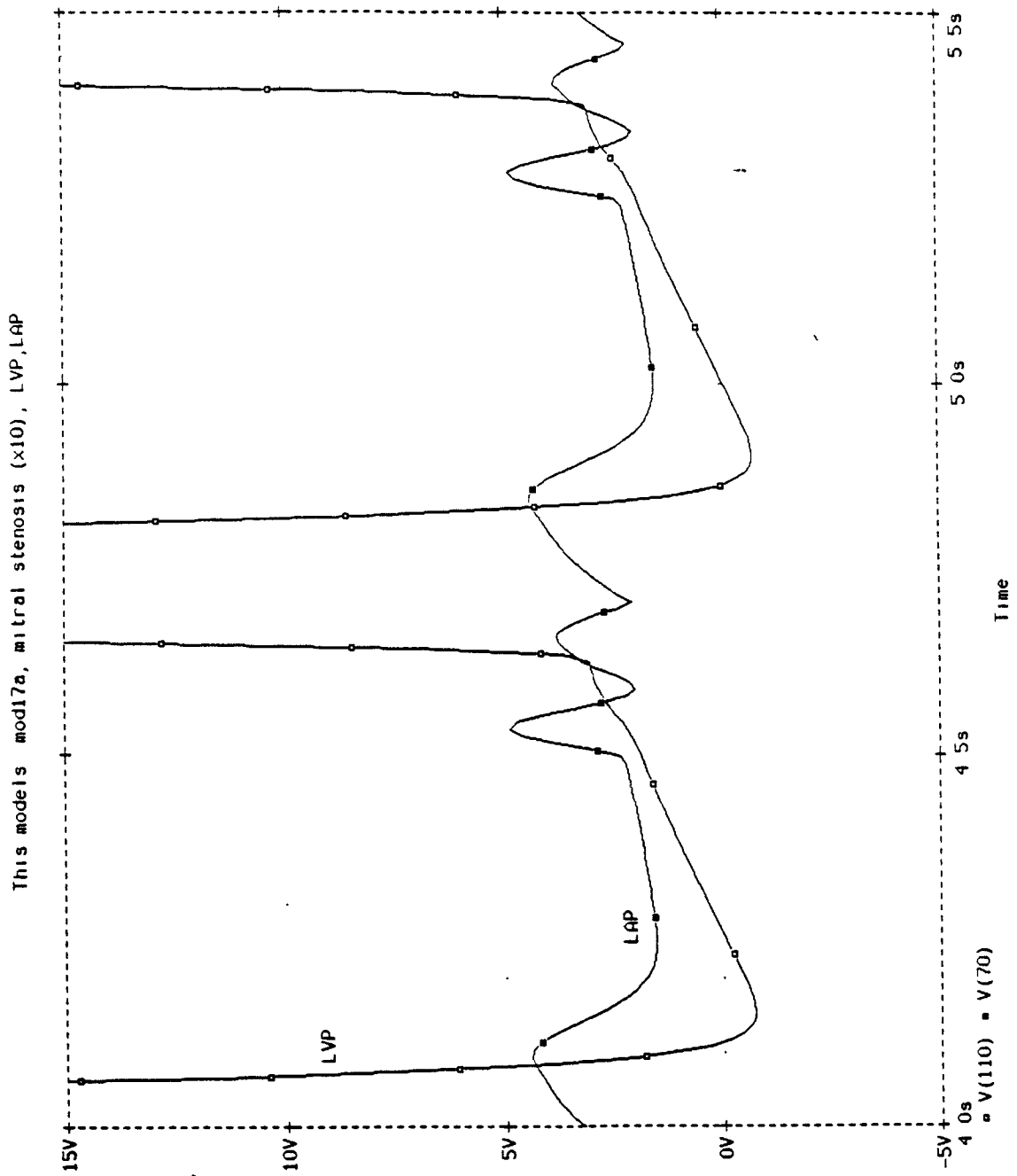
This models mod17a, mitral stenosis (x10), MF

MF

Time
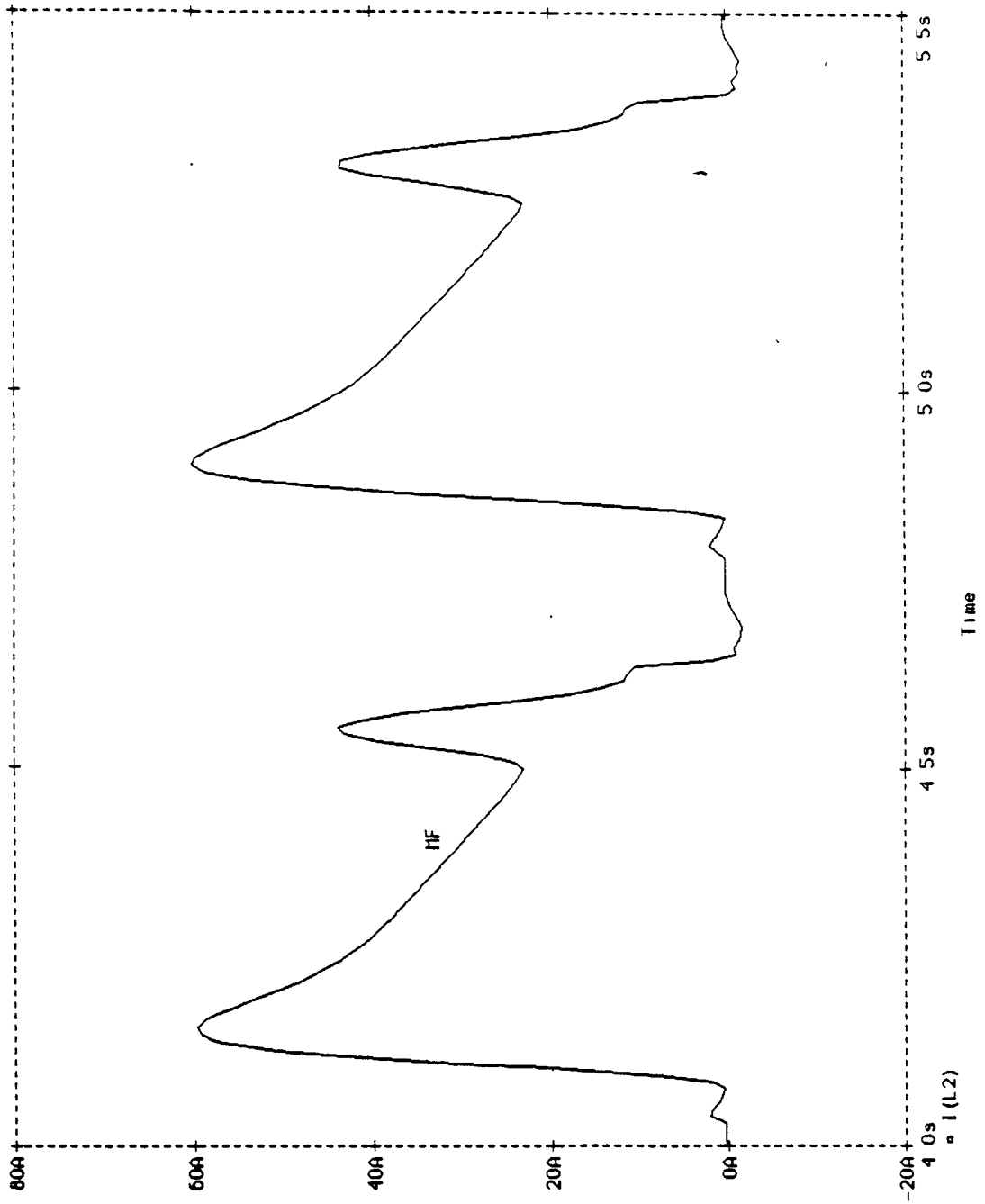
Figure 107

This models mod17a, mitral stenosis (x10), LVV
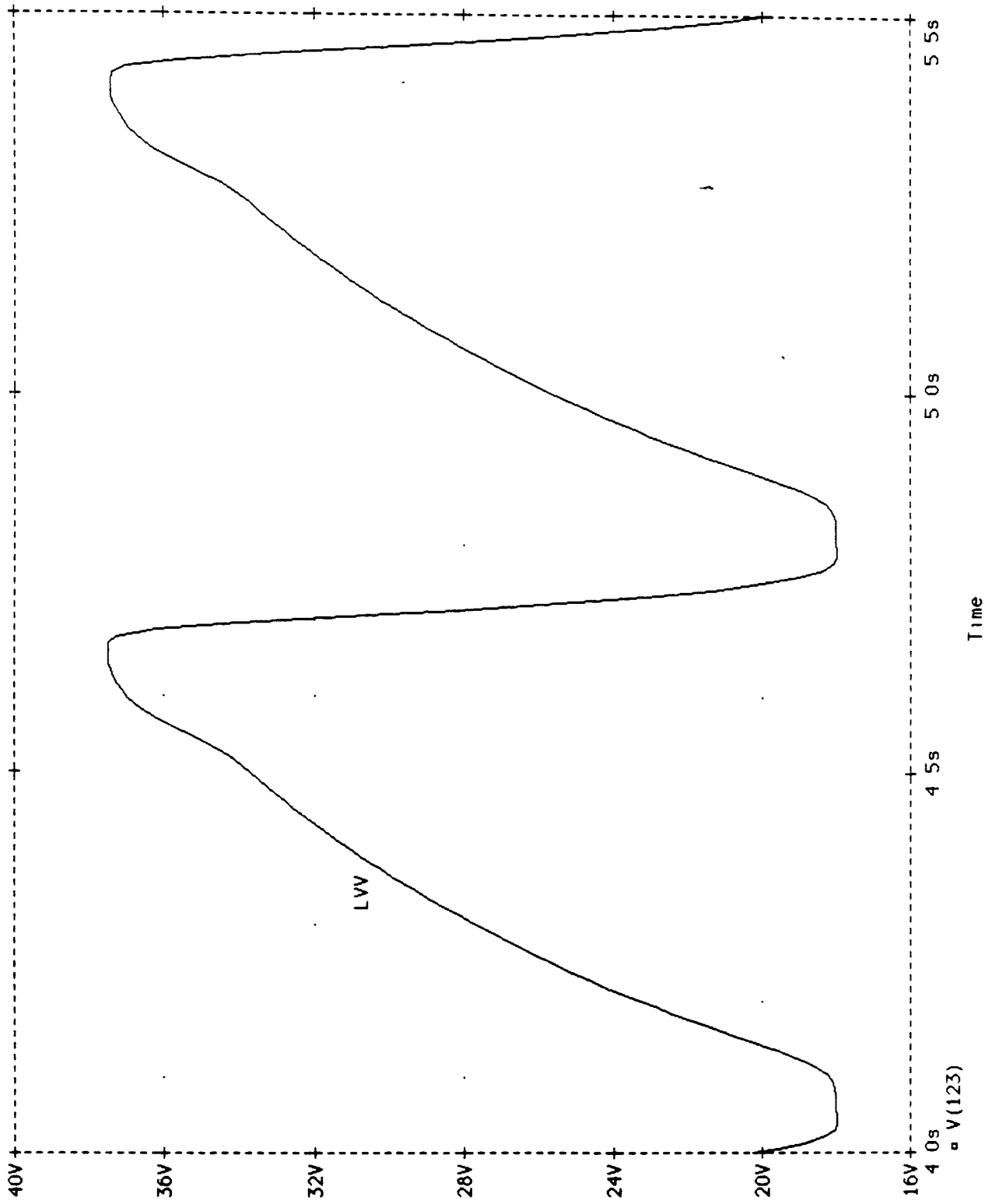
Figure 108

This models mod17a, mitral stenosis (x10), LAV

Figure 109

137

Figure 110

138

Figure 111

139

Figure 112

140
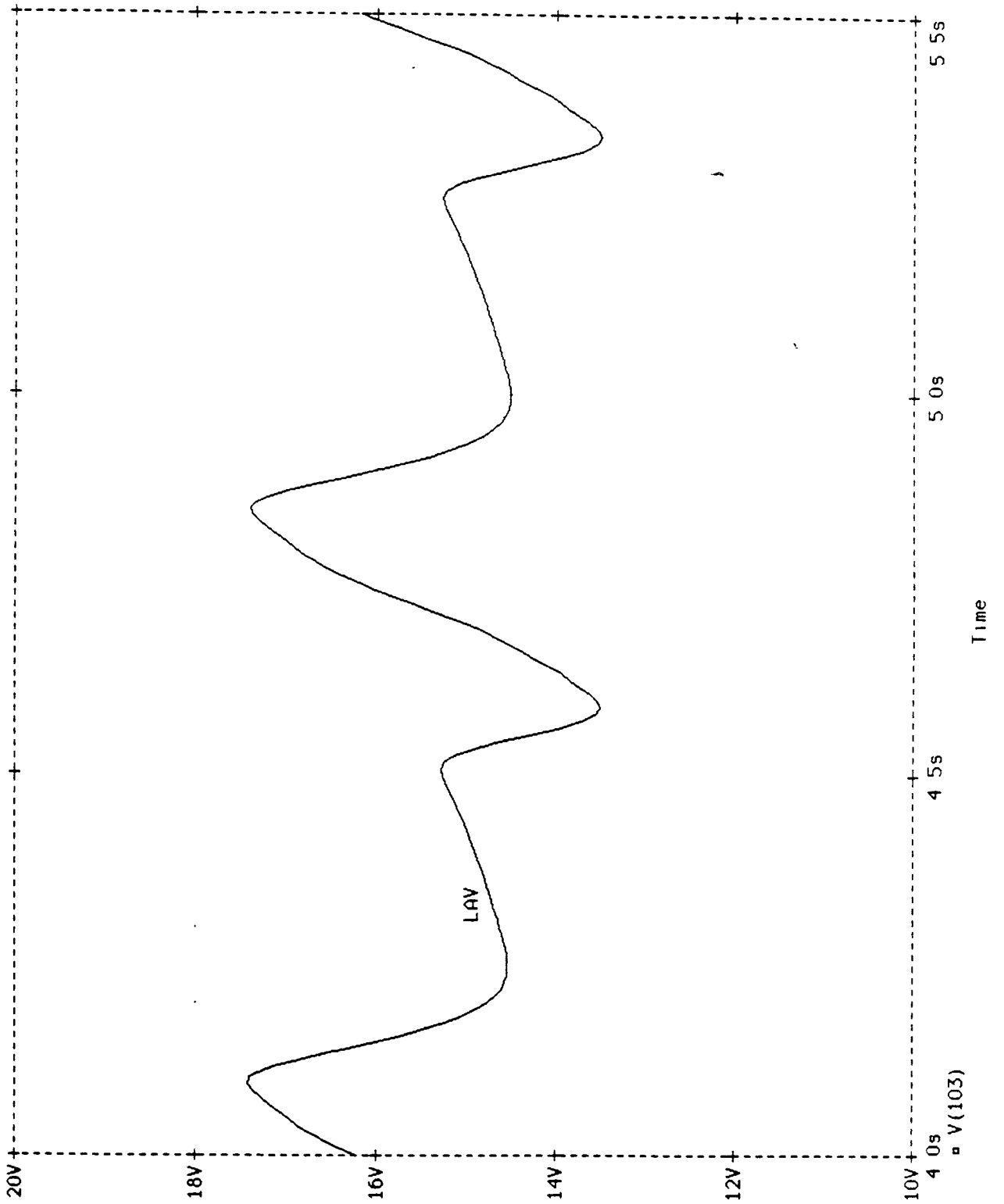
This models mod17a, no atrial kick, LAV
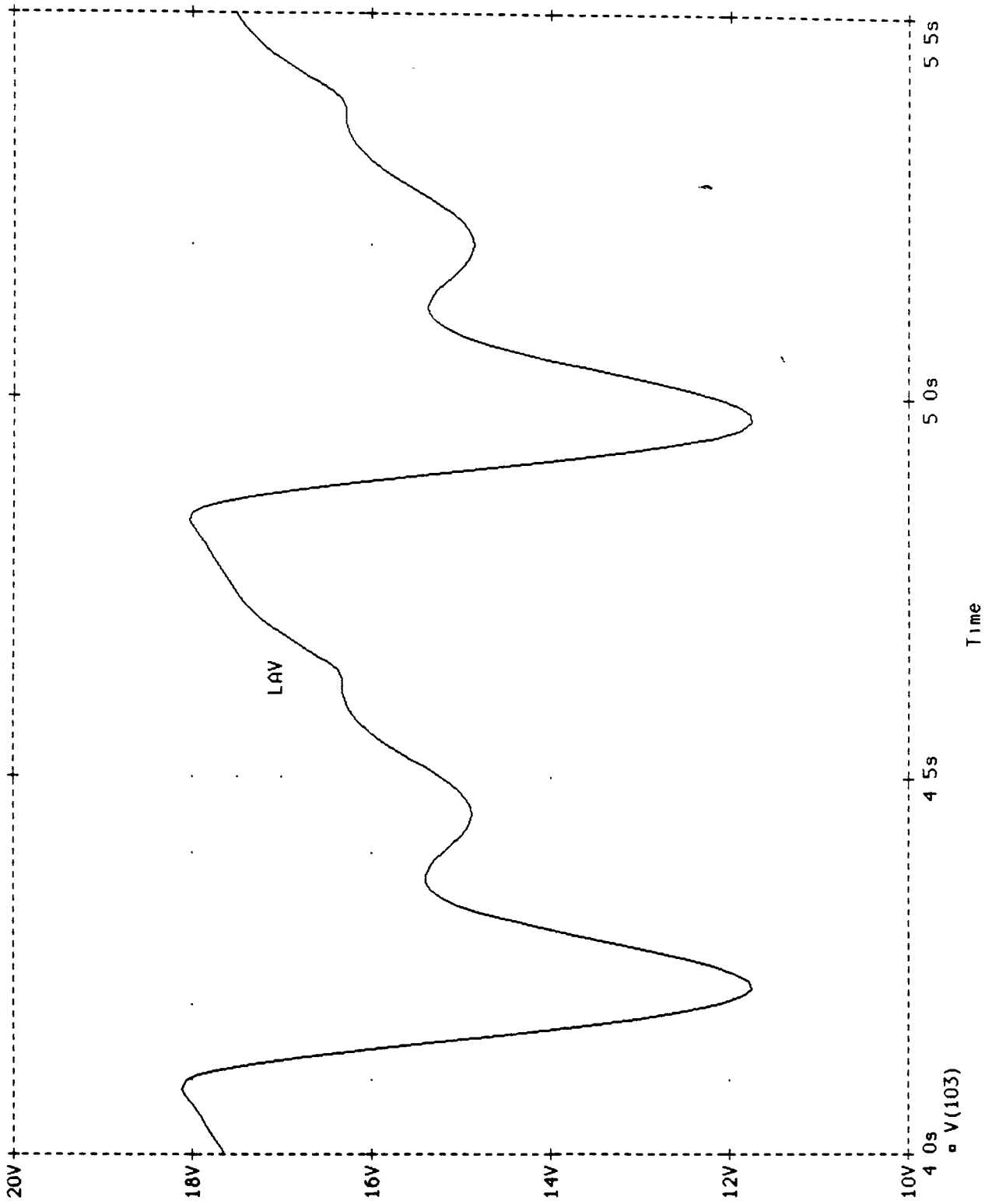
Figure 113

CHAPTER VIII

CONCLUSION:

In the introduction it was asserted that the goal of this thesis was two-fold. One of these goals included modification of the original Meisner program to be able to perform parameter vs. parameter runs in such a way that the output would be usable by a standard spreadsheet package and yield valuable graphs of how output parameters varied with input parameters. The methodology for this was presented in chapter five. Examples of graphs produced by QUATTRO PRO, the spreadsheet package chosen to do the plotting, were also provided in order to validate and demonstrate the success of the modification. Though this first goal was satisfactorily accomplished, there are some further modifications and improvements that could be done to this program. These include appending to the QuickBASIC program a section that would enable the entire set of original run parameters to be formatted so as to be stored in the same "bigfile.dat" as the the experimental output currently is, and sent to QUATTRO PRO. In addition, since QUATTRO PRO has the ability to plot three dimensional graphs, it would be useful if the QuickBASIC program could be further modified to enable the simultaneous variation of two different input parameters.

The second major goal of the thesis involved implementing the model in PSPICE. The lengthy process of this implementation was documented in chapter six and some very successful runs, attesting to the validity of the implementation, were presented in chapter seven. Now that it has been demonstrated that PSPICE can be used to implement this model, including

generating the required excitation functions and using them to control variable capacitors, it leaves opens the door for further improvements. Among the more important ones is figuring out some way to get the PSPICE program to run faster. It currently can take upwards of ten minutes for one run on a 386 with a 33 MHz clock. This is extremely slow and limits the number of experiments that can be performed. A second major improvement involves the ability to more readily vary the excitation functions. Although PSPICE does provide the ability to easily vary all the input parameters that were variable in the original QuickBASIC implementation, modifying an excitation function is a lot more difficult. The imprecise nature of the excitation functions causes that to be an area in which further research should and will be done, and thus to be able to vary them more easily is important.

Finally, everything done herein utilized, except for minor discrepancies, the existing Meisner model. Within that model there is room for modification and addition. These changes could be made in either or both PSPICE and Basic implementations, though for many of these changes it may initially be easier to implement them in PSPICE. Some possible modifications include adding more detail in areas that exist but were "neglected" the first time around, such as aortic inertance, as well as additions of entire new sections such as a right heart.

APPENDIX A

Complete QuickBasic Program

```
'$DYNAMIC
DECLARE SUB PLOTPV ()
DECLARE SUB PLOTT ()
DECLARE SUB JOFF (i!, OFFSET!, J!)
DECLARE SUB printcontrol ()
DECLARE SUB printall ()
DECLARE SUB ANALYSIS ()
DECLARE SUB SETOUT ()
DECLARE SUB SETVENTION ()
DECLARE SUB INITIALIZATION ()
DECLARE SUB SETPAR ()
DECLARE SUB parnames ()
DECLARE SUB outnames ()
DECLARE SUB reiterate (reit, sv, ev, st)
DECLARE SUB setven2 (st, sv, ev, reit1, paramchg)
DECLARE SUB ITERATION (istep)
DECLARE SUB SAVEITER ()
DECLARE SUB SAVCON ()
DECLARE SUB INTERVENTION ()
DECLARE SUB activation ()
COMMON SHARED PLOT, id$, NUMPAR, it, CI, mfww, INRTOT, L8, R8, E8, R0, E0, R1, L
COMMON SHARED MV, VF, avf, AF, v0, V8, V1, V2, P3, P5, P1, P2, P3ST, v0ST, V8ST,
COMMON SHARED RVP, paf, F80, P0, P8, MVST, sv, ev, st, reit, reit1, outprt, part
COMMON SHARED paramchg, cj
DIM SHARED K1(1000), K2(1000), VD1(1000), q11(1000)
DIM SHARED parvpar(40, 50), nmq$(50)
DIM SHARED nm$(50), prm(50), CHNGD(50), INR(50), inrval(50), nmp$(50), NMI$(50),
DIM SHARED YLAV(1000, 1 TO 2), YLAP(1000, 1 TO 2), ylvv(1000, 1 TO 2), YLVP(1000
DIM SHARED YPVF(1000, 1 TO 2), YF80(1000, 1 TO 2), YPAF(1000, 1 TO 2), YP0(1000,
DIM SHARED LVEDV(2), LAPMX(2), LAPMEN(2), LAPMED(2), LAPMES(2), LAPRE(2), LALVMD
DIM SHARED pco(2), FV(2), FVA(2), FVA1(2), FVPCO(2), FVPMF(2), TMFA(2), TMFA1(2)
'*******************************************************************************
'*****************************   MOD17A   **************************************
'*******************************************************************************
'**************************  BY J.S. MEISNER  **********************************
'***********************  MODIFIED BY A.Z. ZIVOTOFSKY  *************************
'************************* NOVEMBER 1991  **************************************
'*******************************************************************************
'
'LEFT HEART MODELING PROGRAM FOR SIMULATION OF PHYSIOLOGIC EXPERIMENTS.
'
'THIS REPRESENTS A MODIFICATION OF PROGRAMS: AMOD16 AND BMOD16, BOTH
'COPYRIGHT 1987, J.S. MEISNER.
'
'MODIFICATIONS INCLUDE:   * VARIABLE TIME CONSTANT OF LV RELAXATION
'                         * LOWER LIMIT OF HEART RATE = 40
'                         * ON-SCREEN PLOT OF VARIABLES VERSUS TIME
'                         * ABILITY TO CHANGE HR OR PR AS INTERVENTIONS
'                         * ABILITY TO PLOT RESULTS ON HP LASER PRINTER
'                         * ABILITY TO DO PARAMETER VS PARAMETER RUNS

CALL parnames

CALL outnames

'Master do-while loop to rerun program

DO

'INITIAL CONDITIONS
```

```
CALL INITIALIZATION

'SET PARAMETERS
CALL SETPAR

'option to vary avariable over a range
CALL reiterate(reit, sv, ev, st)

'SET INTERVENTIONS (IF ANY)
IF reit <> 1 THEN
        CALL SETVENTION

        'SET OUTPUT OPTIONS
        CALL SETOUT
END IF

IF reit = 1 THEN
        paramchg = sv
        FOR drt = 1 TO 1500: q11(drt) = 0: NEXT
        CLS
        PRINT "running the control before the reiterations"
END IF

'LA/LV ACTIVATION FUNCTION SETUP
CALL activation

'CONTROL MODEL RUN FOR ccycle CYCLES/STORE ccycle INTO ARRAY 1 (CONTROL)
CI = 1
mfww = 0
IF OUTSCR = 1 THEN
        SCREEN 8
        COLOR 8
        LOCATE 1, 25: PRINT "CONTROL Cycle # "
        LINE (30, 0)-(30, 200): LINE (30, 179)-(639, 179): LINE (30, 100)-(639,
        LINE (0, 25)-(29, 25): LINE (0, 129)-(29, 129): PSET (0, 32): PRINT "100
END IF
FOR it = 1 TO ccycles
COUNTER = 3
        IF OUTSCR = 1 THEN LOCATE 1, 43: PRINT it
        FOR istep = 1 TO RR
                CALL ITERATION(istep)
                IF COUNTER < 3 THEN
                        COUNTER = COUNTER + 1
                ELSEIF it = ccycles THEN
                        COUNTER = 0
                        y = INT(609 / 1500 * istep)
                        X1 = 100 - INT(avf * .75)
                        IF X1 > 199 THEN X1 = 199
                        IF X1 < 0 THEN X1 = 0
                        X2 = 179 - INT(P1 * 5)
                        IF X2 > 199 THEN X2 = 199
                        IF X2 < 104 THEN X2 = 104
                        X3 = 179 - INT(P2 * 5)
                        IF X3 > 199 THEN X3 = 199
                        IF X3 < 104 THEN X3 = 104
                        IF OUTSCR = 1 THEN
                                PSET (y + 30, X1), 9
                                PSET (y + 30, X2), 9
                                PSET (y + 30, X3), 9
                        END IF
```

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```
                     END IF
           NEXT istep
NEXT it

'CONTROL RUN NO-ATRIAL-CONTRACTION CYCLE/STORE MITRAL FLOW RESULT INTO ARRAY 1
'FIRST, RESET ATRIAL ACTIVATION FUNCTIONS K1,VD1
'NOTE: FUNCTION IS RESET ONLY AFTER POSSIBLE SECOND PORTION OF AC
IF PR > -150 AND PR < 50 THEN
           FOR i = (51 - PR) TO RR
                      K1(i) = K10
                      VD1(i) = VD10
           NEXT i
           ELSE
           FOR i = 1 TO RR
                      K1(i) = K10
                      VD1(i) = VD10
           NEXT i
END IF

CI = 1
mfww = 1
           FOR istep = 1 TO RR
                      CALL ITERATION(istep)
           NEXT istep

'RESET PRE-NO-ATRIAL-CONTRACTION CYCLE 10
           V1 = YLAV(1, 1)
           P1 = YLAP(1, 1)
           V2 = ylvv(1, 1)
           P2 = YLVP(1, 1)
           AF = YAF(1, 1)
           avf = YMF(1, 1)
           VF = YPVF(1, 1)
           F80 = YF80(1, 1)
           paf = YPAF(1, 1)
           P0 = YP0(1, 1)
           P8 = YP8(1, 1)
           P5 = YP5(1, 1)
           P3 = P3ST
           v0 = v0ST
           V8 = V8ST
           RVP = rvpST
           MV = MVST

'ANALYSIS OF CONTROL
CI = 1
CALL ANALYSIS


IF reit = 1 THEN CALL SAVCON

'CHANGE INTERVENTIONAL PARAMETERS AND RERUN LA/LV ACTIVATION FUNCTION

cj = o
DO

IF reit = 1 THEN
       CALL setven2(sv, st, ev, reit1, paramchg)
END IF
```

```
IF INRTOT > 0 THEN
        CALL INTERVENTION
        CALL activation

'INTERVENTION MODEL RUN FOR icycles CYCLES
CI = 2
mfww = 0
IF OUTSCR = 1 THEN
        COLOR 8
        LOCATE 1, 25: PRINT "Intervention Cycle #                         "
        LINE (30, 0)-(30, 200): LINE (30, 179)-(639, 179): LINE (30, 100)-(639,
END IF
FOR it = 1 TO icycles
        COUNTER = 3
        IF OUTSCR = 1 THEN LOCATE 1, 56: PRINT it
        FOR istep = 1 TO RR
                CALL ITERATION(istep)
                IF COUNTER < 3 THEN
                        COUNTER = COUNTER + 1
                ELSE
                        COUNTER = 0
                        y = INT(609 / 1500 * istep)
                        X1 = 100 - INT(avf * .75)
                        IF X1 > 199 THEN X1 = 199
                        IF X1 < 0 THEN X1 = 0
                        X2 = 179 - INT(P1 * 5)
                        IF X2 > 199 THEN X2 = 199
                        IF X2 < 104 THEN X2 = 104
                        X3 = 179 - INT(P2 * 5)
                        IF X3 > 199 THEN X3 = 199
                        IF X3 < 104 THEN X3 = 104
                        IF OUTSCR = 1 THEN
                                PSET (y + 30, X1), 13
                                PSET (y + 30, X2), 13
                                PSET (y + 30, X3), 13
                        END IF
                END IF
        NEXT istep
NEXT it

'RESET INTERVENTION PRE-NO-ATRIAL-CONTRACTION CYCLE 10
        V1 = YLAV(1, 2)
        P1 = YLAP(1, 2)
        V2 = ylvv(1, 2)
        P2 = YLVP(1, 2)
        AF = YAF(1, 2)
        avf = YMF(1, 2)
        VF = YPVF(1, 2)
        F80 = YF80(1, 2)
        paf = YPAF(1, 2)
        P0 = YP0(1, 2)
        P8 = YP8(1, 2)
        P5 = YP5(1, 2)
        P3 = P3ST
        v0 = v0ST
        V8 = V8ST
        RVP = rvpST
        MV = MVST

'RUN NO-ATRIAL-CONTRACTION CYCLE/STORE MITRAL FLOW RESULT INTO ARRAY 1
```

```
'FIRST, RESET ATRIAL ACTIVATION FUNCTIONS K1,VD1
'NOTE: FUNCTION IS RESET ONLY AFTER POSSIBLE SECOND PORTION OF AC
IF PR > -150 AND PR < 50 THEN
        FOR i = (51 - PR) TO RR
                K1(i) = K10
                VD1(i) = VD10
        NEXT i
        ELSE
        FOR i = 1 TO RR
                K1(i) = K10
                VD1(i) = VD10
        NEXT i
END IF

CI = 2
mfww = 1
        FOR istep = 1 TO RR
                CALL ITERATION(istep)
        NEXT istep
END IF


'ANALYSIS OF INTERVENTION (IF DONE)
IF INRTOT > 0 THEN
        CI = 2
        CALL ANALYSIS
END IF

'PRINTER ANALYSIS OF CONTROL/INTERVENTION, IF REQUESTED
IF outprt = 1 THEN
        IF INRTOT < 1 THEN
                CALL printcontrol
        ELSE
                CALL printall
        END IF
END IF
'PLOTTER OUTPUT OF CONTROL/INTERVENTION VS TIME, IF REQUESTED
IF PLTVAR = 1 OR PLTVAR = 2 THEN
        PLOT = 1
        CI = 1
        CALL PLOTT
        IF INRTOT > 0 THEN
                PLOT = 2
                CI = 2
                CALL PLOTT
        END IF

ELSEIF PLTVAR = 3 OR PLTVAR = 4 THEN
'PV LOOP ROUTINE
        CI = 1
        CALL PLOTPV
        IF INRTOT > 0 THEN
                IF PLTVAR = 4 THEN
                        LOCATE 23, 1: PRINT ;
                        LOCATE 23, 1: INPUT "Change plotter paper now and press
                END IF
                CI = 2
                CALL PLOTPV
        END IF
END IF
```

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```
       IF reit = 1 THEN
               cj = cj + 1
               CALL SAVEITER
               IF sv <= ev AND st > 0 THEN
                       'PRINT "sv<=ev"; sv, ev;
                       paramchg = paramchg + st
                       IF paramchg > ev THEN reit = 0
                       'PRINT paramchg, reit
               ELSEIF sv > ev AND st < 0 THEN
                       'PRINT "sv>ev"; sv, ev;
                       paramchg = paramchg + st
                       IF paramchg < ev THEN reit = 0
                       'PRINT paramchg, reit
               ELSE
                       PRINT "will not end, step is wrong sign"
                       EXIT DO
               END IF
END IF
LOOP WHILE reit = 1
IF cj > 0 THEN
       CLS
       QQ$ = CHR$(34)
       'QQ$ is now a double quote
       OPEN "bigfile.dat" FOR OUTPUT AS #1
       PRINT "this run varied  "; nm$(reit1)
       PRINT #1, QQ$; "this run varied"; QQ$; QQ$; nm$(reit1); QQ$; QQ$; "from"
       PRINT #1, QQ$; "output"; QQ$; QQ$; "control"; QQ$
       PRINT #1, QQ$; ""; QQ$;
       FOR y = 0 TO 35
       FOR x = 0 TO cj
               PRINT parvpar(y, x);
               PRINT #1, USING "###.######"; parvpar(y, x);
               PRINT #1, ",";
               IF x = cj THEN WRITE #1, ""
       NEXT
       PRINT
       PRINT #1, QQ$; nmq$(y + 1); QQ$;
       NEXT
       CLOSE #1
END IF

LOCATE 23, 1
DO
       INPUT "When you are done, enter 1 to run program again, or 0 for DOS (0)
LOOP WHILE atorerun < 0 OR atorerun > 1

LOOP WHILE atorerun = 1
END

REM $STATIC
SUB activation
'DEVELOPMENT OF NEW ACTIVATION FUNCTIONS - WITH EXPONENTIAL LV DEACT.
pi = 3.141593
IF PR < -150 THEN PR = RR + PR

'Generate LA elastance and dead volume
IF PR <= 50 THEN
               FOR i = 1 TO (51 - PR)
                       x = (149 + PR + i) * 2 * pi / 200 + 3 * pi / 2
                       K1(i) = K10 + (SIN(x) + 1) * (EMAXLA - K10) / 2
```

```
                          x = (149 + PR + i) * pi / 200
                          VD1(i) = VD10 - SIN(x) * 2
               NEXT i
               FOR i = (51 - PR) TO (RR - 150 - PR)
                          K1(i) = K10
                          VD1(i) = VD10
               NEXT i
               FOR i = (RR - 149 - PR) TO RR
                          x = (i - (RR - 149 - PR)) * 2 * pi / 200 + 3 * pi / 2
                          K1(i) = K10 + (SIN(x) + 1) * (EMAXLA - K10) / 2
                          x = (i - (RR - 149 - PR)) * pi / 200
                          VD1(i) = VD10 - SIN(x) * 2
               NEXT i
      ELSE
               FOR i = 1 TO (RR - 150 - PR)
                          K1(i) = K10
                          VD1(i) = VD10
               NEXT i
               FOR i = (RR - 150 - PR) TO (RR - 150 - PR + 200)
                          x = (i - (RR - 149 - PR)) * 2 * pi / 200 + 3 * pi / 2
                          K1(i) = K10 + (SIN(x) + 1) * (EMAXLA - K10) / 2
                          x = (i - (RR - 149 - PR)) * pi / 200
                          VD1(i) = VD10 - SIN(x) * 2
               NEXT i
               FOR i = (RR - 149 - PR + 200) TO RR
                          K1(i) = K10
                          VD1(i) = VD10
               NEXT i
      END IF

'Generate LV elastance
      FOR i = 1 TO (RR - 150)
                 K2(i) = emaxlv * EXP((-1 * (i - 1)) / tau)
      NEXT i
      FOR i = (RR - 149) TO RR
                 x = 3 * pi / 2 + (i - (RR - 149)) * 2 * pi / 300
                 K2(i) = emaxlv / 2 * (SIN(x) + 1)
      NEXT i

'Generate pulmonary flow function if Cardiac Output (Cout) Specified
IF cout > 0 THEN
      hr = 60000 / RR
      FOR i = 1 TO 150
                 x = pi / 2 + (i / 150 * pi / 2)
                 q11(i) = SIN(x) * pi / 2 / .3 * cout / hr
                 NEXT i

      FOR i = 151 TO RR - 151
                 q11(i) = 0
      NEXT i

      FOR i = (RR - 150) TO RR
                 x = (i - (RR - 150)) / 150 * pi / 2
                 q11(i) = SIN(x) * pi / 2 / .3 * cout / hr
      NEXT i
END IF

END SUB

SUB ANALYSIS
```

```
'Subroutine for Analysis of control or intervention (CI=1/2)
i = 0
DO
        i = i + 1
LOOP WHILE YLAP(i, CI) < YLVP(i, CI) AND i < RR
IF i >= RR THEN BEEP: PRINT "ERROR 101": STOP
pco(CI) = YLAP(i, CI)
TX(CI) = i
TX = i
LAPMEN = 0
FOR i = 1 TO RR
        LAPMEN = LAPMEN + YLAP(i, CI)
NEXT i
LAPMEN(CI) = LAPMEN / RR
LAPMED = 0
LALVMD = 0
FOR i = TX TO RR - 150
        LAPMED = LAPMED + YLAP(i, CI)
        LALVMD = LALVMD + YLAP(i, CI) - YLVP(i, CI)
NEXT i
LAPMED(CI) = LAPMED / (RR - 150 - TX + 1)
LALVMD(CI) = LALVMD / (RR - 150 - TX + 1)
LAPMES = 0
FOR i = 1 TO TX
        LAPMES = LAPMES + YLAP(i, CI)
NEXT i
FOR i = RR - 150 TO RR
        LAPMES = LAPMES + YLAP(i, CI)
NEXT i
LAPMES(CI) = LAPMES / (TX + 150)
lvpmn = 100

i = TX
DO
        i = i + 1
LOOP WHILE YLVP(i + 1, CI) < YLVP(i, CI) AND i < RR
IF i >= RR THEN BEEP: PRINT "Error 102": STOP
lvpmn(CI) = YLVP(i, CI)
TLVPMN(CI) = i - TX

i = TX
DO
        i = i + 1
LOOP WHILE (YLAP(i + 1, CI) - YLVP(i + 1, CI)) > (YLAP(i, CI) - YLVP(i, CI)) AND
IF i >= RR THEN BEEP: PRINT "Error 103": STOP
LALVMX(CI) = YLAP(i, CI) - YLVP(i, CI)
TLALVMX(CI) = i - TX

i = TX + 10
DO
        i = i + 1
LOOP WHILE YMF(i + 1, CI) > YMF(i, CI) AND i < RR
IF i >= RR THEN BEEP: PRINT "Error 104": STOP
PMF(CI) = YMF(i, CI)
TPMF(CI) = i - TX
LVEDP(CI) = YLVP(RR - 150, CI)
LVEDV(CI) = ylvv(RR - 150, CI)
FVPMF(CI) = ylvv(TPMF(CI) + TX, CI) - ylvv(TX, CI)
FVA1(CI) = ylvv(RR - 150 - PR, CI) - ylvv(TX, CI)
MFA1(CI) = YMF(RR - 150 - PR, CI)
```

```
i = RR - 150 - PR + 25
DO
        i = i + 1
LOOP WHILE i < RR AND (YMF(i + 1, CI) > YMF(i, CI) OR YMF(i, CI) < .2 * PMF(CI))
IF i >= RR THEN
        MFA(CI) = 1
        TMFA(CI) = 1
        TMFA(CI) = 1
        LPRINT "UNABLE TO FIND MF-A"
ELSE
        MFA(CI) = YMF(i, CI)
        TMFA(CI) = i - TX
        TMFA = i - TX
END IF

i = RR - 150 - PR + 25
DO
        i = i + 1
LOOP WHILE YMF(i, CI) > 0 AND i < RR
IF i >= RR THEN
        TMFEND = RR - 150 - TX
        TMFEND(CI) = TMFEND
        BEEP: LPRINT "Unable to find MFEND"
ELSE
        TMFEND = i - TX
        TMFEND(CI) = i - TX
END IF

MFASUB(CI) = .01
MFASUB1(CI) = .01
FOR i = (RR - 150 - PR) TO (TMFEND + TX - 1)
        MFASUB(CI) = MFASUB(CI) + .0005 * (ymfa(i, CI) + ymfa(i + 1, CI))
NEXT i
FOR i = (TMFEND + TX) TO (RR - 150)
        MFASUB1(CI) = MFASUB1(CI) + .0005 * (ymfa(i, CI) + ymfa(i + 1, CI))
NEXT i
FVA(CI) = ylvv(TMFEND + TX, CI) - ylvv(RR - 150 - PR, CI) - MFASUB(CI)
TMFA1(CI) = RR - 150 - PR - TX
DFPP(CI) = RR - 150 - TX

i = RR - 120
DO
        i = i + 1
LOOP WHILE YLVP(i + 1, CI) > YLVP(i, CI) AND i < RR
IF i >= RR THEN
        PLVP(CI) = 1
        LPRINT "Unable to find PLVP"
ELSE
        PLVP(CI) = YLVP(i; CI)
END IF

LAPRE(CI) = YLAV(RR - 150 - PR, CI)

i = RR - 150 - PR
DO
        i = i + 1
LOOP WHILE YLAP(i + 1, CI) > YLAP(i, CI) AND i < RR
IF i >= RR THEN
        TLAPMX(CI) = 1
```

```
              LAPMX(CI) = 1
              LPRINT "Unable to find LAP-A"
ELSE
              LAPMX(CI) = YLAP(i, CI)
              TLAPMX(CI) = 1 - TX
END IF
FV(CI) = ylvv(TMFEND + TX, CI) - ylvv(TX, CI)
LVPAMN(CI) = YLVP(RR - 150 - PR, CI)

END SUB

SUB INITIALIZATION
MV = 1
VF = 10
avf = 0
AF = 10
v0 = 30
V8 = 20
V1 = 20
V2 = 40
P3 = .001
P5 = 60
paf = 10
F80 = 10
P0 = 10
P1 = 10
P2 = 50
P8 = 11
END SUB

SUB INTERVENTION
FOR i = 1 TO NUMPAR
        IF INR(i) = 1 THEN
                    SELECT CASE i
                    CASE 1
                    L8 = inrval(i)
                    CASE 2
                    R8 = inrval(i)
                    CASE 3
                    E8 = inrval(i)
                    CASE 4
                    R0 = inrval(i)
                    CASE 5
                    E0 = inrval(i)
                    CASE 6
                    R1 = inrval(i)
                    CASE 7
                    L1 = inrval(i)
                    CASE 8
                    R2 = inrval(i)
                    CASE 9
                    L2 = inrval(i)
                    CASE 10
                    E3 = inrval(i)
                    CASE 11
                    R3 = inrval(i)
                    CASE 12
                    R4 = inrval(i)
                    CASE 13
                    R5 = inrval(i)
```

```
                              CASE 14
                              E5 = inrval(i)
                              CASE 15
                              K10 = inrval(i)
                              CASE 16
                              VD10 = inrval(i)
                              CASE 17
                              VD2 = inrval(i)
                              CASE 18
                              PINF = inrval(i)
                              CASE 19
                              R9 = inrval(i)
                              CASE 20
                              ALPHA = inrval(i)
                              CASE 21
                              ALV = inrval(i)
                              CASE 22
                              EMAXLA = inrval(i)
                              CASE 23
                              RMR = inrval(i)
                              CASE 24
                              LMR = inrval(i)
                              CASE 25
                              DMR = inrval(i)
                              CASE 26
                              ARR = inrval(i)
                              CASE 27
                              MVCLOSE = inrval(i)
                              CASE 28
                              PR = inrval(i)
                              CASE 29
                              RR = inrval(i)
                              CASE 30
                              emaxlv = inrval(i)
                              CASE 31
                              pmaxrv = inrval(i)
                              CASE 32
                              tau = inrval(i)
                              CASE 33
                            - REM change in control cycles not allowed
                              CASE 34
                              REM change in intervention cycles not alllowed
                              CASE 35
                              cout = inrval(i)
                              END SELECT
                  END IF
      NEXT i

      END SUB

      SUB ITERATION (istep)
      'Differentiation/Iteration  Subroutine

      IF paf > 0 THEN
              DPAFDT = (RVP - P8 - paf * R8) / L8
      ELSE
              DPAFDT = (RVP - P8) / L8
              IF DPAFDT < 0 THEN DPAFDT = 0
      END IF
      DV8DT = paf - F80
```

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```
DV0DT = F80 - VF
DVFDT = (P0 - P1 - VF * R1) / L1
DV1DT = VF - avf
IF MV = 1 AND avf < 0 THEN MV = 0
IF MV = 0 AND P3 >= 0 AND avf > 0 THEN MV = 1
IF RMR > 0 AND MV = 0 THEN
        DAVFDT = (P1 - P2 + avf * avf * (RMR - DMR * V2 / 50 * RMR)) / LMR
        DP3DT = 0
        P3 = .001
ELSEIF MV = 1 THEN
        DAVFDT = (P1 - P2 - avf * avf * R2) / L2
        DP3DT = 0: P3 = .001
        ELSE
                avf = (P1 - P2 - P3) / (R2 + R3)
                DAVFDT = 0
                DP3DT = E3 * avf
END IF
DV2DT = avf - AF
DP5DT = E5 * (AF - P5 / R5)
RVP = pmaxrv * K2(istep) / emaxlv
IF cout > 0 THEN
        paf = q11(istep)
ELSE
        paf = paf + DPAFDT * .001
END IF

V8 = V8 + DV8DT * .001
v0 = v0 + DV0DT * .001
VF = VF + DVFDT * .001
P8 = E8 * V8
P0 = E0 * v0
F80 = (P8 - P0) / R0
V1 = V1 + DV1DT * .001
avf = avf + DAVFDT * .001
P3 = P3 + DP3DT * .001
V2 = V2 + DV2DT * .001
IF ARR > 0 AND P2 < P5 THEN
        AF = (P2 - P5) / ARR
ELSE
        AF = (P2 - P5) / R4
        IF AF < 0 THEN AF = 0
END IF
IF AF < 0 THEN AF = 0
P5 = P5 + DP5DT * .001
P1 = K1(istep) * (V1 - VD1(istep))
P2 = ALV * (EXP(ALPHA * V2) - 1) + K2(istep) * (V2 - VD2) + R9 * avf + PINF

IF (it = ccycles AND CI = 1) OR (it = icycles AND CI = 2) THEN
        YLAV(istep, CI) = V1
        YLAP(istep, CI) = P1
        ylvv(istep, CI) = V2
        YLVP(istep, CI) = P2
        YAF(istep, CI) = AF
        YMF(istep, CI) = avf
        YPVF(istep, CI) = VF
        YF80(istep, CI) = F80
        YPAF(istep, CI) = paf
        YP0(istep, CI) = P0
        YP8(istep, CI) = P8
        YP5(istep, CI) = P5
```

```
                    IF istep = 1 THEN
                            P3ST = P3
                            v0ST = v0
                            V8ST = V8
                            rvpST = RVP
                            MVST = MV
                    END IF
            END IF

            IF mfww = 1 THEN ymfa(istep, CI) = avf

            END SUB

            SUB JOFF (i, OFFSET, J)
            J = (i - OFFSET) / 3
            END SUB

            SUB outnames
            nmq$(1) = "PCO": nmq$(2) = "LVPmin": nmq$(3) = "LVEDP": nmq$(4) = "LVEDV"
            nmq$(5) = "EF": nmq$(6) = "(LAP-LVP)max": nmq$(7) = "PLVP"
            nmq$(8) = "M-(LA-LV)-diast": nmq$(9) = "MLAP": nmq$(10) = "MLAP-diast"
            nmq$(11) = "MLAP-syst": nmq$(12) = "LVP-a-min": nmq$(13) = "LAP-a-max"
            nmq$(14) = "LAV-a-min"
            nmq$(15) = "PMF": nmq$(16) = "MF-a-min": nmq$(17) = "MF-a-max"
            nmq$(18) = "MF-a-max/PMF"
            nmq$(19) = "FV": nmq$(20) = "FV-PMF": nmq$(21) = "FV-a-min": nmq$(22) = "FVA(Yel
            nmq$(23) = "FVA(clin)": nmq$(24) = "FV-lost after MF=0"
            nmq$(25) = "FVA(Y)/FV": nmq$(26) = "FVA(Y)-FVlost/FV"
            nmq$(27) = "FV-PMF/FV"
            nmq$(28) = "t-LVPmin": nmq$(29) = "t-(LAP-LVP)max": nmq$(30) = "t-PMF"
            nmq$(31) = "t-MF-a-min": nmq$(32) = "t-MF-a-max"
            nmq$(33) = "DFP-f": nmq$(34) = "DFP-p": nmq$(35) = "DFP-f/RR"


            END SUB


            SUB parnames
            'Subroutine for Parameter and Initial Condition Name Set-Up

            nmp$(1) = "L8": nmp$(2) = "R8": nmp$(3) = "E8": nmp$(4) = "R0"
            nmp$(5) = "E0": nmp$(6) = "R1": nmp$(7) = "L1": nmp$(8) = "R2"
            nmp$(9) = "L2": nmp$(10) = "E3": nmp$(11) = "R3": nmp$(12) = "R4"
            nmp$(13) = "R5": nmp$(14) = "E5": nmp$(15) = "K10": nmp$(16) = "VD10"
            nmp$(17) = "VD2": nmp$(18) = "Pinf": nmp$(19) = "R9": nmp$(20) = "ALPHA"
            nmp$(21) = "ALV": nmp$(22) = "Emax-LA": nmp$(23) = "MR-R": nmp$(24) = "MR-L"
            nmp$(25) = "MR-LVVdep": nmp$(26) = "AR-R": nmp$(27) = "MVclosed"
            nmp$(28) = "PR": nmp$(29) = "V-V": nmp$(30) = "Emax-LV": nmp$(31) = "Pmax-RV": n
            nmp$(33) = "#Con": nmp$(34) = "#Int": nmp$(35) = "CO"
            NMI$(1) = "MFic": NMI$(2) = "VFic": NMI$(3) = "AVFic": NMI$(4) = "AFic"
            NMI$(5) = "V0ic": NMI$(6) = "V8ic": NMI$(7) = "V1ic": NMI$(8) = "V2ic"
            NMI$(9) = "DUMMY": NMI$(10) = "P3ic": NMI$(11) = "P5ic"

            END SUB

            SUB PLOTPV
            'Subroutine to Plot P-V Loops    LA and LV
            OPEN "COM1:9600,S,7,1,RS,CS65000,DS,CD" FOR RANDOM AS #1
            PRINT #1, "SP1;IP500,500,4500,6000;SC100,0,0,50;PU100,0;PD0,0;PD0,50;PU;"
            PRINT #1, "PU"; : PRINT #1, USING "###.##"; YLVP(1, CI); : PRINT #1, ","; : PRIN
            FOR i = 1 TO RR
```

```
        PRINT #1, "PD"; : PRINT #1, USING "####.####"; YLVP(i, CI); : PRINT #1,
NEXT i
PRINT #1, "PU;"
PRINT #1, "SP1;IP5500,500,9500,6000;SC20,0,0,50;PU20,0;PD0,0;PD0,50;PU;"
PRINT #1, "PU"; : PRINT #1, USING "###.##"; YLAP(1, CI); : PRINT #1, ","; : PRIN
FOR i = 1 TO RR
        PRINT #1, "PD"; : PRINT #1, USING "####.####"; YLAP(i, CI); : PRINT #1,
NEXT i
PRINT #1, "PU;"
CLOSE #1

END SUB

SUB PLOTT
'Subroutine to Plot Data vs. Time
nm$(1) = "L8    "
nm$(2) = "R8    "
nm$(3) = "E8    "
nm$(4) = "R0    "
nm$(5) = "E0    "
nm$(6) = "R1    "
nm$(7) = "L1    "
nm$(8) = "R2    "
nm$(9) = "L2    "
nm$(10) = "E3    "
nm$(11) = "R3    "
nm$(12) = "R4    "
nm$(13) = "R5    "
nm$(14) = "E5    "
nm$(15) = "K10   "
nm$(16) = "VD10  "
nm$(17) = "VD2   "
nm$(18) = "Pinf  "
nm$(19) = "R9    "
nm$(20) = "ALPHA"
nm$(21) = "Acoef"
nm$(22) = "EmxLA"
nm$(23) = "MR-R  "
nm$(24) = "MR-I  "
nm$(25) = "MR-D  "
nm$(26) = "AR-R  "
nm$(27) = "MV 0  "
nm$(28) = "PR    "
nm$(29) = "RR    "
nm$(30) = "EmxLV"
nm$(31) = "PmxRV"
nm$(32) = "tau"


OPEN "COM1:9600,S,7,1,RS,CS65000,DS,CD" FOR RANDOM AS #1
'Separate windows are used for each variable
PRINT #1, "SP1;"
IF PLOT = 2 AND PLTVAR = 1 THEN
        OFFSET = RR * 3 + 100
ELSE
        OFFSET = 0
END IF
'LAP
PRINT #1, "IP8000,0,9750,7000;SC17.8,-4,0,7000"
PRINT #1, "PU0,"; 3 + OFFSET; ";PD0,"; RR * 3 + OFFSET; ";"
```

```
PRINT #1, "SP2;"
PRINT #1, "PU"; YLAP(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO RR * 3
'LVP
PRINT #1, "SP1;PU;IP8000,0,9750,7000;SC17.8,-4,0,7000"
y = YLVP(1, CI)
IF y > 20 THEN y = 20
PRINT #1, "PU"; y; ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO RR * 3 + OFFSET S
PRINT #1, "PD"; : PRINT #1, USING "###.##"; y; : PRINT #1, ","; i; ";": NEXT i
'DELTA P
PRINT #1, "IP6500,0,8000,7000;SC10,-8.75,0,7000"
PRINT #1, "PU0,"; 3 + OFFSET; ";PD0,"; RR * 3 + OFFSET; ";"
GHTY = YLAP(1, CI) - YLVP(1, CI)
IF GHTY > 9.99 THEN
        GHTY = 9.99
ELSEIF GHTY < -4 THEN
        GHTY = -4
END IF
PRINT #1, "PU"; GHTY; ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO RR * 3 + OFFSE
PRINT #1, "PD"; : PRINT #1, USING "##.##"; y; : PRINT #1, ","; i; ";": NEXT i
'REM MF
PRINT #1, "IP4800,0,6800,7000;SC80,-20,0,7000"
PRINT #1, "PU0,"; 3 + OFFSET; ";PD0,"; RR * 3 + OFFSET; ";"
PRINT #1, "PU"; YMF(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO RR * 3 +
PRINT #1, "PD"; : CALL JOFF(i, OFFSET, J): PRINT #1, USING "###.##"; YMF(J, CI);

DO WHILE partplot = 0

'AoP=YP5
        PRINT #1, "IP3000,0,4200,7000;SC120,0,0,7000"
        PRINT #1, "PU"; YP5(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO
        PRINT #1, "PD"; : CALL JOFF(i, OFFSET, J): PRINT #1, USING "###.##"; YP5
'AF
        PRINT #1, "IP3000,0,4200,7000;SC600,0,0,7000"
        PRINT #1, "SP1;PU0,"; 3 + OFFSET; ";PD0,"; RR * 3 + OFFSET; ";"
        PRINT #1, "SP2;PU"; YAF(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET
'LOW GAIN LVP
        PRINT #1, "SP1;IP3000,0,4200,7000;SC120,0,0,7000"
        PRINT #1, "PU"; YLVP(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO
'dP/dt (derived here)
        REM PRINT #1,"SP1;IP2900,0,3500,7000;SC750,-750,0,7000"
        REM PRINT #1,"PU";(1000/TIMSTP*(YLVP(TIMSTP+1)-YLVP(1,CI)));","; (TSTART+
        REM FOR I=TSTART+1 TO TSTART+999 STEP TIMSTP:GOSUB 1800:PRINT #1,"PD";:Y
'LOW GAIN LAP
        PRINT #1, "SP1;IP3000,0,4200,7000;SC120,0,0,7000"
        PRINT #1, "PU"; YLAP(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO
'LVV
        PRINT #1, "SP1;IP2000,0,3000,7000;SC50,0,0,7000"
        PRINT #1, "PU0,"; 3 + OFFSET; ";PD0,"; RR * 3 + OFFSET; ";"
        PRINT #1, "PU"; ylvv(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO
'LAV
        PRINT #1, "SP2;IP2000,0,3000,7000;SC50,0,0,7000"
        PRINT #1, "PU"; YLAV(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO
'PVF
        PRINT #1, "IP0,0,1000,7000;SC100,-50,0,7000"
        PRINT #1, "PU0,"; 3 + OFFSET; ";PD0,"; RR * 3 + OFFSET; ";"
        PRINT #1, "PU"; YPVF(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO
'F80
        PRINT #1, "SP2;IP0,0,1000,7000;SC100,-50,0,7000"
        PRINT #1, "PU"; YF80(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO
'PO
```

```
            PRINT #1, "SP1;IP1000,0,2000,7000;SC18,6,0,7000;"
            PRINT #1, "PU6,"; 3 + OFFSET; ";PD6,"; RR * 3 + OFFSET; ";"
            PRINT #1, "PU"; YP0(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO
'p8
            PRINT #1, "SP2;IP1000,0,2000,7000;SC18,6,0,7000;"
            PRINT #1, "PU"; YP8(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + OFFSET TO
            IF nac = 1 THEN
                    'MF-A
                    PRINT #1, "SP2;IP4800,0,6800,7000;SC80,-20,0,7000"
                    PRINT #1, "PU"; ymfa(1, CI); ","; 3 + OFFSET; ";": FOR i = 3 + O
                    PRINT #1, "PD"; : PRINT #1, USING "###.##"; ymfa(J, CI); : PRINT
                    PRINT #1, "SC;SP1;PU500,6100;SI;DI0,1;"
            END IF

LOOP

PRINT #1, "SC;SP1;PU500,6100;SI;DI0,1;"
IF PLOT = 2 OR (PLOT = 1 AND INRTOT = 0) THEN
        PRINT #1, "IP800,0,9750,7000;"
        PRINT #1, "LBJSM MODEL V.17"; CHR$(3)
        PRINT #1, "CP;LB"; DATE$; CHR$(3)
        PRINT #1, "CP;LB"; : PRINT #1, USING "RR #####"; RR; : PRINT #1, CHR$(3)
        PRINT #1, "CP;LB"; : PRINT #1, USING "PR #####"; PR; : PRINT #1, CHR$(3)
        PRINT #1, "CP;CP;LB"; id$; CHR$(3); "CP;";

        OPEN "param1.dat" FOR INPUT AS #2
                FOR i = 1 TO NUMPAR
                        INPUT #2, prm(i), CHNGD(i)
                NEXT i
        CLOSE #2

        PRINT #1, "CP;LBC:"; CHR$(3)
        FOR i = 1 TO NUMPAR
                IF CHNGD(1) = 1 THEN
                        PRINT #1, "CP;LB"; : PRINT #1, USING "& ###.#####"; nm$(
                END IF
        NEXT i

        IF INRTOT > 0 THEN
                PRINT #1, "CP;CP;CP;LBI:"; CHR$(3)
                FOR i = 1 TO NUMPAR
                        IF INR(i) = 1 THEN
                                PRINT #1, "CP;LB"; : PRINT #1, USING "& ###.####
                        END IF
                NEXT i
        END IF
END IF
CLOSE #1
END SUB

SUB printall
'Subroutine to print control, intervention, and their differences
LPRINT "JSM MODEL V.17    ANALYSIS - CONTROL AND INTERVENTION";
LPRINT USING "    RR=#### ms HR=### bpm  PR=#### ms"; RR; 60000! / RR; PR
LPRINT id$

OPEN "param1.dat" FOR INPUT AS #2
FOR i = 1 TO NUMPAR
        INPUT #2, prm(i), CHNGD(i)
NEXT i
```

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```
CLOSE #2
LPRINT "Non-default CONTROL parameter(s):"
        FOR i = 1 TO NUMPAR
                IF CHNGD(i) = 1 THEN
                        LPRINT USING "     & ###.#####"; nm$(i); prm(i)
                END IF
        NEXT i

        IF INRTOT > 0 THEN
                LPRINT "INTERVENTION parameter(s):"
                FOR i = 1 TO NUMPAR
                        IF INR(i) = 1 THEN
                                LPRINT USING "     & ###.#####"; nm$(i); inrval(
                        END IF
                NEXT i
        END IF
LPRINT
LPRINT "Parameter               C              I      I-C    (I-C)/C"
LPRINT
LPRINT USING "PCO                 ###.#   mmHg  ###.#  ####.#   ##.###"; pco(1); p
LPRINT USING "LVPmin              ###.#         ###.#  ####.#   ##.###"; lvpmn(1);
LPRINT USING "LVEDP               ###.#         ###.#  ####.#   ##.###"; LVEDP(1);
LPRINT USING "LVEDV               ###.#   ml    ###.#  ####.#   ##.###"; LVEDV(1);
i = 100 * FV(1) / LVEDV(1)
J = 100 * FV(2) / LVEDV(2)
LPRINT USING "EF                   ##.#          ##.#    ##.#    ##.###"; i; J; J -
LPRINT USING "(LAP-LVP)max        ###.#   mmHg  ###.#  ####.#   ##.###"; LALVMX(1)
LPRINT USING "PLVP                ###.#         ###.#  ####.#   ##.###"; PLVP(1);
LPRINT USING "M-(LA-LV)-diast     ###.##        ###.## ####.##  ##.###"; LALVMD(1)
LPRINT USING "MLAP                ###.##        ###.## ####.##  ##.###"; LAPMEN(1)
LPRINT USING "MLAP-diast          ###.##        ###.## ####.##  ##.###"; LAPMED(1)
LPRINT USING "MLAP-syst           ###.##        ###.## ####.##  ##.###"; LAPMES(1)
LPRINT USING "LVP-a-min           ###.#         ###.#  ####.#   ##.###"; LVPAMN(1)
LPRINT USING "LAP-a-max           ###.#         ###.#  ####.#   ##.###"; LAPMX(1);
LPRINT USING "LAV-a-min           ###.##        ###.## ####.##  ##.###"; LAPRE(1);
LPRINT
LPRINT USING "PMF                 ###.#   ml/s  ###.#  ####.#   ##.###"; PMF(1); P
LPRINT USING "MF-a-min            ###.#         ###.#  ####.#   ##.###"; MFA1(1);
LPRINT USING "MF-a-max            ###.#         ###.#  ####.#   ##.###"; MFA(1); M
i = MFA(1) / PMF(1)
J = MFA(2) / PMF(2)
LPRINT USING "MF-a-max/PMF         #.###         #.###  ##.###  ##.###"; i; J; J -
LPRINT
LPRINT USING "FV                  ###.#   ml    ###.#  ####.#   ##.###"; FV(1); FV
LPRINT USING "FV-PMF              ###.#         ###.#  ####.#   ##.###"; FVPMF(1);
LPRINT USING "FV-a-min            ###.#         ###.#  ####.#   ##.###"; FVA1(1);
LPRINT USING "FVA (Yellin)        ###.#         ###.#   ###.#   ##.###"; FVA(1); F
i = FV(1) - FVA1(1)
J = FV(2) - FVA1(2)
LPRINT USING "FVA (clin)          ###.#         ###.#  ####.#   ##.###"; i; J; J -
i = MFASUB1(1)
J = MFASUB1(2)
LPRINT USING "FV-lost after MF=0 ###.#         ###.#  ####.#   ##.###"; i; J; J -
i = FVA(1) / FV(1)
J = FVA(2) / FV(2)
LPRINT USING "FVA(Y)/FV            #.###         #.###  ##.###  ##.###"; i; J; J -
i = (FVA(1) - MFASUB1(1)) / FV(1)
J = (FVA(2) - MFASUB1(2)) / FV(2)
LPRINT USING "FVA(Y)-FVlost/FV     #.###         #.###  ##.###  ##.###"; i; J; J -
i = FVPMF(1) / FV(1)
```

```
J = FVPMF(2) / FV(2)
LPRINT USING "FV-PMF/FV               #.###        #.### ##.### ##.###"; i; J; J -
LPRINT
LPRINT USING "t-LVPmin            ###    ms    ###    ####    ##.###"; TLVPMN(1)
LPRINT USING "t-(LAP-LVP)max       ###          ###    ####    ##.###"; TLALVMX(1
LPRINT USING "t-PMF               ###          ###    ####    ##.###"; TPMF(1);
LPRINT USING "t-MF-a-min          ###          ###    ####    ##.###"; TMFA1(1);
LPRINT USING "t-MF-a-max          ###          ###    ####    ##.###"; TMFA(1);
LPRINT USING "DFP-f               ###          ###    ####    ##.###"; TMFEND(1)
LPRINT USING "DFP-p               ###          ###    ####    ##.###"; DFPP(1);
i = TMFEND(1) / RR
J = TMFEND(2) / RR
LPRINT USING "DFP-f/RR                #.###        #.### ##.### ##.###"; i; J; J -

END SUB

SUB printcontrol
'Subroutine to print control only
LPRINT "JSM MODEL V.17    ANALYSIS - NO INTERVENTION";
LPRINT USING "    RR=####  ms HR=### bpm  PR=#### ms"; RR; 60000! / RR; PR
LPRINT id$
OPEN "param1.dat" FOR INPUT AS #2
FOR i = 1 TO NUMPAR
       INPUT #2, prm(i), CHNGD(i)
NEXT i
CLOSE #2
LPRINT "Non-default CONTROL parameter(s):"
       FOR i = 1 TO NUMPAR
               IF CHNGD(i) = 1 THEN
                       LPRINT USING "        & ###.#####"; nm$(i); prm(i)
               END IF
       NEXT i
LPRINT
LPRINT USING "PCO                   ###.#   mmHg"; pco(1)
LPRINT USING "LVPmin                ###.#"; lvpmn(1)
LPRINT USING "LVEDP                 ###.#"; LVEDP(1)
LPRINT USING "LVEDV                 ###.#   ml"; LVEDV(1)
i = 100 * FV(1) / LVEDV(1)
LPRINT USING "EF                     ##.#   percent"; i
LPRINT USING "(LAP-LVP)max          ###.#    mmHg"; LALVMX(1)
LPRINT USING "PLVP                 ####.#"; PLVP(1)
LPRINT USING "M-(LA-LV)-diast       ###.##"; LALVMD(1)
LPRINT USING "MLAP                  ###.##"; LAPMEN(1)
LPRINT USING "MLAP-diast            ###.##"; LAPMED(1)
LPRINT USING "MLAP-syst             ###.##"; LAPMES(1)
LPRINT USING "LVP-a-min             ###.#"; LVPAMN(1)
LPRINT USING "LAP-a-max             ###.#"; LAPMX(1)
LPRINT USING "LAV-a-min             ###.## ml"; LAPRE(1)
LPRINT
LPRINT USING "PMF                   ###.#   ml/s"; PMF(1)
LPRINT USING "MF-a-min              ###.#"; MFA1(1)
LPRINT USING "MF-a-max              ###.#"; MFA(1)
LPRINT USING "MF-a-max/PMF           #.###"; MFA(1) / PMF(1)
LPRINT
LPRINT USING "FV                    ###.#   ml"; FV(1)
LPRINT USING "FV-PMF                ###.#"; FVPMF(1)
LPRINT USING "FV-a-min              ###.#"; FVA1(1)
LPRINT USING "FVA (Yellin)          ###.#"; FVA(1)
LPRINT USING "FVA (clin.)           ###.#"; FV(1) - FVA1(1)
IF MFASUB1(1) = .01 THEN
```

```
        LPRINT
ELSE
        LPRINT USING "FV-lost after MF=0 ###.#"; MFASUB1(1)
END IF
LPRINT USING "FVA(Y)-FVlost/FV      #.###"; (FVA(1) - MFASUB1(1)) / FV(1)
LPRINT USING "FVA(Y)/FV             #.###"; FVA(1) / FV(1)
LPRINT USING "FV-PMF/FV             #.###"; FVPMF(1) / FV(1)
LPRINT
LPRINT USING "t-LVPmin              ###    ms"; TLVPMN(1)
LPRINT USING "t-(LAP-LVP)max        ###"; TLALVMX(1)
LPRINT USING "t-PMF                 ###"; TPMF(1)
LPRINT USING "t-MF-a-min            ###"; TMFA1(1)
LPRINT USING "t-MF-a-max            ###"; TMFA(1)
LPRINT USING "DFP-f                 ####"; TMFEND(1)
LPRINT USING "DFP-p                 ####"; DFPP(1)
LPRINT USING "DFP-f/RR              #.###"; TMFEND(1) / RR

END SUB


SUB reiterate (reit, sv, ev, st)
LOCATE 23, 1: PRINT "
LOCATE 23, 1: PRINT "parameter vs parameter run ? (N)";
INPUT r$
IF r$ = "y" OR r$ = "Y" THEN reit = 1 ELSE reit = 0
IF reit = 1 THEN
        LOCATE 23, 1: PRINT "  ";
        INPUT "what parameter do you want to vary "; reit1
        INPUT ; "starting value"; sv
        INPUT ; "    end value"; ev
        INPUT "      step"; st
END IF
END SUB

SUB SAVCON

PRINT "running savcon"

parvpar(0, 0) = prm(reit1)

parvpar(1, 0) = pco(1)
parvpar(2, 0) = lvpmn(1)
parvpar(3, 0) = LVEDP(1)
parvpar(4, 0) = LVEDV(1)
parvpar(5, 0) = 100 * FV(1) / LVEDV(1)
parvpar(6, 0) = LALVMX(1)
parvpar(7, 0) = PLVP(1)
parvpar(8, 0) = LALVMD(1)
parvpar(9, 0) = LAPMEN(1)
parvpar(10, 0) = LAPMED(1)
parvpar(11, 0) = LAPMES(1)
parvpar(12, 0) = LVPAMN(1)
parvpar(13, 0) = LAPMX(1)
parvpar(14, 0) = LAPRE(1)
parvpar(15, 0) = PMF(1)
parvpar(16, 0) = MFA1(1)
parvpar(17, 0) = MFA(1)
parvpar(18, 0) = MFA(1) / PMF(1)
parvpar(19, 0) = FV(1)
parvpar(20, 0) = FVPMF(1)
parvpar(21, 0) = FVA1(1)
```

```
parvpar(22, 0) = FVA(1)
parvpar(23, 0) = FV(1) - FVA1(1)
parvpar(24, 0) = MFASUB1(1)
parvpar(25, 0) = FVA(1) / FV(1)
parvpar(26, 0) = (FVA(1) - MFASUB1(1)) / FV(1)
parvpar(27, 0) = FVPMF(1) / FV(1)
parvpar(28, 0) = TLVPMN(1)
parvpar(29, 0) = TLALVMX(1)
parvpar(30, 0) = TPMF(1)
parvpar(31, 0) = TMFA1(1)
parvpar(32, 0) = TMFA(1)
parvpar(33, 0) = TMFEND(1)
parvpar(34, 0) = DFPP(1)
parvpar(35, 0) = TMFEND(1) / RR


END SUB

SUB SAVEITER

parvpar(0, cj) = paramchg
parvpar(1, cj) = pco(2)
parvpar(2, cj) = lvpmn(2)
parvpar(3, cj) = LVEDP(2)
parvpar(4, cj) = LVEDV(2)
parvpar(5, cj) = 100 * FV(2) / LVEDV(2)
parvpar(6, cj) = LALVMX(2)
parvpar(7, cj) = PLVP(2)
parvpar(8, cj) = LALVMD(2)
parvpar(9, cj) = LAPMEN(2)
parvpar(10, cj) = LAPMED(2)
parvpar(11, cj) = LAPMES(2)
parvpar(12, cj) = LVPAMN(2)
parvpar(13, cj) = LAPMX(2)
parvpar(14, cj) = LAPRE(2)
parvpar(15, cj) = PMF(2)
parvpar(16, cj) = MFA1(2)
parvpar(17, cj) = MFA(2)
parvpar(18, cj) = MFA(2) / PMF(2)
parvpar(19, cj) = FV(2)
parvpar(20, cj) = FVPMF(2)
parvpar(21, cj) = FVA1(2)
parvpar(22, cj) = FVA(2)
parvpar(23, cj) = FV(2) - FVA1(2)
parvpar(24, cj) = MFASUB1(2)
parvpar(25, cj) = FVA(2) / FV(2)
parvpar(26, cj) = (FVA(2) - MFASUB1(2)) / FV(2)
parvpar(27, cj) = FVPMF(2) / FV(2)
parvpar(28, cj) = TLVPMN(2)
parvpar(29, cj) = TLALVMX(2)
parvpar(30, cj) = TPMF(2)
parvpar(31, cj) = TMFA1(2)
parvpar(32, cj) = TMFA(2)
parvpar(33, cj) = TMFEND(2)
parvpar(34, cj) = DFPP(2)
parvpar(35, cj) = TMFEND(2) / RR
```

```
END SUB

SUB SETOUT
'Quiery for output options
CLS
PRINT "                              MODEL OUTPUT OPTIONS"
LOCATE 5, 1: PRINT "Screen monitoring? (Y)";
INPUT a$
IF a$ = "N" OR a$ = "n" THEN OUTSCR = 0 ELSE OUTSCR = 1
LOCATE 5, 1: PRINT "                                              "
LOCATE 5, 1: PRINT "Output to printer? (Y)";
INPUT a$
IF a$ = "N" OR a$ = "n" THEN
        outprt = 0
ELSE
        outprt = 1
END IF
PLTVAR = 0
LOCATE 5, 1: PRINT "Output plots to plotter/laser printer? (Y)";
INPUT a$
IF a$ <> "N" AND a$ <> "n" THEN
        DO
                        LOCATE 14, 40: PRINT "          "
                        LOCATE 7, 1
                        PRINT "Plot  1. Variables versus time with control/interven
                        PRINT "      2. Variables versus time with control/interven
                        PRINT "      3. Atrial and ventricular pressure-volume loop
                        PRINT "                  control/intervention on separate pag
                        PRINT "      4. Atrial and ventricular pressure-volume loop
                        PRINT "                  control/intervention overlayed"
                        LOCATE 14, 25: INPUT "Enter choice (1)"; a$
                        IF a$ = "" THEN PLTVAR = 1 ELSE PLTVAR = VAL(a$)
        LOOP WHILE PLTVAR > 4

        DO
                LOCATE 16, 33: PRINT "          "
                LOCATE 16, 1: INPUT "Enter plotter time step in ms (4) "; a
                IF a = 0 THEN a = 4
                TIMSTP = INT(a)
        LOOP WHILE TIMSTP < 1 OR TIMSTP > 50 OR TIMSTP <> a

        LOCATE 16, 33: PRINT "          "
        LOCATE 16, 1: INPUT "Plot no-atrial contraction baseline? (Y)"; a$
        IF a$ <> "N" AND a$ <> "n" THEN nac = 1 ELSE nac = 0

        LOCATE 16, 33: PRINT "              "
        LOCATE 16, 1: INPUT "Plot ONLY LAP/LVP/MiF? (N)"; a$
        IF a$ <> "Y" AND a$ <> "y" THEN partplot = 0 ELSE partplot = 1

END IF
IF PLTVAR > 0 OR outprt = 1 THEN
        DO
                LOCATE 16, 50: PRINT "              "
                LOCATE 16, 1: INPUT "Enter identifier for printout (up to 10 cha
        LOOP WHILE LEN(id$) > 10
END IF

END SUB

SUB SETPAR
```

```
SCREEN 0
'SETPAR1      SETS UP PARAMETERS FOR JSM MODEL
'TO ADD PARAMETERS, CHANGE NUMPAR
NUMPAR = 35

nm$(1) = "L8-PA inertance"
nm$(2) = "R8-PA resistance"
nm$(3) = "E8-PA elastance"
nm$(4) = "R0-Pcap resistance"
nm$(5) = "E0-Pcap elastance"
nm$(6) = "R1-PV resistance"
nm$(7) = "L1-PV inertance"
nm$(8) = "R2-MV resistance"
nm$(9) = "L2-MV inertance"
nm$(10) = "E3-MV bulge elastance"
nm$(11) = "R3-MV bulge resistance"
nm$(12) = "R4-Ao resistance"
nm$(13) = "R5-periph resistance"
nm$(14) = "E5-Ao elastance"
nm$(15) = "K10-LA passive elast."
nm$(16) = "VD10-LA dead vol."
nm$(17) = "VD2-LV dead vol."
nm$(18) = "Pinf - LVP asymptote"
nm$(19) = "R9-LV viscous res."
nm$(20) = "ALPHA-LV passive exp."
nm$(21) = "A-LV passive coef."
nm$(22) = "Emax-LA"
nm$(23) = "MR-Res. (0=no MR)"
nm$(24) = "MR-Inertance"
nm$(25) = "MR-LVV dependence"
nm$(26) = "AR-Res   (0=no AR)"
nm$(27) = "MV 0=closed 1=open"
nm$(28) = "PR"
nm$(29) = "RR"
nm$(30) = "Emax-LV"
nm$(31) = "Pmax-RV"
nm$(32) = "tau"
nm$(33) = "con. cycls"
nm$(34) = "int. cycls"
nm$(35) = "CO"

OPEN "param1.dat" FOR INPUT AS #1
        FOR i = 1 TO NUMPAR
                INPUT #1, prm(i), CHNGD(i)
        NEXT i
CLOSE #1

CLS
PRINT "CONTROL Parameter Set-Up Routine      flashing=non-default": PRINT
FOR i = 1 TO NUMPAR

        IF i > 18 THEN
                I1 = i - 18
                J = 40
        ELSE
                I1 = i
                J = 1
        END IF

        LOCATE I1 + 3, J
```

```
            COLOR 15
            PRINT USING "## "; i;
            IF CHNGD(i) = 1 THEN
                    COLOR 31
            ELSE
                    COLOR 15
            END IF
            PRINT USING "####.##### "; prm(i);
            COLOR 15
            PRINT nm$(i);
NEXT i

DO
        DO
                COLOR 15
                LOCATE 23, 64
                PRINT "          "
                LOCATE 23, 1
                PRINT "Enter # to be changed or "; NUMPAR + 1; " to default all
                INPUT a
        LOOP WHILE a < 0 OR a > (NUMPAR + 1)

        SELECT CASE a
                CASE NUMPAR + 1
                        prm(1) = .004: prm(2) = .02: prm(3) = .32: prm(4) = .18:
= 13: prm(17) = 8: prm(18) = -4: prm(19) = .00001
                        prm(20) = .05: prm(21) = 1.09: prm(22) = 2: prm(23) = 0:
                        FOR i = 1 TO NUMPAR
                                CHNGD(i) = 0
                        NEXT i
                        OPEN "param1.dat" FOR OUTPUT AS #1
                                FOR i = 1 TO NUMPAR
                                        PRINT #1, prm(i); CHNGD(i)
                                NEXT i
                        CLOSE #1

                        FOR i = 1 TO NUMPAR
                                IF CHNGD(i) = 1 THEN
                                        COLOR 31
                                ELSE
                                        COLOR 15
                                END IF

                                IF i > 18 THEN
                                        I1 = i - 18
                                        J = 40
                                ELSE
                                        I1 = i
                                        J = 1
                                END IF

                                LOCATE I1 + 3, J
                                PRINT USING "## ####.##### &"; i; prm(i); nm$(i)
                        NEXT i

                CASE 1 TO (NUMPAR + 1)
                        LOCATE 23, 1
                        PRINT "
                        INPUT B1
                        b(1) = .004: b(2) = .02: b(3) = .32: b(4) = .18: b(5) =
```

```
19) = .00001: b(20) = .05: b(21) = 1.09: b(22) = 2
                b(23) = 0: b(24) = .002: b(25) = 0: b(26) = 0: b(27) = 1
        IF b(a) = B1 THEN
                CHNGD(a) = 0
                ELSE
                CHNGD(a) = 1
        END IF
        prm(a) = B1
        OPEN "param1.dat" FOR OUTPUT AS #1
        FOR i = 1 TO NUMPAR
                PRINT #1, prm(i); CHNGD(i)
        NEXT i
        CLOSE #1
        IF a > 18 THEN
                I1 = a - 18
                J = 40
        ELSE
                I1 = a
                J = 1
        END IF

        IF CHNGD(a) = 1 THEN COLOR 31 ELSE COLOR 15
        LOCATE I1 + 3, J
        PRINT USING "## ####.##### &"; a; prm(a); nm$(a);
        LOCATE 23, 1
        PRINT
        END SELECT

LOOP WHILE a <> 0

L8 = prm(1)
R8 = prm(2)
E8 = prm(3)
R0 = prm(4)
E0 = prm(5)
R1 = prm(6)
L1 = prm(7)
R2 = prm(8)
L2 = prm(9)
E3 = prm(10)
R3 = prm(11)
R4 = prm(12)
R5 = prm(13)
E5 = prm(14)
K10 = prm(15)
VD10 = prm(16)
VD2 = prm(17)
PINF = prm(18)
R9 = prm(19)
ALPHA = prm(20)
ALV = prm(21)
EMAXLA = prm(22)
RMR = prm(23)
LMR = prm(24)
DMR = prm(25)
ARR = prm(26)
PR = prm(28)
RR = prm(29)
emaxlv = prm(30)
pmaxrv = prm(31)
```

```
tau = prm(32)
ccycles = prm(33)
icycles = prm(34)
cout = prm(35)




END SUB

SUB setven2 (sv, st, ev, reit1, paramchg)

INRTOT = 0

OPEN "param1.dat" FOR INPUT AS #1
        FOR i = 1 TO NUMPAR
                INR(i) = 0
                INPUT #1, prm(i), CHNGD(i)
        NEXT i
CLOSE #1

PRINT "performing a parameter vs. parameter run"
PRINT "reiterating:"; INT(ABS((sv - paramchg) / st)) + 1; "out of"; INT(ABS((sv
PRINT

FOR i = 1 TO NUMPAR

        IF i > 18 THEN
                I1 = i - 18
                J = 40
        ELSE
                I1 = i
                J = 1
        END IF

NEXT i

        a = reit1
        INRTOT = INRTOT + 1
        INR(a) = 1
        inrval(a) = paramchg
        IF a > 18 THEN
        I1 = a - 18
        J = 40
        ELSE
        I1 = a
        J = 1
        END IF




END SUB

SUB SETVENTION
INRTOT = 0

OPEN "param1.dat" FOR INPUT AS #1
        FOR i = 1 TO NUMPAR
                INR(i) = 0
                INPUT #1, prm(i), CHNGD(i)
```

```
        NEXT i
CLOSE #1

CLS
PRINT "INTERVENTION - Parameter Set-Up Routine      flashing=INTERVENTION": PRIN
FOR i = 1 TO NUMPAR

        IF i > 18 THEN
                I1 = i - 18
                J = 40
        ELSE
                I1 = i
                J = 1
        END IF

        LOCATE I1 + 3, J
        COLOR 15
        PRINT USING "## "; i;
        PRINT USING "####.##### "; prm(i);
        PRINT nm$(i);
NEXT i

DO
        DO
                COLOR 15
                LOCATE 23, 1
                PRINT "
                LOCATE 23, 1
                PRINT "Enter INTERVENTION #  or <RETURN> to END ";
                INPUT a
        LOOP WHILE a < 0 OR a > (NUMPAR + 1) OR a = 33 OR a = 34

        IF a > 0 THEN
                INRTOT = INRTOT + 1
                INR(a) = 1
                LOCATE 23, 1
                PRINT "
                LOCATE 23, 1
                PRINT "Enter INTERVENTION value for "; nm$(a);
                INPUT inrval(a)

                IF a > 18 THEN
                        I1 = a - 18
                        J = 40
                ELSE
                        I1 = a
                        J = 1
                END IF

                IF INR(a) = 1 THEN COLOR 31 ELSE COLOR 15
                LOCATE I1 + 3, J
                PRINT USING "## ####.##### &"; a; inrval(a); nm$(a);
                LOCATE 23, 1
                PRINT
        END IF

LOOP WHILE a > 0

END SUB
```

APPENDIX B

Complete PSPICE Program

This models mod17a

```
.PARAM RR8=.02
.PARAM RR0=.180
.PARAM RR1=.10
.PARAM RR2=.0001
.PARAM RR3=8.0
.PARAM RR4=.10
.PARAM RR5=2.4
.PARAM RR9B=.00001
.PARAM LL8=.004
.PARAM LL1=.002
.PARAM LL2=.002
.PARAM PR=.13
.PARAM RR=.75
.PARAM E8=.32
.PARAM E0=.48
.PARAM E3=1280
.PARAM E5=1.25
.PARAM LAV0=13 ;is same as VD10
.PARAM LVVD=8     ;is same as VD2
.PARAM PINF=-4
.PARAM AY=1.09
.PARAM ALPHA=.05
.PARAM TAU=.02
.PARAM K10=1.0
.PARAM PMAXRV=25
.PARAM RVDUR=300   ;duration of rv contraction in ms
.PARAM EMAXLA=2.0
.PARAM EMAXLV=8

XIN 10 0 RV

DA 10 20 DA
R8 20 30 {RR8}
L8 30 40 {LL8} IC=100
C8 40 0 {1/E8} IC=6.667
R0 40 50 {RR0}.
C0 50 0 {1/E0} IC=15

R1 50 60 {RR1}
L1 60 70 {LL1} IC=25

XC1 101 102 103 65 0 yx
CREF 103 0 1
ELA2 101 102 VALUE={1/V(62)}
RH1 101 0 10K
RH2 102 0 10K

XVA1 62 0 LA
R62 62 0 10K
ELA1 70 65 VALUE={(-LAV0)*(V(62))}

C3 70 80 {1/E3}
R3 80 90 {RR3}
DB 70 80 DA
VZERO 80 90 0
*R2 90 100 .0001
HIR2 90 100 POLY(1) VZERO 0 0 .0001
L2 100 110 {LL2} IC=30
```

```
XLV1 82 0 LV
R82   82 0 10K

R9 110 112 (RR9B)

EEXLV 112 114 VALUE={AY*EXP(ALPHA*(10000*V(114,115)))}
CQMEASURE 114 115 10K

ELV1 115 120 VALUE={(-LVVD)*(V(82))}
RHUGE 120 0 100G

XC2 121 122 123 120 125 yx
CREF2 123 0 1
ELV2  121 122 VALUE={1/V(82)}
RH3   121 0 100K
RH4   122 0 100K

EVPINF 125 0 VALUE={PINF}

DC 110 130 DA
R4 130 140 (RR4)
C5 140 0 (1/E5)
R5 140 0 (RR5)

.SUBCKT yx 1 2 3 4 5
ECOPY 3 6 POLY (2) (1,2) (4,5) 0 0 0 0 1
FOUT 4 5 VSENSE 1
RIN 1 2 1G
VSENSE 0 6 0
.ENDS yx


*This models an ideal diode
.MODEL DA D(N=.001)

*Creates function used in the right ventricle
.SUBCKT RV 299 298
VSIN1  201 0 SIN(0 {PMAXRV}  {1/(2*(RVDUR/1000))} {PR})
VCHOP1 202 0 PULSE(0 1 {PR} 1U 1U {RVDUR/1000} 14)
EPROD1 203 0 POLY(2) 201 0 202 0 0 0 0 0 1
R201   201 0 10K
R202   202 0 10K

R203   203 400 10K

T11  400 0 301 0 Z0=10K TD={RR}
ES1  308 0 POLY(2) 203 0 301 0 0 1 2
R301 301 0 10K
R308 308 313 10K

T12  313 0 317 0 Z0=10K TD={2*RR}
ES2  318 0 POLY(2) 308 0 317 0 0 1 2
R317 317 0 10K
R318 318 323 10K

T13  323 0 327 0 Z0=10K TD={4*RR}
ES3  328 0 POLY(2) 318 0 327 0 0 1 2
R327 327 0 10K
R328 328 333 10K
```

```
T14   333 0 337 0 ZO=10K TD={8*RR}
ES4   338 0 POLY(2) 328 0 337 0 0 1 2
R337 337 0 10K
R338 338 0 10K


EOUT   299 298 VALUE={V(338)}
R299   299 0 10K
R298   298 0 10K
.ENDS

*creates function used in the left atrium
.SUBCKT LA 299 298
VSIN1  110 0 SIN(0 {EMAXLA-K10} {1/(2*PR)})
VCHOP1 111 0 PULSE(0 1 0 1U 1U {PR} 14)
EPROD1 112 0 POLY(2) 110 0 111 0 0 0 0 0 1
R10    110 0 10K
R11    111 0 10K


R12   112 300 10K

T11 300 0 301 0 ZO=10K TD={RR}
ES1 308 0 POLY(2) 112 0 301 0 0 1 2
R301 301 0 10K
R308 308 313 10K


T12 313 0 317 0 ZO=10K TD={2*RR}
ES2 318 0 POLY(2) 308 0 317 0 0 1 2
R317 317 0 10K
R318 318 323 10K


T13 323 0 327 0 ZO=10K TD={4*RR}
ES3 328 0 POLY(2) 318 0 327 0 0 1 2
R327 327 0 10K
R328 328 333 10K


T14 333 0 337 0 ZO=10K TD={8*RR}
ES4 338 0 POLY(2) 328 0 337 0 0 1 2
R337 337 0 10K
R338 338 0 10K


VK10     198 0 {K10}
ETOTAL   199 0 POLY(2) 198 0 338 0 0 1 1
R98      198 0 10K
R99      199 0 10K


EOUT   299 298 VALUE={V(199)}
R298    298 0 10K
R299    299 0 10K
.ENDS

*CREATES function used in LEFT VENTRICLE
.SUBCKT LV 399 398
VSIN1  201 0 SIN({EMAXLV/2} {EMAXLV/2} 3.3333333 {RR+PR-.225})
VCHOP1 202 0 PULSE(0 1 {RR+PR} 1U 1U .15 15)
EPROD1 203 0 POLY(2) 201 0 202 0 0 0 0 0 1
*THIS LINE IS: 0, 0, RR+PR+.15, EMAXLV, RR+PR+.15+(DELAY), EMAXLV
*VLINE  707 0 PWL(0 0 1.03 0 1.030001 8 1.079999 8 1.08001 0)
```

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```
*ADD the delay to the second to last term
VEXP1   204 0 EXP(0 {EMAXLV} {RR+PR} 15M {RR+PR+.15} {TAU})
*add the delay to the third term
VCOP1   205 0 PULSE(0 1 {RR+PR+.15+.000001} 1U 1U {RR-(2*PR)} 15)
EPOD1   206 0 POLY(2) 204 0 205 0 0 0 0 1
ESUM1   207 0 POLY(2) 203 0 206 0 0 1 1
R201    201 0 10K
R202    202 0 10K
R203    203 0 10K
R204    204 0 10K
R205    205 0 10K
R206    206 0 10K
*R707    707 0 10K

R207    207 500 10K

T11  500 0 301 0 Z0=10K TD={RR}
ES1  308 0 POLY(2) 207 0 301 0 0 1 2
R301 301 0 10K
R308 308 313 10K

T12  313 0 317 0 Z0=10K TD={2*RR}
ES2  318 0 POLY(2) 308 0 317 0 0 1 2
R317 317 0 10K
R318 318 323 10K

T13  323 0 327 0 Z0=10K TD={4*RR}
ES3  328 0 POLY(2) 318 0 327 0 0 1 2
R327 327 0 10K
R328 328 333 10K

T14  333 0 337 0 Z0=10K TD={8*RR}
ES4  338 0 POLY(2) 328 0 337 0 0 1 2
R337 337 0 10K
R338 338 0 10K


VFIRST 688 0 EXP(0 {EMAXLV} {PR} 18M {PR+.15} {TAU})
*V122    688 0 PWL(0 0 15 0)
R688 688 0 10K      .

ESUM10 689 0 POLY(2) 338 0 688 0 0 1 1
R689    689 0 10K

EOUT    399 398 VALUE={V(689)+.001}
R98     398 0 10K
R99     399 0 10K


.ENDS

.TRAN .02 8 0 .02 UIC
*.PLOT TRAN V(70)
*.PRINT TRAN V(70) V(110)
.PROBE
.OPTIONS NOPAGE  ITL4=20 ITL5=0 ABSTOL=1U RELTOL=.01 VNTOL=.5M PIVTOL=.01F CHGTO
.END
```

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