A MODEL OF HEART CONTRACTILITY FOR CONDITIONS OF STRESS

A Thesis

Presented to

the Faculty of the Department of Mechanical Engineering

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Master of Science in Mechanical Engineering

---

by

Timothy John Hattenbach

August, 1974

ACKNOWLEDGMENTS

I wish to acknowledge with deep appreciation Dr. Franklin J. Kay, whose assistance and guidance was necessary for the successful completion of this work.

I extend many thanks to my parents, Jeanette and Lottie Hattenbach, for providing the incentive and opportunity for me to complete my undergraduate degree, which allowed me to further my education.

Deepest love and affection are extended to Whatley Langham and Billy James for their invaluable assistance in helping me maintain a proper balance and perspective in my life during this work.

This thesis is dedicated to my beautiful and loving companion in life, Sharon.

to Sharon

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ABSTRACT

Mathematical modeling has become an important tool in research disciplines that defy traditional laboratory experimentation. The study of the human heart is ideally suited for this approach. This paper develops a model of heart contractility for conditions of stress, formulated from a mathematical and physiological background, which is incorporated into a proven cardiovascular model. The combined model simulates the transient and steady-state response to exercise and is in good agreement with published experimental data. Also, when compared with previous work, the present model provides much improved fidelity in the response of important cardiac variables to exercise.

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CHAPTER I

INTRODUCTION

In recent years, the disciplines of engineering and physiology have been combined with new computer techniques to produce a new area of research - physiological systems modeling. The goal of this work is to create accurate mathematical models of complex physiological systems that will predict the behavior of these systems. Models are important since they provide a measure of the understanding of the process in question and its interaction among other systems. The most important benefit that models provide is the ability to mathematically simulate phenomena that otherwise would be hazardous or exceedingly difficult to perform with living organisms.

The response of the human heart to exercise provides a system that is ideally suited to mathematical modeling. For obvious reasons, the human heart is not suited for experimentation. Direct measurements of important variables are difficult, if not impossible, to make and often effects must be recorded and the causes inferred. Basically, the heart is a variable output pump for which the pressure and flow equations can be easily formulated. The greatest difficulty in modeling arises in determining how and to what degree the heart's properties change in response to exercise.

One of the most important details of any heart model is the description of the heart's contractility. The strength of

each heart beat is normally constant; but when subjected to stress, the contractility of the heart is greatly enhanced. The object of this study is to provide a model that will simulate the transient and steady state response to various exercise rates of the heart's contractility.

CHAPTER II

LITERATURE REVIEW

Most work concerning the contractility of myocardium has been carried out in two separate but related fields. Medical researchers have centered their quest on a reliable index of contractility for clinical purposes; while researchers attempting to mathematically describe the cardiovascular system have sought an adequate model of contractility for their simulations. The goal of each group, divergent as they may seem, is really the same, for two reasons. Any physiological index of contractility, when incorporated into a systems model, should yield results observed in experiments. Also, any mathematical model of contractility should have some physiological basis for its existence.

Clinicians and physiologists have observed for some time that in response to various stimuli the strength of contraction of the heart, i.e., contractility, is enhanced. Over the years, the measurement of many quantities has been proposed to give an index of contractility [1,2,3,4,5].* Some of the quantities are peak left ventricular dp/dt, time from R wave to peak dp/dt, peak dp/dt divided by developed left ventricular pressure, and time from start of aortic flow ejection to peak flow velocity.

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*Numbers in brackets indicate references.

Patterson, et al., [6], have conducted experiments in which they evaluated and compared ten indices of contractility. They concluded each index had some merit but no one was without fault. Karliner and Ross [7] reached essentially the same conclusion when they found that a combination of several indices may be necessary to adequately describe cardiac contractility. However, one quantity in particular, the peak derivative of left ventricular pressure, has received wider acceptance than any of the other indices.

The peak derivative of left ventricular pressure (peak dp/dt) was first suggested as an index of contractility by Wiggers [8] in 1927. He reported that the application of epinephrine to myocardium produced an increase in peak dp/dt. These early results were qualitative in nature and it was nearly 40 years later before quantitative relationships were established. This is not to say peak dp/dt had no drawbacks and was immediately accepted, quite the contrary.

The first obstacle to be overcome was the actual measurement of dp/dt in the left ventricle. The standard catheter-manometer was grossly inadequate because of artifacts inherent in pressure recording made by this type of system. In the mid 1960's, however, the development of special catheters with high-fidelity micromanometers at their tips removed this first hurdle. The next barrier to be eliminated was the most crucial: Could a change in peak dp/dt be elicited by means other than increased contractility? Several researchers [1,9,10,11,12] have reported

peak dp/dt is affected by left ventricular preload, afterload and heart rate in varying degrees.

Mason [1], in 1969, concluded that peak dp/dt was a sensitive measure of contractility but that it was affected by preload, afterload, and heart rate. The objection to preload was eliminated when Furnival, Linden and Snow [9] in 1970 reported that changes in preload were not accompanied by changes in peak dp/dt. Their conclusions were substantiated by Grossman, et al., [11] in 1971. Also that same year, Mason, et al., [10] reported that when peak dp/dt occurs before ejection, it is independent of afterload. In 1973, Barnes, et al., [13] considered the entire problem of the effects of preload, afterload, and heart rate. In confirming previous work, they concluded that, in canine studies, peak dp/dt was a reliable index of myocardial contractility and was minimally influenced by changes in preload, afterload, and heart rate. Finally, 46 years after it was first suggested by Wiggers, peak dp/dt was established as an index of contractility.

Experiments reported in the literature that concern the relation between peak dp/dt and contractility are very scarce. In most cases, the information regarding peak dp/dt is incidental and not a crucial portion of the experiment. For these reasons, only a qualitative trend can be obtained from the experimental results. The following researchers have reported that peak dp/dt increases during exercise: Wiener, et al., [14], O'Brien, et al., [15], Glancy, et al., [16], and Vatner, et al., [17].

One other measure of contractility has recently been shown to be independent of loading and rate - the left ventricular pressure-volume ratio, i.e., the ventricular elastance. Suga [2] in 1971 and Suga, et al., [18] in 1973 reported that in the canine left ventricle the peak value of the elastance function explicitly reflects contractility. It will be developed later that this is not an entirely different concept from that of peak dp/dt, but that the two are intimately related.

Most work in modeling the cardiovascular system has been done since the early 1950's. Steady-state models were the first to be developed and accordingly time-dependent contractility functions were not included. The complexity of models increased but with the emphasis placed on the improved description of the systemic portion of the model. The results were still, however, for a steady-state system. Dick [19] in 1968 developed one of the first models to simulate the major transients in the canine cardiovascular system.

In the development of cardiovascular models, one of the last factors to be included was that of contractility. As late as 1972, Guyton, et al., [20] had considered contractility only as a constant in their model of the human circulatory system. The first model to explicitly describe the contractility function was developed by Croston [21] in 1972. His model was based on the quantity of circulating metabolites that varied during the simulation of exercise.

CHAPTER III

DESCRIPTION OF STUDY

A review of the mathematical cardiovascular models and physiological experiments contained in the references listed in the Bibliography indicates that, to explain the cardiac performance, it is necessary to fully understand myocardial contractility. This is essential since changes in the contractile behavior of the heart can be elicited by two distinct mechanisms. One is the variation in length of myocardial muscle fibers (i.e., myofilament overlap), and the other is the increase in vigor of the active state of the myocardium (i.e., contractility). It is of utmost importance that a model of contractility should have a strong physiological basis for its formulation which will differentiate between the above two phenomena. Therefore, the objective of this research is to formulate a physiologically acceptable mathematical model of myocardial contractility which, when incorporated into a proven cardiovascular model, will accurately describe the cardiovascular response to exercise.

CHAPTER IV

DESCRIPTION OF CARDIOVASCULAR MODEL

The cardiovascular model used in this study was developed by Croston [21] in 1972. It is a mathematical model and digital computer simulation of the human cardiovascular system with controls developed to simulate the transient responses to bicycle ergometer exercises. The model has complex control models for the control of heart period, peripheral flow resistances, venous tone, and other controlled variables. Metabolic control models are also included to indicate the transient metabolic state and simulate other chemical factors.

The model also contains equations describing pulsatile blood flows, pressures, and volumes for 28 sections of the uncontrolled cardiovascular system. Figure 1 illustrates the major arteries and veins that are modeled while Figure 2 is the circulatory model block diagram. The circulatory system model is combined with models of the controlling systems to simulate transient responses to exercise. Other characteristics of the combined model include gravity effects, muscle pumping, venous tone, venous valves, respiratory frequency, and intrathoracic pressure effects. The model has been verified and when compared with experimental data yields satisfactory results for a broad range of exercise simulations. However, as suggested by Croston [21], one area of the model needing refinement is the contractility model, and this suggestion is the origin of this research.

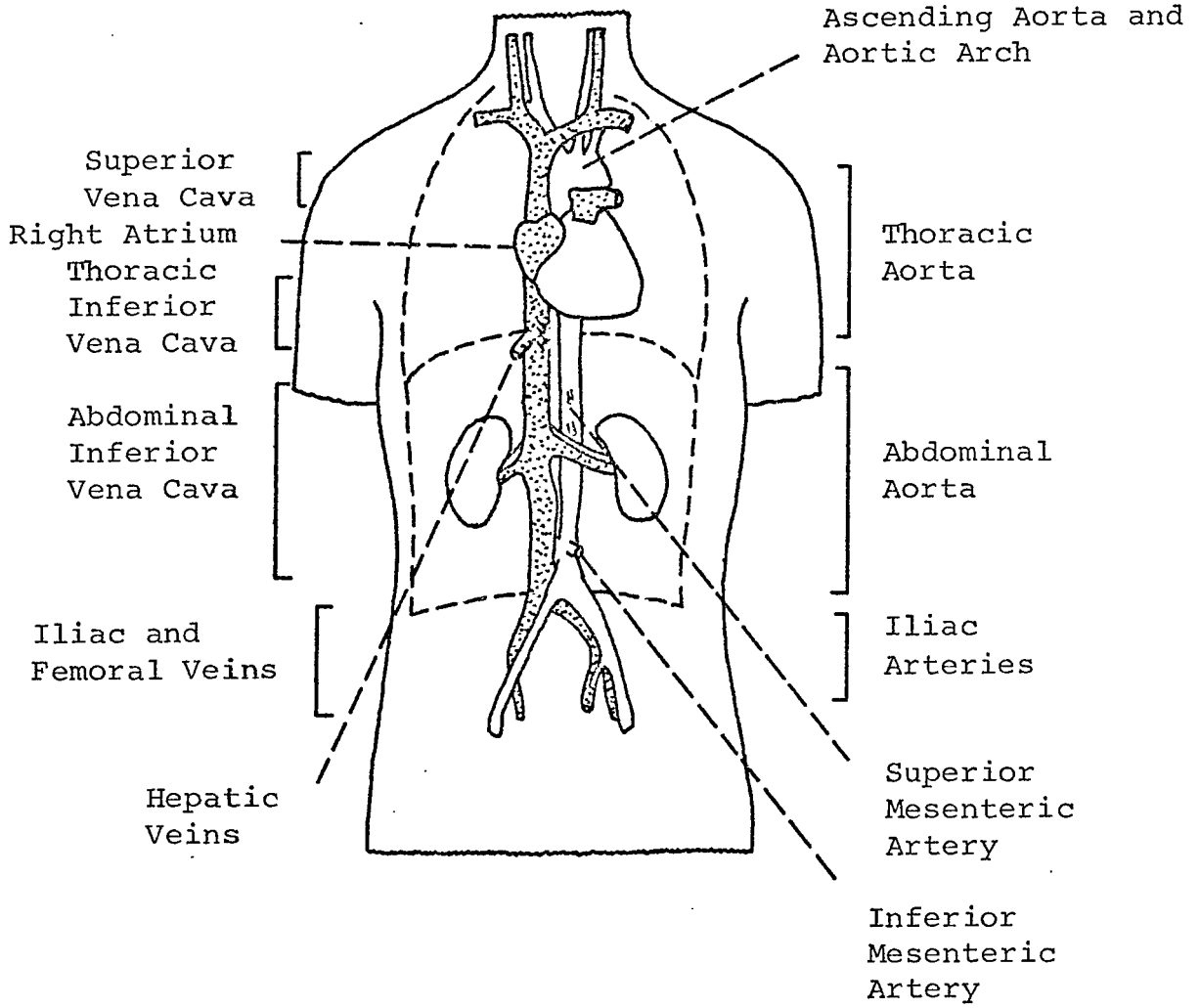

Figure 1

Major Arteries and Veins

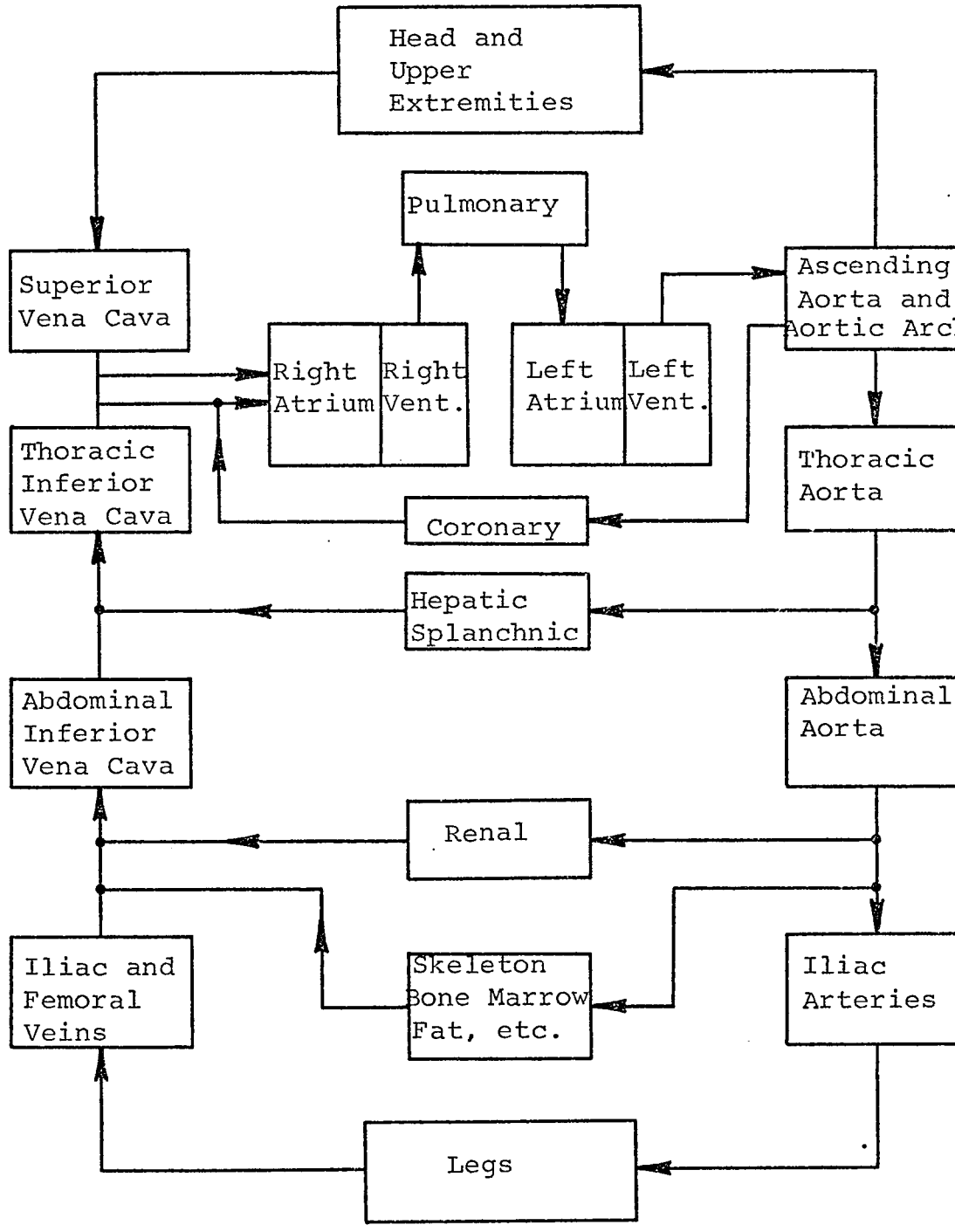

Figure 2

Circulatory Model Block Diagram

CHAPTER IV

DEVELOPMENT OF CONTRACTILITY MODEL

The requirements necessary to simulate the heart's function are those of any pumping system. Equations must be written that accurately relate the pressure-volume characteristics of the heart. This task is made more difficult since the elastance (pressure-volume ratio) varies throughout each heart beat and may vary in response to physiological demands. This latter phenomenon provides the basis for this research.

Equations, similar to those formulated by Croston [21], which describe the pumping characteristics of the heart are as follows:

$$P(t) = E(t)V_s(t) \ , \tag{1}$$

$$E(t) = A_D + A_s(\sin t/T_{vs}) \ , \tag{2}$$

$$V_s(t) = \int (Q_{IN} - Q_{OUT})dt + V_s(0) \ , \tag{3}$$

where Q_{IN} and Q_{OUT} are the flows applicable to a chamber, $V_s(0)$ is the initial chamber volume, $V_s(t)$ is the instantaneous volume, t is the time from the onset of systole, T_{vs} is the period of systole, A_D and A_s are diastolic and peak systolic elastances respectively, E(t) is the total elastance and P(t) is the pressure. The use of a sinusoid to represent elastance is not novel. References [22] and [23] have used this approach previously and

data reported by Suga [2] and Suga, et al., [18] substantiate this assumption. These equations are applicable to each chamber of the heart when the appropriate values of the constants are substituted. Based on the physiological discussion (see [24], p. 187) that all four heart chambers are augmented in strength by an increase in contractility, Croston has included a contractility function in the elastance function. The goal of this research is to provide a mathematical definition of the contractility function and justify its place in the heart model.

As previously stated, any valid mathematical model of a living system must have a physiological basis for its existence. In the case of myocardial contractility, substantial research has been done in an attempt to define and quantitatively describe this phenomenon. The development of the peak derivative of left-ventricular pressure (peak dp/dt) as an index of contractility was presented in the literature survey. Following the conclusions of Barnes, et al., [13] that peak dp/dt is minimally influenced by preload, afterload, and heart rate, peak dp/dt will be used to develop the contractility model.

Considering the heart model equations, forming the time derivative of pressure and recalling that the volume is constant during the period of interest yields

$$\frac{dP(t)}{dt} = \frac{A_s V_s(0)}{T_{vs}} (\cos t/T_{vs}) \tag{4}$$

with

$$\text{peak } \frac{dP(t)}{dt} = \frac{A_s V_s(0)}{T_{vs}} . \tag{5}$$

These results provide the basis for the contractility model. Inspection of equations (4) and (5) reveals several important facts. First, peak dp/dt is not a constant, rather it depends upon the value of $V_s(0)$ and T_{vs}, both of which vary according to physiological demands. Secondly, it has been reported [2,18] that A_s is not a constant. Lastly, the peak value is reached harmonically with a direct dependence upon T_{vs}.

Extending these results in a general sense, a contractility function may be defined as

$$f(c) = c_1 (\cos t/T) + c_2 , \qquad (6)$$

where t is the time from the onset of increased contractility and c_1, c_2 and T are dependent upon the intensity of the physiological demands (i.e., exercise). This is a rational approach since physical systems are often observed to behave in a harmonic manner.

Following the development of the contractility function, its inclusion in the elastance function is not an arbitrary step. The foundation for this assumption lies in the work by Suga [2] and Suga, et al., [18]. They reported that peak ventricular elastance explicitly reflects contractility. This does not contradict the previous establishment of peak dp/dt as a contractility index, rather it enhances the acceptance of both. As illustrated by equation (5), the two quantities are inextricably related, a change in one being reflected in the other. Therefore, in studying contractility, researchers should not look upon left

ventricular peak dp/dt and elastance as divergent approaches, but, through equation (5), as the same approach.

The major assumption of this model is that the contractility function reaches a steady-state value during exercise and that a harmonic function can be defined that will describe the transient response at the beginning and end of exercise. Further development of the contractility model requires that the variables in equation (6) be defined. It will be assumed that the quantities c_1, c_2, and T are dependent upon the intensity of exercise.

Following this approach, it can be noted that c_1 and c_2 control the amplitude of the contractility function and thus the peak value of the elastance. Since the elastance directly affects several hemodynamic variables, correlations between these quantities can be made for various work rates to verify the value of the functions involved. Figures 3 and 4 illustrate the values of c_1 and c_2 obtained in this manner for specific work rates and least squares regression results for the data.

A similar technique can be used to determine the defining functions for the length of the transient periods at the beginning and end of exercise (T_1 and T_2, respectively). As before, the length of these transient periods will depend upon the work rate. Figures 5 and 6 show values of the transient periods for various work rates and least squares regression results for the data.

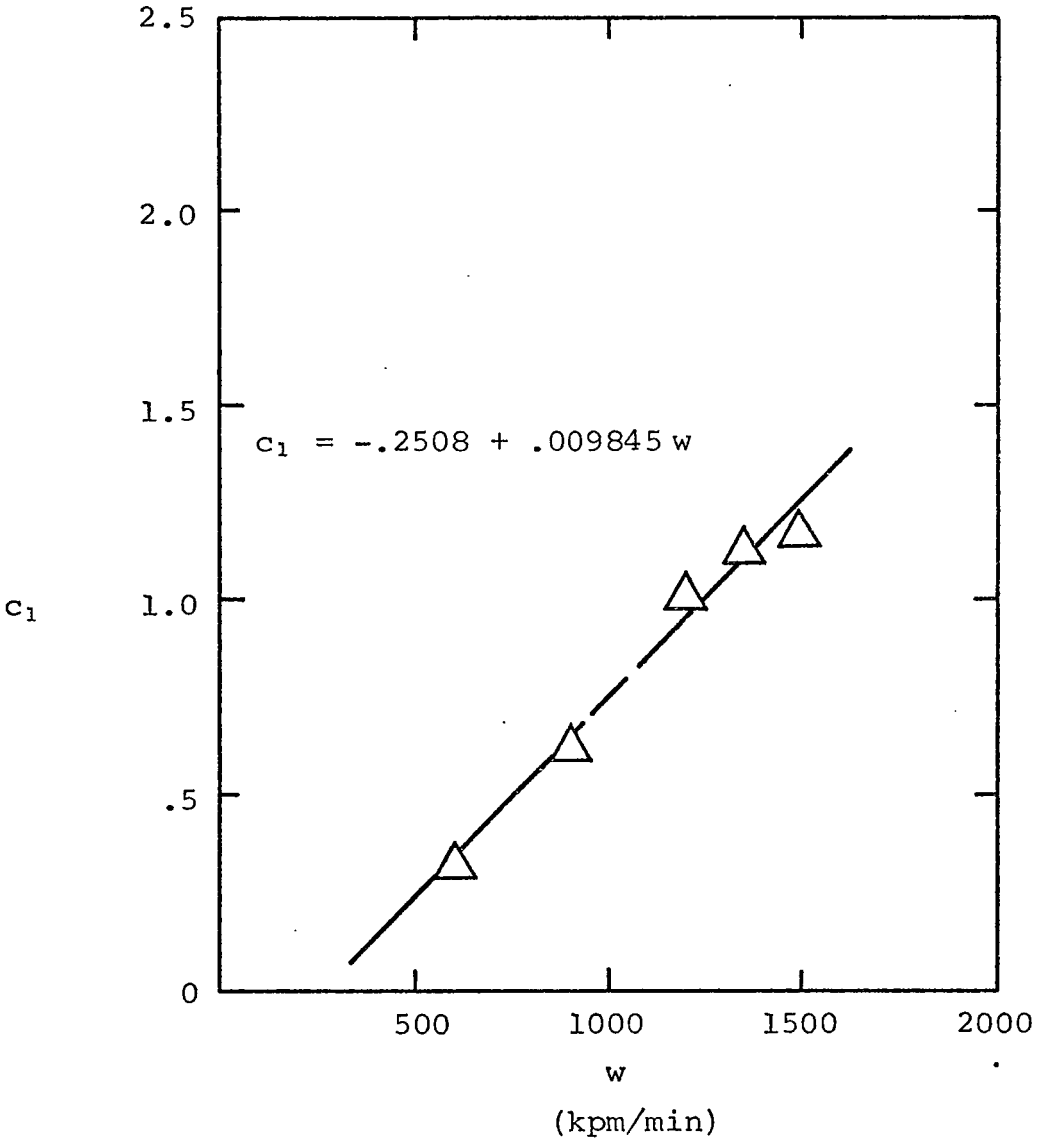

Figure 3

Plot of c_1 Coefficient
vs. Work Rate

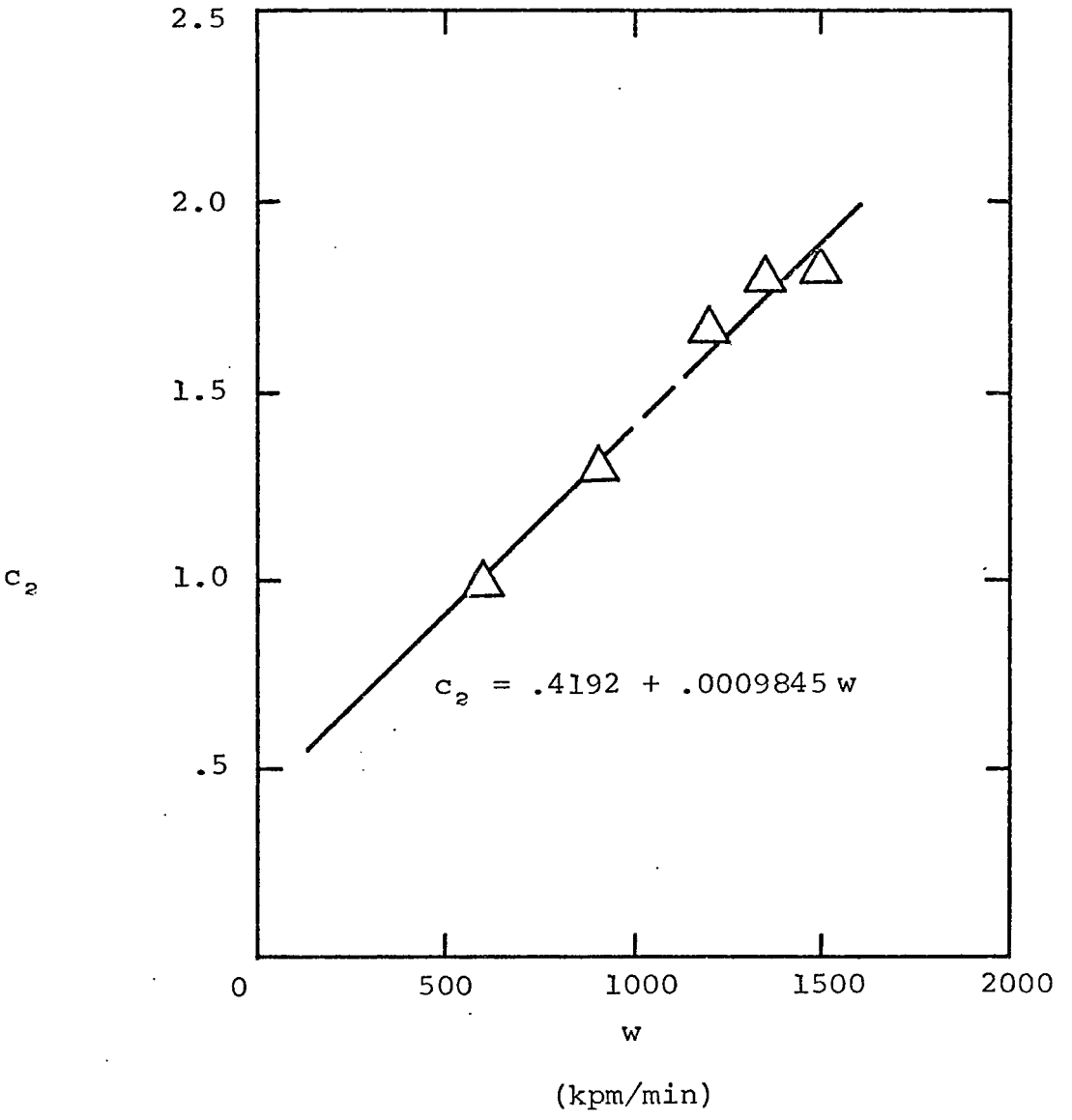

Figure 4

Plot of c_2 Parameter
vs. Work Rate

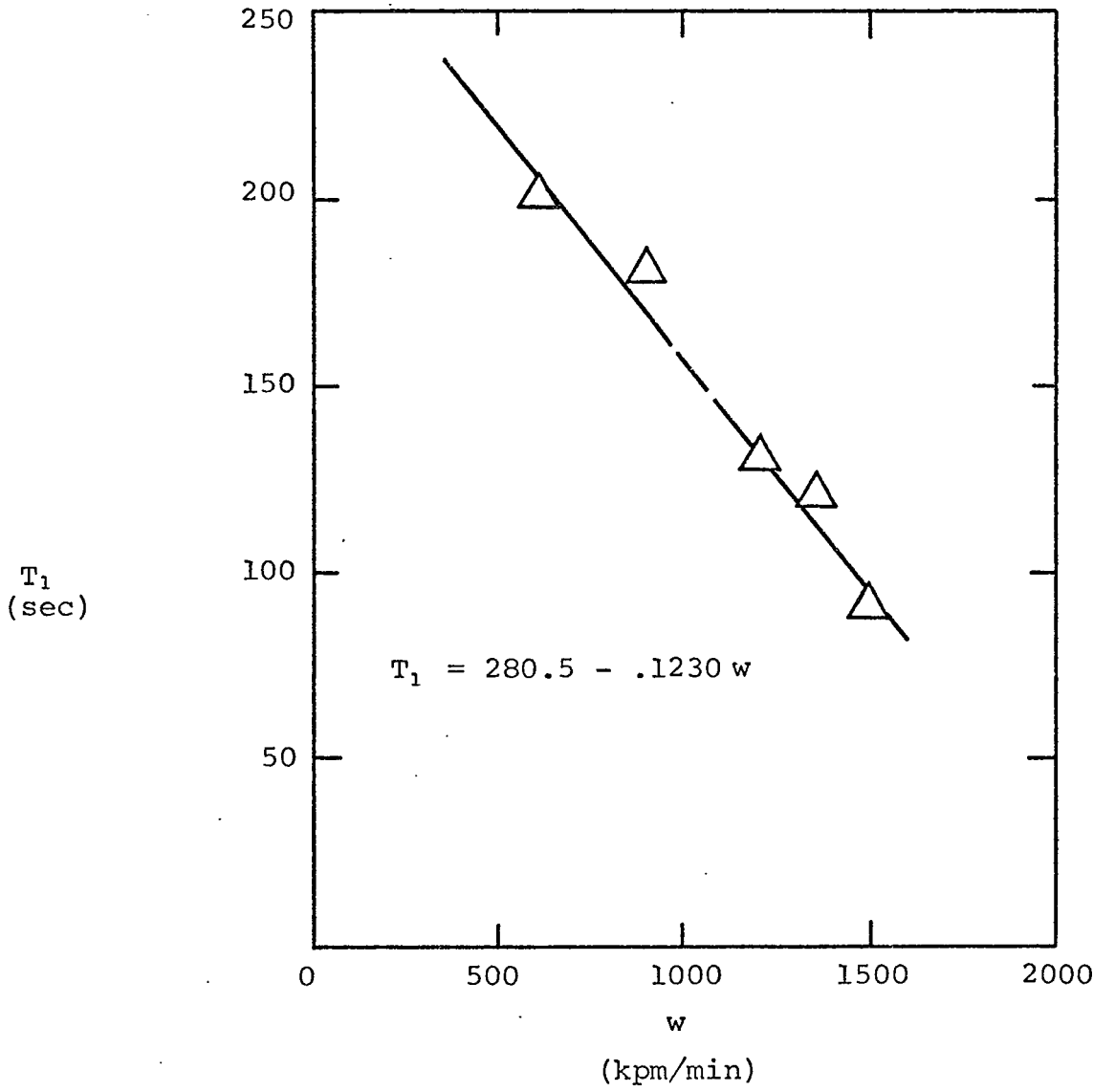

Figure 5

Plot of Rise Time Constant
vs. Work Rate

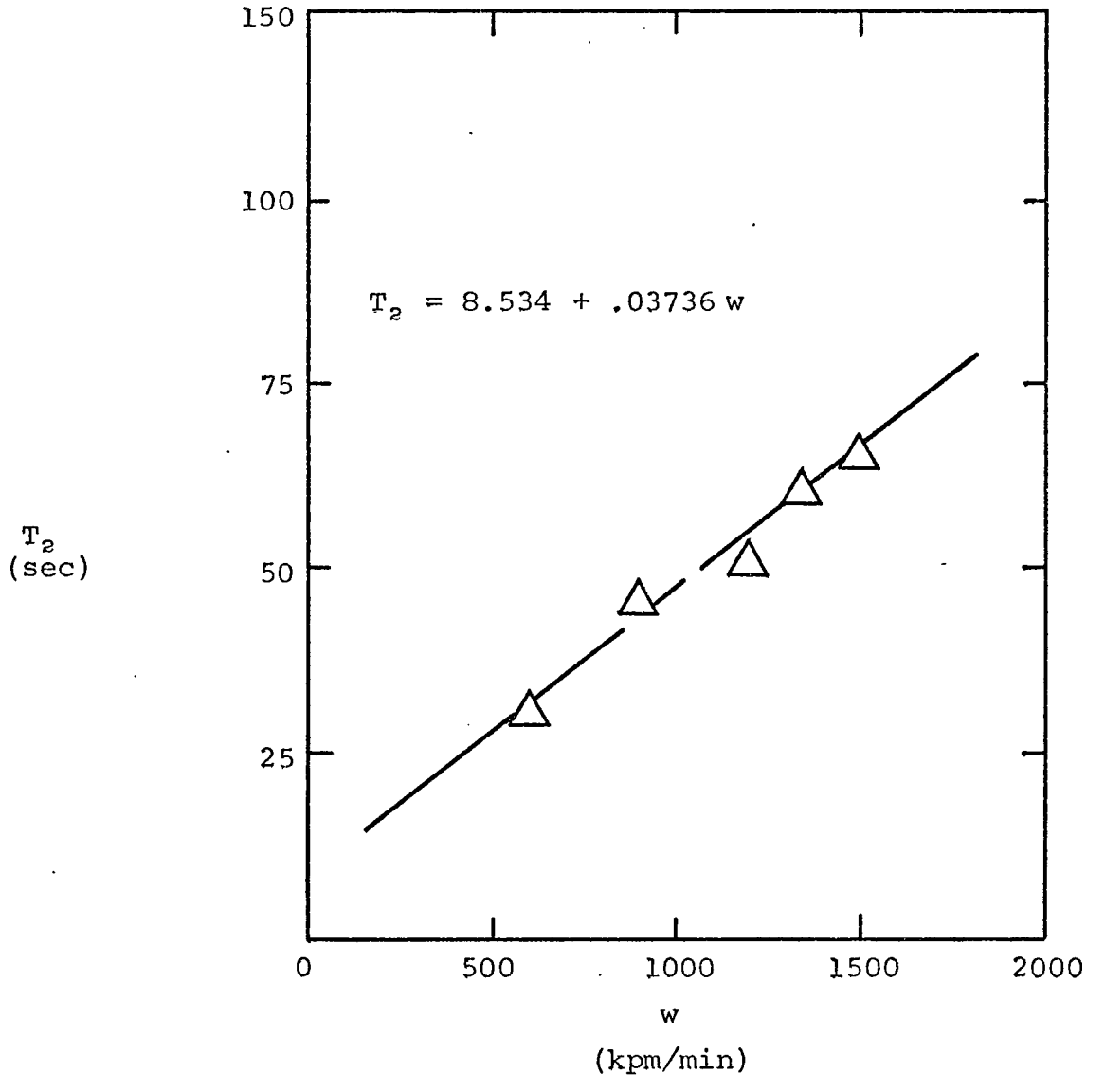

Figure 6

Plot of Delay Time Constant
vs. Work Rate

CHAPTER V

MODEL RESULTS AND COMPARISON WITH EXPERIMENTAL DATA

The steady model values are compared with a set of experimental data and with the Croston [21] model. The experimental data was published by Ekblom, et al., [25] and is for a group of eight male students, aged 19-27 years old, exercising on a bicycle ergometer. Experimental tests were made before and after training. Data taken before training are used to compare with the model.

Simulation runs were made at 300, 600, 900, 1200, and 1500 kpm/min (100 kpm/min = 723 ft-lbf/min = 16.35 watts). These work rates cover the physiological range from moderate to maximal exercise. All exercise simulation runs are for a five minute exercise period. Since a precise steady-state does not exist, steady values were obtained by averaging values taken at 10 second intervals during the last minute of exercise.

Figures 7 through 11 summarize the steady-state values obtained from the computer models and compare them with the experimental data. The charts are prepared for a comparison on the basis of oxygen uptake which is a conventional way of presenting laboratory test data. The simulation results show very good agreement with the experimental data since the model results are within the one standard deviations shown. This particular experimental data was chosen because it provides a consistent set that has small variations with respect to overall

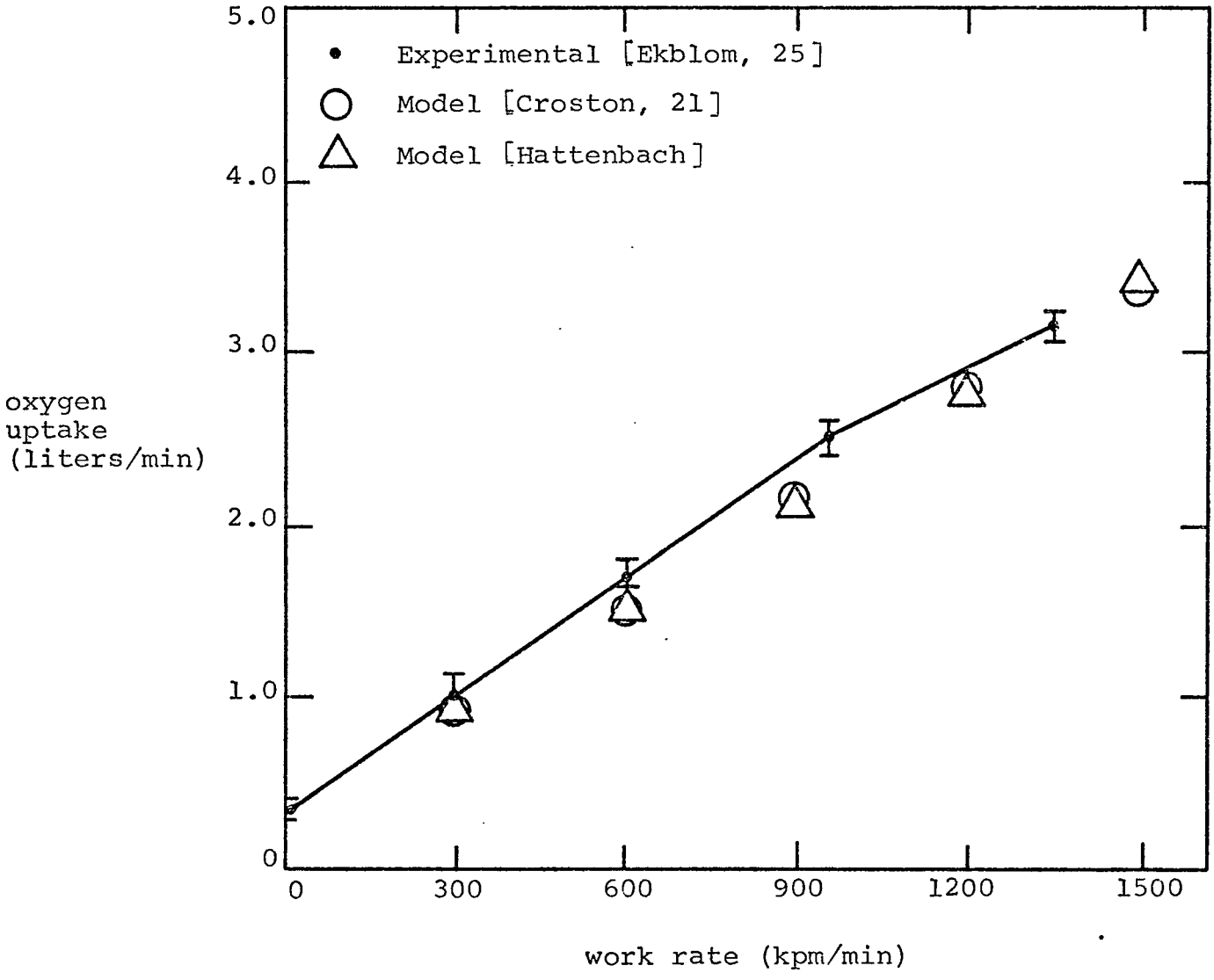

Figure 7

Comparison of Steady Values of Oxygen Uptake vs. Work Rate

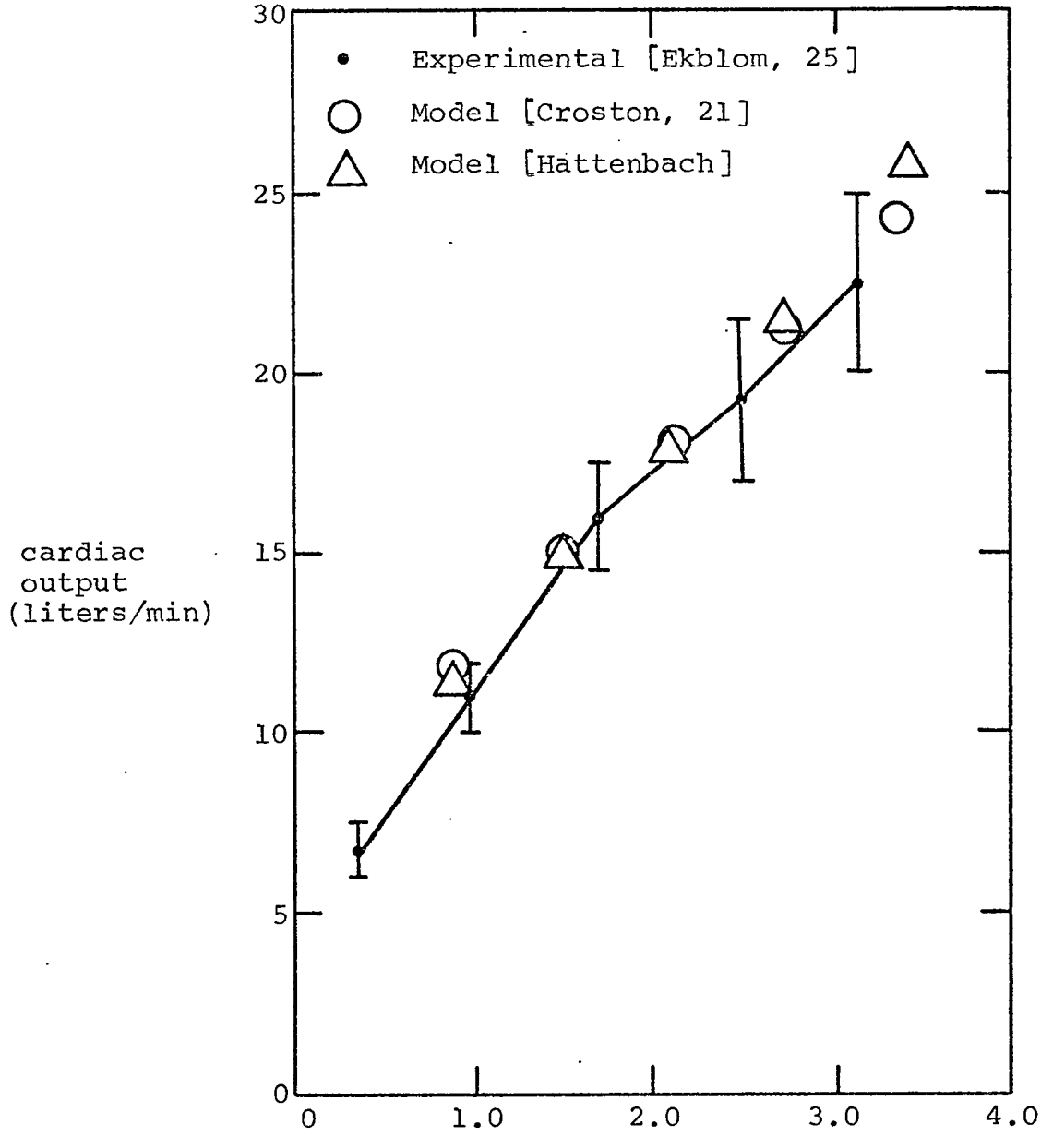

Figure 8

Comparison of Steady Values of Cardiac Output vs. Oxygen Uptake

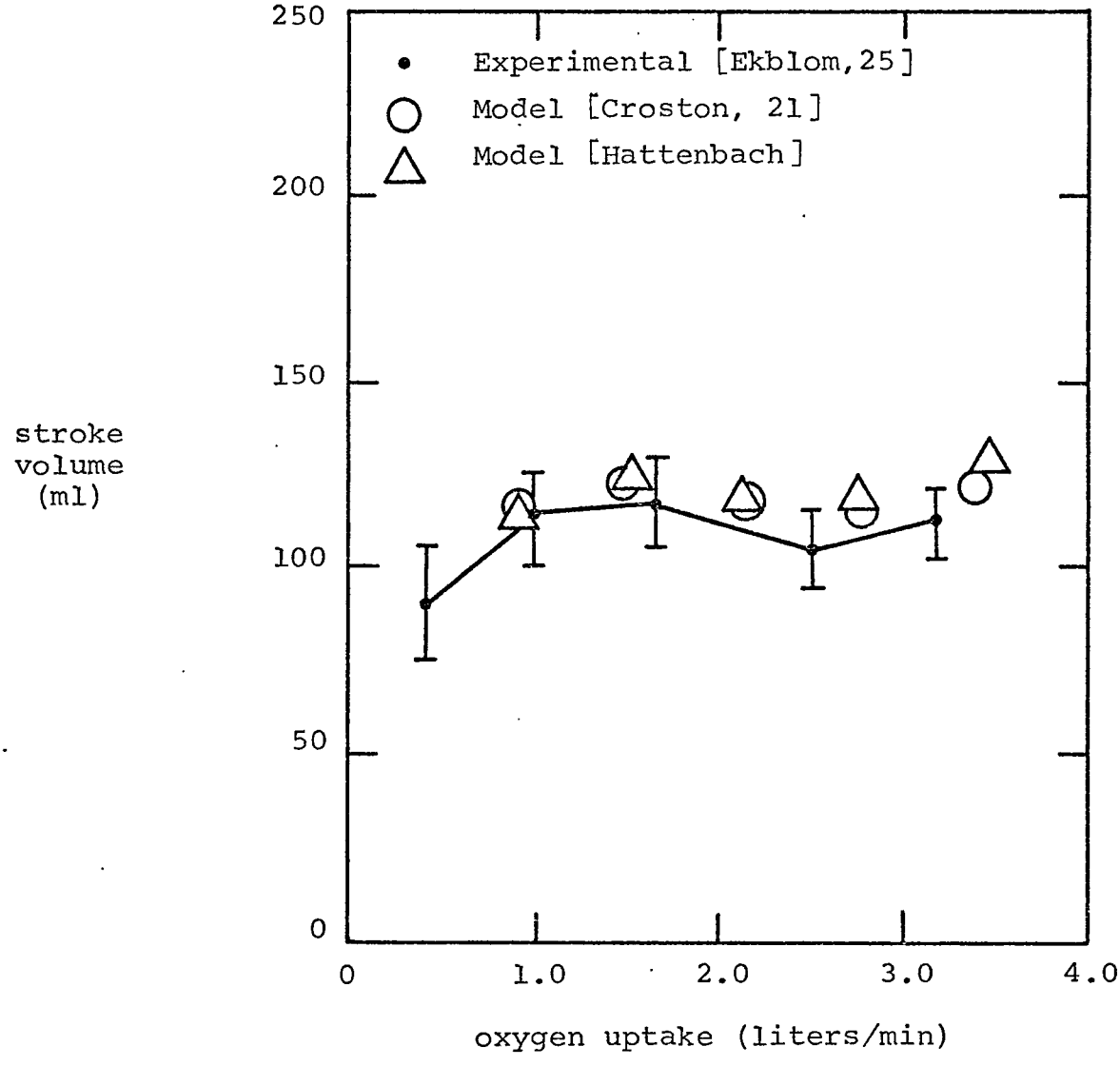

Figure 9

Comparison of Steady Values of Stroke Volume vs. Oxygen Uptake

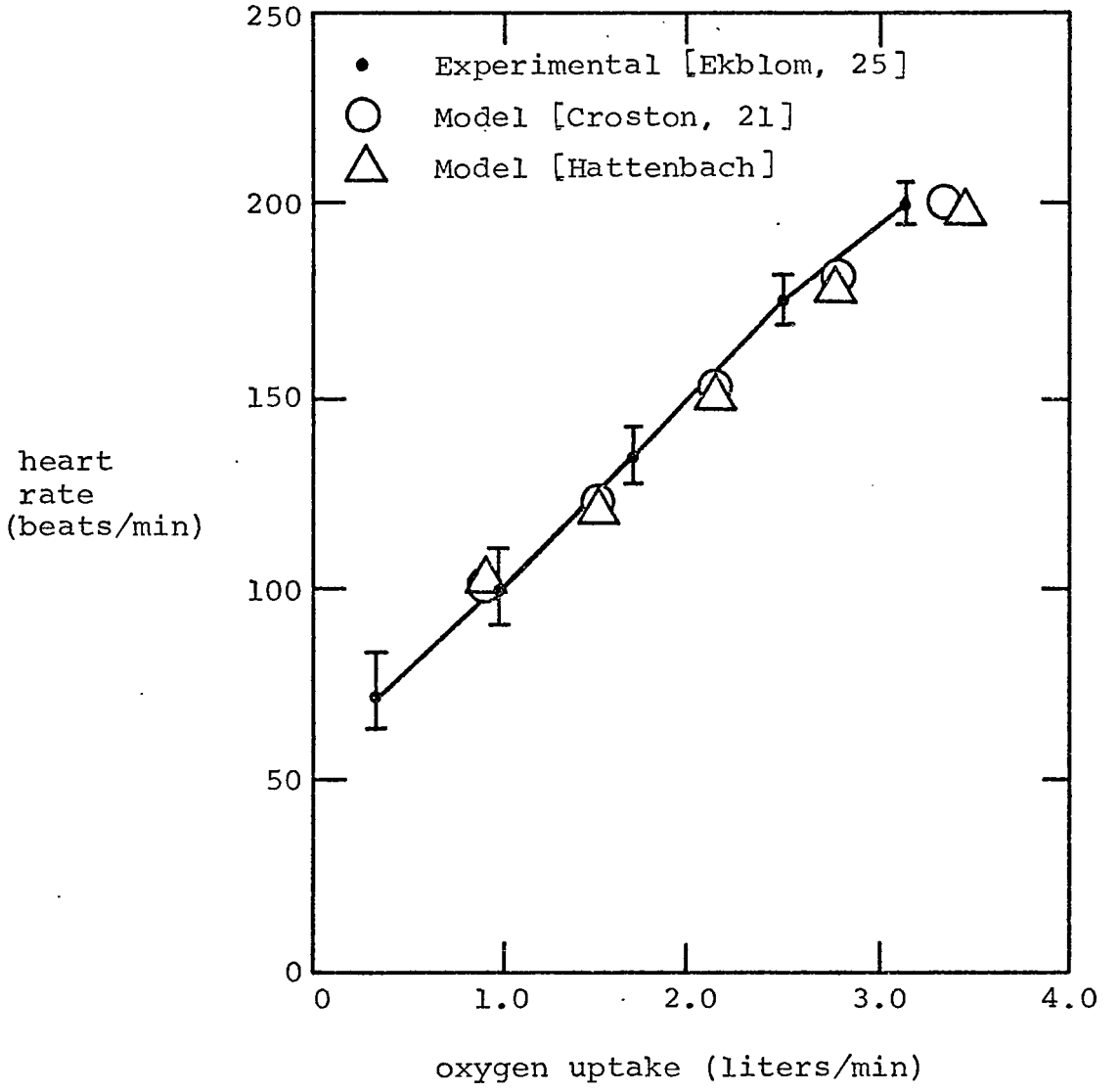

Figure 10

Comparison of Steady Values for
Heart Rate vs. Oxygen Uptake

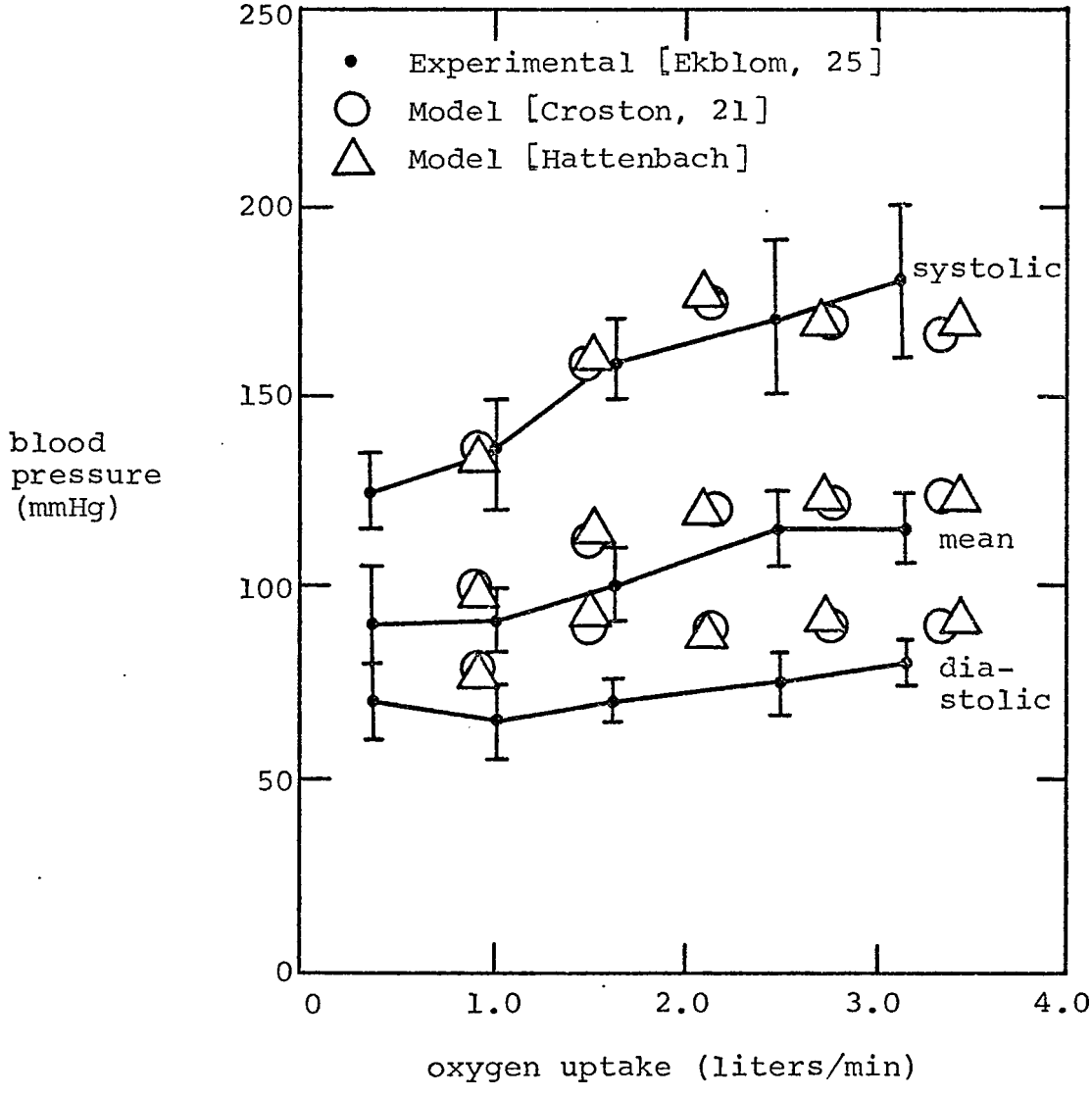

Figure 11

Comparison of Steady Values of
Blood Pressure vs. Oxygen Uptake

population variations. This allows a close comparison for model values over the entire exercise range.

This model's improvement over previous work [21] is best illustrated by Figures 12 and 13. One of the weak points in Croston's [21] model was the erratic behavior of the important cardiac variables during the transient response to moderate exercise. As the figures show, the fidelity of the transient response is much improved in the present model.

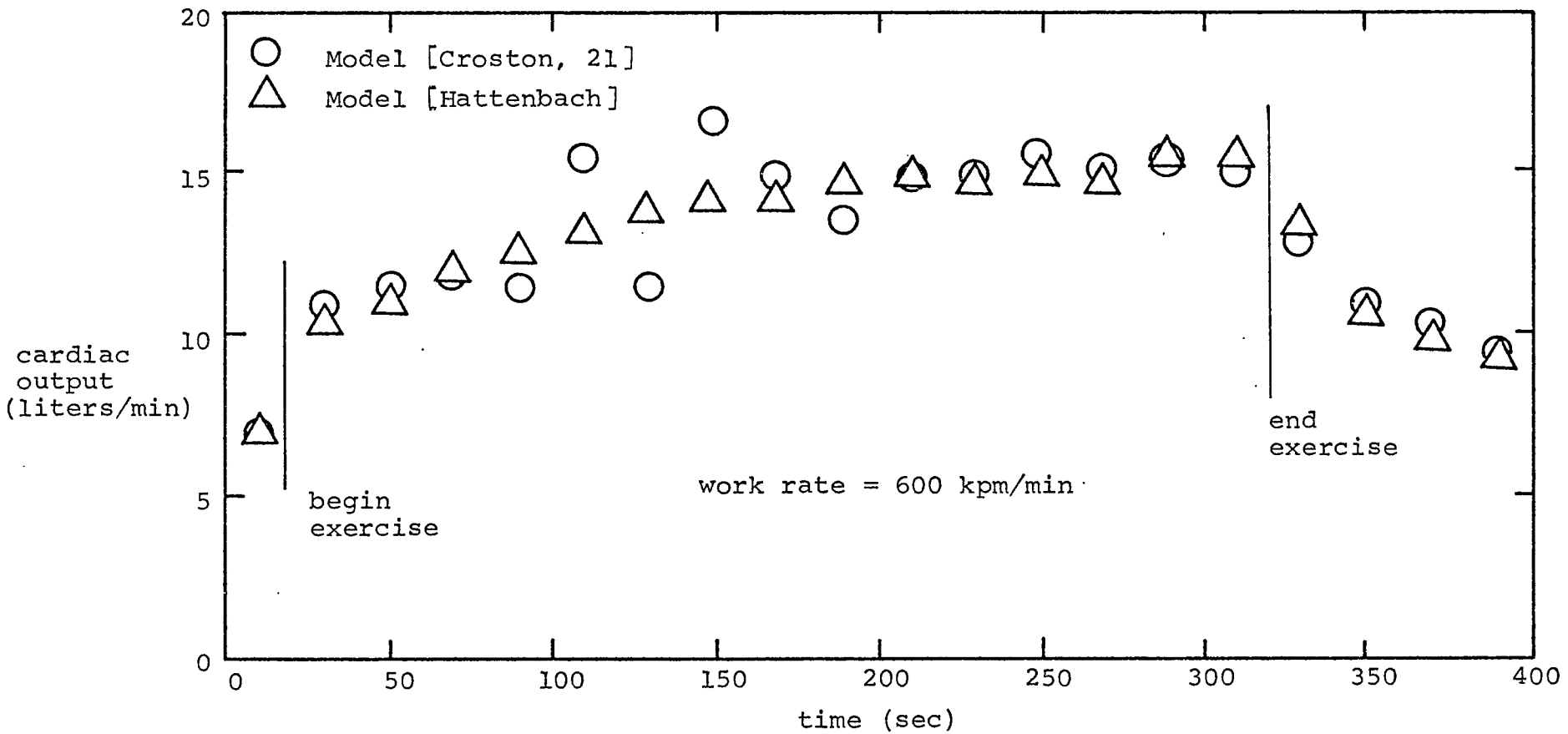

Figure 12

Comparison of Transient Values of Cardiac Output vs. Time

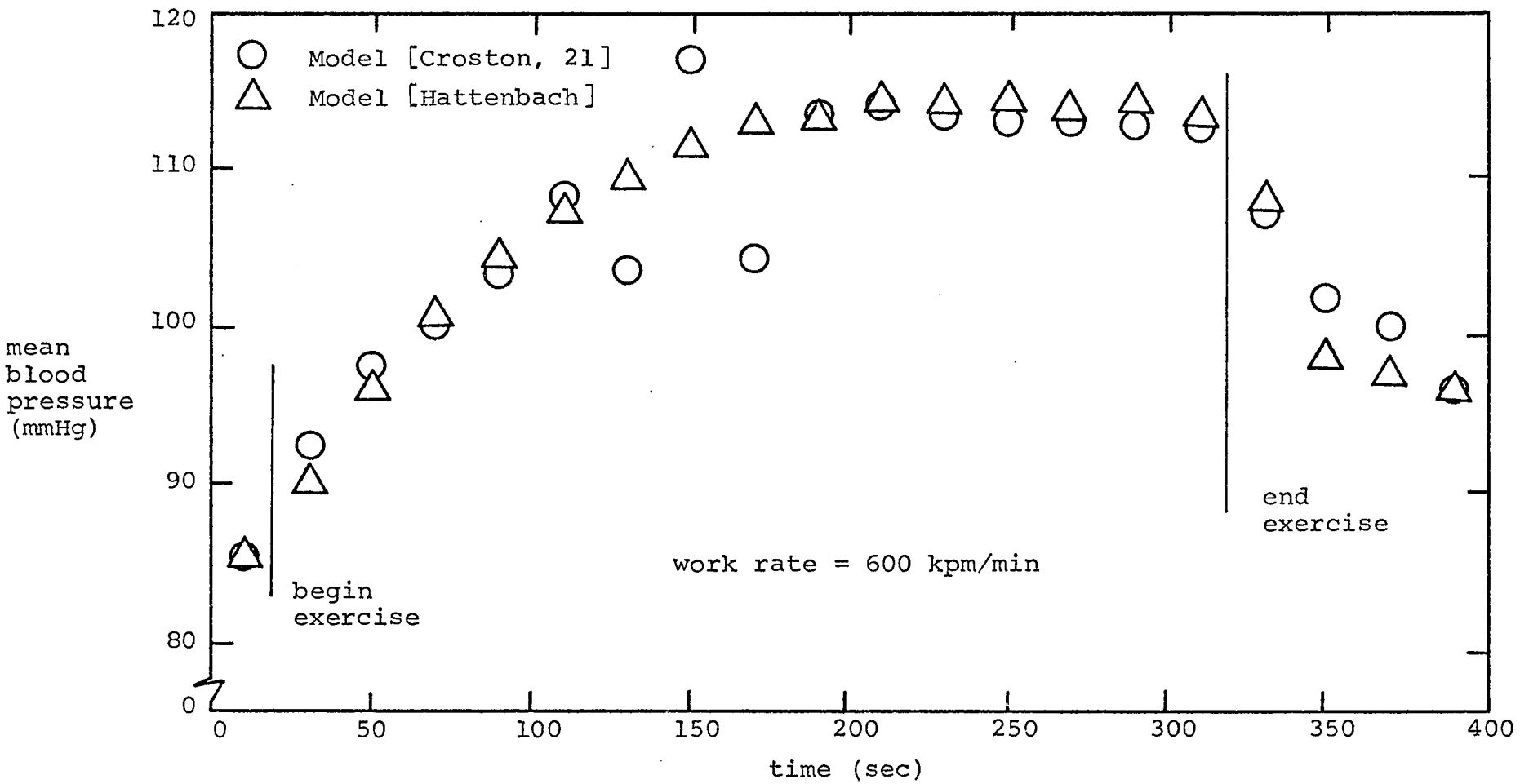

Figure 13

Comparison of Transient Values of Mean Blood Pressure vs. Time

CHAPTER VI

CONCLUSIONS

A model of contractility for the human heart has been formulated from a mathematical and physiological background. The contractility model is incorporated into a proven cardiovascular system model [21]. The combined model simulates the transient and steady-state response to exercise and is in good agreement with published experimental data. Also, when compared with the only other model available [21], the present model provides much improved fidelity in the response of important cardiac variables to exercise.

SUGGESTIONS FOR FURTHER STUDY

One problem encountered in researching the topic of myocardial contractility was the lack of data directly relating increased contractility to various rates of exercise. It is suggested that an experimental study be performed to quantify peak dp/dt or peak elastance with the rate of exercise. The study should include the transient periods at the beginning and end of exercise as well as the steady-state period obtained during exercise.

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