MYOCARDIAL CONTRACTILE FORCE AS MONITORED BY STRAIN GAGE TRANSDUCERS ON THE INTACT DOG HEART

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ABSTRACT

MYOCARDIAL CONTRACTILE FORCE AS MONITORED BY STRAIN GAGE TRANSDUCERS ON THE INTACT DOG HEART

by William E. Elzinga

The output of blood from the heart is directly dependent upon myocardial force and/or velocity of contraction. The first derivatives of cardiac force and ventricular pressure (indirectly) should quantify this "contractile velocity" of the myocardium. This study was designed to investigate the first derivative of cardiac contractile force (df/dt) as an index of heart performance; further, to investigate the relationship between maximal df/dt and maximal dp/dt (the first derivative of pressure). To monitor cardiac contractile force, a tension transducer (gage) was constructed. The transducer consists of two strain gages (each 350 ohms) attached by epoxy resin copper beryllium shim stock (6mm x 14mm). The transducer was then encapsulated (in silastic sheeting) to reduce tissue reaction. The shim (and thus the transducer) was arched to approximate the curvature of the heart. To study heart muscle tension, the strain gage transducer (S.G.T.) was sutured firmly to the epicardium. The ability of the S.G.T. to sense changes in heart performance was tested (3 dogs). The S.G.T. was energized by and its output recorded by a Grass Model 5 polygraph. In addition, to facilitate data analysis, on some occasions gage output was stored on magnetic tape

(Sanborn Model 2000) from which signals could be displayed subsequently upon a Tektronix Model 564 dual beam storage oscilloscope. Differentiation was done electronically.

When myocardial contractility was increased (epinephrine), the transducer registered an increased contractile force (after 2.5 ug epinephrine, cardiac force increased from 9.8 gm to 21.2 gm tension). Occlusion of large vessels (venae cavae, descending and ascending aorta and pulmonary artery) near the heart also were used to vary cardiac performance. Again, the S.G.T. detected the altered myocardial contractility. These results suggest that the tension transducer is capable of detecting variations in cardiac contractility in the intact dog. The gage data correlate highly with intracardiac pressure data ($r = .7$ to $.9$).

The first derivative of cardiac contractile force (df/dt) was found (18 dogs) to quantify the heart's ability to alter readily its velocity of contraction. The results show that (1) chloroform . . . hinders, (2) epinephrine facilitates and (3) ouabain slowly potentiates the ability of the myocardium to alter cardiac contractile force and thus the intraventricular blood pressure. A high degree of correspondence ($r = .6$ to $.9$) between dp/dt and df/dt was found throughout the investigation. This suggests that df/dt and dp/dt are actually measuring similar aspects of myocardial performance: the rate function of tension build-up in cardiac muscle. The high degree of correlation between the two means of estimating cardiac

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TABLE OF CONTENTS

LIST OF TABLES

Table | Page

LIST OF FIGURES

LIST OF APPENDICES

CHAPTER I

INTRODUCTION

The study of muscle physiology has occurred in two separate directions, the molecular and mechanical. The former is concerned with protein structure and chemical reactions of muscle (60). The latter approach seeks to describe the physical performance of muscle fibers.

The investigation of the structural changes in muscle during contraction has taken place to a large extent with the electron microscope. It has been demonstrated that the smallest unit of a muscle fibril is composed of proteins, actin and myosin, and muscle shortening results when these two proteins in some way slide together (81). The chemical process underlying this movement is unknown. However, the energy source is adenosine triphosphate (61).

The chemical nature of muscular contraction has been investigated indirectly. These studies have utilized metabolic and thermal techniques, whereby the oxygen uptake and/or heat liberated by the tissue reflects the energy used in chemical reactions of shortening.

The mechanical properties of muscles have been studied under a variety of different conditions (66). Great strides have been made in the understanding of skeletal muscle performance. Recently, that which is known about skeletal muscles has been applied to cardiac muscle mechanics

and in many instances, this approach has given a better understanding of cardiac contractility (82, 84).

There are essentially two ways to study muscle mechanics. First, by directly measuring the force generated by the muscle and/or the rate at which the fibers shorten, and secondly, by indirectly measuring changes in the object or substance that the muscle has acted upon. For example, skeletal muscles move appendages and cardiac muscles move blood.

Cardiac performance is usually investigated by considering the heart either as a pump which is made of muscle or as a muscle which is acting as a pump. Some scientists are concerned mainly with how much blood the heart is capable of pumping and express their results in terms of cardiac output or stroke volume. Still others are concerned with how the heart, as a muscle, can vary its output of blood.

Numerous researchers have studied the heart as a muscle. It has been demonstrated that the myocardium can increase its force and velocity of contraction (86). By increasing its force, the myocardium provides a higher systolic intraventricular blood pressure; by increasing its velocity, the ejection of blood from the ventricle occurs more rapidly.

This investigation is a study of these two properties, force and velocity, of the myocardium. Its purpose is to describe in detail the manner in which the cardiac

contractile force and the velocity of contraction change in relation to variations in the intraventricular blood pressure. Chloroform, epinephrine and ouabain were used to alter the contractility of the heart in order to provide changes in force and pressure measurements.

For direct measurement of cardiac contractile force, a specially designed strain gage transducer was constructed. The transducer was sutured firmly to the epicardium of the heart. The ability of the transducer to measure changes in cardiac contractile force was investigated.

CHAPTER II

SURVEY OF LITERATURE

Muscle Mechanics

Thermal Aspects of Muscle Contraction

Much was already known about the concept of energy when studies of muscle physiology were only beginning. The laws of thermodynamics were well established by this time. It was known that transformations of energy are associated with the liberation of heat and that chemical compounds probably contain energy which is used for many biological phenomena. It was most likely then, because so much was known about energy, that the first studies on muscles were thermal. It was hoped that such thermodynamic studies would provide useful clues to the intimate mechanisms involved in muscle contraction and would give some insight to the relation of the mechanical event and chemical changes.

Strictly from a historical stand-point, it is of interest that the earliest work done on muscle heat production dates back to Heidenhain in 1864. He discovered that if weights were hung on a muscle (not after-loaded) that the heat production, caused by the contraction of the muscle and the lifting of the weight, increased with increasing weights. In 1878 Fick supplied evidence that the contraction heat also increased with increasing load even if the muscle always contracted from the same initial

position. It was further demonstrated by Blix in 1901 that a muscle gives off more heat in an isometric contraction than in an isotonic one.

Many of the modern heat production studies were by A. V. Hill and Hartree (57). One of the major problems confronting them, and one which confronts scientists today, was the construction of an apparatus which would give highly accurate readings of temperature changes occurring in the contracting muscle. Hill, after many years of experimentation with thermocouple, perfected a highly sensitive galvanometer which was quite satisfactory.

Muscle contraction is accompanied by the liberation of heat under aerobic conditions in two principal phases, the initial and delayed heats (37). The maximal initial heat production lasts for a very short time and was described by Hill as being instantaneous (36, 38). The maximal delayed heat phase occurs after the mechanical event is over and lasts for a longer time. The delayed heat is at least as great as the total heat liberated during the contraction (initial heat). Hill explained that initial heat production was associated with the energy used in actual muscle contraction, i.e., the shortening of fibers in isotonic contraction or build-up of tension in isometric contraction. He suggested that delayed heat was the restoration of initial heat. It was later shown (39), that if heat measurements were carried out in nitrogen, in

place of oxygen, only an initial burst of energy was released. This indicates, as pointed out by Hill, that energy required for contraction of muscle is derived from nonoxidative reactions. The restoration of this energy, on the other hand, depends exclusively on oxidative processes. This was the first recording of the phenomenon of oxygen debt.

The time course of heat production in contracting muscles was well defined by Hill's early experiments (37, 41). The second step in the study of muscle mechanics was the search for factors that caused the initial heat production to vary. Fenn's investigations of the relationship between work performed and energy released (24, 28), opened this so called "second stage." He found that the amount of actual energy liberated by a muscle is not constant for any given initial condition of the muscle but varies with the load. A large load resulted in the liberation of more energy than a small load. This concept came to be known as the "Fenn Effect," which states that the muscle in some way can adjust its output of energy to the task required of it.

The discovery that heat production in contracting muscle depends largely on the conditions to which it is subjected, led to investigation of the effect of varying the muscle length on the amount of heat produced during an isometric contraction. It was found (34) that if a muscle is allowed to shorten before or during the development of

tension, the heat production may be 20 to 30 percent smaller than it would have been had the muscle never been allowed to shorten. If, however, the muscle is allowed to shorten only when the tension has already reached its maximum value, then the heat production is in no way affected by the shortening. This led Hill to suggest that after the tension is maximal, the muscle acts as a purely elastic body with potential energy capable of doing work or of being liberated in the form of heat.

From results of the previous study, Hill (38) proposed a theory to explain events that occur in a muscle contraction. He states that in an isometric contraction a "damped element" (contractile element) shortens and stretches an elastic element. In this way the overall length of the isometrically contracting muscle does not change. The tension generated by the muscle reflects the recoil properties of the elastic elements. Hill suggests that the contractile elements in a muscle develop a maximal "active state" or force almost instantaneously. The "active state" is associated with the initial stage of heat production. The contractile elements deliver a certain quantity of energy for a finite period of time and immediately thereafter relaxation takes place. During the "active state" of the contractile elements, the elastic elements are being stretched and tension (force) of the muscle builds up in direct proportion to the degree of stretch.

The total force that a muscle can develop depends to a large extent on the duration of the fully "active state" of the contractile elements. If the contractile elements remain in the fully "active state" for a longer period of time (during repetitive stimulation), more of the available energy would be used and more stretching of the elastic elements would occur giving a greater tension developed by the muscle. For example, during a tetanic muscle contraction, the developed force is greater than that which occurs for a single muscle twitch.

The above theory was tested by changing a muscle length physically before and during a muscle twitch (31). By stretching a muscle at various intervals after stimulation, it should be possible to prestretch the elastic elements and the contractile elements then should develop a greater force than if no prestretching had occurred. That is, the total force developed by the muscle should be equal to the physically prestretched elastic elements plus the force developed by the contractile element.

Gasser and Hill (31) discovered that the sooner the muscle is stretched after it is stimulated, the greater the developed force. It was concluded that the contractile elements develop their full force (fully "active state") almost instantaneously after the stimulus is applied. The prestretching in succeeding intervals after the stimulus, gives a smaller force because some of

the energy is already dissipated in stretching the elastic elements prior to the prestretching.

From the results of the previous study, Gasser and Hill (31) formulated a definition of the "active state" of muscle contraction as follows:

> The stimulus is followed by a wave of depolarization followed within some mill-seconds by a sudden decrease in extensibility of the muscle, a decrease of extensibility that is presumable the mechanical sign of a vigorous shortening of the contractile elements; this change which is called the development of the "active state" lasts for only a short time during which the elastic elements are stretched.

Associated with the "active state" of muscle contraction which characterized the initial phases of contraction, it was also found desirable to find some expression that would cover all phases of the isometric contraction. This expression was determined by Hill (44) to be the "tension-time" measurement, or the total areander the tracing of an isometric contraction curve. The total area was found to be directly proportional to the total energy used in the contraction (42). Hill used the "tension-time" index because during isometric contraction of muscles no external work is done. However physiologically, work is being done to promote the internal "shortening" and to maintain a tension. In isometric contractions the extra rate of energy turnover is directly proportional to the tension developed. Muscles demand an increased rate of

energy consumption proportional to the tension developed even if no external work is done.

Perhaps the most striking discovery by A. V. Hill is that muscle heat production is a simple linear function of the degree of fiber shortening (39, 46). When a muscle was allowed to shorten at variable velocities, the force and heat production diminished considerably as the speed of shortening increased. The faster an active muscle shortens, the further the tension fell or as the speed of shortening of the muscle increased, the work done (or the tension developed) fell off linearly according to the equation $W = W_o - kV$, where W is the work done, W_o the potential energy, K a constant and V the velocity of contraction (43).

Since the inverse "force-velocity" or "heat-velocity" characteristic of muscle contraction was presumed to be a linear phenomenon, a model was proposed for skeletal muscle (45). A muscle is a simple spring in a viscous medium. This model accounted for the linear inverse relationship between "force-velocity" in that when the velocity of shortening increased the frictional resistance to shortening increased in direct proportion (24).

It was soon demonstrated however, that a simple linear relationship between the velocity of shortening and force generated or heat dissipated does not generally

exist (53). As the speed of shortening increased, it was found, the force decreased not in a linear fashion as would be the case if viscosity alone were concerned, but rather in an exponential fashion. To explain the exponential "force-velocity" relationship, Hill (28) altered his muscle model somewhat. He proposed that a muscle has active contractile elements in series with passive elastic ones. The former obeys Hill's equation of linearity; the elastic elements caused the nonlinear exponential relationship.

However, it was again shown that Hill's equation was inadequate to explain the inverse "force-velocity" relationships. Levin and Wyman (53) devised a method whereby the elastic components of a muscle were held constant during a muscle twitch. In this way the contractile elements could be studied alone. They found that the "force-velocity" graphs were not linear but exponential. It was, therefore, concluded that the inverse exponential "force-velocity" characteristics of contracting muscles were not due solely to the elastic component but also to the contractile elements.

Hill (46) stated that the viscous theory of muscle contraction must be dismissed. The muscle may still have viscoelastic properties but they are less important in muscle behavior than the other properties of shortening heat and energy regulation. He concluded that the active muscle is a two component system containing an apparent damped element (contractile element) in series with the undamped elastic one.

Functional Anatomy and Movements of the Heart

Anatomy

Knowledge of the functional anatomy of cardiac contraction is essential for an understanding of cardiac action. Actually, the two ventricles have different anatomical and functional characteristics. The energy released during systole of the heart represents the combined effects of various bundles of myocardial fibers. Contribution of each bundle depends not only on its contractile power but also on its anatomical orientation with the cardiac walls (69, 75).

Four valve rings of dense connective tissue join to form a fibrous skeleton of the heart. The atrial and arterial trunks are attached to the superior surface of this fibrous skeleton; to its inferior aspect are fastened the arteriovenous valves and ventricular chambers (69). The atrial musculature is thin and arranged as bands radiating from the sulcus terminalis. The atria have two muscular systems, one common to both atria and encircling them, the other arranged at right angles and independent for each atrium (75). From a functional point of view, the ventricular musculature has two groups of myocardial bundles, the spiral muscles and the deep constrictor muscles (71). The superficial spiral muscles, which arise from the mitral and tricuspid rings cover very thinly almost the entire surface of both ventricles to a depth of about 1 mm. They course

diagonally around the surface of both ventricles to converge at the apex where they are strongly twisted and where they make up the full wall thickness. They penetrate to the interior of both ventricles to form its inner thin layer of spiral muscle and the lower third of the interventricular septum. They spiral upward in reverse directions to form the papillary muscles from which fibrous tendons attach to the valve leaflets. The inner and outer spiral muscles follow oblique directions about 90° apart since they spiral in opposite directions. As they contract, the oblique traction by the outer layer is opposed by tension in the opposite direction by the inner layer. The net result of their action is a shortening of the ventricular cavities longitudinally rather than a rotation of the ventricles (70). Interposed between the thin exterior and interior spiral muscles, are the deep constrictor muscles which make up the basilar two-thirds of the septum and lateral wall of the left ventricle. In the right ventricle these deep circular fibers form a thin middle layer but its contribution to thickness is small compared to that of the inner and outer spiral layer. Because the left ventricular wall contains a large mass of circularly arranged constrictor fibers, its contraction would be expected to result predominantly in a reduced ventricular diameter with minimal shortening from apex to base whereas in the right ventricle with its dominance of spiral muscle, the ventricle should shorten with little movement of its lateral wall (72, 73, 74).

The configuration and contraction of the right and left ventricular chambers are very different. The right ventricle resembles a pocket fastened to the periphery of the convex intra-ventricular septum. During contraction, the free wall conforms more closely to the convex septum, ejecting blood into the pulmonary artery and at the same time evacuating most of the blood contained around the periphery of the chamber (75).

The left ventricle resembles more of a cylinder with a conoid segment at the apical end. Systole produces primarily a reduction in the diameter of the chamber. Shortening of the ventricle plays a minor role in the systolic ejection (75).

Ejection of blood by the right ventricle is accomplished primarily by a shortening of the free wall drawing the tricuspid ring toward the apex of the heart. Changes in the width of the right ventricular chamber are relatively slight but may be significant due to the large surface area between the interventricular septum and the free wall of the ventricle (74).

The thick constrictor muscles encircling the left ventricular cavity are probably responsible for a major portion of the left ventricular wall thickness.

Movements of the Heart During Contraction

In studies on muscle movement of the heart (69, 73), tiny metal markers were placed on the epicardium and their

movements investigated. It was shown that the movement of the markers located in the free walls of the ventricles may be described in two directions: (1) toward the apex (parallel with the wall); (2) toward the interventricular septum. In the right ventricle longitudinal shortening of the free wall was the predominant movement with little reduction in right ventricular width. Thus, metal markers on the free wall moved primarily toward the right ventricular apex.

In contrast, the markers on the free wall of the left ventricle moved obliquely toward the apex and toward the interventricular septum indicating a simultaneous reduction in width and length of the chamber.

According to Rushmer, et al. (74), there are but two functional groups of muscle in the heart: (1) the spiral muscle which forms the internal and external investment; (2) the deep constrictor muscles. Simultaneous shortening of the internal and external layers of the spiral muscle do not produce rotation since the oblique tension exerted by each layer is mutually counteracted. The result of their combined action is to shorten the long axis of the chambers. On the other hand, the deep constrictor muscles act to reduce circumference. Since the deep constrictor muscles are much more powerful in the left ventricle than in the right, the left tends to be compressed in width to a greater extent than the right.

The different muscle layers, because of their arrangement in the heart, must slide past one another. However, it has been impossible to demonstrate this since the individual muscle layers are very difficult to locate and/or separate.

Evidence has been presented by Rushmer, et al. (74) that during systole, the myocardial fibers in different layers do pull against each other and apply stretch to the connections between them. This fiber stretching represented potential energy which was wasted as far as systolic ejection was concerned. However, as the ventricles begin to relax, this potential energy was used to return the ventricular chambers toward their diastolic dimensions, and ventricular filling began immediately. This mechanism was more effective in the thick walled left ventricle.

Changes in left ventricular diameter during the cardiac cycle in unanesthetized dogs, using variable inductance gages, has been described by Rushmer (70). He found that there was an increased ventricular diameter during the early filling period, followed by a plateau-duration of slow filling, terminated by a small increase during artial contraction and a rapid increase at the beginning of systole. After this, the ventricular diameter decreased during systole.

Rushmer's (70) data on ventricular diameter suggested that no real isometric stage of cardiac contraction (as first suggested by Wiggers) existed. He concluded that a

more appropriate term would be isovolumic. The volume of blood in the ventricles remained constant, however, the shape of the heart changed during the period of isovolumic contraction. Most hollow elastic structures tend to assume a more spherical shape as their internal pressure increases and the abrupt increase in ventricular diameter, shown by Rushmer to occur at the onset of ventricular systole, might be due to a rounding and shortening of the chambers (13).

Application of Skeletal Muscle Mechanics to Heart Muscle

Force-Velocity Relationships of Skeletal and Heart Muscle

In the past few decades, much information has been recorded concerning the mechanics of skeletal muscles (10). Only recently this information has been applied to heart muscle (30, 82). The acquisition of data for analysis of heart muscle mechanics, on a level comparable to that for skeletal muscle, is limited by the relatively complicated geometry of the heart and the consequent difficulty of making certain (isotonic or isometric) measurements. The use of isolated heart papillary muscle (a segment of the myocardium with parallel fibers, reasonable dimensions and stable performance when studied *in vitro* (1, 39), though possibly introducing other limitations (removal from the body and not perfusing), appreciably diminishes the problems present when examining the intact heart muscles.

It is well known (28) that an increase in skeletal muscle fiber length strenghtens the force of contraction. Sonnenblick and McCallum (82) have shown that cardiac muscle increases its force of contraction when the fiber length is increased.

The inverse relationship between force and velocity of shortening comprises one of the most fundamental properties of the contractile system of skeletal muscle (48, 49). The papillary muscle of the feline heart also is reported to show an inverse relationship between force and velocity of shortening (82).

There are differences, however, between cardiac and skeletal muscle mechanics. Sonnenblick (83) has demonstrated with papillary muscles that an increased initial length of the cardiac muscle increased the maximal rate of tension rise. This does not occur in skeletal muscle. An increased frequency of stimulation of the papillary muscle also increased the maximal rate of tension rise. Again, this is not true of skeletal muscle (83).

None of the physical factors that changed the contractile force in skeletal muscle (except temperature) altered its maximal velocity of contraction. In cardiac muscle an increased initial muscle fiber length, higher frequency of stimulation, or a change in chemical environment (calcium, norepinephrine) all may alter the maximal rate of force rise (58, 82, 87, 85).

Myocardial Contractility

The Need for Definition of Terms

Though the term myocardial contractility is often used, it is seldom defined and almost never in terms that are generally applicable. Most workers appear to think of changes in myocardial contractility in terms of some index appropriate to the conditions of their experiments rather than in terms of the fundamental properties of the muscle itself. For example, investigators (57, 19, 52, 65, 74, 77, 78) have defined myocardial contraction in terms of cardiac output, stroke volume output, work done, ventricular pressure, as an increase in external stroke work, as an increase in external stroke power from a given end-diastolic fiber length and finally as a combination of ventricular diameter and pressure as well as accumulated work and power. While these definitions and many others are useful under the conditions of the experiments for which they were devised, they are not suited to experiments in which isometric or isotonic contractions take place. These indices all give some indication of heart performance. However, the measurements are indirect and may not be measuring what the heart muscle is doing at all. For example, cardiac output is not necessarily dependent upon only the force or velocity of contraction of the heart muscle, but also is dependent upon such factors as peripheral resistance, venous return, and end-diastolic volume.

A Useful Definition of Myocardial Contractility

It is not easy to describe myocardial contractility in terms that are generally applicable. A complete description of the contractility of a muscle, whether skeletal or cardiac, seems to require the use of four variables, all of which may change simultaneously during the course of a single contraction. The usual four variables are: (1) tension in the muscle; (2) the velocity of shortening; (3) fiber length, and (4) the time after excitation (85).

Blinks and Koch-Weser (8) believe that similar considerations can be applied to cardiac muscle but because there may be no plateau of full activity, it seems more meaningful to formulate them somewhat differently. They suggest that changes in myocardial contractility be defined as changes in the performance of the heart that arise from changes in the relationships among force, velocity, fiber length and the time after excitation.

Most investigators of myocardial contractility are inclined to believe that variation in heart performance arising simply from a change in physical conditions outside the contractile system (changes in the tension developed, the work done, or the distance shortened) does not necessarily reflect a change in myocardial contractility. For example, changes in the tension developed with changing fiber length (Frank-Starling phenomena) are not considered to represent variations in myocardial contractility, nor are differences

in the work performed by isotonic contractions against differing afterloads (81). When the duration of the "active state" changes, a contractility change is thought to occur, whether or not the maximum isometric tension increases. Changing fiber length does not alter the duration of the active state (87).

The "active state," which characterizes the properties of the activated contractile elements is very important in defining myocardial contractility. The definition of myocardial contractility lies within the chemical processes (from which the "active state" is derived) which cause the contractile elements to shorten and develop tension. Very little is known about these chemical processes. The passive series elastic elements in heart muscle are characterized by the heart's load-extension properties (13, 87). The active contractile elements are best characterized in the terms of four dimensions: force, velocity, instantaneous muscle length and time. The identification of the four variables of the "active state" and their quantification provides a framework for the evaluation of myocardial performance (87) and is a rational basis for defining myocardial contractility.

Myocardial Contractility as Defined by Changes in the First Derivative of Ventricular Pressure Pulses

Some investigators, in attempting to define myocardial contractility, have used the first derivative of the intraventricular blood pressure curve as an index of heart

performance (23, 63, 64, 70, 76, 79, 90, 91). The first derivative of the intraventricular blood pressure pulse for a complete cardiac cycle simply gives the rate of change of pressure as a function of time. In other words, the first derivative gives the velocity of pressure build-up during systole expressed as mm. Hg./sec. The velocity of pressure change is usually not constant during any phase of systole but is accelerating for approximately one-half of systole and decelerating for the remainder. In one particular study (33), a summary of the changes in the first derivative of the intraventricular pressure pulse are given for a complete cardiac cycle. This was done during human open chest surgery. A needle, connected to a pressure sensing transducer, was inserted into the left ventricle. It was found that during ventricular diastole, when the rate of change of ventricular pressure is slow, the first derivative (dp/dt) is flat and about zero. With the onset of contraction in the left ventricle, dp/dt increased slowly for several milliseconds and then rose smoothly to reach its peak derivative near the midpoint of the isovolumic contraction period. In the right ventricle it was found that dp/dt exhibited either a notch or an inflection on its ascending limb. The dp/dt fell abruptly to values far below zero during late systole. The peak values for rate changes in left ventricular pressure (dp/dt) were within the range from 841 to 3,239 mm. Hg./sec. The authors stated

that the rate at which ventricular pressure developed was a fundamental property of the contracting myocardium.

Sonnenblick (87) has previously demonstrated on cat papillary muscle, that the initial fiber length at the onset of contraction greatly influenced the maximal rate of force rise. Reeves, et al. (63) were interested in determining how much initial fiber length influenced maximal rate of pressure rise in the intact dog. The data suggest that the maximal rate of pressure rise (dp/dt) is altered by the same mechanical conditions in the intact heart as Sonnenblick has described for the isolated papillary muscle. Contraction of isolated heart muscle demonstrates two prominent characteristics.

First, under constant load, steady frequency of stimulation and constant inotropic state, the rate of force development increases with increased fiber length. In the intact ventricle, maximum dp/dt increased as left ventricular end-diastolic-pressure was elevated. Second, in isolated heart muscle, at constant initial length, the rate of force development increases during norepinephrine infusions and by digitalization. In each instance, a marked increase of maximum dp/dt occurred despite a fall of left ventricular end-diastolic-pressure.

Some of the factors that influence the maximum dp/dt are fiber length, mean aortic pressure and heart rate changes

without changes in left ventricular end-diastolic pressure and aortic diastolic pressure.

It was suggested by Reeves and Hefner (64) that changes in maximum dp/dt are not a specific index of myocardial contractility. However, changes in maximum dp/dt can, and frequently do, reflect changes in myocardial contractility. The authors preferred to define myocardial contractility as follows: when, from any lowered or constant end-diastolic pressure, the maximum dp/dt rose, an increase of myocardial contractility was considered to have occurred.

In the open chest dog, Reeves and Hefner (64) investigated three cardiac variables: (1) end-diastolic stretch (using Rushmer's variable resistance gages); (2) contractility (Brodie-Walton strain gage); and (3) intraventricular pressure. The results show that the maximal rate of pressure rise in the ventricle during isometric systole is a direct linear function of the product of the end-diastolic stretch and contractility of the ventricular myocardium (measured with strain gage transducer). The maximal slope of the isometric contraction phase of the left ventricular pressure pulse was found to range from 456 to 6,610 mm. Hg./sec.

Other investigators (63, 64, 79) have studied the rate of rise of ventricular blood pressure in an attempt to quantify contractility of the myocardium. Their results suggest that the ratio dp/dt:integrated isometric tension

is such a quantification. This ratio was used because it gave an index of myocardial contractility which was independent of changing end-diastolic pressure, afterload and myocardial work. This index then facilitates a distinction between the Frank-Starling mechanism and true inotropic shifts in myocardial function.

Siegal and Sonnenblick (79) suggest that the ratio of dp/dt, to instantaneous pressure should be considered a good index of contractility. They concluded that fiber length is the most important factor in determining the maximum velocity of muscle shortening.

Measurements of Cardiac Performance by Strain Gage Transducers

Types of Strain Gage Transducers

In investigating the mechanical properties of ventricular muscle, two types of strain gage transducers have been used: the Walton-Brodie strain gage arch (9) and the spring Cushny lever (92, 55). The Cushny lever was used for both isotonic and isometric studies. The Walton-Brodie gage measured only isometric tension. Both gages were sutured directly to the surface of the heart, and usually sensed isometric systolic tension of approximately fifty grams (6, 17, 28, 92).

In a particular experiment (17), on the open chest dog, the Walton-Brodie gage was sutured on various sites of both the left and right ventricle. The results of the

investigation have shown that recordings of percent change of contractile force from any given area of the ventricles are representative of the contractile activity of the entire syncytium.

The authors (17) have further demonstrated that increasing the initial length of the muscle segment between the two points of attachment to the strain gage arch results in an increase in the force recordings. However, at a 30 percent increase in initial length, the force plateaus and a further increase in muscle length had no effect. Stretching the segment of muscle under the transducer by approximately 30 percent reduced the variations of force recordings between different sites of attachment of the gage as well as between dogs.

With chronically implanted strain gage arches (9), the systolic force commonly recorded at the time of surgical attachment of the arches was on the order of 50 grams. This force was found to be reduced with time after surgery due, supposedly, to the gradual loosening of the suture attachments. It was for this reason that, in the closed-chest observations, results were expressed in terms of percent change in contractile force rather than in gram tension.

In suturing the strain gage arch onto the heart most investigators used the following technique: an incision was made between the left 4th intercostal space. The heart was rotated to expose fully the anterior aspects of the right ventricle and the pericardium was resected over this area.

The arch was attached to the anterior surface of the right ventricle by cotton thread sutures, one set near the A-V sulcus and the other near the septum. Two to three sutures were laid at each point, threaded through the drilled holes in the "feet" of the arch and tied.

Potential Limitations of the Strain Gage Transducers

One of the potential limitations of the strain gage arch (Walton-Brodie strain gage arch) for investigating the mechanical properties of ventricular muscle is that the muscle segment actually under the gage is probably not functionally independent of the remainder of the heart and may therefore by influenced by the activity of the adjacent myocardium. It has been shown, however, that the electrical and mechanical activity of the entire heart remained constant while the length of the small segment of myocardium under study was altered (6). The response of the transducer is undoubtedly influenced by the absolute quantity of myocardium to which the strain gage arch is attached, i.e. the number of muscle fibers included within the sutures.

The chief complication of the chronic implantations of strain gage arch thus far has been adhesions which tear out the sutures holding the strain gage to the muscle and break the lead wires.

Characteristic Investigations with the Strain Gage Transducer

The effects of catecholamines on myocardial contractility during experimental adrenal insufficiency, were tested by Lefer and Sutfin (51). A modified Walton-Brodie strain gage arch was sutured to the epicardium of the left ventricle between the main coronary branches. The sutures holding the gage were inserted into the ventricular wall to a depth of 4-6 mm. The muscle segment was stretched about 33 percent of its normal diastolic length. The stretching increased the absolute value of the contractile force, but since relative changes were tested, this did not effect the results of the measurements. The stretching was said to reduce possible artifacts produced by excessive dilatation of the heart. The ventricular systolic contractile force was about 59 grams of tension and the diastolic about 16 grams post surgery.

In other typical studies (4, 52) the strain gage arch (Walton-Brodie) was sutured to the left ventricle, the chest was closed and the dog was allowed to breathe spontaneously. The effects of quinidine and procaine on myocardial contractility (contractile force) were tested. Results were again stated as relative change in contractile force. The authors maintain that at present the recorded curve from the strain gage is the most direct measure of myocardial contractility.

Reeves and Hefner (64) have investigated the relationship of contractile force and myocardial contractility in the intact mammalian heart. The strain gage was sutured to the heart and the chest remained open during the experiment. Recordings from the strain gage were differentiated electrically and also integrated manually. The maximal rate of tension development was measured before and after injection of epinephrine. It was found that not only did the total tension increase, but the rate of development of tension increased. The correlation between contractile force and the maximal rate of force rise was $r = .45$.

CHAPTER III

CHANGES IN RIGHT CARDIAC CONTRACTILE FORCE AND RIGHT INTRAVENTRICULAR BLOOD PRESSURE IN RESPONSE TO EPINEPHRINE AND LARGE VESSEL OCCLUSION

Purpose of Investigation

The purpose of this portion of the present study is to investigate the capabilities and limitations of a strain gage transducer (S.G.T.), when sutured onto the surface of the heart, for evaluating myocardial performance.

First, a comparison was made of simultaneous changes in right ventricular contractile force, as sensed by the S.G.T., and right intraventricular blood pressure after injections of epinephrine. If a good correlation exists between the force and pressure variables, the S.G.T. probably is measuring correctly then, one aspect of cardiac performance.

Next, the blood pressure within the ventricle was altered and its effects on myocardial contractile force (by the S.G.T.) were studied. In the first experiments of the study, the force of contraction was augmented by the addition of epinephrine. The independent variable was the force of contraction and a pressure change within the ventricle was the dependent variable. In the second portion of the study, the pressure was indirectly or mechanically altered in the ventricle and was, therefore, the independent variable.

In this case then, the S.G.T. force data were examined as a function of pressure changes in the ventricle.

Materials and Methods

Experimental Animals

Three mongrel dogs were used in these experiments. The dogs were anesthetized with a 6% solution of sodium pentobarbital (30 mg./Kg.).

Surgical Techniques

The heart was exposed by a midsternal incision and artifical respiration was maintained. The pericardium was opened to expose the right ventricle. Two similar strain gage transducers (appendices A and B) were sutured to the surface of the right ventricle. One gage was positioned parallel to the most obvious direction of myocardial shortening. The other gage was adjacent and perpendicular to the first. Sutures attaching the strain gage transducers to the surface of the heart penetrated the entire wall of the right ventricle. The suturing material was 000 Mersilene.

Instrumentation

The right ventricular blood pressure was monitored by a Statham blood pressure transducer (model P 23 A) to which was attached a piece of polyethylene tubing (6 inches long) with an 18 gauge needle (1 1/2 inches) fastened to one end. The needle was inserted directly into the apical portion of the right ventricle.

Left carotid blood pressure was monitored by a Statham blood pressure transducer (model P 23 A), attached to a polyethylene cannula (9 inches long). All recordings were made on a Grass Model 5 ink writing oscillograph.

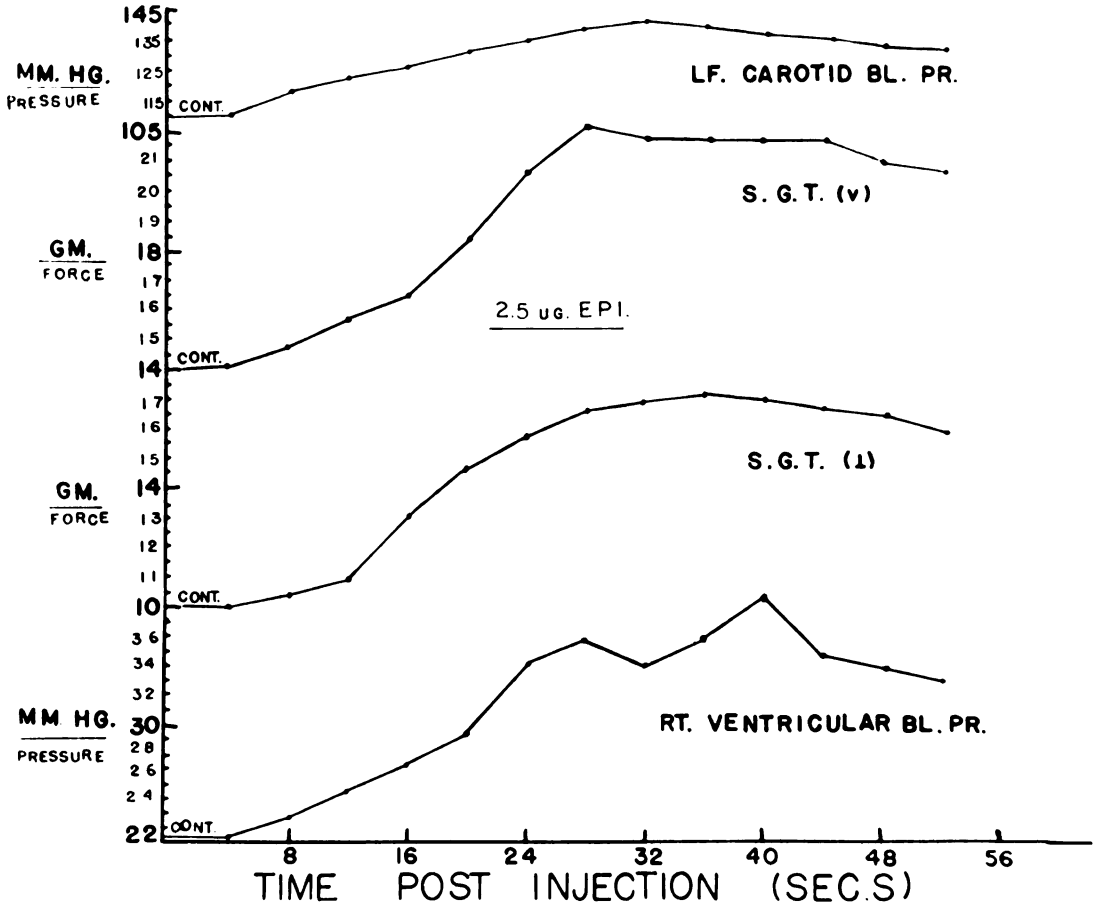
Epinephrine was injected intravenously into the left femoral vein. To occlude the venous and arterial vessels, lifting ligatures (cotton thread) and glass tubing were used (Rumel tourniquet). Both free ends of the lifting ligature were passed through the glass tube and by pulling the vessel toward the glass, occlusion occurred.

Results

Force and Pressure Response to Epinephrine

Approximately 15 seconds after the injection of 2.5 ug epinephrine into the left femoral vein, the force of contraction, detected by the S.G.T., and the pressure in the ventricle began to rise as shown in Figure 1. The force and pressure values rose rapidly, plateaued and began to decline in a simultaneous manner. The force generated by the myocardium, under the S.G.T., was found to be higher for the gage attached parallel to the direction of most obvious ventricular shortening, (S.G.T.v) than for the gage sutured perpendicular and adjacent to (S.G.T.$\perp$) the first. However, the S.G.T.$\perp$ sensed a 70 percent increase in force of contraction, after injection of 2.5 ug epinephrine, as compared to 57 percent sensed by the S.G.T.v.

Figure 1.--Intravenous injection of 2.5 ug epinephrine: Response of (from above downwards); (a) left carotid blood pressure, (b) contractile force in direction of most obvious contraction (S.G.T.v), (c) contractile force perpendicular to b. (S.G.T.⊥), (d) right ventricular blood pressure.


MM. HG.
PRESSURE
GM.
FORCE
GM.
FORCE
MM. HG.
PRESSURE
CONT.
CONT.
CONT.
CONT.
LF. CAROTID BL. PR.
S. G. T. (v)
2.5 ug. EPI.
S. G. T. (1)
RT. VENTRICULAR BL. PR.
TIME POST INJECTION (SEC.S)

The right ventricular blood pressure increased by 70 percent from its control value. Under the conditions of this experiment then, the percent increase in force and pressure were almost identical. The carotid blood pressure rose from its control value of 110 mm. Hg. to a maximum of 140 mm. Hg. for the three dogs, an increase of 27 percent (Table 1).

Figure 2 shows a plot of the increase in myocardial contractile force compared to the increase in right ventricular blood pressure. The relationship is compared for both gages. The results show a linear relationship between force and pressure, S.G.T.v, r = .95 and for the S.G.T.$\perp$, r = .92.

The above study was repeated with increased dose of epinephrine to 5 ug. Results are shown in Figure 3. Force and pressure variables again appear to change simultaneously. The force sensed by the S.G.T.v was again greater (5 grams) than from the S.G.T.$\perp$, Table 1.

In plotting the rise of force against the rise of pressure for both strain gages, Figure 4, again a good linear relationship is shown, S.G.T.v, r = .94, and for the S.G.T.$\perp$, r = .96.

Force and Pressure Response to "Venous Occlusion"

The effect of clamping the superior vena cava, inferior vena cava and the azygos vein ("venous occlusion") on the intraventricular blood pressure and myocardial contractile force sensed by the S.G.T.'s is shown in Figure 5.

Figure 2.--Comparison of changes in cardiac force and ventricular blood pressure in response to 2.5 ug epinephrine.

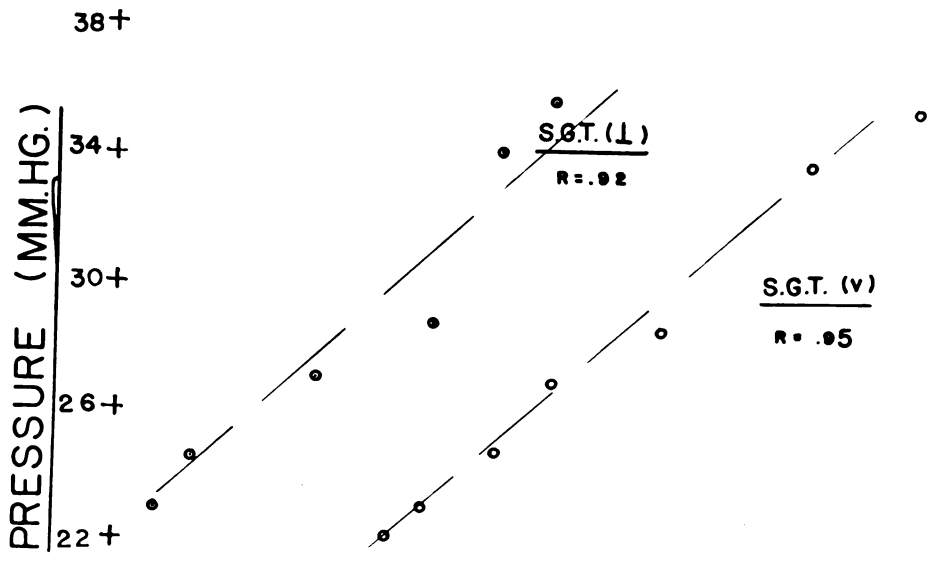

38+
34+
30+
26+
22+
PRESSURE (MM.HG.)
S.G.T. (⊥)
R=.92
S.G.T. (v)
R=.95
10
12
14
16
18
20
22
FORCE (GM.S)

Figure 3.--Intravenous injection of 5.0 ug epinephrine:Response of (from above downwards);(a) left carotid blood pressure, (b) contractile force in direction of most obvious contraction (S. G.T.v), (c) contractile force perpendicular to b. (S.G.T.$\perp$), (d) right ventricular blood pressure.

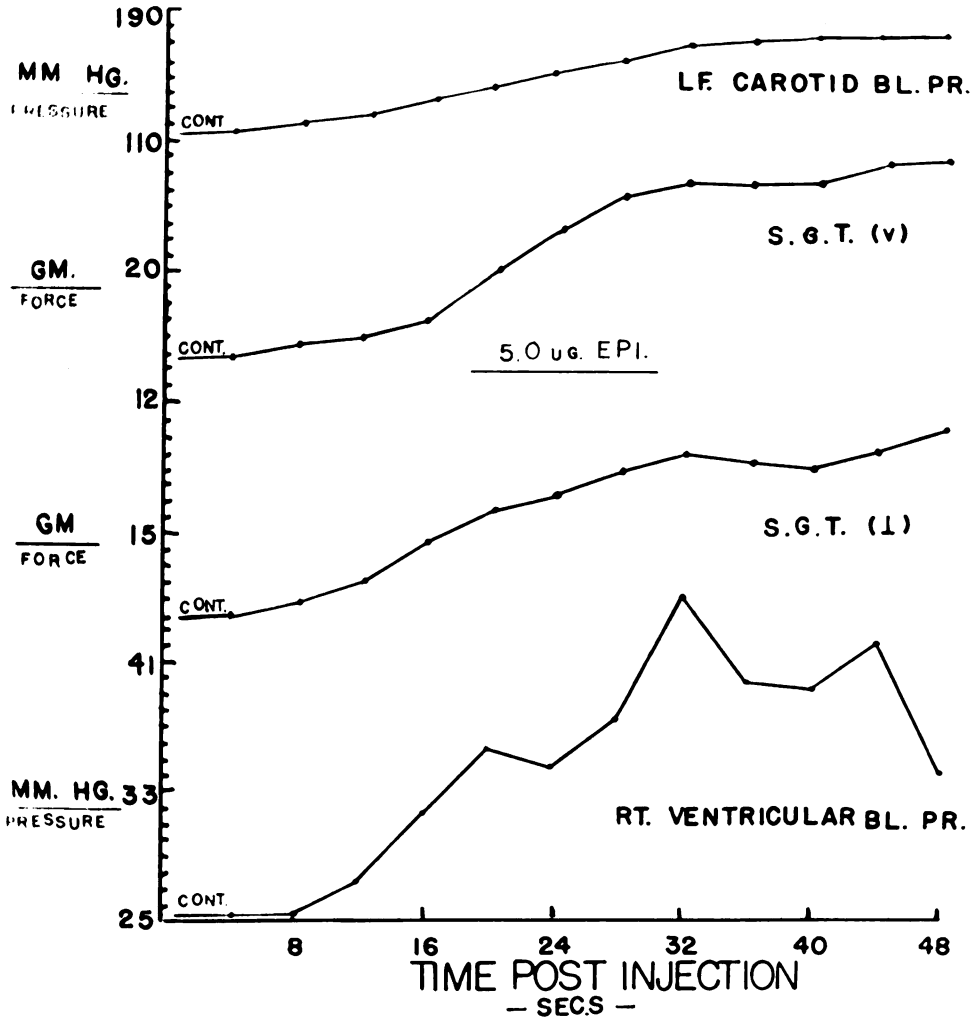

190
MM HG.
PRESSURE
110
LF. CAROTID BL. PR.
CONT
GM.
FORCE
20
S.G.T. (v)
CONT.
5.0 ug. EPI.
12
GM
FORCE
15
S.G.T. (⊥)
CONT.
41
MM. HG.
PRESSURE
33
RT. VENTRICULAR BL. PR.
CONT.
25
8
16
24
32
40
48
TIME POST INJECTION
— SECS —

Figure 4.--Comparison of changes in right cardiac force and ventricular blood pressure in response to 5.0 ug epinephrine.

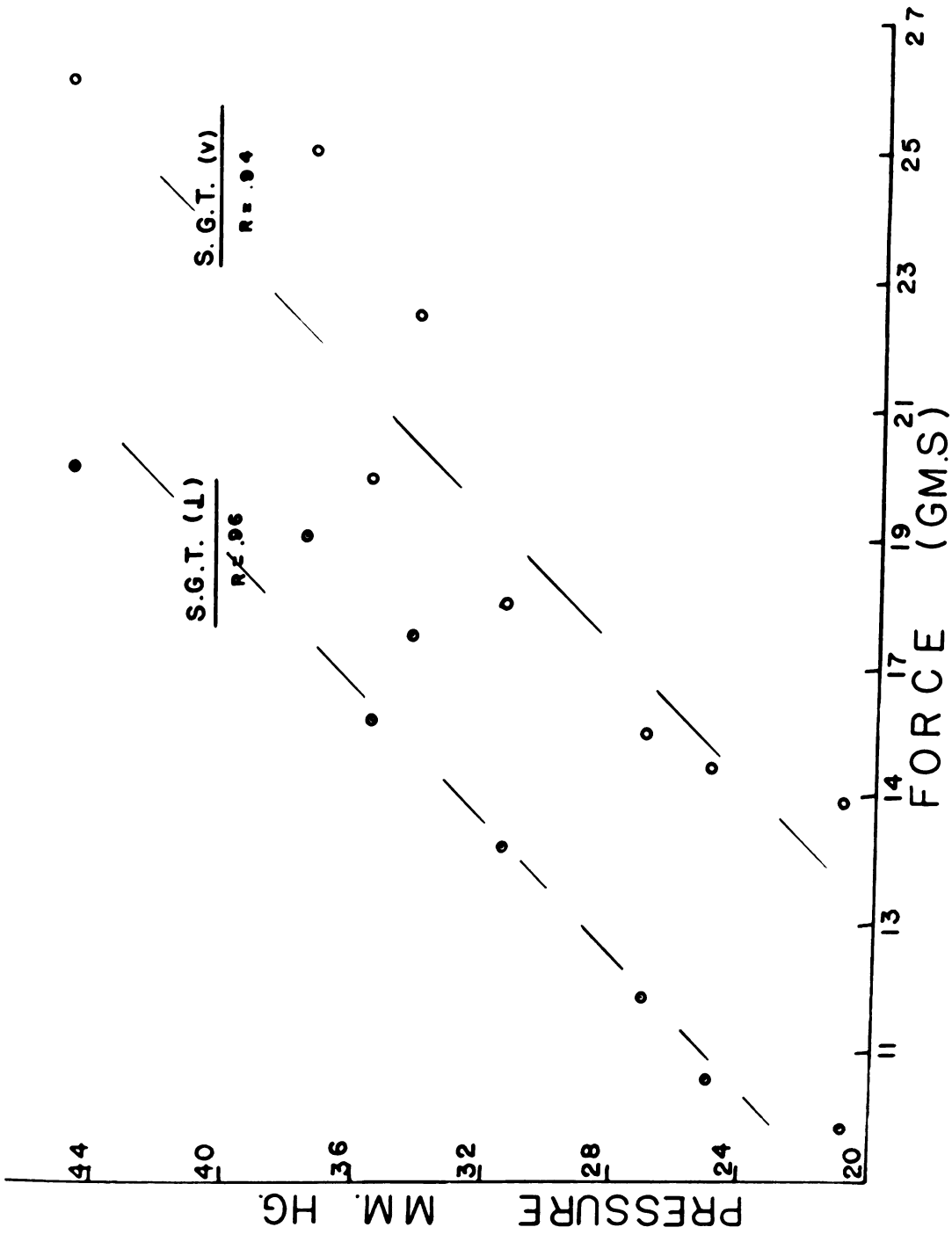

S.G.T. (V)
R=.94
S.G.T. (L)
R=.96
PRESSURE MM. HG.
FORCE (GM.S)
20
24
28
32
36
40
44
11
13
14
17
19
21
23
25
27

Figure 5.--Occlusion of superior and inferior venae cava and azyzos veins: Response of (from above downwards); (a) left carotid blood pressure, (b) contractile force in direction of most obvious contraction (S.G.T.v), (c) contractile force perpendicular to b, (S.G.T.⊥), (d) right ventricular blood pressure.

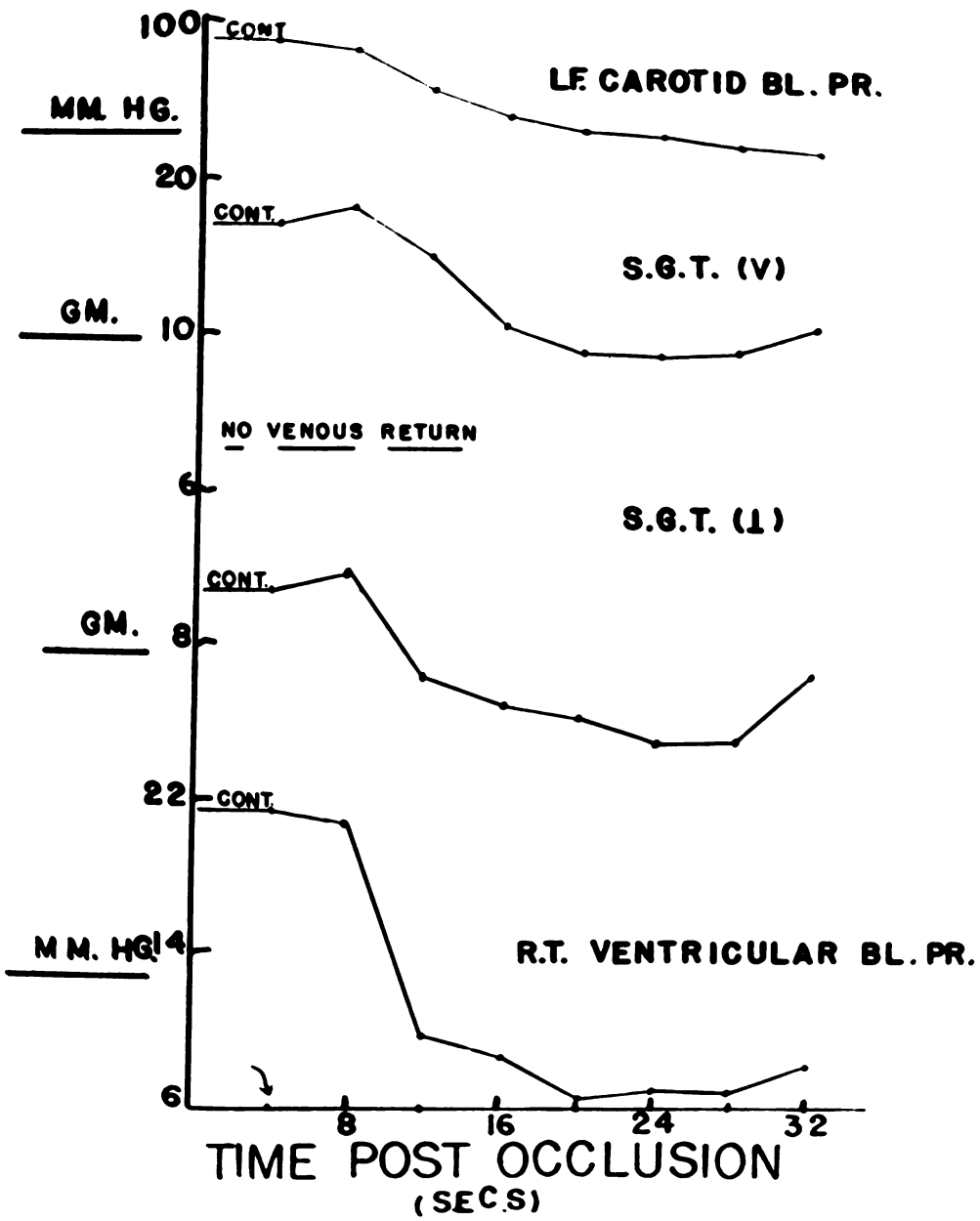

100
CONT
LF. CAROTID BL. PR.
MM. HG.
20
CONT.
S.G.T. (V)
GM.
10
NO VENOUS RETURN
6
S.G.T. (1)
CONT.
GM.
8
22
CONT.
MM. HG.
14
R.T. VENTRICULAR BL. PR.
6
8
16
24
32
TIME POST OCCLUSION
(SECS)

Table 1.--Effects of epinephrine on right cardiac contractile force and right intraventricular blood pressure.

		2.5 ug Epinephrine				5.0 ug Epinephrine	
Variable	Control Value	Maximum Value	% Incr.	Variable	Control Value	Max. Value	% Incr.
Force S.G.T.v	14 gm.	22 gm.	57%	Force S.G.T.v	14.7 gm.	27 gm.	84%
Force S.G.T.⊥	10 gm.	17 gm.	70%	Force S.G.T.⊥	9.8 gm.	21.2 gm.	116%
Pressure Rt. Vent.	22 mm. Hg.	37 mm. Hg.	70%	Pressure Rt. Vent.	21 mm. Hg.	45 mm. Hg.	114%
Pressure Carotid	110 mm. Hg.	140 mm. Hg.	27%	Pressure Carotid	115 mm. Hg.	170 mm. Hg.	48%

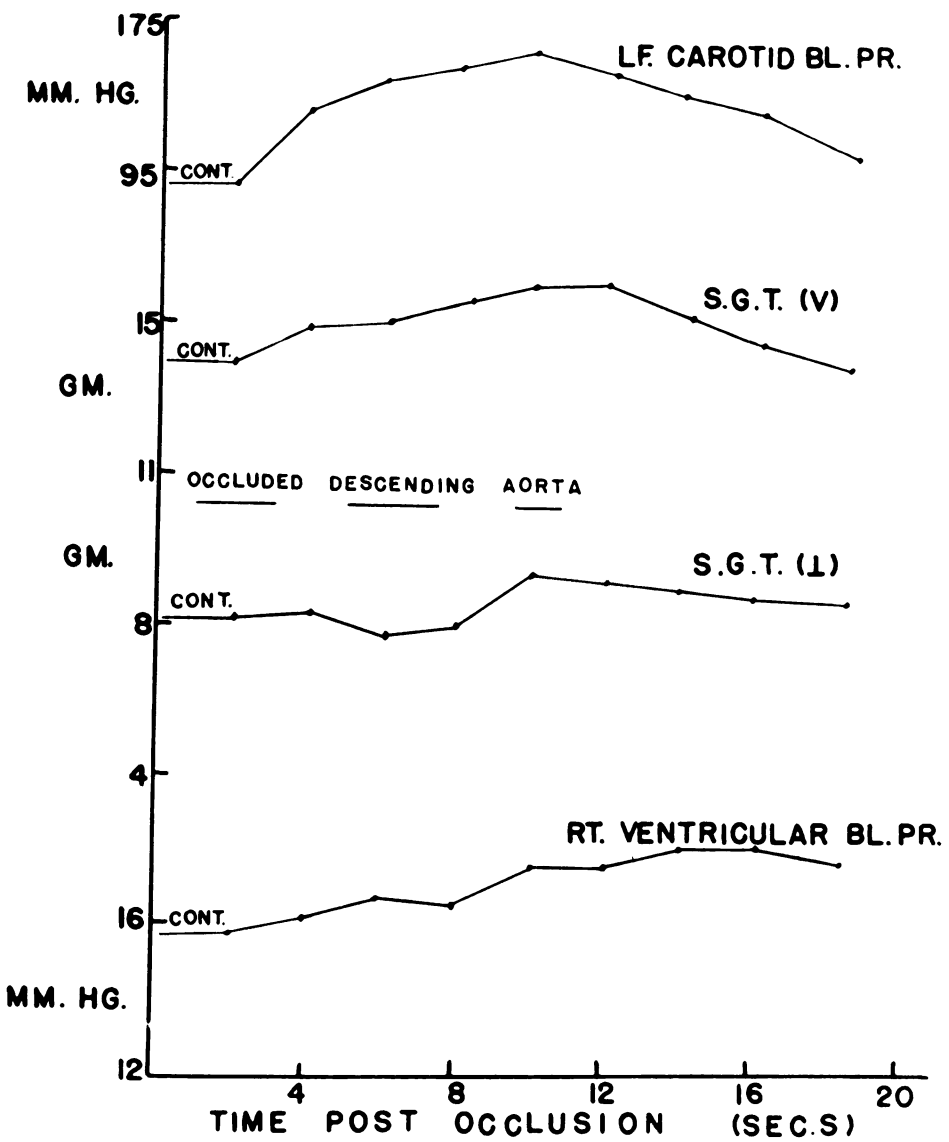
The experiment shows that both pressure and force measurements decline almost simultaneously. The right ventricular blood pressure dropped rapidly from a control of 21.4 mm. Hg. to 6.3 mm. Hg. The myocardial contractile force, as sensed by the S.G.T.v, declined from a control of 12.8 grams to 9.4 grams. A drop from 9.4 grams to 5.4 grams was registered by the S.G.T.⊥.

A drop in myocardial contractile force during venous occlusion to the heart is probably due in part to a lowering of the pressure in the ventricle or a decrease stretch on the heart muscle (Frank-Starling phenomenon). However, various other parameters such as decreased coronary flow and nervous reflexes should be considered before any conclusive statement can be made. Therefore, a drop in pressure within the ventricle does not necessarily mean that the pressure directly influences the recordings of the S.G.T., there may in fact be an actual drop in force as generated by the myocardium.

In this experiment ("venous occlusion") the force as sensed by the S.G.T.v was greater than that sensed by the S.G.T.⊥, again showing a quantitative force difference due to gage placement on the heart.

The correlation coefficients comparing force and pressure data were $r = .85$ for the S.G.T.v and $r = .96$ for the S.G.T.⊥. This again shows a close relationship between the two variables.

Figure 6.--Occlusion of the descending aorta (mid-thoratic): Response of (from above downwards); (a) left carotid blood pressure, (b) contractile force in direction of most obvious contraction (S.G.T.v), (c) contractile force perpendicular to b, (S.G.T.$\perp$), (d) right ventricular blood pressure.


175
MM. HG.
95
CONT.
LF. CAROTID BL. PR.
15
CONT.
S.G.T. (V)
GM.
11
OCCLUDED DESCENDING AORTA
GM.
S.G.T. (⊥)
CONT.
8
4
RT. VENTRICULAR BL. PR.
16
CONT.
MM. HG.
12
4
8
12
16
20
TIME POST OCCLUSION (SEC.S)

Force and Pressure Response to Occlusion of the Descending Aorta

The occlusion of the descending aorta (mid-thoracic region) resulted in a rise in both carotid and ventricular blood pressure as well as a slight rise in right ventricular contractile force.

The carotid blood pressure rose from a control value of 90 mm. Hg. to a maximum of 160 mm. Hg. The force (by S.G.T.v) rose from a control of 13.9 grams to a maximum of 16 grams. The "perpendicular" gage (S.G.T.$\perp$) indicated control force of 8.2 grams, which rose to a maximum of 9.3 grams. The right ventricular pressure increased from a control of 15.7 mm. Hg. to a high of 18 mm. Hg., Table 2.

Table 2.--Occlusion of large veins to heart, effects upon right myocardial contractile force and right intraventricular blood pressure.

Variable	Contr. Value	Minimum Value	% Change
Force S.G.T.v	12.8 gm.	9.4 gm.	- 27%
Force S.G.T.v	9.4 gm.	5.4 gm.	- 42%
Pressure Rt. Vent.	21.4 mm. Hg.	6.3 mm. Hg.	- 71%
Pressure Carotid	90.0 mm. Hg.	32.0 mm. Hg.	- 64%

Table 3.--Occlusion of descending aorta, effects upon right myocardial contractile force and ventricular pressure.

Variable	Contr. Value	Max. Value	% Change
Force S.G.T.v	13.9 gm.	16 gm.	15%
Force S.G.T.⊥	8.2 gm.	9.3 gm.	13%
Pressure Rt. Vent.	15.7 mm. Hg.	18 mm. Hg.	14%
Pressure Carotid	90 mm. Hg.	160 mmg. Hg.	77%

Force and Pressure Response to Occlusion of the Ascending Aorta

The occlusion of the ascending aorta resulted in a fall in both carotid and right ventricular blood pressures and a rise in ventricular force recordings, Figure 7. The carotid blood pressure dropped from a control value of 90 mm. Hg. to a low of 15 mm. Hg. The right ventricular pressure dropped from a control value of 11.6 mm. Hg. to a minimum of zero. The force, from S.G.T.v, shows a rise from 13.9 grams to 21.2 grams, whereas the S.G.T.⊥ rose from 9.7 grams to 17.9 grams, Table 4.

When the ascending aorta is occluded suddenly it appears that the force of myocardial contraction is increased probably by sympathetic discharge by way of the

Figure 7.--Occlusion of the ascending aorta: Response of (From above downwards); (a) left carotid blood pressure, (b) contractile force in direction of most obvious contraction (S.G.T.v), (c) contractile force perpendicular to b, (S.G.T.$\perp$), (d) right ventricular blood pressure.

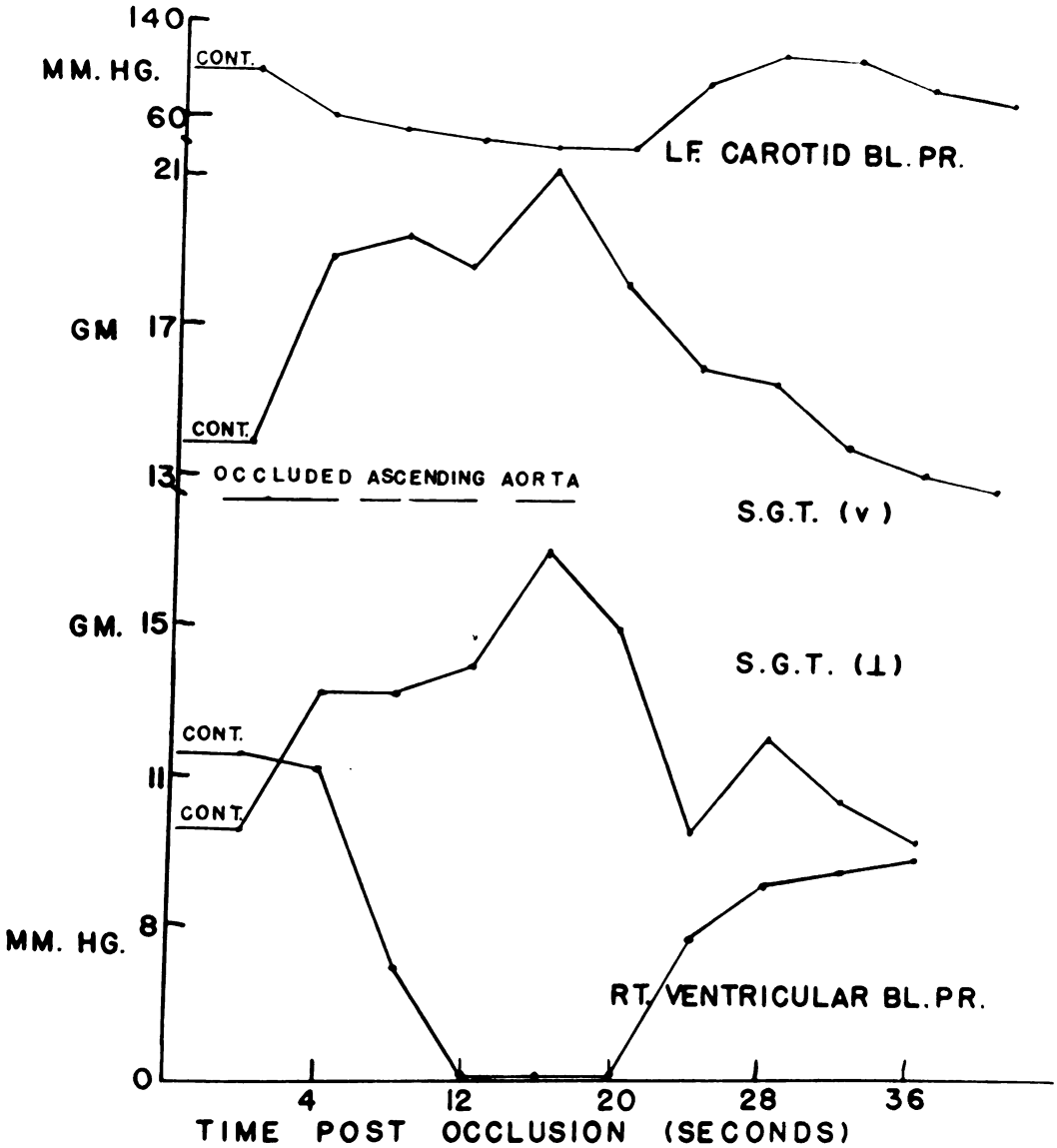

140
MM. HG.
CONT.
60
21
LF. CAROTID BL. PR.
GM 17
CONT.
13
OCCLUDED ASCENDING AORTA
S.G.T. (v)
GM. 15
S.G.T. (⊥)
CONT.
11
CONT.
MM. HG. 8
RT. VENTRICULAR BL. PR.
0
4
12
20
28
36
TIME POST OCCLUSION (SECONDS)

Table 4.--Occlusion of ascending aorta, effects upon right myocardial contractile force and ventricular pressure.

Variable	Contr. Value	Max. or Min. Value	% Change
Force S.G.T.v	13.9 gms.	21.2 gms.	+ 53%
Force S.G.T.⊥	9.7 gms.	17.9 gms.	+ 84%
Pressure Rt. Vent.	11.6 mm. Hg.	0.0 mm. Hg.	- 100%
Pressure Carotid	90.0 mm. Hg.	15.0 mm. Hg.	- 83%

carotid sinus reflex. The factors involved in this kind of response will be discussed later.

Force and Pressure Response to Occlusion of the Pulmonary Artery

The occlusion of the pulmonary artery resulted in a fall of carotid blood pressure and a rise in the myocardial contractile force and right ventricular blood pressure, Figure 9. The carotid pressure declined from a control value of 100 mm. Hg. to 60 mm. Hg. since no blood was being pumped to the systemic vessels. The myocardial contractile force, from the S.G.T.v, rose from a control of 10.2 grams to a maximum of 13.9 grams, whereas the S.G.T.⊥ indicated a rise from 10.4 grams to 24.1 grams. The right ventricular pressure rose from a control value of 19.3 mm. Hg. to a maximum of 65.7 mm. Hg. or a 235 percent increase, Table 5.

Figure 8.--Occlusion of the pulmonary artery: Response of (from above downwards);(a) left carotid blood pressure, (b) contractile force in direction of most obvious contraction (S.G.T.v), (c) contractile force perpendicular to b, (S.G.T.$\perp$), (d) right ventricular blood pressure.

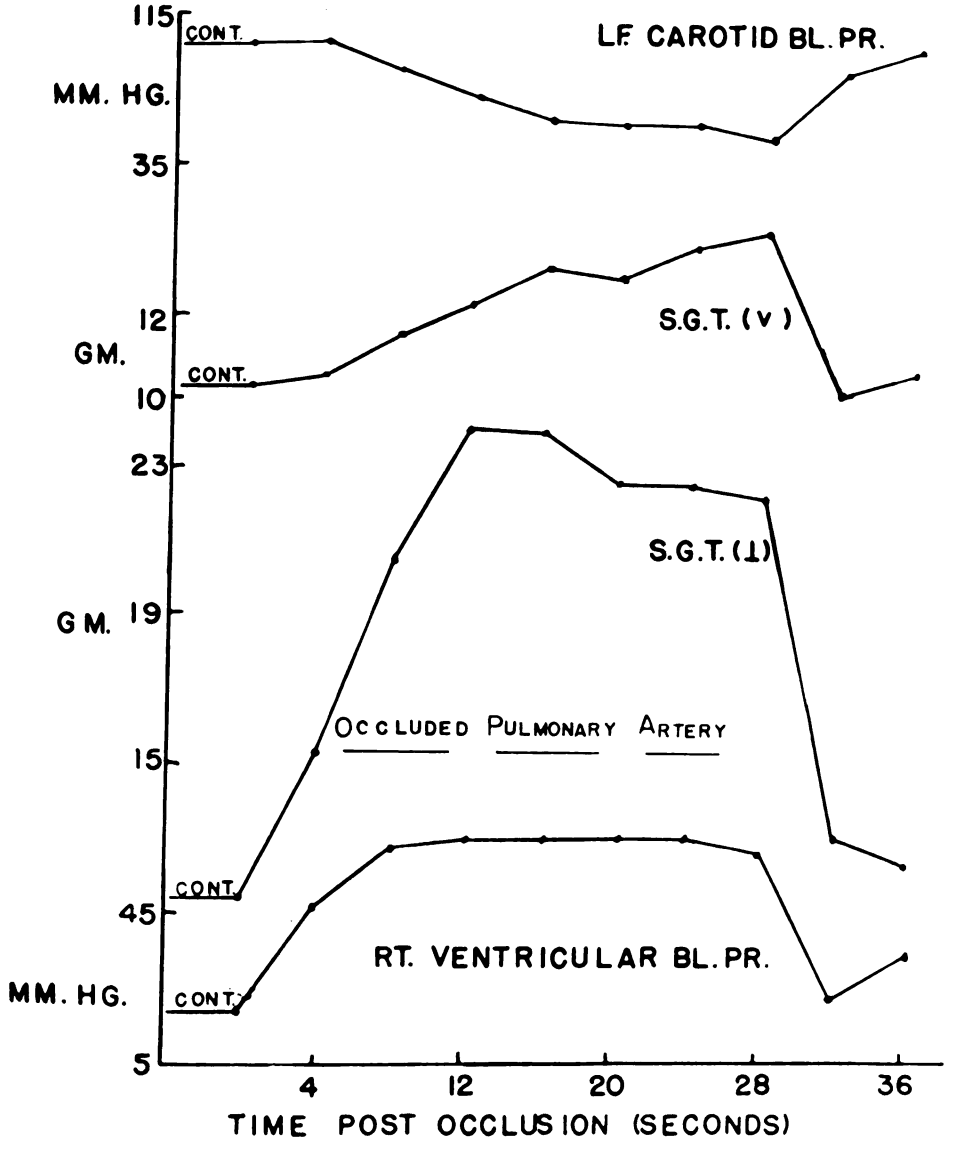

115
CONT.
LF CAROTID BL. PR.
MM. HG.
35
12
S.G.T. (V)
GM.
CONT.
10
23
S.G.T. (⊥)
GM. 19
OCCLUDED PULMONARY ARTERY
15
CONT.
45
RT. VENTRICULAR BL. PR.
MM. HG.
CONT.
5
4
12
20
28
36
TIME POST OCCLUSION (SECONDS)

Figure 9.--Graph showing comparison of force displacement transducer (F.D.T.) and strain gage transducer (S.G.T.) when sutured on the surface of frog gastrocnemius muscles. Ordinate is percent increase in force. Abscissa is stimulus strength at 6 msec and 0.5 cycle per second.

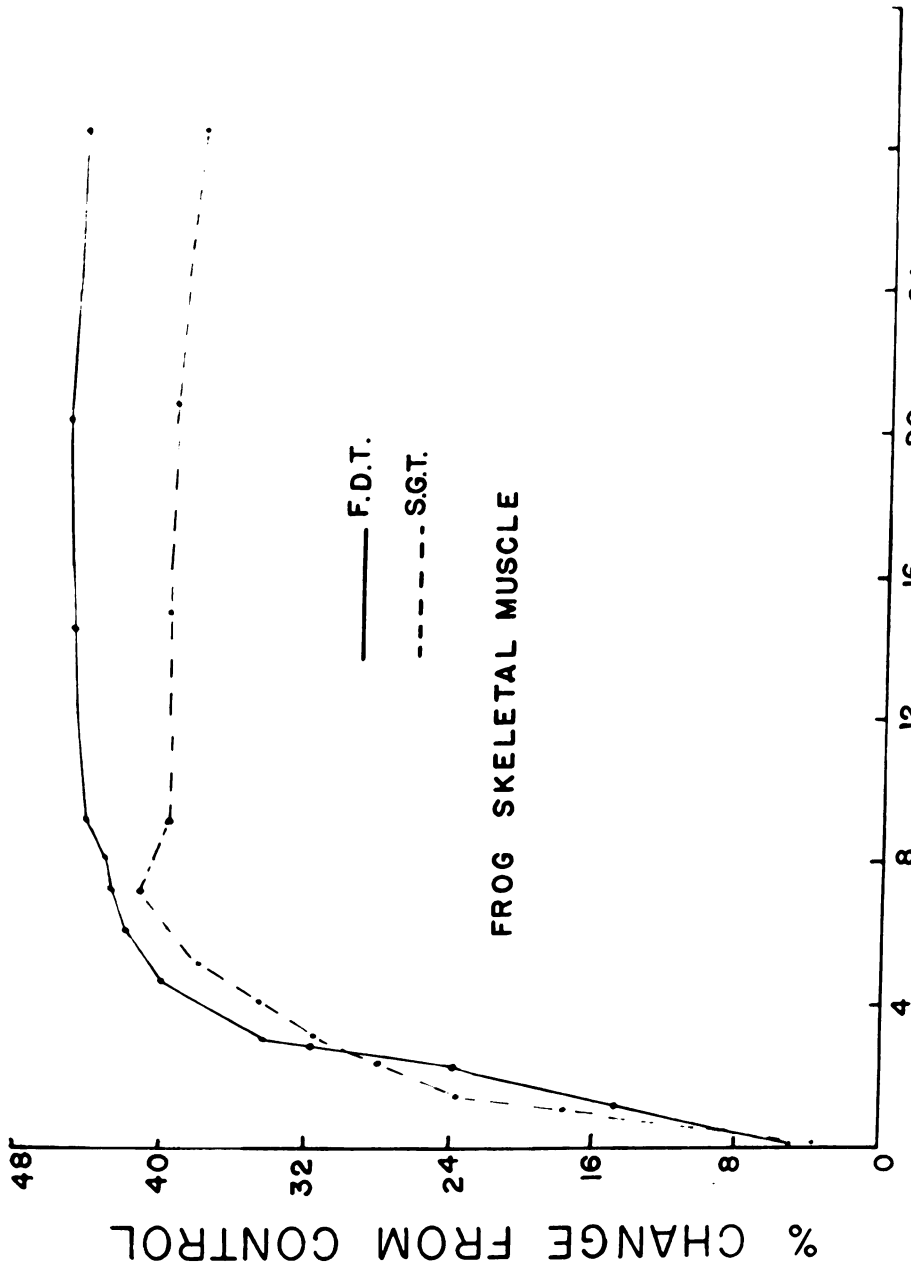

% CHANGE FROM CONTROL
48
40
32
24
16
8
0
4
8
12
16
20
24
28
STIMULUS VOLTAGE (VOLTS)
F.D.T.
S.G.T.
FROG SKELETAL MUSCLE

Table 5.--Occlusion of pulmonary artery, effects upon right myocardial contractile force and ventricular blood pressure.

Variable	Contrs. Value	Peak Value	% Change
Force S.G.T.v	10.2 gms.	13.9 gms.	36%
Force S.G.T.⊥	10.4 gms.	24.1 gms.	131%
Pressure Rt. Vent.	19.3 mm. Hg.	65.7 mm. Hg.	235%
Pressure Carotid	100.0 mm. Hg.	60.0 mm. Hg.	- 40%

Discussion and Conclusions

The ability of the strain gage transducer (S.G.T.) to sense changes in heart muscle performance has been demonstrated by increasing myocardial contractility with 2.5 and 5.0 ug epinephrine, Figures 2 and 4. There is a high correlation between myocardial force changes (strain gage) and ventricular pressure following epinephrine. The degree of correspondence between the two means of estimating cardiac contractility affirms the adequacy of these particular strain gages in the heart studies.

The vessel occlusion experiments were designed to test the transducer, as a sensor for cardiac performance, when large pressure fluctuations occurred within the ventricles. When venous return to the heart was decreased, the transducer detected a fall in cardiac fiber contractility. It is assumed that this fall is mainly due to a decreased fiber

length (Frank-Starling, phenomenon). Other factors such as decreased ejection resistance and lowered coronary perfusion pressure possibly contribute. The carotid systolic blood pressure decreased during venous occlusion. This should activate the carotid sinus reflex and increase cardiac contractile force. Since the transducer did not detect an increase in myocardial force, but a decrease instead, it is suggested that the Frank-Starling phenomenon overrides the carotid sinus reflex under the conditions of this experiment.

Occlusion of the ascending aorta, descending aorta pulmonary artery (individually but not simultaneously) increases the perpheral resistance the heart must pump against. In response, the right heart increases its force of contraction as indicated by the S.G.T. This occurred even when the end-diastolic pressure increased (pulmonary artery occlusion) or decreased (ascending aorta occlusion) and therefore, is due not solely to changes in cardiac fiber length.

During ascending aorta occlusion, the right ventricular blood pressure (R.V.B.P) fell to zero and myocardial contractile force greatly increased, Figure 8. If one were monitoring only R.V.B.P. as an indicator of cardiac performance, it is possible that a decrease in myocardial contractility could be erroneously reported. In this case the S.G.T. is the better sensor of cardiac function.

When the pulmonary artery was occluded contractile force was greatly increased, Figure 7. The increase in force as sensed by the S.G.T.⊥ was over four fold greater than with the S.G.T.v. Although it is not possible to ascertain from the experiment, the reasons for this, it is, however, suggested that certain groups of muscles in the right ventricle may respond differently from one another. More specifically, the S.G.T.v probably senses the force developed mainly by the myocardial spiral muscles and the S.G.T.⊥ the constrictor bundles. The latter is more responsive in all cases in this study.

Two transducers were sutured to the cardiac fibers at opposing (right) angles to test their ability in sensing myocardial performance at different sites on the right ventricle. Contrary to the data published by Walton and Brodie (17) in a similar study, this investigation shows that quantitative and qualitative differences existed between the S.G.T.v and S.G.T.⊥, Tables 5 and 6. The S.G.T.v always detected a greater force by cardiac fibers than the S.G.T.⊥. However, the S.G.T.⊥ always sensed a larger change (percent) in force in response to epinephrine and vessel occlusion than the S.G.T.v.

Rushmer, et al. (74) have demonstrated that ejection of blood by the right ventricle is accomplished primarily by a shortening of the free wall drawing the tricuspid ring toward the apex of the heart. The two strain gage transducers

(S.G.T.v, S.G.T.⊥) in this study also show that a predominant contractile force (S.G.T.v) is developed by those cardiac fibers pulling the tricuspid ring toward the apex of the heart.

The strain gage transducer described here has been found capable of detecting variations in cardiac contractility in the intact dog under a variety of experimental circumstances (including observations on skeletal muscle, Figure 9). The gage data correlate highly with intracardiac pressure data. The tension transducer (gage) technique appears to be acceptable and could make feasible cardiac motility studies on the intact unanesthetized animal.

CHAPTER IV

A COMPARISON OF THE RATES OF CHANGE (FIRST DERIVATIVES) IN CARDIAC CONTRACTILE FORCE AND INTRAVENTRICULAR BLOOD PRESSURE WHEN ALTERED BY CHLOROFORM, EPINEPHRINE AND OUABAIN

Introduction and Purpose

Importance of the First Derivative of Intraventricular Blood Pressure Pulses

The ability of the myocardium to alter its rate of contraction and, consequently the rate of ventricular pressure change, is one of its most important properties (64). It is this ability which allows the period of isovolumic contraction to remain essentially constant even though the diastolic pressure in the aorta or pulmonary artery may change markedly. If the rate of contraction could not be adjusted, the period of isovolumic contraction would vary as does the diastolic pressure in the aorta. For example, an increase in aortic diastolic pressure from 60 to 120 mm. Hg. would double the isovolumic phase of contraction and the ejection phase would be proportionately reduced if the remainder of the cardiac cycle remained constant.

The velocity of blood ejection from the ventricles is in major part a function of the difference in instantaneous pressures between the ventricle and its adjacent artery (64). This difference is largely a function of the slope of the ventricular pressure pulse. It is, therefore, apparent that

the rate of increase in pressure within the ventricle, reflected in the slope of the ventricular pressure pulse, is a primary factor in the ability of the heart to increase or decrease the velocity of blood ejection. For example, when stroke volume is increased (or the ejection period is decreased as in tachycardia), the velocity of cardiac blood ejection is normally increased to maintain a constant ratio between emptying and filling times.

Historical Aspects of the Use of the First Derivative, A Qualitative Approach

The importance of the capacity of heart muscle to alter its rate of contraction was recognized very early in the development of cardiac physiology. Frank (29) included the rate of change in pressure in his analysis of the frog ventricle during isometric contractions. Similarly, Wiggers (95) noted that when the initial (end-diastolic) intraventricular pressure increased, so did the steepness of the ascending limb of the ventricular pressure pulse. Starling (59) also emphasized the fundamental importance of the rate of change in pressure in the heart.

Since these early investigations, frequent qualitative estimates of changes in ventricular contractility have been made on the basis of alterations in the rate of change in pressure. Wiggers (98), using high frequency optical pressure manometers, demonstrated that elevated ventricular end-diastolic filling pressure (increased venous return), or epinephrine (50, 96, 101) or digitalis (99) injection increased

the rate of pressure rise. This rate increased despite a fall in ventricular end-diastolic pressure (produced by digitalis). On the other hand, with myocardial ischemia, Wiggers (100) found a decreased slope in the ventricular pressure curves despite a rising end-diastolic pressure.

Quantitative Analysis of the First Derivative of Pressure Pulses

Wiggers has clearly and thoroughly demonstrated the qualitative aspects of the rate of rise in ventricular pressure pulses under a variety of circumstances (95, 101). Recently, with the use of computers, it became possible to quantify exactly the rate of rise of intraventricular pressure tracings. Computerized quantifications give a continuous record of the instantaneous pressure change in the ventricles.

The first derivative of intracardiac pressure reaches a peak in early systole (63). This means that the pressure within the heart builds up slowly, accelerates to a maximum and declines, sequentially, throughout the early part of a cardiac systole. Many investigators have included the first derivative of pressure (dp/dt) when studying cardiac performance. Rushmer, et al. (44) measured dp/dt when dogs were exercising on a treadmill. It was demonstrated by Tolman and Young (98) that dp/dt was comparable to ventricular function curves* in predicting heart performance. In human

*Ventricle function curve illustrates the relationship between cardiac end-diastolic volume (abscissa) and stroke work (ordinate).

patients, Gleason and Braunwald (33) were able to demonstrate that interventions which acutely augmented myocardial contractility (muscular exercise, norepinephrine, epinephrine and atropine) resulted in an increased maximal derivative of pressure. On the other hand, when cardiac performance is decreased (acute left ventricular failure) dp/dt decreased (100).

Changes in the maximum derivative of ventricular blood pressure were considered, therefore, by many early investigators (74, 89, 33, 29, 95, 59, 98, 65) to be a good indication of a change in myocardial contractility. Recently, this concept has been popular in associating changes in cardiac performance with changes in maximum dp/dt (3,90,94, 88, 79). There is evidence, however, that certain variables tend to alter maximum dp/dt even though cardiac contractility is unchanged. For example, it has been shown by Wallace, et al. (91), Sarnoff and Mitchell (78), and Akre (3) that a near linear relation exists between heart rate and maximum dp/dt. Wallace, et al. (91), Levy, et al. (54), and Wiggers (97) have pointed out that elevation of aortic diastolic pressure increased maximum dp/dt. This change occurred with constant left ventricular end-diastolic pressure. They concluded that aortic diastolic pressure can influence maximal dp/dt in the absence of changes in cardiac contractility. Reeves, et al. (63) disagree with the above studies (91, 54, 97). They contend that maximal dp/dt does not change when aortic diastolic pressure was elevated. Sarnoff and Mitchell (77)

have further shown that several beats after the onset of elevated aortic pressure, heart contractility increased. They called this "homeometric autoregulation."

Maximum dp/dt is influenced by changes in cardiac end-diastolic volume (90). Theoretically increased dp/dt maximum in response to increased fiber length is not an appropriate indicator of increased myocardial contractility (83). If it were possible to eliminate the effect of changing fiber length on dp/dt a true index of contractility would result. Siegel, et al. (79) have shown this to be the case in an isovolumic contracting ventricle. They found that dividing the maximal dp/dt by the area under the ventricular pressure curve (A) no change occurred in such an "index of contractility" when fiber length was altered.

$$\frac{\text{Maximum dp/dt}}{\text{A}} = \text{"index of contractility"}$$

The peak derivative of ventricular pressure (dp/dt) must not be considered a specific index of myocardial contractility. Changes in this measurement should be interpreted with caution if any significant alterations of heart rate, aortic pressure and fiber length occurs.

Relationship of Myocardial Contractile Activity and the First Derivative of Pressure

Changes of maximal dp/dt in response to alterations in muscle fiber length were not measured directly prior to 1960. Often these changes were inferred from variations in end-

diastolic volume or end-diastolic pressure (90, 79, 98). Recently, Reeves and Hefner (64) have compared heart fiber length (strain gauge arch) to the first derivative of cardiac force (df/dt). When fiber length was increased, while maintaining heart rate and end-diastolic volume constant, a linear increase in df/dt maximum occurred. When maximal dp/dt was compared to cardiac contractile force, Reeves, et al. (63) discovered a good (sic) correlation (r = .45). It was further shown (63) that an excellent correlation (r = .79) existed between the maximal rate of pressure rise and the product of the contractile force times the end-diastolic circumference of the left ventricle.

In summary, the reliability of dp/dt as a good index of cardiac contractility has not been well established. However, investigators continue to relate changes in maximum dp/dt to altered myocardial contractility. Very few data are available to substiate that changes in dp/dt reflect alterations in muscle contractility or df/dt. The fact that heart rate, aortic pressure and fiber length consistently alter maximal dp/dt suggests that this rate function of pressure should be interpreted with care.

It is the purpose of this study to investigate (a) the first derivative of cardiac contractile force (df/dt) as an index of heart performance, and (b) the relationship between maximal df/dt and maximal dp/dt.

Materials and Methods

Experimental Animals

Eighteen mongrel dogs were used in the study. The dogs were anesthetized with 6 percent solutions of sodium pentabartital (30 mg/kg) via the cephalic vein.

Surgical Techniques

The technique for strain gage attachment to the right ventricle has previously been described (Chapter 3 page 31). Briefly, the heart was exposed by a midsternal incision. The pericardium was opened to expose the right ventricle. A strain gage transducer was sutured firmly to the surface of the right heart (Gage calibration saline and data in Figure 10).

A Statham pressure transducer (model P 23 A) was used to record intraventricular pressure curves. For heart puncture an 18 gauge needle (1 1/2 inches long) was used. The syringe needle was connected to the pressure sensing transducer with polyethylene tubing (6 inches long). The needle was inserted directly into the apical region of the right ventricle.

Data Collection

ECG measurements were recorded from silver electrodes sutured under the skin on both sides of the chest.

The first derivatives of intraventricular blood pressure and myocardial contractile force tracings were obtained by electrical differentiation (Appendix, Figure 24).

All recordings of data were made on a Grass model 5 ink writing oscillograph (Figure 11). All data were also recorded on a Sanborn (model 2000) tape recorder.

The maximum rate of change of pressure and force with respect to time (dp/dt, and df/dt) was measured by noting the height, in millimeters, of the differentiated signal recorded on the Grass chart paper (Figure 23). The maximal deflections of the differentiated signals were then converted to velocity (mm/sec. or g/sec.) from a standard curve. The standard curve was made by generating a "saw tooth" signal. By feeding this into the electrical differentiator, the relation between distance and time (tangent of the "saw tooth wave") was calculated.

Ideally, to record intraventricular pressure pulses, the blood pressure transducer should have a natural frequency response of 4 to 5 times the smallest wave component of the pressure pulse. In the ordinary intraventricular pressure pulse this component has been shown to be 25 cycles per second (95). Therefore, the pressure transducer ought to have a natural frequency response of 100 to 125 cycles per second. Moreover, the differentiator should respond at least twice as fast as the blood pressure recorder and thus have a natural frequency of 200 to 250 cycles per second (minimum). The frequency response of the system used in the present experiments was linear only up to 35 cycles per second. This limitation was set by the Grass recorder.

The time interval between the peak of the ECG R-wave and the peak of the diffentiated signal of the maximum rate of pressure or force rise was measured on a Tektronix

oscilloscope (Figure 21). The procedure was to play back simultaneously from the tape recorder, the ECG and differentiated signals onto the oscilloscope screen. The distance between the two variables (ECG R-wave and df/dt or dp/dt) was measured directly from the oscilloscope grid. Knowing the sweep speed (50 msec/cm), the measured distance was converted to a velocity.

The areas under the force and pressure tracings (Figure 12) were measured directly from the Grass chart paper using a calibrated planimeter.

Epinephrine and ouabain were injected via the right femoral vein. Chloroform was given by inhalation. A glass jar, containing cotton and paper towelling saturated with chloroform, was connected between the respirator and the endotracheal tube. The amount of chloroform inhaled by each dog was kept relatively constant by always disconnecting the chloroform bottle after the developed cardiac force, read from the recorder tracings, declined to 50 percent of the control values.

Results

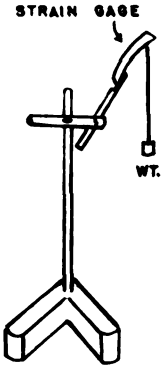
Effects of Chloroform Inhalation on Cardiac Force and Pressure

The normal ability of the myocardium to alter readily systolic intraventricular blood pressure and contractile force is greatly reduced by chloroform inhalation (Figures 13, 14). The use of first derivatives of intraventricular blood pressure (dp/dt) and cardiac contractile force (df/dt)

Figure 10.

A.--Diagram showing the technique of calibrating the strain gage transducer.

B.--A plot of pen deflection (ordinate) and weight in grams (abscissa) for calibration of the strain gage. Sen. 2, 5, 10, 20 refer to sensitivity settings on the Grass preamplifier.


STRAIN GAGE
WT.

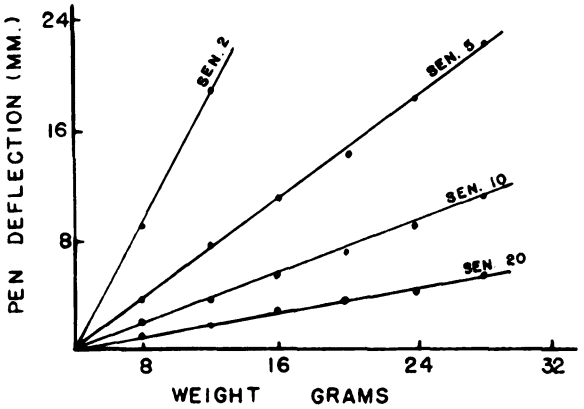

PEN DEFLECTION (MM.)
24
16
8
SEN. 2
SEN. 5
SEN. 10
SEN 20
8
16
24
32
WEIGHT GRAMS

Figure 11.--A scheme of the data collection and analysis system. From upper left to the right.
(a) right ventricle with gage attached.
(b) force and pressure transducers.
(c) grass amplifiers.
(d) computer (electrical differentiator).
(e) data record diagram.

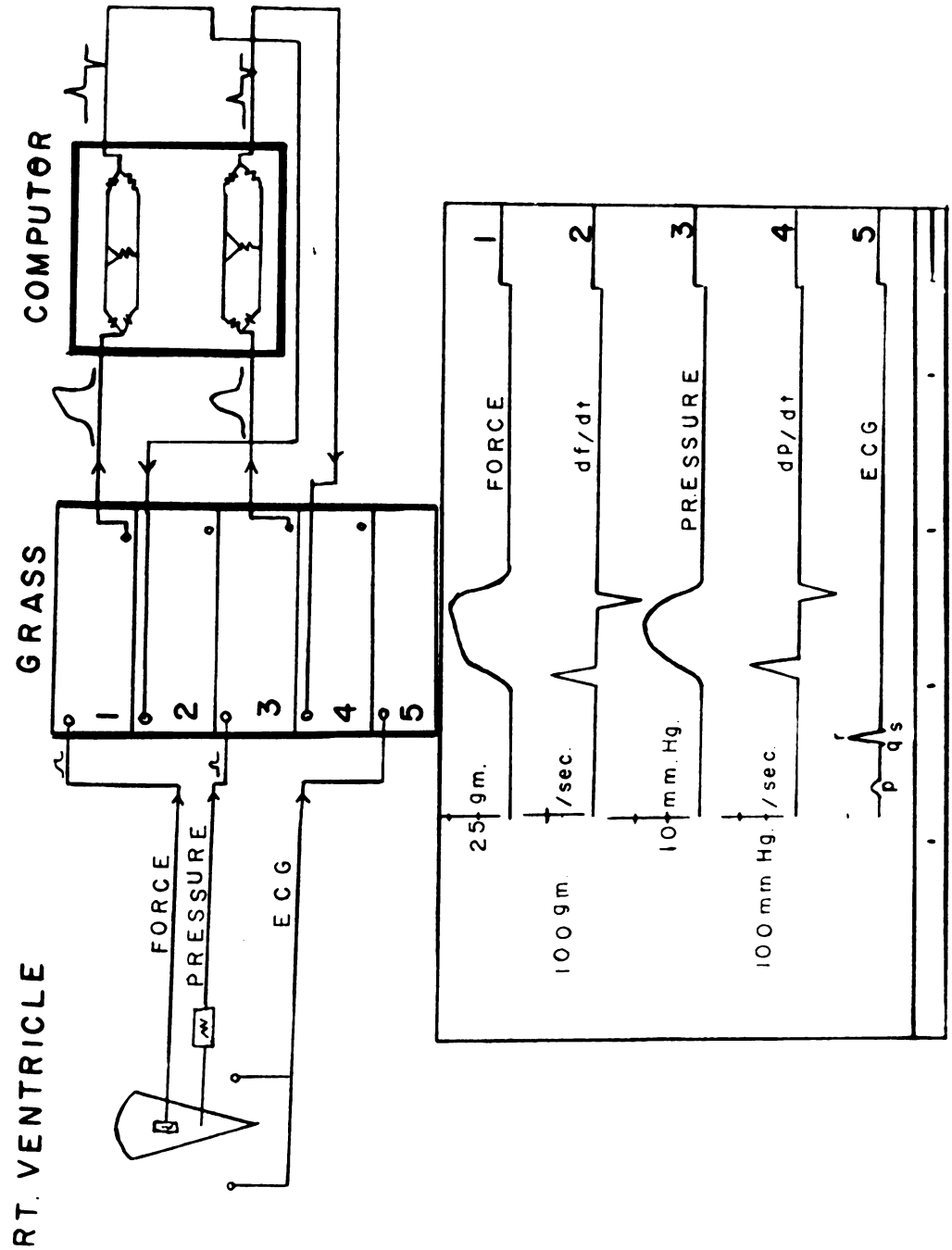
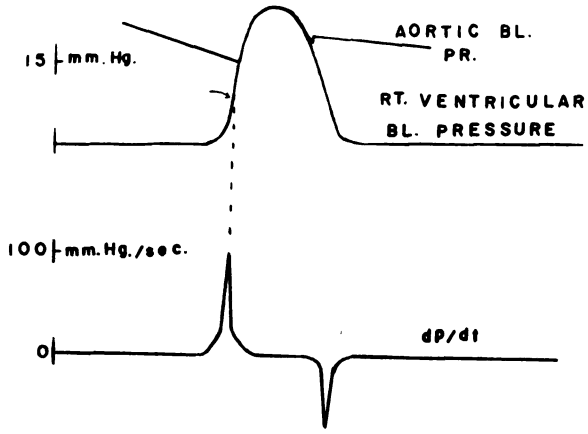

RT. VENTRICLE
FORCE
PRESSURE
ECG
GRASS
COMPUTOR
1
2
3
4
5
FORCE
df/dt
PRESSURE
dP/dt
ECG
25 gm.
100 gm
/sec.
10 mm. Hg.
100 mm Hg.
/sec.
p
q
s

Figure 12.

A.--A scheme showing the relation between (a) aortic blood pressure (b) right ventricular blood pressure, and (c) its derivative (dp/dt) for a complete cardiac cycle. Listed are three parameters measured in the study.

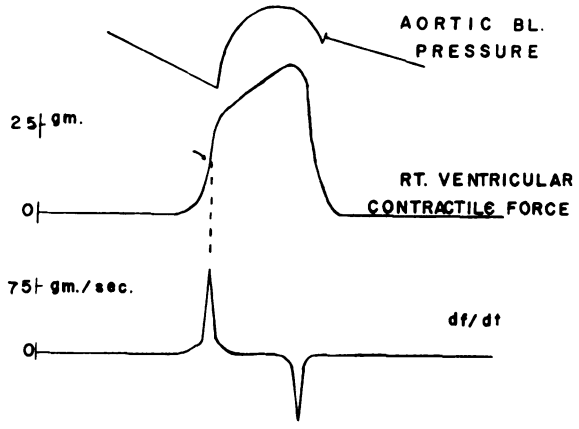
B.--A scheme showing the relationship between (a) aortic blood pressure, (b) right ventricular contractile force and (c) its derivative (df/dt) for a complete cardiac cycle. Listed are three parameters measured in the study.



1. TIME INTEGAL OF PRESSURE $\left(\int_{t}^{t} P\,dt\right)$

2. % CHANGE IN MAX. dP/dt

3. PRESSURE AT MAX. dP/dt



1. TIME INTEGRAL OF FORCE $\left(\int_{t}^{t} F\,dt\right)$

2. % CHANGE IN MAX. df/dt

3. FORCE AT MAX. df/dt

facilitates quantification of this ability of the myocardium to vary its rate of contraction. The results of this study indicate that maximal dp/dt and maximal df/dt (Figure 13) are equally "good" indicators of a decrease in heart performance during chloroform inhalation. The correlation ($r = .73$) between the force and pressure derivatives is good. Not only did maximal dp/dt and maximal df/dt decline during chloroform inhalation, they required a longer period of time after the onset of systole to reach these maximal values. This is shown in the increased durations of the time intervals (T.I.) from the peak of the ECG R-wave until maximal dp/dt and df/dt are developed (Figure 13).

The areas under the right cardiac force curves were found to vary differently from those for the right intraventricular blood pressure during chloroform inhalation ($\int F dt$ and $\int P dt$) (Figure 13). Part of this is due to the weakness of the contracting myocardium which in turn increases end-systolic volume promoting right heart congestion. Therefore, chloroform causes an increased right intraventricular pressure and/or fiber length, as shown by the increased area under the pressure pulse curves.

Cardiac Effects of Epinephrine on Force and Pressure

Epinephrine has a pronounced faciliatory effect on the ability of the myocardium to alter its rates of contraction and intraventricular pressure rise (Figure 15, 16, 17).

Figure 13.

A.--Inhalation of chloroform: Percent change from control (ordinate), time in sec. after beginning drug inhalation (abscissa) from above downwards.

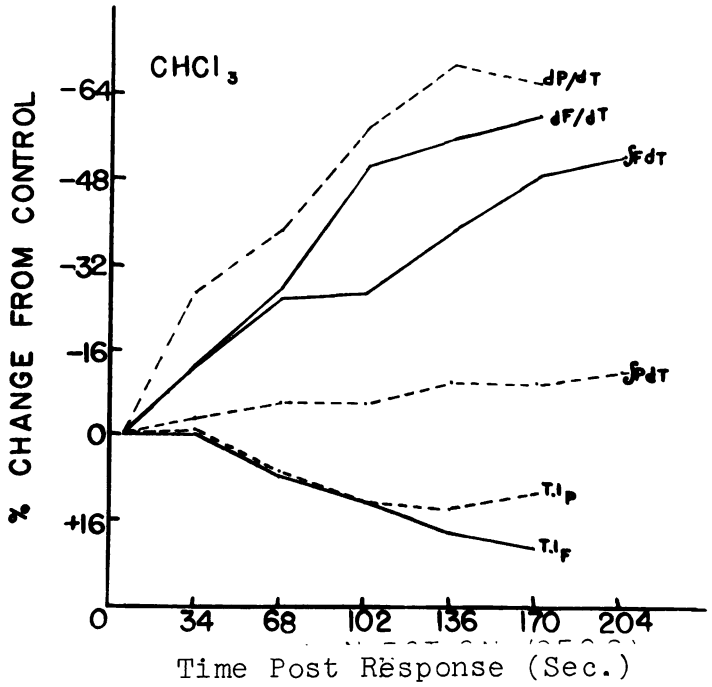
a. first derivative of pressure (dp/dt)
b. first derivative of force (df/dt)
c. time integral of force ($\int$Fdt)
d. time integral of pressure ($\int$Pdt)
e. time interval pressure $T.I._p$
f. time interval force $T.I._f$

Typical changes for one dog with measurements every 20th heart beat (see Tables 6, 7, 8, 9, Appendix G).

B.--Inhalation of chloroform: Percent change from control (Ordinate), time in sec. after beginning drug inhalation (abscissa) from above downwards.

a. time interval pressure (T.I.p)
b. time interval force (T.I.f)
c. time integral pressure ($\int$Fdt)
d. first derivative of pressure (dp/dt)
e. first derivative of force (df/dt)
f. time integral force ($\int$Fdt)

Mean for six dogs where measurements were made every 20th heart beat (see Tables, 6, 7, 8, 9, Appendix G).


CHCl 3
dP/dT
dF/dT
∫Fdt
∫Pdt
T.I P
T.I F
% CHANGE FROM CONTROL
-64
-48
-32
-16
0
+16
0
34
68
102
136
170
204
Time Post Response (Sec.)

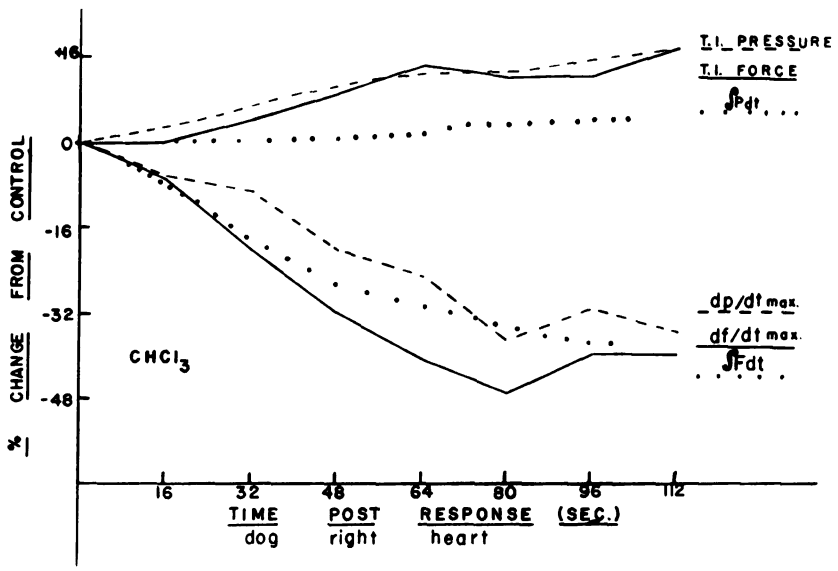
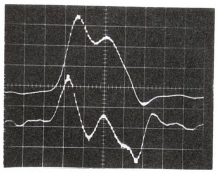

T.I. PRESSURE
T.I. FORCE
∫Pdt
dp/dt max.
df/dt max.
∫Fdt
% CHANGE FROM CONTROL
+16
0
-16
-32
-48
CHCl3
16
32
48
64
80
96
112
TIME POST RESPONSE (SEC.)
dog right heart

Figure 14.

A.--Right contractile force response to chloroform:
Top, oscilloscope tracing of control and its derivative contractile force (df/dt).
Bottom, tracing of experimental contractile force and its derivative (df/dt).
(Sweep speed 50 msec./cm. (abscissa); contractile force 1 cm. equals 15 gms. ordinate).

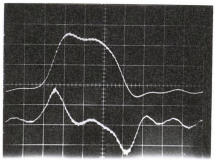
B.--Response of right ventricular pressure to 0.7 mg ouabain:
Top, oscilloscope tracing of control ventricular pressure and its derivative (dp/dt).
Bottom, oscilloscope tracing of experimental ventricular pressure and its derivative (dp/dt).
Scope sweep speed 50 msec./cm. (abscissa); Intraventricular blood pressure 1 cm equals 10 mm. Hg. (ordinate).



Contractile Force

df/dt

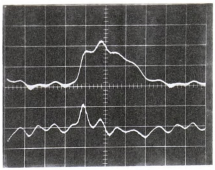
Control



Contractile Force

df/dt

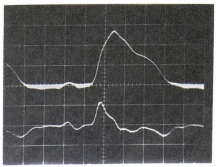
Experimental



Pressure

dp/dt

Control



Pressure

dp/dt

Experimental

Figure 15.

A.--Effects of intravenous ephinephrine (5 ug): Percent change from control (ordinate); time in sec. after drug injection (abscissa), from above downward.

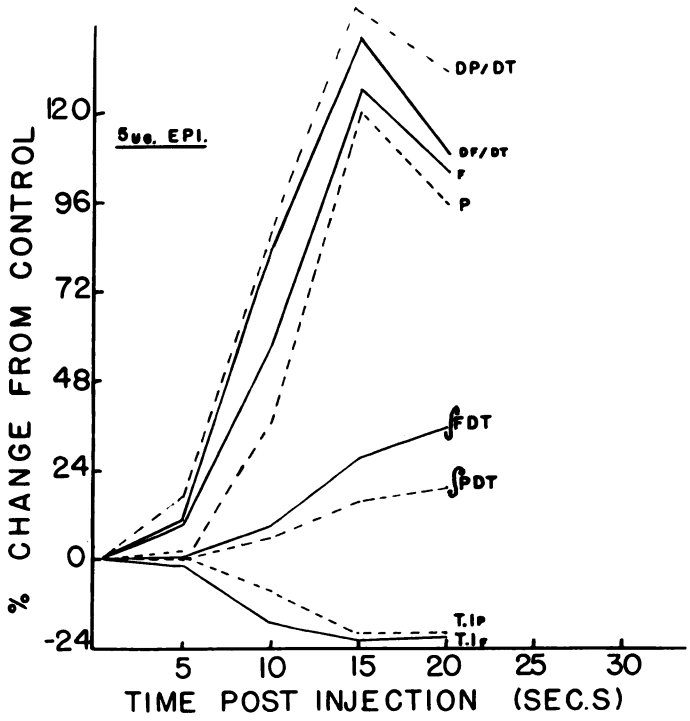
a. first derivative of pressure (dp/dt)
b. first derivative of force (df/dt)
c. force at maximal df/dt
d. pressure at maximal dp/dt
e. time integral of force ($\int$Fdt)
f. time integral of force ($\int$Pdt)
g. time interval pressure (T.I.p)
h. time interval force (T.I.f)

Typical changes for one dog with measurements every fourth hear beat (see Tables 10, 11, 12, 13, Appendix G).

B.--Effect of intravenous epinephrine.

a. first derivative of pressure to 5 ug, 2.5 ug and 1.25 ug doses.
b. first derivative of force to 5 ug, 2.5 ug, and 1.25 ug doses.

Plot of mean values for 3 dogs from measurements every fourth heart beat (see Table 13, Appendix G).


DP/DT
5ug. EPI.
DF/DT
F
P
∫FDT
∫PDT
T.Ip
T.If
% CHANGE FROM CONTROL
120
96
72
48
24
0
-24
5
10
15
20
25
30
TIME POST INJECTION (SEC.S)

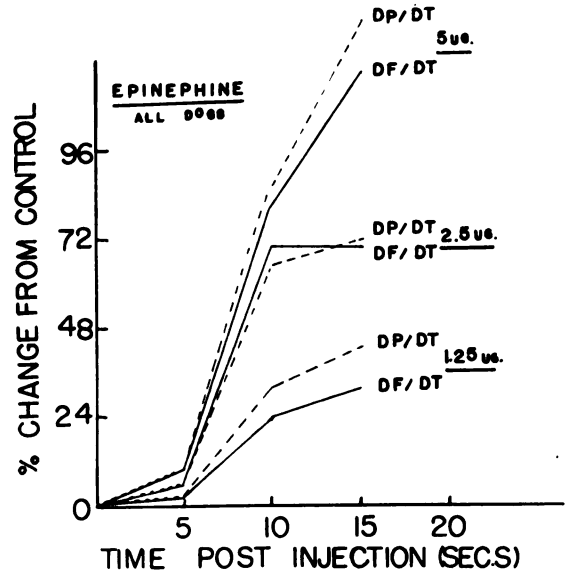

DP/DT
5ug.
DF/DT
EPINEPHINE
ALL DOSES
DP/DT 2.5ug.
DF/DT
DP/DT
1.25ug.
DF/DT
% CHANGE FROM CONTROL
96
72
48
24
0
5
10
15
20
TIME POST INJECTION (SEC.S)

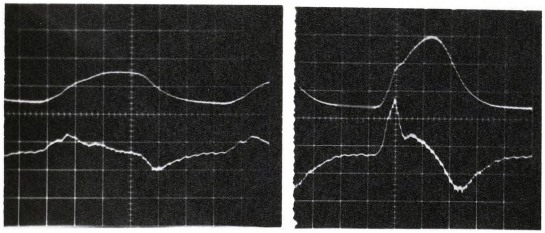
Figure 16.--Response of right contractile force and ventricular pressure to 2.5 ug epinephrine.

top, oscilloscope tracing of control and experimental cardiac force and its first derivative (df/dt).

bottom, oscilloscope tracing of control and experimental right ventricular pressure and its first derivative (dp/dt).

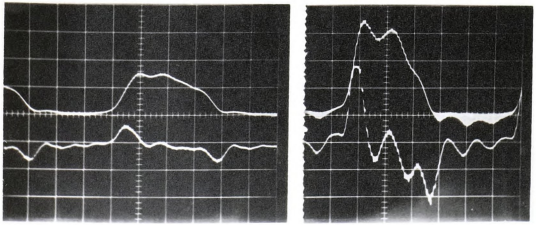
Sweep speed 50 msec/cm. (abscissa), contractile force, 1 cm. equals 15 gms. (ordinate).

Intraventricular blood pressure, 1 cm. equals 17 mm Hg. (ordinate).



Control Experimental

a.--Force
b.--df/dt



Control Experimental

a.--Pressure
b.--dp/dt

Figure 17.

A.--Effects of intravenous epinephrine: Percent change from control (ordinate), time in sec. after drug injection (abscissa), from right to left.

a. changes in time interval of force data to 10 ug, 5 ug, 2.5 ug and 1.25 ug doses.

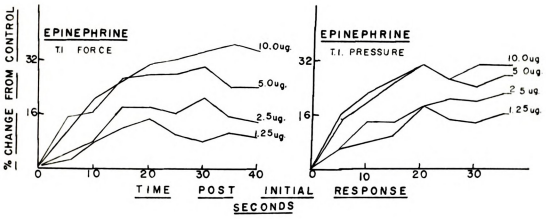
b. changes in time interval of pressure data to 10 ug, 5 ug, 2.5 ug and 1.25 ug doses.

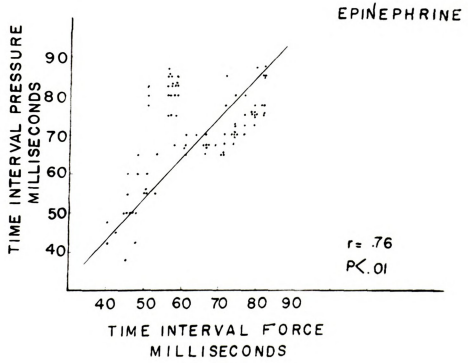
Mean for three dogs, measurements every fourth heart beat (see Table 11, Appendix G).

B.--Effects of intravenous epinephrine (5 ug) on duration of time interval (T.I.).

a. duration of time interval (milliseconds) for pressure data (ordinate).

b. duration of time interval (milliseconds) for force data (abscissa).


% CHANGE FROM CONTROL
EPINEPHRINE
TI FORCE
10.0ug.
5.0ug.
2.5ug.
1.25ug.
32
16
1
0
10
20
30
40
TIME POST INITIAL RESPONSE
SECONDS
EPINEPHRINE
T.I. PRESSURE
10.0ug
5.0ug
2.5ug
1.25ug
32
16
0
10
20
30


EPINEPHRINE
TIME INTERVAL PRESSURE
MILLISECONDS
90
80
70
60
50
40
r= .76
P<.01
40 50 60 70 80 90
TIME INTERVAL FORCE
MILLISECONDS

The results indicate, again, that the maximal dp/dt and maximal df/dt are comparable indicators of an increase in heart performance for all dose levels of epinephrine tested (Figure 15, 16). The correlation between these two variables is r = .97.

Epinephrine not only promotes an increase in the maximal rate of pressure rise (dp/dt) and force rise (df/dt), it also shortens the period of time, after the onset of systole necessary to reach these maximal values. Figure 17 illustrates the decreased duration of this time interval (T.I.) It is measured from the peak of the ECG R-wave to maximal dp/dt or df/dt. The correlation (r = .71) between these two variables (T.I.p and T.I.f) for all dose levels is good.

The change in areas under the right cardiac contractile force tracings and right intraventricular pressure pulse tracings, in response to all doses of epinephrine, was found to increase in a similar manner (Figure 15, $\int$Fdt, $\int$Pdt).

Effects of Ouabain on Cardiac Force and Pressure

The ability of the myocardium to alter intraventricular blood pressure and contractile force is slowly potentiated by the cardiac glycoside ouabain (Figures 18, 19, 20). First derivatives of cardiac pressure (dp/dt) and force df/dt) quantify this potentiation. The results of this study again show that both dp/dt and df/dt indicate an increase in myocardial performance. The correlation between the two variables is r = .69.

Figure 18.--Effects of intravenous ouabain (.7 mg): Percent change from control (Ordinate), time in sec. after drug injection (abscissa), from above downwards.

a. time integral of force ($\int Fdt$)
b. first derivative of force df/dt
c. force at maximal df/dt
d. time interval of force (T.I.f)

Typical change for one dog with measurements every 20th heart beat (see Table 14, Appendix G).

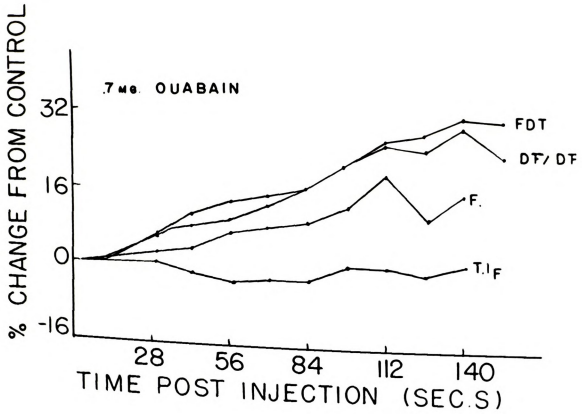

.7 MG. OUABAIN
% CHANGE FROM CONTROL
32
16
0
-16
28
56
84
112
140
TIME POST INJECTION (SEC.S)
FDT
DF/DF
F.
T.I F

Figure 19.

A.--Effects of intravenous ouabain (.7 ug): Percent change from control (ordinate), time in sec., after drug injection (abscissa), from above downwards.

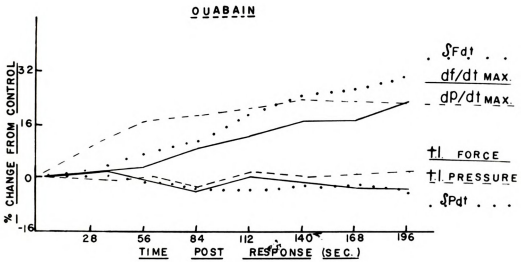
a. time integral of force ($\int Fdt$)
b. first derivative of force (df/dt)
c. first derivative of pressure (dp/dt)
d. time interval of force (T.I.f)
e. time interval of pressure (T.I.p)
f. time integral of pressure ($\int Pdt$)

Mean for five dogs with measurement every 10th heart beat (see Tables 14, 15, 16, 17, Appendix G).

B.--Effects of intravenous ouabain (.7 ug): Percent change from control (ordinate), time in sec., after drug injection (abscissa), from above downwards.

a. first derivative of pressure (dp/dt)
b. pressure at maximal dp/dt
c. time interval of pressure (T.I.p)
d. time integral of pressure ($\int Pdt$)

Typical changes for one dog with measurements every 20th heart beat(see Table 14, Appendix G).


OUABAIN
% CHANGE FROM CONTROL
32
16
0
-16
28
56
84
112
140
168
196
TIME POST RESPONSE (SEC.)
∫Fdt
df/dt MAX.
dP/dt MAX.
TI FORCE
TI PRESSURE
∫Pdt

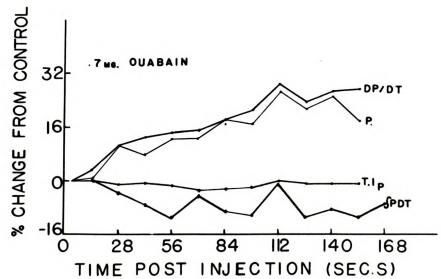

.7 mg. OUABAIN
% CHANGE FROM CONTROL
32
16
0
-16
0
28
56
84
112
140
168
TIME POST INJECTION (SEC.S)
DP/DT
P
T.I P
∫PDT

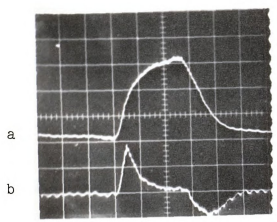
Figure 20.--Response of right contractile force to 0.7 mg ouabain.

top right, oscilloscope tracing of control cardiac force and its derivative (df/dt).

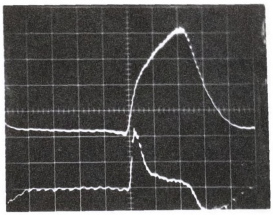
top left, oscilloscope tracing of experimental cardiac force and its derivative (df/dt).

bottom, oscilloscope tracing of experimental cardiac force and its derivative (df/dt).

Sweep speed 50 msec/cm (abscissa), contractile force, 1 cm equals 15 gms (ordinate).

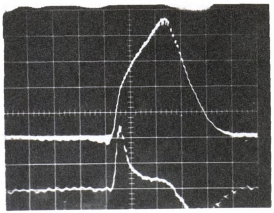


Control



Experimental
(Fifteen minutes post injection)

a.--Force
b.--df/dt



Experimental
(Thirty minutes post injection)

a.--Force
b.--df/dt

Although ouabain increases maximal dp/dt and maximal df/dt, it does not change the time required after the onset of systole for these maximal differentials to be developed by the myocardium. This is evident in that no significant change occurred in the duration of the time intervals (T.I.p and T.I.f) (Figures 18, 19). The correlation between the two variables is r = .21.

The areas under the right cardiac contractile force tracings were found to increase, whereas, the area under the intraventricular pressure did not change significantly in response to ouabain (Figure 19).

Discussion and Conclusions

Widely divergent views have been expressed in regard to the usefulness of the first derivative of intraventricular blood pressure tracings in assessing the performance of the myocardium (33, 64, 70). Two major objections to the use of maximal dp/dt as a specific index of myocardial contractility are: first, with increasing heart rate, there is a near linear increase in dp/dt (3) and second, at a constant heart rate but with increasing fiber length, there is a similar linear increase in dp/dt (63). However, if heart rate and fiber length are controlled, or remain constant, maximal dp/dt is an excellent indicator of cardiac contractility (12, 79).

In this present investigation the first derivatives of myocardial force (df/dt) and ventricular pressure (dp/dt)

were compared. During altered heart performance (with $CHCl_3$, epinephrine and ouabain), a high positive correlation between force and pressure derivatives was discovered ($r = .76$). This indicates that changes in muscle tension are reflected in both df/dt and dp/dt, and that df/dt is a specific index of cardiac contractility (when heart rate and fiber length are controlled).

For monitoring heart performance, it is suggested here that the strain gage technique is superior and has many advantages compared to the needle heart puncture method. It is very difficult to prevent needle movement within the ventricle of the heart. Since the ventricle is not spherical the pressure varies from site to site within the cardiac chambers (13). If during cardiac systole the needle's position is altered within the heart, a portion of the recorded pressure fluctuations is due to this movement. Also, during cardiac systole, pressure waves are reflected from the walls of the heart chamber and interfere with pressure measurements, therefore with dp/dt . None of these factors (reverberating pressure waves or movements of the indwelling needle) interfere with the measurement of contractile force and its derivative (df/dt). In the chronic investigation of myocardial contractility (using dp/dt as an index) intraventricular pressure measurements (thus dp/dt) are difficult to obtain. No reliable technique is available for chronic intracardiac pressure measurements. The present study

demonstrates that the strain gage technique is applicable to chronic measurements of cardiac force (thus df/dt).

The time integral, or area under intraventricular pressure and contractile force curves, is also important in defining the performance of the heart. Siegel and Sonnenblick (79, 80) have shown that the area under the ventricular pressure tracings increases directly with increasing fiber length or end-diastolic volume. Reeves, et al. (63) have demonstrated that the integrated isometric tension also varies directly with changes in the duration of systole.

The results of this present study indicate that the area under the force tracings ($\int$Fdt) does not always change in a similar manner with respect to the pressure area ($\int$Pdt). This suggests that these indices of heart performance ($\int$Fdt and $\int$Pdt) are measuring two entirely different aspects of cardiac contractility. For example, chloroform decreased the area under the contractile force tracings while the area under the pressure curves remained the same or increased slightly (Figures 13, 14). A probable reason for this is that chloroform causes right heart congestion resulting in a rise of ventricular pressure and increased fiber length increased area under pressure tracings). In the ouabain experiment, integrated systolic force ($\int$Fdt) increased whereas ventricular pressure ($\int$Pdt) remained constant or declined (Figure 19). Ouabain influences the heart both

indirectly and directly. The cardiac glycoside increases aortic blood pressure (22, 15), decreases left and right atrial pressure (20) and finally, by its direct action on arteriolar smooth muscle, increases total systemic resistance (67, 68, 11, 20). The increased total systemic resistance results in a decreased venous return, a reduction in end-diastolic fiber length (22) and a decline in the area under the intraventricular pressure curve.

The effect of digitalis glycosides on failing and normal hearts of dogs and humans has been extensively investigated. While there is general agreement that digitalis improves the contractile properties of the failing myocardium, the actions of these drugs on the nonfailing heart are less clear. In the absence of heart failure, acute digitalization either depresses or produces no significant change in cardiac output (20, 67, 88, 94), whereas in the failing heart, cardiac output is greatly increased (88).

Although it has been reported that cardiac output remains constant in the nonfailing heart, the present investigation (using S.G.T.s) demonstrates that myocardial contractile force greatly increases in response to ouabain (Figure 20). This agrees with similar studies where cardiac contractile force, measured by a Brodie-Walton strain gage arch, was always increased (11, 16, 20, 21, 88, 93).

The effects of digitalis on the first derivative of intraventricular blood pressure has recently been investigated

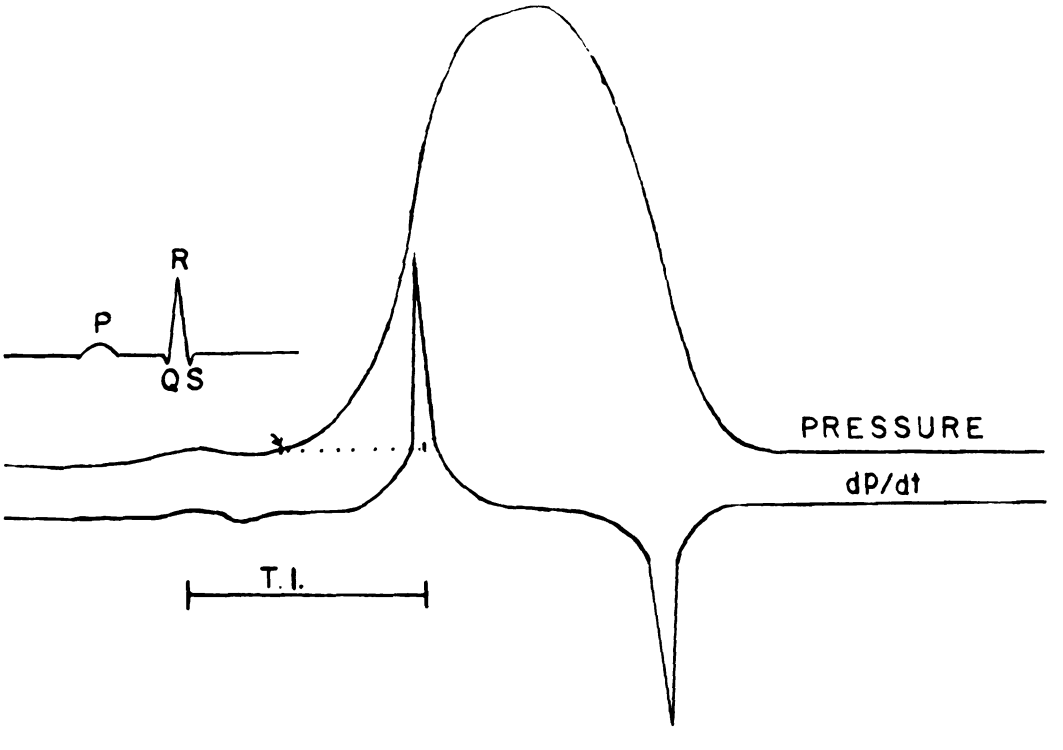
(15, 18, 22, 88). These studies by others are corroborated by the present research. Both indicate that maximal dp/dt increases in the nonfailing dog heart in response to ouabain. Furthermore, strain gage transducer studies in this research indicate that ouabain potentiates the rate of force development (df/dt) by the myocardium. The response of df/dt to ouabain might have been inferred but has not been reported previously.

Following ouabain injection heart rate remains almost constant (56, 88), the period of systolic contraction decreases (7, 11, 18, 94, 99), myocardial oxygen consumption increases and integrated systolic tension is reduced (22) in the noncongested dog. The present data, contrary to Covell, et al. (22), indicate an increase in the integrated area under the cardiac contractile force tracings in response to ouabain. The reason for this disagreement may be due, in part, to different animal preparations. Their procedure included a canine right heart by-pass in which heart rate, stroke volume and mean aortic pressure were held constant. They also observed that the end-diastolic volume and mean aortic pressure decreased in response to ouabain. A decreased time integral of pressure (Figure 19) in the present investigation indicates a drop in end-diastolic volume.

The time interval (Figure 21 and Tables 8, 11, 15) from onset of mechanical systole to development of maximal dp/dt or maximal df/dt is usually 30 to 60 milliseconds of duration. The fact that maximal df/dt and maximal dp/dt are

Figure 21.--A diagram of the time interval from the peak of the ECG R-wave to the development of the maximal rate of pressure rise. From above downwards.

a. intraventricular blood pressure
b. E.C.G.
c. first derivative of pressure (dp/dt)
d. time interval (T.I.)



T.I = TIME INTERVAL FROM PEAK OF ECG·R·WAVE

TO THE DEVELOPMENT OF MAX. dp/dt

DOG RIGHT HEART

attained somewhat after onset of contraction and prior to onset of ejection (about the middle of the isovolumic stage of the cardiac cycle) makes the measurement of the time interval of particular interest. The reason for this is that according to the force-velocity relationship of muscle contraction (83), the maximal velocity of shortening of the contractile elements should occur at the very onset of contraction when the stretch (load on the muscle) of series elastic elements is least. However, seen quantitatively in the present study, and qualitatively by Reeves, et al. (63), considerable time elapses between the development of the first visible increase in tension in the heart muscle and the attainment of maximum df/dt and/or dp/dt (Figure 21).

Why then, is there such a delay in the development of maximal df/dt and/or dp/dt in cardiac muscle? One of the reasons may be the means whereby heart muscle is stimulated (Purkinje system). Rushmer (73) has shown that all of the ventricular myocardium cannot begin to contract simultaneously because all of it is not excited simultaneously. The first portion of the ventricle to contract is the trabeculae carnae and papillary muscles (73). According to Rushmer, the delay in the "time interval" is caused by an asynchronous stimulation of the cardiac fibers. During systole more and more fibers are being stimulated and come into play in the tension build-up. Reeves, et al. (63) stated that a definite increase in the duration of this "time interval" (10 to 30

milliseconds) was noted when the initiation of the heart beat was transferred from the normal pacemaker conducting system (S.A. node) to a pair of pacing electrodes. Wiggers (97), Gilmore, et al. (32) and Chardack, et al. (14) have also demonstrated that when the heart was paced by ventricular stimulation, the maximal rate of pressure rise was less.

Priola and Randall (62) have studied alterations in cardiac synchrony induced by cardiac sympathetic nerve stimulation. They have demonstrated that measurements from the ECG P-wave to the onset of mechanical systole shortened when the stellate ganglion was stimulated in the dog. They (62) suggested that stellate stimulation increased the conduction velocity over atria nodal tissues and ventricles. They concluded that sympathetic stimulation may promote greater synchrony in the cardiac contraction.

Abbott and Ritchie (2) have demonstarted with skeletal muscles, that at the end of the latent period, the part of the muscle at the point of stimulation begins to shorten with its maximal speed. They found that when the stimulus was applied to one end of a muscle, the part of the muscle distant from the electrodes became active only after an extra delay representing the time taken for activity to spread along the muscle to that part. They interpreted this to mean that the shortening of the whole muscle begins gradually. The abrupt change in each fiber is masked by a time dispersion between the fibers.

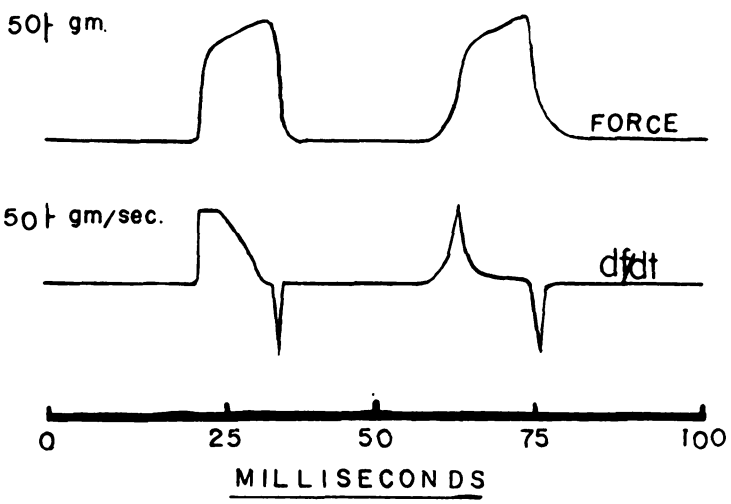
The results of these studies (83, 73, 62, 2) suggest that: a.--each muscle fiber upon stimulation instantaneously contracts with a maximal velocity; b.--all myocardial fibers are not stimulated simultaneously (synchronously) thus, the long duration of the time interval.

Theoretically then, if it were possible to stimulate the heart in such a manner that all of the cardiac fibers contracted in perfect synchrony (stimulation of all fibers simultaneously), the first derivative of cardiac force should reach its peak almost instantaneously (Figure 22).

These observations on the time interval lead to certain assumptions about the measurement of cardiac contractility. It may be unwise to consider altered cardiac performance as being due solely to a change in contractility of each fiber without considering the possibility that the change was due to a more or less synchronous activation. A change in synchrony of activation is not the same as a change in cardiac fiber contractility.

In the present investigation chloroform increased the duration of the time interval in both force and pressure tracings (Figures 13, 14, Table 8) in all experiments and on all dogs. It is possible that chloroform decreases the conduction velocity of the electrical impulse in the heart. Therefore, the decreased contractility of the heart during inhalation of chloroform may, in part, be caused by greater asynchrony in the cardiac contraction resulting from a

Figure 22.--A diagramatic illustration of the right ventricular contractile force and its first derivative. From left to the right the force tracing and its derivative (as it would likely look if all fibers in the heart were able to contract simultaneously or synchronously). The normal force and its derivative.


50 gm.
FORCE
50 gm/sec.
df/dt
0
25
50
75
100
MILLISECONDS

decreased conduction velocity. Since ventricular pacing (63) and chloroform prolong the time interval, it is suggested here that both may cause asynchrony of heart muscle contraction.

Epinephrine decreased the duration of the time interval from the peak of the ECG R-wave to the development of the maximal rate of force and/or pressure rise (Figure 15, Table 11). Priola and Pnadall (62) demonstrated that stimulation of the stellate ganglion increases the conduction velocity of the heart muscle. It is likely that epinephrine produces a similar increase in conduction velocity in the heart. Thus, both stellate stimulation and epinephrine injection probably increase the synchrony of cardiac contraction (reflected in the decreased duration of the time interval).

The time interval was not altered significantly by ouabain in the present study. However, it did cause an increase in both maximal df/dt and maximal dp/dt. Apparently, therefore, ouabain increases myocardial contractility without altering the synchrony of the cardiac contraction.

From the limited evidence presented here, it is likely that the measurement of the time interval between the onset of systole to the development of maximal rate of force and/or pressure rise is important in the measurement of myocardial contractility. The data so far indicate that this time interval may provide some quantitative information concerning the degree of cardiac synchrony.

In summary, it is suggested here, that changes in the time interval, maximal df/dt and maximal dp/dt provide a complete quantitative description of an important property of the myocardium, namely, its ability to vary its rate of contraction.

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APPENDICES

APPENDIX A

STEPWISE CONSTRUCTION OF STRAIN GAGE TRANSDUCER USED TO MEASURE THE MYOCARDIAL CONTRACTILE FORCE*

Shim Stock Preparation

1. Cut the 2.5% beryllium copper sheeting, into 4 mm. x 12 mm. using a large paper cutter-
2. Flatten all edges, using scalple handle and a hard surface.
3. Drill four small holes in each corner of the metal shim (a dental drill with a #30 drill).
4. The metal shim is then molded into the form of an arch, using a cylindrical iron pipe with a piece of metal, of the same curvature as the cylindrical pipe. The metal shim is placed between the pipe and metal and clamped in a vice.
5. The arched shims are then placed in a muffle furnace for two hours at 600° F. Quench immediately afterwards in cold water.
6. When cool, remove all sharp edges with a file.
7. Soak filed arches in metal conditioner for approximately one half hour with frequent shaking.
8. Sand the metal shim with Silicon Carbide (180 Grit) until shim is free of any imperfections.
9. Rinse sanded shims in isopropyl alcohol to degrease. Store. Shim is now ready for bonding.

Strain Gage Preparation

1. The entire strain gage is covered with mylar tape.
2. The strain gage is then taped to a solid surface and the epoxy backing is trimmed away from the edges using a new razor blade.

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*Transducer construction published by: Reinke, D. A., Rosenbaum, A. H. and Bennett, D. R. Patterns of Dog Gastrointestinal Contractile Activity Monitored in Vivo with Extraluminal Force Transducers. American Journal of Digestive Diseases 12:113 (1967).

3. The back of the strain gage is cleaned, using a cotton tipped swab, with neutralizer.

4. The strain gage is now ready for bonding.

Bonding Procedure

1. The bonding material is GA-5 epoxy adhesive and activator. It is mixed according to directions provided. The activator and adhesive should be mixed thoroughly. However, care should be taken to keep the amount of bubbles in the solution to a minimum.

2. A small drop of activated adhesive is placed on both surfaces of the metal shim. Spread evenly over the entire shim.

3. Place strain gages on both sides of the shim. Press the strain gage down firmly to remove all bubbles from under it.

4. The shim and its two strain gages are than placed under pressure using two carefully placed Silastic rubber-aluminum plates, on both sides of the shim, held together with two 1 lb. negator clamps.

5. The package (plates, clamps, shim and gages) is placed in an oven and heated at 200-220° F. for one hour.

6. Dismantle the package upon cooling and cut away excess cement, and remove mylar tape from upper surface of strain gage and soldering tabs.

Soldering Procedure

1. The soldering tabs are cleaned with methyl ethyl Ketone and plumice to promote a better soldering surface.

2. The teflon insulated 11-A wire (36 gauge, 3 conductor) is inserted into a solution of Tetra Eche to promote the bonding of the teflon to silastic. After rinsing in water, the ends of the teflon insulated wire are stripped and tinned for 2.5 millimeters.

3. A small drop of solder, on the tip of the soldering iron is placed on each of the four soldering tabs.

4. The teflon insulated wire is firmly held over the solder and with the iron, the attachment is made for three of the four tabs on the two strain gages.

5. To complete the 1/2 wheat stone brigde, a small wire (7-A, #34 Soldi cu, one conductor, Solderеze insulated) is soldered from the solder tabe of the above strain gage to soldered tape of the lower strain gage.

6. After soldering, the strain gage and wires are cleaned using rosin solvent.

7. Another thin layer of activated GA-5 adhesive is applied to the upper surface of the strain gage, solder joints, and shim. Allow to air dry for 24 hours.

8. After drying, a protective water coating material is applied to the surface of the transducer and teflon insulated wires. The water coating used was Gage Kote #2 (mixed 1:5 with melhylethylkeytone). Several layers should be appled.

Encapsulation Procedure

1. Silastic tubing (Medical-Grade tubing .058" ID by .077" OD) is cut and cleaned with Ivory Flakes.

2. The lead wires from the gages are coiled within the silastic tubing. The ends of the tubing containing the coiled wires are plugged or filled with G.-E. adhesive sealant (silicone rubber).

3. Silastic sheeting (non-reinforced) is used to encapsulate both the transducer and a portion of the silastic tubing containing the lead wires.

4. The Silastic sheets (2 x 2 cm. by .040 inch.) are cut and cleaned with Ivory Flakes detergent and rinsed in water.

5. Medical Adhesive is generously applied to one surface of each piece of the cut silastic sheeting. There should be no bubbles. The transducer and

lead out tube is then sandwiched between the two pieces of silastic sheeting and held under pressure for at least 12 hours.

6. After adhesive has dried, the transducer is trimmed using a razor.

7. The gage is now ready for attachment to the Animal Sensor Plug.

Construction of the Animal Sensor Plug

1. The animal sensor plug consist of a female cannon electric plug mounted in silastic sheeting.

2. The procedure is to solder the free ends of the coiled lead wires, from the strain gage transducer, to the appropriate connectors of the cannon plug. The solder joints are cleaned with the rosin solvent and several coats of Gage-Kote (diluted 1:5) #2 is applied.

3. The cannon plug connector are then bent perpendicular to the plug.

4. Medical grade silastic sheeting (.080 inch.) is cut such that it is larger than the bent cannon plug. A second piece of silastic is cut with a small hole, size of the female end of cannon plug, in the center. The silastic sheeting is cleaned with Ivory Flakes and a generous amount of medical adhesive is applied to one side of each of the cut pieces of silastic sheeting. The cannon plug and silastic tubing, containing the coiled lead wires, are sandwiched between the two silastic sheets and held for 12 hours or more under pressure.

Construction of Receiving Coil
(From animal sensor plug to bridge box).

1. A piece of tygon tubing (1/2" ID-10' long) is coiled around an iron pipe (1 1/2" OD) and placed in hot water overnight. After the tygon tubing is dried and removed from the iron pipe, it retains its shape-that of a spring coil.

2. Four wires (15-B -3 conductor-Teflon insulated) are pulled through the tygon tube.

3. One end of the tubing, with the 4 wires, is a attached (soldered) to a male cannon plug. This plug fits into the female animal sensor plug.

4. The other end of the tygon coil leads to the wheatstone bridge adaptor box which goes directly to the input of the grass polygraph (circuitry of input bridge 2K).

APPENDIX B

LIST OF MATERIALS

Metal for Shim Stock Cement

2.5% beryllium copper sheeting, .004 and .008 inch thick in the "quarter-hard" state.

Meier Brass and Aluminum Co., 1471 E. 9 Mile Rd., Hazel Park, Michigan.

Lead Wire

#36 gauge stranded copper wire, three conductor, Teflon insulated, Code no. 11-A.

#34 gauge solid copper wire, 1 conductor, solderize insulated, Code no. 7-A.

#34 gauge solid copper wire, 3 conductor, Teflon insulated, Code no. 15-B.

William T. Bean, 18915 Grand River Ave., Detroit 23, Michigan.

Waterproofing

Gagekote #2, nitrile rubber solution.

William T. Bean, Detroit 23, Michigan.

Cement

GA-5 Epoxy Cement.

Instruments Division, Budd Co., Phoenixville, Pennsylvania.

Soldering Accessories

Strain gage solder, 300° F., .015 inch diameter American Beauty Soldering Iron #B-2000 w/B-3 tips.

William T. Bean, Detroit 23, Michigan.

Accessories for Cleaning Metal Sheeting and Bonding

Neutralizer 2 oz. BtLS
Cotton applicator-Pg. of 100
Pumice 1/2 oz. Jar
Code 7-A Wire 100" roll
Cellophane tape 3/4" x 400" rolls
Silicon carbide (180 grit) pkg. of 12
Metal conditioner 2 oz. bottle
Rosin solvent 1/2 oz. bottle
Silicon Carbide (800 grit)
Tetra-etch 2 oz. bottle
N/A, 1 lb. Neg-Ator Clamp
N/A, 300° F. Strain Gage Solder Lot
N/A, Mylar Tape, 1/2" x 200" Roll
Metal Conditioner, 1 qt.
Gage Kite 32 1 kit of 12 oz. btl.
Teflon Sheet (.003 x 2 x 60")

William T. Bean, Detroit 23, Michigan

Strain Gages

Gage type MD-DV-090 DG-350
Gage type SA-09-090 DH-350
(epoxy on both sides of gage).

William T. Bean, Detroit 23, Michigan

Tube Filler

G. E. 113 RTV Silicone Rubber

Silicone Products Department, General Electric Company, Waterford, New York 12188.

Adhesive

Dore Adhesive and Catalyst 2 lbs.

John L. Dore Co., 5406 Schuler, P. O. Box 7772, Houston 7, Texas.

Cannon Plug

MD 1-15SL 1
Electrical Connector (female)
051403-0001

MD1-15PLI
Electrical Connector (male)
051402-0001

Newark Ferguson, 20700 Hubbell Ave., Detroit, Michigan 48237.

Needles and Sutures

Double Needle 000 Merisilene suture

Ethicon, Inc., Sommerville, New Jersey.

Silicone Rubber Tubing

3H5-10610 Silicone Rubber Tubing
.058" I.D. x .077" O.D. 10' coil
3H5 10618 Silicone Rubber Tubing
.132" I.E. x .183 O.D. 10' coil

V. Mueller and Company, 330 S. Honore St., Chicago, Illinois 60612.

Silastic Sheeting

Medical Adhesive Type A
(Silicone) 1 two oz. Tube

Silastic Brand Sheeting (Med. Grade)

1 pk. Nonreinforced .040"
1 pk. Nonreinforced .080"
(Extra Firm Grade)
1 pk. Reinforced .040"

V. Mueller and Company, 330 S. Honore St., Chicago, Illinois 60612.

APPENDIX C

CHRONIC EXPERIMENT

Purpose

It was one of the objectives of this thesis to study cardiac contractile force of the dog in his undisturbed cage environment. This chronic experimental data was to be compared to the acute anesthetized dog data. However, because of various complications only partial success was achieved on the chronic dog preparations.

Presurgery Conditioning of Dogs

The dogs had been conditioned to their cages (in which recordings took place) for approximately six months before surgery. Four weeks before surgery, ropes hanging from the tops of the cages were tied to the dogs in harness each evening. This conditioning accustomed each dog to the plug-in coil which was used for collecting force data post-surgery.

All data collections were recorded in an adjacent room such that the dog did not experience any distraction during the procedure.

Methods

In five healthy dogs (beagles) under sterile conditions, the following was performed: After anesthetization (sodium pentobarbital 30 mg./kg.), clipping and intubation, two incisions were made. The first was between the scapulae for

implantation of an animal sensor plug and the second was in the right 4th. intercostal space. The right lung was packed down with wet gauze pads for better exposure of the right heart. The right ventricle was exposed by a three inch incision in the pericardium. The transducer and its cable were inserted under the skin, with the aid of a troca, from the incision between the two scapulae to the rib incision. The skin was then sutured around the animal sensor plug (button) leaving exposed only the female connectors of the button. The strain gage transducer was next sutured firmly to the right ventricle. Two ECG electrodes were sutured under the skin on each side of the chest. The incisions were closed and penicillin (10^6 units/day) was administered up to four days postsurgery.

Results

Three days postsurgery four out of five dogs gave good right heart contractile force recordings. The ECG recordings from the dogs were very noisy because of difficulties in grounding the animals in their cages. Five days postsurgery only one of the five strain gage transducers gave good heart force recordings. The seventh day post-surgery the remaining gage also detected large interferences.

After post mortem on each dog it was discovered that the cause of the poor contractile force recordings was adhesions in the chest. Between four and five days post-surgery, when the strain gage transducer produced many

abnormal recordings, adhesions had formed around the gage, between the gage and the pericardium. In many instances these were connected to the lungs and in two cases to the diaphram thus making the force recordings impossible to interpret.

However, some significant data were obtained before severe adhesions had developed, that is, three days post-surgery.

In comparing the contractile force recordings of the dog in the supine position to that of the standing position, it was noticed that in all four dogs tested, a definite arrhythmia occurred in thesupine position. When the dog stands, this arrhythmia immediately disappears (Figure 23).

Each day after surgery the right heart contractile force was found to be less than that recorded the previous day. For example, immediately post-surgery, (closed chest; anesthetized) the cardiac peak systolic force was approximately 50 grams. The first day after the operation, unanesthetized dog, the peak force was 40 grams and the second day 35 grams and the fifth day it declined to 25 grams.

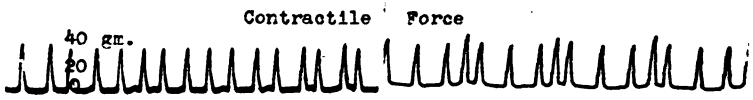
The response of the unanesthetized dog to 2.5 ug epinephrine as compared to the anesthetized open-chest animal is shown in (Figures 23). The results suggest that the percent change in cardiac force in response to 2.5 ug epinephrine in the unanesthetized dog is less than in the acute preparation.

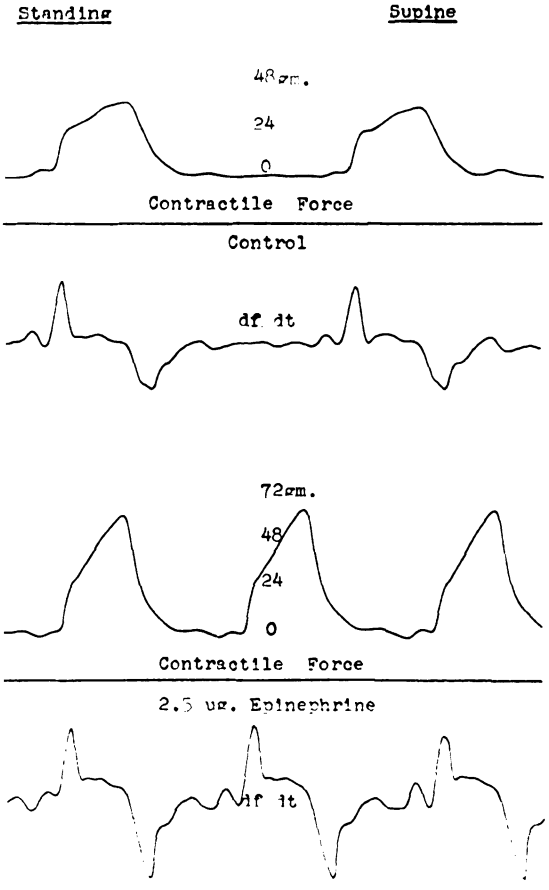
Figure 23.

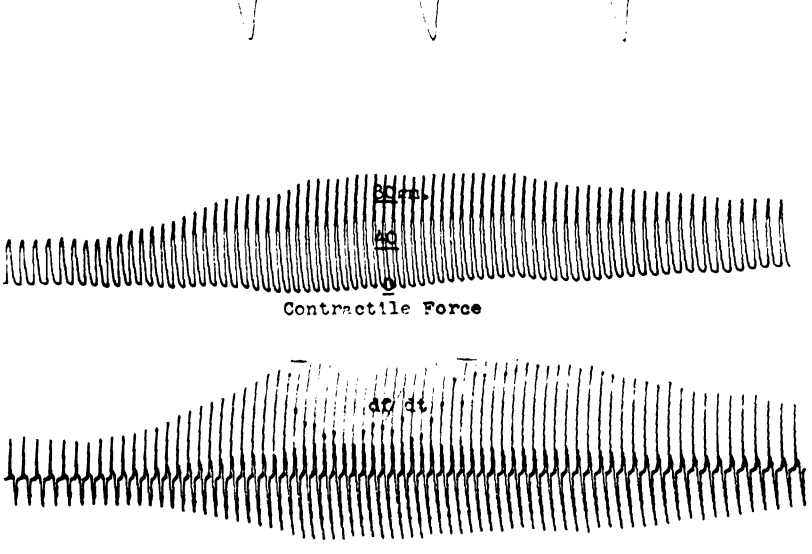
A.--Changes in the contractile force in response to 2.5 ug. epinephrine. Closed chest, unanesthetized dog. From above downwards, control force as recorded from the strain gage transducer (S.G.T.) and the simultaneous recording of the first derivative (df/dt). The rise in force and the simultaneous recording of the first derivative (df/dt) in response to 2.5 ug. epinephrine.

B.--Changes in the contractile force in response to 2.5 ug. epinephrine. Open chest, anesthetized dog. recorded at a speed of 5 mm./sec. From above downwards, force as recorded from the strain gage transducer (S.G.T.), and the simultaneous recording of the first derivative (df/dt) of the force tracings.

C.--Changes in the heart rhythm of the closed chest unanesthetized dog, as observed by the force recordings from the strain gage transducer. Reocrder at a speed of 5 mm./sec.


Contractile Force
40 gm.
20
0


Standing
Supine
48 gm.
24
0
Contractile Force
Control
df dt
72 gm.
48
24
0
Contractile Force
2.5 ug. Epinephrine
df dt


80 gm.
40
0
Contractile Force
df dt

There was no significant response or change in contractile force in the unanesthetized dog due to 0.7 mg. (I.V.) ouabain, with the exception that the dog regurgitated on the investigator.

Discussion and Conclusions

It is possible that better surgical techniques would eliminate some of the adhesions between the heart, gage, pericardium, lungs and diaphram of the dog, and permit better heart contractile force recordings (S.G.T.). However, another investigator (17) has reported similar adhesion problems in the chronic dog preparation.

The fall in the peak cardiac force each days after surgery is probably caused by a gradual loosening of the attachments of the gage to the myocardium and/or possibly because of the interference due to adhesions around the gage itself. The response of the heart to 2.5 ug epinephrine in the unanesthetized dog was noticably smaller as compared to the open chest anesthetized dog (Figure 23). The reason for this is probably the adhesions.

In conclusion the author suggest that by overcoming the problems of adhesion, possibly by better surgical techniques, (or by any other means) the strain gage transducer should provide a technique whereby the heart muscle can be studied directly in chronic dog preparations for long periods of time.

Figure 24.--Circuitry for coupling the strain gage transducer to the Grass amphifiers.

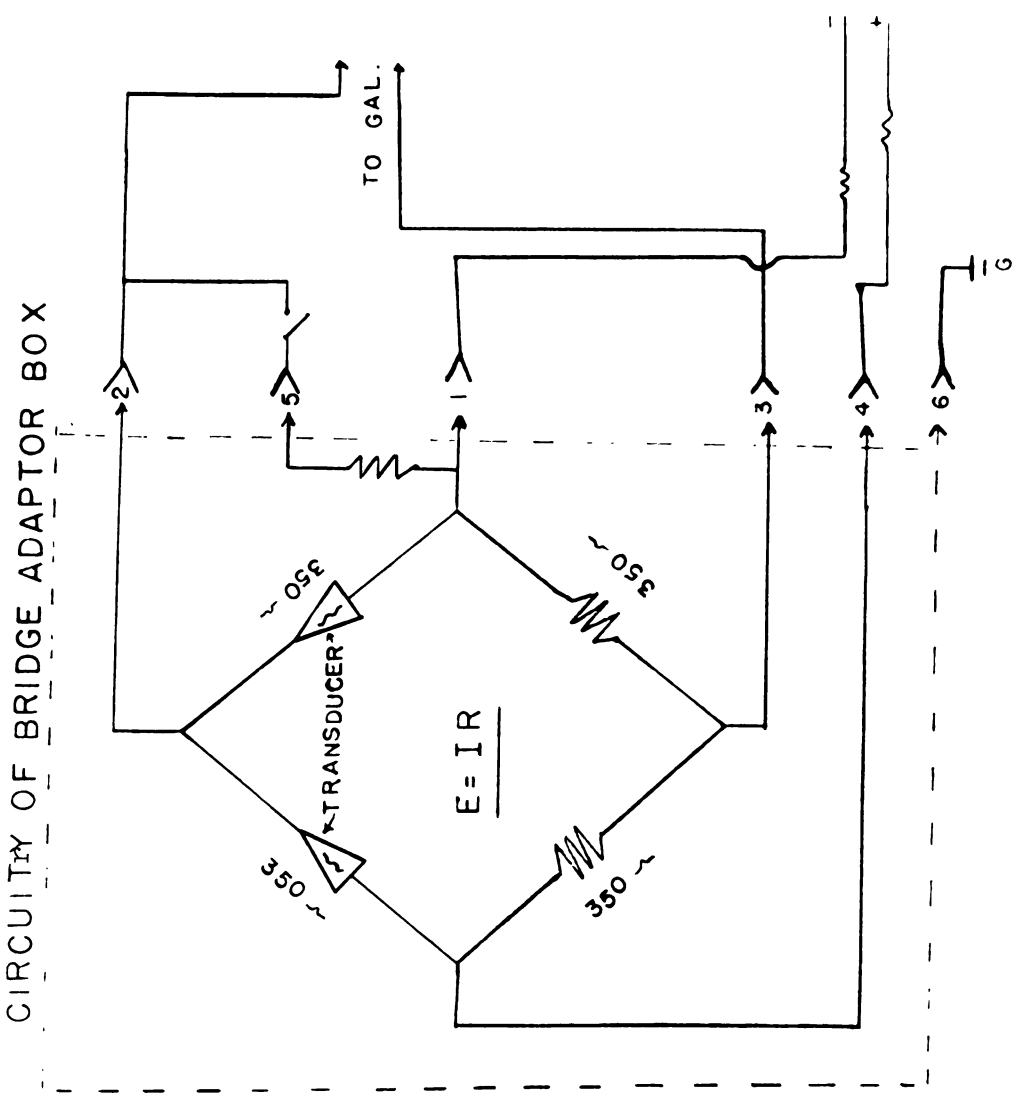
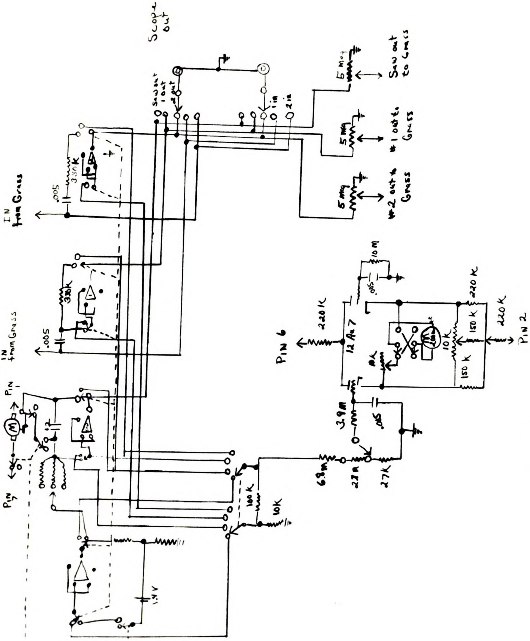

CIRCUITRY OF BRIDGE ADAPTOR BOX
TO GAL.
2
5
1
3
4
6
G
350 Ω
350 Ω
TRANSDUCER*
E = IR
350 Ω
350 Ω
-
+

Figure 25.--Circuitry of the electrical differentiator.


Scope out
Saw out
1 out
2 out
1 in
2 in
5 meg
Saw out to Grass
5 meg
#1 out to Grass
5 meg
#2 out to Grass
IN from Grass
.005
330K
IN from Grass
.005
330K
PIN 1
PIN 7
M
1.4 V
100 K
10K
6.8 M
27K
3.9 M
.005
PIN 6
220 K
12 AU 7
10 M
.005
220 K
150 K
150 K
10 K
220 K
PIN 2

APPENDIX D

STATISTICAL FORMULAE

Product-moment coefficient of correlation

$$r = \frac{N\varepsilon XY - (\varepsilon X)(\varepsilon Y)}{\sqrt{[N\varepsilon X^2 - (\varepsilon X)^2][N\varepsilon Y^2 - (\varepsilon Y)^2]}}$$

Testing the significance of the correlation

$$z = \sqrt{\frac{r^2 (N - 2)}{1 - r^2}}$$

Test of significance "t"

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{\varepsilon(x_1 - \bar{x})^2 + \varepsilon(x_2 - x_2)}{N_1 + N_2 - 2} \left(\frac{1}{N} + \frac{1}{N}\right)}}$$

Table 6.--The effects of Chloroform inhalation on the maximal rate of force rise and maximal rate of pressure rise in the right ventricle of dogs.*

Maximal rate of force rise						Maximal rate of pressure rise					
Control Values											
Gms./sec						mm. Hg./sec.					
Dogs	IV	IV	IV	V	V	III	IV	IV	IV	V	V
III											
125	80	55	60	60	90	110	107	90	97	65	90
120	85	55	65	60	95	120	105	87	95	65	95
120	82	55	60	60	10	110	107	90	92	65	100
120	80	55	60	60	10	115	105	90	92	60	110
110	80	55	60	60	10	115	107	90		62	100
---	90	55	--	--	--	115	110	87	---	--	---
---	90	55	--	--	--	---	112	87	---	--	---
---	85	--	--	--	--	---	110	---	---	--	---
During Inhalation Chloroform											
100	90	55	60	60	87	120	110	90	100	62	90
150	82	57	65	--	--	115	110	100	100	--	---
130	85	70	65	60	85	115	115	95	100	67	100
135	80	65	60	--	--	105	117	95	92	--	---
110	70	47	60	55	80	105	110	82	92	75	105
100	65	45	55	--	--	110	100	85	90	--	---
105	57	45	47	50	72	120	95	77	87	70	102
105	55	40	50	--	--	130	87	77	82	--	---
100	50	37	40	47	67	120	85	78	75	60	90
105	45	35	42	--	--	130	80	70	72	--	---
100	45	35	37	45	70	125	80	70	70	57	80
100	40	32	40	--	--	120	77	60	70	--	---
95	--	30	35	42	70	120	---	55	65	55	77
100	--	--	25	--	--	110	---	---	60	--	---
95	--	--	--	40	--	110	---	---	---	55	---
95	--	--	--	--	--	107	---	---	---	--	---
85	--	--	--	--	--	107	---	---	---	--	---
90	--	--	--	--	--	100	---	---	---	--	---
90	--	--	--	--	--	95	---	---	---	--	---
90	--	--	--	--	--	100	---	---	---	--	---
90	--	--	--	--	--	100	---	---	---	---	---
95	--	--	--	--	--	100	---	---	---	---	---
87	--	--	--	--	--	100	---	---	---	---	---
95	--	--	--	--	--	100	---	---	---	---	---
90	--	--	--	--	--	100	---	---	---	---	---

*In each column, from above downward, each datum is derived from every 20th heart beat after beginning control observations and following drug administation.

Table 7.--The effects of chloroform inhalation on the time integral (area) of the right ventricular contractile force and pressure tracing.*

Dogs	Time Integral of Force					Time Integral of Pressure					
	II	III	IV	IV	V	II	II	III	IV	IV	V
	Gram-Seconds			Control Values		Millimeter-Hg.-Seconds					
	1.34	4.37	1.38	1.43	1.26	4.21	2.04	2.67	3.93	3.03	2.88	2.34
	1.28	4.15	1.41	1.41	1.17	4.21	1.95	2.75	3.93	3.21	2.79	2.36
	1.30	4.08	1.39	1.38	1.21	4.04	2.08	2.75	3.80	3.03	2.88	2.42
	1.31	4.38	1.38	1.40	1.19	4.10	2.02	2.89	3.96	2.88	2.80	2.33
	----	4.35	1.38	1.39	1.24	4.01	----	2.86	3.96	3.16	3.04	2.62
	----	----	1.37	1.36	1.21	----	----	----	3.96	3.01	2.80	----
	----	----	1.41	1.37	1.21	----	----	----	----	3.07	2.88	----
	----	----	----	1.35	----	----	----	----	----	----	----	----
	During Chloroform Inhalation											
	1.20	4.21	1.44	1.43	1.25	4.13	1.98	2.63	3.94	3.00	2.93	2.36
	1.20	4.04	1.40	1.39	1.35	4.15	2.01	2.75	3.84	2.95	3.08	2.49
	1.01	3.45	1.37	1.39	1.13	3.84	1.85	3.01	3.67	3.01	3.01	2.75
	1.04	3.45	1.28	1.42	1.18	4.06	1.89	3.03	3.55	3.09	2.95	2.65
	0.95	3.20	1.15	1.31	1.09	3.15	1.85	3.14	3.56	3.01	3.14	2.72
	0.91	2.86	1.14	1.27	1.10	2.78	1.76	3.17	3.93	3.01	3.00	2.63
	1.04	2.95	1.13	1.23	0.99	2.75	1.73	3.26	3.95	3.01	3.01	2.59
	0.96	----	1.07	1.19	0.91	2.58	1.80	----	4.19	3.17	3.14	2.63
	0.88	----	0.99	1.11	0.91	----	1.35	----	4.33	3.16	2.95	----
	0.88	----	0.98	1.13	0.87	----	1.30	----	4.43	3.22	2.95	----
	0.81	----	0.98	1.11	0.87	----	1.25	----	4.26	3.28	2.99	----
	0.73	----	0.94	1.07	0.79	----	1.10	----	4.19	3.10	2.75	----
	0.76	----	0.97	----	0.80	----	1.17	----	4.19	----	2.86	----
	0.65	----	0.97	----	----	----	1.10	----	4.15	----	----	----
	0.61	----	0.92	----	----	----	0.99	----	4.31	----	----	----
	0.62	----	0.91	----	----	----	1.02	----	4.06	----	----	----
	0.63	----	0.91	----	----	----	0.97	----	4.08	----	----	----
	----	----	0.92	----	----	----	----	----	3.93	----	----	----
	----	----	0.89	----	----	----	----	----	3.98	----	----	----
	----	----	0.94	----	----	----	----	----	4.02	----	----	----
	----	----	0.95	----	----	----	----	----	3.96	----	----	----
	----	----	0.91	----	----	----	----	----	4.18	----	----	----
	----	----	0.90	----	----	----	----	----	4.09	----	----	----
	----	----	0.89	----	----	----	----	----	----	----	----	----

*Same as Table 6.

Table 8.---The effects of chloroform inhalation on the length of the time intervals between the peak of the ECG-R-wave and the maximal rate of pressure and force rise.*

Dogs	Time interval between the peak of ECG-R-wave and the maximal rate of force rise							Time interval between the peak of ECG-R-wave and the maximal rate of pressure rise						
	II	II	III	IV	IV	IV	V	V	II	II	III	IV	IV	IV	V	V
	Milliseconds							Control Values	Milliseconds							
60	66	80	57	60	65	52	55	65	80	85	67	70	65	83	83
62	66	80	57	60	65	52	55	65	80	82	67	70	67	85	85
60	67	80	60	60	55	57	57	65	77	82	65	70	67	82	80
60	67	80	57	60	60	52	57	67	80	80	65	67	67	82	80
62	67	80	57	55	55	52	57	65	75	85	65	70	70	85	80
57	67	82	57	60	60	52	55	65	77	85	65	70	70	--	82
60	66	82	55	60	--	52	55	67	77	85	67	67	70	--	80
55	67	--	55	60	--	52	55	67	75	85	--	--	70	--	--
62	66	--	57	--	--	52	60	62	77	85	--	--	--	--	--
60	67	--	57	--	--	--	57	65	75	--	--	--	--	--	--
60	--	--	--	--	--	--	55	67	77	--	--	--	--	--	--
57	--	--	--	--	--	--	55	65	--	--	--	--	--	--	--
60	--	--	--	--	--	--	--	65	--	--	--	--	--	--	--
--	--	--	--	--	--	--	--	67	--	--	--	--	--	--	--
								65	--	--	--	--	--	--	--
	During Chloroform Inhalation															
60	67	80	57	60	60	55	60	60	80	82	67	65	70	85	80
62	65	80	60	55	60	52	55	62	75	82	67	67	67	85	82
60	68	80	57	55	60	50	55	65	75	85	70	70	70	85	85
62	71	77	55	60	60	52	60	67	77	85	65	67	70	80	82
61	73	77	60	60	60	50	55	75	85	85	75	50	70	82	82
62	73	80	57	57	60	50	55	75	85	85	70	75	72	82	85
65	75	80	57	62	60	52	60	75	85	85	70	72	72	80	85
67	75	82	60	62	65	55	57	80	90	87	75	75	75	85	85
71	76	80	60	65	65	55	53	77	87	85	75	75	75	82	85
67	80	80	65	65	62	67	60	77	90	85	80	80	77	82	82
71	82	80	60	60	67	55	60	75	90	82	77	80	77	80	80
71	75	80	--	--	--	57	57	80	85	85	--	--	77	82	85
71	82	80	--	--	--	57	57	80	87	85	--	--	80	87	82
70	80	85	--	--	--	57	60	77	85	85	--	--	--	82	82
73	--	85	--	--	--	60	60	80	--	87	--	--	--	85	82
75	--	82	--	--	--	57	55	82	--	87	--	--	--	85	80
75	--	80	--	--	--	60	62	80	--	90	--	--	--	87	82
75	--	82	--	--	--	60	55	80	--	90	--	--	--	87	85
70	--	80	--	--	--	60	55	82	--	90	--	--	--	87	80
72	--	87	--	--	--	57	60	82	--	90	--	--	--	87	82
70	--	82	--	--	--	57	57	82	--	87	--	--	--	85	85
70	--	85	--	--	--	57	57	82	--	92	--	--	--	87	85
70	--	82	--	--	--	57	--	82	--	--	--	--	--	87	--
77	--	80	--	--	--	57	--	80	--	95	--	--	--	85	--

*Same as Table 6.

Table 9.--The effects of chloroform inhalation on the force and pressure df/dt maximum and dp/dt maximum respectively.*

Dogs III	Force at df/dt maximum					Pressure at dp/dt maximum					
	IV	IV	IV	V	V	III	IV	IV	IV	V	V
	Grams					Control Value	Millimeters of Hg.				
8.1	4.2	3.3	3.3	4.2	4.2	12	15	14	14	12	13
8.7	3.6	3.6	3.0	3.9	4.2	13	17	13	13	14	14
7.8	3.6	3.6	3.0	3.9	4.2	14	16	14	12	12	14
8.4	4.2	3.6	3.6	4.2	4.8	12	15	13	14	13	15
7.5	4.5	3.0	3.3	3.9	4.2	13	16	13	13	12	15
8.4	4.2	3.3	---	---	---	13	18	14	--	--	--
---	4.5	3.3	--	--	--	--	17	13	--	--	--
--	--	--	--	--	--	--	16	--	--	--	--
	During Chloroform Inhalation										
7.8	4.2	3.3	3.0	3.9	3.9	13	16	16	13	12	13
7.5	4.5	3.6	3.3	3.6	3.6	13	16	14	13	14	13
7.2	4.2	3.3	3.0	3.6	3.3	13	18	14	14	12	13
8.1	4.2	3.3	3.3	3.3	3.6	12	16	14	13	12	12
6.9	4.2	3.3	3.3	3.0	2.6	12	16	17	13	10	11
6.6	3.6	3.0	3.0	2.8	2.6	14	15	13	14	10	11
7.2	3.0	2.3	2.3	2.6	3.0	12	12	12	12	10	10
7.2	3.0	2.3	2.3	2.6	---	13	13	12	13	10	--
7.8	2.4	2.0	2.0	---	---	14	13	12	12	--	--
7.5	3.0	1.6	2.3	---	---	14	12	12	12	--	--
7.5	2.6	1.6	2.3	---	---	15	12	11	11	--	--
7.2	---	2.3	2.0	---	---	15	--	12	10	--	--
7.1	---	1.6	1.6	---	---	16	--	11	10	--	--
7.8	---	---	1.3	---	---	14	--	--	--	--	--
7.2	---	---	---	---	---	14	--	--	--	--	--
6.7	---	---	---	---	---	15	--	--	--	--	--
6.6	---	---	---	---	---	14	--	--	--	--	--
6.4	---	---	---	---	---	14	--	--	--	--	--
6.3	---	---	---	---	---	14	--	--	--	--	--
6.6	---	---	---	---	---	14	--	--	--	--	--
6.0	---	---	---	---	---	14	--	--	--	--	--
6.9	---	---	---	---	---	14	--	--	--	--	--
6.3	---	---	---	---	---	14	--	--	--	--	--
6.0	---	---	---	---	---	14	--	--	--	--	--
6.6	---	---	---	---	---	13	--	--	--	--	--

*Same as Table 6.

Table 10.--The effects of epinephrine on the maximal rate of pressure rise (dp/dt) and the maximal rate of force rise (df/dt) in the dog right heart.*

	df/dt maximum gm/sec.						dp/dt maximum mm. Hg./sec.					
	Control Values											
Dogs V	VI	V	VI	V	VI	V	VI	V	VI	V	VI	
	1.25 ug.		2.5 ug.		5.0 ug.		1.25 ug.		2.5 ug.		5.0 ug.	
60	57	70	57	70	60	105	75	80	70	55	70	
65	60	75	57	72	60	100	70	80	70	55	75	
65	60	70	60	70	65	110	70	80	75	57	75	
65	57	70	57	70	60	110	75	82	75	57	75	
70	60	70	57	70	60	110	72	80	77	57	75	
67	--	70	---	70	---	100	---	80	---	55	---	
70	--	70	---	65	---	120	---	80	---	55	---	
--	--	---	---	70	---	---	---	---	---	---	---	
	Following Epinephrine Injection											
77	70	85	95	100	115	120	90	87	100	60	112	
80	80	97	110	160	145	120	97	105	135	90	170	
75	80	105	110	170	135	115	100	120	140	160	125	
77	75	110	100	165	110	125	90	132	120	160	142	
80	--	115	---	170	135	120	---	137	---	165	---	
80	--	115	---	160	110	120	---	140	---	150	---	
82	--	110	---	155	110	140	---	135	---	155	---	
90	--	110	---	140	---	140	---	130	---	145	---	
85	--	---	---	130	---	140	---	130	---	---	---	
80	--	---	---	---	---	130	---	---	---	---	---	
85	--	---	---	---	---	140	---	---	---	---	---	
95	--	---	---	---	---	140	---	---	---	---	---	
85	--	---	---	---	---	160	---	---	---	---	---	
90	--	---	---	---	---	140	---	---	---	---	---	
90	--	---	---	---	---	150	---	---	---	---	---	
90	--	---	---	---	---	135	---	---	---	---	---	
85	--	---	---	---	---	150	---	---	---	---	---	
90	--	---	---	---	---	160	---	---	---	---	---	
85	--	---	---	---	---	160	---	---	---	---	---	
90	--	---	---	---	---	150	---	---	---	---	---	
85	--	---	---	---	---	160	---	---	---	---	---	
85	--	---	---	---	---	180	---	---	---	---	---	
90	--	---	---	---	---	160	---	---	---	---	---	
90	--	---	---	---	---	150	---	---	---	---	---	
90	--	---	---	---	---	160	---	---	---	---	---	
--	--	---	---	---	---	140	---	---	---	---	---	
						150						

*Same as Table 6.

Table 11.--The effects of epinephrine on the duration of the time interval between the peak of the ECG-R-wave to the development of the maximal rate of force (df/dt) and pressure (dp/dt) rise in the dog right heart.*

Time Interval (msec.)						Time Interval (msec.)					
Control Values											
Dogs II	II	III	III	IV	IV	II	II	III	III	IV	IV
1.25 ug.		2.5 ug.		5.0 ug.		1.25 ug.		2.5 ug.		5.0 ug.	
55	77	55	82	55	80	85	77	80	75	80	85
55	80	57	80	55	80	82	77	82	75	80	82
57	72	55	80	55	80	87	80	80	75	82	85
55	77	57	85	55	80	87	77	82	75	82	85
57	75	52	80	55	80	82	77	82	77	80	87
55	77	55	80	55	80	85	77	82	77	80	85
--	82	55	80	55	--	85	77	--	77	80	--
--	77	55	80	--	--	85	77	--	80	82	--
--	77	57	80	--	--	--	--	--	75	82	--
--	80	55	--	--	--	--	--	--	77	--	--
Following Epinephrine Injection											
57	77	57	80	55	80	85	75	80	75	82	85
55	77	55	80	50	75	82	77	85	72	82	87
55	77	57	80	55	75	82	80	80	75	80	85
55	80	57	77	55	75	85	77	82	77	80	87
57	80	57	80	50	77	82	77	82	77	80	85
55	80	55	70	50	75	85	77	75	75	77	85
55	75	50	72	47	80	85	72	55	75	50	72
52	77	45	--	40	77	75	70	50	70	47	75
55	75	45	57	40	70	65	65	50	72	42	--
52	75	45	--	42	67	55	65	55	70	45	--
52	70	47	60	45	67	55	65	50	70	45	67
50	72	45	57	47	67	60	65	60	67	37	67
50	70	47	60	45	67	75	67	65	70	42	67
52	72	--	--	50	65	75	70	--	70	50	67
55	72	--	62	47	65	75	70	--	70	55	--
55	72	--	60	--	65	--	70	--	70	60	70
--	72	--	60	--	67	--	72	--	72	--	70
--	72	--	65	--	--	--	--	--	--	--	65
--	70	--	--	--	--	--	--	--	--	--	--

*Same as Table 6.

Table 12.--The effects of epinephrine on the time integral (area) of pressure and force tracings in the dog right heart.*

Dogs	Time Integral of Force (gm./sec.)						Time Integral of Pressure (mm. Hg. sec.)								
	(1.25 ug.)		(2.5 ug.)			(5.0 ug.)			(1.25 ug.)			(2.5 ug.)			(5.0 ug.)		
	IV	V	VI	IV	V	VI	IV	V	VI	IV	V	VI	IV	V	VI	IV	V	VI
Control Values																		
	2.33	1.27	4.01	1.89	1.39	4.1	2.02	1.39	3.99	3.13	3.47	2.75	3.33	3.77	2.62	3.01	3.54	2.67
	2.36	1.23	4.03	2.01	1.19	3.9	2.26	1.34	4.18	3.02	3.30	2.63	3.36	3.41	2.63	3.07	3.60	2.74
	2.33	1.23	4.16	1.19	1.29	3.9	----	1.36	4.11	3.09	3.38	2.75	3.12	3.49	2.75	----	3.28	2.75
	----	1.21	4.18	----	1.32	3.9	----	1.38	4.75	----	3.37	2.49	----	3.54	2.69	----	3.87	2.67
	----	1.23	4.04	----	1.27	3.9	----	1.38	4.89	----	3.38	2.62	----	3.67	2.84	----	3.60	2.76
	----	----	----	----	1.27	---	----	----	----	----	----	----	----	3.42	----	----	----	----
Following Epinephrine Injection																		
	2.36	1.27	4.13	2.18	1.29	3.9	2.11	1.31	3.89	3.15	3.47	2.62	3.46	3.54	2.54	3.59	3.67	2.72
	2.53	1.31	4.13	2.38	1.31	4.0	2.68	1.42	3.91	3.30	3.45	2.72	3.70	3.62	2.75	3.33	3.44	2.75
	2.72	1.31	3.93	2.48	1.39	4.3	2.68	1.43	3.99	3.36	3.74	2.57	3.57	3.54	2.63	3.62	3.93	3.01
	2.83	1.27	4.21	2.43	1.43	4.3	2.64	1.56	4.37	3.26	3.47	2.62	3.54	3.70	2.75	3.80	3.67	2.62
	2.73	1.47	4.62	2.53	1.59	4.9	2.67	1.67	5.06	3.12	3.66	3.01	3.47	3.67	2.95	3.54	3.74	2.86
	2.73	1.50	4.45	2.53	1.60	5.2	----	1.83	6.00	3.02	3.80	3.12	3.42	3.77	3.41	----	4.59	3.33
	2.80	1.44	4.18	----	1.59	4.9	----	1.89	5.90	2.99	4.08	3.28	----	3.93	3.73	----	4.26	3.35
	2.67	1.43	4.18	----	----	4.5	----	1.92	5.26	2.81	4.13	3.14	----	----	3.63	----	4.33	4.30
	----	1.39	----	----	----	---	----	1.79	5.21	----	4.13	----	----	----	----	----	4.26	4.21
	----	----	----	----	----	---	----	----	5.27	----	----	----	----	----	----	----	----	4.26

*Same as Table 6.

Table 13.--The effects of epinephrine on the force at df/dt maximum and the pressure at dp/dt maximum.*

Dogs	Force at df/dt maximum (gms.)							Pressure at dp/dt maximum (mm. Hg.)				
						Control Values						
V	VI	V	VI	V	VI	V	VI	V	VI	V	VI	
1.25 ug.		2.5 ug.				1.25 ug.		2.5 ug.		5.0 ug.		
2.9	3.6	3.0	3.7	3.3	3.9	10.8	13.5	12.6	13.4	14.2	13.3	
						Following Epinephrine Injection						
3.1	3.7	3.3	3.7	3.3	4.0	11.2	13.0	12.6	13.5	13.3	13.0	
3.2	3.7	3.7	4.0	3.4	3.7	11.2	13.2	12.8	14.0	13.5	14.7	
3.1	4.5	4.8	6.1	5.4	7.8	11.0	16.5	15.0	15.0	19.5	15.5	
3.3	4.3	5.9	5.8	7.7	9.3	11.3	17.0	17.3	18.0	31.6	17.5	
3.4	---	5.1	---	6.9	5.6	12.4	----	17.3	----	28.1	18.2	
4.1	---	---	---	---	---	13.8	----	----	----	----	----	
4.2	---	---	---	---	---	14.7	----	----	----	----	----	
4.6	---	---	---	---	---	16.2	----	----	----	----	----	
4.5	---	---	---	---	---	15.3	----	----	----	----	----	

*Same as Table 6.

Table 14.--The effects of ouabain on the maximal rate of pressure rise (dp/dt) and the maximal rate of force rise (df/dt) in the dog right heart.*

df/dt maximum gm./sec.						dp/dt maximum mm. Hg./sec.			
Control Values									
Dogs I	II	III	V	VI	I	II	III	V	VI
85	125	102	120	100	70	125	95	155	95
80	125	105	115	100	65	120	97	145	97
80	127	105	120	100	65	120	97	140	102
85	130	105	120	100	65	125	98	140	100
85	130	105	120	97	70	122	96	135	97
---	---	105	125	97	--	---	100	145	97
---	---	---	120	100	--	---	---	140	95
---	---	---	120	100	--	---	---	140	90
---	---	---	115	105	--	---	---	135	95
---	---	---	---	100	--	---	---	---	105
---	---	---	---	110	--	---	---	---	100
Following Ouabain Injection									
80	130	100	120	100	67	140	95	135	92
85	135	99	125	100	67	150	97	150	97
80	135	105	125	107	88	150	100	145	102
80	130	107	130	105	70	155	102	145	110
85	127	100	130	105	75	155	107	155	115
85	130	110	125	100	70	157	108	150	115
85	135	105	130	105	75	160	107	155	110
85	135	107	130	100	75	160	107	160	120
90	140	110	130	100	70	155	105	145	115
92	140	115	120	110	80	185	106	135	115
90	145	105	130	100	70	135	102	140	110
90	177	102	120	100	75	150	100	135	110
92	140	110	120	100	80	162	105	145	110
95	155	110	120	100	80	180	105	145	110
90	155	110	120	100	75	170	107	145	110
90	180	116	120	82	77	190	105	140	110
90	180	110	110	100	80	147	105	145	110
90	---	120	115	100	70	---	110	140	115
95	---	110	130	100	75	---	105	140	115
90	---	120	115	95	80	---	108	140	115
95	---	110	120	100	80	---	107	140	115
96	---	112	120	100	70	---	107	140	110
90	---	120	105	105	75	---	107	145	110
95	---	125	115	100	80	---	110	140	110
100	---	120	115	105	80	---	115	145	110
100	---	120	115	110	75	---	120	150	110
95	---	127	115	100	80	---	120	145	110
95	---	135	120	105	80	---	120	145	110
100	---	125	120	110	85	---	118	145	110
95	---	128	120	107	75	---	118	140	110
100	---	135	120	110	80	---	115	145	110
100	---	130	120	95	80	---	118	165	105
103	---	---	120	105	85	---	---	170	105
100	---	---	140	92	80	---	---	165	105
95	---	---	130	105	80	---	---	165	105
105	---	---	135	105	85	---	---	170	100
105	---	---	135	110	90	---	---	180	105
100	---	---	145	110	80	---	---	170	105
100	---	---	145	105	85	---	---	170	105
110	---	---	150	110	90	---	---	170	100
100	---	---	150	105	77	---	---	155	100
100	---	---	135	105	85	---	---	175	110
110	---	---	135	105	--	---	---	175	---

*Same as Table 6.

Table 15.--The effects of ouabain on the duration of the time interval between the peak of the ECG-R-wave to the development of the maximal rate of force (df/dt) and pressure (dp/dt) rise in the dog right heart.*

	Time Interval (msec.)					Time Interval (msec.)			
				Control Values					
Dogs I	II	III	V	VI	I	II	III	V	VI
68	55	67	55	55	77	65	70	55	52
60	55	60	55	57	70	70	70	55	55
70	52	57	57	55	75	75	72	57	55
67	55	62	55	57	77	75	72	55	52
67	52	67	55	57	77	77	72	50	55
62	55	62	55	57	75	75	75	55	55
65	52	70	55	55	80	75	75	50	52
65	55	60	57	60	75	77	75	50	52
65	55	65	57	60	75	75	75	52	52
67	57	65	57	55	--	77	--	50	55
70	55	65	55	57	--	75	--	52	--
--	55	60	--	57	--	80	--	52	--
--	55	--	--	60	--	77	--	--	--
--	55	--	--	57	--	77	--	--	--
--	--	--	--	60	--	77	--	--	--
--	--	--	--	57	--	77	--	--	--
--	--	--	--	--	--	75	--	--	--
				Following Ouabain Injection					
65	55	57	57	57	77	75	75	52	50
70	55	60	57	57	75	75	75	52	52
67	55	57	60	57	80	77	70	50	52
65	55	62	57	55	75	75	72	55	52
65	55	65	55	55	72	75	72	50	52
65	52	62	55	55	75	77	70	52	52
60	55	70	52	60	75	77	70	52	52
60	57	60	57	60	77	72	72	52	52
62	55	65	50	57	73	77	72	52	55
72	65	67	52	60	75	75	70	50	50
65	52	62	57	55	73	75	75	50	52
65	50	67	57	57	75	75	70	50	52
65	52	67	55	55	77	75	72	50	50
70	55	70	52	60	77	70	70	50	52
70	52	67	57	57	75	--	75	55	52
70	55	70	57	60	80	--	70	52	52
70	50	70	55	60	77	--	72	50	52
67	52	70	55	57	77	--	75	52	52
65	--	70	52	55	75	--	72	50	52
65	--	62	55	57	80	--	70	55	55
70	--	70	57	57	77	--	75	55	52
70	--	65	55	60	77	--	75	55	55
70	--	67	57	57	80	--	75	50	55
65	--	65	55	57	75	--	75	50	50
67	--	67	57	57	80	--	75	55	55
67	--	60	55	55	77	--	72	55	52
65	--	65	57	57	77	--	80	50	55
70	--	65	57	57	75	--	75	50	55
70	--	67	--	57	80	--	72	52	50
67	--	65	--	60	75	--	70	52	55
--	--	70	--	57	77	--	75	50	52
--	--	--	--	--	--	--	72	50	--

*Same as Table 6.

Table 16.--The effects of ouabain on the time integral (area) of pressure and force measurements in the dog right heart.*

Time Integral of Force (gm./sec.)					Time Integral of Pressure (mm. Hg. sec.)				
Control Values									
Dogs I	II	III	V.	VI	I	II	III	V	VI
1.79	1.63	1.66	1.18	1.67	1.75	3.01	2.91	4.36	3.30
1.73	1.66	1.64	1.19	1.76	1.74	2.95	2.88	4.39	3.28
1.75	1.59	1.66	1.18	1.71	1.79	2.91	3.01	4.19	3.31
1.77	1.66	1.67	1.16	1.79	1.83	2.88	2.08	4.10	3.21
1.85	1.60	1.66	1.19	1.75	1.98	2.86	2.88	4.59	3.14
1.75	----	----	1.15	1.82	1.81	----	----	4.29	3.14
----	----	----	1.19	1.69	----	----	----	4.26	3.34
----	----	----	1.19	1.82	----	----	----	4.13	3.25
----	----	----	1.11	1.82	----	----	----	4.46	3.21
----	----	----	----	1.87	----	----	----	----	3.20
Following Ouabain Injection									
1.70	1.65	1.67	1.23	1.82	1.78	3.00	2.99	4.39	3.41
1.70	1.67	1.60	1.23	1.91	1.73	3.14	2.87	4.29	4.05
1.77	1.63	1.67	1.27	1.83	1.82	3.01	3.03	4.20	3.77
1.81	1.69	1.79	1.34	1.91	1.84	2.89	2.93	4.22	3.60
1.83	1.63	1.74	1.27	1.83	1.96	3.05	2.93	4.29	3.54
1.78	1.67	1.71	1.27	1.75	1.74	3.01	3.01	4.23	3.67
1.85	1.73	1.76	1.27	1.78	1.73	3.01	2.89	4.03	3.76
1.82	1.75	1.90	1.23	1.91	1.69	3.16	2.91	4.13	3.91
1.97	1.78	1.81	1.27	1.99	1.74	3.16	3.00	3.93	3.88
1.98	1.85	1.86	1.27	1.99	1.85	3.18	2.91	3.93	3.81
1.89	1.82	1.91	1.34	1.92	1.62	3.14	3.07	4.19	3.60
1.91	1.83	1.96	1.43	1.91	1.70	3.04	2.91	4.46	3.73
1.91	1.91	2.07	1.43	2.05	1.57	3.10	2.86	4.36	3.93
2.07	2.02	2.07	1.47	2.76	1.87	3.20	2.88	4.49	3.94
1.99	1.99	1.96	1.43	2.31	1.69	3.13	2.91	4.29	3.94
2.02	2.29	2.02	1.51	2.31	1.61	3.80	2.88	4.29	4.33
2.02	2.32	2.07	1.59	2.23	1.67	3.16	2.75	4.46	3.67
2.06	----	2.14	1.59	2.39	1.58	----	2.88	4.26	4.59
1.98	----	2.09	1.58	2.47	1.60	----	2.80	4.26	4.06
2.13	----	2.16	1.68	2.55	1.61	----	2.82	4.16	4.22
2.12	----	2.08	1.66	2.54	2.07	----	2.75	4.85	4.06
1.94	----	2.25	1.66	2.40	1.54	----	2.86	4.62	4.46
2.01	----	2.27	1.71	2.23	1.62	----	2.84	4.92	4.98
1.99	----	2.31	1.69	2.56	1.70	----	2.79	4.59	4.94
2.09	----	2.39	2.03	2.54	1.73	----	2.79	4.78	4.59
2.01	----	2.39	1.66	----	1.56	----	2.74	4.62	----
2.01	----	2.41	1.69	----	1.57	----	2.74	4.88	----
2.06	----	2.53	1.69	----	1.58	----	2.88	4.29	----
2.17	----	2.85	1.67	----	1.96	----	2.86	4.62	----
2.07	----	2.72	1.68	----	1.54	----	----	4.69	----
2.02	----	2.75	1.69	----	1.57	----	----	4.30	----
2.10	----	2.72	1.63	----	1.61	----	----	4.98	----
2.19	----	2.63	1.72	----	1.70	----	----	4.78	----
2.17	----	----	2.48	----	1.57	----	----	4.69	----
2.17	----	----	2.66	----	1.88	----	----	4.46	----
2.30	----	----	2.59	----	1.96	----	----	4.27	----
2.30	----	----	2.39	----	1.61	----	----	4.56	----
----	----	----	----	----	1.58	----	----	----	----
----	----	----	----	----	1.96	----	----	----	----
----	----	----	----	----	1.53	----	----	----	----

*Same as Table 6.

Table 17.--The effects of ouabain on the force at df/dt maximum and the pressure at dp/dt maximum. *

Force at df/dt maximum (gms.)					Pressure at dp/dt maximum (mm. Hg.)				
Control Values									
Dogs I	II	III	V	VI	I	II	III	V	VI
5.1	3.9	3.3	4.8	4.3	8.0	17.7	9.5	18.2	13.2
4.6	4.8	3.3	4.5	4.8	8.0	16.0	8.5	18.2	14.0
5.1	4.3	2.5	4.5	5.4	8.0	17.2	10.0	18.2	13.5
5.4	5.1	2.3	4.3	5.1	8.2	16.5	10.0	18.2	13.0
5.7	5.4	3.3	4.2	4.8	9.0	18.2	9.0	18.2	14.0
---	---	2.0	3.9	4.8	----	----	9.0	18.2	12.0
---	---	---	4.5	5.1	----	----	----	20.0	13.5
---	---	---	4.5	5.2	----	----	----	18.2	12.0
---	---	---	4.5	4.9	----	----	----	18.2	15.0
---	---	---	---	4.8	----	----	----	----	13.0
---	---	---	---	5.7	----	----	----	----	12.5
Following Ouabain Injection									
5.1	5.1	2.7	4.8	4.8	8.0	19.2	9.0	18.2	13.0
5.1	5.1	2.3	4.2	5.4	7.5	20.0	10.0	21.0	15.5
4.8	5.1	3.4	4.5	5.1	8.2	19.5	9.5	18.2	14.2
5.7	5.1	2.6	4.8	5.4	7.5	19.5	10.0	18.2	13.0
4.5	5.2	2.6	4.8	4.8	10.0	19.5	9.5	18.2	17.0
5.2	4.8	2.6	5.4	4.8	9.0	19.7	11.0	20.0	14.0
6.0	6.0	3.0	5.1	4.8	8.7	19.5	10.5	21.0	14.0
4.8	5.4	3.1	5.1	5.4	9.0	19.5	10.7	21.0	12.0
5.4	4.8	3.3	5.1	4.8	10.0	18.5	10.2	21.0	10.0
5.1	5.4	3.4	4.8	5.4	9.0	21.7	9.5	18.2	11.7
4.8	4.8	3.0	4.2	5.2	8.5	20.0	9.2	18.2	12.2
5.4	5.4	3.1	4.5	5.5	8.5	18.0	10.9	16.0	16.0
6.0	5.8	3.0	4.8	4.8	8.5	21.5	9.7	21.0	16.0
5.2	5.7	3.5	4.8	4.8	10.0	19.5	10.7	18.2	17.0
4.8	6.0	3.6	5.1	5.4	9.0	17.5	9.0	20.0	16.0
6.4	7.3	4.2	4.8	5.4	8.5	13.5	10.8	18.2	10.5
5.7	6.6	4.2	4.8	5.1	9.0	23.0	10.0	16.0	11.0
5.4	---	3.7	4.2	4.8	9.5	----	8.7	18.2	11.0
5.4	---	4.0	4.5	5.4	9.5	----	10.0	18.2	10.0
6.3	---	4.2	4.5	4.5	9.7	----	9.7	15.0	13.0
5.4	---	4.2	4.5	5.7	10.0	----	9.0	18.2	12.0
5.2	---	3.0	4.8	5.1	8.5	----	11.2	18.2	11.0
5.7	---	4.8	4.2	5.1	9.5	----	10.0	20.0	12.5
6.6	---	3.9	4.5	5.8	9.7	----	10.7	18.2	13.0
5.7	---	4.8	4.5	5.1	8.5	----	12.0	18.2	13.0
6.0	---	4.5	4.5	5.4	9.7	----	11.0	16.0	12.0
5.8	---	4.6	4.8	6.0	9.7	----	10.5	20.0	13.0
5.4	---	4.2	4.5	4.8	10.0	----	12.0	18.2	12.0
5.4	---	4.2	4.8	5.1	8.7	----	11.0	18.2	10.5
6.0	---	4.8	4.8	7.8	9.5	----	11.2	21.0	10.5
5.7	---	4.8	4.8	5.7	9.0	----	10.2	21.0	11.5
6.0	---	4.2	4.8	5.7	10.0	----	9.0	21.0	12.0
6.0	---	---	4.5	4.9	9.5	----	----	18.2	10.0
5.4	---	---	4.8	5.4	10.0	----	----	18.2	10.5
6.0	---	---	5.1	5.4	10.0	----	----	24.0	10.0
6.6	---	---	5.1	5.4	9.5	----	----	18.2	12.0
6.3	---	---	5.4	5.1	10.0	----	----	18.2	11.0
5.7	---	---	5.7	5.7	10.0	----	----	----	----

*Same as Table 6.