



1968

A Direct Examination of Papillary Muscle Function in the Canine Left Ventricle

Robert Emmet Cronin
Loyola University Chicago

Follow this and additional works at: https://ecommons.luc.edu/luc_theses

 Part of the [Medicine and Health Sciences Commons](#)

Recommended Citation

Cronin, Robert Emmet, "A Direct Examination of Papillary Muscle Function in the Canine Left Ventricle" (1968). *Master's Theses*. 2081.
https://ecommons.luc.edu/luc_theses/2081

This Thesis is brought to you for free and open access by the Theses and Dissertations at Loyola eCommons. It has been accepted for inclusion in Master's Theses by an authorized administrator of Loyola eCommons. For more information, please contact ecommons@luc.edu.



This work is licensed under a [Creative Commons Attribution-NonCommercial-No Derivative Works 3.0 License](#).
Copyright © 1968 Robert Emmet Cronin

A DIRECT EXAMINATION OF PAPILLARY MUSCLE FUNCTION
IN THE CANINE LEFT VENTRICLE

by

Robert Emmet Cronin

A Thesis Submitted to the Faculty of the Graduate School
of Loyola University in Partial Fulfillment of
the Requirements for the Degree of
Master of Science

June

1968

Library -- Loyola University Medical Center

LIFE

Robert E. Cronin was born in Chicago, Illinois, on March 26, 1942.

He attended St. Ignatius High School, in Chicago, Illinois, and then Holy Cross College in Worcester, Massachusetts, where he received his Bachelor of Arts degree in 1964.

Since September, 1964, he has been a medical student at Loyola University, Stritch School of Medicine, and will receive his M.D. degree in June, 1968. For the past three years he has been enrolled in the combined Master of Science - Medical Doctor Program, supported by the National Institutes of Health, under the supervision of Dr. Walter C. Randall, Chairman, Department of Physiology.

In April, 1968, he presented a paper based upon his thesis at the Student American Medical Association - University of Texas Research Forum, in Galveston, Texas. An abstract of this presentation will appear in the Texas Reports of Biology and Medicine, in June, 1968.

ACKNOWLEDGEMENTS

I wish to express my sincere appreciation to Dr. Walter C. Randall, Chairman of the Department of Physiology, for his understanding, personal guidance, and example during the course of the studies and research which led to the writing of this thesis.

I would like also to acknowledge the generous assistance of Dr. Michael P. Kaye who helped in solving many of the technical difficulties encountered.

Finally, I thank the faculty, staff, and students of the Physiology Department for the friendship and inestimable help they have given to me during the past three years.

TABLE OF CONTENTS

Chapter	Page
I. INTRODUCTION	1
II. LITERATURE REVIEW	3
A. Anatomical Studies	3
B. Valve Function	4
C. Papillary Muscle Investigations	6
D. Clinical Studies	11
III. METHOD	15
IV. EXPERIMENTAL RESULTS	22
V. DISCUSSION	35
VI. SUMMARY	45
BIBLIOGRAPHY	47

LIST OF FIGURES

Figure	Page
1. GROSS DESIGN OF STRAIN GAUGE	17
2. GRAPH SHOWING LINEAR RELATIONSHIP OF GAUGE RESPONSE AND CHANGES IN TENSION	18
3. POSTMORTEM VIEW OF STRAIN GAUGE PLACED ON ANTERIOR PAPILLARY MUSCLE OF LEFT VENTRICLE	19
4. CONTROL TRACES OF ANTERIOR PAPILLARY MUSCLE	23
5. EFFECTS OF NOREPINEPHRINE INFUSION	26
6. EFFECTS OF ISOPROTERENOL INFUSION	28
7. POST EXTRASYSTOLIC POTENTIATION	31
8. OCCLUSION OF THORACIC AORTA	32
9. ARTERIAL PUMP INFUSION	33

CHAPTER I

INTRODUCTION

It is convenient to speak of the atrioventricular valve mechanism as composed of three parts, the valve cusps, the chordae tendineae, and the papillary muscles. Early investigations in this area were of necessity indirect, with perfused hearts, isolated valves, and the dying beats of excised hearts giving the earliest clues into the dynamic nature of these structures. With the advent of better recording devices for intracardiac pressures, electrical activity, and heart sounds, knowledge and theories about valve closure and function grew. The function of the valve cusps seemed clear enough--by closing over the atrioventricular opening during systole, they insured that blood flow from the ventricle would be unidirectional. The chordae tendineae prevented the cusps from being everted under the high pressure gradient generated by systolic contraction. Perhaps the most impressive structures were the papillary muscles which dominated the valve area, and in a most logical fashion early observers assumed that their contraction was important in valve closure.

It has now been clearly shown by a number of investigators that the most important single event in effective a-v valve closure is a properly timed atrial systole and under normal circumstances the valve is closed and competent before ventricular contraction occurs.

It seemed worthwhile then to reexamine the function of the papillary muscle. Is it merely a passive structure acting as a "guy rope" (41) to prevent eversion of the valve cusps during systole, or is it actively involved in preventing regurgitation during the rise of intraventricular pressure? It is the purpose of this paper to describe the activity of the papillary muscle in the intact left ventricle of the dog and relate it to well-documented events of the normal cardiac cycle using left ventricular, left atrial, and aortic pressures as points of reference.

CHAPTER II

LITERATURE REVIEW

A. Anatomical Studies.

Thomas, in describing the anatomy of dog myocardium showed that the myocardium was made up of a number of fascicles which had their origin and insertion in the ventricular base (40). The left ventricular cavity was described as being made up of a cylindrical band of fibers which was covered on its inner surface by the papillary muscles and the trabeculae carneae. The trabeculae carneae inserted directly into the ventricular base, but the papillary muscles inserted on the left ventricular ring indirectly through the intermediation of the mitral valve flaps and the chordae tendineae. Thomas also noted that the orientation of fibers in the papillary muscles was longitudinal, while that of the cylindrical layer was spiraling. Robb and Robb reported that the superficial muscles of the ventricles possessed an internal portion which constituted the papillary muscles (24). In view of the observations by other workers that the time of initial electrical negativity at the interior and exterior at the apices of the two ventricles was early, these authors suggested that these facts gave anatomic and physiologic support to the concept that the superficial muscles had two definite functions, namely: 1) to fix the apical fulcrum and 2) to fix the a-v valve leaflets. To prevent the a-v

valves from bulging into the auricle, the valve leaflets must be fixed, and to accomplish this, the papillary muscles must be contracted in order to keep the chordae tendineae tense.

Ross et al using a technique for rapid fixation of the dog heart in systole and diastole reported that the papillary muscle volume averaged 5.0% of ventricular volume at end-diastole and 14.7% at end-systole (26). Priola et al injected plaster of paris into hearts during diastole and during systole, froze them instantaneously in liquid nitrogen and found that during systole the papillary muscles became more prominent and actually separated the ventricular chamber into a functional inflow and outflow tract (22).

B. Valve Function.

In 1912 Henderson and Johnson proposed two modes of closure for the a-v valves using an isolated valve preparation (14). The first type of closure resulted from a negative pressure generated at the ostium by the breaking of a jet of blood due to cessation of the force from behind or increased resistance in front. He noted that the part of the valve flap nearest the base was the first to move in and this closure showed no regurgitation. The second mode of closure was always associated with regurgitation and was due to static back-pressure on the valve, such as in a ventricular systole not preceded by an atrial systole. In the normal heart, then, atrial systole assured a non-leaking mode of closure, while an isolated ventricular systole was probably always associated with regurgitation. He also concluded that the a-v valve was normally closed before the onset of ventricular contraction, and that atrial systole need not inject any considerable quantity of blood into the ventricle to achieve closure.

Dean disagreed with Henderson's idea that the valve was normally closed before ventricular systole, since he was unable to explain the first heart sound otherwise (5). Using an isolated, perfused heart preparation and recording tension on a human hair attached to the septal leaflet of the mitral valve, he described two separate closures of the mitral valve; the first due to atrial systole and the second due to ventricular systole. If the interval between atrial systole and ventricular systole was 0.147 to 0.272 seconds, the closures summated and no regurgitation occurred. If the interval was greater than 0.272 seconds, the leaflets had time to drift apart resulting in two separate closures.

Since Dean made his observations, a number of investigators have studied the effect of atrial systole on valve closure. Little criticized Dean's work because he kept left atrial pressure constant with a reservoir preventing physiologic pressure changes in the atrium (20). Little was able to show that with normal left atrial pressures, atrial systole would reverse the atrioventricular pressure gradient and completely close the valve before the onset of ventricular systole. With an increased venous return and an increased left atrial pressure, the atrioventricular pressure gradient was reduced and the valves would reopen as left atrial pressure rose, allowing a small regurgitation before ventricular systole again closed the valves. In the case of heart block where a ventricular systole might not be preceded by an atrial systole, a large regurgitation through the valve occurred.

In a heart-blocked preparation, Sarnoff reported that the mitral valve could be closed solely as a result of atrial activity with vagal stimulation depressing the effect and stellate stimulation enhancing it (34). The

more vigorous and rapid the contraction and relaxation of the atrium, the greater likelihood the mitral valve would be closed independently of ventricular activity. In the same type of preparation, Skinner showed that mitral regurgitation occurred with improperly timed atrial systoles, but that properly timed, effective atrial activity could enhance ventricular filling and pre-close the a-v valve (38). Paul demonstrated diastolic regurgitation of contrast media injected into the left ventricles of normal dogs occurring during periods of long ventricular diastasis such as occurred during bradycardia, sinus arrhythmia and compensatory pauses after an extrasystole (21).

It is significant in all these studies that little is mentioned of papillary muscle or chordae tendineae involvement in closure, the inference being that the valve leaflets open and close freely in spite of these structures.

C. Papillary Muscle Investigations.

The time of papillary muscle contraction is an elusive entity, and investigators have reported sighting it at various locations in the cardiac cycle. Roy and Adami used lever writing pens attached to two small hooks, one being anchored to the external left ventricular wall and the other to a mitral valve cusp and brought out through the atrial appendage (28). They reported that the external ventricular fibers approximated the base and apex before the free edges of the a-v valves were pulled toward the apex by the contraction of the papillary muscles. Further, they felt that the papillary muscles contracted in two phases, the first one which rapidly straightened the valve-chordae structure, and then a slower phase when this structure was stretched. They suggested that the peak in the left ventricular trace occurring

approximately at the height of rapid ejection was due to summation of left ventricular pressure with the papillary muscle contraction. They also felt that papillary muscle contraction could be specifically identified in the femoral artery pressure curve. While it appears now that these conclusions far outstripped the sensitivity of the instruments used and the actual data shown, they did have the salutary effect of promoting investigation in this area.

In the following year, Fenwick and Overend criticized the work of Roy and Adami on the basis of their own work with excised rabbit hearts (7). They showed that within four minutes of death the papillary muscle contracted one-twentieth of a second after the left ventricular apex. Reasoning that during a normal ventricular contraction the ventricle was closed for one-tenth of a second, it was difficult for them to see how the papillary muscle contraction could occur as late in the cycle as the earlier workers had described. Haycraft and Paterson, using a similar preparation to Fenwick and Overend, reported that in a heart where recordings were taken within one minute and a half, the papillary muscle and the ventricular wall contracted simultaneously, shedding further doubt on Roy and Adami's conclusions (13).

Puff demonstrated in high speed films of a surgically exposed heart that the papillary muscle and inflow tract contracted very early and were followed by contraction of the outflow tract (23). Hider et al described the sequence of contraction of the left ventricle in dogs using high speed cinephotography through ventriculotomy incisions made from different approaches until a composite picture of the contraction sequence could be made (15). The anterior papillary muscle and adjacent part of the septum were found to contract first and from here contraction spread rapidly to produce maximum contraction

of both papillary muscles and the wall of the left ventricular inflow tract within 50 msec. The muscles relaxed in the same order of excitation with the papillary muscles starting to relax first at 60-75 msec, and the outflow tract starting to relax last at 150 msec. Kantrowitz made high speed films of mitral valve motion in a dog heart during left heart bypass and showed that a momentary shortening of the chordae tendineae occurred with the onset of ventricular contraction (18). He also showed the mitral valve ring contracting and decreasing the orifice diameter with systole. The papillary muscles were noted to ascend toward the valve orifice and become more prominent in late systole. Salisbury, however, measured tension in a single chorda tendinea in the open-chest dog with a transverse displacement transducer and concluded that the initial tension began at the same instant as left ventricular systole and terminated at the moment of aortic valve opening (33). He concluded that the chorda tendinea tension he measured was the sum of several stresses: traction exerted by the contracting papillary muscle and traction exerted in the opposite direction from the pressure on the mitral valve leaflet held by the chorda. In addition, elongation of the ventricle might shift the base of the papillary muscle irrespective of its state of contraction or relaxation. Burch, in theorizing about tension in the papillary muscle, described the dynamic nature of papillary muscle function and believes that the papillary muscles are activated before the free left ventricular wall, so that when the sudden rise in pressure associated with isometric contraction occurs, the papillary muscles are already in a state of tension and therefore prepared to support the forces acting on the mitral valve (3).

The notion that the papillary muscles aid in ventricular emptying in addition to supporting the valve structure is not new. William Harvey in his classic work De Motu Cordis described the papillary muscles in the following way:

There are also so-called braces in the heart, many fleshy and fibrous bands, which Aristotle calls nerves (De Respirat., & De Part. Animal. Lib 3). They are stretched partly from place to place, and partly in the walls and septum, where they form little pits. Little muscles are concealed in these furrows which are added to assist in a more vigorous expulsion of blood. Like the cleaver and elaborate arrangement of ropes on a ship, they help the heart to contract in every direction, driving blood more fully and forcibly from the ventricles (11).

It was interesting that he did not mention that these structures might have a function in valve closure or competence. In discussing ventricular contraction, he again mentioned the papillary muscles:

The ventricles are not constricted only by virtue of the direction and thickening of their walls. The walls contain solely circular fibers, but there are also bands containing only straight fibers, which are noted in the ventricles of larger animals and which are called nerves by Aristotle. When they contract together, an excellent system is present to pull the internal surfaces closely together, as with cords, in order to eject the blood with greater force.

Burch expanded the papillary muscle role in ventricular contraction when he suggested that the wrinkled nature of the ventricular cavity allowed greater ventricular emptying, since the trabeculae carneae and papillary muscles by occupying a progressively greater volume of the cavity during systole, displaced a proportionally greater volume of blood into the systemic circuit. If the endocardium were smooth on the other hand, wrinkling would occur with systole and the danger of injury to subendocardial muscle would be high (2).

Rushmer proposed the concept of "asynchronous contraction" to explain the internal and external length and circumference changes in the left

ventricle during the cardiac cycle that he and later Hawthorne observed using mercury strain gauges and internal inductance gauges (30). In his explanation the first event was strong contraction of the papillary muscles and the trabeculae carneae which pulled down on the mitral valve. This was a fact he had previously documented by attaching metal clips to the mitral valve edges in chronically prepared dogs and noting during cinefluoroscopy that the mitral valve cusps generally displayed limited lateral motion during the cardiac cycle, but instead moved predominantly along the longitudinal axis of the ventricular chamber (31). He proposed that this downward movement of the valve displaced blood laterally causing the left ventricular circumference to enlarge and the base to apex diameter to decrease. After these events, the circumferentially oriented muscles contracted leading to ventricular ejection and a reduction in the ventricular circumference. During diastole, the valves move laterally and then rapidly reascended towards the atrium as the mitral valve ring moved in the same direction. He suggested that observations in open-chest dogs showing valve cusps which "flapped" and "floated" were due to the thoracotomy procedure which he had shown shrunk the heart and most likely put slack on the chordae (32). He concluded that the papillary muscles exerted continuous tension on the cusps except during the rapid filling phase. In support of Rushmer's observations is the data of Scher and Young showing that the earliest points of myocardium activated were on the endocardial surfaces of the ventricles and that electrical activity moved outward to excite the rest of the heart (36).

In a recent abstract, Fisher et al reported attaching mercury strain gauges to the left ventricular papillary muscles through a

ventriculotomy while on total bypass and noted five phases in the length changes in the papillary muscle: lengthening during rapid filling; plateau during slow filling; further lengthening during isovolumetric contraction; slow shortening during ejection; more rapid shortening during isovolumetric relaxation (8). They concluded that lengthening during rapid filling was due to ventricular enlargement. More recent work by this same group reported similar findings in the right ventricle, with the exception that the right ventricular papillary muscle lengthened throughout ventricular contraction and shortened only after complete unloading (10).

D. Clinical Studies.

Clinical investigators have recently become interested in the papillary muscle, primarily in regard to mitral valve surgery. Lillehei and his co-workers found that when prosthetic (Starr) valves were implanted without removing the valve leaflets or papillary muscles as had formerly been done, there was a decreased incidence of post operative "low output" syndrome (19). Lillehei, in agreement with Rushmer, felt that the intact cusp-chordae-papillary muscle structure promoted better ventricular emptying by pulling down the a-v valve ring during systole. Rastelli studied the morphology of the papillary muscle in the left ventricle of dogs after replacement of the mitral valve with a Starr-Edwards prosthesis. If the chordae tendineae and leaflets were excised at operation, the papillary muscle underwent atrophy and was replaced by fibrous tissue. If the chordae tendineae and leaflets were left intact, the papillary muscles remained morphologically normal (27). Hider studied the immediate and late effects on valve competence of injecting 95% alcohol into the papillary muscle of dogs (16). Five of the nine surviving

dogs had incompetence after fourteen days, while only one in nine of the surviving controls which had 95% alcohol injected into left ventricular wall adjacent to the papillary muscle had mitral incompetence. Since only three of eleven dogs developed immediate incompetence and this was only mild as judged by the increase in size of the "c" wave, he used this to support the view that any role which the papillary muscles played in the prevention of valve inversion and incompetence was predominantly passive. He suggested that the maximal contraction of the papillary muscle occurred during the isometric phase of ventricular systole. In this event, he concluded, maximum shortening of the ventricular wall at the end of the ejection phase occurred at a time when the papillary muscles were already relaxing.

Seidel and Grossin using an isolated dog heart preparation showed an asymmetric dilatation of the myocardium on the side of unilateral resection of the chordae, indicating that the mural chordal apparatus strengthened the lateral ventricular wall in the longitudinal direction. The strengthening effect of the preserved papillary muscle-chordal mechanism was mainly explained as a longitudinal mechanical support of the myocardial fibers, which preferably ran in a circular direction. They suggested this may be important in preventing failure in the early post operative period after mitral valve replacement (37).

Burch discussed the entity of papillary muscle dysfunction with its associated mitral valvular incompetence and stated that in uncomplicated cases with no ventricular dilatation the murmur produced tended to be "soft to only moderately loud, to have somewhat of a blowing quality, and to be predominantly mid-systolic with a crescendo-decrescendo character" (4). However,

he also noted that due to the variety of dysfunctions that could occur, the murmur might be mid or late systolic or pansystolic. Burch felt that characteristic ECG alterations were associated with ischemia of the papillary muscles. The three basic types were depression of the junction "J", depression or inversion of the T-U segment or U waves. He stated that previously these patterns were often diagnosed as indicating acute subendocardial infarction.

To summarize current thinking, the papillary muscle role in the approximation and closure of the valve leaflets is entirely passive and these events normally occur before the onset of ventricular systole. In the papillary muscle acutely inactivated by 95% alcohol injection, valve function and competence is not seriously compromised, indicating a passive rather than active role for the papillary muscles in the cardiac cycle. The papillary muscle is one of the earliest portions of the myocardium to be depolarized, and high speed cinephotography of the open contracting ventricle and cinefluoroscopy of the closed heart both indicate early mechanical activation of the papillary muscles. Force recordings from a chorda tendinea show that peak tension in this structure, and by inference the associated papillary muscle, occurs at the end of isovolumetric contraction. Most of the current theorizing on papillary muscle function has the papillary muscle initially shortening with the onset of ventricular systole and describes such clinical entities as mitral regurgitation or a poor ventricular contraction when this sequence is altered either by a disease process or surgical intervention. Recent work, however, shows that the papillary muscle initially lengthens with ventricular systole suggesting that forces are at work in the ventricle which are capable of overcoming the shortening process in the depolarized papillary muscle.

It is the purpose of this work to examine and describe the mechanical functioning of the left ventricular papillary muscle in a preparation which closely approximates a normally functioning and anatomically intact myocardium.

CHAPTER III

METHOD

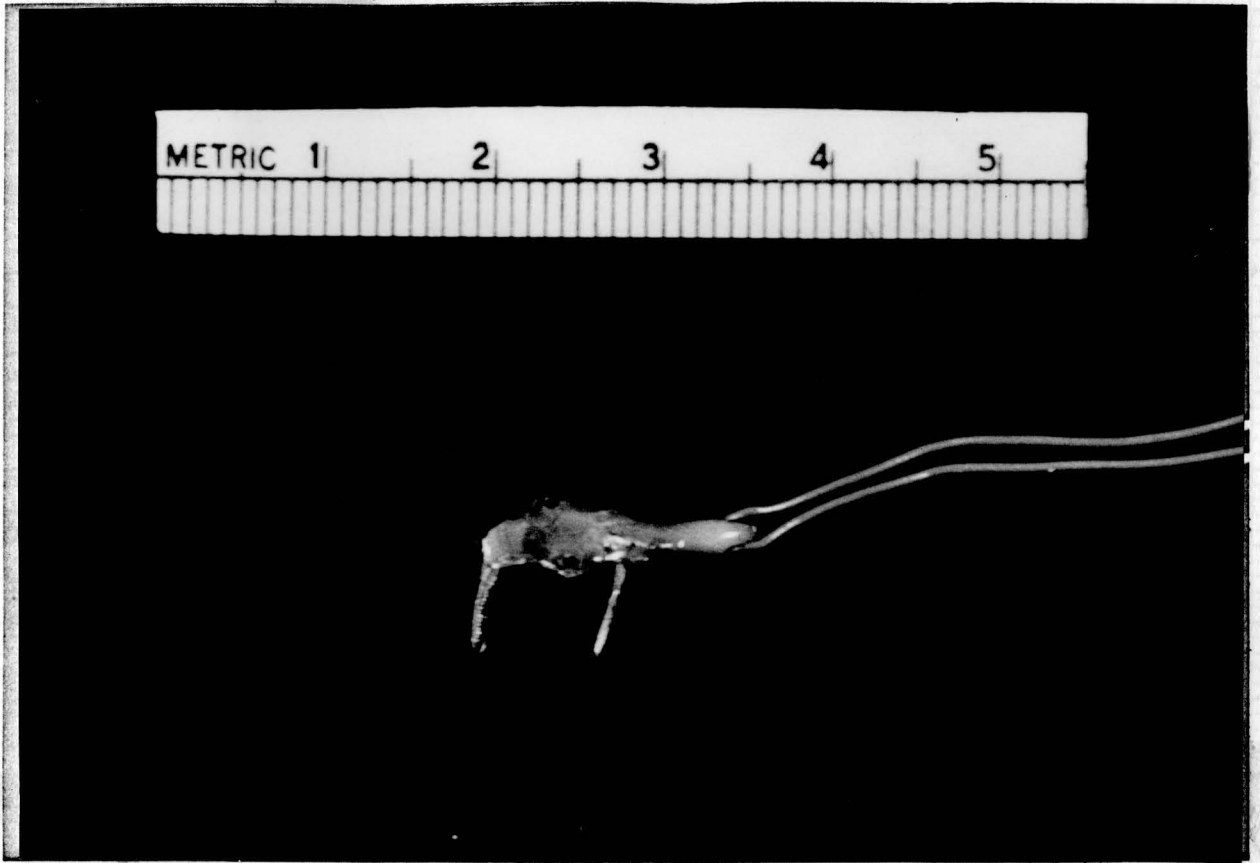
Thirty mongrel dogs of either sex, weighing from 15-26 Kg, were anesthetized with phencyclidine HCl (Sernylan) 2 mg/Kg given intramuscularly and alpha chloralose 80 mg/Kg given intravenously. A bilateral thoracotomy was performed and the internal thoracic artery was cannulated to record systemic blood pressure. The stellate ganglia and cervical vagi were isolated.

The animal was prepared for total cardiopulmonary bypass in the following manner: a single 3/8" id Tygon tube was inserted into the right atrial appendage and gravity drained venous blood to a Travenol model U 230 disposable bubble oxygenator bag. Arterialized blood was returned via a single femoral artery Bardic #14 catheter using a Sarns model 3500 portable pump. During intracardiac surgery continuous suction with a duplicate Sarns pump kept the left ventricular cavity free of blood. A water bath at 38-40 degrees centigrade warmed the arterial blood before it was returned to the animal. Donor dogs were bled and 500-1000 cc of blood were recovered, heparinized, and used to prime the oxygenator and tubing. The experimental animal was given 200-500 units of Sodium Heparin per Kg intravenously. In a few experiments varying combinations of Ringer's Solution, 5% Dextrose and Saline, and Normal Saline were used to prime and also used later in the experiments if additional volume was required. Adequacy of perfusion was monitored by means of arterial blood

pressure which was kept at or above 60 mm Hg during perfusion, and by pump flows of 60-100 cc/Kg/min. Length of perfusion varied from thirty-five to ninety minutes averaging about sixty minutes.

While on total bypass, the left atrium was entered from the animal's right side at the interatrial groove. The left ventricle was immediately decompressed and the mitral valve made incompetent. Ventricular fibrillation was effected with a 3 volt, 100 cps current applied to the ventricular apex.

The SR-4 BLH strain gauge (modified Walton gauge) was constructed with two eye holes flanking the long axis of the 8 mm long arch back (figure 1). These were used for the securing suture. The gauge legs measured 8 mm in length, and in a typical placement, approximately 6 mm of the leg was buried in the muscle. The gauge was calibrated by adding known increments in weight across the legs. The changes in weight and in pen deflection were found to be linearly related within the range of length changes seen in this study. During the experiments an amplifier sensitivity was chosen which gave approximately a 1-2 cm pen deflection. In a typical experiment the length changes were equivalent to a calibration weight of 60-80 gms (figure 2). Under direct vision the strain gauge was imbedded into the papillary muscle and secured with a single suture (figure 3). The gauge leads exited the left ventricle through a small hole punctured in the ventricular apex insuring a competent mitral valve once the heart was closed. The gauge was always put on during fibrillation which was used as a baseline position, obviating any difficulty which might arise if it were put on a contracted versus a relaxed muscle. The gauge needed no initial tension such as epicardial gauges require, since it was wedged into the muscle and the legs were buried. This reasoning was vindicated by the traces



GRAMS OF TENSION

FIGURE 1

GROSS DESIGN OF STRAIN GAUGE

GRAPH SHOWING LINEAR RELATIONSHIP OF GAUGE RESPONSE

AND CHANGES IN TENSION

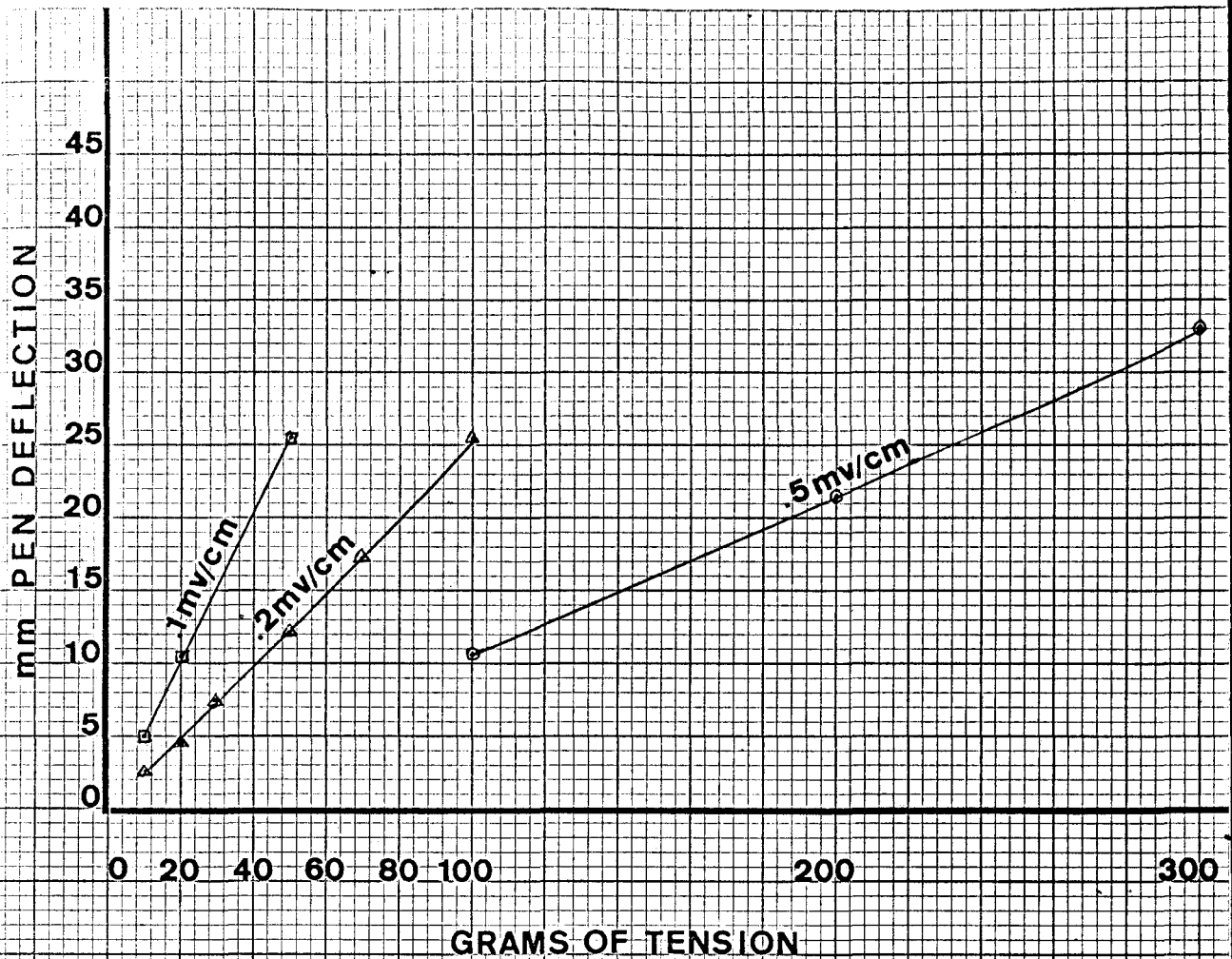


FIGURE 2
GRAPH SHOWING LINEAR RELATIONSHIP OF GAUGE RESPONSE
AND CHANGES IN TENSION



FIGURE 3

POSTMORTEM VIEW OF STRAIN GAUGE PLACED ON ANTERIOR
PAPILLARY MUSCLE OF LEFT VENTRICLE

The heart was defibrillated with a direct current defibrillator and the atriotomy was sutured closed. Left ventricular pressure was recorded with a button type catheter implanted in the left ventricular apex. Statham Model P 23 db transducers were used for all pressures, but pressure was recorded with a no. 19 needle. A catheter of 55-100 catheter inserted into the aortic root. Left atrial pressure was taken via a left pulmonary vein. All pressures are in millimeters of Hg. Strain gauge activity, pressures, and CG were recorded on an Offner Type R Dynograph. Stellate stimulations were performed with a Grass S-5 stimulator with rectangular pulses of 4-8 volts, 10

obtained which rarely show a flat segment even during slow diastolic filling where the gauge was consistently seen to be lengthening.

Since the objection that the gauge legs might actually be protruding through the papillary muscles into the left ventricular wall was anticipated, during three experiments the papillary muscle was cut away from the left ventricular wall with the gauge still in place and it was noted that the legs did not protrude through, but were imbedded entirely in papillary muscle fibers. It was also noted during dissection of the endocardial surface that the fibers in both papillary muscles were running exclusively in one direction, i.e., from base to apex whereas the fibers of the ventricular wall immediately adjacent to the papillary muscles ran in several directions in a basket-weave pattern. Because of this anatomical finding, it was felt that the gauge measured not a vector sum of myocardial contractile forces as an epicardial gauge does due to the different fiber orientations beneath it, but rather a single force with its direction running parallel to the long axis of the papillary muscle.

The heart was defibrillated with a direct current defibrillator and the atriotomy was sutured closed. Left ventricular pressure was recorded with a button type catheter implanted in the left ventricular apex. Statham model P 23 db transducers were used for all pressures. Aortic pressure was recorded with a no. 19 needle on a 7 cm length of PE 100 catheter inserted into the aortic root. Left atrial pressure was taken via a left pulmonary vein. All pressures are in millimeters of Hg. Strain gauge activity, pressures, and ECG were recorded on an Offner Type R Dynograph. Stellate stimulations were performed with a Grass S-5 stimulator with rectangular pulses of 4-8 volts, 10

cps, and 5 msec duration. Stimulation voltage was monitored on an oscilloscope.

During the course of this study, thirty experiments were performed, however, thirteen of these were excluded from analysis for one or more of the following reasons: a) the animal had deteriorated to such an extent that it was impossible to get it off the bypass, b) at autopsy the gauge was found to be poorly placed or had actually fallen out of the muscle during the experiment, c) the securing suture was looped about one of the legs of the gauge possibly restricting gauge movement, and d) the gauge developed a short in its electrical connections during the course of the experiment.

Gauge polarity was carefully checked following each experiment.

CHAPTER IV

EXPERIMENTAL RESULTS

In a typical control trace (figure 4) the initial movement in the papillary muscle was consistently a lengthening which coincided with the period of isovolumetric contraction. This finding was confirmed in seventeen experiments. The maximum rate of lengthening occurred during isovolumetric contraction with maximum length being reached just before the opening of the aortic valve. Shortening began with ventricular ejection, the maximum rate being reached during the rapid ejection phase. Shortening then slowed somewhat, reaching the shortest length immediately prior to the opening of the a-v valve as indicated by the descent of the "v" wave in the left atrial pressure trace. The papillary muscle lengthened slowly during diastolic filling, the rate being most rapid during the first one-third of this period. In experiments where activity from both papillary muscles was recorded, the traces were identical in their shape and correlation with the cardiac events. When fibrillation was induced during control traces, the resting papillary muscle baseline most closely approximated the end-diastolic length of a normal trace, indicating that this was the state of least papillary muscle tension.

To determine the effect of a positive inotropic agent on the papillary muscle trace, norepinephrine 5 $\mu\text{g}/\text{Kg}$ was injected into a femoral vein

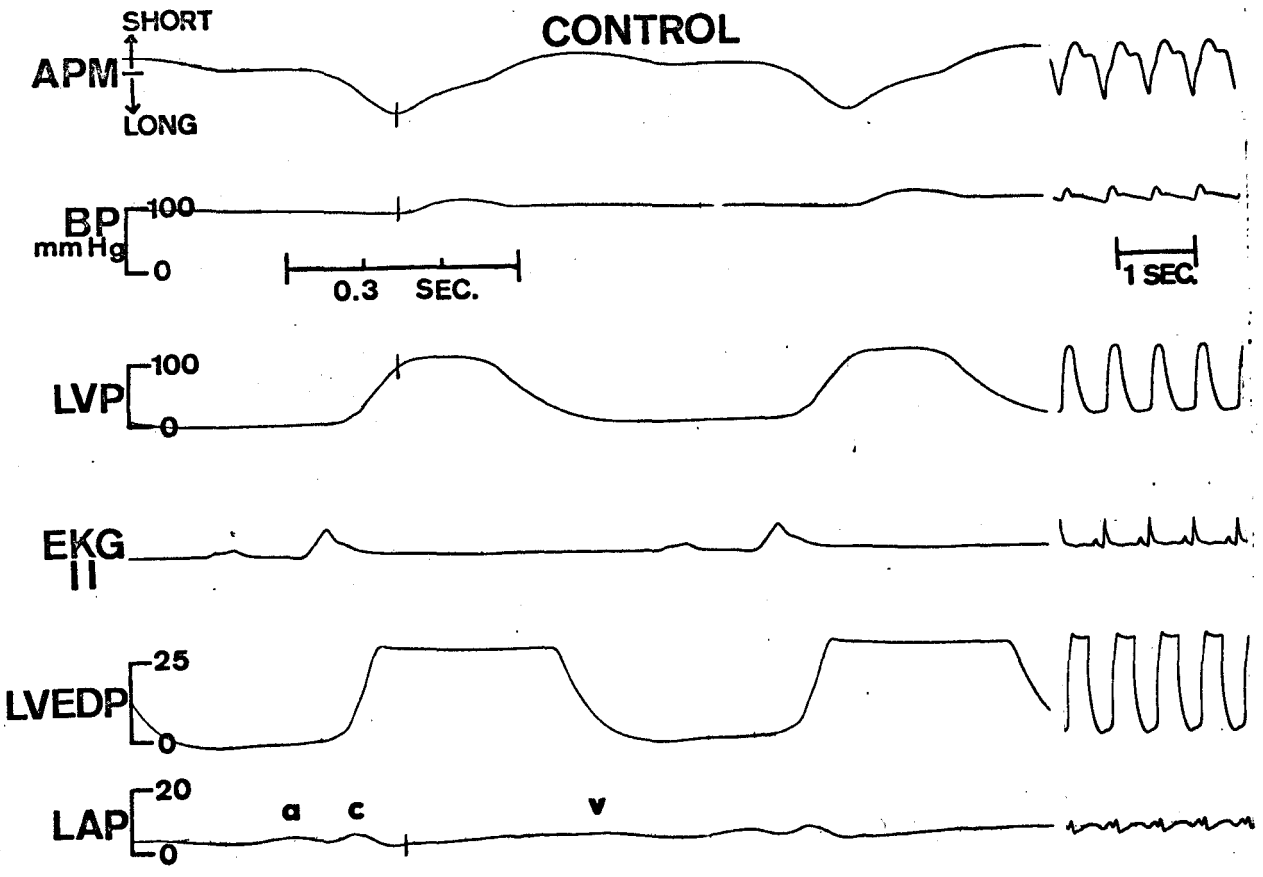


FIGURE 4

CONTROL TRACES OF ANTERIOR PAPILLARY MUSCLE

LEGEND FOR FIGURE 4

APM, anterior papillary muscle; "short" and "long" indicate shortening or lengthening from the baseline or end-diastolic papillary muscle length; BP, internal thoracic artery blood pressure; LVP, left ventricular pressure; EKG, electrocardiogram lead 2; LVEDP, left ventricular end-diastolic pressure; LAP, left atrial pressure.

(figure 5). The expected augmentation of ventricular contraction was evident in the left ventricular pressure trace, with the dp/dt changing from a control of 1.078 mm Hg/msec to 3.290 mm Hg/msec at peak response. In the papillary muscle the increased contractility resulted in a decrease in the lengthening phase, an increase in the shortening phase, and a shift upward in baseline, indicating that the myocardium worked from a shorter fiber length. The early papillary muscle response to the norepinephrine was closely associated with the drop in LVEDP. Comparable responses were noted with other positive inotropic agents, such as sympathetic cardiac nerve stimulation, and calcium chloride. Two minutes after injection a reversal of the papillary muscle trace appeared in the face of a sustained norepinephrine effect. The lengthening phase again became the predominant aspect of the trace and was greatly increased over the control. The dp/dt value dropped to 2.448. Closely associated with this reversal in the trace was a marked rise in arterial blood pressure and a slight rise in LVEDP to a level greater than control.

Injection of isoproterenol 1 μ g/Kg into a femoral vein gave a response that was directionally like that seen in the early norepinephrine response but only to a much greater degree, i.e., the initial lengthening phase rapidly diminished until shortening occurred as the initial event in the papillary muscle (figure 6). As the response wore off, the trace quickly returned toward the pre-injection contour. In this experiment an identically constructed gauge was attached to the left ventricular wall over the anterior papillary muscle. Traces from this external gauge consistently shortened while the internal papillary muscle gauge was lengthening. In every respect this epicardial gauge responded as the more conventional strain gauge arches which

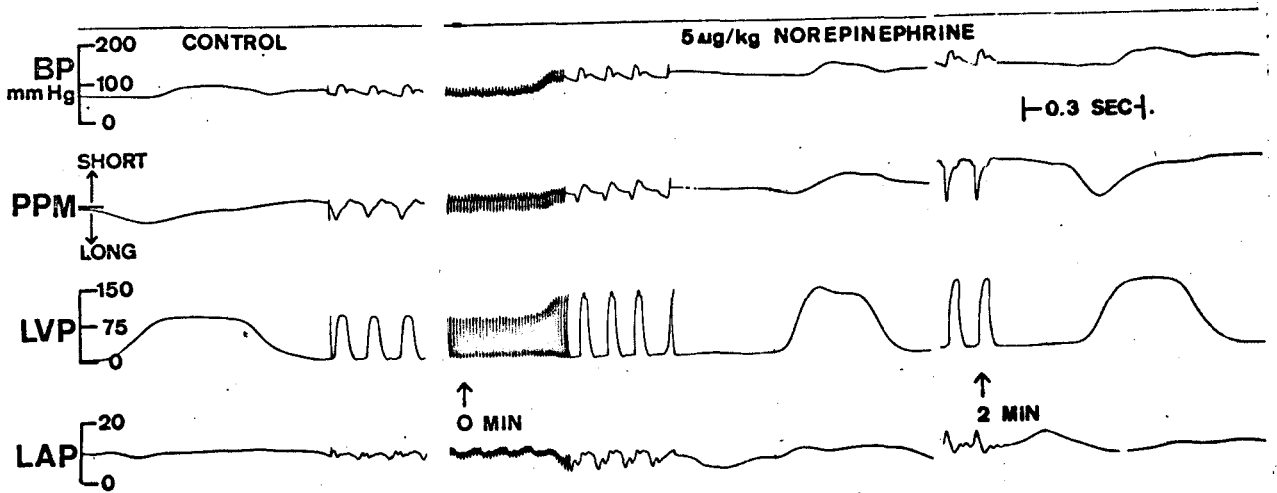


FIGURE 5
EFFECTS OF NOREPINEPHRINE INFUSION

LEGEND FOR FIGURE 5

PPM, posterior papillary muscle; zero minutes marker indicates infusion of drug, followed by early norepinephrine response; two minute marker indicates presence of delayed norepinephrine response.

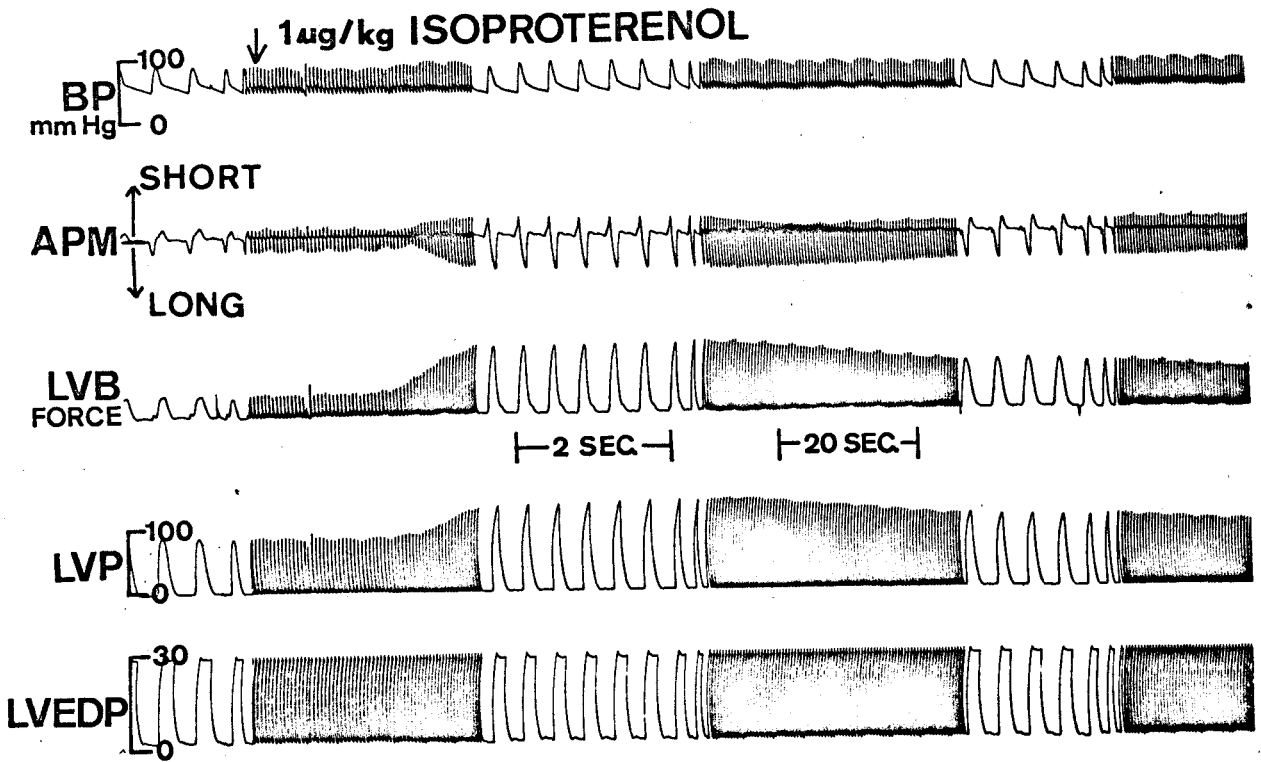


FIGURE 6
EFFECTS OF ISOPROTERENOL INFUSION

LEGEND FOR FIGURE 6

LVB FORCE, represents strain gauge force recorded from the epicardial surface of the ventricular base with a gauge identically made and attached as that on the papillary muscle.

are attached by two sutures across a stretched segment of myocardium. The polarity of both gauges was confirmed at autopsy. Thus the possibility that the type of gauge construction or attachment could enter an artifact was excluded.

In a few traces spontaneously occurring extra systoles exhibited the phenomenon of post extrasystolic potentiation (figure 7). The alteration in the papillary muscle traces in the potentiated beats was consistent with the changes seen in the augmentation occurring from the early effect of norepinephrine and that of isoproterenol, i.e., a decrease in the lengthening phase and a marked increase in the shortening phase. Although ventricular filling and LVEDP was increased before the potentiated beat, the lengthening phase was decreased rather than increased as will be shown to occur with an increase in total blood volume.

With occlusion of the thoracic aorta, arterial pressure rose abruptly and there was a moderate rise in LVEDP (figure 8). The alteration in the papillary muscle trace was quite similar to the delayed norepinephrine response, i.e., a marked increase in the lengthening phase with no change in the shortening phase. A slight drop in baseline can be seen in this trace suggesting that the papillary muscle was operating from a longer resting length.

Volume depleted animals responded to arterial pump infusion with a marked increase in the papillary muscle lengthening phase with no change in the shortening phase (figure 9). The end-diastolic papillary muscle length increased progressively during the infusion as did the amount of lengthening and the maximum length achieved on each beat. When the infusion was stopped, the new pressure level plateaued and was steady, as was the papillary muscle trace. With the increased filling pressure caused by the infusion, the effect

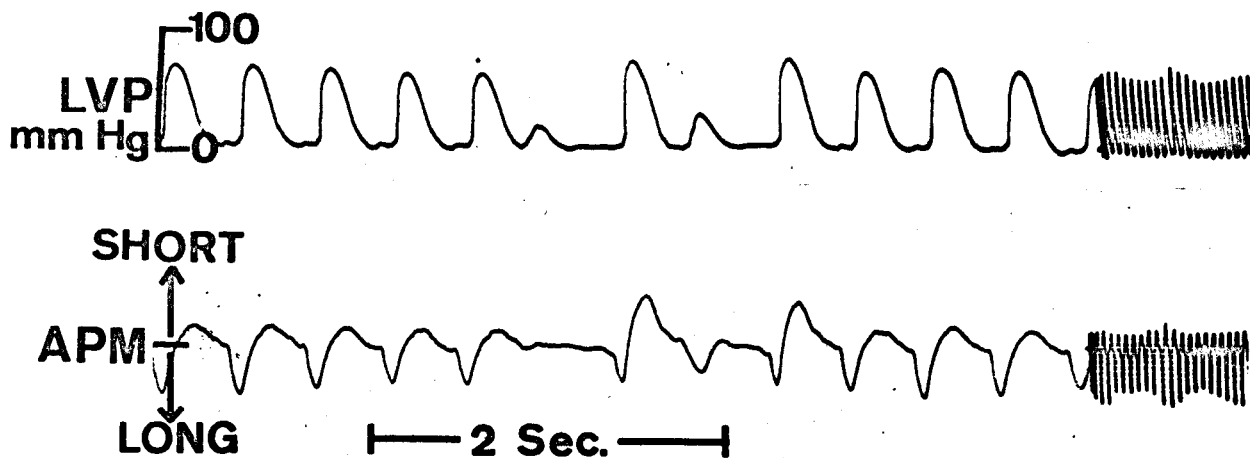
POST EXTRASYSTOLIC POTENTIATION

FIGURE 7

POST EXTRASYSTOLIC POTENTIATION

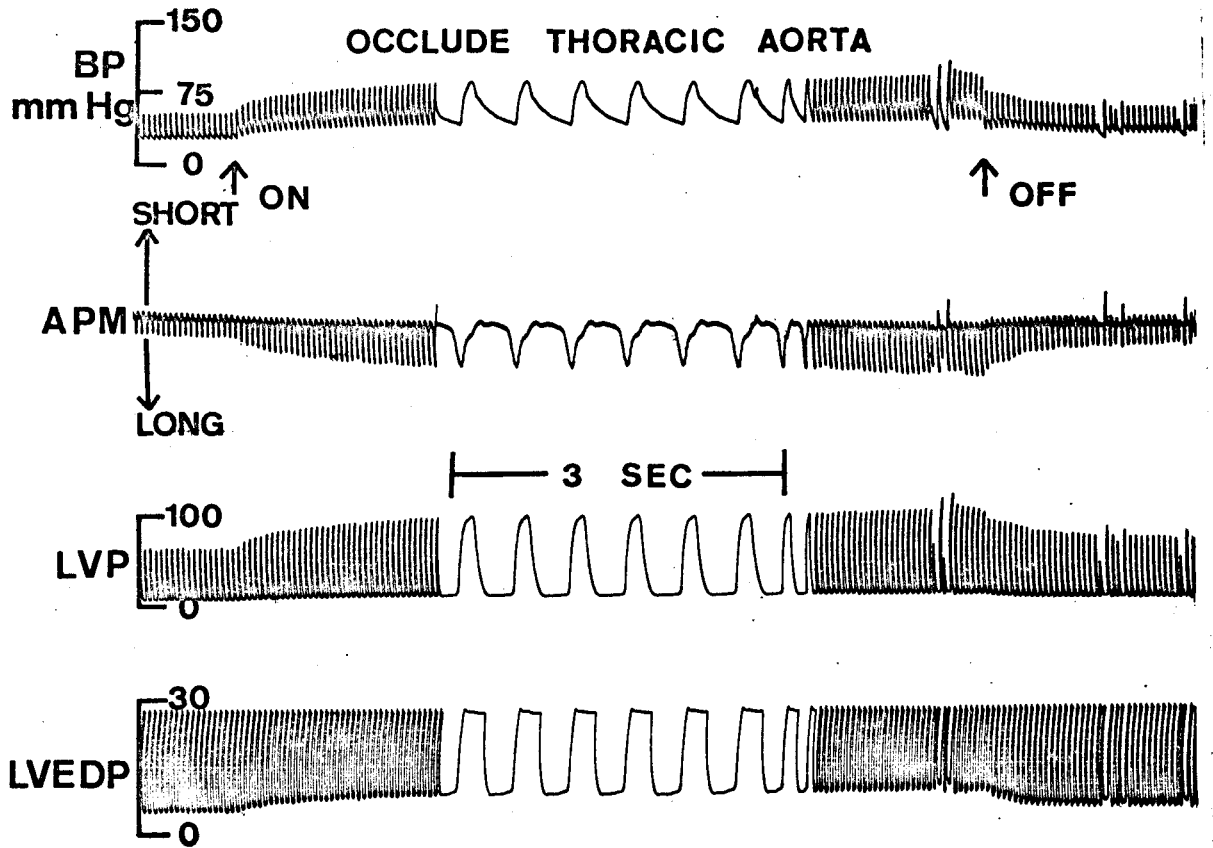


FIGURE 8

OCCLUSION OF THORACIC AORTA

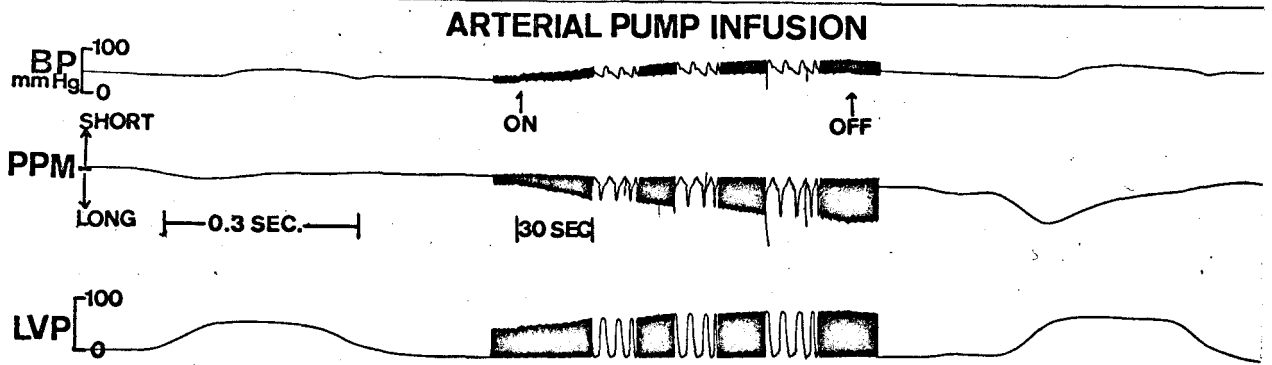


FIGURE 9

ARTERIAL PUMP INFUSION

of atrial systole on ventricular systole became prominent in the left ventricular pressure trace. In the papillary muscle trace, it caused a momentary lengthening, a rebound shortening, and finally the major lengthening phase associated with isovolumetric contraction.

CHAPTER V

DISCUSSION

The most significant and originally least expected finding from this data was that the papillary muscle did not shorten at the onset of ventricular contraction, but rather was passively stretched. Fisher et al were the first to report this observation, but have not to date published their data in other than abstract form (8). These authors attached their gauge through a ventriculotomy incision, an approach also attempted by this author but abandoned because of the damage it caused to the myocardium and the cardiac failure that resulted so frequently. The present approach through the left atrium allowed easy access to the papillary muscles and did not damage the myocardium or obstruct the mitral valve. After bypass the ECG, pressure levels and responses to inotropic agents indicated the presence of an electrically and mechanically sound myocardium.

The present findings indicate that the role of the papillary muscle in valve closure and isovolumetric contraction is passive, but that active shortening does occur during ejection. The origin of the initial stretch is probably multiple. As Burch pointed out, when the left ventricle contracts, its internal surface area decreases while internal pressure rises (2). Since pressure is applied equally on all areas of the endocardium and valves, the

papillary muscle is put under tension both from its origin in the apical free wall and its insertion into the mitral valve. The resultant of these two oppositely directed forces is a stretch of the papillary muscle. In addition one must also consider the geometric changes occurring during contraction which may alter the spatial relationship of the valve ring to the papillary muscle. In a few experiments, an attempt was made to assess the role of the chordae tendineae in the initial lengthening phase by cutting these structures, but this produced severe valvular incompetence and the heart failure which rapidly ensued made interpretation difficult. Rushmer's hypothesis that early papillary muscle and trabeculae carnae contraction caused asynchronous contraction (30) was arrived at by exclusion rather than direct evidence. His cine films showed the mitral valve being pulled into the left ventricular cavity during isovolumetric contraction and he felt this was due to papillary muscle contraction. The present work does not support this, but rather suggests another muscular origin for the pressure rise and the internal length changes of the endocardial surface. Direct data concerning internal chamber lengths during the cardiac cycle is scant. Rushmer was only successful in attaching an aortic root to apex inductance gauge on two occasions and noted no change in one and a slight shortening in the other which he felt was due primarily to the septum. It should be noted that his gauge was in the outflow tract (29). His hypothesis might be sounder had he been able to measure length changes of the inflow tract where the papillary muscles and the mitral valve reside. The external apex to base length was recorded by both Rushmer and Hawthorne using mercury strain gauges, but with opposite findings as to the direction of change. Hawthorne's work showed that left ventricular length

decreased with isovolumetric contraction and he felt his deeply placed securing sutures revealed the change in the whole left ventricular wall length whereas Rushmer's superficially placed securing sutures showed only the superficial muscle which lengthens with isovolumetric contraction (12). Fisher et al reported that their internal and external apex to base mercury gauges most commonly lengthened during isovolumetric contraction, but pointed out that considerable variability existed between experiments (9). From these contradictory findings, it is apparent that the definitive method and measurements of internal cardiac dimensions is yet to be discovered.

The role of the papillary muscles in valve closure is clearly passive and in conjunction with the chordae tendineae the papillary muscles act as limiting struts on the valve leaflets as they rise toward the atrium during ventricular filling. Even during isovolumetric contraction they perform passively and probably allow slight bulging of the valve leaflets into the atrium, since early lengthening occurs at the same instant as the "c" wave appears in the left atrial pressure curve (figure 4). The length alterations produced in the papillary muscle by atrial systole as indicated by the atrial filling wave in the left ventricular pressure are consistent with a purely passive papillary muscle at the time of valve closure (figure 9). Following the stretch on the papillary muscle produced by atrial systole, the slight shortening that occurred probably represented a rebound of the chamber shape after the distortion from atrial systole. Atrial systole closed the mitral valve as is evident by the sustained pressure elevation in the left ventricular pressure trace prior to ventricular systole.

Burch enumerated twenty-four causes of papillary muscle dysfunction, including myocardial ischemia, ventricular dilatation, disturbances in the time course of papillary muscle activation and contraction, and rupture of the papillary muscle or chordae tendineae all of which are manifested clinically by varying grades of mitral incompetence (4). The present data do not entirely support the cause and effect relationship made between papillary muscle dysfunction and clinical findings. Burch assumes that for a competent valve the papillary muscle must actively contract in proper sequence, but the present work indicated that the first movement in the papillary muscle was consistently passive. In animals in acute cardiac failure with elevated LVEDP or in relatively strong hearts exhibiting occasional ectopic beats, the papillary muscle continued to initially lengthen showing no gross changes in mechanical function as Burch suggested. Our conclusions are more in agreement with those of Hider cited above regarding the passive role of the papillary muscles in valve competence (16). Thus the initial passive lengthening of the papillary muscle is a safety device insuring a competent valve regardless of the functional state of the myocardium or the pattern of myocardial excitation.

The high speed film techniques give little practical information about normal ventricular dynamics since the ventricles are open and not contracting against a load. The observation by Kantrowitz that a momentary shortening of the chordae tendineae occurred at the onset of ventricular contraction has little meaning for a physiologic preparation since this observation was from a perfused heart with a "dry" ventricle. Neither our data nor Salisbury's (33) support this concept, but show that the tension which causes the lengthening increases immediately with the onset of ventricular contraction.

The role of the papillary muscles in active ventricular emptying and whether it can be separated from a role in valve competence is difficult to assess. The present work and the studies cited above all suggest that the papillary muscles stabilize and prevent over-dilatation of the ventricular chamber by acting as internal supports. If active papillary muscle shortening did add significantly to ventricular contraction, it would have to be through its insertion in the ventricular base via the chordae tendineae and valve leaflets. However, figure 4 does not reveal any pressure alterations in the left atrium at the time of papillary muscle shortening to indicate a downward pull of the valve out of proportion to that required to maintain proper alignment of the cusps during ejection. It is concluded then, that the importance of the papillary muscle in total myocardial performance is dependent on its presence as a structural support rather than as an active participant in contraction.

The papillary muscle response to changes in preload and afterload, and to cardiac pressor drugs demonstrated three important control mechanisms for increasing contractility: 1) the heterometric, or Starling type, autoregulation which is also defined as preload, 2) the homeometric autoregulation which is seen with increases in aortic impedance or afterload (35), and 3) the extrinsically induced change in contractility which accompanies positive inotropic drugs and cardiac nerve stimulation. The early papillary muscle response to norepinephrine was characteristic of an extrinsic change in contractility. Since the coronary vascular bed was among the first to receive the drug, it was reasonable to expect initially a purely beta-adrenergic cardiac response. As the norepinephrine reached the periphery causing arteriolar

vasoconstriction, a rise in systemic blood pressure, and thus an increase in afterload, a delayed norepinephrine effect appeared which changed both the left ventricular pressure and the papillary muscle trace contour. The papillary muscle responded to isoproterenol, a pure beta-adrenergic drug, and post extrasystolic potentiation, a phenomenon which strikingly augments the level of myocardial contractility (17), with changes consistent with the early norepinephrine response. Occluding the thoracic aorta produced a sudden rise in peripheral resistance and the papillary muscle responded in a fashion consistent with the delayed norepinephrine response. Arterial pump infusion had the dual effect of increasing ventricular filling by increasing total blood volume and increasing afterload by increasing arterial pressure. The summated effect was a change in contractility consistent with the delayed norepinephrine effect.

Brady concluded from quick stretch experiments with isolated papillary muscles that contractility in cardiac muscle was relatively slow in its onset with maximum capacity to shorten occurring about midway through the rising phase of isometric tension development (1). He noted that the time course of tension development following a stretch was dependent only on the magnitude of the stretch and not on the velocity or the time of the stretch so long as the stretch occurred either before or within 150-200 msec after excitation. Volume changes imposed upon the ventricle, or in this case stretches of the in situ papillary muscle, as late as ventricular ejection would result in tension development consistent with Starling's Law. Therefore, Starling's Law held not only for changes in diastolic fiber length, but also for length changes occurring halfway through systole. These findings have application in explaining papillary muscle function in situ. Initial papillary muscle

movement was the resultant of two opposing forces, a passive stretch and an active contraction. It is well known that myocardium contracts more forcefully when it contracts from a longer resting length and in the papillary muscle we have the very desirable situation of a muscle contracting at the same time that it is being passively stretched, allowing it to develop very great tension. Under control situations the stretch that the papillary muscle underwent with the initial rise of intraventricular pressure was of greater force than the force developed by the contracting papillary muscle. Shortening of the papillary muscle developed a force greater than the total load on it, i.e., when left ventricular pressure was greater than aortic pressure, or at the time of aortic valvular opening. Therefore, a length-tension control mechanism for papillary muscle shortening and tension development exists in the heart and is determined by and dependent upon the degree of stretch the muscle undergoes prior to the opening of the aortic valve. Under normal conditions, the degree of stretch is determined by the preload as represented by LVEDP, but may be altered by factors changing the myocardial force-velocity relationship. Factors which increased the LVEDP increased the lengthening phase. Factors which increased the force-velocity relationship as measured by changes in dp/dt decreased the lengthening phase by increasing the velocity of fiber shortening in the shortening phase. Arterial pump infusion (figure 9) increased the preload or end-diastolic volume through increased filling causing a progressive increase in papillary muscle lengthening. The infusion secondarily increased afterload since it also raised systemic pressure. The increased lengthening seen with the late norepinephrine effect was associated with a downward shift in the dp/dt from the early norepinephrine response which was probably due to a

diminishing of the beta effect with a sustained peripheral effect. It is obvious that under normal conditions neither preload nor afterload effects can be isolated, since a change in one alters the other. The same holds true for the effects of positive inotropic drugs. The early effect of norepinephrine caused an augmented shortening phase with an overshoot of the baseline and this encroached upon and decreased the lengthening phase. The dp/dt value changed from a control of 1.078 to 3.290 mm Hg per msec at peak response. Since norepinephrine, isoproterenol, and post extrasystolic potentiation all shift the force-velocity curve upward (39), the traces recorded during these interventions showing that the stretch phase was much abbreviated or even absent can be explained as due to a more rapid and greater force development in the shortening phase than the passively developed force of the stretch phase. The papillary muscle change may not be due solely to the effect on the force-velocity relationship, however, since with better ventricular emptying the preload and thus the length-tension relation is altered. The potentiated post extra-systole beat, however, vividly separated and defined the passive and active components of the papillary muscle trace and indicated their independence of one another. The augmented shortening phase is clearly an intrinsically induced change in contractility (25), and independent of preload and afterload, since the lengthening phase was reduced in spite of an increased preload resulting from the increased filling during the compensatory pause. The active contractile nature of this augmented shortening phase is evidenced by the marked overshoot of the resting papillary muscle length in the potentiated beats and by the absence of this in the inefficient, low pressure, extra-systole beats.

In dissecting the endocardium, the fibers comprising the trabeculae carnae could be seen running obliquely towards the papillary muscle fibers, whose direction was consistently longitudinal in a base to apex orientation. When the papillary muscle was cut away from the wall the trabeculae carnae fibers continued their oblique direction behind the papillary muscles. Anatomical evidence, then, suggests functionally different roles for the papillary muscles and trabeculae carnae. Rastelli's work graphically pointed up the importance of the chordae tendineae tension in maintaining the papillary muscle because without this tension it soon atrophied (27).

In two experiments inotropic intervention produced the frequently seen late systolic pressure peak in the left ventricular pressure curve. In conjunction with this, the papillary muscle gauge registered a forceful late systolic lengthening. Since neither occurred in the control trace, it seemed they might be related. That these events were confined to the ventricle was apparent from the unaffected aortic pressure contour. Dieudonne suggested that the late systolic pressure peak was due to compression of myocardium about the catheter tip, however, he did not see this phenomenon with the type pressure catheter used in the present study (6). Recent work mentioned above (26,22,2) has shown that the papillary muscle and trabeculae carnae become more prominent in the left ventricular cavity with systole. Burch emphasized that at the end of ventricular systole, the ridges of muscular trabeculae are squeezed together and the valleys in the endocardial wall are reduced in volume (2). Therefore, a possible explanation for the late systolic pressure rise is the formation of high pressure pockets by the papillary muscle and trabeculae carnae as they occupy an increasingly greater fraction of the

left ventricular cavity late in the ejection phase, isolating and compressing a pocket of blood about the catheter tip. The late lengthening in the papillary muscle may be the result of the strong contraction of the basal constrictor fibers, or may represent compression of the papillary muscle against the septum which would tend to lengthen it.

CHAPTER VI

SUMMARY

The mechanical function of the canine left ventricular papillary muscles was assessed using modified Walton-Brodie strain gauges. Under control conditions the papillary muscle initially lengthened with isovolumetric contraction and actively shortened during ejection. This pattern was altered by positive inotropic agents such as norepinephrine which showed a decrease in the initial passive lengthening phase, an increase in the shortening phase and a shift to a shorter resting fiber length. Changes in afterload as occurred with the delayed, vasoconstrictor effect of norepinephrine and with occlusion of the thoracic aorta caused an increase in the lengthening phase, no change in the shortening phase, and a shift to a longer resting fiber length. Changes in blood volume exerted their effect on the lengthening phase and resulted in a longer resting fiber length. It was concluded that the papillary muscles were normally passive during isovolumetric contraction, but actively contracted during this period when their force-velocity curve was shifted upward by a positive inotropic agent. The origin of the lengthening was probably due to rising intraventricular pressure causing the papillary muscle to be stretched at its origin in the ventricular apex and at its insertion in the valve leaflets via the chordae tendineae. The initial lengthening of the

papillary muscle was described as a safety device preventing or minimizing regurgitation in normal and diseased hearts. The degree of lengthening of the papillary muscle with ventricular filling determines the degree of subsequent shortening according to Starling's Law.

BIBLIOGRAPHY

1. Brady, A.J. Onset of Contractility in Cardiac Muscle. J. Physiol. 184: 560-580, 1966.
2. Burch, G.E., C.T. Ray, and J.A. Cronvich. Certain Mechanical Peculiarities of the Human Cardiac Pump in Normal and Disease States. Circulation 5: 504-513, 1952.
3. Burch, G.E. and N.P. DePasquale. Time Course of Tension in Papillary Muscles of Heart. JAMA 192: 701-704, 1965.
4. Burch, G.E., N. DePasquale, and J.H. Phillips. The Papillary Muscle Syndrome. JAMA 204: 249-252, 1968.
5. Dean, A.L. The Movement of the Mitral Cusps in Relation to the Cardiac Cycle. Amer. J. Physiol. 40: 206-217, 1916.
6. Dieudonne, J.M. Artificial Nature and Site of the Systolic Pressure Drop During Inotropic Stimulation of the Normal Ventricle. Canad. J. Physiol. and Pharm. 44: 829-836, 1966.
7. Fenwick, W.S. and W. Overend. The Contraction of the Papillary Muscles and Its Relation to the Production of Certain Abnormal Cardiac Sounds. British Medical Journal 1: 117, 1891.
8. Fisher, V.J., J.H. Stuckey, R.J. Lee, and F. Kavalier. Length Changes of Papillary Muscles of the Canine Left Ventricle During the Cardiac Cycle. Fed. Proceedings, vol. 24, no. 2, March-April, 1965.

9. Fisher, V.J., R.J. Lee, Gourin, Anatole, H. Bolooki, J.H. Stuckey, and F. Kavalier. Muscle Fiber Length: A Determinant of Left Ventricular Contraction. Amer. J. Physiol. 211: 301-306, 1966.
10. Hartstein, M.L., J.H. Stuckey, V.J. Fisher, and F. Kavalier. Length Changes of Papillary Muscle of the Canine Right Ventricle During the Cardiac Cycle. Fed. Proceedings, vol. 27, no. 2, March-April, 1968.
11. Harvey, W. Exercitatio Anatomica De Motu Cordis Et Sanguinis in Animalibus. Translated by Chauncey D. Leake. Charles C. Thomas, Springfield, p. 119-120, 1928.
12. Hawthorne, E.W. Instantaneous Dimensional Changes of the Left Ventricle of Dogs. Circ. Res. 9: 110-119, 1961.
13. Haycraft, J.B. and D.R. Paterson. The Time of Contraction of the Papillary Muscle. J. of Physiol. 19: 262-265, 1895-1896.
14. Henderson, Y. and F.E. Johnson. Two Modes of Closure of the Heart Valves Heart 4: 69-82, 1912.
15. Hider, C.F., D.E.M. Taylor, and J.D. Wade. Sequence of Mechanical Contraction of the Left Ventricle of the Dog. J. Physiol. 178: 34 P., 1965.
16. _____, _____, and _____.
The Effect of Papillary Muscle Damage on Atrioventricular Valve Function in the Left Heart. Quart. J. Expt. Physiol. 50: 15-22, 1965.
17. Hoffman, B.F., E. Bindler, and E.E. Suckling. Post Extrasystolic Potentiation of Contraction in Cardiac Muscle. Amer. J. Physiol. 185: 95-102, 1956.
18. Kantrowitz, A., A.S. Hurwitt, and A. Herskovitz. A Cinematographic Study of the Function of the Mitral Valve In Situ. Surgical Forum 2:204-6, 1951

19. Lillehei, C.W., M.J. Levy, and R.C. Bonnabeau. Mitral Valve Replacement with Preservation of Papillary Muscle and Chordae Tendineae. J. Thoracic C-V Surgery 47: 532-543, 1964.
20. Little, R.C. Effect of Atrial Systole on Ventricular Pressure and Closure of the A-V Valve. Amer. J. Physiol. 166: 289-295, 1951.
21. Paul, R.E., M.J. Oppenheimer, P.R. Lynch, and H.M. Stauffer. Regurgitation of Radiopaque Contrast Material Through Normal Mitral Valves in Cine-fluorographic Studies of Dogs. J. Appl. Physiol. 12: 98-104, 1958.
22. Priola, D.V., C.E. Osadjan, and W.C. Randall, Functional Characteristics of the Left Ventricular Inflow and Outflow Tracts. Circ. Res. 17: 123-129, 1965.
23. Puff, A. Die Morphologie des Bewegungsablaufes der Herzkammern. (Eine Untersuchung über die wechselseitige Beeinflussung des Kontraktionsablaufes im rechten und linken Ventrikel). Anat. Anz. 108: 342, 1960.
24. Robb, J.S. and R.C. Robb. The Normal Heart Anatomy and Physiology of the Structural Units. Amer. Heart J. 23: 455-467, 1942.
25. Ross, J. Jr., J.W. Covell, E.H. Sonnenblick, and E. Braunwald. Contractile State of the Heart Characterized by Force-Velocity Relations in Variably Afterloaded and Isovolumic Beats. Circ. Res. 18: 149-163, 1966.
26. Ross, J. Jr., E.H. Sonnenblick, J.W. Covell, G.A. Kaiser, and D. Spiro. The Architecture of the Heart in Systole and Diastole: Technique of Rapid Fixation and Analysis of Left Ventricular Geometry. Circ. Res. 21: 409-421, 1967.
27. Rastelli, G.C. Fate of Papillary Muscle after Prosthetic Replacement of Mitral Valve. Mayo Clinic Proceedings 42: 210-217, 1967.

28. Roy, C.S. and J.G. Adami. Heartbeat and Pulse-Wave. Practitioner 44-45: 82-94, 1890.
29. Rushmer, R.F. Continuous Measurements of Left Ventricular Dimensions in Intact, Unanesthetized Dogs. Circ. Res. 2: 14-21, 1954.
30. Rushmer, R.F. B.L. Finlayson, and A.A. Nash. The Initial Phase of Ventricular Systole: Asynchronous Contraction. Amer. J. Physiol. 184: 188-194, 1956.
31. _____, _____, and _____. Movements of the Mitral Valve. Circ. Res. 4: 337-342, 1956.
32. _____, _____, and _____. Shrinkage of the Heart in Anesthetized, Thoracotomized Dogs. Circ. Res. 2: 22-27, 1954.
33. Salisbury, P.F, C. E. Cross, and P.A. Rieben. Chorda Tendinea Tension. Amer. J. Physiol. 205: 385-392, 1963.
34. Sarnoff, S.J., J.P. Gilmore, and J.H. Mitchell. Influence of Atrial Contraction and Relaxation on Closure of Mitral Valve. Observations on Effects of Autonomic Nerve Activity. Circ. Res. 11: 26-35, 1962.
35. Sarnoff, S.J., J.P. Gilmore, and A.G. Wallace. The Influence of Autonomic Nerve Activity on Adaptive Mechanisms in the Heart. In Nervous Control of the Heart. Edited by W.C. Randall, 251 pp. Baltimore: Williams & Wilkins, Chapter 4, PP. 54-129, 1965.
36. Scher, A.M., A.C. Young, A.L. Malmgren, and R.R. Paton. Spread of Electrical Activity Through the Wall of the Ventricle. Circ. Res. 1: 539-547, 1953.
37. Seidel, W., and W. Gross. Experimental Investigations on the Function of Papillary Muscles after Prosthetic Mitral Valve Replacement. Surgery

- 61: 802-807, 1967.
38. Skinner, N.S., J.H. Mitchell, A.G. Wallace, and S.J. Sarnoff. Hemodynamic Effects of Altering the Timing of Atrial Systole. Amer. J. Physiol. 205: 499-503, 1963.
39. Sonnenblick, E.H. Implications of Muscle Mechanics in Heart. Fed. Proceedings 21: 975-990, 1962.
40. Thomas, C.E. The Muscular Architecture of the Ventricles of Hog and Dog Hearts. Amer. J. Anat. 101: 17-58, 1957.
41. Wiggers, C.J. In Physiology in Health and Disease. Fifth Edition. London: Henry Krimpton, PP. 584-585, 1934.

APPROVAL SHEET

The thesis submitted by Robert E. Cronin has been read and approved by three members of the faculty of the Graduate School.

The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the thesis is now given final approval with reference to content, form and mechanical accuracy.

The thesis is therefore accepted in partial fulfillment of the requirements for the Degree of Master of Science.

May 27, 1968

Date

Walter C. Randall

Signature of Advisor