MYOCARDIAL RELAXATION: THE EFFECT OF EPINEPHRINE ON UNIT SYNCHRONIZATION

DISSERTATION

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I. INTRODUCTION

A. Inotropic activity of epinephrine

From the time when Oliver and Schafer (1) first showed the effects of extracts of the suprarenal capsule on the frog's heart the drug, epinephrine, has probably been used more than any other in physiological research. It has especially enriched the volume of literature in cardiovascular physiology. The inotropic and chronotropic potentiating abilities of the drug have been demonstrated many times since this first experiment. Wiggers and Katz (2) demonstrated an increased stroke volume and rate of ejection following administration of the drug; they also noted that it increased diastolic distension. The positive inotropic action of epinephrine has been demonstrated on other cardiac tissues. Utilizing the papillary muscle of the cat, S. Krop in 1944 (3) and later Garb in 1950 (4) demonstrated the characteristic augmentation of systole produced by epinephrine. The introduction of strain gauge arches as an instrument of cardiovascular research has enabled other workers to determine the positive inotropy of epinephrine in both open chest and intact unanesthetized dogs (5). In this work Cotton and Pincus reported that injection of 2-4 μg./Kg. of epinephrine produced maximal increase in contractile force as measured by these gauges. These arches were used subsequently
by Cotton and Maling (6) to establish that a linear relationship exists between ventricular contractile force and ventricular stroke work. This relationship remained linear during changes in aortic and atrial pressures and during the action of l-norepinephrine. Previous to this, Cotton (7) demonstrated in dogs that accelerator nerve stimulation produced significant increases in both heart rate and myocardial contractile force. The increase in contractile force elicited by nerve stimulation was equivalent to that obtained by injection of approximately 2 μg./Kg. of commercial epinephrine (Adrenalin).

Sympathetic stimulation was also shown to increase contractility by Anzola and Rushmer (8). In both open chest dogs and chronically operated animals they found consistent changes in heart rate, in ventricular and aortic pressures, and in heart dimensions. The systolic pressure was greatly elevated while both systolic and diastolic dimensions were reduced. The aorta was clamped to prevent outflow; upon sympathetic stimulation there was a further elevation in left ventricular pressure indicating a change in contractile characteristics of the myocardium. Thus the positive inotropic action of epinephrine has been well documented.

The effects of epinephrine noted above are concerned primarily with its action on the systolic portion of the pressure and tension curves. There is also a very pronounced effect of epinephrine on
the relaxation process. It is this phase of the myocardial response which is the salient point of this dissertation.

B. **Relaxation process and ventricular filling**

The ventricular relaxation process has long been considered capable of playing an important role in determining the ventricular stroke output. Perhaps the first reference to relaxation rate as a possible determinant of ventricular stroke behavior was by Henderson in 1923 (9). He asserted that the rate of relaxation in skeletal muscles undergoing strenuous activity is an important factor in their ability to continue to perform work. He then remarked "in similar fashion in the heart, the velocity and extent of relaxation, in other words, the ease with which the muscle stretches under the distending force of venous pressure, is probably quite as important a factor in the heart's behavior as the force and rapidity of the systolic contraction." He also mentioned the probable increase in relaxation rate which accompanies physical exertion. Certainly a great deal of attention has been paid the process of ventricular relaxation in relation to its effect on the subsequent filling cycle. Katz in 1930 (10) using the isolated turtle ventricle emphasized the role of the relaxation process in ventricular filling. In his experiments he measured intraventricular pressure and found that it continued to decrease during the phase of rapid inflow. He concludes from these experiments that this fall in
intraventricular pressure in the face of a rapid inflow of fluid can only be explained by the fact that the ventricle is relaxing at a faster rate than it can fill.

Later the relaxation phase was again investigated in an attempt to determine its role in ventricular filling. The series of papers by Ogden et al. (11, 12, 13) emphasize the mechanical impedance of the ventricle during the filling periods. In one of these papers (12) a slight effect of epinephrine on the relaxation rate is indicated; the major effect, however, seems to be a decrease of impedance during the midfilling period. In the subsequent paper (13) epinephrine is also reported to have an effect on the rate at which the impedance to inflow is decreased. Here it is clearly shown that epinephrine increases the rate of fall of the mechanical impedance. It is stated that "it is probable that any stimulus speeding the rate of relaxation of the ventricle would speed the rate of impedance fall".

The relaxation process under the influence of epinephrine was again studied using a slightly different approach. The term "impedance" introduced in the papers mentioned above has been objected to and so the term "renitence" has been substituted by Hennacy and Ogden (14). Hennacy (15) undertook the task of clarifying the specific effects of epinephrine on ventricular relaxation. Using isolated frog ventricles he again studied the pressure flow relationships. His
findings substantiate those of other workers previously mentioned. In the isochoric preparation epinephrine increases the maximum rate of relaxation to a greater extent than it increases the developed pressure. It was concluded that epinephrine thus has the ability to increase relaxation rate independently of its inotropic effect on pressure. He intimates that this more rapid relaxation is due to a more synchronous behavior of the myocardial elements.

The process of ventricular relaxation and its role in determining the extent of filling during diastole is presented from still another viewpoint by those who subscribe to the mechanism of diastolic ventricular suction. In the work to be subsequently discussed it should be remembered that the question of whether or not there is indeed a suction process which contributes significantly to the normal stroke output is not yet settled. However, the volume of literature concerned with this subject is so abundant that some mention should be made concerning the research which supports such a mechanism. The work below which substantiates diastolic ventricular suction have one fact in common: all experiments which demonstrate suction were performed at ventricular residual volumes considered to be significantly below the normal.

The question of the ventricle filling by the process of suction was dispelled by Harvey. In Leake's translation (16) of his "Exercitatio Anatomica De Motu Cordis et Sanguinis in Animalibus", it is stated
"it is not true... that the heart by its own action or distension draws blood into its ventricles" p. 33. This inability of the ventricles to aid their own filling is mentioned once again in this work. In the portion dealing with the function of the auricles it is stated that ventricular filling occurs by auricular contraction and not by any suction or dilatation of the ventricles (p. 41).

More recently, however, a considerable body of information which indicates that a ventricular diastolic suction does indeed exist has been obtained. In 1956 Bloom (17) demonstrated that the excised rat heart was able to propel itself about a beaker while immersed in saline; during diastole fluid was drawn into the ventricle and then ejected from it during systole. An inherent elasticity of the non-beating heart was also demonstrated when external compression was applied to it - the removal of the external force permitted the ventricle to draw in fluid from the surrounding medium. In an attempt to demonstrate that negative intraventricular pressure is established during diastole Bloom and Ferris (18) measured intraventricular pressures and electrocardiograms in excised beating rat hearts. It was shown that with the collapsible auricle intact no ventricular filling could occur during diastole. However, excision of this collapsible compartment permitted some fluid to enter the ventricle during diastole. They also attempted to demonstrate a negative intraventricular pressure in open chest dogs. If inflow into the
ventricles was obstructed left ventricular pressures fell to -15 to -20 mm.Hg. Mention is made of two possible sources of this negative pressure, i.e., elastic recoil caused by distortion of interfacial planes or an active lengthening of the myocardium following a full contraction.

From the studies just cited the authors were led to believe that there existed an inverse relationship between the systolic pressure developed during contraction and the negative pressure determined during diastole. The more forceful the heart beat, the more negative was the intraventricular pressure during diastole. Subsequently, the relationship between the systolic pressure and the diastolic pressure was studied under three conditions (19): spontaneous weakening of contraction, ventricular alternans, and during the increase in systolic pressure resulting from injection of epinephrine and nor-epinephrine. From the results of these experiments they concluded that the negative pressure caused by elastic recoil of the relaxing ventricle is inversely proportional to the end systolic volume of the preceding beat.

Further evidence supporting ventricular diastolic suction was presented by Kraner and Ogden (20). Using isolated turtle hearts they estimated that at zero filling pressure the preparation was filled to about 10% of its normal stroke output. At approximately the same time Brecher (21) presented evidence for ventricular diastolic
suction in open chest dogs. The heart was immersed in fluid by filling the chest with saline; a reservoir was connected to the left ventricle at a level below that of the saline in the chest. If the ventricle was prevented from filling via the atrium the ventricle aspirated fluid from the reservoir. Brecher also found that suction was more pronounced during diastoles following strong heart beats. In discussing these results Brecher admits that no quantitative significance can be attached to them since residual volumes were quite low. The study of this problem was continued by Brecher and Kissen in a subsequent paper (22). Here the immersed dog heart pumped blood against a normal arterial pressure so maintained by a perfusion pump. With extirpation of the left atria it was found that in the absence of a positive ventricular filling pressure the ventricle was indeed able to eject a certain amount of blood against the existing aortic pressure. If the aortic pressure was raised the ventricle was unable to eject any blood against this elevated resistance; however, with the addition of epinephrine the increased force of ventricular contraction overcame this high outflow resistance and ejection was again possible. Obviously, if the ventricle ejected, it also had to fill; this occurred by suction. The addition of epinephrine had the same effect in a failing heart; i.e., one that was unable to eject and hence fill at normal arterial pressures regained the ability to do both when epinephrine was added. These results are qualitative and the percent
contribution of diastolic suction to ventricular filling remains unknown. It is mentioned by the authors that perhaps with epinephrine the prime contribution to filling shifts from \textit{vis a tergo} to a \textit{vis a fronte}. Also discussed is the fact that a negative intraventricular pressure need not be demonstrated in order for the phenomenon of diastolic ventricular suction to exist. The next paper concerned with the problem of ventricular suction was published in 1959 by Kraner (23). He again used the excised turtle heart immersed in saline. It was demonstrated that these hearts were able to eject fluid against fairly reasonable outflow pressures (16 cm. saline). The effect of epinephrine on this particular preparation was usually to increase the volume output of the ventricle; again it was established that a more complete systolic ejection enabled more fluid to be taken into the ventricle during the subsequent diastole. The statement is made that "epinephrine appears usually to act on the heart, so that the relaxation phase is modified allowing an increase in diastolic ventricular suction".

C. Synchronicity of the myocardium

The effect of epinephrine on the ventricular isometric relaxation phase of the cardiac cycle has been known for many years. This increased rate of relaxation under the influence of epinephrine is mentioned whenever the dynamics of the ventricular relaxation process are discussed; inevitably in these discussions it is stated
that perhaps this specific effect on the myocardial relaxation process is due to a more synchronous behavior of the individual myocardial units. The purpose of this dissertation is then to answer the question, does epinephrine increase the synchronicity of the individual myocardial contractile elements and so bring about a more rapid ventricular relaxation? Since it is the purpose of this paper to determine whether epinephrine increases synchronicity of the individual myocardial units, the work which first considered an altered synchronization of the myocardium as responsible for changes in the intraventricular pressure curve will be discussed. The effect of epinephrine on the myocardium was viewed by Wiggers to be one which altered the rate of entry of fractionate contractions into the contraction process. This view was not a new one and had been considered responsible for alterations in the myocardiograms of frog ventricles by Koch in 1920 (24). The work by Wiggers was begun after the discovery by Lewis and Rothschild (25) that the appearance of negativity on the ventricular surface appeared at distinct times at different points of the myocardium. Depolarization was coupled to the process of contraction in cardiac muscle by Kavaler (26); he demonstrated that depolarization is followed by development of tension and that the phase of rapid repolarization is nearly coincident with the beginning of the tension decline.
The results obtained by Lewis and Rothschild were confirmed by Wiggers (27); he then investigated the genesis of the intraventricular pressure curve on the assumption that it is caused by an algebraic summation of fractionate contractions. A more rapid summation of these unit contractions would explain the alterations in the intraventricular pressure curve and would cause a steeper pressure gradient, an earlier termination of systole, and a more rapid rate of isometric relaxation (28). He had earlier observed that if the ventricle of a dog was stimulated directly rather than through the normal conduction pathways there was a slower initial rise of pressure, a lengthening of the isometric contraction phase, a lower pressure maximum, and an increase in the duration of systole (29). It was concluded that these effects on the intraventricular pressure curve were induced by changes in the order of excitation.

The study on the mechanism of cardiac stimulation by epinephrine published in 1927 by Wiggers (30) was also based on this hypothesis of a more rapid summation of unit contractions. He measured interpunctal intervals (time differences between appearance of negativity at various myocardial locations) in hearts maintained at a constant rate by atrial pacing. The differences were small and not consistent. Later (31, pg. 264) the hypothesis that the intraventricular pressure curve was a resultant of rapidly summated fractionate contractions was abandoned by Wiggers.
The general order of excitation of the ventricular epicardium originally mapped out by Lewis and Rothschild has been confirmed many times by different workers and the notion of an altered synchronization of the myocardial units has persisted in the literature.

In a paper previously mentioned (30) Wiggers demonstrated a specific effect of epinephrine on the relaxation process, and consequently, the view that a change in synchronization may affect the process of relaxation became evident in the literature. He showed that the gradients of both contraction and relaxation were increased by the drug and recognized the more complete and rapid relaxation of the ventricle as being one of the major forces which tend to regulate the initial tension of the ventricle at the beginning of the next systole. The effect of epinephrine on ventricular relaxation was confirmed later by Opdyke (32); using dog hearts isolated "in situ" and doses of epinephrine around 4 μg, he demonstrated that during the maximum effect of the drug the rapid relaxation phase decreased by as much as 0.16 second. Although he does not claim that increased rate of relaxation is the result of a more synchronous behavior of myocardial fibers he enumerated it as being one possibility.

This specific effect on the relaxation process was again demonstrated in 1960 by Randall and Kelso (33). They recorded pressure pulses from the aorta, the carotid artery and from either one or both of
the ventricles of an anesthetized open-chest dog. Upon stimulation
of the stellate ganglion (right or left) there was a marked increase
in the rate of intraventricular pressure rise and fall. In one animal
the rate of pressure rise increased from a control value of 0.9 to
2.3 mm. Hg./msec. at the time of maximal effect. The effect on
the rate of pressure decline, although not as marked, was neverthe­
less quite significant. During isometric relaxation the rate of fall
of pressure increased from 0.7 to 1.3 mm. Hg./msec. Thus, the
effect of the hormone on the relaxation rate has been amply demon­
strated irrespective of whether it is administered by I. V. injection,
by injection into a perfusion set up, or by perhaps the most physio­
logically sound method, i.e., stellate ganglion stimulation.
II. MATERIALS AND METHODS

A. Operative procedure

1. Surgery. -- The experiments were performed on a total of 21 mongrel dogs of both sexes, anesthetized with 30 mg./Kg. Veterinary Nembutal (Pentobarbital Sodium, Abbott Laboratories, North Chicago, Illinois). A tracheotomy was performed and a Y-shaped tracheal cannula was inserted. At this time the left carotid artery and the left vagus nerve were isolated for future procedures. With the dog lying on its back the sternum was split longitudinally; immediately prior to opening the thorax the tracheal cannula was attached to an "Ideal" Respiration Pump (C. F. Palmer (London) Ltd.) using oxygen. The tidal volume was varied from about 225-350 ml. depending upon the size of the animal. The respiration rate was maintained at a constant 16/minute. The chest walls were widely spread and securely tied to the operating table; both internal thoracic arteries and veins were ligated. The phrenic nerves were severed just cephalad to the base of the heart; these nerves were then stripped toward the diaphragm and extirpated slightly above their penetration of the muscle. This was done so as to eliminate any attempt by the animal to breathe spontaneously during the recording procedure. The final surgical manipulation prepared the heart for the attachment of
the recording devices. The pericardium was first cut longitudinally. The free edges of the pericardium were then grasped with hemostats at approximately the mid-point between the apex and base of the heart. The pericardial opening was completed by two lateral incisions at right angles to the first and extending from it as far as possible. The four leaflets so obtained were then sutured to the thoracic wall in such a manner to form a cradle capable of supporting the heart in a reasonably normal position. The preparation was now ready for placement of the recording instruments.

2. Parameters. — Before proceeding to a description of the attachment and insertion of the recording transducers and their associated elements, the variables recorded will be stated. In each animal the same phenomena were registered; namely, the aortic blood pressure and the tension changes from three areas of the left ventricle. From these the heart rate and systolic and diastolic blood pressures were determined for each cardiac cycle. The three tension curves recorded with strain gauges were used to determine whether epinephrine produced a more synchronous myocardial relaxation. Aortic blood pressure was recorded with a Statham P23Db Pressure Transducer. A long (21 cm.) metal cannula (I.D. = 1 mm.) was slipped down through the left carotid artery until the tip of the cannula was palpated in the ascending aorta. In each animal an attempt was made to place the
cannula tip in mid-stream just distal to the aortic valves. As a further precaution to avoid blockage of the cannula two openings were provided; one at the extreme tip of the metal tube, the second drilled into the side of the cannula ca. 4 mm. back of the first. A three-way Luer Stopcock was placed between the end of the cannula and the pressure transducer. If it was thought necessary a few ml. of saline were flushed from the stopcock through the cannula to insure a patent passageway.

3. Strain gauge attachment and characteristics. -- The strain gauges used were sutured onto the left ventricle of the dog's heart with size 0 (A-56) Ethicon silk thread (see figure 1). This size was sufficiently heavy so that the gauges were securely held to the myocardium while the danger of cutting through the muscle when fastening the gauges in place was minimized. At the end of each experiment the gauges were carefully checked to make certain they had remained firmly attached. In experiments from which data were collected (Group I and Group II) at no time did the gauges become loosened from the myocardium.

To attach the gauges the following procedure was used. Because of the position of the heart in the pericardial cradle, and the desire to avoid rotating the heart to any measurable extent, the space on the left ventricular surface available for attachment of these gauges was rather limited. Moreover, it was deemed
FIGURE 1

LOCATION OF STRAIN GAUGES AFTER ATTACHMENT TO MYOCARDIUM

(Photograph of a sketch by Mrs. Carol Woike, Department of Surgery, University Hospital, Columbus, Ohio)
absolutely essential that the sutures used for this attachment not
occlude any of the major branches of the left descending coronary
artery as they emerged from or very near the anterior longitudinal
sulcus. Thus, to a considerable degree the gauges were placed in
positions dictated by the peculiar coronary architecture of each
animal. After the approximate location of each gauge had been deter­
mined the silk was threaded through the myocardium. Each suture
was placed into the ventricular muscle at a depth varying from about
3-5 mm. The depth of these sutures is of little importance for the
response of the arches (34); they were placed at this depth only to
insure a firm attachment to the myocardium. The threads for each
gauge were placed from 7-9 mm. apart parallel to each other. In
every instance but one, this distance provided a sufficient amount
of initial tension and stretch of the muscle segment under the re­
spective gauge. In the one situation mentioned, one foot of the gauge
was loosened and another thread inserted at a closer distance to the
secure foot; this remedied the situation and a satisfactory recording
was obtained.

The first gauge attached was the one closest to the apex of the
heart; its orientation was usually parallel, or nearly so, to the
cranial-caudal axis of the dog's body. The second gauge was us­
ually slightly more cranial than the first (1-3 mm.); it was also
nearly parallel to the craniad-caudad axis but this orientation varied a bit more than it did in the case of the first gauge attached. This was so because this second gauge always had to be placed between two major branches of the left descending artery, hence, it was parallel to these branches as a matter of prime importance. The distance between these two gauges also varied widely; a good average estimation would be 6 mm. Again this distance was primarily determined by the branching of the major artery. The third gauge was attached still further toward the base of the heart at a distance lateral to the second and greater than that between the first and second. This length of separation between the second and third gauges was from 1-3 cm; the orientation of the gauge varied considerably, sometimes being nearly parallel to the second, other times being nearly perpendicular to the second. In one experiment the second or middle gauge was nearly perpendicular to the other two. These differences in orientation seemed to have no effect on the recordings obtained as was previously demonstrated by Cotton (7). It was shown that the cardiac response to infusion of catecholamines was little affected by orientation of the gauges.

The strain gauges used in this work were made by O. J. Brodie at the Medical College of South Carolina. These gauges were of the type described by Boniface et al. (35). They were the open type
arch with the distance between the center of their feet approximately
11 mm. The insulation on this type arch is a phenolic resin. The
characteristics of these instruments are described elsewhere (7).
Their uses and limitations are described by Cotton and Bay (34).
In this work it was deemed necessary to calculate the phase angle
shift between these gauges. The gauges were attached to the myo-
cardium as described above. The heart was then removed from the
animal and a cannula with a condom rubber on the end was securely
tied into the aorta. The cannula system was fluid filled and then
attached to a piston pump. Peak to peak tensions were examined in
one of the three gauges and the cycle time determined; phase angle
shift in the other two gauges was calculated to be zero degrees
from 0 to 14 CPS.

Given a reasonable amount of care these arches have proven
to be quite reliable and very sturdy. The original three arches
have been used throughout this work with the only repair being the
addition of a small amount of insulating material to each gauge.
The arches were calibrated several times and the response was
linear at all attenuations used in this work.

The strain gauges were first balanced before attachment to the
myocardium; since the gauges were elongated after being sutured
to the myocardium it was necessary to again adjust the current flow
to zero. This was accomplished by stopping the heart for a brief period of time by stimulation of the left vagus nerve. For this purpose a monophasic pulse was applied with standard classroom platinum electrodes at a frequency and intensity which varied slightly from dog to dog. It was sometimes possible to balance the three gauges with only one cessation of the heart; however, it more often required two or three heart stoppages to balance all three gauges. In no case was the vagus stimulated for longer than 30 seconds without permitting the heart to resume its beat. If during this time the gauges were not balanced we waited 4-6 minutes and stimulated the nerve again. As mentioned above the gauges were always balanced after the third period of cardiac inactivity. This balancing procedure was followed in both groups of animals.

Five to ten minutes after the gauges were sutured to the myocardium, the dogs were heparinized; 0.5 ml./Kg. of Panheparin was used for this purpose (Abbott Laboratories, 1000 units/ml.). The next step was the insertion of the cannula for measurement of aortic blood pressure; this procedure was previously described.

B. Instrumentation

The recorder used was a Recording Oscillograph, Type S-14C, Hathaway Instrument Co., Denver, Colorado. Hathaway Oscillograph Galvonometers were used; the characteristics of these galvonometers were the same for both blood pressure and tension
gauges. Their D.C. sensitivity is 330 mm./ma./m., frequency response is 180 CPS. The response of the three galvanometers was flat up to 110, 116, and 120 CPS respectively. The photographic recording paper used was DuPont Lino-Writ 2, Type W, Spec. #124, (E. I. DuPont DeNemours & Co., Wilmington 98, Delaware).

Blood pressure was recorded with a Statham transducer as mentioned previously. In Group two the output from the amplifier was split so that the pressure could be monitored on a direct writing recorder; the direct writing recorder used was an Ink Writing Oscillograph, Model 5-C, Grass Instrument Co. The output from the amplifier was connected to a Grass 5P5 Input Cable; this was coupled to the Low-Level D.C. Preamplifier of the recorder.

The strain gauges served as one arm of a Wheatstone bridge; the remainder of the bridge was constructed in the department. For this purpose 120 ohm (±1%) wire wound precision resistors (I.R.C.) were used; temperature coefficient of the resistors is 0.00 25%/°C. The output from the gauges as well as from the Statham transducer was fed into a Consolidated Carrier Amplifier (Type 1-118), Consolidated Engineering Corporation. The stimulator used to stop the heart so that the gauges could be balanced was an SD5 Stimulator (Grass Instrument Co.).
C. Experimental procedure

As stated above 21 animals were used in this work. Of these, seven were used in preliminary experiments in which no data suitable for final analysis were collected. These seven animals served to perfect the experimental procedure; this, of course, includes the surgical manipulation, the method of attachment of the strain gauges, etc. It was originally planned to suture these three gauges to the right ventricle, since a much larger area is exposed here than is available on the left ventricular surface. The first three dogs were sacrificed in an attempt to suture these gauges to this area. Because of the longitudinal movement of the right ventricular surface when the pericardium was slit the placement of three gauges was extremely difficult. It was especially trying when one attempted to place the sutures a uniform distance apart for the attachment of a particular gauge. Because of this it was frequently impossible to attach the gauges properly and record isometrically the tension changes of the right heart. This effort was abandoned and on the subsequent four animals the method of attachment to the left ventricle was advanced to a satisfactory state.

1. Group 1.--The procedure in a first group of animals was as follows: at intervals of either five or ten minutes two control records were taken; in some cases a third control was obtained. Immediately
after the last control record the experimental drug was given. In this group one ml. of a 1:50,000 or 1:25,000 solution of Suprarenin (Synthetic Epinephrine, Winthrop Laboratories, New York 18, N.Y.) was injected directly into the superior vena cava. The experimental drug was diluted with saline just prior to its injection. Records were obtained every 15 or 20 seconds after the first appearance of the drug effect until its subsidence some two to four minutes later. Thus, five to eight records of the epinephrine effect upon the myocardium were taken. Another control record was taken 10-15 minutes after the drug had been injected. Both the control and experimental recording time was from six to eight seconds. In all cases the paper speed was 10 in./second; the time lines marked 0.01 second. This recording procedure was followed in six animals. Because of the extremely long records obtained the recording procedure was slightly modified in the second group of animals.

2. Group II. --Control one and control two were taken at five minute intervals. Immediately after two, 1 µg./Kg. of the drug was injected directly into the superior vena cava. The effect of the drug was now recorded at two definite points of the heart's response. The maximum effect was recorded for a period of 15-18 seconds; the declining portion of the response was recorded for about 12-15 seconds. The declining phase occurred within one to two minutes
after the Suprarenin was injected. The maximum and declining effects of the drug were indicated by recording aortic blood pressure on a direct writing recorder; by thus monitoring the response of the pressure it was possible to significantly reduce the volume of data to be analyzed and at the same time get sufficient information on the effect of the drug. A third control record was taken from 10-12 minutes after the drug had been administered; the recording time for the controls lasted about eight seconds each.

D. Analysis of records

After each experiment the blood pressure transducer was calibrated. Systolic and diastolic pressures were measured in each cycle; in some instances the systolic pressure went off scale during the peak phase of the response and so in these cases the systolic pressure is given only as being greater than the maximum value in the calibration curve. Heart rate was likewise measured in each cycle; the cycle length was taken from the beginning of the rising phase of the aortic pressure curve to the same point in the succeeding pressure curve.

The analysis of the strain gauge curves required the use of a magnifying lens. To establish the more or less synchronous activity of the myocardium under the influence of epinephrine, the tension curves were divided into four parts. Hereafter in this description
we will talk of only one curve, remembering that all three were treated in exactly the same fashion.

As just mentioned the curve was divided into four distinct phases (figure 2). These phases will first be described and a short-hand way of discussing them will be introduced. The first phase consists of the time interval which begins at the point where the tension curve leaves the base line and ends at the peak tension of that particular gauge; this period of time will henceforth be referred to as Zero-Peak. The second phase begins at the peak tension and ends at the closure of the aortic valves - the incisura of the pressure curve was used as the indicator of valve closure; this phase will now be signified as Peak-V.C. The third phase of the tension curve assumes the prime role in the determination of whether or not epinephrine increases myocardial synchronization; this period commences at valve closure, its end point assumes the preponderant role in this experimental work. This point was determined as follows: the slope of the isometric relaxation curve was approximated as nearly as possible using a straight edge; a line was then drawn which represented the average relaxation rate of the particular segment of the myocardium to which the gauge was attached. The point at which the tension curve deviated from this line was designated the end point of the third phase. This phase is termed the period of Rapid
FIGURE 2

TRACE OF A CONTROL SEGMENT
OF RECORD (EXP. 5/9/62)

(a = O - Peak, b = Peak - V.C., c = Rapid Relaxation,
d = Slow Relaxation, e = Total Contraction Time)
Relaxation and will be abbreviated R. R. The final phase of the tension curve begins at the point just described and ends at the beginning of relative ventricular quiescence. This period of time is termed Slow Relaxation and quite naturally abbreviated S. R.

Of the four periods determined the end point of phase four was usually the most troublesome; this was especially true at rapid heart rates and so in some instances it was not at all possible to delineate this phase. The first and second phases were added together and termed Total Contraction Time and abbreviated T. C. T.

As was stated, the major consideration in this work will be given to the third period described above, i.e., R. R. The other periods of activity mentioned will be used only to confirm the effects of epinephrine described by other authors, i.e., the synchronization of myocardial units during ventricular systole. For this reason the periods of O-Peak and Peak-V.C. were not measured in every set of tension curves; rather, a spot check was made at every third or fourth cardiac cycle. It was occasionally impossible to determine the instant of valve closure; however, it was still possible to determine the end point of R. R. and as will be shown next this is the major consideration.

The alteration of myocardial synchronization by epinephrine was determined by measuring the synchronization of the end points
of R. R. The time differences between these end points were subtracted one from the other and an average value established; this figure is hereafter designated the average time difference ($\Delta T$).

The larger the value the less synchronous, the smaller the value, the more synchronous was the myocardial relaxation. This problem of synchronization, no-synchronization could also be looked at as one involving splay of the relaxation curves of the three gauges. The more splay the less the synchronization. A superimposition of the three curves would mean that the highest possible degree of muscular synchronization had been achieved. The results of these experiments will be presented in the manner just described, i.e., a demonstration of the decreased average time difference between the three gauges and a graphic presentation of the ability of epinephrine to cause a superimposing of one tension curve on the other.
III. RESULTS

A. Effect on cycle length

The typical alterations of cycle length were obtained in these experiments. Tables 1 and 2 depict these results from two separate experiments. The shortening of systole is quite significant in both tables. This amounts to approximately 86 msec. in table 1 and to about 56 msec. in table 2. Note that this effect is observed at the peak response of the myocardium to epinephrine. The figures for the declining phase of the epinephrine response in table 2 are presented to demonstrate that the values are approaching the control level. In connection with these two tables it is noteworthy to mention the effect of epinephrine on the duration of diastole. This is of major importance for the maintenance of an adequate stroke volume at rapid heart rates. In table 1 the average control value for the sum of R.R. and S.R. is 92 msec. while the average value for the same period at the peak effect of epinephrine is 61 msec. Less effect is observed in the experiment reported in table 2; the values are 92 and 83 msec. respectively for control and experimental phases. More significant, however, is the constancy of the control diastolic interval during the epinephrine effect irrespective of an increase in heart rate. These data are summarized in table 3. In one experiment (4/9/62) during the peak response to epinephrine
TABLE 1

CONTROL AND EXPERIMENTAL TIMES FOR PHASES OF CYCLE - TIMES IN MSEC.

Experiment - 11/21/62

Control

Cycles 1, 5 and 9

<table>
<thead>
<tr>
<th></th>
<th>O-Peak</th>
<th>Peak-V.C.</th>
<th>T.C.T.</th>
<th>R.R.</th>
<th>S.R.</th>
<th>ΔT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gauge 1</td>
<td>161</td>
<td>70</td>
<td>231</td>
<td>49</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Gauge 2</td>
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<td>55</td>
<td>222</td>
<td>46</td>
<td>41</td>
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<td>Gauge 3</td>
<td>181</td>
<td>43</td>
<td>224</td>
<td>56</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Gauge 1</td>
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<td>69</td>
<td>232</td>
<td>51</td>
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<td></td>
</tr>
<tr>
<td>Gauge 2</td>
<td>167</td>
<td>56</td>
<td>223</td>
<td>50</td>
<td>34</td>
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<td>46</td>
<td>224</td>
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<td></td>
</tr>
<tr>
<td>Gauge 1</td>
<td>167</td>
<td>67</td>
<td>234</td>
<td>50</td>
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<td>224</td>
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</tr>
</tbody>
</table>

Epinephrine (Peak)

Cycles 1, 5 and 8

<table>
<thead>
<tr>
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<th>O-Peak</th>
<th>Peak-V.C.</th>
<th>T.C.T.</th>
<th>R.R.</th>
<th>S.R.</th>
<th>ΔT</th>
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<td>23</td>
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<td>Gauge 1</td>
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<td>2</td>
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<td>Gauge 3</td>
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<td>62</td>
<td>144</td>
<td>26</td>
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</tr>
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</table>
TABLE 2
CONTROL AND EXPERIMENTAL TIMES FOR PHASES OF CYCLE - TIMES IN MSEC.

Experiment - 4/9/62

Control
Cycles 3 and 5

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<td>142</td>
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<td>166</td>
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Epinephrine (Peak)
Cycles 9 and 12

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Epinephrine (Decline)
Cycles 6 and 11

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<td>37</td>
<td>206</td>
<td>43</td>
<td>47</td>
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<td></td>
</tr>
</tbody>
</table>
TABLE 3

RELATIONSHIP BETWEEN TOTAL CYCLE LENGTH, T.C.T., AND DURATION OF DIASTOLE - TIMES IN MSEC.

(Average times obtained from phases in tables 1 and 2)

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Total Cycle Length</th>
<th>T.C.T.</th>
<th>Duration of Diastole</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/9/62</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>422</td>
<td>204</td>
<td>218</td>
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<tr>
<td></td>
<td>416</td>
<td>205</td>
<td>211</td>
</tr>
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<td>Epinephrine</td>
<td>365</td>
<td>150</td>
<td>215</td>
</tr>
<tr>
<td></td>
<td>365</td>
<td>147</td>
<td>218</td>
</tr>
<tr>
<td>11/21/62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>370</td>
<td>226</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>377</td>
<td>226</td>
<td>151</td>
</tr>
<tr>
<td></td>
<td>379</td>
<td>227</td>
<td>152</td>
</tr>
<tr>
<td>Epinephrine</td>
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<td>134</td>
</tr>
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<td></td>
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<td>195</td>
</tr>
<tr>
<td></td>
<td>333</td>
<td>144</td>
<td>189</td>
</tr>
</tbody>
</table>
the duration of diastole is maintained near the control value; moreover, in the other group of data (11/21/62) it is shown that in spite of an increase in heart rate from an average control level of 160 beats/min. to an average experimental value of 200 beats/min. the average duration of diastole is increased by approximately 23 msec. At the most rapid heart rate (219 per min. - cycle length 274 msec.) the effect of epinephrine on diastole is such as to permit only a 15 msec. shortening of this period.

Thus, it has been verified by these experiments that epinephrine shortens systole and preserves the diastolic duration so that filling is sufficient to maintain a near normal stroke output. The data in tables 1 and 2 also demonstrate that epinephrine causes the peak tension in each gauge to be attained more synchronously. This is evident by the clustering of the Peak-V.C. times when the drug is exerting its maximum effect on systolic blood pressure.

B. Effect on synchronization of myocardial relaxation

In all experiments epinephrine caused a more synchronous behavior of the myocardium during the process of relaxation. This result was determined at the peak response of the ventricle (as judged by the maximum increase in systolic blood pressure) to the drug. A minimum increase in systolic blood pressure of 30 mm. Hg. was arbitrarily designated as being requisite before the effect
of the drug was considered adequate. If the dose of epinephrine employed failed to elicit this minimum increase in systolic blood pressure the data were not analyzed. In the seven experiments completely analyzed (see tables 4 and 5, figure 3) the average \( \Delta T \) values were 8.6 msec. for controls 1 and 2 and 4.4 msec. for the peak response to epinephrine.

The pattern of recovery took two forms. In the one case the recovery was exhibited as a gradual restoration of the \( \Delta T \) to its pre-epinephrine control level; i.e., the synchronization of the myocardial units gradually decreased and approached the control levels (see figure 3, 11/19/62, 11/21/62, and 4/16/62; also table 4). In the second general pattern of recovery there was a marked decrease in synchronization as evidenced by the increase in \( \Delta T \) during the restoration of blood pressure to its control level. For this response see table 5 (Epinephrine, decline) and figure 3 (11/26/62, 4/9/62, 5/9/62, and 12/7/62).

A consecutive beat to beat correlation of heart rate, systolic blood pressure, and \( \Delta T \) is presented in figure 4. In this experiment the recovery from the epinephrine effect falls into the second category mentioned above.

Because of the possibility that these changes in synchronization may have occurred only as a result of the chronotropic effect of
## TABLE 4

COMPOSITE DATA OF EXPERIMENTS COMPLETELY ANALYZED - AVERAGE VALUES

<table>
<thead>
<tr>
<th></th>
<th>Experiment - 4/16/62</th>
<th></th>
<th>Experiment - 11/19/62</th>
<th></th>
<th>Experiment - 11/21/62</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SP/DP</td>
<td>H.R.</td>
<td>ΔT ± s.d.</td>
<td>SP/DP</td>
<td>H.R.</td>
</tr>
<tr>
<td><strong>Control 1</strong></td>
<td>107/72</td>
<td>113</td>
<td>16 ± 2.6</td>
<td>93/80</td>
<td>128</td>
</tr>
<tr>
<td><strong>Control 2</strong></td>
<td>114/80</td>
<td>128</td>
<td>12.7 ± 1.4</td>
<td>92/81</td>
<td>129</td>
</tr>
<tr>
<td><strong>Epinephrine (Peak)</strong></td>
<td>170/120</td>
<td>134</td>
<td>7.5 ± 2.4</td>
<td>123/106</td>
<td>126</td>
</tr>
<tr>
<td><strong>Epinephrine (Decline)</strong></td>
<td>137/92</td>
<td>120</td>
<td>9.2 ± 3.9</td>
<td>96/78</td>
<td>113</td>
</tr>
<tr>
<td><strong>Control 3</strong></td>
<td>129/85</td>
<td>128</td>
<td>12.8 ± 1.4</td>
<td>92/80</td>
<td>122</td>
</tr>
</tbody>
</table>

(Values represent mean ± standard deviation)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SP/DP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>H.R.</strong></td>
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</tr>
<tr>
<td><strong>ΔT±s.d.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control 1</strong></td>
<td>118/94 142 4.3 ±1.6</td>
<td>119/99 101 8.1 ±1.9</td>
<td>98/81 162 8.7 ±3.0</td>
<td>121/98 175 6.4 ±1.4</td>
</tr>
<tr>
<td><strong>Control 2</strong></td>
<td>114/90 138 4.2</td>
<td>125/104 107 8.3</td>
<td>95/77 164 8.3</td>
<td>127/101 160 7.0</td>
</tr>
<tr>
<td><strong>Epi. (Peak)</strong></td>
<td>148/118 164 2.1 ±0.6</td>
<td>160/142 169 5.2 ±1.1</td>
<td>131/90 191 3.1 ±1.0</td>
<td>175/140 168 2.9 ±1.2</td>
</tr>
<tr>
<td><strong>Epi. (Decline)</strong></td>
<td>134/105 138 5.4 ±2.0</td>
<td>140/129 129 18.3 ±1.0</td>
<td>116/86 158 14.2 ±3.4</td>
<td>129/99 155 15.9 ±3.0</td>
</tr>
<tr>
<td><strong>Control 3</strong></td>
<td>114/89 141 4.1 ±1.4</td>
<td>115/88 106 9.4 ±1.3</td>
<td>109/90 172 13 ±3.1</td>
<td>130/103 166 8.6 ±1.8</td>
</tr>
</tbody>
</table>
FIGURE 3

\[ \Delta T \] BETWEEN GAUGES FOR ALL EXPERIMENTS -

CONTROLS, EPINEPHRINE (PEAK), AND

EPINEPHRINE (DECLINE) AS

INDICATED

(Average values for consecutive cardiac cycles;
Controls = 9 - 15 cycles, Epinephrine = 12 - 18 cycles)
FIGURE 4

BEAT BY BEAT CORRELATION OF SYSTOLIC BLOOD PRESSURE, HEART RATE, AND $\Delta T$

(Average $\Delta T$ for each Experimental Condition Indicated by Solid Line)
<table>
<thead>
<tr>
<th>HEART RATE</th>
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<th>150-</th>
<th>200-</th>
<th>250-</th>
<th>300-</th>
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</thead>
<tbody>
<tr>
<td>SBP-mm Hg</td>
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<td>125-</td>
<td>150-</td>
<td>175-</td>
<td>200-</td>
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<td>ΔT-msec</td>
<td>5-</td>
<td>10-</td>
<td>15-</td>
<td>20-</td>
<td>25-</td>
</tr>
</tbody>
</table>

control 1  control 2  epi(peak)  epi(fall)  control 3

CONSECUTIVE PULSES

11/26/62
epinephrine on the sinoauricular node the ratio of $\Delta T$ to total cycle
duration was calculated (table 6). In all cases but one (5/9/62) this possibility seems to be eliminated and the effect of the drug on synchronization appears to be either on the contractile elements or on the conduction system of the heart.

Finally, the reduced splay in the relaxation curves of the three strain gauges when the epinephrine action is at its peak is depicted in figure 5. Here the vertical line represents valve closure and the curves are traces of the relaxing myocardium as recorded by the gauges. During the phase of rapid relaxation the curves of the control recordings are separated to a certain extent. With epinephrine this splay is decreased and the curves are nearly superimposed on one another.
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
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<td>0.0252</td>
<td>0.0301</td>
<td>0.0102</td>
<td>0.0235</td>
<td>0.0186</td>
<td>0.0136</td>
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<tr>
<td>Control 2</td>
<td>0.0172</td>
<td>0.0244</td>
<td>0.0271</td>
<td>0.0097</td>
<td>0.0227</td>
<td>0.0186</td>
<td>0.0148</td>
</tr>
<tr>
<td>Epinephrine (Peak)</td>
<td>0.0096</td>
<td>0.0147</td>
<td>0.0168</td>
<td>0.0058</td>
<td>0.0098</td>
<td>0.0081</td>
<td>0.0147</td>
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<tr>
<td>Epinephrine (Decline)</td>
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<td>0.0375</td>
<td>0.0410</td>
<td>0.0394</td>
</tr>
<tr>
<td>Control 3</td>
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<td>0.0185</td>
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<td>0.0096</td>
<td>0.0373</td>
<td>0.0238</td>
<td>0.0166</td>
</tr>
</tbody>
</table>
FIGURE 5
SUPERIMPOSITION OF TENSION CURVES DURING RELAXATION (VERTICAL LINE REPRESENTS INCISURA)
IV. DISCUSSION

A. Methodology

1. Determination of synchronization.--The method of data collection permitted two possibilities for the demonstration of a more synchronous relaxation with epinephrine. The method chosen was the measurement of the average time difference (ΔT) at which the tension recorded by the three strain gauges deviated from a point. The point selected was established by determining the instant that the tension curve of each of the three gauges deviated from the straight line representing the average relaxation rate of the segment of myocardium under the respective gauge.

Alternatively, the maximum time difference between any two of the gauges could have been used as indicative of a more synchronous unit behavior. In the theoretically ideal situation which would include the relaxation curves of every individual unit, the determination of maximum time difference would probably be most satisfactory since this time would then be that difference between the most rapidly relaxing unit and the slowest relaxing unit. Changes in this time would be an excellent indication of increased or decreased synchronization. Quite obviously, this situation is not nearly approximated when only three curves are available.
Since only three curves are available for analysis it was thought that an average value would be more meaningful and more inclusive of the actual alterations occurring in these units. Moreover, it was noted occasionally that the maximum time difference shifted from one set of gauges to another indicating possible changes in impulse propagation. Although this could not be stated with any degree of certainty from the data collected, it must be considered a possibility. For these reasons then, the $\Delta T$ was selected as a more accurate measurement. In fact, the value of $\Delta T$ was a constant fraction of the maximum time difference and so tended to minimize unavoidable errors of measurement in this analysis.

2. Consideration of valve closure as commencement of relaxation.

In the discussion above allusion is made to the end point of the phase designated in this work as R.R. It now seems necessary to describe considerations which led to the selection of aortic valve closure as the initial moment of relaxation as opposed to the peak tension recorded by the gauges. In this respect the factors which determine ventricular wall tension must be considered and so the Law of Laplace is necessarily introduced. Although not strictly applicable to the ventricle this law ($T=\rho R$) serves as a guideline so that deductions can be made regarding the
relationship between ventricular wall tension, intraventricular pressure, and the radius of the chamber.

The wall tension required to maintain a given level of intraventricular pressure decreases as the radius of the ventricle diminishes during ejection. Thus, it is probable that concomitantly with a continuing contraction of many myocardial units the ventricular wall tension falls during the late phase of ejection as a result of a decrease in ventricular size. Although valve closure is determined by several factors opposing contraction, i.e., myocardial viscosity, interfascicular tension, as well as the degree of relaxation, it is most likely that the initial tension fall beginning at peak tension is influenced more by decreased radius, increased viscosity, and increased interfascicular tension than it is by the actual process of ventricular relaxation. For this reason closure of the aortic valves as indicated by the incisura was selected as the beginning of the rapid relaxation phase. In addition to the above mentioned factors, there was a two-phase cycle representing the fall in tension in most of the strain gauge recordings. The first and most rapid portion of the tension fall preceded valve closure; the second portion became evident after valve closure and so indicated that the decrease in tension now observed represented a new balance of forces.

The impossibility of stating with confidence that valve closure represents the beginning of relaxation in all myocardial elements
is recognized. In reality, this is most certainly not the case. Because it is experimentally impossible to determine the beginning of relaxation in all myocardial units the incisura was selected as an average starting point with admitted inaccuracy. In the determination of synchronization the precise moment of valve closure is not of great importance since it only represents an arbitrarily selected zero point.

B. Results

1. Confirmation of previous work.--These experiments confirm the alterations observed by others (33, 36, 37) which epinephrine and/or sympathetic stimulation produce on the cardiac cycle. Thus, the duration of systole is abbreviated and the isometric relaxation phase (essentially corresponding to R. R.) is shortened. Also confirmed by this work is the more synchronous contraction of the myocardium as reported by Randall and Kelso (33). They obtained this result by stimulation of the stellate ganglion. Sarnoff et al. (37) discuss the effects of synchronicity on stroke work. They varied the synchronicity of ventricular contraction by changing the site of pacing without altering the norepinephrine background. They state that a less synchronous ventricular contraction produced a decrease in external stroke work at any given end-diastolic pressure. However, no data on this work is presented in the paper.
The phenomenon of synchronous ventricular contraction is later discussed by Sarnoff and Mitchell (38). They present data which indicate that a more synchronous ventricular contraction does indeed cause a greater stroke work by altering the rate of development of tension in the myocardium. They also mention that the \( VFC_{LV} \) would be shifted to the right if the pacing were changed from atria to ventricle; they have obtained evidence which indicates that this is precisely what occurs (39). Asynchronism of ventricular contraction is stressed by Angelokos and Hegnauer (40) as responsible for the decreased contractility of hypothermic dog hearts. Myocardial tension curves were recorded and under hypothermia displayed a decrease in peak tension as well as a decreased rate of isometric contraction and relaxation. This asynchronism is attributed in part to decreased conduction velocity.

The attainment of peak tension is used as an indicator of synchronicity in the present work. If this is a reliable guide, the clustering of Peak - V. C. times of the tension curves at the peak response to epinephrine certainly indicates a more synchronous contraction of the myocardial units.

2. **Synchronization of relaxation.** - With the instrumentation used in these experiments it was demonstrated without doubt that epinephrine does indeed cause a more synchronous relaxation of
the myocardial units as indicated by a decrease in the average time difference ($\Delta T$) between the three strain gauges. This effect occurred in all animals and was quite pronounced at the peak response of the myocardium to epinephrine. The increase in synchronization is believed to be partly responsible for the preservation of the diastolic interval, thus permitting adequate time for ventricular filling to occur. In both these experiments a significant increase in heart rate resulted from epinephrine (from ca. 140-164 in one case, from 160-200 in the second), nevertheless the duration of diastole was either slightly increased or maintained at the control level. It is probable then, that the increase in synchronization is in part responsible for the preservation of diastole up to heart rates of about 200 beats/minute. It must be remembered that although the changes in synchronization amounted to only 2-5 msec. in these experiments, the region for attachment of the gauges to the myocardium was largely limited to the anterior aspect of the left ventricle. For technical reasons it was not possible to explore the alterations in $\Delta T$ which would occur if the gauges had been more widespread in their distribution; however, it can be assumed that these values for $\Delta T$ would be greater if the posterior ventricular surface, and particularly that region closest to the base of the heart, were included in the investigation. Present evidence
indicates that the activation of the epicardium proceeds from apex to posterior basal portions of the left ventricle (25, 41, 42, 43).

It is possible that the alterations in $\Delta T$ with epinephrine were solely a consequence of the chronotropic effect of the drug. If this were so then a given percentage decrease in total cycle length would be accompanied by a similar percentage decrease in $\Delta T$ and the ratio of $\Delta T$/total cycle length would be a constant. That this is not so is shown in table 3; with but one exception (5/9/62) this ratio is markedly decreased at the peak response of the myocardium to epinephrine. This table clearly demonstrates the lack of dependence on heart rate for the manifestation of an increased myocardial synchronization. In this connection it might also be mentioned that an increase in synchronization can occur without a concomitant increase in heart rate (table 4, experiment 11/19/62).

The recovery of the myocardium from the epinephrine effect on synchronization seems to occur in one of two ways. One mechanism could be nothing more than the utilization of the injected drug and the consequent subsidence of its effect on the muscle; this implies a gradual return of the altered synchronization to its control level. The second mechanism would involve a reflexly mediated process with overshoot of the restoration response and a resultant value of $\Delta T$ greater than the control figure. The return to control levels would then depend on subsidence of the reflex as
well as destruction of the injected drug. The reflex mechanism most likely involved would originate in the carotid sinus and would involve an increase in parasympathetic discharge and/or a decrease in sympathetic discharge to the myocardium.

The effect of vagal stimulation upon the ventricular myocardium is not established with certainty. It has been shown that vagal stimulation has no negative inotropic effects on the ventricular myocardium (37, 44, 45). These results were obtained in both dogs and man. However, a negative inotropic effect of vagal stimulation on the myocardium has also been reported (46, 47). Peterson (46) elicited his results by stimulation of the carotid sinus nerve thus simulating an elevated arterial pressure. The apparent lack of vagal distribution to the ventricular myocardium would tend to support the concept that indeed there is no direct effect of vagal stimulation on the ventricular myocardium.

The process of recovery could be attributed to a decrease in normal sympathetic tone as a result of pressoreceptor stimulation. That carotid sinus stimulation by elevated arterial pressure can induce a decrease in sympathetic activity has been adequately demonstrated (48, 49). The effects of altered vagal tone are manifested by changes in atrial contractility. It must be acknowledged that it is possible that there is indeed only one pathway of recovery from
the effects of epinephrine. The dual mechanism of recovery would then be attributed to the fact that the recordings were not continuous and so part of the epinephrine effect was lost.

The decrease in splay elicited by epinephrine is demonstrated in figure 5. This figure in reality is a plot of tension disappearance vs. time for each of the three gauges. Since the three curves originate at the same point in time the ordinate represents the percent fall in tension for each unit of myocardium - in most cases a different scale must be applied to each curve since the initial tension on each strain gauge is not equal. In one experiment (11/19/62) scales were constructed for the tension curves and marked off in percentage of total tension - 100% tension is at incisura. Two arbitrary times were selected and the percentage of the tension dissipated at these times was estimated for each myocardial unit. At the first time chosen the values were as follows: 50%, 58%, and 64% for controls; with epinephrine the values were 76%, 80%, and 74%. At the second time chosen the control values were 74%, 78%, and 83%, while those with epinephrine were 92%, 92%, and 93%. In this example the increased synchronization of the myocardium is demonstrated not by determining time differences but by analysis of the curves at arbitrarily selected times for the proportion of tension dissipated. It is shown that when the myocardium is
stimulated by epinephrine the fraction of tension lost in each unit at a given time approaches the same value. This is certainly a more synchronous relaxation of the myocardial units.

C. General considerations

The importance attributed to the relaxation process in ventricular filling has been mentioned quite extensively in the introduction to this paper. Epinephrine has been shown to increase ventricular diastolic suction and to decrease the impedance with which the ventricle resists filling. It was demonstrated in this work that epinephrine also acts to preserve the diastolic interval at rapid heart rates and so permits adequate filling to take place. The increased synchronization of relaxing units is believed to play an important role in this process. This increased synchronization could affect ventricular filling in one of two situations: at rapid heart rates a more rapid relaxation would maintain a nearly normal stroke output and so contribute to increase the cardiac output; at slower heart rates a longer than normal time interval would be available for the ventricle to fill and in this manner the filling of the ventricle would increase. This increase in filling is necessary to maintain an elevated stroke output which would occur as a result of the increase in myocardial contractility elicited by epinephrine injection or by sympathetic stimulation. Thus, the two mechanisms by way of which the heart is capable of responding to an increased
demand necessitates, in one case, the maintenance of a normal stroke output and, in the other case, an increase in stroke output. In both these instances the increase in synchronization elicited by epinephrine and the consequent prolongation of diastole must play a vital role.

It now remains to ascribe an explanation to this increased synchronization of myocardial units. In this respect we will discuss the specificity of this effect to the process of relaxation. The possibilities of a more synchronous relaxation have been mentioned by other workers (15, 32) and it is more or less implied that this synchronization is manifested only during the process of relaxation. However, in this work and in others (33, 50) it has been demonstrated that sympathomimetic amines (epinephrine and levarterenol) affect the myocardium so as to cause a more synchronous contraction. The problem then arises as to whether the synchronization during relaxation is a specific effect or whether it is in fact a continuation of a process initiated during systole. The possibility definitely exists that the improved synchronization elicited during relaxation is in fact initiated at the onset of the contractile period and is continued throughout the period of diastole.

If this is so then the alteration of $\Delta T$ at the commencement of systole should approximate that value obtained at the end of R. R.
both in the control and experimental periods. To establish this as a possible explanation for the results obtained, the \( \Delta T \) at the initiation of systole was calculated in three experiments (for technical reasons it was not possible to calculate this value for all experiments). These results are presented in table 7. They strongly indicate that the effect of epinephrine on the process of myocardial relaxation is in reality a continuation of its effect during systole.

It is postulated that epinephrine via its effect on conduction velocity (51, 52) produces a more synchronous initiation of contraction in the myocardium and that the manifestation of this more synchronous behavior during systole is a more synchronous relaxation of the myocardial units.
TABLE 7

COMPARISON OF $\Delta T$ AT INITIATION OF CONTRACTION WITH $\Delta T$ AT END OF RAPID RELAXATION - TIMES IN MSEC.

<table>
<thead>
<tr>
<th></th>
<th>$\Delta T$ (Systole)</th>
<th>$\Delta T$ (Diastole)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experiment - 11/21/62</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 1</td>
<td>6.6</td>
<td>6.4</td>
</tr>
<tr>
<td>Control 2</td>
<td>7.1</td>
<td>6.4</td>
</tr>
<tr>
<td>Epinephrine (Peak)</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Experiment - 4/9/62</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 1</td>
<td>4.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Control 2</td>
<td>4.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Epinephrine (Peak)</td>
<td>3.8</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Experiment - 5/9/62</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 1</td>
<td>4.5</td>
<td>8.1</td>
</tr>
<tr>
<td>Control 2</td>
<td>4.4</td>
<td>8.3</td>
</tr>
<tr>
<td>Epinephrine (Peak)</td>
<td>2.3</td>
<td>5.2</td>
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</tbody>
</table>
V. SUMMARY AND CONCLUSIONS

An attempt was made to demonstrate an effect of epinephrine on the synchronization of myocardial units during ventricular relaxation. The experiments were performed on open chest mongrel dogs. Myocardial tension was recorded by 3 strain gauges sutured onto the left ventricle; the degree of synchronization was determined by calculating the average time difference ($\Delta T$) between the three tension curves.

With this method it was unequivocally demonstrated that epinephrine causes a more synchronous relaxation of the ventricular units. For the area of the ventricle under study the increase in synchronization produced a 35-60% decrease in the control $\Delta T$. This increase in synchronization contributed 2-5 milliseconds to the preservation of the rapid filling period. It is believed that the inclusion of the entire ventricle in this study would significantly raise this value so that the altered synchronization could play an important role in the maintenance of an adequate filling period at rapid heart rates.

This effect of epinephrine on synchronization is not limited to diastole and thus is not specific to the relaxation process. The data indicated that the altered synchronization is evident at the beginning of the tension rise. It must then be concluded that the
effect on relaxation is a manifestation of a phenomenon common to the entire contraction process.

The increase in synchronization is most probably a consequence of the alterations in conduction velocity elicited by epinephrine.
BIBLIOGRAPHY


I, Lawrence Thomas Paul, was born in Wiconisco Township, Pennsylvania on June 17, 1933. I received my secondary education in the public school system at Lykens, Pennsylvania. I entered Muhlenberg College in 1951 and was awarded the degree B.S. in June, 1955.

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I will continue my research training in Physiology with Dr. Heinz Pieper as a post-doctoral fellow sponsored by the Bremer Foundation.