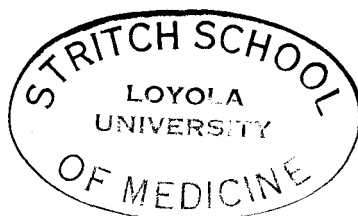


SUBENDOCARDIAL HEMORRHAGE PRODUCED BY STIMULATION
OF CARDIAC SYMPATHETIC NERVES

by

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A Thesis Submitted to the Faculty of the Graduate School
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the Requirements for the Degree of
Master of Science

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BIOGRAPHY

Michael P. Kaye was born in Chicago, Illinois February 10, 1935. He was graduated from St. Ignatius High School, Chicago in June, 1952. In September of the same year, he entered St. Louis University, Missouri. Here, he received his pre-medical training.

He enrolled in the Stritch School of Medicine of Loyola University, Chicago in 1955 and during his sophomore year in Medical School he started work in the Graduate School of Loyola University.

At the present time, he has received an appointment to a surgical internship at the University of Minnesota, in Minneapolis.

INTRODUCTION

Within the past few years, it has been demonstrated that stimulation of the cardiac sympathetic nerves may cause considerable augmentation of the force of myocardial contraction. (1-5) This augmentor action has been found to be most prominent when the left cardiac sympathetic nerves are stimulated; whereas, stimulation of the cardiac nerves on the right side induces more prominent changes in the heart rate. Further experiments have demonstrated that experimental hypertension may be induced in the open chest dog and maintained by continuous, low frequency stimulation of the cardiac sympathetic nerves for periods up to eleven hours. (5)

Since the sympathetic innervation of the heart is normally functional in intact animals and known connections exist between the higher levels of the central nervous system and the sympathetic outflow to the heart, it has been postulated that this mechanism may participate in the induction of neurogenic hypertension of emotional or psychic origin. (5)

With this knowledge as a background for our work, we undertook the project of developing a method by which we would be able to maintain this hypertensive state for more prolonged periods. A technique for implantation of a bipolar electrode on either stellate ganglion and subsequent closure of the thorax was developed. This having been accomplished, a series of experiments was performed with the animals under a hypnotic dose of pentobarbital sodium to determine if the responses would be similar to those obtained in an open

chest animal and to determine how long this stimulation could be maintained before the preparation deteriorated.

Because of a pulsus alternans and electrocardiographic changes which developed in the first experiment in which this new technique was used, the heart was removed and examined after a period of nine hours—during the experiment the animal was maintained under anesthesia and the left stellate ganglion continuously stimulated at a rate of three per second.

Upon examination of the heart, a number of small subendocardial hemorrhages were noted in the left ventricle situated mainly over the posterior papillary muscle. Microscopic examination of section taken through the involved areas confirmed that these hemorrhages were confined to the subendocardial area.

Because of the electrocardiographic changes and the finding of subendocardial hemorrhages at postmortem examination, we began to further investigate the possible role of the sympathetic cardiac nerves in the production of these hemorrhages.

It was pointed out that these lesions were distinctly reminiscent of those observed following hemorrhagic hypotension. (6,7) The similarity was puzzling in so far as in these two procedures the hemodynamic events are so different. On the other hand, certain physiological and biochemical changes are found to be similar in both procedures. Indeed, they have in common a massive excitation of the sympathetic terminations in the myocardium as well as an increase in the arterial epinephrine-norepinephrine levels. (8)

Jemings and Wartman and others (9) have reported similar areas of subendocardial necrosis following ligation of the left circumflex coronary artery in dogs and identical myocardial necrosis has been elicited in animals

by enforced exercise (10,11) and by faradization, (12) as well as by the infusion of epinephrine and norepinephrine. (13,14,15)

These experiments strongly indict the sympathetic nervous system, and more specifically, the epinephrine-norepinephrine levels in the blood perfusing the myocardium as well as the myocardial concentration of these catecholamines as the causative agents for the severe pathological changes. Their obvious significance required careful study of the circumstances in which they appear during nerve stimulation, and this serves as the principle objective of this thesis.

MATERIAL AND METHODS

In all experiments, mongrel dogs were anesthetized with pentobarbital sodium (32.5 mgm/kgm) and the stellate ganglion isolated.

The stellate ganglion was approached by a median sternotomy or by a thoracotomy incision through the second intercostal space. In those instances where a median sternotomy was employed, the experiment was carried out in its entirety with the chest opened and respiration supported by a positive pressure respirator through a tracheal cannula. In those cases in which a thoracotomy was performed, endotracheal intubation was first performed and the animal's respiration was supported by a positive pressure respirator during the operative procedure. Following completion of the surgical procedure, in the latter instances, the chest wall was closed, normal intrathoracic pressure re-established and the animal breathed spontaneously during the remainder of the experiment.

In experiments in which open-chest animals were used, a unipolar electrode was attached to the stellate ganglion; whereas in the case of the "closed-chest" animals a bi-polar electrode was used. The two procedures have provided essentially similar data.

The parameters of stimulation included pulses of either 2.0 or 5.0 msec duration and 3.0 to 5.0 volts as read directly from a cathode ray oscilloscope monitoring across the stimulating electrode. Frequency of stimulation was systematically varied as indicated in Table 1.

TABLE I

STIMULATION 3.0 Volts 5 msec.	NUMBER OF EXPERIMENTS	PULSE PRESSURE AVERAGE mm. Hg.
LEFT STELLATE 1/sec.	8	8
LEFT STELLATE 3/sec.	11	23
LEFT STELLATE 10/sec.	11	33
LEFT STELLATE AND BILAT. VAGOTOMY 10/sec.	6	25.4
RGT. STELLATE 10/sec.	6	6.0

Pressure pulses were recorded on a Sanborn recorder model 127 through a Statham pressure transducer P23Db connected to a polyethylene catheter passed into the femoral artery in those instances in which the closed-chested techniques were used.

In the open chest animals, critically damped pressure pulses were recorded from Statham (P23Db) transducers on an optical Kymograph. Again essentially similar results were obtained with either recording technique.

The experiments may be divided into three general groups:

1. Those in which the left stellate ganglion was stimulated
2. Those in which the right stellate was stimulated and
3. Those in which the left stellate ganglion was stimulated following a bilateral high cervical vagotomy

By any of the afore mentioned procedures the stellate ganglion was stimulated for periods up to ten hours.

Due to the realization that the induction of anoxia may be a significant factor in causing the subendocardial hemorrhages the following procedure was carried out at the termination of the experiment. While respiration was maintained, Stage IV anesthesia was rapidly induced in the animal with pentobarbital sodium, the thorax opened, great vessels clamped and the heart and lungs excised en bloc.

Following removal, the heart was immediately rinsed and opened according to standard pathological procedure. The endocardial surface, as well as the remainder of the heart was carefully examined for the presence of any macroscopic lesion. In cases in which a lesion of any type was observed, sections were taken for microscopic examination.

To serve as a control group for this series of experiments, the hearts of animals taken from the medical student laboratory or from other departmental experiments not involving sympathetic or catacholamine stimulation were examined to ascertain the appearance of the endocardium of the stock supply of animals.

RESULTS

In only three of the 93 "control" hearts examined were even slight subendocardial hemorrhages observed. Petechial hemorrhages were occasionally observed at the base of the mitral valve and small thrombi were frequently found adherent to the valves in the control group.

In eight animals, the left stellate ganglion was continuously stimulated at a frequency of 1 per second for several hours. Figure 1 illustrates the cardiovascular responses. In contrast to responses to higher frequency stimulation, augmented arterial pulses developed gradually but were sustained throughout the period of stimulation. Remarkable augmentation occurred instantaneously upon transection of the vagi during the stellate stimulation. Heart rate accelerated early in the stimulation period but was a less consistent response than the increase in the pulse pressure. In none of these eight animals did subendocardial hemorrhages appear, although small thrombi were sometimes found on the mitral valve, as in the control animals.

In 11 animals, the left stellate ganglion was stimulated as in the above series except that the frequency was 3 per second. The cardiovascular responses were more prompt and generally more profound in that both the systolic and pulse pressure changes were greater (fig. 2). These responses also appeared more promptly after the initiation of stimulation. The augmented pressure pulses were well sustained for the early portions of the stimulation period but deteriorated somewhat more rapidly than did the one per second stimulation group. In this group of experiments (11) all but two showed

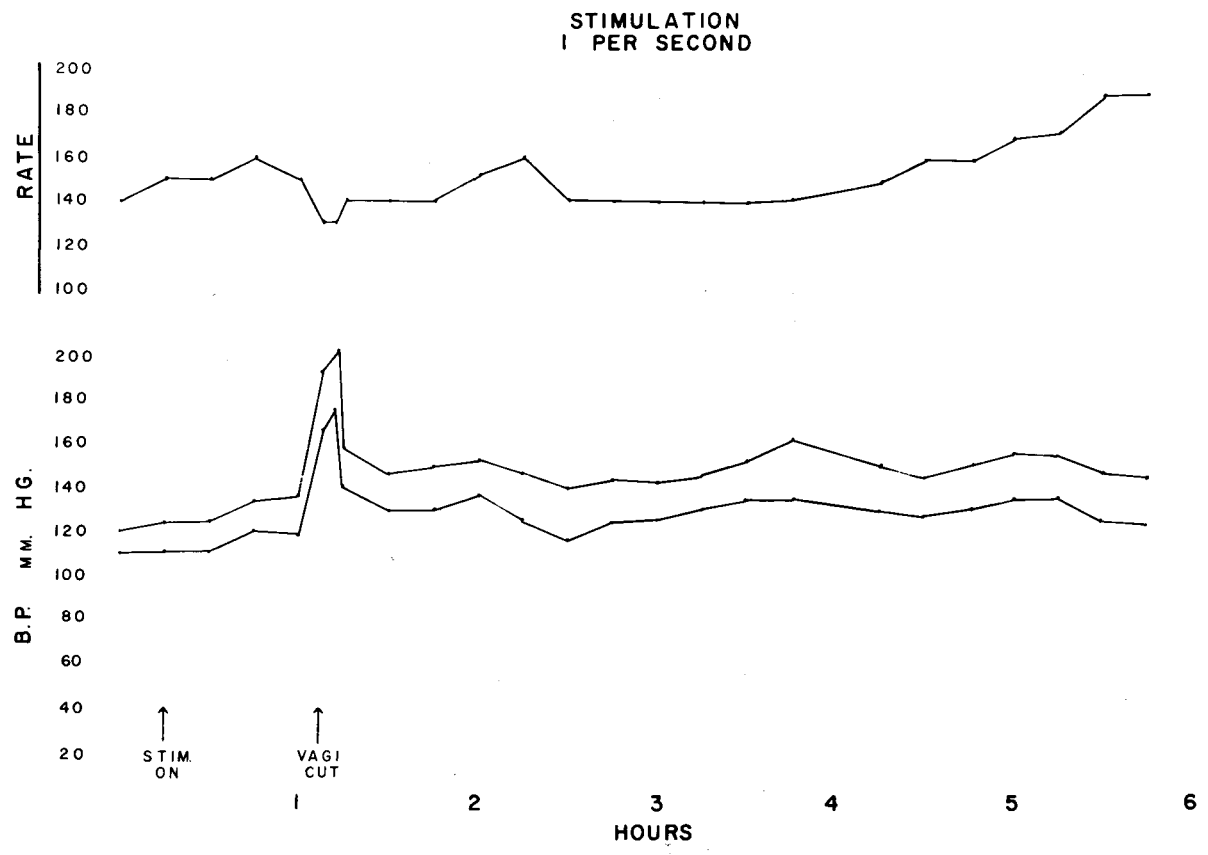


Figure 1

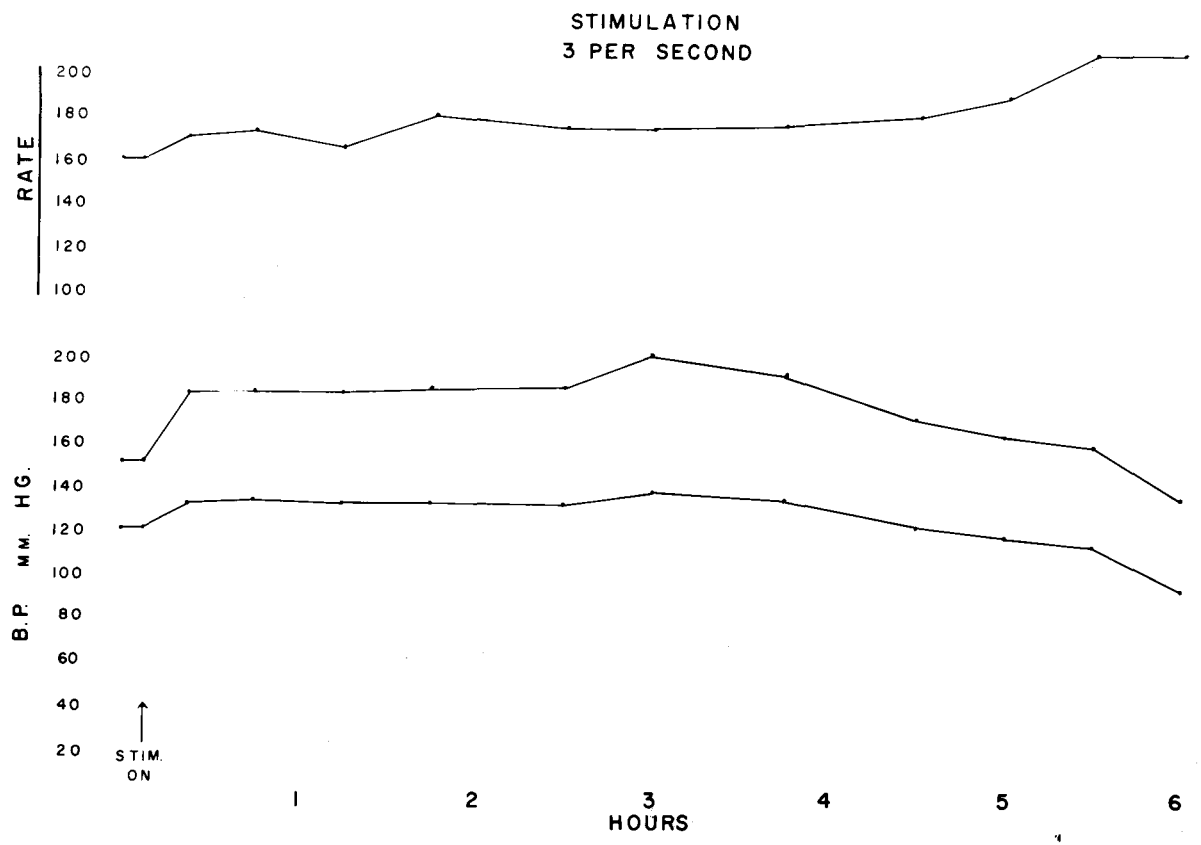


Figure 2

definite subendocardial hemorrhages. The hemorrhages were not massive in any of these hearts, but usually consisted of macroscopic hemorrhagic streaks along the longitudinal aspects of the trabeculae carneae and the papillary muscles of the left ventricle. In one experiment, a few small areas of subendocardial hemorrhage appeared in the right ventricle.

In a group of 11 animals, the left stellate ganglion was stimulated at a frequency of 10 per second. In these animals, the cardiac response was prompt (starting within 2 or 3 seconds) and much more pronounced than in either of the earlier groups (fig. 3). The response was primarily augmentor, resulting in an increase in pulse pressure of twenty to eighty mm Hg. In some of these animals the pressure pulse remained augmented for many hours, but in most, the initial augmentation slowly and gradually deteriorated as marked by a progressive decline in the amplitude of the pressure pulse. Electrocardiographic tracings were obtained in a number of these animals stimulated at a frequency of 10 per second and it was noted that with the onset of stimulation there were usually S-T segment changes as well as changes in the T wave. The T wave changes were either flattening, diphascity or inversion in the standard leads I and II. There was shortening of the P-R interval as would be expected with an increase in conductivity as well as an increase in the amplitude of the R wave with stimulation. Following the cessation of stimulation, the electrocardiogram usually returned to its initial pattern (fig. 4).

The hearts of all of the animals stimulated at 10 per second for prolonged periods (3-12 hours) showed moderate to massive subendocardial hemorrhages in the left ventricle. These hemorrhages were distributed along the long axis of the trabeculae carneae and the posterior papillary muscle with the

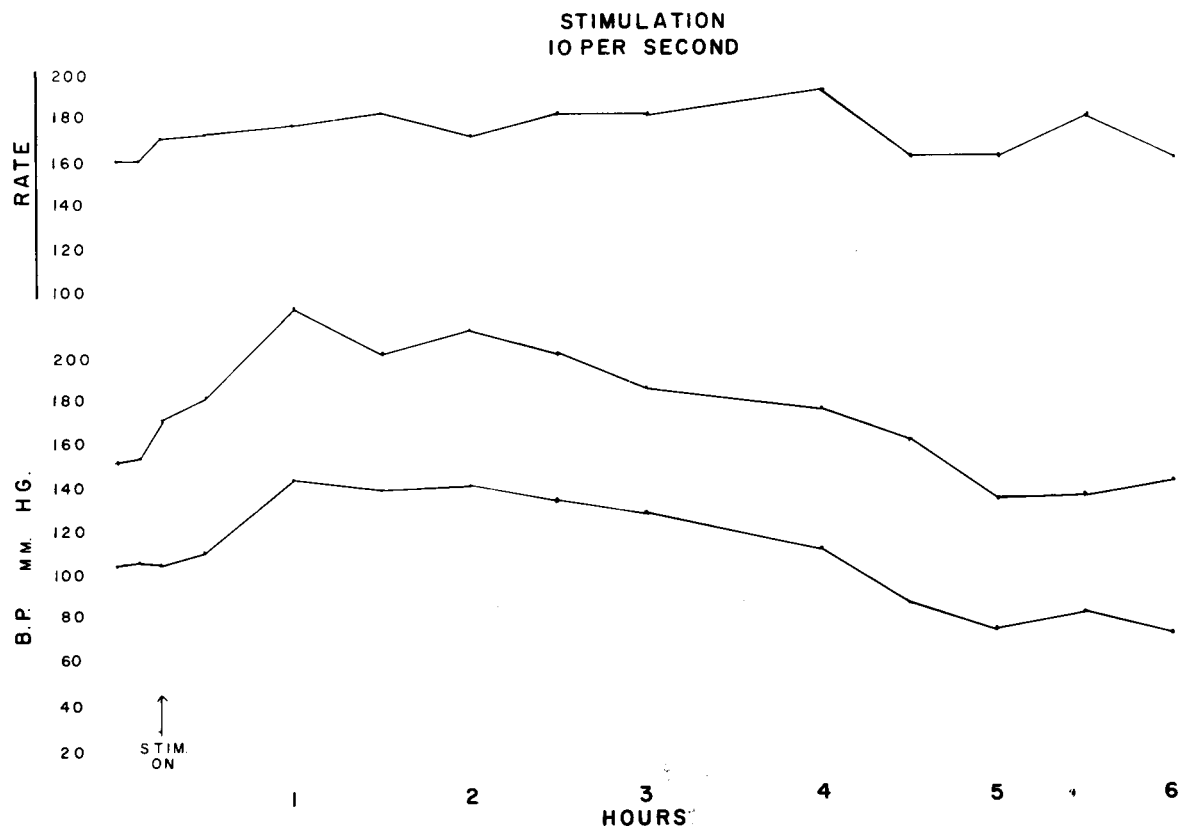


Figure 3

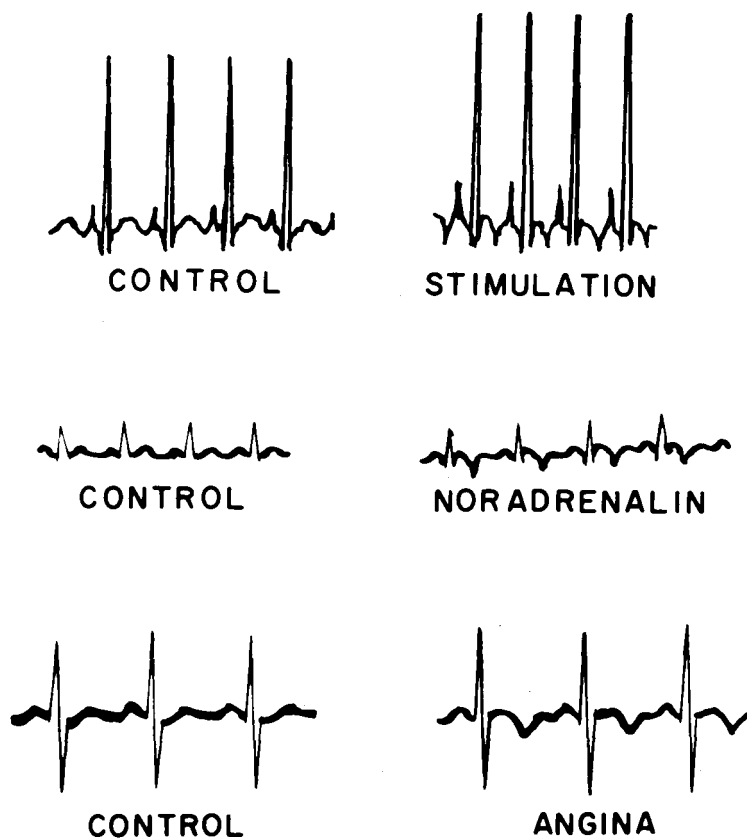


Figure 4

Figure 4 illustrates EKG changes as seen during left stellate ganglion stimulation, infusion of noradrenalin and angina pectoris.

most common site of occurrence being the point of attachment of the chordae tendinae to the papillary muscle. Only rarely was hemorrhage observed in the right ventricle, regardless of whether the right or left stellate ganglion was stimulated, and it has never been observed in the atrial walls.

Microscopic examination of the hearts in which these lesions were found showed moderate extravasation of blood in areas of the endocardium and in the interstitial tissue of the adjacent myocardium. The amount of hemorrhage varied directly with the frequency of stimulation. Occasional neutrophilic infiltration was noted. Some of the myocardial fibers, which were surrounded by blood, were non-straited and hyalinized but there were no definite nuclear changes indicative of necrosis seen.

In marked contrast to the above results obtained by stimulation of the left stellate ganglion were those obtained with stimulation of the right stellate ganglion. A summary of the results obtained in the first twenty-five experiments is seen in table 2. Blood pressure responses and heart rate changes were similar to those reported in an earlier publication. The average increase in pulse pressure in these experiments was 24.4 mm. Hg. during stimulation of the left stellate ganglion, with increases in the systolic pressure ranging from 24-88 mm. Hg. The average increase in the heart rate during this series of experiments was only 6 beats per minute.

In the animals in which the right stellate ganglion was stimulated the average increase in the pulse pressure was only 6.0 mm. Hg. but the average increase in the heart rate was 90 beats per minute. It is also remarkable that the hearts of the animals in which the right stellate ganglion was stimulated when examined following the termination of the experiment showed no

TABLE 2

STIMULATION PROCEDURE	NO. OF EXPER.	DURATION (Hrs.)	MAX. P. P. mm. Hg.	MAX. HEART RATE	PATHOLOGY
LFT. STELLATE GANGLION	13	3.5 - 10	24.4	6.2	SEH LEFT VENTRICLE 12 DOGS
BILAT. VAGOTOMY	3	4 - 5	22.7	3.3	NO LESIONS
LFT. STELLATE GANGLION	3	3 - 5	28.0	6.3	SEH LEFT VENTRICLE
RGT. STELLATE	6	5	6.0	90.0	NO LESIONS

SEH = Subendocardial Hemorrhage

Table 2 is a summary of the first 25 experiments demonstrating the different response to right and left stellate ganglion stimulation and the effect of vagotomy.

lesions regardless of the frequency of stimulation.

DISCUSSION AND CONCLUSIONS

These experiments establish that the experimental hypertension which may be induced in the open chest dog by prolonged, continuous, low frequency stimulation of the cardiosympathetic nerves may also be induced in a similar fashion in the intact (closed-chest) animal. However, it has been impossible to maintain this hypertensive state by continuous stimulation, as previously intended, for more than about twelve hours. It has been found that with this continued stimulation, the pressure pulse, after a period of 6-8 hours, gradually decreases, assumes the appearance of the pulse in shock, and the animal eventually expires. Such results have been attained in animals in which the vagi have been sectioned bilaterally and the sympathetic trunk has been cut immediately caudal to the stellate ganglion as well as in animals with the vagi and sympathetic trunks intact. Hence, some of the preparations were neurally isolated in such a way that direct excitation of the splanchnic vascular bed and the adrenal medulla was eliminated.

Because of other important aspects of this experiment and because of the great number of possible contributing factors, the actual cause of death in these animals has not yet been fully determined.

These experiments also point out that the response to stimulation of the left and right stellate ganglion is remarkably different. Stimulation of the left stellate ganglion results primarily in an increase in the pulse pressure with little change in the heart rate; whereas, stimulation of the

right stellate ganglion causes a more marked change in the heart rate with smaller changes in the pulse pressure.

Again the ultimate action of the cardiac sympathetic nerves is not known but the inotropic action of these nerves is best explained as a result of a marked increase in the force of contraction of the ventricular musculature with a consequent elevation in the volume of the systolic ejection. Since we have noted no significant alteration of electrical conductivity within the heart during stimulation of the right stellate ganglion—as determined electrocardiographically—we believe the increased heart rate to be a simple sinus tachycardia.

In attempting to explain the etiology of the subendocardial lesions seen in our experiments we need consider both mechanical and metabolic factors as possible causes. Considered among the mechanical causes are those factors which may lead to a break in the continuity of the subendocardial arterioles and/or venules. Intraventricular pressures and systemic blood pressures can be dismissed as the sole causative factor since the lesions produced may be found regardless of the height of the pressure pulse. We have also mentioned that the stimulation of the cardiac sympathetic nerves results in an increase in the force of contraction of the ventricular musculature. It is considered possible that with this increased contraction the subendocardial vessels may be sheared, or be subjected to such increases in pressure as to be caused to rupture.

Lastly, we know that with the increased force of contraction of the heart there is a more complete emptying of the ventricle. It is possible that the lesions result from forceful apposition of the endocardial surfaces under

the conditions of sympathetic nerve excitation.

It is apparent that we cannot dismiss these mechanical factors as unimportant in the production of the subendocardial lesions, but we believe that the role they play, if any, is only secondary to some metabolic alteration caused by the stimulation of the cardiac sympathetic nerves.

As was mentioned earlier, it was the cardiac arrhythmias and the electrocardiographic changes that first caused us to examine the heart for possible pathology. Our stimulation procedures of the left stellate ganglion at a rate of 10 per second caused flattening, diphascity or inversion of the T wave in leads I and II as well as some S-T segment changes. These changes reverted to normal following discontinuation of the stimulation for a period of a few minutes.

Such EKG changes as noted in these experiments are similar to those seen with the infusion of epinephrine and norepinephrine (16,17) or in patients with angina pectoris. Johansson and Vendsalu have reported that with low doses of epinephrine ($2.73 \times 10^{-7}M$) only slight S-T segment changes were noted. At higher doses ($1.36 \times 10^{-3}M$) S-T segment changes occurred which could be above or below the isoelectric line and the previously positive or negative T waves became less negative or less positive respectively. At higher doses, the downward and upward T deflections diminished considerably and diphasic forms appeared. Occasionally, directional changes in the T occurred. These authors comment that the accompanying S-T deviations resembled an injury current with their monophasic complex. They also note that in their experiments the T wave changes preceded the displacement of the S-T segment. (16)

Again, these changes are not at all unlike the changes seen in

patients in whom angina pectoris is provoked by exercise or during the inhalation of low oxygen concentrations. (18,19,20) In these individuals there is also noted depression of the S-T segment and flattening, diphascity and/or inversion of the previously positive T in leads I and II (and in some of the precordial leads). A comparison of the EKG changes obtained in our experiments, in epinephrine-norepinephrine infusion and in angina pectoris is seen in figure 4.

The question then arises as to how stimulation of the stellate ganglion can produce the EKG changes which have been described and how this procedure produces the subendocardial lesions which have been found in almost every animal in which it was employed.

To date, there has been no report of such lesions produced by direct stimulation of the cardiac sympathetic nerves. However, these lesions have been described following hemorrhagic shock, (6-7) following infusion of catecholamines (13,14,15) following forced exercise (10) and faradisation in animals (12) and following intracranial lesions. (21) Since these situations (except intracranial lesions) have been shown to have in common a resultant increase in the myocardial and circulating concentration of catecholamines, it appears most worthwhile to consider the possible role of these substances in the production of the areas of myocardial damage.

Stimulation of the cardiac sympathetic nerves has been shown to lead to an increase in the total concentration of myocardial catecholamines. Increases have also been demonstrated following injection into the circulation of epinephrine and norepinephrine, following muscular exercise and exposure to cold, by direct stimulation of the cardiac sympathetic nerves as well as in

similar situations in which there was a sympathetic nervous discharge. (10) Although in the early reports, there appeared to be a considerable amount of confusion as to the substance or substance liberated at the cardiac sympathetic postganglionic nerves which terminated within the heart, it has been shown recently that this increase in myocardial catecholamines is due specifically to an accumulation of norepinephrine, while the concentration of epinephrine remains the same. (10)

Further evidence for the fact that the cardiac sympathetics play an important role in the regulation of myocardial catecholamine concentration is offered by the fact that sympathectomy is followed by a diminution of the total myocardial catecholamines. (22)

It is also suggested by our present series of experiments that the frequency of stimulation may play an important role as regards the amount of these substances liberated at the sympathetic nerve endings within the heart. In table 2 is shown the incidence and severity of the subendocardial lesions occurring with varied frequency of stimulation. It will be noted that with stimulation of a very low frequency (1/sec) lesions are seldom produced in the heart. Stimulation of the cardiac sympathetic nerves at a rate of three per second causes lesions which are relatively small; whereas stimulation at a rate of ten per second results in the production of lesions in the hearts of all of the animals with the lesions ranging in size from moderate to massive. In figure 5 is shown a heart in which are present subendocardial lesions which have been described.

In 1957 Jennings and Wartman described the occurrence of myocardial infarction following the ligation of the left circumflex coronary artery in



Figure 5

Figure 5 shows a heart in which is seen subendocardial hemorrhagic lesions typical of those obtained by stimulation of the left stellate ganglion at a frequency of 10 per second.

dogs. (9) The areas of the heart musculature which were affected in their procedure were almost identical with those described in our experiments. It was pointed out by these authors that experiments with tagged red blood cells showed that less blood entered the posterior papillary muscle than entered the lateral wall of the left ventricle. They concluded that the posterior papillary muscle apparently received most of its blood from the left circumflex coronary artery alone, so that when this vessel was occluded, greater ischemia developed in this area than elsewhere.

Other authors have also proposed that the subendocardial area is more susceptible to anoxia due to the higher intramyocardial pressures which are found in this area. (23,24) The present evidence therefore leads us to suspect that the lesions found in our experiments are in some way related to hypoxia of the subendocardial region which is induced by sympathetic discharge. The disruption of the continuity of the vessels in this area may also be enhanced by the mechanical factors which are associated with this sympathetic discharge.

Within the past few years, numerous authors have demonstrated that epinephrine and norepinephrine have a definite effect on the myocardial oxygen consumption. Gollwitzer-Meier and Witzleb (31) have demonstrated that norepinephrine has a marked augmenting influence on the cardiac oxygen consumption. This effect exerted by norepinephrine is approximately one-quarter of the effect exerted by epinephrine. Gollwitzer-Meier and her associates have also ascertained the oxygen consumption of the myocardium during direct stimulation of the cardiac sympathetic nerves. (25) Eckstein (26) as well as Shipley and Gregg (27) are in complete agreement with her conclusions in which it was found that the oxygen consumption is greatly intensified during sympathet-

ic stimulation. In experiments in which the cardiac output was controlled during the sympathetic stimulation, Eckstein and his co-workers found that the increase in oxygen consumption is not necessarily due to an increase in the work of the heart. His findings are in close agreement with those of similar experiments performed with epinephrine and his conclusion is in harmony with that offered by Evans, (28) Gollwitzer-Meier, (29) Gremels and Garcia Ramos. (30)

Further evidence that these cardiac lesions appear as a result of anoxia is offered by the fact that the chemistry of the involved area is identical with that of the area of infarction which is produced by ligation of the arterial supply to this area. It has been demonstrated that lactic acid concentration in the area is increased while the glycogen as well as the creatinine and adenylypyrophosphoric acid is decreased. (10)

These facts lead to the implication that the sympathetic neuro-hormonal action aside from causing obvious mechanical responses, also plays an important role in altering the oxygen consumption of the myocardium.

It has been suggested in the past by some authors that the vagi exert an oxygen sparing effect upon the myocardial tissue (10) and by other authors, that these nerves may be the agents solely responsible for the subendocardial hemorrhages. (21) It is shown in our experiments that the vagi have no apparent influence on the appearance of these lesions. Neither the size nor the severity of the subendocardial lesions was altered in our experiments in which the vagi were sectioned.

Our experiments have also revealed that in animals in which the right stellate ganglion was stimulated, no visible lesions occurred in the heart. No electrocardiographic changes were noted in these experiments except those

which would be expected with the change in heart rate. The cardiovascular responses obtained in these experiments have been mentioned earlier.

Since we are not equipped to determine levels of the catecholamines and since no definitive work of this kind has yet been reported upon stimulation of the left and right stellate ganglion in dogs, we are unable to offer a satisfactory explanation for these results at this time.

We are aware of the fact that no adequate explanation for the ultimate action of the catecholamines upon the cellular metabolism of the heart has yet been offered. Be that as it may, the fact remains that these hormones are secreted as a result of stimulation of the cardiac sympathetic nerves and result in a marked increase in the myocardial oxygen consumption. The end results, as seen in our experiments, are the electrocardiographic changes suggestive of myocardial hypoxia and the subendocardial hemorrhages found at post-mortem examination.

SUMMARY

- I. The right or left stellate ganglion of dogs was stimulated at varying frequencies (1,3, or 10/sec) for periods up to 10 hours. This procedure was carried out in vagotomized animals as well as in animals with the vagi intact.
- II. The present experiments are in complete agreement with earlier experiments in which it was demonstrated that the augmentation of myocardial contraction is most prominent during stimulation of the left sympathetic trunk and its associated pathways, whereas excitation of the right trunk induces more prominent cardiac acceleration.
- III. It has been demonstrated that stimulation of the left stellate ganglion at a frequency of 3 per second or greater consistently results in the occurrence of subendocardial hemorrhages of the left ventricle.
- IV. A possible explanation for the occurrence of these subendocardial lesions is offered in which the "anoxiating" action of the catecholamines liberated by sympathetic stimulation is implicated.

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APPROVAL SHEET

The thesis submitted by Michael P. Kaye has been read and approved by three members of the faculty of the Stritch School of Medicine, Loyola University.

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.

5-28-59

Date

Walter C. Randall

Signature of Adviser