STUDIES ON THE EFFECTS OF METHOXAMINE HCl ON THE DOG WITH PARTICULAR REFERENCE TO THE EXPERIMENTALLY DAMAGED HEART

by

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A THESIS

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INTRODUCTION

The purpose of this investigation was to develop a safe and simple therapy for hypotension and shock in the presence of a damaged heart. The importance of shock in association with a damaged heart, particularly in cases of myocardial infarction need hardly be stressed. One only need review the mortality figures under such circumstances: The average mortality in patients with myocardial infarction without shock rarely exceeds ten to fifteen per cent, in cases with severe hypotension and prolonged shock the mortality approximates eighty per cent.

The sympathomimetic amines are widely used to prevent and treat normovolemic shock states by maintaining normal blood pressure. The use of these drugs in cases of hypotension and shock following myocardial infarction has been controversial. Recently, however, some light may have been shed on this subject by the diagnostic classification proposed by Fink et al(1). This group divides patients of this type into two groups:

1. Those with low venous pressure (below 5 cm. of water).
2. Those with high venous pressure (above 12 cm. of water).

The first group of patients is considered to have a shock condition similar to that following severe trauma. These patients seem to respond best to vasopressors with plasma as an adjuvant.

The second group is considered to have a congestive failure type of shock and as such seemed to respond better to lanatoside C. The use of plasma and vasopressors is held to be contraindicated in this group.

Disadvantages of using many of the common vasopressor drugs and excessive fluid administration in either of the two groups of patients are (Tovell, Bannister and Brown[2]):

a. The hypotension is not the result of decreased blood volume.

b. Hypervolemia (resulting from fluids or plasma administration) causes increased work load on the heart with unnecessary strain and pulmonary edema.

c. Many vasopressor drugs increase cardiac output and rate of metabolism at the expense of increased cardiac irritability and pulse rate.

As pointed out by Miller et al[3], the ideal pressor drug should:

1. increase peripheral resistance
2. elevate blood pressure
3. cause proportionate increase in coronary flow
4. not decrease cardiac output or produce serious arrhythmias
5. have minimal side effects
6. have freedom from local damage to myocardium or blood vessel walls.

For cases of shock with otherwise normal hearts, (e.g., following gastrointestinal hemorrhage, etc.) the treatment is more clearly indicated. The best results are usually obtained from transfusions of whole blood or plasma. In persons with seriously damaged hearts, transfusions are attended with serious risk; congestive failure with pulmonary edema and death may be precipitated by this procedure. It is true that more recently the use of intra-arterial transfusions has been reported as

being successful in minimizing these complications. However, instances of gangrene in the extremity distal to the point of the arterial puncture have been observed and death from air embolism has also been reported.

It is obvious therefore that an agent which can be administered by the relatively safe and simple procedure of a glucose infusion is highly desirable. Such an agent has been sought in the employment of a pressor amine. Unfortunately, those pressor amines which have been used have not been entirely free from unfavorable side effects. As pointed out by Nathanson, even those considered relatively safe, such as Neosynephrine and norepinephrine (Levophed), may cause increased cardiac rhythmicity resulting in dangerous arrhythmias (ventricular tachycardia, etc.).

Methoxamine (Vasoxyl) was selected for this study because of the indications that it caused little or no stimulation of the myocardium either directly or indirectly (Stutzman)[4]. This characteristic in a vasopressor drug would seem to be a distinct advantage especially when used in myocardial infarction.

The lack of stimulation of the myocardium of methoxamine was demonstrated by Nathanson[5]. The effects of methoxamine were studied on the following groups of patients:

a. Patients on whom carotid sinus pressure produced cardiac standstill.

1. Vasoxyl caused a blood pressure rise but cardiac standstill could still be produced.
2. Epinephrine raised the blood pressure but cardiac standstill could not be produced.

b. Patients with complete heart block.

1. Methoxamine caused blood pressure rise but no change in heart rate.
2. Epinephrine caused blood pressure rise and increased ventricular rate.

c. Patients with paroxysmal tachycardia.

1. Methoxamine caused immediate slowing with establishment of sinus rhythm.
2. Phenylephrine usually had the same effect but occasionally caused signs of myocardial stimulation.

All the above groups demonstrate the apparently complete lack of myocardial stimulation of methoxamine. The pressor effect is claimed to be purely the result of peripheral vasoconstriction.

The principle actions of methoxamine are claimed to be as follows (Tovell[2], Steven[6] and Kistler[7]):

1. causes increased total peripheral resistance thus raising the blood pressure.
2. causes no cerebral stimulation.
3. produces a sinus bradycardia which can be abolished by atropine.
4. does not increase cardiac muscle irritability.
5. raise coronary blood flow.
6. does not increase cardiac output or stroke volume.
7. salivation.
8. pilomotor activity is noted.
9. occasionally headaches occur.

10. respiratory depression in large doses.
11. causes no nausea, vomiting, tremors, nervousness, giddiness or other signs of CNS stimulation.

We were interested, in this preliminary study, in determining the toxic and minimal effective doses of methoxamine in dogs on weight-time basis. Once the optimun dose was determined it was planned to extend the studies to dogs with artificially damaged and infarcted hearts.

METHODS

Constant Infusion of Vasoxyl

The purpose of these experiments was to determine the effects of Vasoxyl when injected at a constant rate over an extended period of time on the anesthetized animal.

The animal was anesthetized with barbital sodium (250 mg./Kg.) or Nembutal sodium (35 mg./Kg.) administered intraperitoneally. After a suitable level of anesthesia had been attained, incision over a femoral vein was made and the vein exposed. A small polyethylene catheter was inserted via the femoral vein into the inferior vena cava. This catheter was then connected to a 30 cc. syringe mounted in a constant rate injection machine. A "T" valve was inserted between the catheter and syringe through which normal saline was injected periodically to prevent clotting of blood in the catheter until the control records had been taken. The syringe was filled with a solution of Vasoxyl in normal saline. These Vasoxyl solutions were of varying concentrations in the different experiments of this type but the volume of solution injected per minute was maintained at 1 cc. per minute for all the animals.

An incision was then made in the neck and the trachea and a carotid artery exposed. A cannula was inserted into the trachea and connected to an impulse tambour and writing arm which traced respirations on a smoked drum kymograph. The carotid artery was cannulated and connected to a mercury manometer to record mean damped blood pressures in the usual manner.

The kymograph used was capable of recording for approximately two hours. The recordings inscribed on the smoked paper were; respirations, blood pressure, zero blood pressure, time in five second and one minute intervals, and periods when the EKG was running were also indicated (see example tracing).

After all the apparatus was connected and checked, controls were taken on respiration, blood pressure, heart rate and six leads of the EKG. The constant injector was then started. Short tracings from lead II were taken throughout the experiments as changes occurred in the animal's status or at approximately 5 minute intervals. Vasoxyl was infused for approximately two hours or until death occurred.

At the conclusion of each experiment the EKG was correlated with the kymograph tracings and the effects of injecting Vasoxyl at various dosage levels tabulated.

Several control experiments were performed following identically the above details so that a decision could be reached as to whether the effects observed were due to the Vasoxyl or might have arisen through some artifact of the technique. Normal sterile saline was injected for two hours at the rate of 1.0 cc./min. and the effects observed to see if hypervolemia were a factor.

Cyclopropane Anesthesia

A fasted dog was anesthetized with cyclopropane without premedication. Induction was accomplished with 60% oxygen and 40% cyclopropane or with 60% oxygen, 20% nitrous oxide and 20% cyclopropane. After the

animal reached Plane III stage I, it was intubated with a cuffed Magill endotracheal tube and anesthesia continued via closed circuit. Anesthesia was maintained with 70% oxygen and 30% cyclopropane. A 30 minute period was allowed for stabilization. Respiration was supported by bag breathing wherever indicated in order to avoid the effects of hypoxia. A lead II electrocardiogram was recorded with a Sanborn Visocardiette throughout the experiment. After the stabilization period, brief control EKG's were taken in leads I, II, III, AVR, AVF and AVL.

A femoral vein was then exposed and a small polyethylene catheter inserted through this vein into the inferior vena cava as close to the right auricle as possible.

Vasoxyl in varying doses was then injected via the femoral catheter. After the acute effects of Vasoxyl had disappeared, as determined by EKG and respiratory status, epinephrine was injected via the polyethylene catheter in doses ranging from 10 micrograms per kilogram to 20 micrograms per kilogram. The effects of the epinephrine on the EKG were again followed by a lead II tracing taken intermittently.

The EKG tracings taken after Vasoxyl administration were than compared with those following epinephrine.

Melville Technique[8]

Fasting dogs were weighed and anesthetized with Nembutal sodium (35 mg./Kg.) administered intraperitoneally. After anesthesia was attained, a cuffed Magill endotracheal tube was inserted into the trachea and control EKG's were taken with a Sanborn Visocardiette in leads I, II,

III, AVR, AVF and AVL. Tracings taken throughout the experiment were lead II. These were recorded at five minute intervals or as the animal's condition changed.

After the controls were taken, the animal was subjected to chloroform inhalation through a gauze mask for five minutes. The chloroform administration was not intended to deepen the level of anesthesia. Following the chloroform, a femoral vein was exposed and a small polyethylene catheter was inserted through this vein high into the inferior vena cava so its tip lay as near the right auricle as possible. Intravenous injections of Vasoxyl were given through this catheter. The doses of Vasoxyl varied from 0.02 mg./Kg. to 1 mg./Kg. for the animals used in these experiments. The animals received assisted respirations with the bag on the gas machine as needed using a closed circuit system with oxygen.

Following the injection of the Vasoxyl, the animals received epinephrine in doses ranging from 10 micrograms to 20 micrograms per kilogram. The epinephrine was administered into the inferior vena cava through the catheter as described above. Varying periods of time were allowed to elapse between the administration of the Vasoxyl and epinephrine (from 5 to 20 minutes). No attempt was made to measure the duration of the effect of Vasoxyl as related to epinephrine results.

There were control experiments conducted in which Vasoxyl was omitted and Levophed or Neosynephrine substituted for the epinephrine "challenge" dose as described by Melville. Part of these control experiments were recorded by means of a single channel EKG and part by means of the four channel machine recording leads II & III and a carotid

pulse wave. The carotid pulse wave was obtained using an electromanometer connected to a carotid artery. Vagotomy was not performed on these animals.

Another modification of this method was utilized in which the vagus nerves were severed bilaterally as high in the neck as possible before administering the chloroform or Vasoxyl. In part of these animals the recording was limited to a lead II EKG as described above. In the other group the recording was accomplished by means of a 4 channel Sanborn electrocardiograph. Two channels were utilized to record leads II and III of the EKG and a third channel recorded the pulse wave of a carotid artery as transmitted through a Sanborn electromanometer.

Vagotomy

Fasted dogs were anesthetized with Nembutal sodium administered intraperitoneally. After suitable anesthesia was attained, control EKG's were taken in leads I, II, III, AVR, AVF and AVL. A cuffed Magill endotracheal tube was inserted into the trachea. Then an incision was made in the anterior midline of the neck and both vagus nerves exposed as high in the neck as possible. The nerves were then severed and Vasoxyl injected intravenously into a superficial leg vein. The status of the animal was recorded by a lead II EKG tracing throughout the experiment. The animal was subjected to five minutes of chloroform inhalation. The dose of Vasoxyl used varied from 0.25 mg./Kg. to 0.5 mg./Kg. in the different animals used in these experiments. At varying time intervals following the Vasoxyl, epinephrine in doses of 20 micrograms/Kg. was given intravenously into a superficial leg vein.

Assisted breathing by means of the bag on the gas machine was given as indicated throughout these experiments. Oxygen was also given as indicated. Due to the short period of time involved in these experiments anoxia or carbon dioxide depletion did not become a problem.

The effects of Vasoxyl and epinephrine as indicated by the EKG were compared and tabulated.

Myocardial Infarction by Means of Intramyocardial Injection of Zinc Hydroxide (Meyer)[9]

Fasted dogs were anesthetized with Nembutal sodium (35 mg./Kg.) given intraperitoneally. The animals were placed supine with legs extended. The left chest wall was shaved, cleansed and the fifth intercostal space marked. Electrodes were attached to all four legs so that intermittent EKG's in lead II could be recorded throughout the experiment. The animal was intubated with a cuffed Magill endotracheal tube so that assisted breathing could be instituted with the re-breathing bag on the anesthetic machine if indicated. Control EKG's were taken in leads I, II, III, AVR, AVF and AVL.

The infarct was then produced. A 20 gauge lumbar puncture needle was inserted through the left fifth interspace about 1/4 to 1/3 the distance from the sternum to the spine. The needle was directed so as to pierce the left ventricular wall. The apex of the heart could be pierced by directing the needle about 45° caudad and the needle could be directed to hit the superior portion of the ventricle wall by turning it

30° cephalad. Since the septum lies in a frontal plane more than in a sagittal plane, the needle must be kept parallel to the table top or at least less than 30° ventralward. The needle could be inserted to lie in the right ventricle wall, the septum, or left ventricular wall by varying the direction and depth of insertion. After the ventricle was pierced, the stylus was withdrawn. If the needle was in a chamber, blood was ejected from the end of the needle. Then the needle was slowly withdrawn until blood no longer flowed from it. This indicated that the needle lay in a ventricular wall or septum depending on the direction and depth.

The zinc hydroxide suspension used was freshly prepared by mixing equal volumes of 0.25 N NaOH and zinc sulfate 5%. Three cc's of this suspension was injected into the myocardium at the rate of 1 cc./10 sec. Between each cc. injected, the needle was aspirated to determine if it were still in the myocardium.

EKG's were recorded every minute. In animals in which an infarct had been formed, the damage was signified by an abnormal EKG tracing within 20 minutes. If, at the end of 30 minutes after the injection, there were no significant change in the EKG, the procedure was repeated. In no case was more than two attempts necessary to produce a cardiac infarction.

As soon as abnormal tracings were noted, Vasoxyl was injected into a superficial vein. The doses of Vasoxyl varied from 0.25 mg./Kg. to 1 mg./Kg.

EKG tracings were taken every minute thereafter to determine the effects of Vasoxyl on the abnormal pattern which had been noted following

the zinc hydroxide injection. After the effects of the Vasoxyl have been dissipated, another EKG was taken and the experiment terminated. In the same manner epinephrine was used instead of Vasoxyl.

Myocardial infarction produced by ligation of the anterior coronary vessels was attempted in one experiment but this method was felt to be unsatisfactory and was discarded.

FIGURE 1

Composite graph illustrating the effects of constant infusion of Vasoxyl in various concentrations on the blood pressure of dogs. All blood pressures have been converted to a common control level of 120 mm. of mercury.

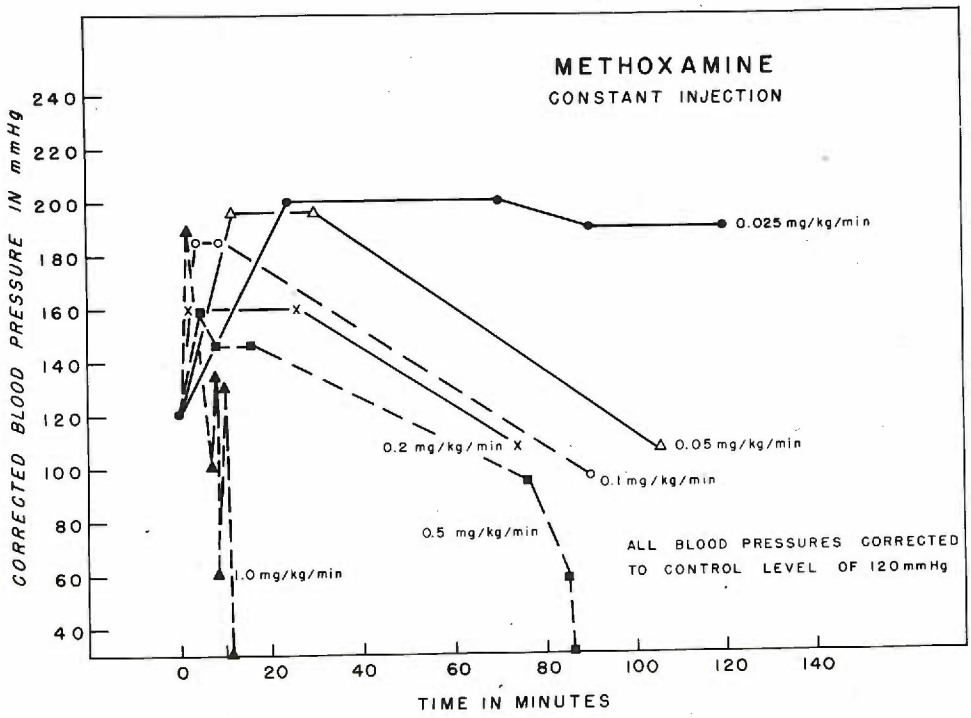
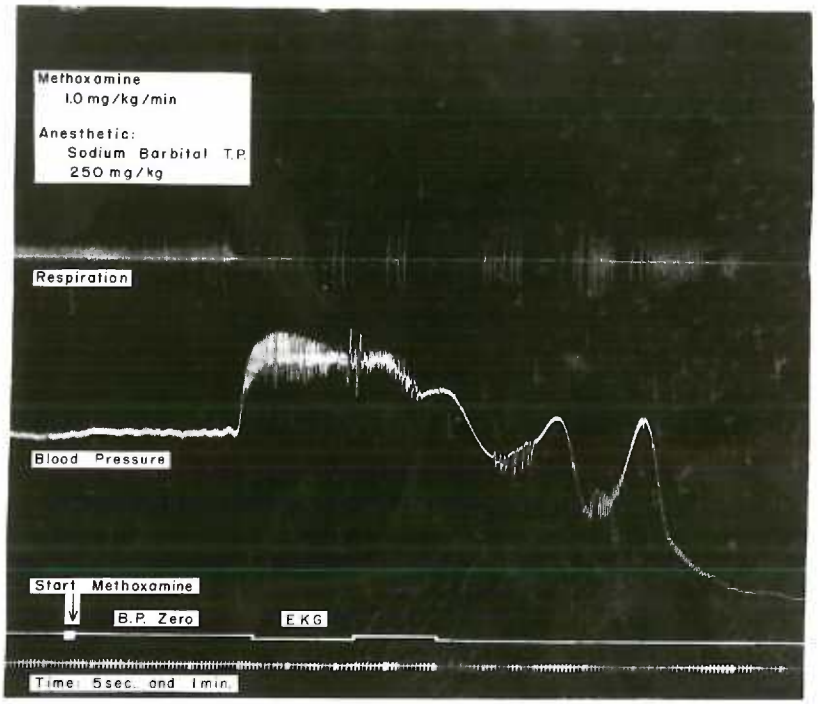

METHOXAMINE
CONSTANT INJECTION
CORRECTED BLOOD PRESSURE IN mmHg
240
220
200
180
160
140
120
100
80
60
40
0
20
40
60
80
100
120
140
TIME IN MINUTES
0.025 mg/kg/min
0.05 mg/kg/min
0.1 mg/kg/min
0.2 mg/kg/min
0.5 mg/kg/min
1.0 mg/kg/min
ALL BLOOD PRESSURES CORRECTED
TO CONTROL LEVEL OF 120 mmHg

FIGURE 2

Section of kymograph record showing the effects of constant intravenous infusion of Vasoxyl on blood pressure and respirations of a dog.


Methoxamine
1.0 mg/kg/min
Anesthetic:
Sodium Barbital T.P.
250 mg/kg
Respiration
Blood Pressure
Start Methoxamine
B.P. Zero
E.K.G.
Time 5sec. and 1min.

RESULTS

Constant Infusion Experiment

The methoxamine solutions used were all made up for each dog so that each ml. of solution contained the required mg./Kg. The constant injector machine was then set to deliver 1 ml. per minute so that the same volume of solution was administered to each dog per minute.

Doses of methoxamine used:

a. 0.01 mg./Kg./min.
b. 0.025 "
c. 0.05 "
d. 0.1 "
e. 0.2 "
f. 0.5 "
g. 1.0 "
h. control 1 ml. sterile normal saline/min.

A. Cardiac effects.

Changes in the blood pressure are summarized in figure 1. Doses of 0.025 mg./Kg./min. caused a sustained rise in blood pressure for as long as the drug was administered. Doses below 0.025 mg./Kg./min. (i.e. 0.01 mg./Kg./min.) are considered to be sub-minimal even though they produced a significant rise in blood pressure. This dosage did not cause a maximal response and the resulting bradycardia seemed to follow roughly that which would be expected in a normal carotid sinus reflex. But in doses above that it would appear that this bradycardia is independent of blood pressure and the vagal reflex (see figures 9 and 10).

As the dose was increased the tachyphylaxis produced by this drug became more and more apparent (King)[10]. At doses of 0.5 to 1.0 mg./Kg./min. the maximal dosage range was being reached. At these doses the height of the blood pressure rise tends to vary from dog to dog although the duration of blood pressure rise remained remarkably constant for each particular dosage used.

There were no significant changes in the electrocardiogram other than the above noted sinus bradycardia. At near lethal doses of 0.5 to 1.0 mg./Kg./min. occasional sinus pauses began to appear interspersed with bursts of nodal rhythm. These periods of nodal rhythm were never seen to exhibit rates more rapid than control rates.

B. Effects on respiration.

One of the more constant effects noted was a respiratory depression. This appeared coincident with the initial blood pressure rise (see figure 2). In the smallest dosage ranges only brief, transient, slowing of respiration occurred after which the respiration returned to essentially control state. In doses of 0.025 mg./Kg./min. and over a Cheyne-Stokes type of respiration appeared. As the dose was increased, the respiratory depression became more severe until doses of 0.5 to 1.0 mg./Kg./min. caused death by respiratory depression (see table 1).

C. Other effects.

An increase in salivation was noted to a slight degree in most dogs but only one dog showed excessive salivation.

All dogs exhibited clonic movements, often quite violent, particularly in the higher dose ranges. The lid reflex and the

TABLE I

Respiratory Effects of Continuous Infusion of Vasoxyl.

Dose Vasoxyl mg./Kg./min.	Time of Maximum B.P. Rise (min.)	Time to Appearance of 1st Respiratory Depression (min.)	Time to Appearance of Cheyne-Stokes (min.)
0.025	24		40
0.05	12	14	22.5
0.1	3.5	3.5	14
0.2	3	4	6
0.5	4.5	3.5	4.5
1.0	2	2	3

corneal reflex returned but the light reflex remained absent. The pupils were dilated in all cases.

The animals, though they gave the appearance of coming out of the anesthesia, showed a marked sensitivity to any further barbiturates. For instance, one animal which had been anesthetized with sodium barbital six hours previously began to have convulsive movements (after one hour of methoxamine) so violent that 1 gr. of sodium pentobarbital was given intraperitoneally. This caused immediate cessation of respiration and severe fall in blood pressure and death followed within minutes. This animal was still receiving methoxamine but evidently was refractory to any pressor action of this drug.

Effects of Methoxamine Overdosage on the Normal Heart. Death was the result of respiratory arrest and falling blood pressure. The accompanying electrocardiographic signs were bradycardia with occasional sinus pauses and slow atrioventricular nodal rhythm. Bradycardia continued despite the falling blood pressure. Late signs did indicate a myocardial hypoxia which could be effaced using artificial ventilation with oxygen.

These continuous perfusion studies indicate that adequate warning symptoms appear long before lethal doses of methoxamine are reached. At any rate of injection greater than 0.025 mg./Kg./min. a Cheyne-Stokes type of respiration appeared when a total dose of 1.0 to 1.4 mg./Kg. had been reached. A second sign of methoxamine overdosage is the occurrence of tachyphylaxis; despite continuing administration of methoxamine the blood pressure declines. With methoxamine administered at 0.2 mg./Kg./min.

or 0.05 mg./Kg./min. the initial drug-induced hypertension disappears and blood pressure returns to the preinjection level when a total dose of 12 mg./Kg. and 4.5 mg./Kg. respectively had been injected. A sustained increase in blood pressure in dogs could be maintained only if the perfusion rate were less than 0.02 mg./Kg./min. Finally, although slowing of the heart rate occurs early, frequent sinus pauses and periods of AV nodal rhythm are related to methoxamine overdosage.

Failure of Vasoxyl to Incite Ventricular Arrhythmias during Cyclopropane Anesthesia. Single doses of Vasoxyl, 0.2-10 mg./Kg., were injected intravenously into non-premedicated dogs anesthetised with 30 per cent cyclopropane and 70 per cent oxygen for thirty minutes. Neither ventricular tachycardia nor ventricular fibrillation was observed. There occurred instead a sinus bradycardia; with 0.5 mg./Kg. the heart rate was approximately two-thirds of the initial rate and at doses of 1.0 mg./Kg. or greater the rate was approximately one-half the control value. With the larger doses, 0.5 mg./Kg. and greater, sinus pauses appeared and there was also transitory episodes of sinus arrest and slow rhythms. Consistent with a picture of vagal stimulation, the larger doses of Vasoxyl were followed by an increase in the PR interval; control values of 0.10 sec. were increased to 0.16 sec. There appeared also an apparent increase in ST interval in many experiments though the interpretation must also include the appearance of a U wave. This is summarized in table II.

Vasoxyl, in doses of 2.5 mg./Kg. and greater, caused apnea and decreased respiratory movements which required assisted respiration for periods of time as long as twenty minutes. It is not believed that this

TABLE II

Effects of Vasoxyl on Cardiac Rhythm in Dogs Anesthetized with Cyclopropane as Shown on Electrocardiogram

Dose of Vasoxyl (mg./Kg.)	Control Period				Vasoxyl					Epinephrine 10 microgm./Kg.	
	Heart Rate (per min.)	QRS (sec.)	PR (sec.)	ST (sec.)	Heart Rate (per min.)	(% decr.)	QRS (sec.)	PR (sec.)	ST (sec.)	Maximum Heart Rate	Duration of Ventricular Tachycardia
0.2	120	0.04	0.10	0.18	100	16.6	0.03	0.12	0.20	200	6 sec.
0.5	144	0.03	0.11	0.14	90	37.5	0.03	0.14	0.15	218	18 sec.
1.0	120	0.03	0.08	0.18	60	50.0	0.03	0.10	0.18	160	Occasional premature beat
2.5	210	0.03	0.10	0.16	100	52.4	0.03	0.16	0.16	100	Sinus pauses eliminated
5.0	152	0.04	0.10	0.16	80	47.4	0.03	0.16	0.16	150	None
10.0	140	0.14	0.10	0.16	60	57.1	0.04	0.16	0.16	240	Single ectopic beat

apnea was the result of increased depth of anesthesia since muscular twitchings and limb movements continued. Marked pilomotor activity was occasionally noted also with doses of 2.5-10 mg./Kg. of Vasoxyl.

When epinephrine hydrochloride, 10 microgram/Kg., is administered to dogs anesthetized with cyclopropane under the same conditions, ventricular arrhythmias are provoked. If the injection of epinephrine is made through a femoral vein catheter so inserted that its tip lies just below the inferior vena cava, ventricular tachycardia appears in 75-80 per cent of the dogs tested. The tachycardia is then followed by rapid rhythms having various ventricular pacemakers, then sinus tachycardia with return to normal rhythm in about ten minutes. The other 20-25 per cent of the dogs die of ventricular fibrillation. If a larger dose of epinephrine is given, the ventricular arrhythmias are prolonged and the incidence of ventricular fibrillation increased.

Using this experimental procedure, a large number of pressor amines have been compared with epinephrine. Most of them have been found to institute ventricular tachycardia and ventricular fibrillation (Orth, Leigh, Mellish and Stutzman, 1939)[11]. However, Stutzman, Pettinga and Fruggiero[4] found in dogs anesthetized with cyclopropane that Vasoxyl in doses of 1-1.5 mg./Kg. failed to elicit ventricular arrhythmias. Similarly, in our studies neither ventricular tachycardia nor ventricular fibrillation was observed with doses of Vasoxyl varying from 0.2-10 mg./Kg. It should be noted that the largest dose (10 mg./Kg.) given is some 35 to 70 times the recommended human adult intramuscular dose.

A surprising finding was the protection afforded by Vasoxyl against epinephrine-cyclopropane ventricular arrhythmias. The usual 10 microgram/Kg.

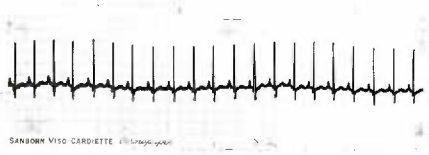
challenge dose of epinephrine was injected nine to twenty-eight minutes after the Vasoxyl had been given (no attempt was made to estimate the duration of Vasoxyl's "protection"). When 1-10 mg./Kg. of Vasoxyl had been injected, epinephrine caused transient periods of an occasional premature ventricular systole, sinus tachycardia or bigeminal rhythms. With smaller doses of Vasoxyl, the duration of epinephrine's ventricular tachycardia was significantly less. There was no ventricular fibrillation when epinephrine had been preceded by 0.2 mg./Kg. of Vasoxyl or more.

Chloroform "stress": Methoxamine was injected immediately following or preceding five minutes of chloroform inhalation at 0.2, 0.5, 1.0, 2.5, 5.0 and 10.0 mg./Kg. Even with the largest methoxamine dose ventricular fibrillation never appeared. Instead methoxamine was followed by slowing of the heart rate, sinus pauses, slow AV nodal rhythm and an increase in the PR interval (see figure 3).

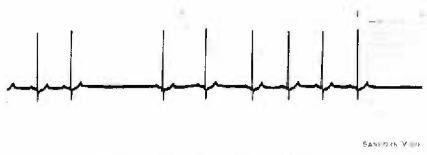
As seen with the cyclopropane experiments, methoxamine prevented chloroform-epinephrine ventricular fibrillation. Ventricular fibrillation never occurred following challenge with 20 microgram/Kg. epinephrine if methoxamine in doses greater than 0.1 mg./Kg. had been given previously. Protection, however, is not complete (see table III). Pretreated with methoxamine, epinephrine still provoked transitory period of rapid AV nodal tachycardia, bigeminal rhythms, premature ventricular systoles and sinus tachycardia. Melville[12] reports similar protection for ephedrine against epinephrine-chloroform fibrillation although he states that it alone may provoke premature ventricular contractions. Methoxamine in the above listed dosage range still prevented epinephrine-chloroform

FIGURE 3

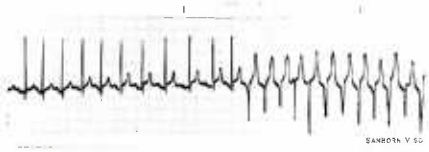
Section of EKG illustrating the effect of Vasoxyl on a dog's heart which has been subjected to the Melville procedure of cardiac sensitisation with chloroform.



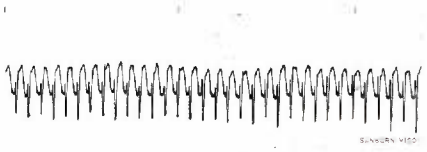
CONTROL



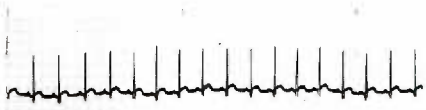
1 MIN. POST METHOXAMINE



30 SEC. POST EPINEPHRINE



1 MIN. POST EPINEPHRINE



RECOVERY

TABLE III

Protection by Methoxamine Against Chloroform - Epinephrine Induced Ventricular Fibrillation

Methoxamine dose mg./Kg.	Number of dogs used	Characteristic arrhythmia following chloroform-epinephrine "challenge"
0	5	Ventricular fibrillation
0.1	1	1 ventricular fibrillation
0.2	1	No ventricular fibrillation
0.25	1	Ventricular tachycardia followed by fast AV nodal rhythm
0.5	3	Rapid AV nodal rhythm followed by premature ventricular systoles
1.0	1	Brief period bigeminal rhythm and premature ventricular systoles

ventricular fibrillation after bilateral vagotomy (see table IV). Methoxamine did not prevent the pressor effect of epinephrine.

In three animals subjected to this procedure, with the substitution of Levophed for Vasoxyl, ventricular fibrillation occurred in all three immediately following the injection of Levophed. This is in accord with the findings of Melville.

Three animals received Neo-Synephrine as a substitute for Vasoxyl in this procedure and in no case did ventricular fibrillation occur.

Myocardial infarct: Myocardial infarcts produced by injecting zinc hydroxide suspensions are not followed by cardiac arrhythmias. The ST junction or segment and T wave alterations typical of myocardial infarcts were the only changes. Dogs included in this report had lesions in the anterior wall of the left ventricle (verified at autopsy). Methoxamine, 0.5-2.5 mg./Kg., did not incite any cardiac arrhythmias. Rather, there was the usual cardiac slowing with occasional sinus pauses. The ST junction was elevated and inverted T wave reversed to an upright position. These electrical indications of improved function which followed methoxamine administration may be due to a restoration of normal intraventricular pressures.

In contrast epinephrine, 10 microgram/Kg., administered to dogs with myocardial infarcts was followed by frequent premature systoles, bigeminal and trigeminal rhythm and ventricular tachycardia from shifting and variable ventricular foci, and even ventricular fibrillation (see figure 4).

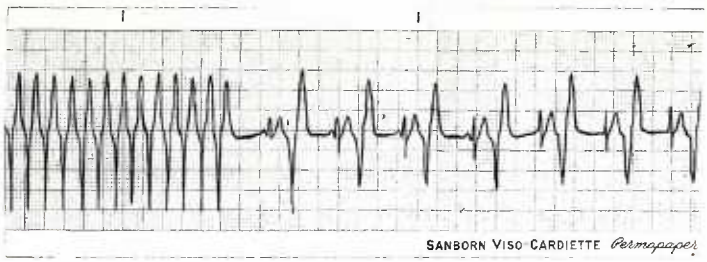
TABLE IV

Results of Vasoxyl in Melville Procedure After Bilateral Vagotomy

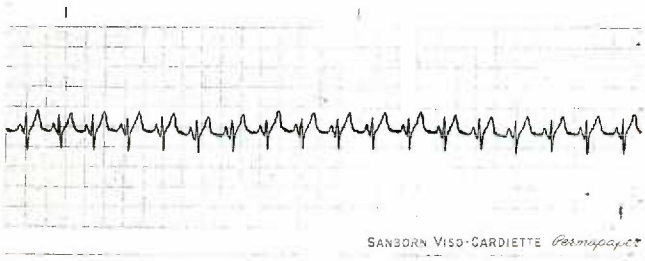
Dose of Vasoxyl mg./Kg.	No. of dogs.	Effect on the EKG
0	2	2 ventricular fibrillation
0.1	1	Ventricular fibrillation
0.2	1	Ventricular tachycardia and ectopic beats followed by complete recovery
0.25	2	2 ventricular tachycardia; complete recovery
0.5	1	Ventricular tachycardia; complete recovery
1.0	1	Ventricular tachycardia; complete recovery

FIGURE 4

Section of EKG of a dog which has received a myocardial infarction with $Zn(OH)_2$ according to Meyer's method. This section illustrates typical effects of epinephrine in these animals.



One minute post epinephrine I.V.
20μ/kg



Two minutes post epinephrine

DISCUSSION

Constant Injection - Undamaged Hearts

Respiratory depression was evident in nearly all instances almost immediately following the injection of Vasoxyl. The degree of depression roughly followed the strength of dose used (see table I). In all but one case the most severe period of respiratory depression coincided with the period of maximum blood pressure rise. The initial severe depression was followed by a somewhat improved respiration in all dogs except the 0.8 mg./Kg./min. and 1 mg./Kg./min. dosage during which the animals died. The respiratory depression in these cases was definitely a factor in their death. The possibility must be considered whether the respiratory depression mirrors a general central nervous system depression. Another facet is the possibility of the late fall in blood pressure being due to anoxia of the vessel walls secondary to respiratory depression. This is not probable because higher doses cause rapid fall in blood pressure following the initial rise; the blood pressure fall is too rapid to be the result of anoxia.

The Cheyne-Stokes type respiration which occurred is thought not to be due to shock. The appearance of the Cheyne-Stokes respiration consistently occurred at a time when the blood pressure was high. I believe it is due directly to cardio-respiratory reflexes with some degree of depression of the central nervous system by Vasoxyl. Furthermore, in a dog which received intermittent doses of Vasoxyl, Cheyne-Stokes respirations rapidly appeared following Vasoxyl injection and disappeared as the effects of the drug wore off. Subsequent doses of Vasoxyl in this animal showed less and less effect on

blood pressure but always showed signs of respiratory depression. This intermittent dosage work should be followed up. Respiratory distress was noted by deBeer and associates[13].

It was further noted that injection of Vascoxyl caused wakefulness and movements of extremities in animals under barbital sodium anesthesia. This is probably due to increased flow of blood to the brain. This, of course, was proportional to the degree of blood pressure rise. Examination of the animals showed lid reflex present, corneal reflex present, pupils dilated but an absent light reflex. At the same time, though these animals appear to be coming out of anesthesia, they are very sensitive to further doses of barbiturates. It is hypothesized that the increased oxygenation of the brain causes wakefulness though the barbiturate is still present in the tissues and if Vascoxyl is causing some central depression, additional barbiturate might prove synergistic in action.

The characteristic signs of emerging from anesthesia may be due to merely increased intracranial blood flow. Certain areas of the cortex may be actively depressed by methoxamine but most of the signs of this be masked by better oxygenation through increased blood flow. Thus when the dog receives more barbiturate, the depressant action may become predominant. The theory that methoxamine has a depressant phase on the cortex is based on the constant appearance of respiratory depression and the respiratory deaths. No conclusions can be drawn definitely on this at this time.

One of the first clinical signs of overdosage in dogs is a depression of respiration which is considered a distinct advantage of this drug. Respiratory distress becomes evident at drug levels well below fatal levels.

Blood Pressure - Reference is made to figures 1 and 2. The blood pressure response was progressively less with increasing dosage, especially in duration. At this time this is thought to be tachyphylactic in nature. This was also noted in animals by deBeer et al[13], though in a private communication Dr. deBeer states tachyphaxis has not been reported in patients. There is some indication that in doses of 0.5 mg./Kg./min. and greater that the per cent rise may be greater than that for low doses but the duration of effect is much less.

The optimum dosage range for maximum sustained effect in normal dogs is about 0.025 mg./Kg./min. The sub-minimal dose is 0.01 mg./Kg./min. and below. Doses of 0.5 mg./Kg./min. and over are the toxic range and may cause varying blood pressure rises and death from respiratory depression.

Effects on the Heart - Reference is made to figures 5 and 6. All doses produced bradycardia, the severity of which apparently increased with the dose (within limits).

Using 0.025 mg./Kg./min. there was an initial drop in heart rate and the coinciding blood pressure rose to slightly above control levels where it was maintained.

In all other doses as the blood pressure fell, there was no compensatory rise in heart rate. This leads one to question whether the bradycardia is due to the carotid sinus reflex. According to Fassett and Toube[14] the pulse rate was almost invariably slowed and the degree of slowing was proportional to the extent of pressor response. No such correlation was seen in my work. Fassett and Toube also abolished the

FIGURE 5

Graphic representation of the relative effects on blood pressure and heart rate of constant infusion of Vasoxyl in a low concentration (0.01 mg./Kg./min.).

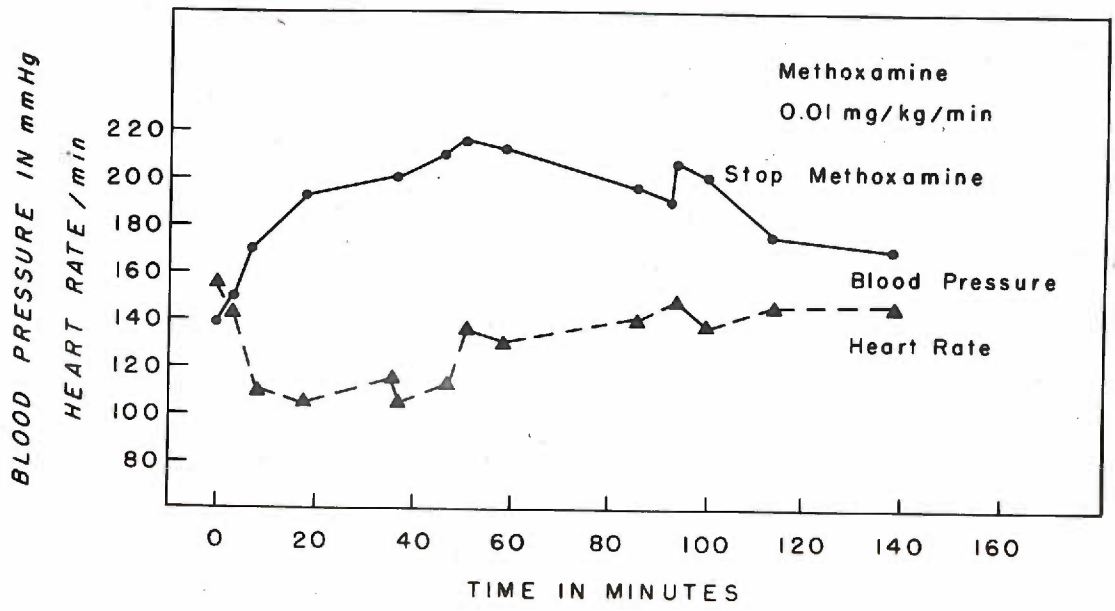
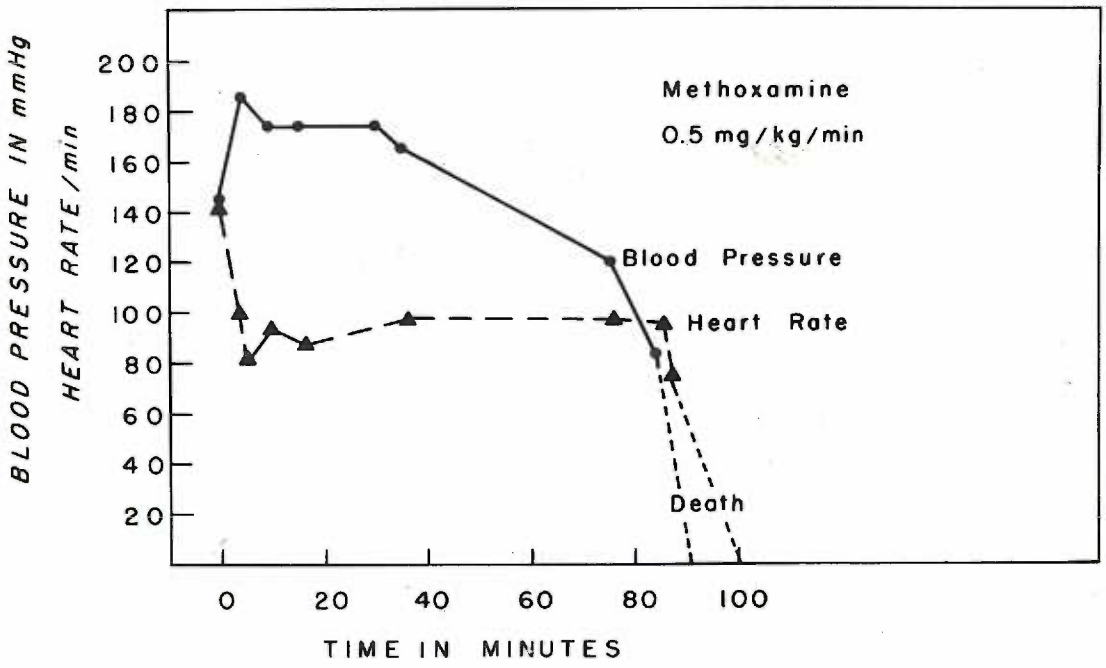

BLOOD PRESSURE IN mmHg
HEART RATE / min
220
200
180
160
140
120
100
80
0
20
40
60
80
100
120
140
160
TIME IN MINUTES
Methoxamine
0.01 mg/kg/min
Stop Methoxamine
Blood Pressure
Heart Rate

FIGURE 6

Graphic representation of the relative effects on blood pressure and heart rate of constant infusion of Vasoxyl in a high concentration (0.5 mg./Kg./min.).


BLOOD PRESSURE IN mmHg
HEART RATE/min
200
180
160
140
120
100
80
60
40
20
0
20
40
60
80
100
TIME IN MINUTES
Methoxamine
0.5 mg/kg/min
Blood Pressure
Heart Rate
Death

bradycardia with atropine indicating that heart rate slowing was due to one or more of the following:

(1) stimulation of vagal center

(2) hypertonicity of vagus

(3) depressant effect on myocardium and intrinsic conducting nerves

(4) depressant or competitive action on enzyme systems of vagal system of myocardial conduction bundles.

Bradycardia was the most consistent effect of Vasoxyl on the heart. No other significant constant effects were noted in the electrocardiogram at low dosages.

Other workers[5] have shown that atropine abolishes the bradycardia which indicates that whatever the origin of the bradycardia it is mediated through the vagus nerve. In low doses it may be, to a degree at least, a normal carotid sinus reflex but in doses of 0.025 mg./Kg./min. and above it is not the result of carotid sinus reflex alone. This cardiac slowing is evidence again of the lack of irritation of the myocardium of this drug. We believe that unlike most of the pressor agents available methoxamine causes no stimulation of the heart and thus should be of value in hypotension of myocardial infarction.

Though bradycardia was a constant effect, our records indicate an initial increase in stroke volume followed eventually by diminished stroke volume (see figure 8). This was particularly noteworthy in the higher dosage ranges. This aspect is to be studied further with more accurate methods. The ultimate decrease in stroke volume was somewhat more severe with higher doses. The stroke volume was only slightly increased with

a dose of 0.025 mg./Kg./min. the optimum dose in our experiment. We believe that the cardiac output is not significantly changed at this dose level.

The apparent decrease in stroke volume of the heart which occurred following the initial increase late in each dog could be due to fatigue or anoxia secondary to respiratory depression.

Toxicity - Death could be produced so far only in animals receiving 0.5 mg./Kg./min. and over. This work indicates that death is primarily due to respiratory distress directly and indirectly through anoxia.

CYCLOPROPANE

These experiments indicated again the lack of irritating effect of Vasoxyl on the myocardium. This is described more fully in the discussion of the Melville Technique immediately following.

In no case in this group of experiments did epinephrine cause ventricular fibrillation when it had been preceded by Vasoxyl.

Though there was no attempt made in these experiments to determine the length of time which Vasoxyl would inhibit or alter the cardiac effects of epinephrine, there are indications that sooner the epinephrine is given following the Vasoxyl, the less the effect. In one experiment epinephrine was given about 9 minutes following the Vasoxyl and no increase in heart rate was seen. However, in this same animal a subsequent dose of epinephrine given approximately 50 minutes following the Vasoxyl produced a significant rise in heart rate. This relationship was seen several times. Other experiments frequently showed that the

first dose of epinephrine following Vasoxyl would cause less of a rise in heart rate than the second dose. The same effect was found to be true regarding the incidence and severity of cardiac arrhythmias due to epinephrine.

Melville Technique

The observation that Vasoxyl produced a bradycardia which was apparently independent of blood pressure and that Vasoxyl apparently had no significant irritant effect on the myocardium, led us to study the drug in animals whose hearts had been "sensitized" by chloroform. It is well known that during this procedure as originally described by Melville[8] epinephrine will produce ventricular fibrillation in all the dogs tested.

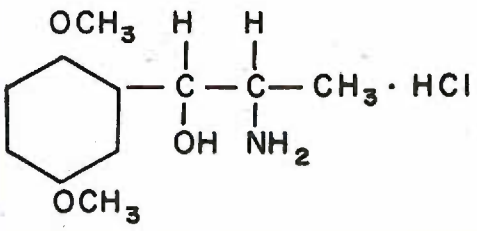
The facts that not only did the administration of Vasoxyl to these animals fail to evoke serious cardiac arrhythmias but further would effectively prevent epinephrine-induced fibrillation, make this pressor amine unique. This effect of preventing epinephrine-induced fibrillation provokes a consideration of the mechanism by which epinephrine causes this phenomenon. It is obvious that it is a direct irritant effect on the myocardium for ventricular fibrillation will occur in the heart which has been isolated from its nerve supply. Determination of the exact nature of this irritant effect is, however, beyond the scope of this investigation. One can suggest the possibility of epinephrine altering enzyme systems or destroying or altering intracellular electrolyte balance.

Vasoxyl, as has been noted before, produces a bradycardia independent of blood pressure and, therefore, independent of the vagal reflex as it is commonly accepted. Now, in these Melville procedures, further evidence is shown that not only does Vasoxyl fail to incite arrhythmias, but it actually may be protective to the myocardium against certain arrhythmias. By blocking, at least in part, the direct irritant action of epinephrine on the myocardium, it may be postulated that Vasoxyl is also acting directly on the myocardium in this respect.

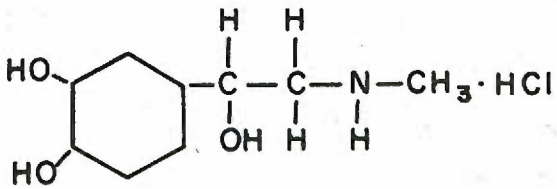
Further evidence of the active protective action of Vasoxyl on the myocardium is shown in that identical results were obtained in animals that received bilateral vagotomy and then were subjected to the Melville procedure. In these animals ventricular fibrillation could not be produced by epinephrine when preceded by Vasoxyl. In the light of present knowledge, it is therefore proposed that Vasoxyl has at least one effect on the myocardium directly.

The exact nature of this "protective action" of Vasoxyl cannot be stated since the exact nature of the mechanism by which epinephrine produces ventricular fibrillation is not yet clear. It is also proposed, however, that this protection against epinephrine-induced fibrillation may be a competitive inhibition type of mechanism. Comparison of the chemical structures of the two compounds as illustrated below indicate that this is not an impossibility.

Methoxamine
(Vasoxyl)



Epinephrine



The duration of this so-called protective action of Vasoxyl was not studied.

$Zn(OH)_2$ - Infarcts

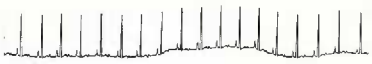
The lack of irritant qualities of this amine on the myocardium is illustrated again by these experiments. In the animals in which we felt we had been successful in producing an infarct, Vasoxyl did not provoke any significant arrhythmias even when administered in doses greater than are used clinically. This can best be illustrated by referring to a representative EKG from one of these animals (see figure 7). It is to be noted that, as compared to the effects of epinephrine in this animal, Vasoxyl was relatively benign.

Due to the many variables which are readily apparent in this type of experiment, it is difficult to draw any exact conclusions from them. This difficulty is compounded by the lack of time and funds needed to perform enough of this type of experiment to make even the above vague impressions statistically significant. All we have attempted to state regarding these experiments is that there is an <u>indication</u> here that Vasoxyl is not likely to cause arrhythmias in animals subjected to Meyers' method of producing infarction.

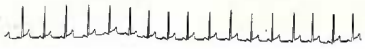
Lack of untoward effects of methoxamine used in animals with experimentally damaged hearts tends to discredit the warning against the use of <u>all</u> pressor amines in clinical heart disease. The failure of this amine to excite ventricular arrhythmias in cyclopropane sensitized hearts is a factor favoring choice of this agent to maintain adequate

FIGURE 7

Sections taken from EKG of a dog in which a myocardial infarct had been produced by $Zn(OH)_2$ according to the method of Meyer. These sections show typical effects of Vasoxyl and epinephrine.

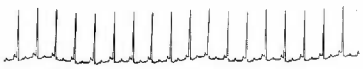


3:40 P.M. CONTROL LEAD II

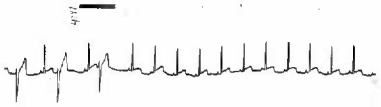


4:30 P.M. LEAD II

$Zn(OH)_2$ INJECTED AT 3:54 P.M.

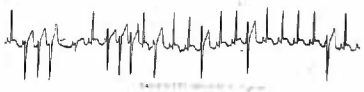


4:00 P.M. LEAD II

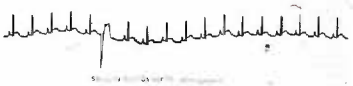


4:47 P.M. LEAD II

2nd INJECTION OF $Zn(OH)_2$ GIVEN AT 4:14 P.M.

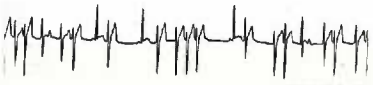


4:21 P.M. LEAD II



5:01 P.M. LEAD II

5:10 P.M. 20 mg/kg EPINEPHRINE INJECTED I.V.



4:27 P.M. DURING INJECTION OF VASOXYL

5:11 P.M. LEAD II

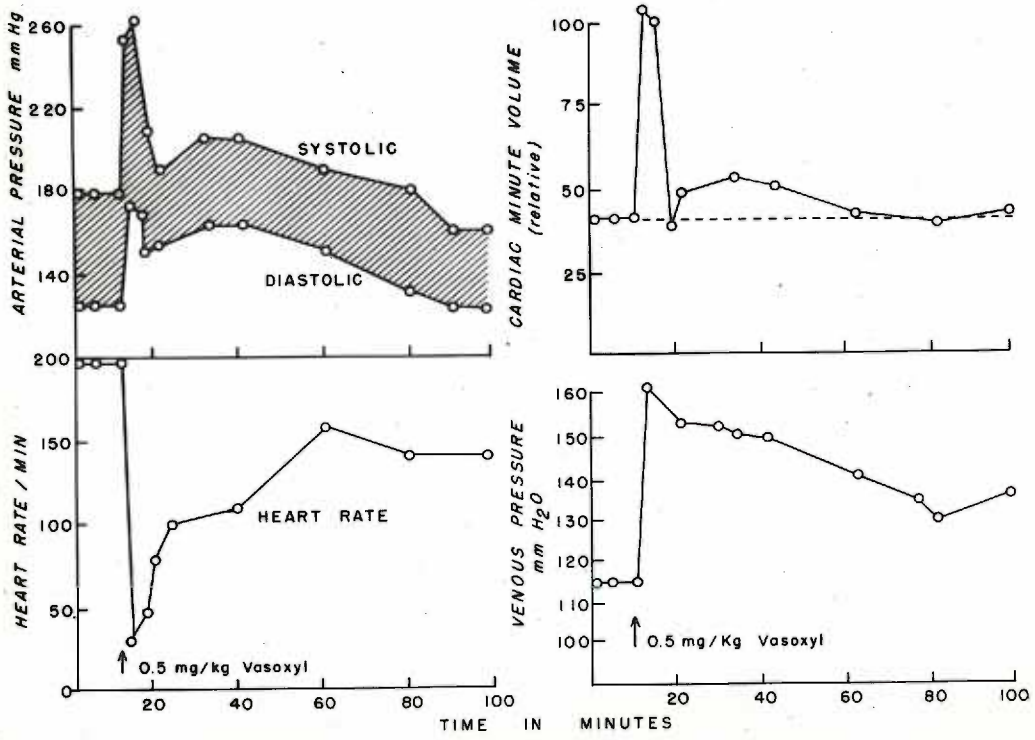
blood pressures during surgery. Particularly pertinent is the finding that methoxamine can prevent epinephrine induced ventricular arrhythmias. This action is apparently independent of the drug's pressor action or vagal stimulation. Our observations indicate that methoxamine should be given extensive clinical trial to prevent or arrest cardiac arrhythmias. According to a few case reports, methoxamine was used with success in arresting supraventricular tachycardia (Nathason and Miller[5]; Berger and Rackliffe[15]), though these authors indicated this effect was thought to be due to a vagal reflex.

A more detailed analysis of the cardiovascular actions of a single intravenous dose of 0.5 mg./Kg. methoxamine was made using electromanometers and multiple recording. The results are illustrated in figure 8. The initial period of high arterial pressures and bradycardia are related to the rapid rate of injection. It would appear that the hypertensive action of methoxamine is related to the increased venous pressure - a reflection of increased peripheral resistance. The cardiac output, calculated by the indirect method of Hamilton and Remington[16] was maintained despite an evident slowing of heart rate. Following bilateral vagotomy and the same dose of methoxamine, the slowing of heart rate was not as marked. As a consequence the cardiac output could not be maintained at the initial rate during methoxamine's hypertensive action. This would indicate that methoxamine has no direct myocardial stimulating action, i.e. there is no positive inotropic effect.

Youmans and Goodman, both then at the University of Oregon Medical School, first described the use of Neosynephrine (phenylephrine) for the reduction of supraventricular tachycardia to normal sinus rhythm[17].

FIGURE 8

Effect of methoxamine hydrochloride, 0.5 mg./Kg., in a dog anesthetized with sodium barbital. All pressures were recorded with "isometric" electromanometers. The cardiac output was obtained by the indirect method from pulse pressures.


ARTERIAL PRESSURE mm Hg
260
220
180
140
SYSTOLIC
DIASTOLIC
CARDIAC MINUTE VOLUME (relative)
100
75
50
25
HEART RATE / MIN
200
150
100
50
0
HEART RATE
0.5 mg/kg Vasoxyl
VENOUS PRESSURE mm H_2O
160
150
140
130
120
110
100
0.5 mg/Kg Vasoxyl
20
40
60
80
100
TIME IN MINUTES

The mechanism of antiarrhythmia action for this drug was proposed as a stimulation of pressor receptors in the carotid sinus and reflex discharge of the vagus nerve. The action of the vagus endings on the sino-auricular node slow its repetition rate and normal sinus rhythm supervenes. Massage of the carotid sinus region and performing the Valsalva maneuver in patients with supraventricular tachycardia also invokes reflex discharge of the vagus.

Vasoxyl by causing an increased pressure in the carotid sinus also will cause reflex vagal discharge in patients with supraventricular tachycardia. The experiments reported in this thesis indicate that, in addition, Vasoxyl acts directly on the myocardium to cause slowing of heart rate. Thus, because of the dual action of Vasoxyl to cause cardiac slowing, it was considered advisable to give it a therapeutic trial in patients with supraventricular tachycardias; and to compare it with Neosynephrine.

It has been reported in the literature as being used for this condition before. Berger[15] reported two cases which were refractory to the usual methods of treating supraventricular tachycardia that responded to 10 mg. doses of Vasoxyl. He felt that the successful results were due to carotid sinus reflex activity in contrast to our feeling.

CASE HISTORIES

Clinically, this drug has been employed in several cases of supraventricular tachycardia. Five such cases are briefly summarized as follows:

Case 1. A sixty-four year old janitor of Italian birth was admitted to St. Vincent's Hospital 9/19/53 for treatment of paroxysmal tachycardia. He had had intermittent attacks of tachycardia since 1920, at intervals of one week to five months. For the past four years he had been taking 0.2 gm. of quinidine three times daily, increasing the dose to 0.4 gm. every four hours when an episode of tachycardia occurred. He was not taking digitalis.

Past history was negative for rheumatic fever, hypertension or any other condition which might cause heart disease.

The present attack began three weeks prior to admission, and unlike previous episodes did not respond to quinidine, carotid sinus pressure or Valsalva maneuver. During this attack congestive failure developed for the first time.

On physical examination there were signs of congestive failure as indicated by breathlessness, distended neck veins, enlarged liver and bilateral ankle edema. Heart was enlarged to percussion, action was regular and rapid with an apical rate of 180 per minute. Blood pressure: 108/94. Electrocardiogram showed a paroxysmal supraventricular tachycardia. Chest X-ray showed passive congestion and an enlarged cardiac silhouette measuring 16 1/2 cm. in transverse diameter. Administration of morphine and phenobarbital sodium relieved apprehension but had no

effect on the ectopic rhythm. Carotid sinus massage, eyeball pressure and Valsalva procedure were likewise without effect.

On 9/20/53 he received 0.6 mg. of digitoxin intramuscularly at 10:30 A.M. and 0.4 mg. intramuscularly at 2:30 P.M. At 5:00 P.M. his apical heart rate was 64 per minute. At 1:30 A.M., 9/21/53, his heart rate again increased to 160 and 0.2 mg. digitoxin was administered. Normal heart rate was resumed at 7:00 A.M., 9/21/53.

Chest X-ray was repeated on 9/21/53 and showed no evidence of congestion and a heart size of 15.9 cm. An electrocardiogram taken at this time was within normal limits.

On 9/24/53 the heart rate again increased to 180 per minute with a blood pressure of 108/102. An intravenous infusion of 50 mg. Vasoxyl in 500 cc. glucose in water was started after the tachycardia had persisted for one hour despite attempts at conversion by using carotid sinus massage and the Valsalva maneuver. Twelve minutes after the infusion was started the blood pressure suddenly increased to 162/140 and the cardiac rate dropped to 52 per minute. The infusion was discontinued. The patient had received approximately 8 mg. of Vasoxyl at the time of conversion to normal sinus rhythm. Within fifteen minutes the blood pressure had returned to 138/78. A normal heart rate was maintained until two hours later when tachycardia of 160 began. After four and one-half hours of tachycardia which did not respond to mechanical maneuvers nor to intramuscular administration of 0.4 mg. digitoxin, Vasoxyl infusion was started. Blood pressure was 102/92. Six minutes after infusion was begun, the blood pressure increased to 168/100 and

the heart rate dropped to 56. The patient had received 4 mg. Vasoxyl. Ten minutes later the blood pressure was 142/86. The electrocardiogram exhibited normal sinus rhythm.

The patient had one other transient episode of tachycardia lasting a few minutes. He was discharged from the hospital on maintenance dosage of digoxin.

Case 2. A 70 year old white female was admitted to St. Vincent's Hospital 10/16/53 with a history of having had nothing to eat for one week; during this time had nausea, vomiting and diarrhea.

Family history: Mother died of diabetes; father died at 73 years of kidney stones and cancer.

Past history revealed that patient had paroxysmal auricular tachycardia for the past 25 years. Attacks last minutes to days. Last attack was 1 month ago, lasted 30 hours. Attacks previously stopped with digitalis and quinidine. Mechanical measures have always failed at conversion. For the past few years the patient has had exertional dyspnea.

Physical examination revealed a few moist rales in the bases of both lungs, a soft systolic murmur in left second to fourth interspaces, and hypotonic reflexes. Pedal pulses were not palpable. No edema. The electrocardiogram showed a supraventricular tachycardia; rate of 200 per minute associated with myocardial ischemia.

All mechanical measures failed to convert the arrhythmia. Lanatocide, 0.8 mg. (Cedilanid), was given without effect. Two hours later 10 mg. morphine was administered; sometime within an interval of two hours conversion took place; rate 98 per minute.

On 10/24/53 the rate increased to 174. Morphine, 8 mg., 1/8 was given with no effect. Rate further increased to 200. Vasoxyl, 8 mg. was given intravenously with abrupt change to a rate of 112 per minute.

On 10/27/53 rate was 224 per minute. Digitalis was started but because of subjective complaints - chest pain and dyspnea - Vasoxyl was again given. At start of Vasoxyl intravenously the blood pressure was 110/70, pulse 220. There was abrupt conversion after 4 mg. of Vasoxyl. After conversion blood pressure was 172/94, pulse 84.

Patient was digitalized and has had no recurrence of the tachycardia up to time of discharge (11/2/53).

Case 3. This patient was in moribund condition when first seen. The history suggested acute myocardial infarction but there was no opportunity for an electrocardiographic confirmation of the diagnosis. The patient had been in shock for several hours and no pulse could be detected at the time when first seen. The blood pressure could not be obtained. Under Vasoxyl infusion the pulse became palpable and the blood pressure rose to 120/80. However, death followed within a few minutes and no autopsy was obtained. This case is included to show that, in a case of extreme shock probably in association with a badly damaged heart, Vasoxyl was at least temporarily effective in raising the blood pressure and improving the quality of the pulse.

Case 4.* A sixty year old white man was admitted to St. Vincent's Hospital on 12/16/52 in shock from an acute posterior wall myocardial infarct. The blood pressure on admission was 135/80 but dropped below 70/52 (the last measurable reading) in 7½ hours. Two units of plasma

and ½ unit of blood were administered during the next 5½ hours resulting in a blood pressure of 62/50.

Vasoxyl was administered at approximately 0.25 mg./min. (50 mg. Vasoxyl, 500 cc. 5% glucose, 40 ggt./min.) maintaining a pressure of approximately 80/60 with some slowing of pulse rate. Lanatocide 1.2 mg. (6 cc. Cedilanid) was administered during this time and resulted in some slight further improvement 90/72. Lanatocide C was readministered to maintain digitalization and sodium heparin and sodium phenobarbital also administered.

It was believed that Vasoxyl was primarily of value in maintaining a normotensive state. At initiation of Vasoxyl administration the blood pressure was almost 62/50 which was maintained between 104/72 and 122/78 by adjusting drip rate. Pressures fell below 80/50 when Vasoxyl administration was stopped. A total of 320 mg. Vasoxyl was administered during a 41½ hour period of time. At the time Vasoxyl was discontinued the blood pressure was 110/74 and it was maintained between 110/74 - 118/70.

The patient expired 26½ hours after cessation of Vasoxyl. Autopsy indicated a ruptured posterior wall infarct.

Case 5* A 75 year old woman was admitted to St. Vincent's Hospital 11/16/53. A diagnosis of extension of anterior wall myocardial infarct was made. Vasoxyl was administered in an effort to raise blood pressure which on admission was 87/?. Five mg. Vasoxyl raised the pressure to 110/78 which was maintained until patient was discharged. There were no arrhythmias other than the expected bradycardia. A slight increase in dyspnea was observed but was not believe caused by the pressor amine.

Comment: These five patients are presented primarily to show that elevation in blood pressure can be obtained by the use of Vasoxyl without the development of cardiac arrhythmias.

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* Cases 4 and 5 were obtained through the courtesy of Dr. H. L. H. Dick.

SUMMARY

1. Methoxamine caused a sustained rise in blood pressure when administered in the dose of 0.025 mg./Kg./min. in normal dogs. Higher doses exhibited correspondingly rapid production of refractoriness which is assumed to be tachyphylactic in nature. Thus, excessive increases in blood pressure in dogs are difficult to produce with this drug.

2. One of the first clinical signs of overdosage in dogs is a depression of respiration which is usually considered a distinct advantage. Respiratory distress becomes evident at drug levels far below fatal levels. Thus, any respiratory interference may be used to advantage as a warning sign against possible overdose and toxicity.

3. Bradycardia is constantly seen when methoxamine is administered. In low doses it may be, to a degree at least, a normal carotid sinus reflex but in doses of 0.025 mg./Kg./min. and above it is not the result of carotid sinus reflex alone. This cardiac slowing is evidence again of the lack of irritation of the myocardium of this drug. We believe that unlike most of the pressor agents available methoxamine causes no stimulation of the heart and thus should be of value in hypotension of myocardial infarction.

4. There is some indication that the stroke volume of the heart is initially increased especially with higher dosages. The stroke volume was only slightly increased with a dose of 0.025 mg./Kg./min., the optimum dose in our experiment. We believe that the cardiac output is not significantly changed, however, at this dose level.

5. In these dogs care must be observed to administer additional anesthetic, especially barbiturates, carefully. The animal's tissues are saturated or nearly so with barbiturate and also seem to be exceedingly sensitive to any additional anesthetic of this type when receiving methoxamine. This drug may cause depression of certain areas of the cortex.

6. In the animals whose hearts were made susceptible to cardiac arrhythmias, methoxamine failed to provoke such arrhythmias. The experimental techniques used included cyclopropane or chloroform sensitization, myocardial infarcts and diphtheria toxin myocarditis. Methoxamine, moreover, prevented epinephrine-cyclopropane or epinephrine-chloroform ventricular tachycardia and ventricular fibrillation. Epinephrine-chloroform induced ventricular fibrillation was effectively blocked by pre-treating with Vasoxyl even after bilateral vagotomy.

7. Methoxamine in overdoses causes sinus pauses and brief periods of AV nodal rhythm. At lethal dosage of methoxamine when death occurs from respiratory arrest cardiac action is still maintained satisfactorily. Methoxamine's pressor effects appear due to increased peripheral resistance; there was no evidence of direct myocardial stimulation.

8. The results obtained with Vasoxyl by constant rate of injection indicate that it may be used by the intravenous drip technique, although the usual recommendation is for intramuscular administration. The use of Vasoxyl by drip appears to have several advantages in addition to eliminating the need for precise titration of dose. Overdosage signs

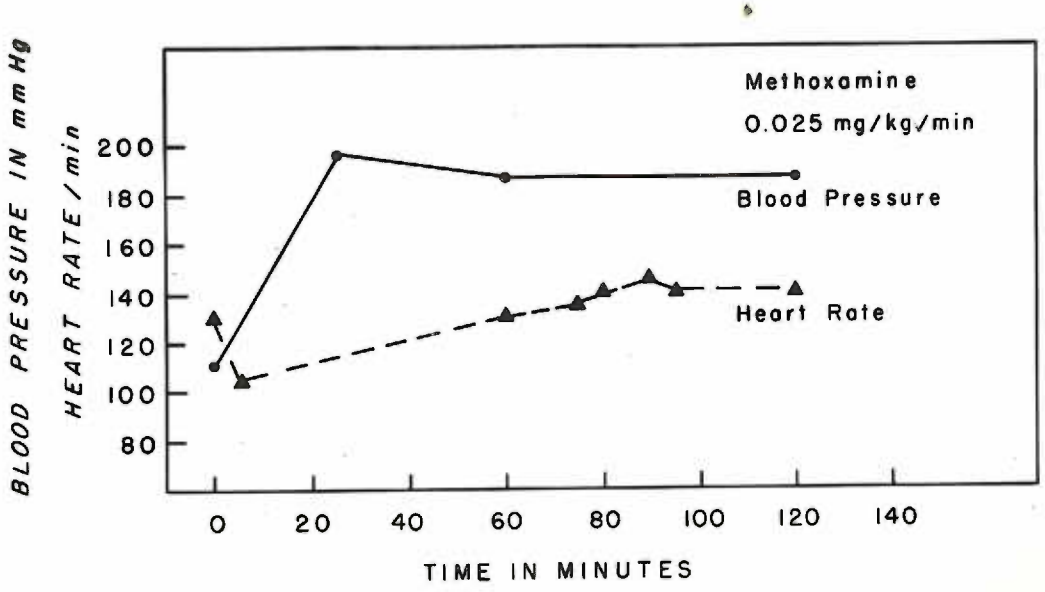
and symptoms, sinus pauses, extrasystole, and irregular breathing appear very early before any serious toxic effects become manifest. Tachyphylaxis to the drug's pressor action is a buffer preventing dangerous hypertensions.

APPENDIX

Summaries of experiments reported in this thesis.

FIGURE 9

Graphic representation of the results of the Constant Injection Experiment using Vasoxyl on February 26, 1953.


BLOOD PRESSURE IN mm Hg
HEART RATE / min
200
180
160
140
120
100
80
0
20
40
60
80
100
120
140
TIME IN MINUTES
Methoxamine
0.025 mg/kg/min
Blood Pressure
Heart Rate

February 26, 1953. Constant Injection Experiment Using Vasoxyl. See figure 9.

A 6.04 Kg. fasted female dog was anesthetized at 2:15 P.M. with sodium barbital given intraperitoneally in a dose of 250 mg./Kg. The animal was placed supine on an animal board and an incision made over the femoral vein. This vein was exposed and cannulated with a small polyethylene cannula to which was attached a syringe from the constant rate injection machine. The syringe contained a solution of Vasoxyl calculated to deliver a dose of 0.025 mg./Kg. The solution was adjusted so as to deliver this dose in 1 cc. volume every minute. The recording in this experiment was done by means of a smoked drum kymograph which recorded carotid blood pressures and respirations. A blood pressure zero line and a time scale were also inscribed on the drum. A single channel Sanborn electrocardiograph was attached to the animal and intermittent lead II EKG's were taken throughout the experiment. Control EKG's were taken in leads I, II, III, AVR, AVL and AVF. The controls were as follows: Respirations regular, see accompanying figure; blood pressure, 116 mm. of mercury; heart rate, 130 per minute, regular; EKG patterns were within normal limits and no abnormalities were noted except for an inverted P wave.

At 3:20 P.M. the injection of Vasoxyl was started. The first blood pressure rise was noted within 80 seconds. The blood pressure continued to rise at a constant rate until 23.3 minutes after the start of the injection when it was maintained at a level of 196 mm. of mercury the remainder of the experiment.

Forty minutes following the start of the injection, the respirations became irregular assuming the pattern of a Cheyne-Stokes respiration. This respiratory pattern was noted throughout the remainder of the experiment.

No alterations in the electrocardiographic pattern were noted other than the P wave becoming upright within about 5 minutes following the start of the injection and remaining so for about an hour. At that time the P wave returned to control height and pattern. The heart rate dropped to 119 per minute and remained regular within 25 minutes following the start of the experiment. At one hour following the start of the experiment the heart rate was 130 and in one and one-quarter hours it was 135. This continued to rise until at one hour and thirty-five minutes following the start of the injection when the heart rate was 140 per minute where it remained for the remainder of the experiment. No other changes were noted during this experiment. The dog was returned in good condition.

March 7, 1953. Constant Injection Experiment Using Vasoxyl.

A 7.7 Kg. male dog was anesthetized with sodium barbital in the dose of 250 mg./Kg. given intraperitoneally at 9:10 A.M. The femoral vein was exposed and cannulated with a polyethylene cannula to which was attached a syringe mounted on a constant rate injection machine. This syringe contained a solution of Vasoxyl in the dose of 0.025 mg./Kg. This solution was adjusted so that this dose was contained in 1 cc. and 1 cc. to be delivered every minute. Recordings for this experiment

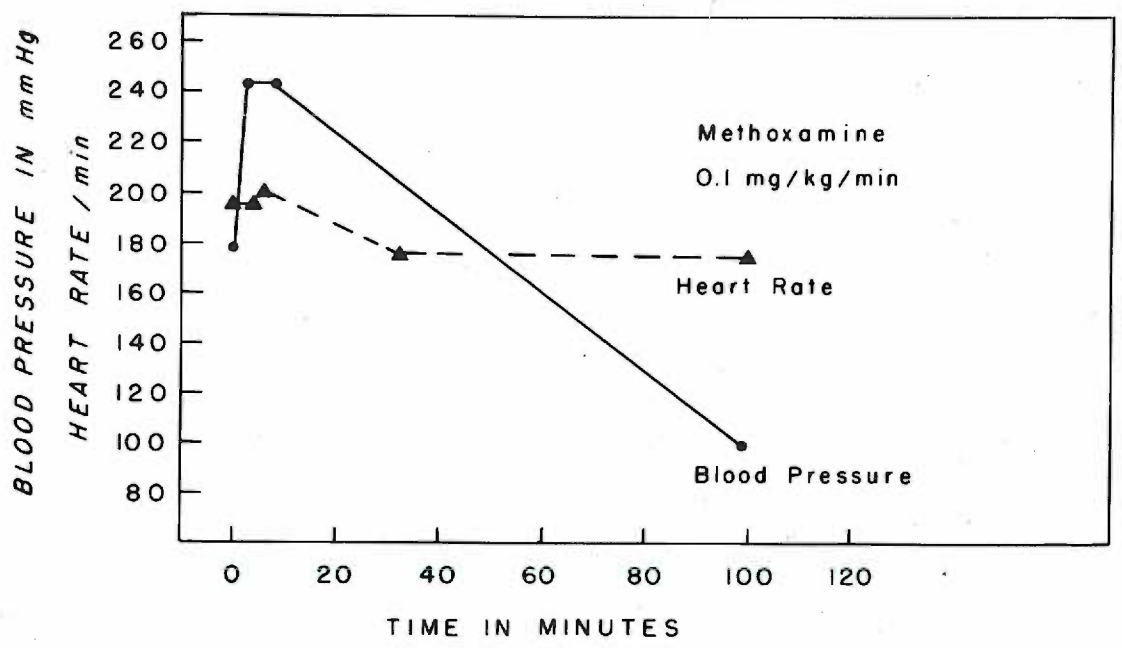
were made on a smoked drum kymograph on which was indicated respirations and carotid blood pressures. Also transcribed on this smoked drum were a blood pressure zero line and a time scale. A lead II electrocardiogram was taken intermittently throughout the experiment on a single channel Sanborn electrocardiograph. The intervals during which the electrocardiograph was being run were also indicated on the kymograph by depressions on the blood pressure zero line.

The injection of Vasoxyl was started at 12:20 P.M. Control EKG's taken during this experiment contained considerable 60 cycle interference. The blood pressure during the control period was 148 mm. of mercury; respiration (control) was 16 per minute, regular; blood pressure rise was noted within 2½ minutes after Vasoxyl was started. This rose steadily for 12 minutes until it reached a point of 224 mm. of mercury. At 30 minutes after the injection of Vasoxyl was started the blood pressure began to decline. At 35 minutes the blood pressure was 194 mm. of mercury. This continued to decline steadily throughout the remainder of the experiment. At one hour it was 170 mm. of mercury; at 1½ hours, 140; at 1 3/4 hours following the start of the injections the blood pressure was 136 mm. of mercury.

Respirations were noted to be markedly depressed at 14 minutes following the injection. A typical Cheyne-Stokes pattern appeared at 22½ minutes. This pattern of respirations became progressively worse throughout the remainder of the experiment.

FIGURE 10

Graphic representation of the results of the Constant Injection Experiment using Vasoxyl on March 25, 1953.


BLOOD PRESSURE IN mm Hg
HEART RATE / min
260
240
220
200
180
160
140
120
100
80
0
20
40
60
80
100
120
TIME IN MINUTES
Methoxamine
0.1 mg/kg/min
Heart Rate
Blood Pressure

March 25, 1953. Constant Injection Experiment Using Vasoxyl. See figure 10.

A fasted female dog weighing 7.95 Kg. was anesthetized at 9:30 A.M. with sodium barbital given intraperitonsally in the dose of 250 mg./Kg. A femoral vein was exposed and cannulated with a polyethylene cannula to which was attached a syringe mounted on a constant rate injection machine. This syringe contained a solution of Vasoxyl adjusted to deliver a dose of 0.1 mg./Kg. in 1 cc. The constant rate injector was adjusted so as to deliver 1 cc. per minute. The recording in this experiment was done on a smoked drum kymograph on which was inscribed blood pressure, taken from a carotid artery; and respirations, taken from a cannula in the trachea. A lead II electrocardiograph was also taken intermittently throughout this experiment. The kymograph was also inscribed with a line indicating zero blood pressure and a time scale. The intervals at which the electrocardiogram was being taken were indicated by depressions on the zero blood pressure line. Controls were taken at 12:05 P.M. and were as follows: EKG heart rate, 195 per minute, regular (other measurements of the EKG were within normal limits); blood pressure, 178 mm. of mercury; respirations, 5 per minute and regular.

Injection of the Vasoxyl was started at 12:10 P.M. The blood pressure started to climb within 1 minute after the start of the injection of Vasoxyl. At 3½ minutes the blood pressure was 242 mm. of mercury. At 6½ minutes the blood pressure was 230 mm. of mercury. At 9 minutes following the start of the injection of the Vasoxyl the blood pressure started to fall. It continued downward steadily until at 100 minutes following the start of the injection the blood pressure was 98 mm. of mercury.

The respirations became more rapid (15 per minute) at 3½ minutes following the start of the experiment. These were also very shallow. At 6½ minutes the respirations had slowed down to 7 per minute, very strong and very slightly irregular. At 14 minutes the respirations assumed a Cheyne-Stokes pattern. This pattern was present throughout the remainder of the experiment.

No alteration was noted in the EKG until 5½ minutes following the start of the injection. At this time the heart rate was 200 per minute with no other significant alteration in the EKG. The heart rate gradually declined until 32 minutes following the start when it stabilized at 175 per minute. The experiment was terminated at 2 o'clock with the animal in the status as noted above.

April 2, 1953. Constant Injection Experiment Using Vasoxyl. See figures 11 and 12.

A fasted 12.05 kg. male dog was anesthetized with sodium barbital given intraperitoneally at 3:00 P.M. in the dose of 260 mg./Kg. A femoral vein was exposed and cannulated with a polyethylene cannula to which was attached a syringe mounted on a constant rate injector machine. This syringe contained Vasoxyl solution adjusted so as to contain 0.2 mg./Kg. per cc. The constant rate injector was adjusted so as to deliver 1 cc. per minute. The recording in this experiment was done by means of a smoked drum kymograph on which was inscribed blood pressure taken from a carotid artery, respirations taken from the cannula in the trachea, a blood pressure zero line, and a time scale. A lead II

FIGURE 11

Graphic representation of the results of the Constant Injection Experiment using Vascuyl on April 2, 1953.

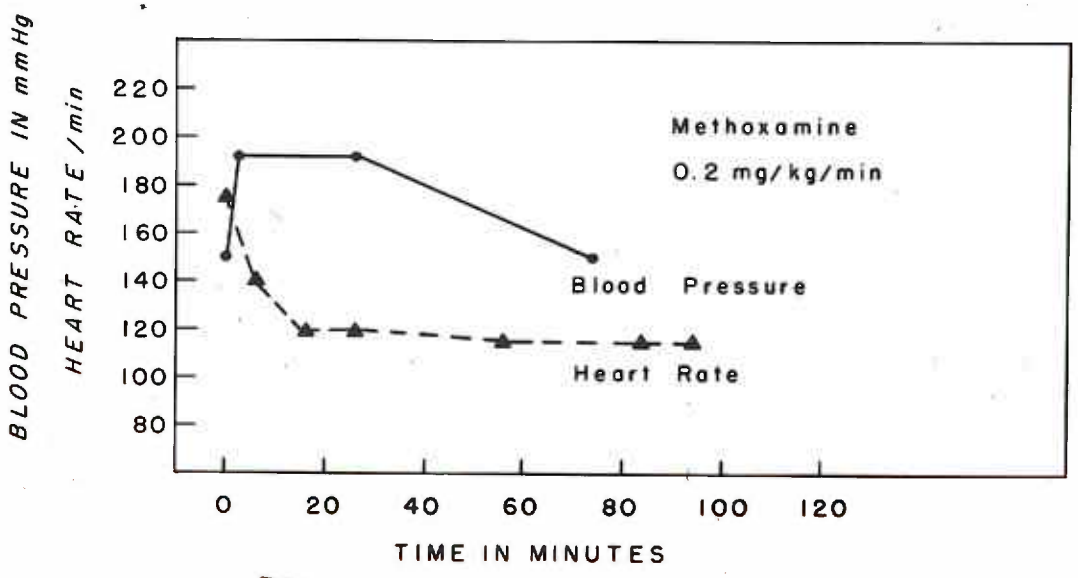
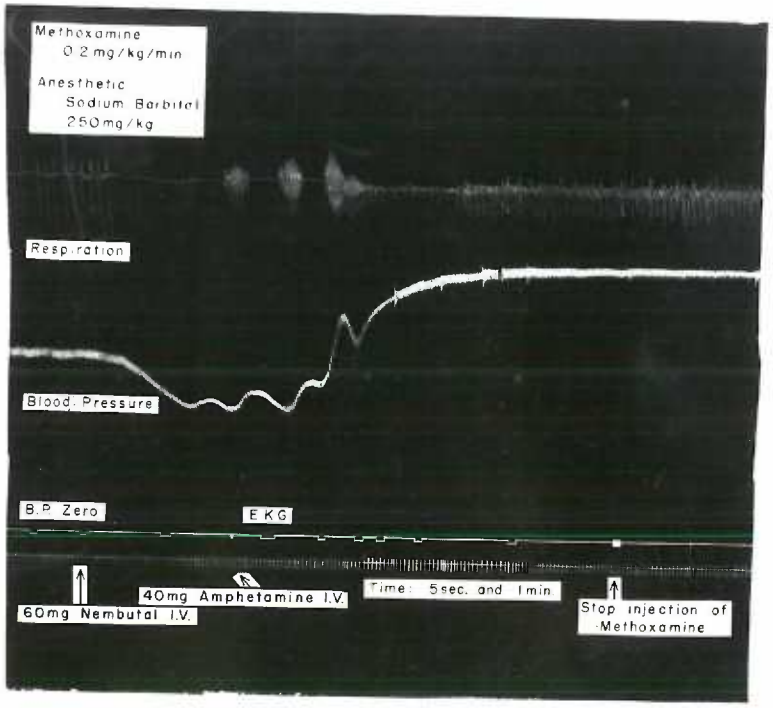

BLOOD PRESSURE IN mmHg
HEART RATE /min
220
200
180
160
140
120
100
80
0
20
40
60
80
100
120
TIME IN MINUTES
Methoxamine
0.2 mg/kg/min
Blood Pressure
Heart Rate

FIGURE 12

Section of kymograph showing effects of amphetamine in Constant Injection Experiment using Vasoxyl on April 2, 1953.


Methoxamine
0.2 mg/kg/min
Anesthetic
Sodium Barbital
250mg/kg
Respiration
Blood Pressure
B.P. Zero
E.K.G.
60mg Nembutal I.V.
40mg Amphetamine I.V.
Time: 5sec. and 1min
Stop injection of Methoxamine

electrocardiogram was also taken intermittently throughout this experiment. The intervals during which the EKG was being taken were indicated by depressions on the blood pressure zero line on the kymograph.

Controls were taken at 4:10 P.M. and they were: Blood pressure, 152 mm. of mercury; respirations, 24 per minute and regular; EKG, heart rate, 175 per minute, regular; no other abnormalities noted in the EKG pattern.

At 4:15 the injection of the Vasoxyl was started. The blood pressure started to rise immediately. Six minutes following the start of the injection, the blood pressure was 182 mm. of mercury. At 11 minutes following the start the blood pressure varied from 190 to 182 mm. of mercury with variations coinciding with the Cheyne-Stokes respiration. Sixteen minutes following the start, the blood pressure varied from 200 to 188 mm. of mercury. Twenty-six minutes following the start of the experiment, the blood pressure started to fall. At 56 minutes the blood pressure varied from 174 to 166 mm. of mercury. At 84 minutes the blood pressure had fallen to 108 mm.

The heart rate started to fall almost immediately following the start of the experiment. By 18 minutes it had reached a level of 120 per minute and became relatively stabilized at approximately that level for the remainder of the experiment (up to the point that amphetamine was administered; see below).

Cheyne-Stokes type respiration appeared within 6 minutes following the start of the experiment. This pattern was maintained until about 80 minutes following the start when the respirations became very irregular. At 87 minutes the respirations were almost negligible. They were weak and extremely irregular.

At 88 minutes, 40 mg. of amphetamine were given intravenously (see figure 12). This resulted in an immediate rise in blood pressure to 126 mm. of mercury, the respirations becoming regular and strong at 23 per minute. The heart rate had climbed to 200 per minute immediately with no other alterations in the EKG pattern. The injection of the Vasoxyl was stopped at this point. Respirations, blood pressure and EKG were all strong and regular. The experiment was terminated.

April 30, 1953. A Constant Rate Injection Experiment Using Vasoxyl.

A fasted 10 Kg. male dog was anesthetized with sodium barbital intraperitoneally at 2:26 P.M. in a dose of 250 mg./Kg. A femoral vein was exposed and cannulated with a polyethylene cannula to which was attached a syringe mounted in a constant rate injector machine. The syringe contained a solution of Vasoxyl adjusted so as to contain a dose of 1.0 mg./Kg. in 1 cc. The constant rate injector was adjusted so as to deliver 1 cc. per minute. The recording in this experiment was accomplished on a smoked drum kymograph on which was inscribed blood pressures taken from the carotid artery, respirations taken from a tracheal cannula, zero blood pressure line, and a time scale. A lead II electrocardiogram was taken intermittently throughout this experiment. The intervals during which the EKG was being taken were indicated on the smoked drum kymograph by depressions in the zero blood pressure line. Shortly after the start of this experiment, the electrocardiograph quit

recording for reasons unknown. Hence, no EKG's are available for this experiment. Controls were as follows: Blood pressure, 120 mm. of mercury; and respirations, 20 per minute and regular.

The injection of the Vasoxyl was started at 5:05 PM. At 2 minutes following the start of the injection, the blood pressure had started to rise. A maximum height of 267 mm. of mercury was obtained by the blood pressure within 5 minutes following the start of the injection. Seventeen minutes following the start of the experiment, the blood pressure had started to decline. The blood pressure continued falling until at one hour following the start of the experiment, it was 196 mm. of mercury.

Respirations showed significant alterations at 2 minutes following the injection. At this time they became somewhat shallower and slower though still regular. By 17 minutes the repirations exhibited Cheyne-Stokes characteristics. Forty-seven minutes following the start of the injection of Vasoxyl the respirations were even more depressed. One hour following the start, the animal exhibited severe respiratory depression. The experiment was terminated one hour and 10 minutes following the start of the injection of Vasoxyl.

June 29, 1953. A Constant Injection Experiment Using Vasoxyl.

In this experiment the animal was anesthetized with barbital sodium given intraperitoneally in the dose of 250 mg./Kg. A femoral vein was exposed and cannulated with a polyethylene cannula to which is attached a syringe mounted in a constant rate injector machine. This syringe contained Vasoxyl in the solution adjusted to contain a dose of

0.5 mg./Kg. in 1 cc. The constant rate injector was adjusted so as to deliver 1 cc. per minute. Recording was accomplished by means of a smoked drum kymograph on which was inscribed the carotid artery blood pressure, respirations from a tracheal cannula, zero blood pressure line and a time scale. A lead II electrocardiograph was taken intermittently throughout this experiment. Intervals during which the EKG was being taken were indicated on the kymograph by means of a depression in the zero blood pressure line. A fasted 9.1 Kg. male dog was anesthetized at 8:45 A.M. Controls were taken at 10:58 A.M. and were as follows: EKG, heart rate, 145 per minute and regular, no abnormalities noted in other EKG measurements; respirations were 56 per minute and regular; blood pressure was 146 mm. of mercury.

At 10:59 A.M., Vasoxyl injection was started. Two minutes following the start of the injection, the blood pressure started to climb. At 2½ minutes the blood pressure was 166 mm. of mercury. The heart rate was 95 per minute and regular. The respirations were 13 per minute and regular even though the respirations did exhibit a decreasing amplitude. Four and a half minutes following the start of Vasoxyl the blood pressure was 186 mm. of mercury. The EKG indicated a heart rate of 82 per minute. This was a sinus bradycardia. No other alterations in the EKG were noted. The respirations exhibited early signs of Cheyne-Stokes characteristics. At 9½ minutes following the start of the injection the blood pressure was 174 mm. of mercury with occasional wave-like periods of variations. The EKG exhibited a heart rate of 94 per minute with a regular sinus bradycardia. Occasional sinus pauses were noted. The QRS complex

apparently declined slightly in height. At this point the respirations were definitely Cheyne-Stokes in character. At 16 minutes the blood pressure was 174 mm. of mercury. The EKG indicated a heart rate of 88 per minute with no further alterations in the pattern noted. The respirations were now 25 per minute and regular. The blood pressure continued to decline steadily throughout the remainder of the experiment.

At 85 minutes following the start of the injection the blood pressure was 84 mm. of mercury. The heart rate was 96 per minute and regular. As indicated above, this was a sinus bradycardia. The only other alteration in the EKG pattern noted was a very small amplitude of QRS complex. Respirations at this point were 39 per minute, regular but very shallow. At 86 minutes following the start of the injection of Vasoxyl the animal suffered respiratory arrest. The blood pressure at this time was 58 mm. of mercury and falling rapidly. The EKG showed severe irregular bradycardia with prolonged sinus pauses. Occasionally absence of the P wave was noted. The QRS complex was extremely small in amplitude. The experiment was terminated.

July 6, 1953. A Constant Injection Experiment With Vasoxyl. See figures 13 and 14.

The anesthetic in this experiment is sodium barbital given intraperitoneally in the dose of 250 mg./Kg. A femoral vein of the animal was exposed with a polyethylene catheter inserted. This catheter was attached to a syringe mounted in a constant rate injector machine.

FIGURE 13

Graphic representation of the results of the Constant Injection Experiment using Vasoxyl on July 6, 1953.

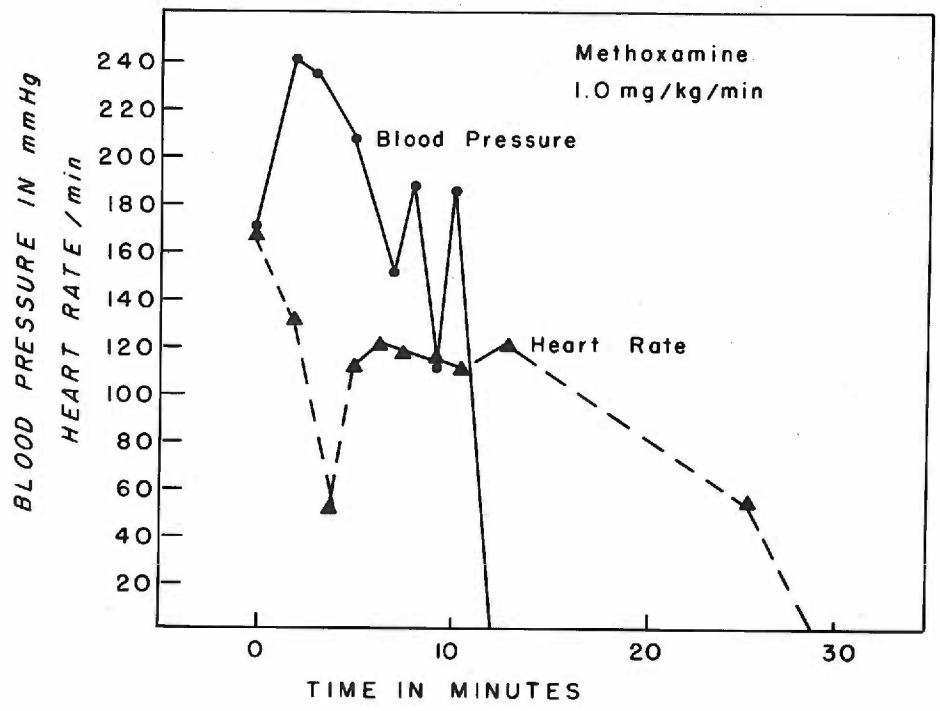
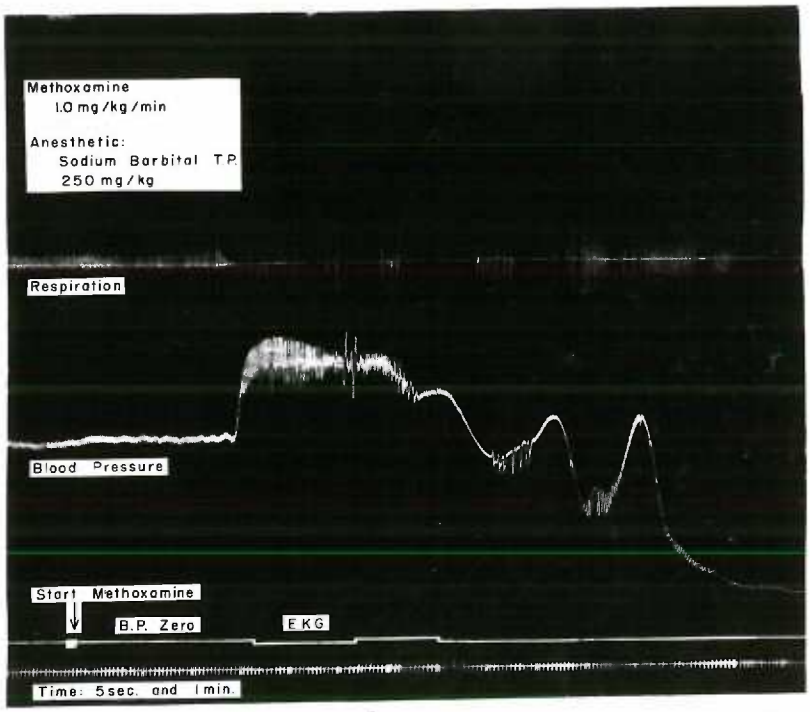

Methoxamine
1.0 mg/kg/min
Blood Pressure
Heart Rate
BLOOD PRESSURE IN mmHg
HEART RATE / min
240
220
200
180
160
140
120
100
80
60
40
20
0
10
20
30
TIME IN MINUTES

FIGURE 14

A section of kymograph showing the results of the Constant Injection Experiment using Vasoxyl on July 6, 1953.

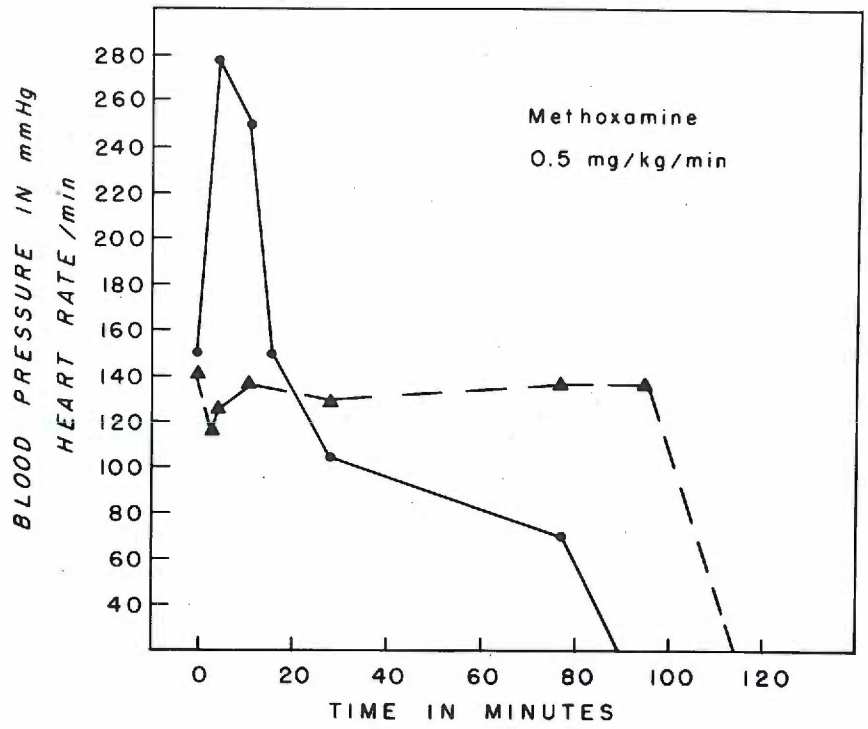

Methoxamine
1.0 mg/kg/min
Anesthetic:
Sodium Barbital T.P.
250 mg/kg
Respiration
Blood Pressure
Start Methoxamine
B.P. Zero
EKG
Time: 5sec. and 1min.

The syringe contained a solution of Vasoxyl adjusted so as to contain a dose of 1 mg./Kg. per cc. The constant rate injector was adjusted so as to deliver 1 cc. per minute. Recording for this experiment was accomplished by means of a smoked drum kymograph on which was inscribed carotid blood pressures, respirations from a tracheal catheter, a zero blood pressure line and a time scale. A lead II EKG was taken intermittently throughout this experiment. Intervals at which this EKG was being taken were indicated on the kymograph by means of depressions in the zero blood pressure line. A fasted 9.32 Kg. female dog received the anesthetic at 11:50 A.M. Controls were taken at 1:41 P.M. and were as follows: Blood pressure, 170 mm. of mercury; the EKG indicated a regular heart rate of 75 per minute; no other alterations were noted in the EKG pattern; respirations were 63 per minute and regular.

At 1:47½ P.M., the Vasoxyl injection was started. Within 1 minute the blood pressure started to rise. Two minutes following the injection the blood pressure was 240 mm. of mercury. The EKG indicated a heart rate of 130 per minute and was regular. No other alterations in the pattern were noted. Respirations were 7 per minute and irregular. Two and one-half minutes after the start of the injection the EKG indicated a heart rate of 85 per minute which was in the pattern of a sinus bradycardia. At 3 minutes the blood pressure was 234 mm. of mercury. The heart rate was 49 per minute and a sinus bradycardia was occasionally noted. Respirations were 12 per minute and irregular. At 5 minutes following the injection of Vasoxyl the blood pressure was 206 mm. of mercury. The only alteration noted in the EKG was a heart rate of 115 per minute which was still regular. There was no alteration in the respirations.

FIGURE 15

Graphic representation of the results of the Constant Injection Experiment Using Vasoxyl on July 8, 1953.


BLOOD PRESSURE IN mmHg
HEART RATE/min
280
260
240
220
200
180
160
140
120
100
80
60
40
Methoxamine
0.5 mg/kg/min
0
20
40
60
80
100
120
TIME IN MINUTES

At 6½ minutes the blood pressure was still falling and was now 150 mm. of mercury. The heart rate was 120 per minute with still no further alterations in the EKG pattern. Respirations were now 10 per minute. At 8 minutes following the start of the injection the blood pressure was 112 mm. of mercury. The EKG indicated a heart rate of 120 per minute which was still regular. A slightly widened PR interval was noted in that it measured 0.14 sec. Respirations were 3 per minute and Cheyne-Stokes in character. At 9 minutes following the start of the experiment the blood pressure averaged 184 mm. of mercury. There were large wave-like variations in blood pressure. The EKG indicated a heart rate of 110 per minute and was regular. The PR interval was still widening and was now 0.16 sec. Respirations were 21 per minute. In eleven minutes the blood pressure was 40 mm. of mercury. There was no visible pulse pressure. EKG indicated occasional sinus pauses. The heart rate was 120 per minute. The QRS indicated a very slight broadening. There were no other abnormalities noted in the EKG. The respirations ceased at this point. The experiment was terminated.

July 8, 1953. A Constant Injection Experiment With Vasoxyl. See figure 15.

A fasted 7.7 Kg. male dog was anesthetized with barbital sodium given intraperitoneally in the dose of 250 mg./Kg. at 11:20 A.M. Results of this experiment were recorded by means of a single channel EKG lead II and a smoked drum kymograph on which was inscribed blood pressure, respirations, a blood pressure zero line and a time scale.

Intervals at which the EKG was being run were indicated on the smoked drum kymograph by means of a depression in the blood pressure zero line. The dose of Vasoxyl used in this experiment was 0.5 mg./Kg./min. This was administered by means of a polyethylene catheter inserted in the inferior vena cava via a femoral vein. This catheter was connected to a syringe mounted on a constant injector machine. The syringe contained a solution of Vasoxyl adjusted so that each cc. contained 0.5 mg./Kg. The constant injector machine was adjusted so as to deliver 1 cc. per minute.

Controls were taken at 1:20 and they were as follows: Blood pressure, 150 mm. of mercury; EKG showed a heart rate of 140 per minute and regular with no abnormalities noted in the tracings; respirations were 21 per minute and regular.

The Vasoxyl was started at 1:25 P.M. By 1:26 the blood pressure had started to rise. Four minutes and 40 seconds following the start of the injection the blood pressure was 280 mm. of mercury; the EKG indicated a heart rate of 125 per minute and respirations were extremely rapid and violent. There was a first appearance of Cheyne-Stokes type respiration. Ten minutes following the start of the injection the EKG showed indications of a bundle branch block. At 11 minutes the blood pressure was 260 mm. of mercury. The heart rate remained 142 per minute and regular. The previously noted "bundle branch block" had disappeared. Respirations were still very violent and rapid. Twenty-eight and one-half minutes following the start of the experiment the blood pressure was now 104 mm. of mercury. The blood pressure also showed wave-like appearance. The heart rate was 128 mm. of mercury and the EKG showed no abnormalities

other than an increased height in the QRS complex. The respirations became more regular though they were still somewhat Cheyne-Stokes in character. The rate of respiration was 19 per minute. Seventy-seven minutes following the start of the experiment the blood pressure was 70 mm. of mercury and very irregular. The EKG indicated a heart rate that was extremely irregular, varying between 130 and 200 per minute with an average of 135 per minute. The QRS complex had now become only 20 mm. in height. There was a depressed ST segment with coving (curving) of the ST segment. No other abnormalities in the EKG were noted. Respirations were 44 per minute. They were still somewhat Cheyne-Stokes in character.

At 94 minutes the blood pressure was 14 mm. of mercury. The EKG was similar in appearance to that noted of the 77th minute. The heart rate was 135 per minute and not irregular. Respirations now were 90 per minute; extremely rapid and difficult to count. At 96 and a half minutes following the start of the injection of the Vasoxyl, respirations ceased and blood pressure was at zero.

July 19, 1953. Constant Injection Experiment Using Vasoxyl. See figure 16.

A fasted 6.36 Kg. female dog was anesthetised with sodium barbital in the dose of 250 mg./Kg. given intraperitoneally at 11:34 A.M. Recording in this experiment was by means of a single channel EKG lead II and a smoked drum kymograph on which was indicated blood pressure, respirations, blood pressure zero line and a time scale.

Intervals during which the EKG was being taken were indicated on the smoked drum kymograph by means of depression on the blood pressure zero line. The dose of Vasoxyl was 0.01 mg./Kg./min. This was administered by polyethylene catheter into the inferior vena cava via a femoral vein. The polyethylene catheter was connected to a syringe mounted in a constant injector machine. The syringe contained a solution of Vasoxyl adjusted so as to contain a dose of 0.01 mg./Kg. per cc. The constant injector machine was adjusted so as to deliver 1 cc. per minute.

Controls were taken at 1:42 P.M. They were as follows: Blood pressure, 140 mm. of mercury; EKG, heart rate, 155 per minute, regular, no other abnormalities noted in the tracings; respirations, 32 per minute.

The injection of the Vasoxyl was started at 1:44 P.M. Seven minutes following the start of the experiment the blood pressure was 170 mm. of mercury with a widened pulse pressure. The EKG indicated a heart rate of 115 per minute. Respirations were 22 per minute and regular. At 18 minutes the blood pressure was 192 mm. of mercury. EKG indicated a heart rate of 105 per minute with a somewhat irregular sinus rhythm. No other abnormalities in the EKG were noted. Respirations were 18 per minute.

Thirty-seven minutes after the start of the experiment the blood pressure was 200 mm. of mercury. The EKG indicated a heart rate of 105 with continuous sinus irregularity. Respirations were 15 per minute. At 51 minutes following the start of the injection the blood pressure was 216 mm. of mercury. The EKG indicated a heart rate of 135 per minute

with a disappearance of the previously noted sinus irregularity. Respirations were 42 per minute with irregular amplitude.

Fifty-eight and a half minutes following the start of the experiment the blood pressure was 212 mm. of mercury. The EKG indicated a heart rate of 130 per minute with slight appearance of sinus irregularity. The respirations were very shallow and slow. There was an indication that they were somewhat Cheyne-Stokes in character. At 94 minutes following the start of the experiment the blood pressure was 206 mm. of mercury. The EKG showed a heart rate of 148 per minute which was regular. No persistent, significant changes in the appearance of the lead II tracings were noted throughout the experiment. Respirations were still very weak and Cheyne-Stokes in character and about 16 per minute.

At the 100 minute mark the blood pressure was 200 mm. of mercury. The EKG showed some sinus irregularity with a heart rate of 138 per minute. Respirations were still very weak and Cheyne-Stokes in character. The Vasoxyl was stopped. At 139 minutes following the start of the experiment and 39 minutes following the cessation of Vasoxyl injection the blood pressure was 170 mm. of mercury. The EKG showed a heart rate of 145 per minute and regular. There was no alteration in the EKG tracing of significance. Respirations were still very weak and of a Cheyne-Stokes type.

FIGURE 16

Graphic representation of the results of the Constant Injection Experiment Using Vasoxyl on July 19, 1953.

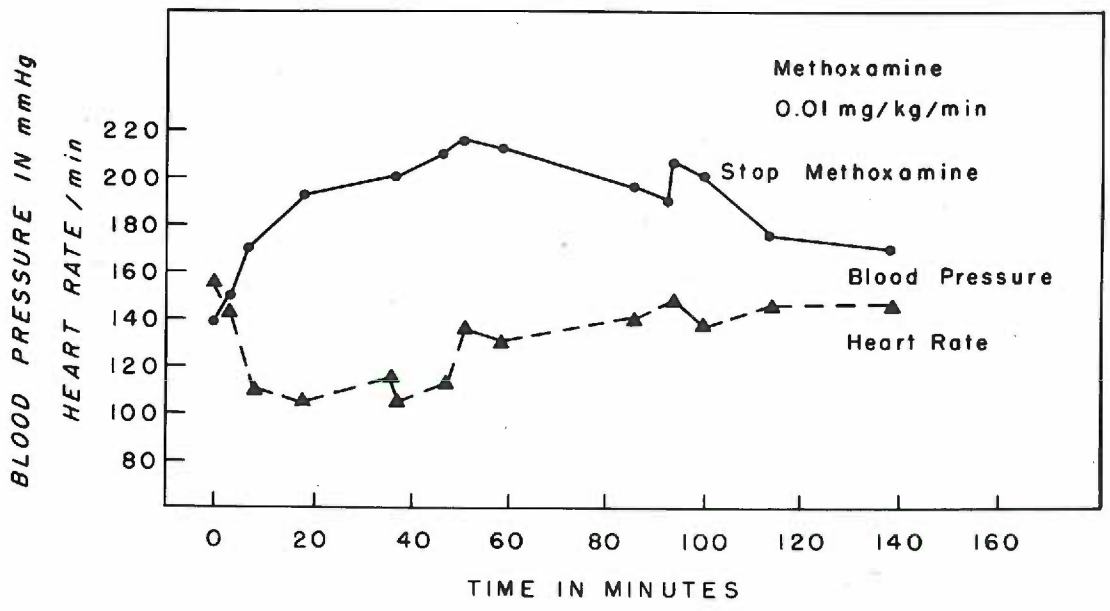
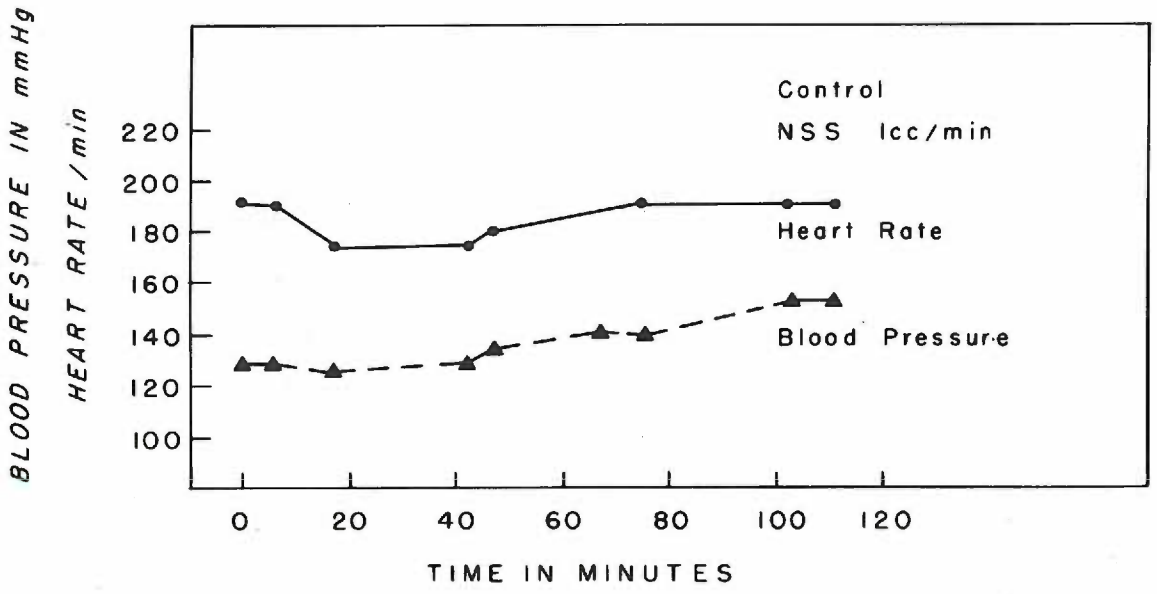

BLOOD PRESSURE IN mmHg
HEART RATE / min
220
200
180
160
140
120
100
80
0
20
40
60
80
100
120
140
160
TIME IN MINUTES
Methoxamine
0.01 mg/kg/min
Stop Methoxamine
Blood Pressure
Heart Rate

FIGURE 17

Graphic representation of the results of the Constant Injection Experiment Using sterile normal saline on August 5, 1953.


BLOOD PRESSURE IN mmHg
HEART RATE / min
220
200
180
160
140
120
100
0
20
40
60
80
100
120
TIME IN MINUTES
Control
NSS Icc/min
Heart Rate
Blood Pressure

August 5, 1953. Constant Injection Experiments Using Normal Saline. See figure 17.

A fasted 10.9 Kg. female dog anesthetized with sodium barbital in a dose of 250 mg./Kg. administered intraperitoneally at 12:14 P.M. The results of this experiment were recorded by means of a single channel EKG lead II and a smoked drum kymograph on which was inscribed blood pressure, respirations, a blood pressure base line and a time scale. Intervals at which the EKG was being run were indicated on the smoked drum by means of depression in the blood pressure zero line. A femoral vein was exposed. A polyethylene catheter was inserted through the femoral vein to lie in the inferior vena cava and was connected to a syringe mounted in a constant injector machine. The syringe contained normal saline. The constant injector was adjusted so as to deliver 1 cc. per minute.

Controls were taken at 2:20 P.M. and they were as follows: Blood pressure, 128 mm. of mercury; heart rate, 192 per minute, regular; all measurements of EKG tracings were within normal limits; respirations were 12 per minute and regular.

At 2:30 P.M. the injection of the normal saline had started. The normal saline was injected at the rate of 1 cc. per minute for 1 hour and 51 minutes. Blood pressure remained relatively constant until about 67 minutes following the start of the injection when it started to rise slightly. At this time it was 140 mm. of mercury. At 75 minutes following the start of the injection the blood pressure was still 140 mm. of mercury. At 103 minutes the blood pressure was 102 mm. of mercury where it remained until the experiment terminated at 111 minutes.

At no time throughout the experiment was there any change noted in measurements of the EKG tracing. A slight drop in heart rate was noted at 17 minutes following the start of the injection. At this time the heart rate was 175 per minute. This rate was held until the 3 minute point at which time it started to increase. At 47 minutes the heart rate was 180 per minute and at 67 minutes it was 187 per minute. At 75 minutes following the start of the experiment, the heart rate was 190 per minute. Thereafter, there was no change in the heart rate until the experiment was terminated.

At no time throughout the experiment was there any significant alterations in respirations noted.

August 10, 1953. Constant Infusion Experiment Using Vasoxyl.

A fasted 12.05 Kg. male dog was anesthetized with barbital sodium in the dose of 250 mg./Kg. administered intraperitoneally at 11:00 A.M. In addition, 100 mg. of sodium barbital was administered at 12:20 P.M. and 300 mg. at 12:44 P.M. The results of this experiment were recorded by means of a single channel EKG lead II and a smoked drum kymograph on which was inscribed blood pressure, respirations, a blood pressure zero line and a time scale. Intervals at which the EKG was being taken are indicated on the smoked drum kymograph by means of depressions in the blood pressure zero line. A femoral vein was exposed and a polyethylene catheter was inserted through it into the inferior vena cava. This catheter was connected to a syringe mounted in a constant rate injector

machine. The syringe contained a Vasoxyl solution adjusted so as to contain 0.025 mg./Kg. per cc. The constant rate injector was adjusted so as to deliver 1 cc. per minute.

Controls were taken at 2 P.M. They were as follows: blood pressure, 124 mm. of mercury; heart rate, 200 per minute and regular; EKG showed no alterations from normal; respirations were regular and 18 per minute.

The injection of the Vasoxyl was started at 2:05 P.M. Due to the length of the tube being used to inject the Vasoxyl in this particular experiment, immediate effects due to Vasoxyl were not noted. It was calculated that about 3 minutes were required before the normal saline was emptied and the Vasoxyl began to enter the vein. Six minutes following the start of the injection, the blood pressure was 129 mm. of mercury. The heart rate was 95 per minute and there was a widening of the PR interval. Control PR interval was 0.12 sec.; at this time the PR interval was 0.16 sec. Respirations were 11 per minute.

Twenty-five and a half minutes following the start of the experiment the blood pressure was 154 mm. of mercury. The heart rate was approximately 90 per minute with some variation in rate. This appeared to be a sinus alteration. There was no change in the measurements of the EKG tracing. Respirations were 13 per minute. There was some suggestion of Cheyne-Stokes breathing. At 36 minutes the blood pressure had started to decline and was now 150 mm. of mercury. The heart rate was 110 per minute.

At 48 minutes the blood pressure was 144 mm. of mercury and the heart rate was 115 per minute and regular. PR interval had now declined to 0.14 sec. Respirations had increased to 40 per minute and somewhat

irregular. At the 65 and a half minute point the blood pressure was 138 mm. of mercury and regular. The heart rate was 140 per minute and regular. The PR interval was now at control level, 0.12 sec. Respirations were extremely rapid. At 79 and a half minutes following the start of the injection of Vasoxyl, the blood pressure was 132 mm. of mercury. The heart rate was 150 and there was no change noted in the EKG. Respirations were 40 per minute and noticeably irregular.

At 98 and a half minutes the blood pressure was 122 mm. of mercury and the heart rate 150 again. There was no change in the EKG picture. At this time, however, respirations appeared definitely Cheyne-Stokes in type. This pattern lasted for approximately six minutes. One hundred and ten minutes following the start of the experiment, the Vasoxyl injection was stopped. At this time the blood pressure was 126 mm. of mercury. The heart rate was 155 per minute and regular. The PR interval was now 0.10 sec. Respirations were 17 per minute and somewhat irregular in their amplitude. At the 115 minute point or five minutes following the stopping of the Vasoxyl injection, 20 mg. of Vasoxyl was injected into the inferior vena cava by means of the previously noted catheter. There was no change produced in heart rate, blood pressure, respirations or EKG picture in the following ten minutes.

August 13, 1953. The Effects Of Vasoxyl On An Animal Anesthetized With Cyclopropane.

A fasted 5.8 Kg. male dog, without premedication, was anesthetized with cyclopropane. Anesthesia was induced with 40% cyclopropane and 60% oxygen. This was started at 10:18 A.M. At 10:30 A.M. nitrous oxide was used to complete the induction. Surgical anesthesia was reached at 10:34 A.M. The animal was returned to cyclopropane in the concentrations of 40% cyclopropane and 60% oxygen at 10:35 A.M. Intubation was complete at 10:40 A.M. and cyclopropane concentration was reduced to 30% and administered through the cuffed Magill endotracheal tube. The animal was allowed to stabilize for the next 30 minutes. Recording in this experiment was by a single channel EKG lead II.

The control EKG was taken at 11:13 A.M. and was as follows: heart rate, 145 per minute and regular; PR interval, 0.12; QRS, 0.03 sec. A notched QRS was noted in the control EKG.

At 11:18 A.M., Vasoxyl was injected into a peripheral limb vein. The dose of Vasoxyl was 10 mg./Kg. Fifteen seconds after the injection of Vasoxyl, the heart rate was 66, the PR interval was 0.16, with no change in the QRS. One minute following the injection the heart rate was 67 per minute and regular. The PR interval was not measurable. There was a slight broadening of the QRS in that it measured 0.04 sec. Four minutes following the injection of Vasoxyl, respirations had ceased. EKG at this point showed evidence of nodal depression with severe bradycardia and sinus pauses. Evidence of muscular tremors were noticeable in the tracing. The heart rate was 27 per minute. The PR interval was

0.18 and the QRS showed no change and measured 0.04 sec. Eleven minutes following the start of the experiment, the heart rate was 16 per minute, the PR interval, 0.16; and QRS, 0.04 sec. The animal was receiving bag breathing during this period.

At the 19 minute point the heart rate had increased to 67 to 70 per minute. There was no change in the PR interval or the QRS complex. An occasional ectopic ventricular contraction was noted. By 32 minutes the heart rate was 138 per minute and regular, the PR interval was unobtainable, and the QRS complex measured 0.03 sec. No P or T waves were visible due to muscular tremor. At the 52 minute mark the heart rate was 155 per minute, the PR interval was 0.12 sec. and the QRS complex measured 0.04 sec. There was a slightly depressed ST segment.

At 12:52 P.M. an injection of epinephrine, 10 microgram/Kg., was administered intravenously into a peripheral limb vein. One minute following this injection the heart rate was 250 per minute. The P wave could not be identified. The QRS complex measured 0.06. The rhythm was identified as ventricular tachycardia with electrical alternans. Four minutes following the injection of the epinephrine, the heart rate was 180 per minute and regular. The PR interval was still unobtainable. The QRS complex measured 0.02. The depression of the ST segment was still present at 12:51.

At 12:57 another injection of epinephrine in the dose of 15 microgram/Kg. was administered intravenously. One mimute following this injection the heart rate was 320 per minute. No P or T waves were

identifiable. The QRS complex measured 0.08. Occasional ectopic ventricular beats were noted and a cyclic variation in the QRS height was noted.

At 1:00 P.M. a third injection of epinephrine was administered intravenously. The dose this time was 20 microgram/Kg. One minute following the injection of epinephrine the heart rate was 350 per minute. Again the PR interval was not measurable. The QRS complex measured 0.08. An extreme variation in the height of the QRS complex was noted. Occasional ectopic ventricular beats were again present. Four minutes following the third injection of epinephrine the heart rate measured 72 per minute and was regular. No P or T waves were as yet visible. The experiment was terminated.

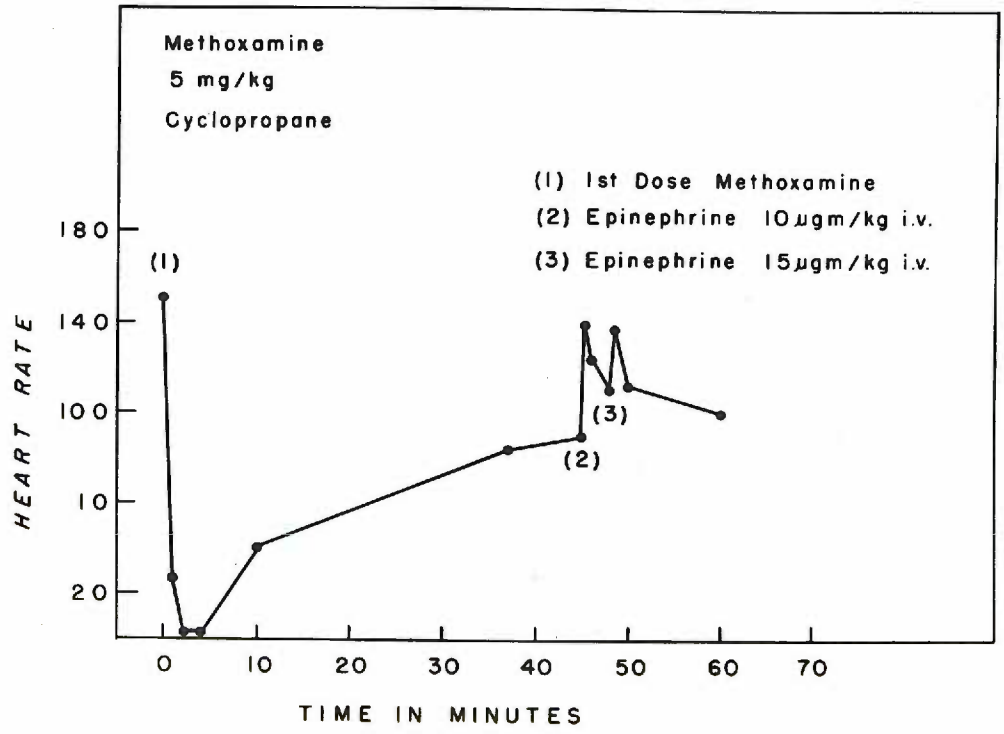
August 17, 1953. The Effects Of Vasoxyl On The EKG Of An Animal Anesthetized With Cyclopropane. See figure 18.

A fasted 5.9 Kg. female dog without premedication was anesthetized with cyclopropane. Induction of anesthesia was started at 2:30 P.M. using concentrations as follows: cyclopropane, 40%; oxygen, 60%. Surgical anesthesia and intubation was completed at 2:40 P.M. At this time the concentrations were cyclopropane, 30% and oxygen, 70%. Recording in this experiment was by means of a single channel EKG lead II.

The control EKG was taken at 3:25 P.M. The heart rate was 152 per minute and regular. The PR interval was 0.10 sec. and the QRS complex measured 0.04 sec.

FIGURE 18

Graphic representation of the results of the Cyclopropane Experiment on August 17, 1953.


Methoxamine
5 mg/kg
Cyclopropane
(1) 1st Dose Methoxamine
(2) Epinephrine 10 µgm/kg i.v.
(3) Epinephrine 15 µgm/kg i.v.
HEART RATE
180
140
100
10
20
(1)
(2)
(3)
0
10
20
30
40
50
60
70
TIME IN MINUTES

At 3:30 P.M., 5 mg./Kg. of Vasoxyl was administered intravenously into a peripheral vein. One minute following this the heart rate was 27 per minute; the PR interval measured 0.20 sec. and the QRS measured 0.04 sec. Two minutes following the injection of Vasoxyl, there was evidence in the EKG of severe nodal depression. An occasional ectopic ventricular beat appeared. Two and a half minutes following the injection of Vasoxyl, the ectopic ventricular beats were noted every six seconds. There was a coincident severe bradycardia. Five minutes following Vasoxyl a complete absence of auricular complex was noted. Ectopic ventricular beats were then occurring every 9 seconds. Ten minutes following Vasoxyl, ectopic ventricular beats were occurring at the rate of 40 per minute. However, the auricular complex was now present. At the 15 minute point the heart rate was 50 per minute. The PR interval measured 0.20 sec. with no change in the QRS complex. There were still appearances of slightly irregular sinus rhythm. Thirty-seven minutes following Vasoxyl the heart was 84 and regular, the PR interval measured 0.20 and the QRS complex measured 0.04 sec.

At 4:15 P.M., 10 microgram/Kg. of epinephrine were administered to the aimal through a peripheral vein. One-half minute later the heart rate was 140 per minute. The PR interval measured 0.16 sec. and there was no change in the QRS complex. The heart rate fell rapidly for the next three minutes until at that point it measured 110 per minute. No change was noted in the PR interval or the QRS complex.

At this time 15 microgram/Kg. of epinephrine were administered intravenously through a peripheral vein. One-half minute later the heart rate measured 138 per minute and was regular. This fell rapidly

until one and a half minutes following the second injection of epinephrine when the heart rate was 112 per minute. There was no change in the PR interval or the QRS complex. It will be noted in this instance that the two injections of epinephrine failed to give the marked increase in heart rate that is usually observed with these doses. Experiment terminated.

August 19, 1953. The Effects Of Vasoxyl On The EKG Of An Animal Anesthetized With Cyclopropane. See figure 19.

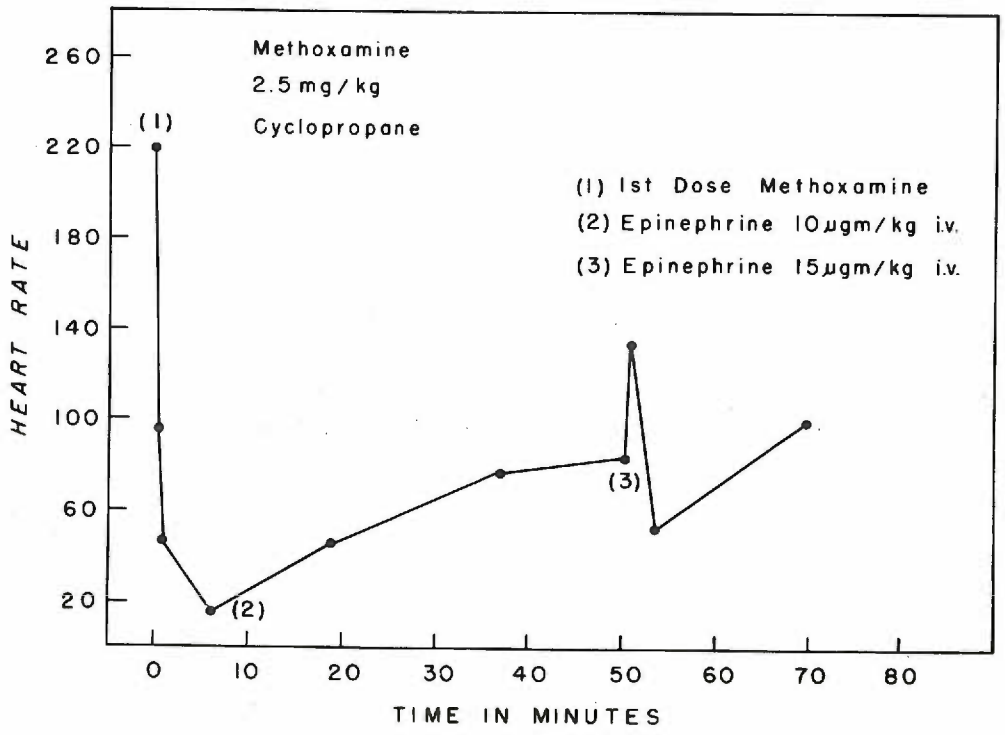
A fasted 7.5 Kg. male dog was anesthetized without premedication with 40% cyclopropane and 60% oxygen. Induction of anesthesia was started at 1:07 P.M. Surgical anesthesia was obtained at 1:15 P.M. The animal was intubated and anesthesia was maintained with 30% cyclopropane and 70% oxygen. Results in this experiment were recorded by means of a single channel EKG lead II. After anesthesia was attained, a 30 minute stabilization period was allowed.

At 1:54 P.M. the control EKG was taken. It was as follows: heart rate, 220 per minute and regular; PR interval, 0.12 sec.; QRS complex, 0.03 sec.

At 2:10 P.M., 2.5 mg./Kg. of Vasoxyl was administered intravenously through a peripheral vein. One-half minute later the heart rate was 96 per minute. PR interval measured 0.16 sec. There was no change in the QRS complex. One minute later the heart rate was 47 per minute. No auricular complex was discernible and the QRS interval measured 0.04 sec. Six minutes following the injection of Vasoxyl, the EKG showed

FIGURE 19

Graphic representation of the results of Cyclopropane Experiment on August 19, 1953.


Methoxamine
2.5 mg/kg
Cyclopropane
(1) 1st Dose Methoxamine
(2) Epinephrine 10µgm/kg i.v.
(3) Epinephrine 15µgm/kg i.v.
(1)
(2)
(3)
HEART RATE
260
220
180
140
100
60
20
0
10
20
30
40
50
60
70
80
TIME IN MINUTES

sinus block. No auricular complexes were noted. Ectopic ventricular beats were occurring every 24 seconds. The animal was apneic and bag breathing was necessary. Nine minutes following the injection of Vasoxyl, 10 microgram/Kg. of epinephrine were injected intravenously through a peripheral vein. There was no effect following this injection of epinephrine.

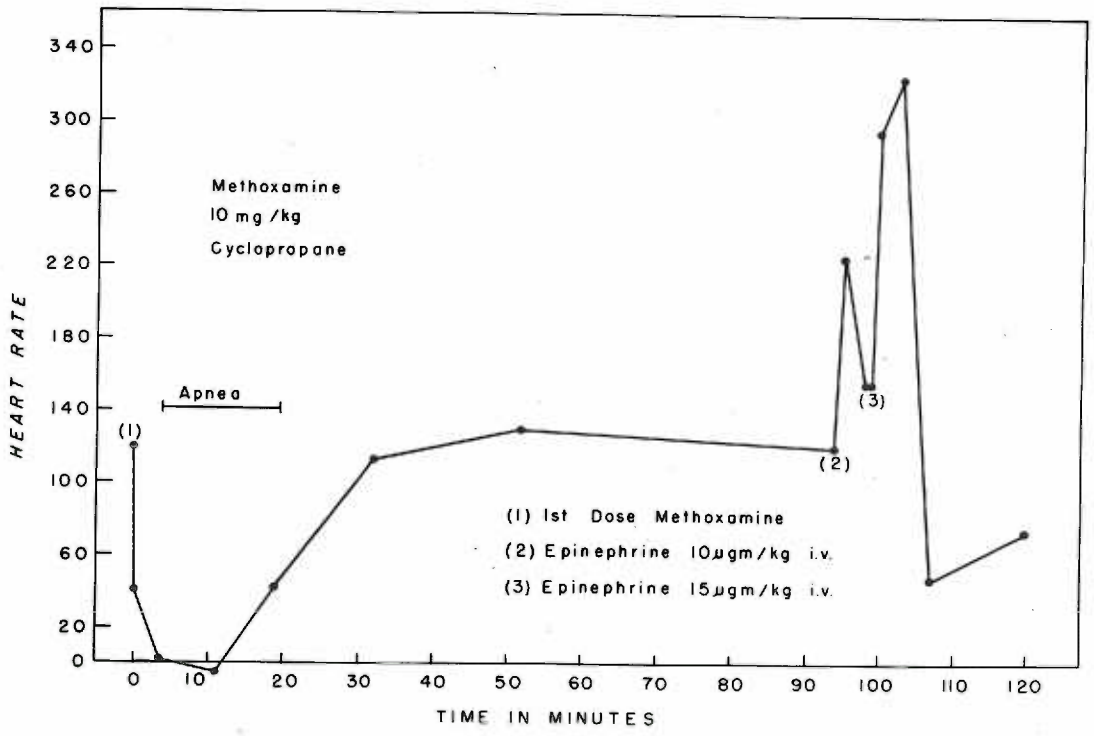
At 2:47, or 30 minutes, following the injection of the Vasoxyl, the heart rate was 78 per minute and regular. At this time the PR interval measured 0.18 sec. and the QRS complex measured 0.02 sec. At 3:00 P.M., 15 microgram/Kg. of epinephrine were injected intravenously into a peripheral vein. Thirty seconds later the heart rate was 135 per minute. The PR interval measured 0.12 sec. and there was no change in the QRS. Three minutes later the heart rate was back to 53 per minute. The PR interval was 0.14 sec. and the QRS complex had increased to 0.04 sec. It will be noted that the first injection of epinephrine given immediately following the Vasoxyl produced no effect whatsoever. The second injection of epinephrine given 37 minutes following the Vasoxyl produced a rise in heart rate though not to a degree that would be expected with this dose. Experiment terminated.

August 20, 1953. The Effects Of Vasoxyl On The EKG Of An Animal Anesthetized With Cyclopropane. See figure 20.

A fasted 11.5 Kg. female dog was anesthetized without premedication with a mixture of 40% cyclopropane and 60% oxygen. Induction was started at 10:45 A.M. Surgical anesthesia was obtained at 11:02 A.M.

FIGURE 20

Graphic representation of the results of the Cyclopropane Experiment on August 20, 1953.


HEART RATE
340
300
260
220
180
140
100
60
20
0
Methoxamine
10 mg /kg
Cyclopropane
Apnea
(1)
(2)
(3)
(1) Ist Dose Methoxamine
(2) Epinephrine 10µgm/kg i.v.
(3) Epinephrine 15µgm/kg i.v.
0
10
20
30
40
50
60
70
80
90
100
110
120
TIME IN MINUTES

at which time the animal was intubated and anesthesia was obtained on a mixture of 30% cyclopropane and 70% oxygen. Results in this experiment were recorded by means of a single channel EKG, lead II. A fifty minute period was allowed for stabilization.

Control EKG's were taken at 11:57 A.M. and were as follows: heart rate, 120 per minute and regular; PR interval, 0.12 sec.; QRS, 0.04 sec.; no abnormalities were noted.

At 12:05 P.M., 10 mg/Kg. of Vasoxyl was injected into a peripheral leg vein. Thirty seconds later the heart rate was 40 per minute. PR interval measured 0.14 sec. No change was noted in the QRS complex. Severe respiratory depression was noted.

At 12:16½ P.M. the heart rate was approximately 6 to 8 per minute, somewhat irregular, with long sinus pauses. The "P" wave was occasionally absent. The QRS complex measured 0.04 sec. The animal was in complete apnea and bag breathing was necessary for approximately 15 minutes. The animal resumed breathing at 12:24 P.M.

The heart rate gradually rose to control levels over the next 10 minutes where it stabilized. The EKG also returned to normal measurements.

At 1:38½ P.M., or 93 minutes after the injection of Vasoxyl, 10 micrograms/Kg. of epinephrine were injected into a peripheral leg vein. One minute later the heart rate was 228 per minute. The PR interval measured 0.10 sec. and the QRS measured 0.04 sec. At 1:42½ P.M. the heart rate had returned to 160 per minute and the QRS was within control limits.

At 1:43 P.M., 15 micrograms/Kg. of epinephrine were injected into a peripheral leg vein. Thirty seconds later the heart rate was 296 per minute and the EKG showed sinus tachycardia with bursts of ventricular tachycardia. At 1:49 P.M. the heart rate had become too rapid to count but was estimated to be over 320 per minute. The heart rate rapidly fell after this until 1:53 P.M. when it was 30 per minute but was regular. Following this point the heart rate and EKG gradually returned to control levels and the experiment was terminated. No fibrillation occurred.

August 22, 1954. The Effects Of Vasoxyl On An Animal Anesthetized With Cyclopropane. See figure 21.

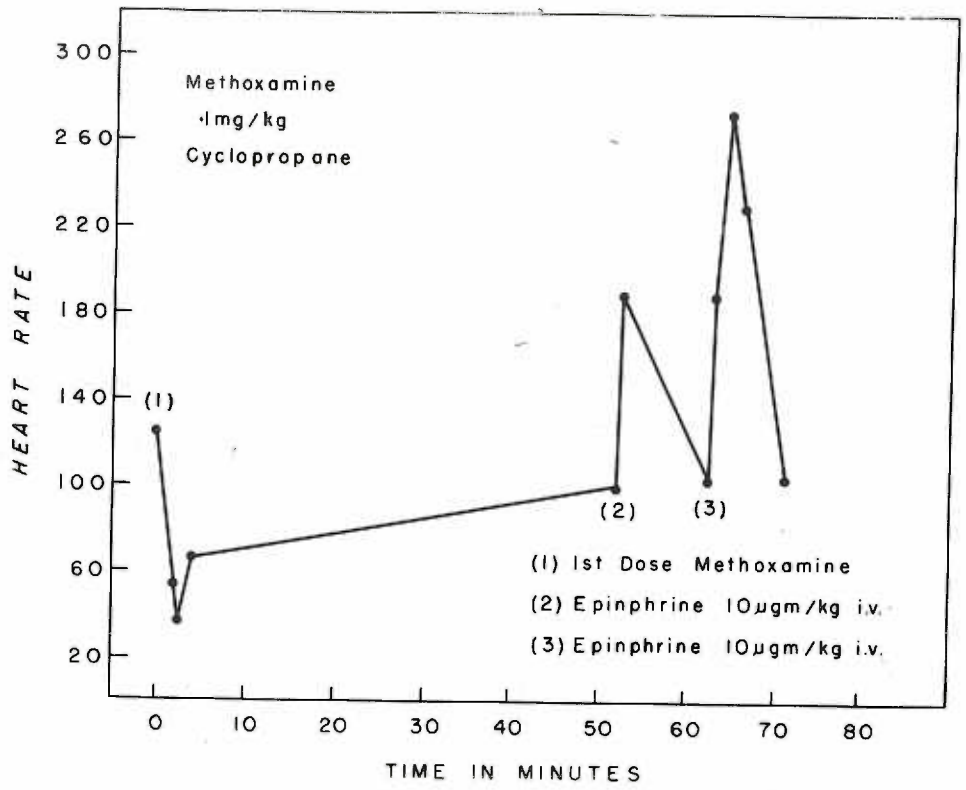
A fasted 11.36 Kg. male dog, without premedication, was anesthetized with cyclopropane. Anesthesia was induced with 40% cyclopropane and 60% oxygen. This was started at 9:31 A.M. At 9:55 A.M. surgical anesthesia had been attained. A cuffed Magill endotracheal tube was installed and anesthesia was maintained through it at 30% cyclopropane and 70% oxygen. A 30 minute stabilization period was allowed. Recording in this experiment was by means of a single channel lead II EKG.

Control EKG was taken at 10:25 A.M. The heart rate was 130 per minute and regular. All measurements of the EKG tracing were within normal limits.

At 10:27 A.M. Vasoxyl was injected into a peripheral leg vein. The dose of Vasoxyl used in this experiment was 1 mg./Kg. This was administered in a total volume of 5.68 cc.

FIGURE 21

Graphic representation of the results of the Cyclopropane Experiment on August 22, 1954.


300
260
220
180
140
100
60
20
HEART RATE
Methoxamine
·1mg/kg
Cyclopropane
(1)
(2)
(3)
(1) Ist Dose Methoxamine
(2) Epinphrine 10µgm/kg i.v.
(3) Epinphrine 10µgm/kg i.v.
0
10
20
30
40
50
60
70
80
TIME IN MINUTES

Two minutes following injection of Vasoxyl the heart rate had fallen to 25 per minute. There was evidence of severe sinus bradycardia with occasional sinus pauses. Five minutes following injection of Vasoxyl the heart rate had risen to 65 per minute. Sinus bradycardia was still present; however, sinus pauses were less frequent.

Fifty-two minutes following the injection of Vasoxyl the EKG tracing had returned to approximately normal limits. The heart rate was just slightly slower being 100 per minute. At this point, 10 microgram/Kg. of epinephrine were injected through a peripheral leg vein. One minute later the heart rate was 190 per minute. The EKG indicated ventricular tachycardia and multiple frequent ventricular ectopic beats.

Approximately 10 minutes later the heart rate had returned to 100 per minute. The EKG tracing was within control limits. At this point a second injection of epinephrine, 10 microgram/Kg. was administered through the peripheral leg vein. One minute later the heart rate was 270 per minute. There was evidence of severe ventricular tachycardia and many ventricular ectopic beats. The EKG tracing appeared to be close to ventricular fibrillation. Eight minutes later the EKG tracing had returned to normal limits.

It is interesting to note that even though epinephrine caused severe ventricular tachycardia, ventricular fibrillation did not occur. Only transient arrhythmias were noted under cyclopropane anesthesia in animals subjected to challenge doses of epinephrine. It is also interesting to note that the first injection of epinephrine caused a

less severe rise in heart rate than the second injection of epinephrine. This is thought to be due to the fact that the effects of the Vasoxyl were gradually wearing off at this point.

August 23, 1953. The Effects Of Vasoxyl On The EKG Of An Animal Anesthetized With Cyclopropane. See figure 22.

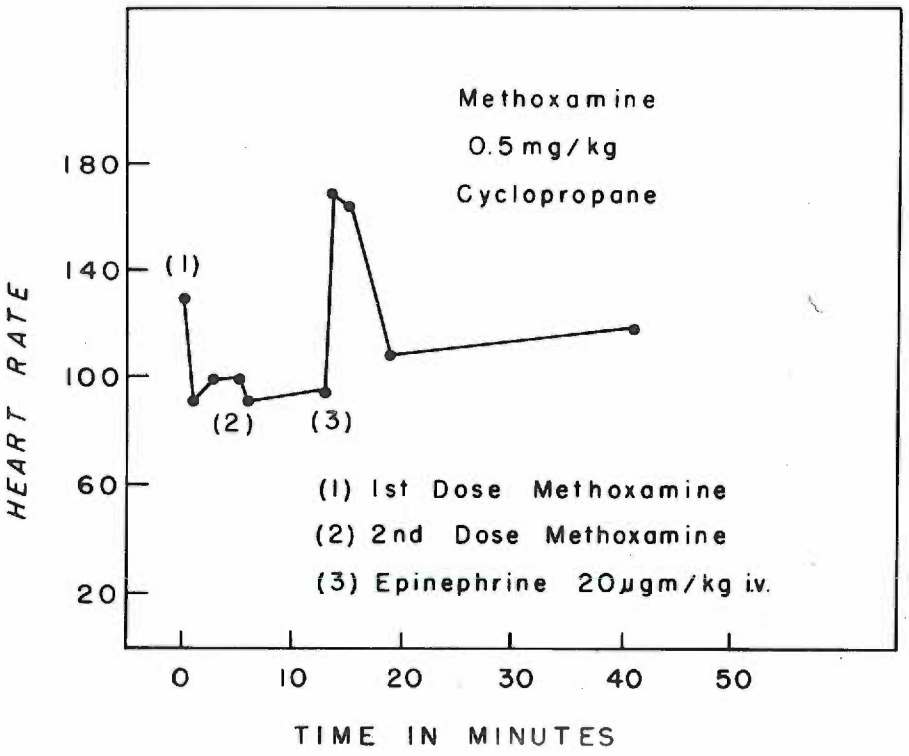
A fasted 7.4 Kg. dog was anesthetized with 40% cyclopropane and 60% oxygen without premedication. Induction was started at 1:32 P.M. Surgical anesthesia was obtained at 1:45 P.M. The animal was then intubated and the concentration of cyclopropane dropped to 30% and oxygen increased to 70% and administered through the tube. A femoral vein was exposed and catheterized with a small polyethylene catheter through which the drugs were administered. A 45 minute stabilization period was allowed. Recording in this experiment was by means of a single channel lead II EKG.

The control EKG was taken at 2:30 P.M. The heart rate was 135 per minute and regular. No abnormalities in the EKG pattern were noted. All measurements were within normal limits.

The dose of Vasoxyl was 0.5 mg./Kg. and was administered into the inferior vena cava through the polyethylene catheter. This was divided in two equal doses to avoid respiratory depression. The first increment of Vasoxyl was administered at 2:40 P.M. Two minutes later the heart rate was 92 per minute. No alterations were noted in the EKG pattern. Six minutes following the injection of the first dose of Vasoxyl, the heart rate was 100 per minute and regular.

FIGURE 22

Graphic representation of the results of Cyclopropane Experiment on August 23, 1953, using 0.5 mg./Kg. of Vasoxyl.


Methoxamine
0.5 mg/kg
Cyclopropane
(1)
(2)
(3)
(1) 1st Dose Methoxamine
(2) 2nd Dose Methoxamine
(3) Epinephrine 20µgm/kg i.v.
HEART RATE
180
140
100
60
20
0
10
20
30
40
50
TIME IN MINUTES

Five minutes following the injection of the first dose of Vasoxyl, the second increment was administered. Two minutes following this dose the heart rate fell to 92 per minute.

At 2:56 P.M., 20 microgram/Kg. of epinephrine was injected through the polyethylene catheter into the inferior vena cava. One minute later the heart rate measured 170 per minute. No abnormalities were noted in the EKG pattern. Eleven minutes following the injection of epinephrine the heart rate was 110 per minute and regular. No significant alterations in the EKG tracing were noted throughout the experiment. No fibrillation occurred.

August 23, 1953. The Effects Of Vasoxyl On The EKG Of An Animal Anesthetized With Cyclopropane. See figure 23.

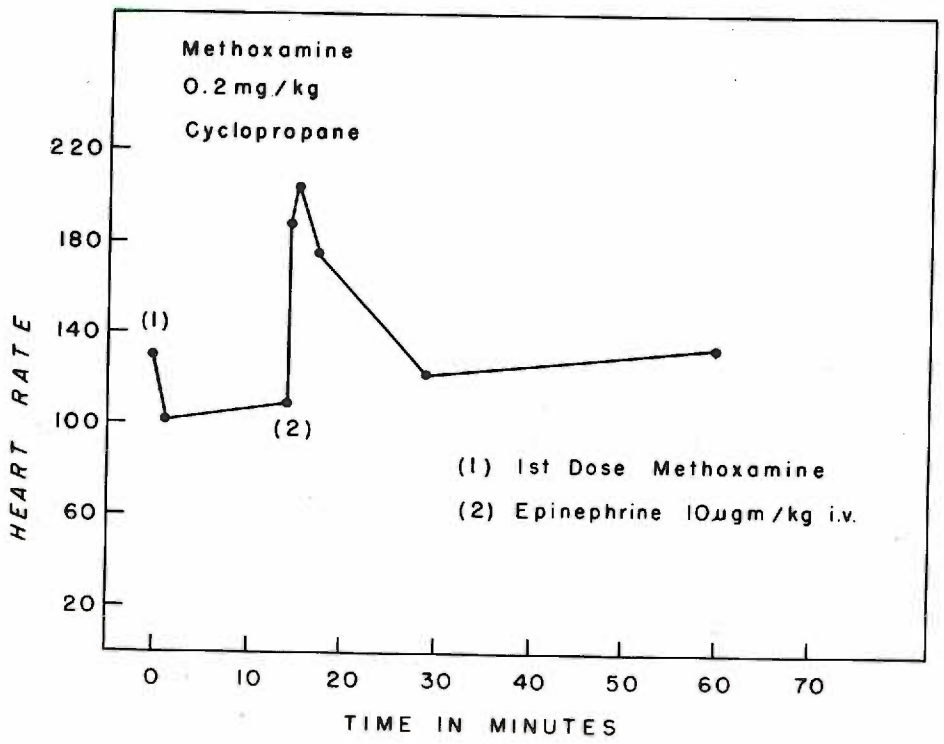
A fasted 9.09 Kg. male dog without premedication was anesthetized with 40% cyclopropane and 60% oxygen. Induction of anesthesia was started at 12:10 P.M. Surgical anesthesia was obtained at 12:20 P.M. At this time the animal was intubated and the concentration of cyclopropane dropped to 30% and oxygen increased to 70%. A 45 minute stabilization period was allowed. Recording in this experiment was by a single channel EKG lead II.

Control EKG was taken at 1:05 P.M. and was as follows: heart rate, 130 per minute and regular; PR interval measured 0.10 sec.; QRS complex measured 0.04 sec.

At 1:11 P.M., 0.2 mg./Kg. of Vasoxyl was injected intravenously through a peripheral vein. Two minutes following the injection of

FIGURE 23

Graphic representation of the results of Cyclopropane Experiment on August 23, 1953, using 0.2 mg./Kg. of Vasoxyl.


Methoxamine
0.2 mg/kg
Cyclopropane
220
180
140
100
60
20
HEART RATE
(1)
(2)
(1) Ist Dose Methoxamine
(2) Epinephrine 10µgm/kg i.v.
0
10
20
30
40
50
60
70
TIME IN MINUTES

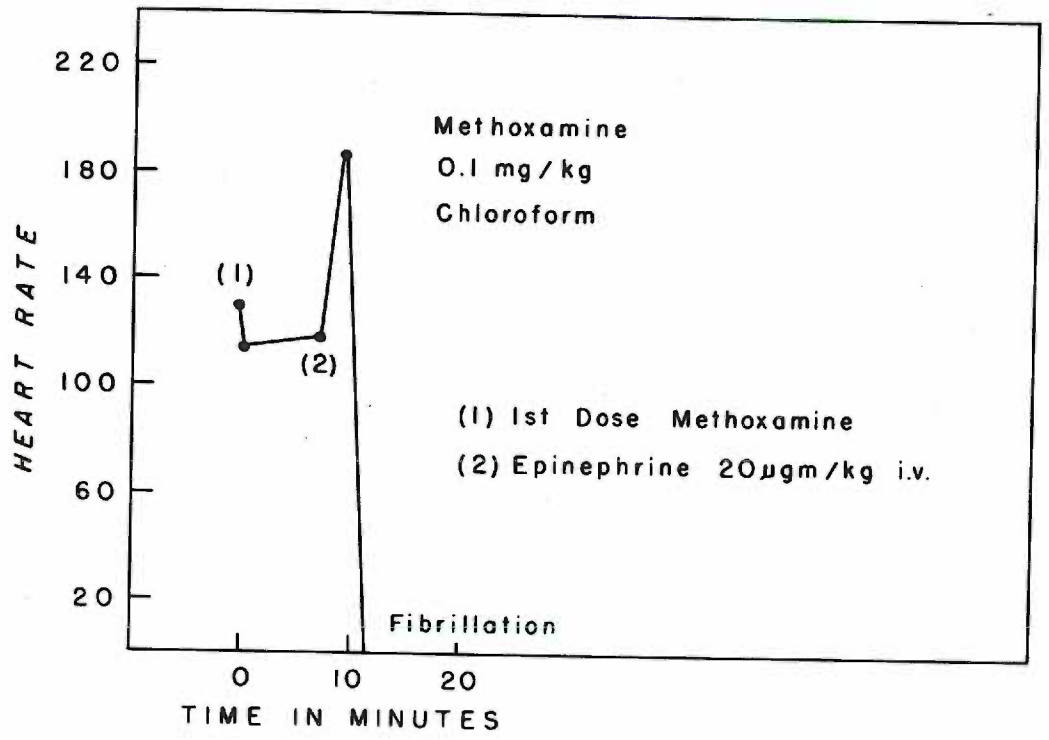
Vasoxyl the heart rate was 102 per minute. The PR interval measured 0.14 and the QRS complex showed no change. Five minutes following the injection of Vasoxyl, the heart rate was 108 per minute. The PR interval measured 0.12 sec. and there was still no change noted in the QRS complex. At 1:24 P.M., or 13 minutes following the injection of Vasoxyl, 10 microgram/Kg. of epinephrine was administered intravenously through a peripheral vein. Thirty seconds later the heart rate measured 188 per minute. There was no change in the PR interval or the QRS complex. Forty-five seconds later there were many ectopic ventricular beats noted in an extremely rapid rate. The rate was so rapid it was uncountable and could be considered close to fibrillation. Two minutes following the injection of epinephrine the heart rate was 175 per minute and regular. The PR interval and the QRS complex were within control limits. Sixteen minutes following epinephrine the heart rate was 122 per minute with no change noted in the PR interval or the QRS complex. It is to be noted that this light dose of Vasoxyl apparently did not completely inhibit the effects of epinephrine as previously noted in other experiments. End of experiment.

August 31, 1953. The Effects Of Epinephrine On The EKG Of An Animal Anesthetized With Cyclopropane.

A fasted 7.73 Kg. female dog without premedication was anesthetized in the usual manner with cyclopropane. This animal appeared to be severely depressed following the stabilization period allowed after surgical anesthesia was reached. The animal died immediately following the administration of epinephrine. This was apparently a respiratory death.

FIGURE 24

Graphic representation of the effects of Vasoxyl and epinephrine in the cardiac sensitization experiment of September 2, 1953.


220
180
140
100
60
20
HEART RATE
Methoxamine
0.1 mg/kg
Chloroform
(1)
(2)
(1) 1st Dose Methoxamine
(2) Epinephrine 20µgm/kg i.v.
Fibrillation
0
10
20
TIME IN MINUTES

September 2, 1953. The Effects Of Vasoxyl In The Melville Technique. See figure 24.

A fasted 6.59 Kg. female dog was anesthetized with Nembutal in the dose of 35 mg./Kg. administered intraperitoneally. This was given at 12:47 P.M. The results in this experiment were recorded on a single channel EKG lead II.

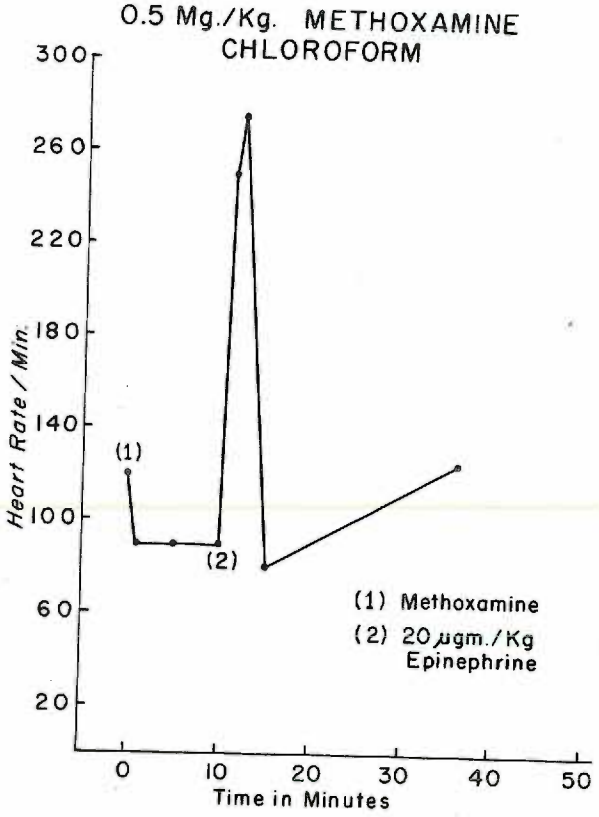
After anesthesia had been attained and the animal stabilized, chloroform inhalation was administered for five minutes in a concentration just strong enough to avoid changing the level of anesthesia. This was completed at 1:52 P.M.

Control EKG results were: heart rate, 130 per minute and regular; PR interval, 0.10 sec.; QRS complex, 0.03 sec.

At 1:55 P.M., 0.1 mg./Kg. of Vasoxyl was administered intravenously through a peripheral vein. One-half minute following the Vasoxyl, the heart rate was 115 per minute. The PR interval measured 0.08 sec. and there was no change in the QRS complex. Seven minutes following the Vasoxyl the heart rate was 118 per minute. There was no further change in the PR interval or the QRS complex. At this time 20 microgram/Kg. epinephrine were injected intravenously. Thirty seconds later ventricular fibrillation occurred and the animal died.

FIGURE 25

Graphic representation of the effects of Vasoxyl and epinephrine in the cardiac sensitization experiment of September 2, 1953.


0.5 Mg./Kg. METHOXAMINE
CHLOROFORM
300
260
220
180
140
100
60
20
Heart Rate / Min.
(1)
(2)
(1) Methoxamine
(2) 20 µgm./Kg
Epinephrine
0
10
20
30
40
50
Time in Minutes

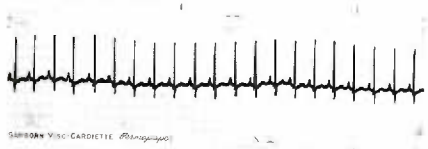
September 2, 1953. The Effects Of Vasoxyl In The Melville Technique. See figure 25.

A fasted 7.73 Kg. male dog was anesthetized with 35 mg./Kg. of Nembutal administered intraperitoneally. This was given at 1:45 P.M. The animal was allowed to stabilize for one hour. Recording in this experiment was done by means of a single channel EKG lead II. A femoral vein was exposed and a polyethylene catheter inserted through it into the inferior vena cava, filled with saline, and clamped. At 3:04 P.M. the control EKG was taken. It was as follows: heart rate, 130 per minute and regular; PR interval measured 0.10 sec.; QRS complex measured 0.02 sec. At 3:08 P.M. chloroform was administered to the animal in a concentration just strong enough to avoid changing the level of anesthesia. Chloroform was discontinued at 3:13 P.M.

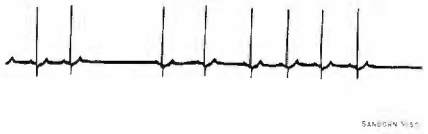
At 3:15 P.M., 0.5 mg./Kg. of Vasoxyl was administered intravenously through the polyethylene catheter in the femoral vein. The animal became apneic within two minutes following the Vasoxyl and assisted respirations were necessary the next three minutes. At this time the animal resumed breathing. At 3:21, 20 microgram/Kg. of epinephrine was administered via the polyethylene catheter. There was a marked increase in heart rate but no fibrillation occurred. End of this experiment.

FIGURE 26

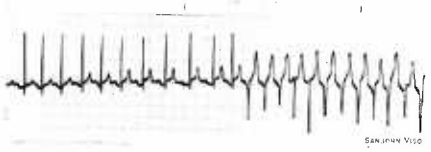
Sections from the EKG taken in the cardiac sensitization experiment of September 3, 1953, using 0.5 mg./Kg. of Vasoxyl.



CONTROL

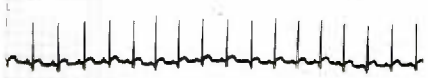


1 MIN. POST METHOXAMINE



30 SEC. POST EPINEPHRINE

1 MIN. POST EPINEPHRINE



RECOVERY

September 3, 1953. The Effects Of Vasoxyl In The Melville Technique. See figure 26.

A fasted 6.8 Kg. female dog was anesthetized with 35 mg./Kg. of Nembutal administered intraperitoneally at 9:35 A.M. The animal was allowed to stabilize for one hour. Recording in this experiment was by means of a single channel EKG lead II. A femoral vein was exposed and a small polyethylene catheter inserted through it into the inferior vena cava. This catheter was filled with saline and clamped.

At 10:36 A.M. the control EKG was taken and the results were as follows: heart rate, 130 per minute and regular; PR interval measured 0.10 sec.; and QRS complex measured 0.02 sec.

At 10:38 A.M. five minutes of chloroform inhalation were administered in a concentration just strong enough to avoid changing the level of anesthesia. This was concluded by 10:43. At this point the animal seemed to be coming out of the anesthesia so one-half cc. of Nembutal solution was administered intraperitoneally. This represents 15 mg. of Nembutal.

At 11:14 A.M. chloroform inhalation was administered again. Since Vasoxyl in high doses apparently depresses respiration, it was felt wiser to administer our Vasoxyl in two doses. This was done in an attempt to avoid excessive respiratory embarrassment. At 11:21 A.M. the first dose of Vasoxyl was administered via the polyethylene catheter. At 11:27, the second dose of Vasoxyl was administered.

The total dose of Vasoxyl administered at this time represented 0.5 mg./Kg. The heart rate at this time was 92 per minute; PR interval, 0.14 sec.; and with no change noted in the QRS complex. At 11:35 A.M. 20 microgram/Kg. of epinephrine were administered into the inferior vena cava by the way of the catheter installed in the femoral vein. A marked increase in heart rate resulted; however, fibrillation did not occur.

September 3, 1953. The Effects Of Vasoxyl In The Melville Technique.

A 6.8 Kg. male dog was anesthetized with 35 mg./Kg. of Nembutal administered intraperitoneally at 10:30 A.M. At 12:55 P.M. an additional 60 mg. of Nembutal was administered intraperitoneally. Recording in this experiment was by means of a single channel EKG lead II. A femoral vein was exposed and a polyethylene catheter inserted through it into the inferior vena cava. This was filled with saline and clamped.

At 1:29 P.M. the control EKG was taken. It was as follows: heart rate, 130 per minute; PR interval, 0.10 sec.; and QRS complex, 0.02 sec. At 1:48 P.M. chloroform inhalation was administered in a concentration just strong enough to avoid changing the level of anesthesia. This was discontinued at 1:53 P.M.

The Vasoxyl (0.25 mg./Kg.) was to be administered intravenously, divided into two equal doses. The first dose was administered into

the inferior vena cava at 1:59 P.M. One minute later the heart rate was 92 per minute and regular, the PR interval measured 0.14 sec. and there was no change in the QRS complex. At 2:05 P.M., or six minutes following the first dose of Vasoxyl, a second dose of Vasoxyl was administered. There was no alteration in the heart rate or EKG noted following the second dose of Vasoxyl as compared to the EKG following the first dose.

Seven minutes following the injection of Vasoxyl, 20 microgram./Kg. of epinephrine was administered into the inferior vena cava. Thirty seconds later the heart rate was 170 per minute and very irregular. The PR interval was unmeasurable due to an absent P wave. The QRS complex measured 0.04 sec. The QRS complex also was of irregular height and occasional ectopic beats were noted. Six minutes following the injection of epinephrine, the heart rate was 110 per minute and regular. The remainder of the EKG was similar to the control. The experiment was terminated. No fibrillation occurred.

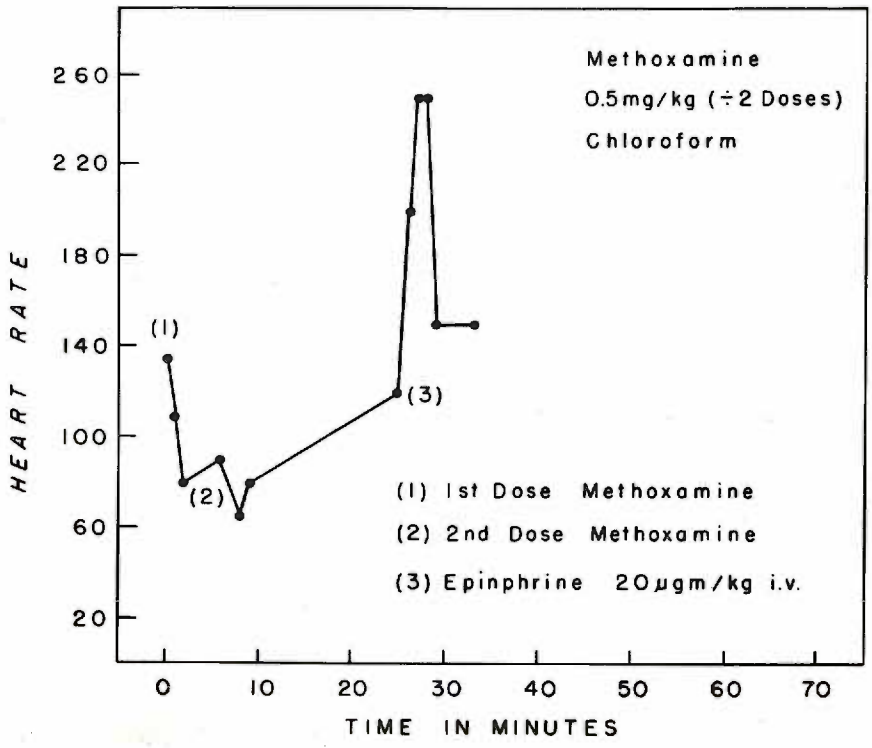
July 2, 1954. The Effects Of Vasoxyl In The Melville Technique. See figure 27.

A fasted 9.5 Kg. male dog was used for this experiment. The anesthetic used was chloroform administered by face mask. Surgical anesthesia was attained by 10:35 A.M.

Recording in this experiment was by means of a single channel lead II EKG. Control heart rate was 134 per minute and was regular. All other EKG measurements were within normal limits.

FIGURE 27

Graphic representation of the results of cardiac sensitization experiment of July 2, 1954.


Methoxamine
0.5mg/kg (÷2 Doses)
Chloroform
HEART RATE
260
220
180
140
100
60
20
(1)
(2)
(3)
(1) 1st Dose Methoxamine
(2) 2nd Dose Methoxamine
(3) Epinphrine 20µgm/kg i.v.
0
10
20
30
40
50
60
70
TIME IN MINUTES

A femoral vein was exposed and a saline filled polyethylene catheter inserted through it into the inferior vena cava.

The dose of Vasoxyl used in this experiment was 0.5 mg./Kg. This was administered in two doses through the catheter into the inferior vena cava. The Vasoxyl dose was divided so as to avoid the respiratory depression common to excessive dosages of the drug.

The first increment of Vasoxyl was administered at 10:50 A.M. The heart rate fell immediately and four minutes later was 80 per minute. No abnormalities were noted in the EKG.

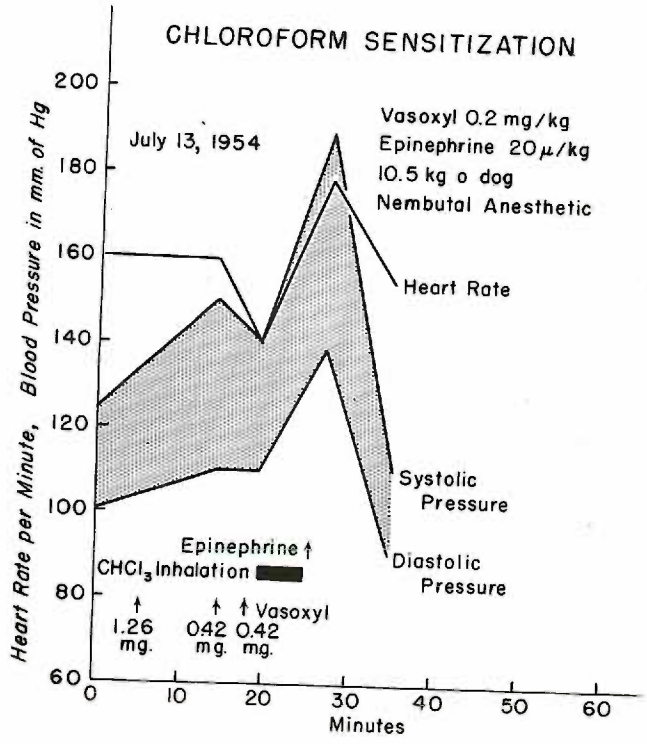
Seven minutes following the first dose of Vasoxyl the heart had risen to 90 per minute. At this point the second dose of Vasoxyl was administered. The heart rate again declined to a low point of 64 per minute four minutes following the second dose of Vasoxyl.

Thereafter the heart rate increased steadily until 11:15 A.M. (25 minutes following the first dose of Vasoxyl) when it was 120 per minute and regular. At this point 20 microgram/Kg. of epinephrine were administered in the inferior vena cava. Four minutes later the heart rate was 250 per minute. Many bursts of ventricular tachycardia and ectopic beats were noted on the EKG tracing.

However, by eight minutes after the epinephrine injection the heart rate had declined to 150 per minute and the EKG tracing was within control limits. This rate was observed to be regular for the next eight minutes and the experiment was terminated. No fibrillation occurred.

FIGURE 28

Graphic representation of the results of the cardiac sensitization experiment of July 13, 1954.


CHLOROFORM SENSITIZATION
July 13, 1954
Vasoxyl 0.2 mg/kg
Epinephrine 20μ/kg
10.5 kg o dog
Nembutal Anesthetic
Heart Rate
Systolic Pressure
Diastolic Pressure
Epinephrine
CHCl3 Inhalation
1.26 mg.
0.42 mg.
0.42 mg.
Vasoxyl
Heart Rate per Minute, Blood Pressure in mm. of Hg
200
180
160
140
120
100
80
60
0
10
20
30
40
50
60
Minutes

July 13, 1954. The Effects Of Vasoxyl In The Melville Procedure. See figure 28.

A fasted 10.5 Kg. male dog was anesthetized with 35 mg./Kg. Nembutal sodium intraperitoneally at 12:00 noon. A femoral vein was exposed and a small polyethylene catheter was inserted through it into the inferior vena cava. This catheter was filled with normal saline and clamped. A carotid artery was exposed and cannulated. This cannula was connected to an electro-manometer. Recording from the electro-manometer was done by means of a single channel Sanborn electrocardiogram. In this manner carotid artery pulse waves were recorded throughout the experiment. After surgical anesthesia was obtained, 45 minutes was allowed as a stabilization period. Controls were taken at 1:45 P.M. They were: Blood pressure, 125/100; heart rate, 160 per minute and regular.

The dose of Vasoxyl used in this experiment was 0.2 mg./Kg. This was administered in divided doses to avoid respiratory depression. The Vasoxyl was injected into the inferior vena cava by means of the polyethylene catheter. At 1:51 P.M. the first dose of Vasoxyl was administered.

At 1:59 P.M. the second increment of Vasoxyl was administered and at 2:03 P.M. the third dose of Vasoxyl was given. At 2:04 P.M. the blood pressure was 140/110. The heart rate was 140 per minute and regular.

At 2:05 P.M. chloroform inhalation was administered in a concentration just strong enough to avoid changing the level of anesthesia.

At 2:10½ P.M., 20 microgram/Kg. of epinephrine were administered into the inferior vena cava through the catheter.

At 2:10 P.M. the blood pressure was 190/140. The heart rate was 180 per minute. At 2:20 P.M. the blood pressure was 110/90.

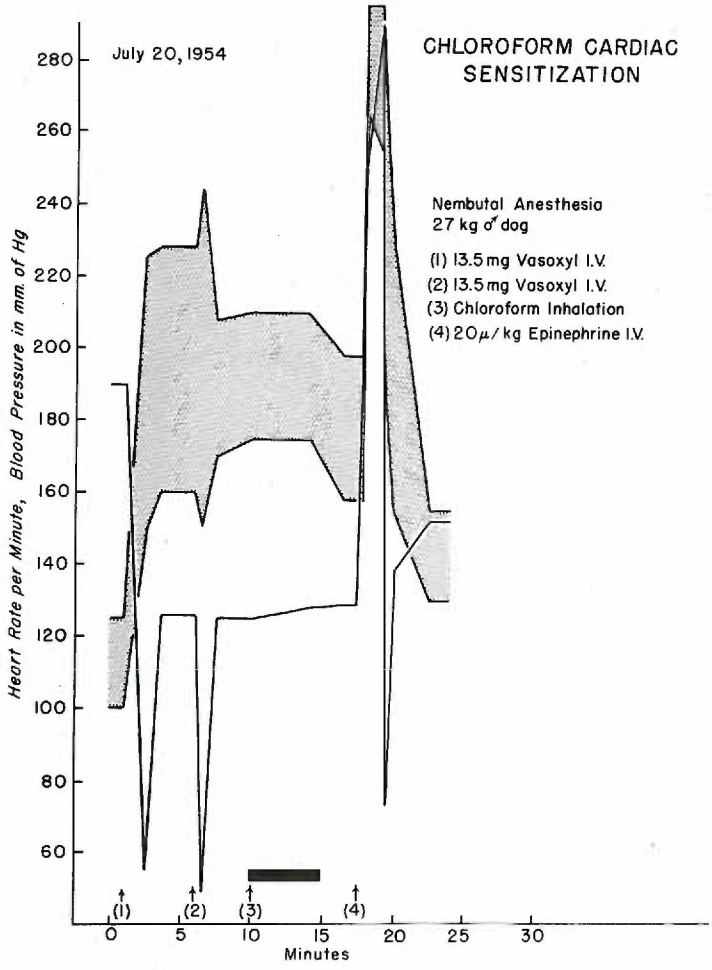
No fibrillation was observed.

July 20, 1954. The Effects Of Vasoxyl In The Melville Technique. See figure 29.

A fasted 27 Kg. male dog was anesthetized with 35 mg./Kg. of Nembutal sodium administered intraperitoneally at 12:45 P.M. A femoral vein was exposed and a small polyethylene catheter inserted through it into the inferior vena cava. This catheter was filled with normal saline and clamped. A carotid artery was exposed and cannulated. This cannula was connected to an electro-manometer which recorded on the visocardiette. In this manner the carotid artery pulse waves were recorded throughout the experiment. After surgical anesthesia was obtained, a 45 minute period was allowed for stabilization. Controls were taken at 2:34 P.M. They were as follows: Heart rate, 190; blood pressure, 125/100. The dose of Vasoxyl given to this animal was 1 mg./Kg. This was administered in two equal doses into the inferior vena cava by means of the catheter. The first increment of Vasoxyl was administered at 2:35 P.M. One and one-half minutes later the heart rate was 55 and blood pressure, 225/150. Slightly irregular heart rate was also noted.

FIGURE 29

Graphic representation of the results of the cardiac sensitisation experiment of July 20, 1954.


July 20, 1954
CHLOROFORM CARDIAC SENSITIZATION
Nembutal Anesthesia
27 kg ♂ dog
(1) 13.5 mg Vasoxyl I.V.
(2) 13.5 mg Vasoxyl I.V.
(3) Chloroform Inhalation
(4) 20μ/kg Epinephrine I.V.
Heart Rate per Minute, Blood Pressure in mm of Hg
280
260
240
220
200
180
160
140
120
100
80
60
(1)
(2)
(3)
(4)
0
5
10
15
20
25
30
Minutes

This was apparently due to sinus pauses. Two and one-half minutes following the Vasoxyl, the heart rate was 126 and the blood pressure, 228/160. The heart rate was now regular.

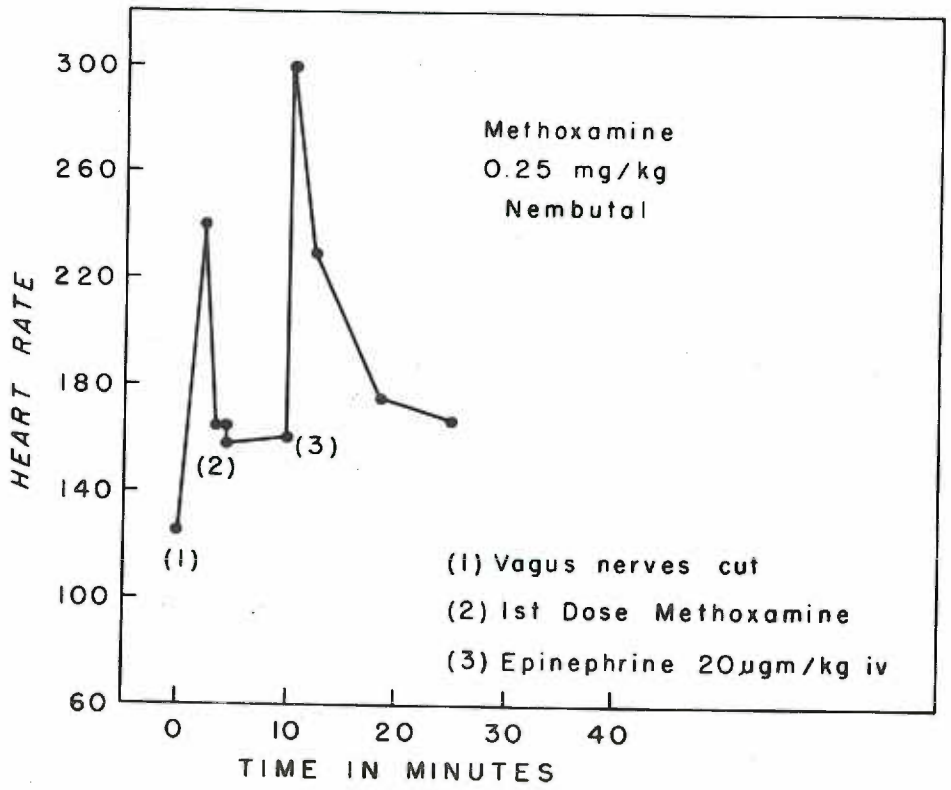
At 2:40 P.M. the second dose of Vasoxyl was administered. Thirty seconds later the heart rate was 48 per minute and the blood pressure, 244/151. There was also a slightly irregular heart rate noted. Three minutes following the second dose of Vasoxyl, the heart rate was 125 per minute and regular and the blood pressure was 210/175.

Starting at 2:44 P.M. five minutes of chloroform inhalation was administered in a concentration just strong enough to avoid changing the level of anesthesia. One minute following the chloroform inhalation the heart rate was 129 and the blood pressure was 198/158. The tracing of the pulse wave was interpreted to represent occasional incomplete ventricular filling though the rate was regular.

At 2:51½ P.M., 20 microgram/Kg. of epinephrine was injected into the inferior vena cava through the catheter. One and one-half minutes later the heart rate was 190 per minute and the blood pressure was 305/255. The pulse wave was interpreted to indicate occasional prolonged diastole. Two minutes following the injection of epinephrine, the heart rate was 73 per minute and the blood pressure was 275/165. At this time the pulse wave tracing was interpreted to represent coupled rhythm. One contraction was normal followed by one with prolonged diastole. Five minutes following the injection of the challenge dose of epinephrine the heart rate was 152 per minute and regular. The blood pressure was 155/130. No fibrillation occurred. Experiment terminated.

FIGURE 30

Graphic representation of the results of cardiac sensitization and vagotomy experiment of September 20, 1953, using 0.25 mg./Kg. of Vasoxyl.


300
260
220
180
140
100
60
HEART RATE
Methoxamine
0.25 mg/kg
Nembutal
(1)
(2)
(3)
(1) Vagus nerves cut
(2) Ist Dose Methoxamine
(3) Epinephrine 20µgm/kg iv
0
10
20
30
40
TIME IN MINUTES

September 20, 1953. The Effects Of Vasoxyl On The Vagotomized Dog. See figure 30.

A fasted 9.54 Kg. male dog was anesthetized with 35 mg./Kg. Nembutal administered intraperitoneally at 9:30 A.M. Results of this experiment were recorded by means of a single channel EKG lead II. A femoral vein was exposed and a polyethylene catheter was inserted through it into the inferior vena cava. This was filled with normal saline and clamped. One hour and 15 minutes was allowed as a stabilization period.

10:45 A.M. the control EKG was taken. It was as follows: heart rate, 125 per minute and regular; PR interval, 0.10 sec.; QRS complex, 0.04 sec.

At 10:48 A.M. both vagus nerves were severed.

At 10:50 A.M. the heart rate was 240 per minute and regular. The PR interval measured 0.08 sec. but the QRS complex showed no change. At 10:51 the heart rate was 165 per minute. There was no additional change in the PR interval or the QRS complex.

At 10:51½ Vasoxyl was administered into the inferior vena cava. The dose of Vasoxyl used was 0.25 mg./Kg. Thirty seconds later the heart rate was 168 per minute and regular. There was no change in the PR interval or the QRS complex.

At 10:57½, 20 microgram/Kg. of epinephrine was administered into the inferior vena cava. Thirty seconds later the heart rate was 300 per minute. The PR interval measured 0.06 sec. and there was no change in the QRS complex. One minute following the epinephrine the heart rate

was very irregular and too rapid to count. Many ectopic ventricular beats were noted. Nine minutes following the epinephrine the heart rate was 175 per minute. The PR interval measured 0.08 sec. and the QRS complex measured 0.03 sec. No fibrillation occurred. End of experiment.

September 20, 1953. The Effects Of Vasoxyl In The Melville Technique After Bilateral Vagotomy. See figure 31.

A fasted 10 Kg. male dog was anesthetized with 35 mg./Kg. Nembutal administered intraperitoneally at 10:20 A.M. This experiment was recorded by means of a single channel EKG lead II. A femoral vein was exposed and a small polyethylene catheter was inserted through it into the inferior vena cava. This was filled with normal saline and clamped. A 45 minute stabilization period was allowed.

At 12:07 P.M. the control EKG was taken. The results were as follows: heart rate, 175 per minute and regular; PR interval measured 0.08 sec.; and QRS complex measured 0.03 sec. No abnormalities in the EKG tracing were noted.

At 12:08 P.M. both vagus nerves were severed as high in the neck as possible.

One minute later the heart rate was 230 per minute. There was no change noted in the PR interval or the QRS complex. Two and a half minutes following the vagotomy the heart rate was 185 per minute and regular. No change was noted in the PR interval or the QRS complex.

The dose of Vasoxyl that was administered in this animal was 0.5 mg./Kg. This was given in two equal doses into the inferior vena cava. Divided dosage was used in an attempt to lessen the depressant effects on respiration of Vasoxyl. This first dose of Vasoxyl was administered at 12:11 P.M. One minute later the heart rate was 170 per minute. There was no change in the PR interval or the QRS complex. Two and a half minutes later the heart rate was 165 per minute and regular. No other alterations in the EKG were noted.

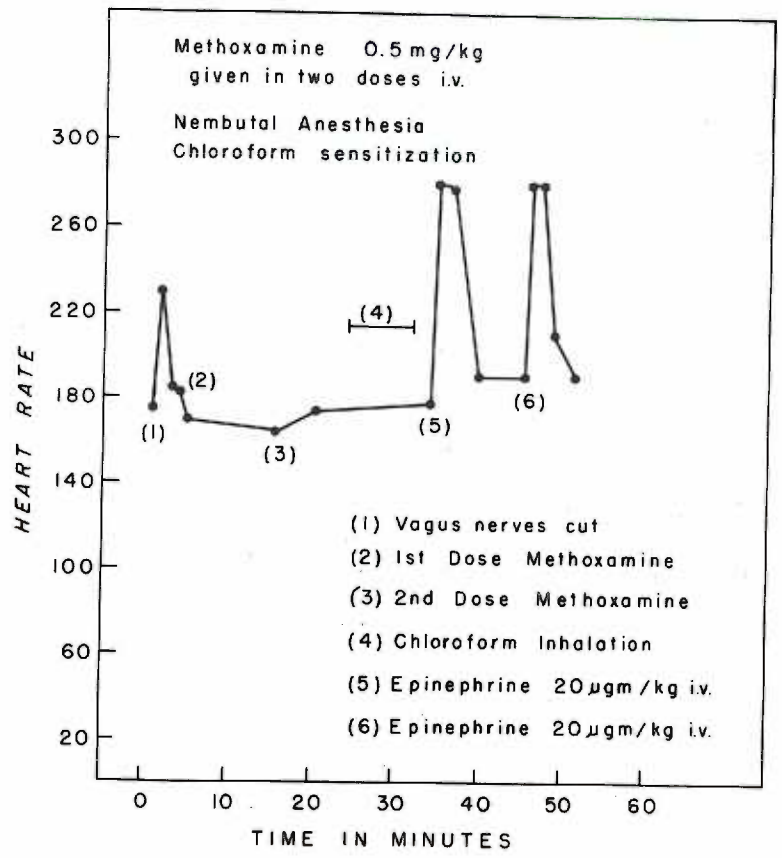
At 12:23 P.M. the second dose of Vasoxyl was administered. One minute later there was a brief period of time during which the EKG indicated a shifting ventricular pacemaker. Four and a half minutes following the second dose of Vasoxyl, the heart rate was 174 per minute and regular. There was no change noted in the PR interval or the QRS complex.

At 12:42 P.M., 20 microgram/Kg. of epinephrine were administered into the inferior vena cava. Thirty seconds later the heart rate was 280 per minute. There was no change noted in the PR interval or the QRS complex. One minute following the epinephrine the EKG showed many ectopic ventricular beats. One and a half minutes following epinephrine the EKG indicated ventricular tachycardia. Five minutes later the heart rate was 190 per minute and regular. No other alteration in the EKG was apparent.

At 12:52½ P.M., 20 microgram/Kg. of epinephrine was administered into the inferior vena cava for the second time. Thirty seconds later the heart rate was 280 per minute. The PR interval and the QRS complex

FIGURE 31

Graphic representation of the results of cardiac sensitization and vagotomy experiment of September 20, 1953, using 0.5 mg./Kg. of Vasoxyl.


Methoxamine 0.5 mg/kg
given in two doses i.v.
Nembutal Anesthesia
Chloroform sensitization
HEART RATE
300
260
220
180
140
100
60
20
(1)
(2)
(3)
(4)
(5)
(6)
(1) Vagus nerves cut
(2) Ist Dose Methoxamine
(3) 2nd Dose Methoxamine
(4) Chloroform Inhalation
(5) Epinephrine 20 µgm/kg i.v.
(6) Epinephrine 20 µgm/kg i.v.
0
10
20
30
40
50
60
TIME IN MINUTES

showed no change. One minute following the second dose of epinephrine ventricular tachycardia appeared. Four minutes following the second administration of epinephrine, the heart rate was 210 per minute, PR interval measured 0.07 sec. and there was no change in the QRS complex. The experiment was terminated. No fibrillation occurred.

August 17, 1954. Effects Of Vasoxyl In The Melville Technique Following Bilateral Vagotomy. See figure 32.

A fasted 17 pound female dog was anesthetized with Nembutal sodium in the usual dosage administered intraperitoneally at 12:05 P.M. After surgical anesthesia was obtained, an incision was made in the neck. Both vagus nerves were isolated as high in the neck as possible. A femoral vein was exposed. Following these procedures one hour was allowed for stabilization. Recording in this experiment was by means of a single channel EKG lead II.

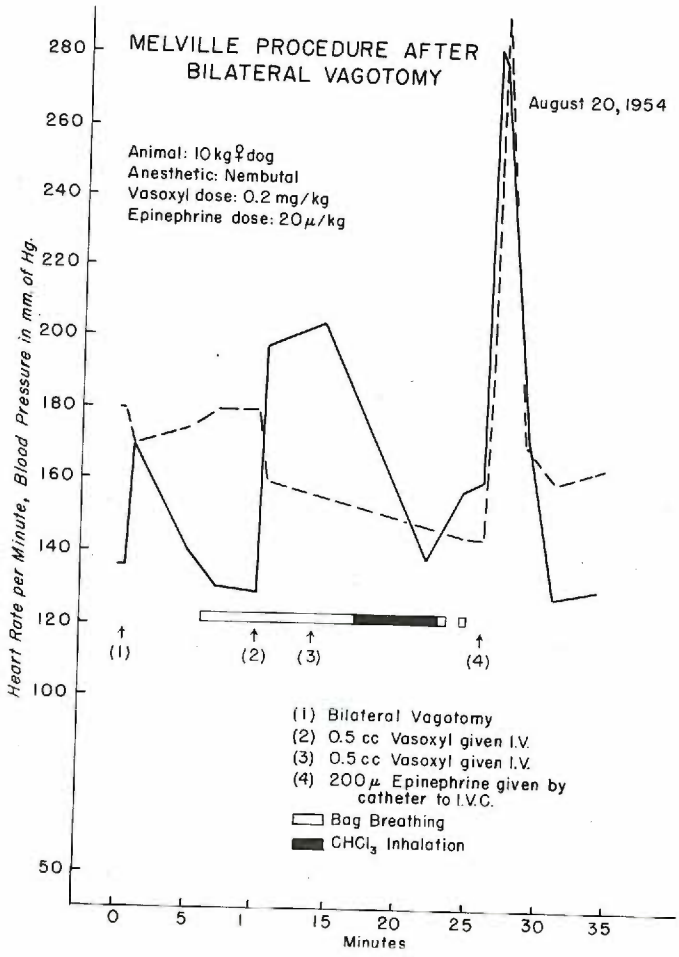
Controls were taken at 3:23 P.M. They were as follows: heart rate, 174 per minute; the lead II EKG picture was within normal limits.

A dosage of Vasoxyl of 1 mg./Kg. was administered into the exposed femoral vein in five increments so as to avoid respiratory depression. These doses of Vasoxyl were given at 3:24 P.M., 3:26 P.M. and 3:28 P.M. At 3:29 P.M. the heart rate was 150 per minute and regular. Two more doses of Vasoxyl were given at 3:35 P.M. and 3:38 P.M. At 3:39 P.M. the heart rate was 138 per minute and regular.

The right vagus nerve was severed at 3:42 P.M. and the left at 3:43 P.M. One minute later the heart rate was 144 per minute and regular.

FIGURE 32

Graphic representation of the results of cardiac sensitization and vagotomy experiment of August 17, 1954.


MELVILLE PROCEDURE AFTER
BILATERAL VAGOTOMY
August 20, 1954
Animal: 10 kg ♀ dog
Anesthetic: Nembutal
Vasoxyl dose: 0.2 mg/kg
Epinephrine dose: 20μ/kg
Heart Rate per Minute, Blood Pressure in mm of Hg.
280
260
240
220
200
180
160
140
120
100
50
(1)
(2)
(3)
(4)
(1) Bilateral Vagotomy
(2) 0.5 cc Vasoxyl given I.V.
(3) 0.5 cc Vasoxyl given I.V.
(4) 200μ Epinephrine given by catheter to I.V.C.
Bag Breathing
CHCl3 Inhalation
0
5
1
15
20
25
30
35
Minutes

At 3:44½ P.M. five minutes of chloroform inhalation was started in a dosage just strong enough to avoid changing the level of anesthesia. At the end of the chloroform inhalation the heart rate was 96 per minute. The EKG was now showing depressed ST segments, inverted T waves and frequent sinus pauses. Also, P waves were absent and there was evidence of nodal rhythm.

At 3:50 P.M. epinephrine in the dosage of 20 microgram/Kg. was administered into the inferior vena cava through the femoral vein. Ten seconds later the heart rate was 216 per minute. Twenty seconds later the heart rate was too rapid to count and there was ventricular nodal tachycardia. One minute later the heart rate was 240 per minute. The EKG showed a regular sinus rhythm though the ST segment was depressed and there was probably a retrograde P wave and an inverted T.

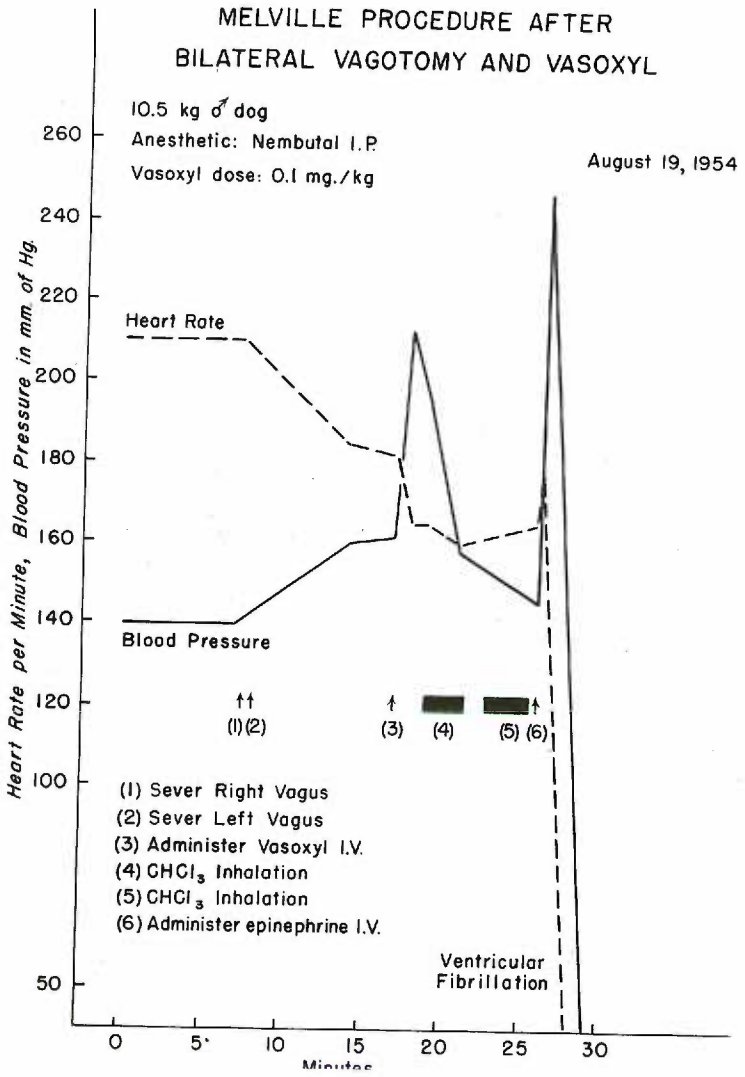
At 3:57 P.M. the heart rate was 156 per minute with a regular sinus rhythm. The ST segment was still depressed however. One minute later the experiment was terminated. No fibrillation occurred.

August 19, 1954. Effects of Vasoxyl In The Melville Technique Following Bilateral Vagotomy. See figure 33.

A fasted 10.5 Kg. male dog was anesthetized with Nembutal in the usual dosage administered intraperitoneally at 8:50 A.M. A second dose of 135 mg. of Nembutal was administered intraperitoneally at 12:45 P.M. After surgical anesthesia was obtained, a cuffed Magill endotracheal tube was installed in the trachea. A midline incision was made in the ventral surface of the neck and both vagus nerves were isolated as high

FIGURE 33

Graphic representation of the results of cardiac sensitization and vagotomy experiment of August 19, 1954.


MELVILLE PROCEDURE AFTER
BILATERAL VAGOTOMY AND VASOXYL
10.5 kg ♂ dog
Anesthetic: Nembutal I.P.
Vasoxyl dose: 0.1 mg./kg
August 19, 1954
Heart Rate
Blood Pressure
(1)(2)
(3)
(4)
(5)(6)
(1) Sever Right Vagus
(2) Sever Left Vagus
(3) Administer Vasoxyl I.V.
(4) CHCl3 Inhalation
(5) CHCl3 Inhalation
(6) Administer epinephrine I.V.
Ventricular Fibrillation
Heart Rate per Minute, Blood Pressure in mm. of Hg.
260
240
220
200
180
160
140
120
100
50
0
5
10
15
20
25
30

in the neck as possible. A femoral vein was exposed and a small polyethylene catheter inserted through it into the inferior vena cava. This catheter was filled with normal saline and attached to a syringe through which drugs were administered. Recording in this experiment was done by means of a single channel EKG lead II and a smoked drum kymograph on which blood pressure and a time scale were inscribed. After the animal was prepared, a one hour stabilization period was allowed.

Controls were taken at 1:44 P.M. and they were as follows: blood pressure, 140 mm. of mercury; heart rate, 210 per minute; QRS, 0.04 sec.; PR interval, 0.08 sec.

The right vagus nerve was severed as high in the neck as possible at 1:57½ P.M. and the left vagus nerve severed at 1:62 P.M. Apnea followed and bag breathing was started at 1:55 P.M. This was necessary for three minutes.

At 1:58 P.M. the blood pressure was 160 mm. of mercury and the heart rate 185 per minute and regular. There was no significant change in the EKG tracing. The PR interval measured 0.010 sec. and was the only significant change in the EKG tracing.

At 2:01 P.M., 0.1 mg./Kg. of Vasoxyl was administered by catheter into the inferior vena cava. One minute later the blood pressure was 212 per minute, and the heart rate 165 per minute. There was no other change in the EKG.

At 2:03 P.M. five minutes of chloroform inhalation was given in a concentration just strong enough to avoid changing the level of anesthesia.

Following the chloroform inhalation, the blood pressure was 158 mm. of mercury and the heart rate 160 per minute and regular. There were no significant changes in the EKG. Bag breathing was necessary at an interval during the chloroform inhalation.

At 2:10 P.M., 20 microgram/Kg. of epinephrine was administered into the inferior vena cava. Thirty seconds later ventricular fibrillation occurred. Vasocyl in this dosage did not prevent ventricular fibrillation. End of experiment.

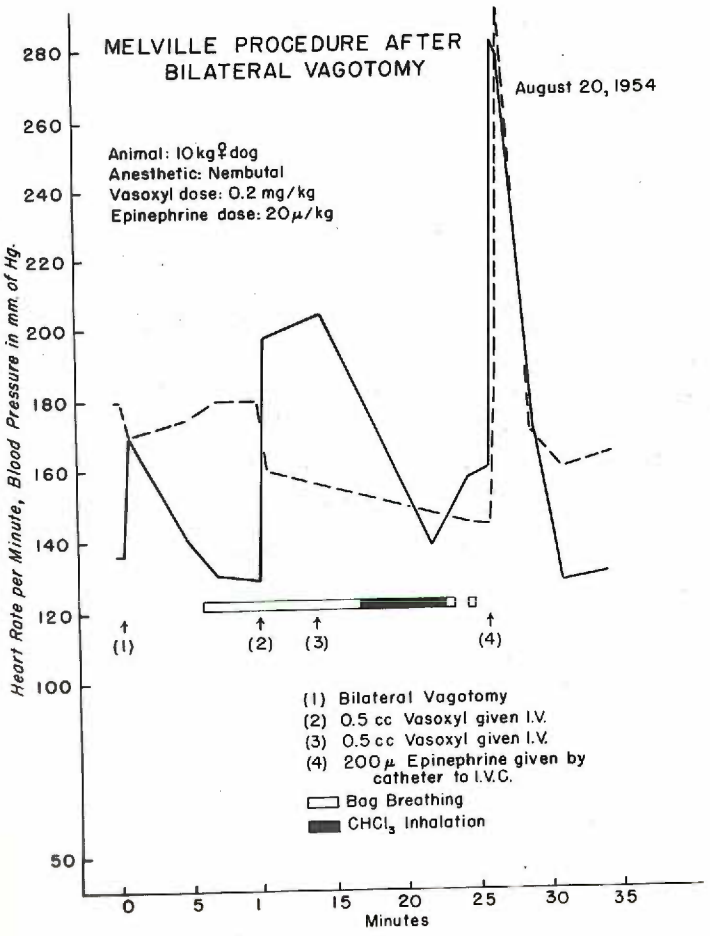
August 20, 1954. Effects Of Vasocyl In The Melville Technique Following Bilateral Vagotomy. See figure 34.

A fasted 10 Kg. female dog was anesthetized with Nembutal in the usual dosage administered intraperitoneally at 9:50 A.M. A cuffed Magill endotracheal tube was installed in the trachea. A ventral midline incision was made in the neck and both vagus nerves isolated as high in the neck as possible. A femoral vein was exposed and through it a polyethylene catheter was inserted into the inferior vena cava. This catheter was filled with normal saline connected to a syringe through which the drugs were given. Recording in this experiment was by means of a single channel EKG lead II and a smoked drum kymograph on which blood pressure and a time scale were inscribed. After the animal was prepared, one hour was allowed for stabilization.

Controls were taken at 11:44 A.M. and they were as follows: blood pressure, 136 mm. of mercury; heart rate, 180 per minute and regular; QRS, 0.04 sec.; PR interval, 0.08 sec.; and respirations, 23 per minute and regular.

FIGURE 34

Graphic representation of the results of cardiac sensitization and vagotomy experiment of August 20, 1954.


MELVILLE PROCEDURE AFTER
BILATERAL VAGOTOMY
August 20, 1954
Animal: 10 kg ♀ dog
Anesthetic: Nembutal
Vasoxyl dose: 0.2 mg/kg
Epinephrine dose: 20μ/kg
Heart Rate per Minute, Blood Pressure in mm of Hg.
280
260
240
220
200
180
160
140
120
100
50
(1)
(2)
(3)
(4)
(1) Bilateral Vagotomy
(2) 0.5 cc Vasoxyl given I.V.
(3) 0.5 cc Vasoxyl given I.V.
(4) 200μ Epinephrine given by catheter to I.V.C.
Bag Breathing
CHCl3 Inhalation
0
5
1
15
20
25
30
35
Minutes

At 11:44½ A.M. both vagus nerves were severed as high in the neck as possible. At 11:49 A.M. the blood pressure was 140 mm. of mercury and the heart rate 175 per minute and regular and respirations 17 per minute, shallow and regular. At 11:50 assisted breathing by means of a bag on the anesthesia machine was necessary.

Vasoxyl in the dose of 0.2 mg./Kg. was administered through the catheter into the inferior vena cava in two equal doses, at 11:54 A.M. and 11:58 A.M. The Vasoxyl was administered in two doses in an attempt to avoid respiratory depression. At 11:58½ A.M. the blood pressure was 206 mm. of mercury and the heart rate 156 per minute and regular. There was no significant change in the EKG tracings.

At 12:01 P.M. assisted breathing was discontinued and five minutes of chloroform inhalation was commenced. Chloroform was administered in a concentration just strong enough to avoid changing the level of anesthesia. Following the chloroform inhalation assisted bag breathing was required. This was necessary for approximately one minute. After this, the animal was breathing spontaneously.

At 12:08½ the blood pressure was 150 mm. of mercury and the heart rate was 145 per minute. At this time the QRS measured 0.03 sec. and the PR interval 0.12 sec.

At 12:10 P.M., 20 microgram/Kg. of epinephrine was administered by catheter into the inferior vena cava. Thirty seconds later the blood pressure was 280 mm. of mercury and the heart rate, 190 per minute. The QRS interval measured 0.02 sec. and the PR interval measured 0.06 sec. There was a 20 second period of apnea. At 12:11 the blood pressure measured 278 mm. of mercury and the heart rate was 290 per minute.

The EKG indicated ventricular tachycardia with occasional extrasystoles and was regular. The respirations improved at this time to 19 per minute.

At 12:15 P.M. the blood pressure measured 128 mm. of mercury and the heart rate was 160 per minute. The EKG picture was within control limits. Respirations were 12 per minute, regular and adequate. The experiment was terminated. No fibrillation occurred.

August 24, 1954. The Effects Of Vasoxyl In The Melville Technique After Bilateral Vagotomy.

A fasted 10 Kg. female dog was anesthetized with Nembutal sodium in the usual dosage administered intraperitoneally at 12:54 P.M. After surgical anesthesia was obtained, a ventral midline incision was made in the neck and both vagus nerves isolated as high as possible. A cuffed Magill endotracheal tube was installed in the trachea. A femoral vein was exposed and a small polyethylene catheter inserted through it into the inferior vena cava. This catheter was filled with normal saline and connected to a syringe through which the drugs were administered. Recording in this experiment was by means of a polyviso electrocardiograph. One channel of the polyviso recording AVR and another channel, lead II, of the EKG. A third channel of the polyviso was utilized to record blood pressure through a pressure transducer. This pulse wave was obtained from a catheterized carotid artery. After the animal was prepared, one hour was allowed for stabilization.

Controls were taken at 2:40 P.M. and they were as follows: heart rate, 185 per minute; lead II EKG measurements, QRS, 0.04 and PR interval, 0.08 sec.; blood pressure was 150/100 mm. of mercury.

At 2:42 P.M. the left vagus nerve was severed as high in the neck as possible and at 2:43 P.M. the right vagus nerve was severed. At 2:58 P.M. the heart rate was 160 per minute and the blood pressure was 180/140. There was no significant changes in the EKG tracings.

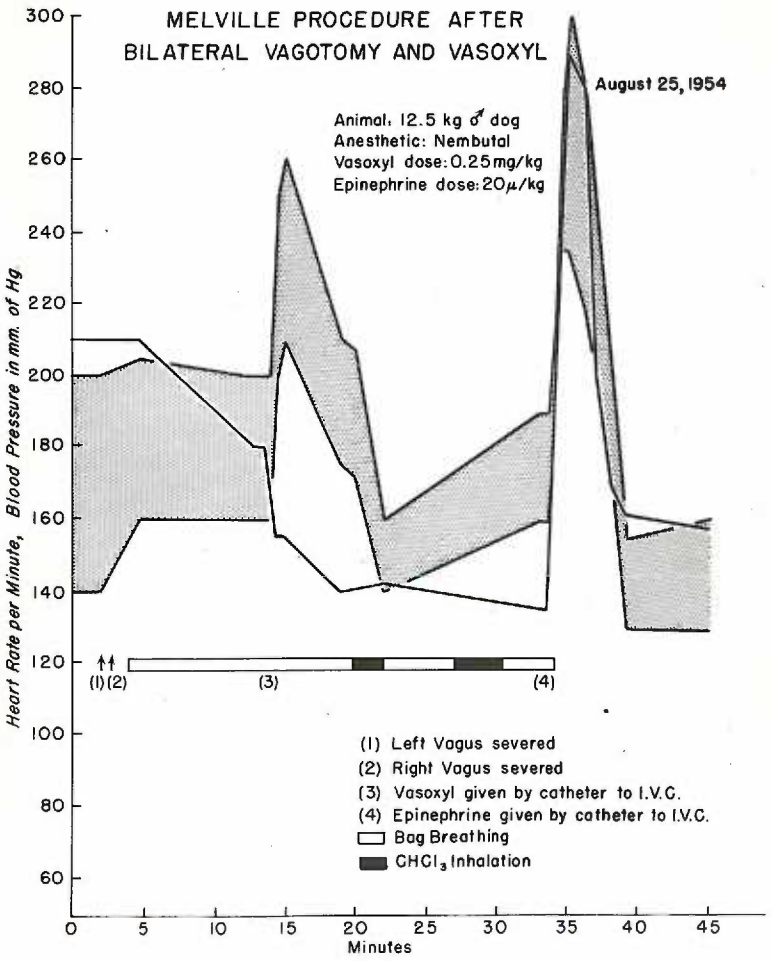
At 3:00 P.M., 0.4 mg./Kg. of Vasoxyl was administered into the inferior vena cava through the catheter in the femoral vein. Thirty seconds later the heart rate was 180 per minute and the blood pressure was 248/200. One and one-half minutes following the administration of the Vasoxyl the EKG showed occasional ventricular beats and an irregular recurring bigeminal pulse, apparently originating from a sinus node. Occasionally the P waves were absent.

At 3:12 P.M. chloroform was administered in a concentration just strong enough to avoid changing the level of anesthesia. The chloroform was discontinued at 3:17, started at 3:19 P.M. again, and finally discontinued at 3:21 P.M.

At 3:22 P.M., 20 microgram/Kg. of epinephrine was administered into the inferior vena cava. No blood pressure rise occurred. Rather the blood pressure fell to 40 mm. of mercury. The animal was in respiratory arrest. No attempt was made to bag breath this animal since there was strong evidence that this animal was suffering from a severe gastrointestinal disease. Respirations were abnormally depressed following the vagotomy and the chloroform inhalation caused complete apnea. The experiment was terminated.

FIGURE 35

Graphic representation of the results of cardiac sensitization after vagotomy experiment of August 25, 1954.


MELVILLE PROCEDURE AFTER
BILATERAL VAGOTOMY AND VASOXYL
August 25, 1954
Animal, 12.5 kg ♂ dog
Anesthetic: Nembutal
Vasoxyl dose: 0.25mg/kg
Epinephrine dose: 20μ/kg
Heart Rate per Minute, Blood Pressure in mm. of Hg
300
280
260
240
220
200
180
160
140
120
100
80
60
(1)(2)
(3)
(4)
(1) Left Vagus severed
(2) Right Vagus severed
(3) Vasoxyl given by catheter to I.V.C.
(4) Epinephrine given by catheter to I.V.C.
Bag Breathing
CHCl3 Inhalation
0
5
10
15
20
25
30
35
40
45
Minutes

August 25, 1954. The Effects Of Vasoxyl In The Melville Technique Following Bilateral Vagotomy. See figure 35.

A fasted 12.5 Kg. male dog was anesthetized with Nembutal in the usual dosage administered intraperitoneally at 9:55 A.M. A ventral midline incision was made in the neck and both vagus nerves isolated as high in the neck as possible. A carotid artery was cannulated. This was connected to a pressure transducer through which the carotid pulse pressure was recorded. A cuffed Magill endotracheal tube was installed in the trachea. A femoral vein was exposed and through it a small polyethylene catheter was inserted into the inferior vena cava. Recording in this experiment was by means of a polyviso four channel EKG. One channel was utilized for lead II of the EKG, another channel for AVR of the EKG and the third channel was utilized to record the carotid pulse wave through the pressure transducer.

After the animal was prepared, one hour was allowed for stabilization.

Controls were taken at 11:15 A.M. All EKG descriptions measured hereafter are of lead II. Controls were as follows: blood pressure, 200/140 mm. of mercury; heart rate, 210 per minute and regular; QRS, 0.04 sec.; PR interval, 0.08 sec.

At 11:17 A.M. the right vagus nerve was severed. At 11:18½ A.M. the heart rate was 210 per minute and regular. Blood pressure was 206/160. There was no other significant change in the EKG. Hereafter, only significant changes in the EKG tracings will be described.

At 11:19 A.M. assisted bag breathing was started. Respirations tend to become severely depressed by this procedure and assisted breathing was utilized intermittently throughout this experiment.

At 11:28 A.M. the heart rate was 180 per minute and regular and the blood pressure was 200/160.

At 11:29 A.M., 0.25 mg./Kg. of Vasoxyl was administered into the inferior vena cava through the polyethylene catheter. Thirty seconds following the administration of Vasoxyl the heart rate was 155 per minute and regular and the blood pressure was 250/200. At 11:44 A.M. the heart rate was 142 per minute and regular and the blood pressure was 210/175.

At 11:35 A.M. chloroform inhalation was administered in the usual manner. After two minutes of chloroform inhalation, it was necessary to discontinue the chloroform and bag breath the animal. At 11:42 A.M. the bag breathing was discontinued and chloroform inhalation was commenced once again. The chloroform was finally discontinued at 11:45½. Bag breathing was administered once again for a brief period.

At 11:48 A.M. the heart rate was 135 per minute and the blood pressure was 190/160.

At 11:48¾ A.M., 20 microgram/Kg. of epinephrine was administered into the inferior vena cava. At 11:49 A.M. the heart rate was 190 per minute. The blood pressure was 220/190. The only significant change noted in the EKG was an absence of the P wave. At 11:49 the EKG indicated severe irregular ventricular tachycardia. The rate was not measurable. The blood pressure at this time was 280/240.

At 11:50 A.M., or 1½ minutes following the injection of epinephrine, the heart rate was 290 per minute and there was regular sinus rhythm. The blood pressure was 300/240. The QRS interval measured 0.03 sec. and the PR interval measured 0.06 sec.

At 12:00 noon the heart rate was 158 per minute and regular. The blood pressure was 160/130. The QRS interval measured 0.03 sec. and the PR interval measured 0.08 sec. This dosage of Vasoxyl in this animal prevented ventricular fibrillation from appearing. End of experiment.

September 13, 1954. The Effects Of Vasoxyl Following Infarction Produced By Injection Of Zinc Hydroxide Into The Myocardium.

Using the method described by F. H. Meyers for creating myocardial infarcts by means of injection of zinc hydroxide, shock due to myocardial damage was produced. After EKG evidence of myocardial damage appeared, Vasoxyl in the dose of 0.25 mg./Kg. was administered intravenously.

An 11.3 Kg. female dog was anesthetized with Nembutal in the usual dosage administered intraperitoneally at 1:15 P.M. After anesthesia was obtained, a cuffed Magill endotracheal tube was installed in the trachea. Recording in this experiment was by means of a single channel electrocardiograph recording lead II. The left half of the thorax was shaved and sterilized. The point of maximum impact was marked on the chest wall. Approximately one hour was allowed for stabilization. The

hydroxide suspension was freshly prepared in the manner described by Meyers. Controls were taken at 2:46 P.M. They were as follows: heart rate, 123 per minute and regular; QRS, 0.04 sec.; PR interval, 0.10 sec. The EKG tracing showed an inverted T wave in lead II.

At 2:52 P.M., 3 cc. of a 3% suspension of zinc hydroxide was injected into the myocardium through the intact chest wall. The method described by Meyers was followed.

At 2:59 P.M. the heart rate was 94 per minute, with no significant change in the EKG tracing. However, occasional ectopic ventricular beats began to appear at this point at irregular intervals. There were approximately 17 or 18 ectopic ventricular beats per minute. Ectopic ventricular beats would appear in bursts of 4 or 5.

At 3:01 P.M., 0.25 mg./Kg. of Vasoxyl was administered intravenously into a peripheral superficial leg vein.

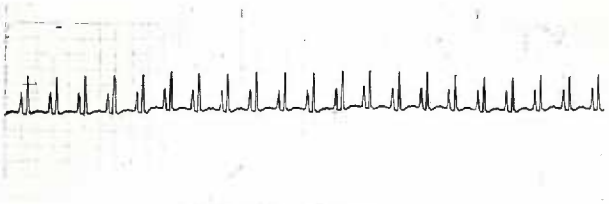
At 3:03 P.M. the heart rate was 88 per minute and regular. The PR interval measured 0.11 sec. The T wave was now normal in size and upright. No ectopic beats appeared since Vasoxyl was administered.

At 3:15 P.M. heart rate was 82 per minute, QRS interval, 0.03; and PR interval was 0.14 sec. The rhythm was regular and no ectopic beats have appeared.

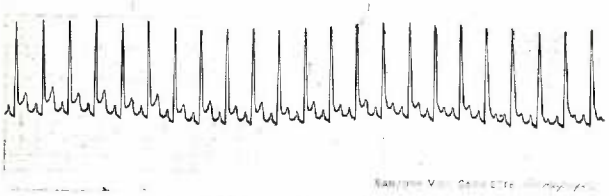
At 3:33 P.M. the animal appeared severely depressed and expired from respiratory distress. No attempt at assisted respiration was made. End of experiment.

FIGURE 36

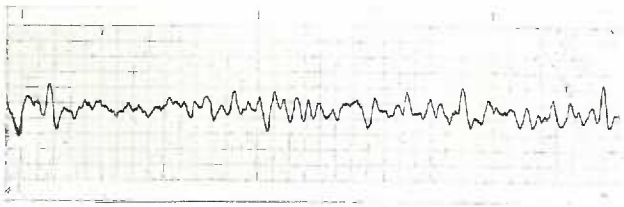
Representative sections of the EKG taken in the myocardial infarction experiment of September 21, 1954.



CONTROL LEAD II



LEAD II FOLLOWING $Zn(OH)_2$ INFARCT



LEAD II FOLLOWING $Zn(OH)_2$ INFARCT

September 21, 1954. The Effects Of Vasoxyl On The EKG Of An Animal In Which An Acute Myocardial Infarct Has Been Produced. See figure 36.

A fasted 8.2 Kg. male dog was anesthetized with Nembutal sodium given intraperitoneally in the usual dosage. Recording in this experiment was done by means of a single channel lead II electrocardiogram. After surgical anesthesia was obtained, an infarct was produced in the manner described by Meyers. A fresh suspension of zinc hydroxide was injected through the intact chest wall into the myocardium. Three cc. of this suspension was used.

At 1:30 P.M. the control EKG was taken.

At 1:38 P.M. the zinc hydroxide suspension was injected into the myocardium. One minute later ventricular fibrillation occurred and the animal died.

Autopsy disclosed a needle hole in the intraventricular septum anteriorly near the AV junction.

September 28, 1954. The Effects Of Vasoxyl On The EKG Of An Animal In Which An Acute Myocardial Infarct Has Been Produced.

A fasted 9.54 Kg. male dog was anesthetized with Nembutal sodium given intraperitoneally in the usual dosage. This was accomplished at 11:45 A.M. Recording in this experiment was done by means of a single channel lead II electrocardiogram.

After surgical anesthesia was obtained, an acute myocardial infarction was produced after the manner prescribed by Meyers. Three cc. of a 3% suspension of zinc hydroxide freshly prepared was injected through the intact chest wall into the myocardium. The control EKG was taken at 1:15 and was found to be within normal limits.

The zinc hydroxide was injected into the myocardium at 1:30 P.M. At 1:38½ P.M. ventricular fibrillation occurred and the animal expired.

Autopsy disclosed a needle hole and an infarct in the intraventricular septum near the auricular ventricular junction somewhat anteriorly.

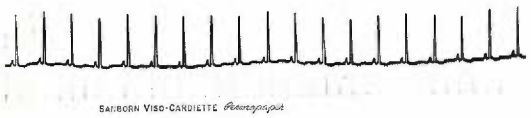
December 20, 1954. The Effects Of Vasoxyl On The EKG Of An Animal In Which An Acute Myocardial Infarction Had Been Produced.
See figure 37.

A fasted 6.8 Kg. female dog was anesthetized with Nembutal sodium given intraperitoneally in the usual dosage. The initial anesthetic dose was given at 11:35 A.M. This was followed by 0.5 cc. of Nembutal given intraperitoneally at 1:20 P.M. Recording in this experiment was by means of a single channel lead II electrocardiogram.

The infarction was accomplished after the manner described by Meyers. Three cc. of a 3% of a freshly prepared zinc hydroxide suspension was injected through the intact chest wall into the myocardium. The effects of the zinc hydroxide on the myocardium were determined clinically and by following the EKG. Approximately 15 to 20 minutes following the appearance of myocardial damage on the EKG, Vasoxyl in the dose of 0.25 mg./Kg. was injected intravenously.

FIGURE 37

Representative sections of the EKG taken in the myocardial infarction experiment of December 20, 1954.

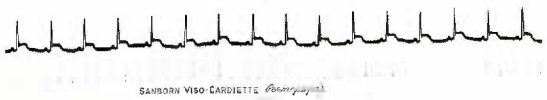


2:10 P.M. CONTROL LEAD II

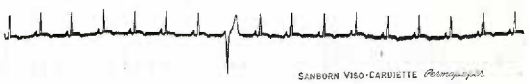
VASOXYL INJECTED AT 2:49 (0.25 mg/kg I.V.)

2:49 1/2 P.M.

$Zn(OH)_2$ INJECTED AT 2:15 P.M.



2:40 P.M.



3:20 P.M.

At 2:10 P.M. the control EKG was taken and this was found to be within normal limits.

At 2:15 P.M. 3 cc. of a 3% suspension of zinc hydroxide was injected into the myocardium. Evidence of acute myocardial damage appeared on the EKG tracing very shortly thereafter.

At 2:19 P.M. 0.25 mg. of Vasoxyl was injected intravenously. The electrocardiogram showed no damaging effects from the Vasoxyl. Rather, it would appear that the EKG was improved.

December 21, 1954. The Effects Of Vasoxyl On The EKG Of An Animal In Which An Acute Myocardial Infarction Is Produced. See figure 38.

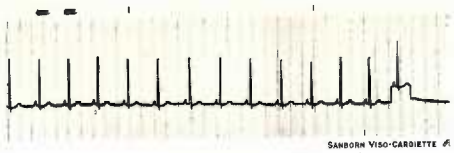
A fasted 8.6 Kg. male dog was anesthetized with Nembutal sodium given intraperitoneally in the usual dosage. This was accomplished 11:45 A.M. After surgical anesthesia was obtained, an acute myocardial infarction was produced in the manner described by Meyers. Three cc. of a freshly prepared 3% suspension of zinc hydroxide was injected into the myocardium through the intact chest wall. The effects of the zinc hydroxide on the myocardium were followed clinically and by a single channel lead II electrocardiogram. Fifteen to twenty minutes following the appearance of evidence of myocardial damage on the EKG, Vasoxyl was injected intravenously.

At 1:30 P.M. the control EKG, all leads, was taken and found to be within normal limits.

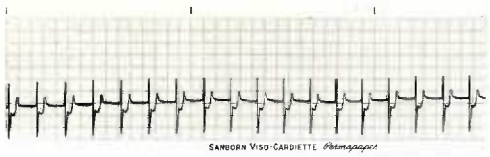
At 1:38 P.M. the zinc hydroxide was injected into the myocardium. Within 3 minutes evidence of an acute myocardial damage appeared on the EKG tracing.

FIGURE 38

Representative sections of the EKG taken in the myocardial infarction experiment of December 21, 1954, using 0.25 mg./Kg. of Vasoxyl.

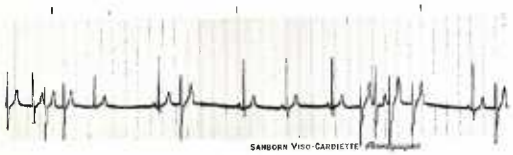


1:30 P.M. CONTROL LEAD II

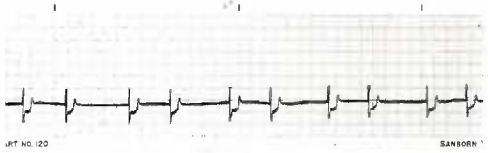


1:43 P.M. LEAD II

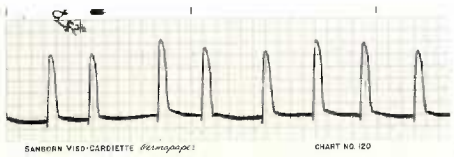
$n(OH)_2$ BEING INJECTED LEAD AVF



1:38 P.M.



1:45 VASOXYL ALL INJECTED



2:50 P.M. LEAD II

At 1:45 P.M. 0.25 mg./Kg. of Vasoxyl was injected intravenously. The Vasoxyl caused no apparent damage to the EKG.

At 3:00 P.M. the animal suddenly died and it was the impression that death was due to acute cardiac failure.

Autopsy disclosed needle wound in an area of discoloration in the left ventricle and in the anterior portion of the intraventricular septum near the auricular ventricular junction.

December 21, 1954. The Effects Of Vasoxyl On The EKG Of An Animal In Which An Acute Myocardial Infarction Is Produced. See figure 39.

A fasted 8.64 Kg. female dog was anesthetized with Nembutal sodium given intraperitoneally in the usual dosage at 9:30 A.M. Recording in this experiment was done by means of a single channel lead II electrocardiogram. The myocardial infarction was produced in the manner described by Meyers in which a freshly prepared suspension of zinc hydroxide was injected through the intact chest wall into the myocardium.

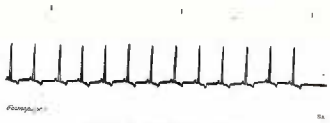
At 10:20 A.M. the control EKG was taken, in all leads, and was found to be within normal limits.

At 10:35 A.M. 3 cc. of the zinc hydroxide suspension was injected into the myocardium. By 10:55 A.M. no damage to the myocardium was apparent from the EKG.

At 11:00 A.M. a second injection of 3 cc. of zinc hydroxide was injected into the myocardium. By 11:10 A.M. evidence of myocardial damage appeared on the EKG.

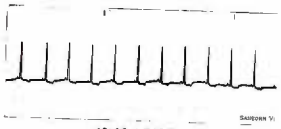
FIGURE 39

Representative sections of the EKG taken in the myocardial infarction experiment of December 21, 1954, using 0.5 mg./Kg. of Vasoxyl.

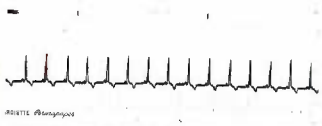


10:20 A.M. CONTROL LEAD II

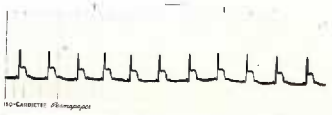
1st $Zn(OH)_2$ INJECTED AT 10:35 A.M.



10:46 LEAD II

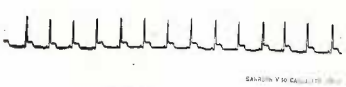


11:00 A.M. END OF 2nd INJECTION $Zn(OH)_2$ LEAD II

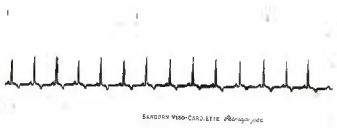


11:10 A.M. LEAD II

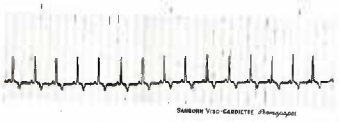
VASOXYL 0.5 mg/kg GIVEN I.V. AT 11:19 A.M.



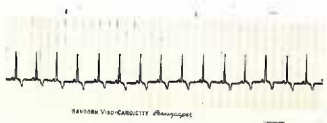
11:20 A.M. LEAD II



11:39 A.M. LEAD II



12:05 P.M. LEAD II



1:00 P.M. LEAD II

At 11:19 A.M. 0.5 mg./Kg. of Vasoxyl was administered intravenously. There was no evidence on the EKG that the Vasoxyl caused further myocardial irritation. Rather, the EKG gave the appearance of being improved following the Vasoxyl.

At 1:00 P.M. the experiment was terminated and the animal returned to the kennels in satisfactory conditions.

On January 3, 1955, the animal died. Autopsy disclosed severe pulmonary congestion with the appearance of vast pneumonitis and edema. Pericardial adhesions and a scarred myocardium was noted in the left ventricle anteriorly near the intraventricular septum.

December 27, 1954. The Effects Of Vasoxyl And Epinephrine On The EKG Of An Animal On Which An Acute Myocardial Infarct Has Been Produced. See figure 40.

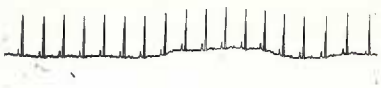
A fasted 6.8 Kg. female dog was anesthetized at 2:50 P.M. with Nembutal sodium given intraperitoneally in the usual dose.

Recording in this experiment was done by means of a single channel lead II electrocardiogram. At 3:40 P.M. the control EKG was taken, in all leads, and found to be within normal limits.

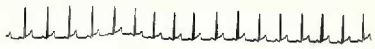
At 3:54 P.M. myocardial infarction was produced in the manner described by Meyers. Three cc. of a freshly prepared 3% suspension of zinc hydroxide was injected into the myocardium through the intact chest wall. By 4:10 P.M. no significant alteration in the electrocardiogram was noted.

FIGURE 40

Representative sections of the EKG taken in the myocardial infarction experiment of December 27, 1954.

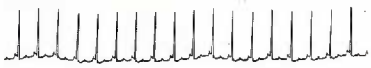


3:40 P.M. CONTROL LEAD II

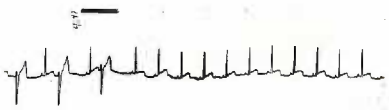


4:30 P.M. LEAD II

$Zn(OH)_2$ INJECTED AT 3:54 P.M.

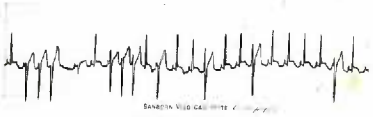


4:00 P.M. LEAD II

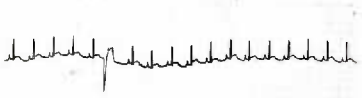


4:47 P.M. LEAD II

2nd INJECTION OF $Zn(OH)_2$ GIVEN AT 4:14 P.M.

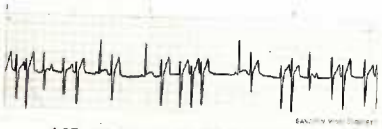


4:21 P.M. LEAD II

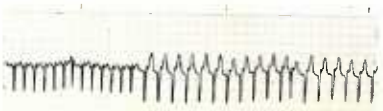


5:01 P.M. LEAD II

5:10 P.M. 20 mg/kg EPINEPHRINE INJECTED I.V.



4:27 P.M. DURING INJECTION OF VASOXYL



5:11 P.M. LEAD II

At 4:14 P.M. a second attempt was made to cause myocardial infarction. By 4:21 P.M. the electrocardiogram showed severe myocardial damage.

At 4:29 P.M. one mg./Kg. of Vasoxyl was injected intravenously. The EKG tracing showed no evidence that the Vasoxyl caused further myocardial damage. It is the impression, rather, that Vasoxyl improved the EKG tracing.

At 5:10 P.M. 20 microgram/Kg. of epinephrine was injected intravenously. Following the epinephrine, the EKG showed the usual severe effects on the myocardium.

At 5:20 P.M. the experiment was terminated and the animal was returned to the kennels in satisfactory condition. The animal was followed by EKG tracings taken every second day. These continually showed abnormal tracings.

The animal expired on January 7, 1955.

Autopsy disclosed completely congested lungs; pus and mucoid fluid were present in all lobes. Pericardial adhesions were noted over the anterior surface of the left ventricle. There was evidence of scarring in the myocardium in the anterior surface of the left ventricle especially near the superior half of the intraventricular septum. End of experiment.

May 14, 1953. Intermittent Injections Of Massive Doses Of Vasoxyl.

In this experiment an anesthetized animal is to receive 20 mg. of Vasoxyl intravenously at varying intervals of time. The animal was anesthetized with sodium barbital in the dose of 250 mg./Kg. given intraperitoneally. A femoral vein was exposed and cannulated with a polyethylene cannula attached to a syringe mounted on a constant rate injector machine. This syringe contained normal saline solution. The Vasoxyl was injected into this cannula by means of a T tube. The recording was accomplished by means of a smoked drum kymograph on which was inscribed a carotid artery blood pressure, the respiration from a tracheal cannula, a zero blood pressure line, and a time scale. A lead II electrocardiograph was taken intermittently throughout the experiment. The intervals at which the EKG was being taken are indicated on the kymograph by means of depressions on the zero blood pressure line. A fasted 11.4 Kg. male dog was the subject of this experiment. The anesthetic was administered at 9:30 A.M. At 1:25 P.M. the saline injection was started.

Controls were taken at 1:28 P.M. They were as follows: heart rate, 170 per minute and regular, and no abnormalities were noted in the EKG pattern; respiration, 36 per minute and regular; blood pressure, 179 mm. of mercury.

At 1:35, 20 mg. of Vasoxyl was injected intravenously. One minute following the injection of the Vasoxyl the blood pressure was 260 mm. of mercury. Two minutes following the injection of Vasoxyl the blood pressure started to decline. At 11 minutes the blood pressure was

160 mm. of mercury. At 14 minutes the blood pressure was 148 mm. of mercury. At 15 minutes the blood pressure had returned to 164 mm. of mercury at which point it stabilized for the next few minutes. At 28 minutes following the injection of Vasoxyl the blood pressure had fallen again to 128 mm. of mercury. At 47 minutes the blood pressure was 134 mm. of mercury.

One minute following the injection of Vasoxyl the respirations showed sharp drop in rate and amplitude. Four minutes following the injection of Vasoxyl the animals respirations were severely depressed. The respirations gradually improved until 47 minutes following the injection of Vasoxyl when they were approximately 16 per minute though Cheyne-Stokes in character.

The EKG showed a marked bradycardia one minute following the injection of Vasoxyl though 60 cycle interference made it difficult to evaluate. At 3 minutes the EKG showed irregular bradycardia with sinus pauses. At 14 minutes the 60 cycle interference had been cleared. The heart rate was now 88 per minute. No other significant alterations in the EKG measurements were noted. Sixteen minutes following the injection of Vasoxyl the heart rate was 107 per minute and regular. At 27 minutes the heart rate was 125 per minute and regular. At this point the animal received 0.5 gm. of sodium barbital intravenously. At 47 minutes the heart rate was 140 minutes and regular.

At 2:21 P.M. 48 minutes following the injection of Vasoxyl, a second 20 mg. injection of Vasoxyl was accomplished. One minute following the injection of Vasoxyl the heart rate was 84 per minute and regular. The blood pressure varied between 164 and 129 mm. of mercury. The respirations

were Cheyne-Stokes in character. At 3 minutes the heart rate was 77 per minute and regular. No significant alteration in the EKG was noted. Blood pressure was still exhibiting marked wave-like variations, varying between 172 and 112 mm. of mercury. There was no change in the condition of the respirations.

At 26 minutes following the second injection of Vasoxyl the heart rate was 110 per minute and regular. The blood pressure still exhibited marked variations though the waves became progressively smaller. The blood pressure now varied between 144 and 130 mm. of mercury. The respirations were still Cheyne-Stokes in character. At 33 minutes the heart rate was 150 per minute and regular. There was no significant alterations in other aspects of the EKG. The blood pressure was 154 mm. of mercury and somewhat stabilized. The animal exhibited extremely violent hypernea.

At 2:56½ P.M., or 35 minutes following the second injection of Vasoxyl, a third injection of Vasoxyl of 20 mg. was given intravenously. Three minutes following the injection of the Vasoxyl for the third time the heart rate was 150 per minute and regular. No other alteration in the EKG was noted. The blood pressure was 135 mm. of mercury with a very narrow pulse pressure. No alteration in respirations was noted following this injection of Vasoxyl. In other wrods, the third injection of Vasoxyl caused no significant alterations in any of the quantities being measured. Subsequent to the third injection of Vasoxyl no change was noted for the next 30 minute period. A fourth and last intravenous injection of Vasoxyl was attempted at this time but no alterations were noted whatsoever. The experiment was terminated.

FIGURE 41

Graphic representation of results of ligation of coronary vessels experiment of September 5, 1951.

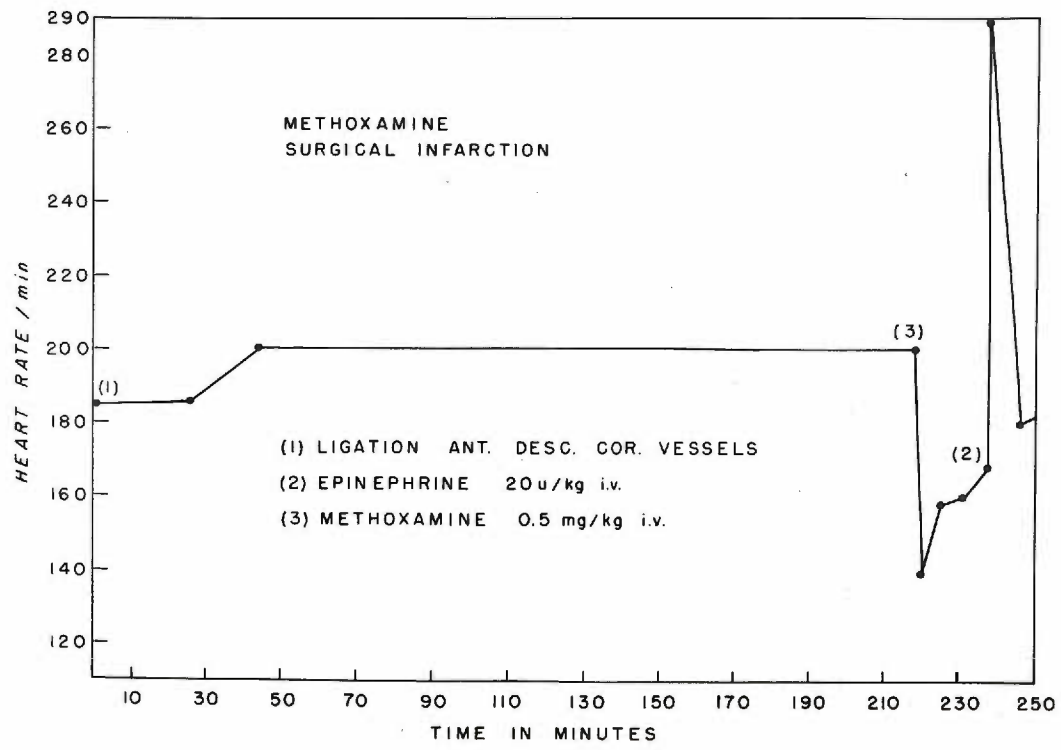
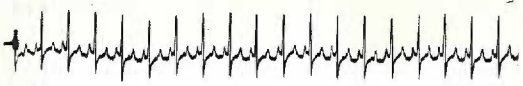

METHOXAMINE
SURGICAL INFARCTION
(1) LIGATION ANT. DESC. COR. VESSELS
(2) EPINEPHRINE 20u/kg i.v.
(3) METHOXAMINE 0.5 mg/kg i.v.
HEART RATE / min
TIME IN MINUTES
290
280
260
240
220
200
180
160
140
120
10
30
50
70
90
110
130
150
170
190
210
230
250

FIGURE 42

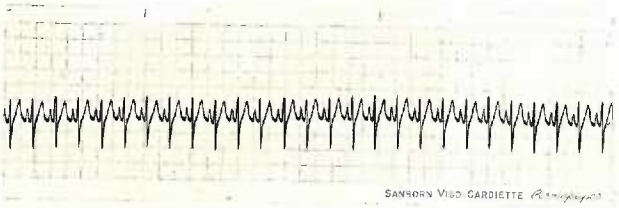
Representative sections of the EKG taken during ligation of coronary vessels experiment of September 5, 1954.

METHOXAMINE CORONARY LIGATION

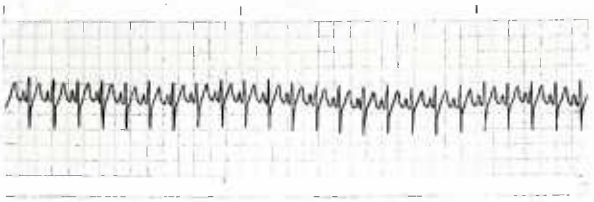


Control

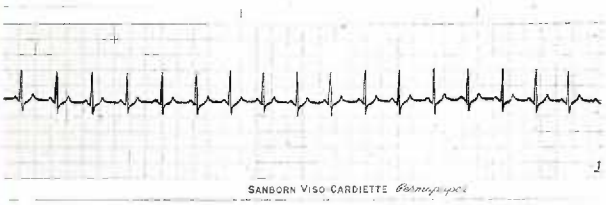
One hour post ligation



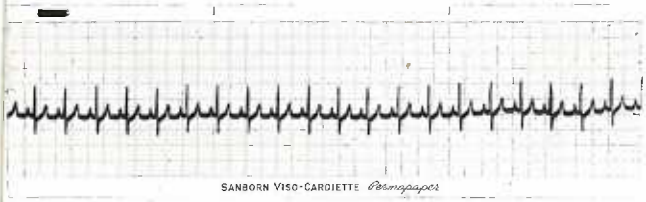
Two hours post ligation



Three hours post ligation



One minute post Methoxamine I.V.
0.5 mg/kg



Six minutes post Methoxamine I.V.

September 5, 1954. The Effects Of Vasoxyl On The EKG Of An Animal Following Ligation Of The Anterior Descending Coronary Vessels.
See figures 41 and 42.

A fasted 12 Kg. female dog was anesthetized in the usual manner and dosage. Surgical anesthesia was obtained at 1:00 P.M. The animal was then intubated with a cuffed Magill endotracheal tube which was connected to an anesthesia machine. Oxygen and supported respiration was supplied as needed. The thorax was opened and the heart exposed and suspended in a sling of pericardium. A femoral vein was exposed and cannulated with a small polyethylene cannula inserted so that its tip lay high in the inferior vena cava. This was filled with normal saline and clamped. Recording in this experiment was by means of a single channel lead II EKG. Control EKG's were taken at 1:15 P.M. The heart rate at this time was 185 per minute and regular. All measurements of the EKG tracings were within normal limits.

At 1:18 P.M. the anterior descending coronary arteries were ligated with doubled silk sutures. No immediate response was noted on the EKG tracing. Twenty-five minutes following ligation, the heart rate was 192 per minute and regular. However, by 43 minutes following the ligation, the heart rate had risen to 200 per minute and regular. No abnormalities were noted in the EKG. This picture was maintained at this level of heart rate, and with no abnormalities, for the next hour and a half.

At 3:36 P.M. 0.5 mg./Kg. of Vasoxyl were administered through the polyethylene catheter into the inferior vena cava. Two minutes later,

the heart rate was 138 per minute. Alterations in the pattern of the EKG tracing were as illustrated in the attached reproduction. The heart rate gradually tended to return toward control level for the next 10 minutes.

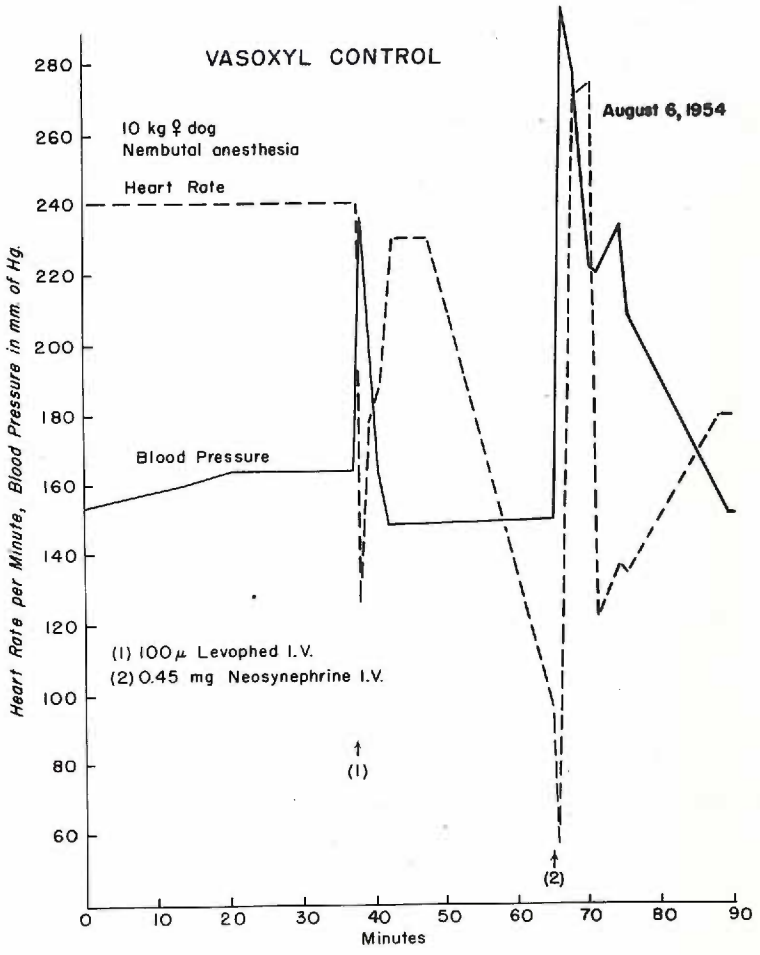
At 3:55 P.M. 20 microgram/Kg. of epinephrine were administered through the inferior vena cava through the polyethylene catheter. One minute later the heart rate was 294 per minute. Severe alterations in the pattern of the EKG tracing were noted. However, at 9 minutes following the injection of epinephrine, the heart rate had fallen again to 180 per minute and the picture of the tracing had returned towards control level. It is to be noted that even in this damaged heart this dose of epinephrine did not cause fibrillation.

August 6, 1954. Vasoxyl Control Experiment; Blood Pressure, EKG And Respiratory Effects Of Levophed And Neo-Synephrine. See figure 43.

A fasted 10 Kg. female dog was anesthetized with Nembutal sodium in the usual dose administered intraperitoneally at 9:10 A.M. Recording in this experiment was by means of a smoked drum kymograph on which was inscribed carotid artery blood pressure, respiration, a blood pressure zero line and a time scale. A single channel EKG lead II was also taken throughout this experiment and intervals during which the EKG was being run are indicated on the smoked drum kymograph by depressions on the blood pressure zero line. After surgical anesthesia was obtained, a femoral vein was exposed and a small polyethylene catheter was inserted through it into the inferior vena cava. The catheter was filled with

FIGURE 43

Graphic representation of the results of experiment demonstrating the effects of Levophed and Neo-Synephrine.


VASOXYL CONTROL
August 6, 1954
10 kg ♀ dog
Nembutal anesthesia
Heart Rate
Blood Pressure
(1) 100μ Levophed I.V.
(2) 0.45 mg Neosynephrine I.V.
(1)
(2)
Heart Rate per Minute, Blood Pressure in mm. of Hg.
280
260
240
220
200
180
160
140
120
100
80
60
0
10
20
30
40
50
60
70
80
90
Minutes

normal saline connected to a syringe mounted on a constant injector machine. A carotid artery was exposed connected to the blood pressure indicator. The tracheal cannula was inserted and connected to the indicator on the kymograph. A 45 minute stabilization period was allowed.

Controls were taken at 11:25 A.M. They were: blood pressure, 154 mm. of mercury; heart rate, 240 per minute and regular; QRS, 0.04 sec.; PR interval, 0.08 sec.; respirations, 20 per minute and regular.

At 12:02½ P.M. 100 microgram/Kg. of Levophed Bitartrate was administered intravenously. The expected rise in blood pressure occurred, going to 236 mm. of mercury. The EKG indicated, at first, the vagal reflex, as would be expected, with a sinus bradycardia. The heart rate slowed initially to 125 per minute but 4 minutes following the injection of Levophed the heart rate was 175 per minute and 7 minutes following the injection of Levophed the heart rate was back to 230 per minute. Initially, the QRS complex was shortened to 0.04 sec. and the PR interval was shortened to 0.06 sec. However, by four minutes following Levophed, the PR interval and QRS complex had returned to normal limits. The only significant alterations in the EKG picture occurred approximately four minutes after the injection of Levophed. At this time there was apparent a coupled rhythm. Also, a depressed ST segment was noted and an occasional ectopic ventricular contraction. This was transient, however, and by 5½ minutes following Levophed, the entire EKG was within normal limits.

There was also noted a brief period of severe respiratory depression immediately following Levophed. This ranged from initial transient complete apnea to merely depressed respirations for the next five minutes.

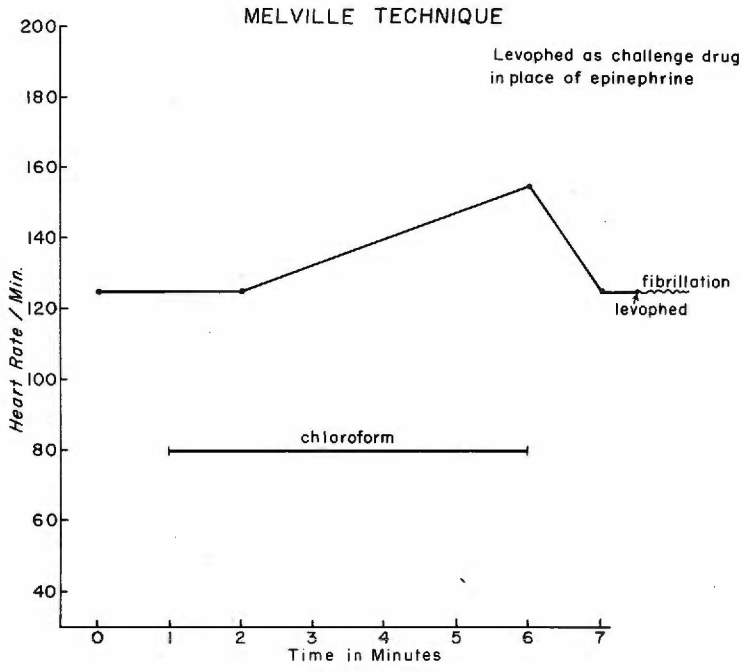
At 12:30½ P.M. 0.45 mg. of Neo-Synephrine was administered intravenously. Thirty seconds following the injection of Neo-Synephrine there occurred the expected rise in blood pressure. The heart rate was severely depressed, 57 per minute. The EKG picture was similar to that occurring 4 minutes after the injection of Levophed in that there was a coupled rhythm. Also, respirations were extremely shallow and irregular. Two and one-half minutes following the injection of Neo-Synephrine, blood pressure was 276 mm. of mercury and ventricular tachycardia had appeared. The heart rate was 290 per minute. Respirations were even more severely depressed and irregular.

Five minutes following the Neo-Synephrine, the heart rate was approaching normal limits though the blood pressure was still 220 mm. of mercury. The EKG indicated a coupled rhythm which was probably a premature complex. There was also occasional evidence of an electrical alternans pattern in the EKG.

Nine minutes following Neo-Synephrine, the heart rate, QRS complex, PR interval and entire EKG had returned to normal again. However, the blood pressure was still markedly elevated in that it was 234 mm. of mercury. Thirty-four minutes following Neo-Synephrine all factors had returned to control levels.

FIGURE 44

Graphic representation of the results of cardiac sensitization experiment using Levophed on July 16, 1954.


MELVILLE TECHNIQUE
Levophed as challenge drug
in place of epinephrine
200
180
160
140
120
100
80
60
40
Heart Rate / Min.
fibrillation
levophed
chloroform
0
1
2
3
4
5
6
7
Time in Minutes

July 16, 1954. Melville Technique Using Levophed Instead of Epinephrine As Challenge Drug. See figure 44.

An 11.5 Kg. female dog was anesthetized with 35 mg./Kg. of Nembutal administered intraperitoneally at 1:40 P.M. Results in this experiment were recorded by means of a single channel Sanborn Cardiette in lead II.

Control EKG was taken at 2:46 P.M. with all measurements within normal limits. Heart rate was 124 per minute and was regular.

Starting at 2:52 P.M. five minutes of chloroform inhalation was administered in the usual manner. At 2:57 P.M., when the chloroform was discontinued, the heart rate was 152 per minute and was regular.

One minute later the heart rate had returned to control levels.

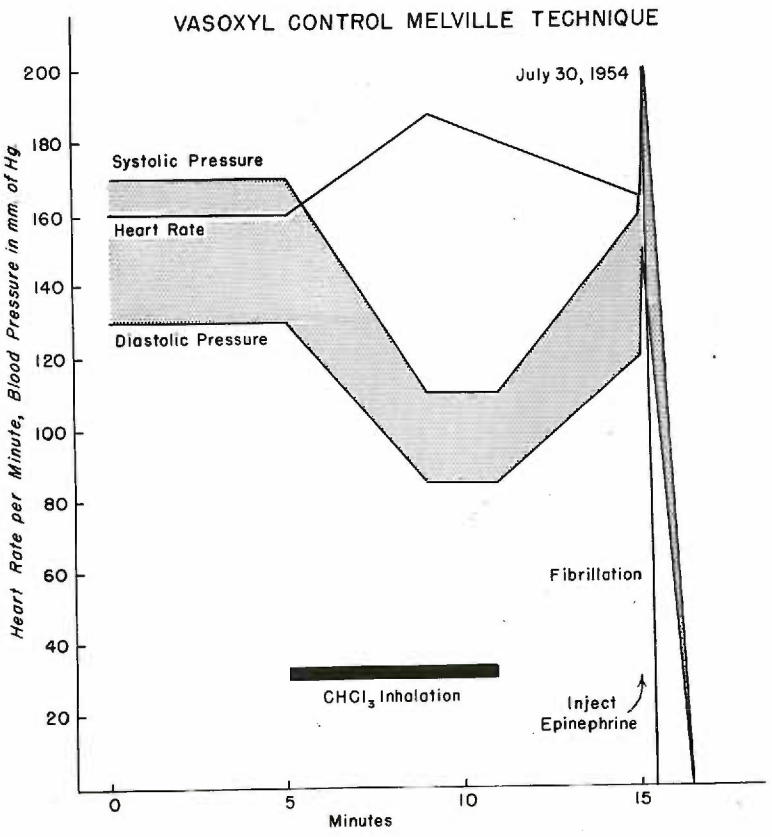
At 2:58½ P.M. 10 microgram/Kg. of Levophed were administered intravenously into an exposed femoral vein. Thirty seconds later ventricular fibrillation occurred.

July 30, 1954. Melville Technique: Control Experiment Without Vasoxyl. See figure 45.

A fasted 7.7 Kg. female dog was anesthetized with 35 mg./Kg. of Nembutal sodium administered intraperitoneally at 9:12 A.M. After surgical anesthesia was obtained, a femoral vein was exposed and a catheter inserted through it into the inferior vena cava. This catheter was filled with normal saline and clamped. A carotid artery was exposed and cannulated. This cannula was connected to an electro-

FIGURE 45

Graphic representation of the results of a cardiac sensitization experiment using epinephrine on July 30, 1954.


VASOXYL CONTROL MELVILLE TECHNIQUE
July 30, 1954
Heart Rate per Minute, Blood Pressure in mm. of Hg.
200
180
160
140
120
100
80
60
40
20
Systolic Pressure
Heart Rate
Diastolic Pressure
Fibrillation
CHCl3 Inhalation
Inject
Epinephrine
0
5
10
15
Minutes

manometer which in turn was connected to a single channel electrocardiograph. In this manner carotid artery pulse waves were recorded throughout this experiment. A 45 minute stabilization period was allowed. Controls were taken at 10:45 A.M. They were as follows: Heart rate, 160 per minute and regular; blood pressure, 170/130.

At 10:50 A.M. 5 minutes of chloroform inhalation was administered in a concentration just strong enough to avoid changing the level of anesthesia. Chloroform inhalation was completed at 10:56 A.M.

At 11:00 A.M. the heart rate was 165 per minute and regular. The blood pressure was 160/120. At this point 20 microgram/Kg. of epinephrine was administered into the inferior vena cava through the catheter.

Nine seconds following the injection of epinephrine the heart rate was 200 per minute and the blood pressure was 200/150. Ten seconds following the injection of epinephrine, ventricular fibrillation occurred. End of experiment.

August 27, 1954. The Effect Of Levophed As The Challenge Drug In The Melville Technique In Place Of The Epinephrine. See figures 46 and 47.

A fasted 9.77 Kg. male dog was anesthetized with Nembutal in the usual dosage administered intraperitoneally at 9:35 A.M. After surgical anesthesia was obtained, a ventral midline incision was made in the neck and both vagus nerves isolated as high as possible. A carotid artery was cannulated and this cannula was connected to a pressure transducer. A femoral vein was exposed and a small polyethylene catheter

FIGURE 46

Graphic representation of the results of a cardiac sensitization experiment using Levophed on August 27, 1954.

MELVILLE PROCEDURE USING LEVOPHED AS CHALLENGE DOSE

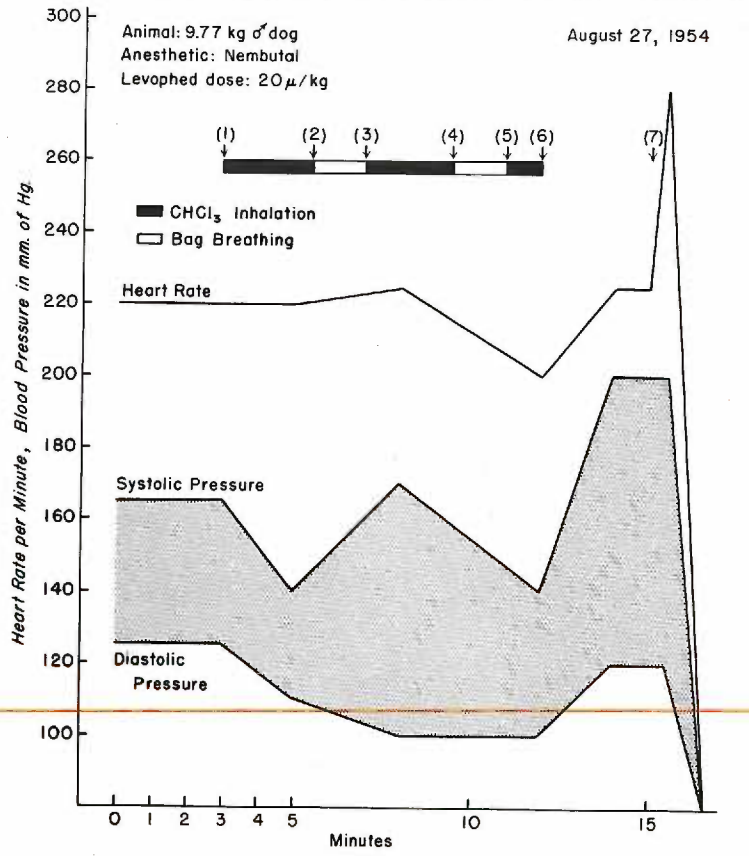
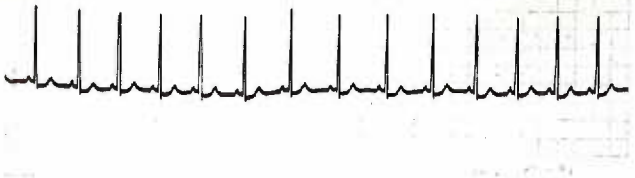


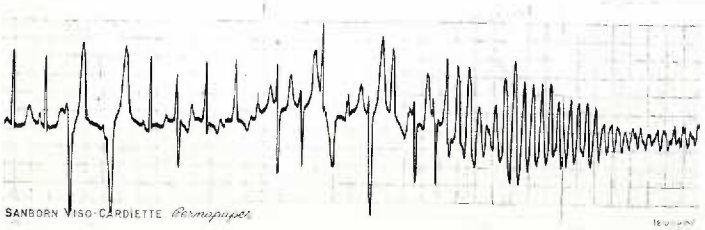
FIGURE 47

Representative sections of the EKG taken during the cardiac sensitization experiment of August 27, 1954.

LEVOPHED



Control



One minute post nor-epinephrine

inserted through it into the inferior vena cava. This catheter was filled with normal saline and connected to a syringe through which the drugs were administered. A cuffed Magill endotracheal tube was installed in the trachea. Recording in this experiment was by means of a polyviso electrocardiograph. One channel was utilized for EKG lead AVR, one channel utilized for lead II, and one channel was utilized to record carotid pulse waves in the pressure transducer. After the animal was prepared, approximately one hour was allowed for stabilization.

Controls were taken at 11:13 A.M. They were as follows: heart rate, 220 per minute and regular; QRS interval, 0.04 sec.; PR interval, 0.08 sec.; blood pressure, 165/125 mm. of mercury.

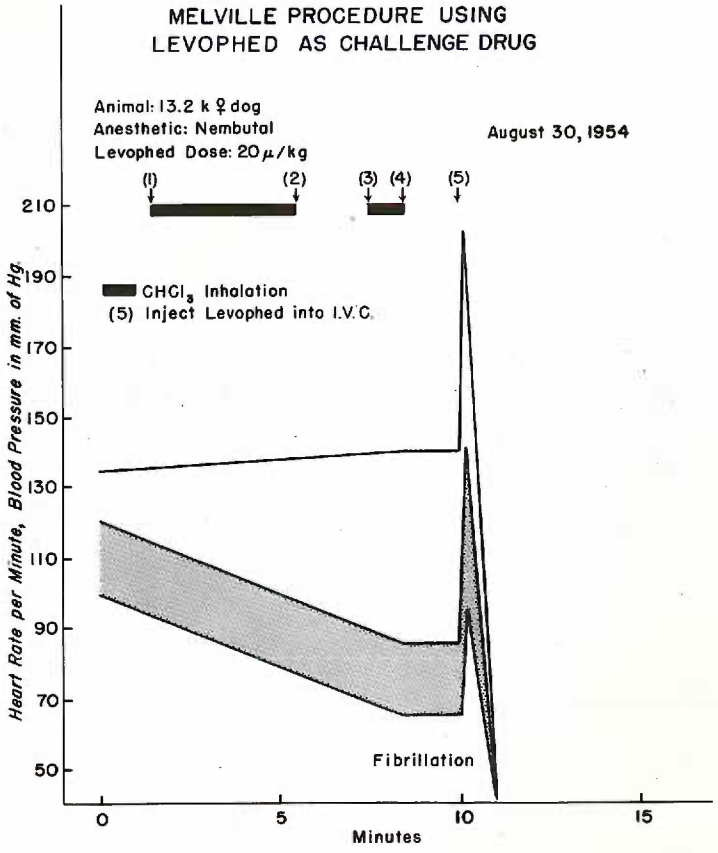
At 11:16 A.M. chloroform inhalation was started. This was administered intermittently until a total of five minutes of chloroform inhalation had been administered. Due to occasional periods of repiratory depression it was necessary to discontinue the chloroform inhalation and assist the animal's respiration by bag breathing. By 11:25 A.M. five minutes of chloroform inhalation had been administered.

At 11:29 A.M. the heart rate was 225 per minute and regular. The blood pressure was 200/120. There was no other significant change in the EKG.

At 11:30 A.M. 20 microgram/Kg. of Levophed was administered into the inferior vena cava by means of the catheter. One minute following the administration of the Levophed, ventricular fibrillation occurred.

FIGURE 48

Graphic representation of the results of a cardiac sensitization experiment using Levophed on August 30, 1954.


MELVILLE PROCEDURE USING
LEVOPHED AS CHALLENGE DRUG
Animal: 13.2 k ♀ dog
Anesthetic: Nembutal
Levophed Dose: 20 μ/kg
August 30, 1954
(1)
(2)
(3)
(4)
(5)
CHCl3 Inhalation
(5) Inject Levophed into I.V.C.
Fibrillation
Heart Rate per Minute, Blood Pressure in mm. of Hg.
210
190
170
150
130
110
90
70
50
0
5
10
15
Minutes

August 30, 1954. The Effects Of Levophed As A Challenge Drug In The Melville Technique In Place Of Epinephrine. See figure 48.

A fasted 13.2 Kg. female dog was anesthetized with Nembutal sodium in the usual dosage administered intraperitoneally at 9:28 A.M. After surgical anesthesia was obtained, a midline incision was made ventrally in the neck. A carotid artery was isolated and cannulated. This cannula was connected to a pressure transducer. A femoral vein was exposed and a small polyethylene catheter inserted through it into the inferior vena cava. This catheter was filled with normal saline and was attached to a syringe in which the drugs were administered. A cuffed Magill endotracheal tube was installed in the trachea. Recording in this experiment was by means of a polyviso electrocardiograph. One channel was utilized for lead II of the EKG, another channel was for lead III of the EKG and a third channel was utilized to record the carotid pulse wave. Following preparation of the animal, approximately one hour was allowed for stabilization.

Controls were taken at 11:00 A.M. They were as follows: heart rate, 135 per minute; QRS, 0.04 sec.; PR interval, 0.10 sec.; blood pressure, 120/100 mm. of mercury. All EKG measurements mentioned hereafter are from lead II.

At 11:01½ chloroform inhalation was started. This was administered at intervals from this point until 11:08½ at which time a total of five minutes of chloroform inhalation had been administered.

At 11:08½ the heart rate was 140 per minute and regular. The blood pressure was 85/65. The PR interval measured 0.12 sec. There was no other change in the EKG.

At 11:10 A.M. 10 microgram/Kg. of Levophed was administered into the inferior vena cava.

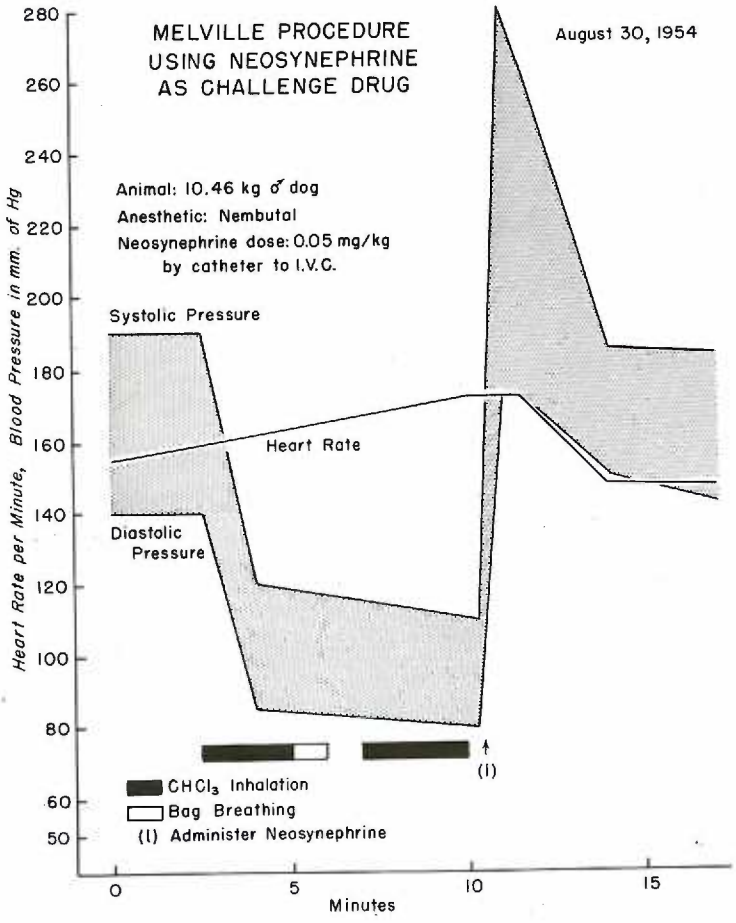
Fifteen seconds following the injection of the Levophed, ventricular fibrillation occurred. End of experiment.

August 30, 1954. The Effects Of Neo-Synephrine In The Melville Technique In Place Of Epinephrine As A Challenge Drug. See figure 49.

A fasted 10.46 Kg. male dog was anesthetized with Nembutal in the usual dosage given intraperitoneally at 1:06 P.M. After surgical anesthesia was obtained, a ventral midline incision was made in the neck and a carotid artery was exposed. This was cannulated and connected to a blood pressure transducer. A cuffed Magill endotracheal tube was installed in the trachea. A femoral vein was exposed with a small polyethylene catheter inserted into the inferior vena cava. This catheter was filled with normal saline and connected to a syringe. Recording in this experiment was done by means of a polyviso electrocardiogram. One channel was utilized to record lead III of the EKG, one channel utilized for lead II of the EKG, and a third channel was utilized to record blood pressure from the carotid artery through the pressure transducer. After the animal was prepared, approximately one hour was allowed for stabilization.

FIGURE 49

Graphic representation of the results of a cardiac sensitization experiment using Neo-Synephrine on August 30, 1954.


MELVILLE PROCEDURE
USING NEOSYNEPHRINE
AS CHALLENGE DRUG
August 30, 1954
Animal: 10.46 kg ♂ dog
Anesthetic: Nembutal
Neosynephrine dose: 0.05 mg/kg
by catheter to I.V.C.
Systolic Pressure
Heart Rate
Diastolic
Pressure
(I)
CHCl3 Inhalation
Bag Breathing
(I) Administer Neosynephrine
Heart Rate per Minute, Blood Pressure in mm. of Hg
280
260
240
220
200
180
160
140
120
100
80
60
50
0
5
10
15
Minutes

Controls were taken at 2:15 P.M. They were as follows: heart rate, 155 per minute and regular; QRS, 0.04 sec.; PR interval, 0.08 sec.; blood pressure, 190/140 mm. of mercury. All EKG measurements are from lead II.

At 2:17½ P.M. chloroform inhalation was started. This was administered intermittently until a total of five minutes of chloroform had been administered. Throughout the administration of the chloroform the animal's respirations were assisted by bag breathing whenever indicated. By 2:25 P.M. a total of five minutes of chloroform inhalation had been administered. At this time the heart rate was 172 per minute and regular. The blood pressure was 110/80.

At 2:25½ P.M. 0.05 mg./Kg. of Neo-Synephrine was administered into the inferior vena cava by means of the catheter. One minute following the injection of the Neo-Synephrine the heart rate was 172 per minute. The blood pressure measured 265/175. There was no significant change in the EKG tracing.

At 2:29 P.M. the heart rate was 148 per minute and regular. The blood pressure was 185/150. No fibrillation occurred using Neo-Synephrine. End of experiment.

<u>September 4, 1953</u>. The Effect of Neo-Synephrine In The Melville Technique.

A fasted 6.36 Kg. female dog was anesthetized with 35 mg./Kg. Nembutal sodium administered intraperitoneally at 9:30 A.M. Recording in this experiment was done by means of a single channel EKG lead II.

A femoral vein was exposed and a small polyethylene catheter was inserted through it into the inferior vena cava. A 45 minute stabilization period was allowed.

At 10:12 A.M. the control EKG was taken and found to be within normal limits. The dose of Neo-Synephrine to be used was 0.5 mg./Kg. This was to be administered intravenously through the catheter in two equal doses. At 10:26 A.M. the first dose of Neo-Synephrine was administered. The second dose was administered at 10:42 A.M.

At 10:40 A.M. 20 microgram/Kg. of epinephrine was administered into the inferior vena cava. No fibrillation occurred.

At 10:44 chloroform inhalation was administered for the second time. The animal died almost immediately from respiratory arrest.

The animal used was very young. It was felt that the first dose of chlorform was very inadequate for the purposes of this experiment. End of experiment.

September 4, 1953. The Effect Of Neo-Synephrine In The Melville Technique.

A fasted 8.73 Kg. female dog was anesthetized with 35 mg./Kg. of Nembutal administered intraperitoneally at 10:04 A.M. The results of this experiment were recorded by means of a single channel EKG lead II. A femoral vein was exposed and a small polyethylene catheter was inserted through it into the inferior vena cava. Forty-five minutes stabilisation period was allowed.

11:48 A.M. the control EKG was taken. This was found to be within normal limits.

At 11:50 A.M. five minutes of chloroform inhalation was administered in a concentration just strong enough to avoid changing the level of anesthesia.

The dose of Neo-Synephrine to be used was 0.5 mg./Kg. to be administered in two equal doses intravenously. The first dose of Neo-Synephrine was administered at 12:00 noon. At 12:05 P.M. the second dose of Neo-Synephrine was administered. Seven minutes later 20 microgram/Kg. of epinephrine was administered into the inferior vena cava. No fibrillation occurred.

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The following references represent an epitomized list of publications consulted. No attempt was made to include the myriad of papers which deal with the effects of adrenergic drugs on the heart. All publications, however, involving a study of methoxamine on the heart of man or animals, it is believed, have been included. In addition is listed all pertinent papers dealing with the experimental methods used for this thesis study.

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