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Studies of Cardiovascular Energy Changes Occurring With Drug Administration under Normal Acid Base Balance and During Hypercapnia, Ischemia, and Metabolic Acidosis

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STUDIES OF CARDIOVASCULAR ENERGY CHANGES OCCURRING WITH DRUG ADMINISTRATION UNDER NORMAL ACID BASE BALANCE AND DURING HYPERCAPNIA, ISCHEMIA, AND METABOLIC ACIDOSIS

BY

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OBJECTIVES

Reflex autonomic changes occurring with the use of cardiovascular drugs may, as a side effect, increase cardiac work and oxygen demand. Improvement of coronary flow and/or a decrease in myocardial work load without increasing oxygen utilization are the desired effects of drugs used in the treatment of coronary insufficiency. The improvement of cardiac function is the purpose of drugs used in the treatment of heart failure. In either case the therapeutic effect may be accomplished through a direct myocardial effect and/or a decrease in cardiac pressure work load through extracardiac action. Through animal experimentation and patient correlation of the many parameters involved, a better understanding of the cardiodynamic effect of these drugs may be determined. This in turn may lead to drug therapy which is more apt to alleviate symptoms than those now used for specific treatment.

The following studies will be included:

1) cardiovascular changes occurring during the administration of several drugs used in the treatment of cardiovascular disease will be evaluated. 2) correction of cardiovascular depression accompanying both metabolic and respiratory acidosis will be attempted with the use of several buffers and their relative efficiency determined.

CHAPTER I

CORRELATION OF CHANGES IN VARIOUS PHASES OF CARDIOVASCULAR DYNAMICS ACCOMPANYING THE ADMINISTRATION OF SEVERAL AUTONOMIC DRUGS

INTRODUCTION

Drugs which produce physiologic responses similar to those of the autonomic nervous system have varying effects on cardiovascular dynamics. The direction and magnitude of the changes depend on the autonomic tone prior to drug administration. Drugs used in the therapy of cardiovascular disease when administered under normal conditions have different end effects than when administered under diseased conditions. This is particularly true in considering changes in blood flow and cardiac output.

Each drug used in this study invariably produced characteristic directional changes in blood pressure and ventricular contractile force although the magnitude of these changes varied. On the other hand, changes in cardiac output were not consistant. The effect of autonomic drugs on blood flow therefore cannot be categorically stated.

Changes in heart rate and ventricular filling time along with changes in total peripheral resistance or resistance to systolic ejection play an important part in control of cardiac output. During drug administration the reflex response to cardiovascular changes are of prime concern in the maintenance of homeostasis. It can then be said that the algebraic sum of the drug effect and the reflex homostatic response to the drug determines the end changes in cardiovascular dynamics.

In man, epinephrine increases cardiac output while arterenol (norepinephrine) may decrease it.[1] This can be explained on a pressor-heart rate relationship which has a pronounced effect on venous return. Guyton et al[2] have shown epinephrine to increase cardiac output by increasing mean circulatory pressure which in turn increases the pressure gradient forcing blood toward the right atrium. Collier and associates[3] further verified an increase in cardiac output occurring with epinephrine in dogs but found that arterenol usually decreases cardiac output or caused no change.

Alterations in coronary flow depend on many parameters, the two most important being changes in vessel caliber and coronary perfusion pressure. Autonomic drugs have the ability to alter both of these. Variations in systolic and diastolic blood pressure, heart rate, ventricular contractile force, neurohumoral changes, etc. all affect coronary flow either directly or indirectly. It is well known that the reserve oxygen capacity of the myocardium is very small and its potential oxygen debt low. Therefore, it is essential that the coronary vessels adjust in such a way as to supply oxygen in accordance with changes in myocardial metabolism. Drugs used in the treatment of coronary insufficiency should improve coronary flow and/or decrease myocardial work load without increasing oxygen utilization.

This statement should be emphasized because many drugs used for this purpose increase cardiac work and oxygen demand. This does not suggest that such drugs should necessarily increase efficiency of myocardial oxygen utilization but only that changes in coronary flow and oxygen extraction adjust in such a way as to meet the existing metabolic requirement. Thus there may be an increase or a decrease in efficiency of oxygen extraction and utilization. As long as adequate oxygen is present, the heart utilizes the aerobic path of metabolism.[4] If adequate oxygen is not present, there will be an accumulation of the products of anaerobic metabolism and a consequent myocardial depression. Variations in oxygen demand appear to be the most important factor in the regulation of coronary flow. Metabolic and neurohumoral changes are very important in the control of coronary vasomotor tone whereas mechanical factors play an important role in blood flow changes.

This first group of experiments attempt to correlate the various parameters effecting changes in cardiovascular dynamics under normal experimental conditions. The second group (Chapter II) relates ventricular isometric systolic tension changes with acidemia and myocardial ischemia.

METHODS

The following two groups of experiments were conducted in 65 open chest dogs weighing 8 to 14 kg. Anesthesia was attained with 10 mgm/kg morphine subcutaneously, followed in 30 minutes by 20 mgm/kg of sodium pentobarbital intravenously.

Group I

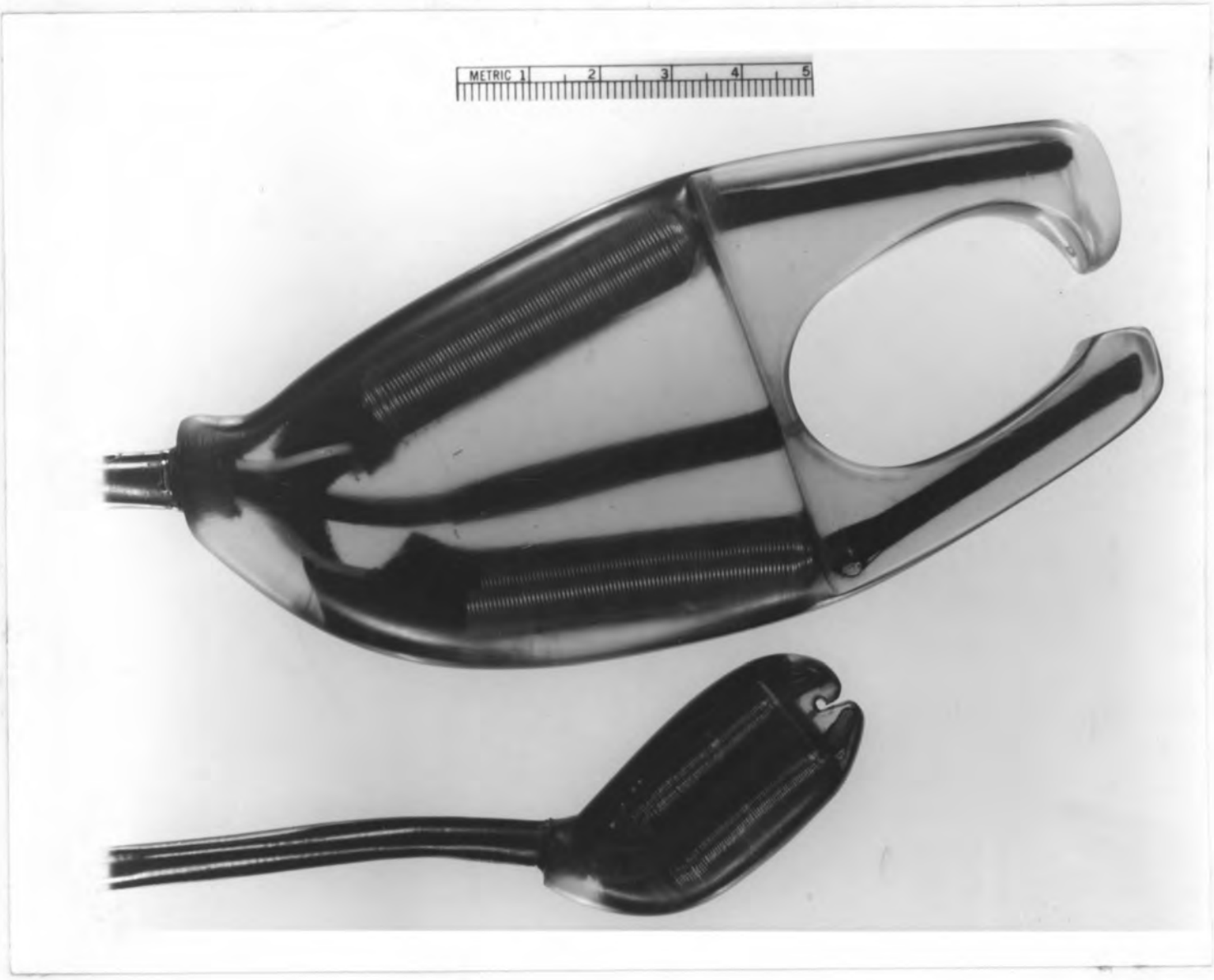
In 38 experiments cardiac output (CO), stroke volume (SV), ventricular contractile force (VCF), aortic blood pressure (ABP), heart rate (HR) and in some experiments right (RAP) and left atrial (LAP) and left ventricular (LVP) pressures were measured. The right femoral artery and vein were cannulated for the measurement of ABP and drug administration respectively. A cannula was inserted to the level of the thoracic aorta via the femoral artery. A mid sternal thoracotomy was performed and VCF, CO, SV, RAP, LAP, and LVP were measured. A strain gage arch was sutured to the right ventricle.[5-8] The sutures for attachment of the strain gage were placed approximately 15 mm. apart. The two feet of the arch were placed approximately 20 mm. apart. When the strain gage was attached to the ventricle, the muscles between the two legs of attachment ware thus stretched by approximately 30% of the end diastolic length. The VCF changes measured have been shown to be primarily due to humoral and neurogenic

changes.[7-8] Myocardial adjustments secondary to hemodynamic changes were minimal because of the fixed initial length of the muscle segment. Atrial and ventricular pressures were measured from cannulas inserted directly into the atrial and ventricular chambers and held in place with purse string sutures. Statham transducers (P-230) were used to measure all pressure changes. SV and CO were measured with a square wave electromagnetic flow meter.[9-10] The magnectic electrode assembly is C-shaped, molded in plastic, can be made of different sizes to fit various size vessels, and can be sterilized by emersion in a detergent solution (Figure I). HR was measured with a tachometer. All BP's, HR, CO, SV, and VCF changes were recorded by an 8 channel Grass ink recorder. The drugs used in these experiments, arterenol, epinephrine, isoproterenol, methoxamine and nitroglycerin, were administered via the right femoral vein.

Group II

Coronary flow (CF) was measured in 27 open chest dogs under barbiturate anesthesia. ABP and VCF were measured as indicated above. Total cardiopulmonary bypass was established by draining vena caval blood into a Mark disc oxygenator and pumping the oxygenated blood back into the arterial circulation with a DeBakey pump. The cannulation procedure for total cardiopulmonary bypass was essen-

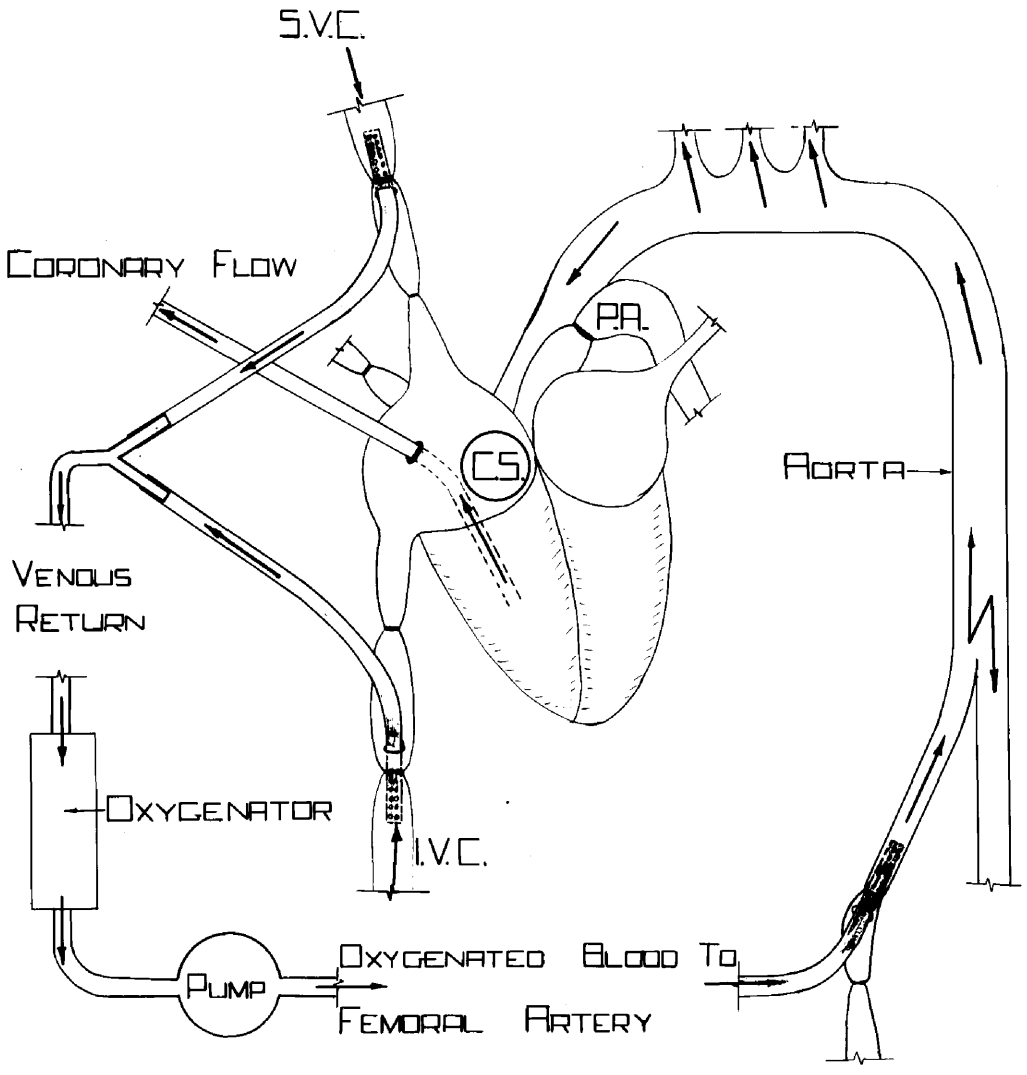
Figure 1



This illustration compares the relative sizes of magnetic flow meter probes. The upper probe is used for measuring blood flow in large vessels such as the human aorta whereas the lower probe may be used to measure flow in small vessels such as coronary vessels. The flow meter operates on the principle that if a conductor of electricity moves through a magnetic field so as to cut the lines of force, a voltage will be generated which is proportional to the velocity of motion, the strength of the magnet, and the length of the conductor (10).

tially the same as previously described.[11-12] The right ventricle was isolated as shown in Figure II. Van Slyke[13] determinations of the oxygen content of the coronary venous blood from the isolated right ventricle and blood from the aorta, provide a measure of myocardial oxygen consumption (QO_2). Arteriovenous (A-V) oxygen difference per cc of blood multipled by minute coronary flow equals oxygen consumption per minute. ABP and VCF changes were recorded with a four channel Sanborn model 150. Arterenol, epinephrine, phenylephrine (neosynephrine), nitroglycerin, and isoproterenol were either injected into the arterial circulation or directly into the pump reservoir.

Figure 2



Cardiopulmonary by-pass procedure was used to measure coronary flow. ---- Vena caval blood was allowed to drain by gravity flow into a Mark disc oxygenator. The oxygenated blood was pumped back in the arterial circulation with a Debakey pump. Blood obtained from the cannulated right ventricle following ligation of the azygos vein and pulmonary artery (PA) was a measurement of coronary flow. CS represents coronary sinus, SVC and IVC the superior and inferior vena cava respectively.

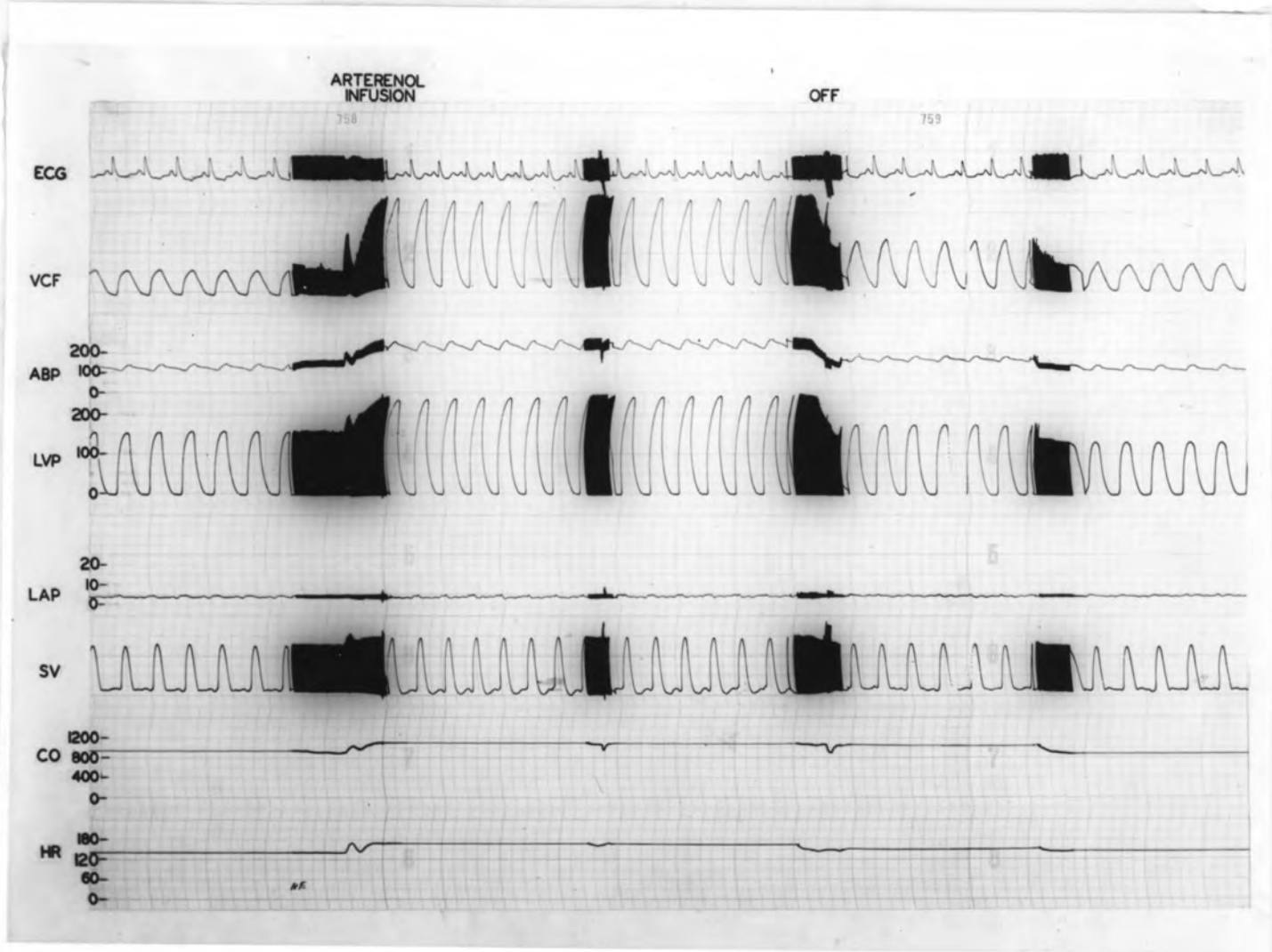
RESULTS

Group I

Arterenol

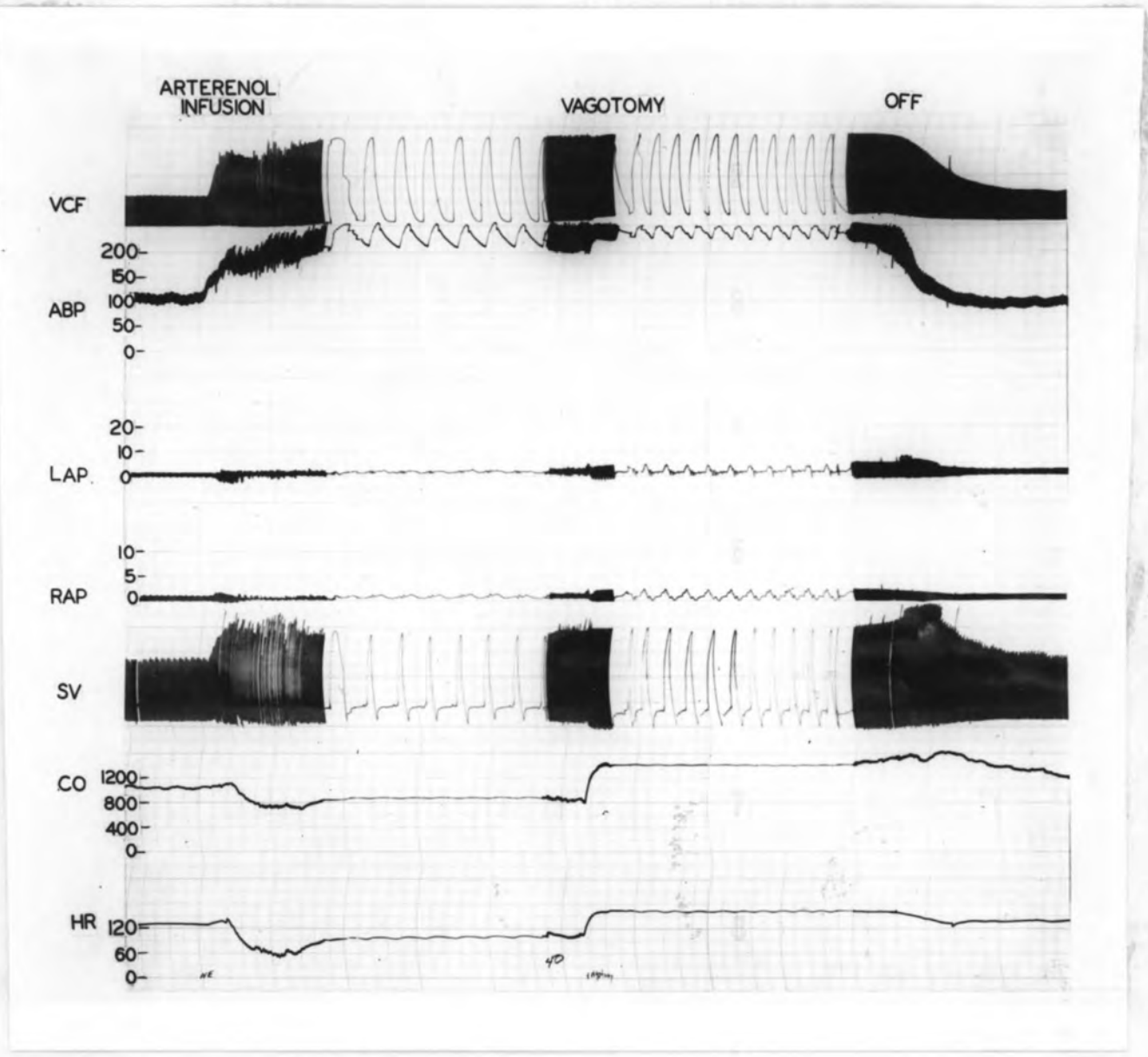
Following a control recording arterenol was infused into dogs. The changes in the parameters shown in Figure III are typical. There was a pronounced increase in myocardial contractile force, aortic blood pressure and left ventricular pressure with a marked increase in the velocity of systolic ejection. There was only a slight increase in cardiac output and this appeared to be the result of augmented heart rate rather than increased stroke volume. Arterenol often causes a reflex decrease in heart rate because of the increase in peripheral resistance. EKG changes consisted of T wave reversal accompanied by a slightly increased S-T depression. There was little change in left atrial pressure. Figure IV shows the effect of vagotomy on the response to arterenol. With intact vagi, a reflex bradycardia occurred because of the increased peripheral resistance. This caused a marked decrease in cardiac output. Following vagotomy heart rate increased with a consequent rise in cardiac output. Pulse pressure decreased markedly due to the decrease in blood run off time during diastole. However, there was a slight increase in stroke volume which would not have been expected from the pulse pressure changes observed. The

Figure 3



The effects of arterenol on the cardiovascular system.
ECG - electrocardiogram
VCF - right ventricular contractile force
ABC - aortic blood pressure (mm Hg)
LVC - left ventricular pressure (mm Hg)
LAP - left atrial pressure (mm Hg)
SV - stroke volume
CO - cardiac output (cc/min)
HR - heart rate
Paper Speed - .25 and 25 mm/sec with each vertical space between lines representing .2 sec. at the faster speed

Figure 4



The effect of vagotomy on the cardiovascular response to arterenol.
VCF - right ventricular contractile force
ABC - aortic blood pressure (mm Hg)
LAP - Left atrial pressure (mm Hg)
RAP - right atrial pressure (mm Hg)
SV - Stroke volume
CO - cardiac output (cc/min.)
HR - heart rate
Removal of vagal tone produced a marked increment in CO.
Paper Speed - .25 and 25 mm/sec.

slight increase in right and left atrial pressure following vagotomy is probably a result of increased venous return.

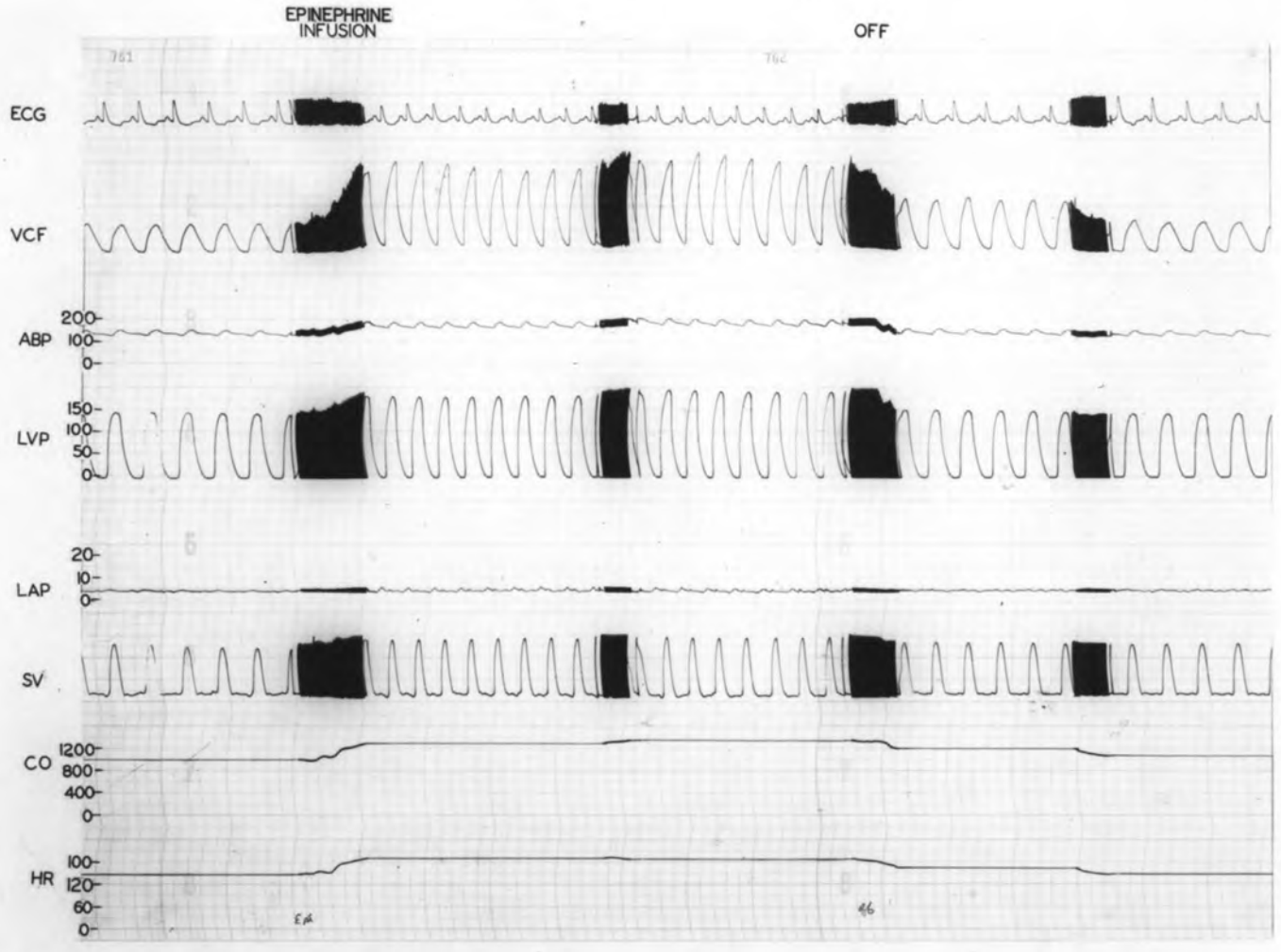
Epinephrine

Epinephrine produces approximately the same changes in VCF, LVP, and EKG as those occurring with arterenol (Figure V). The pressor effect of epinephrine is generally less than that of arterenol. Arterenol, therefore, more often causes reflex bradycardia. The direct sympathomimetic effect of epinephrine on heart rate is therefore more often apparent than that of arterenol. There is little change in stroke volume but the increase in heart rate is responsible for the increment in cardiac output.

Isoproterenol

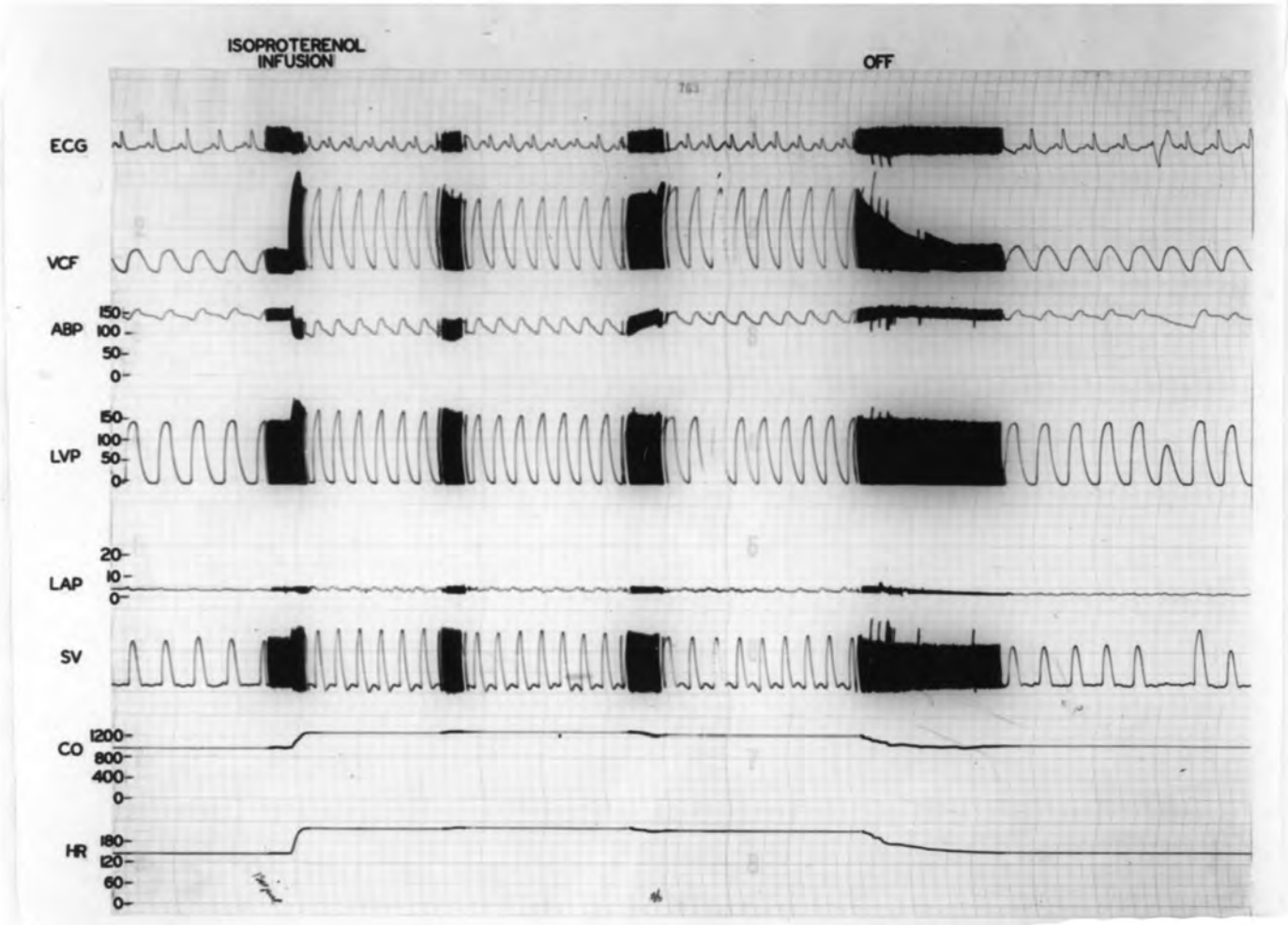
Isoproterenol is a vasodilator but in addition has a powerful positive inotropic effect on the heart similar to arterenol and epinephrine.[14] This drug also produces a positive chronotropic effect (Figure VI). This may be attributed to the direct effect of isoproterenol on the cardiac accelerator nerves and the reflex activity of the pressor receptors to the fall in blood pressure. The left ventricular systolic pressure is usually higher than the aortic systolic pressure and appears to be related directly to contractile force. This may be due to the aortic valves offering a resistance to systolic ejection occurring with the

Figure 5



The effects of epinephrine on the cardiovascular system.
ECG - electrocardiogram
VCF - right ventricular contractile force
ABP - aortic blood pressure (mm Hg)
LVP - left ventricular blood pressure (mm Hg)
LAP - left atrial pressure (mm Hg)
SV - stroke volume
CO - cardiac output (cc/min.)
HR - heart rate
Paper Speed - .25 and 25 mm/sec.

Figure 6



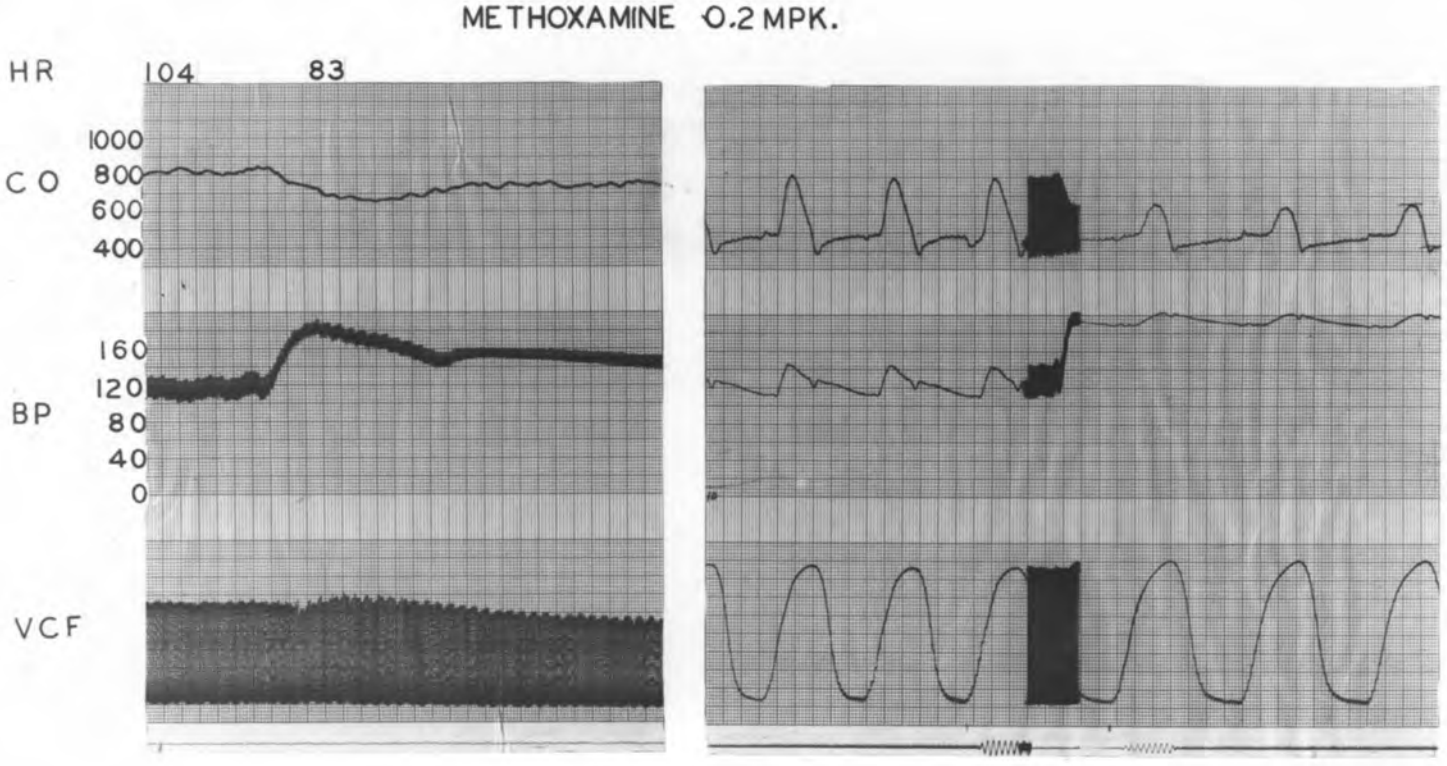
The effect of isoproterenol on the cardiovascular system.
ECG - electrocardiogram
VCF - right ventricular contractile force
ABP - aortic blood pressure (mm Hg)
LVP - left ventricular pressure (mm Hg)
LAP - left atrial pressure (mm Hg)
SV - stroke volume
CO - cardiac output (cc/min.)
HR - heart rate
Paper Speed - .25 and 25 mm/sec.

marked increase in velocity and force of contraction. In addition, the immediate venous pooling and increased peripheral run off of blood from the aorta may result in a time lag in elevation of aortic pressure to ventricular pressure. The increment in cardiac output is primarily attributed to the chronotropic effect. There was little change in left atrial pressure. It is interesting to note the ventricular extrasystole at the right of Figure VI. This ectopic beat produced an adequate increase in myocardial isometric systolic tension, however, due to the prematurity of contraction, the resistance to systolic ejection was greater than usual thereby preventing blood ejection during the contraction. On the contrary, the beat following the extrasystole produced an increase in stroke volume probably due to the time increment in diastole run off. This caused an increase in ventricular filling and a decrease in resistance to systolic ejection.

Methoxamine

Figure VII is an illustration of the cardiovascular effects of Methoxamine (Vasoxyl). Methoxamine is primarily a vasopressor agent with little direct effect on the myocardium.[15] The pressor action of methoxamine causes a decrease in cardiac output. The reason being a reflex slowing of the heart and a decreased stroke volume accompanying the increment in resistance to ventricular ejection. This

Figure 7



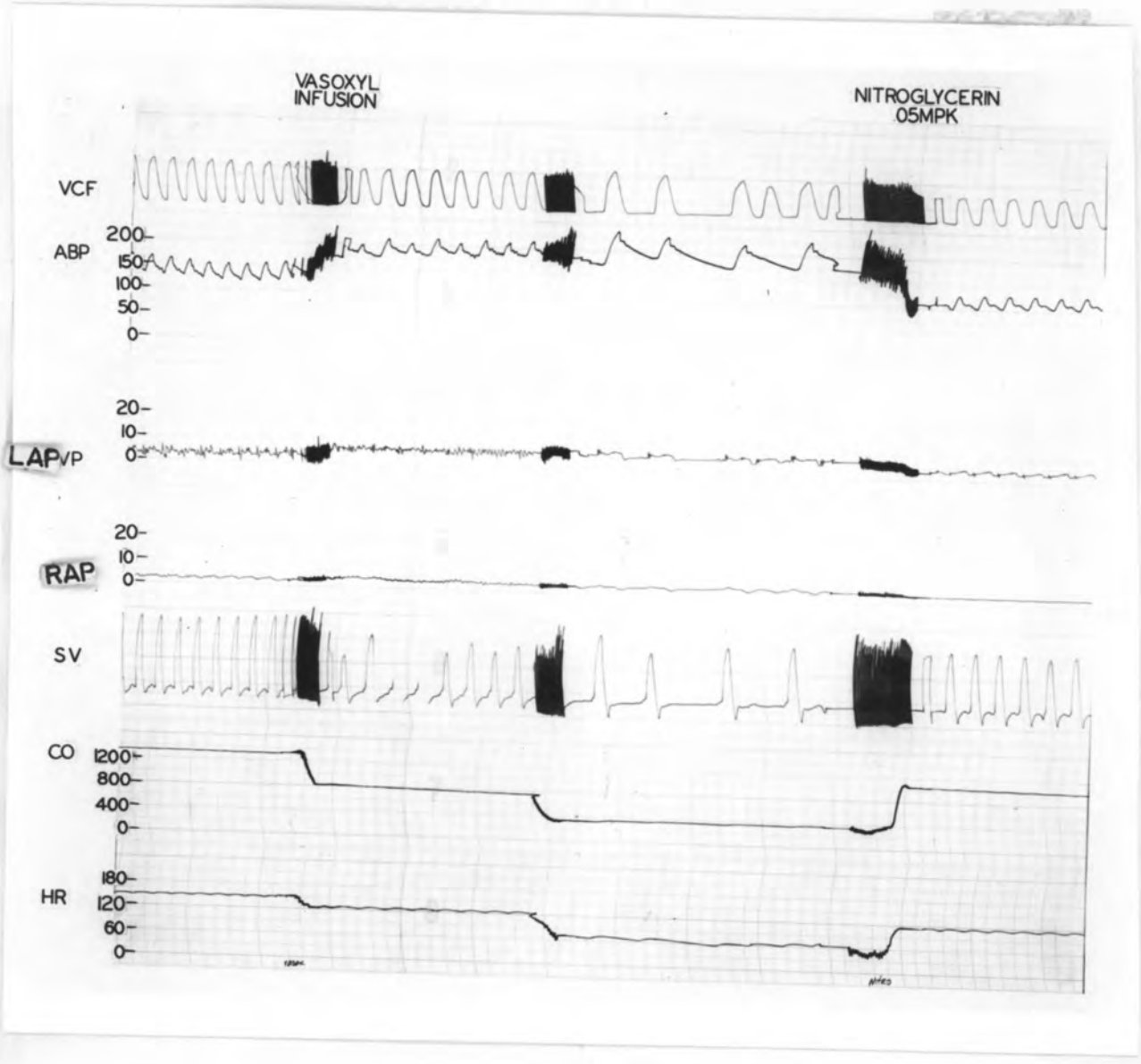
The effect of vasoxyl (methoxamine) on the cardiovascular system.
HR - heart rate
CO - cardiac output (cc/min.)
BP - blood pressure (mm Hg)
VCF - right ventricular contractile force
Paper speed - .25 and 50 mm/sec.

in turn causes an increase in isometric ventricular contraction with a consequent decrease in tension available to perform external work. Figure VIII shows the effect of relieving the myocardial work load produced by methoxamine. Nitroglycerin reduced pressure work load and reflex vagal tone thereby causing cardiac output to increase three-fold.

Nitroglycerin

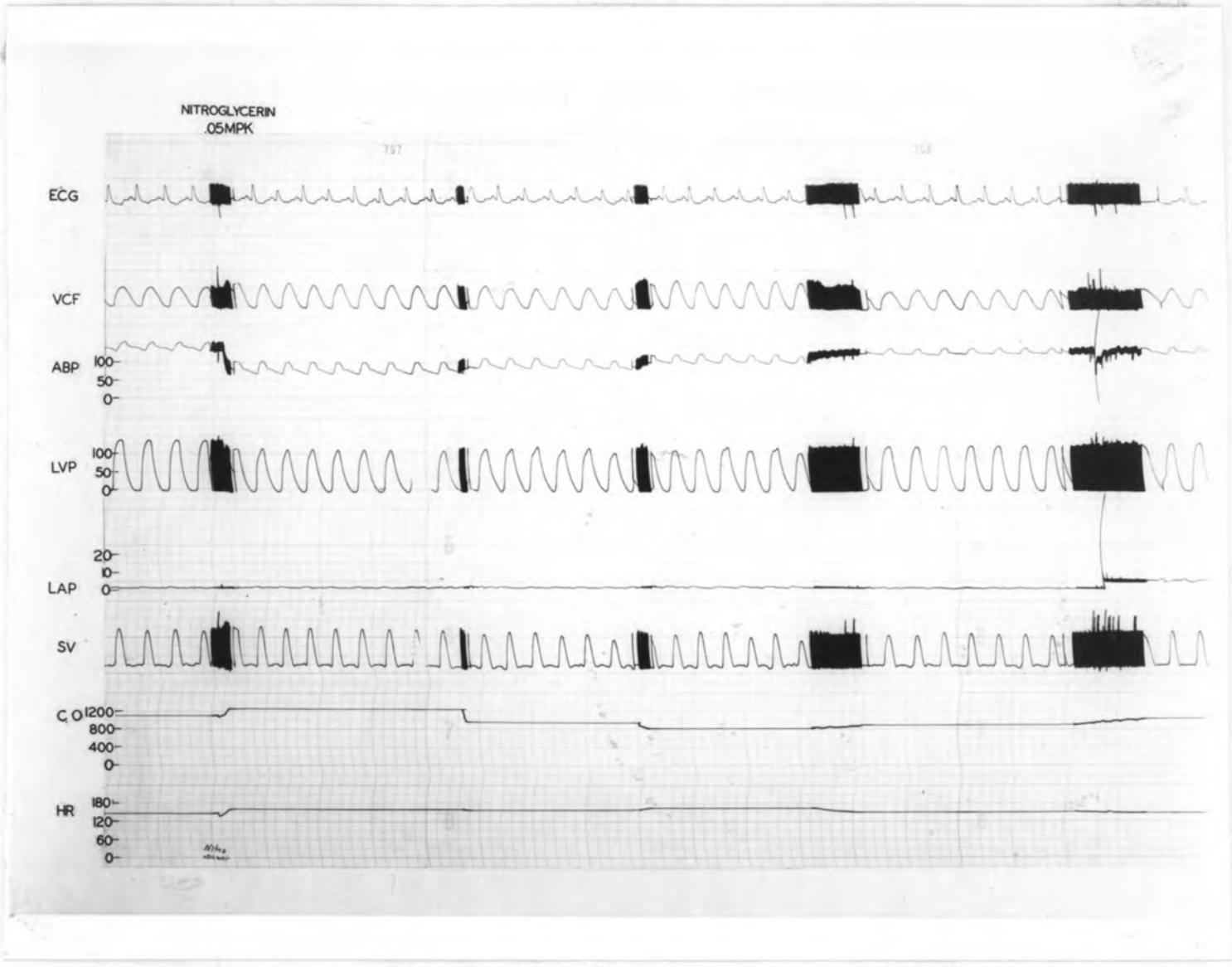
Figure IX represents typical cardiovascular effects of nitroglycerin. This drug has a direct vasodilating action.[16-17] The fall in blood pressure causes a reflex decrease in vagal tone and a sympathoadrenal release. This in turn attempts to maintain hemeostasis through an increase in heart rate, blood pressure and myocardial contractile force. The increase in contractile force in this case is minor and may be attributed to an increment in coronary flow as well as sympathetic hormones. ECG and left atrial pressure changes were negligible. Usually there was an initial increase in cardiac output followed by a prolonged decrease. Similar to isoproterenol the left ventricular systolic pressure was greater than aortic systolic pressure during drug administration. This may be attributed to a decreased resistance to ejection. Table I summarizes the results discussed above.

Figure 8



Effect of nitroglycerin on vasoxyl induced hypertension.
VCF - right ventricular contractile force
ABP - aortic blood pressure (mm Hg)
LAP - left atrial pressure (mm Hg)
RAP - right atrial pressure (mm Hg)
SV - stroke volume
CO - cardiac output (cc/min.)
HR - heart rate
The decrease in cardiac work load and reflex increase in heart rate produced by nitroglycerin during vasoxyl infusion caused a marked increment in CO.
Paper Speed - .25 and 25 mm/sec.

Figure 9



Effect of nitroglycerin on the cardiovascular system
ECG - electrocardiogram
VCF - right ventricular contractile force
ABP - aortic blood pressure (mm Hg)
LVP - left ventricular pressure (mm Hg)
LAP - left atrial pressure (mm Hg)
SV - stroke volume
CO - cardiac output (cc/min.)
HR - heart rate
Paper Speed - .25 and 25 mm/sec.

Table 1

Percent changes above control values in cardiac output (CO), ventricular contractile force (VCF), systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) occurring during admistration of the indicated drugs. (38 experiments)

	Norepinephrine	Epinephrine	Isoproterenol	Vasoxyl	Nitroglycerin
CO	+19% SD ±27	+38% SD ±32	+30% SD ±23	-44% SD ±43	+16% SD ±17 —— -21 SD ±6
VCF	+147% ±72	+141% ±26	+184% ±87	-10% ±19	+14% ±30
SBP	+71% ±50	+61% ±21	-33% ±16	+96% ±40	-49% ±20
DBP	+85% ±52	+60% ±28	-42% ±11	+90% ±37	-47% ±8
HR	-6% ±19	+12% ±17	+31% ±11	-29% ±12	+16% ±6

Control heart rate —— 128 beats/min. SD ±23

Control blood pressure —— $\frac{114 \text{ SD } \pm 27}{87 \quad \pm 21}$ mm Hg

Group II

Coronary Flow

In 27 experiments, following a four minute control period with BP maintained at 80 mm. Hg. during bypass, sympathomimetic amines and nitroglycerin were infused into the pump reservoir or injected directly into the femoral artery. In 19 experiments myocardial oxygen consumptions (QO_2) were determined during arterenol responses. As indicated in Table II arterenol was administered in concentrations sufficient to increase BP 100%. This was accompanied by an increase in VCF of approximately 145% above control. When the pressure was allowed to increase, there was a marked increase in QO_2 which was usually accompanied by a slight decrease in A-V oxygen difference. This change in A-V oxygen difference was due to an increase in venous oxygen content and may be attributed to the marked increment in coronary flow. While continuing the arterenol infusion, BP was reduced to control levels by reducing pump outflow. This reduction in coronary perfusion pressure decreased the existing increment in CFl approximately 50% with a similar decrease in QO_2. This decrease in CFl and QO_2 was accompanied by only a slight fall in the VCF response to arterenol. The increase in coronary flow during arterenol administration may be primarily attributed to the vasopressor response with a consequent increased head of pressure in the aorta. Figure X illustrates

Table 2

Percent changes above control values in coronary flow (CFl), arterio-venous oxygen difference in volume percent (A-V), total myocardial oxygen consumption (QO_2), aortic blood pressure (BP), and ventricular contractile force (VCF) during norepinephrine infusion. (19 experiments)

	CFl	A-V	QO_2	BP	VCF
Norepinephrine	+194 SD ±98	-15 SD ±11	+161 SD ±48	100	145 SD ±70
Norepinephrine *	+91 ±42	-7 ±8	+83 ±29	0	131 ±61

* With blood pressure controlled by decreasing total body perfusion.

Table 3

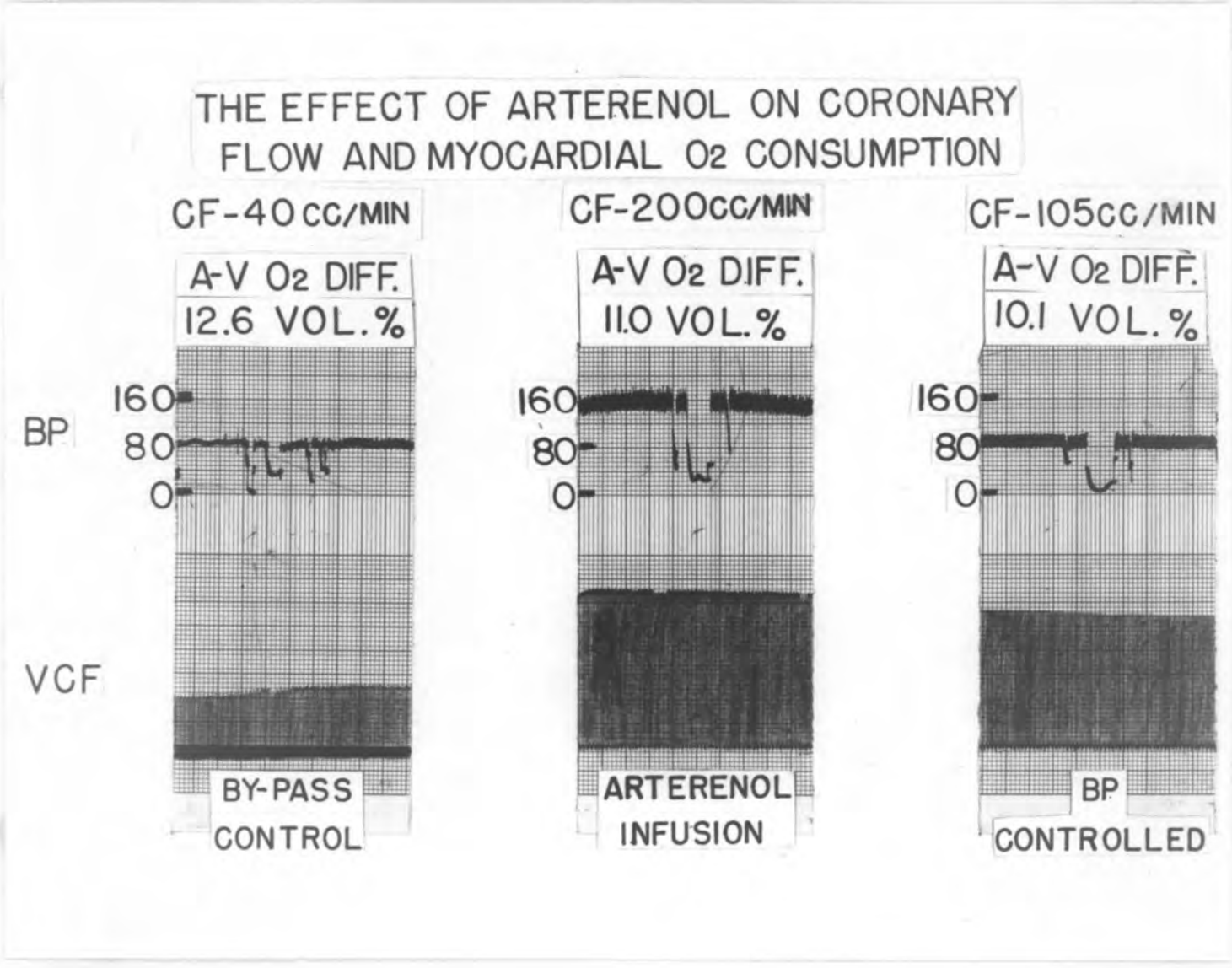
Percent changes above control values in coronary flow (CFl) and ventricular contractile force (VCF) during the administration of the indicated drugs in concentration sufficient to increase aortic blood pressure 50%. (5 experiments)

	CFl **	VCF **
Neosynephrine	61 (51 - 109)	22 (2 - 59)
Neosynephrine *	11 (-4 - +22)	
Norepinephrine	93 (86 - 163)	151 (108 - 230)
Norepinephrine *	22 (15 - 41)	
Epinephrine	148 (117 - 258)	144 (116-237)
Epinephrine *	51 (32 - 120)	

* With blood pressure controlled by decreasing total body perfusion.

** Range of values

Figure 10



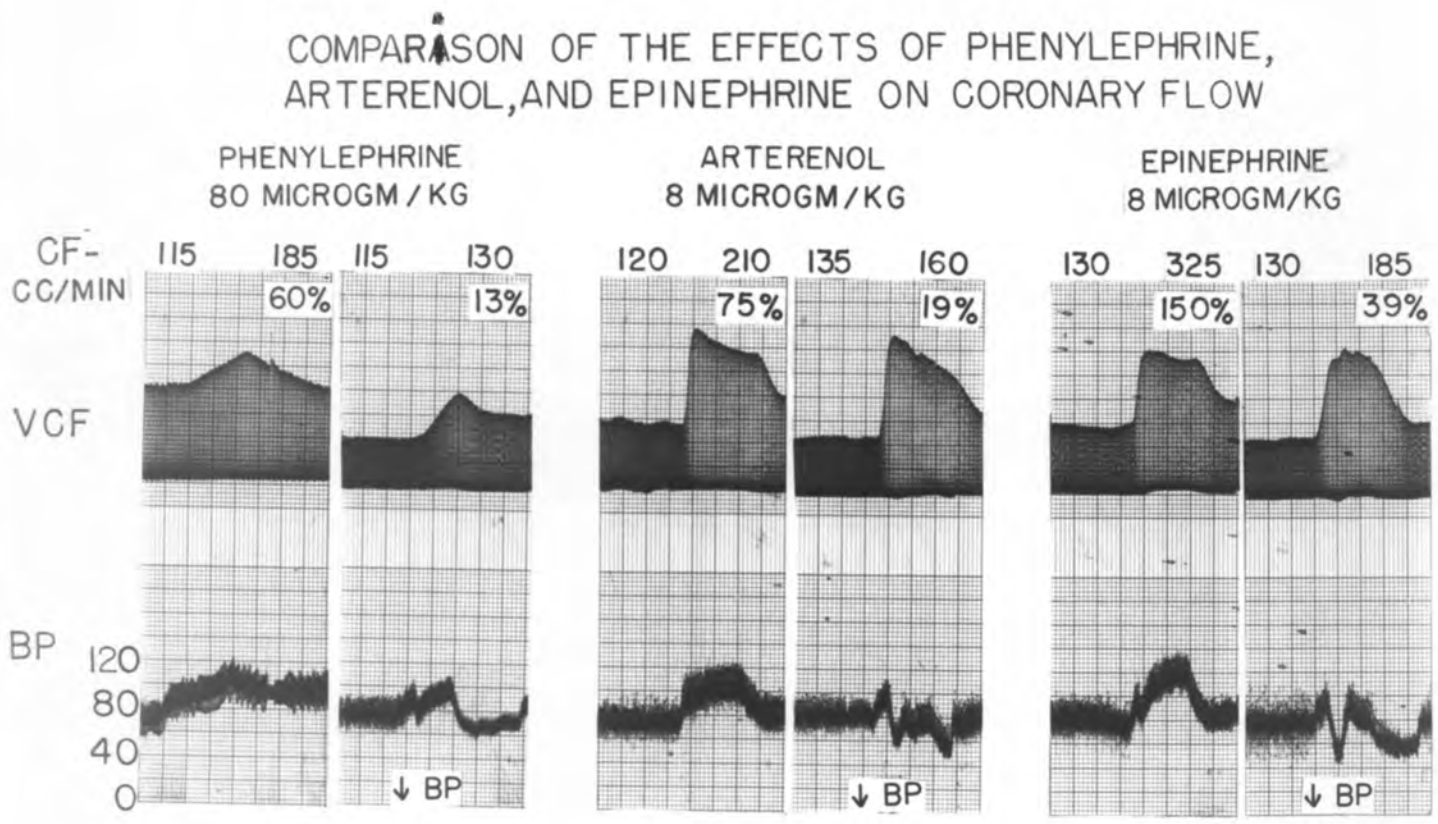
CF - coronary flow (cc/min.)
A-V - artereo-venous oxygen difference (vol. %)
BP - aortic blood pressure
VCF - left ventricular contractile force
BP was maintained at the control level by decreasing total body perfusion with the by-pass pump.

typical results of the above discussed experiments.

In 5 experiments, equipressor doses of phenylephrine (neosynephrine), epinephrine, and arterenol were injected into the femoral artery during cardiopulmonary bypass. Figure XI is a recording representative of the results in this group of experiments. Each drug produced approximately a 50% increase in aortic blood pressure when using the concentration indicated. Phenylephrine produced a 60% increase in CFl which, however, fell to 13% above control when BP was reduced to control levels with the pump oxygenator. When blood pressure was returned to control levels during the injection of arterenol, the CFl decreased from 75% to 19% above control. During the injection of epinephrine CFl increased 150%. This decreased to 39% above control values when the blood pressure was maintained at control levels. Since epinephrine produced approximately the same increments in BP and VCF as arterenol, the higher CFl was apparently due to a greater dilating effect on the coronary vessels. Table III summarizes the results of these experiments.

Two vasodilators, nitroglycerin and isoproterenol, were administered to three dogs. Figure XII exemplifies one of these experiments. Following administration of the indicated drug, the BP decreased over 50%. The coronary perfusion pressure was therefore

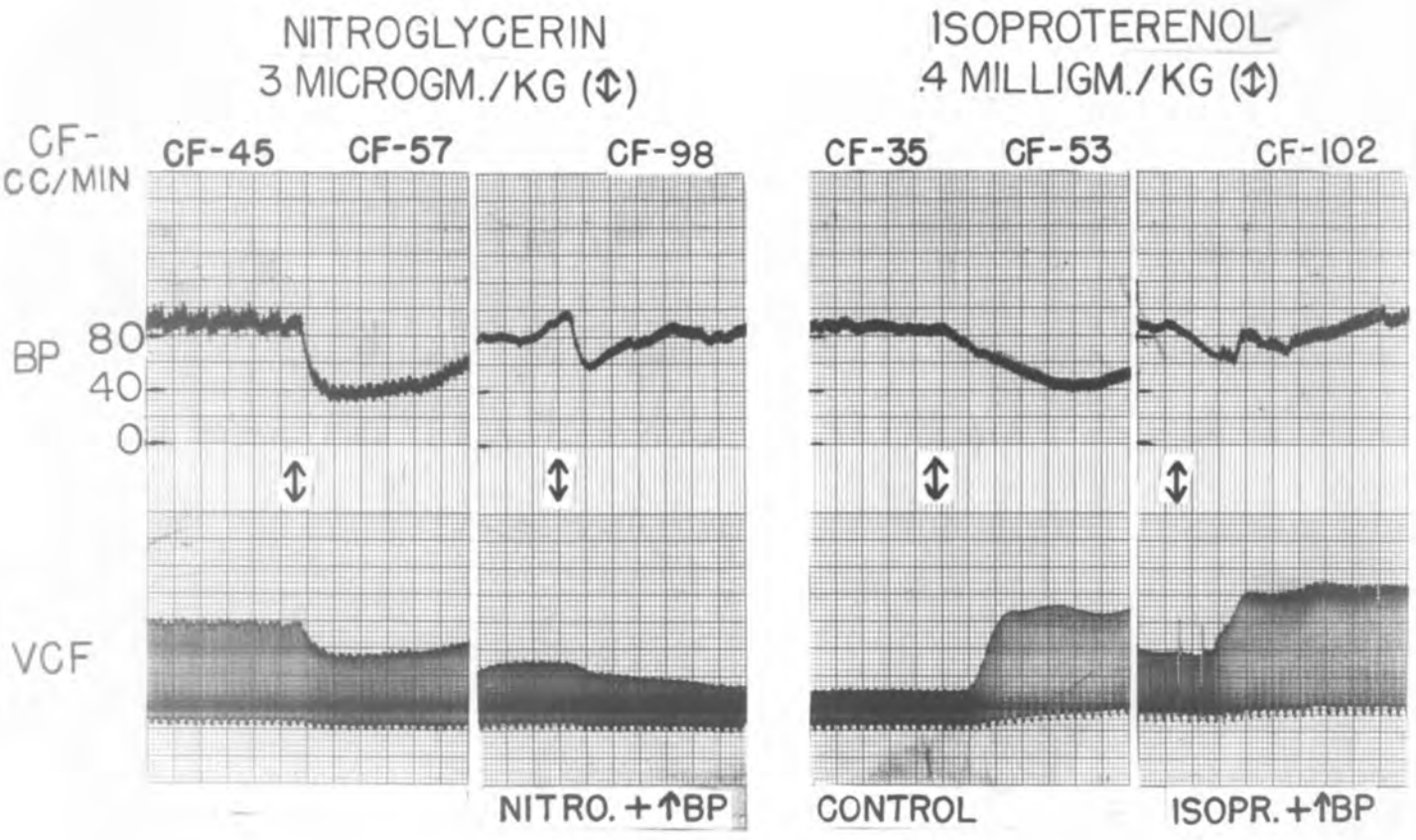
Figure 11



CF - coronary flow
VCF - left ventricular contractile force
BP - aortic blood pressure
BP was maintained at control levels by decreasing total body perfusion with the by-pass pump.
Percents - equal percent increase in CF over control values.

decreased. The increment in coronary flow thus indicated a direct dilatation of the coronary arteries. When the pressure was maintained at control levels by increasing pump perfusion, the CFl increment with nitroglycerin was twofold and isoproterenol threefold. This was consistent in these experiments. The greater increase in CFl occurred with isoproterenol. This may be due to the increment in VCF which in turn causes a more complete filling and emptying of the coronary vessels. Isoproterenol also has a direct positive chronotropic effect.

Figure 12



The effect of nitroglycerin and isoproterenol on coronary flow.
CF - coronary flow
BP - aortic blood pressure
VCF - right ventricular contractile force
BP was maintained at control levels by increasing total body perfusion with the by-pass pump.

DISCUSSION

In these studies several simultaneous cardiovascular changes occurring during the administration of drugs with conspicious cardiovascular effects were recorded and analysed. The parameters observed appear to be intimately interrelated with one another. Normal cardiovascular tone is the result of a balance between the excitatory and inhibitory influence of the autonomic nervous system. During deviations away from the normal, this system attempts, primarily through reflex activity, to maintain homeostasis. Of prime importance in these studies was the ability of the myocardium to increase its efficiency and pumping capacity in the face of abnormally high work loads. Drugs stimulating the myocardium, such as epinephrine and arterenol, were able to overcome the large increases in total peripheral resistance. This was accomplished through their direct positive inotropic and chronotropic effects. Vasopressor drugs, such as methoxamine, administered to the normotensive animal produced an increase in total peripheral resistance of such magnitude that reflex bradycardia and resistance to systolic ejection caused the stroke volume and heart rate changes to decrease cardiac output over 40%.

Changes in venous return alter cardiac output. The difference between mean circulatory filling pressure which is the pressure within

the circulatory system measured at end systole, and right atrial pressure is the pressure gradient for venous return. Increasing arterial resistance does not decrease venous return appreciably whereas slight increases in venous resistance, right atrial pressures above 0, decreases venous return tremendously with little effect on total peripheral resistance.[18] Therefore, it appears that venous vasomotor tone is of prime importance in controlling cardiac output. The capacitance of the venous system has been shown to be much greater (20-30 times) than that of the arterial system.[19] There were only slight changes in right atrial pressure occurring during drug administration in the above experiments. The changes in cardiac output attributed to vascular changes appear to be due to changes in mean circulatory filling pressure rather than venous vascular tone.

Cardiac output depends on stroke volume and heart rate. Stroke volume in turn depends on length of diastole, effective filling pressure, aortic blood pressure, ventricular distensibility, ventricular contractile force, and venous return. The left atrial pressure and therefore ventricular filling pressure remained constant during the above experiments. The duration of diastolic blood runoff decreased with all of the above drugs except methoxamine. However, positive inotropic vasopressor drugs produced no change or a slight increase in stroke volume which

may be attributed to an increase in ventricular contractile force (VCF). Accompanying the increment in VCF was an increased velocity of systolic ejection as indicated by changes in the slopes of the stroke volume and VCF curves. There was also an increase in the rate of ventricular relaxation. Brewster and associates have reported that the rate of myocardial relaxation is directly related to rate of metabolism with the active transfer of chemical bond energy occurring during relaxation.[20] He implies contraction is a passive state. With epinephrine, arterenol, and isoproterenol the angle between the slope of the relaxation curve and the base line approaches 90°. This indicates an increase in the rate of myocardial metabolism. In the present experiments the drugs exerting a positive inotropic effect were accompanied by an increase in the rate of ventricular relaxation and therefore length of diastole despite the decrease in peripheral diastolic run off time. This in turn should decrease the impedance to ventricular filling. Rushmer found ventricular diameter and circumference at end diastole to be increased by epinephrine and arterenol.[21] In these experiments the slight rise in the VCF base line occurring during the positive inotropic effect indicates a change in length tension relationship not due to changes in diastolic heart size. This could have been due to an increase in ventricular distensibility elicited by an

intrinsic action of the drug on myocardial metabolism. Since VCF was measured with the strain gauge arch at a fixed length, the recorded changes in VCF are primarily intrinsic ones.[7-8] Szent-Gyorgyi states that isometric contraction is an indication of the maximum working capacity of muscle and depends on free energy change which is the portion of total energy available for the performance of work.[22] The positive inotropic drugs used in these experiments appear to increase the free energy release during systole. Olson and Piatnek divide the metabolic processes in heart muscle into three general phases.[23] They are energy liberation, conservation and utilization. It seems likely that an increase in free energy change would accompany an increase in metabolism of any one of these three phases.

The immediate increase in cardiac output occurring with nitroglycerin may be attributed to an increase in venous return. The decrease in output which follows is probably due to the extreme hypotension accompanying peripheral pooling of blood. There appeared to be little change in free energy release as indicated by an almost constant VCF. The rate of metabolism was not altered significantly. The de-decrease in stroke volume may be due to a decrease in ventricular filling time as well as venous return.

Of the group of drugs used in these experiments, isoproterenol produced the largest increment in VCF and heart rate. The VCF change is due to a direct inotropic effect while the heart rate change is due to both a direct drug and hypotensive reflex effect. Although there was a marked decrease in blood pressure the above changes in VCF and rate produced an increase in cardiac output. There was little change in stroke volume. Of particular interest with isoproterenol was the left ventricular blood pressure change when compared with aortic blood pressure change. In all cases the ventricular systolic pressure was higher than the aortic systolic pressure during the drug response. This may be attributed to a combination of an increase in velocity and strength of VCF as well as an increase in peripheral vascular removal of blood from the arterial system. The impedance to systolic ejection was thereby decreased. Therefore, the ventricle may have been compressed at a greater velocity and force than necessary to complete ventricular emptying.

Nitroglycerin relieved the increased cardiac work load produced by methoxamine. Invariably methoxamine produced a decrease in cardiac output resulting from the pressor and reflex bradycardia effects. During methoxamine infusion, administration of nitroglycerin decreased blood pressure to near control levels with a consequent increase in cardiac output. There was also an increase in heart rate be-

cause of the decrease in the pressor reflex bradycardia. Vagotomy during arterenol infusion produced similar results. The vagal effect was removed thereby increasing heart rate with a consequent increase in cardiac output.

Since heart muscle extracts almost a maximal amount of O_2 under normal conditions, the coronary flow is the first line of defense against increased cardiac load. Gregg has shown oxygen extraction from the left coronary to range from 7.9 to 15.2 vol.% under normal conditions.[24] Coronary flow depends on the caliber of the coronary vessels, aortic blood pressure,[25] heart rate,[26,27] VCE,[28-30] cardiac output,[31] and changes in CO_2 production[32] and O_2 consumption.[33,34]

Two important variables control the caliber of the coronary vessels. One is the active vasomotor changes in the vessels induced by nerve and/or chemical influence. The other being extravascular compression and relaxation accompanying ventricular contraction. A third may be passive changes as a result of perfusion pressure changes. Changes in right atrial pressure may effect coronary sinus drainage and therefore coronary inflow.

The in situ heart used in the coronary flow studies was subjected to reflex neural and humoral influences while retaining those advantages of hemodynamic control which characterize the isolated heart

preparation. Arternol produced large increments in coronary flow and QO_2 (Table II). When the blood pressure was maintained at control levels, there was a marked decrease in both coronary flow and QO_2 despite little change in the force or tension of ventricular contraction. Ventricular contractile force appears to depend only minimally on coronary flow if the flow rates are above a critical level, assuming arterial oxygen content is sufficient. This was indicated in that only a slight decrease in VCF accompanied a marked decrease in QO_2. It was stated that arterenol produced an increase in myocardial metabolism as shown by the increased tension and rate of relaxation of contraction. This was also related to free energy change and rate of metabolism. Since in this preparation, the myocardium is not performing any external work, the ratio of internal efficiency between the actual total tension developed by the myocardium and its O_2 consumption is markedly increased when the blood pressure is maintained at control levels during arterenol infusion. Sarnoff and associates, using a tension-time index, state that the primary determinant of O_2 utilization by the myocardium is the total tension developed by the heart during contraction.[35] Stimulation of the stellate ganglion of the sympathetic nervous system in the dog causes a marked increase in the ventricular contractile force accompanied by increased cardiac work, coronary flow, and myocardial oxygen consumption.[36] These effects are essentially the same as those described above for arterenol.

Both phenylephrine and epinephrine produced increments in coronary flow. The greater increase occurring with epinephrine was attributed to increased metabolism accompanying an increased vigor of contraction as occurred with arterenol. Epinephrine also appears to dilate the coronary vessels directly. The flow increase occurring with phenylephrine appears to be almost entirely due to the increment in aortic blood pressure which in turn increased coronary perfusion pressure.

Of the two vasodilators nitroglycerin and isoproterenol, the latter produced the greatest increment in coronary flow. This may be attributed to an increased myocardial metabolism occurring with the increased ventricular tension.

These observations suggest that the primary cause of increased coronary flow during the administration of arterenol, epinephrine and phenylephrine is an increased head of pressure in the aorta which forces blood through the coronary bed. Positive inotropic action produces an increment in coronary flow through a greater oxygen demand and accumulation of metabolites which produces an intrinsic coronary dilation. The relaxation period is also increased which may cause a more complete filling, and in turn emptying of the coronary vessels. At end diastole extravascular compression is at a minimum while at the height of intraventricular pressure, ventricular contractile force and

compression are at a maximum. These effects may predominate over direct vasoconstrictor effects with a net effect of coronary vasodilatation.

Regardless of the immediate effect of drugs on the myocardium, the consequent changes in cardiac tension and the accompanying changes in metabolism are probably largely responsible for changes in coronary vascular tone. Therefore, flow changes may be taken to be the net effect from changes in extravascular support, metabolism, and any direct effect the drug may have on the coronary vasculature.

SUMMARY

Epinephrine, isoproterenol and arterenol increased cardiac output, rate of myocardial metabolism, and free energy change. Methoxamine and nitroglycerin had little effect on myocardial force, rate of metabolism and free energy change. Both drugs decreased cardiac output, methoxamine to the greater degree. The major factor influencing augmented coronary flow during administration of phenylephrine, arterenol and epinephrine is the increased coronary perfusion pressure as a result of increased aortic pressure. Another factor is the direct increment in ventricular contractile force, therefore metabolism, occurring with arterenol, epinephrine and isoproterenol. An additional factor occurring with nitroglycerin, isoproterenol and possibly epinephrine is direct coronary vasodilatation. Myocardial oxygen utilization appears to be primarily associated with myocardial tension rather than external work.

CHAPTER II

CARDIOVASCULAR RESPONSE TO SYMPATHOMIMETIC AMINES DURING RESPIRATORY AND METABOLIC ACIDOSIS AND FOLLOWING THE ADMINISTRATION OF SEVERAL BUFFERS TO CORRECT THE ACIDOSIS

INTRODUCTION

Normal concentrations of blood gases depend largely on pulmonary function and an adequate circulating blood volume. Severe hypoxic acidosis is a common complication of inadequate tissue perfusion which may be due to hypovolemia, cardiac failure or a reduction in venous return.[37-39] Hyperglycemia usually occurs early in conditions associated with a reduction in circulating blood volume.[37] The degree of hyperglycemia seems to follow closely the level of catechol amine liberation.[40-42] There is a progressive increase in blood lactate and pyruvate production found under these conditions with a greater increase in lactate.[37, 39, 43] As lactic acid is formed, there is an immediate reaction with the bicarbonate buffer system. This reaction results in the formation of lactate and carbonic acid.[44] The carbonic acid dissociates to form CO_2 and water. An increase in ventilation allows respiratory compensation for the increase in hydrogen ion production. However, as the bicarbonate buffer system is gradually depleted, there is a progressive increase in hydrogen ions derived from both anaerobic and aerobic metabolism since the blood loses its ability to carry CO_2.[39, 45] This reduction in CO_2-carrying capacity is analogous to hypoxia caused by a decrease in hemoglobin-combining power. While ventilation is adequate, the ability of the blood to carry CO_2 from the tissues to the lungs is greatly impaired.

The changes occurring with sympathoadrenal stimulation would indicate a marked increase in carbohydrate metabolism with an increase in the anaerobic phase. Energy production by glycogenolysis involves reversible reactions; therefore, the increase in the end products of these reactions would decrease the rate of the reactions according to the law of mass action. In the present investigations this hypothesis has been tested. Hypoxia produced by limiting cardiac output to the venous return supplied by the azygos vein resulted in an increase in lactate production and a decrease in total arterial blood CO_2 concentrations. Correction of the acidosis with 2-amino-2-hydroxymethyl, 1, 3-propane diol (THAM),[46,47] a hydrogen ion acceptor, resulted in a greater increase in lactate production with a corresponding increase in free energy change, as judged from the isometric tension developed with myocardial systole. A decrease in the bicarbonate buffer system of the blood elicited by lactic acid infusion resulted in changes closely similar to those associated with hypoxic acidosis. The inhalation of CO_2 similarly reduced the free energy change. Correction of the increase in the hydrogen ion concentration by the administration of the hydrogen ion acceptor, THAM, without reducing the inspired CO_2 concentration resulted in an increase in the free energy change. This control of the accumulation of hydrogen ions also resulted in a

greater response to the administration of levarterenol. Such an increase in free energy release should improve the ability of the body to maintain homeostasis in emergency situations.

During operative trauma, the cardiovascular system frequently becomes refractory to endogenous releases of epinephrine and levarterenol and to administration of the sympathomimetic amines. Such refractoriness usually follows periods of diminished cardiac output and hypotension, which are concomitant with metabolic acidosis or alkali deficit.[48-52] Hypotension reflexly elicits an increase in sympatho-adrenal activity.[17,51,53] Sympathetic stimulation is generally believed to increase anaerobic metabolism with notable increase in acid metabolites. Relative refractiveness to injected or infused catechol amines accompanying high circulating plasma levels of these amines is probably due to both the high existing amine levels and the concomitant metabolic acidosis produced.

ANIMAL STUDIES

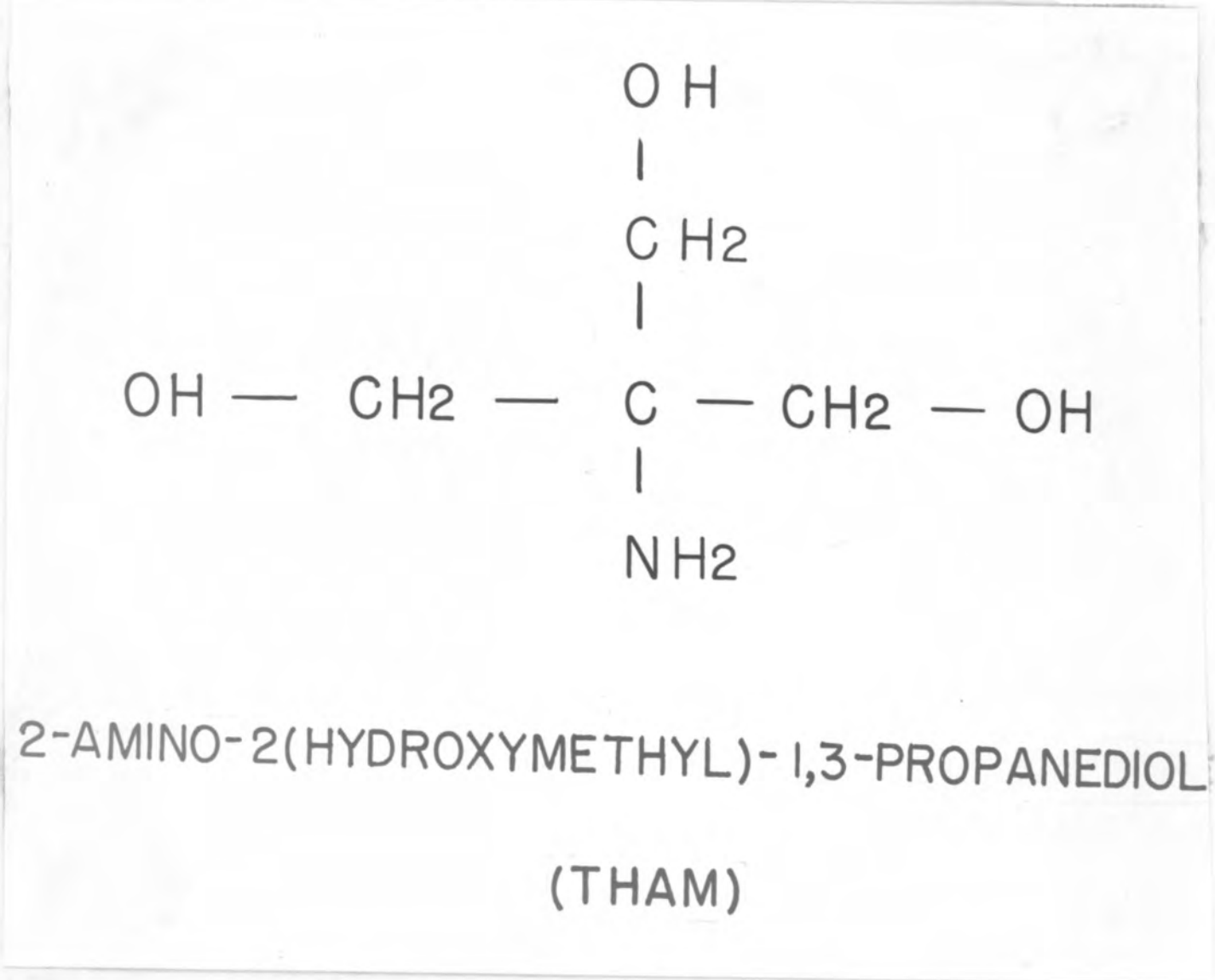
METHODS.

The following experiments were conducted in 98 apparently healthy mongrel dogs weighing 8 to 13 Kg.

Group I: This group consisted of 39 "azygos flow" experiments produced by occlusion of the venae cavae, thus limiting venous return to that supplied by the azygos vein and coronary vessels for periods of 10 minutes.

This group of experiments was divided into 6 subgroups: (a) In 10 animals the response to a test dose of 1 microgram per Kg. levarterenol was determined during the control period, within 1 to 3 minutes after release of the venae cavae and at approximately 20 minute intervals for a period of 1 hour. (b) In 4 experiments preganglionic sympathetic blockade was established prior to establishment of "azygos flow." The duration of "azygos flow" in these animals was 5 minutes. (c) In 14 animals after a period of at least 1 hour following the first "azygos flow" study, the animals were subjected to a second period of "azygos flow". A solution of 2-amino-2-hydroxymethyl, 1, 3-propane diol (THAM) (Figure 13) in a concentration of 0.3 M was infused during 5 to 10 minutes of the second period of "azygos flow". (d) In 3 experiments 2 periods of "azygos flow" were carried out without THAM administration. (e) In 4 experiments THAM was administered prior

Figure 13



Structural formula of THAM. The buffering ability of THAM is due to the presence of the amino group. Under acid conditions, THAM acts as a proton acceptor and is readily ionized. It removes hydrogen ions from solution which combine with amino groups producing an ionization of the molecule with a charge of +1 (46).

to a second period of "azygos flow." (f) In 4 animals left atrial perfusion was carried out through a no. 20 French Bardic catheter placed in the left auricular appendage and connected to a reservoir. Boiled saline, a solution of THAM in boiled saline and blood were separately infused rapidly into the left atrium after 10 minutes of "azygos flow".

Group II: In 7 animals total body perfusion was controlled by extracorporeal circulation with cardiopulmonary bypass, utilizing a Kay-Cross disc oxygenator.* In the procedure the heart and lung circulation was separated from the peripheral circulation. The quantity of blood traversing all or part of the heart and pulmonary circulation was limited to coronary flow and bronchial artery flow. The cannulation procedure for the extracorporeal circulation experiments has been described.[11,12]

Group III: The response to an arterenol test dose of 1 microgram per Kg. was obtained during a control period in 19 dogs. The animals were then placed on an infusion of 2 M lactic acid at a rate determined by degree of cardiovascular depression. The pH was determined at 5 to 25 minute intervals, and injections of test doses of arterenol were administered at each reduction of 0.1 pH units. An infusion of 0.3 molar THAM, 0.9 molar sodium bicarbonate, molar

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* Mark Instrument Company, Boston, Mass.

sodium lactate, or 3% sodium chloride was started during the lactic acid infusion. The pH and arterenol response was obtained until the pH had reached control values of near 7.50.

Group IV: Arterenol or epinephrine was infused into 12 dogs in quantities sufficient to produce and maintain VCF approximately 100% above control levels. This produced a metabolic acidosis with pH values near 7.1. As in group III, the response to test doses of several sympathomimetic amines was determined before and after attempted correction of the acidosis with THAM, sodium lactate, and sodium bicarbonate.

Group V: In 12 animals the response to levarterenol was tested during a control period, after which an increase in CO_2 ventilation was established by supplying a mixture of 15 per cent CO_2 in oxygen to the respirator. During the period of marked myocardial depression, a second test dose of levarterenol was administered. While the CO_2 ventilation concentration remained at 15 per cent, THAM was infused in a concentration of 0.3 M. The response to a test dose of levarterenol was again established. In 4 of these experiments $NaHCO_3$ infusion was compared with THAM.

Group VI: In 6 dogs the cardiovascular response to THAM was tested before and after preganglionic sympathetic blockade. In 3

experiments the effects of THAM on cardiac output was determined by a square wave electromagnetic flow meter.[9,10] The ascending aorta was isolated from the pulmonary artery, and the probe or sensing unit was placed around the ascending aorta.[54] The unit constricted the vessel slightly but had little effect on the pulse pressure or the contour of the pulse wave. In addition, THAM was administered to 5 isolated rabbit hearts (Langendorff preparations) and 3 cat papillary muscle preparations.

Anesthesia was the same as used in Chapter I. Ventilations were controlled by means of a Harvard respirator which provided positive pressure. The chest was opened in the midline, and a strain gage arch was attached to the right ventricle.[5-8] Ventricular contractile force (VCF) and aortic blood pressure (ABP) were measured and recorded on a Sanborn polyviso (model 150) as described in Chapter I. A second polyethylene catheter was placed in the descending aorta for blood sampling. Arterial pH, whole blood CO_2 combining powers, CO_2 content and lactate blood levels were determined from samples of blood obtained anaerobically from the second arterial catheter.[13] A Beckman Model G pH meter equipped with a Beckman hypodermic electrode assembly part number 40311 was used for pH determinations. Periodic check duplicate pH determinations were obtained from different pH meters (both Beckman G and Cambridge Research models). The pH meter con-

tinuously used was standardized after at least each 2 determinations. The pH values reported are believed to be correct to within 0.05 pH units. Similarly, precautions were taken with other determinations.

"Azygos flow" was established by occlusion of the superior and inferior venae cavae with umbilical tapes placed around each vena cava. The ends of the tapes were then inserted through a rubber tube which was depressed lightly against the vena cava and held securely in place with hemostats. Care was taken to occlude these vessels completely with a minimal amount of pressure to prevent venous spasm.

In the Group III animals additional polyethylene catheters were passed into the inferior vena cava via the right and left femoral veins, one for drug injections and the other for drug infusions. A 2 M solution of lactic acid was infused into the venous catheter at an infusion rate varying from 0.4 to 2 ml./min.

Preganglionic sympathetic blockade was produced according to the technic of Brewster et al[55] but modified to the extent that 0.05 per cent tetracaine was used in place of 0.5 per cent procaine.

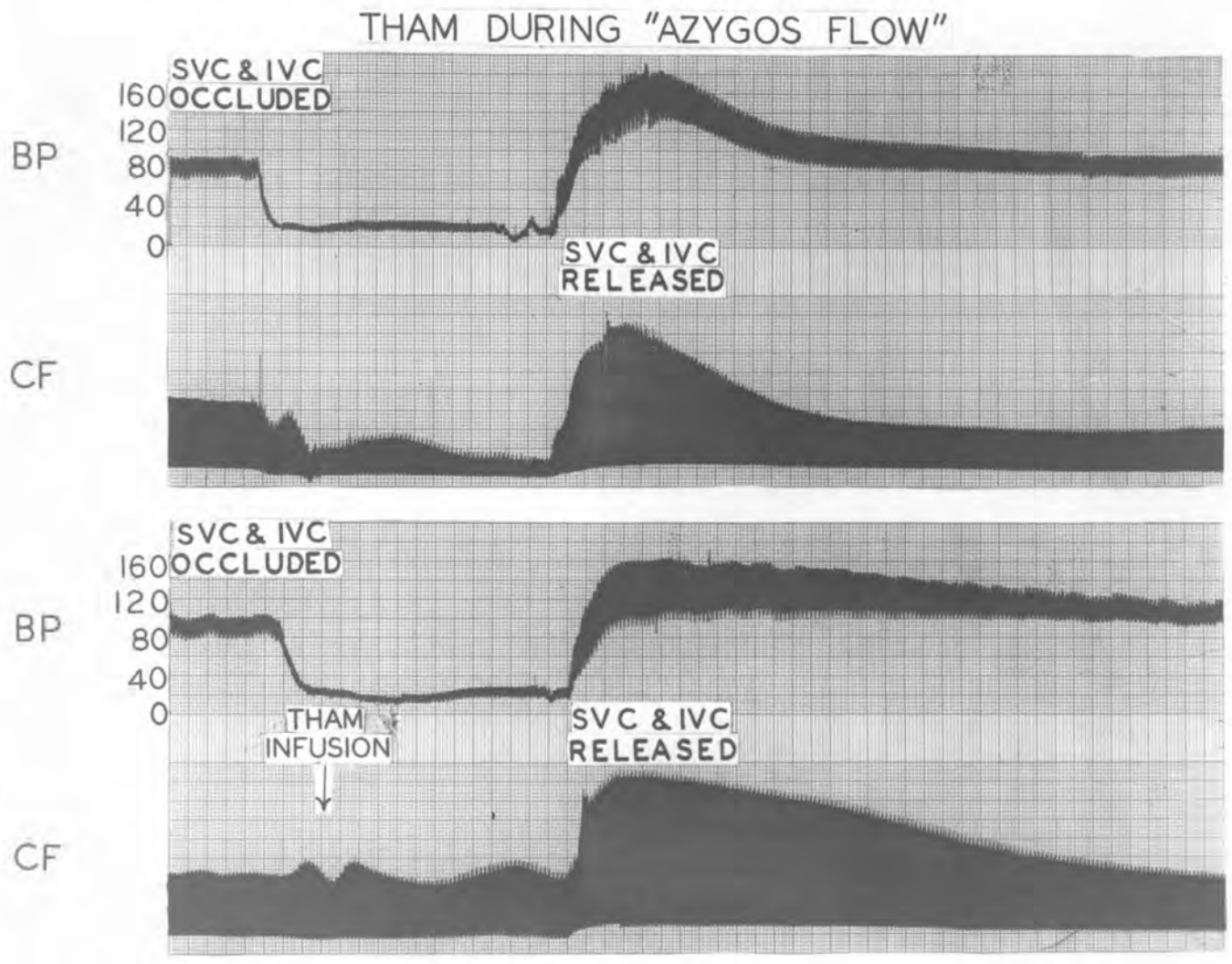
RESULTS

AZYGOS FLOW.

The effect of 10 minutes of "azygos flow" on the cardiovascular system have been reported previously.[11,56,57] The upper 2 tracings of Figure 14 show the typical changes occurring with 7 minutes of superior and inferior vena caval occlusions. The reduction in circulating blood volume is accompanied by a decrease in arterial pH during the period immediately following release of the superior and inferior venae cavae. Measurements of lactate levels show an increase of 2 to 4 times normal (0.7-1.6 mM/L to 3.3-5.8 mM/L) during the "rebound" stimulation in VCF and arterial blood pressure. Catechol amine plasma levels have been reported to reach a maximum after 7 minutes of azygos flow.[56] These levels are 15 to 50 times normal (100 to 300 microgram/L of plasma).

Ventilation was regulated so that the rate and depth was excessive in order to allow near maximal respiratory compensation for the expected increment in acid metabolites. During the control period with an arterial pH which ranged from 7.53 to 7.68 a response to a test dose of levarterenol, 1 microgram per Kg., was obtained. Following 8 minutes of "azygos flow" there was no response to a second test dose of levarterenol. After 10 minutes of occlusion the venae cavae were re-

Figure 14



Effects of "azygos flow" on VCF and blood pressure without and with correction of hypoxic acidosis. The upper pair of tracings show blood pressure (in mm. Hg) and VCF changes occurring with "azygos flow" without correction of acid-base changes. The lower pair of tracings illustrate the changes in blood pressure and VCF in the same animal occurring with a second period of "azygos flow". However, in this instance THAM, 0.3 M, was infused following vena caval occlusion. The increase in VCF during the period of "azygos flow" and the longer time interval of the rebound response in the lower pair of tracings occurred with a greater increase in blood lactate levels. While the pH and total blood CO_2 were reduced in the upper response, these values were increased in the lower response. The time interval between the heavy vertical lines represents 20 seconds.

leased. Within 3 minutes after the release of the venae cavae, the animals were relatively refractory to a third test injection. The decrease in pH to values near 7.30 during the "rebound" phase of cardiovascular stimulation may be largely due to the tissue washout of metabolic acids produced during the period of low systemic blood flow. The decrease in alkali reserve supports this hypothesis. After 35 minutes the percentage of cardiovascular responses to levarterenol returned to near the control values, although the existing contractile force was generally 20 to 30 per cent below preocclusion levels. The CO_2 combining power and pH were also near control levels. The plasma levels of catechol amines have been reported to be elevated for at least 20 minutes following 10 minutes of "azygos flow".

In these studies correction of the acid-base changes occurring with "azygos flow" prevented the marked depression of the myocardium during the period of reduced cardiac output as shown in the lower 2 tracings of Figure 14. The "rebound" stimulation of ventricular contractile force and arterial blood pressure lasted from 2 to 4 times the uncorrected period of stimulation as shown in Table 4. It is evident that correction of the acidosis, which occurred with reduced cardiac output, greatly increased the free energy released with systole. The lactate levels which followed 10 minutes of reduced cardiac output with

Table 4

Percentage Increase in Ventricular Contractile Force (VCF) Following 1μg./Kg. of Levarterenol at Average pH Indicated (Group I, A)

	Control	3 min. after "azygos flow"	30 min. after "azygos flow"
pH	7.52	7.31	7.51
VCF	142%	41%	287%

Two "Azygos Flows", First Without Corrective Measures and the Second with THAM (Group I, C)

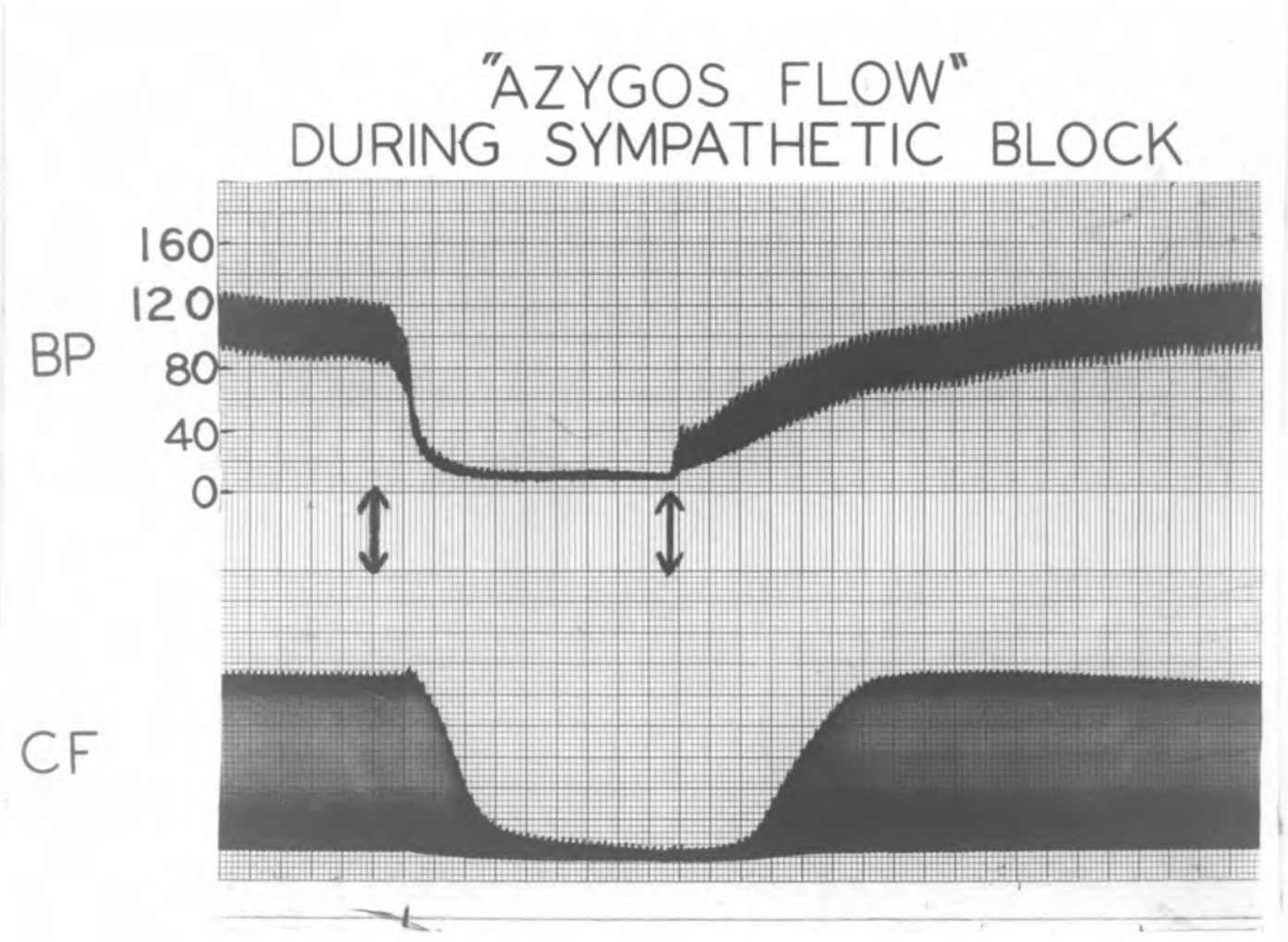
	Rebound in VCF (%)	Duration of rebound (min.)	Pulse pressure during rebound *	pH		CO_2 (mM/L.)		Lactate (mM/L.)	
				control	rebound	control	rebound	control	rebound
First azygos flow	74	4.3	94%	7.51	7.37	19	21	2.6	6.2
Second azygos flow (with THAM)	84	12.4	204%	7.49	7.76	18	31	3.6	12.7

* Increase above pre-"azygos flow" level.

an infusion of 0.3 M THAM (500 to 750 mg./Kg.) ranged from 9 mM/L to 14.2 mM/L. These results would seem to indicate that with control of the buffer base and hydrogen ion concentration there is a greater increment in the oxygen debt incurred during the period of reduced cardiac output. The increment in ventricular contractile force (VCF) seems to indicate better metabolic function provided the acidosis is corrected. When the THAM infusion was started before occlusion of the superior and inferior venae cavae, the results were not so striking as in the cases where the THAM infusion was started from 3 to 5 minutes after the occlusion. Alkalosis occurs with THAM infusions during the period prior to "azygos flow". In 4 experiments boiled saline was perfused into the left atrium during the period of "azygos flow". The atrial pressure was raised to 6 cm. of water. This infusion caused an increase in arterial blood pressure and VCF to 75 per cent of control. In 3 experiments conducted in the same 4 animals, THAM was added to the saline solution. There was a rebound increment in VCF to 35 per cent above control. This would seem to indicate that removal of the hydrogen ions present in the coronaries aids in restoring VCF following periods of reduced coronary flow.

Figure 15 illustrates the effects of "azygos flow" on the animals deprived of sympathetic stimulation. Under these conditions 5 minutes of "azygos flow" greatly depressed both the myocardium and

Figure 15



Effects of "azygos flow" on VCF and blood pressure (in mm. Hg) in a dog during a period of preganglionic sympathetic blockade. The superior and inferior venae cavae were occluded at the first arrow and released at the second. Notice the absence of a secondary rise in VCF and the lack of a "rebound" response following release of the venae cavae. These changes would stress the need for sympathetic stimulation for an increase in VCF during and following periods of reduced circulating blood volume. The time interval between the heavy vertical lines is 20 seconds.

arterial blood pressure. It should be noticed that there was no rebound stimulation in VCF or arterial blood pressure. In contrast to the experiments in the animals with intact innervation, arterial blood pressure increased considerably before improvement in myocardial function. This would seem to indicate that removal of metabolites and a supply of oxygen are necessary for the return of intrinsic myocardial function.

EXTRACORPOREAL CIRCULATION:

The results obtained in the control tissue perfusion studies were different from those obtained in the "azygos flow" experiments. The "azygos flow" experiments produced a more drastic reduction in circulating blood volume. Correction of the acidosis in the control tissue perfusion experiments did not prevent the decrease in VCF. The "rebound" increments in VCF were not so great as those seen in the "azygos flow" experiments. The animals receiving THAM developed higher lactate levels, as did the animals with correction of the acidosis in the "azygos flow" studies. Prevention of the acidosis could reduce or prevent sympathoadrenal stimulation. The reduction in total body perfusion flow rates decreases coronary artery perfusion pressure and has been shown to reduce substantially coronary flow.[58] The reduction

in VCF occurred independent of intraventricular pressure and volume changes since the heart and lungs were bypassed except for coronary and bronchial artery flow. The removal of acid metabolites from the myocardium by the marked increase in cardiac output following release of the superior and inferior venae cavae seems to be of greatest importance in the "rebound" myocardial stimulation. In the extracorporeal experiments total body blood flow was only returned to control values; therefore, the removal of the hypoxic metabolites could be slower.

LACTIC ACID INFUSION.

A 2 M solution of lactic acid was infused slowly in quantities governed by the degree of cardiovascular depression. When the arterial pH was depressed to values near pH 7.10 by the lactic acid infusions, there was approximately a 50 per cent decrease in VCF and arterial blood pressure. The response to injected arterenol at this reduced pH level was significantly less in amplitude and duration than that observed in the same animal prior to the lactic acid infusion (Table 5). At pH values below 7.0 both epinephrine and levarterenol usually failed to produce a response. There was a concomitant diminution in alkali reserve to values less than 50 per cent of control levels (a 13 to 21 mM/L decrease) at the time of development of near 50 per cent refrac-

Table 5

Lactic Acid Infusions

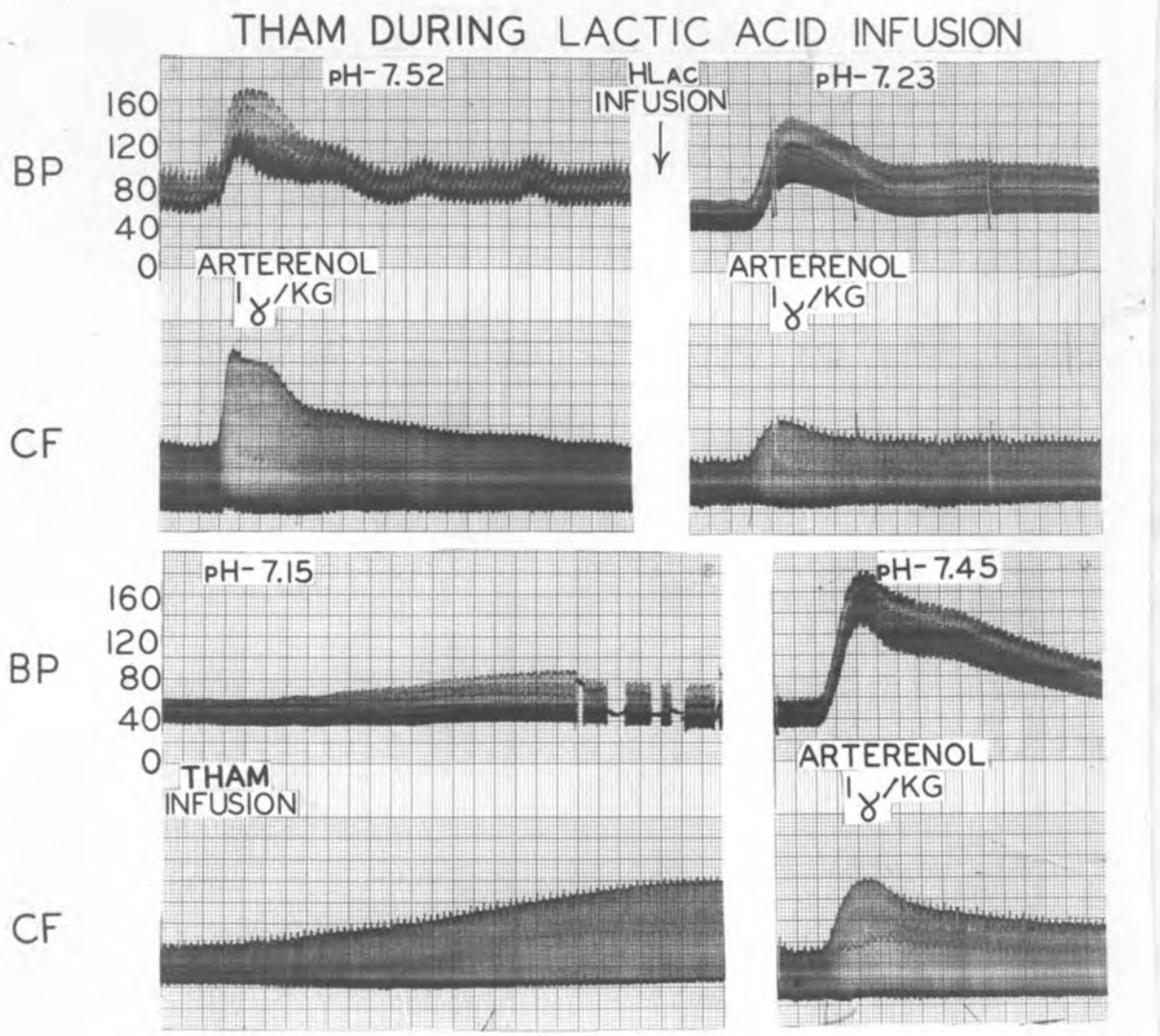
	Levarterenol response (%)	pH	Total CO_2 (mM/L.)
Control	148	7.55	22
Lactic acid depression	89	7.13	2
Lactic acid + THAM*	154	7.53	19

* With the infusion of THAM, there was an initial increase in VCF of 188 per cent above the acid depression level.

tiveness to levarterenol injection and to levels as low as 2 mM/L at the time of complete refractiveness. Shortly after the period of complete refractiveness was reached, cardiovascular collapse and death occurred. Houle, Campbell and their associates have reported a similar reduction in the pressor responses of arterenol, epinephrine, and metaraminol during respiratory acidosis.[49,59] The animals were hyperventilated in these experiments to prevent respiratory acidosis.

In 7 animals, as the pH was reduced by lactic acid infusion to levels near 7.10, a 5 to 8 mg./Kg./min. infusion of THAM was administered. Figure 16 illustrates the typical response of the cardiovascular system to infusions of lactic acid and correction of the arterial pH changes by an infusion of THAM during the lactic acid infusion. There was an initial increase of nearly 100 per cent in VCF. The continued infusion of lactic acid and THAM resulted in a second gradual depression of VCF concomitant with the improvement in arterial pH. Nahas et al have shown that correction of respiratory acidosis results in a decrease in sympathetic stimulation as evidenced by a decrease in the plasma catechol amine levels.[47] This could account for the secondary VCF depression. With the contractile force stimulation elicited by THAM infusion, there was usually an increase in systolic blood pressure without much change in diastolic blood pressure. When the arterial pH had re-

Figure 16



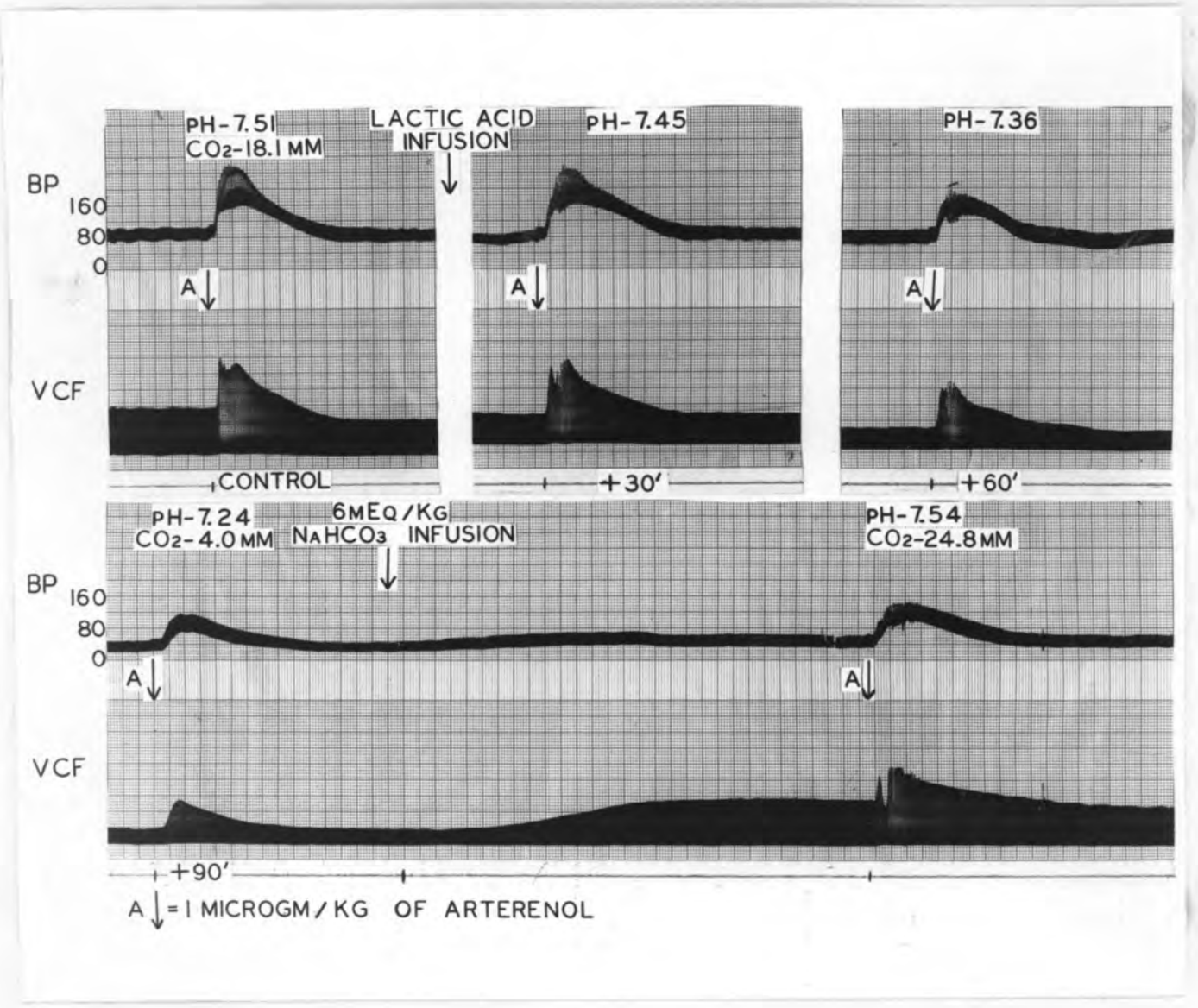
Typical cardiovascular response to a test dose of 1 μg. of levarterenol at the control pH value of 7.52. An infusion of lactic acid 2 M was started at the arrow. After approximately 40 minutes the pH had reached a value of 7.23; the VCF was depressed to a value of only 50 per cent of control, and there was a marked depression in the response to a second test dose of levarterenol. At pH 7.15 a THAM, 0.3 M, was started along with the continued lactic acid infusion. The immediate increase in VCF and systolic blood pressure can be seen. As the pH returned to near control values, there was a secondary depression of VCF, and the levarterenol response was markedly improved. The time required for the correction of the pH values was nearly 20 minutes. The pH values reflect changes in alkali reserve since ventilation of the animals was controlled. The time interval between the heavy vertical lines represents 20 seconds.

turned to control levels near pH 7.4, the amplitude and duration of the VCF response to levarterenol had returned to within 80 per cent of normal. However, the blood pressure response was usually greater than that seen in the control.

Figure 17 illustrates the typical response to lactic acid infusion with the VCF and blood pressure changes during correction of the acidosis by sodium bicarbonate infusion. The improvement in cardiovascular function following an infusion of 6 mEq/kg sodium bicarbonate as with THAM seemed to be largely due to an increase in VCF which increased from 50% below the prelactic-acid control to as high as 150% above this level. From 15 to 30 minutes after the administration of either THAM or sodium bicarbonate there was a substantial improvement in both VCF and blood pressure responses to test injection of levarterenol, the responses being similar to those seen in the control period. With THAM, the duration of the responses were 1 1/2 to 2 times those observed prior to lactic acid infusion. Infusions of 3% sodium chloride and molar sodium lactate had little effect on the cardiovascular depression resulting from infusion of lactic acid. Both agents failed to improve the VCF or blood pressure response to levarterenol. As a matter of fact, molar sodium lactate seemed to hasten death.

Sodium bicarbonate and THAM raised pH to near control levels. Both of these agents raised arterial total CO_2 and CO_2 combining

Figure 17



Lactic acid infusion with production of acidosis and correction with $NaHCO_3$. The upper pair of tracings show the typical decrease in arterial blood pressure (BP) and ventricular contractile force (VCF) response to injections of arterenol after 30 minutes and 60 minutes of lactic acid infusion. The lower pair of tracings show the typical improvement in cardiovascular response following $NaHCO_3$ infusion which seems to be largely due to an increase in VCF. There was also a substantial improvement in VCF and BP response to test injections of levarterenol similar to that in the prelactic-acid control period. While pH and total CO_2 were reduced during lactic acid infusions, these values increased with administration of $NaHCO_3$. The time interval between the heavy vertical lines represents 20-second time intervals.

power. Continued infusion of THAM produced an alkalosis. Sodium chloride (3%) and molar sodium lactate increased arterial pH slightly, but molar sodium lactate increased pH more than sodium chloride. These agents had little effect, however, on the arterial total CO_2 or the CO_2 combining power. The results of these studies are summarized in Table 6.

EFFECTS OF HYPERCAPNEA ON VENTRICULAR CONTRACTILE FORCE WITH CORRECTION BY THAM.

Figure 18 shows the effects of THAM correction of hypercapnea compared with that produced by sodium bicarbonate. Ventilation with 15 per cent CO_2 produced a marked decrease in VCF (35 per cent of control).

The initial decrease in VCF was followed in 3 to 7 minutes by a secondary increase in VCF. This increase in VCF was slow but progressive, and within 30 minutes the VCF had usually returned to near pre-CO_2 ventilation levels. This secondary rise in VCF is thought to be due to sympathetic stimulation.[5, 60] Sympathetic blockade prevents this increase. Hypercapnea also decreased the myocardial response to injections of levarterenol. While the percentage increase in VCF produced by levarterenol was closely similar to that produced in the control injections, the total amplitude of the VCF response was obviously

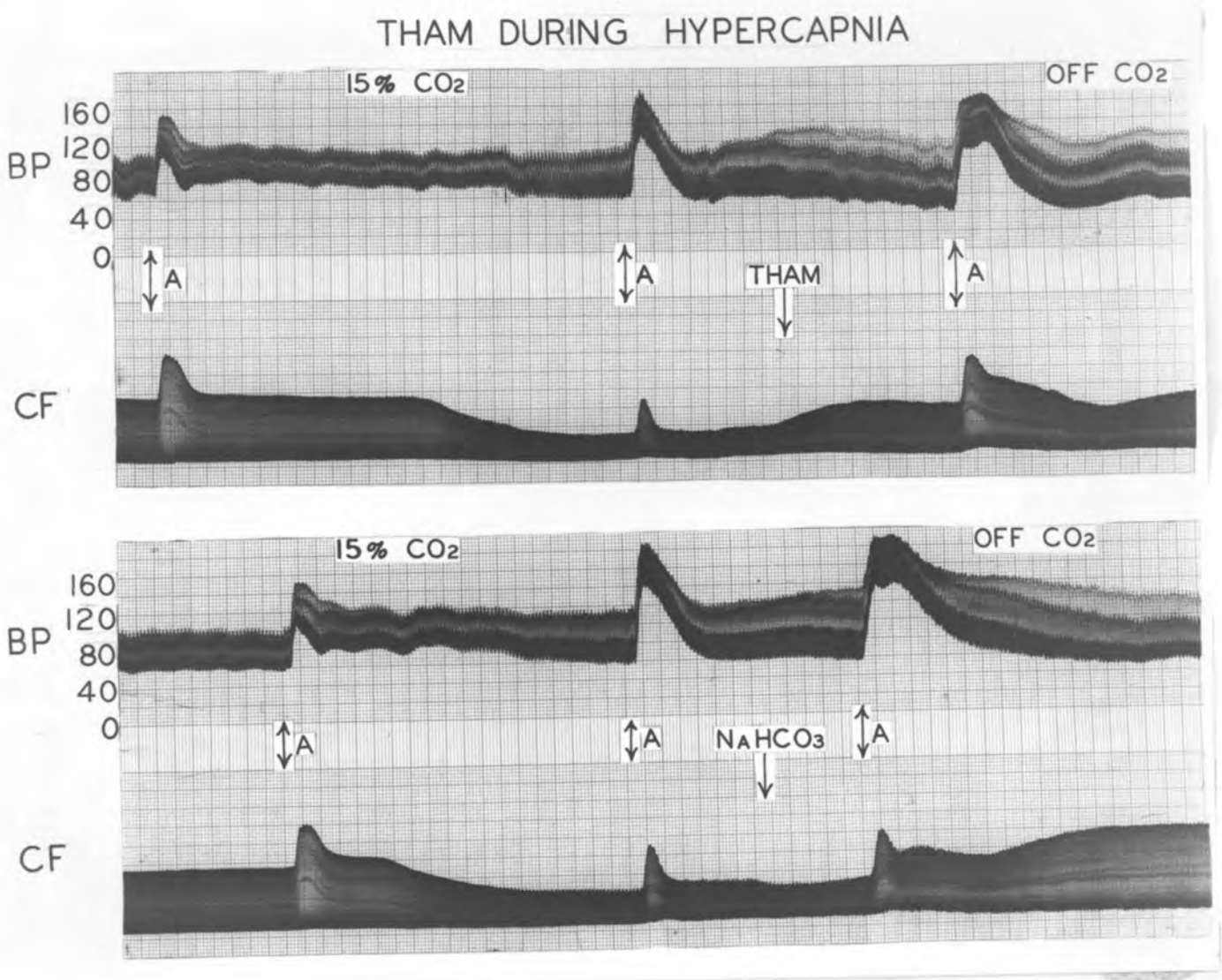
Table 6

Buffer Correction of Lactic Acid Induced Acidosis.

	pH	Total CO_2	Arternol Response BP	Arternol Response CF	Number of Experiments
THAM	+++	+++	+++	+++	7
$NaHCO_3$	+++	++	++	++	4
NaLac	+	0	0-+	0	4
NaCl	0-+	0	0-+	0	4

+++ - returned to or above control values
++ - returned almost to control values
+ - moderate effect
0-+ - slight effect
0 - no effect

Figure 18



Comparison of the effects of THAM and $NaHCO_3$ on the depression of VCF elicited by forced CO_2 inhalation. The "A" denotes injections of 1 μg./Kg. of levarterenol. These results were obtained in the same animal. The second period of increased CO_2 ventilation occurred approximately 30 minutes after the first. The time interval between the heavy vertical lines represents 20 seconds.

less than that produced in the control response. A 5 to 8 mg./Kg./min. infusion of a 0.3 M solution of THAM during the period of hypercapnea produced an immediate increase in VCF to within 90 per cent of control. In some instances VCF was increased above the control recording. The amplitude of the VCF response to 1 microgram per Kg. of arterenol was closely similar to that produced in the control period when administered during the THAM infusion. The duration of action was, however, approximately 1 1/2 times greater than the duration of action during control (table 7). Restoration to normal ventilation caused a rebound increment in VCF and arterial blood pressure which lasted from 5 to 15 minutes but was not so great as that seen following 10 minutes of "azygos flow". Sodium bicarbonate infusions, 2 mEq./min., during the period of hypercapnea usually slightly decreased VCF and failed to improve the response to levarterenol.

EFFECTS OF THAM ON VENTRICULAR CONTRACTILE FORCE AND ARTERIAL BLOOD PRESSURE.

THAM (100 mg./Kg.) administration in the normal animal usually produced a very short period of VCF stimulation, the duration being less than 1 minute. The amplitude increased to a level of approximately 10 to 25 per cent above control. THAM also produced a sharp decrease in both diastolic and systolic pressure. The decrease in diastolic pressure exceeded that of systolic pressure, resulting in an increase in pulse pressure. The degree of these changes seems to de-

Table 7

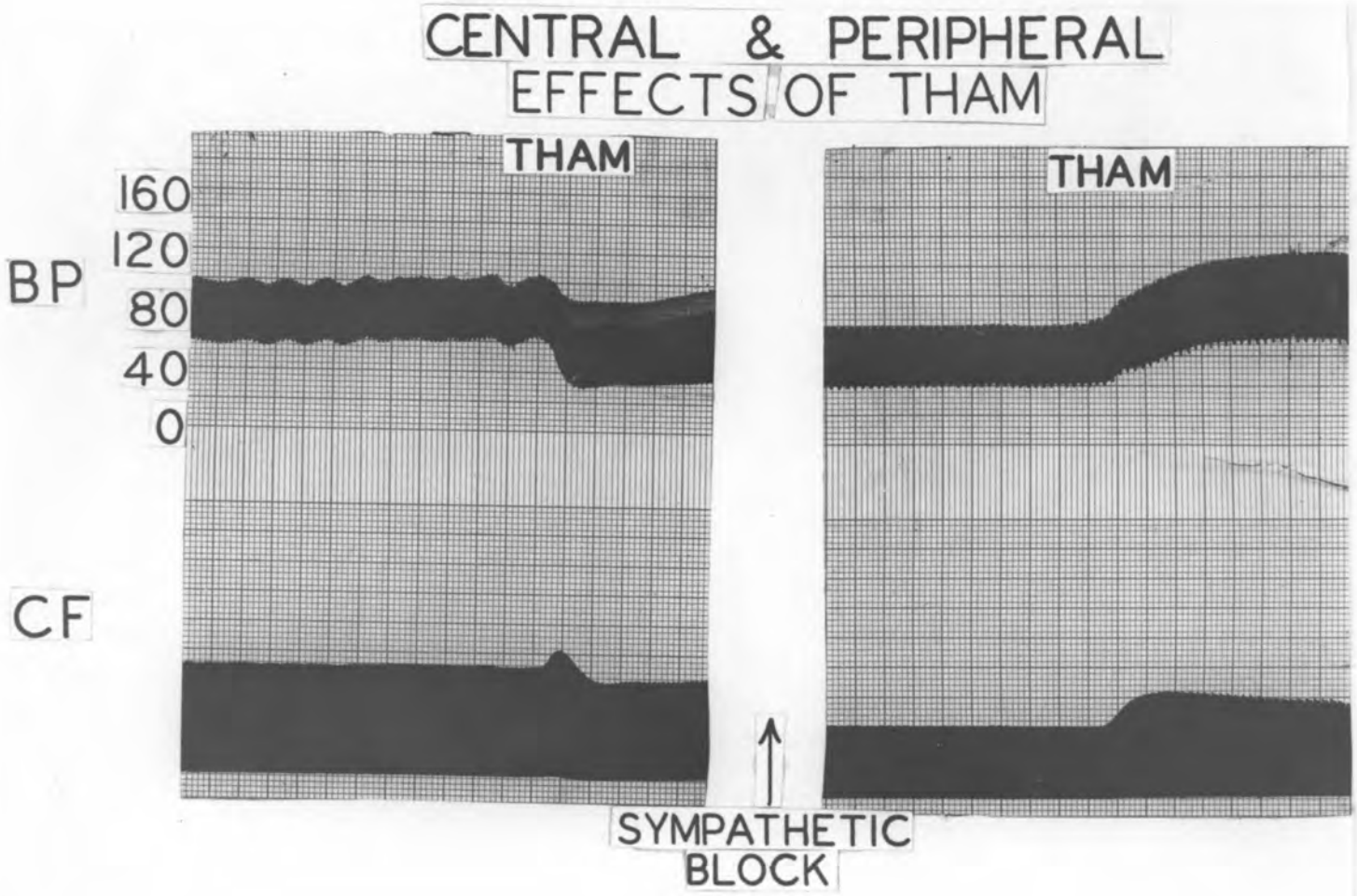
Levarterenol Response During Fifteen Per Cent CO_2 Ventilation

	Increase in VCF above control (%)*	% of initial control response of VCF	Duration of response (min.)
Levarterenol	157	100	2.1
CO_2 + arterenol	192	48	1.5
CO + THAM + arterenol	178	94	2.9

* Prior to each levarterenol injection.

pend largely on the status of the animal prior to the injection of THAM. As shown in Figure 19 sympathetic blockade increased the amplitude and duration of the THAM myocardial response. Following sympathetic blockade an injection of 100 mg. per Kg. of THAM usually produced an increase in diastolic pressure of 10 to 20 mm. Hg and a greater increase in systolic pressure 20 to 40 mm. Hg, again resulting in an increase in pulse pressure. In animals under conditions of hypercapnea usually an increase in pulse pressure was observed during the period of THAM infusion. This was also true under conditions of addition acidosis produced by infusions of lactic acid or by reductions in total circulating blood volume. In a limited number of experiments (3) direct measurements of aortic flow showed an increase (15 to 20 per cent) following THAM administration in the normal animal and greater increments (25 to 50 per cent) in the animal under conditions of hypercapnea. This increment is largely due to an increase in stroke volume. There was very little change in heart rate observed during the THAM infusions. The administration of 5 mg. of THAM to 5 isolated rabbit hearts (Langendorff preparations) and 3 cat papillary muscles resulted in an immediate and sustained increment in the amplitude of contraction which was nearly 250 per cent greater than the control amplitude.

Figure 19



Effects of 100 mg./Kg. of THAM on blood pressure (mm. Hg) and VCF. The first response was obtained prior to preganglionic sympathetic blockade, and the second response was obtained in the same animal following sympathetic blockade. The central reflex response to an increased pH produced by THAM appears to be greater than the local vascular effect.

CATECHOL AMINE INFUSION.

Infusion rates of levarterenol or epinephrine had to be continually increased after the first 30 to 45 minutes to maintain VCF 100% above control. After about 90 minutes the VCF usually failed to increase with increased infusion rates. Relatively large amounts (10 microgram/kg.) of levareterenol could be injected intravenously as test doses without affecting BP or VCF. Generally, there was a decrease in VCF responsiveness prior to a decrease in BP responsiveness. The response to test injections of 1 microgram/kg. of levareterenol was usually lost within the first hour of infusion. This loss of responsiveness paralleled a decrease in plasma CO_2 combining power. The arterial pH also declined with the diminution in CO_2 combining power. There was no significant difference in the response obtained with epinephrine as compared with levarterenol. Preganglionic sympathetic blockade had no significant effect on the observed changes.

ATTEMPTS AT CORRECTION OF THE ACIDOSIS.

In 4 animals, after approximately 150 minutes of levarterenol infusion, a mean arterial pH of 7.0 was obtained. Sodium lactate (1 molar) was then infused in the opposite femoral vein from that used for the levarterenol infusion. There was an increase in arterial pH, but there was no effect on the CO_2 combining power of the plasma.

Cardiovascular response to levarterenol test injections was unaffected by the correction of the pH alone.

In 4 other animals receiving levarterenol by infusion, again at approximately 150 minutes and near arterial pH 7.0, $NaHCO_3$ was infused in the same manner as that described for the sodium lactate. This agent not only corrected the arterial pH but also increased the CO_2 combining power to normal or elevated levels, and increased the responsiveness of the cardiovascular system to endogenous levels of catechol amines as well as to test injections of levarterenol.

In 4 additional animals THAM was used as the buffer solution. There was an increase in pH, CO_2 combining power, VCF, heart rate and pulse pressure. The latter was due primarily to an increase in systolic pressure, normally accompanied by a decrease in diastolic pressure. Sodium lactate failed to affect the levarterenol response and $NaHCO_3$ affected it only minimally (20%). THAM decidedly improved the response (50%).

SUBSTITUTION OF OTHER SYMPATHOMIMETIC AMINES FOR TEST INJECTIONS OF LEVARTERENOL DURING INFUSION.

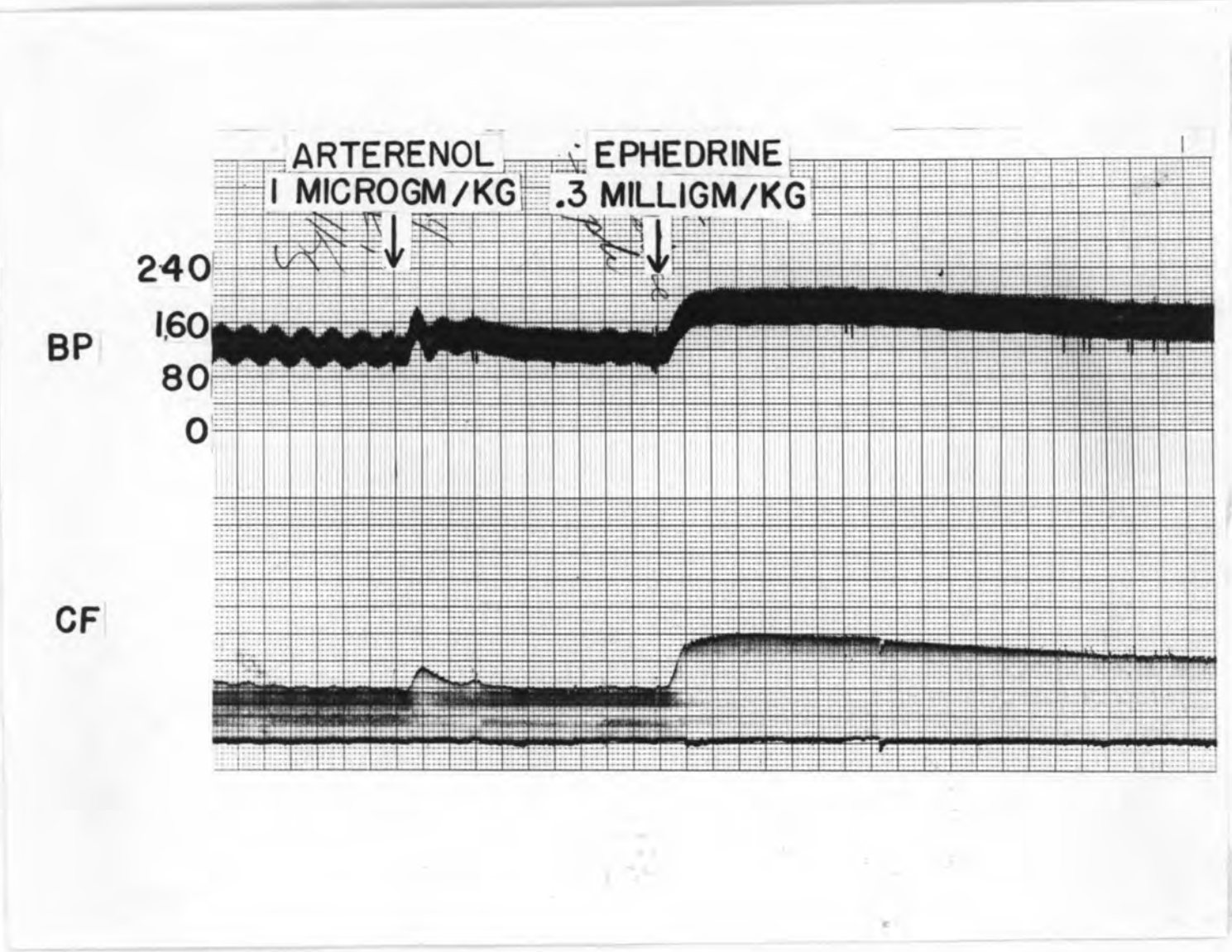
After the animal had become markedly refractory to infusions of levarterenol, single injections or infusions of wyamine, aramine, and ephedrine were administered. These agents seemed to have a decidedly better effect than large doses of levarterenol on VCF

and BP. The effect on BP was more pronounced than on VCF. When the animal became refractory to these agents, often a levarterenol infusion could be re-started with an increase in responsiveness. During administration of these amines responsiveness to injected levarterenol seemed to increase. The animals responded best to ephedrine following the levarterenol infusion (Figure 20). Wyamine was somewhat more effective than aramine in maintaining VCF and BP following the levarterenol infusion, but the animal seemed to become refractory to wyamine more quickly than to aramine.

HEMATOCRIT.

Hematocrit determinations showed an increase in volume of packed cells during periods of acidosis. In terminal states the loss of circulating plasma volume was marked, as judged from the packed cell values of 80 to 90 per cent. Preliminary results seem to indicate that the loss of plasma is a consequence of tissue acidosis. Correction of the acidotic state decreased the volume of packed cells. In vitro studies with blood indicated that some of the increase in cell volume was related to red cell swelling.

Figure 20



The effect of ephedrine on blood pressure (BP) and ventricular contractile force (CF) compared with that of arterenol during arterenol infusion.

CLINICAL STUDIES

Methods

Ten patients were studied who exhibited shock characterized by most of the following findings: marked hypotension, tachycardia, weak pulse, pallor and sweating, scant urine output, apathy, weakness, restlessness, or coma. The patient had these symptoms for at least 24 hours despite receiving sympathomimetic amines and the usual shock therapeutic regimens and was considered terminal prior to the administration of THAM. Serial determinations of arterial pH, total CO_2, CO_2 combining power, serum electrolytes, and lactate blood levels were obtained prior to initiation of THAM therapy and at intervals of 1 to 12 hours over a period as long as 4 days. In 3 patients, arteriovenous oxygen saturations were determined at least twice.

RESULTS

All patients were being supported by large doses of sympathomimetic amines and were considered terminal. The results are summarized in Table 8. A hypoxic or metabolic acidosis, which was characterized by an increase in blood lactate, a reduction in arterial total CO_2 and a decrease in CO_2 combining power was found. Initially, arterial pH was frequently normal or slightly elevated. This was largely due to a respiratory compensation for a metabolic acidosis. When the arterial blood was equilibrated at a pCO_2 of 40 mm. Hg, there was a reduction in pH which provided further evidence for respiratory compensation. Correction of the acidosis with THAM resulted in a decrease in the concentration of the pressor amine required to maintain normal blood pressure. In patients with normal kidney function prior to THAM administration, an increase was observed in urinary output which equaled or slightly exceeded the amount of fluid infused. In one patient, with acute renal failure, no improvement in urinary output was observed. THAM was administered in a 0.33 molar solution. The amount of solution required to correct the acidotic state varied from 300 to 750 ml. and was administered over a 3 hour period. In 3 patients, 72 gm. of THAM was infused over a 3 day period. When discontinued, there was a gradual decrease in arterial total CO_2, CO_2 combining power, and terminally a marked decrease in arterial pH.

Table 8

Average and Range of Values Obtained from Patients Who Received 2-Hydroxymethyl, -2-Amino-1, -3-Propanediol (THAM)

	Before	After
pH	7.26 (7.03-7.32)	7.48 (7.40-7.52)
Total CO_2	13 mM/L (10-16)	28 mM/L (25-32)
Whole blood CO_2 combining power	15 mM/L (11-18)	34 mM/L (28-42)
Lactate	4.2 mM/L (3.6-5.7)	4.0 mM/L (3.1-5.2)

Although the hematocrit was observed to be normal or slightly elevated in 4 patients, there was a decrease from normal in oxygen capacity of the blood and a marked increase in the A-V oxygen difference. The decrease in oxygen capacity despite normal hematocrit values points out the possible chance of error in calculating oxygen-carrying capacity from hematocrit determinations under these conditions. Red cell swelling under conditions of acidosis is well known, but the degree of hemoconcentration is difficult to determine.[32] Despite artificial respiration with 50% oxygen, arterial oxygen saturation was decreased below normal. The decrease in oxygen capacity produces a marked decrease in oxygen content in the arterial blood to as low as 15 vol. % which was obtained during artificial respiration at a rate and depth judged to be more than normal with no obstruction to ventilation. At this point the arterial total CO_2 and the CO_2 combining power were extremely low.

In 2 patients who were judged to be normovolemic, but hypotensive postoperatively, arterial total CO_2 was 25 mM/L, and the pH was 7.38. Serum Na, K, and Cl levels were within normal limits, but Na was low normal and the K was high normal. Despite these essentially normal acid-base findings, 44 mEq. of sodium bicarbonate were given with a good response in arterial blood pressure.

DISCUSSION

As Szent-Gyorgyi has pointed out, the isometric tension developed with each contraction of the muscle indicates the quantity of free energy spent.[22] The isometric systolic tension then represents the maximum work capacity of the muscle. Therefore, the amplitude of the VCF recording, as determined by the strain gage arch method, indicates the quantity of free energy change with systole. Olson and Piatnek have suggested that myocardial metabolism might be divided in to 3 general phases: (1) energy liberation, (2) energy conservation and (3) energy utilization.[23] Therefore, the relationship between the amplitude of the VCF recording and free energy change would mainly be related to energy utilization. Brewster and associates have stated that an inverse exponential relationship existed between the metabolic rate and the duration of the contracted state as well as the time required for relaxation of the heart muscle.[20] Such experiments utilized strain gage arch recordings similar to those obtained in this investigation. These investigators showed that relaxation has the kinetic characteristics of an enzymatic reaction associated with and dependent on chemical bond energy or electron transfer. Therefore, the relaxation phase of the contractile force curve appears to be more closely related to the energy liberation phase of metabolism.

However, in the present study only the amplitude of the isometric systolic tension was considered. Root and his associates have shown that there is a striking correlation between pH decreases and increments in plasma phosphate.[39] The increase in phosphate occurs when the blood volume is decreased in excess of 20 per cent and rises progressively to higher values with further decrements in circulating blood volume. This increase in phosphate could be related to a reduction in stored energy due to a deficit in energy liberation, as well as the decreased ability of cardiovascular utilization of energy. These changes would lead to a decrease in free energy change with each contraction of the myocardium.

The oxygen debt which the heart can incur is believed to be limited since the heart muscle is embedded in well-developed oxidative machinery. Carbon dioxide, the end product of aerobic metabolism, is markedly depressant to the myocardium.[5] This gas is liberated as a result of the bicarbonate buffering of lactic acid. Lundholm has presented excellent evidence that the vasodilator action of epinephrine is related to the release of CO_2 from the bicarbonate buffer system.[44] The formation of sodium lactate would decrease the ability of the blood to buffer CO_2 production and lead to an increase in dissolved CO_2. This

increment in CO_2 would depress anaerobic energy liberation as a result of the law of mass action. Earlier experiments dealing with the changes in myocardial contractility occurring with extracorporeal circulation and the reduction in the response of the myocardium to sympathetic stimulation gave rise to the supposition that metabolic changes leading to a decrease in pH were largely responsible for these changes.[12] The present studies, as well as observations in past experiments designed to study the effects of sympathetic stimulation in angina pectoris, lead to the conclusion that the metabolic production of hydrogen ions may be of extreme importance in the changes in myocardial contractility occurring with myocardial ischemia.[61]

Sympathetic stimulation and hypoxia in the "azygos flow" experiments also support the hypothesis stated in the introduction. There was an increase in the free energy change, as evidenced by the increase in VCF, in the animals with high lactate levels following the administration of THAM.

The decrease in the VCF occurring with lactic acid infusion paralleled the reduction in bicarbonate buffer base. There was an increase in the calculated dissolved CO_2 since the total CO_2 was extremely low and the arterial pH was near 7.0. Correction of the acidosis with restoration of CO_2 combining power resulted in an immediate increase in VCF and improvement in the myocardial response to levarterenol injections. A decrease in sympathoadrenal stimulation due to the rise in pH could account for the decrease in VCF (occurring with the

continued infusion of lactic acid and THAM); the pH returned to near normal values, however. Woods and Richardson[62] have shown adrenal stimulation with lactic acid injections. With the administration of THAM Nahas and coworkers[47] have shown a decrease in the sympathoadrenal response to CO_2. Increased concentrations of CO_2 in the ventilation gas would tend to increase the CO_2 gradient across the cell membrane, and the experiments showed a decrease in energy release. The increase in blood pCO_2 would result in a CO_2 retention within the cells. The accumulation of the products of metabolism should result in a decrease in the energy metabolism in accordance with the law of mass action. The gradual increase in VCF following an initial decrease during the administration of CO_2 and the "rebound" stimulation of VCF following the withdrawal of CO_2 could be related to sympathoadrenal stimulation[5, 60] and an increase in anaerobic metabolism. The administration of THAM resulted in an immediate increase in the amount of free energy release with each contraction. This agent also improved the response to levarterenol.

During the infusion of lactic acid the hematocrit was observed to increase progressively up to 155 per cent above control values. This increase may indicate a loss of plasma volume with an increase in size and possibly number of red blood cells. Rosenthal

and DiPalma have reported that the spleen does not increase its liberation of red blood cells during acidosis accompanying arterenol infusion.[63] They consistently found a rise in hematocrit in splenectomized dogs. Loss of circulating plasma volume may possibly be attributed to electrolyte compensation for an extravascular acidosis. Correction of this acidosis caused a decrease in hematocrit.

The changes observed in hematocrit due to shifts of water from the intravascular compartment are important in connection with fluid therapy during shock. With relief of shock or the correction of extravascular acidosis there should be an increase in the fluid volume shifted to the intravascular compartment and a concomitant increase in the cardiovascular response to catechol amines. Such changes would result in an increase in pulmonary blood volume and pulmonary edema. This presumed sequence agrees with clinical experience.

These results coupled with a review of the literature lead to the conclusion that much of the energy released in response to sympathoadrenal stimulation is derived from carbohydrate metabolism.[48, 52, 64, 65, 66] Anaerobic metabolism seems to play an important part in this response. The buffering of lactic acid leads gradually to a decrease in CO_2 carrying capacity of the blood. This was evidenced by an

increase in dissolved CO_2, not only in the late stages of the lactic acid infusions but also following long-term infusions of levarterenol and epinephrine. Since the oxygen debt which the heart can incur is thought to be extremely limited, the decrease in CO_2 carrying capacity of the blood would be detrimental to myocardial energy metabolism. In either case, anaerobic or aerobic metabolism, the limiting factor of metabolism seems to be the ability of the body to buffer hydrogen ions produced by metabolism.

Infusions of large amounts of levarterenol or epinephrine gradually led to a marked decrease in total CO_2, alkali reserve and pH of the blood. Since approximately 50% of the CO_2 of tissue respiration is carried as bicarbonate, such changes would be expected to decrease markedly the ability of the blood to remove CO_2 from the tissues. An increment in CO_2 tension at the tissue level leads to an increase in the diffusion gradient across the cell membranes and to a decrease in tissue metabolism. Corrective therapy of this condition would depend largely on the ability of the agent used to increase the CO_2 carrying capacity of the blood. With the administration of sodium lactate and sodium chloride under the conditions of these experiments, there was an increase in blood pH without a concomitant increase in the ability of the plasma to combine CO_2. $NaHCO_3$ increased the bicarbonate

level of the blood, elevated the alkali reserve and reacted with the acid metabolites to form additional CO_2. THAM, on the other hand, combined directly with CO_2 released by the tissue to form a carbamino compound and thereby increased the CO_2 carrying capacity of the blood.

THAM successfully corrected the acidosis in 10 patients but it was not until marked irreversible shock was evidenced. In each case the dose of levarterenol or the number of injections of metaraminol the patient received could be reduced. Urinary output improved in all but one patient who had acute renal failure. While urinary pH was markedly acid prior to THAM, it became alkaline before the blood pH returned to normal. Correction of the acidosis did not relieve the shock state. The chief advantage of correction of the marked acid-base derangements in these patients would appear to be the gaining of time during which the usual therapeutic regimen of supportive therapy might correct underlying factors causing shock. In other studies in 12 patients with circulatory arrest a similar severity of acidosis was directly related to the difficulty of cardiac resuscitation. The use of intracardiac THAM here resulted in successful resuscitation in 9 of 12 where other measures had failed.[67]

A hydrogen ion acceptor like THAM that appears to traverse the cell membrane in the unionized form seems to be an ex-

cellent buffer. Since the body relies on sympathoadrenal stimulation when there is an immediate need for an increase in cardiac output, the greater increase in free energy change following administration of THAM could be very significant. Since the successful therapy of many emergencies frequently depends on the myocardial response to sympathomimetic amines, the recognition and correct treatment of acidosis are of crucial importance.

SUMMARY

Hyperglycemia and hypoxia acidosis are known to occur during periods of shock. The plasma levels of catechol amines have been reported to be elevated during periods of shock. Injection of epinephrine or levarterenol can produce increments in blood glucose. In the present studies the effects of reducing circulating blood volume or infusion of lactic acid or adrenal hormones and of forced CO_2 inhalation on ventricular isometric systolic tension (VCF) and the cardiovascular response to test injections of levarterenol were determined. The experiments with a reduction in circulating blood volume and with lactic acid infusions resulted in a decrease in arterial pH, whole blood total CO_2 and whole blood CO_2 combining power. Concomitant with these changes there was a marked depression of VCF and the response to test injections of levarterenol. Correction of the acid-base changes with 2-amino-2-hydroxymethyl, 1, 3-propane diol resulted in an immediate improvement in VCF and in the response to levarterenol. This change occurred despite a greater increase in blood lactate levels. Anaerobic metabolism with lactate production leads to a decrease in total blood CO_2 and an increase in dissolved CO_2. This decrease in the CO_2 carrying capacity would

lead to anincrease in tissue CO_2. Since the heart is markedly depressed by CO_2, this increment could be largely responsible for the myocardial depression. The oxygen debt which the heart can incur is thought to be limited. Therefore, the build-up of CO_2, one of the end-products of aerobic metabolism, would depress oxidative metabolism according to the law of mass action. This hypothesis was further tested by forced CO_2 ventilation which resulted in a marked depression of VCF and the response to levarterenol. Correction of the respiratory acidosis by the administration of THAM which increased the CO_2 carrying capacity of the blood resulted in an immediate improvement in VCF and the levarterenol response.

Acid-base derangements were studied in 10 patients with terminal shock from various causes. The metabolic studies included calculations of arterial pH, total CO_2, CO_2 combining power, and pCO_2. Blood samples were also equilibrated with a pCO_2 of 40 mm. of Hg and pH determined. There was a marked metabolic acidosis as a complication of this shock state. Death and metabolic profile were similar to those produced in the animal experiments. Again, a decrease in the vascular response to infusions of levarterenol was noted during the periods of acidosis. Correction of the metabolic

acidosis with an increase in the carbon dioxide combining power could be achieved with an organic buffer (THAM) and sodium bicarbonate. The vascular response to levarterenol was observed to increase in the patient as in the dog. The results seemed to indicate that death and shock may be due to a decrease in the ability of the blood to carry carbon dioxide, which leads to a build up of acid cellular products, CO_2 narcosis, and death.

The frequent substitution of levarterenol by other sympathomimetic amines in the therapy of shock might be advantageous. If hypotension has been present for any length of time prior to therapy, metabolic acidosis is often a complicating factor. Correction of this condition should improve cardiac contractibility and thereby overall cardiovascular function.

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