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A Study of the Influence of Acid-Base Changes on Myocardial and Vasopressor Responses to Arterenol and Epinephrine

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A STUDY OF THE INFLUENCE OF ACID-BASE CHANGES ON MYOCARDIAL AND VASOPRESSOR RESPONSES TO ARTERENOL AND EPINEPHRINE.

BY

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A thesis submitted to the Graduate School of the Medical College of the State of South Carolina in partial fulfillment of the requirements for the degree of Master of Science.

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OBJECTIVES.

It is well known that when the body is subjected to various stress conditions there is almost always a reflex release of certain neurohumoral substances in an attempt to compensate for these abnormal conditions. Acid-base changes, for example, are some of the most frequent occurring under these conditions. As mentioned throughout this thesis there is a direct correlation between acidosis and extreme hypotension or shock. The objective of these experiments was to investigate and determine the influence of acidosis on the cardiovascular response to the sympatho-adrenal hormones, arterenol and epinephrine, which are released in large amounts during shock.

These studies included: 1) the influence of metabolic acidosis on the responsiveness of the myocardium to epinephrine and arterenol, 2) the role of endogenous release of epinephrine and arterenol in contributing to metabolic acidosis and loss of responsiveness to these amines and 3) the production of acidosis by exogenous intravenous infusion of lactic acid, arterenol or epinephrine.

INTRODUCTION

Shock, a term often used by many clinicians to denote a syndrome and to describe a condition produced by various unrelated causes, is simply a term denoting the clinical symptoms of the patient. Because of the wide indiscriminate use of the term many investigators have attempted to classify shock as to its primary specific cause and these classifications, although still somewhat broad, have definitely narrowed the term down to a meaningful one. Some examples are cardiogenic shock, hemorrhagic shock, peripheral vascular failure shock, hypovolemic shock and many more. Therefore shock in itself is a symptomatic term and cannot adequately be used to describe a clinical syndrome but is a very significant and descriptive term when used specifically.

Clinically, before adequate treatment for a patient can be prescribed by the physician, the underlying causes for the particular disease have to be determined, and shock, although not considered a disease but as a product of chronic disease or some acute malfunction, is no exception. There are no consistent pathognomonic signs in shock (1), therefore for correct diagnosis it is almost always necessary to consider first the general symptoms

and then determine one by one the specific mechanism which is evident for any one specific type. In obvious hemorrhagic shock the treatment can be determined immediately as being that of blood replacement therapy, elimination of the cause of hemorrhage and normal supportive therapy. Some types of hemodynamic shock however may have many similar clinical symptoms but still have different manifestations which may alter treatment considerably. Therefore, it is essential to determine the specific cause of shock in each clinical case if ideal therapy is to be accomplished.

The diagram of the circulatory system in figure I illustrates various clinical conditions which may produce states of shock and their effect on the hemodynamics of the cardiovascular system. As can be seen from table I more than one specific cause may be listed under any specific group heading - exemplified by hypovolemia which may be caused by 1) hemorrhage, 2) dehydration, 3) loss of protein, 4) capillary leakage and so on. Table I classifies the six specific causes of shock illustrated in figure I.

In hypovolemia a critical point is reached when the volume of blood present in the circulatory system is no longer adequate to fill the vascular bed; as a consequence the arterial blood pressure is lowered due to a

Table I.*

Clasification of Specific Causes of Shock

1. Hypovolemia
   Hemorrhage, dehydration, loss of protein

2. Cardiac failure
   Myocardial infarction, cardiac dysrhythmia

3. Hypersensitivity
   Anaphylaxis, reaction to drugs

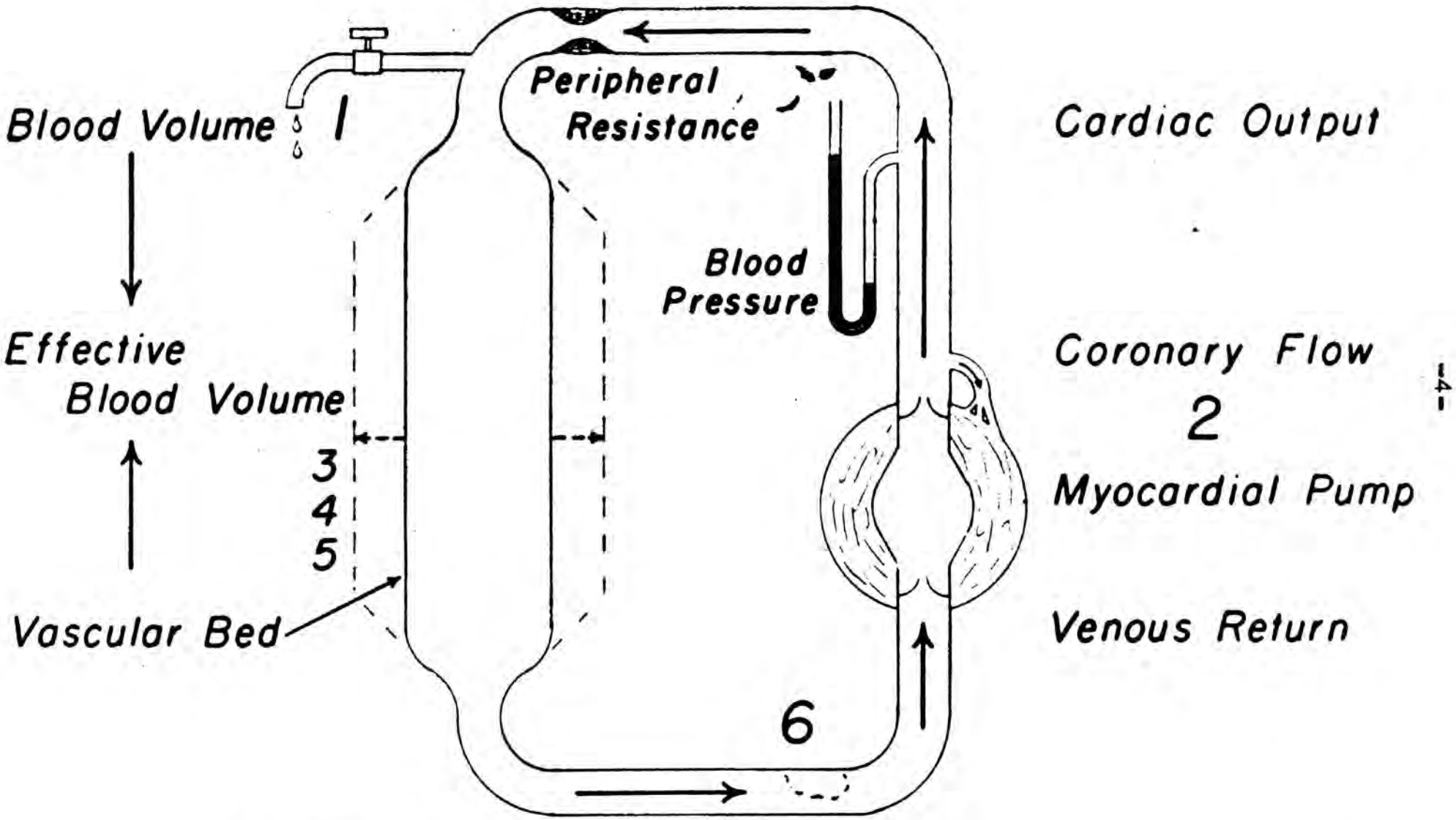
4. Bacteremia
   Bacterial toxins (endotoxin)

5. Neurogenic factors
   Vasomotor paralysis, spinal shock, ganglionic blockade

6. Impediment to blood flow
   Pulmonary embolism, dissecting aneurysm

* Circulation 16: 1098, 1957

Figure 1*



Schematic of the circulatory system indicating the six main defects causing Shock.

* Circulation 16: 1098, 1957.

decrease in venous return and cardiac output. A late secondary feature is myocardial ischemia as evidenced by electrocardiographic changes attributed to coronary insufficiency. The myocardial ischemia may lead to defective myocardial contractility causing the cardiac output to decline further and thereby cause the arterial pressure to fall even lower. From the diagram in figure I it is evident that two vicious cycles are present due to the above mentioned hemodynamic features brought about by a reduction in effective volume of circulating blood. One is related to the pooling of blood as in shock produced by hypersensitivity, bacteremia and neurologic factors. The other is propagated by a gradual increasing degree of coronary insufficiency which is the terminal outcome of each of the specific causes listed in table I.

In heart failure due to myocardial infarction the heart fails as a pump causing a severe reduction in cardiac output sometimes producing shock (2). The failure of the heart to pump an adequate volume of blood into the circulatory system leads to peripheral vascular collapse which aggravates the condition by producing a further decrease in an already diminished coronary flow. It has been known for some time that the circulating blood volume is not significently reduced in myocardial infarction in man (3), although as mentioned above the cardiac output is decreased. Although myocardial infarction is

the cardiac condition most frequently accompanied by shock there are other cardiac conditions that produce acute circulatory failure such as : 1) tachycardia, 2) terminal phases of chronic congestive heart failure, 3) acute coronary insufficiency, 4) cardiac tamponade, 5) dissecting aneurysm of the aorta, 6) aortic aneurysm, 7) arterio venous fistula and 8) ball valve obstruction of the mitral orifice (4).

Shock due to hypersensitivity reactions are not at the present time completely understood. It is thought to be mainly the result of sudden constriction of small hepatic veins followed by pooling of large quantities of blood in the portal venous bed, which leads to sudden reduction in venous return and cardiac output (5). Therefore the initial hemodynamic action of shock due to hypersensitivity is very similar to bacteremic shock (6-8) followed by the secondary hemodynamic action of coronary insufficiency as explained above.

Impediment to blood flow, such as that encountered in pulmonary embolism and dissecting aneurysm, may produce physical obstruction of a main vessel so that circulation is lessened due to the inadequate blood flow. Consequently, venous return and cardiac output are insufficient and a state of shock persists.

The value of pressor amines in the treatment of shock has been recognized for some time. The choice of the

drug for therapy indeed requires experience and sufficient knowledge of the pharmacologic action and physiologic effect of the drugs available. For example, in cardiogenic shock, arterenol or metaraminol would be preferred over phenylephrine or methoxamine. Although all four of these drugs are pressor agents, only arterenol and metaraminol possess the additional wanted characteristic of increasing the contractile force of the heart (9). In hypovolemic shock such drugs alone are insufficient and treatment must be aimed at restoring the effective circulating blood volume with blood or a substitute which will expand blood volume (10).

Previous work from this department (11) shows that the ability of some of the sympathomimetic amines such as arterenol to increase heart contractile force is an important basis for their use in shock accompanying myocardial infarction. Other investigators (12) have shown that the beneficial effects of metaraminol, although due in part to increased coronary flow accompanying the increase in blood pressure, are also due to an increase in myocardial contractile force.

In anaphylactic type shock epinephrine is the drug of choice because of its ability to dilate the bronchiole in addition to increasing the heart contractile force, cardiac output and blood pressure. Epinephrine has

also long been the drug of choice in cardiac arrest, although generally it is of little practical value (13).

Vasopressor drugs are seldom indicated in shock due to hypovolemia or impediment to blood flow and are only used as a support to fluid replacement therapy. Normal volumes of fluid are re-established by the use of blood, plasma and electrolytic fluids. If shock perisits after fluid therapy it is possible this secondary shock is due to a pooling of blood or myocardial failure. This is sometimes wrongly referred to as irreverible shock because vasopressor agents may be helpful. Further vasoconstriction in shock due to impediment to blood flow is of little or no value unless, of course, complications arise that necessitate an increased vasoconstriction. Actually isoproterenol, a powerful cardiac stimulant and a systemic vasodilator (14-15) may be of value in cardiogenic shock as an adjunct to arterenol (16). In this case isoproterenol produces a decrease in reflex vagal slowing and pressor effect. Therefore, as indicated with isoproterenol, an increase in the cardiac stimulatory action and heart rate alone, even with a slight decrease in arterial blood pressure, has proven useful in some types of shock, since it is the blood flow and not the blood pressure that is responsible for oxygenation and removal of metabolites from tissue.

Even though the pressor amines have been used favorably in shock therapy, there are many factors limiting

the effectiveness of pressor activity. Some of these possible reasons have been discussed by Eckenhoff and Dripps (17) such as inadequate dose, failure of drug to reach its site of activity, heart failure, hypovolemia, mechanical blockage of blood flow, and failure of the vascular smooth muscles to contract. Hormones, electrolytes and acid-base balance play an important role in the progression and treatment of shock. Many investigators have shown that the corticosteroids (18-20) and thyroid hormones (21) potentiate the vasopressor and cardiac stimulant action of epinephrine and norepinephrine in animals and humans. These findings are related to potassium depletion from the heart and vessels that respond to arterenol (22-24) which seem to indicate there is a possible interference with organ cationic shifts when there is a depletion of the corticosteroids causing the sympathomimetic amines to become less active.

Other workers have reported that acid-base imbalance, particularly acidosis, has a profound influence on the cardiovascular response to some of the pressor amines. Burget and Visscher (25) noted that the adrenalin response of the vascular system of the pithed cat may be made to vary at any time by varying the pH of the blood from 6.7 to 8.0 - the response progressively increased with an increase in pH. These investigators attributed

the increased response either to an increased irritability of the sympathetic nervous system or to the possibility that the adrenalin is oxidized more rapidly and completely thereby constituting a stronger stimulation at its seat of action. More recently other investigators (26,27) have investigated the effect of respiration on the pressor action of epinephrine and norepinephrine and have shown that in the presence of respiratory acidosis the pressor response to injections of norepinephrine and epinephrine were decreased.

Previous studies from this laboratory by this investigator and associates have shown a reduction in the responsiveness to arterenol in patients following total cardio-pulmonary bypass for surgical correction of congenital abnormalities. It was mentioned earlier that certain reflex mechanisms attempt to compensate for physiological conditions other than those which normally occur. This is exemplified by the initial hypotension and decreased myocardial contractility usually accompanying bypass procedures. These abnormal conditions are thereby partially compensated for by sympatho-adrenal releases. The more recent studies presented in this thesis attempt to establish some of the metabolic changes that occur as a result of these neurohumoral compensatory mechanisms.

EXPERIMENTAL

Methods.

The following groups of experiments were conducted in 46 healthy mongrel dogs weighing 8 to 13 kilograms.

Group I 17 lactic acid intravenous infusions with sympathetic blockade in 5.

Group II 16 epinephrine or arterenol intravenous infusions with sympathetic blockade in 5.

Group III Epinephrine or arterenol intravenous infusion in 5 closed chest animals.

Group IV 8 azygos flow experiments.

Groups I, II and IV were performed in open chest animals.

Moderate anesthesia was produced with 10 mg/kg morphine injected subcutaneously followed in 30 minutes by 15 mg/kg of sodium pentobarbital. Additional sodium pentobarbital was administered as necessary in order to maintain anesthesia. Respiration and left carotid blood pressure (BP) were measured with Statham transducers and recorded by a Sanborn Poly Viso, Model 154 amplifier-recorder. The open chest animals were mechanically respired with atmospheric air under positive pressure. The contractile force (CF) of the heart was measured with the strain gauge arch described in detail in previous publications(28-31) and recorded along with blood pressure and respiration by the Sanborn machine mentioned above. The strain gauge arch was sutured directly to the myocardium of the right ventricle

with approximately 50 percent stretch of the segment of the muscle between the two legs of the arch producing an initial tension of 75 to 100 grams above end diastolic tension. The contractile force changes measured and recorded were those produced by neurohumoral stimulation of the myocardium, Starlings law changes being insignificant because of the 50 percent increase in initial diastolic length.

A polyethylene catheter was inserted in the right femoral artery for withdrawing blood samples to determine pH values with a Beckman pH meter, Model G, and pCO_2 values with a Van Slyke manometric blood gas apparatus (32-34). Additional polyethylene catheters were placed in the right and left femoral veins, one for drug injection and the other for drug infusion from a drip apparatus connected to a salvarsan tube. A tracheotomy was performed and a T tube inserted with a screw clamp on one of the exposed ends to regulate respiration and the respirator connected to the other open end to supply the respiratory gases. In some of the experiments the chest was closed and the animal allowed to respire through his own efforts.

Sympathetic preganglionic block was performed by inserting three polyethylene cannulae into the epidural space advancing one to the sacral, thoraco-lumbar and cervical region of the spinal cord respectively. The

epidural space was then flooded with 30 cc of .05 percent tetracaine at 20 minute intervals until the animals sympathetics were blocked, this being evident when no change in blood pressure or contractile force accompanied epidural injection. Azygos flow was induced by occlusion of the superior and inferior vena cavae, accomplished by inserting umbilical tape around the vena cavae through individual rubber tubes which were depressed lightly against the vessels and held in place by hemostats holding the tapes securely against the open ends of their respective rubber tubings.

RESULTS AND DISCUSSION

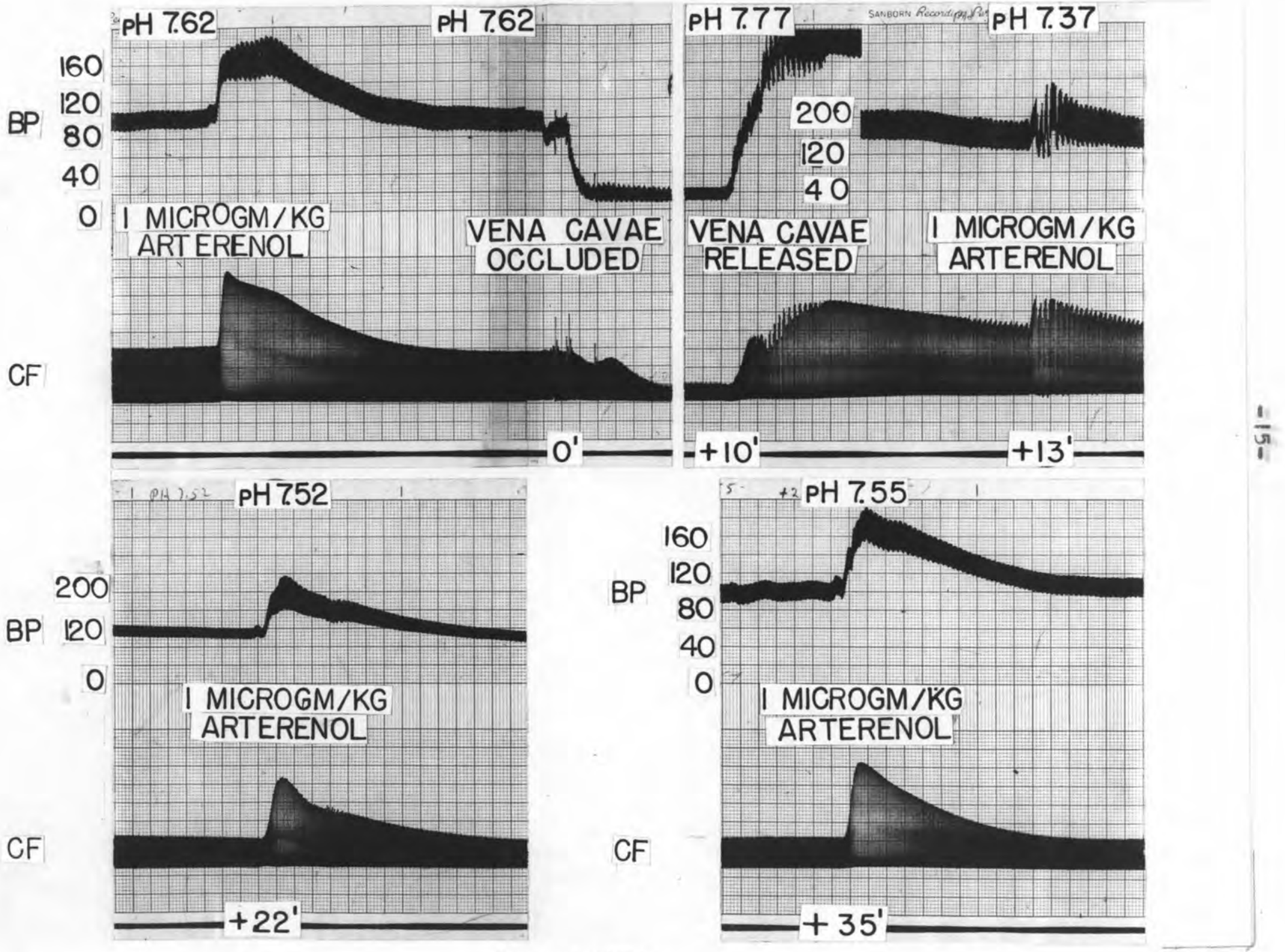
The following three groups of experiments were designed to further investigate some previous work by this author and associates (35) in an attempt to illuminate some of the factors contributing to acid-base derangement under various stress conditions.

Group I - Azygos Flow

A group of eight azygos flow experiments was conducted to produce a large endogenous release of catechol amines as reported by Woods and associates (36). By using the method described previously the total venous return was reduced by approximately 80 percent during azygos flow. The venous return being solely that from the coronary and azygos veins produced a decrease in cardiac output to approximately 20 percent of the normal output. This situation of decreased cardiac output during azygos flow experiments simulated low flow rates during cardio-pulmonary bypass (35,37) enabling further study in this field. Studies by Pontius and associates (38) have shown arterial pH to be directly proportional to total body perfusion flow rates during cardio-pulmonary bypass. They further indicated this acidosis may be of a metabolic nature.

Fig. 2 is a typical illustration of results from a dog

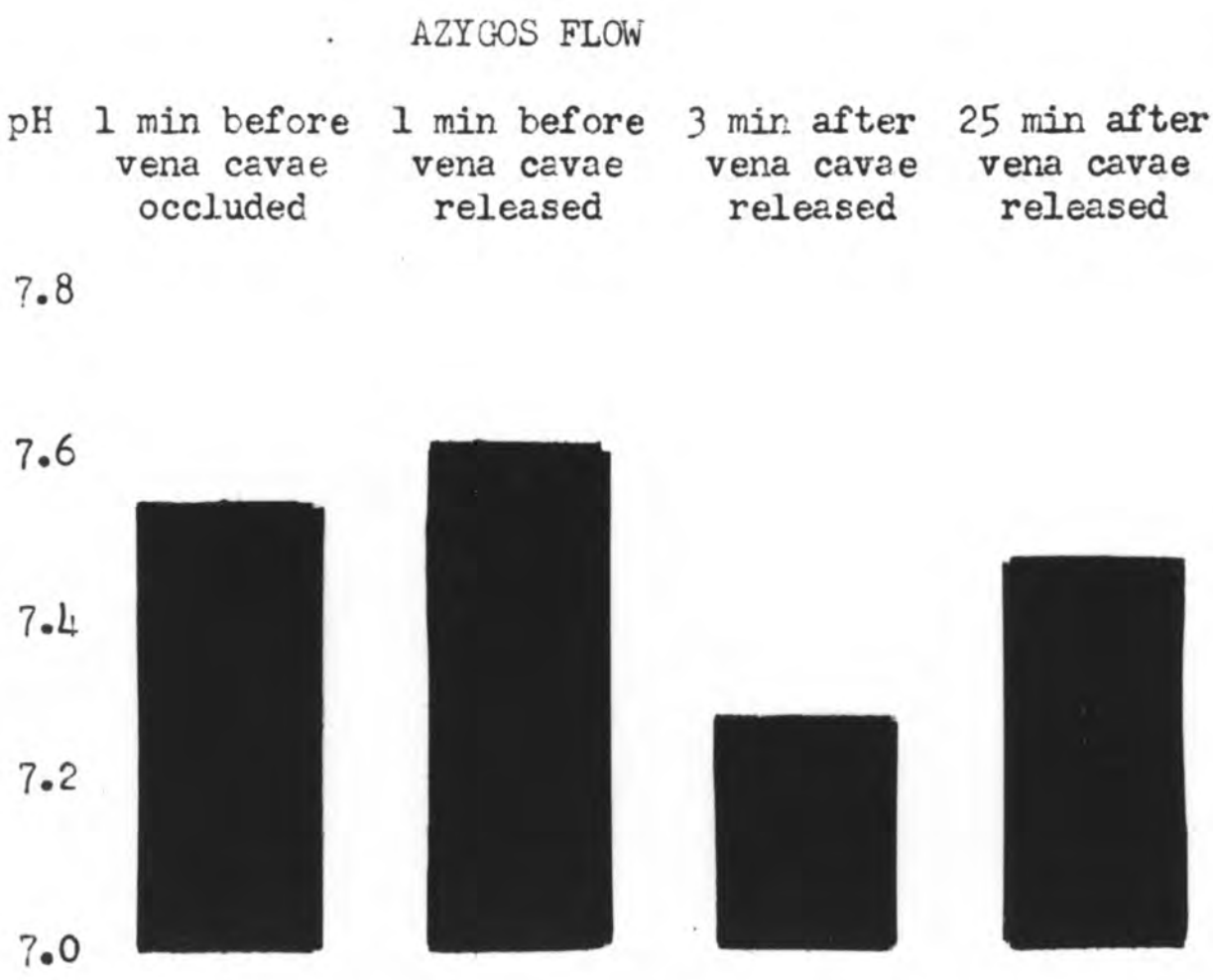
Figure 2.



Azygos Flow.

subjected to azygos flow. During the control period, pH 7.62, a test dose of arterenol was administered producing a normal response. However, during azygos flow there was no response to injected arterenol. This lack of responsiveness may be caused by the high degree of myocardial ischemia as brought out later in the discussion of figure 4. Even though there are large amounts of catechol amines present (36) they are physiologically inactive, possibly due to the above mentioned ischemia produced by the tremendous diminution in coronary blood flow. Upon releasing the vena cavae there is a great increase in venous return and coronary blood flow containing large quantities of oxygen and catechol amines thereby producing the marked positive inotropic and blood pressor response shown at plus 11 minutes. At plus 13 minutes the animal is relatively refractive to an injection of arterenol. This refractiveness is possibly caused by two factors: 1) increased catechol amine levels and 2) the decrease in arterial pH from 7.62 to 7.37 presumably due to the increased circulating catechol amines as indicated in the discussion of the experiments performed in group 2. The catechol amine and pH levels at plus 35 minutes have almost returned to the control level. Consequently, the blood pressure and contractile force responses to 1 microgm/kg is relatively normal. Figure

Figure 3.



This graph shows average pH changes during and after azygos flow in eight experiments ($P > .01$).

3 is a graph showing the changes in pH occurring during the above eight experiments.

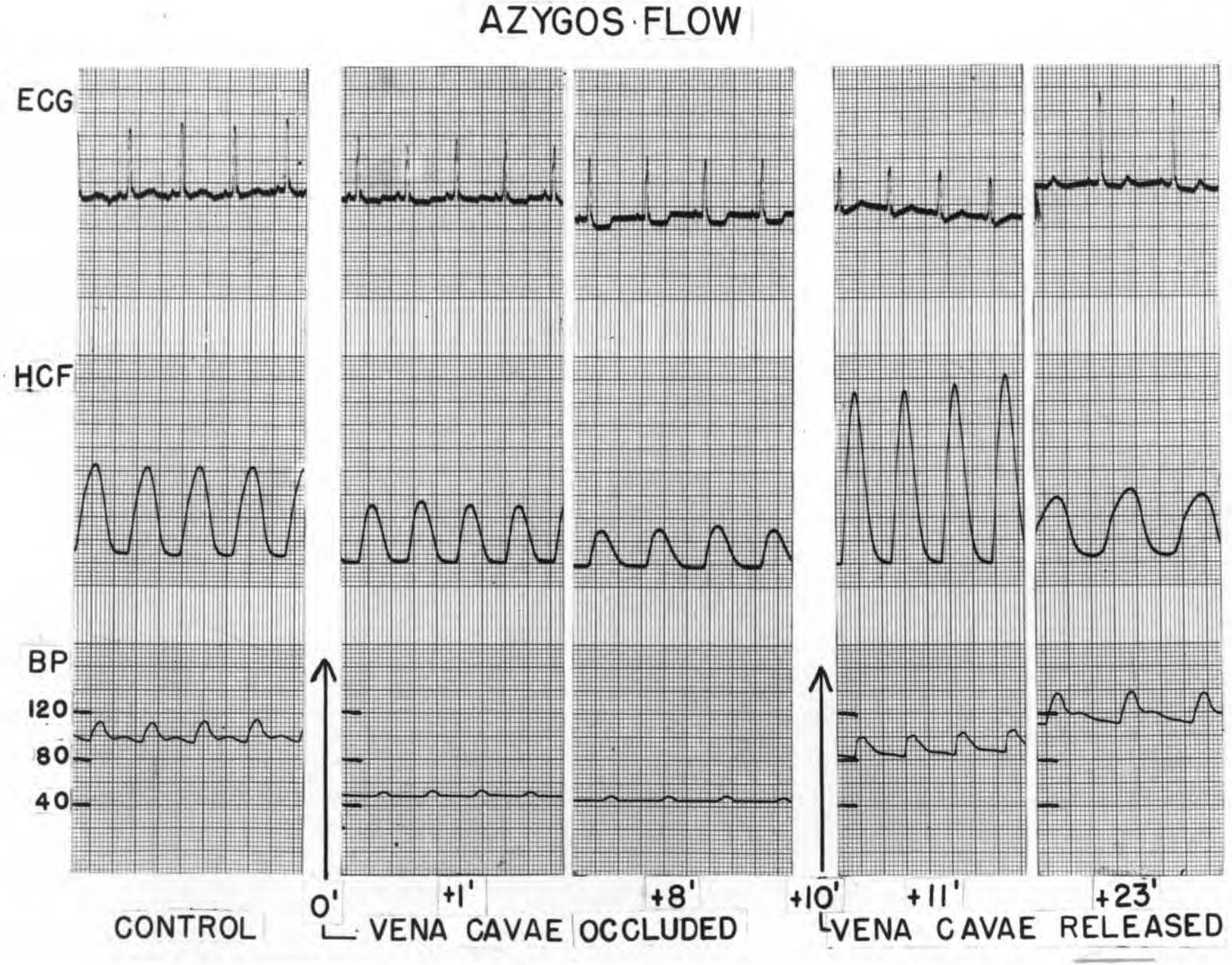
Figure 4 is an illustration of a tracing produced at a fast recording speed (25 mm/sec). An electrocardiogram is recorded in addition to contractile force and blood pressure. It is evident from the electrocardiogram recording that during azygos flow myocardial ischemia is present as indicated by the pronounced S-T depression at plus 8 minutes. As explained earlier this is presumably due to the diminished venous return and cardiac output leading to a decreased coronary flow. Consequently this produces a relative hypoxia and build up of metabolites within the tissues of the myocardium.

To rule out any major role of right atrial stretch receptors being responsible for the "rebound" phenomenon following release of the vena cavae in the above group of experiments, three additional experiments were performed. These experiments indicated that reflex action from increased right atrial pressure contributed only a small part of the total increase in contractile force after release of the vena cavae. This has also been shown by Cotten (31) without the benefit of azygos flow.

Group 2 - Catechol Amine Infusion

Arterenol or epinephrine was infused in sixteen dogs to determine the ability of these catechol amines to

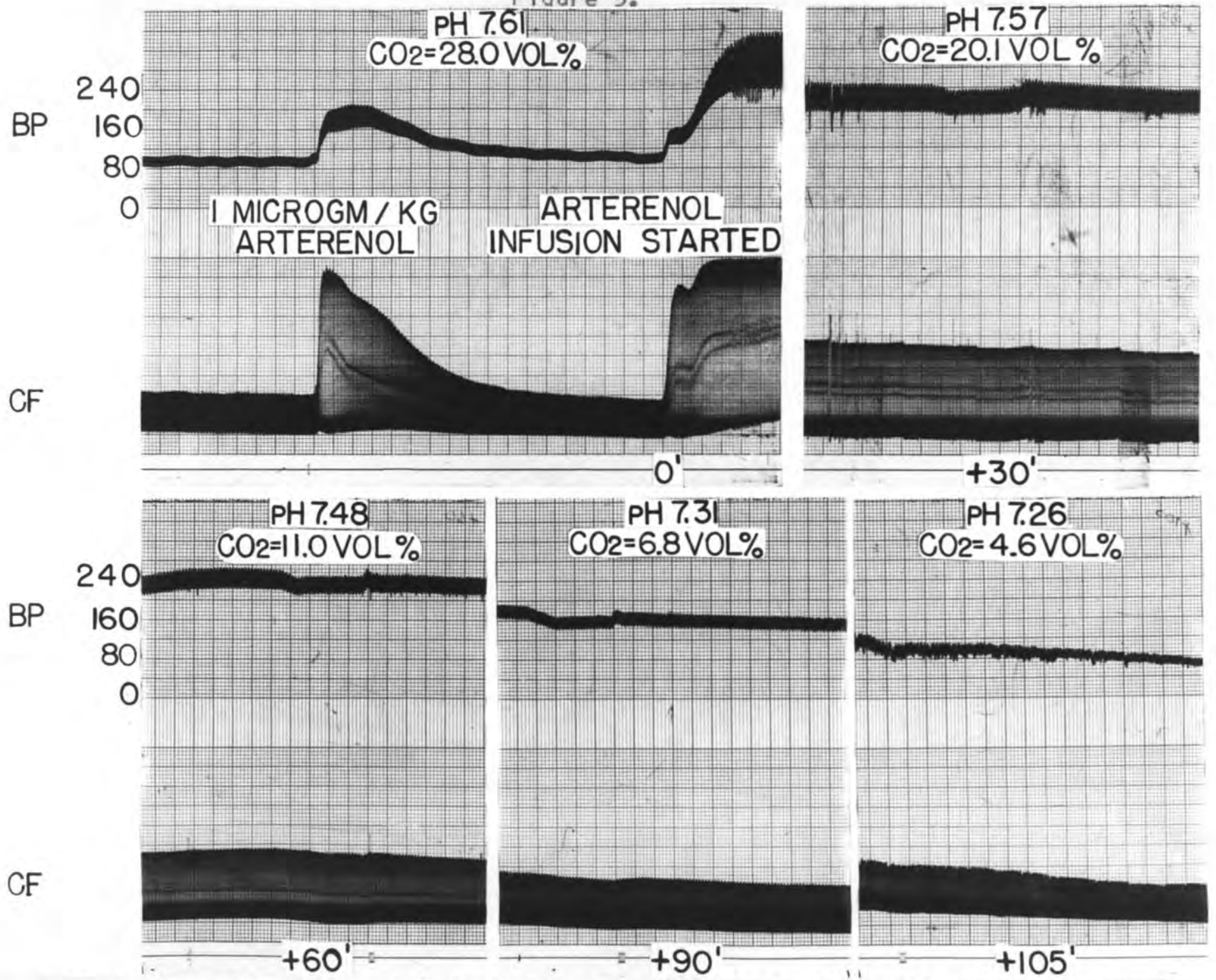
Figure 4.


AZYGOS FLOW
ECG
HCF
BP
120
80
40
0'
+1'
+8'
+10'
+11'
+23'
CONTROL
VENA CAVAE OCCLUDED
VENA CAVAE RELEASED

produce acidosis and cardiovascular refractiveness to injected catechol amines. The sympathetics were blocked in ten of these animals (See Methods). There was no significant difference in experimental results between the animals with sympathetic blockade and those without. In the blocked animals intravenous arterenol or epinephrine infusions raised sympathetic tone to and maintained it at control levels by dripping the amines at a rate determined by blood pressure and contractile force observations. A further increase in infusion rate will increase the sympathetic tone just as in the unblocked animal. According to Bulbring and Burn (39) sympathetic tone seems to be absent when a norepinephrine drip is stopped, perhaps because of ganglionic blockade. Therefore an infusion of catechol amines will decrease to a very minimum all normal sympathetic release.

During the discussion of the azygos flow experiments it was mentioned that large quantities of catechol amines may possibly be the cause of a relative acidosis following release of the vena cavae. Figure 5 illustrates this ability of arterenol to produce acidosis. The control tracing shows the pH to be 7.61 and the plasma CO_2 combining power 28.0 volumes percent. It is evident in further recordings at thirty minute intervals that the animal becomes progressively acidotic during

Figure 5.

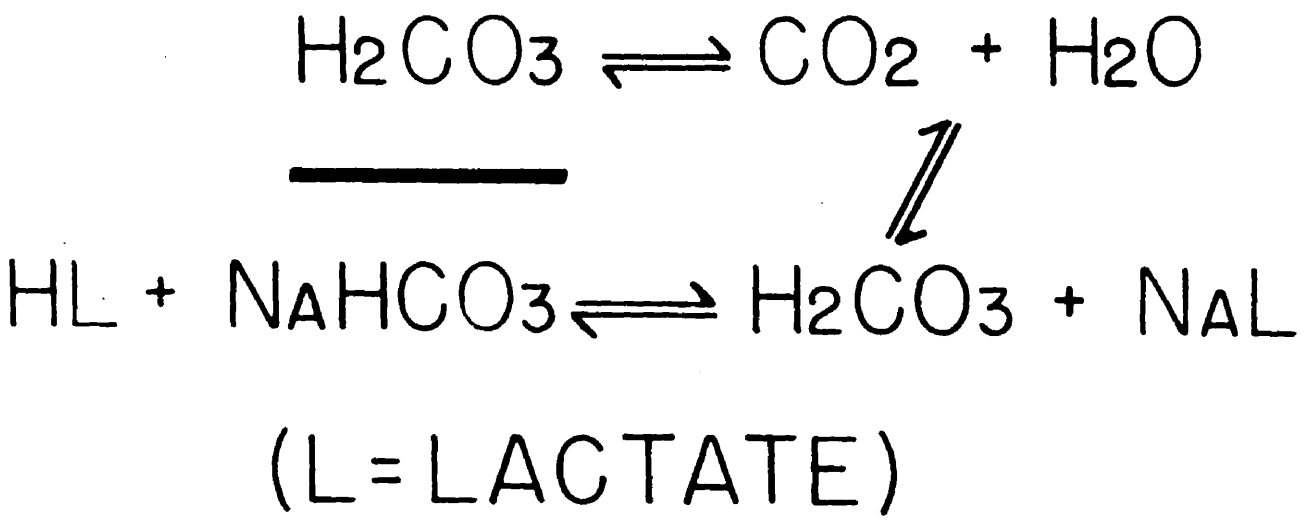


Effect of rapid arterenol infusion on arterial blood pH and CO_2 combining power.

infusion of arterenol. A total of 31.5 mgm of arterenol was infused during an hour and thirty five minutes (25 microgm/kg/min average) at a continuously increasing rate in order to try to maintain a relatively high vasopressor and positive inotropic response. The animal became completely refractory to the infusion at the end of ninety minutes. The final recording, plus 105 minutes, shows a decrease in pH and CO_2 combining power to 7.26 and 4.6 volumes percent respectively.

This acidosis accompanying the infusion of arterenol may be attributed to a build up of lactic acid within the tissues. According to Lundholm (40), lactic acid is removed from the body tissues as shown in figure 6. Lactic acid accumulates in the tissues and combines with sodium bicarbonate in the carbonate buffer system producing sodium lactate and carbonic acid which liberates carbon dioxide. The carbon dioxide diffuses into the blood stream and in turn is released through respiration. It is evident that the sodium bicarbonate can only combine with so much lactic acid to produce sodium lactate and carbonic acid. When the available sodium ions are depleted the lactic acid builds up within the tissues producing a metabolic acidosis. At this point the acidosis is further potentiated by the loss of sodium bicarbonate and increase in carbonic acid.

Figure 6.

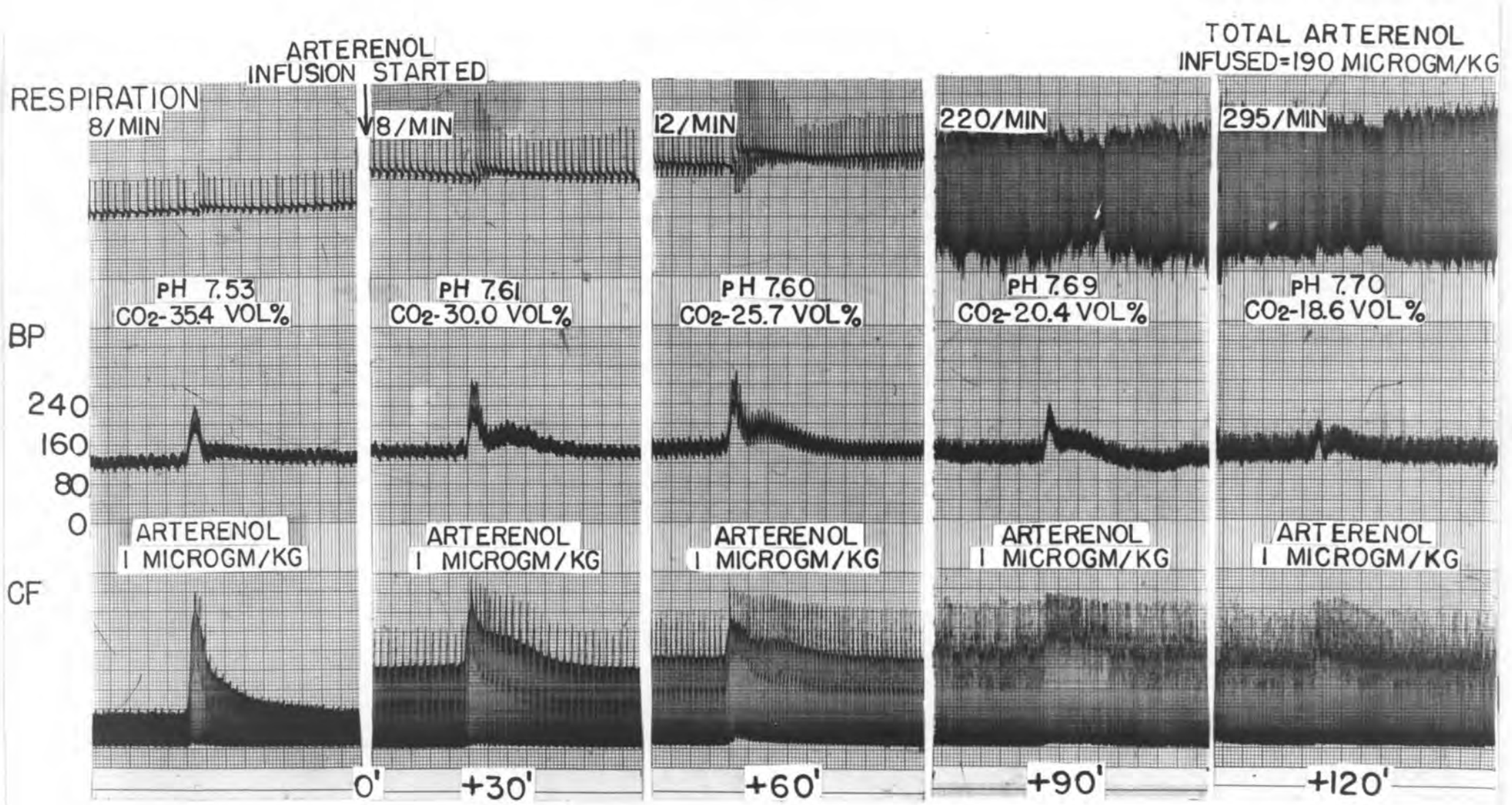


This figure illustrates Lundholm's theory of lactic acid breakdown and its removal from the body at the expense of sodium bicarbonate in the carbonate blood buffer system.

From the discussion of figure 6 it can be said that the compensatory mechanisms mentioned above are taking place during arterenol infusion. In figure 5 there was a decrease in pH with a concomitant fall in plasma CO_2 combining power. This decrease in CO_2 combining power may possibly be due to sodium depletion in an attempt to compensate for the metabolic acidosis being produced. This experiment, along with the rest in this group, was conducted in an open chest animal thereby producing a rapid acidosis due to the build up of carbon dioxide along with lactic acid. The reason for this is that the increased carbon dioxide production is not compensated for by an increase in respiration such as would occur if the animal were able to respire through his own efforts.

The above sixteen experiments were compared with five other experiments in which the chest was closed and the animals allowed to respire without the help of positive pressure respiration. In this way the animals could compensate for the increased carbon dioxide by an increase in respiration as shown in figure 7. In this experiment the animal received an average of 1.6 microgm/kg/min for a period of two hours with the infusion rate being increased as necessary to maintain a constant elevation in contractile force throughout the experiment. The control pH was 7.53 and after two hours of arterenol infusion it had risen to 7.70. This rise in pH may be attributed to

Figure 7.



Effect of slow arterenol infusion on arterial blood pH, CO_2 combining power and respiration.

respiratory over-compensation which is evident by: 1) the tremendous increase in respiration from 8 to 295 per minute and 2) the decrease in plasma CO_2 combining power of 35.4 volumes percent at control to 18.6 volumes percent at the end of two hours. A study of figure 6 will review the metabolic and respiratory processes having taken place.

As the arterenol infusion progresses the myocardium and the overall peripheral vascular system becomes more and more refractive to injected doses of arterenol. Obviously this refractiveness is not caused by a decrease in pH or acidosis but probably is caused by an increased level of circulating arterenol. Possibly toward the end of the infusion there is a tendency toward intracellular metabolic and respiratory acidosis because of the more rapid build up of lactic acid and the increasing diminution of sodium as shown by the continuous decline in plasma CO_2 combining power.

The hematocrit was found to increase progressively during the arterenol infusion. This seemed to indicate a loss of circulating plasma volume and may possibly be due to electrolyte shifts accompanying compensatory measures. Studies are planned to evaluate the possibility of sodium diffusing into the intracellular spaces taking fluid along with it thereby decreasing the circulating blood volume. Scholz (41) has shown an increase in hematocrit with

adrenalin infusion. He attributes this to either or a combination of: 1) a loss of plasma into the tissue, 2) a release of red blood cells from the spleen and splanchnic area or 3) withdrawal of plasma into the surface films in small vessels by vasoconstriction. More recently Rosenthal and DiPalma (42) ruled out an increase in red blood cells liberated by the spleen. They consistently found a continuous rise of the hematocrit in normal as well as spleenectomized dogs during three hours of arterenol infusion. Therefore from other reports and the present findings in this investigation, the loss of circulating plasma volume may possibly play an important role in the development of cardiovascular refractiveness to catechol amines.

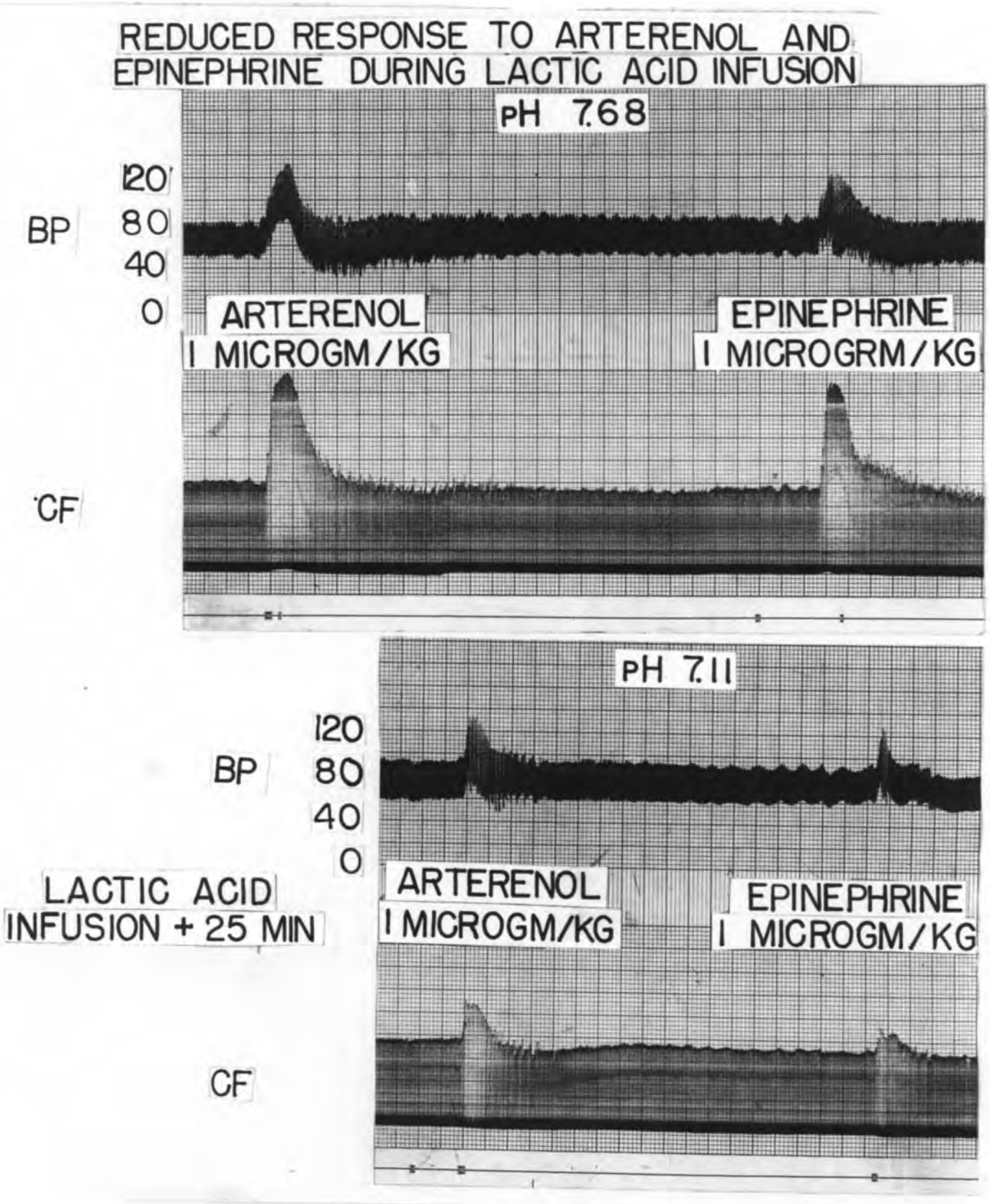
Nickerson (43) has reported that following 2 microgm/kg/min of arterenol infused over a period of four hours only one of eleven dogs survived although some recovered for as long as forty eight hours. Gross hemorrhage of the lungs and intestine was observed upon autopsy. Other investigators have shown this hemorrhage phenomenon (44), myocardial changes (45) and serum transaminase changes (46) to take place after large doses of catechol amines. Maling (46) found in her experiments that the serum glutamic oxalacetic-transaminase was elevated which indicated myocardial and possibly skeletal muscle damage rather than hepatic damage.

Group 3 - Lactic Acid Infusion

In order to produce acidosis in a group of seventeen experimental animals, lactic acid was infused into the femoral vein. Lundholm (40) postulates lactic acid has a twofold effect in the production of acidosis: 1) it supplies hydrogen ions and 2) the concentration of lactic acid in the blood is increased, therefore increasing the concentration gradient between the blood and the tissues. This caused a decrease in the rate of lactic acid diffusion from the tissues into the blood, the rate of diffusion being directly proportional to the concentration gradient. Under normal conditions lactic acid is continually being produced by the muscle systems of the body. Ordinarilly the body easily compensates to maintain an equilibrium between the amount of lactic acid produced and the amount leaving the cells by diffusion. However, during stress states such as shock, tremendous amounts of lactic acid are produced in the tissues due to an increase in sympathetic activity attempting to maintain homeostasis. During this period of compensation there is always a tendency toward respiratory as well as metabolic acidosis - refer to figure 6.

Burget and Visscher (25) have shown a fall in the adrenalin pressor response of the pithed cat when the pH is decreased. In figure 8 a decrease in the pressor

Figure 8.

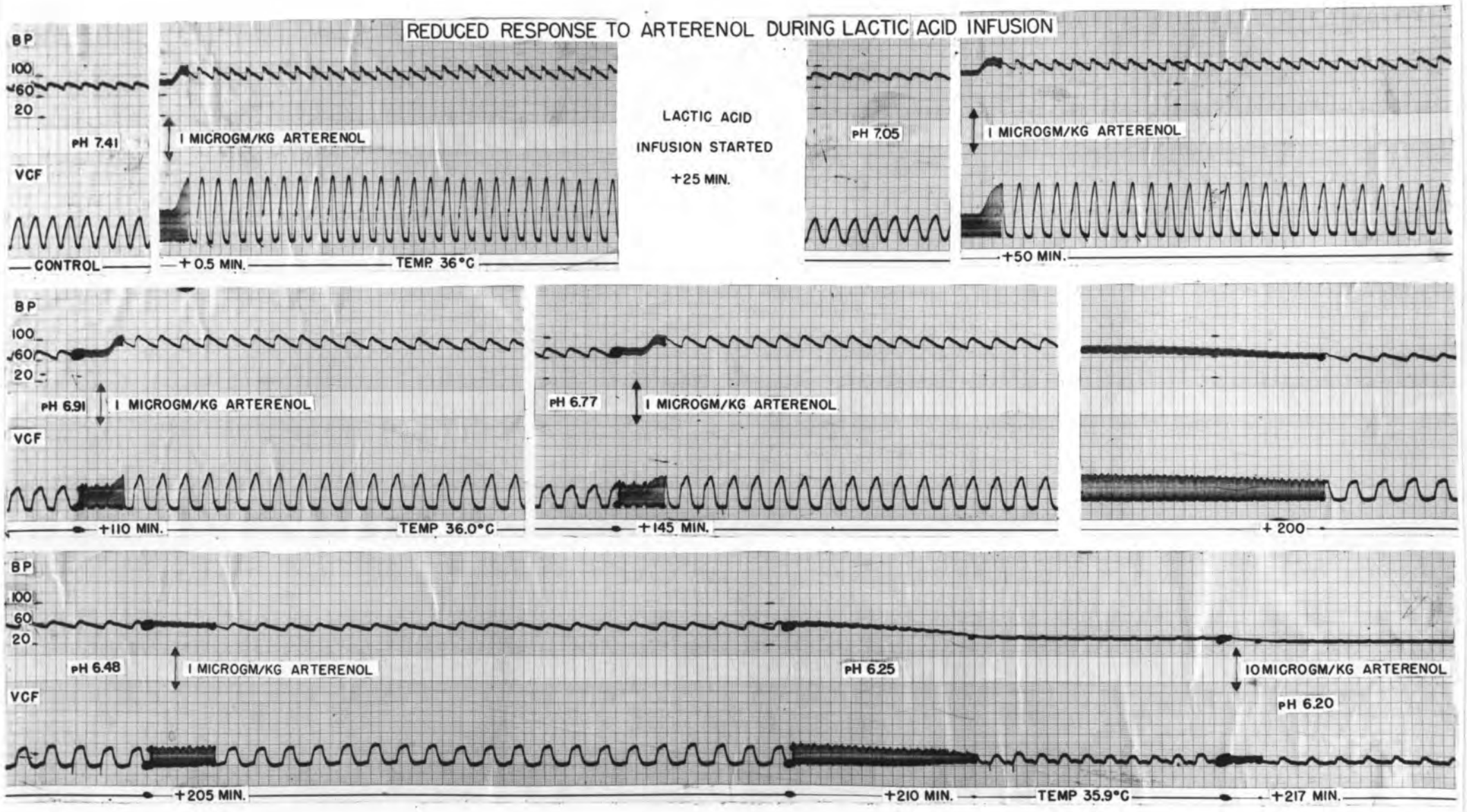

REDUCED RESPONSE TO ARTERENOL AND EPINEPHRINE DURING LACTIC ACID INFUSION
pH 7.68
120
BP 80
40
0
ARTERENOL
1 MICROGM/KG
EPINEPHRINE
1 MICROGRM/KG
CF
pH 7.11
120
BP 80
40
0
LACTIC ACID
INFUSION + 25 MIN
ARTERENOL
1 MICROGM/KG
EPINEPHRINE
1 MICROGM/KG
CF

response to arterenol and epinephrine is evident during infusion of lactic acid. There is a concomitant decrease in the positive myocardial inotropic response which is much more pronounced than the reduced pressor response. There is no concrete explanation for the greater percentagewise refractiveness of the myocardium. This may possibly be attributed to the intrinsic ability of the smooth muscle of the blood vessels to tolerate stress to a higher degree than the myocardium. Referring to the experiments in group I this is particularly well illustrated in figure 2, a typical azygos flow experiment. This diminution in responsiveness has also been shown by Darby and associates (37).

Figure 9 is an illustration of a high speed tracing, 25 mm/sec, of an arterenol response during lactic acid infusion. This shows a similar decrease in vasopressor and myocardial contractile force response as in figure 8 along with a continuous decrease in heart rate. Weil and associates (27) have reported a similar effect on the pressor responses of epinephrine, norepinephrine and metaraminol during respiratory acidosis. Apparently there have been no reports correlating the effect of acidosis on the myocardial contractile force response to the adrenal hormones.

In animals with preganglionic sympathetic blockade, lactic acid infusion produced death almost

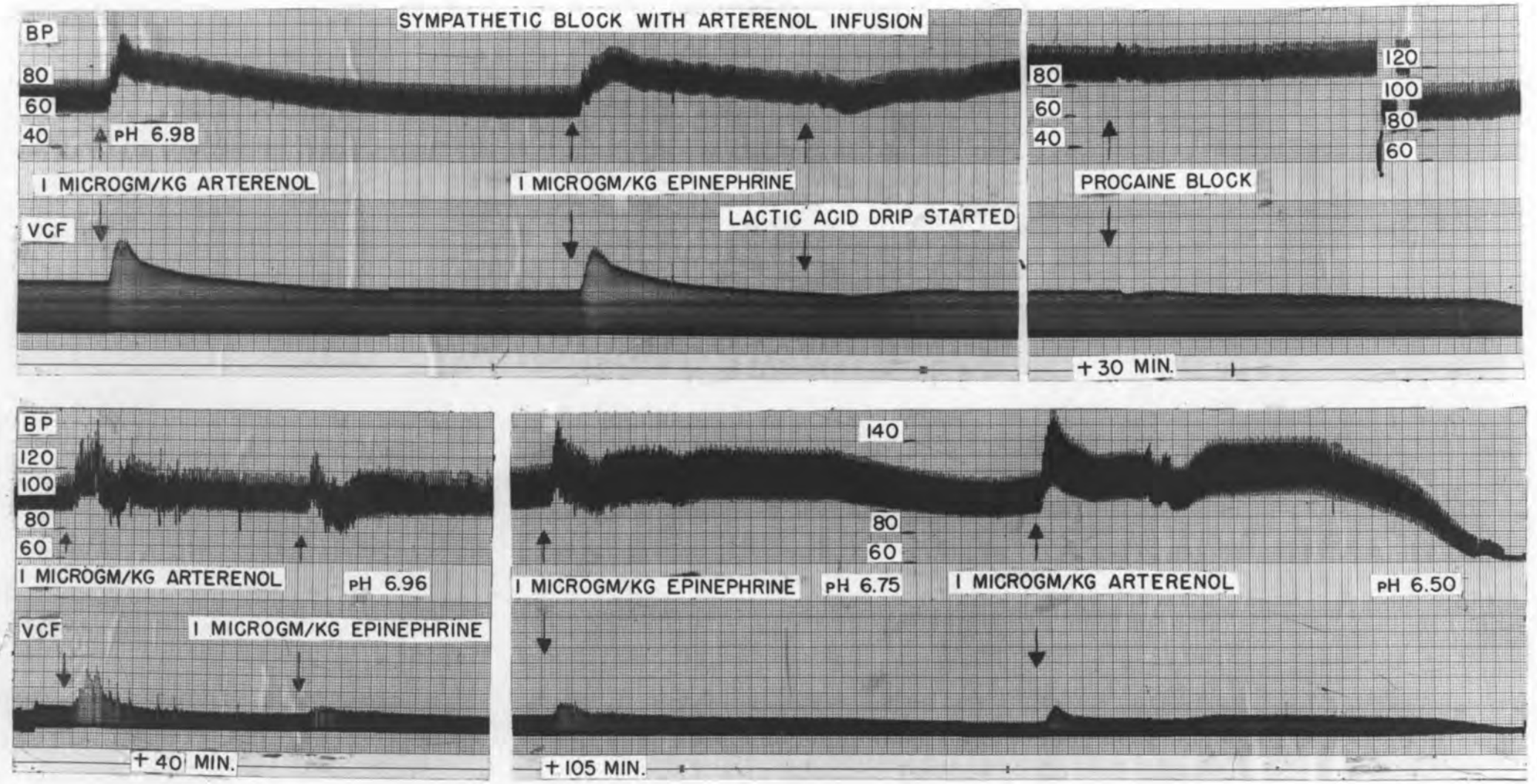
Figure 9.


REDUCED RESPONSE TO ARTERENOL DURING LACTIC ACID INFUSION
BP
100
60
20
pH 7.41
VCF
CONTROL
1 MICROGM/KG ARTERENOL
+0.5 MIN.
TEMP 36°C
LACTIC ACID
INFUSION STARTED
+25 MIN.
pH 7.05
1 MICROGM/KG ARTERENOL
+50 MIN.
BP
100
60
20
pH 6.91
1 MICROGM/KG ARTERENOL
VCF
+110 MIN.
TEMP 36.0°C
pH 6.77
1 MICROGM/KG ARTERENOL
+145 MIN.
+200
BP
100
60
20
pH 6.48
1 MICROGM/KG ARTERENOL
VCF
+205 MIN.
pH 6.25
+210 MIN.
10 MICROGM/KG ARTERENOL
pH 6.20
TEMP 35.9°C
+217 MIN.

immediately indicating a need for compensatory sympathetic release during acidosis. This demand for adrenal hormones was further substantiated in five additional experiments in which vascular tone was maintained with infusions of one of the sympathomimetic amines, epinephrine or norepinephrine, after endogenous release of these amines was terminated by preganglionic sympathetic blockade. In these experiments the animals did not develop refractiveness to the amines until the terminal stages of the experiment. This loss of responsiveness of the cardiovascular system to the adrenal hormones during lactic acid infusion appears to be twofold: 1) the acidosis produced by increased hydrogen ion concentration brought about by both lactic acid infusion and production and 2) the increase in circulating catechol amines due to compensatory release by the adrenal glands and sympathetic nervous system. Page and Olmsted (26) have shown that the onset of vascular refractiveness to sympathomimetic amines in dogs respired with high concentrations of carbon dioxide is completely prevented only by total sympathectomy.

A typical experiment in this group, figure 10, illustrates the effect of lactic acid infusion on the arterenol responsiveness of a blocked dog with the sympathetic tone being maintained by arterenol infusion.

Figure 10.


SYMPATHETIC BLOCK WITH ARTERENOL INFUSION
BP
80
60
40
pH 6.98
1 MICROGM/KG ARTERENOL
VCF
1 MICROGM/KG EPINEPHRINE
LACTIC ACID DRIP STARTED
80
60
40
120
100
80
60
PROCAINE BLOCK
+30 MIN.
BP
120
100
80
60
1 MICROGM/KG ARTERENOL
pH 6.96
VCF
1 MICROGM/KG EPINEPHRINE
+40 MIN.
140
80
60
1 MICROGM/KG EPINEPHRINE
pH 6.75
1 MICROGM/KG ARTERENOL
pH 6.50
+105 MIN.

It can be seen that percentagewise the cardiovascular response to injections of arterenol does not decrease nearly as readily as during the lactic acid infusion in the unblocked animals in figures 8 and 9. Such changes in refractiveness are probably produced because of a smaller total circulating catechol amine level in the blocked animals as compared to higher circulating levels in the unblocked animals due to endogenous releases of sympathomimetic amines. Watts (47) has reported high peripheral blood levels of epinephrine during intravenous infusion of this amine. Therefore an injected dose of 1 microgm/kg of arterenol is only a small incremental increase in the presence of tremendously large amounts of endogenously released catechol amines. This may possibly account for the increased refractiveness in the unblocked animals.

SUMMARY

In the introduction various clinical symptoms and causes of shock were discussed along with some possible methods of treatment. The terminal outcome of all the types of shock mentioned may be death if not properly treated. The cause of this irreversible phase of shock was attribtued to a gradual increasing degree of coronary insufficiency and finally complete circulatory failure. The advantages of some of the sympathomimetic amines over others in the treatment of shock were brought out. The ability of some of these amines to increase the myocardial contractile force as well as blood pressure is an important basis for their use in the treatment of shock, particularly shock accompanying myocardial infarction. Some investigators have shown hormones, electrolytes and acid-base balance to play an important role in the progression and treatment of shock. Other workers have shown acidosis to correlate inversely with the vasopressor response to the catechol amines.

From the foregoing groups of experiments it has been shown that acid-base balance indeed plays a most important role in the response of the cardiovascular system to the sympatho-adrenal hormones. Experiments utilizing azygos flow as a means of endogenous release of catechol amines and production of acidosis produced a tremendous

decrease in contractile force and blood pressure during vena cavae occlusion even though large amounts of catechol amines were present. Possibly this is partly due to a hypoxic condition causing the catechol amines to become physiologically inactive. The stores of norepinephrine are depleted at a slower rate than epinephrine (36) and the myocardium is relatively refractive to normal endogenous releases of catechol amines after release of the vena cavae. This seems to indicate the myocardium may have been injured during the short period of hypoxia. During the rebound phase the contractile force and blood pressure were relatively refractive to norepinephrine probably because of an increased catechol amine level and a subsequent decrease in pH. From this group of experiments it is evident that proper oxygenation is a necessity for normal catechol amine response.

The experiments utilizing lactic acid infusion as a source of exogenously produced acidosis causes the cardiovascular system to become refractory to injected doses of arterenol and epinephrine. The group of experiments producing endogenous acidosis by infusion of catechol amines also caused a loss of responsiveness to these amines. In both groups of experiments the loss of responsiveness was thought to be due to the combination of an increase in hydrogen ion concentration and catechol amine levels. It was very interesting to note that the contractile force response became refractory much sooner than the vasopressor

response. The relationship between catechol amine infusion and respiration was correlated in a group of closed chest experiments.

The results of this work show a direct correlation between acidosis and high levels of circulating plasma catechol amines. Under certain conditions such as shock there is a large endogenous release of these amines. This release is caused by a reflex mechanism in an attempt to compensate for the hypotension produced. Initially there is normal cardiovascular response to this sympatho-adrenal release which gradually diminishes causing a decrease in compensation with an eventual fall in blood pressure below the initial shock level. When large amounts of sympatho-adrenal hormones are present over a long period of time their vasopressor and positive myocardial inotropic effect is lost and finally a state of shock will follow. The ability of prolonged high levels of these hormones to eventually produce hypotension may be attributed to the acidosis produced and to the gradual depletion of substances required for the energy release and utilization occurring during this increased metabolic activity.

Other factors such as electrolyte, hormonal and enzymatic changes or deficiencies are thought to play an important role in shock. Sodium, potassium and chloride shifts or losses may have a profound effect on fluid balance and possibly myocardial activity during shock. Acidosis is enhanced by a rise in the total pCO_2 and the enzyme carbonic

anhydrase may play an increasingly important role in CO_2 transport during this rise in pCO_2. Further studies are planned to evaluate the possible role of these electrolytes and enzymes during acidosis. Experiments are now being conducted using a buffer to maintain a normal pH even when the CO_2 content is more than twice as great as normal. This is accomplished by maintaining the $\frac{NaHCO_3}{H_2CO_3}$ ratio at the normal value of $\frac{20}{1}$. The electrolyte shifts during an increase in CO_2 content of the body is relatively unchanged due to the sparing action of the buffer.

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