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.1-3 Hyper-glycemia usually occurs early in conditions associated with a reduction in circulating blood volume.1 The degree of hyper-glycemia seems to follow closely the level of catechol amine liberation.4-6 There is a progressive increase in blood lactate and pyruvate production found under these conditions with a greater increase in lactate.1-3 As lactic acid is formed, there is an immediate reaction with the bicarbonate buffer system. This reaction results in the formation of lactate and car-bonic acid.8 The carbonic acid dissociates to form CO₂ 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 CO₂.3,9 This reduction in CO₂-carrying capacity is analogous to hypoxia caused by a decrease in hemoglobin-

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combined power. While ventilation is adequate, the ability of the blood to carry CO₂ 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 glycolysis 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 CO₂ concentrations. Correction of the acidosis with 2-amino-2-hydroxymethyl, 1, 3-propane diol (THAM),10-11 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 CO₂ 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 CO₂ 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 levaterenol. Such an increase in free energy release should
improve the ability of the body to maintain homeostasis in emergency situations.

Methods

The following experiments were conducted in 78 apparently healthy mongrel dogs weighing 8 to 13 Kg.

Group I: This group consisted of 41 "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 mg. per Kg. of levartenerol 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 a second period of "azygos flow," after a period of at least 1 hour following the first "azygos flow" study, the animals were subjected to a period of "azygos flow." A solution of 2-amino-2-hydroxymethyl, 1, 3-propane diol (THAM) 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 to 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.12

Group III: (a) The response to a levartenerol test dose of 1 μg. per Kg. was obtained during a control period in 12 dogs. The animals were then placed on an infusion of lactic acid. The concentration of lactic acid was 2 M, and the rate of infusion was determined by degree of cardiovascular depression. The pH was determined at 5 to 25-minute intervals, and injections of test doses of levartenerol were administered at each reduction of 0.1 pH units. (b) In 7 animals, when the pH had reached approximately 7.10, an infusion of THAM was started while the lactic acid infusion was continued. The pH and levartenerol response was obtained until the pH had reached control values of near 7.50.

Group IV: In 12 animals the response to levartenerol was tested during a control period, after which an increase in CO₂ ventilation was established by supplying a mixture of 15 per cent CO₂ in oxygen to the respirator. During the period of marked myocardial depression, a second test dose of levartenerol was administered. While the CO₂ ventilation concentration remained at 15 per cent, THAM was infused in a concentration of 0.3 M. The response to a test dose of levartenerol was again established. In 4 of these experiments NaHCO₃ infusion was compared with THAM.

Group V: 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. The ascending aorta was isolated from the pulmonary artery, and the probe or sensing unit was placed around the ascending aorta.13 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.

In each of the dog experiments anesthesia was provided by 10 mg. per Kg. of morphine sulfate injected subeutaneously, followed in 30 minutes by 15 mg. per Kg. of sodium pentobarbital administered intravenously. 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.14-16 The sutures for attachment of the strain gage arch were placed approximately 15 mm. apart. The 2 feet of the arch were placed approximately 20 mm. apart. When the strain gage arch was attached to the ventricle, the muscle between the 2 points of attachment was thus stretched by 33 per cent of the end-diastolic length. The ventricular contractile force (VCF) changes which were measured and recorded have been shown to be primarily due to humoral and neuropogenic changes.15, 16 Myocardial adjustments secondary to hemodynamic changes were insignificant because of the fixed initial length of the muscle segment. Arterial

*Circulation Research, Volume VIII, November 1960

Mark Instrument Company, Boston, Mass.
"Azygos flow" was established by occlusion of the superior and inferior vena 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., 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 effects of 10 minutes of "azygos flow" on the cardiovascular system have been reported previously. The upper 2 tracings of figure 1 show the typical changes occurring with 7 minutes of superior and inferior venae caval occlusions. The reduction in VCF and arterial blood pressure 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. These levels are 15 to 50 times normal (100 to 300 μg./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 μg. 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 released. 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 seemed to 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 preclosure levels. The CO₂ 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 1. 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 1. 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 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 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 to 75 per cent of control. There was a slight increase, however, in VCF which did not reach control levels (60 to 80 per cent of control levels). 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 coronary aids in restoring VCF following periods of reduced coronary flow.

**Table 1**

| Percentage Increase in Ventricular Contractile Force (VCF) Following 1 µg./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             | 145%           | 41%            | 387%           |

**Table 2**

<table>
<thead>
<tr>
<th>Two &quot;Azygos Flows,&quot; First Without Corrective Measures and the Second with THAM (Group I, C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebound of VCF (%)</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>First azygos flow</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Second azygos flow (with THAM)</td>
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</tbody>
</table>

*Increase above pre-"azygos flow" level.

Circulation Research, Volume VIII, November 1960
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.

"Azygos flow" on the animals deprived of sympathetic stimulation. Under these conditions 5 minutes of "azygos flow" greatly depressed both the myocardium and 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 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 experiment 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 lactic acid 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. 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 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 2). 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.

**Table 2**

<table>
<thead>
<tr>
<th>Levartenol response (%)</th>
<th>pH</th>
<th>Total CO2 (mM/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>148</td>
<td>7.55</td>
</tr>
<tr>
<td>Lactic acid depression</td>
<td>89</td>
<td>7.13</td>
</tr>
<tr>
<td>Lactic acid + THAM*</td>
<td>154</td>
<td>7.33</td>
</tr>
</tbody>
</table>

*With the infusion of THAM, there was an initial increase in VCF of 188 per cent above the acid depression level.
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(a 13 to 21 mM/L decrease) at the time of development of near 50 per cent refractiv-ness to levarterenol injection and to levels as low as 2 mM/L at the time of complete re-fractiveness. 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. 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 ad-ministered. Figure 3 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 continued infusion of lactic acid. 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. 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 returned 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.

Effects of Hypercapnea on Ventricular Contractile Force with Correction by THAM

Figure 4 shows the effects of THAM correction of hypercapnea compared with that produced by sodium bicarbonate. Ventilation with 15 per cent CO₂ 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 pro-gressive, and within 30 minutes the VCF had usually returned to near pre-CO₂ ventilation levels. This secondary rise in VCF is thought to be due to sympathetic stimulation. 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 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 in-
Figure 4
Comparison of the effects of THAM and NaHCO₃ on the depression of VCF elicited by forced CO₂ inhalation. The “A” denotes injections of 1 μg./Kg. of levarterenol. These results were obtained in the same animal. The second period of increased CO₂ ventilation occurred approximately 30 minutes after the first. The time interval between the heavy vertical lines represents 20 seconds.

crease 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 μg. 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, 1½ times to 2 times greater than the duration of action during control (table 3). 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. An injection of 100 mg. per Kg. of THAM 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 depend largely on the status of the animal prior to the injection of THAM. As shown in figure 5, 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 blood 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 prepara-

Table 3
Levarterenol Response During Fifteen Per Cent CO₂ Ventilation

<table>
<thead>
<tr>
<th></th>
<th>Increase in VCF above control (%)</th>
<th>% of initial control response of VCF</th>
<th>Duration of response (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levarterenol</td>
<td>157</td>
<td>100</td>
<td>2.1</td>
</tr>
<tr>
<td>CO₂ + arterenol</td>
<td>192</td>
<td>48</td>
<td>1.5</td>
</tr>
<tr>
<td>CO₂ + THAM + arterenol</td>
<td>178</td>
<td>94</td>
<td>2.9</td>
</tr>
</tbody>
</table>

*Prior to each levarterenol injection.
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.

Discussion

As Szent-Gyorgyi has pointed out, the isometric tension developed with each contraction of the muscle indicates the quantity of free energy spent. 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 into 3 general phases: (1) energy liberation, (2) energy conservation and (3) energy utilization. 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 heart muscle. 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. 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. 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. 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. 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 re-
duction 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. 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.

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 CO₂ since the total CO₂ was extremely low and the arterial pH was near 7.0. Correction of the acidosis with restoration of CO₂ combining power resulted in an immediate increase in VCF and improvement in the myocardial response to levarte'eno! injections. A decrease in sympathoadrenal stimulation 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 have shown adrenal stimulation with lactic acid injections. With the administration of THAM Nahas and coworkers have shown a decrease in the sympathoadrenal response to CO₂. Increased concentrations of CO₂ in the ventilation gas would tend to increase the CO₂ gradient across the cell membrane, and the experiments showed a decrease in energy release. The increase in blood pCO₂ would result in a CO₂ 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 CO₂ and the "rebound" stimulation of VCF following the withdrawal of CO₂ could be related to sympathoadrenal stimulation 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 15% 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 Di-Palma have reported that the spleen does not increase its liberation of red blood cells during acidosis accompanying arterenol infusion. 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. Anaerobic metabolism seems to play an important part in this response. The buffering of lactic acid leads gradually to a decrease in CO₂-carrying capacity of the blood. This was evidenced by an increase in dissolved CO₂, not only in the late stages of the lactic acid infusions in this study, but also following long-term infusions of levarterenol and epinephrine in other stud-
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Since the oxygen debt which the heart can incur is thought to be extremely limited, the decrease in CO₂-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.

A hydrogen ion acceptor like THAM that will traverse the cell membrane in the unionized form seems to be an excellent buffer. Dehydrogenase reactions play an important role in metabolism, and the ability of THAM to accept hydrogen ions may affect these reactions. For instance, this agent is known to enhance the Qo₂ values obtained with ophio-1 amino acid oxidases (snake venom). The formation of RNH₂ compounds and their participation in nitrogen metabolism are known. The effects of THAM on these reactions have not been taken into consideration in this discussion. However, 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 and have been shown to elicit a metabolic acidosis. In the present studies the effects of reducing circulating blood volume or infusion of lactic acid and of forced CO₂ inhalation on ventricular isometric systolic tension (VCF) and the cardiovascular response to test injections of levarterenol were studied. The experiments with a reduction in circulating blood volume and with lactic acid infusions resulted in a decrease in arterial pH, whole blood total CO₂ and whole blood CO₂ 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 CO₂ and an increase in dissolved CO₂. This decrease in the CO₂-carrying capacity would lead to an increase in tissue CO₂. Since the heart is markedly depressed by CO₂, 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 CO₂, 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 CO₂ 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 CO₂-carrying capacity of the blood resulted in an immediate improvement in VCF and the levarterenol response.

Summario in Interlingua

Es cognoscite quo hyperglyceinia e acidosis de hypoxia occurre durante periodos de choc. Il ha esse reportate que le nivellos plasmatic de catecholaminas es elevate durante periodos de choc. Le injection de epinephrina o de levarterenol es capace a producere augmentos del glucos de saigne e il ha esse mostrate que ille agentes evoca un acidosis metabolico. In le presente studios le effecto esses esse investigate que resulta del reducione del circulante volume de saigne o del infusion de acido lactic e del fortia inhalation de CO₂ in le tension systolic isometric ventricular (i.e. le fortia contractile del ventriculo = VCF) e in le responso cardiovascular a injectiones experimental de levarterenol. Le experimentos con le reduction del circulante volume de saigne e con infusiones de acido lactic resultava in un reducione del pH arterial, del total CO₂ de saigne integre, e del fortia combinatori pro CO₂ del parte de
sanguine integre. In concomitants with late alterations, it occurred a marcante depression del FCV e del response a injectiones experimental de leverterenol. Le correction del alterations acido-basa per medio de 2-amino-2-hydroxymethyl-1,3-propano-diol (THAM) resultava in un immediato mellioration del FCV e del response a leverterenol. Iste alteration occurred in despecto de un plus grande augmento del niveles sanguine de lactato. Metabolismo anaerobe con production de lactato resulta in un reduction del total CO₂ del sanguine e in un augmento del dissolvite CO₂. Iste reduction in la capacitate de portar CO₂ resultarea responsa a levarterenol. Un correction del acidose resultava in un marcate depression del FCV e del consequente, le accumulation de CO₂, un del productos in despecto de un plus grande augmento del nivellos de CO₂, iste augmento in un augmento del ventilation de CO₂, lo que redue massa. Tste hypotliese esseva testate additional-mente. Le correction del alterationes acido-basie per medio sanguine de lactato. Metabolismo anaerobe con production terminal del metabolismo aerobic, deprimerea le metabolismo oxidatori de acido con le lege del action de massa. Iste hypothese essa evase testate additionalmente per un fortiate ventilation de CO₂, lo que resultava in un marcate depression del FCV e del response a leverterenol. Le correction del acidosis respiratori per medio del administration de THAM (que augmentava le capacitate de portar CO₂) resultava in un immediate mellioration del FCV e del response a leverterenol.

References
METABOLIC ACIDOSIS AND VENTRICULAR CONTRACTION


Effects of Metabolic Acidosis on Ventricular Isometric Systolic Tension and the Response to Epinephrine and Levarterenol

THOMAS D. DARBY, EARL E. ALDINGER, RICHARD H. GADSDEN, WENDELL B. THROWER, Sidney H. Westbroo and James M. Tenneii

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