Vasopressor Agents

Influence of Acidosis on Cardiac and Vascular Responsiveness

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• **Clinical observations have indicated that patients who are in shock and who have coexisting acidosis respond relatively poorly to sympathomimetic amines. In experiments with dogs, it was found that, in the presence of acidosis, the pressor action of epinephrine, norepinephrine and metaraminol was considerably reduced. The effect on cardiac rhythm was also considerably lessened after the pH value of the blood had been lowered.**

In view of these observations in animals, six human patients with profound shock and acidosis were studied. All had a considerably lessened pressor response to vasopressor agents; then, after elevation of the blood pH by intravenous infusion of a 1-molar solution of sodium lactate, responsiveness was restored.

These observations emphasize the desirability of close observation of the acid-base status, and early treatment of acidosis, as an important aspect in the management of patients with shock.

QUESTION AS TO THE EFFECT of acidosis on the effectiveness of vasopressor agents suggested itself at the bedside during studies on the value of drugs such as norepinephrine (Levophed®) and metaraminol (Aramine®) for the treatment of patients with bacteremia and shock. It was noted that patients who were in acidosis at the time of onset of the shock state were relatively resistant to the action of these sympathomimetic drugs. Moreover, a progressive decrease in pressor effectiveness on the part of patients who had at first responded well was frequently related to the development of acidosis.

These observations were in harmony with phenomena noted in earlier studies in animals. In 1927, Burget and Visscher[3] noted in experiments with pithed cats that the response of the vascular system could be altered by changing the pH of the blood and that response to epinephrine progressively increased as the pH was elevated from 6.9 to 8.0. More recently Page and Olmsted[6] demonstrated that the pressor action of epinephrine and norepinephrine was diminished in dogs with respiratory acidosis.

Blumenthal, Brown and Campbell[2] observed that the cardioaccelerator response to epinephrine in human subjects was diminished during respiratory acidosis and increased during respiratory alkalosis. These investigators also noted that the bronchodilator action of epinephrine in patients with bronchial asthma was frequently improved following the intravenous administration of molar sodium lactate. These facts suggested that similar considerations would pertain to patients with shock and acidosis.

In experiments that have been published in greater detail elsewhere,[5] epinephrine, norepinephrine and metaraminol were administered to dogs in doses that were calculated to produce moderate elevation in arterial pressure. The arterial pressure and electrocardiogram were recorded and the pH of the arterial blood was measured. After the response to each of these drugs was determined as a control measurement, acidosis was produced by allowing dogs anesthetized with thiopental to breathe a gas mixture containing 30 per cent carbon dioxide and 70 per cent oxygen. The test procedure with vasopressor agents was then repeated.

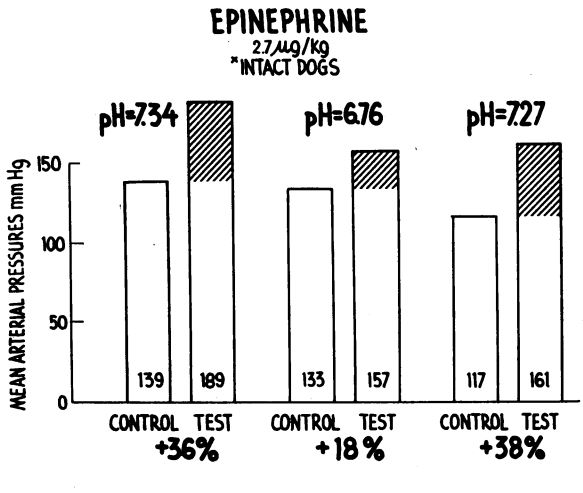

Chart 1.—Relationship of responsiveness to vasopressor agents at normal pH values of arterial blood, and during acidosis in intact dogs.

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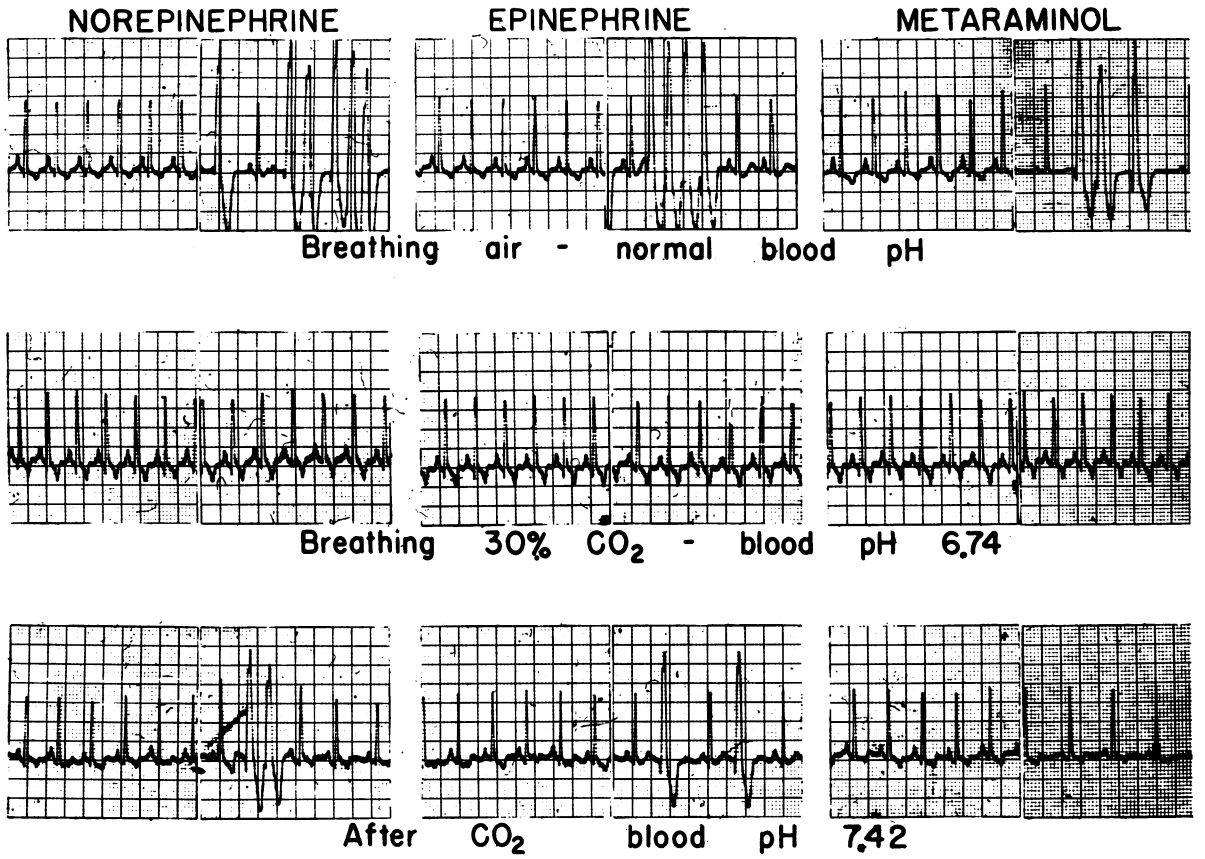


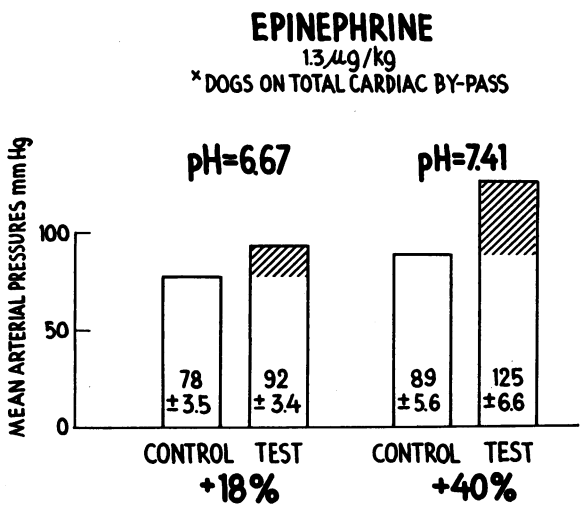
Figure 1.—Electrocardiographic changes following administration of vasopressor agents during acidosis and when the blood pH was at normal values.

Figure 1 is reproduced from the Proceedings of the Society for Experimental Biology and Medicine[5] with permission.

It was found that, in the presence of respiratory acidosis, the pressor responses to each of the three sympathomimetic drugs were diminished (Chart 1). Following the intravenous injection of 2.7 micrograms of epinephrine per kilogram of body weight in five animals with the pH of the arterial blood in the normal range, there was an increase in mean arterial pressure from 139 to 189 mm., which represents an increase of 36 per cent of the control value. However, at pH 6.76 the responsiveness was decreased to 18 per cent. After the pH was raised to 7.27 the pressor response was again increased in this instance to 38 per cent. Corresponding results were obtained with norepinephrine and metaraminol. Pressor responses produced by epinephrine, norepinephrine and metaraminol were also diminished in a similar group of intact animals under condition of metabolic acidosis produced by infusion of a dilute solution of hydrochloric acid.

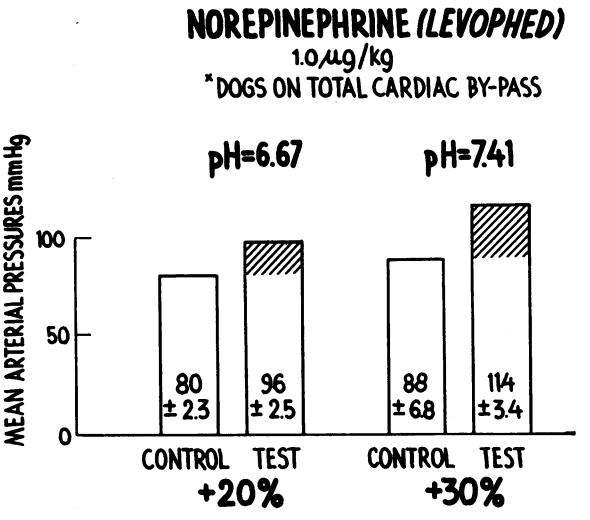
The electrocardiographic tracings (Figure 1) were of considerable interest. Multiple ventricular extrasystoles and even runs of ventricular tachycardia were produced by each of the sympathomimetic amines when the blood pH was within normal limits. However, no ventricular dysrhythmias followed administration of the same dose of these drugs in dogs with respiratory acidosis. After blood pH was returned to or near normal values, the cardiac irregularity usually reappeared. Dogs with metabolic acidosis gave a similar response. These observations are being studied in greater detail. We have postulated that the increased ventricular activity which follows administration of lactate solution in patients with complete heart block, as reported by Bellet, Wasserman and Brody,[1] may be related to augmented action of endogenous epinephrine brought about by elevation of the blood pH.

In order to separate the effects on the heart from effects on the peripheral vascular bed, a series of experiments was performed during which the sympathomimetic drugs were administered to dogs subjected to total cardiac by-pass. The method described by Campbell, Crisp and Brown[4] was followed: A homologous lung was used as an oxygenator and Sigmamotor units as pumps in the extracorporeal circuits. The extracorporeal lung was ventilated with the 30 per cent carbon dioxide and 70 per cent oxygen mixture. The response of the animal during



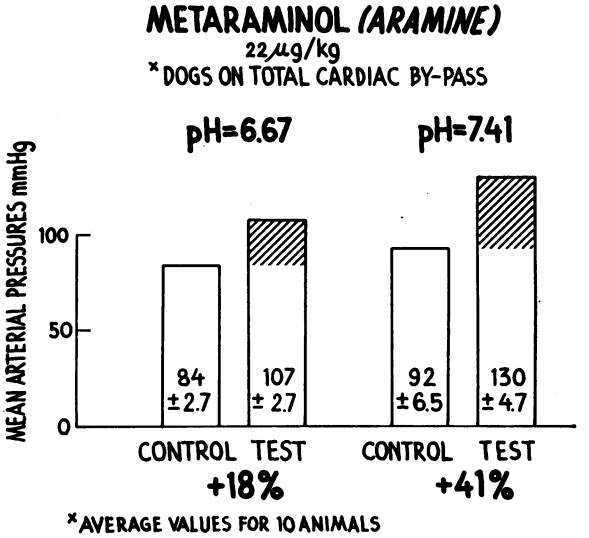
*AVERAGE VALUES FOR 10 ANIMALS

Chart 2.—The effect of pH on pressor responsiveness to *epinephrine* in dogs on total cardiac by-pass.



*AVERAGE VALUES FOR 10 ANIMALS

Chart 3.—The effect of pH on pressor responsiveness to *norepinephrine* in dogs on total cardiac by-pass.



*AVERAGE VALUES FOR 10 ANIMALS

Chart 4.—The effect of pH on pressor responsiveness to *metaraminol* in dogs on total cardiac by-pass.

acidosis was determined first and the control portion of the experiment, in which the pH of the blood was near normal, was performed subsequently. Thus, we were assured that any decrease in reactivity during acidosis would not be confused with a possible decrease in reactivity of the preparation related to prolonged cardiac by-pass.

After the heart was excluded from the circulation, pressor responses under conditions of respiratory acidosis were uniformly much less than those of the same animals after pH was returned to or near normal levels. Thus, when epinephrine was injected into dogs that had total cardiac by-pass after the arterial blood pH had been depressed to 6.67, the pressor response was 18 per cent of the control value (Chart 2). After pH had been elevated to 7.41, the pressor response increased to 40 per cent. The average mean pressure in ten dogs and the standard error of the mean is indicated within the bars of the graph. Similarly in the case of norepinephrine, responsiveness was 20 per cent of the control value at pH 6.67, and 30 per cent at pH 7.41 (Chart 3). Following injection of metaraminol at pH 6.67, responsiveness was 18 per cent and at pH 7.41 it was 41 per cent (Chart 4). Statistical analysis of these data indicates that the differences in pressor responsiveness during acidosis and at normal blood pH for all three agents were significant—the chances of accidental occurrence being less than 1 in 1,000.

In view of these findings in experimental animals, the value of correcting acidosis by infusion of a molar solution of lactate was studied at the bedside. Six patients who had coexisting bacteremic shock and acidosis were treated. All six had received large doses of norepinephrine or metaraminol before these studies, but in spite of this the mean arterial blood pressure was 40 to 60 mm. of mercury. The pH of arterial blood before treatment was as low as 7.06. Following administration of 300 to 1,000 ml. of 1-molar sodium lactate by continous intravenous infusion, the pH was elevated to a maximal value of 7.51. During and after this therapy the blood pressure returned to near the normal range even though the infusion of vasopressor agents was decreased or discontinued. However, none of the patients lived more than seven days in spite of this treatment. It was significant and gratifying that responsiveness to the vasopressor agents was restored by sodium lactate after the usual measures had failed.

In view of the limited accumulation of clinical experience on the use of 1-molar sodium lactate in

the treatment of shock, conclusions regarding its value and possible dangers involved in its employment must await additional observations. However, these studies have alerted us to close observation of the acid base status and early treatment of acidosis as one important facet in the management of patients with shock.

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