ANNALS OF SURGERY

Vol. 163 February 1966 No. 2

Effect of Acute Respiratory and Metabolic Acidosis on Cardiac Output and Peripheral Resistance

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IT IS commonly assumed that acute acidosis, either respiratory or metabolic, has an adverse effect on circulatory dynamics; however, clinical evidence of beneficial cardiac effect from treatment of acidosis has been inconclusive and numerous experimental studies have produced conflicting results.

Clinical evidence that cardiovascular depression is caused by acidosis is usually based on the association of metabolic acidosis with low cardiac output and hypotension. However, low cardiac output is a primary cause of metabolic acidosis, and it is therefore difficult to distinguish between cause and effect. It is also frequently assumed that correction of metabolic acidosis by appropriate alkalinizing agents will produce improvement in cardiovascular performance, although there is clinical evidence that an acidotic state may be completely corrected in respect to hydrogen ion concentration without improvement in cardiac output.[4] Since therapy of acidosis is usually accompanied by other supportive measures, subsequent improvement may be a result of either the correction of pH or associated therapy.

Measurement of cardiac output as an index of cardiovascular performance has yielded conflicting results in various experimental studies. Opinion seems evenly divided as to whether respiratory acidosis produces an increase or decrease in cardiac output; however, the majority opinion appears to be that metabolic acidosis has either no effect or a depressant effect on the myocardium.

A series of experiments was therefore carried out in dogs in which extraneous factors known to affect circulatory dynamics were rigidly controlled in order to document the isolated effect of acute respiratory and metabolic acidosis on cardiac output and peripheral resistance.

Submitted for publication March 12, 1965.

This study was supported by research grants from the U. S. Public Health Service (H-3720) and the Erie County Heart Association.

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Methods

Experiments were performed on 59 adult mongrel dogs with more than 600 individual determinations of cardiac output.

Anesthesia was induced by a single injection of sodium pentobarbital given intraperitoneally, with an initial supplement administered intravenously. This method previously has been found to produce adequate anesthesia and to maintain the animal in a quiet state with good circulatory stability during a 2½- to 3-hour experimental period.[1] After induction of anesthesia an endotracheal tube was inserted and artificial ventilation maintained with alternating positive-negative pressure, employing the same rate and pressure throughout the experimental period. During the control periods and recovery periods the animals were ventilated with a mixture of 3% carbon dioxide–97% oxygen, a proportion which has been found to maintain the pH in a normal range during adequate ventilation or moderate hyperventilation, and which insures full oxygenation of the arterial blood.

Aortic and vena caval catheters were introduced through femoral vessels for blood sampling and pressure monitoring. Cardiac output was measured by the dye dilution technic, using Cardiogreen dye with a Colson densitometer and a photographic recorder. Dye was injected into the inferior vena cava near the right atrium and arterial blood withdrawn from the aorta for recording of output curves. Arterial blood samples were drawn for pH measurements immediately prior to each output curve. Arterial blood pressure and pulse rate were monitored continuously on a photographic recorder and recorded simultaneously with each dye curve.

Three control measurements of cardiac output and arterial pressure were obtained at 10-minute intervals in each animal to verify stability of baseline values. Subsequent measurements were obtained at 15-minute intervals during the acidotic periods and during recovery.

Respiratory Acidosis. After control determinations during ventilation with the 3% CO_2–97% O_2 mixture, respiratory acidosis was induced by switching directly to various increased concentrations of CO_2 in O_2 while maintaining the same ventilatory characteristics as during the control period. The following concentrations of CO_2 were employed: 5, 10, 15, 18, 25 and 35%. When one concentration of CO_2 was used throughout the acidotic period, serial measurements of cardiac output were obtained at 15-minute intervals during a 2-hour test period. When more than one concentration of CO_2 was employed, three output determinations were obtained at 10-minute intervals with each new concentration. After the acidotic period, final studies were performed during a 30- to 60-minute recovery period.

Metabolic Acidosis. Lactic acid was chosen as the agent for induction of metabolic acidosis as a more physiologic acid than others such as hydrochloric acid. Acidosis was induced by repeated injections of lactic acid in dosages of either 25 ml. of 8.5% solution or 50 ml. of 3.4% solution. After each injection, three determinations of cardiac output were obtained at 15-minute intervals. Artificial ventilation with the 3% CO_2–97% O_2 mixture was maintained throughout the experiments to eliminate respiratory effects and ensure full oxygenation.

Control Studies with Sodium Chloride. A series of control experiments was carried out in which sodium chloride was administered in the same amount in milliequivalents and fluid volume and with the same study sequence as in the experiments with metabolic acidosis.

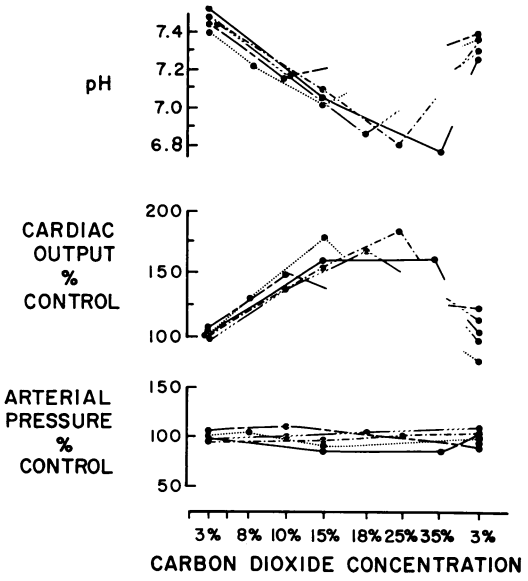

FIG. 1. Respiratory acidosis: mean values from five groups of animals. Concentrations of CO_2 at which measurements were made are plotted against pH, cardiac output and atrial pressure. Each point represents the mean value of three determinations for each animal in the group.

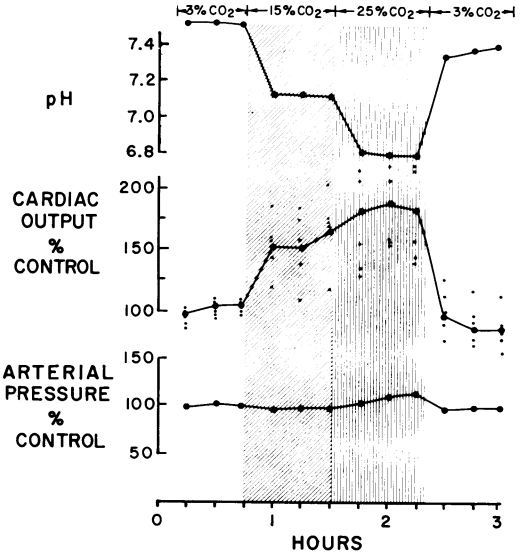

FIG. 2. Respiratory acidosis: mean values from five animals receiving 15% and 25% CO_2. Individual cardiac output determinations are also illustrated.

Results

Respiratory Acidosis. Animals subjected to respiratory acidosis were divided into five groups, each group beginning with a 3% CO_2 gas mixture during the control period, receiving from one to three separate increased concentrations during the acidotic period and returning to the 3% mixture during recovery. Each group was composed of five to nine animals.

Mean values for pH, cardiac output and arterial blood pressure for all groups are shown in Figure 1. In each curve the concentrations of CO_2 at which measurements were made are shown as individual points. The pattern of response in all groups was similar. With decreasing pH, reaching a minimal level of 6.7, there was a generally progressive increase in cardiac output, reaching a maximum of 182% of control levels. In all groups the cardiac output fell toward control levels during the recovery period.

In all experiments the arterial pressure remained essentially constant throughout the study period, indicating a significant decrease in peripheral resistance.

Pulse rate remained near control levels throughout the acidotic period, showing a tendency toward a slight decrease, indicating that the increase in cardiac output was accomplished by increased stroke volume.

Figure 2 illustrates in more detail the sequence of events and individual data in a group of dogs with initial ventilation with 3% CO_2, followed successively by 15% and 25% and then returning to a 3% mixture. After changing to 15% CO_2 there was a prompt increase in cardiac output which remained constant throughout a 1-hour period at this degree of acidosis, with a further increase when the CO_2 was changed to a 25% concentration. The pattern of change was similar in each individual experiment although varying somewhat in degree.

Figure 3 illustrates the effect of continued acidosis at one level over a longer interval, with 10% CO_2 employed throughout the 2-hour test period. Immediately after changing to the 10% mixture the

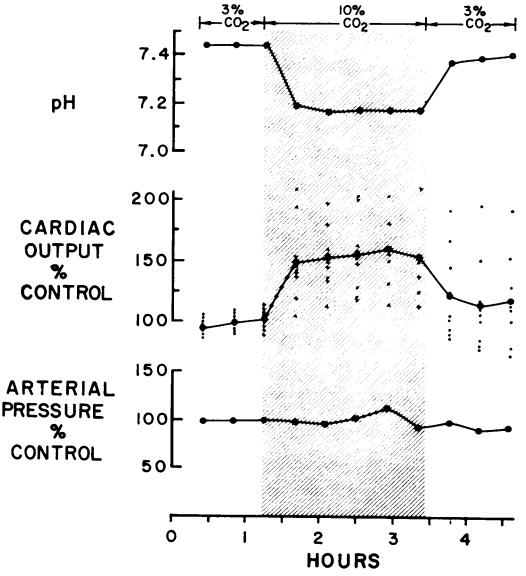

FIG. 3. Respiratory acidosis: mean values from eight animals receiving 10% CO_2. Individual values for cardiac output are shown as well as the means.

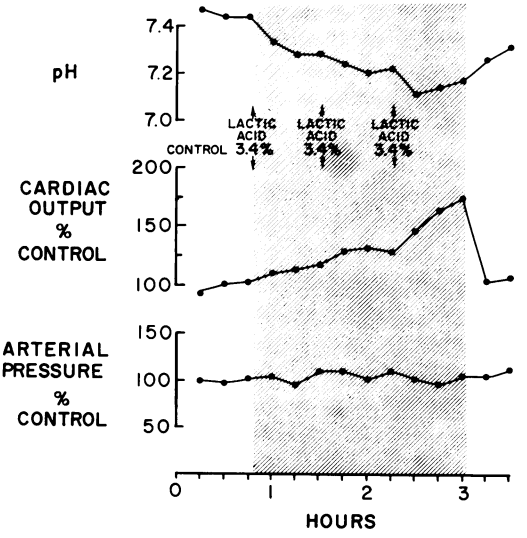

FIG. 4. Metabolic acidosis: mean values from ten animals receiving 3.4% lactic acid.

pH fell to a mean of 7.17 and remained constant throughout the acidotic period. Similarly, cardiac output rose to approximately 155% of control values and remained relatively stable at this elevated level. With return to the 3% CO_2 mixture there was a progressive decrease in cardiac output returning to near control levels.

Metabolic Acidosis. Figure 4 illustrates the results in the animals receiving 3.4% lactic acid. With repeated injections of lactic acid there was a progressive fall in pH, reaching a minimum mean level of 7.12. Beginning with the first injection there was a progressive increase in cardiac output, reaching a maximum value of 175% after the third injection. As the pH gradually returned toward normal, cardiac output again fell to control levels. As in the experiments with respiratory acidosis, arterial pressure remained essentially unchanged.

A second group of animals received 8.5% lactic acid injections (Fig. 5). In this group a more severe acidosis was produced, reaching a minimum level of pH 6.8. Again, a more or less progressive increase in cardiac output occurred with increasing acidosis, with the cardiac output reaching 185% of control levels at pH 6.8. As the pH returned toward normal the cardiac output fell sharply to normal levels.

Control Studies with Sodium Chloride Injection. Figure 6 illustrates the results obtained in the group of animals receiving injections of sodium chloride in amounts comparable to the injections of lactic acid in the previous group. A slight decrease in pH occurred, with a progressive rise in cardiac output which averaged 144% of control levels following the third injection of sodium chloride. Cardiac output subsequently declined toward control levels. In this group of animals the arterial pressure showed a modest but consistent elevation but pulse rate remained constant.

Acute Deaths during Metabolic Acidosis. During the earlier phase of these experiments rapidly progressive hypotension and sudden death occurred in several dogs during the course of the lactic acid injections with no apparent relation to the degree of acidosis. In each instance autopsy disclosed massive thrombosis or thromboembolism in the right ventricle and pulmonary arteries, with a curious granular type

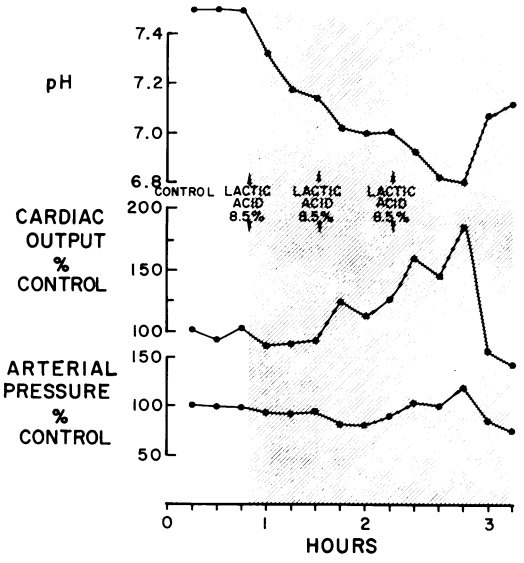

FIG. 5. Metabolic acidosis: mean values from eight animals receiving 8.5% lactic acid.

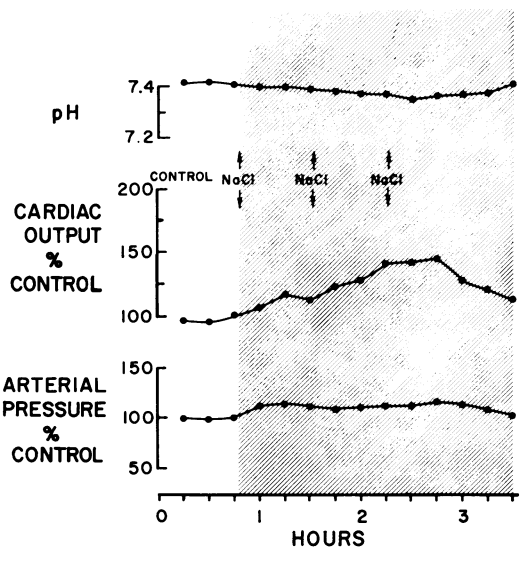

FIG. 6. Control studies with NaCl. Mean values from five animals are illustrated.

of thrombus enmeshed in the chordae tendinae of the tricuspid valve. This was believed due to the rapid injection of a bolus of concentrated acid and in subsequent experiments a slower injection with positioning of the catheter in the main stream of the central vena cava eliminated this occurrence. No similar deaths occurred in dogs subjected to respiratory acidosis.

All other animals subjected to either respiratory or metabolic acidosis recovered without therapy.

Discussion

Since "shock," inadequate cardiac output, and acidosis so regularly occur together in various clinical states, it is of critical importance in a rational approach to therapy that the cardiovascular effects of acidosis be well defined.

The belief that acidosis has a depressant effect on the heart has gained particular acceptance in the field of cardiac surgery and the frequent development of acidosis in the period during and following extracorporeal circulation has led to the common practice of treating all such acidotic states with alkalinizing or buffering agents, or giving such agents prophylactically. Implicit in such management is the assumption that the acidosis will further depress cardiac output and lead to increased acidosis, and that *elevation of pH* will improve cardiac output and reverse the cycle. Nevertheless, there is little conclusive information on the specific beneficial effect of such therapy. Conclusions derived from such treatment in patients are handicapped by inability to assess the coincidental effect of other therapy such as blood transfusions, and by the natural recovery of the postsurgical heart.

Experimental evidence on the direct effect of acidosis on the cardiovascular system also appears at present to be conflicting.

Clowes et al.,[4] in an extensive study of experimental and clinical acidosis, found that in animals rendered acidotic by hypercapnia or by administration of hydrochloric acid, a significant decrease in *cardiac output* did not occur until the arterial blood pH fell below 7.1. Sudden heart failure took place in animals during hydrochloric acid infusion at pH values below 7.0; however, the possibility exists that emboli—such as occurred in the present

series—may have been a factor, since autopsy findings were not described. Hypercapneic animals usually withstood pH levels as low as 6.6 although all animals with hypercapneic acidosis died within the ensuing 24 hours if the acidosis lasted for more than 20 to 30 minutes.

However, the same authors [4] noted in several postoperative patients and two patients with diabetic acidosis that correction of pH alone did not affect the depressed cardiac output although subsequent improvement occurred with other therapy.

Richardson *et al.*,[13] in studies in normal humans, found an increase in cardiac output during respiratory acidosis but no change in circulatory dynamics during acidosis induced by lactic acid infusions. He concluded that increase in hydrogen ion concentration had a less significant effect than changes in carbon dioxide levels.

Fishman *et al.*[8] studied the effect of *hypercapnia* in humans and found an increase in cardiac output with no evidence of pulmonary vasoconstriction in either normal subjects or patients with pulmonary disease.

Kittle *et al.*[10] found a consistent and marked increase in cardiac output during respiratory acidosis, with minimal increase during metabolic acidosis induced by hydrochloric acid injection. They also demonstated increases in carotid and coronary flow which correlated directly with carbon dioxide tension in the blood, concluding that change in carbon dioxide level was a more significant factor in alteration of circulatory dynamics than change in pH.

The effect of respiratory and metabolic acidosis on *myocardial contractile force* has been studied by several groups with somewhat contradictory results. Darby *et al.*[6] found a decrease in ventricular contractile force and arterial blood pressure and a diminished response to levarterenol and epinephrine; however, in certain of these experiments a period of "azygos flow" was used as the method of induction of acidosis and such a method could be assumed to produce concomitant myocardial hypoxia. Bendixen *et al.*[3] reported that respiratory acidosis diminished the circulatory effect of epinephrine in dogs, with depression of myocardial contractile force, cardiac rate, and mean arterial pressure; however, only the fall in contractile force appeared to show a direct relationship to the degree of acidosis. Greenfield and Eber [9] also found a decreased myocardial contractile force during hypercapnia of only 7 minutes duration.

On the other hand, LaVeen *et al.*[11] concluded from isolated perfusion experiments that acidosis did not appreciably influence myocardial contractility and that cardiac arrest or depression produced in experimental animals during acidosis was secondary to other causes such as potassium release and hypoxia.

Various studies have failed to demonstrate definite circulatory benefit from correlation of the metabolic acidosis accompanying experimental hemorrhagic shock with either bicarbonate or THAM. Selmonosky [15] pointed out that since THAM corrected both extra- and intracellular pH, this drug should have produced improvement in cardiac output if acidosis had a significant depressant effect on the cardiovascular system; however, no such improvement was observed. Baue and McClerkin,[2] who recently studied the effect of coexistent acidosis on the *depressed circulation* in shock following aortic declamping, found no causal relationship between acidosis and impaired circulatory state and observed no benefit from correction of acidosis with THAM.

It is well known that results of experimental studies of cardiac output may be influenced by various factors which affect cardiovascular stability. Repeated injections or continuous infusion of anesthetic drugs tends to produce variations in cardiac output and peripheral resistance, presuma-

bly caused by uncontrolled changes in depth of anesthesia. Similarly, artificial ventilation with varying rate and pressure, or intermixed with periods of spontaneous ventilation, may profoundly alter cardiac output by affecting the rate of venous return and pulmonary vascular resistance. Associated hypoxia may result from reduced ventilation intended to avoid respiratory alkalosis and also may occur with artificially reduced cardiac output. Finally, surgical trauma may affect cardiac dynamics directly or as a result of altered adrenocortical function.

In the present experiments extraneous influences were eliminated insofar as possible in an attempt to obtain valid data. No evidence was found to support the contention that acute acidosis exerts a depressant effect on myocardial function, at least down to the range of approximately pH 6.8. On the contrary a rather striking increase in cardiac output was observed which appeared to grow more pronounced with decreasing pH. This pattern of response was confirmed by a decrease in output when the pH was allowed to return to normal after the acidotic period. It was noted, however, that the increase in output was greater and more prompt during acutely induced respiratory acidosis than during metabolic acidosis. This observation agrees with the conclusion of Kittle *et al.*[10] and Richardson *et al.*[13] that changes in *carbon dioxide tension* exert a greater effect on cardiovascular dynamics than changes in hydrogen ion concentration. The observation that administration of a similar ionic load in the form of sodium chloride produced an increase in cardiac output comparable to that observed with metabolic acidosis, although of lesser degree, suggests that the response to experimentally induced metabolic acidosis may in part be a result of increased intravascular fluid volume.

Mechanisms by which acidosis may stimulate an increase in cardiac output are not completely explained. It has been considered that the vigorous respiratory movements accompanying elevation in blood carbon dioxide tension could be responsible. However, the experiments of Richardson [13] effectively ruled out such a mechanism since comparable degrees of voluntary hyperventilation without change in arterial pCO_2 did not alter cardiac output. In the present experiments the ventilatory rate was kept constant throughout the experiment in a state of moderate hyperventilation, thereby effectively excluding this factor.

It has been demonstrated that inhalation of carbon dioxide in increased concentrations is accompanied by an increase in plasma concentration of norepinephrine and epinephrine,[14] which might produce an increase in cardiac output. This possibility is not entirely contradicted by the observation that in an acidotic state the vascular system may be less responsive to epinephrine, as has been stated in other reports,[3, 6] since an increase in *catacholamines* during acidosis might result in diminished sensitivity to supplementary administration. Such an hypothesis seems attractive but may be inconsistent with the observed decrease in pulse rate and lack of increase in blood pressure. Further studies of the relative effects of endogenous and exogenous catecholamines are needed to clarify the mechanisms of this response.

It is of interest that in previously reported experiments [1] an increase in cardiac output was demonstrated with infusion of sodium bicarbonate but the effect was closely simulated by injection of equivalent amounts of sodium chloride. A rather similar pattern of events in the present experiments suggests that such infusion of ionic solutions exerts an effect in part by acute increase in *intravascular volume* rather than by changes in pH alone. Whether a specific ionic effect exists which may produce a rather profound depression in pe-

ripheral resistance remains open to speculation. However, generally similar results were produced by each of these different solutions—one producing alkalosis, one acidosis, and one maintaining near-normal pH.

Teleologically one might consider that the homeostatic mechanism of the body should compensate for acute abnormalities and initiate self-correcting responses in the presence of an acute physiological derangement such as acidosis. Many aspects of the accumulated evidence suggest that in terms of cardiac output and myocardial performance, acute acidosis of moderate degree does not exert a measurably harmful effect and that, in fact, cardiac output rises in response to this demand. Since acidosis is usually secondary to a primary abnormality, it might temporarily serve a useful function in providing a stimulus for mobilization of the body's defenses against the underlying cause. It may, therefore, be reasonable to suggest a re-evaluation of the practice of artificial correction of a *moderately* depressed pH for presumed cardiac benefits.

Summary

The effect of acute respiratory and metabolic acidosis on cardiac output and peripheral resistance was studied experimentally in dogs.

Respiratory acidosis, with maximal depression of pH to 6.7, produced a marked increase in cardiac output and fall in peripheral resistance.

Metabolic acidosis induced by lactic acid injections, with reduction of pH to 6.8, resulted in a consistent increase in cardiac output and fall in peripheral resistance.

Control injections of sodium chloride produced an increase in cardiac output, although to a lesser degree than observed with lactic acid.

The rationale of therapy of acidotic states as a means of improving cardiovascular function is discussed.

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