Bicarbonate Does Not Improve Hemodynamics in Critically Ill Patients Who Have Lactic Acidosis

A Prospective, Controlled Clinical Study

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Study Objective: To determine whether correction of acidemia using bicarbonate improves hemodynamics in patients who have lactic acidosis.

Design: Prospective, randomized, blinded, crossover study. Each patient sequentially received sodium bicarbonate and equimolar sodium chloride. The order of the infusions was randomized.

Setting: Intensive care unit of a tertiary care hospital.

Patients: Fourteen patients who had metabolic acidosis (bicarbonate < 17 mmol/L and base excess < -10) and increased arterial lactate (mean, 7.8 mmol/L). All had pulmonary artery catheters and 13 were receiving catecholamines.

Measurements and Main Results: Sodium bicarbonate (2 mmol/kg body weight over 15 minutes) increased arterial pH (7.22 to 7.36, $P < 0.001$), serum bicarbonate (12 to 18 mmol/L, $P < 0.001$), and partial pressure of CO_2 in arterial blood (Pa_{CO2}) (35 to 40 mm Hg, $P < 0.001$) and decreased plasma ionized calcium (0.95 to 0.87 mmol/L, $P < 0.001$). Sodium bicarbonate and sodium chloride both transiently increased pulmonary capillary wedge pressure (15 to 17 mm Hg, and 14 to 17 mm Hg, $P < 0.001$) and cardiac output (18% and 16%, $P < 0.01$). The mean arterial pressure was unchanged. Hemodynamic responses to sodium bicarbonate and sodium chloride were the same. These data have more than 90% power of detecting a 0.5 L/min (7%) change in mean cardiac output after administration of sodium bicarbonate compared with that after sodium chloride. Even the 7 most acidemic patients (mean pH, 7.13; range, 6.90 to 7.20) had no significant hemodynamic changes after either infusion.

Conclusions: Correction of acidemia using sodium bicarbonate does not improve hemodynamics in critically ill patients who have metabolic acidosis and increased blood lactate or the cardiovascular response to infused catecholamines in these patients. Sodium bicarbonate decreases plasma ionized calcium and increases Pa_{CO2}.

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Patients who have metabolic acidosis are currently treated with sodium bicarbonate to correct acidemia, to improve myocardial contractility and cardiac output, and to increase the cardiovascular response to circulating catecholamines (1-3). However, the ability of sodium bicarbonate therapy to achieve these goals has never been tested in a controlled clinical study and therefore is debated (2, 4). Many adverse effects of sodium bicarbonate therapy have been described (4, 5). Some of the potentially more important effects include hypercapnia and aggravation of intracellular acidosis (6, 7), hyperosmolality (8), congestive cardiac failure, and ionized hypocalcemia (9, 10). Hypercapnia is likely to occur during sodium bicarbonate therapy when the normally compensating respiratory reflexes are obtunded, which may occur during sedation and mechanical ventilation. Hypercapnia may increase intracellular acidosis because carbon dioxide crosses cell membranes rapidly and thus may decrease myocardial cell function (6, 11-14). Sodium bicarbonate is usually infused as a hypertonic solution and therefore may decrease myocardial contractility (15), increase preload, and alter afterload. Any of these changes may alter cardiac output. Finally, sodium bicarbonate may decrease plasma ionized calcium. By increasing pH, sodium bicarbonate increases the binding between calcium ions and albumin (16) and also directly binds calcium (17). A decrease in plasma ionized calcium may then decrease myocardial contractility (18).

We designed a prospective, controlled clinical study to determine whether the positive or negative hemodynamic effects of sodium bicarbonate therapy predominate when it is used to treat patients who have lactic acidosis. We questioned whether correction of acidemia using sodium bicarbonate infusion improves cardiac output, blood pressure, or other hemodynamic variables or changes plasma ionized calcium and partial pressure of CO_2 in arterial blood (Pa_{CO2}) in critically ill patients who have lactic acidosis.

Patients and Methods

Patients

Fourteen critically ill patients in the intensive care unit of a tertiary-care hospital were studied according to a protocol approved by the Human Ethics Committee of St. Paul's Hospital and the University of British Columbia. Consecutive patients, who had pulmonary and systemic arterial catheters inserted for clinical purposes, were studied if they had

Table 1. *Characteristics of 14 Patients Who Had Lactic Acidosis*

Patient	Sex, Age	Diagnoses	Inotropic Drugs	Site of Infection	Lactate	Creatinine	Outcome
	y				*mmol/L*	*μmol/L*	
1	M, 26	Chronic renal failure, ischemic bowel	dopamine, dobutamine, norepinephrine	Blood (gram-negative bacillus)	2.5	672	Died
2	F, 75	Pneumonia, ischemic bowel	dobutamine, epinephrine	Sputum (*Staphylococcus aureus*)	5.0	68	Died
3	M, 75	Empyema	dobutamine, epinephrine, norepinephrine	Pleural fluid (*Staphylococcus aureus*)	5.7	206	Died
4	M, 35	Septic shock	dopamine, epinephrine, norepinephrine	Blood (*Streptococcus pneumoniae*)	18	400	Died
5	F, 63	Septic shock, cirrhosis	dopamine, epinephrine	Blood (gram-negative bacillus)	21	226	Died
6	F, 65	Septic shock	dopamine, dobutamine, epinephrine	Blood (*Streptococcus pneumoniae*)	2.9	350	Died
7	F, 78	Hemicolectomy	dopamine, dobutamine	Peritoneum (*Bacteroides fragilis*)	4.4	123	Died
8	M, 57	Pneumonia, ethylene glycol	dopamine, epinephrine	Sputum (*Staphylococcus aureus*, gram-negative bacillus)	6.5	389	Survived
9	M, 37	Pneumonia	dopamine, dobutamine, epinephrine	Lavage (*Pneumocystis carinii*)	14	180	Died
10	F, 82	Hypovolemic shock	dopamine, dobutamine	No infection	8.4	101	Died
11	M, 67	Septic shock, acute myeloid leukemia	dopamine, epinephrine	Blood (gram-negative bacillus)	6	93	Died
12	M, 29	Pneumonia	dopamine, dobutamine, epinephrine	Lavage (*Pneumocystis carinii*)	4.7	379	Died
13	M, 61	Cardiac arrest, alcoholism	dopamine, dobutamine, epinephrine	No infection	8	175	Died
14	F, 34	Hypovolemic shock	No inotropic drugs	No infection	4.5	124	Survived

metabolic acidosis (arterial bicarbonate < 17 mmol/L and base excess < -10) and increased arterial lactate (> 2.5 mmol/L). Arterial pH was not used as an inclusion criterion because of the dependence of pH on Pa_{CO2}, which is affected by ventilator settings (19). All patients were being mechanically ventilated, 13 were receiving infusions of dopamine, dobutamine, epinephrine, or norepinephrine, or a combination, and 11 had a proven site of infection (Table 1). Eight patients had renal dysfunction (mean creatinine, 336 mmol/L; range, 175 to 672 mmol/L). The mean blood lactate was 7.8 mmol/L ($n = 14$) and the mean baseline Pa_{CO2} was 32 mm Hg, reflecting hyperventilation.

Protocol

We rigorously attempted to avoid patient variability and therefore studied all patients after their hemodynamic status had stabilized. For the same reason, ventilator settings and fluid infusion rates were kept constant during the 2-hour study period, no new medications were administered, and nursing interventions, particularly patient turning and endotracheal suctioning, were minimized. Each patient received sequentially both sodium bicarbonate (0.9 M, 2 mmol/kg body weight, infused over 15 minutes via either a peripheral or a central line) and sodium chloride (equal dose, volume, and time) during the 2-hour study period. The infusion order was randomized using cards in sealed envelopes, so that 7 patients received sodium bicarbonate first and 7 received sodium chloride first. An assistant was aware of the code and labeled each infusion numerically. When each patient's study was completed the infusions were identified to allow ongoing analysis. The infusions were identical in appearance and the investigator, the patient's nurse, and the patient were all blind to solution identity. Because the patients were all heavily sedated and mechanically ventilated they were unaware of the crossover point between infusions. Because the investigator was aware of the end tidal CO_2 measurements, however, he was no longer effectively blinded after the infusions had started.

All measurements were done immediately before, immediately after, and 30 minutes after the first infusion. After a 20-minute break the protocol was repeated with the second infusion. Thus the total study duration for each patient was less than 2 hours. This duration was chosen because it proved to be the maximum time during which we could avoid medical and nursing interventions and thus maintain constant study conditions. Every patient was studied using the same protocol with the same interval between infusions. There were no dropouts.

We measured arterial and mixed venous blood gases (including measured oxygen saturations), arterial ionized calcium, and hemodynamics (Table 2). End tidal CO_2 (Eng-

Table 2. *Additional Hemodynamic and Blood Gas Variables of 14 Patients Who Had Lactic Acidosis**

Variable	HCO_3 Infusion			NaCl Infusion		
	Before	Immediately after	30 Minutes after	Before	Immediately after	30 Minutes after
Heart rate, (*beats/min*)	111 ± 18	116 ± 24	112 ± 20	112 ± 22	114 ± 22	111 ± 19
Central venous pressure, (*mmHg*)	13 ± 5	15 ± 6	13 ± 6	11 ± 6	15 ± 7	13 ± 6
Pulmonary artery pressure, (*mmHg*)	30 ± 8	32 ± 8	30 ± 9	30 ± 8	31 ± 8	30 ± 9
Arterial oxygen saturation, (*measured %*)	92 ± 6	91 ± 6	92 ± 7	91 ± 7	92 ± 6	91 ± 7
Mixed venous oxygen saturation, (*measured %*)	69 ± 10	69 ± 11	65 ± 12	68 ± 10	69 ± 10	68 ± 11
End tidal CO_2, (*mm Hg*)	23 ± 6	29 ± 6†	25 ± 6†	22 ± 6	22 ± 6	22 ± 6
Oxygen delivery, (*mL/min*)	1067 ± 574	1188 ± 517	1023 ± 452	1036 ± 485	1150 ± 456	1055 ± 509
Oxygen consumption, (*mL/min*)	230 ± 66	256 ± 72	266 ± 92	234 ± 64	261 ± 59	242 ± 69

* All values are expressed as mean ± SD.
† $P \leq 0.01$ compared with values measured before HCO_3.

strom Eliza, Bromma, Sweden) was monitored for patient safety to provide an indicator of minute-to-minute changes in Pa_{CO2}. Hemodynamics comprised mean arterial, pulmonary artery, pulmonary capillary wedge and central venous pressures, heart rate, and cardiac output using the thermodilution technique. All measurements were done at end expiration. Cardiac output was measured in triplicate using 10-mL injections of 5% dextrose at room temperature and a cardiac output computer (Marquette Electronics Inc, Milwaukee, Wisconsin). Oxygen delivery and oxygen consumption were calculated using standard formulas (20). Plasma ionized calcium was measured using an ICA 1 analyzer (Radiometer, Copenhagen, Denmark) and was not corrected for pH.

Data Analysis

We tested the principal null hypotheses that there was no difference between sodium bicarbonate and sodium chloride infusions for cardiac output, mean arterial pressure, or ionized calcium using a 2 × 2 crossover design with repeat baseline measurements (21). The measurements after baseline were done both immediately and 30 minutes after each infusion. We also examined the other variables using the same analysis. Because no statistically significant differences in hemodynamics were observed between sodium bicarbonate and sodium chloride, we tested the power of our data (22) to detect a difference of 0.5 and 1.0 L/min between the changes in cardiac output after sodium bicarbonate compared with sodium chloride. These differences are 7% and 15%, respectively, of the mean cardiac output measurements ($n = 14$). We chose to test for a 15% change in cardiac output because previous investigators have accepted this change as clinically significant (23). We also chose to test for a smaller change in cardiac output (7%) because we recognize that the change considered to be "clinically significant" is dependent on clinical judgment.

Crossover designs with repeat baseline measurements differ from the more traditional crossover design whose weaknesses have been recently discussed (24). A 2 × 2 crossover design with repeat baseline measurements has only two possible carryover effects. First, a difference in baseline measurements can occur, and second, the treatment effect may be altered by treatment order. Kenward and Jones (21) have described a method that has a high power to test for carryover effects. In contrast, the method used to test for carryover effects in a traditional crossover design has a low power (24). Therefore, following the method of Kenward and Jones, we tested for both types of carryover. In the event that carryover was detected, only first-period data were used. In addition, because some investigators hesitate to use crossover analyses at all (24), we also tested for treatment effect using all the first-period data only. In this analysis we avoided any potential carryover problems but lost some of the statistical power of the crossover design. Finally, in order to search for a benefit for bicarbonate in very acidemic patients, we also separately examined the subgroup of seven patients who had an initial pH of 7.20 or less. Crossover study results are presented as estimates of the effect and with 95% confidence intervals (CI).

Results

There was no difference at any time between the effects of sodium bicarbonate and sodium chloride infusions on cardiac output, blood pressure, or pulmonary capillary wedge pressure (Figure 1). Immediately after both infusions pulmonary capillary wedge pressure increased (15 to 17 mm Hg and 14 to 17 mm Hg; both $P < 0.001$) and cardiac output increased (6.7 to 7.5 L/min and 6.6 to 7.3 L/min; both $P < 0.01$), whereas mean arterial pressure and heart rate were unchanged. The differences in effects between sodium bicarbonate and sodium chloride at 30 minutes were 0.15 L/min (CI, −0.06 to 0.36) for cardiac output, −0.29 mm Hg (CI, −2.43 to 1.85) for mean arterial pressure, and 0.44 mm Hg (CI, −1.10 to 0.46) for pulmonary capillary wedge pressure. None of these differences at 30 minutes was statistically significant.

In this study, the dose of sodium bicarbonate used (2 mmol/kg) was adequate to significantly improve acidemia throughout the study period. After sodium bicarbonate infusion, the mean arterial pH increased from 7.22 to 7.36 ($P < 0.001$) and the mean serum bicarbonate increased from 12 to 18 mmol/L ($P < 0.001$). Both measurements then gradually decreased (Figure 1). At 30 minutes, however, both were still increased compared with their baselines ($P < 0.001$). Unlike our hemodynamic measurements, the baseline measurements of serum bicarbonate in the sodium bicarbonate and sodium chloride groups were not identical. We therefore also present the data by order of infusion (Figure 2) to demonstrate that the hemodynamic effects were the same regardless of the infusion order.

Bicarbonate decreased plasma ionized calcium (Figure 3). Plasma ionized calcium was low in all patients at baseline (mean, 0.95 mmol/L; normal range for our laboratory, 1.17 to 1.29 mmol/L). After sodium bicarbonate infusion, plasma ionized calcium decreased further (to 0.87 mmol/L, $P < 0.001$) but after sodium chloride infusion, it was unchanged. Bicarbonate increased Pa_{CO2}. During the sodium bicarbonate infusion, Pa_{CO2} increased from 33 to 39 mm Hg ($P < 0.001$). End tidal CO_2 increased from 23 to 29 mm Hg ($P < 0.001$) over the same time and peaked toward the end of the infusion. Arterial and end tidal CO_2 then decreased, but both were still elevated at 30 minutes. None of these changes were seen after sodium chloride.

The power of our design to detect a difference in cardiac output between sodium bicarbonate and sodium chloride infusions was 99.9% to detect a difference of 1.0 L/min, and over 90% to detect a difference of 0.5 L/min. When we examined the first period only (no crossover), seven patients received sodium bicarbonate and seven received sodium chloride. The conclusions are the same as in the larger study–no difference was seen between sodium bicarbonate and sodium chloride for any hemodynamic response. In this more restricted analysis, the power was 95% to detect a 1.0 L/min difference but less than 50% to detect a 0.5 L/min difference.

Finally, we separately analyzed the seven most acidemic patients (arterial pH < 7.20; Figure 4). These patients had a mean arterial pH of 7.13 (range, 6.9 to 7.2) and a mean arterial lactate of 10.1 mmol/L (range, 2.6 to 21 mmol/L). Even in these patients, however, although bicarbonate increased arterial pH significantly (Figure 4, *left*), it did not increase cardiac output or mean arterial pressure. The hemodynamic responses (Figure 4, *right*) were the same as those for the whole group.

Discussion

Our study shows that in critically ill patients who have metabolic acidosis and increased blood lactate, correction of acidemia using sodium bicarbonate does not increase cardiac output, blood pressure, or other hemodynamic variables even when the arterial pH is less

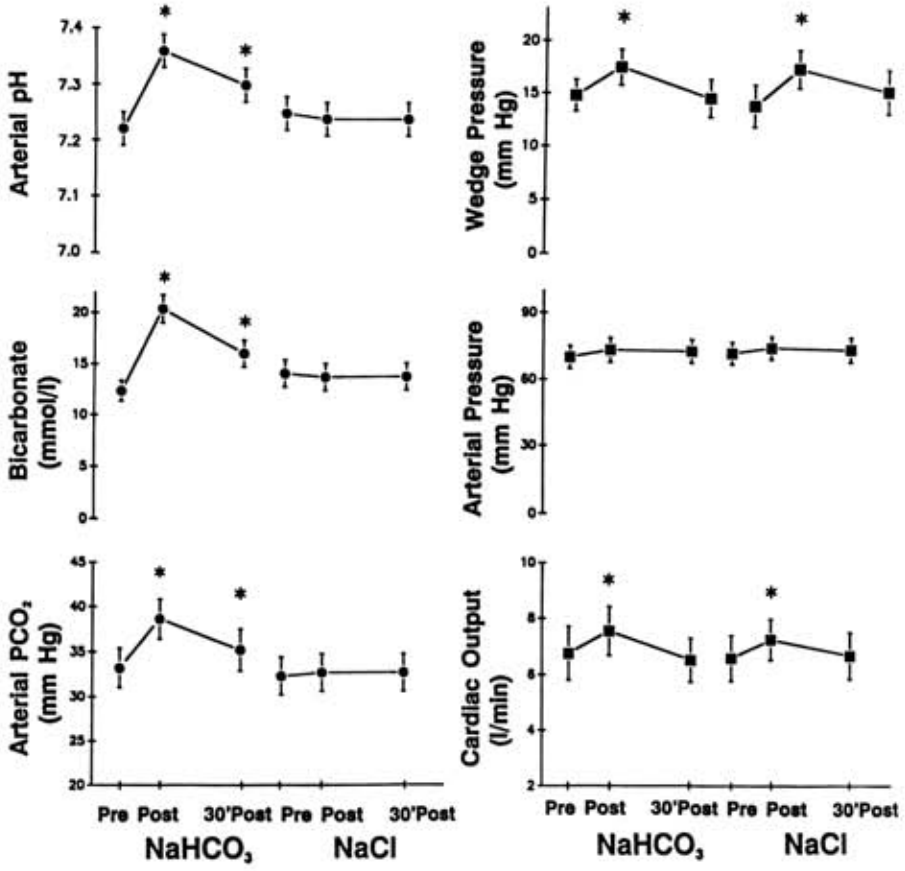

Figure 1. Acid-base (*left*) and hemodynamic (*right*) measurements before (*Pre*) and after (*Post*) sodium bicarbonate and sodium chloride in critically ill patients who had lactic acidosis ($n = 14$). The increases in pulmonary capillary wedge pressure and cardiac output were not caused by pH correction because identical changes were observed after sodium chloride. All values are mean ± SE. Asterisk indicates $P < 0.01$ compared with Pre.

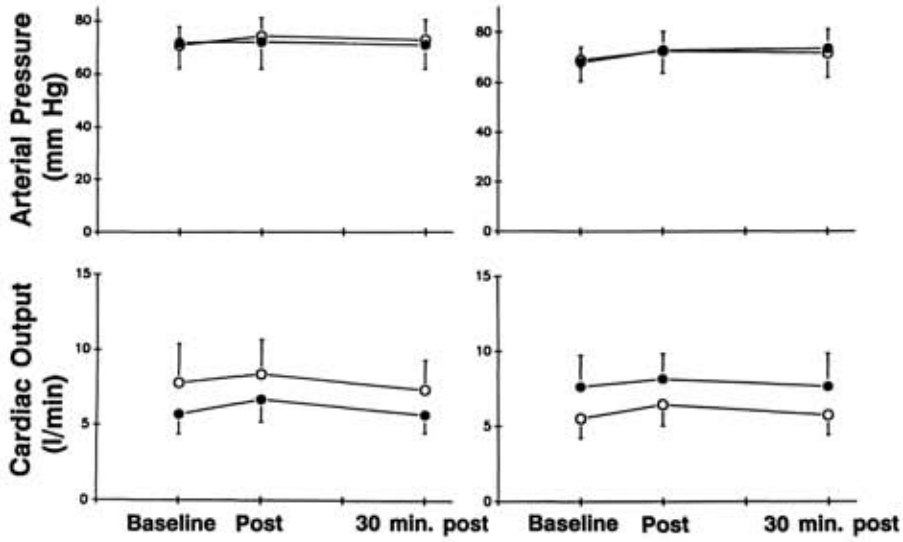

Figure 2. Influence of infusion order on hemodynamic measurements before (*Baseline*) and after (*Post*) sodium bicarbonate and sodium chloride in 14 patients who had lactic acidosis. In each case patients who received an infusion first are represented with open circles and those who received an infusion second are represented with closed circles. There were no changes in cardiac output or blood pressure and the trends were the same regardless of infusion order. All values are mean ± SE.

than 7.20. Unexpectedly, we also found that sodium bicarbonate infusion does not increase the cardiovascular response to circulating catecholamines in these patients. This study identifies two side effects of sodium bicarbonate infusion that may explain its lack of efficacy: Sodium bicarbonate decreases plasma ionized calcium and increases Pa_{CO2}. Finally, this study suggests that transient hemodynamic responses to sodium bicarbonate infusion are not caused by increases in pH, but instead are caused by the infusion of a hypertonic, sodium-containing solution.

Many clinicians believe that correction of acidemia using sodium bicarbonate is most likely to improve hemodynamics in patients who have a very low pH, and an arterial pH of 7.20 is often the point at which sodium bicarbonate therapy is recommended (25, 26). However, in our patients who had an arterial pH less than 7.20, there was no difference between the hemodynamic effects of sodium bicarbonate and sodium chloride. Thus, it appears that even in very acidemic patients, an increase in pH using sodium bicarbonate does not improve hemodynamics.

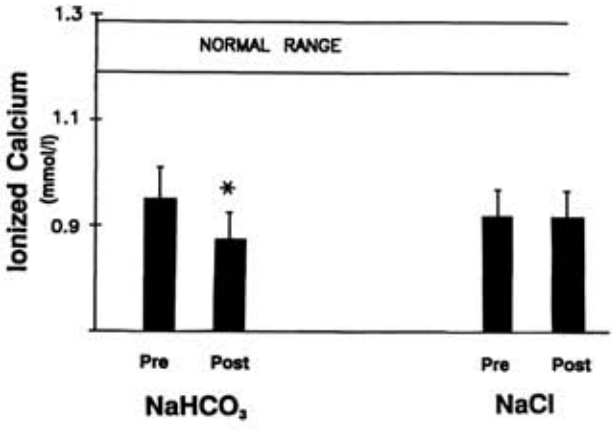

Figure 3. Changes in plasma ionized calcium after sodium bicarbonate and sodium chloride in critically ill patients who have lactic acidosis ($n = 10$). Ionized calcium decreased after sodium bicarbonate but not after sodium chloride infusion. All values are mean ± SE. Asterisk indicates $P < 0.001$ compared with Pre.

Because 13 of our 14 patients were receiving catecholamine infusions, we were also able to examine the hypothesis that correction of acidemia increases the cardiovascular response to circulating catecholamines (27, 28). We found that it did not. The notion that acidemia decreases the cardiovascular response to circulating catecholamines is widely held among clinicians and is based largely on animal models using extremely severe acidosis (29). We measured no difference in the hemodynamic responses after sodium bicarbonate and sodium chloride in our patients who were receiving catecholamines, despite a large increase in pH using sodium bicarbonate. Therefore, we conclude that in critically ill patients who have lactic acidosis, sodium bicarbonate infusion does not improve the cardiovascular response to catecholamines.

Our study identifies two important side effects of sodium bicarbonate therapy: decreased ionized calcium and increased Pa_{CO2}. Sodium bicarbonate may decrease ionized calcium by two mechanisms. First, an increase in pH increases the binding between ionized calcium and proteins and thereby decreases the physiologically active, ionized fraction (16). Second, bicarbonate may directly complex calcium in vivo as it does in vitro (16, 17). Although several investigators (9, 10) have recently raised this issue as potentially important in humans, we know of no data that have been published on the effect of sodium bicarbonate therapy on plasma ionized calcium in either animals or patients who have lactic acidosis. A decrease in plasma ionized calcium in these patients may decrease myocardial contractility as it did in a recent study (18) in which myocardial contractility, measured non-invasively in humans, decreased as plasma ionized calcium decreased. In that study plasma ionized calcium decreased by 24%. Our patients' mean plasma ionized calcium at baseline was 20% below the normal range for our laboratory. Sodium bicarbonate infusion further decreased plasma ionized calcium by 8.5% ($P < 0.001$). Thus, we believe that the low ionized calcium levels in our patients may have decreased myocardial contractility, and we also suspect that so-

dium bicarbonate administered to our patients before the study may have contributed considerably to the baseline plasma ionized calcium levels we observed. A number of associations of ionized hypocalcemia in critically ill patients have been described (30, 31). Our study identifies another cause–sodium bicarbonate therapy–in critically ill patients who have lactic acidosis. The other important side effect of sodium bicarbonate infusion that we recognized in these mechanically ventilated patients was hypercapnia, which may also decrease myocardial contractility. We did not measure intracellular pH in this study but an increase in extracellular P_{CO_2} may decrease intracellular pH and thus decrease myocardial cell function (6, 13, 14).

Our study also suggests that anecdotal reports (32) of sodium bicarbonate improving hemodynamics during acidosis may be explained by effects common to both sodium bicarbonate and sodium chloride infusions, and not to pH changes. The increase in extracellular fluid osmolality and in sodium content can both affect myocardial contractility (15). Furthermore, the increase in intravascular volume after hypertonic solutions may be much greater than the infused volume owing to fluid shifts from the extravascular compartment. Thus, increased preload may then increase cardiac output. Our equimolar sodium chloride control was received by all patients, and therefore we were able to clearly separate the effects of increased pH from these other factors. We found that all the changes in hemodynamics that we observed were accounted for by factors common to both solutions and not to changes in pH.

Our conclusions differ from previously published reports that suggest a beneficial effect of sodium bicarbonate. There are three likely reasons for these differences. First, most previous studies have not been in humans, and because large interspecies differences exist (33) these studies may not be directly extrapolated to humans. A prospective, controlled human study has not previously been reported. Second, most previous studies did not examine endogenous lactic acidosis (34, 35), and those studies that did examine endogenous lactic acidosis used drugs and anesthetic agents known to depress myocardial contractility (36, 37). Finally, of those studies that have examined sodium bicarbonate therapy, most have been unable to reach a definitive conclusion about hemodynamics because of difficulty increasing pH with the dose and regimen of sodium bicarbonate used (36, 38).

We believe that our patients are typical of those who currently receive sodium bicarbonate therapy in many critical care settings. Our patients had severe cardiac dysfunction. Despite high preload (mean pulmonary capillary wedge pressure, 14 mm Hg), low afterload (mean arterial pressure, 70 mm Hg), and infusion of inotropic drugs in 13 patients, cardiac output was only marginally above normal (mean, 6.7 L/min, Figure 1). In contrast, a normal patient who had no cardiac dysfunction but who had the same high preload, low afterload, and inotrope infusions would be expected to have a much greater cardiac output. Cardiac dysfunction may have been caused by acidemia but there are other possible causes. Our patients had a very high mortality (86%, Table 1). However,

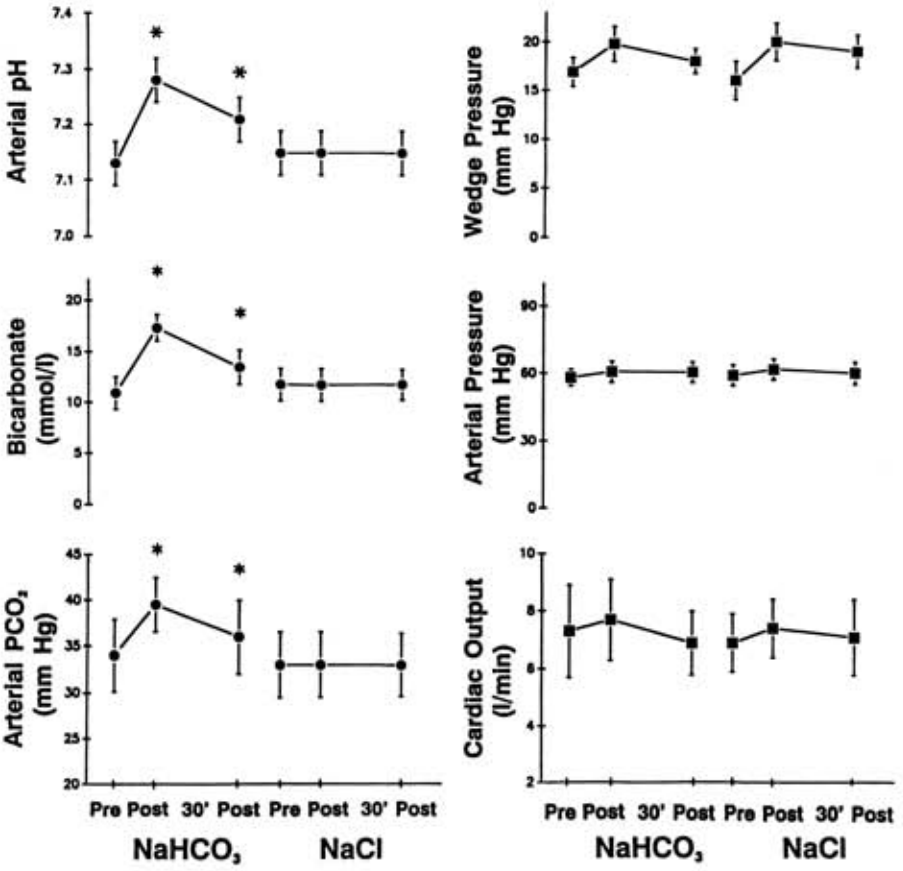

Figure 4. Acid-base (*left*) and hemodynamic (*right*) measurements before (*Pre*) and after (*Post*) sodium bicarbonate and sodium chloride in seven, critically ill patients who had severe lactic acidosis (arterial pH < 7.20). The changes and the trends were the same as in the larger group (Figure 1). All values are mean ± SE. Asterisk indicates $P < 0.05$ compared with Pre.

the mean survival time of nonsurvivors after the study was 48 hours. Therefore, although these patients were all critically ill, had cardiac dysfunction, and had a high mortality, they were stable at the time of the study. It is exactly this type of patient who currently receives sodium bicarbonate therapy in many different critical care settings in North America today.

Correction of acidemia using sodium bicarbonate infusion does not improve cardiac output, blood pressure, or other hemodynamic variables in critically ill patients who have lactic acidosis. Correction of acidemia also does not improve the cardiovascular response to circulating catecholamines in these patients. Sodium bicarbonate infusion decreases plasma ionized calcium and increases Pa_{CO2}, and we speculate that these side effects may override the beneficial effects that pH correction may have on hemodynamics.

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References

1. **Olivia PB.** Lactic acidosis. *Am J Med.* 1970;**48:**209-25.
2. **Narins RG, Cohen JJ.** Bicarbonate therapy for organic acidosis: the case for its continued use. *Ann Intern Med.* 1987;**106:**615-8.
3. **Narins RG, Jones ER, Dornfield LP.** Alkali therapy of the organic acidoses: a critical assessment of the data and the case for judicious use of sodium bicarbonate. In: Narins RG, ed. *Controversies in Nephrology and Hypertension.* New York: Churchill Livingstone; 1984:359-76.
4. **Stacpoole PW.** Lactic acidosis: the case against bicarbonate therapy. *Ann Intern Med.* 1986;**105:**276-9.
5. **Graf H, Leach W, Arieff AI.** Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. *Science.* 1985;**227:**754-6.
6. **von Planta M, Gudipati CV, Weil MH, Kraus LJ, Rackow EC.** Effects of tromethamine and sodium bicarbonate buffers during cardiac resuscitation. *J Clin Pharmacol.* 1988;**28:**594-9.
7. **Graf H, Leach W, Arieff AI.** Metabolic effects of sodium bicarbonate in hypoxic lactic acidosis in dogs. *Am J Physiol.* 1985;**249:**F630-5.
8. **Mattar JA, Weil MH, Shubin H, Stein L.** Cardiac arrest in the critically ill. II. Hyperosmolal states following cardiac arrest. *Am J Med.* 1974;**56:**162-8.
9. **Cooper DJ, Worthley LI.** Adverse haemodynamic effects of sodium bicarbonate in metabolic acidosis. *Intensive Care Med.* 1987;**13:**425-7.
10. **Graf H, Arieff AI.** The use of sodium bicarbonate in the therapy of organic acidosis. *Intensive Care Med.* 1986;**12:**285-8.
11. **Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI.** Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. *N Engl J Med.* 1988;**315:**153-6.
12. **Falk JL, Rackow EC, Weil MH.** End-tidal carbon dioxide concentration during cardiopulmonary resuscitation. *N Engl J Med.* 1988;**18:**607-11.
13. **Ng ML, Levy MN, Zieske HA.** Effects of changes in pH and of carbon dioxide tension on left ventricular performance. *Am J Physiol.* 1967;**213:**115-20.
14. **Steenbergen C, Deleeuw G, Rich T, Williamson JR.** Effect of acidosis and ischemia on contractility and intracellular pH of rat heart. *Circ Res.* 1977;**41:**849-58.
15. **Kozeny GA, Murdock DF, Euler DE, et al.** In vivo effects of acute changes in osmolality and sodium concentration on myocardial contractility. *Am Heart J.* 1985;**109:**290-6.
16. **Pederson KO.** Binding of calcium to serum albumin. II. Effect of pH via competitive hydrogen and calcium ion binding to the imidazole groups of albumin. *Scand J Clin Lab Invest.* 1972;**29:**75-83.
17. **Oberleithner H, Greger R, Lang F.** The effect of respiratory and metabolic acid-base changes on ionized calcium concentration: in vivo and in vitro experiments in man and rat. *Eur J Clin Invest.* 1982;**12:**451-5.
18. **Lang RM, Fellner SK, Neumann A, Bushinsky DA, Borow KM.** Left ventricular contractility varies directly with blood ionized calcium. *Ann Intern Med.* 1988;**108:**524-9.
19. **Stacpoole PW, Harman EM, Curry SH, Baumgartner TG, Misbin RI.** Treatment of lactic acidosis with dichloroacetate. *N Engl J Med.* 1983;**309:**390-6.
20. **Shoemaker WC.** Relation of oxygen transport patterns to the pathophysiology and therapy of shock states. *Intensive Care Med.* 1987;**13:**230-43.
21. **Kenward MG, Jones B.** The analysis of data from 2×2 crossover trials with baseline measurements. *Stat Med.* 1987;**6:**911-26.
22. **Zar JH.** *Biostatistical Analysis.* 2d ed. Englewood Cliffs, New Jersey: Prentice Hall; 1984:150-60.
23. **Stetz CW, Miller RG, Kelly GE, Raffin TA.** Reliability of the thermodilution method in the determination of cardiac output in clinical practice. *Am Rev Resp Dis.* 1982;**126:**1001-4.
24. **Woods JR, Williams JG, Tavel M.** The two-period crossover design in medical research. *Ann Intern Med.* 1989;**110:**560-6.
25. **Cohen RD, Woods HF.** Lactic acidosis revisited. *Diabetes.* 1983;**32:**181-91.
26. **Mizock BA.** Controversies in lactic acidosis. Implications in critically ill patients. *JAMA.* 1987;**258:**497-501.
27. **Davies AO.** Rapid desensitization and uncoupling of human beta-adrenergic receptors in an in vitro model of lactic acidosis. *J Clin Endocrinol Metab.* 1984;**59:**398-405.
28. **Campbell GS, Hale DB, Crisp NW, Weil MH, Brown EB.** Depressed response to intravenous sympathomimetic agents in humans during acidosis. *Dis Chest.* 1958;**33:**18-22.
29. **Thrower WB, Darby TD, Aldinger EE.** Acid-base derangements and myocardial contractility. Effects as a complication of shock. *Arch Surg.* 1961;**82:**76-85.
30. **Desai TK, Carlson RW, Geheb MA.** Prevalence and clinical implications of hypocalcemia in acutely ill patients in a medical intensive care setting. *Am J Med.* 1988;**84:**209-14.
31. **Zaloga GP, Chernow B.** The multifactorial basis of hypocalcemia during sepsis. Studies of the parathyroid hormone-vitamin D axis. *Ann Intern Med.* 1987;**107:**36-41.
32. **Chazan JA, Stenson R, Kurland GS.** The acidosis of cardiac arrest. *N Engl J Med.* 1968;**278:**360-4.
33. **Downing SE, Talner NS, Gardner TH.** Cardiovascular responses to metabolic acidosis. *Am J Physiol.* 1965;**208:**237-42.
34. **Fisher DJ.** Acidaemia reduces cardiac output and left ventricular contractility in conscious lambs. *J Dev Physiol.* 1986;**8:**23-31.
35. **Jeffrey FM, Malloy CR, Radda GK.** Influence of intracellular acidosis on contractile function in the working rat heart. *Am J Physiol.* 1987;**253**(6 Pt 2):H1499-505.
36. **Arieff AI, Gertz EW, Park R, Leach W, Lazarowitz VC.** Lactic acidosis and the cardiovascular system in the dog. *Clin Sci.* 1983;**64:**573-80.
37. **Arieff AI, Leach W, Park R, Lazarowitz VC.** Systemic effects of $NaHCO_3$ in experimental lactic acidosis in dogs. *Am J Physiol.* 1982;**242:**F586-91.
38. **Iberti TJ, Kelly KM, Gentili DR, et al.** Effects of sodium bicarbonate in canine hemorrhagic shock. *Crit Care Med.* 1988;**16:**779-82.