Improved hemodynamic function during hypoxia with carbicarb,* a new agent for the management of acidosis

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ABSTRACT Carbicarb is a mixture of Na₂CO₃/NaHCO₃ that buffers similarly to NaHCO₃, but without net generation of CO₂. We studied the effects of carbicarb in an animal preparation of hypoxic lactic acidosis (HLA). HLA was induced by ventilating dogs with an hypoxic gas mixture (8% O₂/92% N₂). Dogs with HLA (n = 28) were then treated with 2.5 meq/kg of either NaHCO₃ or carbicarb over 1 hr. Measurements were made, after 1 hr of hypoxia and 1 hr of therapy, of: cardiac hemodynamics, blood gases, liver intracellular pH (pHi), oxygen consumption, and regional lactate production. After therapy, the arterial pH rose with carbicarb (7.22 to 7.27, p<.01), and fell with NaHCO₃ (7.18 to 7.13, p<.01). Mixed venous PCO₂ did not change with carbicarb but increased with NaHCO₃ (p<.05). Arterial lactates stabilized with carbicarb but rose with NaHCO₃ (by 3.1 mmol/liter, p<.005). Lactate use by muscle, gut, and liver all improved with carbicarb and decreased with NaHCO₃. The liver pHi (normal = 6.99, hypoxia = 6.80) improved with carbicarb (to 6.92), but decreased further with NaHCO₃ (to 6.40). Muscle O₂ consumption rose with carbicarb, whereas it decreased with NaHCO₃. Arterial pressure fell less with carbicarb (–12 vs –46 mm Hg, p<.006) and the cardiac output was stable with carbicarb but decreased with NaHCO₃ (from 143 to 98 ml/kg/min, p<.004). Stroke volume also improved with carbicarb but there was no change in pulmonary capillary wedge pressure, suggesting that carbicarb had a beneficial effect on myocardial contractility. These data demonstrate that administration of carbicarb to dogs with HLA results in improvements in the arterial blood gases, tissue pH, lactate production, and cardiac hemodynamics. These findings are in contrast to the effects of NaHCO₃ and may be related to less systemic CO₂ generation by carbicarb. Carbicarb thus appears to be superior to NaHCO₃ for the treatment of hypoxic states in the presence of lactic acidosis.


THE MOST COMMON causes of metabolic acidosis are cardiopulmonary arrest and other states characterized by impaired cardiac performance and reduced tissue perfusion.¹ In these states, hypoxia and circulatory insufficiency combine to reduce tissue oxygen availability, causing anaerobic metabolism and lactic acidosis.²

The lactic acidosis in turn appears to have direct negative effects on myocardial function.³–⁵ Indeed, this effect appears to be most pronounced when the acidosis is due to hypoxia, since myocardial contractile function is depressed more by the combination of hypoxia and lactic acidosis than by either process alone.⁶,⁷ Since tissue oxygen delivery is critically dependent on cardiac output in hypoxic states and cardiopulmonary arrest, the negative inotropic effect of lactic acidosis assumes a critically important role in determining clinical outcome in these situations. Because of this, the goal of cardiopulmonary resuscitation has been to correct both the hypoxia and the lactic acidosis simultaneously in order to restore myocardial function as rapidly as possible.¹¹

The correction of lactic acidosis in hypoxic states has traditionally been accomplished with the administration of sodium bicarbonate (NaHCO₃). However, investigations from our laboratory and others¹²–¹⁶ suggest that the administration of NaHCO₃ in this setting may be counterproductive. Using an animal preparation of hypoxic lactic acidosis (HLA) in dogs,
demonstrated that the administration of NaHCO₃ was associated with depression of cardiac function, acceleration of lactate production, and a paradoxical lowering of the blood pH and bicarbonate concentrations. The potential mechanisms by which bicarbonate may have these deleterious consequences include: (1) the production of CO₂ as a result of bicarbonate administration, which may then aggravate intracellular acidosis, and (2) enhanced glycolysis, which may stimulate or accelerate lactic acid production as the pH increases. (3) increased oxygen-hemoglobin binding, which may then impair tissue oxygen availability. This latter phenomenon assumes particular importance in hypoxic states and cardiopulmonary arrest.

However, both an increase in glycolysis and a shift of the oxygen-hemoglobin binding curve are predicted on an increase of the blood pH as a result of NaHCO₃ administration. If the blood pH is not increased, then these two mechanisms cannot explain the effects of NaHCO₃ on hemodynamic function and lactate production. Rather, a likely mechanism for these effects is the generation of CO₂ resulting from an administration of NaHCO₃.

To test this hypothesis, we compared NaHCO₃ to a new agent, carbicarb, in an animal preparation of HLA. Carbicarb is an equimolar solution of sodium carbonate and sodium bicarbonate. It buffers excess hydrogen ions in the blood in a manner similar to that of NaHCO₃, but it does so without changing PCO₂ levels. Thus, a comparison of these two agents allows one to determine the importance of CO₂ production to the observed effects of NaHCO₃ on cardiovascular function, tissue oxygen delivery, and lactate metabolism.

**Methods**

Studies were carried out in two groups of mongrel dogs, mean weight of 20 kg, as follows. HLA was induced both groups of dogs by delivery of low oxygen gas mixtures under general anesthesia. Dogs were anesthetized with sodium pentobarbital (18 to 20 mg/kg iv), intubated, and mechanically ventilated with anesthesia machine (Harvard). The anesthesia machine was adjusted to deliver a mixture of nitrogen and oxygen gas to each animal. In preliminary experiments, it was found that there was marked individual variation among dogs such that the percent flow of oxygen required to establish hypoxia in each dog was critical and required individual adjustment. If the oxygen content of the gas mixture and the resultant arterial PO₂ were too high, lactic acidosis did not occur, even with an arterial PO₂ as low as 30 mm Hg. If the PO₂ was too low (below 20 mm Hg), the animals suffered fibrillatory arrest and died. The optimum gas mixture was found to be a mean of 8% oxygen and 92% nitrogen, which served to maintain arterial PO₂ between 25 and 30 mm Hg. With an arterial PO₂ of 25 to 30 mm Hg, metabolic acidosis was established rapidly (less than 30 min), with the arterial pH achieving a steady state of 7.20 ± 0.05 and the arterial lactate rising to a plateau above 5 mmol/liter. Thereafter, the blood pH changed little and the arterial lactate rose more slowly, generally at a rate of 1 to 2 mmol/liter/hr as continuous hypoxia was maintained. Minute ventilation was also individually adjusted to normalize the arterial PCO₂ at 37 ± 2 mm Hg and once adjusted was kept constant throughout the experimental protocol.

After 1 hr of continuous hypoxia, measurements were made of: (1) circulatory hemodynamics, including cardiac output, mean right atrial pressure, pulmonary arterial systolic, diastolic, and mean pressures, pulmonary capillary wedge (PCW) pressure, hind limb blood flow, and hepatic portal vein blood flow, (2) blood gases, regional oxygen consumption, 2,3-diphosphoglyceric acid (2,3-DPG), and the p50 of blood, (3) regional net lactate metabolism, and (4) liver intracellular pH (pHi). Blood gases, oxygen saturations, and lactate were measured in samples from the aorta, pulmonary artery, inferior vena cava, femoral vein, hepatic portal vein (HPV), and hepatic vein.

Cardiac output was measured in triplicate with the thermodilution technique by insertion of a balloon-tipped, flow-directed catheter into the pulmonary artery and by use of a cardiac output computer (Instrumentation Laboratories, Lexington, MA). Hind limb muscle flow was estimated by measurement of femoral artery blood flow with the use of Statham flowmeters (Gould Statham Model SP202, Oxnard, CA). Gut blood flow was estimated similarly by measurement of HPV flow. Right atrial mean pressure and pulmonary arterial pressures were recorded from the pulmonary artery catheter. Central aortic mean pressure was recorded with a catheter placed in the abdominal aorta via a femoral artery. All pressures were measured in millimeters of mercury with Gould pressure transducers and a physiologic monitor (Electronics for Medicine Model IM-4, Honeywell Systems). Total peripheral resistance (TPR) was calculated with the formula: TPR = (MAP × 80)/CO, where MAP is mean arterial pressure and CO is cardiac output. Similarly, pulmonary vascular resistance (PVR) was calculated with the formula: PVR = (PAM – PCW)/80/CO, where PAM is mean pulmonary arterial pressure. The electrocardiogram and heart rate were monitored continuously with the use of a three-lead system and the physiologic monitor.

Blood gases were measured at 37°C with an automated blood gas analyzer (Model ABL-30, Radiometer, Copenhagen, Denmark). Oxygen saturations and hemoglobin contents were measured simultaneously on the same blood samples with an automated oximeter (Model OSM-3, Radiometer, Copenhagen, Denmark). Oxygen contents (vol%) were calculated with the formula: O₂ content = 1.34 × hemoglobin content × % O₂ saturation. Systemic oxygen consumption was then calculated with the formula: systemic O₂ consumption = (aortic-pulmonary artery) O₂ content difference × CO. Similarly, hind limb oxygen consumption was estimated with the formula: hind limb oxygen consumption = (femoral artery – femoral vein) O₂ content difference × femoral artery flow. Liver oxygen consumption was estimated with the formula: liver oxygen consumption = [HPV + 0.41 aortic – 1.41 hepatic vein] O₂ content × HPV flow, based on direct measurement of HPV flow and the observation that hepatic artery flow is normally 41% of total hepatic blood flow, as previously published. The p50 of blood was calculated on arterial samples corrected for temperature with the use of directly measured oxygen saturations, oxygen tensions, blood pH, and published tables. Measurements of 2,3-DPG (mmol/ml) were made on 0.5 ml samples of arterial blood deproteinized immediately with 1.0 ml 0.55M perchloric acid and frozen at −5°C. The 2,3-DPG content was then measured spectrophotometrically on these sam-
samples by the NADH oxidation method (Sigma Chemicals, St. Louis).**26 Blood lactates were also measured spectrophotometrically on deproteinized samples from all sites sampled (Sigma Chemicals, St. Louis).**27 Net lactate production by the gut and hind limb was estimated by determining the difference in blood lactate levels in the appropriate arteries and veins and by multiplying the differences by the organ blood flow. For net hepatic lactate extraction, addition of (0.71)(HPV lactate) + (0.29)(aortic lactate) yields the afferent hepatic lactate. The efferent (venous) lactate is the hepatic vein lactate. Subtraction of the efferent (venous) from afferent lactate multiplied by the liver blood flow yields the liver lactate uptake. Systemic lactate production was determined by the formula: (pulmonary artery – arterial) lactate difference × CO.

Liver pH was estimated by the 14C-dimethadione (DMO) technique.**28 A dose of 50 to 75 mCi of 14C-DMO was injected intravenously 1 hr before determination of liver pH. At the time of determination of pH, blood samples were taken from the hepatic vein and HPV to establish the extracellular reference pH, lactate concentration, and whole blood 14C-DMO activity. A tissue sample was then obtained and processed for 14C-DMO activity and lactate. Corrections for the liver extracellular space were made by measurement of the endogenous chloride space, as previously described.**28

After measurement of the above variables during continuous hypoxia, each dog was randomly assigned to one of two treatment groups. In group I, the dogs were administered 2.5 meq/kg body weight of 1M NaHCO3 by continuous infusion over 1 hr. Group II animals received 2.5 meq/kg body weight of 1M carbicarb by continuous infusion over 1 hr. At the end of each 1 hr infusion, the above-mentioned measurements were all repeated to determine end-therapy values.

Statistical analyses were made by comparing end-therapy values to individual hypoxic values with use of paired t tests to determine significant effects of therapy within treatment groups. Comparisons between treatment groups were made by unpaired t tests of net changes from individual hypoxic values. Differences between treatment groups were considered significant when p < .05. Statistical analysis was accomplished with Macintosh Plus computer and a Statview 512 + Statistical Software package (Calabassas, CA).

Results

A total of 28 dogs were studied, 13 in the NaHCO3 treatment group (group I) and 15 in the carbicarb group (group II). The pretreatment room-air (normoxic) values for each measured variable were not significantly different between groups.

Blood gas analysis. The arterial pH improved significantly with carbicarb (from 7.22 to 7.27, p < .01), whereas it declined with NaHCO3 (from 7.18 to 7.13, p < .01) (figure 1). Likewise, the arterial bicarbonate concentration increased with carbicarb an average of 1 mmol/liter for each millimole per kilogram body weight administered (from 14.4 to 16.6), whereas it fell paradoxically with NaHCO3. The arterial Pco2 did not change with either carbicarb (from 35.0 to 35.2, p = NS) or NaHCO3 (from 34.4 to 33.6, p = NS). However, the mixed-venous Pco2 showed a differential response. With carbicarb, the mixed-venous Pco2 did not vary (from 39.2 to 39.1, p = NS). With NaHCO3, on the other hand, the mixed-venous Pco2 rose significantly (from 38.5 to 40.8, p < .05).

The arterial Po2 was reduced from 96 to 25 mm Hg with the establishment of hypoxia. Corresponding arterial oxygen contents fell from 18.9 to 6.6 vol%. Despite the low arterial Po2 in both groups, systemic oxygen extraction remained normal (4.1 vol% at room air vs 4.1 vol% with hypoxia, p = NS) and systemic oxygen consumption did not fall (from 4.5 to 5.2 ml O2/min/kg body weight, p = NS). Therapy did not change the arterial Po2 (mean net change +1 mm Hg in group I vs + 4 mm Hg in group II, p = NS) or arterial oxygen content (+ 0.7 vs + 0.2 vol%, p = NS). Arterial 2,3-DPG levels did not change (+ 0.43 vs – 0.22 mmol/g hemoglobin, p = NS) and the p50 of blood remained normal throughout the experiment in both treatment groups (from 28.9 with hypoxia to 28.3 with therapy, p = NS; normal = 29.0). Thus, neither blood oxygen carrying capacity nor blood oxygen-hemoglobin binding was affected by either therapy.

Hemodynamics. With the establishment of hypoxia, the cardiac output increased by 24% from 115 to 143 ml/min/kg body weight. With the administration of NaHCO3, the cardiac output fell substantially to 98 ml/min/kg body weight (p < .004), whereas with carbicarb the cardiac output did not change (150 ml/min/kg body weight, p = NS) (figure 2). There were no significant differences in the pulmonary arterial

![Figure 1](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.77.1.229?journalCode=circ)
pressures, PVR, PCW pressure, or heart rates in group I vs group II dogs. Thus, the fall in cardiac output with NaHCO₃ was due to a primary reduction in stroke volume, whereas the improvement in cardiac output with carbicarb was attributable to a modest improvement in stroke volume (figure 3).

The TPR fell modestly with both infusions (−475 vs −480 dynes·sec·cm⁻⁵, p = NS). As a result, changes in arterial pressure reflected primary changes in cardiac output. Since administration of NaHCO₃ resulted in a significant reduction in cardiac output, arterial pressure fell precipitously (from 105 to 59 mm Hg, p < .001). With carbicarb, on the other hand, cardiac output improved as peripheral resistance fell, and thus arterial pressure did not change (figure 4).

With administration of NaHCO₃, changes in the cardiac output with therapy correlated with changes in the mixed venous PCO₂. As mixed venous PCO₂ rose, the cardiac output fell, and vice versa (figure 4). A positive correlation was also found between the arterial pH and cardiac output after NaHCO₃, so that as arterial pH fell, so did the cardiac output (figure 4). However, even in the few animals in which NaHCO₃ raised the arterial pH, the cardiac output still tended to fall unless the arterial pH was restored to normal. Significant correlations between mixed venous PCO₂, arterial pH, and cardiac output were not present after carbicarb.
since the mixed venous Pco2 did not vary and the mean arterial pH and cardiac output improved.

Both therapeutic agents reduced hepatic portal blood flow to the same degree (−92 vs −82 ml/min, p = NS). However, hind limb blood flow was reduced substantially more by NaHCO3 than by carbicarb (−53 vs −19 ml/min).

Oxygen delivery and consumption. Whole body oxygen delivery was reduced by 1.7 ml O2/min/kg body weight (23% decrease) as a result of administration of NaHCO3. Whole body oxygen consumption also decreased, although to a lesser extent (−0.5 ml O2/min/kg body weight, 8% decrease) than oxygen delivery (figure 5). Systemic oxygen extraction increased (+1.3 vol%) to partially offset the decrease of cardiac output. In contrast, carbicarb increased whole body oxygen delivery by 1.3 ml O2/min/kg body weight (p<.05) and oxygen consumption by 1.1 ml O2/min/kg body weight (figure 5). Systemic oxygen extraction did not change (−0.2 vol%, p = NS). Oxygen delivery, extraction, and consumption by the liver and gut did not differ with the two infusions. However, hind limb oxygen delivery and consumption decreased significantly with NaHCO3 and increased with carbicarb.

Lactate metabolism. With the establishment of hypoxia, the arterial lactate concentration rose from 1.97 to 7.18 mmol/liter. After NaHCO3, the arterial lactate continued to rise at an accelerated rate, whereas with carbicarb, the arterial lactate rose at a much slower rate (+3.14 vs +1.21 mmol/liter/hr, p<.03) (figure 6). Lactate concentrations in the HPV and liver followed the same pattern (figure 7), as did lactate concentrations in the hepatic vein, vena cava, and femoral vein. Net hepatic lactate clearance did not change with NaHCO3, whereas it improved significantly with carbicarb (+245 vs +4087 μmol/kg body weight per hour). Net gut lactate production was reduced more by carbicarb than by NaHCO3. Net lactate production by carcass was also improved with carbicarb, but worsened with NaHCO3 (+1544 versus −2061 μmol/kg body weight per hour).

Liver pH. The liver pH was 6.99 during normoxia and 6.80 during hypoxia. With administration of NaHCO3, the liver pH declined to 6.40, whereas with carbicarb it improved to 6.92 (p<.04) (figure 1). A factor analysis demonstrated that the two best predictors of changes of liver pH were the HPV pH and Pco2. As HPV pH fell and the Pco2 rose with NaHCO3, the liver pH fell. Although liver intracellular lactate concentrations rose at the same rate as blood lactate levels, they did not appear to predict changes in liver pH.

Discussion

These studies demonstrate that in dogs with HLA, the administration of carbicarb — a mixture of 50% sodium carbonate and 50% sodium bicarbonate — improves arterial pH and elevates the blood HCO3− concentration without changing the blood Pco2, stimulating lactate production, or affecting cardiovascular...
performance. Systemic oxygen delivery and consumption also improve with administration of carbi-carb. In contrast, in dogs with similar degrees of HLA, the administration of NaHCO₃ results in a decline of arterial pH and HCO₃⁻ concentrations, increased venous Pco₂ concentrations, accelerated lactate production, and reduced cardiac index and mean arterial pressure. Both the delivery and consumption of oxygen decline.

The most striking finding of this study was the depression of both cardiac output and blood pressure with NaHCO₃ administration, an observation that was not made after carbi-carb. The reduction of cardiac output after NaHCO₃ appears to be the result of a primary reduction in left ventricular contractility. Left ventricular preload (PCW) did not change. Left ventricular afterload (TPR) decreased modestly. The heart rate did not change. Thus, stroke volume decreased primarily at a time when the loading conditions of the left ventricle were constant, suggesting that contractility was depressed. Although dP/dt was not measured, the peak systolic arterial pressure fell, on the average, by more than 60 mm Hg. With no change in heart rate, dP/dt most likely decreased.

The mechanisms by which myocardial contractility is impaired after administration of NaHCO₃ are not known, but may involve the generation of CO₂. The inverse correlation found between the mixed venous Pco₂ and cardiac output would suggest that the generation of CO₂ as a result of administration of NaHCO₃ might be a factor in the observed depression of contractile function. Such depression of myocardial contractile function might be related to a decrement of cardiac pH brought about by a greater increase of the Pco₂ in the myocardium than other tissues.

In the present study, arterial Pco₂ did not change with the administration of either NaHCO₃ or carbi-carb. However, the mixed venous (pulmonary artery) Pco₂ rose with NaHCO₃ administration and did not change with carbi-carb. Other studies suggest that when hypoxic states are complicated by circulatory failure, such as in cardiopulmonary arrest, there is indeed a significant component of respiratory acidosis that is only reflected by the venous blood gases. Weil et al. showed that in patients in cardiopulmonary arrest, the mixed venous Pco₂ was on average 36 mm Hg higher than the arterial Pco₂, confirming that even at times when the arterial blood gases are normal, respiratory acidosis may be present at a cellular level. Furthermore, Caparelli et al. demonstrated that respiratory acidosis may be more pronounced in the coronary vascular bed than in other vascular beds. In dogs with experimental cardio-
on myocardial function or the circulation, whereas bicarbonate does not. Carbicarb appears to be superior to NaHCO₃ in therapy of experimental HLA and trials of the therapy of acidicotic states in man, particularly cardiopulmonary arrest, are warranted.

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