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The Effects of Sodium Bicarbonate on Brain Blood Flow and O_2 Delivery during Hypoxemia and Acidemia in the Piglet

ABBOT R. LAPTOOK

University of Texas Health Science Center at Dallas, Department of Pediatrics, Dallas, Texas 75235

ABSTRACT. Metabolic acidosis in the neonate is often secondary to hypoxemia and cardiopulmonary disturbances. Sodium bicarbonate, an agent used to treat metabolic acidemia in newborns, is often administered during hypoxemia. In the absence of acid-base alterations, during hypoxemia a reciprocal relationship exists between arterial O_2 content (CaO_2) and brain blood flow (BBF). However, when hypoxemia is compounded by acidemia it is unclear whether the increase in arterial pH achieved by infusions of sodium bicarbonate alters BBF. To investigate this, BBF (microsphere technique), arterial blood gases, and CaO_2 were measured in 14 ventilated piglets. Variables were assesed during a control period, a period of hypoxemia (50 min) associated with metabolic acidemia (hypoxemia + acidemia), and after infusions of either saline ($n = 6$) or $NaHCO_3$ ($n = 8$, 2 mEq/kg) during continued hypoxemia. Arterial pH was similar in both groups at control, and hypoxemia + acidemia resulted in comparable reductions of pH in both saline- and $NaHCO_3$-treated piglets (7.21 ± 0.02 *versus* 7.21 ± 0.03, respectively). $NaHCO_3$ infusions produced a significant rise in pH, 7.30 ± 0.03 *versus* 7.15 ± 0.03, $p < 0.05$. In each group CaO_2 paralleled changes in pH but did not differ between groups. In all animals BBF increased more than 2-fold during hypoxemia + acidemia and was unaltered by infusions of either saline or $NaHCO_3$. Brain O_2 delivery decreased in both groups during hypoxemia + acidemia and was unchanged by infusions of saline or $NaHCO_3$. During hypoxemia + acidemia the change in arterial pH induced by $NaHCO_3$ (2 mEq/kg) does not alter BBF or brain O_2 delivery. (*Pediatr Res* 19: 815–819, 1985)

Abbreviations

CaO_2, arterial oxygen content
BBF, brain blood flow
CBF, cerebral blood flow
CO_{2TOT}, total carbon dioxide content
ECF, extracellular fluid
BBB, blood-brain barrier
MAP, mean arterial pressure

Sodium bicarbonate has been recommended for the treatment of metabolic acidemia in neonates (1). In both preterm and term infants metabolic acidemia is commonly secondary to cardiopulmonary disorders (*e.g.* hyaline membrane disease, pneumonia, asphyxia neonatorum, sepsis, etc.) and often hypoxemia accompanies metabolic acidemia. In the absence of acid-base alterations hypoxemia results in increases of CBF (2), the increments of which are reciprocally related to reductions in CaO_2 (3). CaO_2 represents the total O_2 carried by arterial blood and is a function of PaO_2, hemoglobin concentration, and hemoglobin-O_2 saturation. Studies of hypoxia in newborn lambs, produced by either hypoxemia or acute normovolemic anemia, demonstrate that CaO_2 appears to be a good predictor and possibly a regulator of cerebral vascular responses (4). During hypoxemia the fall in CaO_2 is exacerbated when there is an associated metabolic acidemia because of a pH mediated shift (down and rightward) in the hemoglobin-O_2 saturation curve (5). The role of hydrogen ion per se in the control of CBF remains controversial. Conflicting results have been obtained from both newborn (6) and adult animal models (7), and human adults (8) with respect to correlations between CBF and changes in arterial pH of metabolic origin. In contrast, it has been demonstrated using the cranial window technique in cats (9) and ventriculocisternal perfusion in dogs (10), that CBF varies directly with changes in cerebral extracellular fluid acidity.

Liberal use of sodium bicarbonate in neonates has been temporized by associated alterations of serum osmolality (11), a role in the pathogenesis of intracranial hemorrhage (12), and effects on the BBB (13). Despite prominent effects within the CNS it remains unclear whether sodium bicarbonate alters CBF. Sodium bicarbonate could potentially affect CBF via osmolar effects (14), transient elevations of arterial CO_2 tension (2, 15), and BBB disruption with secondary change in cerebral interstial fluid pH (9). Since sodium bicarbonate is often administered during hypoxemia and acidemia, another potential mechanism is that the rise in arterial pH induced by sodium bicarbonate may improve hemoglobin-O_2 saturation sufficiently to increase CaO_2 and thus, CBF may decrease. Reductions in CBF during hypoxemia and acidemia would appear to be detrimental considering the cerebral vascular response to hypoxemia. However, evaluation of tissue O_2 delivery, which is dependent on both blood flow and CaO_2, may be important to assess whether changes in CBF are appropriate. Therefore, to determine if sodium bicarbonate alters brain blood flow and O_2 delivery, piglets with metabolic acidemia secondary to hypoxemia were studied before and after alkali treatment.

METHODS

Fourteen miniature swine were the subjects of this investigation. Pregnant sows were housed and farrowed in the Animal Resources Center of The University of Texas Health Science Center at Dallas. Newborns were kept with the sow until the morning of the study at which time one piglet was removed from

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Reprint requests to Abbot R. Laptook M.D., University of Texas Health Science Center at Dallas, Department of Pediatrics, 5323 Harry Hines Boulevard, Dallas, TX 75235.
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the litter. Premedication consisted of a single dose of intramuscular ketamine (5 mg/kg) after which a tracheostomy was performed with placement of a 3.0-mm endotracheal tube. The piglet was ventilated (Harvard Apparatus Rodent Respirator, model 680) with 70% nitrous oxide and 30% oxygen, using a tidal volume of 12 ml/kg and rates of 40–50 breaths/min. Polyethylene catheters were placed in the left ventricle (via the left common carotid artery), abdominal aorta (via a femoral artery), inferior vena cava (via a femoral vein), and the left axillary artery. A 22-gauge Teflon catheter was inserted into the sagittal sinus through a burr hole in the midline of the exposed calvarium.

All procedures were performed while maintaining rectal temperature between 38.5–39.5° C. Following catheter placement, the inspired gas was changed to 70% nitrogen and 30% O_2, 0.3 mg/kg D-tubocurarine was given intravenously, and a 1-h stabilization period commenced. After stabilization a control measure of BBF was obtained during normoxemia. Hypoxemia was then induced by decreasing the inspired O_2 to 13%. Hypoxemia was continued until arterial pH was less than 7.25 (assessed by serial blood gases), at which time a second BBF determination was performed. Once completed, the piglets were randomly divided into two groups; eight piglets received an infusion of 0.5 M $NaHCO_3$ (2 mEq/kg) over 3 min via the femoral vein catheter, whereas the remaining six piglets received a comparable volume of 0.9% NaCl (4 ml/kg) over 3 min. Hypoxemia was continued during the respective infusions. The third blood flow determination was performed 10 min following the completion of either $NaHCO_3$ or saline infusion. The ventilator rate was adjusted to maintain $PaCO_2$ constant (~35–40 mm Hg) throughout the experiment. Immediately prior to each microsphere injection, blood was obtained for measurement of hematocrit, plasma osmolality and sodium concentration, CO_{2TOT} and cerebral arteriovenous differences of O_2 content, blood gases, and pH. At each blood flow measurement 4.0 ml of blood was removed for blood analyses and the microsphere reference sample. After each microsphere injection packed red blood cells previously obtained from a donor piglet of the same litter and stored with ACD were slowly administered to replace blood loss.

Organ blood flow was measured using 15 ± 5 μ microspheres labeled with ^{57}Co, ^{46}Sc, and ^{85}Sr (3M Co., St. Paul, MN and New England Nuclear, Boston, MA). The specific method is that of Heymann *et al.* (16). Briefly, for each measurement approximately 7–8 × 10^5 microspheres suspended in 3.5 ml of dextran were injected into the left ventricle over 30 s and the catheter flushed with 1.0 ml of isotonic saline. Starting prior to the microsphere injection an arterial reference sample was withdrawn from the axillary artery catheter into counting vials under oil at a rate of 1.03 ml/min for 2 min with a Harvard pump. All samples of brain tissue and reference samples contained more than 400 microspheres.

MAP and heart rate were monitored with Gould Statham pressure transducers and recorded on a Beckman Dynograph Recorder. An Instrumentation Laboratory Micro 13-03/213-05 blood gas analyzer was used to measure pH, PaO_2, and $PaCO_2$; a Lex-O_2-Con (Lexington Instruments, Waltham, MA) was used to determine O_2 content. Plasma osmolality was measured by an Advanced Instruments Osmometer, and CO_{2TOT} was measured by a Natelson Microgasometer. An Instrumentation Laboratory Spectrophotometer was used to determine plasma sodium concentration.

At study completion the piglets were sacrificed and catheter placement verified. The entire brain was removed, cut into sections, and the weight of each section determined. All brain tissue and blood reference samples were counted in a Packard 3-Channel Auto-Gamma Spectrometer (Model 5385). BBF was computed by the following:

$$\text{BBF (ml/min)} = \frac{\text{brain tissue cpm}}{\text{reference sample cpm}} \times \text{withdrawal rate (ml/min)}$$

Wet tissue weight was used to express blood flow as ml/min · 100 g. Regional brain blood flow (cerebrum, cerebellum, brainstem) was calculated by the above formula using the respective regional cpm in lieu of brain tissue cpm. Brain O_2 delivery was derived by the product of BBF and CaO_2. By the Fick principle, cerebral O_2 uptake was equivalent to the product of cerebral blood flow and the cerebal arteriovenous difference of O_2 content.

Statistical analysis was performed by analysis of variance with repeated measures (SAS Statistical Package) to compare the measured variables between groups. Significant interactions were localized by a Newman-Keuls multiple comparison procedure. Statistical significance was designated at $p < 0.05$. Values reported are the mean and 1 SE. In one saline-infused piglet the reference sample withdrawal apparatus malfunctioned and blood flow analysis was limited to the 13 animals with complete data.

RESULTS

Age and weight were comparable between groups at the time of study (8 ± 2 *versus* 8 ± 1 days and 1.54 ± 0.12 *versus* 1.77 ± 0.13 kg for the saline- and bicarbonate-treated piglets, respectively). The changes in PaO_2, arterial pH, and CO_{2TOT} are shown in Figure 1. Values for PaO_2 were comparable between groups throughout the study. For all animals a significant reduction in PaO_2 was observed at 10 min after initiation of 13% oxygen, falling to 37.7 ± 1.3 mm Hg and was unchanged thereafter. The time necessary for hypoxemia to result in metabolic acidemia varied, ranging from 41 to 62 min; however, there were no differences between groups (48 ± 7 *versus* 51 ± 9 min for the saline- and bicarbonate-treated piglets, respectively). Therefore, values for hypoxemia with acidemia are plotted as the mean value for all animals, at 50 min after the onset of hypoxemia. Arterial pH was comparable in both groups at control and fell during hypoxemia to similar values at 60 min; however, during continued hypoxemia the respective infusions resulted in differ-

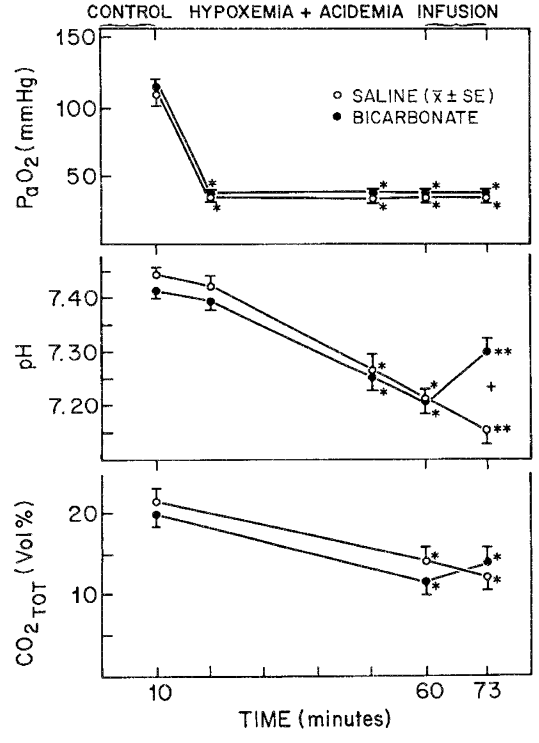

Fig. 1. The effects of hypoxemia and acidemia with and without bicarbonate therapy on arterial O_2 tension (PaO_2), pH, and CO_{2TOT}. Values are plotted at the time of each blood flow measurement with two additional points for PaO_2 and pH during hypoxemia and acidemia. * $p < 0.05$ compared to control values. ** $p < 0.05$ compared to control and hypoxemia with acidemia. † $p < 0.05$ for comparisons between the two groups.

ent pH values (7.154 ± 0.029 *versus* 7.302 ± 0.024 for the saline- and bicarbonate-infused piglets, respectively, $p < 0.05$). In both groups CO_{2TOT} was reduced during hypoxemia with acidemia. Although CO_{2TOT} appeared to increase in the bicarbonate-treated group and decrease in the saline-infused piglets, the differences were not significant.

No differences occurred between groups in MAP. Both groups demonstrated an increase in MAP during hypoxemia with acidemia ($p < 0.05$) which returned to control values following respective infusions. MAP for control, hypoxemia with acidemia and following infusions were 89 ± 3, 97 ± 4, and 94 ± 5 mm Hg for the saline-treated piglets, and 89 ± 3, 97 ± 2, and 90 ± 2 mm Hg for the bicarbonate-infused animals. $PaCO_2$ remained unchanged throughout the study by adjusting the ventilator rate. The rate was increased by a mean of 9 breaths/min during bicarbonate infusions but was not altered when saline was given. $PaCO_2$ for control, hypoxemia with acidemia and following infusions were 38.2 ± 2.0, 37.7 ± 2.2, and 37.4 ± 2.5 mm Hg for the saline group and 41.7 ± 1.1, 36.9 ± 2.1, and 39.2 ± 1.6 mm Hg for the bicarbonate group.

The changes in BBF, CaO_2, and brain O_2 delivery are shown in Figure 2. In each group BBF was comparable at control and increased to similar values during hypoxemia with acidemia. Infusions of either saline or bicarbonate during continued hypoxemia resulted in BBF which was unchanged from measurements obtained during hypoxemia with acidemia. CaO_2 was reduced more than 60% in each group during hypoxemia with acidemia. Although CaO_2 appeared to increase during bicarbonate infusions and decrease during saline infusions, the magnitude of these changes were small and not significantly different. Brain O_2 delivery did not differ between groups throughout the study. Reductions in brain O_2 delivery were present in both groups during hypoxemia with acidemia. Following infusions of either saline or bicarbonate, brain O_2 delivery remained unchanged from that during hypoxemia with acidemia. There were no differences between groups in cerebral O_2 uptake (ml/min·100 g); for control, hypoxemia with acidemia and following infusions cerebral O_2 uptake was 6.5 ± 0.5, 6.2 ± 0.4, and 4.9 ± 0.4 for the saline-infused piglets and 6.4 ± 0.4, 6.0 ± 0.4, and 5.3 ± 0.2 for the bicarbonate-infused piglets. The decrements in cerebral O_2 uptake following infusions of either saline or bicarbonate were of similar magnitude. Although the data are not shown, cerebral venous O_2 tension and regional blood flow did not differ between groups.

Table 1 lists the hematocrits, plasma osmolality, and sodium concentrations for both groups during each experimental period. Although hematocrit decreased at study completion in both groups, the tendency for bicarbonate-infused animals to have lower hematocrits was not significant and no differences were present between groups. No alterations were found in either osmolality or sodium when measured 10 min after the completion of either saline or bicarbonate infusions.

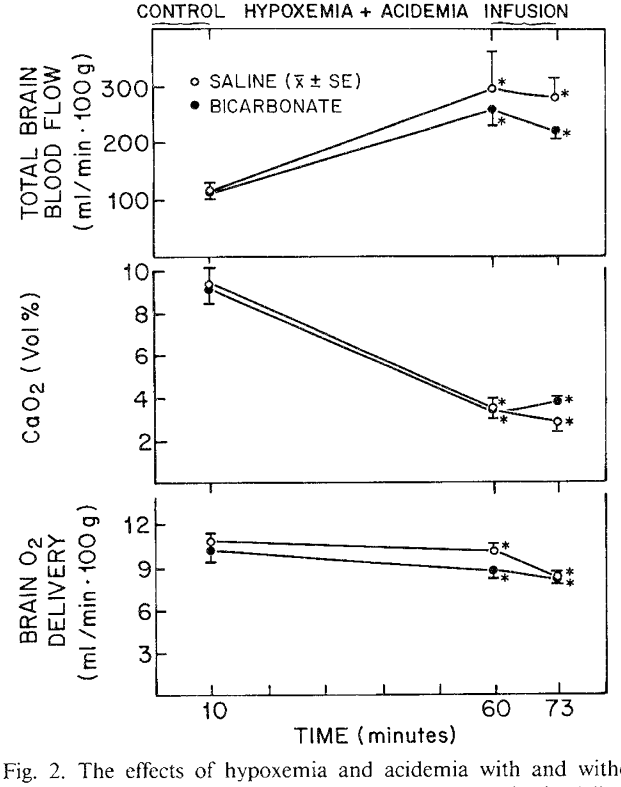

Fig. 2. The effects of hypoxemia and acidemia with and without bicarbonate therapy on brain blood flow, CaO_2 and brain O_2 delivery. * $p < 0.05$ when compared to control values.

DISCUSSION

In this investigation $NaHCO_3$ was administered to correct metabolic acidemia associated with hypoxemia. A dose of 2 mEq/kg diluted with sterile H_2O (0.5 M) was utilized since this amount and concentration is often employed in clinical settings. To determine whether $NaHCO_3$ alters BBF, microsphere measurements were performed 10 min following completion of the infusions, at a time when $NaHCO_3$ has prominent effects on pH and intravascular fluid shifts. Siegel *et al.* (11) have reported that in preterm infants alterations in hematocrit, plasma osmolality, and sodium concentration occurred 3 min following a $NaHCO_3$ infusion (mean dose 2.8 mEq/kg) but baseline values were reestablished for all three variables 30-min postinfusion. In the present investigation a $NaHCO_3$ effect was substantiated by the observed rise in arterial pH and CO_{2TOT}. However, no differences between groups were noted in osmolality, hematocrit, or sodium which likely reflects the time of sampling (10 min following completion of the infusion). Immediately following infusions of hypertonic solutions rapid equilibration of water occurs between the intracellular and extracellular spaces due to osmolality gradients; in addition, there is movement of sodium out of the intravascular space (17).

$NaHCO_3$ potentially may affect CBF by altering variables (osmolality and $PaCO_2$) important for the regulation of cerebral vascular tone. Increments in osmolality increase CBF in adult humans (8) and induce vasodilation of pial vessels in adult cats (14). Osmolality was not important in the present study since the osmolar load of 2 mEq/kg $NaHCO_3$ was small, resulting in rapid equilibration across the vasculature and an unchanged osmolality. Transient elevations in $PaCO_2$ after $NaHCO_3$ infusion is not a consideration since arterial isocapnia was maintained in the present study. However, the increases in CBF in adult humans (8) following $NaHCO_3$ infusions may be related to the PCO_2 which was uncontrolled and unmeasured. Since

Table 1. *The effects of saline or bicarbonate infusions on hematocrit, osmolality, and sodium following hypoxemia and acidemia (H + A) (mean ± SE)*

	Control	H + A	H + A and saline	Control	H + A	H + A and bicarbonate
Hematocrit (%)	25.7 ± 2.0	25.1 ± 1.9	23.5 ± 1.6*	24.3 ± 1.0	23.9 ± 0.9	21.2 ± 1.0*
Osmolality (mosmol/liter)	280 ± 3	283 ± 6	286 ± 4	281 ± 8	292 ± 6	290 ± 5
Sodium (mEq/liter)	132 ± 3	131 ± 5	131 ± 2	131 ± 4	133 ± 2	135 ± 2

* $p < 0.05$.

$NaHCO_3$ was administered during hypoxemia and acidemia, and CaO_2 is important in describing CBF during hypoxemia, $NaHCO_3$ may affect CBF through alterations in CaO_2. Specifically, $NaHCO_3$- induced increases in arterial pH may improve hemoglobin-O_2 saturation sufficiently to increase CaO_2, and thus, reduce CBF. Although the shift in the hemoglobin-O_2 saturation curve following an increase in pH is up and leftward, the improvement in hemoglobin-O_2 saturation, as reflected by an unchanged CaO_2, was obviously small following 2 mEq/kg $NaHCO_3$. Thus, BBF was similar to values observed during hypoxemia with acidemia. Furthermore, a leftward shift of the curve (at a constant CaO_2) is associated with an increase in CBF presumably due to a change in P_{50} (18); however, the magnitude of pH change following 2 mEq/kg $NaHCO_3$ is too small to alter O_2 affinity noticeably (5).

The role of changes in arterial pH of metabolic origin in the control of CBF remains unclear. The present investigation supports the contention that metabolic perturbations of arterial pH, of modest magnitude and short duration, do not alter CBF. Whether larger changes or prolonged changes in pH affect CBF is unclear. However, it is generally accepted that the hydrogen ion concentration $[H^+]$ of cerebral ECF is important in mediating alterations of cerebral vascular tone. Kontos *et al.* (9) used the cranial window technique in adult cats to demonstrate that pial arterioles do not change caliber upon application of cerebrospinal fluid with an unchanged pH but simultaneously altered PCO_2 or HCO_3^- concentration. The results confirm that CO_2 and HCO_3^- do not independently alter vasoactivity of pial vessels but act through changes in ECF pH. Britton *et al.* (10) have made similar conclusions utilizing ventriculocisternal perfusion with artificial cerebrospinal fluid in adult dogs.

The apparent contrast in pH effects on CBF between the cerebral interstium and systemic circulation suggests an important role for the BBB. The BBB has been thought to be relatively impermeable to changes in blood $[H^+]$ or $[OH^-]$, however, transport of $[H^+]$ or its equivalent does not exist from blood to brain. Using brain surface pH electrodes Javaheri *et al.* (19) reported that changes in arterial blood $[H^+]$ are reflected in brain surface pH relatively quickly. In contrast, when Javaheri *et al.* (20) measured brain ECF pH with microelectrodes inserted 5 mm below the cortex during systemic metabolic acid-base perturbations, only small but parallel changes in brain ECF pH occurred. Thus, compared to CO_2 diffusion into the brain the transport of H^+ is a slow process when the BBB is intact, and short intravenous HCO_3^- infusions in animals with an unimpaired BBB would not be expected to alter CBF. The results of Harper and Bell (7) of an unchanged CBF during isocapnic metabolic alkalosis using mechanically ventilated adult dogs are in agreement with this concept and the results of the present investigation.

The effect of $NaHCO_3$ on the cerebral vasculature of human newborns is limited to one study. Lou *et al.* (21) reported striking results of 50% reductions in CBF after variable doses (range 0.8 to 3.0 mEq/kg) of $NaHCO_3$ were infused in seven infants with respiratory distress and metabolic acidemia. The authors postulated the presence of a compromised BBB following asphyxia, which allowed $NaHCO_3$ to alter cerebral ECF pH. The diagnosis of asphyxia is presumably based on a liberal definition (1 min Apgar score $\leq$ 6) but other data indicating asphyxia are not provided. An important consideration is whether $NaHCO_3$ infused via a catheter positioned with the tip in the innominate or left common carotid artery as in the study of Lou *et al.* (21) alters a damaged or normal BBB. Underscoring this reservation is the observation of reversible opening of the BBB by carotid infusions of hyperosmotic agents in adult animals (22).

A number of investigations using adult animals have reported reductions in CBF following $NaHCO_3$ administration. Pannier *et al.* (23) found decreases in CBF after a 60-min $NaHCO_3$ infusion increased arterial pH from 7.25 to 7.56. The duration of the infusion may have been sufficient to alter cerebral ECF pH. Arvidsson *et al.* (24) reported that in hypercapnic anesthetized dogs, intravenous alkali infusions were associated with a reduction of CBF. It has been suggested that hypercapnia alters the BBB, allowing entry of HCO_3^- into the cerebral interstium. Pannier *et al.* (23, 25) have made two corrollary observations in cats and rats: 1) a diminished CBF response to hypercapnia during prolonged intravenous HCO_3^- infusions and 2) a decrease in CBF following intravenous HCO_3^- infusions in animals with prior hypertensive damage to the BBB.

Therefore, the net affect of $NaHCO_3$ on BBF is probably dependent on multiple variables including the quantity administered, the duration of the infusion, and the status of the BBB. In the present experimental design, 2 mEq/kg of 0.5 M $NaHCO_3$ infused over 3 min, as frequently used in neonatal nurseries had no effect on BBF. Although BBF was determined during the experimental protocol, it was recognized that calculation of tissue O_2 delivery may be a more important variable in view of potential alterations of CaO_2. However, significant changes did not occur in CaO_2 and therefore brain O_2 delivery was similar following either saline or $NaHCO_3$ infusions. Despite an apparent lack of effect of HCO_3^- on BBF and O_2 delivery, the potential hazards of $NaHCO_3$ therapy should still be appreciated.

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The Responses of Glutathione and Antioxidant Enzymes to Hyperoxia in Developing Lung

JOSEPH B. WARSHAW, CHARLIE W. WILSON, III, KOTARO SAITO, AND RUSSELL A. PROUGH

Departments of Pediatrics and Biochemistry, The University of Texas Health Science Center at Dallas, Dallas, Texas 75235

ABSTRACT. Total glutathione levels and the activity of enzymes associated with antioxidant protection in neonatal lung are increased in response to hyperoxia. Glutathione levels in developing rat lung decreased from 24 nmol/mg protein on day 19 of gestation to approximately 12 nmol/mg protein at birth. The initial decrease in glutathione may be due to emergence of other antioxidant systems. Newborn rats placed in 100% oxygen showed a rapid and sustained increase in total glutathione levels which was primarily due to an increase in reduced glutathione. Explants obtained from 16-wk gestation human fetal lung or from 17- to 18-day fetal rat lung also showed increased total and reduced glutathione when cultured in 95% oxygen, 5% CO_2 as compared with explants cultured in room air. Type II cells isolated from neonatal rats maintained in oxygen for 6 days also showed glutathione levels twice those found in cells isolated from animals in room air. The activity of antioxidant enzymes (glucose-6-phosphate dehydrogenase, glutathione peroxidase, glutathione reductase) was increased in lungs of newborn rats exposed to 100% oxygen either at birth or 2 days of age. Antioxidant enzyme activity of lung explants cultured in 95% oxygen, 5% CO_2 was also higher than in explants maintained in room air. These results suggest that the increases in glutathione and of antioxidant enzymes *in vivo* and *in vitro* are a direct effect of oxygen exposure in lung and that the increase of both glutathione and antioxidant enzyme activity is intrinsic to the lung cell itself. It is likely that increases in glutathione in lung represent an important protective mechanism against oxidant injury. (*Pediatr Res* 19:819–823, 1985)

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Reprint requests Joseph B. Warshaw, M.D., Department of Pediatrics, The University of Texas Health Science Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75235.
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Abbreviations

SOD, superoxide dismutase
GSH, reduced glutathione
GSSG, oxidized glutathione
PBS, phosphate-buffered saline
G6PHD, glucose-6-phosphate dehydrogenase

Bronchopulmonary dysplasia is a problem of clinical significance in newborns treated with high concentrations of oxygen in the course of therapy for the respiratory distress syndrome. While it is likely that factors such as positive pressure ventilation (1) and patent ductus arteriosis (2) play an important role in chronic lung disease in newborns, the duration and intensity of oxygen exposure is thought to be a central etiological feature of bronchopulmonary dysplasia (3). The sequence of injury resulting initially in lung injury has been well described (4, 5). It has been postulated that highly reactive free radicals of oxygen such as the superoxide anion ($O_2^{-\cdot}$) may cause tissue injury by direct peroxidation of unsaturated fatty acids in membranes and also by oxidation and inactivation of enzymes and other cell constituents essential for cell function. This results in membrane damage with transudation of fluid and formed elements into alveoli and the sequence of injury characterized by fibrosis and chronic clinical impairment.

Protective mechanisms against oxidant injury included SOD and the biological systems associated with glutathione or chemical antioxidants such as α-tocopherol. SOD catalyzes the dismutation of the superoxide anion O_2^- to H_2O_2 and O_2. The H_2O_2 thus formed can be removed by either catalase or glutathione peroxidase. SOD is found in all cells which sustain aerobic metabolism and appears to be a first line defense against oxidant damage. In the glutathione system, GSH provides reducing equivalents necessary for the removal of hydrogen peroxide and perhaps other toxic membrane lipid hydroperoxides through the