Uterine Blood Flow and Fetal Acid–Base Changes after Bicarbonate Administration to the Pregnant Ewe

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Administration of sodium bicarbonate over a 90-minute period to nine normal pregnant ewes near term in order to produce maternal alkalemia (mean arterial pH 7.70, base excess +17 mEq/l) resulted in a 16 percent reduction in uterine blood flow. Bicarbonate was not transferred to the fetus. Maternal and fetal PaCO₂ both increased 7 torr and fetal pH decreased. Fetal PaO₂, oxygen saturation and content also decreased significantly during the period of maternal metabolic alkalosis. (Key words: Uterus; blood flow: alkalosis; Acid–base equilibrium: alkalosis; metabolic; Oxygen: saturation: fetal.)

MILD TO SEVERE ASPHYXIA occurs in all fetuses during delivery.1–5 The magnitude of the asphyxial insult may be aggravated by pre-existing maternal or fetal complications, such as maternal hypotension, umbilical cord compression, or uteroplacental insufficiency.6–9 Maternal acidosis, resulting from prolonged or difficult labor, also is reflected in the fetus and accentuates neonatal acidosis.8–10 Several investigators have advocated prophylactic administration of sodium bicarbonate to parturients to minimize fetal acidosis and possible neonatal depression.10–11

On the other hand, several studies suggest that acute metabolic or respiratory alkalosis may adversely affect fetal oxygenation and, thereby, accentuate neonatal acidosis.12–16 How alkalosis affects fetal oxygenation remains unclear. Postulated causes for decreased oxygenation include a decrease in umbilical or uterine blood flow; mismatching of maternal and fetal bloods in the placenta; and displacement of the maternal oxygen–hemoglobin dissociation curve to the left, thereby increasing the affinity of maternal hemoglobin for oxygen.15 Uterine blood flow during induced metabolic alkalosis has not hitherto been measured. Because of the apparent controversy about maternal use of bicarbonate during parturition, we measured the effect of bicarbonate infusion on uterine blood flow in the nonanesthetized pregnant ewe and related the changes to fetal acid–base alterations.

Methods

Nine pregnant ewes near term (mean gestational age 134 days, range 133 to 141 days, term 147 to 150 days) were studied. Using spinal or local anesthesia, the gravid uterus was exposed, and through a small hysterotomy incision, we extracted a fetal hind limb. A polyvinyl catheter (#4 French, 0.048" O.D.) was inserted into a hind-limb artery, the limb was returned to the uterus, and the uterus closed. Polyvinyl catheters (#8 French, 0.015" O.D.) were placed in both maternal femoral arteries, one femoral vein, and the right atrium via the internal jugular vein. Location of the tip of the atrial catheter was verified by advancing the catheter into the right ventricle, then withdrawing it until an atrial-pressure trace was obtained. An electromagnetic flow probe was secured on a major uterine artery through a groin incision, and a zero-occlusion loop was placed around the aorta and inferior vena cava, as described by Greiss.17 Experiments were performed 24 to 48 hours after the preparatory surgery. Animals breathed room air during the
experiment, while standing quietly in their cages. After maternal and fetal blood pressure, pulse rate, uterine blood flow, pH, and PaCO₂ values had been stable for 45 to 60 minutes, 297 mEq of sodium bicarbonate were given intravenously to the mother over a 5-minute period. This was followed by an infusion of 0.05 to 0.10 mEq/kg/min of sodium bicarbonate for 90 minutes in order to maintain a constant maternal pH. After discontinuing the bicarbonate infusion, we observed all animals for a minimum of 45 minutes, and three animals for as long as 165 minutes. Maternal blood pressure, heart rate, right atrial pressure, and fetal heart rate and blood pressure were measured continuously using Statham P23Dc strain gauges connected to a Grass polygraph recorder. Uterine blood flow was measured with a Statham gated sine-wave electromagnetic flowmeter. The flow probes had been calibrated in vitro with physiologic saline solution. A linear response was obtained over the flow ranges studied. Zero flow obtained was by mechanical occlusion checked against electrical zero several times during the experimental period.

Maternal and fetal arterial bloods were sampled simultaneously 1, 5, 10, and 15 minutes after administration of the bicarbonate bolus, and at 15-minute intervals thereafter. Blood gases were obtained immediately using an Instrumentation Laboratories 313 Blood Gas Analyzer and the values corrected for body temperature measured continuously by a Yellow Springs rectal probe. Maternal and fetal base excess values were obtained using the Severinghaus slide rule. Hemoglobin concentration was measured using a cyanmethemoglobin method and a Bausch & Lomb Spectronic 20 spectrophotometer. Maternal and fetal oxygen saturation and oxygen content values were obtained from Hellegers’ nomogram. Maternal cardiac output was measured every 15 minutes by caridiogreen dye dilution using a Beckman cardiodensitometer. Maternal stroke volume and total peripheral resistance were calculated using the formulas:

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\text{Cardiac output (ml/min)} = \frac{\text{Stroke volume (ml)}}{\text{Heart rate (beats/min)}}
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\[
\text{Total peripheral resistance (dynes/sec/cm}^3\text{)} = \frac{\text{Mean arterial blood pressure (torr)} - \text{Mean right atrial pressure (torr)}}{\text{Cardiac output (ml/sec)}} - 1332
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Control values for maternal and fetal mean arterial blood pressure, heart rate, and maternal central venous pressure and uterine blood flow are averages of determinations made at 5-minute intervals during the 45-60-minute stable period preceding administration of the bicarbonate bolus. Control values for acid-base data and maternal cardiac output are averages of four determinations at 15-minute intervals during the same period. Cardiovascular data obtained following bicarbonate administration were converted to percentage changes from control. Analysis of variance was used to determine statistical significance. P < 0.05 was considered significant. Regression analysis was used where indicated.

**Results**

Bicarbonate infusion increased maternal pH from 7.56 (normal in ewes near term) to approximately 7.70. Maternal pH remained at this level during the ensuing periods (fig. 1). Fetal pH showed a slight, significant decline. Maternal base excess increased 17 mEq/l and remained nearly constant during the experiment, while fetal base excess was unchanged. The three animals followed for 165 minutes after termination of bicarbonate infusion showed no evidence of bicarbonate placental transfer. Maternal and fetal PCO₂’s increased 3 to 5 torr 1 minute after injection of the bicarbonate bolus and continued to rise gradually throughout the bicarbonate infusion. A maternal-fetal PCO₂ gradient of approximately 10 torr was present during the entire experiment. Maternal arterial PO₂ decreased immediately after the bicarbonate bolus and continued to decline thereafter (fig. 2). Maternal oxygen saturation and content did not change, but fetal PO₂, saturation, and content decreased.
Transitory increases in maternal central venous pressure and uterine blood flow immediately followed the bicarbonate bolus (figs. 3 and 4). After 15 minutes central venous pressure returned to and remained at control level. The initial increase in mean uterine blood flow was followed by sustained significant depression to 14 to 20 per cent below control values. Maternal heart rate increased (P < 0.05) after the bicarbonate bolus and remained elevated during bicarbonate infusion. Stroke volume tended to be reduced but neither it nor maternal cardiac output, arterial blood pressure, or total peripheral resistance changed significantly (P > 0.05) during the bicarbonate infusion period from 15 minutes until the end of the experiment.

Wide individual variations in fetal mean arterial blood pressure and heart rate occurred during bicarbonate infusion. Statistical significance by analysis of variance could not be demonstrated. An increase in fetal mean arterial blood pressure occurred during bicarbonate infusion (regression analysis, P < .001). A significant correlation between fetal mean arterial blood pressure and fetal P<sub>CO2</sub> was evident (regression analysis, P < .01).

**Discussion**

The relation of maternal and fetal acid-base balances during pregnancy, labor, and delivery has received considerable attention. Several investigators have induced maternal pH alterations experimentally to observe fetal effects. Blechner and associates infused acid (NH₄Cl) into awake pregnant sheep or goats near term and found a stable maternal-fetal P<sub>CO2</sub> gradient.
over a wide range of maternal $P_{CO_2}$ and $pH$ values. Maternal and fetal bicarbonate, however, were virtually independent of each other over a 24-hour period despite large changes in maternal $pH$, suggesting that hydrogen and bicarbonate ions diffuse slowly, if at all, across the ovine placenta. Motoyama et al.\textsuperscript{15} infused sodium bicarbonate into anesthetized sheep, and found a decrease in fetal $pH$ rather than the increase which should occur if bicarbonate ion readily crossed the placenta. They also found a 24 per cent decrease in umbilical blood flow. Our results confirm the reduction in fetal $pH$ and the barrier to bicarbonate placental transfer in sheep. We were unable to demonstrate significant transfer of bicarbonate to the fetus despite the administration of an average of 762± 47 mEq over a 90-minute period.

The placental barrier to hydrogen or bicarbonate ion is present but less marked in man. Maternal metabolic acidosis is reflected in the fetus after several hours of equilibration. Goodlin and Kaiser\textsuperscript{27} produced immediate metabolic acidosis in the mother with NH$_4$Cl administered orally, and found no fetal acidosis until 4 hours later.

Prolonged or difficult labor may cause progressive maternal metabolic acidosis, which may adversely affect fetal $pH$ and base excess.\textsuperscript{8-10} Rooth administered sodium bicarbonate or diuretic\textsuperscript{10} to the mother, attempting to raise her arterial $pH$, thereby improving fetal or neonatal acid-base status. He found significantly less acidosis in cord blood at delivery in bicarbonate-treated human parturients (mean base excess in umbilical vein blood: $-5.5$ mEq/l; in umbilical artery blood: $-6.7$ mEq/l). Newman et al.\textsuperscript{2} administered a slow infusion of 88 to 125 mEq of sodium bicarbonate to six parturients over 1–3-hour periods and measured fetal bicarbonate levels at the end of infusion. He found increased fetal standard bicarbonate in five of six fetuses, and concluded that maternal infusion of sodium...
bicarbonate, in the absence of placental insufficiency, could increase fetal base excess. Clark et al.11 gave approximately 150 mEq sodium bicarbonate to parturients over a period of 1–5 hours and measured acid–base variables in maternal arterial and umbilical arterial and venous blood at delivery. A good correlation between maternal and fetal base excess at delivery was obtained (r = 0.651). The authors concluded that the use of bicarbonate seems a “safe and effective means of aiding the fetus.”11 Structural differences between human and ovine placentas may account for the variability in bicarbonate placental transfer.30

In agreement with previous findings,15 we found that the rise in maternal Pco2 after bicarbonate administration was reflected in the fetus (fig. 1). The small but significant decrease in fetal pH that occurred was secondary to the rise in fetal Pco2.

The shift to the left of the maternal oxygen–hemoglobin dissociation curve might impede oxygen release at the intervillous space by lowering Paco2 at any given O2 content.21 Consonant with this hypothesis, fetal PO2, oxygen saturation, and oxygen content declined during the marked maternal alkalosis. Motoyama18 similarly found consistent decreases in fetal carotid PO2 and saturation with maternal metabolic alkalosis. In Motoyama’s study, maternal respiratory alkalosis also reduced fetal PO2, but the concomitant decrease in fetal oxygen saturation was less than that seen after maternal metabolic alkalosis. The greater decrease in fetal oxygen saturation seen with maternal metabolic alkalosis may be due in part to the difference in placental permeability to bicarbonate ion and CO2. With maternal alkalosis induced by hyperventilation, both maternal and fetal Pco2 decrease, causing similar shifts in both maternal and fetal oxygen–hemoglobin dissociation curves. Thus, the Po2 gradient between maternal and fetal blood is unaffected. With acute maternal metabolic alkalosis, the maternal dissociation curve shifts to the left, while the position of the fetal curve remains unchanged. The reduction in the Po2 gradient from the maternal to fetal blood impedes placental oxygen transfer.

Maternal cardiovascular changes were biphasic. The initial increases in central venous pressure and uterine blood flow could be attributed to rapid volume expansion. After 15 minutes central venous pressure had returned to control. In contrast, uterine blood flow decreased to significantly below control and remained 15 to 20 per cent below control throughout the remainder of the infusion and observation periods. The mechanism for the decrease in uterine blood flow is not apparent. Uterine blood flow decreases with a fall in mean arterial blood pressure or an increase in uterine vascular resistance. No significant decrease in maternal blood pressure occurred in our experiments, although hypotension after administration of hypertonic glucose, saline, or bicarbonate solution in dogs has been reported.22 The absence of significant alteration in mean arterial blood pressure indicates that myometrial or placental vascular resistance increased. Sympathetic stimulation results in uterine vasoconstriction and a decrease in uterine blood flow.23–25 Maternal Pco22, a potent stimulus to the sympathetic nervous system, increased during bicarbonate infusion. Maternal tachycardia was prominent, and may have been the result of increased sympathetic tone.

In healthy fetuses the stress of increased Pco2 and small decreases in uterine blood flow, fetal Pco2 and saturation is apparently handled without difficulty. Fetal metabolic acidosis did not occur. There is obviously a “critical” fetal Po2 combined with a “critical” blood flow beyond which fetal compensation is not possible. An already-compromised fetus may not be able to tolerate even a minimal reduction in uterine blood flow. Further studies are necessary before prophylactic sodium bicarbonate administration can be recommended for parturients.

We did not study the effects of administration of bicarbonate to the acidotic ewe. Fetal acidosis resulting from maternal acidosis can be corrected in man,9 if enough time elapses for placental transfer of bicarbonate. We recommend, however, that when bicarbonate is administered, oxygen should also be administered to compensate for the potential maternal hypoventilation and thereby prevent decreases in maternal and fetal arterial Po2's.

References