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Effects of Intravenous Hyperosmotic Sodium Bicarbonate on Arterial and Cerebrospinal Fluid Acid-Base Status and Cardiovascular Function in Calves with Experimentally Induced Respiratory and Strong Ion Acidosis

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The objectives of this study were to determine the effects of hyperosmotic sodium bicarbonate (HSB) administration on arterial and cerebrospinal fluid (CSF) acid-base balance and cardiovascular function in calves with experimentally induced respiratory and strong ion (metabolic) acidosis. Ten healthy male Holstein calves (30–47 kg body weight) were instrumented under halothane anesthesia to permit cardiovascular monitoring and collection of blood samples and CSF. Respiratory acidosis was induced by allowing the calves to spontaneously ventilate, and strong ion acidosis was subsequently induced by IV administration of L-lactic acid. Calves were then randomly assigned to receive either HSB (8.4% $NaHCO_3$; 5 ml/kg over 5 minutes, IV; n = 5) or no treatment (controls, n = 5) and monitored for 1 hour. Mixed respiratory and strong ion acidosis was accompanied by increased heart rate, cardiac index, mean arterial pressure, cardiac contractility (maximal rate of change of left ventricular pressure), and mean pulmonary artery pressure. Rapid administration of HSB immediately corrected the strong ion acidosis, transiently increased arterial partial pressure of carbon dioxide (P_{CO_2}), and expanded the plasma volume. The transient increase in arterial P_{CO_2} did not alter CSF P_{CO_2} or induce paradoxical CSF acidosis. Compared to untreated control calves, HSB-treated calves had higher cardiac index and contractility and a faster rate of left ventricular relaxation for 1 hour after treatment, indicating that HSB administration improved myocardial systolic function. We conclude that rapid IV administration of HSB provided an effective and safe method for treating strong ion acidosis in normovolemic halothane-anesthetized calves with experimentally induced respiratory and strong ion acidosis. Fear of inducing paradoxical CSF acidosis is not a valid reason for withholding HSB administration in calves with mixed respiratory and strong ion acidosis.

Key words: Metabolic acidosis; Paradoxical cerebrospinal fluid acidosis; Strong ion difference.

Mixed respiratory and strong ion (metabolic) acidosis is a common finding in calves with perinatal birth asphyxia,[1–5] endotoxemia,[6–9] or diarrhea and hypovolemia.[10,11] Mild to moderate mixed respiratory and strong ion acidosis is a normal physiologic event in newborn calves that is triggered by impaired oxygen delivery to the fetus during delivery and hypoxemia following rupture of the umbilical cord.[1,3–5] Uterine contractions and separation of the fetal membranes during parturition decrease uterine perfusion and umbilical blood flow, subjecting the fetus to hypoxia and hypercarbia.[5] Respiratory acidosis at birth can be complicated by strong ion acidosis from anaerobic production of L-lactate after severe and prolonged reduction of fetal oxygen supply during dystocia at delivery.[1] Almost all calves extracted with forced assistance, and depressed calves delivered without assistance, suffer from mixed respiratory and strong ion acidosis, with venous blood pH $<$ 7.20 and increased blood L-lactate concentration.[3,4]

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Sodium bicarbonate is the alkalinizing agent of choice for treating severe strong ion acidosis in calves.[12–16] Sodium bicarbonate more rapidly alkalinizes the blood compared to metabolizable bases such as sodium L-lactate and sodium acetate.[16,17] Most commercially available preparations of sodium bicarbonate solution are hyperosmotic, with a theoretical osmolality of 1,000 mOsm/L (4.2% hyperosmotic sodium bicarbonate [HSB]) or 2,000 mOsm/L (8.4% HSB). Although these 2 hyperosmotic formulations have been widely used in Europe for the treatment of severe acidemia in calves with or without diarrhea and dehydration,[12,18] isosmotic 1.3% sodium bicarbonate solutions are currently recommended for administration in neonatal calves with diarrhea and dehydration in order to effectively expand the extracellular fluid volume and increase blood pH.[12,14,19] Isosmotic sodium bicarbonate also has been recommended for the treatment of acidemia in newborn calves with mixed respiratory and strong ion acidosis,[9] whereas others have recommended the administration of 8.4% HSB at 1–2 mmol $NaHCO_3$/kg body weight administered as a slow bolus injection.[20]

Sodium bicarbonate is administered to prevent the detrimental effects of severe acidemia (blood pH $<$ 7.20) on the cardiovasular system, thereby improving cardiac contractility and cardiac output (CO), and to provide buffer anions to prevent further decreases in pH as a result of ongoing acid production.[21,22] However, the IV administration of sodium bicarbonate for the treatment of acidemia caused by endogenous acids (L-lactate or ketoacid), and for the treatment of mixed respiratory and strong ion acidosis, remains controversial.[17,21,22] Potentially important adverse effects of HSB administration include hypercarbia, which is suspected to cause a paradoxical intracellular and cerebrospinal fluid (CSF) acidosis,[2,17,23–25] hypernatremia,[26] and

extracellular fluid hyperosmolality,[26] hypocalcemia,[19] hypokalemia,[26] decreased oxygen delivery, intracranial or cerebral hemorrhage due to abrupt changes in osmolality,[27,28] and further exacerbation of lactic acidosis.[29] The main objectives of this study were therefore to determine the safety and efficacy of rapid IV administration of HSB for the treatment of strong ion acidosis in calves with experimentally induced respiratory and strong ion acidosis. We hypothesized that rapid IV HSB administration would rapidly alkalinize the blood, improve cardiovascular function, and not create paradoxical CSF acidosis in spontaneously breathing anesthetized calves. A portion of this manuscript has been previously published as an abstract.[a]

Materials and Methods

Calves

This study was approved by the Institutional Animal Care and Use Committee. Ten colostrum-fed male Holstein-Friesian calves (30–47 kg body weight; 4–10 days old) were obtained from a local source and housed individually in stalls before instrumentation. The calves had free access to freshwater and were fed an all milk-protein milk replacer[b] (crude protein 22%, crude fat 20%, and crude fiber $< 0.15\%$) at 10% of body weight per day, divided into 2 feedings at 12-hour intervals. The calves were acclimatized to their stalls and diet, and determined to be healthy on the basis of physical examination findings.

Instrumentation

Calves were held off feed for 12 hours and anesthesia was induced by IV administration of diazepam[c] (0.25 mg/kg), followed immediately by ketamine[d] (4 mg/kg IV). Calves were then orotracheally intubated, placed in left lateral recumbency on a water-circulating heating pad[e], and mechanically ventilated with 2.5% halothane in 100% O_2 by use of a volume-cycled respirator.[f] During instrumentation and baseline measurements, tidal volume was set at 15 mL/kg and respiratory frequency at 15 breaths/min. A respirometer[g] was placed in the ventilatory circle to measure total ventilation (minute volume). A base-apex ECG was obtained to monitor heart rate (HR) and rhythm.[h] The hair over the right jugular groove, atlanto-occipital region, and the medial region of the left hock was clipped and the sites were surgically scrubbed for aseptic placement of intravascular and atlanto-occipital catheters. A minor surgical cutdown was performed on the right jugular groove to place catheters in the jugular vein and carotid artery. A 90-cm 7-F thermodilution (Swan-Ganz) catheter[i] was advanced until the distal port was in the pulmonary artery and the proximal port was in the right atrium. The Swan-Ganz catheter was connected to calibrated fluid-filled transducers.[j] A 7-F high-fidelity catheter dual-tipped pressure transducer[k] was inserted in the right carotid artery and advanced so that the distal transducer was in the left ventricle and the proximal transducer was in the ascending aorta for measurement of left ventricular pressure and aortic pressure, respectively. Correct positions of cardiac catheters were assessed by monitoring the pressure signals on a strip-chart recorder.[h] A 22-gauge IV catheter was placed in the left saphenous artery for collecting arterial blood and monitoring arterial blood pressure, and a similar catheter was placed in the left saphenous vein for IV administration of fluids (0.9% NaCl at 4 mL/kg/h) during instrumentation. A 20-gauge spinal catheter was placed in the atlanto-occipital space for collection of CSF. Successful placement of the atlanto-occipital catheter was assessed when CSF flowed from the catheter without blood contamination after removing the stylet. When instrumentation was completed, anesthesia was maintained with an end-tidal halothane concentration of 1.04%, which was equivalent to 1.3 times the minimum alveolar concentration.[30] This anesthetic depth was selected to minimize the cardiovascular depressive effects of halothane.

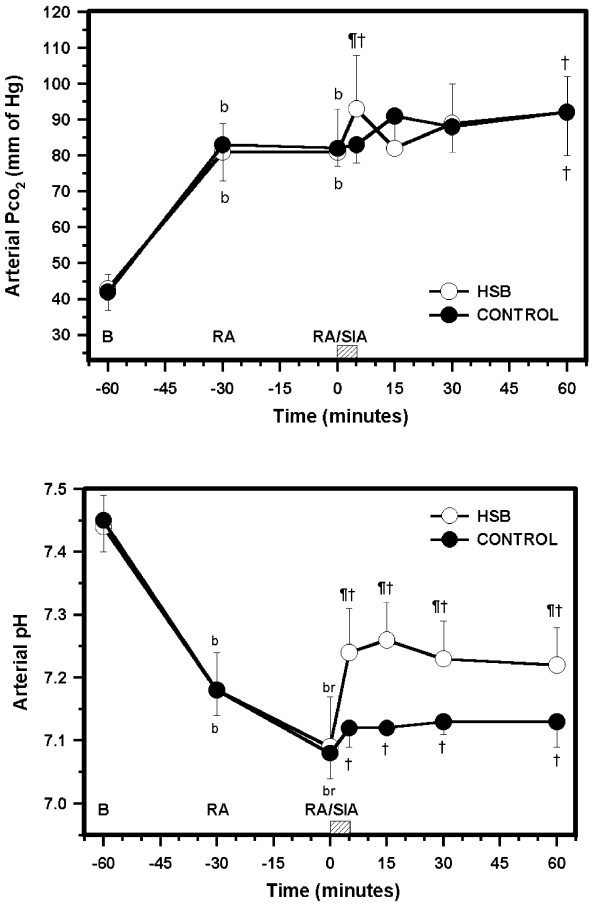

Fig 1. Arterial blood partial pressure of carbon dioxide (P_{CO_2}) and pH in halothane-anesthetized, normovolemic, neonatal calves at baseline (B, time = −60 minutes) and after experimentally induced respiratory acidosis (RA, time = −30 minutes) and mixed respiratory acidosis and strong ion acidosis (RA/SIA, time = 0 minutes). At time = 0 minutes, calves were randomly assigned to receive hyperosmotic sodium bicarbonate (HSB, 8.4% sodium bicarbonate; 5 mL/kg over 5 minutes, IV; n = 5, hatched rectangle) or no treatment (CONTROL, n = 5) and monitored for 1 hour. b, significantly different ($P < .05$) from baseline value; r, significantly different ($P < .05$) from RA value; †, significantly different ($P < .05$) from time = 0 minutes value; ¶, significantly different ($P < .05$) from CONTROL at the same time. Values are mean ± SD; the SD value is smaller than the symbol radius in individual time points with no apparent SD bars.

Experimental Protocol

Calves were monitored for 30 minutes after instrumentation to ensure hemodynamic stability. IV 0.9% NaCl administration was discontinued and baseline hemodynamic values were obtained. Respiratory acidosis was induced by disconnecting the endotracheal tube from the ventilator and allowing the calf to breathe spontaneously for 30 minutes. The ventilator was not reconnected at the end of this 30-minute period, meaning that respiratory acidosis was sustained for the remainder of the study. Light to moderate halothane anesthesia in spontaneously breathing, laterally recumbent calves has been shown to induce a marked respiratory acidosis at 1.0–1.5 times the minimal alveolar concentration.[30] Concurrent respiratory and strong ion acidosis was then induced by IV administration of 300 mM L-lactic acid solution[l] at a rate of 3 mL/kg over 30 minutes. This dosage protocol was adapted from studies describing experimentally induced mixed respiratory and strong ion acidosis in calves.[31] Calves were then ran-

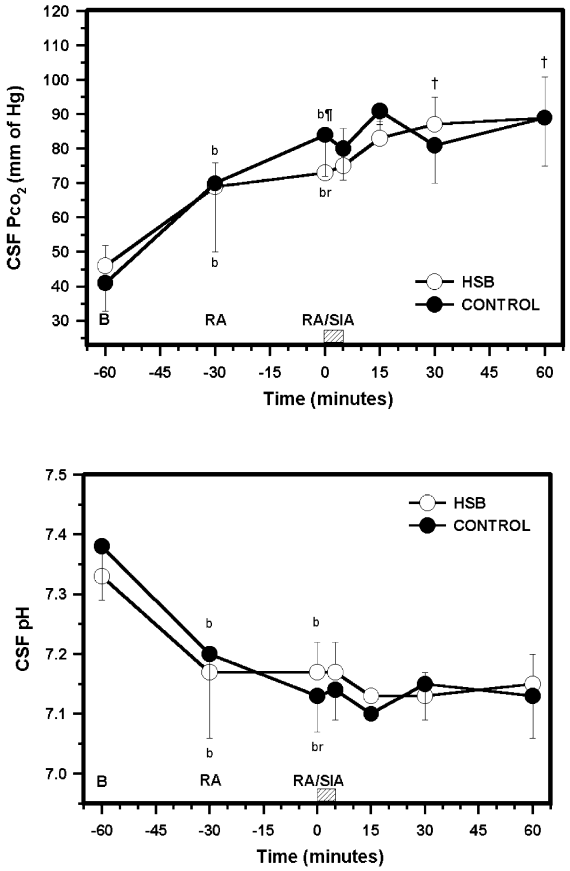

Fig 2. Cerebrospinal fluid (CSF) partial pressure of carbon dioxide (Pco_2) and pH in halothane-anesthetized, normovolemic, neonatal calves at baseline (B, time = −60 minutes) and after experimentally induced respiratory acidosis (RA, time = −30 minutes) and mixed respiratory acidosis and strong ion acidosis (RA/SIA, time = 0 minutes). At time = 0 minutes, calves were randomly assigned to receive hyperosmotic sodium bicarbonate (HSB, 8.4% sodium bicarbonate; 5 mL/kg over 5 minutes, IV; n = 5, hatched rectangle) or no treatment (CONTROL, n = 5) and monitored for 1 hour. b, significantly different ($P < .05$) from baseline value; r, significantly different ($P < .05$) from RA value; †, significantly different ($P < .05$) from time = 0 minutes value; ¶, significantly different ($P < .05$) from CONTROL at the same time. Values are mean ± SD; the SD value is smaller than the symbol radius in individual time points with no apparent SD bars.

domly assigned to 1 of 2 groups (5 calves/group). Calves in the control group (group C) received no treatment. Calves in the treatment group (group HSB) received 5 mL/kg of 8.4% sodium bicarbonate solution through the saphenous vein catheter at a rate of 1 mL/min/kg (total treatment time of 5 minutes). The 8.4% sodium bicarbonate solution had a calculated osmolality of 2,000 mOsm/kg.

HR, respiratory rate (RR), mean aortic pressure (MAP), arterial pulse pressure, maximal rate of change of left ventricular pressure (LV dP/dt_{max}), left ventricular end-diastolic pressure (LVEDP), rate of left ventricular relaxation (tau), minimal rate of change of left ventricular pressure (dP/dt_{min}), mean pulmonary artery pressure (MPAP), mean central venous pressure (CVP), and minute volume were measured at baseline (time baseline), after induction of respiratory acidosis (time RA), after induction of respiratory and strong ion acidosis (time RA/SIA), and 3, 5, 10, 15, 20, 30, 45, and 60 minutes after the start of IV administration of HSB solution or an equivalent time point in control calves. CO measurements were obtained at 10, 15, 30, 45, and 60 minutes after the start of IV administration of HSB solution or equivalent time point in control calves.

Arterial blood and CSF (1 mL) were collected anaerobically into a 3-mL heparinized plastic syringe for blood gas analysis and determination of acid-base status at 5, 15, 30, 45, and 60 minutes after the start of IV administration of HSB solution or an equivalent time point in control calves. Samples for blood gas analysis were kept at 4°C and analyzed[m] within 2 hours. This sampling and storage procedure was selected because storage of heparinized blood in 3-mL plastic syringes on ice causes a smaller change in pH and partial pressure of carbon dioxide (Pco_2) over 6 hours than does storage in glass syringes.[32]

Pulmonary artery blood was collected from the distal port of the Swan-Ganz catheter for determination of blood L-lactate concentration after deproteinization in 8% perchloric acid.

After obtaining the samples and measurements at time = 60 minutes, calves were euthanized by administering sodium pentobarbital (108 mg/kg IV).

Cardiovascular Measurements

CO was measured by the thermodilution technique with the aid of a CO computer.[n] Five milliliters of ice-cold 5% dextrose solution was injected rapidly into the proximal port of the Swan-Ganz catheter for CO measurement, and the mean value of 3 determinations was used as the experimental value for each period. Stroke volume (SV) was calculated from simultaneously determined HR and CO values, and CO and SV were indexed to body weight. Left ventricular pressure was digitized at 500 Hz by a 12-bit microcomputer system, and data were stored on a hard disk for subsequent analysis by commercially available[o] and custom-designed software (used to calculate ventricular relaxation indices). LVEDP was defined as the ventricular pressure at the start of the r wave of the QRS complex, which usually has an rS morphology on the base-apex lead system. LV dP/dt_{max} and dP/dt_{min} were determined by using a 3-point Lagrangian interpolation on digitized pressure data.[33] Tau was calculated as relaxation half-time.[33] MAP, MPAP, and CVP measurements were recorded on a multichannel strip-chart recorder,[h] and all pressure recordings were referenced to the center of the thorax. Mean aortic pulse pressure was the difference between mean systolic and diastolic aortic pressures. Systemic vascular resistance (SVR) was calculated as SVR = (MAP − CVP) × 80/CO, and pulmonary vascular resistance (PVR) was calculated as PVR = (MPAP − LVEDP) × 80/CO.

Determination of pH, Gas Tension, and Electrolyte Concentrations in Blood and CSF

A blood gas analyzer[m] was used for determination of pH, Pco_2, and partial pressure of oxygen (Po_2) in arterial blood and CSF samples, and measurements were corrected for blood temperature by using standard algorithms.[34] Arterial and CSF bicarbonate concentrations [HCO_3^-] were calculated from the temperature-corrected values for pH and Pco_2 by using the Henderson-Hasselbalch equation and temperature-adjusted values for the negative logarithm of dissociation constant of acid (pK_1') and solubility of carbonic acid for plasma[34] and CSF.[35] Blood hemoglobin concentration and plasma concentrations of sodium, potassium, calcium, and chloride were measured by using ion-selective electrodes.[m,p] Blood lactate concentrations were determined by using a spectrophotometric technique[36] and L-lactate dehydrogenase.[q] Hematocrit and plasma protein (PP) concentration were determined from the blood used for blood gas analysis by the microhematocrit technique and refractometry, respectively. Changes in plasma volume (ΔPV) were calculated as $\Delta PV = (PP_{baseline} - PP_t) \times 100/PP_t$ where PP_t is the plasma protein concentration at time t.[37] Total blood O_2 content was calculated to be 1.39 mL of O_2/g of hemoglobin plus dissolved O_2 equal to 0.3 volume %/100 mm Hg. Systemic O_2 delivery was calculated as the product of arterial O_2 content and CO and normalized to body weight.

Statistical Analysis

Data were expressed as mean ± SD and a P value $< .05$ was considered significant. Two-way analysis of variance (treatment, time) with repeated measures on one factor (time) was used for comparison of normally distributed data. Non–normally distributed data were log transformed or ranked before analysis. Appropriate post tests were conducted whenever the F test was significant ($P < .05$). Multiple pairwise comparisons were conducted between or within treatment groups by using the Bonferroni inequality to keep the experimentwise error rate at $P < .05$ for each group of comparisons. Within-group comparisons were made to baseline values for respiratory acidosis (time RA) and strong ion acidosis (time RA/SIA). Additional post-treatment comparisons were made within groups to the value before treatment was initiated (time RA/SIA). Between-group comparisons were made at each time interval. A statistical software program was used for all analyses.[r]

Results

Baseline

The pH, P_{O_2}, and [HCO_3^-] were lower in CSF than in arterial blood (Figs 1, 2; Tables 1, 2), whereas P_{CO_2} was similar in CSF and arterial blood. Sodium concentration was higher and potassium and calcium concentrations were lower in CSF than in plasma.

Respiratory Acidosis

Thirty minutes of spontaneous ventilation under halothane anesthesia successfully induced acidemia and respiratory acidosis, based on the increase in arterial P_{CO_2} and decrease in arterial pH, with a small decrease in arterial base excess that was significant only in the HSB group (Fig 1; Table 1). CSF P_{CO_2} and pH changed similarly to arterial plasma, but to a comparatively smaller extent (Fig 2).

Respiratory acidosis was accompanied by a marked increase in HR, cardiac index, mean arterial pressure, and cardiac contractility (LV dP/dt_{max}) (Fig 3), a small increase in MPAP and oxygen delivery, and a decrease in the rate of left ventricular relaxation (Table 3). These cardiovascular changes were consistent with sympathetic nervous system activation.

Mixed Respiratory and Strong Ion Acidosis

Intravenous administration of 300 mM L-lactic acid solution successfully induced strong ion acidosis, based on an increased blood L-lactate concentration and a decreased arterial pH, base excess, plasma [HCO_3^-], and serum [Cl^-], with no change in P_{CO_2} (Fig 1; Table 1). CSF P_{CO_2} was mildly increased and CSF pH was mildly decreased after administration of L-lactic acid; this most likely reflected continued equilibration of increased arterial P_{CO_2} with the CSF (Fig 2). CSF base excess did not change, indicating that IV administration of L-lactic acid rapidly produced strong ion acidosis in blood, but not in the CSF (Table 2).

Superimposition of strong ion acidosis on the experimentally induced respiratory acidosis was associated with a marked increase in MPAP and pulmonary vascular resistance, and a smaller increase in mean arterial pressure and minute volume (Tables 1, 3).

Administration of 8.4% Sodium Bicarbonate

Intravenous administration of HSB to calves with mixed respiratory and strong ion acidosis caused an immediate and sustained (>60 minutes) increase in arterial pH, base excess, and [HCO_3^-], and a small transient (<15 minutes) increase in mean P_{CO_2} from 81 to 93 mm Hg, with no change in RR or minute volume (Fig 1; Table 1). This indicated that HSB rapidly corrected the strong ion acidosis and created a strong ion alkalosis, while mildly and transiently increasing the severity of the respiratory acidosis. Administration of HSB did not immediately alter CSF pH, base excess, P_{CO_2}, [HCO_3^-], or [Cl^-], but gradually increased CSF base excess and [HCO_3^-] that was significant by 30 and 60 minutes after administration (Fig 2; Table 2). CSF electrolyte concentrations were unchanged in control calves except for a gradual decrease in CSF [Cl^-], and only minor changes were present in CSF electrolyte concentrations of calves after HSB administration.

Administration of HSB caused an immediate and sustained plasma volume expansion, increase in plasma sodium concentration, and decrease in plasma potassium concentration, hematocrit, hemoglobin, and plasma protein concentration (Fig 3; Table 1). Plasma volume expansion in HSB-treated calves was evidenced by calculating the percent change in plasma volume from baseline, and the magnitude and direction of change in hematocrit, hemoglobin concentration, and plasma protein concentration. The rapid IV administration of HSB immediately increased cardiac index, stroke index, mean LVEDP, mean CVP, and oxygen delivery, and decreased MAP and SVR (Fig 3; Table 3). Cardiac contractility (as assessed by LV dP/dt_{max}) after HSB administration was greater than that in the control calves at time = 10, 30, and 60 minutes. Cardiac arrhythmias were not observed in HSB-treated calves. Taken together, these changes indicate that HSB rapidly increased preload and transiently decreased afterload, with the net result being an immediate increase in CO and oxygen delivery.

MPAP and PVR gradually decreased in both groups over 60 minutes (Table 3), associated with the decrease in blood L-lactate concentration (Table 1). Compared to control calves, HSB-treated calves had higher cardiac index and contractility (as assessed by LV dP/dt_{max}; Fig 3), lower LVEDP, and a faster rate of ventricular relaxation, indicating that HSB administration improved myocardial systolic function.

Discussion

The main findings of this study were that rapid IV administration of HSB (5 mmol/kg at 1 mmol/kg/min) in normovolemic, spontaneously breathing, halothane-anesthetized calves with experimentally induced respiratory and strong ion acidosis provided a safe and effective method for systemic alkalinization without changing CSF pH. Administration of HSB caused a transient but nonsignificant increase in mean arterial P_{CO_2} from 81 to 93 mm Hg at 5 minutes after treatment, but paradoxical CSF acidosis was not induced.

A comparison of the acid-base status of arterial blood and CSF at baseline indicated similar values for P_{CO_2} but numerically lower values for pH and [HCO_3^-] in CSF. Our

Table 1. Respiratory rate, minute volume, and arterial blood gas and acid-base status in neonatal calves with experimentally induced respiratory acidosis (RA), mixed respiratory acidosis and strong ion acidosis (RA/SIA), and response to no treatment (C) or treatment with IV hypertonic sodium bicarbonate solution (HSB). Values are mean ± SD.

				Time (minutes) after start of treatment			
Variable	Baseline	RA	RA/SIA	3	5	10	15
Respiratory rate (breaths/min)							
C	15 ± 0	49 ± 13[a]	52 ± 11[a]	50 ± 13	55 ± 8	51 ± 14	49 ± 13
HSB	15 ± 0	52 ± 6[a]	56 ± 7[a]	52 ± 6	52 ± 7	53 ± 7	52 ± 6
Minute volume (L/min)							
C	7.0 ± 0.4	9.5 ± 0.8[a]	11.5 ± 2.3[a,d]	10.7 ± 1.6	11.1 ± 1.0	11.2 ± 0.9	10.7 ± 1.2
HSB	6.9 ± 2.3	8.3 ± 2.3[a]	10.6 ± 3.1[a,d]	9.0 ± 2.5[b,c]	10.3 ± 3.5	9.6 ± 2.7[c]	10.2 ± 2.8
Blood P_{O_2} (mm Hg)							
C	379 ± 94	274 ± 69[a]	286 ± 57[a]	ND	304 ± 67	ND	298 ± 36
HSB	354 ± 132	251 ± 86[a]	236 ± 83[a]	ND	297 ± 118	ND	376 ± 24
Plasma [HCO_3^-] (mmol/L)							
C	27 ± 2	29 ± 1[a]	23 ± 2[a,d]	ND	25 ± 1[b]	ND	27 ± 1[b]
HSB	27 ± 1	28 ± 1	23 ± 1[a,d]	ND	37 ± 1[b,c]	ND	34 ± 1[b,c]
Base excess (mEq/L)							
C	5.1 ± 2.7	4.0 ± 0.9	−3.4 ± 2.1[a,d]	ND	−0.6 ± 1.6[b]	ND	1.6 ± 0.6[b]
HSB	5.0 ± 2.1	3.1 ± 1.3[a]	−3.4 ± 2.2[a,d]	ND	13.5 ± 2.0[b,c]	ND	10.8 ± 0.1[b,c]
Plasma [Na^+] (mEq/L)							
C	134 ± 4	137 ± 1	135 ± 3	ND	135 ± 2	ND	134 ± 4
HSB	135 ± 7	140 ± 9[a]	133 ± 8[d]	ND	141 ± 7[b,c]	ND	144 ± 10[b,c]
Plasma [K^+] (mEq/L)							
C	3.8 ± 0.7	3.9 ± 0.7	3.7 ± 0.5	ND	3.7 ± 0.4	ND	4.2 ± 0.2
HSB	4.0 ± 0.3	4.1 ± 0.2	4.1 ± 0.2[c]	ND	3.5 ± 0.3[b]	ND	3.4 ± 0.6[b]
Plasma [Ca^{2+}] (mEq/L)							
C	3.1 ± 0.4	3.4 ± 0.6	3.6 ± 1.0	ND	3.4 ± 0.6	ND	3.7 ± 0.6
HSB	3.6 ± 0.4	3.6 ± 0.5	3.9 ± 0.4	ND	3.4 ± 0.3	ND	3.7 ± 0.3[b]
Serum [Cl^-] (mEq/L)							
C	101.0 ± 1.4	101.2 ± 1.6	96.8 ± 4.3[a,d]	ND	97.3 ± 2.8	ND	ND
HSB	102.2 ± 0.8	103.6 ± 1.3	98.4 ± 0.9[a,d]	ND	100.0 ± 2.0	ND	ND
Blood L-lactate concentration (mmol/L)							
C	1.0 ± 0.3	0.5 ± 0.5	5.2 ± 1.0[a,d]	ND	3.9 ± 1.2[a,b,d]	ND	ND
HSB	1.2 ± 1.0	0.9 ± 0.6	5.3 ± 0.9[a,d]	ND	3.3 ± 0.7[a,b,d]	ND	ND
Hematocrit (%)							
C	34 ± 6	34 ± 7	36 ± 7	ND	35 ± 7	ND	34 ± 0
HSB	31 ± 5[c]	32 ± 4	32 ± 4[c]	ND	27 ± 2[b,c]	ND	27 ± 2[b,c]
[Plasma protein] (g/dL)							
C	5.0 ± 0.4	4.9 ± 0.5	4.9 ± 0.5	ND	4.9 ± 0.5	ND	4.4 ± 0.0
HSB	4.9 ± 0.5	4.9 ± 0.4	4.8 ± 0.5	ND	4.2 ± 0.5[b,c]	ND	4.2 ± 0.4[b,c]
Blood [hemoglobin] (g/dL)							
C	9.8 ± 1.7	10.0 ± 2.0	10.0 ± 1.6	ND	9.9 ± 1.8	ND	9.7 ± 0.6
HSB	8.4 ± 0.8[c]	8.4 ± 0.6[c]	8.5 ± 0.9[c]	ND	8.1 ± 1.2[b,c]	ND	8.1 ± 1.0[b,c]

P_{O_2}, partial pressure of oxygen; ND, not determined.
[a] Significantly different ($P < .05$) from baseline value.
[b] Significantly different ($P < .05$) from RA/SIA value.
[c] Significantly different ($P < .05$) from value for group C calves at same time.
[d] Significantly different ($P < .05$) from RA value.

observation that CSF pH was lower than arterial blood pH is in agreement with previous studies in calves,[38] neonatal foals,[39] and adult horses,[40] and was attributed to a low CSF strong ion difference. The mean difference between [HCO_3^-] in arterial blood and CSF at baseline was approximately 5 mmol/L; this was also in agreement with previous findings in conscious calves,[38] but the difference was greater than in equine neonates[39] and most mammalian species.[41]

Marked respiratory acidosis was successfully induced after 30 minutes of halothane anesthesia, as indicated by a

Table 1. Extended.

Time (minutes) after start of treatment			
20	30	45	60
47 ± 12	49 ± 12	47 ± 13[b]	45 ± 10[b]
52 ± 6[c]	56 ± 8[c]	52 ± 5[c]	54 ± 6[c]
10.4 ± 1.4	9.6 ± 1.7[b]	9.7 ± 2.5[b]	9.1 ± 2.5[b]
9.2 ± 2.9[b]	9.9 ± 3.7	8.6 ± 2.9[b]	8.9 ± 3.0[b]
ND	307 ± 136	ND	309 ± 89
ND	325 ± 104	ND	307 ± 123
ND	27 ± 1[b]	ND	29 ± 1[b]
ND	35 ± 2[b,c]	ND	35 ± 2[b,c]
ND	1.8 ± 1.2[b]	ND	3.2 ± 1.4[b]
ND	11.0 ± 2.5[b,c]	ND	11.1 ± 2.2[b,c]
ND	135 ± 3	ND	135 ± 4
ND	141 ± 6[b,c]	ND	140 ± 7[b,c]
ND	3.8 ± 0.4	ND	3.7 ± 0.5
ND	3.6 ± 0.3	ND	3.6 ± 0.2[b]
ND	3.6 ± 0.5	ND	3.7 ± 0.4
ND	3.8 ± 0.7	ND	3.7 ± 0.2
ND	99.5 ± 2.6	ND	99.5 ± 5.1
ND	99.5 ± 1.3	ND	99.5 ± 2.5
ND	1.7 ± 0.6[b]	ND	0.4 ± 0.5[b]
ND	1.5 ± 0.4[b]	ND	1.0 ± 0.4[b]
ND	34 ± 5	ND	36 ± 8
ND	28 ± 1[b,c]	ND	28 ± 1[b,c]
ND	4.8 ± 0.5	ND	4.8 ± 0.5
ND	4.7 ± 0.4[b,c]	ND	4.7 ± 0.5[b,c]
ND	10.0 ± 1.8	ND	10.1 ± 1.8
ND	8.0 ± 0.6[c]	ND	8.3 ± 0.4[c]

doubling in arterial P_{CO_2}. This response was similar to that observed in a previous study in calves.[30] Baseline arterial blood P_{CO_2} and CSF P_{CO_2} were similar in the study reported here; however, after induction of respiratory acidosis, the mean increase in P_{CO_2} in CSF was approximately 10 mm Hg smaller than that measured in arterial blood. This finding indicated that equilibration of CO_2 between arterial blood and CSF had not occurred by 30 minutes of halothane-induced respiratory acidosis. Equilibration was essentially complete by 60–120 minutes, as indicated by similar mean values for arterial blood and CSF P_{CO_2} in control calves. Similar results were found in neonatal foals with experimentally induced respiratory acidosis; CSF P_{CO_2} was maximally increased after 75 minutes of hypercarbia.[39] These results are consistent with a CSF turnover rate of 1% per minute,[41] and demonstrate that acute changes in blood P_{CO_2} lead to a delayed, but ultimately similar, change in CSF P_{CO_2}. In other words, even if rapid HSB administration caused an immediate increase in arterial blood P_{CO_2} as a result of buffering of plasma organic acids, the slow turnover of CSF ensures that a much slower increase in CSF P_{CO_2} will always result.

Spontaneous ventilation under halothane anesthesia resulted in hypercarbia, tachypnea, and increased minute volume. This response has been attributed to ventilation-perfusion mismatch secondary to atelectasis in the dependent lung lobes,[30] although it is likely that halothane anesthesia also obtunds the respiratory center response to increased P_{CO_2}. Hypercarbia stimulates the sympathetic nervous system, thereby increasing HR, cardiac contractility, and CO.[42,43] In the study reported here, we observed a progressive improvement in cardiovascular performance after induction of respiratory acidosis, as indicated by an increased HR, cardiac contractility (LV dP/dt_{max}), cardiac index, mean arterial blood pressure, and oxygen delivery, and a decreased rate of left ventricular relaxation (tau).

Intravenous administration of 300 mM L-lactic acid solution to calves with induced respiratory acidosis produced a strong ion acidosis in arterial blood, but not in CSF. This result indicated slow diffusion of L-lactate into CSF or rapid metabolism of L-lactate by cells in the central nervous system. The movement of lactate across the blood-brain barrier has 2 components, a saturable, stereospecific component for L-lactate, and a nonsaturable, nonstereospecific diffusional component for D-lactate.[41,44] When organic acids accumulate in blood as in lactic acidosis, L-lactate diffuses from blood into CSF but penetration is slow, with CSF L-lactate concentration being 60% of the blood L-lactate concentration by 6 hours after a rapid increase in blood L-lactate concentration in rats.[41] Because CSF base excess did not change in the study reported here, and because blood L-lactate concentration rapidly decreased after administration, we suspect that CSF L-lactate concentration did not increase after IV administration of L-lactate.

Intravenous administration of L-lactic acid was successful in inducing acute lactic acidosis, which has been defined as a state where arterial L-lactate concentration exceeds 5 mmol/L.[22] Superimposition of a strong ion acidosis on the experimentally induced respiratory acidosis was associated with a marked increase in MPAP and pulmonary vascular resistance, and a smaller increase in mean arterial pressure and minute volume. The L-lactate–induced pulmonary hypertension was an interesting finding and raises the intriguing possibility that hyper-L-lactatemia may influence the severity of the pulmonary hypertension induced by high-intensity exercise.[45]

HSB was effective at increasing arterial blood pH to above 7.20 but not to within the reference range because of continued respiratory acidosis. Systemic alkalinization occurs after HSB administration because essentially all of

Table 2. Cerebrospinal fluid (CSF) acid-base status and electrolyte concentrations in neonatal calves with experimentally induced respiratory acidosis (RA), mixed respiratory and strong ion acidosis (RA/SIA), and response to no treatment (C) or treatment with IV hypertonic sodium bicarbonate solution (HSB). Values are mean ± SD.

				Time (minutes) after start of treatment							
Variable	Baseline	RA	RA/SIA	3	5	10	15	20	30	45	60
CSF P_{O_2} (mm Hg)											
C	141 ± 36	156 ± 34	169 ± 40	ND	183 ± 39	ND	176 ± 32	ND	208 ± 49	ND	203 ± 52
HSB	141 ± 42	166 ± 56	157 ± 28	ND	205 ± 43	ND	245 ± 73	ND	221 ± 87	ND	194 ± 68
CSF [HCO_3^-] (mmol/L)											
C	23 ± 1	25 ± 1[a]	26 ± 1[a,b]	ND	26 ± 1	ND	26 ± 1	ND	26 ± 1	ND	28 ± 1[c]
HSB	23 ± 1	24 ± 1[a]	25 ± 1[a]	ND	26 ± 2	ND	27 ± 2	ND	27 ± 2[c]	ND	29 ± 2[c,d]
CSF base excess (mEq/L)											
C	−0.7 ± 1.9	−1.0 ± 1.9	−0.4 ± 1.3	ND	−0.2 ± 1.1	ND	−0.6 ± 0.1	ND	0.3 ± 1.0	ND	1.2 ± 1.2[c]
HSB	−1.2 ± 0.8	−1.9 ± 1.0	−0.9 ± 0.8	ND	0.0 ± 2.2	ND	−0.9 ± 2.0	ND	0.8 ± 2.5[c]	ND	2.7 ± 2.2[b,c]
CSF [Na^+] (mEq/L)											
C	144 ± 3	145 ± 5	143 ± 3	ND	144 ± 2	ND	142 ± 0	ND	143 ± 2	ND	142 ± 3
HSB	142 ± 7	148 ± 1[a,d]	145 ± 9[a,b]	ND	147 ± 9[d]	ND	145 ± 9	ND	144 ± 9	ND	143 ± 8
CSF [K^+] (mEq/L)											
C	2.2 ± 0.2	2.3 ± 0.3	2.4 ± 0.2[a]	ND	2.4 ± 0.1	ND	2.4 ± 0.1	ND	2.4 ± 0.1	ND	2.4 ± 0.1
HSB	2.2 ± 0.1	2.3 ± 0.2	2.3 ± 0.2	ND	2.4 ± 0.3	ND	2.6 ± 0.2[c,d]	ND	2.6 ± 0.1[c,d]	ND	2.6 ± 0.1[c]
CSF [Ca^{2+}] (mEq/L)											
C	1.8 ± 0.5	2.6 ± 0.4[a]	2.3 ± 0.4	ND	2.3 ± 0.4	ND	2.2 ± 0.6	ND	2.3 ± 0.4	ND	2.6 ± 0.4
HSB	2.0 ± 0.3	1.9 ± 0.7[d]	1.8 ± 0.7	ND	1.9 ± 0.9	ND	2.8 ± 0.5[c]	ND	2.7 ± 0.7[c]	ND	2.8 ± 0.8[c]
CSF [C1] (mEq/L)											
C	114.8 ± 4.0	111.3 ± 0.5	110.4 ± 1.3	ND	109.2 ± 2.5[a]	ND	ND	ND	107.0 ± 3.3[a]	ND	105.8 ± 3.8[a,d]
HSB	11.6 ± 2.5	113.4 ± 3.6	109.2 ± 3.1	ND	112.3 ± 4.7	ND	ND	ND	100.5 ± 3.1	ND	110.3 ± 3.3

ND, not determined.
[a] Significantly different ($P < .05$) from baseline value.
[b] Significantly different ($P < .05$) from RA value.
[c] Significantly different ($P < .05$) from RA/SIA value.
[d] Significantly different ($P < .05$) from value for group C calves at same time.

the infused bicarbonate is exhaled as CO_2.[46,47] The net result of sodium bicarbonate administration is therefore an increase in plasma strong ion difference (SID) and blood pH, because pH is dependent on P_{CO_2}, SID, and the concentration of nonvolatile buffers in plasma, such as albumin, globulin, and phosphate.[13,48]

Our main interest in conducting this study was to evaluate the safety and efficacy of HSB administration in spontaneously breathing calves with mixed respiratory and strong ion acidosis. The IV administration of sodium bicarbonate at different tonicities and doses has increased arterial and venous blood P_{CO_2} in newborn calves with birth acidosis.[2,20,49] This observation lead to speculation that a rapid increase in P_{CO_2} after bolus administration of HSB could result in paradoxical intracellular and CSF acidosis,[2] because CO_2 generated from the buffer reaction can rapidly diffuse across cell membranes and the blood-brain barrier to increase intracellular and CSF P_{CO_2}. Although paradoxical CSF acidosis has been described in humans,[23] the potential for sodium bicarbonate to induce paradoxical intracellular and CSF acidosis in adequately ventilated animals has been questioned.[50] The results of the study reported here show, for the first time, that the rapid administration of HSB does not cause a clinically or statistically significant increase in P_{CO_2} and pH in CSF, and therefore does not induce paradoxical CSF acidosis during light levels of halothane anesthesia. Interestingly, the rapid decline in arterial P_{CO_2} after bolus administration of HSB in the calves in the study reported here was not due to an increased minute volume (Table 1), because HSB administration slightly decreased minute volume when compared to that for calves with respiratory and strong ion acidosis. This result suggests that halothane anesthesia obtunded the central nervous system response to hypercarbia, or that minute volume increases in response to increased P_{CO_2} or decreased pH. In the latter case, the increase in pH after HSB administration would be expected to ameliorate the effect of decreased pH on minute volume.

Our results agree with those obtained in a randomized blinded clinical study in newborn calves.[20] This study compared bolus administration of 60 mL of 8.4% sodium bicarbonate directly after birth, followed by a 2nd 40-mL bolus 10 minutes later, with the same dosage protocol of 0.9% NaCl solution[20] (for comparison, the calves in our study received 150–235 mL of 8.4% sodium bicarbonate over 5 minutes). The calves were full term and were classified as vigorous (n = 11; pH > 7.20), depressed (n = 15; pH = 7.19–7.00), or comatose (n = 4; pH < 7.00)

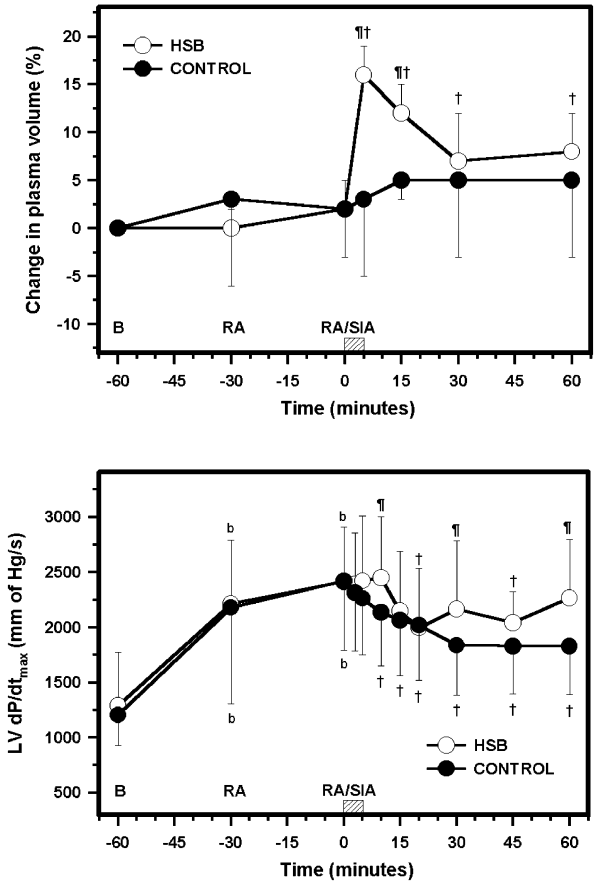

Fig 3. Change in plasma volume from baseline (%) and maximal rate of change of left ventricular pressure (LV dP/dt_{max}) in halothane-anesthetized, normovolemic, neonatal calves at baseline (B, time = −60 minutes) and after experimentally induced respiratory acidosis (RA, time = −30 minutes) and mixed respiratory acidosis and strong ion acidosis (RA/SIA, time = 0 minutes). At time = 0 minutes, calves were randomly assigned to receive hyperosmotic sodium bicarbonate (HSB, 8.4% sodium bicarbonate; 5 mL/kg over 5 minutes, IV; n = 5, hatched rectangle) or no treatment (CONTROL, n = 5) and monitored for 1 hour. b, significantly different ($P < .05$) from baseline value; r, significantly different ($P < .05$) from RA value; †, significantly different ($P < .05$) from time = 0 minutes value; ¶, significantly different ($P < .05$) from CONTROL at the same time. Values are mean ± SD; the SD value is smaller than the symbol radius in individual time points with no apparent SD bars.

based on jugular venous blood gas analysis. Jugular venous P_{CO_2} was transiently (<5 minutes) increased in the 3 groups after treatment with HSB.[20] The rapid decline in venous P_{CO_2} after bolus administration of HSB was attributed to the clinical impression of an increased tidal volume after HSB administration, although this was not measured. All calves treated with HSB survived.[20]

Our results also agree with those obtained when using a hypoxic lactic acidosis model in neonatal rabbits[51] and a cardiac arrest model in dogs under cardiopulmonary bypass with respiratory and metabolic acidosis.[52] Neither study observed the development of paradoxical CSF acidosis after administration of sodium bicarbonate at 10 mmol/kg[51] and approximately 4 mmol/kg.[52] The results of the study reported here are also in agreement with previous findings on the effects of HSB administration in a canine model of cardiac arrest.[53] Dogs in that study received 1 mmol/kg without a significant change of CSF pH and CSF P_{CO_2} despite significant increase of plasma P_{CO_2}.[53] CSF P_{CO_2} and pH were not altered in conscious horses after the IV administration of 5% sodium bicarbonate solution (5 ml/kg body weight over 30 minutes).[54] Taken together, the results of our study and a number of other studies indicate that the rapid administration of sodium bicarbonate does not induce paradoxical CSF acidosis in spontaneously ventilating normovolemic animals. In fact, it appears that paradoxical CSF acidosis after sodium bicarbonate administration only occurs when ventilation cannot increase in response to an increased P_{CO_2}.[23,24,55]

The dosage of HSB in the study reported here was 5 mmol/kg at a dose rate of 1 mmol/kg/min. This dose was selected to assist in comparison to studies administering hypertonic saline (7.2% NaCl; 4.8 mmol/kg at a dose rate of 1.2 mmol/kg/min) to neonatal calves.[6,7,36,56,57] The dosage was similar to the recommended dosage of 5–7 mmol/kg to calves with birth acidosis, administered as an isosmotic 1.3% sodium bicarbonate solution.[9] A recent study used 2 infusions of 60 and 40 mL of HSB at 1 minute and 10 minutes after delivery.[20] Another previous study in calves with birth acidosis used 3 mmol/kg administered within 1–3 minutes.[49]

This appears to be the first study to document the cardiovascular effects of HSB administration in calves during anesthesia. A recent study evaluated the cardiovascular effects of infusing 5, 10, or 15 mL/kg of isoosmotic sodium bicarbonate over 30 minutes in conscious calves with normal acid-base status.[58] Administration of isoosmotic sodium bicarbonate solutions did not significantly alter hemodynamic variables or plasma oncotic pressure in that study.[58] For comparison, the results of this study in calves with respiratory and strong ion acidosis indicated that the rapid IV administration of HSB (5 mL/kg) corrected the strong ion acidosis and induced marked but transient hemodynamic improvement. The hemodynamic response to HSB was characterized by an increase in preload (plasma volume expansion) and a decrease in afterload (decrease in systemic vascular resistance); the latter response is primarily due to hyperosmolar induced relaxation of vascular smooth muscle.[59] The apparent increase in cardiac contractility (as assessed by LV dP/dt_{max}) most likely reflected the increase in plasma volume, because this contractility index is preload dependent.[60]

A potential limitation of the study reported here is the choice of model to induce acute respiratory and strong ion acidosis, in that our model may not necessarily reflect the heterogeneous disorder of neonatal asphyxia or septicemia in calves with severe acidemia. The underlying disease process of combined respiratory and strong ion acidosis in neonatal asphyxia or endotoxemia is alveolar hypoxia, leading to hypoxemia, hypercarbia (respiratory acidosis), and decreased oxygen delivery[6–8]; the latter results in anaerobic metabolism, L-lactate production, and strong ion acidosis. Instead, we specifically sought to determine the in vivo effects of HSB administration on acid-base status in blood

Table 3. Hemodynamic findings in neonatal calves with experimentally induced respiratory acidosis (RA), mixed respiratory acidosis and strong ion acidosis (RA/SIA), and response to no treatment (C) or treatment with IV hypertonic sodium bicarbonate solution (HSB). Values are mean ± SD.

				Time (minutes) after start of treatment			
Variable	Baseline	RA	RA/SIA	3	5	10	15
Heart rate (beats/min)							
C	106 ± 8	144 ± 23[a]	149 ± 16[a]	142 ± 15	140 ± 15	138 ± 13[b]	136 ± 15[b]
HSB	108 ± 25	146 ±24[a]	156 ± 22[a]	154 ± 22[c]	153 ± 26[c]	153 ± 21[c]	139 ± 20[b]
Cardiac index (mL/min/kg)							
C	117 ± 29	169 ± 32[a]	161 ± 19[a]	ND	173 ± 30	ND	166 ± 33
HSB	136 ± 35	173 ± 37[a]	240 ± 50[a,c,d]	ND	240 ± 62[b,c]	ND	197 ± 68[c]
Stroke index (mL/kg/beat)							
C	1.1 ± 0.2	1.2 ± 0.2	1.1 ± 0.1	ND	1.2 ± 0.2	ND	1.2 ± 0.2
HSB	1.3 ± 0.3	1.2 ± 0.1	1.3 ± 0.1	ND	1.6 ± 0.3[b,c]	ND	1.4 ± 0.4
Mean arterial pressure (mm Hg)							
C	93 ± 13	105 ± 14[a]	114 ± 18[a]	118 ± 21	118 ± 21	116 ± 20	118 ± 23
HSB	90 ± 17	105 ± 9[a]	117 ± 13[a,d]	109 ± 18[c]	109 ± 18[c]	111 ± 13	108 ± 8[b,c]
Arterial pulse pressure (mm Hg)							
C	52 ± 5	57 ± 9	55 ± 7	54 ± 5	50 ± 2	52 ± 5	53 ± 5
HSB	57 ± 10	58 ± 5	59 ± 6	59 ± 5	59 ± 3[c]	53 ± 8	55 ± 3
Mean pulmonary artery pressure (mm Hg)							
C	16 ± 2	20 ± 4	37 ± 9[a,d]	34 ± 10	32 ± 10	31 ± 11[b]	31 ± 10[b]
HSB	14 ± 3	19 ± 7[a]	40 ± 7[a,d]	37 ± 10	35 ± 9	34 ± 9	33 ± 8[b]
Mean central venous pressure (mm Hg)							
C	1.0 ± 0.7	1.0 ± 0	0.8 ± 0.5	1.2 ± 0.8	1.2 ± 0.8	1.2 ± 0.5	1.2 ± 0.5
HSB	1.0 ± 0.7	1.2 ± 0.5	1.6 ± 0.6[a,c]	2.2 ± 0.5[b,c]	2.0 ± 0.7[c]	1.8 ± 0.8[c]	1.4 ± 0.6
LVEDP (mm Hg)							
C	11.6 ± 2.4	9.5 ± 3.6	7.6 ± 3.5	10.4 ± 4.8	10.8 ± 4.5	11.7 ± 4.8	12.8 ± 3.8[b]
HSB	12.1 ± 1.3	8.2 ± 4.1	8.7 ± 5.0	17.7 ± 5.2[b,c]	14.8 ± 5.3[b]	10.4 ± 6.3	10.5 ± 5.5
LV dP/dt_{max} (mm Hg/s)							
C	1,205 ± 276	2,179 ± 873[a]	2,419 ± 625[a]	2,311 ± 525	2,261 ± 512	2,135 ± 483[b]	2,064 ± 505[b]
HSB	1,290 ± 486	2,211 ± 582[a]	2,410 ± 496[a]	2,389 ± 469	2,421 ± 586	2,447 ± 559[c]	2,148 ± 540
Tau (ms)							
C	28 ± 4	20 ± 4[a]	22 ± 4[a]	22 ± 4	22 ± 4	23 ± 4	23 ± 4
HSB	27 ± 5	19 ± 3[a]	20 ± 4[a]	21 ± 3[c]	21 ± 4	19 ± 5[c]	21 ± 4[c]
Oxygen delivery (mL O_2/min/kg)							
C	17 ± 3	24 ± 3[a]	23 ± 2[a]	ND	25 ± 4	ND	25 ± 5
HSB	18 ± 6	22 ± 6[a]	26 ± 8[ad]	ND	29 ± 9[bc]	ND	23 ± 10
Systematic vascular resistance (dyne s/cm^5)							
C	1,472 ± 305	1,129 ± 214[a]	1,284 ± 246	ND	1,249 ± 270	ND	1,283 ± 318
HSB	1,408 ± 296	1,283 ± 292	1,225 ± 324	ND	969 ± 292[b,c]	ND	1,295 ± 447
Pulmonary vascular resistance (dyne s/cm^5)							
C	61 ± 65	109 ± 53	336 ± 128[a,d]	ND	230 ± 151[b]	ND	206 ± 145[b]
HSB	25 ± 52	133 ± 106[a]	325 ± 102[a,d]	ND	179 ± 62[b]	ND	220 ± 113

ND, not determined. LV dP/dt_{max}, maximal rate of change of left ventricular pressure.
[a] Significantly different ($P < .05$) from baseline value.
[b] Significantly different ($P < .05$) from RA/SIA value.
[c] Significantly different ($P < .05$) from value for group C calves at same time.

and CSF and cardiovascular function during anesthesia and experimentally induced respiratory and metabolic acidosis.

Acute respiratory acidosis has usually been induced by increasing the fraction of inspired CO_2, with or without the concurrent presence of hypoxemia. Instead, our study used spontaneous ventilation under halothane anesthesia to increase arterial P_{CO_2} and induce respiratory acidosis. However, because halothane causes direct respiratory and cardiovascular system depression, the halothane-anesthetized calf provides a reasonable acute model for calf septicemia, in that many septicemic calves have respiratory acidosis and intrinsic cardiovascular depression that may be tem-

Table 3. Extended.

Time (minutes) after start of treatment			
20	30	45	60
135 ± 16[b]	132 ± 13[b]	132 ± 14[b]	131 ± 15[b]
135 ± 20[b]	140 ± 23[b]	137 ± 13[b]	143 ± 19[b,c]
ND	165 ± 33	177 ± 38	155 ± 36
ND	182 ± 50	200 ± 60[c]	180 ± 39[c]
ND	1.2 ± 0.2	1.3 ± 0.2	1.2 ± 0.2
ND	1.3 ± 0.2	1.5 ± 0.4	1.3 ± 0.1
117 ± 23	113 ± 20	109 ± 17	109 ± 17
108 ± 10[b,c]	112 ± 12	114 ± 17	114 ± 16
53 ± 4	51 ± 6	51 ± 6	52 ± 6
53 ± 3[b]	53 ± 5	53 ± 7	58 ± 6[c]
29 ± 10[b]	29 ± 9[b]	28 ± 8[b]	27 ± 8[b]
29 ± 8[b]	24 ± 7[b]	21 ± 6[b]	20 ± 6[b]
1.2 ± 0.5	1.2 ± 0.5	0.8 ± 0.5	1.0 ± 0
1.2 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5
13.6 ± 2.7[b]	14.6 ± 4.3[b]	13.9 ± 3.3[b]	13.3 ± 4.1[b]
10.8 ± 4.7	10.6 ± 4.4[c]	9.6 ± 2.9[c]	9.1 ± 4.1[c]
2,019 ± 500[b]	1,837 ± 451[b]	1,827 ± 431[b]	1,827 ± 437[b]
1,995 ± 539[b]	2,165 ± 620[c]	2,042 ± 285[b]	2,266 ± 530[c]
23 ± 4	24 ± 4	24 ± 4	24 ± 5
22 ± 4	21 ± 4	11 ± 3[c]	20 ± 4[c]
ND	23 ± 2	ND	23 ± 3
ND	22 ± 6	ND	22 ± 6
ND	1,277 ± 270	1,171 ± 306	1,247 ± 256
ND	1,387 ± 366	1,335 ± 516	1,378 ± 257
ND	172 ± 79[b]	138 ± 79[b]	173 ± 77[b]
ND	169 ± 53[b]	125 ± 44[b]	132 ± 101[b]

porarily reversed by sympathetic activation.[8] Whenever a calf has decreased CO, oxygen delivery, and tissue perfusion (eg, in severely dehydrated, diarrheic calves), it is possible that the CO_2 generated from HSB administration may be stored in the tissues or venous capacitance beds and not effectively removed by alveolar ventilation. It would therefore appear preferable to increase the circulating blood volume before administering HSB. However, because hypertonic saline (7.2% NaCl) provides the most rapid method for initial resuscitation in hypovolemic animals, and because it is the transient hypernatremia and hyperosmolality induced by hypertonic saline administration that rapidly expands the plasma volume and resuscitates the animal,[6,7,36,57] an equimolar dose of HSB would be expected to produce a similar plasma volume expansion as that observed after administration of hypertonic saline. Indeed, HSB produced an immediate increase in plasma volume of more than 15% (Fig 3).

In conclusion, the rapid IV administration of HSB provided an effective and safe method for treating strong ion acidosis in halothane-anesthetized normovolemic calves. Additional studies are needed to determine the effects and safety of HSB administration in conscious calves with naturally occuring birth acidosis and in dehydrated calves with diarrhea.

Footnotes

[a] Berchtold J, Constable PD, Smith G, et al. Acid-base, cerebrospinal fluid, and cardiovascular effects of rapid IV hypertonic sodium bicarbonate in calves with experimentally induced metabolic and respiratory acidosis. J Vet Intern Med 2001;15:282 (abstract).
[b] Agri Master, Supreme All Milk, Blain Supply, Janesville, WI
[c] Diazepam, Elkins-Sinn, Cherry Hill, NJ
[d] Vetaket, Lloyd Inc, Shenandoah, IA
[e] Aquamatic K module, Gormann-Rupp Industries, Bellville, OH
[f] Volume-cycled respirator, Harvard Apparatus Co Inc, Dover, MA
[g] Wright Respirometer, Harris-Lake Inc Medical Equipment, Cleveland, OH
[h] 5/6 Recorder, Gilson Medical Electronics Inc, Middleton, WI
[i] Model 131H-7F Swan-Ganz catheter, Baxter Healthcare Corp, Edwards Critical Care Division, Irvine, CA
[j] P23XL transducer, Viggo Spectramed, Oxnard, CA
[k] 7-F high-fidelity catheter dual-tipped pressure transducer, Millar Instruments, Houston, TX
[l] L-Lactic acid, Sigma Chemical, St Louis, MO
[m] 288 Blood gas system, Ciba-Corning, Medfield, MA
[n] COM-1 cardiac output computer, American Edwards Laboratories, Irvine, CA
[o] CONDUCT-PC, Leycom, Zoetermeer, The Netherlands
[p] Hitachi 704 automatic analyzer, Hitachi, Tokyo, Japan
[q] L-Lactate dehydrogenase, Sigma Chemical, St Louis, MO
[r] SAS 8e, SAS Institute, Cary, NC

References

1. Adams R, Garry FB, Holland MD. Clinicopathologic measurements in newborn beef calves experiencing mild to moderate degrees of dystocia. Agric Pract 1995;16:5–11.

2. Eigenmann UJE, Rüdiger B, Schoon HA, et al. Natriumbikarbonat- und Glucosebehandlung bei der Asphyxie des Kalbes. Dtsch Tierärztl Wochenschr 1982;89:228–234.

3. Herfen K, Bostedt H. Zum Säure-Basen-Status bei neugeborenen Kälbern in den ersten Lebenstagen unter Berücksichtigung differenter Vitalitätssituationen. Berl Münch Tierärztl Wochenschr 1999;112:166–171.

4. Szenci O. Role of acid-base disturbances in perinatal mortality of calves. Acta Vet Hung 1985;33:205–220.

5. Varga J, Szenci O, Dufranse I, et al. Respiratory mechanical function in newborn calves immediately postpartum. Vet J 1998;156: 73–76.

6. Constable PD, Schmall LM, Muir WW, et al. Hemodynamic re-

sponse of endotoxemic calves to treatment with small-volume hypertonic saline solution. Am J Vet Res 1991;52:981–989.

7. Constable PD, Schmall LM, Muir WW, et al. Respiratory, renal, hematologic, and serum biochemical effects of hypertonic saline solution in endotoxemic calves. Am J Vet Res 1991;52:990–998.

8. Constable PD. Acute endotoxemia increases left ventricular contractility and diastolic stiffness in calves. Shock 1999;12:391–401.

9. Kasari TR. Weakness in the newborn calf. Vet Clin North Am Food Anim Pract 1994;10:167–180.

10. Berchtold J, Hartmann H, Hofmann W. Bedeutung respiratorischer Kompensationsvorgänge bei Azidosen des Kalbes. Dtsch Tierärztl Wochenschr 2000;107:10–16.

11. Groutides C, Michell AR. Changes in plasma composition in calves surviving or dying from diarrhoea. Br Vet J 1990;146:205–210.

12. Berchtold J. Intravenous fluid therapy of calves. Vet Clin North Am Food Anim Pract 1999;15:505–531.

13. Constable PD. Clinical assessment of acid-base status: Strong ion difference theory. Vet Clin North Am Food Anim Pract 1999;15: 447–471.

14. Constable PD. Fluids and electrolytes. Vet Clin North Am Food Anim Pract 2003;19:1–40.

15. Constable PD, Stämpfli HR, Navetat H, et al. Use of a quantitative strong ion approach to determine the mechanism for acid-base abnormalities in calves with and without diarrhea. J Vet Intern Med 2005. In press.

16. Kasari TR, Naylor JM. Clinical evaluation of sodium bicarbonate, sodium L-lactate, and sodium acetate for the treatment of acidosis in diarrheic calves. J Am Vet Med Assoc 1985;187:392–397.

17. Hartsfield SM, Thurmon JC, Corbin JE, et al. Effects of sodium acetate, bicarbonate and lactate on acid-base status in anaesthetized dogs. J Vet Pharmacol Ther 1981;4:51–61.

18. Grove-White DH, White DG. Diagnosis and treatment of metabolic acidosis in calves: A field study. Vet Rec 1993;133:499–501.

19. Grove-White DH, Michell AR. Iatrogenic hypocalcemia during parenteral fluid therapy of diarrhoeic calves. Vet Rec 2001;149:203–207.

20. Herfen K. Überprüfung Verschiedener Therapiemodelle bei der Neonatalen Atemdepression des Kalbes unter Besonderer Berücksichtigung Klinischer und Blutgasanalytischer Vitalitätskriterien. Gießen, Germany: Justus-Liebig-Universität Gießen; 1997. Thesis.

21. Cooper DJ, Walley KR, Wiggs BR, et al. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. Ann Intern Med 1990; 112:492–498.

22. Swenson ER. Metabolic acidosis. Respir Care 2001;46:342–353.

23. Posner JB, Plum F. Spinal-fluid pH and neurologic symptoms in systemic acidosis. N Engl J Med 1967;277:605–613.

24. Bishop RL, Weisfeldt ML. Sodium bicarbonate administration during cardiac arrest. J Am Med Assoc 1976;235:506–509.

25. Fanconi S, Burger R, Ghelfi D, et al. Hemodynamic effects of sodium bicarbonate in critically ill neonates. Intensive Care Med 1993; 19:65–69.

26. Chew DJ, Leonard M, Muir WW. Effect of sodium bicarbonate infusion on serum osmolality, electrolyte concentrations, and blood gas tensions in cats. Am J Vet Res 1991;52:12–17.

27. Papile LA, Burstein J, Burstein R, et al. Relationship of intravenous sodium bicarbonate infusions and cerebral intraventricular hemorrage. J Pediatr 1978;93:834–836.

28. Wheeler AS, Sadri S, Gutsche BB, et al. Intracranial hemorrhage following intravenous administration of sodium bicarbonate or saline solution in the newborn lamb asphyxiated in utero. Anesthesiology 1979;51:517–521.

29. Graf H, Leach W, Arieff AI. Evidence of detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. Science 1985;227:754–756.

30. Steffey EP, Howland D. Halothane anesthesia in calves. Am J Vet Res 1979;40:372–376.

31. Michaelis B. Experimentelle Erzeugung einer Respiratorisch-Metabolischen Azidose beim Kalb bei Gleichzeitiger Überprüfung des Therapeutischen Wertes von Natriumhydrogenkarbonat- und Trispufferlösungen. Berlin, Germany: Freie Universität Berlin; 1982. Thesis.

32. Wu EY, Barazanji KW, Johnson RL. Sources of error in A-aDo_2 calculated from blood stored in plastic and glass syringes. J Appl Physiol 1997;82:196–202.

33. Constable PD, Muir WW, Sisson D. Clinical assessment of left ventricular relaxation. J Vet Intern Med 1999;13:5–13.

34. Gabel RA. Algorithms for calculating and correcting blood-gas and acid-base variables. Respir Physiol 1980;42:211–232.

35. Alexander SC, Gelfand R, Lambertsen CJ. The pK′ of carbonic acid in cerebrospinal fluid. J Biol Chem 1961;236:592–596.

36. Constable PD, Gohar HM, Morin DE, et al. Use of hypertonic saline-dextran solution to resuscitate hypovolemic calves with diarrhea. Am J Vet Res 1996;57:97–104.

37. Beaumont W van, Greenleaf JE, Juhos L. Disproportional changes in hematocrit, plasma volume, and proteins during excercise and bed rest. J Appl Physiol 1972;33:55–61.

38. Singh M, Mirakhur KK, Prasad B, et al. Acid-base status and gases in cerebrospinal fluid of healthy calves and buffalo calves. Zentralbl Veterinarmed A 1981;28:131–134.

39. Geiser DR, Andrews FM, Rohrbach BW, et al. Cerebrospinal fluid acid-base status during normocapnia and acute hypercapnia in equine neonates. Am J Vet Res 1996;57:1483–1487.

40. Muir W, Swanson C, Reed S, et al. Cerebral spinal fluid acid-base balance in adult conscious and anesthetized horses. Vet Surg 1985;14:339.

41. Fencl V. Acid-base balance in cerebral fluids. In: Cherniack NS, Widdicombe JG, eds. Handbook of Physiology, Section 3: The Respiratory System, Vol II: Control of Breathing, I. Bethesda, MD: American Physiological Society; 1986:115–140.

42. Wagner AE, Bednarski RM, Muir WW III. Hemodynamic effects of carbon dioxide during intermittent positive-pressure ventilation in horses. Am J Vet Res 1990;51:1922–1929.

43. Epstein SK, Singh N. Respiratory acidosis. Respir Care 2001; 46:366–383.

44. LaManna JC, Harrington JF, Vendel LM, et al. Regional blood-brain lactate influx. Brain Res 1993;614:164–170.

45. Olsen SC, Coyne CP, Lowe BS, et al. Influence of furosemide on hemodynamic responses during exercise in horses. Am J Vet Res 1992;53:742–747.

46. Kornberg HL, Davies RE, Wood DR. The metabolism of ^{14}C-labelled bicarbonate in the cat. Biochemistry 1952;51:351–357.

47. Clugston GA, Garlick PJ. Recovery of infused [^{14}C]bicarbonate as respiratory $^{14}CO_2$ in man. Clin Sci 1983;64:213–233.

48. Constable PD. Calculation of variables describing plasma nonvolatile weak acids for use in the strong ion approach to acid-base balance in cattle. Am J Vet Res 2002;63:482–490.

49. Ayers MW, Besser TE. Evaluation of colostral IgG1 absorption in newborn calves after treatment with alkalinizing agents. Am J Vet Res 1992;53:83–86.

50. Roussel AJ, Kasari TR. Using fluid and electrolyte replacement therapy to help diarrheic calves. Vet Med 1990;85:303–311.

51. Sessler D, Mills P, Gregory G, et al. Effects of bicarbonate on arterial and brain intracellular pH in neonatal rabbits recovering from hypoxic lactic acidosis. J Pediatr 1987;111:817–823.

52. Rosenberg JM, Martin GB, Paradis NA, et al. The effect of CO_2 and non–CO_2-generating buffers on cerebral acidosis after cardiac arrest: A 31P NMR study. Ann Emerg Med 1989;18:341–347.

53. Sanders AB, Otto CW, Kern KB, et al. Acid-base balance in a canine model of cardiac arrest. Ann Emerg Med 1988;17:667–671.

54. Pedrick TP, Moon PF, Ludders JW, et al. The effects of equivalent doses of tromethamine or sodium bicarbonate in healthy horses. Vet Surg 1998;27:284–291.

55. Berenyi KJ, Wolk M, Killip T. Cerebrospinal fluid acidosis complicating therapy of experimental cardiopulmonary arrest. Circulation 1975;52:319–324.

56. Constable PD. Hypertonic saline. Vet Clin North Am Food Anim Pract 1999;15:559–585.

57. Walker PG, Constable PD, Morin DE, et al. Comparison of hypertonic saline-dextran solution and lactated Ringer's solution for resuscitating severely dehydrated calves with diarrhea. J Am Vet Med Assoc 1998;213:113–121.

58. Suzuki K, Abe I, Iwabuchi S, et al. Evaluation of isotonic sodium bicarbonate solution for alkalizing effects in conscious calves. J Vet Med Sci 2002;64:699–703.

59. Constable PD, Muir WW, Binkley PF. Effect of hypertonic saline solution on left ventricular afterload in normovolumic dogs. Am J Vet Res 1995;56:1513–1521.

60. Constable PD, Muir WW, Binkley PF. Hypertonic saline is a negative inotropic agent in normovolumic dogs. Am J Physiol 1994; 267:H667–H677.