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Comparative Effects of Metabolic Acidemia and Hypoxemia on Cardiac Output and Regional Blood Flows in Unanesthetized Newborn Lambs

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ABSTRACT. We studied the comparative effects of HCl-induced metabolic acidemia (pH = 7.11 ± 0.03, mean ± SE) and hypoxemia (PO_2 = 28 ± 1 torr) on cardiac output and regional blood flows in newborn lambs 3 days after the surgical placement of catheters in the left atrium and aorta and pacing wires on the left atrium. Cardiac output decreased by 49 ± 6% during metabolic acidemia in contrast to the 12 ± 2% increase during hypoxemia. The adrenal glands and the diaphragm were the only organs that received increased blood flows during acidemia and hypoxemia. Cerebral and myocardial blood flows decreased during acidemia but increased during hypoxemia. Blood flows decreased to the carcass and gastrointestinal tract during acidemia but did not change significantly during hypoxemia. Renal and splenic blood flows decreased during both stresses, but the reductions were more severe during acidemia. The changes in regional blood flows were not a passive result of the respective changes in cardiac output. HCl-induced metabolic acidemia and hypoxemia each result in significant redistributions of available blood flows which are quantitatively and qualitatively different from each other. (*Pediatr Res* 20: 756–760, 1986)

Birth asphyxia can result in significant injury to multiple body organs (1–5). Asphyxia also is frequently associated with metabolic disturbances such as hypoxemia and acidemia (6, 7). As clinical and necropsy data from asphyxiated newborns have suggested that the organ injury of birth asphyxia is consistent with perinatal ischemia and/or tissue hypoxia (5, 8–10), experimental studies have focused on the relationship between the metabolic abnormalities that occur during asphyxia and total cardiac output as well as regional organ blood flows. Many studies have demonstrated that neonatal and fetal ovine hypoxemia results in reductions in renal, gastrointestinal, splenic, and hepatic blood flows (11–13). However, as severe hypoxemia also produces increases in cerebral, myocardial, adrenal, and diaphragmatic blood flows, these experiments suggest that hypoxemia may be partially but not completely responsible for the ischemic and hypoxic changes that may occur during birth asphyxia. Thus, the purpose of this study was to consider the influence of an additional metabolic stress on the asphyxiated newborn by comparing the effects of metabolic acidemia with hypoxemia on cardiac output and regional organ blood flows in unanesthetized newborn lambs.

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METHODS

Surgical technique. We operated on 24 Western newborn lambs at 1 to 8 days (5 ± 1, mean ± SE) after birth. The weight at surgery was 5.6 ± 0.2 kg. We performed a thoracotomy under halothane anesthesia in the left fourth intercostal space and inserted polyvinyl catheters (inside diameter 0.10 cm; outside diameter 0.15 cm) directly into the left atrium, and into the ascending aorta via the left internal thoracic artery (14). A pair of stainless steel pacing wires were sutured onto the left atrial appendage (A5633 hookup wires, Cooner Wire Co., Chatsworth, CA). Separate catheters were placed in a leg vein and artery, and advanced into the distal inferior vena cava and abdominal aorta, respectively. The wounds were sutured and postoperative care was given as described previously (14).

Experimental protocols. Studies were performed 3 days after surgery, which is a duration that allows for the recovery of a normal cardiac output after a thoracotomy and halothane anesthesia in newborn lambs (15). The lambs were blindfolded, placed in a nylon-mesh animal sling, and a continuous recording was begun of a lead II electrocardiogram, aortic mean blood pressure, and heart rate. After the lambs had been resting quietly for 30 min, we withdrew 0.5 ml of aortic blood for the measurement of oxygen saturation, hemoglobin concentration, PO_2, pH, and PCO_2. Immediately after obtaining the blood sample, we measured cardiac output and regional blood flows with radionuclide-labeled microspheres (16).

After the control measurements were made, each lamb was subjected to 20 min of either reduced arterial blood oxygen content (hypoxemia) or reduced arterial pH (metabolic acidemia). Hypoxemia was produced in 12 lambs by placing each lamb's head in a polyethylene bag through which we administered 7% oxygen with the balance as nitrogen (14). Metabolic acidemia was produced in the other 12 lambs with an intravenous infusion of 0.5 N HCl into the distal inferior vena cava at 0.4 ml/min. We increased the infusion rate by 0.1 ml/min every ten minutes until the aortic pH was less than 7.20. The HCl infusion was discontinued at that time and the measurements were repeated after 20 min of metabolic acidemia. The arterial pH decreased by 0.02 ± 0.02 pH units during this period, but this trend was not statistically significant. The acidemia was achieved over 29 ± 2 (mean ± SE) min with a 0.09 ± 0.02 ml/kg/min of HCl.

Previous studies have noted that metabolic acidemia may result in severe sinus bradycardia and an unstable preparation in experimental lambs and dogs (17, 18). Consequently, we paced

the left atrium at the control rate during the HCl infusion in the lambs that developed sinus bradycardia in order to maintain stable hemodynamics in all of the lambs (Model SD9, Grass Instruments). The lambs that developed sinus bradycardia were not distinguished from the lambs that developed tachycardia by their age, weight, control heart rate, control blood pressure, or degree of hyperventilation.

As in our previous studies, there was no suggestion that the lambs experienced any pain during hypoxemia or acidemia, as evidenced by the absence of agitation (12, 14). All of the lambs hyperventilated during hypoxemia and metabolic acidemia, but otherwise rested quietly in the animal sling during the studies. Using one of the above protocols, a single study of either hypoxemia or metabolic acidemia was performed in each lamb. The lambs were killed with euthanasia solution after the completion of each experiment. Correct placement of the catheters was verified at necropsy.

Measurements and calculations. PO_2, PCO_2, and pH were measured with a blood gas analyzer (Model 158, Corning Instruments, Medfield, MA). All values for PO_2 were corrected to 39° C, the average body temperature of sheep (19). Blood oxygen contents were calculated by multiplying measured oxygen saturations and hemoglobin concentrations (Hemoximeter OSM2, Radiometer, Copenhagen, Denmark), using a capacity factor of 1.36 ml oxygen per gram of hemoglobin (19). Aortic blood pressure was measured with a Statham P23Db transducer referred to atmospheric pressure with zero obtained at the midchest position.

Cardiac outputs and regional blood flows were measured as previously described with 15 micron diameter microspheres labeled with ^{57}Co, ^{113}Sn, ^{114m}In, ^{85}Sr, ^{95}Nb, or ^{46}Sc (16). During the left atrial injection of microspheres, reference samples were withdrawn continuously from the ascending thoracic aorta and the descending abdominal aorta into preweighed syringes for 2 min at a rate of 4 ml/min. Cardiac outputs were calculated by summating the radioactivity of all body parts. Each sample contained at least 400 microspheres, thereby providing an accuracy for counting statistics of ±10% (16). There was no more than 10% variability of blood flows between paired cerebral hemispheres and kidneys, thereby demonstrating adequate mixing of microspheres within the circulation (16). Oxygen deliveries were calculated by multiplying the arterial blood oxygen content with the appropriate blood flow. Systemic vascular resistance was estimated by dividing aortic mean blood pressure by cardiac output. This may induce a small error by omitting central venous pressure from the calculation. Central venous pressure was not measured.

The mean ± SE was calculated for each variable. Significant differences were determined with *t* tests for the parametric data analyses, and with the Wilcoxon signed rank test or the Mann-Whitney test for the nonparametric (percentage cardiac output) data analyses (20). When a variable was subjected to two different statistical comparisons, the critical level of significance (p) was reduced to 0.025 (21).

RESULTS

The control measurements (Table 1) were similar to previous measurements for conscious newborn lambs (2, 12–14, 19). There were no significant differences between any of the control measurements in the two groups of lambs (Tables 1 and 2, Fig. 1).

Our protocols were designed to produce significant reductions in arterial blood oxygen content in one group of lambs, and in the arterial pH in another group of lambs (Table 1). There was no significant change in the arterial pH in the hypoxemia group. Acidemia produced a shift in the hemoglobin-oxygen dissociation curve in that the arterial PO_2 did not change but there was a mild reduction in the measured blood oxygen saturation (Table 1). Both protocols produced hyperventilation with similar reductions in the arterial carbon dioxide tensions. Hypoxemia was associated with tachycardia while left atrial pacing was necessary to normalize the heart rate in the eight lambs that developed sinus bradycardia during metabolic acidemia. There were no significant changes in the aortic mean blood pressure or in the arterial blood hemoglobin concentration in either groups of lambs (Table 1).

Table 1. *Systemic oxygen transport and hemodynamic data at rest, during hypoxemia, and during acidemia**

	Control	Hypoxemia	Control	Acidemia
PO_2	81 ± 2	25 ± 1†	77 ± 2	78 ± 2§
pH	7.40 ± 0.02	7.46 ± 0.02	7.40 ± 0.02	7.11 ± 0.03†·§
PCO_2	40 ± 1	28 ± 1†	38 ± 1	27 ± 1†
SaO_2	95 ± 1	35 ± 2†	95 ± 1	88 ± 1‡·§
Hg	10.3 ± 0.2	10.7 ± 0.2	10.1 ± 0.2	10.6 ± 0.2
CaO_2	6.0 ± 0.2	2.3 ± 0.2†	5.8 ± 0.1	5.4 ± 0.1‡·§
CO	247 ± 14	277 ± 16†	263 ± 16	124 ± 16†·§
DO_2	1434 ± 82	642 ± 81†	1523 ± 83	671 ± 81†
HR	191 ± 12	255 ± 16†	196 ± 11	205 ± 14§·‖
Ao	70 ± 2	67 ± 3	69 ± 2	65 ± 3
SVR	0.29 ± 0.03	0.21 ± 0.02‡	0.27 ± 0.03	0.49 ± 0.4†·§

* Results are means ± SE, $n = 12$ for each group. PO_2 and PCO_2 are arterial O_2 and CO_2 tensions, respective, in torr. SaO_2 and CaO_2 are arterial blood oxygen saturation (%) and content (m mol/liter), respectively. Hg = arterial blood hemoglobin concentration in g/dl. HR = heart rate in beats per minute. Ao = aortic mean blood pressure in mmHg. CO = cardiac output in ml/min/kg of body weight. DO_2 = systemic oxygen delivery in m mol/min/kg body weight. SVR = systemic vascular resistance in mm Hg/ml/min/kg. There were no significant differences between the control groups in any of the variables.

†·‡ $p < 0.001$ and 0.01, respectively, compared with its control value.

§ Measurements during hypoxemia are significantly different from acidemia at $p < 0.001$.

‖ Data during acidemia represents the combined heart rates of the four lambs that developed mild sinus tachycardia and the eight lambs that were atrially paced to prevent sinus bradycardia (see "Methods").

In agreement with previous studies in lambs of a similar age (13), hypoxemia produced an average 12% increase in cardiac output (Table 1). In contrast, acidemia produced an average 49% reduction in cardiac output (Table 1). The cardiac output was 128 ± 22 ml/min/kg during acidemia in the eight lambs that were paced as compared to 121 ± 20 ml/min/kg in the four remaining acidemia lambs that were not paced because they developed mild sinus tachycardia. Similarly, the left atrial mean pressures were 7 ± 2 mm Hg in the acidemia lambs that developed sinus tachycardia and 6 ± 1 mm Hg in the lambs that were paced because they developed sinus bradycardia.

There were significant qualitative as well as quantitative differences in many of the regional blood flow responses to metabolic acidemia as compared to hypoxemia (Table 2, Fig. 1). Cerebral and myocardial blood flows decreased during metabolic acidemia but they increased during hypoxemia. The increase in adrenal blood flow was more limited during acidemia than during hypoxemia. Blood flow to the carcass and gastrointestinal tract decreased during acidemia but was unchanged during hypoxemia (Table 2). Renal blood flow decreased more during acidemia. As there were significant differences in the percentage of cardiac output flowing to each of the organs except the brain and spleen, the differences in the regional blood flow responses during the two protocols did not appear to be a passive result of the differences in the cardiac output responses (Fig. 1).

There also were many significant differences in the regional oxygen delivery responses during hypoxemia and acidemia (Table 2). Cerebral oxygen delivery decreased during acidemia but did not change significantly during hypoxemia. Myocardial oxygen delivery decreased during acidemia but increased during hypoxemia. Adrenal oxygen delivery increased during both stresses, but the increases were significantly greater during aci-

Table 2. *Regional blood flows and oxygen deliveries at rest, during hypoxemia, and during acidemia**

	Control	Hypoxemia	Control	Acidemia
Blood flows				
Brain	85 ± 11	195 ± 15	89 ± 6	61 ± 4†·‖
Heart	196 ± 11	774 ± 32†	212 ± 10	150 ± 15‖·§
Adrenals	192 ± 34	668 ± 60†	166 ± 20	344 ± 44†·‡
Diaphragm	27 ± 3	69 ± 9†	27 ± 3	59 ± 8§
Carcass	18 ± 1	20 ± 2	18 ± 1	8 ± 1†·‡
Kidneys	273 ± 28	216 ± 31§	257 ± 26	126 ± 18†·‡
Gastrointestinal tract	168 ± 26	160 ± 30	151 ± 27	100 ± 18†·‡
Spleen	297 ± 28	111 ± 19†	285 ± 33	99 ± 31†
Oxygen deliveries				
Brain	445 ± 34	399 ± 47	518 ± 36	328 ± 20†·‡
Heart	1239 ± 71	1574 ± 161§	1340 ± 64	819 ± 86†·‖
Adrenals	1034 ± 250	1450 ± 134§	963 ± 118	1852 ± 247†·‖
Diaphragm	154 ± 14	159 ± 34	155 ± 13	316 ± 48§·‡
Carcass	106 ± 8	45 ± 7†	106 ± 7	44 ± 3†
Kidneys	1462 ± 184	545 ± 134†	1371 ± 112	688 ± 96†
Gastrointestinal tract	892 ± 86	548 ± 70†	876 ± 94	538 ± 48†
Spleen	1726 ± 148	268 ± 69†	1638 ± 174	529 ± 157†·‡

* Results are means ± SE, $n = 12$ for each group. Blood flows are in ml/min/100 g tissue. Oxygen deliveries are in m moles/min/100 g tissue. There were no significant differences between the control groups in any of the variables.

†·§ $p < 0.001$ and 0.01, respectively, compared with its control value.

‡·‖ Measurements during hypoxemia are significantly different from acidemia at the $p < 0.01$ and 0.001 levels, respectively.

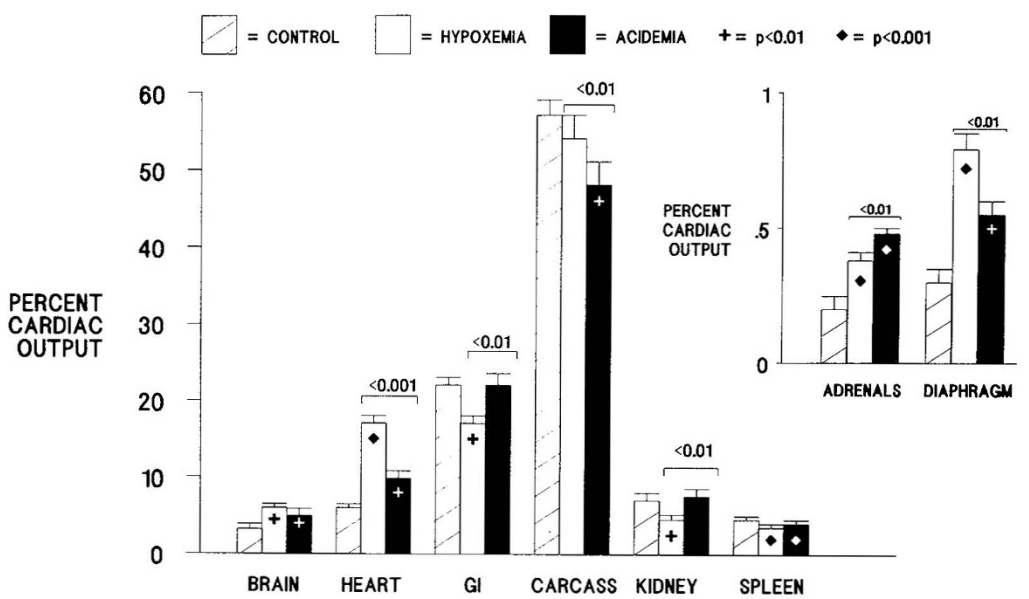

Fig. 1. The effect of hypoxemia and metabolic acidemia on the percentage of cardiac output flowing to each organ. Values are means ± SE. There were no significant differences in the two control groups, and all of the control data points were pooled to simplify the graphic presentation. ◇ or + within a column indicate a significant difference between hypoxemia or acidemia output compared to its paired control group, as demonstrated by the Wilcoxin signed rank test. A p value associated with a *bracket* indicate a significant difference between hypoxemia and acidemia, as indicated by the Mann-Whitney test. *GI*, gastrointestinal.

demia. Diaphragmatic oxygen delivery increased during acidemia but did not change significantly during hypoxemia. Splenic oxygen delivery decreased less severely during acidemia. In contrast, the carcass, kidneys, and gastrointestinal tract developed similar reductions in oxygen deliveries during the two stresses.

DISCUSSION

The model. It is important to note that both groups of lambs were studied at 3 days after surgery, which is a postoperative duration that would allow for the recovery of a normal cardiovascular status (15). Previous studies have addressed the influence of metabolic acidemia on regional blood flows, but they may not be directly comparable to the present study or to metabolic acidemia *in vivo* because anesthetics can exert independent effects on regional blood flows (32). The present study provides the first data on the cardiac output and regional blood flow responses to metabolic acidemia in newborns that are not under the influence of anesthesia.

Although the metabolic acidemia of birth asphyxia is a lactic acidemia, available information suggests that the cardiac responses to metabolic acidemia in a given preparation are similar when lactic acid is infused as compared to HCl (23). There is very little information on the comparative responses in tissues other than the heart, but there apparently are no data to suggest an independent response conditioned by the type of metabolic acid. Thus, we believe that the responses to HCl are likely to be typical of the responses to other types of metabolic acidemia.

In contrast, certain responses to metabolic acidosis may be quite different from the responses to respiratory acidosis. Arterial P_{CO_2} appears to have an important independent effect on certain vascular responses, especially in the cerebral circulation where it is a potent vasoactive agent (24). Thus, cerebral blood flow increased during respiratory acidosis in unanesthetized lambs (24), whereas cerebral blood flow decreased during HCl-induced metabolic acidosis in the present study (Table 2). It is important to note for purposes of comparison that the arterial P_{CO_2} was similar during acidemia and hypoxemia in the present study (Table 1).

An effect of pacemaker location on regional blood flows has been demonstrated in fetal lambs (25), but the use of left atrial pacing should not have had an independent effect on the results in newborn lambs at the ages that were studied because the atrial foramen is functionally closed. However, the reversal of sinus bradycardia to a normal heart rate during acidemia could have prevented a more severe reduction in cardiac output (6), which could have altered the regional blood flow responses. Thus, our study should be viewed as examining the effects of acidemia independent of the associated bradycardia in comparison with hypoxemia with its associated tachycardia. An extension of this proviso is that the differences that occurred in regional blood flows could have resulted from differences in the cardiac output responses as well as from direct vascular responses to hypoxemia and acidemia.

Comparative effects of hypoxemia and acidemia. Our data are consistent with previous studies in newborn and fetal lambs which have demonstrated that hypoxemia results in significant severe reductions in blood flows to the kidneys and the spleen (12, 13, 27). Although the hypoxemic lambs in the present study maintained their control levels of gastrointestinal blood flow, reduced blood flows to the gastrointestinal tract and the liver reproducibly occur at slightly more severe degrees of aortic desaturation than were used in the lambs in this study (12, 28, 29). Central to the interpretation of these blood flow changes, additional studies have demonstrated that the hypoxemia-induced reductions in regional blood flows are accompanied by signs of tissue hypoxia in the kidneys, liver, and gastrointestinal tract in newborn and fetal lambs (27–29). In contrast, studies with arterial oxygen saturations as low as 20–25% have demonstrated that the oxygenation and function of the heart, brain, adrenal glands, and diaphragm appear to be preserved because of a redistribution of the circulation with increased blood flows to these organs (12, 14, 30). Thus, hypoxemia does not reduce blood flow or oxygenation in the heart, brain, adrenal glands, or diaphragm as would be expected if hypoxemia could explain the necropsy data demonstrating ischemic/hypoxic injury after birth asphyxia (5, 8–10).

In the limited context of having measured only blood flows and oxygen deliveries, the present study suggests that the reductions in the cerebral, gastrointestinal, renal, splenic, and carcass blood flows and oxygen deliveries that occur during metabolic acidemia could contribute to the tissue ischemia, hypoxia, and dysfunction that can occur during birth asphyxia (1–5, 8–10). Support for this possibility would be dependent on further studies designed to measure oxygen consumption and function of these organs during metabolic acidemia. The independent effects of acidemia on the loading and unloading of oxygen on hemoglobin also must be considered. Our results regarding the reduction in myocardial blood flow and oxygen delivery are harder to interpret because they were accompanied by reductions in at least two determinants of myocardial blood flow, external cardiac work (the product of cardiac output and aortic mean blood pressure) and contractility (17). Thus, the reductions in myocardial blood flow could be either a passive response to reductions in its determinants or a primary cause of the reductions in contractility and cardiac output. The information available in this study is not sufficient to distinguish between these two possibilities.

It is noteworthy that although acidemia and hypoxemia augment sympathoadrenal activity, the cardiac output responses are opposite in lambs (12, 14, 17, 31, 32). The increase in cardiac output in hypoxemia results from an adrenergically mediated increase in contractility as well as from reduced cardiac afterload, whereas the reduction in cardiac output during HCl-induced acidemia results from reduced contractility as well as from increased cardiac afterload (17). The reduction in cardiac contractility during acidemia may result from an interference with adrenergic receptor binding or from an interference with the intracellular interaction between calcium and troponin (33, 34).

With the data available in this study we are able to eliminate two mechanisms by which acidemia might have produced the redistribution of regional blood flows. Figure 1 indicates that the percentage changes in cardiac output were variable. Thus, the changes in regional blood flows did not occur exclusively as a passive response to the reduction in cardiac output. Similarly, the variable changes in regional blood flows did not occur entirely because of the shift in the hemoglobin-oxygen dissociation curve that occurred during acidemia (Table 1). The results suggest an active process which presumably responds to regional metabolic demands (35). The precise mechanism(s) regulating the changes in regional blood flows during metabolic acidemia and hypoxemia remain to be determined.

In agreement with previous studies, we found that hypoxemia was associated with selective increases in cerebral, myocardial, adrenal, and diaphragmatic blood flows (13, 14, 30). These studies and others have suggested that these organs appear to assume a priority for the available blood flow during hypoxemia. The present study demonstrated that while acidemia was associated with increased blood flows to the adrenal glands and the diaphragm, blood flows decreased to all of the other organs. Thus, cerebral blood flow decreased when other blood flows to certain other organs were increasing (Table 2). These data could imply that there is a further priority for available blood flow when cardiac output is severely reduced. This possibility is supported by data from another study which demonstrated that when cardiac output was decreased by pericardial tamponade, the diaphragm of hyperventilating dogs assumed a priority over cerebral tissue for available blood flow (36). These results do not necessarily imply any further regulatory mechanisms other than local microvascular control of regional blood flows (35).

Our data demonstrate that most regional oxygen deliveries are significantly diminished during an acidemic reduction in cardiac output, but these results cannot be directly extrapolated to the adequacy of regional oxygenation and function. Although increased blood flows are important for the avoidance of diminished cerebral and myocardial oxygen consumptions during hypoxemia, other organs such as the gastrointestinal tract avoid reduced oxygen consumptions and anerobic metabolism at moderate levels of hypoxemia through increased oxygen extraction (14, 28, 30). Thus the full consequences of the changes in regional blood flows and oxygen deliveries that occur during acidemia remain to be determined. Nonetheless, the importance of these data is in the demonstration that metabolic acidemia produces a reduction in cardiac output, a reduction in blood flows to most organs, and a redistribution of the circulation that is distinct from hypoxemia. However, it is not possible to determine if the differences in cardiac output and regional blood flows during acidemia and hypoxemia resulted from the associated differences in heart rates, or from more direct effects on the heart and/or the regional resistance blood vessels.

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