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Lactate, Pyruvate, and Excess Lactate during Ether and Halothane Anesthesia in Infants and Children

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Arterial blood lactate, pyruvate, and excess lactate (XL) were measured and calculated in 33 patients aged 7 months to 6 years over a period of 2 hours during repair of harelip or cleft palate. When the anesthetic was diethyl ether, lactate and pyruvate levels rose significantly 60 minutes after induction of anesthesia but did not rise thereafter. Excess lactate appeared 60 minutes after induction of ether anesthesia, but it, too, showed no further increase. When the anesthetic was halothane there was no significant change in lactate, pyruvate, or XL. Changes with ether were not age-related, nor could they be correlated with changes in rectal or skin temperature. The responses of lactate, pyruvate and XL to ether anesthesia in the present study were not significantly different from those found by others in adults. (Key words: Anesthesia, pediatric; Anesthetics, volatile, diethyl ether; Anesthetics, volatile, halothane; Metabolism, lactate and pyruvate.)

DURING ETHER ANESTHESIA, blood levels of lactate, pyruvate, and excess lactate increase in adult man.[1] Bunker *et al.* reported that metabolic acidosis was more pronounced in infants and young children than in adult man during ether anesthesia.[2] No study of blood lactate levels in infants and children during ether anesthesia has been done since Bunker's study. In Bunker's study, however, venous blood was used for lactate measurements in infants less than 1 year of age, while arterial blood from those more than 1 year of age was used. Serum lactate levels for infants less than 1 year of age were not given in their report. Also, no data on lactate levels in infants and children during halothane anesthesia have been reported.

The present study was designed to determine whether lactacidemia is more pronounced in younger infants than in older children during ether anesthesia, and to determine the metabolic response to halothane in infants and children.

Materials and Methods

Thirty-three infants between 7 months and 6 years of age undergoing repair of harelip or cleft palate were studied. Parental consent was obtained. Patients with histories of metabolic, respiratory, circulatory or central nervous system disorders, as well as those who had had abnormal temperatures during the preceding week or whose rectal temperatures were above 37.5 C on the morning of the study, were excluded. Infants less than 2 years of age were given clear fluids by mouth until 2 hours (others 4 hours) before induction of anesthesia. Premedication consisted of secobarbital (7 mg/kg in patients less than 1 year of age, 6 mg/kg for those less than 2 years of age, and 5 mg/kg for others), given intramuscularly with 0.015 mg/kg atropine 1 hour prior to induction of anesthesia. Selection of anesthetic agent (ether or halothane) was at random. In the ether group, open-drop ether with oxygen supplementation under the mask was used for induction of anesthesia. In halothane group, a face mask with a Keats nonrebreathing system and halothane–nitrous oxide–oxygen were used for induction in the majority of patients. In a few, open-drop halothane was used for induction. The trachea was intubated without muscle relaxants and anesthesia then maintained with either ether–nitrous oxide–oxygen or halothane–nitrous oxide–oxygen with a Keats nonrebreathing system. Fresh-gas concentrations of nitrous oxide were the same with ether and with halothane (60 per cent). Anesthetic gases were not humidified. Respiration was assisted manually. Intravenous catheters were inserted after induction of anes-

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thesia, and 5 per cent dextrose in water (10 ml/kg/h) was infused through them during anesthesia. Patients who showed excitement (crying and/or vigorous body movement) before or during induction of anesthesia or body movement during operation were excluded from the study. Also excluded were patients who had blood losses of more than 5 ml/kg (as determined by weighing of sponges). Patients were not given any drug other than 5–10 ml physiologic saline solution with epinephrine, 1:200,000, for local vasoconstriction during the 2–4 hours of operation. No transfusion was administered. All operations were performed in the morning.

Arterial blood samples were drawn anaerobically from the dorsalis pedis, posterior tibial, or femoral artery of the right leg immediately after induction and hourly thereafter. Pa_{O_2} and *p*H were measured within 15 minutes of sampling using an Astrup apparatus; Pa_{CO_2} and base excess were calculated using the Siggaard-Andersen nomogram. Arterial blood samples were also placed in chilled 10 per cent trichloroacetic acid within 20 seconds, centrifuged, and analyzed in duplicate for lactic acid by the method of Baker and Summerson[3] and for pyruvic acid by the method of Friedman and Haugen.[4] Excess lactate (XL) was calculated by the method of Huckabee.[5] Mean arterial pressure was calculated from the systolic and diastolic pressures measured by sphygmomanometry.

Rectal temperature was measured by a probe inserted 6 cm and skin temperature by a probe on the ventral aspect of the distal phalanx of the left big toe, held in place with adhesive tape. Temperatures were recorded immediately prior to induction of anesthesia and every 15 minutes thereafter with a Shibaden meter. A dry–wet thermometer was placed on the operating table 1 meter from the patient's toe, and temperatures recorded every 15 minutes.

Patients were divided into two groups according to the anesthetic used. Analysis of variance was used for determination of significance. Results are given as means ± standard errors. Statistical significance was assumed when *P* values were 0.05 or less. Analysis of data for statistical significance using the Welch test, which assumes that the two groups had different population variances, gave similar results.‡

TABLE 1. Distribution of the Study Population by Age, Sex, and Anesthetic Agents Used

Age	Number of Patients	Sex		Agent	
		M	F	Ether	Halothane
7–12 months	10	5	5	5	5
–18 months	8	4	4	5	3
–24 months	10	4	6	5	5
–6 years	5	3	2	2	3
TOTAL	33	16	17	17	16

Results

Distribution of the patients by age, sex, and anesthetic agent is shown in table 1. There was no significant change in mean arterial pressure during the course of anesthesia in the two groups (table 2). Blood losses averaged 2.2 ± 0.1 ml/kg/h. Arterial hemoglobin concentrations were the same in the two groups (table 2). Ambient temperatures were the same in the two groups.

Rectal and skin temperature changes have been reported.[6] There was no significant correlation between changes in rectal or skin temperature and lactate, pyruvate, or XL. Pa_{O_2}, Pa_{CO_2}, *p*H, and base excess are shown in table 3.

In the halothane group, there was no significant change in lactate, pyruvate, or XL during 2 hours of anesthesia compared with control values obtained immediately after induction of anesthesia (table 4).

During ether anesthesia, lactate and pyruvate concentrations were significantly higher ($P < 0.01$) 60 and 120 minutes after induction (table 4), but there was no significant increase in the values thereafter (60 minutes *vs.* 120 minutes). Pyruvate levels also increased significantly, but to a lesser extent. Excess lactate became apparent 60 minutes after induction. No further significant eleva-

‡ Statistical assistance given by Mr. Takashi Miyawaki, Department of Statistics, Yale University, is greatly appreciated. Calculation was done using programs ANOVA and T-Test in the DATATEXT at the Yale Computer Center.

TABLE 2. Mean Arterial Blood Pressures and Rectal Skin Temperatures (Means ± SE)

	Ether			Halothane		
	0	60 Min	120 Min	0	60 Min	120 Min
Mean arterial pressure (torr)	86.5 ± 3.4 (n = 17)	92.9 ± 3.2 (n = 17)	90.2 ± 2.9 (n = 17)	84.9 ± 4.2 (n = 13)	86.8 ± 4.3 (n = 13)	84.9 ± 3.8 (n = 13)
Hemoglobin (g/100 ml)	12.7 ± 0.2 (n = 17)	—	—	12.5 ± 0.3 (n = 13)	—	—
Rectal temperature (C)	37.2 ± 0.1 (n = 16)	37.1 ± 0.2 (n = 14)	37.6 ± 0.3 (n = 13)	37.2 ± 0.2 (n = 15)	36.8 ± 0.1 (n = 14)	37.3 ± 0.3 (n = 10)
Skin temperature (C)	31.6 ± 0.4 (n = 16)	29.6 ± 0.5 (n = 14)	28.4 ± 0.7 (n = 13)	32.5 ± 0.3 (n = 15)	30.8 ± 0.4 (n = 14)	30.3 ± 0.9 (n = 10)

tion in XL was evident at 120 minutes. Increases in lactate, pyruvate, and XL with ether at both 60 and 120 minutes were significantly greater than those observed during halothane anesthesia (table 4). The changes observed with ether anesthesia failed to show significant age-related differences.

Discussion and Conclusion

An increase in lactate that is associated with a proportionate increase in pyruvate can result from increased glycolysis. Glucose administration can increase glycolysis and so lead to elevation of lactate and pyruvate,[5] but in the present study it is unlikely that this was the cause of the observed increases in lactate and pyruvate. The infusion of glucose during ether anesthesia does not increase levels of pyruvate in excess of those expected to occur during ether anesthesia without glucose infusion.[5] Increased glycolysis, reflected in increased lactate and pyruvate levels, is more likely to be caused by increased sympathetic nervous system activity, as evidenced by the fact that lactate and pyruvate levels fail to change during ether anesthesia in the presence of sympathetic denervation.[7]

Excess lactate is produced when tissue hypoxia is present. Tissue hypoxia may be caused by a decrease in Pa_{O_2}, decreased blood flow, or increased O_2 consumption of tissue. In the present study, decreases in Pa_{O_2} can be ruled out as a cause of XL production during ether anesthesia, since there was no XL production during halothane anesthesia with an identical Pa_{O_2}. However, decreased blood flow to some tissue (*i.e.*, liver) and/or increased O_2 consumption could not be ruled out as a cause of XL production in the presence of the increased sympathetic nervous system activity during ether anesthesia. Lowered Pa_{CO_2} may, both because of the Bohr effect and because of vasoconstriction, also reduce tissue oxygenation and so lead to XL production.[8] However, the low Pa_{CO_2} observed in the present study could not be the explanation of XL during ether anesthesia, since with identical Pa_{CO_2} values XL appeared 60 minutes after starting ether anesthesia but had not appeared even after 120 minutes of halothane anesthesia.

Excess lactate in arterial blood during ether anesthesia in the present series might have been due to some factor other than tissue hypoxia.[9,10] For instance, if cytoplasmic NADH/NAD (lactate/pyruvate) relationship did not accurately represent the relationship between mitochondrial NADH and NAD (reduction–oxidation state), false XL production would occur. Ether, like ethanol,[11] might, for example, have affected the shuttle system that transfers hydrogen between cytoplasm and mitochondria and thereby equilibrates NADH/NAD in both compartments. Production of lactate in the presence of oxygen (absence or weak presence of the Pasteur effect[12]) and uncoupling (inadequate

TABLE 3. Results of Blood–Gas Analyses (Means ± SE)

	Ether			Halothane		
	0	60 Min	120 Min	0	60 Min	120 Min
Pa_{O_2} (torr)	107.2 ± 10.7 (n = 13)	147.8 ± 8.7 (n = 12)	137.0 ± 7.6 (n = 12)	133.2 ± 11.5 (n = 16)	127.9 ± 7.3 (n = 14)	138.6 ± 5.7 (n = 12)
Pa_{CO_2} (torr)	41.1 ± 1.7 (n = 15)	32.9 ± 1.5†‡ (n = 12)	31.8 ± 1.3† (n = 12)	40.6 ± 1.5 (n = 16)	40.2 ± 1.6 (n = 14)	35.0 ± 1.7* (n = 13)
*p*H	7.33 ± 0.01 (n = 15)	7.35 ± 0.01 (n = 12)	7.35 ± 0.01 (n = 12)	7.32 ± 0.01 (n = 16)	7.32 ± 0.01 (n = 14)	7.33 ± 0.01 (n = 12)
Base excess (mEq/l)	−4.6 ± 0.5 (n = 15)	−7.1 ± 0.5† (n = 12)	−7.2 ± 0.3† (n = 12)	−5.1 ± 0.3 (n = 16)	−5.8 ± 0.6 (n = 13)	−7.0 ± 0.6* (n = 13)

* Significant change from control, $P < 0.05$.
† Significant change from control, $P < 0.01$.
‡ Significantly greater ($P < 0.01$) compared with halothane.

TABLE 4. Lactate, Pyruvate, and Excess Lactate (Means ± SE)

	Ether			Halothane		
	0	60 Min	120 Min	0	60 Min	120 Min
Lactate (mM/l)	1.57 ± 0.14 (n = 16)	3.33†‡ ± 0.27 (n = 14)	3.77†‡ ± 0.29 (n = 13)	1.52 ± 0.18 (n = 15)	1.79 ± 0.14 (n = 14)	2.19 ± 0.25 (n = 10)
Pyruvate (mM/l)	0.083 ± 0.004 (n = 16)	0.128*‡ ± 0.006 (n = 15)	0.138*§ ± 0.010 (n = 12)	0.085 ± 0.005 (n = 17)	0.092 ± 0.007 (n = 16)	0.107 ± 0.010 (n = 11)
Excess lactate (mM/l)	—	1.02§ ± 0.33 (n = 13)	1.23‡ ± 0.28 (n = 11)	—	0.13 ± 0.22 (n = 14)	0.36 ± 0.32 (n = 9)

* Significant change from control, $P < 0.05$.
† Significant change from control, $P < 0.01$.
‡ Significantly greater ($P < 0.05$) compared with halothane.
§ Significantly greater ($P < 0.01$) compared with halothane.

formation of ATP) are also known to produce arterial XL in the absence of tissue hypoxia.[9] Ether might have had an effect on these mechanisms.

Bunker *et al.*[2] reported that ether anesthesia regularly produced moderate metabolic acidosis in infants less than 1 year of age, but not in older children or adults. However, Bunker *et al.* used heel blood for determination of CO_2 content and venous blood for lactate determination, while arterial blood was used for all studies of children more than 1 year of age. In our study, only arterial blood was used. This may explain why the present data fail to demonstrate any significant age-relted difference in the metabolic responses to ether of infants and children. However, in Bunker's study, five of eight patients less than 1 year of age were less than 6 months old, and these five patients had higher fixed acid levels (5.66 ± 0.43 mEq/l) than did those children 7 to 12 months old (4.50 ± 0.41 mEq/l). In our study all 11 of the patients less than 1 year of age were 7 to 12 months old.

TABLE 5. Lactate, Pyruvate, and Excess Lactate in Arterial Blood during Ether Anesthesia (mM/l)

	Control	30 Min	60 Min	120 Min	Age	Reference
Lactate Pyruvate Excess lactate	0.74 0.152	2.13 0.199 1.164			Adults	Greene[1]
Lactate Pyruvate Excess lactate	1.57 0.083		3.33 0.128 1.016	3.77 0.138 1.229	7 months -6 years	Present study
Lactate Pyruvate	0.90 0.127	1.61 0.130	1.83 0.186	2.22 0.305	Adults	Henneman and Vandam[16]
Excess lactate				0.944*	Adults	Schweizer and Howland[14]

* "At the end of operation."

Data for lactate, pyruvate, and XL in adults during ether anesthesia reported by other authors are compared with the results obtained in the present study in table 5. Although the levels of lactate found in the present study were somewhat higher than those observed in adults by others, there is no statistically significant difference. Similarly, XL levels found in the present study were essentially the same as those of adults.

Lactate, pyruvate, and XL in infants and children during halothane anesthesia were essentially the same as those reported by other authors to occur in adults,[1,13,14] although slightly higher values were found for lactate in the present study. Glucose administration apparently did not affect the blood lactate and pyruvate levels during halothane anesthesia.

The response to 1 mg of epinephrine injected subcutaneously is essentially the same as that observed following the intravenous infusion of epinephrine at a rate of 20 μg/min[15] (approximately 0.3 μg/kg/min), the dose with which the metabolic effect of epinephrine is seen in man.[15] The largest dose of epinephrine given subcutaneously to the patients in the present study was 5 μg/kg over more than 2 hours (approximately 0.03 μg/kg/min), a dose far below that required to produce a metabolic effect. Furthermore, epinephrine was used in both groups, yet metabolic changes were observed only in patients anesthetized with ether. It is unlikely, therefore, that the results obtained during ether anesthesia were caused by the epinephrine infiltration.

Although this study demonstrates definite increases in lactate, pyruvate, and XL during ether anesthesia in infants and children, it should be noted that these pharmacologically induced metabolic changes are relatively small compared with changes occurring during significant metabolic acidosis as seen in circulatory insufficiency.

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Biochemistry

ANESTHESIA AND STRESS The effects of stress due to brief (4–5 min) ether and pentobarbital anesthesia versus decapitation on assays of enzymes in homogenates of rat articular synovium, articular and epiphyseal cartilage, and adjacent bone were compared. Ether caused twofold changes in the enzymes participating in glycolysis, energy production, the citric acid cycle, and collagen synthesis. No difference between enzymatic activities of the several tissues taken from rats that had been decapitated and those anesthetized with pentobarbital could be detected. (*Simons, DJ, Lesker PA: Effects of short term ether and pentobarbital anesthesia on bone and cartilage metabolism. Can J Physiol Pharmacol 53:33–37, 1975.*) ABSTRACTER'S COMMENT: In this article, the ether used for anesthesia was not specified, but it is assumed that it was diethyl ether, which is not used as extensively as formerly. The article does add to the accumulated evidence that ether anesthesia causes more stress reaction than barbiturate anesthesia, and effects of ether anesthetic agents such as methoxyflurane and enflurane have a qualitative, if not quantitative, effect similar to that of diethyl ether. Whether this effect is advantageous or disadvantageous depends on the circumstances.