LACTATE, PYRUVATE, AND EXCESS LACTATE PRODUCTION IN ANESTHETIZED MAN

NICHOLAS M. GREENE, M.D.

THE normal relationship between lactate and pyruvate may be summarized by the equation:

$$\text{Pyruvate} + \text{DPNH}_2 \overset{\text{LDH}}{\rightleftharpoons} \text{Lactate} + \text{DPN}. \quad (1)$$

Lactate levels are accordingly dependent upon two factors: the amount of available pyruvate and the integrity of the so-called lactate dehydrogenase (LDH) system, a term which is used to include not only LDH activity itself but also the relationship between oxidized (DPN) and reduced ($DPNH_2$) diphosphopyridine nucleotide. Under normal circumstances, activity of the LDH system is such that at equilibrium there is more lactate than pyruvate. Maintenance of normal activity of the LDH system is dependent upon amounts of oxygen adequate to maintain the normal DPN:$DPNH_2$ ratio.[1] Because of the dependence of this system on molecular oxygen, the ratio of lactate to pyruvate has been found to be a valuable measure of anaerobic carbohydrate metabolism.[2-7] In the absence of adequate oxygen, Equation 1 is driven to the right with a consequent accumulation of lactate and an increase in the normal lactate: pyruvate ratio. The lactate so accumulated during anaerobiosis is termed "excess lactate" (XL) because it represents the amount of lactate formed in excess of that which can be ascribed to an increase in pyruvate. Calculation of XL is a more precise means of evaluating the integrity of the LDH system than use of the lactate:pyruvate ratio. Equation 2 shows the method of calculating XL.[1]

$$XL = (L_N - L_0) - (P_N - P_0)\ (L_0/P_0) \quad (2)$$

where L_0 and P_0 are, respectively, control values for lactate and pyruvate, and L_N and P_N experimental values.

Accepted for publication January 13, 1961. The author is in the Section of Anesthesiology, Yale University School of Medicine, and the Department of Anesthesiology, Grace-New Haven Community Hospital.

Hyperlactacidemia can, therefore, be the result of two separate processes. In one, an increase in lactate is associated with an increase in pyruvate so that there is no excess lactate formation. This situation occurs either when there is an increase in pyruvate production [1, 8] or, because Equation 1 is reversible, when for some reason there is accumulation of lactate due to exogenous administration of lactate or decreased conversion of lactate to glycogen by the liver or decreased oxidation of lactate by peripheral tissues. Thus, for example, intravenous administration of lactate is accompanied by an increase in pyruvate.[8, 9] The second situation in which hyperlactacidemia occurs, and one which is biochemically completely different than the first, is that in which the activity of the LDH system is impaired with the result that excess lactate is formed without a comparable increase in pyruvate. In studying lactate metabolism, therefore, the important factor is not the level of lactic acid, but rather the ratio of lactate to pyruvate or, even more precisely, excess lactate production.

A review of the literature fails to reveal studies of excess lactate formation during clinical anesthesia. Changes of blood lactate have been reported during ether anesthesia in experimental animals and in man, and all studies are agreed that blood lactate levels rise significantly during ether.[10-20] Cyclopropane anesthesia has also been shown, though less frequently, to be associated with less pronounced rises [12, 14, 20] or even decreases [15] in lactate. Barbiturate (including thiopental) anesthesia has variously been stated as being associated with a rise, [21,22] a decrease,[20, 23] or no change [16, 19, 24] in lactate. Ether anesthesia has also been reported as producing a rise in blood pyruvate,[15-17, 19, 20] while barbiturate anesthesia has been reported as being accompanied by no change [16, 24, 25] or a decrease,[20, 23, 26] and cyclopropane anesthesia, in the one report available, has been said to be associated with

an increase in blood pyruvate.[20] Simultaneous measurements of both lactate and pyruvate during anesthesia have been reported only infrequently.[15, 19, 20, 23] The data in the majority of the above reports, however, are inadequate for determining either the lactate:pyruvate ratio or excess lactate formation in man during clinical anesthesia. Many of the reports are preliminary abstracts. Many deal only with experimental animals, and, as Bunker and his associates have emphasized,[14] it is hazardous to transpose the results of animal metabolic studies to man. Other reports, while of considerable merit, do not have as their primary purpose calculation of the lactate:pyruvate ratio or excess lactate formation, and so the data are presented in such a form as to preclude such calculations. Finally, many of the published reports are based upon venous blood samples. To determine the over-all reaction of the entire organism, such metabolic studies must employ either mixed venous or arterial blood [4] rather than peripheral venous blood draining from a specific area.

The present study was initiated to determine the effects, if any, of three commonly used anesthetic techniques on arterial lactate and pyruvate levels and to relate such changes to alterations in activity of the LDH system as determined by excess lactate production.

Methods

Forty-five patients were studied. Their ages ranged from 14 to 74. Thirteen were males and 32 females. Patients were unselected except for the exclusion of those with hepatic or endocrine disease. All patients were fasting and had received premedication consisting of a barbiturate (pentobarbital or secobarbital, 1.25 to 2.0 mg./kg. of body weight) and atropine or scopolamine (0.4 to 0.6 mg./70 kg.) intramuscularly 40–60 minutes prior to the time the first arterial (brachial) sample was obtained by direct arterial puncture. Immediately after the control sample was drawn, anesthesia was induced. Thirteen patients received thiopental-nitrous oxide (3.5:1 liters per minute), 15 received cyclopropane, and 17 received ether anesthesia. When thiopental was administered, the minimum possible amount was employed consistent with anesthesia deep enough to immobilize the patient and allow insertion of a pharyngeal airway. Surgery in such cases was limited to operations not requiring relaxation of skeletal muscles. Cyclopropane and ether were employed in cases in which the proposed surgery required muscular relaxation. All anesthetics were administered in circle carbon dioxide absorption systems. Ether anesthesia was induced with nitrous oxide-oxygen (3.5 or 4:1 liters per minute) for 4–5 minutes, the oxygen flow remaining one liter per minute after the nitrous oxide had been discontinued. Care was taken to assure a patent airway in all cases, respirations being manually assisted or controlled and pharyngeal airways or endotracheal tubes being inserted when indicated. Additional drugs such as muscle relaxants were not used, nor were intravenous infusions of fluid employed.

Exactly 30 minutes after the start of induction of anesthesia, a second arterial blood specimen was obtained from the contralateral brachial artery by direct puncture. In most cases operations had not commenced at the time the second sample was drawn. In those few in which it had, skin incision only had been made. This was not found to alter the results.

Each blood sample was drawn into specially prepared syringes and within 20 seconds placed in chilled 10 per cent trichloroacetic acid which was then centrifuged, the supernatant being removed and analyzed in duplicate for lactic acid by the method of Barker [27] and for pyruvic acid by the method of Friedman.[28] The results were calculated in terms of m*M* of lactate or pyruvate per liter of whole arterial blood.

Results were analyzed to determine whether the individual anesthetic techniques employed were associated with statistically significant changes in lactate and pyruvate by use of paired "t" tests, with each patient serving as his own control. The effects of one anesthetic on lactate and pyruvate were compared to the effects of another anesthetic by calculating the significance of the difference between the means. If the resultant p values were less than 0.01, the changes are termed "highly significant"; if between 0.01 and 0.05,

TABLE 1

BLOOD LACTATE, PYRUVATE, AND EXCESS LACTATE LEVELS DURING ETHER ANESTHESIA
(m*M*/L. of whole arterial blood)

Patient	Control		Experimental		Excess Lactate*
	Lactate	Pyruvate	Lactate	Pyruvate	
1	1.49	.158	3.24	.174	1.605
2	1.04	.157	2.27	.176	1.095
3	0.79	.122	2.02	.157	1.005
4	0.98	.150	2.38	.166	1.296
5	0.63	.125	1.83	.206	0.791
6	0.18	.166	2.13	.255	1.860
7	1.53	.141	0.83	.192	−1.256
8	0.51	.124	1.67	.174	0.950
9	0.84	.141	1.00	.110	0.340
10	0.80	.069	3.27	.136	1.692
11	0.57	.172	0.91	.147	0.427
12	0.54	.103	5.60	.326	3.884
13	0.42	.115	1.51	.151	0.969
14	0.18	.135	2.02	.198	1.762
15	0.90	.436	4.16	.542	3.038
16	0.23	.122	0.72	.138	0.459
17	0.86	.150	0.66	.136	−0.122
Mean ± Standard Error of the Mean	.74±.10	.152±.006	2.13±.32	.199±.025	1.164±.282

* As calculated from Equation 2.

TABLE 2

BLOOD LACTATE, PYRUVATE, AND EXCESS LACTATE LEVELS DURING CYCLOPROPANE ANESTHESIA
(m*M*/L. of whole arterial blood)

Patient	Control		Experimental		Excess Lactate*
	Lactate	Pyruvate	Lactate	Pyruvate	
1	0.74	.125	1.78	.145	0.913
2	0.60	.118	1.81	.140	1.101
3	1.59	.166	2.09	.185	0.315
4	1.00	.157	1.40	.191	0.182
5	0.78	.101	1.09	.151	−0.074
6	0.64	.169	1.00	.181	0.313
7	0.61	.070	0.76	.092	−0.043
8	1.10	.098	1.39	.107	0.189
9	0.82	.153	0.84	.148	0.052
10	0.67	.131	1.21	.152	0.432
11	0.82	.123	0.88	.102	0.193
12	0.78	.124	1.21	.118	0.469
13	0.88	.121	1.11	.124	0.216
14	0.50	.127	1.20	.180	0.495
15	0.57	.136	0.89	.157	0.237
Mean ± Standard Error of the Mean	.81±.07	.128±.007	1.24±.10	.145±.008	.333±.083

* Derived from Equation 2.

they are termed "significant"; if more than 0.05, they are termed "non-significant."

Results

Ether anesthesia of 30 minutes' duration was associated with a highly significant rise in mean lactate levels from control values of 0.74 ± 0.10 mM/l. to 2.13 ± 0.32mM/l. (table 1). The rise in pyruvate from control values of 0.152 ± 0.006 to 0.199 ± 0.025 mM/l. was also highly significant. Ether anesthesia was also associated with a mean excess of lactate production of $1.164 \pm .282$ mM/l. indicating therefore that the rise in lactate was on the average greater than the rise in pyruvate.

Following 30 minutes of cyclopropane anesthesia (table 2), highly significant changes were also observed in both lactate (from 0.81 ± 0.07 to 1.24 ± 0.10 mM/l.) and pyruvate (from 0.128 ± 0.007 to 0.145 ± 0.008 mM/l.) As with ether, cyclopropane was associated with excess lactate production, the mean value being 0.333 ± 0.083 mM/l.

Thiopental-nitrous oxide anesthesia was not associated with statistically significant changes in either lactate or pyruvate (table 3). Though the tendency was for the blood levels of each of these substances to decrease, the wide variation in response of individual patients prevented such a tendency from being statistically significant.

Changes in lactate during ether anesthesia were highly significantly greater than the changes in lactate during either cyclopropane or thiopental-nitrous oxide anesthesia. The changes in lactate associated with cyclopropane were also highly significantly greater than those observed during thiopental-nitrous oxide anesthesia.

Pyruvic acid increases during ether anesthesia were not statistically significantly different than those observed during cyclopropane anesthesia although they were highly significantly greater than those observed during thiopental-nitrous oxide anesthesia. Statistically, there was no significant difference between the changes in pyruvate during cyclopropane compared to those obtained during thiopental-nitrous oxide anesthesia.

Excess lactate production was highly significantly greater during ether anesthesia than it was during either cyclopropane or thiopental-nitrous oxide anesthesia. The excess lactate production associated with cyclopro-

TABLE 3

Blood Lactate, Pyruvate, and Excess Lactate Levels During Thiopental-Nitrous Oxide Anesthesia
(mM/L. of whole arterial blood)

Patient	Control		Experimental		Excess Lactate*
	Lactate	Pyruvate	Lactate	Pyruvate	
1	0.64	.167	1.00	.133	0.487
2	1.74	.153	1.31	.173	−0.652
3	1.33	.114	0.38	.108	−0.890
4	1.34	.143	1.07	.153	−0.374
5	1.61	.100	0.82	.084	−0.533
6	1.21	.157	0.57	.115	−0.321
7	0.44	.093	0.51	.093	0.067
8	0.94	.183	0.77	.136	0.062
9	0.63	.126	0.57	.123	−0.050
10	0.90	.206	1.00	.197	0.140
11	0.60	.128	0.60	.142	−0.064
12	0.54	.119	0.58	.120	0.028
13	0.44	.155	0.74	.173	0.248
Mean ± Standard Error of the Mean	.95±.12	.142±.009	.76±.07	.135±.009	−.140±.108

* As derived from Equation 2.

pane was also highly significantly greater than it was with thiopental-nitrous oxide.

Discussion

The present results indicate that in man a significant hyperlactacidemia occurs under clinical conditions during both cyclopropane and ether anesthesia which does not occur during thiopental-nitrous oxide anesthesia. The increase in lactic acid associated with ether and cyclopropane is accompanied by an increase in pyruvic acid, but with each the increase in lactate is proportionately greater than the increase in pyruvate, with the result that excess lactate is formed. A portion, therefore, of the increased lactate can be ascribed to an increase in aerobic carbohydrate metabolism during ether and cyclopropane, but a portion must also be ascribed to altered activity of the LDH system.

In a study such as the present one, the experimental design has as its object determining whether clinical anesthesia is or is not associated with changes in LDH system activity. It is, therefore, impossible to prove from the present results how or why the anesthetics studied were associated with impaired LDH activity. Considerable work has, however, been published on the effects of certain central nervous system depressants on carbohydrate metabolism. This has been summarized by Butler,[29] by Brody,[30] and by Hunter and Lowry.[31] Thus, barbiturates have been reported as depressing *in vitro* oxidation of both lactate and pyruvate, not only by brain,[32] but also by other tissues.[33] It has been hypothesized that this depression is caused by impairment of dehydrogenase activity.[34] More specifically, it has been proposed that barbiturates interfere with dehydrogenase activity by altering flavoprotein activity[35] by binding reduced flavoprotein with cytochrome B.[36] This has been disputed and an alternative proposed, namely that pyruvic oxidase is the enzyme affected by barbiturates,[37] though this concept in turn has been questioned by the use of more advanced techniques.[38] There are two major difficulties in interpreting such reports. The first is that the concentrations used in *in vitro* experiments have frequently been in excess of those achieved *in vivo*. Secondly, even when more physiological concentrations are employed, the metabolic effects of central nervous system depressants *in vitro* are frequently found to differ from those found *in vivo*.[39] The concensus is that while barbiturates *in anesthetic concentrations* exhibit an "uncoupling" effect[30, 40] whereby they impair formation of high-energy phosphate bond substances, they do so without altering oxygen consumption and without directly affecting lactate metabolism. The changes in tissue levels of lactate following the administration of a barbiturate are probably the result of decreased activity, and neither the cause of decreased activity nor the result of impaired lactate metabolism. Thus, for example, brain lactate concentration in rats during normal sleep is approximately that found in rats anesthetized with pentobarbital.[41] Accordingly, it is not surprising to find that, as in the present study, thiopental anesthesia in man is associated with either no change in blood lactate and pyruvate or a tendency for both to decrease and that thiopental is not associated with a statistically significant alteration in LDH system activity.

The nitrous oxide administered with the thiopental would not be expected to change the blood levels of these metabolites in view of the fact that *in vitro* nitrous oxide has been reported as having no effect on lactate metabolism[42, 43] unless administered in hypoxic concentrations.[32]

Ether has been shown to alter lactate and pyruvate metabolism *in vitro*, but only in toxic concentrations.[32] In anesthetic concentrations it has slight or no effect on the metabolism of these substances,[44] and little effect on phosphorylative oxidation.[45, 46] The excess lactate production found in the present study during ether anesthesia cannot be ascribed to a direct effect of ether on LDH system activity, even though ether has been reported as having effects on other aspects of carbohydrate metabolism by Henneman and her associates.[17, 47, 48]

The effects of cyclopropane on lactate and pyruvate metabolism have been little studied, but the only report available indicates that at concentrations which block conduction in peripheral nerves there is no significant impairment by cyclopropane of pyruvate metabolism.[49] It is therefore likely that cyclopropane

has, like ether, thiopental, and nitrous oxide, no direct effect on LDH system activity in anesthetic concentrations.

Even though anesthetics in clinically effective concentrations do not affect the LDH system directly, it is possible that they may have indirect effects mediated through hormonal, cardiovascular, or respiratory responses to the anesthetic agent. For example, Brewster *et al.*[50] found that the metabolic response of dogs to light ether anesthesia, including the hyperlactacidemia, was prevented by total preganglionic sympathetic block which prevented the reflex release of epinephrine and norepinephrine normally produced by ether anesthesia. Deeper levels of ether anesthesia were associated, even in the presence of a sympathetic block, with increased blood levels of lactate in these dogs. These changes were ascribed, in the absence of concurrent changes in pyruvate, to peripheral tissue hypoxia secondary to diminished cardiac output caused by the ether. On the basis of such data it appears likely that the release of catechol amines is a contributory factor which may in part explain some of the changes in lactate and pyruvate observed in the present series during ether anesthesia. This is supported by the observation that the intravenous administration of epinephrine to normally oxygenated, non-anesthetized humans is also associated with an increase in blood lactate and pyruvate, and, as in the case of ether anesthesia, the production of excess lactate.[51] As with ether, the hyperlactacidemia due to epinephrine administration is due to two factors. One is an increase in aerobic carbohydrate metabolism with an increase in pyruvate and a proportionate increase in lactate. The other is an increase in anaerobic carbohydrate metabolism exemplified by excess lactate production. The excess lactate production associated with epinephrine can only be ascribed to impaired LDH activity secondary to decreased tissue oxygenation for, like ether, epinephrine has no direct effect on LDH activity.[51] The decreased tissue oxygenation in turn is either due to decreased tissue blood flow due to vasoconstriction in the presence of a constant rate of oxygen utilization, or due to an increased rate of oxygen utilization in the presence of a constant blood flow, or due to both factors.

The implication is, therefore, that insofar as carbohydrate metabolism is concerned the over-all metabolic response of man to ether anesthesia consists of an anaerobic phase superimposed on an aerobic phase and that this response is mediated through epinephrine release. Actual measurements of tissue oxygen tensions during ether anesthesia and during epinephrine administration have so far been limited to skin [52, 53] where both have been shown to be associated with comparable decreases in cutaneous oxygen tension. It is unlikely, however, that changes in cutaneous oxygenation alone can explain the excess lactate production found with ether and epinephrine. It is more likely that biochemically more important organs such as the viscera contribute to excess lactate production more than does skin. This possibility is presently under investigation. It should be remarked, however, that not all of the effects of ether anesthesia on carbohydrate metabolism can be ascribed to concurrent release of epinephrine. Both ether anesthesia and epinephrine, for example, result in an increase in lactate and pyruvate, but whereas ether is associated with a simultaneous increase in serum inorganic phosphorus,[11, 12, 15, 54] epinephrine results in a decrease in phosphorus.[55] In addition, ether anesthesia is associated with increased blood levels of 17-hydroxycorticosteroids [56] which may, as Henneman and Bunker [17] have suggested, alter carbohydrate metabolism much as they do in Cushing's syndrome.

The production of excess lactate during cyclopropane anesthesia also implies that cyclopropane anesthesia is associated with changes in tissue oxygen tensions great enough to alter LDH activity. Cyclopropane anesthesia is known to be accompanied by increased blood levels of norepinephrine,[57] but while norepinephrine infusions have been shown to decrease cutaneous oxygen tension,[53] cyclopropane anesthesia has not.[52] At the present time it is not known which organ or organs contribute to the excess lactate production seen with cyclopropane, nor is it known what the effects of norepinephrine infusions are on excess lactate formation, but it is likely that future investigations will relate excess lactate production during cyclopropane to catechol amine release and consequent vasocon-

striction, much as occurs with ether and epinephrine.

Finally, general anesthesia may be associated with changes in pulmonary ventilation which could contribute to the observed production of excess lactate. If anoxic anoxia were to occur, the metabolic response to it would be comparable to that observed in the present series of cases. However, it is unlikely that the present results can be ascribed to this, for cyanosis was not observed, the anesthetics were administered by skilled persons with high concentrations of oxygen, and meticulous attention was paid to maintenance of a clear airway, with respirations being controlled or assisted as indicated. Changes in carbon dioxide tension, on the other hand, could have occurred and remained clinically unrecognized. Both respiratory acidosis [58] as well as respiratory alkalosis [1, 59] have been shown to be associated with a metabolic acidosis. The exact nature of such metabolic acidosis is, however, not known, especially as regards excess lactate production. Although it is impossible to estimate whether the present results were due to altered carbon dioxide excretion, the changes in fixed acids reported as being due to respiratory acidosis or alkalosis are not great enough over a 30-minute period of time to make such a theoretical possibility a likely explanation for the present results. Intentional hyperventilation to the extent necessary to produce cerebral vasoconstriction and a decreased cerebral oxygen tension [60] was not employed.

Summary

The ratio of lactate to pyruvate and excess lactate production were studied in 45 patients during general anesthesia because of the value of such determinations as an index of the availability of molecular oxygen at the tissue level. The over-all response as determined in arterial blood specimens indicated that anaerobic carbohydrate metabolism occurred during ether and cyclopropane anesthesia but not during thiopental-nitrous oxide anesthesia. It is concluded that the anesthetic agents themselves were not directly causing this effect but rather that they were producing their effect indirectly and primarily through concurrent catechol amine release which resulted in decreased tissue oxygen tensions by altering tissue blood flow or tissue oxygen consumption, or both. The specific organ(s) in which decreased tissue oxygen tensions occurred during ether and cyclopropane anesthesia are not as yet fully defined.

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CORNEAL LESIONS Desiccation of the cornea following nonclosure of the eyelids during anesthesia results in ocular pain, foreign body sensation, photophobia, conjunctival hyperemia and abundant lacrimation. Exophthalmic patients are especially prone to develop this syndrome. If anesthesia is administered by mask, in contrast to endotracheal anesthesia, pressure on the lacrimal sac prevents the loss of lacrimal fluid, and humidification of the eyes is maintained. The incidence of this complication is reported as about 5 in 1,000 cases. (*Baumann, P.: La Conjonctivité Post-anesthésique par Inoclusion Oculaire, Anesth. Analg. (Par.) 18: 356 (June, July, Aug.) 1960.*)

HYPNOANESTHESIA Anesthesia by hypnosis, *per se*, is recommended only for selected patients. These constitute less than 10 per cent of all patients requiring major surgery. Hypnosis has a much wider field of application when used to potentiate or reduce chemoanesthesia or analgesia. In this capacity it can facilitate the induction of anesthesia, due to marked reduction in anxiety, fear, and tension. Additionally, anoxia is greatly diminished. In many patients, the use of hypnosis can obviate the traditional use of preanesthetic medicaments and thus lessen the tendency to the development of respiratory depression. (*Kroger, W.: Hypnoanesthesia in Surgery, West. J. Surg. 68: XXV (Nov.-Dec.) 1960.*)