Lactic acidosis

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Case presentation

A 33-year-old male was admitted to Michael Reese Hospital and Medical Center for evaluation of weight loss, dyspnea, and fever. He had factor VIII-deficient hemophilia and had been chronically ill over several months with a cough productive of scanty sputum, weight loss of 15 lbs, low-grade fever, and progressive dyspnea on exertion. The medical history was notable for right total hip replacement and loss of 15 Ibs, low-grade fever, and progressive dyspnea on exertion. The medical history was notable for right total hip replacement and splenomegaly.

Physical examination revealed a thin white male in no distress. Temperature was 37.2°C; blood pressure, 115/80 mm Hg supine; heart rate, 120 beats/min; and respiratory rate, 36/min. There were white plaques in the mouth, bilateral axillary lymphadenopathy, and splenomegaly. The lungs were clear and the remainder of the examination was within normal limits. Laboratory findings disclosed: hemoglobin, 12.5 g/dl; mean corpuscular volume, 93 μm³; white blood cell count, 7,000/ mm³ with 78% neutrophils, 4% band forms, and 7% lymphocytes; and normal platelets. Other routine chemistry tests were normal. Urinalysis was unremarkable. Chest x-ray was suggestive of early, patchy interstitial infiltrates. An arterial blood sample obtained with the patient breathing room air revealed a pH of 7.44; temperature of 38.2°C. The lungs were clear. An arterial blood sample obtained with the patient breathing room air revealed a pH of 7.44; PCO₂, 32 mm Hg; and PO₂, 63 mm Hg. The patient developed a hectic fever, and treatment with ampicillin and gentamicin was started. Pulmonary function tests showed reduced diffusing capacity and were consistent with a mild restrictive defect. A gallium scan revealed diffuse uptake in the lungs, and chest x-ray showed diffuse interstitial infiltrates. On the sixth hospital day, bronchoscopy yielded biopsy material positive for Pneumocystis carinii. Trimethoprim-sulfamethoxazole was administered, but was discontinued after 8 days because of leukopenia and rash. Pentamidine isethionate, 200 mg/day intramuscularly for 7 days, produced dramatic improvement of interstitial infiltrates. The subsequent hospital course was complicated by a recurrence of pulmonary infiltrates, worsening dyspnea, disabling cough, severe inanition, myoclonus and tremors, abnormal liver function tests, hyponatremia, and hostility and depression. Multiple cultures, including bone marrow, revealed only Candida albicans in the sputum and urine. T-cell studies showed a T4/T8 ratio of 0.4 (normal, 1.7–3.5), consistent with the diagnosis of acquired immunodeficiency syndrome. A second course of pentamidine isethionate was given for 14 days, and the patient died.

Physical examination revealed a chronically ill-appearing male in no distress. The temperature was 36.8°C and the blood pressure was 120/80 mm Hg supine and 60/40 mm Hg standing. The corresponding heart rate values were 68 and 72 beats/min; the respiratory rate was 24/min. Positive findings included oral candidiasis and dullness at the right lung base. No motor, sensory, or reflex abnormalities were present, with the exception of previously known slight weakness of the right hip flexors. Laboratory data revealed: hemoglobin, 8.7 g/dl; mean corpuscular volume, 95 μm³; white blood cell count, 1800/mm³ with 52% neutrophils, 10% band forms, and 21% lymphocytes; platelets, 97,000; serum sodium, 135 mEq/liter; potassium, 4.4 mEq/liter; chloride, 99 mEq/liter; carbon dioxide, 23 mmol/liter; glucose, 157 mg/dl; albumin, 3.3 g/dl; total calcium, 8.8 mg/dl; magnesium, 1.1 mg/dl; SGOT, 182 units; and creatine kinase (CK), 437 units. The urinalysis was unremarkable. Chest x-ray was clear.

The clinical impression was that the patient had volume depletion and probably exophalgeal candidiasis; endoscopy was negative, however. Severe orthostatic hypotension persisted despite volume repletion. Administration of 9-α-fluorocortisol was started on the eleventh hospital day and parenteral hyperalimentation with dextrose, vitamins, and electrolyte solutions was initiated on the thirteenth day. Treatment with trimethoprim-sulfamethoxazole at a low dose was restarted on the fourteenth hospital day.

Two days later, the patient became abruptly tachypneic and had a temperature of 38.2°C. The lungs were clear. An arterial blood sample obtained while the patient was breathing room air revealed a pH of 7.44; PCO₂, 16 mm Hg; and PO₂, 90 mm Hg. Serum sodium was 135 mEq/liter; chloride, 97 mEq/liter; carbon dioxide, 11 mmol/liter; lactate, 17.7 mEq/liter; glucose, 408 mg/dl. A serum Acetest was negative. Tobramycin, cefazolin, ticarcillin, and amphotericin were administered. Hypotension, oliguria and refractory lactic acidosis developed. The patient was intubated on the nineteenth hospital day and vasopressors were required. After more than 250 mmol of sodium bicarbonate was administered over 6 hours, the blood pH was 7.19, lactate concentration 33.5 mEq/liter, and serum carbon dioxide 8 mmol/liter. Hemofiltration was performed for fluid removal. On the nineteenth hospital day the patient died.

Discussion

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Lactic acidosis

Metabolically produced lactate is accompanied by the generation of an equivalent number of protons that are released into the body fluids. These protons, which are titrated by bicarbonate and non-bicarbonate buffer systems, acidify the intracellular and extracellular environments. By contrast, metabolic removal of lactate consumes an equivalent number of hydrogen ions, and thus replenishes the body's alkali reserve.

In this section, I will present a brief account of the biochemical and regulatory aspects of lactate production and utilization. The sole biochemical reaction that generates or consumes lactate in the organism is illustrated by Equation 1:

\[ \text{CH}_3\text{COCOO}^- + \text{NADH} + \text{H}^+ \xrightarrow{\text{LDH}} \text{CH}_3\text{CH(OH)COO}^- + \text{NAD}^+ \]

(pyruvate) (lactate) (1)

This reversible reaction occurs in the cytosol and is catalyzed by the enzyme lactate dehydrogenase (LDH), which is ubiquitous in the cytosol. Lactate is formed when pyruvate reacts with reduced nicotinamide adenine dinucleotide (NADH) and is converted back to pyruvate by reactions with the oxidized counterpart of the dinucleotide (NAD\(^+\)). Lactate is a metabolic end-product, its only metabolic fate being oxidation back to pyruvate. The equilibrium of Equation 1 favors the formation of lactate; thus, under normal conditions the concentration of lactate is approximately tenfold greater than that of pyruvate. Of the two optical isomers, L(+)lactate is the natural form in mammals; LDH is stereospecific for the L(+)lactate reaction and does not catalyze the processing of the levorotatory enantiomer D(-)-lactate.

Lactate production

The presence of the enzyme LDH in sufficient quantities in the cytosol ensures the near-equilibrium position of Equation 1. Recasting Equation 1 to highlight the equilibrium concentrations of lactate yields Equation 2:

\[ [\text{Lactate}] = \frac{K_{eq} \times [\text{pyruvate}] \times [\text{NADH}] \times [\text{H}^+]}{[\text{NAD}^+]} \] (2)

where \( K_{eq} \) is the equilibrium constant of the LDH reaction and \([\text{H}^+]\), refers to the intracellular (cytosolic) hydrogen ion concentration. Consequently, the cytosolic concentration of lactate can be viewed as being determined by three variables: the concentration of pyruvate; the \([\text{NADH}]/[\text{NAD}^+]\) ratio, otherwise referred to as the redox (reduction/oxidation) state; and the intracellular hydrogen ion concentration.

Pyruvate concentration. Assuming no change in the other two determinants, an increment in pyruvate concentration should lead to a proportional increase in lactate concentration. The cytosolic pyruvate concentration is the composite function of a series of metabolic processes, some of which generate and some of which consume pyruvate. The main pathway for cellular production of pyruvate is anaerobic glycolysis (Embden-Meyerhof pathway) (Fig. 1). Glycolysis occurs in the cytosol, and its pace is controlled by the activities of three functionally unidirectional enzymes that catalyze rate-limiting, nonequilibrium steps in an irreversible mode: hexokinase (HK), 6-phosphofructokinase (PFK), and pyruvate kinase (PK). Different enzymes are required to catalyze these nonequilibrium reactions in the "reverse" direction. ATP is an allosteric inhibitor of the PFK reaction; thus, when ATP stores are reduced, flux through this reaction is augmented and the rate of glycolysis is increased. A key step in glycolysis is the oxidation of glyceraldehyde 3-phosphate during which \( \text{NAD}^+ \) is consumed and converted to NADH. Provision of \( \text{NAD}^+ \) therefore is essential to the maintenance of glycolysis. Anaerobic tissues under normal conditions and aerobic tissues under hypoxic conditions replenish \( \text{NAD}^+ \) stores by the cytosolic conversion of pyruvate to lactate (Equation 1). On the other hand, aerobic tissues under normal conditions regenerate \( \text{NAD}^+ \) largely via mitochondrial oxidative reactions. Because the inner mitochondrial membrane is impermeable to both NADH and \( \text{NAD}^+ \), reoxidation of cytosolic NADH in aerobic tissues is accomplished indirectly via transmembrane substrate "shuttles."
cytosol, having converted thereby to its reduced form; this form is transported into the mitochondrion where it is subsequently oxidized by the electron-transfer chain. The end result is the effective transport of hydrogen ions, referred to as reducing equivalents, across the mitochondrial membrane and the reoxidation of cytosolic NADH. The two best-studied such systems are the malate/aspartate shuttle and the glycerol phosphate shuttle. Virtually all body tissues are equipped for glycolysis, but particularly high rates are observed in brain, skeletal muscle, heart, and intestinal mucosa. An additional, although quantitatively smaller, source of pyruvate is the transamination of alanine (released from muscle and small intestine) by the enzyme alanine aminotransferase (AAT), a reaction that occurs virtually exclusively in the liver. Finally, in the kidney, pyruvate is formed from the metabolism of the carbon skeleton of glutamine (alpha-ketoglutarate) following removal of the amide and amino nitrogen groups of glutamine in the process of ammoniagenesis.

On the other hand, consumption of pyruvate in aerobic tissues under normal conditions occurs by means of two oxidative mitochondrial pathways and follows the transport of pyruvate across the mitochondrial membrane (Fig. 1). The first of these is oxidative decarboxylation to acetyl-CoA; that is, there is no way that acetyl-CoA can be converted back to pyruvate. The resultant acetyl-CoA can enter the tricarboxylic acid (TCA) cycle and the electron transfer/oxidative phosphorylation pathway for complete oxidation to CO2 and water, or it can be utilized in various biosynthetic pathways (fatty acids, ketone bodies, cholesterol, steroid hormones, acetylcholine). The second aerobic mitochondrial pathway for pyruvate is gluconeogenesis, that is, the synthesis of glucose or glycogen, a process occurring exclusively in the liver and the renal cortex. It is important to recognize that gluconeogenesis is not a mere reversal of glycolysis; as I have noted, three glycolytic reactions (HK, PFK, and PK) are irreversibly catalyzed only in the "forward" direction. As Figure 1 illustrates, synthesis of glucose from pyruvate (as well as from lactate and alanine) depends on bypassing these key, nonequilibrium reactions. The first step in this process, conversion of pyruvate to phosphoenolpyruvate, involves two components: (1) carboxylation of pyruvate to oxaloacetate within mitochondria, a process catalyzed by pyruvate carboxylase (PC); and (2) cytosolic conversion of oxaloacetate to phosphoenolpyruvate, a process catalyzed by the enzyme phosphoenolpyruvate carboxykinase (PEPCK). Both reactions require ATP. The two additional steps requiring specific catalysis are affected by fructose-bisphosphatase (FBPase) and glucose-6-phosphatase (G-6-Pase). As is the case for the reactions unique to

![Fig. 1. Metabolic pathways of glycolysis and gluconeogenesis.](image-url)
glycolysis, all those unique to gluconeogenesis are irreversible (that is, functionally unidirectional); thus, they constitute the rate-limiting steps of the gluconeogenesis pathway.

Formation of pyruvate (via the PK reaction) completes the segment of the glycolytic pathway that is common to both anaerobic and aerobic metabolism. The conversion of one molecule of glucose to pyruvate or lactate is associated with the net production of two molecules of ATP. The subsequent aerobic oxidation of pyruvate generates 36 additional molecules of ATP, for a total of 38 molecules per completely oxidized molecule of glucose.

Impaired mitochondrial oxidative function, as occurs in hypoxic states, leads to accumulation of pyruvate in the cytosol and thus to increased lactate production. The accumulation of pyruvate reflects both overproduction of pyruvate and reduced utilization of pyruvate through its two pathways (note the NAD⁺ dependence of the PDH reaction and the ATP requirement of the PC and PEPCK reactions). The former occurs because a reduced supply of ATP to the cytosol stimulates the PFK reaction and results in augmented glycolysis (Fig. 2). As noted, ATP constitutes a potent external regulator of the PFK reaction. During anaerobic conditions, glycolysis becomes the main source of energy for the organism; despite the prevailing mitochondrial dysfunction, continuation of glycolysis (via oxidation of glyceraldehyde 3-phosphate) is assured by cytosolic regeneration of NAD⁺ via the conversion of pyruvate to lactate. Thus increased lactate production represents the toll paid by the organism to maintain energy generation during anaerobiosis.

The [NADH]/[NAD⁺] ratio. This ratio is a measure of the redox state of cytosolic pyridine nucleotides. The ratio is affected by the activity of the various cytosolic dehydrogenases that employ pyridine nucleotides for transferring H⁺ (mainly during the processes of glycolysis and gluconeogenesis), but in mitochondria-containing cells it is largely determined by the rate of mitochondrial oxidative reactions; NADH is oxidized to NAD⁺ by the electron-transfer chain, which is coupled to oxidative phosphorylation. Suppression of mitochondrial function through decreased oxygen availability or other mechanisms leads to reduced availability of NAD⁺ within the cytosol; as Equation 2 indicates, the resultant increase in the [NADH]/[NAD⁺] ratio shifts the equilibrium of the LDH reaction toward lactate (Fig. 2).

Intracellular [H⁺]. According to Equation 2 and barring any changes in pyruvate concentration and redox state, an increment in intracellular [H⁺] should lead to increased lactate concentration in the cytosol. In isolated tissue preparations, however, this direct effect of intracellular [H⁺] is overridden by pH-mediated effects on PFK [8] and thus on pyruvate production (Fig. 1). Strong evidence indicates that the activity of PFK is inhibited by intracellular acidosis and stimulated by intracellular alkalosis; consequently, in tissue preparations, lactic acid production falls during acidosis and increases during alkalosis [9–13]. These effects of intracellular [H⁺] on the glycolytic rate and on lactate production have been demonstrated during aerobiosis as well as during anaerobiosis and may well serve an important homeostatic function. Under conditions of tissue hypoxia, stimulation of glycolysis leads to augmented lactic acid production with a resultant decrement in intracellular pH; the acidosis in turn inhibits glycolysis and lactic acid production and thus moderates the acidification of the intracellular milieu. Conversely, this servomechanism blunts the increment in intracellular pH by augmenting lactic acid production during alkalosis [4, 9, 11, 14]. Acidosis and alkalosis thus influence lactic acid production in the direction of minimizing the acid-base disruption. Given the ubiquity of the glycolytic process in mammalian tissues, the cellular machinery may well employ pH-regulated production of lactic acid (and other organic acids) to buffer fluctuations in the prevailing pH, thereby maintaining a measure of stability in intracellular as well as extracellular domains [4, 9, 11, 12].

In-vivo observations on the composition of extracellular fluid corroborate the existence of such a negative feedback mechanism between net lactate production under basal or stimulated conditions and acidity of body fluids. Several investigators have documented that plasma lactate concentration falls during acute respiratory acidosis, thus contributing a small component to the whole body’s buffer response [15–19]. In addition, small decrements in plasma lactate have been observed in acute and chronic metabolic acidosis [20, 21]. On the other hand, small rises in plasma lactate concentration occur during acute respiratory or metabolic alkalosis [4, 9, 15, 16, 22–28]; however, any tendency for a substantial increase is probably tempered by augmented lactate utilization. Whereas plasma lactate concentration is within normal limits during chronic hypocapnia even in the presence of associated hypoxemia [29–34], a mild elevation in lactate persists in chronic metabolic alkalosis [21, 35]. An additional increment in plasma lactate is observed when acute or chronic hypocapnia is superimposed on chronic metabolic alkalosis [36].

Several recent lines of evidence lend strong support to such a homeostatic system of net lactic acid production under conditions of stimulated synthesis. Acute hypocapnia produced by elevating FiCO₂ resulted in marked suppression of exercise-induced hyperlactatemia in volunteer subjects [37–40]. Similarly, administration of either NH₄Cl or NaHCO₃ led to substantial suppression or augmentation, respectively, of the hyperlactatemia of exercise [39, 41]. Muscle lactate concentration and glycogen depletion were less in individuals ingesting NH₄Cl than in those given NaHCO₃. In an experimental model of
hypoxia-induced lactic acidosis in the rat [42], superimposition of either mild respiratory acidosis (PaCO2, 59 mm Hg) or HCl-induced metabolic acidosis (sufficient to decrease pH from 7.27 to only 7.23) resulted in a dramatic blunting of the rise of blood lactate; by contrast, superimposition of respiratory alkalosis (PaCO2, 15 mm Hg) led to an exaggerated rise in blood lactate in the hypoxic animals. Moreover, findings in patients with malignancy-induced chronic lactic acidosis [43, 44] as well as extensive experience with experimental models of hypoxic and nonhypoxic lactic acidosis [45–52] clearly demonstrates that bicarbonate administration augments lactate production and blood lactate levels.

These observations are in full accord with previous findings in fasting obese humans, another state of enhanced endogenous acid release, which revealed an exquisite sensitivity of ketoacid production to chronic mild changes in systemic pH produced by acid or alkali ingestion [12, 53, 54]; a fall in pH suppressed and a rise increased ketoacid production. A similar effect has been observed on the degree of ketonuria in patients with diabetes mellitus [55, 56]. These clinical observations are amplified further by the demonstration of remarkable responsiveness of ketoacid production to acute changes in pH when HCl or NaHCO3 is infused into rats or humans [57–59].

Taken together, these findings suggest the existence of a more generalized homeostatic system that regulates endogenous organic acid production via changes in systemic pH [12]. What is truly remarkable is the impressive responsiveness of this system and the magnitude of the change elicted by relatively small deviations in extracellular pH during probing experimental maneuvers. Obviously, it would be of great interest to apply modern noninvasive technology to monitor the response of intracellular acidity to these relatively modest extracellular changes.

The role of this negative feedback system in the pathogenesis and evolution of clinical lactic acidosis is uncertain, and it represents an exciting area for future investigation. Such a system might be crucial to survival during maximal exercise, a state characterized by marked hyperlactatemia and severe extracellular and intracellular acidosis [60, 61]. On the other hand, this servomechanism is apparently overridden in cases of severe lactic acidosis. Indeed, in hypoxic lactic acidosis, although the prevailing acidemia can exert an inhibitory effect on the magnitude of the evolving metabolic derangement, the acidemia eventually proves impotent in preventing escalation to extreme hyperlactatemia. It appears that any inhibitory effect of acidemia is simply overridden by the hypoxic drive to augmented lactate production. Equally uncertain is whether a clinically relevant interaction exists between this servomechanism and pH-mediated alterations in hepatic and renal gluconeogenesis (and, thus, lactate uptake).

**Lactate utilization**

As I already have noted, the sole pathway for lactate utilization is conversion back to pyruvate, its oxidized counterpart (Equation 1). Consequently, metabolic removal of lactate is equivalent to the metabolic removal of pyruvate. I will examine the factors that influence lactate uptake and utilization in a moment.

Lactate is freely filtered at the glomerulus. At low concentrations it is reabsorbed virtually completely in the proximal tubule. Under conditions of hyperlactatemia, renal excretion contributes to lactate removal. The renal threshold for lactate excretion being approximately 5 to 6 mEq/liter [20, 62]. In lactic acid-loading experiments in humans, rats, and sheep, renal lactate excretion accounted for less than 1.2% of the infused load [20, 62, 63]. In general, lactate excretion represents a small fraction of total lactate uptake by the kidney.

**Physiology and quantitative aspects of lactate metabolism**

Plasma lactate concentration is normally in the range of 1 mEq/liter and that of pyruvate about 0.1 mEq/liter. The normal ratio of these two substances (known as the L/P ratio) is approximately 10:1. Obviously, the stability of plasma lactate concentration implies a precise equivalence between the process of releasing lactate to, and that of removing lactate from, the extracellular compartment. The average basal turnover rate in normal humans has been estimated at about 20 mEq/kg/day with a range of 15 to 25 mEq/kg/day [3, 6, 7, 63–66]. This amounts to approximately 1400 mEq/day per 70 kg subject or approximately 1 mEq/min. Such estimates have been obtained through a variety of techniques including the disappearance of infused lactate, measurements of blood flow and arteriovenous differences for lactate across tissue beds, extrapolations from in-vitro incubation data, and the kinetics of infused isotopically labeled lactate. Methodologic limitations make available estimates gross approximations at best. Estimates of the apparent volume of distribution of lactate range from 270 to 340 ml/kg in humans [63, 67] and about 360 ml/kg in the rat [20]. Unfortunately, available information on quantitative aspects of lactate production and utilization by humans in health and disease is quite limited. Considerably more information is available from studies in experimental animals.

Although all tissues produce lactate during the course of glycolysis, only some of them contribute substantial quantities to the extracellular fluid under normal aerobic circumstances. Table 1 lists the lactate-producing tissues. Whereas the renal medulla normally produces lactate in spite of an adequate substrate and oxygen supply, the renal cortex has a high rate of oxidative metabolism and lactate utilization [68]. Erythrocytes are obligatory producers of lactate because, in the absence of mitochondria, they lack the apparatus for the metabolic processing of pyruvate. During exercise, skeletal muscle is the major source of circulating lactate. The maximal rates of lactate production by various tissues remain unknown. Yet estimates from individuals undergoing short bursts of maximal exercise or having a grand-mal seizure indicate that lactate production can increase by several hundredfold [4, 7, 69]. Under hypoxic conditions, virtually all tissues can release lactate into the circulation. Indeed, during severe hypoxia and acidosis, even the liver—the predominant consumer of lactate under normal conditions—can add lactate to the blood [70, 71]; obviously, such a transition from net utilization of lactate to net production is an ominous sign for the organism.

Liver and renal cortex, the major lactate-consuming organs, can use lactate (via pyruvate) as a substrate for gluconeogenesis and can oxidize it to CO2 and water. Animal studies indicate that of the two pathways, gluconeogenesis is the primary mode of lactate processing in the liver. On the other hand, in the kidney the fraction of lactate that is extracted and converted to glucose as opposed to being oxidized remains unclear; variable
Table I. Lactate-producing and -consuming tissues under basal conditions

<table>
<thead>
<tr>
<th>Producers</th>
<th>Consumers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Liver</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>Renal cortex</td>
</tr>
<tr>
<td>Brain</td>
<td>Heart</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Salivary glands (?)</td>
</tr>
<tr>
<td>Intestinal mucosa</td>
<td></td>
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<tr>
<td>Leukocytes</td>
<td></td>
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<tr>
<td>Platelets</td>
<td></td>
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<tr>
<td>Renal medulla</td>
<td></td>
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<tr>
<td>Tissues of the eye (cornea, lens, retina)</td>
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</tr>
</tbody>
</table>

results have been obtained depending on the experimental conditions employed. Available evidence suggests that about 50% of the renal lactate uptake in the rat and dog is oxidized [11, 21, 72, 73]. Although the interorgan apportioning of lactate utilization remains poorly defined, the relative contribution of the various organs to lactate uptake varies widely according to the prevailing conditions (for example, basal state, exogenous infusions of lactate at rest, vigorous exercise). Estimates for the fractional contribution of the liver to the total basal lactate load in humans vary widely, ranging from 30% to 70%; 50% is probably a reasonable figure [7, 74, 75]. Studies utilizing lactic acid loading in rats and sheep have estimated that the kidney extracts approximately 20% to 30% of the load [20, 62, 76]. Notably, the liver has a large reserve capacity for lactate metabolism that is estimated to be higher than the basal rate by severalfold [77]. Hepatic uptake of lactate exhibits marked concentration dependence [15, 62]. Recent lactate-loading experiments in sheep suggest that hepatic lactate uptake is a saturable process with second-order (Michaelis-Menten) kinetics [62]; whereas the basal rate of hepatic lactate removal averaged 0.57 mEq.kg⁻⁰.⁷⁵.h⁻¹, the V_max was estimated at 5.72 mEq.kg⁻⁰.⁷².h⁻¹, and the Km at 3.06 mEq/liter. Studies in the perfused rat liver have shown saturation of uptake at a plasma lactate concentration of approximately 4 mEq/liter [6]. Observations in humans suggest that during mild exercise (about 30% to 60% of maximum O₂ uptake, with plasma lactate levels up to 2.3 mEq/liter) hepatic lactate uptake is augmented in proportion to the load [78–80]; in contrast, hepatic lactate uptake does not change or even can decrease markedly during strenuous exercise [74, 81]. Despite the prevailing severe hyperlactatemia during maximal exercise, lactate uptake probably is suppressed by the marked diminution in hepatic blood flow that is known to occur; an additional suppressive role might be exerted by the existing, often severe, acidosis [15, 64, 70, 82–86]. Although the hepatic functional reserve for lactate removal is well documented, the fact that hyperlactatemia develops during even mild exercise indicates that the liver (as well as other lactate-consuming sites) cannot keep pace acutely with lactate-producing organs; that is, lactate production at least transiently outstrips utilization.

Similarly, renal consumption of lactate is augmented in hyperlactatemia, thus contributing to the organism’s reserve capacity (20, 72); the excess lactate enters both oxidative and biosynthetic pathways [87]. As I already have noted, renal excretion contributes to lactate removal under such circumstances. In response to an exogenous lactic acid load in the rat and at a plasma lactate concentration of 10 mEq/liter, renal lactate excretion accounted for approximately 12% of the cumulative renal contribution to lactate removal (the latter being about 25% to 30% of the administered load) [20]. During hyperlactatemia the heart’s contribution to lactate removal also increases [88]. Under these conditions, the lung can be involved in lactate utilization [89].

Although normally a lactate-producing organ, resting skeletal muscle also can extract lactate from the blood—and use it primarily as fuel for oxidation—during hyperlactatemia produced by exogenous infusion or by exercise of regional muscle groups [67, 90–92]. Indeed, several studies have shown conversion from lactate output to lactate uptake by resting skeletal muscle following an infusion of a lactic acid load, with an estimated 25% to 35% of the load taken up by muscle [62, 67, 90, 93]. Under such circumstances, skeletal muscle can dispose of more of the lactate load than does the liver [62, 90]. Whereas saturation of hepatic lactate uptake during relatively mild increases in lactate level have been documented [6, 62], one study reported no saturation of extrasplanchnic lactate uptake even at the highest plasma lactate concentration, 20 mEq/liter [62]. In fact, deductions drawn from studies in the isolated perfused rat hind limb, which showed a linear increase in muscle lactate uptake with perfusate concentrations up to 27 mEq/liter [94], suggest that the liver may contribute in only a small way to lactate removal during recovery from maximal exercise. Further, the rate of plasma lactate recovery was augmented if the subject continued exercising at a submaximal level rather than resting; this observation lends strong support to the importance of skeletal muscle in extracting lactate under such circumstances [81]. Limited clinical data suggest a compensatory increase in lactate uptake by skeletal muscle when hepatic lactate uptake is deranged [95]. Nonetheless, the contribution of skeletal muscle to lactate utilization during clinical lactic acidosis remains a matter of considerable debate [3, 6, 7, 64, 67].

The importance of the liver as a lactate-consuming organ is exemplified by observations after functional hepatectomy in the diabetic dog. Functional hepatectomy was produced by diverting the portal circulation to the inferior vena cava and ligating the hepatic artery. Although lactate production due to surgical stress might have contributed to acidosis, 2 and 3 hours following the procedure the plasma lactate increased from a mean control value of 1.4 mEq/liter to average values of 6.0 and 10.7 mEq/liter, respectively; corresponding values for blood pH were 7.20 and 7.13 (mean control value, 7.42) [96].

Turning to the contribution of the kidney to lactate disposal, removal of an exogenous lactic acid load was slower in rats subjected to bilateral nephrectomy as compared with animals subjected to a sham operation; lactate elimination half-life averaged 5.3 minutes, and blood clearance for lactate (at a plasma concentration of 10 mEq/liter) was 45.3 ml/min/kg in sham-operated animals; the corresponding values were 7.1 minutes and 32 ml/min/kg in animals with bilateral nephrectomy [20]. Overall, nephrectomy resulted in approximately a 30% slowing of absolute lactate removal following an intravenous lactic acid load [20].

From the standpoint of the whole organism’s economy, therefore, tissues with glycolytic activity under normal aerobic conditions metabolize glucose to lactate and relinquish it into the circulation. In turn, lactate is extracted by the liver and
renal cortex and is either reconverted to glucose or becomes fuel for oxidation to CO₂ and water. The cyclical relationship between glucose and lactate, embodied in the Cori cycle (Fig. 3), ensures a continuous supply of glucose to tissues requiring this substrate as fuel, such as brain and erythrocytes.

Another important dividend to the body’s economy from the unperturbed function of the Cori cycle is that the cycle provides for the recapturing of hydrogen ions released into the body fluids during glycolysis and thus allows for acid-base balance to be maintained. What follows is a short overview of the acid-base consequences of lactate metabolism.

Exogenously administered lactic acid is virtually completely dissociated in body fluids, because its pKₐ is 3.86. However, lactic acid as such is not produced at any step in the glycolytic process; rather lactate, its conjugate base, is the actual end-product of anaerobic glycolysis. Nonetheless the glycolytic process also results in the release of protons in numbers equivalent to the lactate produced, and the net effect is as if lactic acid were released into the body fluids.

Conversion of glucose to lactate is coupled to the synthesis of two molecules of ATP. The most simplified description of the stoichiometry of this conversion is as follows (Equation 3):

\[
C₆H₁₂O₆ + 2ADP^{3−} + 2Pi^{2−} \rightarrow 2CH₃CH(OH)COO^- + 2ATP^{4−} + 2H₂O
\]

Under steady-state conditions, the ratio of ATP to ADP remains unchanged; consequently, all ATP synthesized in Equation 3 is promptly consumed (Equation 4):

\[
2ATP^{4−} + 2H₂O \rightarrow 2ADP^{3−} + 2Pi^{2−} + 2H^+ \]

Summing up Equations 3 and 4 we obtain Equation 5:

\[
C₆H₁₂O₆ \rightarrow 2CH₃CH(OH)COO^- + 2H^+
\]

Thus, protons are released via the hydrolysis of ATP generated during anaerobic glycolysis and not via dissociation of the lactic acid species [97–99]. Protons freed from this process are titrated by bicarbonate and nonbicarbonate buffers residing in the intracellular and extracellular compartments. For acid-base balance to be maintained, however, the protons released into the body fluids must be removed. This task is achieved during the metabolism of lactate via the two oxidative pathways. When the liver and the renal cortex reconvert lactate to glucose during gluconeogenesis, Equation 5 is reversed and a number of protons equivalent to the number of lactate ions consumed is removed from the body fluids (Equation 6):

\[
2CH₃CH(OH)COO^- + 2H^+ \rightarrow C₆H₁₂O₆
\]

(6)

Gluconeogenesis is an energy-requiring process and consumes ATP and GTP; the aerobic repletion of these high-energy phosphate groups produces the net utilization of protons during gluconeogenesis [97–99]. Similarly, during the combustion of lactate to CO₂ and water, an equivalent number of protons are abstracted from the body fluids (Equation 7):

\[
CH₃CH(OH)COO^- + H^+ + 3O₂ \rightarrow 3CO₂ + 3H₂O
\]

In actuality, consumption of the proton occurs during aerobic mitochondrial ATP synthesis, which may be considered the reverse of ATP hydrolysis [97–99].

In the overall scheme, protons are generated in the cytosol via hydrolysis of synthesized ATP and are consumed in the mitochondria via aerobic reconstitution of high-energy phosphate groups. The recapturing by the liver, and secondarily by the kidney, of protons freed during glycolysis allows for regeneration of bicarbonate and back-titration of the nonbicarbonate buffers, so that no net input of hydrogen ion to body fluids occurs and acid-base balance remains undisturbed. In this sense, lactic acidosis is generated whenever an imbalance between ATP hydrolysis and ATP generation occurs, and results in a net gain of hydrogen ions by the body fluids.

The importance of disposing of the protons produced during glycolysis for the maintenance of acid-base equilibrium can be better appreciated when its magnitude—that is, 15 to 25 mEq of H⁺/kg/day under basal conditions, as much as the lactate produced—is contrasted with the magnitude of net acid excretion by the kidney, approximately 1 mEq of H⁺/kg/day. Moreover, under conditions of lactate overproduction, an even greater burden is placed on the liver and the kidney to maintain acid-base homeostasis. It is apparent therefore that from an acid-base perspective, the liver plays a pivotal, albeit not widely appreciated, role in ensuring the daily miracle of the organism’s survival. This analysis is a sobering reminder to nephrologists, who usually are possessed by a nephrocentric view of acid-base balance.

**Pathogenesis of lactic acidosis**

Lactic acidosis is generated whenever the production of lactic acid outstrips its utilization. The result of such an imbalance is evidenced by the accumulation of lactate in the circulation, often in the company of hypobicarbonatemia and acidemia. From a theoretical standpoint, as I have just stressed, the pathogenesis of this imbalance could reflect overproduction of lactic acid, underutilization, or both.

Overproduction of lactic acid is clearly recognized as the mechanism of transient lactic acidosis in subjects undergoing vigorous exercise and in those who have generalized convulsions [3, 4, 7, 65]. Similarly, for reasons I already have noted, hypoxia constitutes a potent stimulus for lactic acid production. However, given the extensive reserve capacity for lactate

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**Fig. 3. The Cori cycle.**
Additional in vivo studies in the dog have shown that reduction in hepatic blood flow to less than 30% of normal cannot be compensated for and results in diminished hepatic lactate uptake [104]. The weight of the evidence thus suggests that nonhypoxic forms of lactic acidosis are secondary to lactate overproduction [2] is extremely weak [6, 7, 64]. In addition, observations from experimental models of hypoxic [45, 101, 102] and nonhypoxic [103] forms of lactic acidosis have clearly implicated both overproduction and underutilization of lactate in the pathogenesis of the disorder. Thus, although we are far from being able to quantitatively apportion the lactate load into overproduction and underutilization columns, it appears likely that both limbs of lactate metabolism might be defective in most forms of clinical lactic acidosis. Accordingly, I should like to address briefly some factors that are known to affect lactate utilization by the liver and kidney. This knowledge has been derived from experimental studies and its clinical relevance remains uncertain; nonetheless, it allows for the formulation of an insightful perspective of the pathogenesis of the disorder.

As I have already noted, hyperlactatemia produced by exogenous infusion elicits increased utilization of lactate by the liver and kidney [15, 20, 62, 72, 87]. On the other hand, graded hypoxia of the hepatic parenchyma leads to a progressive diminution in hepatic lactate uptake; this reduction converts the liver from a lactate-consuming to a lactate-producing organ [45, 71, 104, 105]. Thus, in early studies in the isolated perfused rat liver, a reduction in hepatic blood flow by 40% to 67% resulted in conversion from lactate uptake to lactate production [45, 105]. By contrast, in a more recent study of the same experimental preparation [106], lactate uptake was reduced only modestly when hepatic blood flow was decreased by 67% of normal; this finding of course reflects an increase in the hepatic extraction ratio of lactate as hepatic blood flow decreases. At more advanced degrees of hypoperfusion, however, severe reductions in uptake were noted. Yet, even when blood flow was reduced by 93%, minimal lactate uptake, but not output, was still observed. At that point, liver intracellular pH averaged 7.03 as compared to a mean value of 7.25 during basal flow [106]. Similarly, in vivo studies in the dog have suggested a large hepatic functional reserve for lactate disposal even during severe ischemia [20]. At plasma lactate concentrations up to 4.2 mEq/liter, reductions in total hepatic blood flow by 70% or less did not elicit a significant decrease in hepatic uptake. However, further hypoperfusion markedly depressed lactate uptake and even caused net lactate production [104]. The weight of the evidence thus suggests that a reduction in hepatic blood flow to less than 30% of normal cannot be compensated for and results in decreased lactate utilization. Indeed, less severe degrees of hypoperfusion might lead to substantial impairment of lactate uptake if accompanied by greater degrees of hyperlactatemia. Additional in vivo studies in the dog have shown that reduction in oxygen tension to a mean PaO₂ of 47 mm Hg decreased hepatic lactate uptake by an average of —5.3 μEq/kg/min (mean control value of 1.7 μEq/kg/min); this change indicated a conversion to net lactate production. When more severe hypoxia was established (mean PaO₂ of 35 mm Hg), net lactate production by the liver was increased (mean of —9.2 μEq/kg/min) [104]. In addition to hypoxia, reduction of the hepatic redox state induced by other means (for example, biguanides, fructose, alcohol) has been shown to lead to impaired lactate removal.

In studies of graded hemorrhage in the dog, renal lactate uptake remained stable up to a blood loss of 30% of the basal volume. Following a 40% blood loss, which resulted in a mean arterial blood pressure of 72 mm Hg and a reduction in renal blood flow by 66% of the prehemorrhage value, renal lactate uptake decreased sharply; lactate production occurred during hemorrhagic shock from a 45% to 50% blood loss at a mean arterial blood pressure of 38 mm Hg and a 94% reduction in renal blood flow [107, 108]. Following reinfusion of shed blood, renal lactate uptake remained below baseline levels, probably reflecting hypoxic tissue damage.

Moreover, strong evidence indicates that either severe metabolic or respiratory acidosis impairs hepatic lactate uptake [15, 64, 70, 82—84, 109, 110]. Lactate uptake by the isolated perfused rat liver decreased progressively at a perfusate pH of less than 7.10; indeed, when the perfusate pH was lowered below 7.0, and liver intracellular pH fell to below 7.05, lactate output, rather than uptake, occurred (Figs. 4 and 5) [70]. Additional studies have revealed that gluconeogenesis from lactate is markedly depressed in the isolated perfused rat liver when the perfusate pH is lowered below 7.10 [83]. By contrast, in vivo and in vitro studies have shown that moderate degrees of acidosis do not significantly change hepatic lactate uptake [15, 62, 64, 70]. The suppressive effect of acidosis on lactate uptake has been attributed to decreased gluconeogenesis from lactate that occurs as a result of a fall in oxaloacetate concentration; the latter could reflect inhibition of pyruvate carboxylase (PC) enzymatic activity, increase in the [malate]/[oxaloacetate] ratio, or both [84, 111]. It is interesting that myocardial lactate uptake decreased by 30% in anesthetized dogs when blood pH was...
lowered to 7.16 to 7.20 by the infusion of hydrochloric acid [112].

Experiments in the isolated perfused rat liver have examined the effects of combined hypoperfusion and acidosis on lactate uptake and gluconeogenesis [85]. The conditions were selected to simulate those prevailing during moderate to severe exercise or during circulatory collapse; in addition, acidosis itself is known to decrease hepatic blood flow [113]. Ischemia and acidosis have separate inhibitory effects on hepatic lactate uptake; thus, both could contribute to the defect in lactate utilization characteristic of those settings [85]. Notably, epinephrine exerted a marked ameliorating effect on lactate uptake under these experimental conditions [86]. This observation might have clinical relevance, in view of the high levels of circulating epinephrine during acidemic states, such as strenuous exercise and shock.

As expected from Equations 6 and 7, the metabolic processing of lactate by gluconeogenesis or oxidation should increase the hepatocyte pH by abstracting intracellular hydrogen ions; by contrast, decreased lactate consumption should decrease intracellular pH. This formulation assumes that at least part of the lactate entering the hepatocyte is not accompanied by an equivalent number of protons; support for this mechanism has been obtained [6, 114]. Experiments in the isolated perfused liver from several species indicate a direct relationship between lactate consumption and a change in intracellular pH [106, 115, 116]. These interrelationships make it evident that the generation of severe acidemia during lactic acidosis carries in itself the potential of initiating a vicious cycle in which the resultant depressed hepatic intracellular pH would suppress lactate uptake, thus leading to further aggravation of intracellular as well as extracellular acidosis (Fig. 6). This ominous cycle would be reinforced further by the depressive effects of acidosis on hepatic blood flow [113].

A potent defense mechanism against a maladaptive positive-feedback system such as this resides in the kidney. Evidence from in-vitro and in-vivo studies suggests that acidosis substantially increases renal lactate uptake and utilization via gluconeogenesis by stimulating the activity of the key gluconeogenic enzyme PEPCK [11, 20, 76, 117]. This adaptation is apparent within 2 to 4 hours from the onset of acidosis [118]. The augmented renal contribution to lactate utilization during acidosis occurs despite the accompanying substantial decrease in renal blood flow [113]. The mechanism underlying the opposite effects of acidosis on lactate utilization by the liver and kidney remains obscure. The overall impact of these responses on the body’s ability to handle a lactic acid load was quantified in rats subjected to either bilateral nephrectomy or to a sham operation and then made acidotic with NH₄Cl. Lactate removal was slowed in nephrectomized animals by approximately 50% during extracellular acidemia at pH 6.75; this result reflected both the suppressed hepatic uptake and the absence of the renal contribution. It was estimated that whereas the contribution of the kidney to lactate removal was 16% at pH 7.45, it rose to 44% at pH 6.75. Consequently, the enhanced ability of the kidney to remove lactate during acidemia was sufficient to compensate for approximately one-half of the concomitant fall in the extra-renal (primarily hepatic) capacity for lactate extraction; the net result was a relatively slight decrease in whole-body lactate removal in the sham-operated animals [20]. It thus appears that

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**Fig. 5.** Relationship between intracellular pH ($pH_i$) and lactate uptake in the isolated perfused rat liver during simulated metabolic acidosis (reprinted by permission from Clinical Science and Molecular Medicine, vol 45, pp 543–549, copyright © 1973, The Biochemical Society, London).

**Fig. 6.** Theoretical positive-feedback mechanism operating to decrease systemic pH under conditions of severe lactic acidosis.

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the finding of an elevated plasma lactate level. The clinical acidemia. Of course, confirmation of the diagnosis rests with (anion gap), often in the company of hypobicarbonatemia and elevation in the concentration of plasma undetermined anions and is supported by the finding of an otherwise unaccounted-for acidosis frequently is strongly suspected on clinical grounds.

The role of the kidney as a lactate-consuming organ becomes progressively more important as extracellular pH falls; in severe acidemia, liver and muscle fall very short of compensating for the absence of kidneys.

The role, if any, of this renal adaptation in the pathogenesis of the many forms of clinical lactic acidosis remains undefined. However, it is intriguing to note that renal dysfunction is often present in patients who develop either hypoxic or non-hypoxic types of lactic acidosis as well as in those with phenformin-induced lactic acidosis [3–7, 65, 77, 119]. Phenformin has been shown to inhibit renal gluconeogenesis both in vivo and in vitro, in addition to its suppressive effect on hepatic gluconeogenesis [4, 120, 121].

Table 2 presents a synopsis of the currently known effects of changes in systemic pH on lactate metabolism. Acidosis inhibits lactate synthesis, retards hepatic lactate uptake, but promotes renal lactate extraction and utilization. On the other hand, alkalosis stimulates lactate generation; no consistent effect of alkalosis on lactate utilization has been identified. As I have noted, experimental observations under basal conditions as well as during stimulated lactate production (exercise, hypoxemia, phenformin administration) reveal suppression of net lactate production in vivo by acidosis and augmentation by alkalosis. Nonetheless, additional research is required to define the aggregated effect of the multitude of influences of acidosis on lactate metabolism. The level of severity of the acidosis, its often rapidly evolving course, and the associated—primary and/or secondary—hemodynamic disturbances are among the factors that add special complexity to this task. It is possible, for example, that during severe acidosis the aggregate effect of these various influences might lead to a pH-induced increase in net lactate production because of the overriding importance of impaired hepatic lactate utilization.

**Clinical features**

The clinical presentation of lactic acidosis is extremely variable and heavily influenced by the manifestations of the underlying disease. Nonetheless, its development is often heralded by the sudden onset of malaise, weakness, anorexia, vomiting, and a deterioration in mental status. Hyperventilation, tachycardia, hypotension, and circulatory instability are common associated findings [3, 4, 65]. The diagnosis of lactic acidosis frequently is strongly suspected on clinical grounds and is supported by the finding of an otherwise unaccounted-for elevation in the concentration of plasma undetermined anions (anion gap), often in the company of hypobicarbonatemia and acidemia. Of course, confirmation of the diagnosis rests with the finding of an elevated plasma lactate level. The clinical significance of lactate levels in the range of 2 to 4 mEq/liter remains unclear. On the other hand, lactate levels of 5 mEq/liter or greater usually point to the seriousness of the clinical condition: the higher the level, the greater the gravity of the patient’s status and the worse the prognosis [122]. I would like to discuss some general aspects of the clinical presentation of lactic acidosis.

**Acid-base**

Although substantial hypobicarbonatemia is a regular accompaniment of lactic acidosis, this need not be the case. If lactic acidosis is superimposed on a preexisting hyperbicarbonatemic state, the accumulated lactic acid may not be sufficient to drive the plasma bicarbonate to frankly subnormal levels. The only laboratory clue to the coexistence of lactic acidosis in this setting is the inappropriately elevated plasma anion gap.

It generally has been assumed that in uncomplicated lactic acidosis (and, in fact, in all types of organic acidosis) reciprocal stoichiometry is maintained between the decrement in plasma bicarbonate and the increment in anion gap. This assumption originates from the expectation that titration precisely replaces bicarbonate with the anion of the offending acid, that is, lactate. Consequently, plasma chloride concentration, unaffected by titration, is assumed to remain normal. As a corollary, when lactic acidosis is found to be associated with hypochloremia (that is, when the increment in anion gap is greater than the decrement in bicarbonate from normal), it has been argued that an antecedent metabolic alkalosis might have been present but presumably is now hidden by the overriding impact of the acidosis. Undoubtedly, in the untreated patient, close correspondence often exists between the decrement in plasma bicarbonate and the increment in anion gap, as well as the rise in plasma lactate. Yet on several occasions we have been puzzled by the occurrence of moderate hypochloremia (in the absence of corresponding hyponatremia) in patients with lactic acidosis but without an identifiable cause for the putative underlying alkalosis. Recent experiments in our laboratory have suggested that some degree of hypochloremia might be an integral part of the prevailing acidosis [123]. A stable degree of lactic acidosis was produced in nephrectomized rats by infusing the racemic mixture of L(+)- and D(−)-lactic acid over a 3-hour period. As Figure 7 illustrates, a decrement in plasma chloride concentration accounted, on average, for 38% and 48% of the increment in plasma anion gap at 1 and 3 hours, respectively. We theorized that this acidosis-induced hypochloremia was due to expansion of the extracellular compartment secondary to the extrusion of cellular cations that occurs in the process of buffering [123]. Although this mechanism provides a plausible explanation for the puzzling hypochloremia I already have referred to, its relevance to the clinical setting remains to be determined. Assuming that this mechanism is operative, one might not expect the generation of acidosis-induced hypochloremia at the very onset of acidosis before substantial ionic shifts have occurred; this prediction is supported by studies of hyperacute, transient lactic acidosis secondary to a single grand-mal seizure in which hypochloremia was not present [69] and by observations in humans following maximal exercise of short duration [60]. By contrast, acidosis of several hours duration might feature this abnormality unless offsetting factors were involved [123].
The degree of acidemia generated by a given level of lactic acidosis-induced hypobicarbonatemia is, of course, determined by the attendant level of PaCO₂. No systematic observations on the magnitude of the ventilatory adaptation to lactic acidosis are available. Retrospective studies have variably reported that this response is greater than, equal to, or less than that associated with other types of metabolic acidosis [3, 124—127]. In an animal model of lactic acidosis, the degree of ventilatory adaptation was virtually identical to that observed in mineral acid-induced metabolic acidosis [123]. Stimulation of carotid and aortic chemoreceptor activities in response to lactic acid-induced metabolic acidosis has been shown in the cat [128]. Although hypocapnia regularly occurs in clinical lactic acidosis [129], it often is difficult to ascribe it entirely to the adaptive response in view of the frequent coexistence of other processes known to stimulate alveolar ventilation, for example, hypoxemia, hypertension, sepsis, pulmonary disease, and hepatic failure. On the other hand, processes that lead to ventilatory failure can limit the ventilatory response to lactic acidosis or superimpose frank hypocapnia; of course, acidemia is compounded under such circumstances.

Plasma potassium concentration

In contrast to mineral acid-induced acidosis, lactic acidosis of comparable severity induced by exogenous infusion of lactic acid is not associated with a significant change in plasma potassium concentration [130—135]. Similarly, hyperkalemia is not observed in patients with grand mal seizure-induced lactic acidosis, and its spontaneous recovery is not accompanied by a significant change in plasma potassium [69]. Although hyperkalemia occurs commonly in patients with various types of lactic acidosis, the level of plasma potassium correlates poorly with the degree of acidemia; moreover, most of the hyperkalemic patients are hypercatabolic, have renal dysfunction, or both [136]. It is doubtful whether organic acidemia in general is a cause of hyperkalemia at all [136]. Despite various hypotheses, the reasons for the disparate response of plasma potassium to lactic acidosis as compared to mineral acidosis remain unknown [132, 133].

Miscellaneous laboratory findings

Serum phosphate concentration is usually increased in patients with lactic acidosis [130, 137, 138]. The pathogenesis of this abnormality is unclear but in all probability reflects a release of inorganic phosphate from cells [139].

Hyperuricemia, another regular feature of lactic acidosis, results from decreased renal excretion of urate owing to competitive inhibition of tubule urate secretion by the lactate ion [140].

Finally, the plasma levels of certain amino acids are frequently increased in patients with lactic acidosis; the most notable increase corresponds to alanine, but proline, valine, lysine, and leucine are also increased substantially [141].

Causes of lactic acidosis

The causes of acquired lactic acidosis are catalogued in Table 3. Increased oxygen demand arises from intense voluntary exercise, which is certainly the most common cause of transient lactic acidosis. Substantial hyperlactatemia also occurs in generalized convulsions, the clinical equivalent of strenuous voluntary exercise. Tissue hypoxia is by far the most common cause of clinically significant lactic acidosis. The decrease in oxygen availability in the tissues results from reduced tissue perfusion, reduced arterial oxygen content, or both. On the other hand, a number of drugs and toxic substances can cause lactic acidosis in the absence of tissue hypoxia. Certain clinical disorders including diabetes mellitus, liver failure, sepsis, and neoplastic diseases predispose the patient to lactic acidosis. Detailed descriptions of the causes of lactic acidosis can be found elsewhere [3—7, 65, 135, 142]. Congenital lactic acidosis results from a variety of relatively rare, congenital enzymatic defects that affect the metabolism of pyruvate and lactate (Table 4).

Treatment

Management of lactic acidosis must be directed at prompt identification and aggressive treatment of the underlying cause or predisposing disorder whenever possible. Although judicious administration of alkali might be warranted to ameliorate the prevailing acidemia and thus possibly prevent catastrophic cardiovascular sequelae, such maneuvers should only be regarded as temporizing and adjunctive to cause-specific measures. Critical tissue hypoxia is the underlying culprit in most cases of clinical lactic acidosis; therapeutic measures therefore should be directed at augmenting oxygen delivery to the tissues. Indeed, focusing one’s efforts on merely treating the acidemia by alkali infusion can be likened to treating diabetic ketoacidosis with bicarbonate while neglecting insulin administration.
and/or hypercapnia; if necessary, artificial ventilation should be administered along with the ventilatory apparatus and the presence of critical hypoxemia. Extreme vigilance rather than administration of inotropic compounds along with vasoconstrictor agents in treating low-cardiac-output states; volume repletion. Every effort should be made to limit the use of such agents. Hypovolemia requires prompt extracellular fluid volume repletion. As a general rule, aggressive hemodynamic monitoring in an intensive care setting should be employed in directing therapeutic measures. Hypovolemia requires prompt extracellular fluid volume repletion. Every effort should be made to limit the use of vasoconstrictor agents in treating low-cardiac-output states; such agents aggravate the ischemia of peripheral tissues, worsening the severity of lactic acidosis and, in turn, prove counterproductive for the patient’s hemodynamic status [3, 4, 65, 143]. Rather, administration of inotropic compounds along with afterload reducing agents should be used. Extreme vigilance should be exercised for the early detection of fatigue of the myocardium to the adverse hemodynamic effects of these sympathetic mediators [149]. These observations, which suggest that pretreatment with α-adrenergic blocking agents sensitizes the myocardium to the adverse hemodynamic effects of acidemia, might have clinical relevance. It therefore should be emphasized that alkali therapy must be administered (1) to possibly avoid the superimposition of severe acidemia-related hemodynamic compromise on that already caused by the underlying disease; and (2) to reinstate cardiac reactivity to endogenous as well as exogenous catecholamines until the underlying condition can be identified and treated. Beyond its direct beneficial effects, such treatment provides a certain measure of safety against the superimposition of additional acidifying stresses; at values below 10 mEq/liter, a further small decline in plasma bicarbonate concentration and/or a small increment in PaCO₂ can cause catastrophic acidemia.

The utility of this time-honored, adjunctive measure in treating lactic acidosis has been criticized strongly in recent years [7, 144]. The outcome of lactic acidosis depends on the severity and reversibility of the underlying condition. If the cause cannot be corrected, lactic acidosis is virtually certain to advance, and the overall prognosis is grim. By contrast, successful treatment of the underlying condition leads to prompt improvement of the systemic acid-base status as the metabolism of the accumulated lactate generates an equivalent amount of endogenous bicarbonate. Typically, the mild to moderate degrees of lactic acidosis accompanying uncomplicated acute alcoholism, acute pulmonary edema, self-limited grand-mal seizures, and diabetic ketoacidosis abate with cause-specific and general supportive measures without the need for treatment of the acidosis itself.

### Alkali therapy

Cause-specific measures should be complemented by alkali therapy whenever the prevailing acidemia is severe, that is, when the pH falls below approximately 7.20 [3, 4, 6, 65, 145]. In the absence of a complicating element of respiratory acidosis (which, if present, warrants prompt efforts at increasing alveolar ventilation), such degrees of acidemia usually imply decrements in plasma bicarbonate concentration below 10 mEq/liter. Intravenous sodium bicarbonate should be administered to raise the plasma bicarbonate concentration to 10 to 12 mEq/liter and to maintain blood pH at or above 7.20. This recommendation is based on strong evidence indicating that severe acidemia—that is, pH below 7.20—exerts adverse hemodynamic effects, including impairment of cardiac contractility; reduction of cardiac output, arteriolar dilation, dangerous degrees of hypotension, and diminution in hepatic and renal blood flow; peripheral venoconstriction leading to central redistribution of blood volume, thereby augmenting the workload of a depressed myocardium; increased pulmonary vascular resistance leading to “shock lung”; and bradycardia and sensitization to various malignant ventricular arrhythmias [75, 113, 145-148]. Although acidemia stimulates the release of catecholamines, it also progressively attenuates the inotropic and chronotropic effects of these sympathetic mediators on the heart; thus, at pH values below 7.20, the direct negative inotropic effect of acidemia becomes dominant. A recent study, which revealed rapid desensitization and uncoupling of human β-adrenergic receptors in an in-vitro model of lactic acidosis, provides a plausible explanation for the characteristic lack of responsiveness to sympathetic mediators [149]. These observations, which suggest that pretreatment with β-adrenergic blocking agents sensitizes the myocardium to the adverse hemodynamic effects of acidemia, might have clinical relevance. It therefore should be evident that alkali therapy must be administered (1) to possibly avoid the superimposition of severe acidemia-related hemodynamic compromise on that already caused by the underlying disease; and (2) to reinstate cardiac reactivity to endogenous as well as exogenous catecholamines until the underlying condition can be identified and treated. Beyond its direct beneficial effects, such treatment provides a certain measure of safety against the superimposition of additional acidifying stresses; at values below 10 mEq/liter, a further small decline in plasma bicarbonate concentration and/or a small increment in PaCO₂ can cause catastrophic acidemia.

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### Table 3. Causes of acquired lactic acidosis

<table>
<thead>
<tr>
<th>Increased oxygen demand</th>
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<tbody>
<tr>
<td>1. Vigorous voluntary exercise</td>
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<tr>
<td>2. Generalized convulsions</td>
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<tr>
<td>Reduced oxygen availability (tissue hypoxia)</td>
</tr>
<tr>
<td>1. Reduced tissue perfusion</td>
</tr>
<tr>
<td>a. Shock or incipient shock</td>
</tr>
<tr>
<td>b. Acute left ventricular failure</td>
</tr>
<tr>
<td>c. Low cardiac output</td>
</tr>
<tr>
<td>2. Reduced arterial O₂ content</td>
</tr>
<tr>
<td>a. Asphyxia</td>
</tr>
<tr>
<td>b. Hypoxemia (PaO₂ &lt; 35 mm Hg)</td>
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<tr>
<td>c. Carbon monoxide poisoning</td>
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<tr>
<td>d. Very severe anemia</td>
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</tbody>
</table>

### Drugs and toxins

1. Ethanol
2. Biguanides (phenformin, metformin, buformin)
3. Various intoxications (e.g., methanol, ethylene glycol, salicylates, isoniazid, streptozocin, cyanide, nitroprusside, papaverine, paracetamol, naldixic acid)
4. Fructose, sorbitol, and xylitol
5. Epinephrine, norepinephrine

### Certain disorders

1. Diabetes mellitus
2. Liver failure
3. Sepsis
4. Neoplastic diseases
5. Renal failure
6. Iron deficiency
7. Short-bowel syndrome [D(—)-lactic acidosis]

### Idiopathic (spontaneous) lactic acidosis

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### Table 4. Causes of congenital lactic acidosis

<table>
<thead>
<tr>
<th>Defects in gluconeogenesis</th>
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<tbody>
<tr>
<td>1. Glucose-6-phosphatase deficiency (type I glycogen storage disease—von Gierke’s disease)</td>
</tr>
<tr>
<td>2. Fructose-bisphosphatase deficiency</td>
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<tr>
<td>3. Pyruvate carboxylase deficiency</td>
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</table>

<table>
<thead>
<tr>
<th>Defects in pyruvate oxidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pyruvate dehydrogenase deficiency</td>
</tr>
<tr>
<td>2. Oxidative phosphorylation defects</td>
</tr>
</tbody>
</table>

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* Adapted from Refs. 3, 4, and 65.
Fig. 8. Effect of 3 treatment options (no treatment, NaCl, or NaHCO₃) on hypoxemia-induced lactic acidosis in the dog. Left panel, changes in blood pH, and bicarbonate and lactate concentrations. Middle panel, production of gut lactate in animals treated with NaCl (clear bars) or NaHCO₃ (hatched bars). Right panel, hemodynamic changes in dogs receiving NaCl (open circles), NaHCO₃ (closed circles), or no treatment (open triangles) (from Ref. 51, copyright 1985 by the AAAS).

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47, 49–51, 142). Critics have argued that despite the established practice of vigorously treating severe lactic acidosis with sodium bicarbonate, mortality rates continue to be overwhelming. This is hardly a persuasive criticism in itself, since the underlying clinical entities—and root causes of the lactic acidosis—are often at grave severity. Alkali administration, although designed to potentially limit the gravity of the metabolic disturbances and their hemodynamic epiphenomena, is not expected to alter materially the course of the background disorder. As I already have emphasized, alkali is used as symptomatic treatment directed at severe, life-threatening acidemia; unless specific measures prove successful in relieving critical tissue hypoperfusion and hypoxia, the outcome is certain to be dismal.

Notwithstanding, an even more serious indictment of bicarbonate therapy has been handed down recently. Its critics charge that such therapy, far from being beneficial, actually exerts a detrimental effect on the course of lactic acidosis [7, 47, 49–51, 142]. I should like to review the chief pieces of experimental evidence supporting this charge.

Hypoxic lactic acidosis was induced in anesthetized dogs with fixed ventilation at an FiO₂ of 8%, with resulting PaO₂ values of 25 to 30 mm Hg [51]. The impact of three treatment options—no therapy, administration of 1 M NaCl at 2.5 mmol/kg/hr, or an equivalent amount of 1 M NaHCO₃—applied for 60 minutes was studied with regard to blood acid-base status, lactate metabolism, and systemic hemodynamics. As Figure 8 shows (left panel), animals in all three treatment groups experienced significant and similar decrements in pH and in plasma bicarbonate concentration during the experimental period. Moreover, although plasma lactate rose further in all groups after one hour of observation, the plasma lactate level was significantly higher in the NaHCO₃ group as compared to the remaining two groups. Skeletal muscle lactate production did not change significantly in any of the three groups. Gut lactate production remained unchanged in the groups receiving either no treatment or NaHCO₃, but it decreased significantly in the NaCl group (Fig. 8, middle panel). Hepatic lactate extraction remained unchanged in all three groups. The baseline mean aortic pressure and blood flow to the gut and liver were normal in all groups, whereas the cardiac index was 130% higher than that in the control animals. No significant changes in blood pressure and cardiac index were noted in the NaCl group during the course of treatment; by contrast, both these parameters fell in the animals receiving either no treatment or NaHCO₃, more so in the latter group (Fig. 8, right panel). Observations on the fate of blood flow to the gut and liver were not provided.

Although interesting, the relevance of these observations to clinical hypoxic lactic acidosis remains unclear. After all, the clinical entity is usually characterized by a decreased, not increased, cardiac output, and by decreased, rather than normal, blood pressure and organ perfusion. In addition, the pathogenesis of the augmentation in the plasma lactate level during NaHCO₃ treatment is somewhat puzzling when viewed in the context of the remaining evidence. Thus, the observed hemodynamic deterioration in the NaHCO₃ group apparently was insufficient to alter either lactate production by gut and skeletal muscle (the main sources of lactate in this model) or hepatic lactate extraction; nonetheless, an exaggerated aggravation of hyperlactatemia was noted. The investigators observed that although systemic acid-base status did not change during the course of the experiment, portal PCO₂ averaged 55 mm Hg after NaHCO₃ treatment—a value significantly higher than the 45 mm Hg after NaCl treatment. It is unclear to what extent the fixed ventilation of the animals affected this result.

Assuming that the basal values of this parameter did not differ between the NaCl- and NaHCO₃-treated groups, it is possible that this degree of portal hypercapnia might have produced excessive intrahepatic acidification, thus adversely affecting hepatic lactate uptake [70]. Yet extraction of lactate by liver remained unaltered by treatment in all groups. Furthermore, the disparate hemodynamic response between the NaCl- and NaHCO₃-treated groups of animals, despite the similarity in the amount of sodium and volume administered and the prevailing
Lactic acidosis, is intriguing but puzzling. No mortality was reported in any of the studied groups [51].

Using a different experimental model, the same group of investigators has produced evidence supporting their thesis of an adverse role of bicarbonate therapy in lactic acidosis [49]. Lactic acidosis was induced in diabetic dogs (having undergone surgical pancreatectomy) via infusion of intravenous phenformin. Following 90 minutes of treatment with either NaHCO$_3$ (1 mmol/min as a 1 M solution) or equivalent amounts of NaCl, systemic acid-base status remained unchanged in both groups; however, plasma lactate remained essentially unaltered in the NaCl-treated group but increased twofold in the NaHCO$_3$-treated animals. Lactate production by the gut doubled in the NaHCO$_3$ group and remained unchanged in the NaCl group; hepatic lactate uptake was unaffected by either treatment. Moreover, cardiac output, hepatic portal venous blood flow, and liver and erythrocyte intracellular pH all decreased in the NaHCO$_3$-treated animals but remained essentially unchanged in the animals given NaCl. However, muscle intracellular pH fell significantly in the NaCl, but not in the NaHCO$_3$, animals. After 4 hours of observation, the same mortality rate, 83%, was seen in both groups.

Again, the relevance of these experimental observations to the clinical disorder is uncertain. Intravenous phenformin in high doses is cardiotoxic and produces consistent decreases in cardiac output and systemic hemodynamics even before any changes in systemic acid-base status are detectable [96, 103]. Why NaHCO$_3$ administration would increase phenformin’s cardiotoxicity as compared to equimolar amounts of NaCl remains unclear. It has been suggested that because phenformin is a strong base, alkalization would intensify its diffusion across plasma membranes to intracellular binding sites [150].

Despite some inconsistencies, the evidence derived from these [49, 51] and other studies supporting the notion that bicarbonate administration or, in general, alkalization (relative or absolute) of body fluids stimulates lactate production is strong. Even massive doses of alkali may not succeed in substantially increasing the plasma bicarbonate level in malignancy-associated chronic lactic acidosis; indeed, a direct stoichiometric relationship between alkali administration and acid production, presumably by the malignancy, has been demonstrated [43, 44]. Moreover, there is a dynamic inverse relationship between the prevailing acidity of body fluids and either ketoacid production during ketoacidosis [12, 53, 54] or lactate production during hypoxemia-induced lactic acidosis [42]. A central difference between clinical hypoxic lactic acidosis and the hypoxemia-induced experimental counterpart is that the latter is a model of relatively controlled lactic acidosis in which the tendency toward continued lactate production apparently is compensated for by salutary hemodynamic adjustments as well as by the negative feedback exerted by the prevailing acidemia. By contrast, clinical hypoxic lactic acidosis is often a precipitous, explosive state in which the prevailing hemodynamic disarray gives rise to rapidly advancing lactic acidosis that, in turn, aggravates the circulatory compromise, diminishes hepatic and renal blood flow, and leads to more severe acidemia by accelerating production and decreasing uptake of lactate. It is thus clear that the negative feedback control system between systemic pH and organic acid production (suggested by experimental studies) is overriden during clinical hypoxic lactic acidosis, and that it gives way to an all-too-familiar lethal vicious cycle. Consequently, I reject any extrapolations of the existing experimental findings to the clinical setting, and I dispute the implication that the clinical use of bicarbonate should be abandoned. Nonetheless, the cumulative experimental evidence has reinforced the clinical dictum that bicarbonate should be administered wisely and cautiously.

I believe strongly, therefore, that judicious administration of bicarbonate along the guidelines given here is imperative. By returning systemic pH above the hemodynamically critical level, the clinician “buys time” that might allow control of the underlying causative illness. This relative alkalinization probably tends to increase lactate production, but this tendency should be offset by the improved state of tissue perfusion and, possibly, by the augmentation of hepatic lactate extraction. For this reason the clinician should take pains to use the smallest possible amounts of bicarbonate that will allow the return of systemic pH to hemodynamically safe levels [144].

No simple prescription exists for predicting the amount of bicarbonate necessary for achieving this goal in the individual patient. The only recourse available to the clinician is to perform an individual titration for each patient. Frequent monitoring of the acid-base status during bicarbonate therapy is essential for a cogent appraisal of additional bicarbonate requirements. That the goal of raising plasma bicarbonate by administering alkali can be achieved is well documented in many forms of clinical lactic acidosis, but widely variable rates of bicarbonate administration are required [3, 65]. This variability in dose requirement largely reflects the fact that the rate of lactic acid production is itself extremely variable. The clinician also should note that the apparent space of distribution for bicarbonate is enlarged in hypobicarbonatemic states [151]; thus, calculating bicarbonate doses on the basis of the normal value of the apparent space of distribution for bicarbonate of 40% to 50% body weight will underestimate the bicarbonate requirements. Indeed, when lactic acid production proceeds extremely rapidly, administered bicarbonate can fail to effect detectable changes in plasma bicarbonate concentration, the apparent space of distribution for bicarbonate becoming essentially infinite.

Administration of large and occasionally massive amounts of bicarbonate entails certain risks [3, 4, 65, 144]. Hypernatremia and marked hyperosmolality, and volume overload are common problems. Establishment of adequate diuresis with potent loop diuretics allows the infusion of large doses of alkali without superimposing iatrogenic circulatory compromise. On the other hand, if renal failure is present, peritoneal dialysis, hemodialysis, or hemofiltration may be required [152-154]. “Overshoot” alkalosis is an extremely undesirable complication of aggressive alkali dosing and underscores the strong recommendation for judicious bicarbonate administration; the swift transition from severe acidemia to alkalemia can produce tetany, altered mental status, generalized convulsions, and cardiac arrhythmias. These complications arise from two mechanisms. The first is the persistence of hyperventilation at levels inappropriate for the newly prevailing plasma bicarbonate concentration—either because of the known delay of medullary chemoreceptors to register the amelioration of acidity in the systemic circulation, or because of pH-independent stimuli of alveolar ventilation. Second, substantial elevations in plasma bicarbonate, occasion-
ally to frankly supranormal levels, can result from the composite effect of inordinately large exogenous alkali loads and from the regeneration of endogenous alkali from the metabolism of the accumulated lactate [3, 4, 65, 144]. Special attention should be paid to the level of plasma potassium to prevent hypokalemia during treatment, especially in patients receiving digitalis. Administration of bicarbonate produces increments in PaCO₂ that originate both from the release of CO₂ during the internal titration of bicarbonate and from pH-mediated suppression of alveolar ventilation [151, 155]. In patients with adequate gas exchange, this small effect is usually inconsequential, but it can be clinically important in patients with borderline oxygenation. Bicarbonate administration during resuscitative efforts in patients with cardiorespiratory arrest prior to the reestablishment of gas exchange may compound the often severe acidemia. This effect occurs due to complete retention of the CO₂ released during the rapid titration of infused bicarbonate by the ongoing lactic acid production [156]. Finally, concerns that the changes in pH induced by judicious alkali administration will produce a clinically significant decrease in tissue oxygen delivery by enhancing hemoglobin’s affinity for oxygen (Bohr effect) are unfounded [144, 157].

Additional measures

Insulin administration has been suggested as a therapeutic measure in diabetic patients with lactic acidosis, whether or not biguanide agents are involved [158, 159]. Theoretically, insulin could exert a beneficial effect by stimulating the oxidation of pyruvate through the pyruvate dehydrogenase (PDH) pathway and by limiting the flow of gluconeogenic amino acids to the liver. Although the evidence supporting this therapy is tenuous, it is probably advisable to include insulin in the treatment plan in this setting [4, 7, 160].

In a single patient with lactic acidosis in association with congestive heart failure, normal cardiac output, and normotension but clinical evidence of severe peripheral vasoconstriction, afterload reduction with sodium nitroprusside led to striking resolution of the metabolic abnormality [161]. No additional experience has been documented in such a setting, however, and the efficacy of this modality thus remains unproven. As I already have mentioned, afterload reducing agents should be used in preference to vasoconstrictors in the treatment of low-cardiac-output states [162, 163].

Methylene blue, an oxidizing agent, was proposed as treatment for lactic acidosis on the premise that it promotes the conversion of NADH to NAD⁺ and thus restores the cellular redox state; however, clinical application of this therapy has not proved successful [164].

Thiamine and lipoic acids, agents that act as coenzymes for the PDH enzyme complex, have been utilized occasionally in the treatment of patients with lactic acidosis, but experience is limited and therefore their utility remains uncertain [3, 4, 165]. However, thiamine represents remarkably effective specific therapy in patients with lactic acidosis in association with fulminant beriberi [165, 166].

Peritoneal dialysis, hemodialysis, or hemofiltration is a useful adjunctive measure in the management of patients with impaired renal function who require large alkali loads [152–154, 167, 168]. In addition to preventing or treating the associated volume overload, dialysis conveniently and reliably provides the needed alkali. Obviously, in view of impaired lactate utilization there is no sense in employing lactate-buffered dialysate. Acetate-buffered dialysate has been used effectively but should be avoided in patients with hemodynamic insufficiency or instability and in those prone to acetate intolerance. Bicarbonate-buffered peritoneal dialysis or hemodialysis has been employed successfully in the management of patients with lactic acidosis [153, 167, 168]. Its attractions include provision of bicarbonate as such, rather than of alkali precursors; avoidance of the risk of further hypobicarbonatemia due to an imbalance between the diffusive losses of bicarbonate in the dialysate and alkali generation from the acetate; the prevention of acetate dialysis-induced hypoxemia; and probably a better hemodynamic profile. Bicarbonate-buffered peritoneal dialysis is particularly suitable in the management of patients with circulatory failure. In addition, dialysis can remove drugs and toxins such as methanol and salicylates; hemodialysis does not remove appreciable quantities of phenformin, however [169]. Finally, dialysis can remove lactate from the body fluids and thus often prevent rebound hyperbicarbonatemia. Recent evidence suggests that hyperlactatemia per se (independent of changes in systemic pH) exerts adverse effects on myocardial contractility. In-vitro studies have shown that increased lactate concentration impairs frog atrial muscle contractility [170], leads to swelling and reduction in oxidative phosphorylation in isolated beef heart mitochondria [171], and inhibits glucose utilization by ischemic rat myocardium at the glyceraldehyde 3-phosphate dehydrogenase step [172]. In addition, hyperlactatemia per se decreased exercise tolerance in normal rats [173]. By contrast, increased lactate concentration did not decrease the contractility of the papillary muscle of the cat [147]. If an adverse hemodynamic effect of hyperlactatemia were confirmed, it would provide a plausible explanation for evidence of hemodynamic deterioration following bicarbonate administration independent of changes in systemic pH [49, 51, 96]. Such confirmation would support therapeutic strategies specifically aimed at reducing plasma lactate.

Finally, dichloroacetate (DCA) is an exciting investigational agent that holds promise as a therapeutic tool in lactic acidosis. Because DCA stimulates PDH activity in many tissues, it augments the oxidation of pyruvate to acetyl-CoA [174, 175]. This effect directs lactate, alanine, and pyruvate into the formation of carbon dioxide, fatty acids, and ketone bodies (Fig. 1) and consequently inhibits hepatic gluconeogenesis from these 3-carbon precursors. Decreases in the plasma levels of lactate, alanine, pyruvate, and glucose occur, whereas plasma ketone-body concentration increases [176–179]. In nonacidotic diabetic patients, DCA decreases lactate levels [180], and it can improve the disordered lactate metabolism in experimental lactic acidosis produced by functional hepatectomy, phenformin administration, exercise, epinephrine infusion, or hypoxemia [52, 175, 177, 181–184]. In one study [52], administration of DCA to diabetic dogs with phenformin-induced lactic acidosis significantly lowered plasma lactate and significantly raised plasma bicarbonate concentration and pH as compared to a similarly prepared group of animals that received NaHCO₃ treatment (Fig. 9). Moreover, whereas treatment with NaHCO₃ could not arrest the progressive fall in the cardiac index, treatment with DCA returned cardiac index to the control value (Fig. 10); mortality during a 4-hour treatment period with either
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modality averaged 91% in dogs receiving NaHCO₃, as compared with 22% in dogs treated with DCA [52]. It is interesting that treatment with DCA resulted in increased liver lactate uptake in association with increased liver intracellular pH; thus, the decreased hyperlactatemia noted could be the composite effect of decreased lactate production due to improved cardiac performance and increased lactate utilization. These authors made similar observations about DCA treatment in dogs with functional hepatectomy and lactic acidosis [52]. The decisively better outcome of DCA therapy compared to NaHCO₃ administration in this study often has been quoted as a potent argument against the utility of NaHCO₃ therapy [7, 49, 51]. I find this argument unconvincing, however. To attempt to draw a parallel, I do not think it valid to conclude that NaHCO₃ has no role in the management of diabetic ketoacidosis on the basis of improved outcome of patients treated with insulin as compared to outcome in those treated with alkali alone.

Two studies have provided evidence in support of a beneficial role of DCA in the treatment of hypoxemia-induced lactic acidosis in rats and dogs [183, 184]. Unlike treatment with sodium chloride, DCA administration resulted in attenuation of the hyperlactatemia, hypobicarbonatemia, and acidemia in hypoxemic rats; moreover, the animals receiving DCA maintained higher mean blood pressures and greater rates of urine flow and sodium excretion [183]. Similarly, administration of DCA to hypoxemic dogs significantly increased plasma bicarbonate and pH, and stabilized plasma lactate concentration; by contrast, progression of hypobicarbonatemia, acidemia, and hyperlactatemia was noted in the group receiving sodium chloride. Additionally, animals given DCA, but not those given NaCl, experienced increased hepatic lactate extraction, decreased liver and muscle lactate levels, and elevated muscle intracellular pH [184].

Some data on DCA are available in humans as well. Thirteen gravely sick, hypotensive patients with lactic acidosis in association with various predisposing illnesses (such as renal and hepatic disease, sepsis, leukemia or lymphoma, arrhythmias) were given DCA [185]. Of the 11 who did not receive concurrent treatment with bicarbonate, each of 7 experienced at least a 20% decrease in plasma lactate (Fig. 11); this subgroup had a significant, mean reduction of lactate of 80% (from an average value of 14.2 to 2.8 mEq/liter) and significant increases in plasma bicarbonate and pH (from 14 to 21 mEq/liter and from 7.24 to 7.39, respectively). The fall in plasma lactate persisted for several hours after treatment with DCA was terminated. In 10 of the 13 treated patients, increases in systolic blood pressure of 10 to 40 mm Hg were noted soon after the initiation of DCA treatment; in 4 patients whose cardiac output was monitored, the increase in systolic blood pressure was accompanied by a significant mean increase in cardiac output of 21% (from 6.2 to 8.4 liters/min). These findings are in accord with previous observations indicating that DCA improves cardiac function in dogs with experimentally induced myocardial ischemia or lactic acidosis [52, 186]. Because the drug is known to augment aerobic oxidative metabolism in cardiac tissue [187], it

Fig. 9. Effect of dichloracetate (DCA) or NaHCO₃ treatment on blood acid-base composition and lactate level during phenformin-induced lactic acidosis in the diabetic dog (reproduced from The Journal of Clinical Investigation, 1982, vol. 70, pp. 853-862 by copyright permission of The American Society for Clinical Investigation).

Fig. 10. Effect of dichloracetate (DCA) or NaHCO₃ treatment on cardiac index during phenformin-induced lactic acidosis in the diabetic dog (reproduced from The Journal of Clinical Investigation, 1982, vol. 70, pp. 853-862 by copyright permission of The American Society for Clinical Investigation).
might improve myocardial contractility. These hemodynamic effects might complement the metabolic action of DCA in decreasing the plasma lactate level. Unfortunately, despite these favorable metabolic and hemodynamic consequences, all but one of the patients in that study died of their underlying disease [185]. Additional human experience with DCA includes observations in 8 adult patients with severe lactic acidosis in association with biguanide therapy, hypotension, sepsis, or malignancy; 3 of the 8 had a greater than 20% reduction in plasma lactate levels, and 2 of the 3 survived [185, 188, 189]. Moreover, of 7 children with congenital forms of lactic acidosis, DCA produced biochemical and/or clinical improvement in 4 [190–194]. In general, no appreciable drug toxicity has been observed in studies of short-term administration of DCA [180, 185, 188, 189, 190–193, 195]. By contrast, serious side effects have been noted with long-term administration, including limb paralysis, cataracts, increased urinary oxalate excretion, tecticular degeneration, neuropathy, mutagenicity, and changes in the white matter of the central nervous system [175]; obviously these findings make DCA unsuitable for extended use [196].

One would hope that the encouraging results of the human studies coupled with those from experimental models would prompt prospective controlled trials of this agent to define its proper role in the management of lactic acidosis. In one sense, augmentation of lactate utilization during lactic acidosis by DCA resembles restoration by insulin of the disordered metabolism during diabetic ketoacidosis. Although the underlying disease is clearly the main determinant of the eventual outcome of the patient, alleviation of the lactic acidemia by DCA or an analogue coupled with judicious administration of alkali for severe acidemia should at least allow the clinician the opportunity to apply other therapeutic measures directed at the inciting disorder. It is currently unknown whether the beneficial effect of DCA on lactic acidosis would be translated into a favorable alteration of the natural course of the underlying disease and thus to decreased mortality. Indeed, the so-far disappointing survival data with DCA therapy should restrain the critics of NaHCO3 therapy who have denounced bicarbonate therapy on the charge that high mortality rates from lactic acidosis persist despite alkali provision.

Conclusion

Advances in the understanding of lactate metabolism have allowed insights into the pathogenesis of lactic acidosis. Despite this progress, however, the development of hyperlactatemia remains an index of the gravity of the patient’s condition and is commonly the harbinger of the patient’s impending demise. The mainstay of therapy for lactic acidosis continues to center around efforts to improve or eradicate the underlying cause or predisposing condition, coupled with the careful and restrained administration of sodium bicarbonate to prevent or treat critical acidemia. Clinical research should continue with the promising investigational agent DCA to define its proper role in the treatment of the various forms of lactic acidosis.

Questions and answers

DR. JOHN T. HARRINGTON: You alluded to the hyperlactatemia of respiratory alkalosis. Could you be a little more quantitative on this issue?

DR. MADIAS: Several investigators have attributed a major component of the reduction in plasma bicarbonate during acute respiratory alkalosis to the accumulation of lactic acid (on the order of 50% to 75%). This conclusion was based on studies in anesthetized animals subjected to mechanical ventilation sufficient to achieve severe hypocapnia (PaCO2 less than 15 mm Hg) [18, 197, 198]. By contrast, studies in unanesthetized animals and in humans subjected to milder degrees of hypocapnia (PaCO2 of 20 to 30 mm Hg) have reported only a slight and short-lived elevation in plasma lactate concentration (in the range of 0.5 to 1.5 mEq/liter). Indeed, the hyperlactatemia vanishes within 8 hours despite the persistent hypocapnia [23, 24, 28]. Additional studies in anesthetized animals and humans confirm the presence of only a mild degree of hyperlactatemia during moderate grades of acute respiratory alkalosis [22, 25–27]. Moreover, during chronic hypocapnia, plasma lactate concentration is within normal limits even in the presence of associated hypoxemia [29–34]. The large increase in lactate observed by some probably reflected a degree of circulatory insufficiency consequent to the cardiovascular effects of anesthesia and vigorous mechanical ventilation.

DR. VINCENT J. CANZANELLO (Division of Nephrology, NEMCH): Do changes in hormones affecting the transcellular distribution of potassium account for the lack of hyperkalemia during experimental lactic acidosis?

DR. MADIAS: To my knowledge, this attractive possibility has not been investigated systematically. In this regard, recent observations have uncovered a role of the endocrine pancreas to account for the different response of plasma potassium to experimental ketoacidosis (normokalemia or hypokalemia) as compared to mineral acidosis (hyperkalemia): Whereas ketoacidosis was associated with hyperinsulinemia, HCl-induced acidosis was accompanied by elevated glucagon levels [199].
Dr. Richard L. Tannen (Director, Division of Nephrology, the University of Michigan Medical Center, Ann Arbor, Michigan): Dr. Madias, I agree with your comments and your recommendations about bicarbonate administration in patients with acute lactic acidosis. However, in considering the adverse effects on the circulation that clearly have been shown to attend treatment with bicarbonate in studies of experimental lactic acidosis [49, 51], I would like to propose that factors other than bicarbonate itself or changes in the hydrogen ion concentration might be at fault. It seems quite possible, for example, that these adverse effects might be caused by metabolic intermediates, the concentrations of which are stimulated by the administration of bicarbonate.

Dr. Madias: I agree that changes in acid-base status consequent to bicarbonate administration cannot explain the adverse hemodynamic effects reported in these studies [49, 51, 96, 103]. These reports have implied that the hemodynamic deterioration might arise from bicarbonate-induced intracellular acidosis. But this suggestion runs counter to available experimental evidence. First, whole-body intracellular pH increases following sodium bicarbonate infusion in the dog [200]. Second, cardiac and skeletal muscle intracellular pH of the rabbit increases in response to sodium bicarbonate infusion [201]. Moreover, myocardial contractility and cardiac output increase consistently following an intravenous or intracoronary infusion of sodium bicarbonate in the dog [112, 202, 203]. Your suggestion that one or more metabolic intermediates of stimulated glycolysis might be at fault is an attractive one and deserving of future investigation.

I should like to reemphasize the important insights in the physiology of lactic acid metabolism that these studies have provided [47—51]. The findings on the hemodynamic effects of bicarbonate treatment have raised important questions that merit further investigation. On the other hand, I maintain strongly at present that any extrapolation from the findings of these studies to patients is inappropriate. I have presented in detail the reasons for my position, chief of which are the questionable relevance of the experimental models to the clinical circumstances and the strong evidence indicating that severe acidemia triggers a series of adverse hemodynamic effects. I should add that regarding mortality, even no treatment at all appears to make no difference in these experimental models [49, 51]. I suggest that leaving severe lactic acidosis untreated is not a viable option in the clinical setting.

Dr. Andrew S. Levey (Division of Nephrology, NEMCH): Could you expand your comments about the potential toxicity of the lactate ion itself?

Dr. Madias: Our thinking has been dominated by the concept that the deleterious effects of lactic acidosis stem exclusively from the outpouring of hydrogen ions into the body fluids, whereas the lactate ions themselves are thought to be innocuous. Yet, some [170—173] but not all [147] of the recent pieces of evidence I have reviewed cast doubt on this concept and argue for a direct adverse effect of the lactate ion on myocardial contractility. I believe that this may be an issue of great importance, and it certainly warrants intensive investigation.

Dr. Canzanello: A number of recent studies suggest that administration of either NH₄Cl or NaHCO₃ induces a substantial decrease or rise, respectively, of the hyperlactatemia of exercise. Have these maneuvers affected exercise tolerance?

Dr. Madias: Careful studies have documented that treatment with oral NH₄Cl is associated with markedly diminished endurance during high-intensity, cycle-ergometer exercise; by contrast, treatment with oral NaHCO₃ led to enhanced endurance [41, 204, 205]. In contrast to these studies of prolonged exercise, changes in acid-base status induced by these maneuvers have not produced appreciable effects on maximal power output and fatigue during short-term, maximal exercise [39]. In both types of exercise however, NH₄Cl-induced acidosis has decreased the post-exercise plasma lactate concentration, whereas NaHCO₃ has augmented the hyperlactatemia. In addition to inducing changes in net lactate production, alterations in acid-base status probably influence plasma lactate levels by affecting the rate of lactate efflux from muscle; several observations suggest that acidosis impairs and alkalosis promotes the efflux of lactate [206—208].

Dr. Ronald D. Perrone (Division of Nephrology, NEMCH): Would you comment on the treatment of the lactic acidosis associated with malignancies?

Dr. Madias: Although lactic acidosis in the company of circulatory insufficiency, liver failure, or sepsis is a common occurrence in the preterminal stage of many neoplastic diseases, it occasionally develops in the absence of such factors and may pursue a relatively chronic course [3, 4, 65]. Such a “paraneoplastic” metabolic derangement usually is seen in patients with leukemia or other myeloproliferative disorders; it also occurs in association with lymphomas and with several solid tumors. Overproduction of lactic acid by the neoplastic tissue has been implicated in the pathogenesis of this syndrome. Because leukocytes and neoplastic cells have a high glycolytic rate, increased production of lactate would be expected if the tumor burden were large. In some instances, lactic acidosis has developed only in association with high-glucose, total parenteral nutrition. In addition, rapidly proliferating tumors may suffer from an inadequate blood supply, producing severe hypoxia and an increased dependence on anaerobic glycolysis. Also, oxygenation can be decreased in a tightly packed bone marrow, thus favoring the accumulation of lactate. The pathogenetic role of lactate overproduction is supported by the observation that lactic acidosis resolves with successful treatment of the underlying malignancy [209—211]. Furthermore, a role for hepatic underutilization of lactate has been suggested in some cases of lactic acidosis in patients with massive replacement of the liver by tumor [3, 4, 65, 211].

With regard to alkali administration, the general restraint I suggested for its use in hypoxic states should be exercised also in this setting. As I have mentioned, even massive doses of alkali may not succeed in substantially increasing plasma bicarbonate in these patients because of a direct stoichiometric relationship between alkali administration and acid production, presumably by the malignancy [43, 44]. In addition to the well-known risks stemming from the administration of large bicarbonate loads, aggravation of the prevailing cachexia may also occur in the patient with cancer and poor dietary intake because the body's glycogen and protein stores may be depleted as a consequence of stimulated lactate production [44]. Consequently, such patients should receive the smallest possible amount of bicarbonate that is sufficient to prevent or treat life-threatening
acidaemia and always in the company of an adequate nutrient supply.

Dr. Harrington: What is your opinion regarding the phenomenon referred to as idiopathic lactic acidosis?

Dr. Madias: As you know, the terms "idiopathic" and "spontaneous" have been applied to cases of lactic acidosis that develop presumably in the absence of evidence for an established cause or associated condition [1, 2, 212]. Although as yet unrecognized cause(s) may be at play, well-founded reservations have been raised about the validity of this designation [4, 213]. Close scrutiny of published reports suggests that many such patients probably suffered from circulatory insufficiency too subtle for clinical detection [135, 213, 214]. In addition, a substantial fraction of patients classified as having "idiopathic" lactic acidosis was taking phenformin. Indeed, in the great majority of cases, the clinical picture quickly advanced to overt circulatory collapse, often in the company of sepsis or liver failure, and had a catastrophic outcome [4, 213, 216]. It therefore appears that the development of so-called idiopathic lactic acidosis is usually a warning sign presaging the appearance of circulatory failure. Although I have included it in Table 3 for completion, I suspect that idiopathic lactic acidosis does not exist.

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