L-lactic acidosis: pathophysiology, classification, and causes; emphasis on biochemical and metabolic basis

Kamel S. Kamel[1,2], Man S. Oh[3] and Mitchell L. Halperin[1,2]

[1]Renal Division, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; [2]Keenan Research Center in the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada; and [3]State University of New York, Downstate Medical Center, Brooklyn, New York, USA

L-lactic acidosis (L-LA) is the most common cause of metabolic acidosis in the critical care setting, which has been associated with a large increase in mortality. The purpose of this article is to provide clinicians with an overview of the biochemical and metabolic background required to understand the different pathophysiological mechanisms that may lead to the development of L-LA. We propose a classification based on whether the pathophysiology of L-LA is due predominantly to increased production or decreased removal of L-lactic acid. In this article, we provide an overview of the biochemical and metabolic aspects of glucose oxidation, the production and removal of L-lactic acid, and a discussion of the pathophysiology of the various causes of L-LA.

Kidney International (2019) ■, ■–■; https://doi.org/10.1016/j.kint.2019.08.023

KEYWORDS: glycolysis; hypoxia; L-lactic acidosis; oxidative phosphorylation

L-lactic acidosis (L-LA) is defined by a blood L-lactate level of >5 mmol/l. A blood pH of <7.35, and a plasma bicarbonate concentration of <20 mmol/l are commonly included in this definition; the absolute value of these parameters, however, is determined by coexisting respiratory and/or metabolic acid–base disorders.[1,2] The accumulation of L-lactic acid in the extracellular fluid leads to the loss of bicarbonate anions (HCO_3^-) and the gain of L-lactate anions. The presence of new anions in plasma is detected by an increase in the plasma anion gap (P_{AG}).[3] A significant increase in blood L-lactate level may be present, however, without an appreciable increase in the P_{AG}.[4,5] This may reflect the wide range of what is considered a normal value of the P_{AG}, failure to correct the baseline value of the P_{AG} for the plasma albumin concentration, as hypoalbuminemia is frequently present in these patients, and/or perhaps a change in the net negative anionic valence on plasma albumin.[6]

L-LA is the most common cause of metabolic acidosis in hospitalized patients, particularly in the critical care setting. L-LA is associated with a large increase in mortality[7–10] that directly correlates with the blood lactate level.[7,11,12] L-LA is not a diagnosis but a manifestation of deranged glucose and energy metabolism that may be the result of a number of disorders. The increased mortality associated with L-LA likely reflects the severity of cellular dysfunction due to deranged energy metabolism. Severe acidemia may also lead to cardiovascular collapse.[13–15] This may be due to the effects of the binding of hydrogen ions (H^+) to cellular proteins, impairing their functions.

Almost 50 years ago, Cohen and Woods proposed a classification of L-LA into type A (where there is clinical evidence of tissue hypoxia) and type B (where there is no clinical evidence of tissue hypoxia).[16,17] The assumption made in this classification is that tissue hypoxia can be detected with the usual clinical parameters used to assess global oxygen delivery. A number of diverse disorders that may lead to the development of L-LA via different pathophysiological mechanisms are lumped together into 1 category: type B L-LA.

L-LA may be caused by an increased rate of production or a decreased rate of removal of L-lactic acid. Although both mechanisms are involved in many cases, usually one predominates. We, therefore, propose a classification based on whether the pathophysiology of L-LA is due predominantly to increased production or decreased removal of L-lactic acid.

Correspondence: *Kamel S. Kamel, University of Toronto, Division of Nephrology, St. Michael's Hospital, Toronto, Ontario, M5B 1W8, Canada. E-mail: kamel.kamel@utoronto.ca*

Received 10 April 2019; revised 1 August 2019; accepted 20 August 2019; published online 6 September 2019

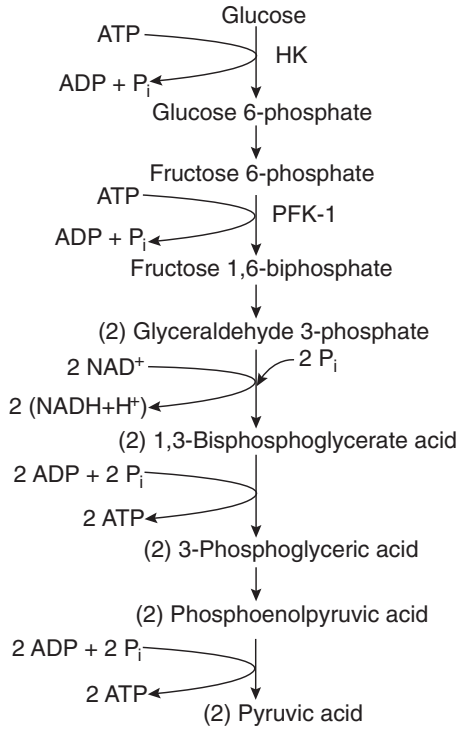

Figure 1 | Glycolysis. The process of glycolysis can be viewed as occurring in 2 stages. In the first stage, glucose is phosphorylated and split into 2 molecules of glyceraldehyde 3-phosphate; 2 molecules of adenosine triphosphate (ATP) are consumed in this stage. In the second stage, the 2 molecules of glyceraldehyde 3-phosphate are converted into 2 molecules of pyruvate, with concomitant regeneration of 4 molecules of ATP. Hence, there is net regeneration of 2 molecules of ATP. Two molecules of nicotinamide adenine dinucleotide (NAD^+) are reduced to 2 molecules of $NADH+H^+$, in the step in which 2 molecules of glyceradehyde 3-phosphate are made into 2 molecules of 1,3 bisphosphoglycerate. The enzyme phosphofructokinase-1 (PFK-1), which catalyzes the irreversible conversion of fructose 6-phosphate to fructose 1-6 bisphosphate, is a key regulatory enzyme in glycolysis. ADP, adenosine diphosphate; HK, hexokinase; P_i, inorganic phosphate.

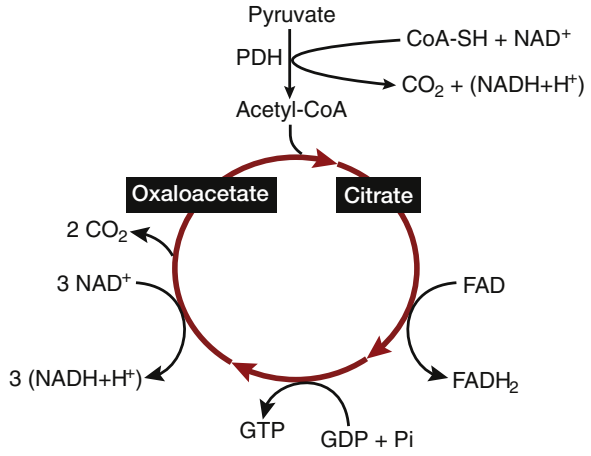

Figure 2 | The formation of acetyl-CoA and the citric acid cycle. Pyruvate is transported into the mitochondria where it is converted into acetyl-CoA in the presence of CoA-SH (coenzyme A with functional sulfhydryl group), a reaction catalyzed by the enzyme pyruvate dehydrogenase (PDH). One molecule of CO_2 is produced, and 1 molecule of nicotinamide adenine dinucleotide $(NAD)^+$ is reduced to $NADH+H^+$. Acetyl-CoA combines with oxaloacetate to form citric acid. Citric acid then undergoes a series of reactions in the citric acid cycle, which leads to the oxidation of the acetyl group to 2 molecules of CO_2 and the regeneration of oxaloacetate. In these reactions, 3 molecules of NAD^+ are reduced to $NADH+H^+$, 1 molecule of flavin adenine dinucleotide (FAD) is made into its hydroxyquinone form $FADH_2$, and 1 molecule of guanosine triphosphate (GTP; equivalent to adenosine triphosphate) is regenerated. Since 2 molecules of pyruvate are made from 1 molecule of glucose, in total, 8 molecules of $NADH+H^+$, 2 molecules of $FADH_2$, and 2 molecules of GTP are produced from 1 molecule of glucose in the process of the formation of 2 molecules of acetyl-CoA from 2 molecules of pyruvate and the oxidation of 2 molecules of acetyl-CoA in the citric acid cycle. GDP, guanosine diphosphate; P_i, inorganic phosphate.

We begin this discussion with a synopsis of the biochemistry of glucose oxidation. This is followed by a discussion of the biochemical and metabolic basis for the development of L-LA. With this background, we proceed to a discussion of the pathophysiology of the various causes of L-LA.

BIOCHEMISTRY OF GLUCOSE OXIDATION IN SKELETAL MUSCLES

Oxidation of glucose occurs in 4 steps; glycolysis, the formation of acetyl- CoA, the citric acid cycle, and the electron transport chain (ETC).

Glycolysis

In this process, which takes place in the cytosol, 1 molecule of glucose is split into 2 molecules of pyruvate[18] (Figure 1). Two molecules of adenosine triphosphate (ATP) are utilized in the initial reactions catalyzed by hexokinase and phosphofructokinase-1 (PFK-1). Four molecules of ATP are ultimately generated; hence, there is net generation of 2 molecules of ATP per each molecule of glucose metabolized. In the metabolic reactions of glycolysis, 2 molecules of nicotinamide adenine dinucleotide (NAD^+) are converted to their reduced form $NADH+H^+$ (in this reaction, 2 electrons but only 1 H^+—that, is a hydride ion (H^-)—are transferred to each NAD^+, forming NADH plus a free H^+).

While it is common to use the terms aerobic and anaerobic glycolysis, since there is no molecular oxygen utilized in this step of glucose oxidation, all glycolysis is in fact anaerobic.

The process of glycolysis results in the formation of pyruvic acid. The production of a proton first occurs when glycerol aldehyde-3 phosphate (an aldehyde) is converted to 1,3 bisphosphoglyceric acid (an acid). The proton, however, is consumed as the carboxylic acid moiety of this compound forms an anhydride bond with phosphoric acid. Net proton production occurs when this anhydride bond is broken at the next step with the conversion of 1,3 bisphosphoglyceric acid to 3-phosphoglyceric acid, which is subsequently converted to pyruvic acid. Because the pH in cells is ~7.1 and the pK of pyruvic acid is ~2.8, pyruvic acid donates its H^+, resulting in formation of pyruvate anions. These H^+ are removed when the pyruvate anions are metabolized to neutral end products

($CO_2 + H_2O$ or glucose/glycogen). Hence, there is a net gain of H^+ only when pyruvate anions accumulate in the cytosol and are converted to L-lactate anions. L- lactate anions, with their H^+, exit cells on the monocarboxylic acid cotransporter, causing acidosis in the extracellular fluid compartment.

Formation of acetyl-CoA

Pyruvate crosses the outer mitochondrial membrane, through the voltage-dependent anion channel,[19] and the inner mitochondrial membrane, through the mitochondrial pyruvate carriers MPC1 and MPC2.[20]

In the mitochondrial matrix, pyruvate is metabolized by the multiprotein enzyme complex pyruvate dehydrogenase (PDH) (Figure 2).[21] The activated form of thiamine—thiamine pyrophosphate—is an important cofactor for PDH. Pyruvate is first irreversibly decarboxylated (1 molecule of CO_2 is produced in this process); then 2 hydrogen atoms are removed, creating acetyl-CoA. One NAD^+ is reduced to $NADH+H^+$.

The citric acid cycle

Acetyl-CoA (a 2-carbon compound) combines with oxaloacetate (a 4-carbon compound) to form citrate (a 6-carbon compound; Figure 2). Citrate then enters the citric acid cycle (also called the tricarboxylic acid cycle or the Krebs cycle),[22] where it undergoes a series of reactions, catalyzed by a number of enzymes, leading to the oxidation of the acetyl group into 2 CO_2 molecules, and the regeneration of the 4-carbon molecule oxaloacetate. The source of oxygen atoms in the molecules of CO_2 is not molecular O_2 but is derived from water molecules. As the acetyl group is metabolized, the released electrons reduce 3 molecules of NAD^+ to 3 molecules of $NADH+H^+$, and 1 molecule of flavin adenine dinucleotide (FAD) to its hydroxyquinone form $FADH_2$. In this process also, 1 molecule of guanosine diphosphate and 1 molecule of inorganic phosphate (P_i) are made into 1 molecule of guanosine triphosphate (equivalent to 1 molecule of ATP).

The ETC and oxidative phosphorylation

The ETC consists of a sequence of linked oxidation-reduction reactions, in which electrons are transferred from an electron donor to an electron acceptor, with O_2 as the final electron acceptor[22] (Figure 3).

The ETC consists of 4 large, multi-protein complexes (I–IV). These complexes consist of electron carriers including: (i) flavin-containing dehydrogenases; (ii) iron as part of peptides containing iron–sulfur clusters; (iii) iron as part of a porphyrin prosthetic group of heme in the cytochromes; and (iv) copper in complex IV. Unlike the iron in the heme of hemoglobin or myoglobin, which remains as Fe^{2+} during oxygen transport, iron in the peptides containing iron–sulfur clusters and in the heme of cytochromes can be in an oxidized (Fe^{3+}) or a reduced (Fe^{2+}) form.

In addition to these stationary complexes, there are 2 electron carriers that are not tightly associated with one individual complex but function as shuttles between them;

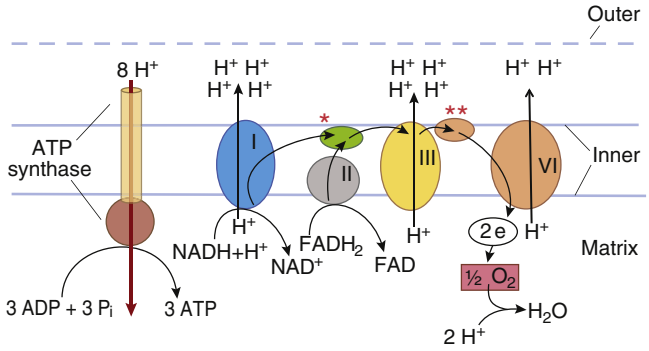

Figure 3 | The electron transport chain and oxidative phosphorylation. The horizontal structure represents the inner mitochondrial membrane with its inner and outer bilayers. The dashed line represents the outer mitochondrial membrane. The electron transport chain consists of 4 large multi-protein complexes (I–IV), and 2 electron carriers that function as shuttles between the complexes—coenzyme Q (denoted by *) and cytochrome C (denoted by **). The electron transport chain consists of a sequence of linked oxidation-reduction reactions, in which electrons are transferred from an electron donor to an electron acceptor, and finally to O_2. Complexes I, III, and IV use the energy generated from electron flow to pump H^+ from the mitochondrial matrix to the intermembrane space. The accumulation of protons in the intermembrane space creates a large electrochemical gradient favoring H^+ re-entry into the mitochondrial matrix. This electrochemical energy is recaptured as H^+ flows through the adenosine triphosphate (ATP) synthase and is coupled to the regeneration of ATP from adenosine diphosphate (ADP) and inorganic phosphate (P_i). e, electron; FAD, flavin adenine dinucleotide; $FADH_2$, hydroxyquinone form of FAD; NAD^+, nicotinamide adenine dinucleotide; $NADH+H^+$, reduced form of NAD^+.

ubiquinone/ubiquinol (reduced form), also known as coenzyme-Q, and cytochrome C. Coenzyme-Q carries electrons from complexes I and II to complex III. Cytochrome C shuttles electrons between complex III and complex IV.

$NADH+H^+$ can only donate electrons in pairs, whereas the iron-containing redox cofactors can only accept single electrons. In complex I, this switch from a 2-electron carrier to a 1-electron carrier is achieved by flavin nucleotides, which can accept or donate a single electron or a pair of electrons. The 2 electrons and 2 H^+ are transferred to FAD, reducing it to $FADH_2$. The electrons are then passed into the iron of the peptides containing iron–sulfur clusters, while the 2 H^+ leak into the mitochondrial matrix. The 2 electrons are subsequently transferred to ubiquinone, reducing it to ubiquinol. Ubiquinol in turn passes them to complex III.

Complex II oxidizes succinate to fumarate (hence, it is also known as succinate dehydrogenase); 2 electrons and 2 H^+ are transferred to FAD, reducing it to $FADH_2$, which in turn transfers the electrons via the iron–sulfur clusters to ubiquinone.

Complex III accepts electrons from ubiquinol, oxidizing it to ubiquinone, and delivers them to cytochrome C. Complex IV accepts the electrons from cytochrome C. This complex contains 2 heme groups and 3 copper ions that hold an oxygen molecule very tightly until it is completely reduced. Reduced

Table 1 | Metabolic products of glucose oxidation

	NAD^+ to $NADH+H^+$	FAD to $FADH_2$	CO_2	H_2O	ATP
Glycolysis	2				2
Formation of acetyl-CoA	2		2		2
Citric acid cycle	6	2	4		
Electron transport chain				12	30.5

ATP, adenosine triphosphate; CoA, coenzyme A; FAD, flavin adenine dinucleotide; $FADH_2$, hydoxyquanine form of FAD; NAD^+, nicotinamide adenine dinucleotide; $NADH+H^+$, reduced form of NAD^+.
The numbers in the table are per molecule of glucose. In total, 10 molecules of $NADH+H^+$ and 2 molecules of $FADH_2$ are produced per 1 molecule of glucose. Approximately 2.7 molecules of ATP are produced when 1 molecule of $NADH+H^+$ is oxidized to NAD^+, and ~1.6 molecules of ATP are produced when 1 molecule of $FADH_2$ is oxidized to FAD. Thus, a total of ~30.5 molecules of ATP are regenerated per molecule of glucose in oxidative phosphorylation. Adding to that, 2 molecules of ATP are generated in glycolysis, and 2 molecules of ATP are generated in the oxidation of 2 molecules of pyruvate in the citric acid cycle (assuming that guanosine triphosphate and ATP are equivalent); there is net regeneration of approximately 34.5 molecules of ATP from the oxidation of 1 molecule of glucose. While 12 molecules of H_2O are produced in the electron transport chain, 6 molecules of H_2O are consumed in glycolysis and the citric acid cycle; hence, only 6 molecules of H_2O are produced per 1 molecule of glucose oxidized.

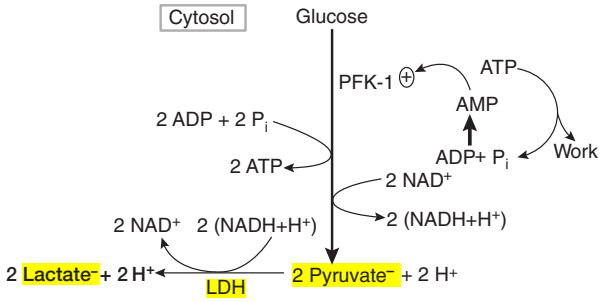

Figure 4 | The production of L-lactic acid. In the cytosol, the energy needed to perform biological work is provided by hydrolysis of the terminal high-energy bond of adenosine triphosphate (ATP). This results in the formation of adenosine diphosphate (ADP). ADP enters the mitochondria on the adenine nucleotide translocator in exchange for ATP. Under conditions of a diminished rate of regeneration of ATP, the concentration of ADP in the cytosol rises. Two molecules of ADP are converted back to 1 molecule of ATP in a near-equilibrium reaction catalyzed by the enzyme adenylate kinase, and 1 molecule of adenosine monophosphate (AMP) is generated. The increase in AMP concentration provides a robust signal, for it leads to a large increase in phosphofructokinase 1 (PFK-1) activity and the flux in glycolysis. The accumulation of pyruvate in the cytosol, coupled with an increase in the ratio of the reduced form of nicotinamide adenine dinucleotide ($NADH+H^+$) to its oxidized form (NAD^+) drives the near-equilibrium reaction catalyzed by the enzyme lactate dehydrogenase (LDH), whereby pyruvate is reduced to L-lactate and $NADH+H^+$ is oxidized to NAD^+. P_i, inorganic phosphate.

O_2 atoms bind H^+ to form H_2O. Four electrons are required to reduce 1 molecule of O_2 and produce 2 molecules of H_2O.

Complexes I, III, and IV use the energy generated from electron flow to pump H^+ from the mitochondrial matrix, across the inner mitochondrial membrane to the intermembrane space. Four H^+ are ejected by each of complexes 1 and III, and 2 are ejected by complex IV. The amount of energy liberated in reactions in complex II is insufficient to pump H^+, so it serves as a source for electrons but does not contribute to the H^+ motive force.

The accumulation of H^+ in the intermembrane space creates both a charge gradient and a chemical gradient favoring H^+ re-entry into the mitochondrial matrix. This electrochemical energy is recaptured as H^+ flow through the ATP synthase. ATP synthase, located in the inner mitochondrial membrane, consists of 2 domains—the F0 domain, which provides the channel for the flow of H^+, and the F1 domain, which has the binding sites for adenosine diphosphate (ADP) and P_i and catalyzes the regeneration of ATP.[22,23] F1 has a gamma subunit, which forms its central core, and 3 beta subunits. The energy generated by the flow of H^+ from F0 to F1 causes the gamma subunit to rotate. This rotatory movement results in conformational changes in the 3 beta subunits, causing the binding of ADP and P_i to 1 subunit in a loose conformation, bringing the second subunit into a tight conformation, where the synthesis of ATP occurs, and promoting the release of tightly bound ATP from the third subunit. This process is termed "coupled oxidative phosphorylation."[24]

The binding of ADP to ATP synthase induces the flow of H^+ from the intermembrane space into the mitochondrial matrix through F0. Hence, the rate of ATP utilization (availability of ADP) regulates the rate of ATP synthesis.

Ten protons are pumped to the intermembrane space during the transfer of 2 electrons from $NADH+H^+$ to O_2, but only 6 protons are pumped to the intermembrane space during the transfer of 2 electrons from $FADH_2$ to O_2. In vertebrates, the flow of 8 protons through ATP synthase is required to regenerate 3 ATP molecules.[25] The actual rate of ATP regeneration is actually a bit lower. Because each ATP requires the transport of 1 $H_2PO_4^-$ from the cytosol into the mitochondria using a proton-coupled phosphate transporter,[26] and ATP^{4-} generated in the mitochondria is transferred into the cytosol in exchange for ADP^{3-} on the adenine nucleotide translocase, there is a waste of the electrochemical gradient of 1 proton for each ATP produced and translocated into the cytosol. We calculated that about 2.7 molecules of ATP are produced per molecule of $NADH+H^+$ oxidized to NAD^+, and about 1.6 molecules of ATP are produced per molecule of $FADH_2$ oxidized to FAD.

The process of oxidation of glucose is summarized in Equation 1 and Table 1 (Pi = inorganic phosphate):

$$\text{Glucose } (C_6H_{12}O_6) + 6\,O_2 + 34.5\,\text{ADP} + 34.5\,\text{Pi} \rightarrow 6\,CO_2 + 6\,H_2O + 34.5\,\text{ATP}. \quad (1)$$

SYNOPSIS OF THE BIOCHEMISTRY OF L-LA

Under physiological conditions, L-lactate is a crucial intermediary in metabolism of carbohydrate and non-essential amino acids, with ~20 mmol/kg body weight (~1500 mmol in a 70-kg subject) produced each day.[27,28] Glycolysis is an obligatory pathway for the regeneration of ATP in red blood cells because they lack mitochondria. L-lactic acid is also produced by the skin, adipose tissues,[29] the central

nervous system, muscle, and the gastrointestinal tract.[30] This load of L-lactic acid is removed largely via gluconeogenesis in the liver (~60%) and the kidney cortex (~30%), and to much lesser extent via oxidation in many organs (liver, kidney, muscle, heart, and brain).[31] This internal recycling of L-lactate with production by some tissues and removal via gluconeogenesis by the liver and the kidneys is known as the Cori cycle. During exercise, the heart and skeletal muscle use L-lactate as their main source of energy.[27,32] The renal threshold for the excretion of lactate is 6–10 mmol/l, so renal excretion is only significant with severe hyperlactatemia.[33]

Accumulations of L-lactic acid can be caused by an increased rate of its production and/or a decreased rate of its removal.

Increased rate of production of L-lactic acid

Increased production of L-lactic acid occurs when the rate of regeneration of ATP in mitochondria is insufficient to meet the requirement for ATP to perform biological work (Figure 4).

In the cytosol, the energy needed to perform biological work (e.g., ion pumping by the Na-K-ATPase pump) is provided by hydrolysis of the terminal high-energy bond of ATP. This results in formation of ADP. ADP enters the mitochondria on the adenine nucleotide translocase in exchange for ATP produced in the mitochondria in coupled oxidative phosphorylation. Under conditions of diminished rate of regeneration of ATP, the concentration of ADP in the cytosol rises. This provides a signal for activation of PFK-1, which is a key regulatory enzyme in glycolysis in skeletal muscle, as it catalyzes an important committed step—the conversion of fructose 6-phosphate and ATP to fructose 1,6-bisphosphate and ADP (Figure 1). The activity of PFK-1 is regulated by a signal related to the concentration of ATP in the cytosol (i.e., when the concentration of ATP falls, PFK-1 is activated). Changes in the concentration of ATP, however, are too small to provide a robust signal for PFK-1 activation. When ADP accumulates in the cytosol, it is converted back to ATP in a near-equilibrium reaction catalyzed by the enzyme adenylate kinase, and adenosine monophosphate (AMP) is generated:

$$2\ \mathrm{ADP} \Leftrightarrow \mathrm{ATP} + \mathrm{AMP}. \qquad (2)$$

Because in muscle cells the concentration of ATP is substantially higher than the concentration of ADP, a small percentage decrease in ATP concentration causes a greater percentage increase in ADP concentration. Furthermore, since AMP concentration is related to the square of ADP concentration, there is an even greater percentage increase in AMP concentration. Therefore, the signal of decreased ATP concentration is markedly amplified via an increase in AMP concentration, resulting in a large increase in PFK-1 activity.

To maintain flux in glycolysis, however, $NADH+H^+$ must be converted back to NAD^+, as NAD^+ is required for the reaction that converts glyceraldehyde 3-phosphate to 1,3 bisphosphoglyceric acid (Figure 1). Normally, $NADH+H^+$ is oxidized to NAD^+ in the mitochondria. Under conditions of defective oxidative phosphorylation, $NADH+H^+$ is oxidized to NAD^+ in the cytosol in an equilibrium reaction catalyzed by the enzyme lactate dehydrogenase, while pyruvate is converted to L-lactate:

$$\mathrm{Pyruvate} + \mathrm{NADH} + \mathrm{H}^+ \Leftrightarrow \mathrm{Lactate} + \mathrm{NAD}^+. \qquad (3)$$

Looking at Equation 3, it was suggested by some that the conversion of pyruvate to lactate is a proton-consuming process, as protons are consumed when $NADH+ H^+$ is converted to NAD^+, and hence should have an alkalinizing effect. The continuous production of L-lactate and therefore the consumption of protons is possible only, however, if there is a continuous supply of $NADH+ H^+$. This requires the conversion of NAD^+ to $NADH+H^+$, which is a proton-producing process. Therefore, there is no net production or consumption of H^+ in the sum of these 2 reactions.

Although only 2 molecules of ATP are regenerated per molecule of glucose in glycolysis, the rate of glycolysis can increase 2 or 3 orders of magnitude faster than the rate of ATP production by oxidative phosphorylation during rest. The price paid, however, is the production of 1 mmol of L-lactic acid per 1 mmol of ATP regenerated. This increase in H^+ concentration inhibits PFK-1. Although this minimizes the drop in intracellular pH, it may lead to a critical shortage of energy production, which may result in detrimental effects, especially in cells of vital organs (e.g., the brain and the heart).[34]

It is not our intent in this review to discuss issues related to management of L-LA, which have been recently reviewed elsewhere,[35–38] but a brief comment on the use of $NaHCO_3$ is warranted. The main-stay of therapy in patients with L-LA is effectively addressing the underlying cause; however, the administration of $NaHCO_3$ might provide a beneficial temporary measure to allow time for direct interventions to be employed.

The detrimental effect of the rise in intracellular H^+ concentration could be the result of the binding of H^+ to cellular proteins, which may change their charge, alter their shape, and possibly affect their functions (e.g., as enzymes, transporters, contractile elements, and structural compounds). One argument against the use of $NaHCO_3$ is that its administration in some animal models of L-LA led to an increase in blood L-lactate level. This increase, however, may be viewed as beneficial if it reflects de-inhibition of PFK-1, increased flux in glycolysis, and increased rate of ATP regeneration in vital organs, providing that the added H^+ load is titrated by the bicarbonate buffer system and not by intracellular proteins.[34] Another argument against the use of $NaHCO_3$ is that the administered HCO_3^- reacts with H^+, leading to increased production of CO_2, which enters cells and causes a fall in intracellular pH. Given that there are few H^+ in either a free or a bound form in the extracellular fluid

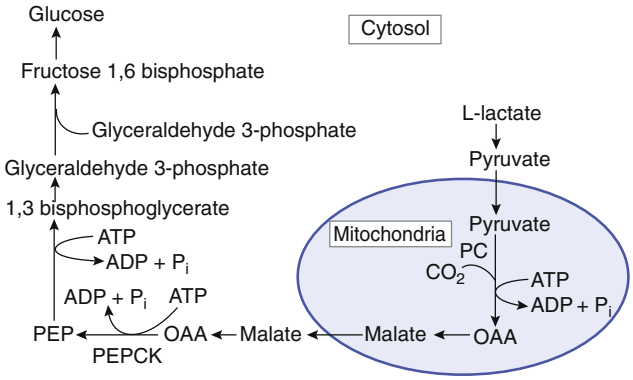

Figure 5 | The removal of L-lactic acid via gluconeogenesis. Lactic acid can be made into glucose in the liver and in the kidney cortex. The key reaction in gluconeogenesis is the conversion of pyruvate to phosphophenol pyruvate (PEP), which occurs in 2 steps. The first step is the metabolism of pyruvate in the mitochondria into oxaloacetate (OAA) by the enzyme pyruvate carboxylase (PC). OAA is then reduced to malate, which is transported into the cytosol by the malate transporter. Once in the cytosol, malate is made back into oxaloacetate. The second step is the conversion of OAA to PEP, in a reaction catalyzed by the enzyme phosphenol pyruvate carboxykinase (PEPCK). Three molecules of adenosine triphosphate (ATP) are consumed in the reactions of converting 1 molecule of L-lactate into 1 molecule of glyceraldehyde 3-phosphate. Since 2 molecules of glyceraldehyde 3-phosphate are required to make 1 molecule of glucose, a total of 6 molecules of ATP are consumed in converting 2 molecules of L-lactate into 1 molecule of glucose. ADP, adenosine diphosphate; P_i, inorganic phosphate.

compartment, the source of this H^+ titrating the administered HCO_3^- may be H^+ that were bound to intracellular proteins.[39] For this back-titration of intracellular proteins by the administered HCO_3^- to continue, however, a low PCO_2 in cells and the interstitial space should be maintained. This requires both adequate alveolar ventilation and adequate effective circulating volume. A large amount of $NaHCO_3$ is likely to be needed to achieve back-titration of the large H^+ load bound to intracellular proteins. A continuous dialysis modality like veno-venous hemodialysis may provide the means for the administration of a large continuous infusion of $NaHCO_3$, while avoiding the risk of volume overload and pulmonary edema.[40,41]

Decreased rate of removal of L-lactic acid

The first step in the metabolic removal of L-lactate is its oxidation to pyruvate. This occurs mainly in the cytosol, but it also appears that L-lactate can be transported into the mitochondria, where it is converted to pyruvate by mitochondrial lactate dehydrogenase.[42,43] Within the mitochondria, pyruvate may be either converted to acetyl-CoA by PDH and forwarded to the oxidative pathway to regenerate ATP, or metabolized by the biotin (vitamin B_7)-requiring enzyme pyruvate carboxylase to oxaloacetate and forwarded to the gluconeogenesis pathway to produce glucose.

Gluconeogenesis occurs in the liver and in the kidney cortex.[18] The pathway for gluconeogenesis is shown in Figure 5; 3 mmol of ATP are consumed in these reactions. Since 2 molecules of pyruvate are needed to make 1 molecule of glucose, a total of 6 molecules of ATP are consumed in converting 2 molecules of L-lactate into 1 molecule of glucose. Hence, the rate of gluconeogenesis will be limited by the rate of ATP regeneration and the demand for ATP to perform other biological work in the organs involved.

CLINICAL SETTINGS OF DEVELOPMENT OF L-LA

The clinical settings for the development of L-LA are most commonly those that lead to increased production of L-lactic acid. Less commonly, L-LA may develop as a result of a disease process that leads to a decreased removal of L-lactic acid. In many cases, both increased production and decreased removal of L-lactic acid may be present, but one pathophysiology is predominant.

Clinical settings with predominantly overproduction of L-lactic acid

Inadequate delivery of oxygen. Most of the body's O_2 consumption is utilized by complex IV of the ETC. Global oxygen delivery (DO_2) is the total amount of O_2 delivered to the tissues in the whole body per minute, irrespective of the distribution of blood flow. DO_2 is the product of cardiac output and the arterial O_2 content:

$$DO_2 = Q \text{ X } Hb \text{ X } 1.39 \text{ X } \% \text{ saturation} \quad (4)$$

(where Q is the cardiac output in l/min, Hb is the hemoglobin concentration in g/l ,1.39 (Huffner's constant) is the amount of O_2 in ml carried per gram of hemoglobin at sea- level, when it is nearly fully saturated [exposed to a PO_2 >97.5 mm Hg]).

At a Q of 5 l/min, Hb of 150 g/l, and fully saturated hemoglobin, DO_2 is ~1000 ml/min, a 4-fold higher than the oxygen consumption of a conscious adult person at rest (~250 ml/min). This O_2 extraction ratio of only 25% enables a substantial fall in DO_2 without compromising oxygen consumption.[44]

As DO_2 falls or metabolic demand increases, the O_2 extraction ratio increases, but once a maximum ratio is reached (60%–70% for most tissues), a further fall in DO_2 or an increase in metabolic demand leads to tissue hypoxia. The threshold of DO_2 below which there is evidence of tissue hypoxia varies substantially among species.[45–48] In resting, healthy, conscious human subjects aged 19–25 years, critical DO_2 is less than 7.3 ml/kg per min.[49] A value of approximately 5 ml/kg per min was observed in an anesthetized, mechanically ventilated man with neuromuscular blockade.[50] Notwithstanding these results, there may be regional or organ-specific variability in the balance between O_2 supply and demand.

Experimental studies have confirmed the relationship between tissue hypoxia induced by reducing the components of DO_2 (hemoglobin level, arterial PO_2, and cardiac output) and the development of hyperlactatemia.[45,51] Clinical studies have also shown this relationship between a supply-dependent

state of O_2 consumption and the development of hyperlactatemia.[52,53]

A common clinical setting for rapid overproduction of L-lactic acid due to diminished DO_2 is cardiogenic shock.[54] Other examples of conditions that lead to inadequate DO_2 include hypovolemic shock,[55] severe hypoxemia (PO_2 < 30–40 mm Hg), and severe euvolemic anaemia (hemoglobin concentration <45 g/l). L-LA may develop in patients with carbon monoxide poisoning because hemoglobin binds carbon monoxide with greater affinity than that for O_2, producing carboxyhemoglobin, a compound that cannot carry O_2. Furthermore, the oxyhemoglobin dissociation curve is shifted to the left; hence, the availability of oxygen at tissue level is further reduced.[56] Carbon monoxide also inhibits complex IV of the ETC.[57]

The decreased O_2 delivery to the liver and kidneys in these settings also limits the rate of L-lactic acid removal via gluconeogenesis.

Sepsis. L-LA is commonly seen in patients with severe sepsis and septic shock; L-lactate blood levels are directly correlated with mortality.[58,59]

Hyperlactatemia may persist or develop in patients with sepsis despite restoring systemic parameters of adequate DO_2. It is thought that in critically ill patients, O_2 consumption remains supply dependent even at supernormal levels of DO_2. Oxygen supply dependency was demonstrated in patients in early stages of septic shock with hyperlactatemia.[53] This led to the hypothesis that these patients have covert O_2 debt that could be eliminated by increasing O_2 supply, and provided the rationale for an "early goal-directed therapy" strategy in which normalization of the blood lactate level is used as a goal for resuscitation. This O_2 supply dependency, however, was not demonstrated in other studies.[60,61]

In patients with sepsis, tissue hypoxia may be due to disordered regional distribution of blood flow between organs, microcirculatory dysfunction, and defective mitochondrial oxygen utilization, despite the correction of variables of systemic DO_2.[62,63] Regional and microcirculatory distribution of cardiac output is determined by a complex interaction of endothelial, neural, and metabolic factors. In critically ill patients, particularly those with sepsis, loss of normal autoregulation of blood flow causes shunting of cardiac output and tissue hypoxia in some organs. Arteriolar smooth muscle cells lose their adrenergic sensitivity and tone in sepsis.[64] Microcirculatory dysfunction results in heterogeneous abnormalities in blood flow, with some capillary beds becoming under-perfused, whereas others may have normal to high blood flow. The endothelium is both exposed to and itself produces many inflammatory mediators that influence vascular tone and other aspects of endothelial function. For example, nitric oxide production is increased in septic shock following induction of nitric oxide synthase in blood vessel walls. Heterogenous expression of the inducible nitric oxide synthase results in pathologic shunting of blood flow from areas lacking inducible nitric oxide synthase to areas with nitric oxide–induced vasodilation.[65] Activation of the coagulation cascade and increased red blood cell aggregation may cause formation of microthrombi and alter microcirculatory blood flow.[66–68] Reactive oxygen species production by activated leukocytes may directly injure endothelial cells, disrupting microcirculatory function and promoting platelet–endothelial adhesion and microthrombi formation.[69] Altered capillary permeability by inflammatory mediators causes tissue edema, which further impedes O_2 diffusion.[70] Tissue hypoxia may also result from mitochondrial dysfunction and diminished O_2 extraction.[71–73] In addition, these mechanisms may also impair O_2 delivery to the liver and kidneys, and limit the rate of L-lactic acid removal via gluconeogenesis.

Mechanisms other than tissue hypoxia may account for the development of L-LA in patients with sepsis. Inflammatory cytokines increase glucose uptake by cells.[74] Endotoxins may inactivate PDH.[75] β_2-adrenoreceptor activation increases the production of cyclic adenosine monophosphate (cAMP), which stimulates glycogenolysis and hence increases the concentration of pyruvate. cAMP also increases the demand for ATP by activating the Na-K-ATPase.[76–78] A role for β_2-adrenoreceptor blockade in management of patients with L-LA due to sepsis has been suggested.[79] This requires, however, the development of clinical tools to identify patients in whom β_2-adrenoreceptor activation plays a predominate role, as tissue hypoxia may also be present despite adequate parameters of DO_2.

L-LA is commonly seen in patients with mesenteric ischemia.[80,81] In addition to overproduction of L-lactic acid by the ischemic bowel, the mechanisms discussed earlier as a result of sepsis/inflammation may also lead to increased L-lactic acid production by other tissues and decrease its removal by the liver and kidneys.

Increased demand for ATP. L-LA occurs during seizures[82,83] and high-intensity exercise.[84,85] Flux in glycolysis is stimulated as ADP accumulates in the cytosol of exercising muscles and is converted to ATP; AMP is generated and PFK-1 is activated (Equation 2).

Another example of this pathophysiology may be seen in patients with vitamin B_6 (pyridoxine) deficiency. Pyridoxine is a cofactor for the reaction catalyzed by the enzyme glutamic acid decarboxylase, in which glutamate is converted to γ-amino butyric acid. Because γ-amino butyric acid activates inhibitory receptors, a deficiency of this acid could result in increased neuronal excitability, leading to the development of seizures.[86] Pyridoxine deficiency may occur in patients taking the drug isoniazid, commonly used to treat tuberculosis, because of the formation of an isoniazid/vitamin B_6 complex.[87] Patients on hemodialysis are at increased risk of this complication because they tend to be deficient in vitamin B_6 owing to the removal of this water-soluble vitamin by hemodialysis.[88] Pyridoxine deficiency may also occur in patients on total parenteral nutrition if they are not given adequate vitamin B_6 supplementation, as might have been the case with the recent parenteral multivitamin products shortage in the United States.

β_2-adrenoreceptor activation may explain the development of L-LA in patients with severe bronchial asthma,[89–91] especially when they are treated with β_2-adrenoreceptor agonists,[92,93] and in some patients with pheochromocytoma.[94,95]

Clinical settings with increased production of L-lactic acid in the absence of hypoxia or increased demand for ATP

Ethanol intoxication. The development of L-LA in patients with ethanol intoxication reflects the higher $NADH+H^+/NAD^+$ ratio in hepatocytes resulting from the ongoing conversion of NAD^+ into $NADH+H^+$ caused by ethanol metabolism by the enzymes alcohol dehydrogenase and aldehyde dehydrogenase. The sources of pyruvate are the catabolism of certain amino acids and the breakdown of glycogen because of both the high level of epinephrine and the low level of insulin, which may occur in this setting, activate the enzyme glycogen-phosphorylase. The degree of L-LA in patients with ethanol intoxication is usually mild, with a plasma L-lactate concentration of <5 mmol/l, because other organs are capable of removing the L-lactic acid made by the liver.[96,97] A more severe degree of L-LA suggests that there are other causes for L-lactic acid overproduction, which may include hypoxia (e.g., due to hemodynamic collapse because of sepsis, bleeding from the gastrointestinal tract, pancreatitis), thiamine deficiency, seizures (due to alcohol withdrawal, delirium tremens), and/or L-lactic acid underutilization from severe liver disease caused by an acute hepatitis induced by alcohol that is superimposed on chronic liver disease (e.g., fatty liver, liver cirrhosis).

Thiamine deficiency. A derivation of thiamine (vitamin B_1) is a key cofactor for PDH. Thiamine deficiency has been associated with development of L-LA.[98–100]

A severe degree of L-LA may develop rapidly in patients with ethanol intoxication and thiamine deficiency.[101] The site of L-lactic acid production in this setting is likely to be the liver because it is where there is accumulation of pyruvate (caused by the diminished activity of PDH) and a high $NADH+H^+/NAD^+$ ratio (caused by metabolism of ethanol). There is also diminished removal of L-lactic acid by other organs due to diminished activity of PDH, and also the presence of alternative fuels that may be used preferentially to regenerate ATP (e.g., free fatty acids for muscles, ketoacids for the brain).

Malignancy. L-LA has been reported in patients with hematological and solid organs malignancies and is usually associated with poor prognosis, as a marker for highly mitotic and invasive tumors.[102,103] Proposed mechanisms for the development of L-LA in these patients include: increased glycolytic activity of tumor cells (Warburg effect), tumor tissue hypoxia, thiamine or riboflavin deficiency, and decreased clearance of L-lactate due to liver metastases.

"Reprogrammed energy metabolism " with increased flux in glycolysis and increased glutamine metabolism are considered metabolic hallmarks of cancer cells.[104] In the 1920s, Otto Warburg demonstrated that tumor ascites cells have a high rate of glucose consumption and lactate production, despite sufficient availability of O_2 for complete oxidation of glucose.[105]

In humans, glucose is metabolized by 2 pathways: glycolysis, which produces $NADH+H^+$ and ATP, and the pentose phosphate pathway, which produces nicotinamide adenine dinucleotide phosphate (NADPH) and ribose-5-phosphate. NADPH is required for synthesis of fatty acids, used for synthesis of phospholipids required for the formation of cell membranes and membranes of all cellular organelles. Ribose 5-phosphate is a pentose essential for the synthesis of nucleotides, such as those in RNA and DNA. Cancer cells and rapidly proliferating cells have a high demand for both phospholipids and ribose 5- phosphate and hence a need to shuttle glucose into the pentose phosphate pathway.[106–109] The enzyme pyruvate kinase (PK) catalyzes the final step in glycolysis in which a phosphate group is transferred from phosphophenol pyruvate to ADP, yielding 1 molecule of pyruvate and 1 molecule of ATP (Figure 1). There are 4 types of PK; tumor cells and rapidly proliferating cells have high levels of the dimeric form of PKM2, which has a very low catalytic activity[110,111]; hence, glucose is shunted to the pentose monophosphate pathway.

In addition to this shunting of glucose to the pentose monophosphate pathway, the bulk of citrate that is made from glucose that is metabolized in the glycolytic pathway to pyruvate and then to acetyl-CoA is shuttled back into the cytosol to be used for fatty acid synthesis instead of entering the citric acid cycle (Figure 2). Because the yield of ATP from each glucose molecule in glycolysis is only 1/17 that from oxidative phosphorylation, flux in glycolysis must be greatly increased to meet the high demand of these cells for ATP.

It has been shown that in rapidly proliferating cancer cells, more than 90% of glucose utilized is converted to L-lactate as the final product.[112] A number of genes involved in glucose transport and glycolysis are upregulated in different types of tumors. The serine-threonine kinase AKT (protein kinase B), one of the most frequently activated kinases in cancer cells, augments flux in glycolysis by increasing the cell surface expression of the high-affinity glucose transporters, GLUT1 and GLUT4, activating hexokinase 2, and inhibiting glycogen synthase kinase.[113] Loss of function mutation in the P53 tumor suppressor gene leads to a reduction in TIGAR (TP53-induced glycolysis and apoptosis regulator), a fructose 2-6 bi-phosphatase.[114,115] This leads to an increase in the level of fructose 2-6 bisphosphate, which is an allosteric activator of PFK-1. Hypoxia inducible factor-1 (HIF-1) is a heterodimeric complex formed by 2 subunits: a constitutively expressed HIF-1ß, and HIF-1α,which is highly susceptible to oxygen-dependent degradation. In the presence of O_2, HIF-1α is hydroxylated on proline residues, which allows its recognition by von Hippel-Lindau protein and its targeting for proteasomal degradation. Tumor cells achieve stabilization of HIF-1α through some genetic alterations that prevent its degradation by von Hippel-Lindau protein. PKM2 activates a well-known nuclear transcription factor, STAT3, via tyrosine phosphorylation.[116] Activated STAT3 induces HIF-1α

transcription, resulting in an increased HIF-1α protein level.[117] HIF-1α induces the upregulation of a number of genes that encode for glucose transporters and for a number of glycolytic enzymes including hexokinase 2 and PFK-1.[118] HIF-1α also induces upregulation of lactate dehydrogenase-A and PK1; PK1 phosphorylates and inactivates PDH.[119] HIF-1α induces upregulation of the monocarboxylic acid cotransporter 4, which exports L-lactic acid out of cells.

It has been suggested that tumor cells, by maintaining a relatively low pH in their microenvironment, may escape immune destruction by suppressing the anti-cancer immune response.[120] A number of mechanisms have been proposed to link Warburg effect to tumor invasiveness, including extracellular matrix degradation due to activation of proteases by the extracellular acidic milieu.[121] This dependence on glycolysis may also offer survival advantage to tumor cells by making them less susceptible to hypoxic stress.

Propane 1,2-diol (propylene glycol). Propylene glycol is commonly used as a solvent for a number of intravenous and oral drug preparations, some of which are commonly used in critically ill patients (e.g., lorazepam or diazepam, barbiturates, phenytoin, and trimethoprim/sulfamethoxazole). Prolonged administration of large doses of propylene glycol can result in development of lactic acidosis.[122–126]

Propane 1,2-diol is a 50:50 mixture of D- and L-isoforms. Of the administered dose, 40% is excreted unchanged in the urine, and 60% is metabolized in the liver by alcohol dehydrogenase to lactaldehyde. L-lactaldehyde is metabolized by aldehyde dehydrogenase to L-lactic acid. In contrast, D-lactaldehyde is not a good substrate for aldehyde dehydrogenase; it accumulates and leads to many of the toxic effects observed in this setting. D-lactaldehyde can be metabolized to D-lactic acid by an alternate pathway in the liver, which uses reduced glutathione as a cofactor. Because L-lactic acid is metabolized faster than D-lactic acid, the acid that mostly accumulates in this setting is D-lactic acid.[127]

Congenital L-LA. L-LA may be caused by a defect in pyruvate transport from the cytosol to the mitochondrial matrix. Mutations in the gene encoding for the mitochondrial pyruvate carrier MPC1 have been identified in 3 families with congenital lactic acidosis.[20]

Most reported cases of L-LA due to congenital PDH complex deficiency have been due to mutations in the *PDHA1* gene, which encodes for the E1alpha subunit of the enzyme complex.[128] Rarely, genetic disorders affecting the function of the citric acid cycle have been described as causes of L-LA.[129–131]

Mutations in mitochondrial DNA or nuclear DNA may result in defects in any of the multiple components of the mitochondrial ETC.[132] Mutations in a mitochondrial transfer RNA gene, *MT-TL1*, account for most cases of MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes).[133]

Inhibition of the ETC.

Riboflavin deficiency. The active metabolites formed from vitamin B_2 (riboflavin), flavin mononucleotide (FMN) and FAD, are components of Complexes I and II of the ECT. Hence, riboflavin deficiency has been associated with the development of L-LA. Riboflavin is activated via an ATP-dependent kinase to produce FMN and FAD. Tricyclic antidepressant drugs (e.g., amitriptyline and imipramine) inhibit this kinase.[134] The activity of this kinase is also decreased in severe hypothyroidism; patients with myxedema may develop L-LA.[135,136]

Antiretroviral drugs. L-LA has been reported with the use of a number of nucleoside analogue reverse transcriptase inhibitors in patients with human immunodeficiency virus infection.[137–139] Long use of these inhibitors may cause damage of γ-DNA polymerase, leading to mitochondrial DNA depletion.[140,141] This impairs the ETC as mitochondrial DNA encodes for a number of enzymes involved in the ETC. Thiamine and/or riboflavin deficiency may also cause L-LA in some of these patients.[142–144]

In addition to the increased production of L-lactic acid, a severe degree of hepatic steatosis as result of mitochondrial dysfunction and impaired β oxidation of long-chain free fatty acid may develop in patients on nucleoside analogue reverse transcriptase inhibitors, which may decrease the removal of L-lactic acid.[145]

Linezolid. The use of Linezolid, an oxazolidinone antibiotic frequently used to treat infections caused by vancomycin- resistant enterococcus and other gram-positive organisms, has been associated with the development of L-LA.[146] Linezolid binds to bacterial ribosome and inhibits bacterial protein synthesis.[147] L-LA associated with linezolid seems to be due to inhibition of the synthesis of some of the proteins of complex IV by mitochondrial ribosomes.[148,149] This is perhaps because of similarities between bacterial and mitochondrial ribosomes, as mitochondria are thought to be a vestige of a previous symbiotic colonization by aerobic bacteria that provided human cells with the capacity to use O_2.

Propofol. L-LA has been associated with propofol infusion.[150] The mechanism seems to be due to inhibition of complex IV of the ETC.[151,152] Infusion of propofol was associated with an increase in plasma malonylcarnitine, an inhibitor of carnitine palmityl transferase, which transports long-chain free fatty acids into the mitochondria. Increased entry of medium and short-chain fatty acids, which do not require the carnitine transporter, into the mitochondria is thought to inhibit complex II of the ETC.[153]

Methanol intoxication. The increased anion gap metabolic acidosis in patients with methanol intoxication is due to the accumulation of formic acid and L-lactic acid.[154] The plasma L-lactate level often exceeds that of formate.[155] The L-LA is thought to be due to inhibition of complex IV by formate.

Of note, falsely elevated blood lactate levels have been noted in patients with severe ethylene glycol intoxication, when assays for L-lactate are performed using an L-lactate oxidase reaction.[156–158] In this method, L-lactate is oxidized to pyruvate by L-lactate oxidase; hydrogen peroxide generated in this reaction oxidizes a chromogen system, and absorbance of the resulting dye complex is measured

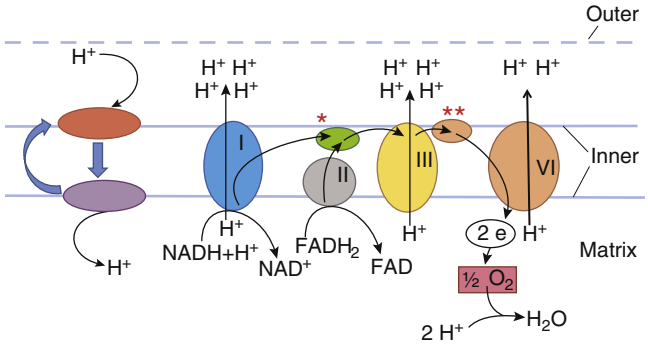

Figure 6 | The uncoupling of oxidative phosphorylation. The horizontal structure represents the inner mitochondrial membrane with its inner and outer bilayers. The dashed line represents the outer mitochondrial membrane. The uncoupling of oxidative phosphorylation occurs when H^+ ions that were pumped out from the mitochondrial matrix through the inner mitochondrial membrane re-enter the mitochondrial matrix through another H^+ ion channel (an uncoupler protein) or via another mechanism that is not linked to the conversion of adenosine diphosphate to adenosine triphosphate (i.e., reactions of the electron transport chain and the phosphorylation of adenosine diphosphate are uncoupled). Most of the compounds that uncouple oxidative phosphorylation are lipophilic weak acids that are capable of translocating H^+ ions across lipid bilayers; in this way, the H^+ gradient is dissipated, and adenosine triphosphate regeneration is diminished. *Coenzyme Q; **cytochrome C. e, electron; FAD, flavin adenine dinucleotide; $FADH_2$, hydroxyquinone form of FAD; NAD^+, nicotinamide adenine dinucleotide; $NADH+H^+$, reduced form of NAD^+.

spectrophotometrically. Because of structural similarity between L-lactate and the ethylene glycol metabolites, glycolate and glyoxylate, L-lactate oxidase reacts with these metabolites, leading to a falsely elevated L-lactate level.[159,160] This interference, however, does not occur when L-lactate is measured using the method that utilizes the reaction catalyzed by lactate dehydrogenase in which lactate is converted to pyruvate, while the added NAD^+ is reduced to $NAH+H^+$, and the latter is measured spectrophotometrically.

Cyanide poisoning. Cyanide binds avidly to Fe^{+3} of heme in the cytochromes and inhibits complex IV of the ETC.[161] Smoke inhalation from domestic fires and occupational exposure (metal extraction in mining, electroplating in jewelry production, photography, and plastic and rubber manufacturing) are the most common causes of cyanide poisoning. Sodium nitroprusside, used in treatment of hypertensive emergencies, contains 5 cyanide groups per molecule. Toxic levels of cyanide may be reached after prolonged infusion of the drug in patients with chronic renal failure, or in pediatric patients.[162,163]

Uncouplers of oxidative phosphorylation. Uncoupling of oxidative phosphorylation occurs when H^+ that were pumped out from the mitochondrial matrix through the inner mitochondrial membrane re-enter the mitochondrial matrix through another H^+ channel (an uncoupler protein)[164] or via another mechanism that is not linked to the conversion of ADP to ATP (i.e., reactions of the ETC and phosphorylation of ADP are uncoupled).[165,166] Most of the compounds that uncouple oxidative phosphorylation are lipophilic weak acids that are capable of translocating H^+ across lipid bilayers.[167] Uncouplers pick up H^+ in the intermembrane space where there is a higher concentration of H^+, then rapidly diffuse into the mitochondrial matrix where they lose H^+, because of the H^+ concentration is lower in this location. Thus, the H^+ gradient is dissipated, and ATP regeneration is diminished (Figure 6).

Metformin is a biguanide that is considered first-line oral antihyperglycemic medication in patients with type 2 diabetes mellitus.[168] The incidence of L-LA attributed solely to use of metformin seems to be very low, with most cases occurring in patients with conditions that predispose them to hypoperfusion or hypoxemia.[169,170] Metformin-associated L-LA is more likely to occur in patients who develop acute renal failure from whatever cause and continue to take metformin,[171–173] as the drug accumulates due to a decrease in its renal clearance. Metformin plasma levels of >5 ug/l (therapeutic <2 ug/l) are generally found in cases when metformin was implicated as the cause of L-LA. The mechanism of L-LA is thought to be due to an effect of metformin to uncouple oxidative phosphorylation[174] and also to inhibit complex I.[175–177] Metformin is also thought to decrease hepatic gluconeogenesis, an effect mediated by a decrease in ATP content in hepatic cells.[178,179]

Salicylic acid is another drug that uncouples oxidative phosphorylation.[175,180] The increased anion gap metabolic acidosis in patients with aspirin overdose is largely due to the accumulation of L-lactic acid and ketoacids.[181]

Clinical settings with predominantly decreased removal of L-lactic acid

This type of L-LA does not have the same urgency as the type with predominantly overproduction of L-lactic acid, because it is not associated with a problem in regenerating ATP. The rate of H^+ accumulation is usually much slower, and a chronic steady state of L-LA is often present. The causes of a low rate of removal of L-LA are usually related to severe liver injury, either due to acute hepatitis (e.g., viral infection or drug toxicity), prior hypoxia (e.g., shock liver), or extensive replacement of normal liver cells (e.g., by tumor cells or large fat deposits).[182]

L-LA in patients with acetaminophen overdose is thought to be due to acute hepatic injury. L-LA may develop, however, in some patients preceding hepatic injury.[183] Down-regulation of both nuclear and mitochondrial genes encoding for proteins involved in the ETC was observed in peripheral blood cells in healthy adults, 48 hours after exposure to a single 4-g dose of acetaminophen.[184]

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Luft D, Deichsel G, Schmulling RM, et al. Definition of clinically relevant lactic acidosis in patients with internal diseases. *Am J Clin Pathol.* 1983;80:484–489.

2. Fall PJ, Szerlip HM. Lactic acidosis: from sour milk to septic shock. *J Intensive Care Med*. 2005;20:255–271.
3. Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol*. 2007;2:162–174.
4. Iberti TJ, Leibowitz AB, Papadakos PJ, Fischer EP. Low sensitivity of the anion gap as a screen to detect hyperlactatemia in critically ill patients. *Crit Care Med*. 1990;18:275–277.
5. Kraut JA, Nagami GT. The serum anion gap in the evaluation of acid-base disorders: What are its limitations and can its effectiveness be improved? *Clin J Am Soc Nephrol*. 2013;8:2018–2024.
6. Kamel KS, Cheema-Dhadli S, Halperin FA, et al. Anion gap: May the anions restricted to the intravascular space undergo modification in their valence? *Nephron*. 1996;73:382–389.
7. Kruse O, Grunnet N, Barfod C. Blood lactate as a predictor for in-hospital mortality in patients admitted acutely to hospital: a systematic review. *Scand J Trauma Resusc Emerg Med*. 2011;19:74.
8. van Beest PA, Brander L, Jansen SP, et al. Cumulative lactate and hospital mortality in ICU patients. *Ann Intensive Care*. 2013;3:6.
9. Pro CI, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370:1683–1693.
10. Kliegel A, Losert H, Sterz F, et al. Serial lactate determinations for prediction of outcome after cardiac arrest. *Medicine (Baltimore)*. 2004;83:274–279.
11. Nichol AD, Egi M, Pettila V, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. *Crit Care*. 2010;14:R25.
12. Bakker J, Nijsten MW, Jansen TC. Clinical use of lactate monitoring in critically ill patients. *Ann Intensive Care*. 2013;3:12.
13. Mitchell JH, Wildenthal K, Johnson RL Jr. The effects of acid-base disturbances on cardiovascular and pulmonary function. *Kidney Int*. 1972;1:375–389.
14. Teplinsky K, O'Toole M, Olman M, et al. Effect of lactic acidosis on canine hemodynamics and left ventricular function. *Am J Physiol*. 1990;258:H1193–H1199.
15. Davies AO. Rapid desensitization and uncoupling of human beta-adrenergic receptors in an in vitro model of lactic acidosis. *J Clin Endocrinol Metab*. 1984;59:398–405.
16. Cohen RD, Woods HF. *The Clinical Presentation and Classification of Lactic Acidosis*. Oxford, UK: Blackwell Scientific; 1967.
17. Cohen RD, Woods HF. *Clinical and Biochemical Aspects of Lactic Acidosis*. Philadelphia, PA: Blackwell Scientific; 1976.
18. Harris AH. Carbohydrate metabolism I: Major metabolic pathways and their control. In: Devlin T, ed. *Textbook of Biochemistry, with Clinical Correlations*. Hoboken, New Jersey: Wiley; 2011:591–646.
19. Lemasters JJ, Holmuhamedov E. Voltage-dependent anion channel (VDAC) as mitochondrial governator—thinking outside the box. *Biochim Biophys Acta*. 2006;1762:181–190.
20. Bricker DK, Taylor EB, Schell JC, et al. A mitochondrial pyruvate carrier required for pyruvate uptake in yeast, Drosophila, and humans. *Science*. 2012;337:96–100.
21. Patel KP, O'Brien TW, Subramony SH, et al. The spectrum of pyruvate dehydrogenase complex deficiency: clinical, biochemical and genetic features in 371 patients. *Mol Genet Metab*. 2012;106:385–394.
22. Beattie SD. Bioenergitics, mitochondria, and oxidative metabolism. In: Devlin TM, ed. *Textbook of Biochemistry, with Clinical Correlations*. Hoboken, New Jersey: Wiley; 2012:541–590.
23. Weber J, Senior AE. ATP synthesis driven by proton transport in F1F0-ATP synthase. *FEBS Lett*. 2003;545:61–70.
24. Rich P. Chemiosmotic coupling: the cost of living. *Nature*. 2003;421:583.
25. Watt IN, Montgomery MG, Runswick MJ, et al. Bioenergetic cost of making an adenosine triphosphate molecule in animal mitochondria. *Proc Natl Acad Sci U S A*. 2010;107:16823–16827.
26. Ferreira GC, Pratt RD, Pedersen PL. Mitochondrial proton/phosphate transporter. An antibody directed against the COOH terminus and proteolytic cleavage experiments provides new insights about its membrane topology. *J Biol Chem*. 1990;265:21202–21206.
27. van Hall G. Lactate kinetics in human tissues at rest and during exercise. *Acta Physiol (Oxf)*. 2010;199:499–508.
28. Connor H, Woods HF. Quantitative aspects of L(+)-lactate metabolism in human beings. *Ciba Found Symp*. 1982;87:214–234.
29. Jansson PA, Smith U, Lonnroth P. Evidence for lactate production by human adipose tissue in vivo. *Diabetologia*. 1990;33:253–256.
30. Wilson TH. The role of lactic acid production in glucose absorption from the intestine. *J Biol Chem*. 1956;222:751–763.
31. Connor H, Woods HF, Ledingham JG, Murray JD. A model of L(+)-lactate metabolism in normal man. *Ann Nutr Metab*. 1982;26:254–263.
32. Hermansen L, Stensvold I. Production and removal of lactate during excercise in man. *Acta Phys Scand*. 1972;86:191–201.
33. Bellomo R. Bench-to-bedside review: lactate and the kidney. *Crit Care*. 2002;6:322–326.
34. Halperin ML, Cheema-Dhadli S, Halperin FA, Kamel KS. Rationale for the use of sodium bicarbonate in a patient with lactic acidosis due to a poor cardiac output. *Nephron*. 1994;66:258–261.
35. Kraut JA, Madias NE. Treatment of acute metabolic acidosis: a pathophysiologic approach. *Nat Rev Nephrol*. 2012;8:589–601.
36. Kraut JA, Madias NE. Lactic acidosis. *N Engl J Med*. 2014;371:2309–2319.
37. Velissaris D, Karamouzos V, Ktenopoulos N, et al. The use of sodium bicarbonate in the treatment of acidosis in sepsis: a literature update on a long-term debate. *Crit Care Res Pract*. 2015;2015:605830.
38. Kraut JA, Madias NE. Intravenous sodium bicarbonate in treating patients with severe metabolic acidemia. *Am J Kidney Dis*. 2019;73:572–575.
39. Gowrishankar M, Kamel KS, Halperin ML. A brain protein centered view of H+ buffering. *J Am Soc Nephrol*. 2007;18:2278–2280.
40. Cerda J, Tolwani AJ, Warnock DG. Critical care nephrology: management of acid-base disorders with CRRT. *Kidney Int*. 2012;82:9–18.
41. De Corte W, Vuylsteke S, De Waele JJ, et al. Severe lactic acidosis in critically ill patients with acute kidney injury treated with renal replacement therapy. *J Crit Care*. 2014;29:650–655.
42. Brooks GA. Intra- and extra-cellular lactate shuttles. *Med Sci Sports Exerc*. 2000;32:790–799.
43. Gladden LB. Muscle as a consumer of lactate. *Med Sci Sports Exerc*. 2000;32:764–771.
44. Nathan AT, Singer M. The oxygen trail: tissue oxygenation. *Br Med Bull*. 1999;55:96–108.
45. Cain SM. Appearance of excess lactate in anesthetized dogs during anemic and hypoxic hypoxia. *Am J Physiol*. 1965;209:604–610.
46. Cain SM. Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. *J Appl Physiol Respir Environ Exerc Physiol*. 1977;42:228–234.
47. Adams RP, Dieleman LA, Cain SM. A critical value for O2 transport in the rat. *J Appl Physiol Respir Environ Exerc Physiol*. 1982;53:660–664.
48. Schou H, Perez de Sa V, Sigurdardottir M, et al. Circulatory effects of hypoxia, acute normovolemic hemodilution, and their combination in anesthetized pigs. *Anesthesiology*. 1996;84:1443–1454.
49. Lieberman JA, Weiskopf RB, Kelley SD, et al. Critical oxygen delivery in conscious humans is less than 7.3 ml O2 x kg(-1) x min(-1). *Anesthesiology*. 2000;92:407–413.
50. van Woerkens EC, Trouwborst A, van Lanschot JJ. Profound hemodilution: What is the critical level of hemodilution at which oxygen delivery-dependent oxygen consumption starts in an anesthetized human? *Anesth Analg*. 1992;75:818–821.
51. Zhang H, Vincent JL. Oxygen extraction is altered by endotoxin during tamponade-induced stagnant hypoxia in the dog. *Circ Shock*. 1993;40:168–176.
52. Ronco JJ, Fenwick JC, Tweeddale MG, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA*. 1993;270:1724–1730.
53. Friedman G, De Backer D, Shahla M, Vincent JL. Oxygen supply dependency can characterize septic shock. *Intensive Care Med*. 1998;24:118–123.
54. Chiolero RL, Revelly JP, Leverve X, et al. Effects of cardiogenic shock on lactate and glucose metabolism after heart surgery. *Crit Care Med*. 2000;28:3784–3791.
55. Akkose S, Ozgurer A, Bulut M, et al. Relationships between markers of inflammation, severity of injury, and clinical outcomes in hemorrhagic shock. *Adv Ther*. 2007;24:955–962.
56. Hampson NB, Piantadosi CA, Thom SR, Weaver LK. Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning. *Am J Respir Crit Care Med*. 2012;186:1095–1101.
57. Alonso JR, Cardellach F, Lopez S, et al. Carbon monoxide specifically inhibits cytochrome c oxidase of human mitochondrial respiratory chain. *Pharmacol Toxicol*. 2003;93:142–146.

58. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med*. 2005;45:524–528.
59. Bakker J, Coffernils M, Leon M, et al. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. *Chest*. 1991;99:956–962.
60. Gilbert EM, Haupt MT, Mandanas RY, et al. The effect of fluid loading, blood transfusion, and catecholamine infusion on oxygen delivery and consumption in patients with sepsis. *Am Rev Respir Dis*. 1986;134:873–878.
61. Ronco JJ, Fenwick JC, Wiggs BR, et al. Oxygen consumption is independent of increases in oxygen delivery by dobutamine in septic patients who have normal or increased plasma lactate. *Am Rev Respir Dis*. 1993;147:25–31.
62. Ince C. The microcirculation is the motor of sepsis. *Crit Care*. 2005;9(suppl 4):S13–19.
63. Spronk PE, Zandstra DF, Ince C. Bench-to-bedside review: Sepsis is a disease of the microcirculation. *Crit Care*. 2004;8:462–468.
64. Price SA, Spain DA, Wilson MA, et al. Subacute sepsis impairs vascular smooth muscle contractile machinery and alters vasoconstrictor and dilator mechanisms. *J Surg Res*. 1999;83:75–80.
65. Morin MJ, Unno N, Hodin RA, Fink MP. Differential expression of inducible nitric oxide synthase messenger RNA along the longitudinal and crypt-villus axes of the intestine in endotoxemic rats. *Crit Care Med*. 1998;26:1258–1264.
66. Revelly JP, Ayuse T, Brienza N, et al. Endotoxic shock alters distribution of blood flow within the intestinal wall. *Crit Care Med*. 1996;24:1345–1351.
67. Baskurt OK, Temiz A, Meiselman HJ. Red blood cell aggregation in experimental sepsis. *J Lab Clin Med*. 1997;130:183–190.
68. Singel DJ, Stamler JS. Chemical physiology of blood flow regulation by red blood cells: the role of nitric oxide and S-nitrosohemoglobin. *Annu Rev Physiol*. 2005;67:99–145.
69. Cerwinka WH, Cooper D, Krieglstein CF, et al. Superoxide mediates endotoxin-induced platelet-endothelial cell adhesion in intestinal venules. *Am J Physiol Heart Circ Physiol*. 2003;284:H535–H541.
70. Fink MP. Intestinal epithelial hyperpermeability: update on the pathogenesis of gut mucosal barrier dysfunction in critical illness. *Curr Opin Crit Care*. 2003;9:143–151.
71. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet*. 2002;360:219–223.
72. Fredriksson K, Hammarqvist F, Strigard K, et al. Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure. *Am J Physiol Endocrinol Metab*. 2006;291:E1044–E1050.
73. Crouser ED, Julian MW, Blaho DV, Pfeiffer DR. Endotoxin-induced mitochondrial damage correlates with impaired respiratory activity. *Crit Care Med*. 2002;30:276–284.
74. Taylor DJ, Faragher EB, Evanson JM. Inflammatory cytokines stimulate glucose uptake and glycolysis but reduce glucose oxidation in human dermal fibroblasts in vitro. *Circ Shock*. 1992;37:105–110.
75. Vary TC, Siegel JH, Nakatani T, et al. Effect of sepsis on activity of pyruvate dehydrogenase complex in skeletal muscle and liver. *Am J Physiol*. 1986;250:E634–E640.
76. Levy B, Desebbe O, Montemont C, Gibot S. Increased aerobic glycolysis through beta2 stimulation is a common mechanism involved in lactate formation during shock states. *Shock*. 2008;30:417–421.
77. James JH, Fang CH, Schrantz SJ, et al. Linkage of aerobic glycolysis to sodium-potassium transport in rat skeletal muscle. Implications for increased muscle lactate production in sepsis. *J Clin Invest*. 1996;98:2388–2397.
78. McCarter FD, Nierman SR, James JH, et al. Role of skeletal muscle Na+-K+ ATPase activity in increased lactate production in sub-acute sepsis. *Life Sci*. 2002;70:1875–1888.
79. Kraut JA, Madias NE. Lactic acidosis: current treatments and future directions. *Am J Kidney Dis*. 2016;68:473–482.
80. Newman TS, Magnuson TH, Ahrendt SA, et al. The changing face of mesenteric infarction. *Am Surg*. 1998;64:611–616.
81. Liao XP, She YX, Shi CR, Li M. Changes in body fluid markers in intestinal ischemia. *J Pediatr Surg*. 1995;30:1412–1415.
82. Lipka K, Bulow HH. Lactic acidosis following convulsions. *Acta Anaesthesiol Scand*. 2003;47:616–618.
83. Orringer CE, Eustace JC, Wunsch CD, Gardner LB. Natural history of lactic acidosis after grand-mal seizures. A model for the study of an anion-gap acidosis not associated with hyperkalemia. *N Engl J Med*. 1977;297:796–799.
84. Stanley WC, Gertz EW, Wisneski JA, et al. Systemic lactate kinetics during graded exercise in man. *Am J Physiol*. 1985;249:E595–E602.
85. Siegel AJ, Januzzi J, Sluss P, et al. Cardiac biomarkers, electrolytes, and other analytes in collapsed marathon runners: implications for the evaluation of runners following competition. *Am J Clin Pathol*. 2008;129:948–951.
86. Gospe SM Jr, Olin KL, Keen CL. Reduced GABA synthesis in pyridoxine-dependent seizures. *Lancet*. 1994;343:1133–1134.
87. Chin L, Sievers ML, Herrier RN, Picchioni AL. Convulsions as the etiology of lactic acidosis in acute isoniazid toxicity in dogs. *Toxicol Appl Pharmacol*. 1979;49:377–384.
88. Siskind MS, Thienemann D, Kirlin L. Isoniazid-induced neurotoxicity in chronic dialysis patients: report of three cases and a review of the literature. *Nephron*. 1993;64:303–306.
89. Appel D, Rubenstein R, Schrager K, Williams MH Jr. Lactic acidosis in severe asthma. *Am J Med*. 1983;75:580–584.
90. Rabbat A, Laaban JP, Boussairi A, Rochemaure J. Hyperlactatemia during acute severe asthma. *Intensive Care Med*. 1998;24:304–312.
91. Prakash S, Mehta S. Lactic acidosis in asthma: report of two cases and review of the literature. *Can Respir J*. 2002;9:203–208.
92. Meert KL, McCaulley L, Sarnaik AP. Mechanism of lactic acidosis in children with acute severe asthma. *Pediatr Crit Care Med*. 2012;13:28–31.
93. Jee R, Brownlow H. Hyperlactaemia due to nebulised salbutamol. *Anaesthesia*. 2007;62:751–752.
94. Madias NE, Goorno WE, Herson S. Severe lactic acidosis as a presenting feature of pheochromocytoma. *Am J Kidney Dis*. 1987;10:250–253.
95. Taliercio JJ, Bravo E. An unusual presentation of pheochromocytoma. *NDT Plus*. 2011;4:331–334.
96. MacDonald L, Kruse JA, Levy DB, et al. Lactic acidosis and acute ethanol intoxication. *Am J Emerg Med*. 1994;12:32–35.
97. Fulop M, Bock J, Ben-Ezra J, et al. Plasma lactate and 3-hydroxybutyrate levels in patients with acute ethanol intoxication. *Am J Med*. 1986;80:191–194.
98. Klein M, Weksler N, Gurman GM. Fatal metabolic acidosis caused by thiamine deficiency. *J Emerg Med*. 2004;26:301–303.
99. Donnino MW, Vega J, Miller J, Walsh M. Myths and misconceptions of Wernicke's encephalopathy: what every emergency physician should know. *Ann Emerg Med*. 2007;50:715–721.
100. Thomas L, Fay D, Moraillon X, et al. [Lactic acidosis treated with thiamine. 3 cases]. *Presse Med*. 1985;14:1871–1875.
101. Shull PD, Rapoport J. Life-threatening reversible acidosis caused by alcohol abuse. *Nat Rev Nephrol*. 2010;6:555–559.
102. de Groot R, Sprenger RA, Imholz AL, Gerding MN. Type B lactic acidosis in solid malignancies. *Neth J Med*. 2011;69:120–123.
103. Munoz J, Mohd K, Amr H, Stoltenberg M. Severe lactic acidosis in a patient with metastatic prostate cancer. *J Cancer Res Ther*. 2011;7:201–202.
104. Hsu PP, Sabatini DM. Cancer cell metabolism: Warburg and beyond. *Cell*. 2008;134:703–707.
105. Warburg O. On the origin of cancer cells. *Science*. 1956;123:309–314.
106. Romero-Garcia S, Lopez-Gonzalez JS, Baez-Viveros JL, et al. Tumor cell metabolism: an integral view. *Cancer Biol Ther*. 2011;12:939–948.
107. Gillies RJ, Gatenby RA. Metabolism and its sequelae in cancer evolution and therapy. *Cancer J*. 2015;21:88–96.
108. Ortega AD, Sanchez-Arago M, Giner-Sanchez D, et al. Glucose avidity of carcinomas. *Cancer Lett*. 2009;276:125–135.
109. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science*. 2009;324:1029–1033.
110. Christofk HR, Vander Heiden MG, Harris MH, et al. The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. *Nature*. 2008;452:230–233.
111. Mazurek S. Pyruvate kinase type M2: a key regulator of the metabolic budget system in tumor cells. *Int J Biochem Cell Biol*. 2011;43:969–980.
112. Lunt SY, Vander Heiden MG. Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. *Annu Rev Cell Dev Biol*. 2011;27:441–464.
113. Robey RB, Hay N. Is Akt the "Warburg kinase"?—Akt-energy metabolism interactions and oncogenesis. *Semin Cancer Biol*. 2009;19:25–31.

114. Bensaad K, Tsuruta A, Selak MA, et al. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell*. 2006;126:107–120.
115. Yalcin A, Telang S, Clem B, Chesney J. Regulation of glucose metabolism by 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatases in cancer. *Exp Mol Pathol*. 2009;86:174–179.
116. Gao X, Wang H, Yang JJ, et al. Pyruvate kinase M2 regulates gene transcription by acting as a protein kinase. *Mol Cell*. 2012;45:598–609.
117. Demaria M, Poli V. PKM2, STAT3 and HIF-1alpha: The Warburg's vicious circle. *JAKSTAT*. 2012;1:194–196.
118. Marin-Hernandez A, Gallardo-Perez JC, Ralph SJ, et al. HIF-1alpha modulates energy metabolism in cancer cells by inducing over-expression of specific glycolytic isoforms. *Mini Rev Med Chem*. 2009;9:1084–1101.
119. Kim JW, Tchernyshyov I, Semenza GL, Dang CV. HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia. *Cell Metab*. 2006;3:177–185.
120. Choi SY, Collins CC, Gout PW, Wang Y. Cancer-generated lactic acid: a regulatory, immunosuppressive metabolite? *J Pathol*. 2013;230:350–355.
121. Han T, Kang D, Ji D, et al. How does cancer cell metabolism affect tumor migration and invasion? *Cell Adh Migr*. 2013;7:395–403.
122. Neale BW, Mesler EL, Young M, et al. Propylene glycol-induced lactic acidosis in a patient with normal renal function: a proposed mechanism and monitoring recommendations. *Ann Pharmacother*. 2005;39:1732–1736.
123. Arbour R, Esparis B. Osmolar gap metabolic acidosis in a 60-year-old man treated for hypoxemic respiratory failure. *Chest*. 2000;118:545–546.
124. Kelner MJ, Bailey DN. Propylene glycol as a cause of lactic acidosis. *J Anal Toxicol*. 1985;9:40–42.
125. Bulathsinghala M, Keefer K, Van de Louw A. Trimethoprim/sulfamethoxazole-induced severe lactic acidosis: a case report and review of the literature. *Medicine (Baltimore)*. 2016;95:e3478.
126. Liamis G, Milionis HJ, Elisaf M. Pharmacologically-induced metabolic acidosis: a review. *Drug Saf*. 2010;33:371–391.
127. Christopher MM, Eckfeldt JH, Eaton JW. Propylene glycol ingestion causes D-lactic acidosis. *Lab Invest*. 1990;62:114–118.
128. Steller J, Gargus JJ, Gibbs LH, et al. Mild phenotype in a male with pyruvate dehydrogenase complex deficiency associated with novel hemizygous in-frame duplication of the E1alpha subunit gene (PDHA1). *Neuropediatrics*. 2014;45:56–60.
129. Bonnefont JP, Chretien D, Rustin P, et al. Alpha-ketoglutarate dehydrogenase deficiency presenting as congenital lactic acidosis. *J Pediatr*. 1992;121:255–258.
130. Quinonez SC, Leber SM, Martin DM, et al. Leigh syndrome in a girl with a novel DLD mutation causing E3 deficiency. *Pediatr Neurol*. 2013;48:67–72.
131. Van Hove JL, Saenz MS, Thomas JA, et al. Succinyl-CoA ligase deficiency: a mitochondrial hepatoencephalomyopathy. *Pediatr Res*. 2010;68:159–164.
132. DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. *N Engl J Med*. 2003;348:2656–2668.
133. El-Hattab AW, Adesina AM, Jones J, Scaglia F. MELAS syndrome: clinical manifestations, pathogenesis, and treatment options. *Mol Genet Metab*. 2015;116:4–12.
134. Pinto J, Huang YP, Rivlin RS. Inhibition of riboflavin metabolism in rat tissues by chlorpromazine, imipramine, and amitriptyline. *J Clin Invest*. 1981;67:1500–1506.
135. Newmark SR, Himathongkam T, Shane JM. Myxedema coma. *JAMA*. 1974;230:884–885.
136. Cimino JA, Jhangiani S, Schwartz E, Cooperman JM. Riboflavin metabolism in the hypothyroid human adult. *Proc Soc Exp Biol Med*. 1987;184:151–153.
137. Falco V, Rodriguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. *Clin Infect Dis*. 2002;34:838–846.
138. Dlamini J, Ledwaba L, Mokwena N, et al. Lactic acidosis and symptomatic hyperlactataemia in a randomized trial of first-line therapy in HIV-infected adults in South Africa. *Antivir Ther*. 2011;16:605–609.
139. Wester CW, Eden SK, Shepherd BE, et al. Risk factors for symptomatic hyperlactatemia and lactic acidosis among combination antiretroviral therapy-treated adults in Botswana: results from a clinical trial. *AIDS Res Hum Retroviruses*. 2012;28:759–765.
140. Claessens YE, Chiche JD, Mira JP, Cariou A. Bench-to-bedside review: severe lactic acidosis in HIV patients treated with nucleoside analogue reverse transcriptase inhibitors. *Crit Care*. 2003;7:226–232.
141. Lewis W, Dalakas MC. Mitochondrial toxicity of antiviral drugs. *Nat Med*. 1995;1:417–422.
142. Schramm C, Wanitschke R, Galle PR. Thiamine for the treatment of nucleoside analogue-induced severe lactic acidosis. *Eur J Anaesthesiol*. 1999;16:733–735.
143. Luzzati R, Del Bravo P, Di Perri G, et al. Riboflavine and severe lactic acidosis. *Lancet*. 1999;353:901–902.
144. Dalton SD, Rahimi AR. Emerging role of riboflavin in the treatment of nucleoside analogue-induced type B lactic acidosis. *AIDS Patient Care STDS*. 2001;15:611–614.
145. Brinkman K. Editorial response: hyperlactatemia and hepatic steatosis as features of mitochondrial toxicity of nucleoside analogue reverse transcriptase inhibitors. *Clin Infect Dis*. 2000;31:167–169.
146. Apodaca AA, Rakita RM. Linezolid-induced lactic acidosis. *N Engl J Med*. 2003;348:86–87.
147. Moellering RC. Linezolid: the first oxazolidinone antimicrobial. *Ann Intern Med*. 2003;138:135–142.
148. Soriano A, Miro O, Mensa J. Mitochondrial toxicity associated with linezolid. *N Engl J Med*. 2005;353:2305–2306.
149. Garrabou G, Soriano A, Lopez S, et al. Reversible inhibition of mitochondrial protein synthesis during linezolid-related hyperlactatemia. *Antimicrob Agents Chemother*. 2007;51:962–967.
150. Kam PC, Cardone D. Propofol infusion syndrome. *Anaesthesia*. 2007;62:690–701.
151. Mehta N, DeMunter C, Habibi P, et al. Short-term propofol infusions in children. *Lancet*. 1999;354:866–867.
152. Schenkman KA, Yan S. Propofol impairment of mitochondrial respiration in isolated perfused guinea pig hearts determined by reflectance spectroscopy. *Crit Care Med*. 2000;28:172–177.
153. Wolf A, Weir P, Segar P, et al. Impaired fatty acid oxidation in propofol infusion syndrome. *Lancet*. 2001;357:606–607.
154. Shahangian S, Ash KO. Formic and lactic acidosis in a fatal case of methanol intoxication. *Clin Chem*. 1986;32:395–397.
155. Smith SR, Smith SJ, Buckley BM. Combined formate and lactate acidosis in methanol poisoning. *Lancet*. 1981;2:1295–1296.
156. Fijen JW, Kemperman H, Ververs FF, Meulenbelt J. False hyperlactatemia in ethylene glycol poisoning. *Intensive Care Med*. 2006;32:626–627.
157. Morgan TJ, Clark C, Clague A. Artifactual elevation of measured plasma L-lactate concentration in the presence of glycolate. *Crit Care Med*. 1999;27:2177–2179.
158. Woo MY, Greenway DC, Nadler SP, Cardinal P. Artifactual elevation of lactate in ethylene glycol poisoning. *J Emerg Med*. 2003;25:289–293.
159. Manini AF, Hoffman RS, McMartin KE, Nelson LS. Relationship between serum glycolate and falsely elevated lactate in severe ethylene glycol poisoning. *J Anal Toxicol*. 2009;33:174–176.
160. Meng QH, Adeli K, Zello GA, et al. Elevated lactate in ethylene glycol poisoning: True or false? *Clin Chim Acta*. 2010;411:601–604.
161. Borron SW, Baud FJ. Antidotes for acute cyanide poisoning. *Curr Pharm Biotechnol*. 2012;13:1940–1948.
162. Tinker JH, Michenfelder JD. Sodium nitroprusside: pharmacology, toxicology and therapeutics. *Anesthesiology*. 1976;45:340–354.
163. Robin ED, McCauley R. Nitroprusside-related cyanide poisoning. Time (long past due) for urgent, effective interventions. *Chest*. 1992;102:1842–1845.
164. Rousset S, Alves-Guerra MC, Mozo J, et al. The biology of mitochondrial uncoupling proteins. *Diabetes*. 2004;53(suppl 1):S130–135.
165. Terada H. Uncouplers of oxidative phosphorylation. *Environ Health Perspect*. 1990;87:213–218.
166. Hanstein WG. Uncoupling of oxidative phosphorylation. *Biochim Biophys Acta*. 1976;456:129–148.
167. Ozaki S, Kano K, Shirai O. Electrochemical elucidation on the mechanism of uncoupling caused by hydrophobic weak acids. *Phys Chem Chem Phys*. 2008;10:4449–4455.
168. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35:1364–1379.

169. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2010:CD002967.
170. Misbin RI. The phantom of lactic acidosis due to metformin in patients with diabetes. *Diabetes Care*. 2004;27:1791–1793.
171. Devetzis V, Passadakis P, Panagoutsos S, et al. Metformin-related lactic acidosis in patients with acute kidney injury. *Int Urol Nephrol*. 2011;43:1243–1248.
172. Laforest C, Saint-Marcoux F, Amiel JB, et al. Monitoring of metformin-induced lactic acidosis in a diabetic patient with acute kidney failure and effect of hemodialysis. *Int J Clin Pharmacol Ther*. 2013;51:147–151.
173. Bruijstens LA, van Luin M, Buscher-Jungerhans PM, Bosch FH. Reality of severe metformin-induced lactic acidosis in the absence of chronic renal impairment. *Neth J Med*. 2008;66:185–190.
174. Andrzejewski S, Gravel SP, Pollak M, St-Pierre J. Metformin directly acts on mitochondria to alter cellular bioenergetics. *Cancer Metab*. 2014;2:12.
175. Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. *Biochem J*. 2000;348:607–614.
176. El-Mir MY, Nogueira V, Fontaine E, et al. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. *J Biol Chem*. 2000;275:223–228.
177. Brunmair B, Staniek K, Gras F, et al. Thiazolidinediones, like metformin, inhibit respiratory complex I: a common mechanism contributing to their antidiabetic actions? *Diabetes*. 2004;53:1052–1059.
178. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: current perspectives on causes and risk. *Metabolism*. 2016;65:20–29.
179. Foretz M, Hebrard S, Leclerc J, et al. Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. *J Clin Invest*. 2010;120:2355–2369.
180. Jorgensen TG, Weis-Fogh US, Nielsen HH, Olesen HP. Salicylate- and aspirin-induced uncoupling of oxidative phosphorylation in mitochondria isolated from the mucosal membrane of the stomach. *Scand J Clin Lab Invest*. 1976;36:649–654.
181. Gabow PA, Anderson RJ, Potts DE, Schrier RW. Acid-base disturbances in the salicylate-intoxicated adult. *Arch Intern Med*. 1978;138:1481–1484.
182. Heinig RE, Clarke EF, Waterhouse C. Lactic acidosis and liver disease. *Arch Intern Med*. 1979;139:1229–1232.
183. Roth B, Woo O, Blanc P. Early metabolic acidosis and coma after acetaminophen ingestion. *Ann Emerg Med*. 1999;33:452–456.
184. Fannin RD, Russo M, O'Connell TM, et al. Acetaminophen dosing of humans results in blood transcriptome and metabolome changes consistent with impaired oxidative phosphorylation. *Hepatology*. 2010;51:227–236.