

racy of the various clinical definitions of ARDS against a histologic reference standard is provocative but conceptually limited, as Ferguson and colleagues acknowledge. Other investigators (10) have evaluated published definitions of ARDS on a physiologic and outcome basis and found that they identify similar patients from at-risk groups. Yet even with this approach, the definitions are imperfect in diagnosing patients with ARDS in the absence of a true gold standard, and they will remain so until ARDS is better understood.

Given this situation, clinicians and investigators alike should use the widely accepted AECC definition in identifying patients with ARDS and determining their eligibility for clinical trials (7). Whether some of the patients actually have bronchiolitis obliterans with organizing pneumonia, acute eosinophilic pneumonia, pulmonary alveolar proteinosis, or other conditions that may respond to specific therapies in addition to supportive measures for ARDS is unclear, although in some cases lung biopsies may help guide treatment. And even

if these conditions are present, the patients generally should benefit from low-tidal-volume ventilation, which has been tested in other patients who met the AECC definition of ARDS and may or may not have had DAD.

John M. Luce, MD, FCCM
 Medical-Surgical Intensive Care Unit
 San Francisco General Hospital
 University of California
 San Francisco, California

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Lactic acidosis in sepsis: Another commentary*

Blood lactate concentration is regarded by many as the simplest marker of tissue dysoxia in the intensive care unit. The trouble with simple things, however, is that one must understand them very well. The interpretation of blood lactate concentration in critically ill patients, in particular patients with sepsis or in septic shock, is not a simple task. Lactate is an enigma. Lactate can be considered either a metabolic fuel or a metabolic waste product. Lactate is produced by hypoxic tissues but also by fully oxygenated tissues. An elevated blood lactate concentration may, or may not, be predictive of mortality. Elevations in blood lactate

concentration may be produced by increased production or by decreased clearance rates (1).

Anaerobic organisms derive their energy from glycolysis by oxidizing and splitting a six-carbon glucose molecule into two three-carbon pyruvate molecules. The energy released during glycolysis is conserved in forming adenosine triphosphate (ATP) and reducing nicotinamide adenine dinucleotide (NAD⁺) to NADH. Lacking a continuous supply of NAD⁺, glycolysis comes to a sudden and disastrous halt. To the delight of wine aficionados, yeast regenerates NAD⁺ by reducing pyruvate to ethanol. Higher organisms reduce pyruvate to lactate via the enzyme lactate dehydrogenase. This reaction averts pyruvate accumulation in the cytosol and supplies glycolysis with the required NAD⁺.

Aerobic organisms dispose of pyruvate in the mitochondria by transferring electrons to oxygen while generating vast quantities of cellular energy. Lactate pro-

duction increases in hypoxia (type A hyperlactatemia) as the rate of glycolysis accelerates, providing normally aerobic cells with a readily available source of nonmitochondrial ATP (Crabtree effect) (2). Lactate production also may occur in fully oxygenated tissues (type B hyperlactatemia) in response to various inducers, such as metformin and epinephrine (3, 4).

The production of lactate does not cause the acidosis associated with heavy exercise or with hypoxia (5). Cellular acidosis in these conditions is produced by the hydrolysis of nonmitochondrial ATP. Each time a molecule of ATP undergoes hydrolysis, a proton is released. When oxygen is readily available, protons, along with the other products of ATP breakdown, adenosine diphosphate and inorganic phosphate, are recycled by mitochondria and cellular pH remains constant. During hypoxia or exercise, mitochondrial turnover rate drops below the rate of ATP hydrolysis. As more pro-

*See also p. 2235.

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tons are produced by the hydrolysis of nonmitochondrial ATP, intracellular pH falls (6). Lactate helps retard cellular acidosis by binding to protons and forming lactic acid (7).

Returning to the example of ethanol-forming yeast, one may ask why higher organisms did not evolve this strategy as a mean to dispose of pyruvate. After all, it may be argued somewhat cynically, ethanol production could make life a bit more pleasant for many of our hypoxic patients. The answer appears to be that, far from being just a metabolic waste product, lactate is also a very busy transport molecule. There is evidence that lactate shuttling from cytosol to mitochondria, bypassing pyruvate oxidation, promotes glycolytic flux and helps preserve mitochondrial redox (8). Lactate also carries protons from actively metabolic tissues to quiescent or fully aerobic tissues as it diffuses in the blood stream as lactic acid. Acidemia facilitates the uptake of lactic acid from blood whereas the opposite occurs with alkalemia (9). Freshwater turtles survive prolonged conditions of anoxia at low temperature and represent an extreme example of lactate as a proton transporter. Lactic acid efflux from anoxic cells is promoted in these animals by forming calcium lactate in blood and incorporating this compound into the turtle's shell and skeleton (10).

A single measurement of lactate concentration in tissue or body fluids is difficult to interpret since it represents the balance between lactate production and removal. The production of lactate occurs commonly in skeletal muscles during heavy exercise. In fact, fully aerobic, working skeletal muscle produces and uses lactate simultaneously as lactate formed in glycolytic fibers is oxidized by adjacent oxidative fibers (11). Other important sources of lactate production are the ischemic gut (12) and acutely injured lungs (13, 14). Several organs participate in lactate removal from blood. The liver efficiently removes lactate from blood, converting it to glycogen (Cori cycle) (15), and septic patients with chronic liver disease are prone to the development of hyperlactatemia (16). The heart is another efficient user of lactate, deriving up to 20% of its aerobic energy from lactate oxidation (17). Other organs capable of removing lactate from blood are the kidneys, the brain, and skeletal muscle (18, 19).

The generally accepted view of lactate as a hypoxia-related noxious metabolite dates to the 19th century when Pasteur noted the association between hypoxia and lactate accumulation in tissue. Data supporting the "harmful" role of lactate are provided by clinical studies showing mortality rates of 83% and 90% for blood lactate concentrations >5 mmol/L on intensive care unit admission (20) or >8 mmol/L after cardiopulmonary resuscitation (21), respectively.

Much of our understanding of lactate accumulation in tissue derives not from studies of tissue hypoxia but from exercise physiology (22). A.V. Hill (23) defined the "oxygen debt" as the "total amount of oxygen used after cessation of exercise in recovery therefrom." Margaria et al. (24) further established the foundations of the lactic oxygen debt by noting lactate's disappearance from blood after exercise with a half life approximately 15 mins long.

Shoemaker and colleagues (25) expanded the concept of *exercise*-related lactic oxygen debt into a *hypoxia*-related lactic oxygen debt and further proposed that hyperlactatemia was evidence of "covert" tissue hypoxia in sepsis. Coupled with the paradigm of pathologic supply dependence (26), the presence of hyperlactatemia served as the rationale for increasing the rate of oxygen delivery to very high values in septic patients. Although an attractive hypothesis, the presence of a persistent, hypoxia-related lactic oxygen debt is difficult to prove since septic patients usually lack evidence of tissue hypoxia, other than hyperlactatemia. Large clinical trials aimed at increasing the rate of systemic oxygen delivery to "supranormal" values were utter failures since patient mortality either increased (27) or did not change (28) when compared with control groups. In our opinion, the failure of these clinical trials to improve survival is related to the notion that septic hyperlactatemia is not tantamount to tissue hypoxia.

There is accumulating evidence that lactate in septic patients is the product of nonhypoxic increases in glycolytic flux, not "covert" tissue hypoxia. Moreover, considerable argument exists as to whether the hyperlactatemia of sepsis results from increased cellular production or from decreased clearance rate. Levraut and colleagues (29) measured lactate clearance in stable septic patients with normal (1.2 ± 0.2 mmol/L) or mildly elevated (2.6 ± 0.6 mmol/L) blood lactate concentrations and noted lower lactate

clearance in the hyperlactatemic patients. A follow-up study in severely ill septic patients with normal or mildly elevated blood lactate concentration (<3 mmol/L) showed that low lactate clearance was predictive of poor outcome (30).

Findings opposite to those of Levraut et al. were reported by Chioloro and colleagues (31) in postoperative cardiogenic shock hyperlactatemia. The latter concluded that hyperlactatemia in their study subjects could be explained by increases in lactate production, with alterations in lactate utilization playing a minor role. Since many of the patients in their study had marked increases in glucose production, Chioloro et al. also concluded that increased rates of glycolysis contributed significantly to the development of hyperlactatemia. It is significant to note that patients in the study by Chioloro et al. had high levels of arterial lactate (7.8 ± 3.4 mmol/L) when compared with those of Levraut et al. (2.6 ± 0.6 mmol/L).

In the present issue of *Critical Care Medicine*, Dr. Revelly and colleagues (32) evaluated lactate production and clearance in patients with septic shock, patients with circulatory failure, and normal volunteers. They infused ^{13}C -labeled sodium lactate and ^2H -labeled glucose in these individuals and calculated the rate of gluconeogenesis from lactate by measuring plasma ^{13}C -glucose and that of lactate oxidation from measurements of expired $^{13}\text{CO}_2$. Lactate clearance was computed using a pharmacokinetic model. The authors found that the increased lactate production in patients with septic or cardiogenic shock was present despite lactate clearance being similar to healthy subjects. Baseline arterial lactate concentrations were 3.2 ± 2.6 mmol/L in septic shock patients, 2.8 ± 0.4 mmol/L in cardiogenic shock patients, and 0.9 ± 0.2 mmol/L in healthy subjects.

Dr. Revelly and colleagues (32) should be congratulated for the care shown in performing these very difficult clinical studies. Given the complexity of the experiments, and as acknowledged in their article, the statistical power of the study is limited by the small number of subjects in each group. A methodological concern is the application of a steady-state pharmacokinetic model that assumes steady state to a condition in which the subjects failed to achieve a lactate concentration plateau. Using the last measured point as an estimate of the plateau value makes the results of the model highly dependent

on the assumption of having reached a steady-state condition. Perhaps it would have been more satisfying, although perhaps not more valid, to extrapolate a fitted mathematical function of the data to a plateau value.

The divergent findings of Dr. Revelly and colleagues (32) and those of Levraut et al. (29) perhaps can be explained by methodological differences in measuring lactate clearance. Dr. Revelly and colleagues used a continuous infusion method, as opposed by the bolus injection method used by Levraut et al. There were also small differences in patient population, with the subjects in Revelly et al. study having higher lactate concentration values.

Except in those individuals with clear evidence of systemic or regional cessation of blood flow, elevations in blood lactate concentration in critical ill patients probably bear little relation to tissue hypoxia. Most likely, the metabolism of lactate and glucose in sepsis is tied to the cellular inflammatory response (33). Some tissues will produce lactate in concert with their degree of inflammation whereas other tissues will consume it. We applaud the efforts of Dr. Revelly and colleagues (32), as well as those of Chiolero et al. (31) and Levraut et al. (29), in attempting to define the complexity of lactate kinetics in critically ill patients.

Guillermo Gutierrez, MD, PhD

Pulmonary and Critical Care
Medicine Division
Department of Medicine
The George Washington University
Medical Center
Washington, DC

Marian E. Wulf, MD

Department of Obstetrics and
Gynecology
Georgetown University Hospital
Washington, DC

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The unpretentious role of 2,3-diphosphoglycerate in critical illness*

The structure of hemoglobin was determined by Perutz and Kendrew (1) with x-ray crystallography almost a century after its discovery by the German chemist Felix Hoppe-Seyler in 1871. The function of hemoglobin as an oxygen carrier was established in the early 20th century by Bohr, Hasselbalch, and Krogh (2), who first described the sigmoid shape of the oxyhemoglobin dissociation curve (ODC).

The hemoglobin protein is a tetramer composed of two α and two β polypeptide chains. Each chain contains a heme group capable of binding reversibly to oxygen. The sigmoid shape of the ODC is characteristic of an allosteric enzyme system, in which the substrate also serves to modulate catalytic activity (3). Fully deoxygenated hemoglobin has low oxygen affinity. Initial binding to an oxygen molecule produces mechanical and chemical stresses that relax the α - β chains of hemoglobin and expose inner oxygen-binding sites. This conformational change increases the affinity of hemoglobin for the next oxygen molecule. As all binding sites are filled, oxygen affinity again decreases. The ability to alter oxygen affinity as a function of oxygen saturation makes hemoglobin an ideal oxygen carrier. Partially deoxygenated venous blood enters pulmonary capillaries, avidly searching for oxygen. Fully oxygenated arterial blood enters tissue capillaries ready to yield its precious cargo.

Alterations in hemoglobin affinity are best characterized by changes in P50, the oxygen tension at which hemoglobin is 50% saturated. Increases in P50 (right shift of the ODC) correspond to lower hemoglobin oxygen affinity. Decreases in P50 (left shift of the ODC) correspond to higher oxygen affinity. Increases in blood temperature, hydrogen ion concentra-

tion, and P_{CO_2} independently lower oxygen affinity through a conformational change in the hemoglobin molecule, albeit to a lesser extent than that produced by heme-to-oxygen binding. Decreased-oxygen-affinity hemoglobin promotes oxygen release in organs with a high metabolic rate, whereas increased-oxygen-affinity hemoglobin facilitates blood oxygen uptake when alveolar P_{O_2} is low.

Cell-free hemoglobin produces substantial vasoconstriction in some endothelial beds (4) since hemoglobin is a potent nitric oxide scavenger (5) with an affinity for nitric oxide 8,000 times that for oxygen (6). Erythrocytes isolate hemoglobin from the endothelial milieu. Furthermore, they do not consume oxygen to generate adenosine triphosphate but instead use glycolysis as their exclusive source of energy. The fermentation of glucose into pyruvate and lactate results in the generation of adenosine triphosphate and in the accumulation of 2,3-diphosphoglycerate (2,3-DPG) (7). Deoxyhemoglobin binds to 2,3-DPG, decreasing hemoglobin oxygen affinity (8, 9). 2,3-DPG also acts on the ODC by altering the Gibbs-Donnan equilibrium in the cell, with consequent lowering of intracellular pH (10).

Unlike the rapid swings in P50 produced by changes in pH or temperature, 2,3-DPG accumulates slowly as a function of the erythrocyte glycolytic rate. Measurable changes in P50 produced by 2,3-DPG require 4–24 hrs to occur (11). Acidosis and reductions in inorganic phosphate decrease blood 2,3-DPG concentration, whereas hypoxia and altitude tend to increase it (12).

Few studies have measured blood 2,3-DPG concentration in critically ill patients or the effect that alterations in 2,3-DPG have on P50 *in vivo*. Of particular interest is the effect that depletion of 2,3-DPG in stored blood (13) has on tissue oxygen delivery (14, 15). Blood transfusions depress overall 2,3-DPG concentration in heart surgery patients (16) but apparently do not affect hemodynamic or oxygen-transport parameters.

Morgan et al. (17) noted decreases in 2,3-DPG concentrations in a mixed group

of critically ill patients but no changes in P50 or in tissue oxygenation. Agusti et al. (18) found higher pH and 2,3-DPG concentrations in a group of mechanically ventilated patients with acute respiratory failure than in a nonventilated cohort. The *in vivo* P50, however, was lower in the ventilated patients. This finding supports the notion that the position of the ODC in critically ill patients is determined primarily by alterations in blood pH, not by changes in 2,3-DPG levels.

The study by Ibrahim and colleagues (19) in this issue of *Critical Care Medicine* explores the relationship between ICU mortality rate and erythrocyte 2,3-DPG concentration. Little is known about this subject, and the authors should be congratulated for their efforts. They measured 2,3-DPG concentrations in a large, heterogeneous cohort of critically ill patients within 24 hrs of ICU admission and compared them with concentrations for a healthy reference group matched by age and sex. They excluded patients who had received a blood transfusion within the previous 24 hrs, ensuring that 2,3-DPG measurements were of either native or *in vivo* rejuvenated erythrocytes.

Ibrahim et al. (19) found no association between ICU mortality and blood 2,3-DPG concentration. Moreover, 2,3-DPG concentration was lower in the ICU patients than in the reference group. This difference could be attributed exclusively to a lower 2,3-DPG concentration in female patients, a remarkable and unexpected finding. A multivariate analysis of the data found no association between gender and 2,3-DPG concentration, so perhaps small but cumulative variances between male and female patient groups were responsible for a lower 2,3-DPG in female patients. This finding certainly merits attention in future investigations.

The study by Ibrahim et al. (19) showed a normal mean *in vivo* P50 (28.5 Torr, or 3.8 kPa) and a reciprocal relationship between blood hydrogen ion and 2,3-DPG concentrations. This relationship appears to be strongest in female patients (Fig. 3 of their article). Ibrahim et al. hypothesize that decreases in 2,3-

*See also p. 2247.

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DPG may affect adversely the unloading of oxygen from blood in tissue capillaries by shifting the ODC curve to the left, or at least by hindering a hydrogen ion-induced rightward shift.

Although it is commonly accepted that decreases in hemoglobin affinity promote the release of oxygen in the tissue capillaries, it is not certain that leftward shift of the ODC impairs tissue oxygen delivery. In fact, Barcroft et al. (20) suggested that acclimatization to a hypoxic environment requires a left shift of the ODC to fully saturate hemoglobin at lower alveolar P_{O_2} values. Subsequent measurements at high altitude, however, showed that acclimatized subjects develop chronic hyperventilation and respiratory alkalosis (21), a response that is accompanied by increases in 2,3-DPG, resulting in constant P50 or even a slight increase in oxygen affinity (22).

As Fairweather et al. (23) proposed >30 yrs ago, perhaps the function of 2,3-DPG is to unobtrusively defend a normal P50 from persistent acid-base disturbances. Increases in hemoglobin oxygen affinity resulting from acidemia are moderated by decreases in 2,3-DPG, whereas the opposite occurs with alkalemia. Avoiding large alterations in P50 might help position the ODC optimally to swing left when loading oxygen and swing right when releasing it. This phasic adjustment in P50 would create the most favorable conditions for oxygen transfer from the lungs to the tissues.

Guillermo Gutierrez, MD, PhD
 Pulmonary and Critical Care
 Medicine Division
 Department of Medicine
 The George Washington University
 Medical Center
 Washington, DC

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