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ED Closing Puts Native Americans at Risk

BY RUTH SORELLE, MPH

"They made us many promises, more than I can remember. But they kept but one. They promised to take our land … and they took it."
— Red Cloud, a Sioux leader (*Native American Tribes: The History and Culture of the Sioux*; CreateSpace, 2013.)

In a series of treaties between the U.S. government and the Sioux tribes of the Great Plains in the late 1800s, the federal government promised a variety of services to the Native Americans who gave up their land and agreed to live on reservations. Promises of food, education, housing, and health care received short shrift in the ensuing years, problems that persist to this day. The situation at the Indian Health Service Rosebud Hospital in an isolated area of South Dakota is an example.

Gio_Banfi/Thinkstock.com

Ambulances drive from Rosebud, SD, to the three closest hospitals that are 44, 53, and 55 miles away. Six patients have died en route.

For at least seven months, a steady stream of ambulances plied the roads between Rosebud, SD, where the ED closed Dec. 5, 2015, and the three closest hospitals: Cherry County Hospital in Valentine, NE (44 miles away); Bennett County Hospital and Nursing Home in Martin, SD (53 miles away); and Winner Regional Hospital in Winner, SD (55 miles away). During that time, they ferried often critically ill patients from the closed emergency department at Rosebud to the closest facilities where they

Continued on page 31

Humans Are Not Yeast

BY PAUL MARIK, MD

Back in the early 1900s, physicians believed that humans made lactate when they didn't have oxygen and that it's not a normal product. This myth continues, as an article from as recently as 2004 showed. (*Circulation* 2004; 110[4]:e27.)

Researchers looking at exercise physiology talk about the anaerobic threshold — which I'll show does not exist — but a normal person who is exercising starts making lactate as he reaches his VO_2 max. They call that the lactate or anaerobic threshold, and as we'll see, it's not anaerobic. Interestingly enough, trained athletes can shift their lactate threshold.

Max Harry Weil, MD, PhD, cemented this concept into critical care. Forty years ago, he showed that the probability of survival increases exponentially as lactate goes down. Or the other way around: As lactate goes up, the chance of survival goes down. (*Circulation* 1970;41[6]:989.)

Continued on page 29

Enemy of the Good: Lowering BP in ICH

BY EVIE MARCOLINI, MD

"The perfect is the enemy of the good." This quote, originally penned by Francois-Marie Arouet under the pseudonym Voltaire, is often used by surgeons encouraging their students to be aware of the dangers of going a bit too far in pursuit of perfection. Perhaps we can apply this maxim to neurology and the pursuit of lower blood pressure in spontaneous intracerebral hemorrhage (ICH).

We know a lot about ICH, but there is even more we don't know. It's only recently that we know that hematoma expansion has been associated with early neurologic deterioration.

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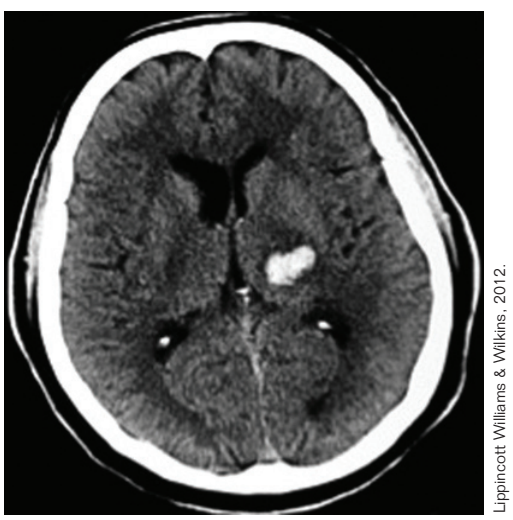

Lippincott Williams & Wilkins, 2012.

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He postulated that this is caused by an oxygen debt and anaerobic metabolism.

I'm sure most people still believe this theory. We have this remarkably scientific document called "Surviving Sepsis," which should really be relabeled "How Not to Survive Sepsis." (www.survivingsepsis.org.) What do they suggest? Target resuscitation to normalize lactate in a patient with elevated lactate as a marker of tissue hypoperfusion. This is such a pervasive concept: Lactate is made anaerobically because patients don't have oxygen. One article titled simply, "Lactic Acidosis," appeared in the *New England Journal of Medicine* (2014;371[24]:2309), but this condition does not exist, even though they subdivided it into type A: hypoxia and type B: non-hypoxia. This is a recent review article on a disease that does not exist.

We need to look at the biochemistry. We all know about glycolysis, glucose, ADP, that phosphorous produces lactate. No hydrogen ions are present in glycolysis. In fact, the conversion of pyruvate to lactate *consumes* hydrogen ions. Prof. Wieland Gevers was the first to document scientifically that the reaction producing lactate consumes a pair of free protons, retarding acidosis. (*J Mol Cell Cardiol* 1997;9[11]:867.)

It is actually a lactic alkalosis. A review in the *American Journal of Physiology Regulatory, Integrative, and Comparative Physiology* reported that lactate production retards — it does not cause — acidosis. (2004;287[3];R502.) The lactic acidosis explanation of metabolic acidosis is not supported by fundamental biochemistry, and has no research basis. Acidosis is caused by reactions other than lactate production. Every time ATP is broken down to ADP, Pi and a proton are released.

Precursor to Gluconeogensis

But the human body does make lactate, about 1,400 mmol per day. The normal serum level is less than 2. Most of it, about 70 percent, is metabolized by the liver and by the kidneys via the Cori cycle. We know the Cori cycle: We have lactate going to pyruvate and glucose. Lactate is the most important precursor to gluconeogenesis. A normal resting person is about 50 percent gluconeogenesis and 50 percent oxidation. When people exercise, lactate is the primary fuel for the brain and the heart, and they oxidize lactate.

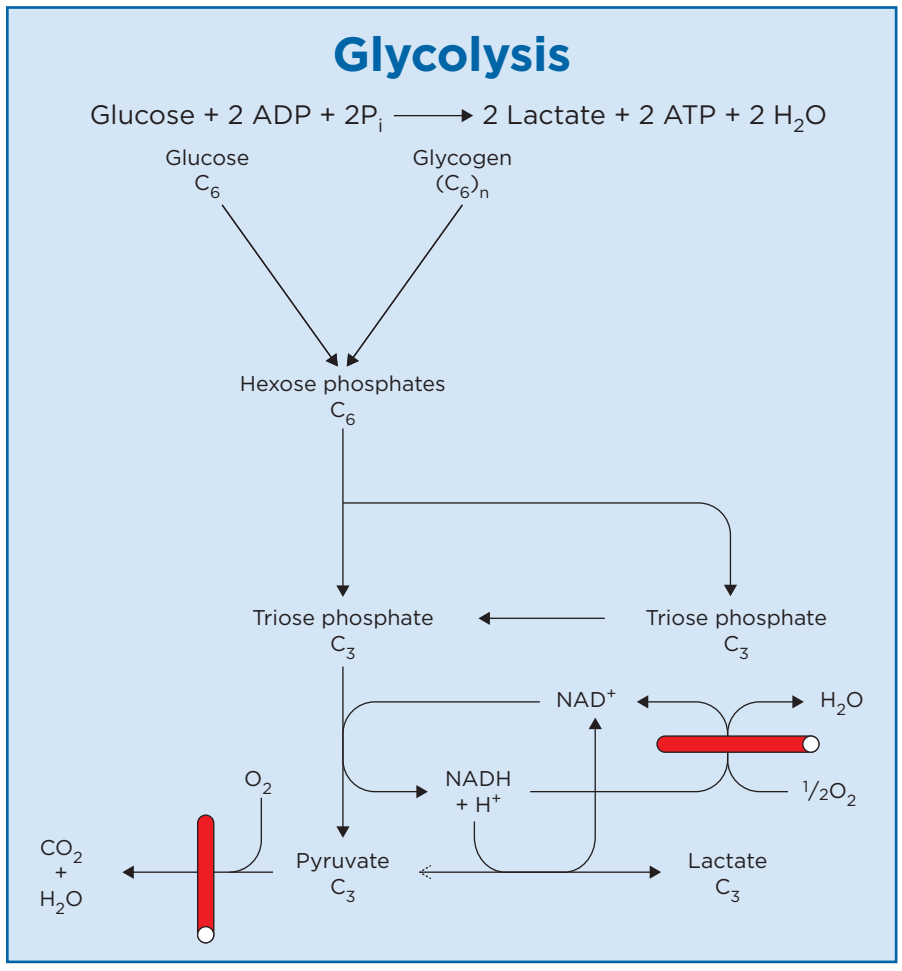
Then there is the tissue hypoxia myth. We know the oxygen-diffusion gradient PO_2 is about 160 in the air, 104 in the alveolus, 109 on the arterial side, and about 40 on the venous side. So we have this oxygen diffusion gradient. The cytosolic PO_2 in the cell is about 5 mm Hg, and the mitochondrial critical O_2 threshold for oxygen aerobic metabolism is about 1 mm Hg. Humans probably develop anaerobic metabolism only when it is less than 1 mm Hg in the mitochondria.

Take, for example, the silly humans who decide to climb Mount Everest without oxygen and then stick a syringe in their femoral artery to take blood when they reach the balcony. (*New Engl J Med* 2009; 360[2]:140.) Some doctors did this outrageous thing, and their mean PaO_2 was 24, and their lactate was normal. *Their lactate was normal*.

Physicians believe the myth that humans make lactate when they don't have oxygen

Another interesting experiment took humans exercising to their VO_2 max. Their leg VO_2 goes up, intracellular O_2 stays the same, yet arterial lactate goes up. As they increase their exercise endurance, however, their skeletal muscles export lactate. This is a brilliant design, and it's not anaerobic. Why did this happen? It's pretty ingenious because we have the lactate threshold. As patients reach about 60 percent of the O_2 max, they start making lactate, which occurs simultaneously with increasing blood epinephrine levels. And you'll see why epinephrine makes lactate.

What happens when someone exercises? The mitochondrion consumes lactate as a source of fuel. People exercise to improve efficiency, and their heart uses lactate. Lactate is a much more efficient bioenergetic fuel than glucose so as someone exercises, the muscles make lactate to fuel the heart. The heart works much more efficiently with lactate. What happens to the brain? The exact same thing. As someone exercises, brain lactate goes up, and the brain starts using lactate preferentially as a source of fuel. This is a brilliant design: Muscles make lactate aerobically as a source of energy for the brain and heart.



Paul Marik, MD

Going back to sepsis: There is this pervasive idea that people with sepsis have cellular hypoxia and bioenergetic failure, but this concept was debunked in 1992. That was more than 25 years ago, and people still don't get it. (*JAMA* 1992;267[11]:150.) Hotchkiss and Karl measured ATP, cellular oxygen levels, and markers of anaerobic metabolism in patients with sepsis; it does not happen. In fact, what happens with sepsis is that it actually goes up if muscle PO_2 is measured. Compared with limited infection, the muscle O_2 goes up in patients with severe sepsis.

Oxygen Delivery

Another intriguing experiment by Ronco, et al., measured the DO_2 or VO_2 in patients who were dying and whose care was being withdrawn. They found humans become supply-dependent at only at 4 mmol/kg. (*JAMA* 1993;270 [14]:1724.) This threshold has been repeated time and time again. They have measured DO_2 and VO_2 in Jehovah Witnesses bleeding to death, and found the exact same threshold: about 3.8 mmol/kg, which works out to about 330 mmol per minute or a cardiac output of about two liters. Patients only reach a critical level as a preterminal state. The study authors said — 25 years ago — that sepsis does not alter critical O_2 delivery for anaerobic metabolism or tissue O_2 extraction. Interventions to increase oxygen delivery to supernormal levels in humans with the hope of increasing oxygen consumption may be inappropriate.

Hayes, et al., did a study (*New Engl J Med* 1994;330[24]:1717) where they iatrogenically tried to drive up oxygen delivery, and the outcome was that they killed people. That's not our goal. Ratcheting up oxygen delivery increases the number of dead people. So this study looked at VO_2 and DO_2 in patients with high lactate; they drove up oxygen delivery, and oxygen consumption stayed exactly the same. Trying to drive up oxygen delivery to make lactate go away does not work.

A more intriguing experiment was done by investigators who gave esmolol to patients with refractory septic shock. (*JAMA* 1992;267[11]:1503.) As we know, esmolol is a beta-1 receptor agonist

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that will decrease heart rate and contractility. Oxygen delivery went down in the esmolol group compared with the control group. Lactate went down in patients whose oxygen delivery was decreased compared with the control group who were treated with placebo. This study demonstrated that decreasing oxygen delivery decreased lactate. This whole idea of trying to get rid of lactate by revving up oxygen delivery is bogus.

A study that Scott Weingart, MD, and I did looked at lactate clearance in patients with sepsis, and we demonstrated that lactate clearance was exactly the same in survivors and nonsurvivors. (http://bit.ly/2aa5DGH.) Titrating treatment to lactate clearance is another bogus myth. Why does someone get a high lactate when septic? It is generated aerobically. It has now been well established that epinephrine released as part of the stress response stimulates Na+/K+-ATPase activity. The hypermetabolic state with increased Na+/K+-ATPase activity results in accelerated glycolysis and generates pyruvate and lactate at an increased rate. If glycolysis occurs at a rate that exceeds that of oxidative metabolism, some pyruvate may not be oxidatively metabolized in the Krebs cycle and will be converted to lactate

Increased lactate may simply occur because of increased production of pyruvate due to increased glycolysis — there is no oxygen debt. We spoke about the muscles exporting lactate; the same thing happens in shock: lactate is used as a fuel for oxidative metabolism. Lactate is transported into the mitochondrion through specific transport proteins, and then is converted to pyruvate in the mitochondrial intermembrane space. Pyruvate then moves into the mitochondrial matrix and undergoes oxidative metabolism.

Lactate is, therefore, a fuel for oxidative metabolism. It's consumed by the brain and heart, and that is absolutely vital to survival when someone is in shock. The body makes lactate, which is then used as a metabolic fuel. We know this in the brain because of the astrocyte-neuron lactate shuttle. The astrocytes make lactate and shuttle it to the neurons used as a fuel. So lactate is good, not bad.

Brain and cardiac muscle increase oxidation during exercise and shock. Lactate removal during shock is associated with cardiovascular collapse. If lactate production is prevented in shock, the risk of death is increased. If lactate is infused, that increases cardiac output in cardiogenic and septic shock. Lactate is a survival advantage. Infusion of lactate improves energy utilization and brain function after traumatic brain injury. Give them lactate; it's your friend, not your enemy.

Ability to Survive

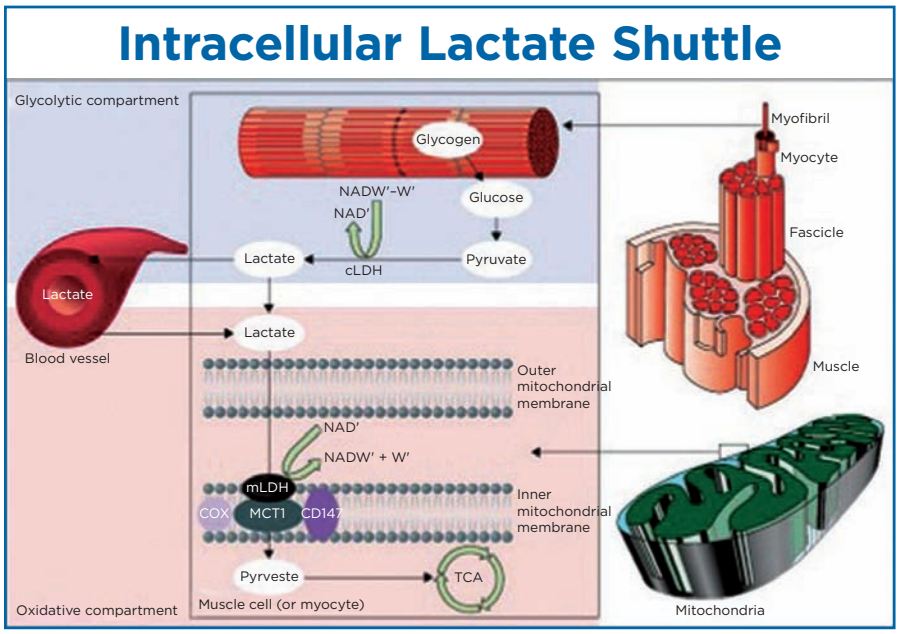
A study using the endotoxic shock model showed that lactate accumulation was prevented by giving a beta-2 blocker and DCA, but preventing lactate increases the risk of death. Animals die if lactate production is prevented. This study gave hypertonic lactate in porcine endotoxic model, and it improved cardiac output and cardiac function. (*Intensive Care Med* 2007;33[3]:495.)

A study done in rats simulated head injury, and then administered lactate. The researchers looked at their ability to perform complex maneuvers, and found that giving lactate to rats improved their ability to survive. (*Brain Res* 2002;928[1-2]:156.)

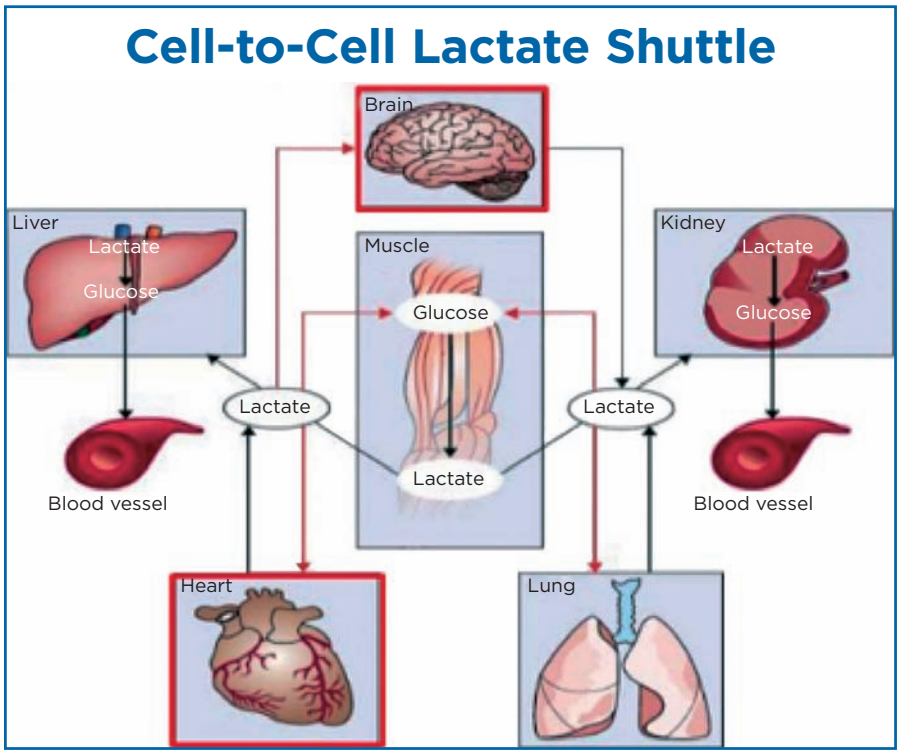
Another study showed that the human brain uses lactate as a source of energy. (*Intensive Care Med* 2014;40[3]:412.) The clinical plausibility was that lactate increases during adrenergic states and in the absence of an oxygen debt. Lactate increases with epinephrine infusion; lactate increases with hyperdynamic sepsis. All of the states have a high cardiac output, high oxygen delivery, and not a single trace of hypoxia. It's driven by epinephrine, not by hypoxia.

Lactate is not an accurate, reliable, robust marker of hypoxia, whatever hypoxia actually is. In fact, the threshold for human survival is 20 mm Hg. PaO_2 below 20 mm Hg is incompatible with survival, and above 20 is adequate for mitochondrial respiration. Lactate's link with hypoxia is biologically implausible, experimentally flawed, and clinically improbable. The only exception would be if a blood vessel is completely occluded. Lactate may be produced if the mesenteric artery is occluded. It's now clear that lactate is a major mitochondrial fuel rapidly utilized in cell-to-cell and intracellular shuttles. It's taken up by mitochondria to optimize bioenergetics. And interestingly, it acts as a hormone and increases the transcription of the enzymes responsible for its transport. It has a powerful effect on protein synthesis.

We do know that lactate is associated with increased mortality because the sicker a patient is, the higher his epinephrine levels. It's a protective mechanism. The association is related to the fact that lactate is a biomarker of physiological stress. And clearly the greater the physiological stress, the greater the risk of death. But lactate itself is a survival advantage, and it's not an evolutionary accident that we make lactate. **EMN**



Paul Marik, MD



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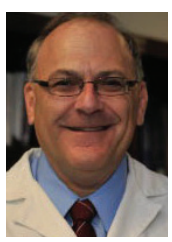
Titrating treatment to lactate clearance is another bogus myth



Dr. Marik *is a professor of medicine and the chief of pulmonary and critical care medicine at Eastern Virginia Medical School in Norfolk. He has written more than 400 peer-reviewed journal articles, 50 book chapters, and four critical care books. Dr. Marik also holds a master's in medicine, a bachelor's in pharmacology, and diplomas in anesthesia and tropical medicine and hygiene. He completed a critical care fellowship, and is board certified in internal medicine, critical care medicine, neurocritical care, and nutrition science.*