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Clinical Use of Lactate Measurements: Comment

To the Editor:

We read with great interest the recent review discussing the clinical interpretation of lactate measurements by Drs. Pino and Singh.[1] The article covered the topic in great detail; however, there are several points which we also feel warrant inclusion when discussing this topic.

An additional source of lactate in surgical patients can be from red blood cell transfusion. As the authors state, red cells are completely anaerobic because they lack mitochondria and require glycolysis for maintenance of adenosine triphosphate. As a result, stored red blood cells are a source of lactate from transfusions; lactate levels and resultant patient lactate loads can increase with the use of stored red blood cells. Although many patients have adequate capability to metabolize lactate loads from transfusion, this may not be the case in massive transfusions, liver transplantation, or pediatric cardiac surgery. In particular, sudden massive boluses of red blood cell–derived lactate in pediatric cardiac surgery from older stored red blood cells can significantly impact more traditional and conventional interpretations of lactate concentration.[2]

Additionally, endogenous overproduction of lactate may represent more than a metabolic waste product. Proponents of the concept contend that lactate can function as a metabolic glucose regulator and regulator of insulin release and insulin resistance.[3] Brooks[4] reviews compelling evidence that endogenous L-lactate is actively involved in aerobic intermediary energy metabolism and signaling effects through hydroxycarboxylic acid receptor 1. In the population with obesity, new evidence suggests hormonally triggered overproduction of lactate is an essential and obligatory feature of adipocytes, even in the absence of hypoxia.[5] Adipocyte lactate production may therefore alter interpretations of elevated lactate levels in obesity and insulin resistance, although this concept is too recent for correlative studies in the perioperative period to define the magnitude and significance of these metabolic pathways.

The authors state that typical measurements of lactate, as conventionally performed with a blood gas machine, do not detect D-lactate, which has been shown to produce numerous deleterious effects. Some formulations of lactated Ringer's solution have historically contained DL lactate,[6] and although most formulations today are likely to contain only L-lactate, compositions may vary between countries and manufacturers. Additionally, although the consumption of fermented foods may contribute only a small proportion of total lactate as D-lactate, the presence and significance of D-lactate in pathologic states is not limited to gut ischemia or short bowel syndrome. Small intestinal bacterial overgrowth, in the absence of short bowel syndrome, has been associated with D-lactic acidosis with central nervous system symptoms. In fact, half of probiotic strains have been shown to ferment carbohydrates to D or DL lactate and may be responsible for gastrointestinal and central nervous system symptoms from D-lactic acidemia in some patients.[7] Because D-lactate levels are not customary measurements, it is conceivable that many cases can be missed with routine laboratory investigations.

Competing Interests

The authors declare no competing interests.

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Clinical Use of Lactate Measurements: Comment

To the Editor:

With great interest, we read the Clinical Focus Review on lactate by Pino and Singh.[1] We strongly agree with the need to decouple an increased lactate level from the mandatory use of fluid infusions.

The authors argue, however, that lactate is a consequence rather than a cause of cellular acidosis and describe the lactate ion as a weak base ("that accepts some of the protons"). This latter statement would imply that increasing lactate levels *per se* would act to decrease acidity, which is in obvious conflict with ubiquitous clinical experience. In this context, we find the quantitative acid–base perspective as described by Stewart and others theoretically more satisfying and clinically useful.[2] The core of the theory states that the concentration of protons (being weak ions) does not change primarily by processes adding or removing these ions (such as when producing lactic acid), but from processes changing the conditions for dissociation of water, which at a concentration of about 55 mol/l (sic) in plasma is a vast potential proton source. As shown by Stewart, the dissociation of water is influenced by carbon dioxide, weak acids, and the strong ion difference, the difference between the sums of strong cations and strong anions. Based on the cutoff value of 4 for the pK of strong electrolytes in biologic systems, lactate in plasma behaves as a strong anion.[2] Therefore, an increase in lactate will decrease the strong ion difference and thereby increase water dissociation and thus increase proton concentration. Contrary to what the authors state, lactate (ion) and not the lactic acid *per se* is a direct cause of acidosis, and increased lactate concentration is reflected 1:1 as a change in base excess. Infusion of sodium lactate does not cause acidosis as the lactate is accompanied by the strong cation sodium, and when the lactate is metabolized (with sodium remaining), the strong ion difference increases, leading to decreased water dissociation and decreased acidity. This perspective on lactate also allows for rapid bedside differentiation of changes in base excess associated with changes in lactate.[3]

Competing Interests

The authors declare no competing interests.

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Clinical Use of Lactate Measurements: Reply

In Reply:

The interpretation of blood lactate results, especially with respect to elevated values, is often based on inaccurate assumptions. We decided upon this topic for the Clinical Focus Review[1] based on our observations of clinicians from all disciplines who routinely gave fluid boluses to normalize the lactate of patients with hemodynamic stability, euvolemia, and normal acid base balances without ruling out the reason for the hyperlactatemia.

We are in agreement with Woehlck *et al.*[2] that lactate can be elevated from stored red blood cells as well as the

inability to clear during massive transfusions. The studies of lactate metabolism in adipocytes were biochemically complex, extensive, and data-rich. However, we feel that the applicability of *in vitro* rat cell results and studies of *Drosophila* to humans is too premature.[3]

The comments of Bahlmann and Werner-Moller[4] from Sweden about our Clinical Focus Review, which was written in Boston, are reminiscent of "The Great Trans-Atlantic Acid-Base Debate" published in 1965.[5] Their opinions are rooted on the role of lactate in the strong ion difference, based on the calculations of Stewart[6] for the determination of acidosis. *In vivo*, the interactions of plasma, erythrocytes, and the interstitium are complex, and the Stewart approach is complementary to other alternatives for acid–base assessments but is not definitive.[7] It is not uncommon to have a metabolic acidosis ruled out with an increased lactate that is inadequate to explain the severity of the acidosis or the elevation in the anionic gap.[8] Critically ill patients may present severe hyperlactatemia with normal values of pH, bicarbonate, and base excess as a result associated with hypochloremic alkalosis.[9]

The key to lactate-associated metabolic acidosis is not necessarily the stoichiometry of acid–base balance but the reason for its elevation.

Competing Interests

Dr. Pino reports financial relationships with Morrison Mahoney (Boston, Massachusetts) and Ratcliff Harten Galamaga LLP (Providence, Rhode Island) for expert legal testimony. Dr. Singh declares no competing interests.

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Anesthetics and Postoperative Cognition: Comment

To the Editor:

In their study, "Intravenous *versus* Volatile Anesthetic Effects on Postoperative Cognition in Elderly Patients Undergoing Laparoscopic Abdominal Surgery," Li *et al.*[1] reported no difference in the incidence of delayed neurocognitive recovery in patients undergoing laparoscopic abdominal surgery with general anesthesia using sevoflurane *versus* propofol. Their secondary outcome involved measuring biomarkers at five prespecified perioperative timepoints to assess their potential to predict delayed neurocognitive recovery. They found that the interleukin-6 concentration at 1 h after the start of surgery (Timepoint 3 [T3]) was significantly different between patients with and without delayed neurocognitive recovery. We have two points of discussion regarding this finding.

First, we wonder about the true significance of interleukin-6 at T3. Thirteen biomarkers were tested at five different timepoints, yielding 65 distinct data points. Testing this many variables increases the likelihood of achieving a "significant" *P* value simply by chance, especially when the alpha level has not been adjusted for multiple testing. Is it more likely that of all the biomarkers tested, only interleukin-6 (and only at 1 h after the start of surgery) would be a true predictor of delayed neurocognitive recovery, or that this one significant value occurred solely by chance? Adding to this question is the fact that the CI of the odds ratio for interleukin-6 at T3 (1.04 [1.01 to 1.07]) nearly encompassed 1.0.

Second, the authors note that both sevoflurane and propofol have been implicated in cellular injury and may play roles in the neuroinflammatory process that occurs with