

However, instead of being a harmful molecule *per se*, lactate is a central molecule in the intra- and interorgan exchange of carbon and redox potential (1). The study by Gattinoni and colleagues, who used a novel approach to analyze data from the ALBIOS (Volume Replacement with Albumin in Severe Sepsis) study, adds to the required change of paradigm concerning lactate metabolism in sepsis (2). The authors nicely demonstrate that there are multiple reasons for hyperlactatemia in sepsis, and that the increased snapshot value we measure reflects an imbalance between increased production and reduced consumption.

By introducing the term “lactic base excess,” the authors also elegantly demonstrate that there is no causal relationship between elevated lactate and metabolic acidosis. We would add that, in fact, lactic acidosis *per se* is a misnomer, a construct that doesn't exist, because there is no lactic acid present in the human body (3). Similarly, we agree that current fluid resuscitation strategies should be modified and perhaps concentrate on organ perfusion rather than targeting hyperlactatemia (4).

We would, however, question the conclusion that impaired tissue oxygen use is the most likely causative factor for hyperlactatemia. Although we are unable to perform correlations without access to the raw data, if we chart the means shown in Table E2 in the online supplement of Reference 2, there seems to be a relationship between lactate levels and epinephrine dose but not between lactate and any variable related to oxygen use (oxygen extraction ratio, Pv_{O_2} , or central venous oxygen saturation). Therefore, we would suggest that exogenous (and likely endogenous) epinephrine via its stimulation of $Na^+ - K^+$ ATPase and glycolysis is likely responsible for the hyperlactatemia in sepsis, rather than impaired tissue oxygen use (5). The possible association of a change in the mean lactate value with the mean PCO_2 gap, from Table E2 in the online supplement of Reference 2, also raises the possibility that increased (not decreased) Krebs cycle activity is associated with hyperlactatemia. Epinephrine-associated hyperlactatemia has also been observed in a prospective randomized trial in septic shock (6). ■

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Understanding Hyperlactatemia in Human Sepsis: Are We Making Progress?

To the Editor:

We have significant concerns about the interpretation of the data presented by Gattinoni and colleagues (1). The reminders that lactic acidosis commonly coexists with renal acidosis and that metabolic acidosis does not necessarily mean acidemia are welcome. Indeed, one should dissociate hyperlactatemia from acidosis because hyperlactatemia can be of hypoxic origin even in the absence of acidosis, and of nonhypoxic origin even when there is acidemia (2). Although we agree with Gattinoni and colleagues that a pH measurement can be misleading, and that lactate concentrations should be measured directly, neither the presence or absence of metabolic acidosis nor the central venous oxygen saturation (Scv_{O_2}) value can help identify the origin of hyperlactatemia.

Gattinoni and colleagues also reemphasize the well-known fact that hyperlactatemia can coexist with any value of $\dot{V}O_2$ /oxygen delivery ($\dot{V}O_2/DO_2$) (or $S[c]v_{O_2}$). This is in part related to timing, because an increase in DO_2 as a result of resuscitative efforts may result in a rapid increase in Sv_{O_2} but a much slower decrease in blood lactate levels. More importantly, a normal or high Scv_{O_2} does not necessarily indicate that tissue perfusion is adequate. It is well known that a high Sv_{O_2} can be a sign of disease severity and worse prognosis (3). However, a high Sv_{O_2} does not always imply a significant alteration in cellular metabolism, as high Sv_{O_2} values can be the result of microcirculatory alterations. In our early study demonstrating the occurrence of microvascular alterations in sepsis (4), Sv_{O_2} values were identical in patients with sepsis and in other ICU patients, but hyperlactatemia was observed only in patients with septic shock (4). Accordingly, it may be erroneous and even potentially harmful to limit resuscitation efforts in a patient with hyperlactatemia just because his or her Scv_{O_2} values are normal or

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high. When associated with signs of tissue hypoperfusion, an elevated Sv_{O_2} (or Scv_{O_2}) does not mean that resuscitation efforts are no longer necessary. We previously reported that elevated Sv_{O_2} values did not exclude fluid responsiveness in patients with sepsis and signs of tissue hypoperfusion (5). Similarly, Monnet and colleagues showed that blood lactate and venoarterial PCO_2 differences, but not Scv_{O_2} , predicted an increase in $\dot{V}O_2$ in fluid-responsive patients (6).

Hence, we do not think that the observations by Gattinoni and colleagues should influence the way in which patients with sepsis are managed. Hyperlactatemia associated with other signs of tissue hypoperfusion should encourage attempts to increase DO_2 with fluids, transfusions, and/or dobutamine administration, even in the absence of acidemia or when Scv_{O_2} is not reduced. ■

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Reply to Nalos and Robergs and to De Backer and Vincent

From the Authors:

We thank Professors Nalos and Robergs for their supportive comments concerning our paper and our hypotheses (1),

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particularly with regard to the lack of a direct causal relationship between elevated lactate and acidemia in patients with sepsis. Moreover, we agree that the cause of hyperlactatemia is often multifactorial and that the use of catecholamines is certainly a well-accepted contributor. In our population, lactate and epinephrine were weakly but significantly related ($R^2 = 0.06$; $P < 0.0001$). Professors De Backer and Vincent disagree with us on several points, which deserve a point-by-point reply.

- They stated that “hyperlactatemia can be of hypoxic origin even in the absence of acidosis, and of nonhypoxic origin even when there is acidemia.” The confusion here might stem from confounding of the terms “acidosis” and “acidemia.” As soon as it is released into the blood, lactate (a strong negative ion) causes acidemia. If the measured pH does not fall, it simply means that other cofactors are operating. In our 1,741 patients with sepsis, the primary cofactor that determined acidemia was kidney function. Therefore, the relationship between acidemia and lactate has nothing to do with lactate origin.
- They stated that “high Sv_{O_2} values can be the result of microcirculatory alterations.” Actually, in their own cited work, they showed that microcirculation was altered in patients with sepsis compared with patients without sepsis, but venous oxygen saturation (Sv_{O_2}) values were similar.
- They stated that elevated Scv_{O_2} is compatible with inadequate perfusion (due to peripheral shunt), thus implying a need for further fluid resuscitation. This argument reflects the common belief that if peripheral shunt increases, the Scv_{O_2} will increase despite inadequate oxygen delivery. The validity of this concept may be tested by considering the periphery as comprised of two compartments: one oxygen consuming ($\dot{V}O_2$) and perfused ($\dot{Q} - \dot{Q}_{sp}$), and one not oxygen consuming but perfused (\dot{Q}_{sp}). Accordingly, the “peripheral shunt” fraction (\dot{Q}_{sp}/\dot{Q}) may be described as:

$$\frac{\dot{Q}_{sp}}{\dot{Q}} = \frac{Scv_{O_2} - Sv_{O_{2id}}}{Sa_{O_2} - Sv_{O_{2id}}},$$

where Scv_{O_2} and Sa_{O_2} are the central venous and arterial oxygen saturations, respectively, and $Sv_{O_{2id}}$ is the oxygen saturation of the blood exiting the $\dot{V}O_2$ consuming/perfused compartment. Therefore:

$$Sv_{O_{2id}} = Sa_{O_2} - \frac{\dot{V}O_2}{\dot{Q} \times \left(1 - \frac{\dot{Q}_{sp}}{\dot{Q}}\right) \times k},$$

where $k = Hb$ (g/L) \times 1.39 ml O_2 /g Hb. The Scv_{O_2} , which derives from the sum of $Scv_{O_{2id}}$ and Sa_{O_2} of the shunted blood, is equal to:

$$Scv_{O_2} = Sa_{O_2} \times \frac{\dot{Q}_{sp}}{\dot{Q}} + Sv_{O_{2id}} \times \left(1 - \frac{\dot{Q}_{sp}}{\dot{Q}}\right).$$

Then, substituting $Sv_{O_{2id}}$: