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Deconstructing hyperlactatemia in sepsis using $ScvO_2$ and base deficit

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For over half a century, clinicians and researchers have endeavored to understand the relationship between oxygen delivery and lactic acidosis (1,2). Or, as discussed later, perhaps more readily considered as “hyperlactatemia with or without acidemia”. In health, pyruvate (the generally-acknowledged end-product of glycolysis) is metabolized by mitochondria to acetyl CoA to feed the tricarboxylic acid cycle. Excess pyruvate is reduced by lactate dehydrogenase to L-lactate. Notably, this reduction consumes a proton: pyruvate + NADH + H^+ ⟷ lactate + NAD^+. Lactate is subsequently oxidized back to pyruvate, either locally or after transfer to organs that utilise lactate as a fuel source (e.g. liver, kidney, brain), or that convert it back to glucose (Cori cycle in the liver). In concert, these processes maintain normal blood lactate levels.

During sepsis, lactate levels frequently rise. Indeed, hyperlactatemia (a measurable surrogate for cellular/metabolic perturbations) is closely associated with sepsis prognosis and is now one of the criteria for septic shock (3). However, it remains challenging to determine clinically when a persistently elevated serum lactate level indicates ongoing inadequacy of oxygen delivery, or when the problem lies elsewhere. The brainstem response to give yet more fluid is often inappropriate and potentially injurious.

Hyperlactatemia during sepsis may result from anaerobic glycolysis. When whole-body oxygen delivery fails to meet cellular demands, tissues transition from mitochondrial aerobic respiration to less efficient ATP generation by glycolysis. This is most common at the time of initial patient presentation and, in many cases, resolves with administration of intravenous fluids ± vasoactive agents. However,

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other factors may also increase serum lactate levels in sepsis, including β_2-receptor stimulation from endogenous/exogenous catecholamines, impaired tissue oxygen extraction (mitochondrial ± microcirculatory dysfunction), liver dysfunction, and thiamine deficiency.

To aid the clinician in his/her decision-making, Gattinoni and colleagues in this issue of the *Journal* propose a conceptual model relating oxygen delivery and utilization, serum lactate concentration, and acidemia (4). They analyzed data from 1741 intensive care unit (ICU) patients enrolled into the Albumin Italian Outcome Sepsis (ALBIOS) trial using serum lactate, central venous oxygen saturation ($ScvO_2$) and blood gas measurements taken at study enrollment (5). Fundamentally, their proposed model frames two clinical questions:

1. Is an elevated lactate level due to inadequate oxygen delivery, and therefore potentially responsive to interventions that increase oxygen delivery?
2. How does an elevated serum lactate affect arterial pH and base excess?

Hyperlactatemia and central venous oxygen saturation

High values of $ScvO_2$ suggest either a systemic oxygen delivery in excess of oxygen demand, impaired cellular (mitochondrial) oxygen utilization, and/or microcirculatory shunting. Low $ScvO_2$ values imply inadequate oxygen delivery that fails to meet metabolic demands. Gattinoni and colleagues propose using $ScvO_2$ to personalize sepsis management, reserving interventions to increase

oxygen delivery only to those patients with low $ScvO_2$ values. Of note, only 35% of patients in the ALBIOS trial had $ScvO_2$ values <70%. Other recent sepsis trials report similar $ScvO_2$ values after initial resuscitation (6).

This proposal is not inherently novel. The concept of early goal-directed therapy (EGDT) (7) and the Surviving Sepsis Campaign recommendations (8) both suggest a low $ScvO_2$ should trigger interventions to increase oxygen delivery (e.g. fluid, inotropes, blood). This concept has a strong physiologic rationale, but the devil is in the detail.

First, the patients in ALBIOS study and the three recent EGDT trials (6) were all enrolled *after* initial resuscitation. On first presentation, many will have impaired oxygen delivery and thus lower $ScvO_2$ values, and a higher likelihood of responding positively to empiric fluid administration. An important caveat is that a low $ScvO_2$ in sepsis does not automatically equate to hypovolemia. Cardiomyopathy can also contribute, and may be worsened by excessive fluid administration.

Second, many patients with sepsis-associated hyperlactatemia have $ScvO_2$ values falling within an indeterminate range; even patients with an elevated $ScvO_2$ may respond physiologically to fluid administration (9). Moreover, $ScvO_2$ is a 'global' (or, rather an 'upper-body') measure of oxygen supply-demand balance, and may miss imbalances in specific tissue beds (10).

Finally, the history of sepsis research is paved with physiologically-rational interventions that nonetheless failed to improve patient outcomes (11). The recent EGDT trials showed no benefit in targeting $ScvO_2$ even among the subset

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of patients with baseline values <70% (6). Interventions to increase oxygen delivery may carry unintended consequences outside the mechanistic pathway assessed by $ScvO_2$ measurement (12,13). Therefore, an $ScvO_2$-based strategy to personalize interventions for patients with sepsis-associated hyperlactatemia requires careful evaluation in clinical trials before any recommendation of standard-of-care implementation in clinical practice.

Hyperlactatemia and arterial pH

Applying strong ion theory, lactate is a strong anion and should thus be completely dissociated from hydrogen in plasma, generating an acidosis. However, some sepsis patients with hyperlactatemia have a concurrently decreased pH (acidemia) whereas others maintain a normal pH. This suggests mechanisms that enable relatively rapid respiratory or metabolic compensation. Gattinoni and colleagues found that the ability to maintain a normal pH despite elevated lactate was more closely correlated with renal function than respiratory compensation. They propose using an indirect measure of the accumulation of renally-excreted fixed acids in plasma - the "*alactic base excess*" – to assess the kidneys' ability to compensate for acid-base disturbances.

Standard base excess, defined as the amount of strong acid that must be added to each liter of oxygenated blood to return the pH to 7.40 at a $PaCO_2$ of 40 mmHg, quantifies the degree of metabolic acidosis or alkalosis independently of respiratory compensation. Contributors to base excess include lactate, strong ions such as sodium and chloride, albumin, and ions that accumulate in renal

failure such as phosphate and sulfate (14). By adding lactate to standard base excess, the authors arrive at the alactic base excess which they assert quantifies *"the role of renal function on acid-base balance in sepsis*."

This suggestion is certainly interesting but requires further thought and investigation. Renal compensation for acid-base disturbances has traditionally been considered to be slower than respiratory compensation. Detailed data on urine output, stage of acute kidney injury (15), minute ventilation, and other physiologic measures would be required before the relative causal effects of kidney injury in compensating for an acidosis could be fully understood. Alactic base excess is not necessarily an explicit measure of renal function. For example, administration of 0.9% sodium chloride decreases base excess, even in the presence of stable renal function and lactate concentrations (16). The impact of concurrent liver dysfunction requires consideration; few such patients were in the ALBIOS database. Nonetheless, the concept of alactic base excess and the role of renal function in modifying acidemia warrant evaluation in future physiologic studies.

In summary, Gattinoni and colleagues are to be congratulated for advancing an ambitious conceptual model relating oxygen delivery, lactate generation, renal function, and acidemia in sepsis. We are eager to see future research to confirm and refine this model – and move us closer to the authors' vision of a more personalized approach to early hemodynamic management for sepsis.

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