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EDITORIAL

Lactate-guided resuscitation saves lives: no

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"For every complex problem, there is an answer that is clear, simple, and wrong".

H.L. Mencken.

Given the competing priorities in the resuscitation of critically ill patients, it is understandable that clinicians would look to simple measures to guide their resuscitation, and lactate clearance has certainly all the hallmarks of such a simple measure. It has been recently postulated as a marker of the adequacy of resuscitation in critically ill patients [1], particularly those with severe sepsis [2]. Nevertheless, the evidence to support the use of lactate clearance to guide resuscitation is still lacking.

The theoretical basis for using lactate to guide resuscitation during shock states is based upon the false premise that hyperlactatemia specifically indicates tissue hypoxia [3]. While the interruption of aerobic glycolysis inevitably leads to increased formation of lactate, there are many reasons why lactate could increase under aerobic conditions (Table 1) [3, 4]. This in part explains why the major trials of lactate-guided therapy have not shown a consistent clinical benefit.

Two relatively recent randomised clinical trials have used protocols based on lactate clearance. In 348 participants with a blood lactate level of ≥3.0 mEq/L [5], Jansen and colleagues compared two algorithms for haemodynamic management, one of which targeted a fall in the lactate level of ≥20 % every 2 h. In the lactate-guided therapy group, the volume of fluid administered over the initial 8 h was slightly but significantly larger and more patients received a vasodilator. There were no differences in lactate levels over the 72-h observation period. There was no significant difference in the unadjusted in-hospital or 28-day mortality rate, even though hospital mortality was reduced when adjusted for risk factors [5].

In the second trial, Jones and colleagues randomised 300 participants with severe sepsis to receive haemodynamic resuscitation based on lactate or central venous oxygen saturation ($ScvO_2$) levels [6]. There were no significant differences in the treatments received by participants in both groups and once again no difference in mortality. Besides these trials, it is also notable that a randomised clinical trial comparing the use of adrenaline to noradrenaline in critically ill patients demonstrated a significant increase in lactate levels, without any differences in clinical outcomes [7]. This provides further evidence that resuscitation guided by changes in lactate levels is very unlikely to improve mortality.

Three reasons may explain why guiding resuscitation of shock states with lactate clearance did not change outcomes in these studies. The first is that lactate is only an imperfect marker of anaerobic metabolism. Many false positives unfortunately arise when using lactate as a marker of tissue hypoxia; therefore using lactate alone to guide haemodynamic resuscitation is in essence limited. Rather than with lactate alone, tissue hypoxia should be assessed in a combined analysis including other indices, such as ScvO2 or indices derived from the venoarterial carbon dioxide pressure gradient [8].

Second, lactate is only a marker of shock severity. So, although the decrease of lactate should be considered a marker for treatment efficacy, lactate clearance should not be the only goal to pursue. As evidenced by the analogy with oliguria in acute kidney injury, oliguria only reflects the severity of the underlying disease and it has become clear that therapy to alter its course, specifically with diuretics, is not only unlikely to change the course of the disease but also potentially harmful [9]. Similarly, it is

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Contrasting viewpoints can be found at: doi:10.1007/s00134-015-4196-0 and doi:10.1007/s00134-016-4220-2.

Table 1 Sources for lactate production under aerobic conditions

Increased aerobic glycolysis
Increased activity of the Na+/K+ ATPase
Liver failure
Decrease in lactate clearance
Renal failure
Decrease in lactate clearance
Mitochondrial dysfunction
Impairment of mitochondrial function during sepsis, mainly related to nitric oxide and peroxynitrites
Lung injury
Metabolic adaptation to inflammatory mediators
Alkalosis
Stimulation of the phosphofructokinase enzyme
Drugs and toxics
Nucleoside reverse transcriptase inhibitors, metformine, cyanide and methanol intoxication

quite probable that the degree of hyperlactatemia reflects the severity of the underlying insult and that therapy to alter lactate levels is potentially harmful rather than beneficial.

Third, lactate is a diagnostic tool and it is unrealistic to expect that medical strategies could alter prognosis differently if the only difference is one diagnostic tool and not therapeutic options. In this regard, lactate clearance has the same limitations as the pulmonary artery catheter. The most rational reason why the latter has never demonstrated any clinical benefit [10] is that in the studies investigating its influence on outcomes, no protocolized treatment was ever attached to its use.

While it remains the Holy Grail of critical care medicine to identify a tool that can improve the resuscitation of acutely unwell patients, this remains elusive. Given the complex physiology and pathophysiology of lactate metabolism and the lack of evidence from randomised clinical trials to show a benefit of lactate-guided therapy, one can only conclude that there is no reason to believe that lactate-guided resuscitation saves lives.

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