Letters and Comments

Lactate and adrenergic signalling in trauma

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COMMENT ON

F Murtuza, AJ Farrier, M Venkatesan *et al.* Is there an association between body temperature and serum lactate levels in hip fracture patients? *Ann R Coll Surg Engl* 2015; **97**: 513–518
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We read with interest the report by Murtuza *et al* investigating a possible relationship between serum lactate levels and body temperature in hip fracture patients. The authors suggest that decreasing temperature could be associated with raised serum lactate owing to the role of lactate in anaerobic metabolism. They determined that there was no continuous relationship between serum lactate and body temperature in their cohort.

We would like to bring to the authors' attention the growing recognition among the intensive care literature that a rise in serum lactate concentrations (in the context of physiological challenge such as septic shock and injury) is unlikely to be due to anaerobic metabolism. Instead, increased lactate levels are likely to be due to activation of adrenergic signalling.¹ It has been demonstrated that shock mediated increases in lactate are abolished by pretreatment with combined adrenergic blockade.² Moreover, in animal studies, adrenaline infusion provokes hyperlactataemia.^{3,4} These studies showed continuous correlations between serum lactate and catecholamine concentrations. This alternative description of lactate biochemistry is, anecdotally, not widely known. We hope that by bringing these ideas to attention, future clinical research questions can be informed by the underpinning basic science.

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AUTHORS' RESPONSE

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The letter by Suddle and Klimach is an instructive contribution to our paper. It raises awareness to a physiological phenomenon that is not widely appreciated. They correctly highlight that catecholamine signalling plays a role in hyperlactataemia in the context of trauma and sepsis.¹ However, it may be premature to suggest that a similar mechanism is operative in the case of hypothermia or in an elderly cohort such as ours.

Adrenergic signalling is not the exclusive means by which lactate increases. Hyperlactataemia can also follow tissue hypoperfusion. The two processes can occur together and are not mutually exclusive.¹ The relative contribution depends on the nature of the insult. The body of evidence suggests that adrenergic signalling activates the sodium–potassium ATPase pump, which consumes considerable quantities of adenosine triphosphate (ATP), generating adenosine diphosphate (ADP).¹ This then accelerates the process of glycolysis with the resultant accumulation of lactate despite adequate oxygenation. This is termed aerobic glycolysis. Lactate accumulation occurs here as glycolysis is much more rapid than the remainder of the aerobic respiration cascade (Krebs cycle and oxidative phosphorylation).² However, it is unclear to what extent this mechanism can occur in hypothermia.

It is well known that falls in body temperature considerably hinder the activity of the sodium–potassium ATPase pump, thereby restricting its ability to generate ADP substrate from ATP, which is necessary for aerobic glycolysis and subsequent hyperlactataemia.^{3,4} Furthermore and significantly, our cohort consisted of a predominantly elderly population. Not only does skeletal muscle mass decline with senescence (sarcopenia)⁵ but there is evidence that the muscles' responsiveness to adrenergic signalling also falls.⁶ In addition, this cohort has a limited physiological reserve. They are more vulnerable to injury, with trauma more likely to cause hypoperfusion and hypoxia. This

effect is compounded by co-morbid disease and polypharmacy such as antihypertensives and antiplatelet agents, which may antagonise an already attenuated physiological response.

With all these factors considered together, the contribution of catecholamine signalling to hyperlactataemia of hypothermia in the senescent hip fracture population is far from clear. Evaluation of this may indeed be a worthwhile endeavour, to help gain a greater understanding of the pathogenic mechanisms involved in the high mortality associated with hip fracture. However, it was beyond the scope of our original study.

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