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EDITORIAL

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Don't take vitals, take a lactate

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The resident internal medicine called from the Emergency Department (ED). "Can you please come and see my patient, I think he is becoming septic and needs admission to intensive care". In the ED we found a confused older patient with an oxygen mask who was clearly dyspnoeic, the urinary catheter was filled with a dark brown fluid, the collecting bag was empty. The resident reported that he admitted the patient 4 h earlier as he suspected pneumonia. On admission the patient was hypoxic but this clearly improved with the supplemental oxygen. The resident was still waiting for all the laboratory results and the chest X-ray. However, now that the patient had developed hypotension he thought the patient was clearly at risk and intensive care admission was required. When we asked why he had not called us earlier, he replied that he intended to admit the patient to the general ward as he was haemodynamically stable and oxygenation had improved on supplemental oxygen so intensive care admission was not required. When reviewing the blood sample that was drawn 30 min following presentation, besides hypoxaemia, an increased lactate level of 4.6 mmol/l was present. The resident pointed out that hyperlactataemia in sepsis is not related to tissue hypoxia but rather is a marker of increased aerobic metabolism. Therefore he thought there was no need to react to this hyperlactataemia. Where did this resident go wrong?

Increased blood lactate levels in critically ill patients are generally associated with increased morbidity and mortality [1, 2]. Even haemodynamically stable patients with raised lactate levels, a condition referred to as compensated shock, are at increased risk of dying [3, 4]. This not only applies to patients admitted to the intensive care unit; also early in the course of illness, increased blood lactate levels are related to increased morbidity and mortality. In a study published in this issue of *Intensive Care Medicine*, Howell et al. [5] evaluated the prognostic value of one single venous lactate measurement shortly after admission to the ED in patients with clinically suspected infection. Their study is a follow-up on a preliminary report [6], where they did not take into account possible confounding factors such as co-morbidities and vital signs. In the current prospective observational cohort study ($n = 1{,}287$), the authors constructed a multivariate model, controlling for age, blood pressure, presence of malignancy, platelet count and blood urea nitrogen level. They showed that venous lactate predicted 28-day in-hospital mortality. The predictive power of the lactate level was independent of blood pressure and co-variates. In patients with normal blood pressure, increased blood lactate levels (>4.0 mmol/l) were associated with a ten times higher mortality rate than normal lactate levels (mortality 26.5%). Others have reported similar results in other patient populations. Lavery et al. [7] measured venous lactate within 10 min following admission to the ED in 375 trauma patients. This study showed that an increased lactate level (> 2.0 mmol/l) was a better predictor of morbidity and mortality than physiological triage criteria (composed of heart rate, blood pressure, Glasgow coma scale and respiratory rate). Rivers et al. [8] also showed that traditional physiological variables did not adequately determine septic patients at risk of increased

mortality. However, when Hucker et al. [9] included all patients admitted to the hospital following presentation at the ED, neither clinical measures nor venous lactate could adequately predict hospital mortality or length of hospital stay. The short-term evolution in blood lactate has also been associated with mortality. In intensive care patients with circulatory shock, Vincent et al. [10] showed that 20 min following fluid resuscitation, non-survivors could already be distinguished from the surviving patients. In the ED, Nguyen et al. [11] observed the evolution of serial lactate levels in patients with severe sepsis during the first 6 h of treatment. In this study, a 10% decrease in lactate levels during the 6-h study period was related to an 11% decrease in the likelihood of mortality. Furthermore, 29% of the patients that did not show a decrease in lactate levels during the study did not have hypotension, where the mortality in this group still exceeded 55% [11]. As venous [7, 12] and capillary [13] blood can be used to reflect arterial blood lactate levels with a turnaround time of less than 2 min [13], the clinician can rapidly identify a group of patients that, irrespective of their haemodynamic stability, has an increased risk of morbidity and mortality. This thus represents a faster and more reliable (independent of inter- and intra-observer variations) severity scoring than commonly used triage and scoring systems.

Two important questions remain, not so much to assess the use of lactate levels as a risk assessment tool, but more to decide what therapeutic measures should be taken when lactate levels are increased. First, why do patients with more often die than patients without increased lactate levels? A systemic imbalance between oxygen delivery (DO_2) and demand causes lactate levels to sharply rise, both in various experimental [14] and in clinical [15] conditions. Increased lactate levels have thus long been used to reflect the presence of tissue hypoxia. Hypoxia results in cell death and thus, if not resolved, leads to organ failure. Increased lactate levels and the duration of hyperlactataemia have indeed been associated with the level of organ failure in patients with septic shock [16]. However, besides this anaerobic mechanism, aerobic processes are also known to raise lactate levels in critically ill patients. First, increased aerobic glycolysis by cytokine-mediated cellular uptake of glucose [17] or by catecholamine-stimulated Na-K pump hyperactivity [18] can result in increased pyruvate production that exceeds the capacity of the pyruvate dehydrogenase enzyme complex (PDH) and thus results in increased lactate levels by mass effect. Second, in sepsis, PDH dysfunction has been reported [19]. Third, the lung is known to produce lactate, probably marking metabolic adaptations in response to inflammatory mediators rather than tissue hypoxia [20, 21]. Finally, reduced clearance of lactate will result in increased levels even when lactate production is not increased. In hemodynamically stable patients with sepsis, impaired clearance has been associated with increased lactate levels [22]. Second, what therapeutic actions should be taken in patients with increased blood lactate levels to improve their prognosis? From earlier studies in the 1980s and 1990s it is clear that correcting lactate levels itself will not improve outcome of critically ill patients [23, 24]. As oxygen supply dependency, as a marker of tissue hypoxia and increased lactate levels, is present in the early phase of critical illness [25], it seems logical to improve tissue oxygen delivery in patients with increased lactate levels. Several studies aimed at improving tissue oxygenation in patients with increased lactate levels have been associated with an improvement in morbidity and mortality [3, 8, 26, 27]. Furthermore, high lactate levels may reflect microcirculatory derangement, hampering oxygen utilization at the tissue level [28]. This is illustrated by the observation that improving capillary perfusion has been shown to decrease lactate levels independent of changes in systemic haemodynamic variables [29]. However, randomized controlled trials in critically ill patients to prove this have not been performed. A recently started randomized controlled multi-centre trial, that is now halfway, is designed to evaluate the value of lactate level-guided therapy early in the course of critical illness (http://www.clinicaltrials.gov/ct/show/NCT00270673?order=1).

However, increased lactate levels, as a marker of tissue hypoxia in critically ill patients, remain a matter of debate [30]. Given the many processes that may affect the ultimate concentration of lactate, both individual lactate levels and the change in level over time may well reflect the general homeostasis of the critically ill patient. The current study by Howell et al. [5] clearly shows that the use of a single measurement of venous lactate, that can be available rapidly following admission to the ED, provides the clinician with better risk assessment, possibly with a clear direction to diagnosis and therapy, than vital signs. In the case presentation the resident could thus have diagnosed a severe disturbance in the homeostasis of his patient, despite the haemodynamic stability for the next few hours, 30 min following admission when the first lactate level became available. The intensivist could then perhaps have made a bigger impact on the outcome of this patient, who died several days following admission.

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