Intensive Care Med (2016) 42:466–469
DOI 10.1007/s00134-015-4196-0

EDITORIAL

Frank Bloos
Zhongheng Zhang
Thierry Boulain

Lactate-guided resuscitation saves lives: yes

Received: 26 November 2015
Accepted: 15 December 2015
Published online: 1 February 2016

Contrasting viewpoints can be found at
10.1007/s00134-016-4220-z and 10.1007/s00134-016-4235-5.

F. Bloos (✉)
Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, 07740 Jena, Germany
e-mail: frank.bloos@med.uni-jena.de
Tel.: +49-3641-9323283

F. Bloos
Center for Sepsis Control and Care, Jena University Hospital, Jena, Germany

Z. Zhang
Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Zhejiang, People's Republic of China

T. Boulain
Medical-Surgical Intensive Care Unit, Centre Hospitalier Régional d'Orléans, Orléans, France

Introduction

Shock is defined as a mismatch between tissue O_2 needs and O_2 delivery. Arterial hypotension is frequently present in patients with shock but may occur late and not all types of shock are associated with arterial hypotension. While blood pressure is easy to measure, true assessment of the adequacy of tissue oxygenation is a challenge. There is an ongoing debate whether the measurement of serum lactate concentration can guide the physician in the diagnosis of shock and use of resuscitation strategies.

Lactate formation in shock: the entangled hypoxic and glycolytic pathways

During glycolysis, a succession of cytosolic enzymatic reactions, which do not need O_2, convert glucose to pyruvate. Pyruvate is either transported into the mitochondria and converted to acetyl-CoA by pyruvate dehydrogenase (PDH) to enter the tricarboxylic acid cycle that, together with O_2, fuels the synthesis of adenosine triphosphate (ATP), the main source of energy for cellular metabolism, or transformed into lactate by the enzyme lactate dehydrogenase (LDH). Formed lactate can be either utilized locally or can be released into the bloodstream. With this pathway (Fig. 1) in mind, it is easy to understand why lactate levels can increase during shock or during other critical illness-related physiological stress.

When tissue O_2 needs are no longer covered by O_2 delivery, cell hypoxia occurs. Cell hypoxia in turn inhibits the mitochondrial respiratory chain and modifies the cellular redox potential by making NADH accumulate, thereby inhibiting PDH. This diminishes the amount of pyruvate entering the mitochondria and favours lactate formation from pyruvate. On the other hand, high inflammatory states such as sepsis are accompanied by a vast array of cytokine or hormone-induced mechanisms that accelerate the cellular glycolytic flux [1]. This accelerated glycolysis necessarily leads to over production of lactate, while the cytosolic lactate/pyruvate ratio remains unchanged until the mitochondrial metabolism is saturated by a too high demand or inhibited by hypoxia. The former pathway has long been the only mechanism put forward to explain hyperlactataemia in shock states. In the recent decades, evidence has accumulated showing that the latter, the accelerated glycolysis, was by far the predominant mechanism, particularly in sepsis, to the point that some argue that cell hypoxia has nothing to do with hyperlactataemia observed during shock states [2].

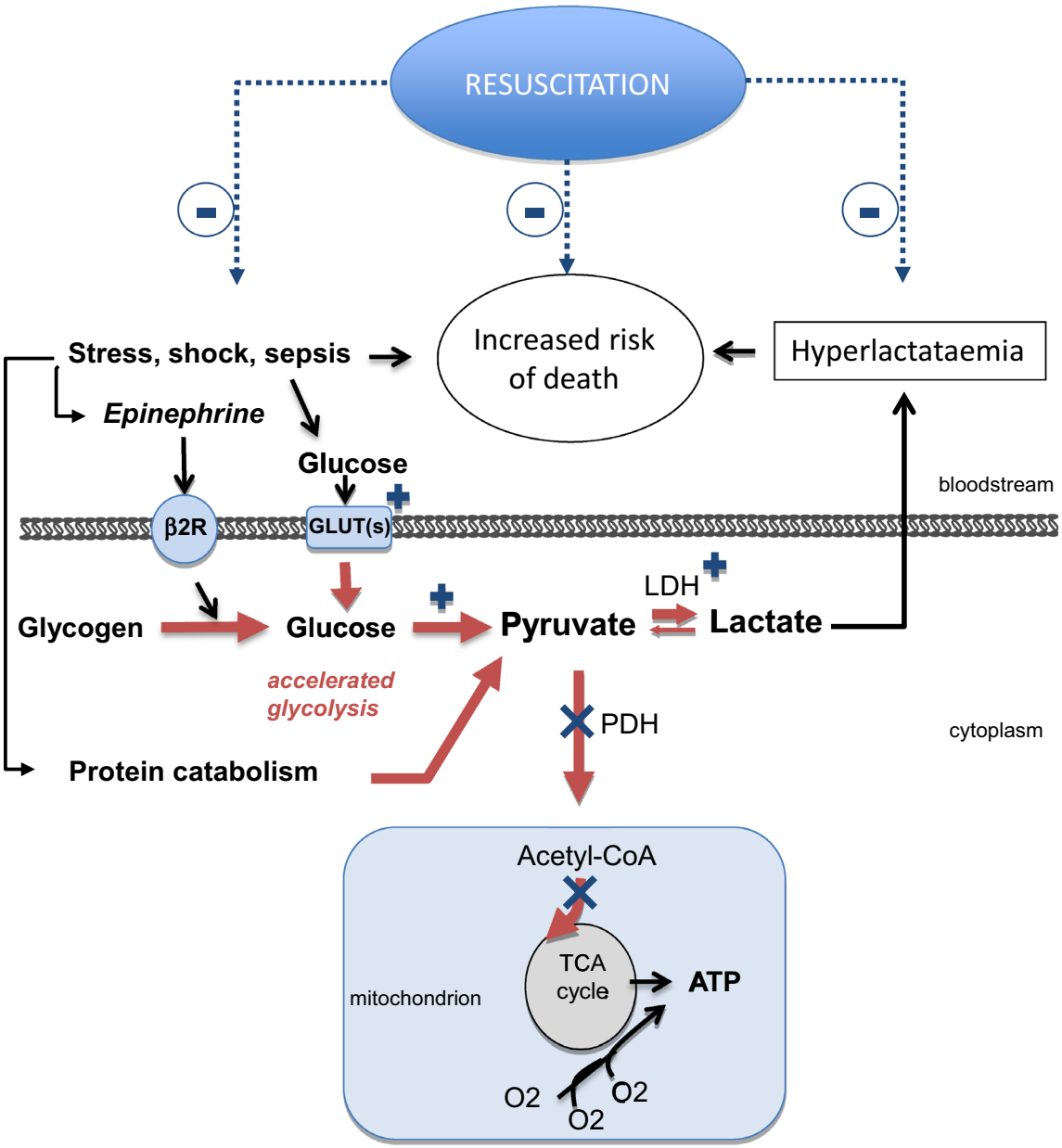

Fig. 1 Sources of blood lactate during shock. *Red arrows* represent the stress-induced accelerated glycolytic flux which results in high energy production (until the TCA and the mitochondrial respiratory chain are saturated) and high lactate production. *Blue plus signs* and *crosses* represent the pathways stimulated or inhibited by hypoxia-induced genomic activity, respectively. *Blue dashed lines* and *minus signs* indicate the expected, parallel, lowering effects of resuscitation on stress, shock, blood lactate level and mortality. *β2R* β2-Adrenergic receptors, *GLUT(s)* glucose transporters, *LDH* lactate dehydrogenase, *PHD* pyruvate dehydrogenase, *TCA* tricarboxylic acid

However, these two pathways can undoubtedly coexist [3]. Notably, hypoxia also enhances glycolysis through hypoxia-inducible factor (HIF-1α) that favours overexpression of genes encoding glucose transporters, glycolytic enzymes, PDH kinase 1 that inhibits PDH, and LDH, all of these resulting in lactate overproduction.

Elevated lactate levels in shock: predictor of adverse outcome

Because serum lactate is a biomarker of tissue hypoperfusion, it is reasonable to assume that its elevation should be associated with poor clinical outcomes. Elevated

serum lactate was observed to be associated with increased risk of short-term death in sepsis and beyond in unselected critically ill patients [4]. In an analysis of a large clinical database by using fractional polynomials, a monotone increasing relationship between lactate and death probability was identified [4]. When lactate levels were categorized into low, intermediate and high subgroups, the in-hospital mortality rates in emergency patients with infection were 15, 25 and 38 %, respectively. Such a dose–response phenomenon confirmed the causal relationship between elevated serum levels and mortality outcome [5]. Likewise, a positive linear relationship was found between lactate and acute-phase death ($\leq$3 days); an initial phase lactate $\geq$4 mmol/L was associated with sixfold increase in short-term death. Lactate elevation was also linked to an increased risk of death in a recent analysis of the Surviving Sepsis Campaign database where elevated lactate of more than 4 mmol/L was independently associated with mortality [6]. Although this association was also given in the absence of arterial hypotension (so-called cryptic shock), the combination of hyperlactataemia and arterial hypotension showed the strongest correlation with mortality. Thus, elevated lactate levels represent an alert situation in patients with shock. The authors concluded that a cutoff value of 4 mmol/L was reasonable to initiate aggressive resuscitation [6].

Achieving early lactate clearance in shock: predictor of survival

If resuscitation is successful in restoring tissue oxygenation, it would be expected that elevated lactate concentration starts to decrease. Early septic shock patients with low central venous oxygen saturation ($ScvO_2$) and hyperlactataemia often show rapid return of $ScvO_2$ and lactate returns to normal values when initial resuscitation succeeds in correcting the initial O_2 demand/delivery mismatch [7]. Lactate clearance is defined as the reduction of lactate levels over time (mostly 2–6 h). Indeed, a recent meta-analysis showed that a sustained elevation in lactate is associated with a high risk of death while a high lactate clearance is a strong predictor of survival with a pooled risk ratio (RR) of 0.38 [8]. Early lactate clearance-guided therapy in patients with sepsis has been prospectively investigated in four randomized controlled trials. A meta-analysis of these studies showed that compared to the control group, early lactate clearance-guided control was associated with a reduction in mortality (RR = 0.65) [9]. However, only 286 patients have received this intervention in studies so far and the quality of the data do not yet allow for conclusive evidence.

In conclusion, lactate metabolism is complex in critically ill patients but tissue hypoxia has a significant contribution to hyperlactataemia which is an independent predictor of death in these patients. However, lactate overproduction per se is not the culprit. It makes no sense in only trying to decrease lactate levels, and in fact we have no means to directly modify an increased lactate synthesis. It is also questionable whether a single biomarker alone can or should guide haemodynamic resuscitation; protocolized haemodynamic resuscitation in patients with septic shock was not superior to usual care [10]. In addition to clinical judgement, lactate should rather trigger the search for potential causes of poor tissue oxygenation accessible to therapeutic manipulation. Then, lactate clearance serves as a dynamic biomarker indicating that resuscitation strategies actually are going in the right direction. In the frame of these considerations, measuring lactate levels saves lives in critically ill patients.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Levy B (2006) Lactate and shock state: the metabolic view. Curr Opin Crit Care 12:315–321
2. Garcia-Alvarez M, Marik P, Bellomo R (2014) Stress hyperlactataemia: present understanding and controversy. Lancet Diabetes Endocrinol 2:339–347
3. Suetrong B, Walley KR (2015) Lactic acidosis in sepsis: it's not all anaerobic. Implications for diagnosis and management. Chest. doi: 10.1378/chest.15-1703
4. Zhang Z, Chen K, Ni H, Fan H (2014) Predictive value of lactate in unselected critically ill patients: an analysis using fractional polynomials. J Thorac Dis 6:995–1003
5. Trzeciak S, Dellinger RP, Chansky ME et al (2007) Serum lactate as a predictor of mortality in patients with infection. Intensive Care Med 33:970–977
6. Casserly B, Phillips GS, Schorr C et al (2015) Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. Crit Care Med 43:567–573
7. Boulain T, Garot D, Vignon P et al (2014) Prevalence of low central venous oxygen saturation in the first hours of intensive care unit admission and associated mortality in septic shock patients: a prospective multicentre study. Crit Care 18(6):609

8. Zhang Z, Xu X (2014) Lactate clearance is a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review and meta-analysis. Crit Care Med 42(9):2118–2125
9. Gu W-J, Zhang Z, Bakker J (2015) Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of randomized controlled trials. Intensive Care Med 41:1862–1863
10. Angus DC, Barnato AE, Bell D et al (2015) A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med 41:1549–1560