

# Reduced oxygen utilization in septic shock: disorder or adaptation?

Alexandre A Steiner\*

Department of Immunology; Institute of Biomedical Sciences; University of São Paulo; São Paulo, SP Brazil

**A fall in oxygen utilization during septic or endotoxic shock is thought to reflect circulatory hypoxia or mitochondrial dysfunction, but these pathology-oriented hypotheses do not explain all clinical observations. Here we discuss an alternative hypothesis of how oxygen utilization could fall as the result of a physiological thermometabolic adaptation.**

This discussion is brought up in light of unexpected findings recently published by our group in a paper by Corrigan et al.<sup>1</sup> In that study, a novel experimental preparation was devised to monitor oxygen delivery and oxygen utilization simultaneously during the early phase of endotoxic shock in rats whose thermoregulation had not been disrupted by anesthetics. Initially, the study revealed that a  $\beta_3$ -adrenergic agonist known to activate metabolic heat production was as effective at increasing oxygen utilization in the endotoxin-challenged rats as it was in their healthy counterparts, thus

indicating that neither oxygen delivery nor mitochondrial function was impaired to the point of directly compromising aerobic metabolism. Yet, oxygen utilization is known to fall early in the course of endotoxic shock. How is that possible? The answer to this question may lie in a physiological downshift of metabolic heat production, which, in turn, drives a reduction in body temperature. Described for the first time by Romanovsky and colleagues,<sup>2</sup> the triggers of this response remain a mystery. Mild-to-moderate circulatory hypoxia is viewed as a probable trigger, given that different types of hypoxia, even if not severe enough to directly limit aerobic metabolism, are capable of suppressing metabolic heat production and lowering body temperature via neuroendocrine mechanisms (see, for example, Tattersall and Milsom<sup>3</sup>). The study by Corrigan et al.,<sup>1</sup> however, has provided striking evidence against the participation of circulatory hypoxia in the hypometabolic, hypothermic response that occurs during the early phase of endotoxin shock. The most crucial piece of evidence was that no fall in cardiac output or oxygen delivery preceded the reduction in metabolic rate in endotoxic shock; oxygen delivery and metabolic rate fell concurrently and to the same extent so the ratio between them remained unaltered. In addition, an analysis of the redox state of nicotinamide adenine dinucleotide provided no indication of tissue hypoxia in the kidney, liver or brain. Only when hypometabolism and hypothermia were prevented by exposure to a warm environment, an imbalance in the ratio between oxygen delivery and oxygen utilization became manifest, and such an imbalance was associated with tissue hypoxia (inferred from a diminished oxidation of nicotinamide adenine dinucleotide).

These findings not only reject circulatory hypoxia and mitochondrial dysfunction as explanations for the reduced oxygen utilization in early endotoxic shock, but they also show that hypometabolism and hypothermia serve as a preemptive strategy to avoid

hypoxia in this case. It is reasonable to propose that this phenomenon could represent a physiological adaptation triggered by heightened or transformed immune-to-brain signaling. We are referring to this idea as the “thermometabolic adaptation” hypothesis. This new hypothesis could be paradigm-shifting for portraying the fall in oxygen utilization in septic and endotoxic shock as a physiological adaptation, as opposed to a pathological event (Fig. 1). While the applicability of this hypothesis to clinical septic shock awaits investigation, it should be kept in mind that approximately 10% of septic patients spontaneously develop hypothermia instead of fever,<sup>4</sup> and it is quite possible that this percentage is higher within the septic-shock subpopulation. Whether hypothermia in clinical sepsis is driven by a physiological suppression of metabolic heat production is uncertain at the moment, as are many other aspects of this phenomenon. For example, an association of spontaneous hypothermia with poor prognosis in septic patients is typically interpreted as if it implies that hypothermia in sepsis is a non-physiological phenomenon with detrimental consequences. However, such an inference overlooks the possibility that the prognostic value of hypothermia may simply reflect its higher prevalence in the most severe cases of sepsis. In our opinion, this dispute can only be settled by a study performed within the hypothermic subset of septic patients, which would need to be randomized into 2 intervention groups: one group subjected to heating as soon as hypothermia is detected (the standard of care in many hospitals); and the other group having hypothermia run its course (perhaps within certain limits). It is interesting that when this design was applied to rats with *E. coli*-induced septic shock, the outcome was more favorable in the group that was allowed to develop hypothermia.<sup>5</sup>

Another important consideration is that the physiological regulation of metabolic rate is unlikely to occur when pathological events are impairing oxygen utilization. The question then arises: when do the

Comment on: Corrigan JJ, et al. Hypometabolism and hypothermia in the rat model of endotoxic shock: independence of circulatory hypoxia. *J Physiol* 2014; 592:3901-16; PMID:24951620; <http://dx.doi.org/10.1113/jphysiol.2014.277277>

**Keywords:** critical care oxygen, hypoxia, hypothermia, LPS, metabolism, sepsis, thermogenesis, temperature, fever

© Alexandre A Steiner

\*Correspondence to: Alexandre A Steiner; Email: [asteiner@usp.br](mailto:asteiner@usp.br)

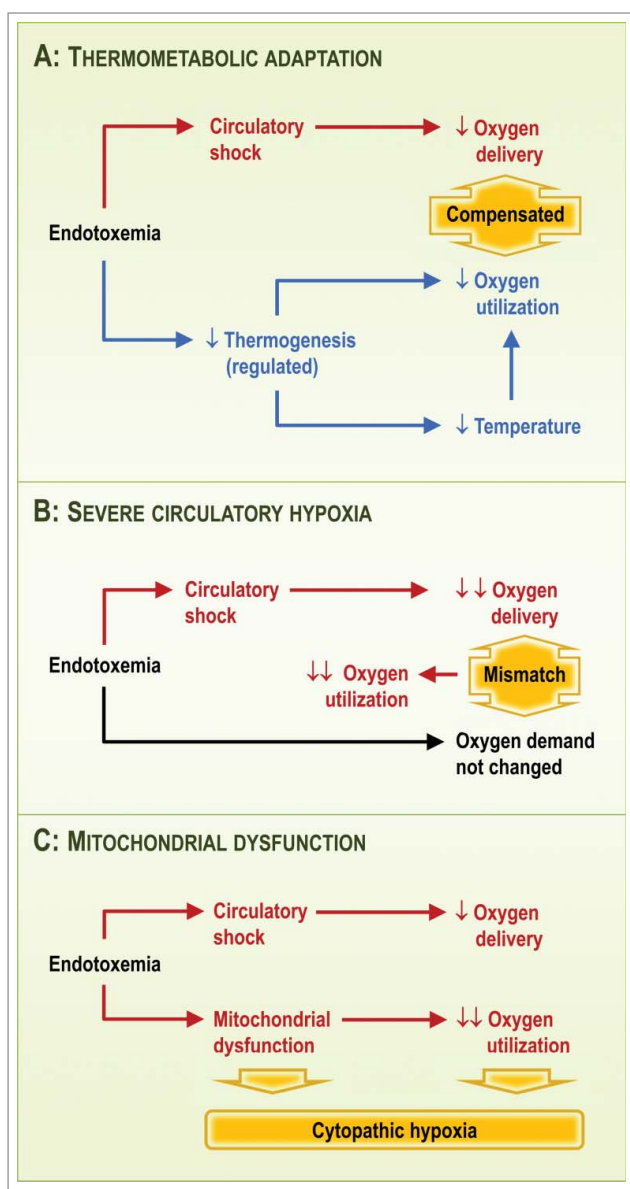
Submitted: 12/04/2014

Revised: 12/05/2014

Accepted: 12/05/2014

<http://dx.doi.org/10.1080/23328940.2014.996484>

This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. The moral rights of the named author(s) have been asserted.



**Figure 1.** Schematic comparison of the hypotheses proposed to explain the decreased oxygen utilization in endotoxic shock. The “thermometabolic adaptation” hypothesis highlighted in this article is shown in (A). The pathology-oriented hypotheses are shown in (B and C). Pathological events are depicted in red; physiological events are depicted in blue.

pathology-oriented hypotheses fail to explain changes in oxygen utilization in clinical septic shock? Even the most diligent advocates of the “mitochondrial dysfunction” hypothesis acknowledge that this hypothesis does not apply to the early stages of sepsis and septic shock.<sup>6</sup> The situation is less clear with regard to the “circulatory hypoxia” hypothesis. The main criticism surrounding this hypothesis is that the occurrence of hypoxia in septic-shock patients has been generally inferred based on an unreliable index of hypoxia

(*i.e.*, plasma lactate levels; *cf.* Corrigan et al.<sup>1</sup>). This is not the only criticism, though. For example, Nimmo et al.<sup>7</sup> have reported that improved oxygen delivery was ineffective at elevating oxygen utilization in at least 50% of the septic-shock patients. This assessment was conducted relatively early in the course of septic shock—during the first 6 hours of resuscitation following admission to the intensive care unit. Therefore, as in rats during early endotoxic shock, it is possible that a hypoxia-independent downshift of aerobic

metabolism occurs in at least a subset of the patients in early septic shock.

From a therapeutic perspective, the existence of a physiological mechanism for the reduced oxygen utilization in septic shock could be transformative. Tests to discriminate physiological from pathological reductions in oxygen utilization could become determinants of therapeutic conduct. Whereas a fall in oxygen utilization would continue to be undesired in patients with metabolic pathology, it would become acceptable, or even desirable, in patients whose lowered metabolic rates seem to be regulated physiologically. In the latter scenario, adrenergic drugs with the potential to elevate metabolic rate would have to be used with caution. Furthermore, in cases where hypometabolism occurs along with hypothermia, the application of external heat to restore body temperature to its “normal” level might prove to be detrimental. The spontaneous development of hypothermia might even serve as a sign for the initiation of a forced hypothermia protocol, such as the protocol for induction of mild hypothermia that is currently under investigation in septic patients (trial No. NCT01455116; [clinicaltrials.gov](http://clinicaltrials.gov)). Only time will tell if these provocative ideas are true or false, but regardless, efforts to reconcile the animal evidence indicative of physiological thermometabolic adaptation in endotoxic shock with data from patients with septic shock are warranted.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest are disclosed.

#### References

1. Corrigan JJ, et al. *J Physiol* 2014; 592:3901–16; PMID:24951620; <http://dx.doi.org/10.1113/jphysiol.2014.277277>
2. Romanovsky AA, et al. *Am J Physiol* 1996; 270:R693–703; PMID:8967396
3. Tattersall GJ, et al. *J Physiol* 2009; 587:5259–74; PMID:19770191; <http://dx.doi.org/10.1113/jphysiol.2009.175828>
4. Clemmer TP, et al. *Crit Care Med* 1992; 20:1395–401; PMID:1395659; <http://dx.doi.org/10.1097/00003246-199210000-00006>
5. Liu E, et al. *Am J Physiol Regul Integr Comp Physiol* 2012; 302:R1372–83; PMID:22513748; <http://dx.doi.org/10.1152/ajpregu.00023.2012>
6. Fink MP. *Crit Care* 2002; 6:491–9; PMID:12493070; <http://dx.doi.org/10.1186/cc1824>
7. Nimmo GR, et al. *Anaesthesia* 1992; 47:1023–8; PMID:1489022; <http://dx.doi.org/10.1111/j.1365-2044.1992.tb04194.x>