Commentary

Sepsis therapy: what's the best for the mitochondria?

Florian Wagner, Peter Radermacher, Michael Georgieff and Enrico Calzia

Sektion Anästhesiologische Pathophysiologie und Verfahrensentwicklung, Universitätsklinik für Anästhesiologie, Universität Ulm, Parkstraße, 89073 Ulm, Germany

Corresponding author: Enrico Calzia, enrico.calzia@uni-ulm.de

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See related research by Regueira *et al*., http://ccforum.com/content/12/4/R88

Abstract

It is suspected that mitochondrial dysfunction is a major cause of organ failure in sepsis and septic shock. A study presented in this issue of *Critical Care* revealed that liver mitochondria from pigs treated with norepinephrine during endotoxaemia exhibit greater *in vitro* respiratory activity. The investigators provide an elegant demonstration of how therapeutic interventions in sepsis may profoundly influence mitochondrial respiration, but many aspects of mitochondrial function in sepsis remain to be clarified.

In this issue of *Critical Care*, Regueira and colleagues [1] report an interesting study of the effects of norepinephrine on mitochondrial respiration in endotoxaemic rats; it should be of particular interest to those involved in sepsis research. During the past decade, failure of energy metabolism at the cellular level has emerged as one of the potentially most important pathophysiological aspects of sepsis [2]. Indeed, the results of a number of experimental and human studies appear to confirm that mitochondrial function is severely compromised in sepsis [2-5], in a phenomenon termed 'cytopathic hypoxia' [6]. Nevertheless, there probably remain more questions than answers in this fairly novel aspect of septic disease, and - from a clinical point of view - the fundamental query is already apparent. If sepsis is a mitochondrial disease, then should we search for a mitochondrial therapy?

The elegant study conducted by Regueira and colleagues may be interpreted as an attempt to address this question. The investigators did not test any new therapeutic approach; rather, they studied how norepinephrine - a standard drug recommended for use in severe sepsis - may directly influence mitochondrial function independent of its haemodynamic effects. The study was conducted in 13 anaesthetized pigs that were receiving endotoxin to simulate human sepsis pathology. The *in vitro* results clearly reveal an increase in respiratory activity in liver mitochondria obtained from norepinephrine-treated animals as compared with control animals not treated with catecholamine. Although a marked decrease in liver perfusion was observed in both groups after administration of endotoxin, no intergroup difference in this parameter was observed. Thus, the norepinephrine-related increase in respiratory activity apparently suggests that this drug exerts a direct and potentially beneficial action on liver cell respiration.

The results reported by Regueira and colleagues are both intriguing and important for several reasons. First, the authors test theoretical reasoning on the effects of catacholamines on intracellular calcium levels. Specifically (and excellently reviewed elsewhere [7,8]), the calcium level is known to increase in myocardial mitochondria after catecholamine release, and this is believed to stimulate mitochondrial respiration. These theoretical mechanisms are entirely consistent with the findings presented by Regueira and colleagues. Conversely, however, Lünemann and coworkers [9] previously presented apparently opposing data; they observed that norepinephrine inhibited oxygen consumption in human peripheral blood mononuclear cells. If this effect were to take place in other tissues as well, then this would have rather detrimental effects, especially in the setting of severe sepsis, in which energetic metabolism is already compromised. However, the study presented by Regueira and colleagues convincingly excludes the possibility that norepinephrine may exert such potential harmful effects, at least in liver tissue.

To summarize, what is the key message of the study? Does it suggest that we should give norepinephrine because it is good for the mitochondria? After all, it appears to 'improve' hepatic mitochondrial respiration. With good reason, Regueira and colleagues are more cautious; their observation of interactions between norepinephrine and mitochondrial respiration is indeed interesting, but the complexity of mitochondrial physiology renders such conclusions unsound. For example, the norepinephrine-induced increase in mitochondrial respiration may also lead to increased oxidative stress, as previously reported in myocardial tissue [10]. Furthermore, despite the

compelling *in vitro* findings, the presented data surprisingly do not reveal any effect of norepinephrine treatment on liver metabolism in intact animals in either group; for instance, both hepatic oxygen consumption and hepatic lactate extraction were equal. Therefore, the advantages of greater mitochondrial activity in the septic animal *in vivo* remain open to question. In this regard, we should not forget that respiratory activity in isolated mitochondria and in intact cells may differ significantly, as was studied in detail years ago by Fontaine [11] and Saks [12] and their colleagues.

Finally, another limitation of the study should be considered; the study was conducted in an endotoxin-induced model of sepsis, which has fundamental differences from human septic shock. As indicated by the data presented by Regueira and colleagues, endotoxin causes acute pulmonary hypertension almost immediately after its application is begun. As a presumable consequence, liver perfusion in the study was almost halved during the early phase of endotoxin administration, and slowly recovered during the course of the experiment, reaching initial values in the final phase only. Clearly, these haemodynamic effects are typical for endotoxin-induced sepsis but not for hyperdynamic sepsis, as is encountered in patients receiving adequate haemodynamic support. Organs, and the liver in particular (the main organ under study), may sustain damage during the initial decrease in perfusion. Of course, the decrease in hepatic perfusion occurred in both groups, and therefore the effects of norepinephrine on mitochondrial respiration were not necessarily affected by this phenomenon. Nevertheless, we do not know whether maintaining or even improving hepatic perfusion, as achieved by other models of endotoxaemic and bacterial sepsis [13,14], may prevent any eventual deterioration in hepatic mitochondrial function, thus neutralizing any beneficial effects of norepinephrine on cellular respiration.

In conclusion, the study by Regueira and colleagues elegantly demonstrates that therapeutic interventions in sepsis may profoundly influence mitochondrial respiration. Because it is suspected that mitochondrial dysfunction is a major cause of organ failure in sepsis, it should be a primary goal of research to elucidate the interaction between therapy and mitochondrial respiration. However, study results will remain difficult to interpret while the targets of mitochondrial therapy are not clearly defined. Efforts in this direction have already been made [15] and may be among the keys to future sepsis therapy.

Competing interests

The authors declare that they have no competing interests.

References

1. Regueira T, Bänziger B, Djafarzadeh S, Brandt S, Gorrasi J, Takala J, Lepper PM, Jakob SM: **Norepinephrine to increase blood pressure in endotoxemic pigs is associated with improved hepatic mitochondrial respiration.** *Crit Care* 2008, **12:**R88.
2. Singer M: **Mitochondrial function in sepsis: acute phase versus multiple organ failure.** *Crit Care Med* 2007, **35(suppl):** S441-S448.
3. Leverve XM: **Mitochondrial function and substrate availability.** *Crit Care Med* 2007, **35(suppl):**S454-S460.
4. Levy RJ, Deutschman CS: **Cytochrome c oxidase dysfunction in sepsis.** *Crit Care Med* 2007, **35(suppl):**S468-S475.
5. Brealey D, Brand M, Hargreaves J, Heales S, Land J, Smolenski R, Davies NA, Cooper CE, Singer M: **Association between mitochondrial dysfunction and severity and outcome of septic shock.** *Lancet* 2002, **360:**219-223.
6. Fink MP: **Bench-to bedside review: Cytopathic hypoxia.** *Crit Care* 2002, **6:**491-499.
7. Hansford RG: **Physiological role of mitochondrial Ca^{2+} transport.** *J Bioenerg Biomembr* 1994, **26:**495-508.
8. McCormack JG, Halestrap AP, Denton RM: **Role of calcium ions in regulation of mammalian intramitochondrial metabolism.** *Physiol Rev* 1990, **70:**391-425.
9. Lünemann JD, Buttgereit F, Tripmacher R, Baerwald CGO, Burmester GR, Krause A: **Norepinephrine inhibits energy metabolism of human peripheral blood mononuclear cells via adrenergic receptors.** *Biosci Rep* 2001, **21:**627-635.
10. Rump AFE, Klaus W: **Evidence for norepinephrine cardiotoxicity mediated by superoxide anion radicals in isolated rabbit hearts.** *Naunyn Schmiedebergs Arch Pharmacol* 1994, **349:** 295-300.
11. Fontaine EM, Keriel C, Lantuejoul S, Rigoulet M, Leverve XM, Saks VA: **Cytoplasmic cellular structures control permeability of outer mitochondrial membrane for ADP and oxidative phosphorylation in rat liver cells.** *Biochem Biophys Res Commun* 1995, **213:**138-146.
12. Saks V, Belikova Y, Vasilyeva E, Kuznetsov A, Fontaine E, Keriel C, Leverve X: **Correlation between degree of rupture of outer mitochondrial membrane and changes of kinetics of regulation of respiration by ADP in permeabilized heart and liver cells.** *Biochem Biophys Res Commun* 1995, **208:**919-926.
13. Barth E, Bassi G, Maybauer DM, Simon F, Gröger M, Öter S, Speit G, Nguyen CD, Hasel C, Möller P, Wachter U, Vogt JA, Matejovic M; Radermacher P, Calzia E: **Effects of ventilation with 100% oxygen during early hyperdynamic porcine fecal peritonitis.** *Crit Care Med* 2008, **36:**495-503.
14. Porta F, Takala J, Kolarova A, Ma Y, Redaelli CA, Brander L, Bracht H, Jakob SM: **Oxygen extraction in pigs subjected to low-dose infusion of endotoxin after major abdominal surgery.** *Acta Anaesthesiol Scand* 2006, **49:**627-634.
15. Protti A, Singer M: **Bench-to bedside review: Potential strategies to protect or reverse mitochondrial dysfunction in sepsis-induced organ failure.** *Crit Care* 2006, **10:**228-235.