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Reactive oxygen species metabolites in sepsis: markers and mediators

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Overproduction of oxygen free radicals and decreased antioxidant capacity has been shown to be a hallmark of severe sepsis more than 20 years ago ¹. In the late 1990's there was a surge of randomised controlled trials trying to modulate this important host response, with predictably negative results ². None of these trials stratified the patients according to their oxygen free radical production, hence it is not surprising that the potential beneficial effect has been diluted in the process ^{3,4}.

Because of these negative studies, clinical researchers became vary of this treatment modality, however there has been an ongoing interest in this part of the pathophysiology of sepsis and septic shock in cellular and molecular level.

In the current issue of the journal, Montini et al. report the results of their pilot study, which adds important data to our understanding of the time-course and potential importance of reactive oxygen species metabolites in sepsis and septic shock ⁵. They found that there was a significant evolution in the reactive oxygen species metabolites (ROM) levels and that diminishing ROM levels showed a negative correlation with the corresponding daily SOFA score and predicted time of death. The authors speculated that this phenomenon could be due to on-going mitochondrial dysfunction as ROMs originating from plasma and mitochondrium showed a growing imbalance as the time passed.

Worsening daily SOFA scores, increased level of oxidative stress and reduced level of antioxidant capacity have been previously shown to correlate with outcome ¹.

This pilot study is the first to actually monitor the evolution of ROMs during the whole course of ICU stay and in that it provides very important insight.

Patients in this pilot study were recruited between the 5th-8th day of ICU stay, with new onset of severe sepsis or septic shock according to the 2012 consensus definition ⁶. They were most likely suffering from ICU acquired infections such as ventilator-associated pneumonia, catheter related urinary tract infection or ICU acquired bacteraemia. Unsurprisingly, most of them suffered from primarily Gram-positive infections and majority of the patients had polymicrobial infection ⁵. There is a growing body of evidence which points towards worse outcomes if the patient

suffers from a “second-hit” infection of Gram-positive origin ⁷ and interestingly the results of Montini et al. may shed some light to one of the possible mechanisms behind this observation.

Gram positive organisms are frequently isolated in clinical samples on the intensive care unit, such as methicillin resistant *Staphylococcus aureus* and possess a sophisticated repertoire to avoid neutrophil killing even if phagocytosis has taken place ⁸. Bacterial pathogens often employ two-component systems (TCSs), typically consisting of a sensor kinase and a response regulator, to control expression of a set of virulence genes in response to changing host environments. In *Staphylococcus aureus*, the SaeR/S TCS is essential for in vivo survival of the bacterium. In an elegant study Guerra et al. demonstrated that the SaeR/S TCS found in *Staphylococcus aureus* species do not inhibit neutrophil superoxide (O₂⁻) production, however, subsequent neutrophil ROS production was significantly reduced and resulted in decreased production of hypochlorous acid/hypochlorite anion (HOCl/⁻OCl) ⁹. *Staphylococcus aureus* already ingested by neutrophils not only undermine oxidant attack but also repair oxidative damage incurred within the immune system’s effector cells. SaeR/S TCS together with other signalling pathways can contribute to the modulation of stress response genes such as Methionine sulfoxide reductases (Msr) ¹⁰. Msr are highly conserved enzymes that support oxidative repair in a wide range of organisms and contribute to survival of bacteria within neutrophils ⁸. The absence of Msr activity increased the susceptibility of *Staphylococcus aureus* to reagent H₂O₂ and HOCl and also to the antimicrobial effects of neutrophils ¹⁰. Together, the combined effects of limiting and repairing

oxidant damage promote survival of Gram positive bacteria within neutrophils ¹⁰.

The results of the clinical study by Montini et al. can add another puzzle to this jigsaw and demonstrate that reduced level of oxidative stress and resulting ineffective bacterial clearance can be demonstrated in the patients with highest risk of unfavourable outcome. Their observation of significantly reduced ROM levels at the last stage of severe sepsis and septic shock not only can signify exhaustion of mitochondrial function but also inadequate host response to the bacterial invasion.

There are several questions remain following this pilot study. One of them is whether the results can be replicated in a much larger cohort? We have seen time and again, that results of small, exploratory studies could not be confirmed in larger trials and this risk runs high with the work of Montini et al ⁵.

The potential role of ROMs in determining the outcome is intriguing and the next logical question is: how can we manipulate this phenomenon? Is there a potential to restore healthy mitochondrial ROM levels to improve the outcome of the critically ill septic patient?

Paradoxically the answer might be to reduce overall oxygen exposure levels and to reduce global oxidative stress and the disturbance of innate immunity. Systemic hyperoxia has been shown to cause peripheral vasoconstriction and, in animal models, increases production of reactive oxygen species. The PROXI trial (Perioperative Oxygen Fraction– Effect on Surgical Site Infection and Pulmonary Complications After Abdominal Surgery) and more recently the Oxygen-ICU study

reported an association between high fraction of inspired oxygen (F_{iO_2}) and an increase in long-term mortality in the perioperative and critical care setting ^{11,12}. The Oxygen-ICU study very convincingly shown a significant reduction in new infections and new incidence of shock, when conservative levels of oxygen therapy was applied on the ICU ¹². Interestingly, the Kaplan-Meier curve started to diverge between the conservative and conventional oxygen administration strategy groups exactly at the time point where Dr Montini recruited their patients into their pilot study. Is it possible that the serial measurement of ROMs could help us minimising external oxygen exposure, whilst maintaining mitochondrial homeostasis? There are many exciting and important questions waiting to be answered, before the role of reactive oxygen species in sepsis is fully elucidated.

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