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# Microcirculatory Analysis in the Management of Sepsis—Occam's Razor or Achilles' Heel?*

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An important feature of critical care–based research is the continual advance in the understanding of the variability of the human responses and the shifting importance of disease biomarkers and their clinical trajectories. The inhalation of nitric oxide (INO) has become a particularly popular procedure in the intensive care, partly because gas delivery to the ventilated patient is relatively easy and partly because this administration route offers a number of advantages for lung-directed therapies. Indeed, INO is used traditionally to treat a variety of conditions marked by hypoxemia secondary to persistent pulmonary hypertension (1). INO was additionally thought to improve ventilation perfusion by regional vasodilation and was therefore usually used as selective pulmonary vasodilator in patients with acute respiratory distress syndrome (1, 2). In contrast with previous knowledge, however, distant extrapulmonary effects of INO have also been demonstrated, probably due to the nitrosylation of plasma proteins and hemoglobin and the formation of nitrite, all of which can improve the systemic microcirculation, as demonstrated by increases in peripheral functional capillary density in patients with hypoxemic respiratory failure (3). Logically, this suggests that INO can also be a method of choice for systemic microcirculatory resuscitation and that the use of INO can be extended as a treatment option for sepsis, where a microcirculatory dysfunction is the key component of the pathogenesis (4, 5).

Nevertheless, there are probably more areas with gaps than confluence in this respect. A recent review revealed that INO can unquestionably improve the level of oxygenation, but does not reduce the mortality in patients with acute respiratory distress syndrome, regardless of the severity (6). Furthermore, IV formulations of nitric oxide (NO) donors, such as nitroglycerine, did not promote the sublingual microcirculatory blood flow in septic shock patients with hemodynamic resuscitation (7).

The article by Trzeciak et al (8) in this issue of *Critical Care Medicine* now offers deeper insight into the effects and limitations of INO therapy in sepsis. The well-chosen aim of this randomized, controlled clinical study was to observe whether INO would improve the peripheral microcirculation in septic patients whose macrocirculation has been optimized with goal-directed therapy, and whether such microcirculatory

***See also p. 2482.**

**Key Words:** perfusion heterogeneity; semiquantitative analysis; sublingual microcirculation

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changes would be associated with an improved organ function, as assessed by the Sequential Organ Failure Assessment score. The primary outcome measure was a change in sublingual microcirculation visualized through standard sidestream dark-field (SDF) videomicroscopy. Interestingly, the inhalation of 40 ppm NO increased the plasma nitrite level significantly, which suggests that NO was delivered systemically and might therefore exert distant microcirculatory effects. However, the interim analysis led to the termination of the trial for futility, in view of the lack of increase in the microcirculatory indices. This dose of NO did not augment the microcirculatory flow index (MFI) or the flow heterogeneity index (FHI) as measured by SDF imaging 2 hours after drug administration. Likewise, no association was found between the microcirculatory variables and the multiple organ dysfunction scores in the INO-treated patient population with sepsis.

This is a welcome study by an authoritative group of clinicians who have provided a conclusion that is absolutely relevant and logical: INO did not exert any significant influence on the sublingual microcirculation after resuscitation and the relation between INO, the sublingual microcirculatory perfusion, and multiple organ failure was therefore not confirmed either. The possible early microcirculatory consequences of INO are still open to discussion, but the interpretation of these findings is well balanced. It may be added that it is perhaps timely to address a somewhat overlooked issue, the analysis method used to quantify the peripheral microcirculatory changes.

Although a clear consensus has been reached that a microcirculatory dysfunction is a pivotal element of critical conditions, the diagnostic power of bedside microcirculatory analyses remains less clear. The terms such as "impaired microcirculation" that are commonly used to describe sepsis or ischemia-induced changes tend to be simplistic and may rather misleadingly suggest that the microcirculatory responses are uniform in nature and similar in extent, whereas pathological microcirculatory alterations can range from transient reductions in capillary red cell traffic with a temporarily reduced velocity to complete capillary stasis with a decreased functional capillary density. A sepsis-induced microvascular failure critically involves a flow redistribution, leading to diverse spatial perfusion heterogeneity in distinct anatomical structures, including the wall of the gastrointestinal tract. To add to the complexity, a second form of perfusion heterogeneity may also be present when time-varying flow fluctuations evolve within the microvascular system.

Continuous or sustained microcirculatory events are easily compared, but this is certainly not the situation for alternating flow conditions in most cases. Not surprisingly, microcirculatory analysis is an extremely difficult task because the conventional variables of spatial heterogeneity (such as functional capillary density) and timewise heterogeneity (such as cycles/min) are insufficiently sensitive to allow subtle microcirculatory alterations to be followed. Further, the comparison of velocities between continuous flow and pulsatile perfusion phases and between different flow patterns is usually impossible by these means, even under well-controlled experimental conditions.

Orthogonal polarization spectral (OPS) imaging and its successor, SDF imaging, have made microcirculatory investigations possible at the bedside, and videomicroscopy now provides easy-to-use approaches with which to recognize peripheral microcirculatory complications in a number of disease processes. The diagnostic value of the intravital imaging technique has been clearly demonstrated in sepsis too (5). Direct visualization of the sublingual microcirculation has become feasible and simple, but the complexity of the problem to be analyzed has not changed. Following OPS or SDF image acquisition, an in-depth analysis of the microcirculation, including the calculation of functional capillary density or the measurement of velocities, can be performed in individual vessels through the use of appropriate software tools. In view of the fact that this approach requires eye-challenging and time-consuming work, automated velocity measurements and new perfusion indicators have been introduced in the clinical routine. After the use of "absent, intermittent, sluggish, and normal" flow to characterize MFI was recommended by a consensus panel of experts (10), many clinical studies have used MFI or other perfusion markers, mostly with regard to their relative simplicity and reduced analysis time. However, "absent, intermittent, sluggish, and normal" are certainly not quantitative variables, and even a numerical derivative such as the FHI (the highest to lowest ratio of MFI at the observation site) is also a basically qualitative descriptor of the microcirculatory perfusion.

In the study by Trzeciak et al (8), the MFI was used to characterize the quality of the flow in the groups of vessels present in the quadrants of the observation area. When the movement of red cells in certain capillaries slows or ceases, the MFI may include perfused and underperfused vessels and (without diameter limitations) arterioles, venules, and capillaries too. The median value of MFI at 0 hour was 1.9 (1.7–2.1) for all groups of patients and was not changed significantly following INO or sham treatment. No flow is awarded a score of 0, intermittent flow a score of 1, sluggish flow a score of 2, and normal flow a score of 3. This means that the sublingual microcirculation was "generally sluggish" in these patients and remained "sluggish" after INO administration. Somewhat similarly, when the capillary refill time was first described in 1947, the definitions "normal," "definite slowing," and "very sluggish" were used to correlate the changes accompanying no, slight/moderate, or severe shock states, respectively (10). This does not disqualify the conclusion that INO is not associated with an improved patient outcome, but the effects on the oral microcirculation are perhaps less clear and subtle changes in microvascular perfusion may definitely not be ruled out. It should perhaps be emphasized that changes which may be subtle numerically are not always unimportant physiologically. Admitting this limitation, it seems clear that the peripheral microcirculation was grossly unaffected in these patients, which does indeed restrict the rationale of INO administration in resuscitated sepsis.

The available clinical techniques cannot provide a complete view of the tissue microcirculation, and none of the techniques available for the evaluation of complex microvascular reactions are perfect. Intravital microscopy serves as a good basis

for estimation of the in situ microcirculatory reactions, but a number of factors may affect the reliability of OPS or SDF measurements, and the analytical method for oral microcirculatory perfusion remains a limiting factor too. The simplicity of an answer as demanded by William of Occam may be desirable as a principle, but accuracy is also important. Novel approaches through which to express numerical changes in microvascular perfusion, including heterogeneity, are surely needed.

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# Prognosis After Cardiac Arrest: Time to Rethink Why, How, and When*


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Why rush to prognosticate after cardiac arrest? Certainly, there is less pressure to issue a rapid and definitive opinion about the long-term prospects of a patient with multitrauma, severe acute respiratory distress syndrome, or septic shock and multiple organ system failure. When confronted with such diseases, most of us would not hesitate, in the absence of futility, advanced age, or severe medical comorbidities, to treat aggressively for a week or more before issuing a formal opinion about prognosis. Yet after cardiac arrest, there has evolved in some centers a practice of early prognostication. As demonstrated by the research of Mulder et al (1) published in this issue of *Critical Care Medicine*, that practice should be reconsidered.

***See also p. 2493.**

**Key Words:** arrest; cardiac; hypothermia; prognosis; severity

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Mulder et al (1) prospectively evaluated 154 comatose survivors of witnessed out-of-hospital cardiac arrest (OHCA) admitted to Hennepin County Medical Center. Seventy-seven percent of those patients were treated with hypothermia, and of the 78 patients (51%) who died, 81% died after withdrawal of life-sustaining therapy. Thirty percent of patients (19 of 63) who died had life support withdrawn within the first 72 hours of therapy, including five treated with therapeutic hypothermia. Yet among survivors, awakening after 72 hours was common (20 of 56; 36%). This demonstrates both the frequency of withdrawal of life support measures as a mechanism of death after cardiac arrest and the need to allow more than 3 days for neurological recovery prior to terminating life support measures.

There are excellent reasons to assess the severity of brain injury early after a cardiac arrest. First, triage to individualized treatment pathways based on the type and severity of brain, cardiac, and systemic injuries, with an analysis of competing risks may improve both outcomes and resource utilization (2). Second, families require accurate information to make informed decisions about the therapeutic options they are offered. Finally, the increasing number of patients surviving an OHCA (3) mandates that effective but expensive therapies like prolonged temperature management and coronary revascularization be targeted to patients likely to benefit, rather than simply anyone rolling through the door with a pulse. We need an early assessment of brain injury to provide, as we like to say, the "right care, right now."