Organ preservation during stress defines the central mission of the clinical practice of anesthesiology. Despite this simple-sounding mandate, any anesthesiologist’s ability to reliably identify when tissues are receiving enough oxygen to function remains inadequate. Currently, no direct measure of oxygen concentration in cells exists in clinical practice. Therefore, surrogate measures of oxygen delivery and organ function guide clinical decisions. These surrogates, although widely utilized, have limited value and rarely offer unambiguous data. Indeed, several recent large trials of sepsis therapy directed to achieve specific values of surrogate markers were not found to be superior to standard care. Because of this, the need for a direct measure of tissue oxygenation remains. A promising effort to meet this need is reported by Romers et al. in the current issue of Anesthesiology.

These investigators used a pig model to study the effect of normovolemic hemodilution on mitochondrial Po2 in live animals. In their model, the investigators employed a technique called delayed fluorescence of protoporphyrin IX (PpIX), which exploits the oxygen-dependent optical properties of a common mitochondrial macromolecule to derive the Po2 noninvasively. Hemodilution was performed in stages, and with each successive step, mitochondrial Po2 decreased. After successive dilutions (to a hemoglobin of about 2.6 g/dl), the Po2 difference between diluted and control animals became significant. This shift to significance was surprisingly abrupt and sharp, and this pattern preceded the hemodynamic instability, which was noted after subsequent iterations. Observed in all 12 experimental pigs, this sharp decline in oxygen tension suggests that a critical mitochondrial Po2 might be discernable, hinting at the possibility of a transfusion trigger. Although the authors plausibly suggest that this sharp decline might represent the exhaustion of each pig’s physiologic compensation to preserve oxygen delivery at declining hemoglobin concentrations, that assertion remains unproven.

The clinical value of mitochondrial Po2 is promising but, so far, unproven, and practical limitations remain. To measure mitochondrial Po2, the authors applied 5-aminolevulinic acid (ALA), a PpIX precursor, and protected it from light by applying aluminum foil to shaved skin for 3 h to enhance mitochondrial synthesis of PpIX. While this method seems impractical for clinicians, oral and intravenous preparations of ALA are in current use, and these authors have reported measuring mitochondrial oxygen tension in human skin using ALA applied to the skin. If 3 h of skin preparation is required to obtain measurements, its clinical utility will be limited, especially in cases of unanticipated tissue hypoxia. ALA itself is not known to be toxic, but high concentrations of PpIX (which it induces) produce singlet oxygen in sunlight and induce apoptosis in all cells, particularly tumor cells. These toxic effects of PpIX appear to depend on the cumulative dose of light applied, and animal data demonstrate that PpIX levels normalize after 24 h, regardless of administration route. Nonetheless, the PpIX toxicity might be a major hurdle to human clinical application. Furthermore, the measurements were performed on each animal’s thoracic skin. In many physiologic as well as disease states, vasoconstriction of the skin occurs. It is unclear whether thoracic skin is really a good early marker (a “canary”) of organ dysfunction seen with severe anemia. In that case, these measurements might not be generalizable to other organs. The current study provided evidence that mitochondrial Pao2 was more sensitive compared to global markers of cellular hypoxia such as lactate and mixed venous oxygen saturation; however, it did not investigate any organ-specific markers. The “canary” hypothesis—that cutaneous mitochondrial Po2 changes foretell changes in other vital organs—while plausible, remains unproven.

“A reliable measure of oxygen tension at the level of the mitochondria might significantly refine transfusion practice in anesthesiology and critical care.”
In cell culture, the use of delayed photoluminescence quenching to measure mitochondrial Po2 is now well recognized, but this study, performed on live large animals with actual compromise to oxygen delivery, is a significant advance. Should we be optimistic that a clinically useful human monitor might be forthcoming? Since direct measurement of mitochondrial oxygen tension has the potential to be a significant improvement over surrogates, the possibilities are enticing. The assumption, for example, that a blood transfusion and subsequent improvement in serum hemoglobin or lactate have actually improved cellular oxygenation after hemorrhage is controversial. A reliable measure of oxygen tension at the level of the mitochondria might significantly refine transfusion practice in anesthesiology and critical care. Indeed, any clinical scenario where cellular oxygenation might be compromised could potentially benefit from this monitor. In the future, a physician might measure mitochondrial Po2 to help manage inotropes for patients with cardiogenic shock, to initiate extracorporeal membrane oxygenation in patients with severe acute respiratory distress syndrome, or to even aim “goal-directed therapy” at a rational and transparent goal. If mitochondrial Po2 can be measured reliably in humans, the potential value of this technique is hard to overestimate.

For clinicians, these results offer a great hope that our clinical interventions will become more judicious and discriminating. Our myriad efforts to deliver oxygen to mitochondria may finally be measurable and guided by a meaningful result. The fact that most of the nuts and bolts required to get this measurement are already available clinically suggests that the interlude between animal and human trials might be a bit shorter this time around. Yet shorter may not mean short. Many fundamental questions—both technical and physiological—remain. The authors have demonstrated convincingly that mitochondrial oxygen tension can be obtained during hemorrhage and that a critical decline appears to present itself before other traditional markers do. This is reassuring, but both recent and distant experience have taught us that the ability to detect and even correct a deranged number does not always yield any improvement in mortality, morbidity, or any other outcome actually meaningful to patients and their physicians. Do we now have a better number near our grasp? Not yet, perhaps, but this study is an impressive proof of concept. For clinicians, the real work has only just begun.

Competing Interests
The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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