Cutaneous Mitochondrial P_{O_2}: A Beginning of a New Era?

To the Editor:

We read with great interest the article about cutaneous mitochondrial P_{O_2} (mito-P_{O_2}) by Römers *et al.* in the July 2016 issue of Anesthesiology. We congratulate them for their hard work in producing this demanding and important proof-of-concept study; it may prove to be revolutionary in transfusion medicine if a safe and feasible monitor of mito-P_{O_2} becomes commercially available.

However, we would like to make the following points. First, the authors administered intravenous anesthetics (ketamine, midazolam, sufentanil, and rocuronium) only and did not use inhalation agents at all.[1] In humans, inhalation anesthetics are used much more frequently. Inhalation agents and ketamine may suppress metabolism differently. Consequently, this can affect the cutaneous mito-P_{O_2} measurements if inhalation agents suppress metabolism and oxygen consumption greater than ketamine. In addition, inhalation anesthetics produce peripheral vasodilation, which may not be the case with ketamine. The result may lead to a different blood flow pattern and hence different oxygen supply.[2] One of the reasons the authors may have chosen intravenous agents is to avoid the vasodilatory and hypotensive effect that accompanies the usage of inhalation agents.

Second, in the shock state, the body will divert most of the cardiac output to the vital organs, including the brain and the heart, as the result of peripheral vasoconstriction.[3] The experiment was performed by heating the measuring site to 38°C to improve/arterialize the regional capillary blood flow.[3] This may not reflect the actual cutaneous blood flow or cutaneous mito-P_{O_2} under real shock condition.

Third, as the authors elaborated in the article, measuring mito-P_{O_2} at the skin may not reflect the oxygen tension (P_{O_2}) in the brain or the heart. Mito-P_{O_2} is variable between different organs and within the same organ under various conditions or at different times.[4] For example; mito-P_{O_2} in the heart muscle varies with different fractional inspired oxygen tension concentrations.[5] Therefore, monitoring the mito-P_{O_2} at the skin may not reflect P_{O_2} in the brain or the heart. Jugular venous oxygen saturation, brain tissue oxygen tension, and/or added additional noninvasive cerebral function monitors such as cerebral near-infrared spectroscopy could have been obtained to monitor the brain oxygenation at the same time and compare its P_{O_2} with the mito-P_{O_2}.[6] Since brain cells have more mitochondria and more adenosine triphosphate consumption than the skin, the brain may have been affected at a different time than the skin with the hemodynamic changes that were induced during the study.

Fourth, mixed venous oxygen saturation and Pa_{O_2} were obtained during the experiment but were not shown in table 1 or fig. 3.[1] These values could have been used to compare different oxygen tensions at the arterial, venous, and mitochondrial levels at the same time. Their inclusion could have been valuable and more informative.

Finally, there is a cell-to-cell variability in mitochondrial number and function. Mitochondria play an important role in cell signaling, differentiation, and death.[4] Cellular P_{O_2} is kept in narrow range under normal conditions as either hypoxia or hyperoxia can result in mitochondrial dysfunction.[7] Indeed, mitochondrial dysfunction may be one of the failing compensation mechanisms that were referred to in the article. With the continuous worsening of cellular hypoxia, mitochondrial dysfunction becomes more apparent and may lead to decreased ability of the mitochondria to utilize oxygen that is reflected by the drop in mito-P_{O_2}. There is some evidence that metabolic reprogramming may cause mitochondrial dysfunction resulting in aberrant gene expression.[7] If this evidence is confirmed, then perhaps transfusion threshold would be detected earlier to avoid the mitochondrial dysfunction and the resulting cell death.

Competing Interests

The authors declare no competing interests.

Marco Mikhael, M.D., Ned Nasr, M.D., Piotr Al Jindi, M.D. Cook County Hospital, Chicago, Illinois (M.M.). mmikhael@cookcountyhhs.org

References

1. Römers LH, Bakker C, Dollée N, Hoeks SE, Lima A, Raat NJ, Johannes T, Stolker RJ, Mik EG: Cutaneous mitochondrial P_{O_2}, but not tissue oxygen saturation, is an early indicator of the physiologic limit of hemodilution in the pig. Anesthesiology 2016;125(1):124–132.
2. Byrne P, Provan JL, Ameli FM, Jones DP: The use of transcutaneous oxygen tension measurements in the diagnosis of peripheral vascular insufficiency. Ann Surg 1984; 200:159–65
3. Yip WL: Evaluation of the clinimetrics of transcutaneous oxygen measurement and its application in wound care. Int Wound J 2015; 12:625–9
4. Guantes R, Díaz-Colunga J, Iborra FJ: Mitochondria and the non-genetic origins of cell-to-cell variability: More is different. Bioessays 2016; 38:64–76
5. Mik EG, Ince C, Eerbeek O, Heinen A, Stap J, Hooibrink B, Schumacher CA, Balestra GM, Johannes T, Beek JF, Nieuwenhuis AF, van Horssen P, Spaan JA, Zuurbier CJ: Mitochondrial oxygen tension within the heart. J Mol Cell Cardiol 2009; 46:943–51
6. Quintard H, Patet C, Suys T, Marques-Vidal P, Oddo M: Normobaric hyperoxia is associated with increased cerebral excitotoxicity after severe traumatic brain injury. Neurocrit Care 2015; 22:243–50
7. Winslow RM: Oxygen: The poison is in the dose. Transfusion 2013; 53:424–37

(Accepted for publication October 5, 2016.)

<zdoi;10.1097/ALN.0000000000001437>