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Application of SPOT chip for transcutaneous oximetry

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Abstract

This response is provided to address the questions raised in the letter to the editor by Henni et al. on our manuscript (Kmiec et al. *Magn Reson Med* 2019;81:781-794) describing the development of a new method for transcutaneous oxygen measurement in humans based on electron paramagnetic resonance (EPR) technology using SPOT chip.

Dear Editor,

We appreciate the interest of Henni et al. (*reference*) in our work developing a new method for transcutaneous oxygen measurement in humans based on electron paramagnetic resonance (EPR) technology (1). We find the authors comments very useful and address the questions raised in the letter to the editor below.

We did not wish to create the impression that all the methods listed in the introduction measure the partial pressure of oxygen. The goal was to list methods, including NIRS, that provide important and useful oxygen data in quantifiable units, which may be related to one another. Interpretation of the data from all these methods requires a clear understanding of what is measured. One advantage of the SPOT chip is that it does measure pO₂ directly.

Currently SPOT chip oximetry is not suitable for use during exercise. The SPOT chip oximetry uses a small (3-mm dia. but could be larger) skin-adhesive sticker as a sensor of free molecular oxygen (diatomic gas), and not oxygen bound to hemoglobin. The sticker stays on the skin and does not need to be physically attached to a cable during measurements

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or while waiting for equilibrium to be reached. The measurement can be done in a totally non-contact mode by holding a loop coil detector (about 1 cm diameter) above the sticker; however, this may be subjected to motion artifacts due to voluntary or involuntary physiological movement of the subject with respect to the loop during measurement. In the first report of the method for skin oxygen measurement (1), we placed the loop over the sticker and connected it with a flexible cable. With this setup, the subject has limited freedom of movement without compromising the data quality. Moreover, the measurement site (skin) has to remain within the boundary of an acceptable magnetic field domain, which is about $20 \times 20 \times 20 \text{ cm}^3$ volume in the center of a large magnet that we currently use for clinical measurements. This requirement is acceptable for the usability of this method to applications such as wound healing, peripheral arterial disease, diabetic ulcer, etc. where we can control the movements within the magnetic field space, but is not suitable for pO_2 measurement during exercise. To address this limitation and to expand the capability of the method for possible real-time measurements during exercise, we are developing a new scanner, by including the magnet and loop in a single, compact hand-held device using pulsed EPR technology for enhanced portability and motion-free data collection (2). We hope the new design of the SPOT chip technology will be potentially useful for real-time monitoring of TcpO_2 during exercise, under ambient conditions.

We appreciate the concern about stating that the electrochemical approach requires heating of the skin. We understand that electrochemical sensors can measure pO_2 without heating. But the electrochemical approach potentially could consume oxygen during operation (3–5), which could underestimate pO_2 , particularly when the skin oxygen is low under ambient temperature without heating. One of the motivations for the development of an alternate technology to the electrode method (TCOM) was to make measurements under ambient conditions. The effect of heating on the skin structure, increased perfusion and diffusion of oxygen through skin, and enhanced vasodilation and blood perfusion in the underlying tissue have been well documented in the literature (5,6). While heating of the skin may help bring the oxygen into the tissue bed beneath the skin to the electrode, the same heating can modify the ‘normal’ level of tissue oxygen at the skin surface and tissue underneath.

Our understanding of the need for skin heating is to increase the diffusion of oxygen through the intact epidermal barrier by reversible lipid melting in the stratum corneum (6). TCOM brochure claims a 20-fold increase in oxygen diffusion at $44\text{--}45^\circ\text{C}$ compared to physiological skin temperature. Whether it is a need or a consequence, the skin heating can induce thermal hyperemia in the capillary bed directly underneath the skin which may increase tissue oxygen levels. As a result, the TCOM method has better sensitivity to oxygen, from virtually undetectable at physiologic skin temperature to $>40 \text{ mmHg}$ in heated healthy skins and significantly shortened waiting time to reach steady state equilibrium of TcpO_2 . Thus, the TcpO_2 values obtained under elevated skin temperatures may not represent true physiological values at ambient conditions. This is evident from the magnitude of measured TcpO_2 values which range from 40 to 90 mmHg in healthy skin (representative of ‘physiological normoxia’) and $<40 \text{ mmHg}$ in unhealthy skin (representative of ‘pathophysiological hypoxia’). In actuality, the tissue pO_2 values are not known to be this high under normal physiological conditions (7). We appreciate that this heating approach is clinically useful and could also be used with the SPOT chips. Our laboratory is studying the

relationship between the pO_2 readings, on the skin versus in the tissue underneath the skin. We think the SPOT chip method, being sensitive to low pO_2 measured under physiological skin temperatures, should be able to relate to pathophysiology. Our results clearly indicate that even without heating, the SPOT chip technology is a valid indicator of pathophysiology related, for example, to oxygen deprivation or hyperoxygenation.

The time to reach initial equilibrium (waiting time) and the response time of the SPOT chip to rapidly changing oxygen levels are two important factors that deserve further clarification. As we described in our manuscript, prior to placement on the skin, the chips were kept in room air (~ 160 mmHg). When the chip is placed on the skin with the oxygen-impermeable surface on top, the ambient oxygen is trapped in the chip and in the space between the chip and skin. The SPOT chip does not consume oxygen, and hence the oxygen trapped in the chip has to diffuse into the skin, possibly driven by pressure gradients, before establishing equilibrium with the transcutaneous oxygen. Further, diffusion of oxygen into the skin is expected to be slow without heating. Thus, the SPOT chip takes up to 60 min depending on the type of skin and conditions including humidity, temperature, etc. In a few cases, we monitored the decrease in pO_2 until it reached equilibrium where we observed that the $TcpO_2$ was stable for more than 3 hours after reaching equilibrium. Hence, in most other cases, we let the volunteers leave the measurement room and then come back 1 to 2 hours later for measurement of $TcpO_2$ with the expectation that the equilibrium would have been reached by this time. Further, the accuracy of our mathematical models for longitudinal changes of our SPOT $TcpO_2$ (Fig. 5 in Ref. 1) allows prediction of the equilibrium value using data from shorter time periods (Supporting Information Figure S1). Alternatively, we can also implement strategies for skin heating during SPOT chip measurements which will allow rapid equilibration as well as match conditions used for TCOM measurement. We are planning to carry out such experiments in our future studies.

Although time is needed for oxygen under the SPOT chip to diffuse away, the SPOT chip is not slow to respond to rapidly changing tissue oxygen levels. A notable advantage of the SPOT chip is its very short response time (< 2 sec) to changes in tissue oxygen levels (Supporting Information Figure S2). We expect that adding a liquid, as suggested by the authors, would not improve the response time since oxygen will just have to diffuse through another medium with a diffusion coefficient lower than air. On the other hand, new sticker designs with a larger surface area or with a heating element may shorten the waiting time considerably. Once equilibrium is reached subsequent measurements, changes in $TcpO_2$ due to physical activity (exercise) or treatment interventions (hyperoxygen treatment), etc. can be monitored almost in real-time.

We used a blood-pressure cuff to reduce the blood flow to the leg or arm temporarily for about 10 min. Our human protocol (approved by Dartmouth College Committee for Protection of Human Subjects) allowed a maximum period of constriction for 10 min; however, the constriction was to be removed if the subject felt pain or discomfort. The study was conducted using healthy human subjects. The blood-flow constriction was used only to validate the operation of the sensor for acute changes in $TcpO_2$ and not meant for or needed for routine use of the SPOT chip for measurement in human subjects.

Hyperemia is a common occurrence in blood reflow following a short-term occlusion (ischemia/reperfusion) in many organs (8–10). The authors state that limb ischemia induced by cuff occlusion for more than 10 min could result in pain or change in experimental conditions which could result in hyperventilation and increase in pO_2 up on restoration of blood flow. We agree with the caution the authors expressed about the use of tourniquet-induced blood flow constriction for extended periods. Nevertheless, flow constriction is not obligatory for the application of the SPOT chip method for $TcpO_2$ measurements in the clinic.

Despite the need to reduce the initial waiting period to reach a steady state $TcpO_2$, the SPOT chip method has the following advantages: (i) measurement without heating when needed, (ii) high oxygen sensitivity, (iii) fast response times, (iv) direct oxygen tension measurements (pO_2), and (v) reliability. The current results are directly applicable to monitoring and treating clinical conditions such as chronic wounds, while future developments may enable broader applications, such as oxygen monitoring of ventilated patients and monitoring of ischemia during exercise.

We thank the editor for the opportunity to provide additional discussion.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Kmiec MM, Hou H, Kuppusamy ML, Drews TM, Praphat AM, Petryakov SV, Demidenko E, Schaner PE, Buckry JC, Blank A, Kuppusamy P. Transcutaneous oxygen measurement in humans using a paramagnetic skin adhesive film. *Magn Reson Med* 2019;81(2):781–794. [PubMed: 30277275]
2. Wolfson H, RA, Twig Y, Kuppusamy P, AB. A miniature electron spin resonance probehead for transcutaneous oxygen monitoring. . *Appl Magn Reson* 2014;45:955–967.
3. Babilas P, Lamby P, Prantl L, Schreml S, Jung EM, Liebsch G, Wolfbeis OS, Landthaler M, Szeimies RM, Abels C. Transcutaneous pO_2 imaging during tourniquet-induced forearm ischemia using planar optical oxygen sensors. *Skin Res Technol* 2008;14(3):304–311. [PubMed: 19159376]
4. Jaszczak P, Sejrsen P. Oxygen tension and consumption measured by a $tc-PO_2$ electrode on heated skin before and after epidermal stripping. *Acta Anaesthesiol Scand* 1987;31(5):362–369. [PubMed: 3630579]
5. Stucker M, Struk PA, Hoffmann K, Schulze L, Rochling A, Lubbers DW. The transepidermal oxygen flux from the environment is in balance with the capillary oxygen supply. *J Invest Dermatol* 2000;114(3):533–540. [PubMed: 10692114]
6. Van Duzee BF. Thermal analysis of human stratum corneum. *J Invest Dermatol* 1975;65:404–408. [PubMed: 1176792]

7. Carreau A, El Hafny-Rahbi B, Matejuk A, Grillon C, Kieda C. Why is the partial oxygen pressure of human tissues a crucial parameter? Small molecules and hypoxia. *J Cell Mol Med* 2011;15(6): 1239–1253. [PubMed: 21251211]
8. Khan M, Mohan IK, Kutala VK, Kotha SR, Parinandi NL, Hamlin RL, Kuppusamy P. Sulfaphenazole protects heart against ischemia-reperfusion injury and cardiac dysfunction by overexpression of iNOS, leading to enhancement of nitric oxide bioavailability and tissue oxygenation. *Antioxid Redox Signal* 2009;11(4):725–738. [PubMed: 18855521]
9. Mohan IK, Khan M, Wisel S, Selvendiran K, Sridhar A, Carnes CA, Bogнар B, Kalai T, Hideg K, Kuppusamy P. Cardioprotection by HO-4038, a novel verapamil derivative, targeted against ischemia and reperfusion-mediated acute myocardial infarction. *Am J Physiol Heart Circ Physiol* 2009;296(1):H140–151. [PubMed: 18978191]
10. Wang W, Winlove CP, Michel CC. Oxygen partial pressure in outer layers of skin of human finger nail folds. *J Physiol* 2003;549(Pt 3):855–863. [PubMed: 12702744]