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LETTER TO THE EDITOR

Mathematical modeling versus experimental data: how to interpret conflicting evidence?

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TO THE EDITOR: We read with interest the mathematical modeling study by Koirala et al. (1), challenging the widely accepted concept that the muscle "deoxygenation" signal [deoxy(Mb + Hb)] obtained by near-infrared spectroscopy (NIRS) is less sensitive to changes of the "total" Hb + Mb signal [oxy + deoxy(Mb + Hb)] (strictly related to blood volume changes) than the "oxygenation" signal [oxy(Mb + Hb)] (2). Whereas we recognize the elegance of the approach, we admit that it was rather difficult for us (and presumably for the average reader of the Journal) to understand the details of the complex mathematical analysis (1). In short, according to Koirala et al. (1) both deoxy(Mb + Hb) and oxy(Mb + Hb) are affected by changes in oxy + deoxy(Mb + Hb). If true, this concept could limit the applications of NIRS in human exercise physiology (2).

We would like to stress the point that the conclusions by Koirala et al. (1), drawn by a mathematical model developed on data obtained in an isolated dog gastrocnemius preparation in situ (in which the NIRS probe is applied directly on the muscle belly, and not on the intact skin overlying the muscle, as in "human" NIRS studies; Ref. 2), go against ample and clear experimental evidence found mainly in exercising humans.

Deoxy(Mb + Hb) is frequently utilized to estimate "fractional O_2 extraction," that is, the ratio O_2 uptake/O_2 delivery, in the tissue (2). Whereas we obviously agree that in ideal conditions, deoxy(Mb + Hb) is an index of fractional O_2 extraction only when oxy + deoxy(Mb + Hb) is constant, the latter condition seldomly occurs in exercise physiology (2). Our contention is, as mentioned above, that in most physiological conditions, deoxy(Mb + Hb) is substantially less influenced than oxy(Mb + Hb) by oxy + deoxy(Mb + Hb) changes.

During constant work rate exercise, the temporal profile of deoxy(Mb + Hb) determined by continuous-wave NIRS ($NIRS_{CW}$) is very similar to that of other indices of fractional O_2 extraction (3), such as venous PO_2 (both in humans and in animal models), microvascular PO_2 determined by phosphorescence quenching, and deoxyMb levels determined by ^{1}H-magnetic resonance spectroscopy (4). The same concept is not applicable to oxy(Mb + Hb), which presents a more complex temporal pattern, presumably related to increased skin blood flow and vasodilation [increased oxy + deoxy(Mb + Hb)] occurring for thermoregulatory purposes (5). Experimental data from our group, shown in Fig. 4 of the study by Ferrari et al. (6), clearly demonstrate the close correlation, during recovery periods, between oxy + deoxy(Mb + Hb) and oxy(Mb + Hb) increases, whereas deoxy(Mb + Hb) increases only during exercise periods, in which oxy + deoxy(Mb + Hb) stays constant. Several other examples along this line could be made as well.

The NIRS data mentioned above have been obtained by the less sophisticated, less expensive, and more diffusely utilized $NIRS_{CW}$ instruments, but the concept can be extended also to the more sophisticated, quantitatively more accurate, and more expensive time-resolved NIRS ($NIRS_{TR}$) instruments. Koga et al. (7), for example, concluded that deoxy(Mb + Hb) determined by $NIRS_{CW}$ or $NIRS_{TR}$ perform better than oxy(Mb + Hb) as an index of fractional O_2 extraction, both in the presence of increased skin blood flow or increased oxy + deoxy(Mb + Hb).

In conclusion, the bottom line of the present Letter could be: should experimental evidence directly obtained in human studies "win" over evidence obtained by complex mathematical modeling constructed upon animal experiments? Our immediate answer would be "yes." Or, perhaps more objectively, every effort should be made to utilize evidence deriving from complex mathematical modeling to better interpret intrinsically imprecise but directly obtained experimental data.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

B.G. and V.Q. drafted manuscript; edited and revised manuscript; and approved final version of manuscript.

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