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Training Increases Muscle O₂ Diffusing Capacity Intrinsic to the Elevated $\dot{V} O_{2max}$

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Dear Editor-in-Chief

Understanding the interdependence between perfusive (cardiac output/blood flow) and diffusive (transmembrane O₂ flux, O₂ extraction) conductances during maximal exercise is fundamental to resolving the mechanistic bases for increased $\dot{V} O_{2max}$ with training. Montero et al. (5) are therefore to be congratulated for spotlighting this issue with their meta-analysis. Based overwhelmingly on studies that measured cardiac output using rebreathing techniques and estimated a-vO₂ difference, they conclude that the "... increase in $\dot{V} O_{2max}$ is associated with increase in cardiac output but not in a-vO₂ difference ...". Thus, muscle O₂ diffusing capacity adaptations are dismissed from contributing to the elevated $\dot{V} O_{2max}$.

These conclusions are surprising and have emerged through skewed selection of studies using technologies (e.g., rebreathing) that render crucial data unbelievable. Technical advances in intravital microscopy, microvascular O₂ measurements, thermodilution, and O₂ diffusion theory have advanced muscle O₂ transport understanding beyond simple O₂ in–O₂ out black box approaches. Substantial heterogeneities of O₂ delivery-to-O₂ utilization at the capillary and intramuscle as well as intermuscle level have the potential to limit $\dot{V} O_2$ kinetics and $\dot{V} O_{2max}$ (3). Moreover, simple measures of cardiac output or even limb blood flow can hide critical training-induced muscle(s) blood flow redistribution.

Peter Wagner's insightful conflation of Fick principle and law demonstrates how muscle perfusive and diffusive O₂ transport combine to achieve $\dot{V} O_{2max}$ in health (8) and disease (6). Thus, as heart failure cripples $\dot{V} O_{2max}$ by impairing perfusive *and* diffusive O₂ transport (6), exercise training does the opposite. These changes can be understood mechanistically through measurements made across exercising muscles (8) and theoretical considerations.

Specific points of concern:

1. Regarding the meta-analysis: As the studies surveyed were interventional not observational Preferred Reporting Items for Systematic reviews and Meta-Analyses rather than Meta-analysis Of Observational Studies in Epidemiology Guidelines are indicated and the Cochrane Risk of Bias Assessment tool is more appropriate than the Systematic Appraisal of Quality for Observational Research (4). Also, the Cochrane Collaboration discourages quality rating scales because they lack empirical support.
2. Inaccurate cardiac output estimates yield implausible a-vO₂ differences (e.g., Montero et al.'s Figure 2 value of 21.07 mL/100 mL is higher than arterial O₂ content!).
3. a-vO₂ difference is *measured* using catheter studies, which have been largely excluded [e.g., Roca et al. (8)]. The two included by Montero et al. (5) demonstrate an *increased a-vO₂ difference* [i.e., Beere et al. (1), Klausen et al. (2)].
4. As cardiac output increases 5–6 L·L⁻¹ $\dot{V} O_2$ with a positive intercept of 5–6 L·min⁻¹, a-vO₂ difference *must* increase hyperbolically with $\dot{V} O_2$ and less fit subjects (lower $\dot{V} O_{2max}$) will increase a- $\dot{V} O_2$ difference more with training than fitter counterparts. Beere et al.'s (1) subjects low pretraining $\dot{V} O_{2max}$ (2.18 L·min⁻¹) left more room for an approximate 20% increase of $\dot{V} O_{2max}$ and 25% increase in a-vO₂ difference posttraining.
5. a-vO₂ difference errors in studies selected by Montero et al. (5) likely arose partially from inaccurate measurements of $\dot{V} O_{2max}$ (7).

Adding further confusion, while deselecting invasive catheterization studies, Montero et al. helpfully point out that "... future studies aiming to determine a-vO₂ difference should assess this invasively to gain accuracy."

We could not agree more!

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