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Capillary Red Cell Transit Time Is Still an Unlikely Contributor to Exercise-Induced Pulmonary Diffusion Limitation: Response to Hopkins, Dempsey, and Stickland

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The impetus for these contrasting perspectives (1,2) originates from a 2023 article summarizing a symposium at the 2022 American College of Sports Medicine Conference (3), which highlighted the underexplored role of rapid red blood cell (RBC) transit times in causing exercise-induced arterial hypoxemia (EIAH). Contrarily, my perspective presents overlooked studies that argue against rapid RBC transit times through pulmonary capillaries as a major factor in EIAH (2), drawing on both animal and human research for support (4–6).

Hopkins and colleagues argue that the Multiple Inert Gas Elimination Technique (MIGET) can detect diffusion limitations by analyzing unexplained differences in alveolar-to-arterial pO_2 ($AaDO_2$) (1). Although MIGET indicates potential diffusion issues as oxygen consumption rises, it cannot specify whether these are due to rapid RBC transit through pulmonary capillaries, alveolar–capillary membrane thickening, or reduced gas exchange surface area. Although MIGET can identify diffusion limitations, it cannot identify the precise cause contributing to EIAH.

As mentioned previously (2), one of the adaptations to endurance training is an increase in total blood volume (7,8), which increases pulmonary blood volume (7). An increase in pulmonary blood volume through endurance training (7) or from artificial means (6) counteracts the increase in cardiac output ($\dot{Q}$) to help prevent whole lung RBC transit times from decreasing below the limit for partial pressure equilibrium.[1] Endurance training also increases resting pulmonary capillary blood volume (Vc) (9), which is higher in aerobically fit individuals (10,11), and rises across fitness levels, regardless of sex (11).[2] With exercise, Vc continues to increase without reaching a plateau, even at maximum effort, a finding supported by methods like the single-breath Roughton–Forster multistep F_IO_2 technique (5,10,12), and the NO–CO double diffusion technique, whether using single-breath (13) or rebreathing approaches (14,15) (Fig. 1). This ongoing increase in Vc challenges Dr. Dempsey's 1986 hypothesis that Vc reaches a peak due to a morphological maximum, beyond which mean pulmonary capillary transit time (PCTT) drops, potentially leading to EIAH (17).

The slope of the oxyhemoglobin dissociation curve between mixed venous pO_2 ($p\bar{V}O_2$) and pAO_2 is ultimately responsible for the rate of diffusion equilibration, and not the pAO_2 or the driving gradient between pAO_2 and $p\bar{V}O_2$ (i.e., the alveolar to mixed venous pO_2 difference) (16). However, the rate of diffusion equilibration of oxygen across the blood–gas barrier does vary with pAO_2 and $p\bar{V}O_2$ but only because the effective slope of the oxyhemoglobin dissociation curve, β, changes (16).

In Figure 1, a variety of studies are presented using various single-breath and rebreathing techniques (5,10,13,14). Although mean PCTT is about 0.90 ± 0.08 s at rest (Fig. 1D; i.e., $p\bar{V}O_2$ = 40 mm Hg), there is complete partial pressure equilibrium after ~0.25 s of gas exchange (18). Thus, there is an inherent evolutionary safety mechanism that allows a threefold reduction in mean PCTT before diffusion disequilibrium occurs. With intense sea-level exercise,[3] the $p\bar{V}O_2$ is 21 ± 2 mm Hg when $\dot{V}O_2$ is 3.7 ± 0.3 $L \cdot min^{-1}$ and $\dot{Q}$ is 25.5 ± 2.9 $L \cdot min^{-1}$ (n = 11) (19,20). Given these parameters, the diffusion disequilibrium across the blood–gas barrier would occur when mean PCTT is ~0.35 s and less (16), which does not occur.

In summary, rapid PCTT is an unlikely contributor to EIAH for the following reasons:

1. Direct measurements in excised rabbit lungs show that paO_2 and pAO_2 remain consistent when $\dot{Q}$ increases and PCTT decreases (4).

[1]There is a strong association between pulmonary capillary transit times and whole lung transit times per Figure 1 of Ref (2).

[2]Vc was calculated from DLNO and DLCO obtained from Zavorsky and Smoliga. Respir Physiol Neurobiol 2017;241;28–35. The θNO = 4.5 mL·(blood·min·mmHg)$^{-1}$and DMNO/DMCO = 1.97.

[3]At sea level, the inspired PO_2 = ~150 mm Hg and alveolar PO_2 (PAO_2) = ~100 mm Hg,

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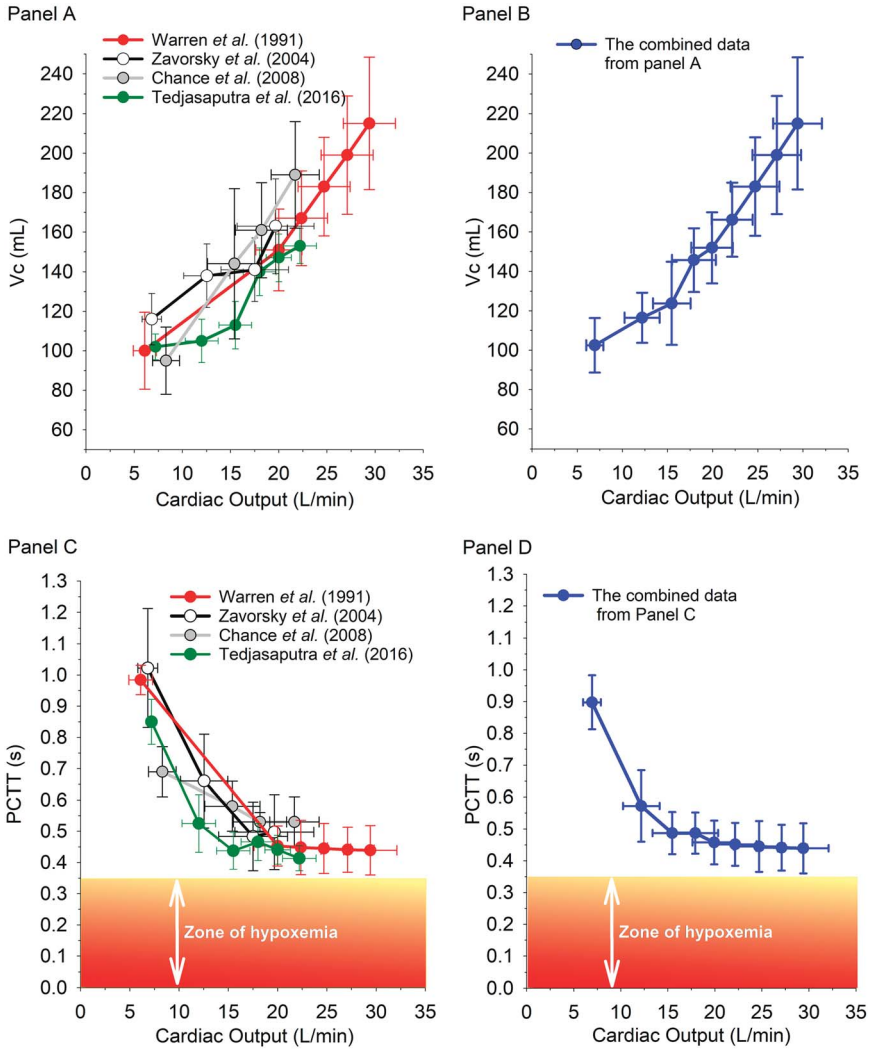

FIGURE 1—This figure illustrates the variations in mean pulmonary Vc and mean PCTT of RBCs as cardiac output increases during sea-level exercise. Maximum oxygen consumption ($\dot{V}O_{2max}$) in these four studies was 4.63 ± 0.48 L·min^{-1} (weighted mean ± SD, n = 47 males). In panels B and D, there are nine exercise intensities with data pooled from panels A and C. The numbers of subjects per exercise intensity are as follows: n = 47 at rest, n = 23 for second- and third-exercise intensity, n = 31 for the fourth-exercise intensity, n = 39 for the fifth- and sixth-exercise intensity, and n = 16 for seventh-, eighth-, and ninth- (maximum) exercise intensity. For an exercise-induced pulmonary diffusion limitation to manifest during intense exercise at sea level, characterized by inspired PO_2 = ~ 150 mm Hg, and alveolar PO_2 (PAO_2) = ~100 mm Hg—for which the limitation is caused by excessively rapid PCTTs—the mean PCTT must be equal to or less than approximately 0.35 seconds when the average mixed venous PO_2 ($P\bar{v}O_2$) is around 20 mm Hg (16). In panels C and D, the shaded area represents the zone of hypoxemia, marked at a PCTT of 0.35 s and less. Even at the highest exercise intensity (mean $\dot{V}O_2$ = 4.32 ± 0.12 L·min^{-1}, or ~93% of $\dot{V}O_{2max}$), the mean PCTT remains above the threshold for EIAH.

2. Vc does not plateau when exercise is maximum effort (Fig. 1). This results in a stabilization of PCTT before the zone of hypoxemia is reached (Fig. 1).
3. Pulmonary blood volume does not plateau with exercise (21). This prevents whole lung RBC transit times from decreasing when cardiac index is ≥8.1 L·min^{-1}·m^{-2} ($\dot{Q}$ ≥ 16 L·min^{-1}) (21).
4. Vc and pulmonary blood volume are inexorably linked (Fig. 1 from Zavorsky [2]), and in turn, so is PCTT and whole lung RBC transit times (2). This is why #2 and #3 above show nearly identical associations between either whole lung transit time or PCTT, volume, and flow.
5. There is no association between $AaDO_2$ or paO_2 and mean whole lung RBC transit times when $\dot{Q}$ ranges from 23 to 37 L·min^{-1} (Figure 2 from Zavorsky [2]).
6. Only 6%–9% of the variance mean PCTT is shared with paO_2 or $AaDO_2$ when $\dot{Q}$ is 29.4 ± 2.7 L·min^{-1} (5).
7. The human body adapts to endurance exercise training in such a way as to prevent EIAH due to β. Exercise training increases total blood volume (7,8), pulmonary blood volume (7), and Vc (9). Thus, an increase in volume will counteract the increase in $\dot{Q}$ to stabilize transit time.
8. The range of times it takes for RBCs to travel through the lungs varies, with some moving very quickly. However, as $\dot{Q}$ increases, the differences in PCTT (4) and whole lung transit times (7,22) tend to become less varied. Therefore, unless there is an abnormal connection allowing blood to bypass the lungs (23), the transit times across the lungs become more consistent with higher $\dot{Q}$. Furthermore, increases in blood volume with regular

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endurance training shifts RBC transit time distribution to the right resulting in fewer RBCs that travel faster than the mean (6).

Hence, the research referenced in this discussion and my initial perspective (2) offer substantial evidence disputing the significance of rapid RBC transit times in EIAH. Unfortunately, these studies were overlooked during the 2022 symposium (3).

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