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Capillary Red Cell Transit Time Is an Unlikely Contributor to Exercise-Induced Pulmonary Diffusion Limitation

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In 1985, Dr. Jerome A. Dempsey delivered the "*Is the Lung Built for Exercise"* lecture at the American College of Sports Medicine National Conference, later published in 1986 (1). About 37 yr later, an updated version of this lecture, "*Revisiting 'Is the Lung Built for Exercise*,'" draws attention to lingering questions surrounding exercise-induced arterial hypoxemia and the increased alveolar pO_2 (pAO_2) to arterial pO_2 (paO_2) difference ($AaDO_2$) that occurs with exercise (2). A contentious issue in this context is the potential contribution of rapid red blood cell (RBC) transit through pulmonary capillaries to diffusion limitation. Although my colleagues suggest a lack of research on this (2), several important investigations involving human and animal subjects have addressed this question over the past three decades.

The average duration of RBC transit through pulmonary capillaries is a function of pulmonary capillary blood volume (Vc) divided by cardiac output ($\dot{Q}$) and is about 0.73–0.79 s at rest (3,4). Under normal conditions (i.e., mixed venous pO_2 or $p\bar{v}O_2$ = 40 mm Hg) partial pressure equilibrium of oxygen in a pulmonary capillary is typically reached after ~0.25 s (5), or one-third along an average capillary distance (6). However, the scenario becomes more complex at high cardiac outputs observed during intense exercise in elite athletes. In such instances, a potential interplay between reduced $p\bar{v}O_2$, leading to a reduced ratio of the diffusing capacity to perfusive conductance ($D/\beta\dot{Q}$), and the maximal capacity of Vc, might precipitate diffusion limitation. Because volume divided by flow equals transit time, should Vc plateau, any further increase in ($\dot{Q}$) will reduce RBC transit time.

Nevertheless, the lack of Vc plateauing during severe exercise is evident in fit endurance athletes (7,8), and the increase in blood volume resulting from endurance training (9) acts as a safeguard, preventing drastic reductions in RBC transit times. Endurance training substantially impacts both red cell and plasma volume (9), allowing Vc to continually increase (without reaching a plateau) even during increased exercise intensities. This mechanism effectively prevents a drop in pulmonary capillary transit times of RBCs below the threshold of approximately 0.4 s in well-trained athletes (Fig. 1). For partial pressure equilibration of oxygen to be maintained during exercise at sea level conditions, characterized by a pAO_2 of 100 mm Hg and a $p\bar{v}O_2$ of around 27 mm Hg, a transit time of approximately 0.35 s is necessary (5). In fact, work published in 1960 demonstrates a similar association between transit time and $\dot{Q}$ with a plateau of transit time of ~0.5 s at a $\dot{Q}$ of ~16 $L \cdot min^{-1}$(3).

Some might criticize studies that measure whole lung RBC transit time using radionuclides as an index of pulmonary capillary transit times of RBCs. However, this is unfounded as there is a direct association between pulmonary capillary transit time and whole lung transit times of RBCs (Fig. 1). Right-to-left-ventricular whole lung RBC transit times and pulmonary capillary transit time of RBCs show the same pattern with respect to increasing cardiac index (Fig. 1), in that when cardiac index increases to ≥ 8.1 $L \cdot min^{-1} \cdot m^{-2}$, cardiopulmonary blood volume increases such that whole lung transit time fails to decrease less than ~2 s (10). Similar to Warren et al. (8), in which there was no association between $AaDO_2$ or paO_2 and the pulmonary capillary transit time of RBCs, we also demonstrated no association between $AaDO_2$ or paO_2 and whole lung RBC transit time approximating maximal exercise (11). This evidence supports the notion that rapid RBC transit is only a minor (if at all) contributor to diffusion limitation[1] at sea level. When raw data from two doctoral theses are pooled together (12,13), there is no association between whole lung RBC transit time and paO_2 or $AaDO_2$ in male endurance athletes who exercise at near-maximal exercise intensities (Fig. 2).

Direct measurements of mean RBC transit time made by *in vivo* fluorescence video microscopy are similar to the RBC transit time obtained from indirect measurement of diffusing capacity (15,16), validating the work of others (8). Further evidence supporting studies in isolated perfused rabbit lungs ventilated with room air shows no change in $AaDO_2$ or paO_2 at a cardiac output of ~18 $L \cdot min^{-1}$ and $p\bar{v}O_2 = 22 \pm 4$ mm Hg

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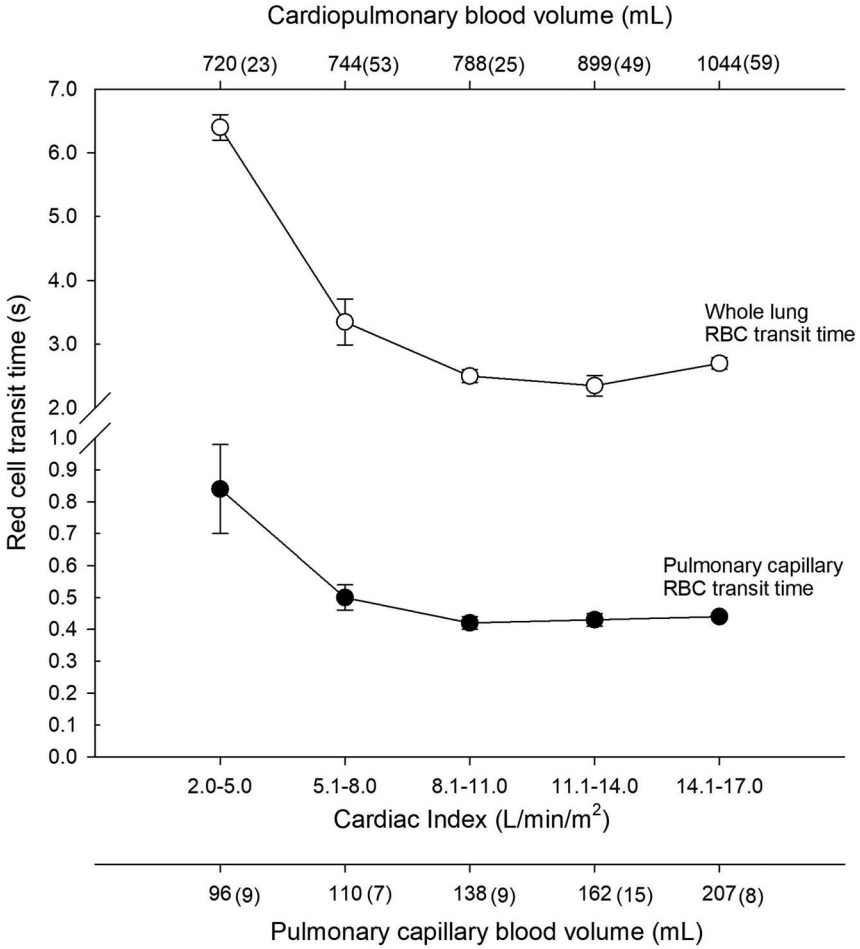

FIGURE 1—This figure demonstrates a robust correlation between pulmonary capillary RBC transit times and whole lung RBC transit times as exercise intensity increases. Notably, capillary and whole lung transit times plateau when cardiac index (CI) reaches ≥ 8.1 L·min^{-1}·m^{-2}. It is important to observe that whole lung RBC transit times consistently remain 6–7 times larger than pulmonary capillary RBC transit times across all CI categories. Data from Warren et al. (8) and Tedjasaputra et al. (7) were used for mean pulmonary capillary RBC transit times and mean Vc, with a sample size of 32–73 subjects per data point. Furthermore, data from Zavorsky et al. (10) provided mean whole lung RBC transit times and mean cardiopulmonary blood volume obtained through first-pass radioactive tracer studies with a sample size of 88 subjects. The error bars represent the SD of means. The numbers values indicated within parentheses for pulmonary capillary blood volume indicate the standard deviation.

compared with rest, despite a significant reduction in RBC capillary transit times (16). When the $\dot{Q}$ of rabbit lungs increased from 80 to 200 to mL·min^{-1}·kg^{-1}, pulmonary capillary transit times of RBCs decreased from 0.62 ± 0.15 s to 0.14 ± 0.01 s, respectively; and when $\dot{Q}$ further increased to 450 mL·min^{-1}·kg^{-1}, transit time remained unchanged (0.17 ± 0.06 s) (16). The consistent paO_2 and pAO_2 values observed at high $\dot{Q}$'s—despite reduction in pulmonary capillary transit times of RBCs (8,16)—reinforce the notion that rapid transit plays a minor role in diffusion limitation.

Also, it may be criticized that, although while mean RBC transit times may not decrease to levels that prohibit paO_2

[1]During my doctoral program, I was mainly influenced by Dr. Susan Hopkins' 1996 study on whole lung RBC pulmonary transit time (PTT) (Respir Physiol. 1996;103:57–73). This research was pivotal in guiding me toward further exploring RBC transit time (Respir Physiol Neurobiol. 2002;131:255–268). Dr. Hopkins' findings in her 1996 article revealed a significant correlation: approximately 33% of the variance in whole lung RBC transit time corresponded with diffusion limitation as indicated by inert gas rebreathing. This was inferred from the differences between observed and predicted $AaDO_2$ correlated to PTT, indicating a rise in the observed versus predicted $AaDO_2$ as PTT decreased. In contrast, my 2002 study did not find a link between whole lung RBC transit time and paO_2 or the observed $AaDO_2$. The variation in our findings could be attributed to Dr. Hopkins' inclusion of both resting and exercise-induced RBC transit time measurements in her 1996 study, among other factors. An analysis of the raw data from her 1992 thesis revealed three subjects exhibiting nonphysiological (negative) observed $AaDO_2$ at rest, potentially affecting the observed versus predicted $AaDO_2$ spread. In addition, her study's significant disparity in PTT during rest (11.75 s) and maximal exercise (2.60 s) emphasized a negative correlation between PTT and diffusion limitation as suggested by inert gas rebreathing. However, when combining data from both studies and focusing exclusively on near-maximal or maximal exercise conditions (cardiac output >23 L·min^{-1} or cardiac index >12.0 L·min^{-1}·m^{-2}), I found no association between whole lung RBC transit times and either $AaDO_2$ or paO_2. This pooled analysis offers a more comprehensive understanding of the dynamics between these physiological variables.[2]The relative dispersion is the coefficient of variation, or the standard deviation of RBC transit times divided by the mean RBC transit time.

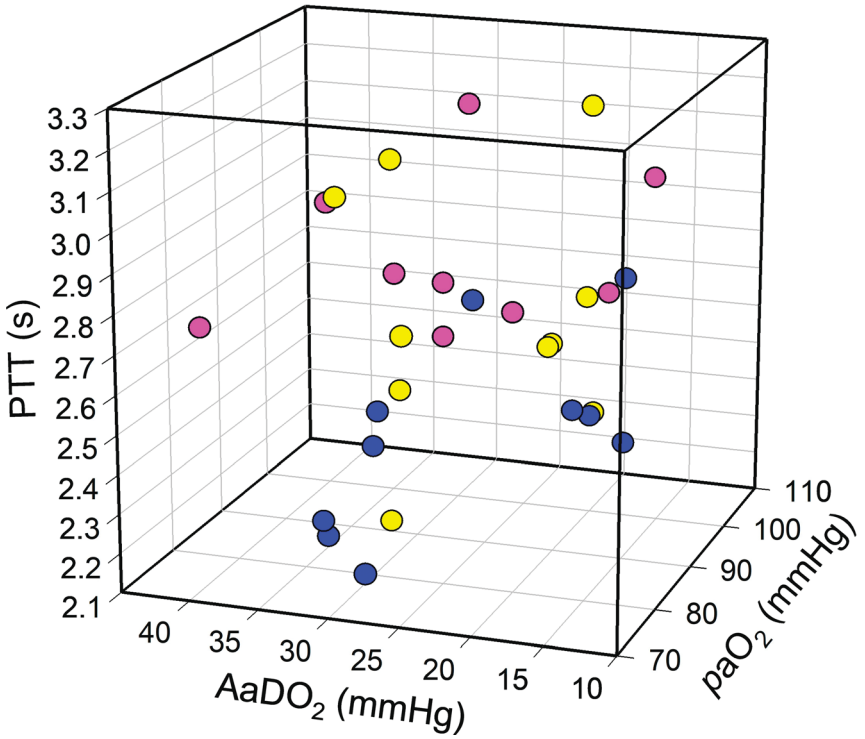

FIGURE 2—A three-dimensional scatter plot that underscores the absence of a significant association between whole lung RBC transit times and $AaDO_2$ ($r = -0.02$; 95% bootstrapped confidence interval (CI), −0.39 to 0.32; $P = 0.901$, $n = 29$ pairs of data) or paO_2 ($r = 0.32$; 95% bootstrapped CI, −0.07 to 0.62; $P = 0.09$, $n = 29$ pairs of data) when cardiac output ranges from 23 to 37 $L \cdot min^{-1}$ during sea level exercise. The association between paO_2 and $AaDO_2$ during maximal exercise was significant ($r = -0.73$; 95% CI, −0.87 to −0.58; $P < 0.0001$, $n = 29$ pairs of data). The data presented in this figure were extracted from two doctoral dissertations (12,13) because of a lack of such data in the published articles (11,14). After excluding one male subject with an outlier RBC transit time of 3.76 s (subject 6 from [12]), the analysis involved 21 subjects with a total of 29 sets of matching "triplets" (PTT, paO_2, $AaDO_2$). There were some typographical errors from Ref. (12) that needed to be rectified. Subject 10 had a PTT and CPBV during maximal exercise of 2.71 s and 1.53 L, respectively, not 2.15 s or 1.53 L, as reported in page 140 of the thesis (12). The pooled subjects had an average age of 28 ± 6 yr, height of 183 ± 7 cm, weight of 73.9 ± 8.4 kg, BMI of 22.1 ± 2.3 $kg \cdot m^{-2}$, maximal oxygen uptake of 5.14 ± 0.55 $L \cdot min^{-1}$, FEV_1/FVC of 0.854 ± 0.062, DLCO at rest of 41.4 ± 5.1 $mL \cdot min^{-1} \cdot mm\ Hg^{-1}$. The $AaDO_2$, paO_2, and whole lung RBC transit times during very strenuous exercise ranged from 16 to 43 mm Hg (mean, 26 mm Hg), 72 to 106 mm Hg (mean, 89 mm Hg), and 2.20 to 3.20 s (mean, 2.64 s), respectively. Note: The individual data that are displayed in solid blue circles is the control condition (non-infusion condition) from the doctoral thesis of Zavorsky (13), and the experimental condition (where a plasma volume expander was infused to increase plasma volume) is displayed in solid yellow circles. The individual data that are displayed as solid pink circles is from the doctoral thesis of Hopkins (12). BMI, body mass index; DLCO, pulmonary diffusing capacity for carbon monoxide; FEV1/FVC, forced expiratory volume in 1 second divided by the forced vital capacity.

from achieving alveolar–capillary equilibrium for pO_2, the distribution of transit times around the mean could result in some RBCs having very short transit times, and those RBCs may not reach alveolar–capillary equilibrium for pO_2. However, even if this were the case, the small number of these RBCs is insufficient to alter paO_2 and $AaDO_2$(8). Furthermore, the distribution of RBC transit times shows decreasing dispersion[2] around the mean with increasing $\dot{Q}$. The relative dispersion of whole lung RBC transit times is about 0.51 at rest decreasing to a dispersion of 0.35 when cardiac index is ~10 $L \cdot min^{-1} \cdot m^{-2}$(17) to 0.29 when cardiac index is ~16 $L \cdot min^{-1} \cdot m^{-2}$(11). Thus, unless a significant left to right shunt exists (18), the distribution of whole lung RBC transit times (19) and pulmonary capillary RBC transit times (16) becomes more homogeneous throughout the lung with increases in $\dot{Q}$. Furthermore, increases in blood volume via colloidal plasma volume expansion shift the distribution of RBC transit times to the right, resulting in significantly fewer RBCs with whole lung RBC transit times <1.8 s (11). Only about 20% of RBCs have a whole lung RBC transit time of <2.0 s during maximal exercise, which decreases to ~13% with plasma volume expansion (11).

Despite the potential influence of alveolar gas fluctuations and pulsatile blood flow on transit times (20,21), their overall impact on gas exchange remains marginal. Regarding the influence of white blood cells (22), evidence remains inconclusive, although limited influence on RBCs transit times is suggested (23).

In conclusion, increased blood volume resulting from chronic exercise training is an important protective mechanism against diffusion limitation arising from rapid RBC capillary transit times during periods of high $\dot{Q}$s. The observed distribution shift in transit times further strengthens the argument that alveolar–capillary equilibrium for pO_2 remains largely unaffected. The cumulative insights derived from exercise training and cardiac output studies converge to suggest that the mechanism of rapid pulmonary capillary RBC transit times has been

[2]The relative dispersion is the coefficient of variation, or the standard deviation SD of RBC transit times divided by the mean RBC transit time.

investigated and is unlikely to be a primary driver of diffusion limitation. The close association between whole lung and pulmonary capillary transit times of RBCs lends further credence to this viewpoint.

Considering these substantial findings, it is evident that the concern expressed by my colleagues regarding a dearth of research on this subject has been addressed by the existing body of work. Although ongoing research is valuable, the existing evidence indicates that capillary RBC transit times do not significantly contribute to diffusion limitation during sea level exercise. This direct alignment between whole lung and pulmonary capillary RBC transit times further enhances the robustness of the accumulated research. The body of evidence presented here emphasizes the significant progress in this field and merits further attention and consideration from my respected colleagues (2).

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