Point: Counterpoint

COUNTERPOINT: THERE IS NOT CAPILLARY RECRUITMENT IN ACTIVE SKELETAL MUSCLE DURING EXERCISE

The notion that a substantial proportion of capillaries do not contain moving red blood cells (RBCs) in muscle at rest but are “recruited,” i.e., begin flowing with RBCs during contractions, is one basis for our present understanding of blood-muscle exchange during exercise (20, 28). This concept emanates, in part, from August Krogh, who showed that many capillaries in resting muscle did not contain India ink after high pressure perfusion (19). Despite Krogh himself recognizing that India ink particles clumped together, more likely to prevent complete perfusion of the capillary bed at rest than during exercise, these experiments, and Krogh’s O2 diffusion model based on them, are still cited by researchers invoking capillary recruitment (e.g., Refs. 3, 7, 25). In his letter to the editor of the American Society is “Nullius in Verba” (Take nobody’s word for it, see page (22).

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Direct evidence for RBC flow in most capillaries in resting muscle. In resting muscle, intravital light microscopy shows that over 80% of capillaries support RBC flow, e.g., in rat spinotrapezius (14, 17, 24), diaphragm (15), and extensor digitorum longus (1), hamster cremaster and sartorius (8), cat sartorius (6), rabbit tenuissimus (30). However, animals in these experiments were anesthetized to facilitate muscle exteriorization and viewing of the capillary beds. To address this, Bailey and colleagues (2) employed minimally invasive techniques to measure blood flow (radioactive microspheres) and microvascular oxygen partial pressure in muscle in situ and neither criterion was altered by exteriorization. Moreover, the dynamic matching of increased O2 delivery and VO2 during contractions in situ was preserved in the exteriorized muscle. It is difficult to conceive how anesthesia might affect arteriolar smooth muscle function at rest (to produce a falsely high %RBC-perfused capillaries) and yet muscles increase their blood flow and VO2 at a ratio of ~6:1 (11), which is precisely that seen in intact voluntary exercising animals and humans (23).

Another valid concern about intravital microscopy is that there are non-RBC containing capillaries at rest that cannot be seen because of their translucency. However, neither observation of contracting (17) nor vasodilated (16) muscles revealed a significant number of such vessels (see also Refs. 8, 14). The technical requirements necessary to observe capillaries within living muscle restrict the procedure to a limited selection of animal muscles so that one question to ask is: How representative of other muscles in the animals’ body and in humans are these? In anesthetized and conscious animals, Snyder et al. (29) used systemic indicator injections and demonstrated that essentially all capillaries in each muscle examined (vastus lateralis, diaphragm, soleus) were perfused within 3–7 s.

Indirect evidence for RBC flow in most capillaries in resting human muscle. Noninvasive near-infrared spectroscopy (NIRS) measures muscle hemoglobin concentration ([Hb]). If there were significant recruitment of previously non-RBC containing capillaries during exercise, say from 20 to 90%, [Hb] would be expected to increase several-fold. However, the rest-to-exercise [Hb] increase is less than onefold (e.g., 10) and can be accounted for by increased capillary hematocrit (18). Thus, as in animal muscles, there is little room for substantial capillary recruitment in human muscle.

Against the evidence for capillary recruitment during exercise. The literature that purports to demonstrate capillary recruitment deserves to be evaluated on its own merits, but the following must be considered as possible explanations for reports of many non-RBC flowing capillaries in resting muscle. 1) Capillaries are fragile structures, subject to damage by blunt trauma, surgery, and/or manipulations such as stretching (24). 2) PO2 within resting muscle is normally very low and raising this will cause arteriolar constriction and capillary flow stoppage (22). 3) Anesthetized preparations are often hypovolemic and hypotensive, which provokes reflex vasoconstriction.

In addition, misinterpretation of histological techniques has supported the notion of capillary recruitment. The conclusion that a RBC in the muscle capillary cross-section indicates RBC flow, whereas its absence supports no flow is erroneous (e.g., Ref. 13). In resting animal muscle observed in vivo, RBC movement in flowing capillaries varies over time, appearing either continuous or stop-start (9). Muscle contractions result...
in more continuously flowing vessels with higher RBC velocities (5). Hargreaves et al. (12) used thioflavine S (a plasma marker) to show that, since all capillaries were perfused, during contractions the increase in muscle blood flow (microspheres) could be accounted for by the increased velocity rather than capillary recruitment. Reduced flow heterogeneity and hence augmented capillary hematocrit from rest to exercise decreases the length of inter-RBC plasma gaps and increases the probability that an RBC will appear in cross section.

Is the concept that most capillaries support RBC flow in resting muscle mathematically possible? In a typical 70-kg human with 31.5 kg of muscle (45% body mass), resting muscle blood flow is estimated as ~1 l/min (or 5.4 × 10^{12} RBCs/min; Refs. 20, 28). Accepting a mean value for capillary density and length of 300/mm^2 and 1,000 μm, respectively, if 80% of the 8.9 × 10^9 capillaries support RBC flow at rest, as in the rat (14, 17, 24), this would be ~12 RBCs per capillary per second—very close to the 15–20 RBCs per capillary/s actually measured in rat muscle (17). Whereas such calculations are certainly not proof that most skeletal muscle capillaries have RBC flow in humans at rest, they support that it is feasible.

Why is it crucial that we question the dogma of capillary recruitment? If most capillaries support RBC flow at rest and are not recruited at exercise onset, increased substrate delivery must occur within already flowing capillaries. Accordingly, is the recruitment of more surface area along the length of already flowing capillaries, rather than de novo flow in previously stagnant capillaries, key to increased blood-myocyte exchange? Diabetes (21), heart failure (27), and chronic ischemia (5) decrease the proportion of RBC-perfused capillaries in resting muscle. If we do not recognize that most capillaries may support RBC flow at rest in healthy muscle, our ability to appreciate the mechanisms for impaired blood-muscle exchange, which may be pathognomonic to these and other diseases, is crippled.

Nullus in verba!

The online version of this article contains supplemental data showing intravital microscopy recordings demonstrating RBC flow in almost all capillaries in healthy resting spinotrapezius muscle (first video, Refs. 24, 27) and diaphragm (third video, Ref. 15). The second video demonstrates the effects of chronic heart failure (CHF; left coronary artery ligation, Ref. 27) on capillary perfusion in spinotrapezius muscle. Note, in the CHF condition, the presence of stopped RBCs in central capillaries and other capillaries that have intermittent RBC flow and/or very low/sporadic RBC flux. Adherence to the misconception that many capillaries do not flow in healthy resting muscle (i.e., capillary recruitment notion) would confound identification of the effects of this disease on capillary hemodynamics and therefore O_2 delivery and substrate exchange.

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REFERENCES

REBUTTAL FROM DRS. POOLE, BROWN, HUDLICKA

My learned colleagues are to be congratulated for considering different techniques (1–5 below) to assess changes in the proportion of flowing capillaries in muscle. However, the resultant data must be judged in light of limitations inherent in those techniques.

It is also important to define precisely what we are talking about. Professor Clark and colleagues’ (1) opening statement that “The key issue here is whether resting skeletal muscle is fully perfused” is clearly erroneous. “Perfusion,” (from the Latin perfusio), infers nothing about the distribution of blood, which, along with the veracity of presumptions made to assess that distribution, is what is at issue here.