

Capillary blood volume increase in already perfused capillaries: role for glycocalyx modulation

To the editor. The viewpoints put forward by both Point (1) and Counterpoint (4) presenters clearly illustrate that there is a potential for recruitment of capillary reserve in muscle during exercise and in response to insulin administration. The question at hand that arises from the Point/Counterpoint discussion is how capillary blood volume can be increased by muscle contractions or insulin (1) when the vast majority of capillaries are supporting blood flow in the resting condition already (4). In line with the original suggestions of Duling and co-workers (e.g., (2)) on how to explain a three- to fourfold increase in capillary tube hematocrit in cremaster tissue during muscle contractions and adenosine superfusion, we are proposing a role for agonist-induced recruitment of glycocalyx volume in mediating increases in capillary blood content in muscle (5). Experimental data has been provided showing that robust exclusion of circulating red blood cells and plasma by the glycocalyx layer causes functionally perfused capillary volume to be greatly reduced in resting muscle (6), but that the exclusion properties of the glycocalyx are greatly diminished in the presence of adenosine, resulting in a recruitment of blood accessible capillary volume upon administration of this vasodilator (2, 5). Modulation of the level of blood exclusion by the glycocalyx might provide a way by which vasoactive substances (e.g., those released during exercise, insulin) can increase functionally perfused capillary volume: the potential impact of glycocalyx volume modulation for capillary blood filling is illustrated by recent estimations of a blood-excluding glycocalyx volume of about 1.5 L in the systemic circulation of healthy human subjects (3).

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Capillary Recruitment In Active Skeletal Muscle During Exercise is Dependent on Muscle Architecture

Techniques are an important issue in the assessment of capillary recruitment (4,6); however, the actual muscles assessed are likely an overdeterminant of findings (4). Muscles typically assessed by intravital microscopy are thin (4,6) and unlikely to have complex fiber and vascular architectures. Thin, and typically parallel-fiber

muscles, are optimized for muscle shortening, with vessel geometries also primarily oriented in parallel, optimizing for blood "flow-through," e.g., the diaphragm (5). This flow-through characteristic would be expected to make recruitment measurements mainly dependent on blood velocity through minimally- compressed parallel channels and beds, rather than recruitment of additional channels and capillary beds. However, pennate-fiber muscles are optimized for high force production rather than shortening, having more complex fiber and vessel arrangements, to "pack in" additional force- generators (fibers), some of which are at significant angles to the long axis of the muscle, across vessels. These complex architecture muscles are not optimized for flow-through, or intravital microscopic analysis, but must have the ability to recruit previously minimally-active fibers, and minimally-perfused vascular channels and capillary beds, when undertaking intense contractile activity. Accordingly, increased local capillary perfusion is dependent on arteriolar relaxation due to nitric oxide (2), coupled with decreases in intramuscular pressure during the relaxation phase of cyclical activity (3), to counter flow-attenuation by intramuscular pressure with high force production (1). These characteristics have been demonstrated in a model of contracting pennate- fiber muscle hyperemia (1-3), with constant resting cardiac output as the major determinant of arterial blood velocity, which would actually underestimate the true capacity for vascular recruitment during exercise.

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Capillary recruitment and the control of VO₂

To The Editor:

One test of the capillary recruitment hypothesis advanced by Clark and colleagues (2) is how well it explains or predicts common physiological observations. For example, the notion that substantial capillary recruitment occurs during exercise is entangled inextricably in the concept that skeletal muscle has two circulations – namely, non-nutritive and nutritive (3). Under this scheme, following the commencement of muscular contraction, blood flow would be diverted to, or preferentially initiated in, so-called nutritive capillaries and it is this process that is considered to enable increased oxygen consumption (VO_2). This scenario places the site of metabolic control within the vasculature rather than the mitochondria and has led to the assertion by Clark and colleagues (3) that muscle VO_2 at rest and during sub-maximal exercise is necessarily limited by O_2 delivery.

If it were correct that VO_2 kinetics or steady-state VO_2 were O_2 delivery-limited, long-established theories of metabolic control, supported by a wealth of experimental evidence in healthy humans and animals, would have to be revised (e.g.,1). For example, there is a substantial range of work rates (from rest through moderate/heavy exercise) where VO_2 kinetics and steady-state VO_2 are not altered by interventions designed to modify O_2 delivery (4,5). Moreover, ^{31}P -MRS analysis of high-energy phosphates provides strong support for an intracellular locus of respiratory control (5). Based upon these and other experimental observations, the contention of Clark and colleagues (2,3) that capillary recruitment is a fundamental determinant of the metabolic response to muscle contractions must be rejected (6).

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Parallel thoughts

Capillary recruitment may explain some aspects of microvascular regulation (1), but there is a dearth of confirmatory data (2). It is easy to fall into this trap. In angiogenesis, the episodic loci of endothelial activation may not be stochastic as generally assumed, but dictated by local differences in shear stress invoked by uneven perfusion of adjacent capillaries instigated by capillary recruitment. Nice idea, but lacking experimental verification. Consider: it is energetically inefficient to have flow arrested for a long time (diving mammals took millions of years to optimise the rheology!) and leads to apoptosis; modelling oxygen transport (eccentric or concentric diffusion) shows the most important element is intercapillary distance; whether supply regions are asymmetric (e.g. mixed skeletal muscle) or have central capillaries (myocardium) determines the pattern of oxygen flux (3); heterogeneity of capillary distribution is maintained during ontogenetic growth (4). Together, these data suggest capillary spacing is sufficiently important to be regulated across time scales, and capillary recruitment would be physiologically detrimental. Of course counter arguments may suggest factors other than oxygen flux are important (the symmorphosis concept is certainly limited) or that intramuscular oxygen tension is buffered (Honig's myoglobin saturation experiments (5) still require verification). But we simply return to the original point: capillary recruitment has not been demonstrated in preparations free from known experimental artefacts. While other descriptions of capillary perfusion (6) cannot be explained by capillary recruitment, and until a physiological benefit for it can be formulated, I see no useful purpose in pursuing this idea.

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Capillary recruitment in skeletal muscle during exercise: how much?

Prof. Clark's interpretation of noninvasive data is that capillaries are recruited during muscle contractions (2). However, that interpretation lacks quantitative information about capillary recruitment. Does the percentage of flowing capillaries increase from 50% to 100%, or 80% to 100%? If the latter is true, animal and human data are consistent: most capillaries are flowing in resting skeletal muscle. Prof. Clark and colleagues (2) use measurement of microvascular bubble ('blood') volume (MBV) as a surrogate for the number of flowing capillaries. An increase in the number of flowing capillaries (recruitment) is not the only explanation for MBV changes during exercise. For example, assume: a) mean values of capillary density and length from

Poole and colleagues (3); b) cylindrical capillaries with mean 'effective' diameter (i.e., available for flow) of $\sim 5 \mu\text{m}$ at rest; c) 1 μm increase in 'effective' capillary diameter with exercise ['thinning' of the glycocalyx layer (4, 5) and capillary distension consequent to arteriolar vasodilation (1)]; d) increase in capillary hematocrit from 20% to 30% with contraction (see citations in Ref. 3); and e) a hypothetical increase from 80% (rest) to 100% (exercise) of capillaries flowing. In this setting MBV would increase 1.7-fold from rest to exercise, close to the 2-fold increase seen in humans (Fig. 1, Ref. 2). Therefore, it is feasible that noninvasive human data are consistent with animal studies and that most capillaries are flowing in resting muscles thereby abrogating the possibility of substantial capillary recruitment during exercise.

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Capillary Rarefaction - A need for Molecular Analysis

The preference of erythrocytes to preferentially enter at bifurcations those capillaries with higher flow rates serves as a mechanism that can lead to the separation of erythrocytes from plasma in the microcirculation. Consequently, individual capillaries or groups of capillaries in muscle supplied by highly contractile terminal arterioles may be perfused by plasma and a depleted number of erythrocytes. Perfusion without erythrocytes tends to be transient and is sensitive to details of microvascular flow regimes and capillary endothelial activity (pseudopod formation, cellular elastic recoil, apoptosis, presence of leukocytes, platelets, etc.). The debate of whether there is or is not capillary recruitment in exercising skeletal muscle (1, 4) hinges on the question whether there are non-erythrocyte-perfused capillaries in resting muscle. Resolution of the issue requires direct measurements of erythrocyte flux in capillaries before and during exercise. Both sides in the debate bring out important shortcomings of current techniques to examine erythrocyte flux at the capillary level in skeletal muscle without anesthesia. Studies that support the presence of non-

erythrocyte-perfused capillaries disagree about its extent (3, 2). The analysis of capillary recruitment needs to be extended, especially at the cellular and molecular level. There is a need to bring to light the implications of any level of capillary recruitment in the framework of chemico- and mechano-transduction mechanisms and signaling pathways in cells that make up the capillary network. Furthermore, only phenomenological connections have been established with the irreversible lack of erythrocytes perfusion in structural capillary rarefaction, e.g. in individuals with arterial hypertension.

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The basics of capillary recruitment in skeletal muscle

As skeletal muscle activity increases from the resting state, venous oxygen content falls dramatically before muscle blood flow increases substantively (1). This increase in oxygen extraction is promoted by the fall in pO₂ within active muscle fibers, which steepens the gradient for oxygen diffusion from surrounding capillaries. Nevertheless, expanding the functional (perfused) capillary surface area will augment oxygen extraction even as capillary pO₂ declines (5). Skeletal muscle capillaries are arranged into 'microvascular units' (3) such that dilation of a terminal arteriole 'recruits' each of the 15-20 capillaries it supplies with red blood cells. Because enhanced extraction alone cannot meet the metabolic demands of working muscle, blood flow into each microvascular unit (and capillary) increases as vasodilation encompasses more proximal arterioles. Regional heterogeneity of capillary perfusion in resting muscle (3, 4, 5) is explained by the cyclic dilation and constriction of terminal arterioles during vasomotion. Such intermittent perfusion of microvascular units promotes more uniform tissue oxygenation over time than does a passive distribution network. Because terminal arterioles are exquisitely sensitive (3), vasomotion is easily 'switched off' thereby allowing capillary perfusion to reach near-maximal levels with even minor perturbations. Thus the key determinant of whether or not an increase in capillary perfusion is observed during an experiment (2, 6) resides in the status of terminal arterioles when the initial baseline data are obtained. If terminal arterioles have already dilated, the flux of red blood cells through perfused capillaries will increase dramatically along with muscle blood flow despite no evidence of capillary recruitment.

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Heterogeneity of capillary blood flow, distensibility of capillary wall, and inflammation

To the Editor:

In addition to the role of glycocalyx (6), there are two other possible mechanisms to explain increased capillary blood volume after muscle contraction (or insulin infusion) (3), without increased number of capillaries carrying blood flow (4) (i.e., capillary recruitment). First, we showed that the "resting" skeletal muscle (i.e., rat extensor digitorum longus, EDL) is associated with marked spatial heterogeneity of blood flow in capillaries (10-20 fold range in red blood cell velocity). This heterogeneity is significantly reduced after muscle contraction (5). Thus, capillaries with initial near-zero flow could see a substantial increase in volume flow after contraction, without being "recruited". Second, it has been shown that capillaries passively distend (~30 %) in vasodilated skeletal muscle (2). This distension will also yield substantial increase in capillary volume flow without recruitment.

The presence/absence of capillary recruitment depends critically on the number of capillaries carrying blood flow in muscle at its resting state. Unfortunately, this state is ill-defined whether or not the animal is subjected to experimental manipulation. Ensuring minimal manipulation of the EDL muscle (i.e., no contact with surgical instruments, but coverage with glass coverslip), we microscopically observed that ~85 % of capillaries carried blood flow continuously at rest (1). Absence of flow in the remaining 15 % was likely due to manipulation-induced inflammation, since subsequent intentional inflammation elevated this number at rest to 40 %. This disagrees with Rebuttal of Clark and coworkers (3), since unavoidable manipulation

of muscle required to visualize capillaries microscopically may actually favour detection of recruitment.

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Capillary recruitment is minimal during exercise

It is apparent that the principal issue at hand here is the definition of capillary recruitment. Clark et al. [1] consider capillary recruitment as synonymous with an increase in blood flow, while Poole et al. [2] posit capillary recruitment as an increase in the number of capillaries that support a given flow. It is clear from the published literature that, in healthy skeletal muscle, 80-90% of capillaries support flow at rest, i.e., the capillaries are already highly "recruited" [3]. Furthermore, Fugelvand & Segal [4] have shown that the capillary bed of skeletal muscle is almost completely perfused at very low levels of activity and that increases in flow result primarily from arteriolar vasodilation. In addition, the notion that relatively few capillaries are 'recruited' at rest can be further debunked using Poiseuille's law. When an increase in flow from rest to exercise, such as reported by Armstrong and Laughlin [5], is kept constant, large increases in capillary recruitment (e.g, 3 to 4 fold) would result in a disproportionately large increase in intramuscular pressure (i.e., arteriolar-venous pressure drop <10 mmHg). Furthermore, for a given pressure drop, large increases in capillary recruitment (e.g., 20% to 90% 'recruited') would result in an increase in flow from rest to exercise that is at least one order of magnitude greater than reported in the literature. Thus, the known increases in muscle blood flow from rest to exercise can be primarily accounted for through changes in arteriolar diameter with minimal capillary recruitment.

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There can/may be capillary recruitment in active skeletal muscle during exercise

The literature cited in (1) and (4) shows that there CAN be capillary recruitment in contracting striated muscle but with the caveat that experimental circumstance and measurement technique MAY cause or preclude recruitment. Even such benign variables as ambient O₂ and sampling time will be determinants of apparent recruitment (2). The critical fact is, that capillary recruitment just can't be measured in an intact working muscle, and there is no way to make a direct comparison between the intra- vital microscopy and intact tissue estimates. Thus, reconciliation of the issue depends on direct measurement of capillary perfusion deep in an intact muscle, a measurement that is not beyond the reach of contrast- enhanced MRI but has yet to be made.

Until such a measurement is made, we must think from a functional perspective. A great inter-capillary distance will render a capillary dysfunctional, even if the flow is brisk, i.e. capillaries are de- recruited. Also, if flow falls below a certain level the capillary becomes dysfunctional. Furthermore, the capillary is not the only exchange vessel (3, 4), and which vessel class is acting as an exchange vessel depends on the molecular species in question. Thus, definition of recruitment or not depends on the question being asked. It brings to mind Tom Robbin's observation that "Philosophers have argued for centuries about how many angels can dance on the head of a pin, but materialists have always known it depends on whether they are jitterbugging or dancing cheek to cheek".

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Letter in response to Point:Counterpoint: There is/is not capillary recruitment in active muscle...

To the editor: This debate reveals difficulties in direct demonstration of capillary recruitment. Problems stem from unknown basal state of the muscles, methods of activating contraction and measuring capillary flow and volume (1, 4). Krogh anticipated recruitment as a means of counteracting limitation of O₂ diffusion into muscle cells (3). Krogh felt that if resting cell Po₂ were low (it is a few mmHg) and muscle venous Po₂ were high (it is 30-40 mmHg) large diffusion distances were indicated. No increase in flow through the same capillaries could supply sufficient O₂ during exercise. But if capillary density at rest were sufficient to provide O₂ during exercise [c.f. (4)] it would be wasteful at rest causing high and almost equal Po₂ in muscle tissue and venous blood (3). At high muscle blood flow (MBF) reaching high O₂ extraction requires increased capillary blood volume in order to increase mean transit time (MTT = thus increasing O₂ diffusion time (5, 6). But if MBF/kg muscle is extremely high [e.g. (6)], becomes higher and extraction less complete [Fig 9-14, 9-16 in (5)]. Despite rising capillary volume, total muscle volume (i.e. Hb) decreases [c.f. (4)] owing to large reduction in postcapillary venous volume by muscle pumping during voluntary contractions (2) unlike during aberrant contractions via electrical stimulation (5). Finally, MBF is heterogeneous [see (5)]. Capillary perfusion is controlled by tonic sympathetic vasoconstriction in arterioles partially opposed by metabolite sensitive α_2 adrenoceptors. Temporal and spatial variations in this tone alter flow to regions of high and low capillary density, different muscle fiber types, etc. depending on O₂ demand. Isn't this recruitment.?

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