

How well does quantifying ‘capillary supply’ assess oxygen transport capacity in skeletal muscle?

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Introduction

This Opinion piece asks a simple but unresolved question: when we quantify “capillary supply”, are we measuring anatomy, oxygen transport capacity, or a mixture of both? We argue that the answer depends on the index used, and that physiological claims about oxygen delivery require indices that capture capillary distribution, not simply capillary number or fibre perimeter. August Krogh’s foundational insight was not simply that capillaries exist to support oxygen delivery, but that their number and spatial arrangement set the boundary conditions for transport within working muscle (Krogh, 1919). More than a century later, the extent of skeletal muscle microcirculation is still routinely summarised with a handful of convenient morphometric indices that are treated, implicitly or explicitly, as read-outs of oxygen supply capacity. While much attention has been paid to central limitations of tissue oxygen supply, the ability to derive physiologically meaningful insight into the local capacity to deliver oxygen underpins attempts to devise effective interventions in health and disease. Capillary remodelling may result from adaptive-physiological and pathophysiological signals, with global counts of capillarity and contact-based indices frequently used to infer exercise tolerance or impaired muscle function. Yet, the field lacks agreement about what individual indices signify, and hence which are appropriate when describing physiological oxygen availability rather than gross anatomy.

Quantification of the geometric arrangement of capillaries (e.g. diffusion distances) has long been used to estimate the capacity for oxygen transport to tissue. Several recent studies have drawn attention to various anatomical determinants of capillary supply in skeletal muscle that may influence oxygen delivery (Blervaque *et al.*, 2025; Degens *et al.*, 2026; Frydenholm *et al.*, 2026), which has prompted this Opinion piece. Here, we place these new reports in the wider context of classical diffusion theory and modern capillary concepts, and argue that many widely used metrics (Table 1) are best interpreted as descriptors of geometry unless they are explicitly tied to distribution-sensitive or transport-validated frameworks. The central issue is therefore not whether indices quantify capillary structure adequately, but whether they reflect oxygen transport under physiologically relevant diffusion constraints.

Index limitations

Commonly reported indices can be grouped into global, contact-based and area-based indices; each captures a different structural feature, but none alone incorporates all haemodynamic, diffusive and metabolic determinants of realised oxygen delivery. Realised oxygen delivery also depends on vascular control, systemic and local blood flow, pressure gradients, red-cell flux, haematocrit, transit time, oxygen extraction and metabolic demand. Many of these indices were developed primarily to describe capillary structure rather than oxygen transport directly (Table 1; Fig. 1). Capillary density (CD) and capillary-to-fibre ratio (C:F) are global summaries that respond strongly to fibre size and regional heterogeneity in muscle composition (Egginton, 1990; Egginton & Ross, 1992) (Fig. 1A). [Here we highlight the lack of descriptive potential of CD by modelling estimates of intra-muscular partial pressure of oxygen \(PO₂\) across a homogeneous and heterogeneous distribution of capillaries \(with identical CD\) which result in distinct PO₂ profiles \(Fig. 1A\). In this example we model a uniform oxygen supply and oxygen demand \(MO₂\) emphasising the impact of spatial distribution with local CD varying inversely with tissue PO₂ \(Fig. 1A\).](#) Perimeter-normalised measures of capillary contact (e.g., CFPE) are often interpreted as quantifying the functional exchange surface, but assume that proximity along a fibre boundary is an adequate proxy for diffusion geometry within the fibre and surrounding interstitium (Al-Shammari *et al.*, 2014; Al-Shammari *et al.*, 2019) (Fig. 1B). These indices remain useful descriptors, but problems arise when they are used to infer oxygen availability or diffusion limitation. Oxygen delivery to tissue is governed by convective supply (e.g., blood flow, haematocrit, red cell flux and transit time), and by diffusion through a heterogeneous microenvironment (Secomb & Pries, 2011; Pries & Secomb,

2014). Histological counts (global, contact-based and area-based) capture none of the haemodynamics, which are only imperfectly represented by diffusive boundary conditions.

As such, geometrical indices and diffusion-based analyses more generally characterise an upper bound on oxygen delivery under idealised perfusion conditions, rather than actual physiological flux. Consequently, these indices may vary with subtle changes in tissue architecture, and the implied maximal oxygen-supply capacity may change with them, even in the absence of any change in the underlying physiological mechanism. For example, capillary density can fall when fibres hypertrophy even if the absolute number of capillaries is unchanged (Kissane *et al.*, 2021). Such indices also neglect additional constraints on capillary organisation, including metabolite removal and heterogeneity in muscle fibre demand (Al-Shammari *et al.*, 2014).

There has been a long history of attempts to directly measure intra-muscular PO₂, which remains fraught with difficulties. Many studies now report the use of near infrared spectroscopy (NIRS) for this purpose, but the technique is poorly validated for intra muscular PO₂ (Pilotto *et al.*, 2022). Until the technical difficulties are resolved, the best readout is currently computer modelling of diffusive O₂ exchange. Although such simulations are not direct physiological measurements, they provide a consistent framework for comparing how well different structural indices capture diffusion-relevant geometry. We have previously highlighted that area-based measures for O₂ delivery perform robustly across a range of geometries and fibre types except under the most extreme conditions, such as excessive capillary clustering (Al-Shammari *et al.*, 2014, 2025). Hence, such indices are well suited as practical, yet very accessible, measures for capillary supply, despite the remaining limitations. Given intravascular haemodynamics (e.g. capillary haematocrit, red cell flux and transit time) are typically represented via averaged boundary conditions, these simulations primarily evaluate diffusive constraints under maximally perfused conditions such as during functional hyperaemia, and thus define an upper bound on oxygen delivery. While there is scope to model sub-maximal physiological flux, it would require modified haemodynamic assumptions. With improvements in sampling resolution and processing capacity there is increasing interest in the use of three dimensional rendering of the muscle capillary bed in order to explore the spatial relations between structures defining supply and demand (Zeller-Plumhoff *et al.*, 2017). However, provided appropriate sampling precautions are taken, 2-D sections can provide a statistically robust estimate of 3-D structure (a fundamental tenet of stereological morphometrics), without extending potential ‘edge effects’ and uncertainty over boundary conditions (Al-Shammari *et al.*, 2019).

Diffusion distance metrics are a step forward, but still require further validation

In a parallel to the minimum diffusion distance across the microcirculation used to determine pulmonary oxygen uptake capacity (e.g. Weibel *et al.* (1993)), it was recently suggested that the mean capillary-to-sarcolemma diffusion distance (mCtSDD) is limiting for oxygen uptake and metabolite exchange in skeletal muscle (Blervaque *et al.*, 2025). While this index showed a strong negative correlation with the maximum oxygen uptake ($\dot{V}O_{2max}$), caution is required before suggesting that capillary density, capillary tortuosity, and/or interstitial space dimensions may determine the capacity for oxygen diffusion. For example, this study used the mean Euclidean distance from the fibre boundary to the nearest capillaries, unlike the harmonic mean utilised by Weibel in his classical stereological approach, and oxygen flux across this carrier-free zone is not evenly distributed across the sarcolemma as it will vary according to the radial proximity of capillaries. Whether the influence of intracellular myoglobin or mitochondrial distribution would further influence the conclusions is unclear. Thus, while mCtSDD incorporates spatial proximity, it remains an averaged geometric descriptor rather than a direct measure of diffusion limitation, with the latter governed by local maxima in path length and heterogeneous flux.

‘Upper limits’ can emerge from geometric assumptions as well as biology

Recognising that adaptive remodelling may involve changes in both the number and location of capillaries around individual fibres, which often occurs alongside changes in fibre size and aerobic

capacity, Degens *et al.* (2026) adopted a more physiologically motivated, area-based approach to quantify capillary supply. Using data from samples with a large range of fibre size and mitochondrial abundance, this study explored the physiological and structural drivers of the *size principle* (aerobic capacity varies inversely with fibre size). They propose upper limits of fibre cross-sectional area (FCSA), concluding that diffusion and physical constraints define an envelope of adequate function beyond which oxidative capacity cannot be supported by increased muscle capillarisation. However, while using succinate dehydrogenase optical density as a surrogate for fibre aerobic capacity and/or mitochondrial content may be adequate for relative comparisons, it is problematic as a surrogate for maximal oxidative demand since maximal enzyme activity measured *in vitro* may not reflect the realised rate of metabolic throughput of the pathway (pathway flux) *in situ*. Also, it has previously been reported that area-based analysis shows a similar distribution of capillaries between species and fibre type, and across a wide range of fibre size (Egginton *et al.*, 1988).

Degens *et al.* (2026) therefore provide a timely and important contribution by formalising how geometric and physical constraints shape the relationship between fibre size, oxidative capacity and capillary supply. In doing so, they argue that physical constraints set an upper limit for the number of capillaries around a fibre (CAF) when normalised for FCSA. Specifically, they report that doubling CAF from 1 to 2 halves the maximal diffusion distance, with little further reduction at higher values, implying diminishing returns beyond locating two capillaries around a fibre (see also (Snyder, 1987, 1990)). This naturally leads to a strong mechanistic interpretation in which diffusion limitation is effectively resolved once a minimal capillary arrangement is achieved. While perimeter crowding is clearly relevant, this argument implicitly treats a symmetric arrangement of capillaries as anatomically representative. As recognised in the paper, *in situ* capillary beds are irregular, and diffusion limitation is likely driven by local pockets created by heterogeneous spacing, capillary sharing and fibre mosaics (Al-Shammari *et al.*, 2014; Kissane *et al.*, 2021). Under such conditions, individual fibre radius is unlikely to be the sole operative constraint; rather, diffusion is likely governed by a complex network of interactions in which distribution of fibre size has a greater influence. A perimeter-based diffusion-distance argument can therefore produce an apparent plateau under symmetric assumptions, even if additional capillaries (by redistributing supply domains) could reduce the worst-case diffusion geometry *in vivo*.

Degens *et al.* (2026) also show that maintaining, for each fibre, the ratio of the CAF to its cross-sectional area requires disproportionately more capillaries around the perimeter for larger fibres. However, this is also an immediate consequence of geometry when considering the ratio of two indices, with one based on fibre perimeter length and the other based on fibre area as area-to-perimeter ratios increase with size. There is a risk therefore that geometric scaling relationships are interpreted as physiological limits, particularly when oxidative capacity is represented by a proxy for mitochondrial enzyme capacity rather than actual oxygen utilisation. This distinction is important because pathway flux cannot be inferred from the maximal activity of an isolated enzyme. Kacser *et al.* (1995) showed that metabolic flux is a system-level property: metabolite pools, enzyme elasticities, and interactions across the pathway determine realised flux, so control is distributed across multiple enzymes rather than residing in a single pacemaker reaction. Their 1973 work (reprinted with updated terminology in 1995), emphasised that enzyme behaviour measured in isolation cannot be translated directly into pathway flux without considering the wider metabolic system. Newsholme *et al.* (1985) provide a related example in rapidly dividing cells, arguing that high glycolytic and glutaminolytic fluxes are not simply required for energy or precursor provision, but help maintain the responsiveness of low-flux biosynthetic branches by stabilising precursor availability. Thus, maximal activities of enzymes such as CS or SDH are better interpreted as indices of potential oxidative capacity, not direct measures of oxygen utilisation. Without validation against fibre oxygen tension, oxygen consumption, or distribution-sensitive indices, proposed

‘upper limits’ may describe the envelope imposed by dataset structure and modelling assumptions rather than a physical constraint on oxygen delivery.

Fibre shape corrections are necessary, but they do not validate perimeter indices as oxygen metrics

While the local capillary supply appears to be insensitive to oxidative demand of muscle fibres, an area-based analysis of capillary supply accommodates the complex interplay between geometric distribution of fibre size and the capillary network. Finally, another potentially important aspect of muscle morphology has been examined: the impact of changing fibre shape on indices of capillarisation (Frydenholm *et al.*, 2026). This study showed that fibre shape changes can inflate perimeter-normalised indices (e.g., capillary-to-fibre perimeter exchange index, CFPE), thus exaggerating apparent age-related capillary rarefaction; adjustment using a shape factor index attenuated age- and fibre-type differences in capillarisation. This again raises the issue of which indices are optimal for functional interpretation. In part this will depend on whether the analysis emphasises eccentric O₂ flux (out of capillaries, the Krogh model) or concentric O₂ flux (into fibres, the Hill model) but focussing on one index of capillarisation that has conceptual problems (Fig. 1B) (Al-Shammari *et al.*, 2025) may simply be an attempt to refine a sub-optimal approach.

Frydenholm *et al.* (2026) identify a genuine bias: CFPE assumes uniform fibre shape, so changes in perimeter relative to area can exaggerate or mask differences between groups. They report greater fibre shape irregularity in older participants and show that adjusting CFPE by a shape factor index reduces apparent age-related differences (from around 22–25% to 19–20%) and attenuates fibre-type differences (from around 12–15% to 8–9%). Normalising to fibre cross-sectional area (CFCE) further attenuates or eliminates most differences, which provides an important methodological warning. However, correcting CFPE for shape does not answer the key physiological question: does CFPE (adjusted or not) track oxygen availability? Perimeter-based indices remain geometry-only surrogates, and require validation before being interpreted as oxygen-transport metrics. Moreover, fibre shape irregularity can itself be a physiological response that alters packing and local distances to capillaries. Treating irregularity purely as a nuisance risks discarding meaningful information about diffusion geometry, particularly in ageing, regeneration or disease where fibre morphology changes (Soendenbroe *et al.*, 2024; Frydenholm *et al.*, 2026); capillary distribution may also adaptively reorganise. While refining a convenient metric may be worthwhile, it is important to first demonstrate that the refined metric is appropriate for understanding oxygen transport. This raises a practical question: how should competing indices be evaluated?

Distribution-sensitive, area-based indices best predict fibre oxygenation

Other papers in the field provide a practical way to adjudicate indices, by comparison to predicted fibre oxygen tension in image-based oxygen transport models (Al-Shammari *et al.*, 2019; Al-Shammari *et al.*, 2025). The latest study evaluated six local supply indices against calculated fibre PO₂ and found that the area-based measures LCD and D_{max} (Table 1, Fig. 1C) were the strongest correlates (linear correlations 0.89 and -0.91 respectively) and robust predictors across distance-correlation and regression frameworks (Al-Shammari *et al.*, 2025). These indices captured the curvilinear, diffusion-limited behaviour of fibre oxygenation and outperformed traditional integer-based metrics. This distinction is critical: indices that predict fibre PO₂ are not merely geometric descriptors, but transport-relevant metrics. Global counts and perimeter summaries miss the defining feature of capillary supply for diffusion, namely spatial heterogeneity. Capillary domains and related planar approaches were developed specifically to represent local supply territories and to quantify how clustering or sparse regions shape diffusion distances (Degens *et al.*, 2006). Even domain approaches have assumptions. In mixed muscles, capillary domains often approximate the areas supplied by individual capillaries (trapping regions) as derived from oxygen transport equations (Al-Shammari *et al.*, 2014), but they can deviate around very large fibres or at sharp interfaces in oxidative demand (Al-Shammari *et al.*, 2014).

Why more capillaries can be misleading; it is 'quality not quantity' that counts

Capillary number and distribution both contribute to the oxygen supply potential, but do so differently. Number sets an upper bound on total exchange capacity and perfusive reserve, while distribution shapes the worst-case diffusion geometry and therefore the risk of local hypoxia. The same CD or C:F can correspond to very different diffusion landscapes if capillaries are clustered or unevenly spaced (Kissane *et al.*, 2021). This distinction helps explain why training, ageing and disease studies can report conflicting capillarisation narratives depending on which metric is chosen. A change in fibre size can reduce CD without any loss of capillaries; a change in shape can shift CFPE without changing oxygenation; a redistribution of capillaries can improve $D_{\max}$ with minimal change in global counts. If researchers treat any one index as the definitive oxygen supply read-out, the literature will continue to accumulate contradictions that are artefactual rather than physiological.

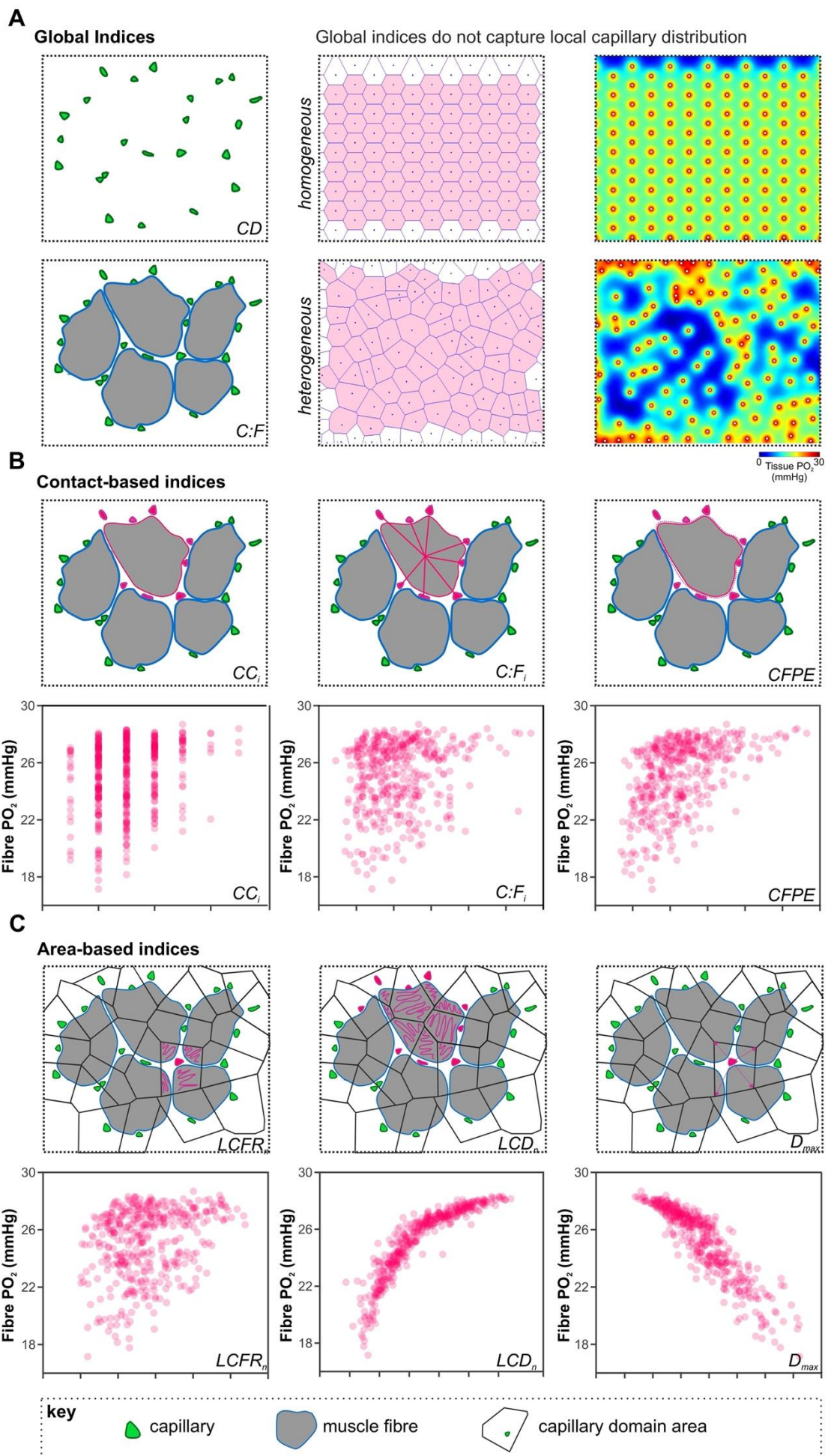
These studies helpfully push the field toward better geometric awareness in the analysis of muscle biopsies, but also illustrate how morphometric surrogates need careful interpretation before their utilisation in quantifying oxygen-transport mechanisms: in the long history of structure-function studies it has always been difficult to avoid conflating correlation with causation. This Opinion argues for a return to basics in the underlying debate: for all the mechanistic complications, the process of O_2 exchange by diffusion is inherently simple. The pertinent question is how does geometric complexity affect this process? Most traditional indices aim to simplify complicated structural variations, with predictable scaling artefacts and conceptual limitations. While they may describe gross structure, they should not be used as stand-alone surrogates for oxygen supply other than perhaps in a comparative manner. When attempting to quantify diffusion constraints and fibre oxygenation, indices must be chosen based on physiological validity and interpreted accordingly. Image-based modelling mitigates many of the issues raised above: local, area-based indices tied to capillary domains best predict calculated fibre oxygen tension across a wide range of phenotypes, outperforming integer-based and perimeter-based metrics (Al-Shammari *et al.*, 2025).

Synthesis

This is not an argument against the use of traditional indices, but against their interpretation as direct measures of oxygen supply. The solution is not to abandon traditional indices, but to align indices with claims. If the argument is anatomical (for example, rarefaction, angiogenesis, gross remodelling), then CD, C:F and contact-based measures remain informative when interpreted alongside fibre size. If the argument is mechanistic and specifically about diffusion limitation or oxygen availability (when considering maximal O_2 supply), then at least one distribution-sensitive, physiologically anchored measure should be reported. A constructive strategy is a two-layer reporting logic: first, utilise a minimal set of global descriptors for context (FCSA distribution, CD, C:F and a sharing-aware contact index such as C:Fi). Second, when making oxygen-transport interpretations, utilise at least one local, area-based distribution metric (LCD and/or $D_{\max}$). While acknowledging the limitations of the modelling framework, such standardisation would nonetheless enable comparability across studies, reduce overreach from geometry-only surrogates, and facilitate future meta-analyses across a disparate database.

Several testable predictions follow. First, group differences reported with the Capillary-Fibre Perimeter Exchange (CFPE) will likely be unstable in contexts that alter perimeter-to-area relationships (e.g. ageing, myopathies, regeneration), and those differences will not necessarily align with oxygenation measures. Second, interventions that redistribute capillaries (altering clustering and heterogeneity) should change LCD or $D_{\max}$ and improve predicted fibre PO_2 even if CD and C:F change little. Third, proposed upper limits based on number of capillaries around a fibre (CAF) and simplified diffusion-distance arguments should weaken when distribution-sensitive indices are analysed in irregular (real) geometries, especially in mixed muscles with large fibres or

275 sharp interfaces in oxidative demand. These predictions are tractable with existing pipelines that
276 provide high-throughput segmentation for domains, and image-based modelling where oxygenation
277 cannot be measured directly. The challenge ahead is therefore not to refine ever more indices, but to
278 ensure that those we use are aligned with the physiology of oxygen delivery that they are intended
279 to represent.



281 **Figure 1. Commonly used capillary supply indices and their correlation with modelled PO₂.**
282 Illustrations of commonly used descriptors of capillary supply including (A) global capillary indices
283 for capillary density (CD) and capillary to fibre ratio (C:F). These global indices lack descriptive
284 insight into the local distribution of capillaries, in this example we highlight the impact of identical
285 capillary densities and C:F in a hypothetical homogeneous vs. heterogeneous distribution, and the
286 impact on estimated tissue oxygenation. Note that about 1-2 capillary separations are excluded in
287 biophysical modelling estimates to avoid boundary artefacts, and hence the extremes of PO₂ at the
288 domain boundaries are not part of the estimates. (B) Top row. Contact-based indices including
289 capillary contacts (CC_i), individual capillary to fibre ratio (C:F_i) and capillary fibre perimeter
290 exchange (CFPE). Bottom row. These show a weak correlation with modelled fibre PO₂. (C) Top
291 row. Supply area-derived capillary indices derived from capillary domain areas (CDA: black
292 tessellating polygons) including the local capillary to fibre ratio (LCFR_n), local capillary density
293 (LCD_n) and D_{max}, Bottom row. These plots particularly highlight the strong correlation between
294 either LCD_n or D_{max} with fibre PO₂. These data are presented in more detail in Al-Shammari *et al.*
295 (2025).

Table 1. List of morphometric indices used to describe capillary supply

‘Capillary supply’ index (units)	Label	Description	Key confounds
Global indices			
Capillary density (mm ⁻²)	CD	$\frac{\text{Number of capillaries (N}_{cap})}{\text{Tissue area}}$	Strongly affected by fibre size distribution and sampling geometry.
Capillary-to-fibre ratio	C:F	$\frac{N_{cap}}{\text{Number of fibres (N}_{fibres})}$	Does not resolve capillary sharing or local heterogeneity.
Contact-based indices			
Individual capillary-to-fibre ratio	C:F _i	The sum of the fractional contribution of each capillary in contact with fibre i	Sharing-aware; still a contact-based surrogate.
Capillary contacts	CC _i	Number of capillaries surrounding muscle fibre i	Highly sensitive to section plane and perimeter geometry; does not encode spacing.
Capillary-fibre perimeter exchange	CFPE	$\frac{C:F_i}{\text{Perimeter of } i^{th} \text{ fibre}}$	Assumes perimeter is a proxy for exchange geometry; sensitive to fibre shape irregularity
Area-based indices			
Capillary domain region	DOM _k	The region of the k th capillary domain	Captures spatial partitioning; approximation quality depends on demand heterogeneity and geometry.
Local capillary-to-fibre ratio of the n th fibre	LCFR _n	$LCFR_n = \sum_{k=1, \dots, N_{cap}} \frac{\text{Area}(\text{DOM}_k \cap \text{FCSA}_n)}{\text{Area}(\text{DOM}_k)},$ where FCSA _n is the cross section of the n th fibre.	Distribution-sensitive; depends on domain construction and overlap definition.
Local capillary density of the n th fibre (μm ⁻²)	LCD _n	$LCD_n = \frac{LCFR_n}{\text{Area}(\text{FCSA}_n)}$	Area-based predictor of fibre oxygenation; less sensitive to integer constraints.

Maximum diffusion distance (μm)	D_{max}	Mean distance between capillaries neighbouring a muscle fibre and the farthest vertex of their capillary domain (DOM)	Distribution-sensitive worst-case geometry index; strongly predictive of fibre PO_2 in modelling.
Note. These indices treat fibres as equivalent sinks, despite oxidative and glycolytic differences. Nonetheless, except for extremes of heterogeneity and capillary clustering, the geometrically-based capillary supply regions underpinning area-based indices provide good approximations to biophysical modelling predictions for capillary supply regions (Al-Shammari <i>et al.</i> , 2014).			

References

- Al-Shammari AA, Gaffney EA & Egginton S. (2014). Modelling capillary oxygen supply capacity in mixed muscles: Capillary domains revisited. *Journal of Theoretical Biology* **356**, 47-61.
- Al-Shammari AA, Kissane RWP, Ashkanani A, Madhoun AA, Al-Mulla F, Gaffney EA & Egginton S. (2025). Utility of local capillary supply indices: Insights from computational image-based modelling. *The Journal of Physiology* **n/a**.
- Al-Shammari AA, Kissane RWP, Holbek S, Mackey AL, Andersen TR, Gaffney EA, Kjaer M & Egginton S. (2019). Integrated method for quantitative morphometry and oxygen transport modeling in striated muscle. *Journal of Applied Physiology* **126**, 544-557.
- Blervaque L, Merlet AN, Maciejewski H, Féasson L & Messonnier LA. (2025). Capillary-to-sarcolemma distance and location of cytochrome c oxidase: Insights for maximal O₂ uptake and muscle lactate release in trained athletes. *The Journal of Physiology* **603**, 3945-3960.
- Degens H, Deveci D, Botto-Van Bemden A, Hoofd LJ & Egginton S. (2006). Maintenance of heterogeneity of capillary spacing is essential for adequate oxygenation in the soleus muscle of the growing rat. *Microcirculation* **13**, 467-476.
- Degens H, Messa GAM, Tallis J, Bosutti A, Venckunas T, Adeniran I, Wüst RCI & Hendrickse PW. (2026). Diffusion and physical constraints limit oxidative capacity, capillary supply and size of muscle fibres in mice and humans. *Experimental Physiology* **111**, 212-225.
- Egginton S. (1990). Morphometric analysis of tissue capillary supply. In *Vertebrate Gas Exchange*, pp. 73-141. Springer.
- Egginton S & Ross H. (1992). Planar analysis of tissue capillary supply. In *Seminar Series - Society for Experimental Biology*, pp. 165-165. Cambridge University Press.
- Egginton S, Turek Z & Hoofd L. (1988). Differing patterns of capillary distribution in fish and mammalian skeletal muscle. *Respiration Physiology* **74**, 383-396.
- Frydenholm JF, Bechshøft CJ, Kjaer M, Mackey AL, Gliemann L & Soendenbroe C. (2026). Capillary differences with age and muscle fiber type are attenuated by accounting for fiber shape. *The FEBS Journal*.
- Kacser H, Burns JA, Kacser H & Fell DA. (1995). The control of flux. *Biochemical Society transactions* **23**, 341-366.
- Kissane RWP, Al-Shammari AA & Egginton S. (2021). The importance of capillary distribution in supporting muscle function, building on Krogh's seminal ideas. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology*, 110889.
- Krogh A. (1919). The number and distribution of capillaries in muscles with calculations of the oxygen pressure head necessary for supplying the tissue. *The Journal of Physiology* **52**, 409-415.

- Newsholme E, Crabtree B & Ardawi M. (1985). The role of high rates of glycolysis and glutamine utilization in rapidly dividing cells. *Bioscience reports* **5**, 393-400.
- Pilotto AM, Adami A, Mazzolari R, Brocca L, Crea E, Zuccarelli L, Pellegrino MA, Bottinelli R, Grassi B, Rossiter HB & Porcelli S. (2022). Near-infrared spectroscopy estimation of combined skeletal muscle oxidative capacity and O₂ diffusion capacity in humans. *The Journal of Physiology* **600**, 4153-4168.
- Pries AR & Secomb TW. (2014). Making Microvascular Networks Work: Angiogenesis, Remodeling, and Pruning. *Physiology* **29**, 446-455.
- Secomb TW & Pries AR. (2011). The microcirculation: physiology at the mesoscale. *The Journal of Physiology* **589**, 1047-1052.
- Snyder GK. (1987). Capillary growth and diffusion distances in muscle. *Comparative Biochemistry and physiology A, Comparative Physiology* **87**, 859-861.
- Snyder GK. (1990). Capillarity and diffusion distances in skeletal muscles in birds. *Journal of Comparative Physiology B* **160**, 583-591.
- Soendenbroe C, Karlsen A, Svensson RB, Kjaer M, Andersen JL & Mackey AL. (2024). Marked irregular myofiber shape is a hallmark of human skeletal muscle ageing and is reversed by heavy resistance training. *Journal of Cachexia, Sarcopenia and Muscle* **15**, 306-318.
- Weibel ER, Federspiel WJ, Fryder-Doffey F, Hsia CC, König M, Stalder-Navarro V & Vock R. (1993). Morphometric model for pulmonary diffusing capacity I. Membrane diffusing capacity. *Respiration Physiology* **93**, 125-149.
- Zeller-Plumhoff B, Roose T, Clough GF & Schneider P. (2017). Image-based modelling of skeletal muscle oxygenation. *Journal of The Royal Society Interface* **14**.