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Exercise-mediated angiogenesis

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Highlights

- Skeletal muscle is heterogeneous in capillary distribution and oxidative demand
- The extent of capillarisation is a key predictor of muscle aerobic capacity
- Exercise-induced angiogenesis is driven by both chemical and mechanical signals
- Simply increasing the number of capillaries may not be an optimal response
- Understanding spatial distribution will facilitate the design of specific exercise regimes

Abstract

Skeletal muscle is among the most plastic of tissues, remodelling to accommodate altered demands. Exercise induces a range of adaptations, notably a growth of capillaries (angiogenesis), while inactivity results in a loss of capillaries (rarefaction). As endurance activity relies on an adequate O_2 supply to support oxidative phosphorylation, hypoxia within working muscle may act as an angiogenic stimulus, but additional candidates include chemical factors such as metabolic by-products (e.g. acidosis) or release of signalling molecules (e.g. VEGF, NO), and mechanical factors including response to muscle contractions (strain) or increased blood flow (hyperaemia). Optimising training interventions, for performance or rehabilitation, will benefit from better understanding of the local environment controlling the pattern of capillary distribution and its consequences for tissue oxygenation. **(120/120 words).**

Keywords: angiogenesis, capillaries, exercise, oxygen transport, skeletal muscle

Introduction

Capillaries are present within almost all organs, with fine structure (continuous, fenestrated, sinusoidal) differing according to functional demand. In skeletal muscle their principal role is gaseous and metabolite exchange at the blood-tissue interface. A capillary has a narrow aperture that produces resistance to blood flow through viscous drag, generating significant levels of shear stress. However, the large cumulative lumen surface area of capillaries actually provides less resistance than that of upstream arterioles. This leads to a lower linear velocity compared to that of larger vessels, which provides a sufficiently long transit time for the diffusive exchange of oxygen and nutrients (Fig. 1). Despite low perfusion velocity, the small diameter combined with low compliance means that individual capillaries may experience high levels of shear stress, which will be elevated during exercise in an intermittent manner determined by the duty cycle involved. The potential exists to mitigate effects of systemic hypoxaemia and/or local hypoxia, and contribute to improved exercise tolerance, by expanding the capillary bed and as a consequence increase surface area and reduce erythrocyte transit time. Growth of capillaries is accomplished by the process of angiogenesis, which shares some similarities but many differences with other forms of vascular growth or remodelling that are often not adequately differentiated by use of loose terminology such as 'neovascularisation'.

Skeletal muscle mass is an independent predictor of peak oxygen uptake (VO_2) in healthy individuals and non-cachectic patients. A variety of skeletal muscle abnormalities contribute to exercise intolerance in those with cardiorespiratory limitations, i.e. may be due to peripheral changes rather than to central haemodynamic dysfunction. As ΔVO_2 during exercise occurs predominantly in the active muscles, due to local vasodilatation and blood shunting from the splanchnic region, this offers a viable therapeutic target. Given this relationship between skeletal muscle mass and exercise capacity, peak VO_2 should increase with training regimes that increase skeletal muscle bulk, hence 'exercise as medicine' is increasingly thought to offer a cost-effective intervention strategy. Aerobic (endurance) muscle performance relies on an adequate arterio-venous O_2 difference, which in turn is limited by either mitochondrial oxidative capacity or blood-tissue diffusive exchange within the microcirculation. Consequently, any supply/demand mismatch needs to have a dynamic response – acutely this may involve metabolic (functional) hyperaemia, but chronically requires growth of new vessels from the existing capillary bed (angiogenesis).

This review aims to summarise current understanding of angiogenic regulation in skeletal muscle, and identify some exciting new avenues of investigation, that may help optimise microvascular performance in health and disease.

Quantification of microvascular supply

Deriving a consensus position on what benefits accrue from exercise-induce angiogenesis, and which training regimes may be most effective, requires agreement on validated methods of quantifying size of the capillary bed. This has been a significant contributor to sometimes wide-ranging estimates of muscle capillary supply in the literature [1]. Histochemical staining has become the most common method of identifying capillaries, where previously injection of dyes into the microvasculature was used [2]. Early identification of capillaries utilised a stain for alkaline phosphatase, an enzyme with high activity in the endothelium [3] but reproducibility differs among staining methods, and its validity as a marker have been questioned [1]. With the development of immunohistochemistry there are an array of antibodies available to probe for endothelial cell components, such as adhesion molecules such as CD31 (PECAM-1), and growth factor receptors such as Flk-1 and Tie-2. An increasingly common marker used to visualise capillary location are various lectins, polysaccharides that bind to the glycocalyx of capillaries, due to the relative simplicity of staining. However, alternative markers for endothelial cells generate disparate results when used to stain the same muscle sections (Fig. 2a). As such, it is important to be aware of the markers used to identify capillaries when using data from the literature, in particular whether they identify newly formed or mature vessels, and the varied sensitivity/specificity of markers among species in comparative studies.

Microvascular sensors

Adaptive tissue remodelling is most likely a result of feedback regulation, so identifying the origin of proximate signals may help direct therapeutic interventions, or optimise training strategies. Key to the integrated exercise response is translation of acute reactions mediated by ergoreceptors [4], that e.g. in the presence of poor capillarisation may promote the sensation of breathlessness and facilitate improved cardiac output, and translation of chronic signals into structural remodelling. Metaboreceptor stimulation by metabolite spillover is accompanied by metabolic heat generation during muscle activity, and passive heat therapy has recently been shown to have angiogenic potential [5]. Three major candidate areas receiving a lot of attention are detection of altered tissue oxygenation, linkage with metabolic activity, and response to haemodynamic

disturbance. These clearly need to invoke an appropriate signalling response on repetition (e.g. part of regular physical activity or structured exercise), as structural remodelling is energetically costly and hence endothelial responses to acute stimuli (e.g. running to catch a bus) are not readily translated into angiogenesis.

1) Endothelial O_2 sensing.

While it is clear that maximal rates of O_2 diffusion in muscle are limited by both the blood carrying capacity and extent of capillarisation, diffusional conductance between the microvasculature and mitochondria represents a significant limitation to maximal VO_2 in health and disease states [6]. The dynamic sensing of changes in local metabolic demand during exercise is therefore key to optimising aerobic capacity, and although the location has been subjected to some debate there is good evidence to suggest this is found at the level of individual capillaries, likely associated with release of ATP from erythrocytes [7]. There is clearly a need to provide both an adequate convective supply of O_2 to working muscle, but also to ensure an effective distribution within a tissue of heterogeneous composition (e.g. different fibre types). Linking endothelial responses to the local environment, e.g. by alteration of metabolism [8], to ascending dilatation within the supplying arterioles [9] provides a mechanism for such coordination. It is likely that such a feedback loop would also include stimulation of angiogenesis, providing the necessary cues to maintain optimal microvascular topology [10-12]. For example, in a recent voluntary running wheel training study on mice, exercise-induced angiogenesis was accompanied by changes in capillary fine structure and tortuosity [13]. Such a downstream response will be mediated by associated changes in the chemical and/or mechanical microenvironment surrounding capillaries.

2) Endothelial chemotransduction

Intimately linked with O_2 sensing is the response to local disturbance in tissue oxygenation by any supply/demand mismatch, leading to pockets of relative hypoxia during muscle activity. This may invoke a range of transcriptional responses [14, 15], orchestrated largely by HIF-1α though requiring a more subtle regulation than implied by the usual description of a hypoxic ‘switch’ [16]. Investigations into release of classical pro-angiogenic signals has centred around the roles of vascular endothelial growth factor (VEGF) [17-23], as both a mitogen and vasodilator. This has expanded in recent years to include the potential involvement of exercise-induced release of endothelial microparticles and changes in microRNAs [24], potentially modifying the response to altered levels of pro-angiogenic or angiostatic factors quantified by e.g. Western blot or ELISA. In addition, there is renewed interest in the role of perivascular cells in regulating adaptive angiogenesis, providing a paracrine influence of e.g. pericytes and

satellite cells on the endothelium [25] offering an additional site for sensing both chemical and physical changes in the local environment and hence influencing the response to exercise. However, the role of endothelial chemotransduction in driving angiogenesis is extensively covered in the literature, largely driven by tumour angiogenesis investigations; the main players in skeletal muscle are summarised in [26] and some new angles explored in [8]. We shall therefore emphasise the less well reviewed concept of mechanotransduction, and identify areas of complementarity.

Mechanotransduction-driven angiogenesis

The ability of endothelium to respond to mechanical stressors is well known, with a majority of studies emphasising the link with atheroma development and inflammation [27]. It has been noted that the signals underlying exercise-induced angiogenesis are likely multi-facetted, in both origin and effects. An impressive functional response of the microvasculature and the skeletal muscle it supports has been demonstrated across a variety of species. As little as four weeks training in humans is required to significantly increase capillary content [28-31], with similar microvascular remodelling seen after four to six weeks of voluntary wheel running or treadmill training in rodents [21, 32-35]. Interestingly some changes in capillarity can be seen as early as seven days [32, 33], suggesting that in these instances angiogenesis precedes the altered fibre type composition [32, 36], and that microvascular changes are permissive for other adaptive responses rather than being simply reactive. However, while changes in fibre type following training usually occur very slowly, exercise-induced alterations in mitochondrial respiration are very fast, and it may be that angiogenesis is reactive to the accompanying stimuli (below).

Attempts to isolate the components largely have concentrated on elements of 1) and 2) (above), but recognition has been growing that the dynamic physical environment experienced by endothelial cells (EC) during a duty cycle (stretch and compression, elevated shear stress, increased transmural pressure) are all factors that may affect EC phenotype in vitro. Isolating these mechanical signals from any accompanying chemical signals in vivo has proved difficult, but there has been a recent surge in the translation of isolated mechanotransductive animal models [35, 37, 38] to human investigation, of particular interest is the use of passive leg exercise [39, 40] and supplementation of the vasoactive α_1 adrenoreceptor antagonist terazosin [41, 42]. Briefly, passive leg movement drives a modest increase in blood flow (hyperaemia) and longitudinal stretch of myofibrils without

the metabolic demand typically induced through active exercise [43]. Passive exercise, with no muscle activity to compound the signal, demonstrates that mechanoreceptors can drive angiogenesis in vivo [44]. Similarly, the well-established shear stress-induced angiogenesis model (typically through prazosin, an α_1 adrenoreceptor antagonist, supplemented in drinking water of rodents) has for the first time been tested in humans. Four weeks of terazosin (another vasodilator) supplementation resulted in a 12.5% increase in capillary to fibre ratio (C:F) and 24% increase in capillary density (CD) within the vastus lateralis of healthy adults. Sustained elevations in shear stress within the microcirculation induced by terazosin, again represent primarily a vascular signal lacking input from surrounding muscle, and parallels the influence of functional hyperaemia on exercise-induced angiogenesis [41]. When applied in a chronic setting, hyperaemia and the accompanying release of endogenous mediators of angiogenesis (VEGF, eNOS and MMP2) increases the microvascular content of skeletal muscle [40]. The associated markers of angiogenesis are also increased both within healthy adults [39] and those with peripheral arterial disease (PAD) [44]. Whether a similar translational benefit of overload-induced angiogenesis [45] could be realised is unknown.

Emphasising quality, not quantity of microvascular supply

The functional relevance of any terazosin-driven angiogenic response (increase in CD) have yet to be fully examined. However, despite the associated increase in capacity for O_2 flux and metabolite removal, key for improved aerobic exercise performance, there is increasing evidence that highlights the importance of fine spatial control of capillary distribution needed to optimise oxygen transport [12, 46, 47]. Terazosin supplementation (an attempt to isolate the exercise hyperaemia response) showed no shift in distribution of the area of muscle supplied by individual vessels (or capillary domain [47]), representing the heterogeneity of capillary spacing, after four weeks (Fig. 3a). This indicates a stochastic location of new vessels that does not affect the microvascular topology seen in controls, suggesting the shear stress driven response is not responding to tissue metabolic demand. In contrast, the exercise response recruits targetted neovascularisation that is seen to reduce the supply area for individual capillaries, and hence optimise muscle oxygenation [46], to support the higher energy demand of active muscle (Fig. 3b). The terazosin data is consistent with findings of prazosin in rodent models of diabetes where, despite a significant increase in microvasculature, there was little or no improvement in the functional readouts reported [35].

The interaction of capillary spatial heterogeneity (supply) and muscle fibre type composition (demand) is becoming a prominent topic of investigation in response to exercise and disease [18, 48-52]. Although strictly the demand is set by mitochondrial function, fibre type is used as a surrogate due to the difficulty of relating dynamic ATP production with capillary location on biopsy sections. We have recently highlighted the importance of spatial heterogeneity in skeletal muscle functional capacity within two distinct components of the rat EDL, a 'mixed' muscle often considered to be of homogeneous composition [50]. Within the same muscle it is possible to have varying functional characteristics and optimum working conditions, which are likely to be driven by functional demand (Fig. 4). These data emphasise the need to understand the functionality of a muscle for the development of effective targetted rehabilitation and therapeutic regimes.

Until recently, the calculation of fine scale indices of capillary supply has been a laborious and undervalued technique, which may explain the lack of attention to this area of morphometric quantification. A handful of research groups have attempted to use more refined indices of capillary supply, specific to individual fibre types [49, 53-55]. However, the methods used to derive these indices are inconsistent, and it is unclear how some offer appropriate representation of local capillary to fibre interactions. The recent boom in semi-automatic software packages for analysis of the phenotypic composition of skeletal muscle [56-59] has yet to allow researchers to extend this analysis and incorporate the fundamental oxygen supply component (capillary) onto muscle fibre boundary outlines, essential if one is to provide an anatomically realistic framework. However, a recent publication has made the first step in providing a means to generate valid local capillary indices, using a semi-automated data pipeline that processes immunohistochemically labelled skeletal muscle tissue, as illustrated in Fig. 4 [51].

Exercise-induced angiogenesis in disease

With national campaigns to increase levels of physical activity, and the drive for exercise as part of healthcare prescriptions, the animal data outlined above may be of particular interest for individuals with reduced exercise tolerance (e.g. chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD) or chronic heart failure (CHF)), who could benefit from treatments that do not impose a large central cardiorespiratory or local metabolic demand, but could rectify poor microvascular supply in the periphery. The initial response in skeletal muscles may then subsequently facilitate a more active exercise program to drive central changes [35].

Skeletal muscle inactivity [49, 51, 60, 61] and ageing [62-64] both result in marked decreases in fibre area and microvascular supply, that corelate highly with a reduced aerobic functional capacity. Interestingly, during healthy aging there appears to be local feedback that coordinates capillary rarefaction in order to preserve appropriate supply to the individual fibre requirements [63]. However, there are a number of pathologies that are accompanied by impaired peripheral microvascular supply that may not maintain this relationship; including COPD [65], CHF [66-68], diabetes [30, 35, 48, 69, 70], PVD [44] and spinal cord injury (SCI) [71]. This supply-demand mismatch is an obvious candidate driving development of the observed exercise intolerance, and hence exercise-induced angiogenesis would appear to be a worthwhile therapeutic goal.

Surprisingly, the microvascular component of SCI is a largely ignored pathology in relation to trauma, and as a potential driver of functional recovery. In chronically injured patients there is a well-maintained hyperaemic response to functional electrical stimulation [72], which points to the microvasculature as the limiting interface leading to impaired fatigue resistance [71]. Following eight weeks of locomotor training combined with epidural stimulation it is possible to significantly blunt the microvascular rarefaction seen in skeletal muscle innervated caudal to the lesion [71]. There is also evidence that passive limb movement [73] and functional electrical stimulation [72] promote muscle hyperaemia, and applied early enough following trauma these may be able to alleviate some of the capillary rarefaction observed. The parallels with exercise-induced angiogenesis are clear, but it remains to be tested whether the signals induced are the same.

Given the established role of skeletal muscle microcirculation in mediating glucose homeostasis exercise-induced angiogenesis is an attractive, non-pharmacological intervention for the burgeoning diabetic population. Again, any exercise-intolerance may be alleviated by invoking shear-stress induced angiogenesis to improve insulin sensitivity [74], with the hope of subsequently encouraging more traditional exercise therapy. The increasing prevalence of diabetes and CHF as comorbidities poses a complex therapeutic niche [75, 76]. As standalone pathologies, both diabetes [30, 35, 48, 69, 70, 77, 78] and CHF [66-68, 79-81] present with modest microvascular rarefaction, and those suffering with both are likely to have more pronounced rarefaction. To further complicate matters the metabolic response to these isolated pathologies is mixed, with evidence that diabetes may preserve [82] or increase oxidative demand of muscle, while CHF tends to present with a reduced oxidative capacity in locomotor muscles [83, 84]. Diabetes [30, 35, 69, 78, 85, 86] and CHF [81, 84] induced rarefaction are both

attenuated with increased activity, with concomitant increases in oxidative demand of skeletal muscles [86, 87], although the functional benefits of these structural and enzymatic changes are still to be determined. When considering the effects of exercise as a holistic response, differences in phenotype among tissues may have important consequences for targetted angiotherapy, e.g. endothelium in the central and peripheral nervous systems are different from skeletal muscle, hence addressing diabetic exercise intolerance may need to distinguish between poor oxygenation and neuropathy [88, 89].

Difficulty in unpicking the proximal causes and subsequent aetiology of many diseases mean that tailoring the most efficient exercise regime represents a significant challenge. It is possible to increase microvascular content using conventional endurance exercise such as cycling and running [29, 30, 78, 85, 90], but often these modalities are poorly tolerated. However, it is also possible to modify microvascular composition and muscle metabolism through moderate intensity interval training (MIIT) [53, 90, 91], high intensity interval training (HIIT) [14, 91, 92] or resistance training [15, 31, 55, 93], offering the potential for disease- and patient-specific interventions. It remains a fine balance between optimising any exercise intervention to avoid overloading the central (cardiorespiratory) systems, while inducing peripheral adaptations to modify the metabolic status (demand) and/or the microvascular composition (supply) sufficiently to impact exercise tolerance. The use of pharmacologically-induced rise in shear stress and/or passive movement to avoid these central challenges are likely to be beneficial, particularly in the early stages of rehabilitation.

Conclusions and future directions

The realisation that even previously assumed ‘homogeneous’ muscles actually contain functionally and structurally distinct regions demands a reappraisal of both the analytical approach when handling biopsies, and interpretation of resulting data describing the outcomes of different training regimes. This will allow improved understanding of the local factors that drive tissue remodelling, and consequently help deliver more effective therapeutic exercise interventions that offer the equivalent of ‘personalised medicine’ for individual conditions. There is a wealth of recent research to suggest that exercise adaptation differs greatly among individuals who receive the same activity stimulus. This may be underpinned by differential molecular responses [94-96], but surprisingly is not accounted for by genetic variation [97]. One unexplored avenue that may complement such studies

is how vicarious events and lifestyle influence the microvascular distribution in skeletal muscle, and the importance of spatial heterogeneity in utilising the intrinsic capacity for oxygen transport to tissue that ultimately may define an individual's endurance exercise performance.

Conflict of Interest Statement:
Nothing declared

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* of special interest

** of outstanding interest

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Figure legends

Figure 0. Vascular cross-sectional area (red line) and mean linear flow (blue line). Note the large cumulative surface area in the capillary bed (exchange vessels), which compensates for the slow perfusion rate to effect adequate diffusive supply of oxygen and other nutrients. Adapted from [98].

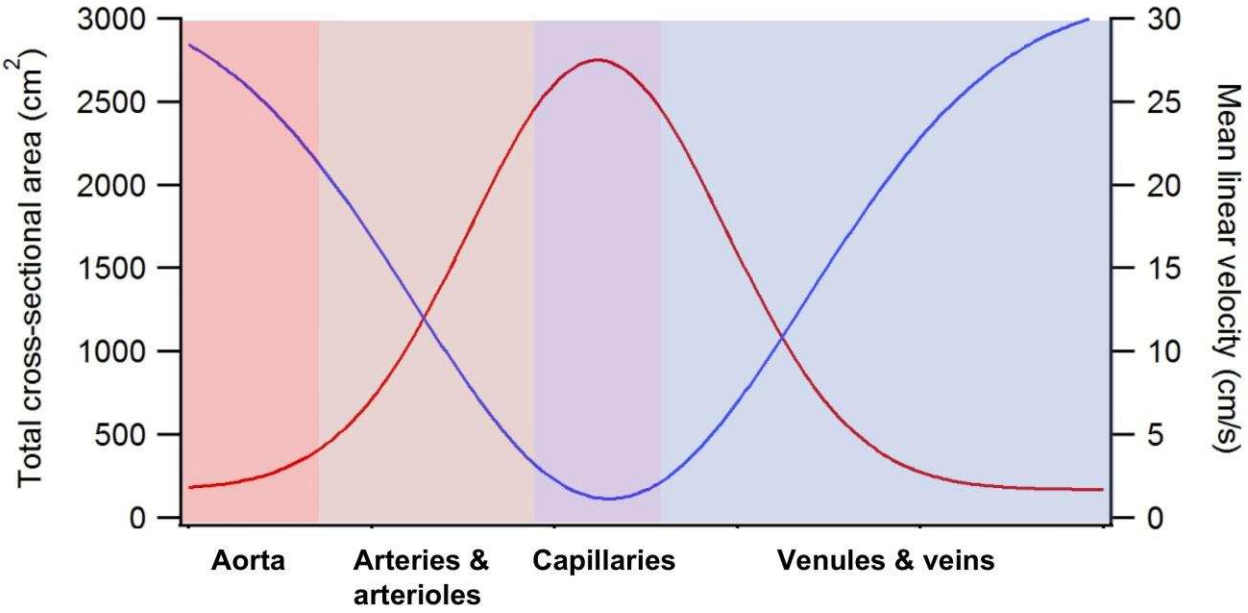


Figure 2. (a) C:F of the mouse EDL using multiple markers for capillary location. Adapted from J Williams, PhD Thesis, University of Birmingham (2005), * P<0.05 from Lectin (n=6). (b) Representative histological samples. There may also be a species effect, as the discrepancy among markers in rat EDL is less pronounced (unpublished data). ALP; alkaline phosphatase, CD31; platelet endothelial cell adhesion molecule (PECAM-1), Lectin; biotinylated Griffonia Simplicifolia Lectin I.

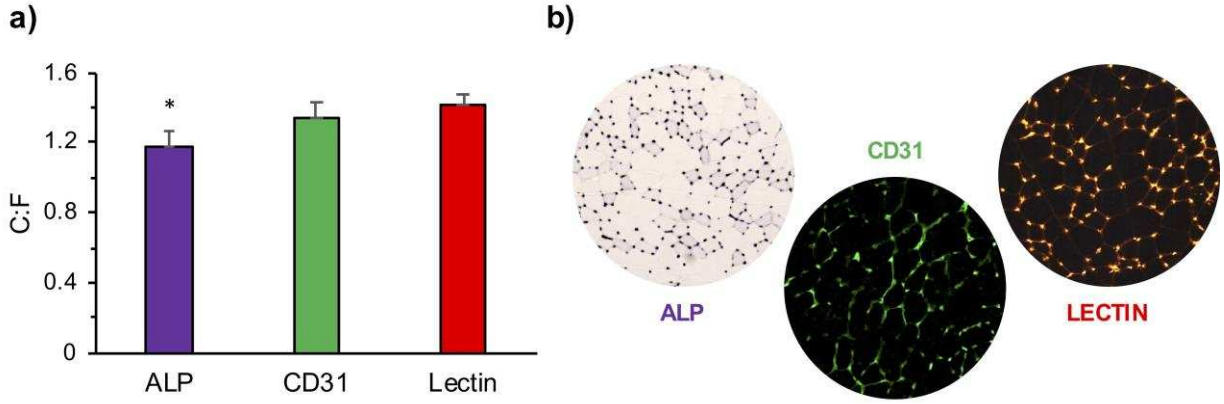


Figure 3. Capillary domain distributions for human angiogenic models. (a) Percutaneous needle biopsies from m. vastus lateralis following supplementation with terazosin for four weeks (modified from Mortensen, et al., 2017). (b) Percutaneous needle biopsies from the lateral quadriceps muscle, pre- and post-isokinetic training at 60% maximum voluntary contraction using a Cybex Orthotron KT2 (Egginton & Jakeman, unpublished data). Note: both interventions produced significant increases in C:F, but the capillary domain area distributions differ greatly.

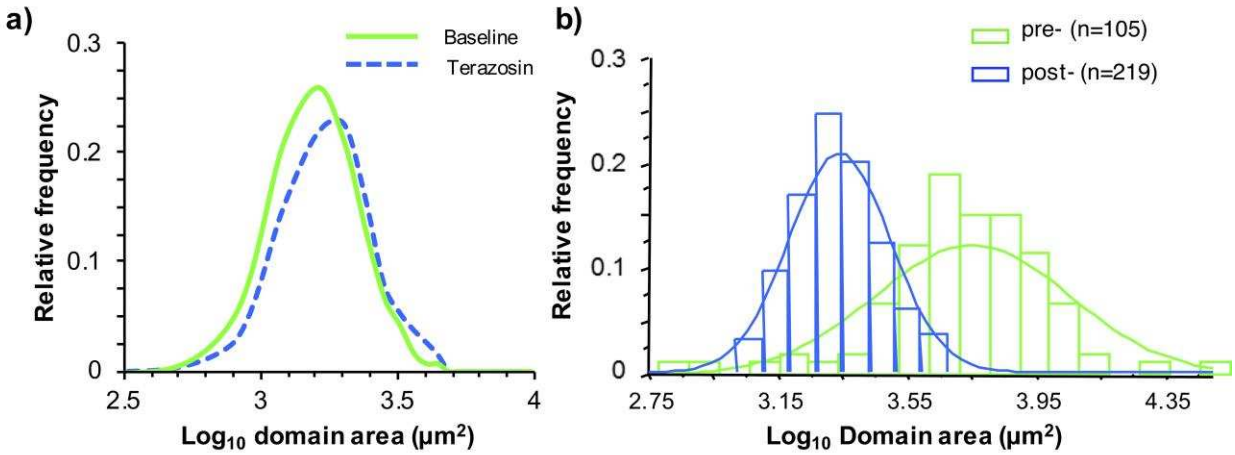
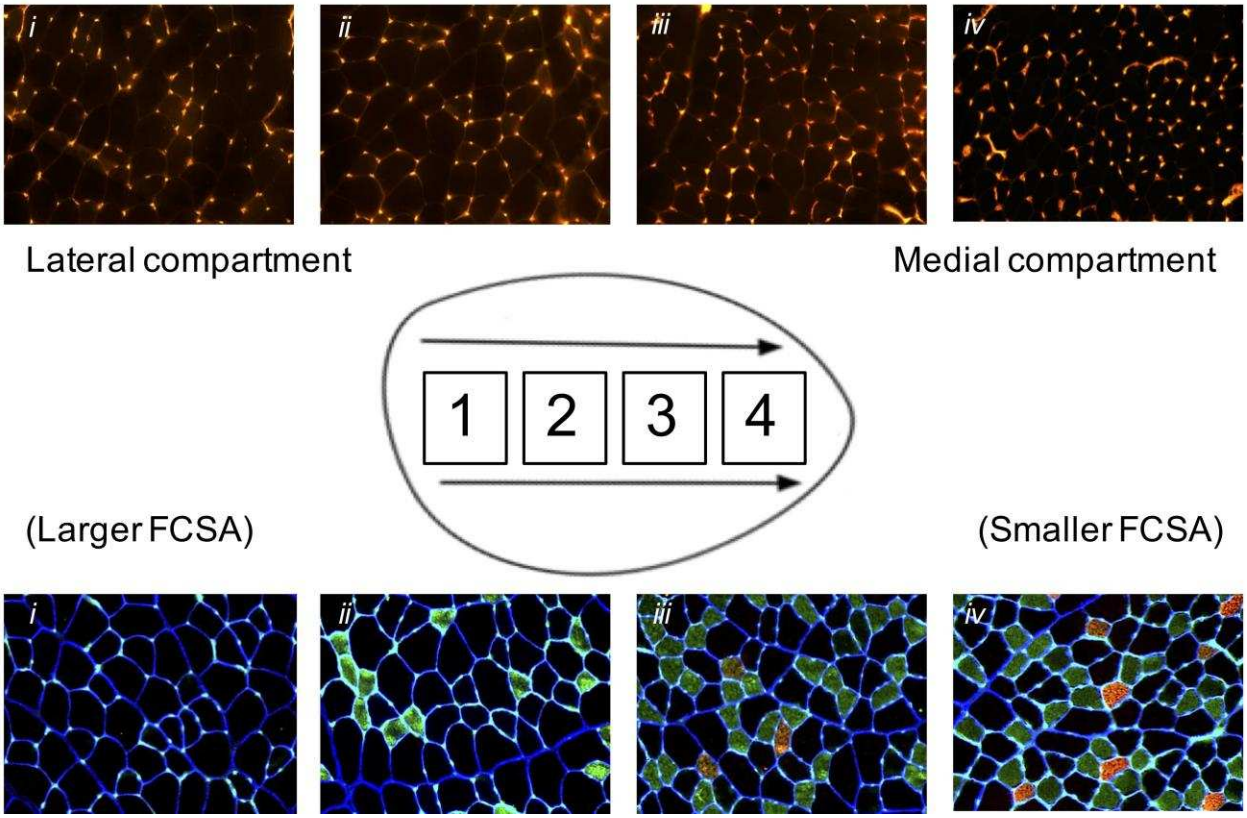


Figure 4. Structural and functional heterogeneity within the EDL. The heterogeneous oxygen supply capacity of the muscle is demonstrated by density of rhodamine labelled capillaries (histology top row, i-iv). The increased oxidative supply medially across the muscle is matched by an increasing oxidative demand, in the form of greater oxidative fibre content (histology bottom row, i-iv).


i
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Lateral compartment
Medial compartment
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(Larger FCSA)
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