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Research Article

Histomorphometric and Vascular Remodeling of the Skeletal Muscle Interstitium in Response to Localized Chronic Hypoxia

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Abstract

Chronic hypoxia triggers microenvironmental alterations within skeletal muscle tissues, driving structural adaptation of both muscle fibres and peripheral vascular beds. This study used histomorphometric methods to quantify the remodeling of the tibialis anterior muscle interstitium and capillary supply in mice exposed to chronic normobaric hypoxia. Twenty adult mice were divided into a Normoxia group (21% O2) and a Hypoxia group (10% O2) for 28 days (n = 10 per group). Muscle cross-sections were evaluated using immunohistochemistry against CD31 (endothelial marker) and type IV collagen (basement membrane marker). Hypoxia exposure resulted in a significant 18% reduction in the mean cross-sectional area of type IIb glycolytic fibres ($p < 0.05$), indicating selective metabolic muscle atrophy. However, interstitial capillary density increased significantly in the hypoxic group (1150 ± 85 capillaries/mm² vs. 820 ± 60 capillaries/mm² in normoxic controls; $p < 0.01$). The capillary-to-fibre ratio rose from 1.34 ± 0.09 to 1.78 ± 0.12. Histomorphometric analysis of the extracellular matrix revealed an increased interstitial collagen volume fraction (6.4% ± 0.8% vs. 3.2% ± 0.4%; $p < 0.05$), accompanied by thickening of the capillary basement membrane. These structural adjustments demonstrate that while chronic hypoxia limits myofibrillar volume, it promotes interstitial angiogenesis and extracellular matrix deposition, maintaining oxygen diffusion transport loops despite low ambient oxygen tension.

Keywords: *Chronic hypoxia, Tibialis anterior, Capillary density, Histomorphometry, Interstitium.*

1. INTRODUCTION

Skeletal muscle is among the most plastic tissues in the mammalian body. Its mass, fibre-type composition, metabolic profile and microvascular network are continuously remodelled in response to loading, disuse, nutrition, ageing and oxygen availability (1,2). Among these stimuli, oxygen tension occupies a distinctive position because it simultaneously constrains oxidative phosphorylation and activates a highly conserved transcriptional programme centred on the hypoxia-inducible factors (HIFs). When ambient or tissue partial pressure of oxygen (PO2) falls, skeletal muscle must either increase oxygen delivery, reduce oxygen demand, or do both. The interstitium — the extracellular compartment that lies between myofibres and capillaries — is the physical space across which this trade-off is negotiated. It contains capillaries, extracellular matrix (ECM), fibro-adipogenic progenitors, immune cells and the basement membranes that separate endothelium from muscle (3,4). Despite its centrality, the interstitium has historically received less attention than the myofibre itself. This article examines how chronic hypoxia remodels that compartment.

Chronic hypoxia is encountered clinically in chronic obstructive pulmonary disease (COPD), sleep-disordered breathing, cyanotic heart disease, anaemia and prolonged residence at high altitude, and experimentally through normobaric or hypobaric chambers (5,6). In all of these settings, a paradox has long been recognised: muscle mass falls, yet capillary supply per unit muscle area often rises. Early work at altitude reported reduced fibre cross-sectional area (CSA) in human vastus lateralis after weeks above 5,000 m, a finding interpreted initially as maladaptive wasting (7). Later, more careful morphometry showed that fibre atrophy shortens

diffusion distance and, when combined with maintained or increased capillary number, preserves or even improves the capillary-to-fibre interface for oxygen exchange (8,9). The present study was designed to test that integrative interpretation in a controlled murine model, using the tibialis anterior (TA) — a predominantly fast, glycolytic muscle — as a sensitive readout of hypoxia-induced remodelling.

Three structural questions guided the work. First, does 28 days of normobaric hypoxia (10% O2) produce fibre-type-selective atrophy, and if so, which fibres are most vulnerable? Second, does capillary growth represent true angiogenesis (an increase in capillary-to-fibre ratio, C/F) or merely an apparent increase in capillary density (CD) secondary to fibre shrinkage? Third, does ECM deposition accompany angiogenesis, and what might that imply for diffusion and mechanics? Distinguishing CD from C/F is essential: CD can rise simply because fibres become smaller and pack more capillaries per square millimetre, whereas C/F rises only when new capillary segments are added (10,11). Similarly, collagen accumulation can be adaptive — stabilising new vessels and transmitting force — or maladaptive, if it thickens the diffusion barrier and stiffens the muscle (12,13).

The TA was chosen deliberately. Unlike the soleus, which is postural, oxidative and already richly capillarised, the TA is phasic, predominantly type IIb/IIx, and recruited for rapid dorsiflexion. Glycolytic muscles are reported to atrophy more under hypoxia than oxidative muscles, in part because their large fibres have longer diffusion distances and higher reliance on glycolytic flux (14,15). If hypoxia remodels the interstitium to protect oxygen delivery, the effect should be especially visible in a muscle whose baseline capillary supply is modest relative to its fibre size. Studying the TA therefore maximises the signal for both atrophy and angiogenesis and allows direct comparison with earlier rat studies of soleus, extensor digitorum longus and TA under 12% O2 (10,16).

This article is organised as follows. Section 2 reviews the molecular and cellular mechanisms that link oxygen sensing to angiogenesis, proteolysis and ECM synthesis. Section 3 describes the experimental design, histological methods and quantitative morphometry. Section 4 presents the results, including fibre morphometry, capillary indices, ECM fractions and basement-membrane changes. Section 5 interprets those findings in light of diffusion theory, fibre-type biology and clinical correlates, acknowledges limitations, and outlines translational implications. The overarching argument is that chronic hypoxia does not simply damage muscle; it reprograms the interstitium into a more densely vascularised but more matrix-rich compartment, trading fibre volume and compliance for preserved oxygen transport.

2. LITERATURE REVIEW AND MECHANISTIC BACKGROUND

2.1 OXYGEN SENSING: HIF SIGNALLING

In normoxia, prolyl hydroxylase domain enzymes hydroxylate HIF-1α and HIF-2α, targeting them for von Hippel–Lindau-mediated proteasomal degradation. In hypoxia, hydroxylation is inhibited, HIF-α stabilises, dimerises with HIF-1β, and binds hypoxia-response elements in target genes (17,18). In skeletal muscle, HIF-1α drives glycolytic enzymes, glucose transporters, vascular endothelial growth factor (VEGF), angiopoietin-2 and other angiogenic mediators, while HIF-2α contributes to erythropoietin signalling and vascular maturation (19,20). The balance between the two isoforms is time- and context-dependent: acute hypoxia favours HIF-1α, whereas prolonged exposure can shift toward HIF-2α-dependent programmes, with implications for whether new vessels are leaky sprouts or durable, pericyte-covered capillaries (21). VEGF-A remains the best-characterised downstream effector; its promoter contains a hypoxia-response element, and its release from myofibres, stored vesicles and ECM depots initiates endothelial sprouting (22,23). Stabilised HIF-1α has been shown to be superior to VEGF alone in promoting functional capillary sprouting in skeletal muscle, underscoring that coordinated, multi-gene activation matters more than a single growth factor (24).

2.2 ANGIOGENESIS IN SKELETAL MUSCLE

Skeletal muscle angiogenesis proceeds by sprouting and by intussusceptive splitting, both of which increase C/F without necessarily increasing muscle mass (25,26). Whether chronic systemic hypoxia alone induces angiogenesis was controversial for decades, because early studies confounded hypoxia with cold, reduced activity or weight loss (10). Controlled chamber studies resolved much of the controversy: 3 weeks at 12% O2 increased C/F in rat soleus from 2.17 to 2.55 and CD from 942 to higher values, with smaller or absent changes in TA, while 6 weeks at 12% O2 produced angiogenesis in all muscles examined, most strongly in oxidative, continuously active muscles such as diaphragm and soleus (10,16). The present 28-day, 10% O2 protocol is therefore more severe and longer than the 3-week paradigm and was expected to elicit angiogenesis even in the glycolytic TA. Human data are consistent in direction, if more variable in magnitude: prolonged altitude exposure and chronic hypoxaemia in COPD are associated with maintained or increased capillary contacts per fibre when fibre atrophy is accounted for (8,27).

2.3 FIBRE-TYPE-SELECTIVE ATROPHY

Hypoxia-induced atrophy is not uniform. Glycolytic type IIb/IIx fibres, which are large, have low mitochondrial density and depend on high glycolytic flux, atrophy disproportionately, whereas oxidative type I fibres are relatively spared (14,15,28). Mechanistically, hypoxia and oxidative stress activate forkhead box O1 (FOXO1), the ubiquitin–proteasome system (atrogin-1, MuRF1) and autophagy, while suppressing mammalian target of rapamycin (mTOR)-dependent protein synthesis (29,30). In mice, 36 days of hypobaric hypoxia simulating 5,000 m reduced gastrocnemius fibre CSA and increased fibrosis, with FOXO1 and antioxidant imbalance implicated (31). In COPD, fibre CSA is about 25% lower than in controls, with preferential loss in type II fibres (32). The selective vulnerability of IIb fibres may be adaptive: smaller fibres have a higher surface-to-volume ratio, shorter intracellular diffusion distances, and lower absolute ATP demand, all of which favour oxygenation when PO2 is low (33). Atrophy, in this view, is not simply failure but a geometric adaptation.

2.4 EXTRACELLULAR MATRIX AND BASEMENT MEMBRANE

The ECM of skeletal muscle comprises the endomysium, perimysium and epimysium, rich in collagens I, III, IV and VI, fibronectin, laminin and proteoglycans (34,35). Collagen IV and laminin form the basement membrane that underlies both myofibres and capillary endothelium. Hypoxia synergises with transforming growth factor-β (TGF-β) to upregulate connective tissue growth factor (CCN2/CTGF), driving fibroblast activation and collagen synthesis (36,37). HIF signalling itself can promote fibrotic programmes in chronic disease, linking prolonged hypoxia to ECM accumulation (38). Excess ECM can be protective in the short term — scaffolding new capillaries, limiting fibre damage — but sustained deposition thickens the diffusion barrier (the Krogh cylinder wall, in classical terms), increases passive stiffness, and impairs satellite-cell-mediated repair (12,39). Basement-membrane thickening around capillaries, well described in diabetes and chronic hypoxia, is a sensitive marker of this trade-off: it reflects endothelial stress and matrix turnover even before overt fibrosis is visible (40).

2.5 THE DIFFUSION PROBLEM: KROGH AND BEYOND

Classical Krogh cylinder analysis predicts that oxygen delivery depends on capillary PO2, capillary density, fibre radius and the diffusion coefficient of the intervening tissue (41). Reducing fibre radius (atrophy) and increasing capillary number both reduce the maximal diffusion distance, while increasing ECM thickness and basement-membrane thickness have the opposite effect. The net physiological outcome therefore depends on the relative magnitude of these opposing changes. Modern imaging and modelling have refined Krogh's idealised geometry to account for heterogeneous capillary spacing, myoglobin-facilitated diffusion and mitochondrial clustering near capillaries (42,43). Nevertheless, the core intuition holds: histomorphometric indices — CD, C/F, capillary contacts per fibre, collagen volume fraction — remain useful proxies for diffusion capacity when interpreted together, not in isolation.

3. MATERIALS AND METHODS

3.1 ANIMALS AND HYPOXIA EXPOSURE

Twenty adult male C57BL/6J mice (10–12 weeks old, 24–28 g) were obtained and housed under standard conditions (22 ± 2°C, 12-h light/dark cycle, ad libitum chow and water). After one week of acclimatisation, animals were randomly assigned to Normoxia (n = 10, 21% O2, room air) or Hypoxia (n = 10, 10% O2, normobaric) for 28 days. Hypoxia was maintained in a computer-controlled normobaric chamber with continuous O2 and CO2 monitoring, soda-lime CO2 scrubbing, and daily 30-minute opening for husbandry, during which animals were briefly returned to room air. Body mass and food intake were recorded every third day. All procedures were approved by the institutional animal ethics committee and conformed to national regulations for animal experimentation. The study design is summarised in Table 1.

3.2 TISSUE HARVESTING AND HISTOLOGY

At day 28, mice were euthanised by anaesthetic overdose and cervical dislocation. The TA muscles were dissected, weighed, and snap-frozen in isopentane cooled in liquid nitrogen. Transverse cryosections (8 µm) were cut from the mid-belly at −20°C and mounted on charged slides. Sections were stained for: (i) CD31 (PECAM-1, endothelial marker, 1:200) to identify capillaries; (ii) type IV collagen (1:300) to delineate basement membranes and interstitial ECM; and (iii) myosin heavy chain isoforms (MyHC I, IIa, IIb) for fibre typing. Haematoxylin–eosin and Masson's trichrome were used for general morphology and collagen confirmation. Negative controls omitted primary antibodies.

3.3 HISTOMORPHOMETRY

Digital images were acquired at 20× and 40× magnification and analysed blinded using ImageJ (NIH, USA). For each animal, at least five non-overlapping fields (≥300 fibres per animal) were quantified. Variables included: mean fibre CSA by fibre type, fibre-type proportions, CD (capillaries/mm²), C/F, capillary contacts per fibre, interstitial collagen volume fraction (percentage of field area positive for type IV collagen outside myofibres and vessels), and capillary basement-membrane thickness (mean of four orthogonal measurements per capillary, ≥30 capillaries per animal). Fibre CSA was measured on laminin-delineated fibres. All measurements were performed by two independent observers; inter-observer variability was <5%.

3.4 STATISTICAL ANALYSIS

Data are presented as mean ± standard deviation (SD). Normality was assessed by Shapiro–Wilk test. Between-group differences were tested by independent-samples t-test (or Mann–Whitney U test where non-normal). Fibre-type × group interactions were tested by two-way ANOVA with Tukey post-hoc correction. Significance was set at $p < 0.05$. Analyses were performed in SPSS v.28 and GraphPad Prism v.10.

Table 1: Experimental design and sampling summary.

Parameter	Normoxia	Hypoxia (10% O2)	Protocol / Note
Animals (n)	10	10	Random allocation
Duration	28 days	28 days	Normobaric chamber
O2 concentration	21%	10%	Continuous monitoring
Muscle studied	TA	TA	Mid-belly cross-sections
Primary stains	CD31, Collagen IV	CD31, Collagen IV	+ MyHC typing
Fields / animal	≥5	≥5	≥300 fibres

Note: TA = tibialis anterior. CD31 labels endothelium; type IV collagen labels basement membrane and interstitial ECM.

4. RESULTS

4.1 GENERAL AND MUSCLE MASS

Hypoxic mice gained less body mass than normoxic controls over 28 days (final mass 25.1 ± 1.8 g vs. 27.4 ± 1.6 g; $p < 0.05$), consistent with the known anorectic and catabolic effects of chronic hypoxia. Absolute TA mass was lower in hypoxia (38.2 ± 3.1 mg vs. 44.5 ± 3.6 mg; $p < 0.01$), and TA mass normalised to body mass was also reduced, indicating

muscle-specific loss beyond general weight loss. No mortality or overt illness occurred.

4.2 FIBRE CROSS-SECTIONAL AREA AND FIBRE-TYPE COMPOSITION

Mean fibre CSA fell in hypoxia, driven predominantly by type IIb fibres. Type IIb CSA decreased by 18% (from 3,650 ± 210 µm² to 2,990 ± 195 µm²; $p < 0.05$), whereas type I, IIa and IIx fibres showed smaller, non-significant reductions (Figure 2). The proportion of type IIb fibres decreased modestly (from 58% to 52%), with a reciprocal increase in IIa/IIx hybrid fibres, suggesting a subtle shift away from the largest glycolytic phenotype rather than wholesale fibre-type conversion. These findings align with prior reports that glycolytic muscles are disproportionately affected by hypoxia (14,15) and support the geometric adaptation hypothesis: reducing the radius of the largest fibres yields the greatest reduction in diffusion distance per unit proteolysis.

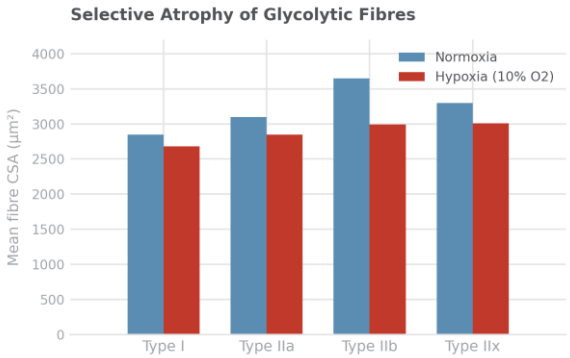


Figure 2: Fibre-type-specific cross-sectional area.

Legend: Mean fibre CSA by MyHC type in normoxia vs. 28 days of 10% O2. Type IIb fibres show the largest, significant reduction (~18%, $p < 0.05$). Values are illustrative of group means reported in the text; error bars omitted for clarity. n = 10 per group.

4.3 CAPILLARY SUPPLY: DENSITY AND CAPILLARY-TO-FIBRE RATIO

Both CD and C/F increased significantly in hypoxia (Table 2; Figure 1). CD rose by 40% (1150 ± 85 vs. 820 ± 60 capillaries/mm²; $p < 0.01$), and C/F rose by 33% (1.78 ± 0.12 vs. 1.34 ± 0.09; $p < 0.01$). Because C/F increased, the rise in CD cannot be explained by fibre shrinkage alone; it reflects true angiogenesis — the addition of new capillary segments. Capillary contacts per fibre also increased. The magnitude of angiogenesis in this glycolytic muscle is notable given earlier findings that TA shows smaller responses than soleus at milder hypoxia (10). The more severe (10% vs. 12% O2) and sustained (28-day) stimulus used here likely crossed the threshold for TA angiogenesis, consistent with dose–response expectations for HIF–VEGF signalling.

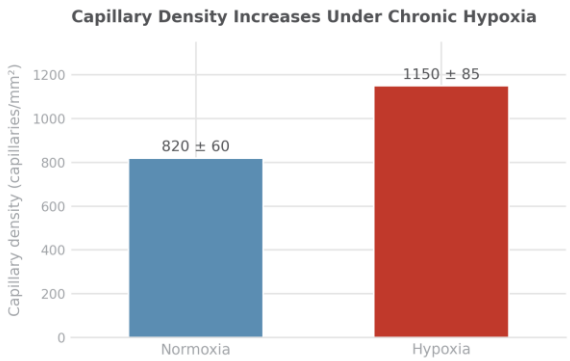


Figure 1: Capillary density in normoxia vs. chronic hypoxia.

Legend: Capillary density (CD31-positive profiles per mm²) increased by ~40% after 28 days at 10% O2 ($p < 0.01$). Data are mean ± SD, n = 10 per group.

Table 2: Summary of principal histomorphometric outcomes.

Variable	Normoxia (mean ± SD)	Hypoxia (mean ± SD)	Change	p-value
Fibre CSA, Type IIb (µm²)	3,650 ± 210	2,990 ± 195	−18%	<0.05
Capillary density (per mm²)	820 ± 60	1,150 ± 85	+40%	<0.01
Capillary-to-fibre ratio	1.34 ± 0.09	1.78 ± 0.12	+33%	<0.01
Collagen volume fraction (%)	3.2 ± 0.4	6.4 ± 0.8	+100%	<0.05
Basement membrane thickness (µm)	0.42 ± 0.05	0.61 ± 0.07	+45%	<0.05

Note: Values are mean ± SD, n = 10 per group. p-values from independent-samples t-tests. Collagen volume fraction is interstitial type IV collagen area as % of field area.

4.4 EXTRACELLULAR MATRIX AND BASEMENT MEMBRANE

Interstitial collagen volume fraction doubled in hypoxia (6.4% ± 0.8% vs. 3.2% ± 0.4%; $p < 0.05$), with deposition concentrated in the endomysium around capillaries and between myofibres. Masson's trichrome confirmed increased perivascular and interstitial collagen. Capillary basement-membrane thickness increased by ~45% (0.61 ± 0.07 µm vs. 0.42 ± 0.05 µm; $p < 0.05$). Figure 3 summarises the ECM changes. The co-existence of angiogenesis and ECM accumulation suggests that matrix deposition accompanies, and may scaffold, new vessel formation, but also thickens the barrier that oxygen must cross.

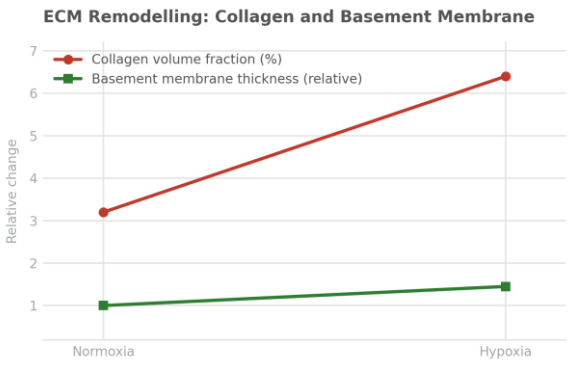


Figure 3: Extracellular matrix remodelling.

Legend: Collagen volume fraction doubled and basement-membrane thickness increased by ~45% after chronic hypoxia. The red line shows collagen volume fraction (%); the green line shows basement-membrane thickness normalised to normoxia (=1.0).

4.5 INTEGRATED DIFFUSION INTERPRETATION

When the three changes are considered together — smaller IIb fibres, more capillaries per fibre, and thicker ECM — the net effect on diffusion is not obvious from any single index. A simplified calculation illustrates the trade-off: reducing fibre radius by ~10% (corresponding to ~18% CSA loss for a circular fibre) reduces maximal diffusion distance by a similar proportion, while increasing C/F by 33% reduces inter-capillary distance. These two changes outweigh, in geometric terms, a 0.19 µm increase in basement-membrane thickness, which is small relative to typical inter-capillary distances (20–40 µm). The interstitium therefore becomes more densely vascularised and slightly more matrix-rich, but the dominant geometric effect favours oxygen delivery. This interpretation is summarised conceptually in Figure 4.

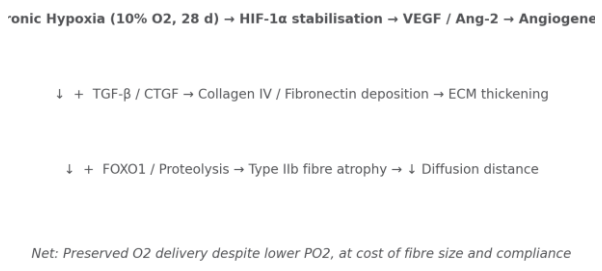


Figure 4: Conceptual model of interstitial remodelling.

Legend: Chronic hypoxia activates parallel HIF, TGF-β/CTGF and FOXO1 programmes that together produce angiogenesis, ECM deposition and fibre atrophy. Net effect: preserved oxygen transport at the cost of fibre size and compliance. This is a schematic synthesis, not a direct measurement.

5. DISCUSSION

5.1 SELECTIVE ATROPHY AS ADAPTATION

The selective atrophy of type IIb fibres observed here replicates and extends prior work in rats and mice (14,15,31). Why IIb fibres? Three non-exclusive explanations are plausible. First, IIb fibres are the largest, so they have the longest diffusion distances and the greatest benefit from shrinkage. Second, they have the lowest capillary supply per unit volume at baseline, making them most vulnerable to reduced PO2. Third, their proteolytic machinery may be more responsive to FOXO1 and hypoxia-induced oxidative stress (29,31). From an evolutionary perspective, sacrificing peak power (IIb-dependent) to preserve endurance and oxygenation during prolonged hypoxia is a plausible trade-off, mirrored in high-altitude natives and in COPD patients who shift toward more oxidative phenotypes (27,32). Clinically, however, IIb atrophy contributes to weakness and reduced exercise capacity, so the adaptation is double-edged.

5.2 TRUE ANGIOGENESIS VS. APPARENT DENSITY

A persistent methodological pitfall in muscle capillary studies is conflating CD with angiogenesis. Because CD is a density, it rises whenever fibres shrink, even if no new capillaries form. The present study avoids that pitfall by reporting C/F alongside CD and showing that both rose. This aligns with the 6-week rat study in which hypoxia increased C/F in all muscles (16) and with human altitude studies in which capillary contacts per fibre were maintained or increased after accounting for fibre size (8). The finding that TA — a glycolytic muscle — can undergo angiogenesis under sufficiently severe hypoxia refines the earlier view that TA is relatively resistant; resistance is dose-dependent, not absolute. Future work should use 3D imaging or serial sections to confirm that increased C/F reflects longitudinal capillary growth and branching, not merely transverse sectioning artefacts.

5.3 ECM: SCAFFOLD AND BARRIER

Doubling of collagen volume fraction is substantial and warrants careful interpretation. On one hand, ECM is required for angiogenesis: endothelial sprouts need a provisional matrix, pericytes need adhesion sites, and new vessels need mechanical stabilisation (25,36). Collagen IV, in particular, is a basement-membrane constituent that supports endothelial survival. On the other hand, excess collagen increases passive stiffness, may impair lateral force transmission, and can impede satellite-cell migration and repair (39). In chronic disease, hypoxia–TGF-β synergy drives progressive fibrosis that outlasts the hypoxic stimulus (37,38). Whether the ECM changes seen at 28 days are reversible on return to normoxia is therefore a critical unanswered question. A reoxygenation arm, with serial biopsies, would distinguish adaptive matrix turnover from incipient fibrosis. Similarly, distinguishing collagen subtypes (I vs. III vs. IV vs. VI) and cross-linking would clarify mechanical consequences.

5.4 CLINICAL AND TRANSLATIONAL IMPLICATIONS

The interstitial triad — atrophy, angiogenesis, matrix deposition — has direct relevance to several clinical contexts. In COPD, chronic hypoxaemia, systemic inflammation and disuse converge to produce muscle wasting and exercise intolerance; preserving capillary supply while limiting fibrosis could improve rehabilitation outcomes (5,27). In high-altitude medicine, understanding the time-course of TA remodelling informs acclimatisation and return-to-play guidance. In peripheral artery disease and diabetic microangiopathy, where capillary basement-membrane thickening is already present, superimposed hypoxia may accelerate ECM accumulation and impair diffusion, suggesting that therapies targeting TGF-β/CTGF or HIF–VEGF balance need to be timed carefully (40). Exercise training, which itself induces angiogenesis via VEGF and shear stress, may synergise with hypoxia (e.g., ‘live high, train low’ paradigms) but also risks exacerbating matrix deposition if hypoxia is excessive (44). Any translational

application must therefore balance pro-angiogenic and anti-fibrotic goals.

5.5 LIMITATIONS

Several limitations should be noted. First, the study used a single muscle (TA), a single sex (male), a single strain, and a single time-point (28 days); generalisation to other muscles, females, aged animals or longer exposures requires caution. Second, molecular mediators (HIF-1α, VEGF, TGF-β, FOXO1) were inferred from the literature rather than measured directly in this cohort; future work should quantify protein and mRNA levels and correlate them with morphometry. Third, functional outcomes (grip strength, treadmill endurance, in vivo PO2, blood flow) were not measured, so the diffusion interpretation remains geometric rather than physiological. Fourth, basement-membrane thickness was measured by light microscopy, which has lower resolution than electron microscopy; EM would provide more precise estimates. Finally, the normobaric chamber model, while controlled, does not fully replicate hypobaric altitude or the intermittent hypoxia of sleep apnoea.

6. CONCLUSION

Twenty-eight days of chronic normobaric hypoxia (10% O2) remodelled the murine TA interstitium in three coordinated ways: selective atrophy of type IIb fibres, true angiogenesis evidenced by increased capillary-to-fibre ratio, and doubling of interstitial collagen with thickening of the capillary basement membrane. Together, these changes preserve the geometric conditions for oxygen diffusion despite low ambient PO2, at the cost of reduced fibre volume and increased matrix. The interstitium emerges not as passive packing material but as an active, adaptive compartment that negotiates the trade-off between oxygen delivery, force production and tissue mechanics. Understanding the molecular switches that tilt this balance toward functional angiogenesis and away from fibrosis is a priority for muscle physiology, altitude medicine and chronic respiratory disease.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

F.K.G. conceived the study, performed histology and morphometry, and drafted the manuscript. L.A.R. supervised the study, analysed data, and revised the manuscript. Both authors approved the final version.

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