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Reframing Skeletal Muscle Angiogenesis: A Determinant, Not a Consequence, of Hypertrophic Adaptation to Resistance Training

Lily D. Bauman, BSc Student [1]*

[1] Department of Kinesiology, McMaster University, Hamilton, ON, Canada L8S 4L8

*Corresponding Author: lilybauman04@gmail.com

Abstract

Introduction: Exercise-induced skeletal muscle angiogenesis is governed by regulators such as vascular endothelial growth factor (VEGF) and thrombospondin 1 (TSP-1) and is classically attributed to aerobic training. While aerobic exercise is well established as a key driver of capillary adaptation, the purpose of capillary expansion during resistance training remains unclear. This review evaluates angiogenic regulation and evaluates whether vascular remodeling functions as a permissive, active contributor to muscle hypertrophy.

Methods: Literature was identified through PubMed, Scopus, and Google Scholar using terms related to skeletal muscle angiogenesis, resistance exercise, VEGF, and TSP-1with studies from 2015 onward prioritized alongside key seminal papers. As a narrative review, studies were selected for relevance to the research objectives rather than predefined inclusion criteria, allowing a comprehensive synthesis of mechanisms underlying vascular adaptation.

Results: Endurance exercise stimulates angiogenesis through mechanical and metabolic signals, with myofiber-derived VEGF acting as the essential driver of endothelial activation and capillary growth. This response is shaped by fiber-type hypoxia, endothelial metabolism, and the VEGF and TSP-1 balance. Resistance exercise also engages VEGF-dependent pathways, and myofiber-specific VEGF deletion demonstrates that preserving the capillary network is necessary for full hypertrophic adaptation. Angiogenesis can precede or scale with muscle growth, and baseline capillarization strongly predicts hypertrophic potential, indicating that vascular remodeling functions as a permissive mechanism supporting adaptation.

Discussion: Detraining rapidly shifts muscle toward an anti-angiogenic state, with early suppression of VEGF and increases in TSP-1 preceding controlled, partially reversible capillary rarefaction. Aging further limits angiogenic potential by reducing baseline capillarization and blunting VEGF responsiveness, producing a vasculature that is less plastic and less capable of supporting hypertrophic adaptation. Metabolic conditions such as obesity also disrupt this balance, as elevated TSP-1 creates an inhibitory endothelial environment even when VEGF expression is preserved.

Conclusion: Overall, the literature shows that skeletal muscle capillarization is essential for functional adaptation, that VEGF and TSP-1 signalling governs exercise-induced angiogenesis, and that vascular expansion acts as a permissive driver of hypertrophy, a relationship that persists across detraining, aging, and obesity.

Keywords: skeletal muscle; angiogenesis; resistance training; hypertrophy

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Introduction

Accounting for roughly 40% of total body mass, the skeletal muscle tissue is tightly linked to overall body health and physical well-being [1, 2]. Skeletal muscle is needed for a wide range of contractile activities ranging from postural balance and respiration to explosive movements during sprinting exercise [3]. Moreover, beyond contractions the skeletal muscle largely influences whole-body metabolic homeostasis, thermoregulation, as well as organ communication via myokines [2, 4, 5]. The skeletal muscle is a highly perfused tissue with an expansive microvascular network. Indeed, numerous capillaries efficiently intercalate between myofibers and as function follows structure, these capillaries are required for the efficient exchange of substrates and metabolites between the myofiber and blood [6, 7]. Therefore, capillaries can be seen as key determinants of skeletal muscle health and in turn, whole body health.

Skeletal muscle angiogenesis, the growth of novel capillary blood vessels, is a well-described physiological response to exercise training [8, 9]. As the capillary network expands, the ability of these conduits to meet the myofiber's metabolic demand improves, thus enhancing the overall functional capacity of the tissue. Classically, the histological parameters of capillary-to-fiber ratio (C:F) and capillary density (CD) serve as indicators of an angiogenic response to training in the skeletal muscle, however, these two parameters are not synonymous [6, 7, 10]. C:F solely reflects the number of capillaries surrounding a myofiber and therefore, increased C:F is the only true indicator of neo-vessel growth in the tissue (angiogenesis). In contrast, CD provides greater information regarding the level of perfusion and oxygen flux to the tissue. Yet, CD can be largely influenced by myofiber cross-sectional area (FCSA) and is thus subject to change in instances such as muscle hypertrophy or atrophy.

Within this context, this review will aim to address a poignant question regarding the skeletal muscle angiogenic response to resistance exercise training. Mainly, whether the angiogenic response (increased C:F) to resistance exercise occurs to improve tissue oxygenation (increased CD) or to maintain a baseline diffusion gradient (no change in CD) that exists prior to training. In doing so, this review will: (1) Briefly summarize the molecular mechanisms that facilitate muscle angiogenesis; (2) Describe how these mechanisms are affected by resistance training and if they result in outcome tissular adaptations; and (3) Explore a new paradigm in which the skeletal muscle angiogenic response is not a passive "passenger" but rather an active "driver" of the hypertrophic response to resistance training.

Methods

To address the three objectives outlined in the introduction, relevant literature was identified through searches conducted in PubMed, Scopus, and Google Scholar using terms related to skeletal muscle angiogenesis, resistance exercise, vascular endothelial growth factor (VEGF), and thrombospondin-1 (TSP-1). Both human and preclinical animal studies were included to integrate mechanistic and translational evidence. No formal language restrictions were applied; however, all included studies were available in English. A total of 37 articles were included in the final synthesis, comprising 27 original experimental studies and 10 review or conceptual papers relevant to the field. Articles published from 2015 onward were prioritized, with exceptions made for seminal studies foundational to the field. Because this review was designed as a narrative and perspective-based synthesis rather than a systematic review, studies were selected based on their relevance to the specific scientific questions rather than predefined inclusion criteria. This approach allowed for a comprehensive yet unbiased integration of key findings, while acknowledging that some manuscripts were not included due to the non-systematic nature of the review.

Results

Mechanisms of Skeletal Muscle Angiogenesis: What do we know from Endurance Exercise Training?

Capillaries are integral to matching the metabolic demands of the myofiber during contractile activity. It surmises therefore, that the myofiber itself may serve as a key-mediator for promoting an angiogenic response. Among a plethora of angiogenic factors, the most potent and well-described is Vascular endothelial growth factor-A (VEGFA) [11]. Indeed, the myofiber is a rich source of VEGFA and actively produces and releases the factor into the muscle interstitial space during contractile activity [12–15]. This myofiber-derived VEGFA can then act on neighbouring skeletal muscle endothelial cells, the main cellular components of capillaries, stimulating their migration, proliferation and formation into complete vascular tubes [11]. In animal models, particularly transgenic mouse models, VEGFA has been shown to be indispensable for exercise-induced angiogenesis. Olfert and colleagues (2010) elegantly supported the important and non-redundant role of VEGFA in skeletal muscle angiogenesis using myocyte specific VEGFA knockout mice (-mVEGF) [16]. Whereas wildtype (WT) animals had an angiogenic response following 6-weeks of treadmill running, no such effect was observed in -mVEGF animals. Additionally, despite having greater levels of oxidative enzymes, -mVEGF performed poorer on treadmill run to exhaustion tests in comparison to WT littermates, further supporting the notion of a dense vascular network being critical to skeletal muscle functional capacity.

Although pro-angiogenic factors are key to capillary formation they are only half of the "balance" that dictate neovessel growth [17]. In rodent models, besides VEGFA, another key regulator of angiogenesis is the endogenous inhibitor TSP-1, which is well recognized for limiting physiological and pathological angiogenesis [17]. For instance, global deletion of TSP-1 increases skeletal and cardiac muscle capillarization concomitant with improvements in exercise capacity [18]. In the context of exercise, TSP-1 is substantially upregulated after a single bout of treadmill running but suppressed with repeated training [19]. This temporary increase may reflect a stress-responsive anti-angiogenic signal that restrains excessive vascular growth immediately after exercise. With chronic endurance exercise, this suppression of TSP-1 permits angiogenesis to proceed. After long-term training, however, TSP-1 expression again rises in response to acute bouts, suggesting a dynamic regulatory reset that stabilizes the expanded capillary network once angiogenesis has occurred [19, 20]. While these molecular systems determine whether angiogenesis proceeds, its magnitude and distribution within the muscle depend on local metabolic and fiber-specific factors.

In rodent endurance models, upregulation of VEGF after exercise is not uniform throughout the muscle but displays clear fiber-type specificity [12]. For instance, VEGF production occurs predominantly in fast glycolytic IIb fibers, which have low oxidative potential and are most susceptible to local hypoxia. Indeed, these fibers have the fewest capillaries, making them particularly prone to oxygen diffusion limitations that stimulate VEGF gene expression [12]. This is non-surprising considering that VEGF transcription is largely governed by the hypoxia-inducible factor 1 (HIF1) signalling pathway [21]. Aligned with this, contractile activity induces a local hypoxic environment in the myofiber as partial pressure of oxygen levels can be rapidly reduced by ~10-fold to 5 mmHg [10].

In humans, work from Ameln and colleagues has supported this hypothesis by demonstrating exercise alone to induce HIF-1α stabilization and VEGF transcription in human vastus lateralis [12]. With respect to tissular adaptations in rodent models, the localized VEGF production promotes early capillary growth around type IIb fibers, which may create the metabolic environment necessary for their subsequent transition to more oxidative type IIa fibers [9]. Collectively, these findings suggest that type IIb fibers form angiogenic ‘hot spots’ within skeletal muscle, where localized VEGF signaling initiates capillary growth that precedes fiber type transitions [9, 13].

Beyond the myofiber, rodent skeletal muscle angiogenesis is also largely dictated by the endothelial cells and their metabolism which is influenced by regional heterogeneity to different myofiber contractile phenotypes [22]. The inhibition of glycolysis or mitochondrial respiration in endothelial cells abolishes an angiogenic response [23, 24]. In the context of skeletal muscle, this is despite preserving muscle contractions and VEGF expression [22–24]. This confirms that metabolic activity within the endothelium is essential for angiogenesis, emphasizing that the endothelium actively contributes rather than relying solely on external stimuli. Interestingly, the endothelium is also the primary source of TSP-1 produced during exercise. Forkhead box O (FOXO) transcription factors regulate anti-angiogenic gene expression and are necessary for exercise-induced TSP-1 production, as endothelial-specific deletion of FOXO prevents TSP-1 induction [20].

Finally, with exercise as a modulator of the angiogenic response, intensity also plays a key role. In human endurance training studies, high-intensity endurance exercise rapidly stimulates angiogenesis in both type I and type II fibers, whereas lower-intensity exercise elicits a smaller or no response [15]. These findings indicate that the activation of pro-angiogenic signalling pathways and the resulting capillary growth are intensity dependent [15]. Collectively, these findings illustrate that endurance exercise stimulates angiogenesis through an integrated network of mechanical, metabolic, and molecular pathways whose activation depends on both local oxygen stress and exercise intensity.

VEGFA and TSP-1, Recurrent Players in the Angiogenic Response to Resistance Training

While endurance exercise has classically been considered the primary driver of skeletal muscle angiogenesis, resistance training also promotes vascular remodeling through distinct but overlapping mechanisms. A single bout of resistance exercise in human studies increases the expression of muscle angiogenic growth factors, including VEGF, demonstrating that pro-angiogenic signaling can be induced without endurance-type loading [25]. Mice studies have shown that myofiber VEGF is also necessary for muscle hypertrophy during resistance exercise, highlighting its role in angiogenesis beyond endurance training contexts. In the absence of myofiber VEGF, hypertrophic adaptation is blunted due to capillary rarefaction, demonstrating that VEGF remains the central driver of angiogenic remodeling even under mechanical overload [26]. By preserving the capillary network, VEGF works as a permissive factor, maintaining the vascular infrastructure necessary to deliver oxygen and nutrients that sustain muscle hypertrophy and contractile performance [26].

Although VEGF is the predominant pro-angiogenic signal, angiogenesis represents a balance between stimulatory and inhibitory influences. Among the latter, TSP-1 is a well-established anti-angiogenic regulator during endurance exercise in rodent studies but remains largely unexplored in resistance training contexts [17]. Limited evidence suggests that TSP-1 may be dynamically regulated alongside VEGF during recovery from disuse with resistance training in humans [27]. Whether similar regulation occurs in healthy resistance-trained muscle remains unknown, leaving the role of TSP-1 unclarified. Overall, resistance training is a legitimate stimulus for muscle angiogenesis, with VEGF serving as an essential mediator of this adaptation, while the contribution of inhibitory regulators such as TSP-1 requires further investigation.

Beyond Compensation: the Proactive Role of Angiogenesis in Muscle Growth

Angiogenesis and hypertrophy are closely linked processes, with rodent-based evidence suggesting that vascular remodeling often accompanies, or even precedes, muscle fiber growth [28, 29]. Historically, vascular adaptation during resistance training was viewed as a secondary or compensatory mechanism, occurring alongside hypertrophy primarily to preserve capillary supply and oxidative capacity [30]. Indeed, Green and colleagues demonstrated in a human study that twelve weeks of high-load resistance training in untrained men to increase fiber cross-sectional area by roughly 17%, with C:F rising across all fiber types while CD remained unchanged [30]. At the time, these findings were interpreted as evidence that capillarization kept pace with muscle growth to maintain oxygen diffusion. Subsequent research, however, has shifted this perspective, indicating that angiogenesis may play a proactive rather than passive role in this hypertrophic process [28, 29]. VEGF expression in rats rises before measurable increases in muscle fiber size, demonstrating that endothelial signaling is initiated early in the hypertrophic response [28]. This early VEGF upregulation likely serves as a preparatory signal for subsequent vascular and myogenic remodeling [28].

In experimental rodent models the relative changes in C:F and/or CD helps distinguish whether vascular remodelling merely maintains or improves oxygen diffusion to the myofiber. For instance, mice performing four weeks of voluntary wheel running exercise have doubled CD in the plantaris muscle and increased C:F from roughly 0.95 to 1.7 [9]. The concurrent rise in both measures indicates true neovascularization and an enhanced capacity for oxygen delivery, representing a functional expansion of the vascular network beyond simple maintenance. Furthermore, this angiogenic response and the increase in the number of capillary-fiber contacts preceded the transition of type IIb to type IIa fibers. Thus, these early findings lended initial support to the notion that skeletal muscle capillaries may promote active remodelling of the myofiber itself.

More recently, in a human resistance training study, older men undergoing twenty-four weeks of progressive resistance training, participants with higher baseline type II fiber capillarization, reflected by greater capillary-to-fiber perimeter exchange index (CFPE), showed significant hypertrophy [31]. Those with lower baseline capillarization exhibited minimal muscle growth despite identical training. In these individuals, capillary number increased only proportionally to fiber enlargement, keeping CD and diffusion capacity stable. Without sufficient vascular support, resistance training failed to induce significant fiber growth, reflecting a maintenance response in which angiogenesis merely matched hypertrophy without improving oxygen delivery per unit area. These human-based findings illustrate that adequate angiogenesis is not only a concurrent adaptation but may be necessary to facilitate and sustain muscle growth in addition to fiber-type transition.

The importance of maintaining adequate capillarization for supporting muscle fiber growth has long been recognized [29]. Early resistance training studies in rodents demonstrated that during the initial weeks of hypertrophy, capillary and muscle fiber growth progress in parallel; however, by roughly one month, capillary proliferation begins to lag behind fiber growth. This discrepancy suggested that vascular expansion could become a rate-limiting factor governing the capacity of skeletal muscle to sustain continued growth and metabolic function [29]. Indeed the recent work of Snijders et al. (2017), builds on these early observations by demonstrating in humans that insufficient baseline capillarization constrains hypertrophic potential, linking early mechanistic findings to contemporary evidence [31].

In human studies, angiogenesis therefore appears to be not only an oxidative adaptation but also an anabolic-supportive process. In young women, testosterone administration led to microvascular expansion in parallel with hypertrophy, suggesting that vascular remodeling may facilitate muscle growth under anabolic stimulation [32]. Consistent with this, individuals with greater baseline microvascular perfusion capacity, reflected by higher type II fiber CFPE, demonstrated greater fiber hypertrophy following resistance training [33]. These results emphasize that superior perfusion supports a stronger hypertrophic response by improving the delivery of oxygen, nutrients, and anabolic hormones to active fibers. Similar findings in older adults show that only individuals with higher initial CFPE exhibit substantial gains in muscle mass and fiber size, whereas those with low baseline capillarization primarily undergo angiogenesis without measurable hypertrophy [34]. Together, these human-based findings highlight that angiogenesis is not a mere byproduct of hypertrophy but a prerequisite that enables, yet ultimately constrains, muscle growth.

Vascular Remodeling to Sustain the Hypertrophic Microenvironment

Having established that angiogenesis and hypertrophy occur concurrently [28–31], the next question is why skeletal muscle elicits this response under predominantly anaerobic resistance exercise conditions, which are not classically oxidative. This likely occurs because angiogenesis expands the supply capacity, not only for oxygen, but also for metabolites, growth factors, hormones, and signaling molecules required for regeneration and fiber enlargement [6, 7]. The angiogenic response supports metabolic clearance, helping to buffer local lactate accumulation and redistribute substrates between oxidative and glycolytic regions, while also facilitating intercellular communication within the muscle [6, 35]. In mouse models, lactate itself acts as a signaling molecule that recruits and reprograms immune cells, establishing an environment that facilitates hypertrophy and tissue remodeling [35]. Collectively, these studies indicate that microvascular capacity determines hypertrophic potential by sustaining the metabolic and signaling environment necessary for muscle growth.

Discussion

While resistance exercise is known to elicit angiogenesis, we can also gain valuable insight into the mechanisms of vascular adaptation by examining instances of myofiber atrophy in humans such as during detraining or bedrest. A study by McIntosh and colleagues found that during two weeks of limb immobilization, the pro-angiogenic signal VEGF fell significantly, while the angiogenesis inhibitor TSP-1 increased, reflecting an early shift toward an anti-angiogenic environment [27]. Although capillary rarefaction was not yet evident, these molecular changes suggest that disuse triggers early suppression of endothelial signaling that may precede vascular regression. Extending this timeline, Hendrickse and colleagues (2022) demonstrated that prolonged inactivity produces vascular rarefaction proportional to muscle fiber atrophy within the first week [36]. However, capillary number stabilizes after 55 days, even as fibers continue to atrophy slightly and oxidative capacity declines considerably. This leaves a surplus of capillary supply compared to oxidative capacity, preserving a vascular scaffold that can support recovery once activity resumes [36]. Together, these human findings suggest that capillary rarefaction during deconditioning is not simply regressive, but rather a controlled, reversible response that emphasizes the resilience of the endothelial network.

In terms of the angiogenic response to resistance exercise in humans, age-related differences are evident. Older men exhibit reduced baseline VEGF protein and mRNA expression, along with a blunted exercise-induced upregulation of VEGF [25]. Even after training, increases in C:F remain lower overall compared to younger adults [25]. These findings suggest that aging is associated with reduced endothelial plasticity, limiting the capacity for vascular remodeling even under the same exercise stimulus. Aging is also accompanied by capillary rarefaction, reflected in reduced CD and C:F [34]. In Moro and colleagues' study, capillary rarefaction was paralleled by reduced oxidative capacity, indicating that vascular decline may precede or exacerbate muscle deterioration rather than merely reflecting it [34]. Together, these findings suggest that aging impairs both the signaling and structural components of angiogenesis, producing a vasculature that is less responsive to exercise stimuli and has a reduced capacity to sustain muscle quality over time.

Metabolic conditions such as obesity disrupt the angiogenic balance within human skeletal muscle by altering the relationship between pro- and anti-angiogenic signals. Obesity alters the angiogenic environment of skeletal muscle by disrupting the balance between pro- and anti-angiogenic signals [37]. In a study by Garner and colleagues (2022), individuals with obesity exhibited a greater increase in TSP-1 compared to healthy controls, while both groups showed similar VEGF mRNA increases, indicating a shift toward inhibition of angiogenesis [37].

Conclusions

Skeletal muscle capillarization is fundamental to supporting muscle function, and exercise training reliably elicits an angiogenic response that expands the vascular network required for efficient perfusion and metabolic exchange. From the literature, it is clear that this response is governed by a balance between the pro-angiogenic influence of VEGF and the inhibitory regulation of TSP-1 across both endurance and resistance training contexts. Based on the findings, the literature supports that capillary expansion occurs because muscle fiber hypertrophy requires enhanced endothelial support to sustain structural remodeling, indicating that angiogenesis functions as a permissive, rather than merely reactive, mechanism that enables contractile adaptation rather than simply maintaining basal capillarization. Finally, evidence from detraining, aging, and metabolic conditions like obesity shows that this coupling between vascular supply and muscle phenotype is preserved across diverse physiological states, highlighting the resilience and necessity of the angiogenesis-hypertrophy relationship.

List of Abbreviations

C:F: capillary-to-fiber ratio
CD: capillary density
CFPE: capillary-to-fiber perimeter exchange index
FCSA: fiber cross-sectional area
FOXO: forkhead box O
HIF-1α / HIF1: hypoxia-inducible factor 1-alpha
-mVEGF: myocyte specific vascular endothelial growth factor a knockout mice
TSP-1: thrombospondin-1
VEGF / VEGFA: vascular endothelial growth factor A
WT: wild type

Conflicts of Interest

The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This manuscript did not require research ethics board approval or participant consent because it is a narrative review that synthesizes previously published studies and does not involve human participants or the collection of new data.

Author's Contributions

LDB: made substantial contributions to the conception and design of the review, conducted the literature search and analysis, drafted and revised the manuscript, and approved the final version for publication while agreeing to be accountable for all aspects of the work.

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