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Computational Network Model Prediction of Hemodynamic Alterations Due to Arteriolar Remodeling in Interval Sprint Trained Skeletal Muscle

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Abstract

Objectives—Exercise training is known to enhance skeletal muscle blood flow capacity, with high-intensity interval sprint training (IST) primarily affecting muscles with a high proportion of fast twitch glycolytic fibers. The objective of this study was to determine the relative contributions of new arteriole formation and luminal arteriolar remodeling to enhanced flow capacity and the impact of these adaptations on local microvascular hemodynamics deep within the muscle.

Methods—The authors studied arteriolar adaptation in the white/mixed-fiber portion of gastrocnemius muscles of IST (6 bouts of running/day; 2.5 min/bout; 60 m/min speed; 15% grade; 4.5 min rest between bouts; 5 training days/wk; 10 wks total) and sedentary (SED) control rats using whole-muscle Microfil casts. Dimensional and topological data were then used to construct a series of computational hemodynamic network models that incorporated physiological red blood cell distributions and hematocrit and diameter dependent apparent viscosities.

Results—In comparison to SED controls, IST elicited a significant increase in arterioles/order in the 3A through 6A generations. Predicted IST and SED flows through the 2A generation agreed closely with in vivo measurements made in a previous study, illustrating the accuracy of the model. IST shifted the bulk of the pressure drop across the network from the 3As to the 4As and 5As, and flow capacity increased from 0.7 mL/min in SED to 1.5 mL/min in IST when a driving pressure of 80 mmHg was applied.

Conclusions—The primary adaptation to IST is an increase in arterioles in the 3A through 6A generations, which, in turn, creates an approximate doubling of flow capacity and a deeper penetration of high pressure into the arteriolar network.

Keywords

angiogenesis; arteriogenesis; exercise training; microcirculation; network model

The purpose of this study was to use a computational network model to examine mechanisms responsible for the increased blood flow capacity we previously reported in white and mixed gastrocnemius skeletal muscle of rats following interval sprint exercise training (high speed, uphill running) (3,10). These previous studies indicate that white and mixed gastrocnemius

muscle of rats trained with this protocol exhibit the largest relative increases in oxidative capacity (10), capillary density (6), and blood flow capacity of the extensor muscles examined in rats (15,28,29). The increased blood flow capacity of white and mixed gastrocnemius muscle does not appear to be mediated solely by increased capillarization (6,29). Based on these previous observations, the focus of the present study was to evaluate the hypothesis that changes in control of vascular resistance and/or increases in the number and/or size of resistance arteries are responsible for these increases in skeletal muscle blood flow capacity (14).

There is evidence that vascular structure and function is matched to muscle fiber characteristics within skeletal muscle (2,7,9,12,14,16). Therefore it seems reasonable to propose that fiber-type related differences in skeletal muscle interact with muscle fiber recruitment patterns during exercise so that the distribution and type of adaptive changes induced by training vary with the type of training performed. Understanding the different strategies for vascular adaptation in skeletal muscle composed of different fiber types requires an appreciation of changes in arterialization and arteriolar density produced by training. Since increases in blood flow capacity cannot be fully explained from changes in capillarity or known changes in control of vascular resistance, we propose that exercise training stimulates arteriogenesis and/or remodeling (5,6,9,15,29). Here, we used computational hemodynamic models of realistic arteriolar networks in specific muscles of sedentary and trained animals to determine the relative importance of structural arteriolar adaptations to changes in blood flow capacity. The results indicate that the primary adaptation to IST is an increase in 3A–6A arterioles, which, in turn, creates an approximate doubling of flow capacity and a deeper penetration of high pressure into the arteriolar network.

EXPERIMENTAL MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (final weight 441 ± 7 g) were obtained from Harlan in groups of 25. Rats were 6 weeks of age when purchased. Rats were ideal for these studies due to the fact that the different types of skeletal muscle fibers are distributed in a highly stratified manner throughout their limbs, thereby facilitating the analysis of selected properties by muscle fiber type composition. Veterinary care was provided by the Office of Animal Resources (OAR) and the College of Veterinary Medicine faculty at the University of Missouri. Animals were observed daily by the OAR staff and housed in pairs in temperature (24°C) and light (12:12-h light:dark) controlled rooms. Rat chow and water were available ad libitum. Treadmill training was performed by highly motivated veterinary or preveterinary students who insured that the rats received proper care. All procedures and animal care fulfilled the *Principles for Use of Animals* and the *Guide for the Care and Use of Laboratory Animals* as approved by the Institutional Animal Care and Use Committee of the University of Missouri.

Experimental Design

We used an interval sprint training (IST) program that increases activity in low-oxidative (FG) white and mixed fast-twitch-oxidative (FOG) and FG gastrocnemius muscle tissue. We used sets of 2 groups of rats: IST and sedentary (SED). At the end of the training programs the rats were anesthetized and the muscle tissue was flushed and perfused with Microfil and processed as described below.

Interval-Sprint Training Program—One to two weeks following delivery from the breeder, 25 rats began a pretraining protocol in which they ran for 5–10 min, 5 days/week at a speed of 30 m/min, 0 incline. After 2 weeks the 5 rats that did not easily adapt to treadmill exercise were removed from the study, and the remaining 20 rats were randomly divided into SED and IST groups, with 10 rats in each group. Following the 2 week pretraining protocol,

the SED group was restricted to cages while the IST group continued the training program. The duration of running and treadmill grade were gradually increased until by 3–4 weeks the rats were able to perform 6 alternating bouts of 2.5 min running at 60 m/min, up a 15% grade, with 4.5 min rest between bouts for 5 days/week. The IST rats continued training at this intensity until the time of study (total training time of 10–12 weeks). This training program has been demonstrated to produce increases in oxidative capacity, blood flow capacity, and capillarity in FG extensor muscles (6,15,29,30).

Citrate Synthase Assay—After euthanasia, samples of triceps brachii muscle were sampled. Muscle samples were frozen in liquid N₂ and stored at –70°C until processed. Citrate synthase activity was measured from whole muscle homogenate using the spectrophotometric method of Srere (30).

Vascular Casting Techniques—Rats were anesthetized with pentobarbital sodium (65 mg/kg IP). A modification of the techniques described by Williams and Segal (32) was used. The femoral artery and vein were cannulated with PE 50 catheters in an anesthetized rat. The limb was fixed at a 90-degree angle at the ankle. Locke's solution, with 0.058% procaine added, was infused into the artery to flush blood from the vasculature. Microfil casting compound (Canton Gio-medical Products, Boulder, CO) was infused through the artery at a pressure of 150 mmHg. Pressure was maintained until the Microfil had polymerized. After 24–72 h the leg muscles were removed and dehydrated progressively in 25, 50, 75, 95, and 100% ethyl alcohol (24 h each solution). The muscles were then cleared by immersion and storage in methyl salicylate. The casts were viewed with a stereo microscope and images of the networks drawn and captured in photomicrographs.

The numbers and dimensions of the branching arteriolar networks were measured and compared among groups. Data were collected from a 5 × 5 × 1-mm section of muscle tissue. We first traced the arterial tree through the various focal planes in the tissue section. Then, we worked through the tissue section recording the branch order, diameter, and length of all the arterioles in the section. Branch orders were assigned using a centrifugal system in which a parent arteriole of order N gives rise to smaller diameter daughter arterioles of order $N + 1$. Branch order classification began by assigning order “1” to the arteriole that is supplied by the feed arteriole and denoted with an arrow in Figure 1A. Following analysis of the 5 × 5 × 1-mm section of tissue, the total number of 2A arterioles in the entire mixed-fiber portion of the muscle was determined and later used to scale computational predictions of flow per 2A arteriole into total muscle flow.

COMPUTATIONAL METHODS

Network Model Dimensions and Topology

Computational network models were generated from the topological and dimensional data presented in Figure 1 using a tree-building algorithm. Ten different network topologies were generated for each group using this algorithm. For each individual network, the total number of arterioles per branch order matched the mean values presented in Figure 1B; however, topological variability between the networks was created by pseudo-randomly altering the number of daughter branches arising from each parent arteriole. Networks had a single input at the 2A arteriole level and multiple outputs, all at the capillary level. Arteriolar diameters and lengths within each branch order were assigned pseudo-randomly from a normal distribution such that the means and standard deviations matched those shown in Figure 1C and D, respectively, and at each node in the network, downstream branch diameters were less than that of the upstream input arteriole. Because Microfil contracts substantially when it cures, the diameters in Figure 1C had to be increased to accurately reflect a state of maximal

vasodilation during exercise. This adjustment was made by comparing maximal diameters of isolated 2A and 3A gastrocnemius muscle arterioles (please see Figure 7 of Laughlin et al. (17)) to those presented in Figure 1C and assuming that the Microfil exhibits a uniform volume reduction upon curing, even though microfilled arteriolar lengths are held at in vivo values by the tissue structure. Based on these conditions, a scaling factor (S) for comparing microfilled arteriolar

$$S = \frac{d_m^2}{d^2}$$

volume to maximal in vivo arteriolar volume was derived using Equation 1, where d_m is the microfilled diameter and d is the maximal diameter.

Applying this equation to the 2A and 3A branch orders for the SED and IST diameters yielded a value of 0.15 for S , which was then used to convert d_m to d throughout the remaining branch orders in each network.

Network Model Solution

The model solution was initiated by assigning pressures at the input and output boundaries. For the first model iteration, the apparent viscosity of each vessel segment (0) was assigned as 4 cP and discharge hematocrit (H_D) was assigned as 0.45. Arteriole segment conductances C were computed assuming Poiseuille flow (Eq. 2), where D is segment diameter and L is vessel segment length:

$$C = \frac{\pi D^4}{128\eta L}$$

Pressure at each node (P) and flow in each segment (Q) were then determined from the

$$\begin{aligned} \text{logit } \psi &= B \text{logit } \frac{\psi - X_o}{1 - 2X_o} + A \\ \text{where } \text{logit } x &= \ln \frac{x}{1-x} \\ A &= -6.96 \ln \left(\frac{D_1}{D_2} \right) / D \\ B &= 1 + \frac{6.98(1-H_D)}{D} \\ X_o &= \frac{0.4}{D} \end{aligned} \quad (3)$$

matrix equation $CP = Q$ using a subroutine that solves sparse matrices as described in detail elsewhere (21). Q values were used to update H_D values with an experimentally derived red blood cell distribution law (Eq. 3) (27). In this relationship, if P was the flow fraction entering a daughter branch and N was the cell flux entering that same branch, then where D is the diameter of the parent branch and D_1 and D_2 are the daughter branch diameters. Computed H_D values are then used in conjunction with D values to update apparent viscosity (0) using Eq. 4 (25):

$$\eta = \left[1 + (\eta^* - 1) \frac{(1-H_p)^{C-1}}{(1-0.45)^{C-1}} \left(\frac{D}{D-1.1} \right)^2 \right] \times \left(\frac{D}{D-1.1} \right)^2$$

where $\eta^* = 6e^{-0.085D} + 3.2 - 2.44e^{-0.06D^{0.645}}$

$$C = (0.8 + e^{-0.075D}) \left(-1 + \frac{1}{1+10^{-11}D^{12}} \right) + \frac{1}{1+10^{-11}D^{12}}$$
(4)

Equation 4 was adjusted for rat erythrocytes by reducing each D to 84% of its original value (25). The 0 values were then inserted back into Eq. 2 and a new network solution was obtained. This process was repeated until 0 values in each segment were less than 0.02 cP different than they were on the previous iteration.

In studies aimed at comparing model predictions of total flow to those obtained experimentally from isolated hindlimbs that were perfused with Tyrode's solution from the abdominal aorta at 40 mmHg (15), input pressure in the 2A arteriole was assigned as 80% of systemic pressure, or 32 mmHg. A constant viscosity of 1.2 cP was chosen to match the viscosity of the Tyrode's solution perfusate; therefore, the calculations in Eqs. 3 and 4 were omitted. For studies aimed at simulating hemodynamics during exercise, 2A input pressure was assigned as 80% of normal systemic pressure (80 mmHg), while diameter- and discharge hematocrit-dependent viscosities were invoked. Output pressures at the capillaries were assigned as 10 mmHg in all simulations.

Statistics

The experimental data in Figure 1 were analyzed using one-way ANOVA followed by pairwise comparisons with Tukey's t tests. The data in Figure 4A and B were analyzed by two-way ANOVA followed by pairwise comparisons with Tukey's t tests. Data in Figures 2, 3, and 4C were analyzed by unpaired Student's t tests. Significance was assessed at $p < .05$.

RESULTS

Arteriolar Adaptations in IST Gastrocnemius Muscle

IST ($n = 5$) and SED ($n = 5$) gastrocnemius muscles were perfused with Microfil, fixed, and dissected and observed as whole mounts. Figure 1A depicts the view of the deep surface of a microfilled medial head of the gastrocnemius muscle of an IST rat. The portion of the muscle at the top of Figure 1A contains mostly white fibers, the portion of the muscle at the bottom contains mostly red fibers, while the muscle tissue in the middle represents the mixed-fiber portion of gastrocnemius muscle. The 1A arteriole supplying this portion of the muscle is denoted with a yellow arrow. From a $5 \times 5 \times 1$ -mm section of muscle tissue in the center-top portion of the muscle in these specimens, measurements of arterioles per branch order (Figure 1B), mean arteriolar diameter per branch order (Figure 1C), and mean arteriolar length per branch order were derived (Figure 1D). Marked increases in arterioles per branch order were observed for IST muscles in comparison to SED controls at the 3A (6.5-fold), 4A (4-fold), 5A (2.8-fold), and 6A (2.6-fold) vessel generations. No significant differences in mean diameter (Figure 1C) or mean length (Figure 1D) per branch order were observed between IST and SED control.

Network Model Validation

To illustrate the predictive power of the computational network model ($n = 10$ networks for both SED and IST), we simulated an experiment in which flow in the mixed-fiber portion of the gastrocnemius muscle was measured in isolated hindlimbs of IST and SED trained rats that

were perfused with Tyrode's solution at the abdominal aorta (15). Under these conditions, total flow per 2A arteriole in the IST was predicted to increase by 81% over SED control (Figure 2A). To facilitate comparison of these results to experimental values that represented total flow in the mixed fiber portion of the muscle, total flow per 2A arteriole was then scaled by the total number of 2A arterioles per mixed-fiber portion of the muscle (Figure 2B). Unlike the data shown in Figure 1B, which were taken from a small and well-defined region of the muscle, the values shown in Figure 2B represent the total number of 2A arterioles in the entire mixed-fiber portion of the muscle. Furthermore, the total number of 2A arterioles per mixed-fiber portion of the muscle in the IST group was observed to be significantly greater than SED control. Predicted total flows per mixed-fiber muscle portion are then shown in Figure 2C, where they are compared to experimentally derived values, which were derived by multiplying flow per unit muscle mass results from Laughlin et al. (15) with muscle mass results presented in Laughlin and Armstrong (11). Note that the model prediction of total flow in the mixed-fiber gastrocnemius shows excellent agreement with experimental values for both the IST and SED groups.

Network Model Flows Under Exercise Conditions

Predicted flow per 2A arteriole in the mixed-fiber portions of SED and IST gastrocnemius muscles were generated using a 2A input pressure of 80 mmHg, corresponding to 80% of systemic pressure in a typical normotensive rat (100 mmHg). Flow per 2A arteriole in the IST group was significantly increased by 81% over SED control (Figure 3A). When these values were scaled by the total number of 2A arterioles per mixed-fiber portion of muscle (Figure 2B), the resultant total flow per mixed-fiber muscle portion was more than 2-fold greater in the IST group, indicating that the formation of new arterioles in response to interval sprint training exerted a substantial impact on muscle flow capacity.

Network Model Pressures Under Exercise Conditions

As illustrated in Figures 4A and 4B, the addition of new arterioles to the network in response to IST caused a shift in the pressure distribution throughout the network. Significant pressure differences were observed between IST and SED at the 3A, 4A, and 5A arteriolar branch orders and in the 30- to 40- μ m, 40- to 60- μ m, and 60- to 80- μ m diameter ranges, with the network model predicting that IST elicits enhanced intraluminal pressure over SED. The consequences of this pressure shift for the distribution of resistances within network are shown in Figure 4C. In the SED networks, on a branch order basis, the 3A arterioles are responsible for 27% of the total pressure drop across the network, whereas the 5A and 6A arterioles account for only about 13% each. However, with interval sprint training, the percentage of total resistance drop across the 3A arterioles falls significantly to about 10% and the contributions of the 5A and 6A arterioles to total network resistance increases dramatically to 24 and 26%, respectively.

DISCUSSION

Blood flow capacity increases with exercise training; however, changes in flow capacity cannot be fully explained by changes in capillarity or known changes in control of vascular resistance (5,6,9,15,29). Therefore, we hypothesized that IST must stimulate arteriolar remodeling responses that serve to significantly enhance flow capacity during exercise. To test this hypothesis, we measured arteriolar densities and dimensions in mixed-fiber regions of rat gastrocnemius muscles following IST. Although mean arteriole length and diameter per order were unchanged from SED control, increases in arterioles/order were observed at the 3A through 6A level. Computational hemodynamic network models, constructed from these topological and dimensional measurements, predicted that arteriolar remodeling in response to IST elicits a shift in the primary site of vascular resistance from the 3A arterioles to the 5A and 6A arterioles. Importantly, the models also predicted that arteriolar adaptations alone create

blood flow capacity increases that are in close agreement with those measured in vivo. When taken in the context of previous findings which suggest that flow capacity is not coupled to capillarity or changes in vascular control, our results are consistent with the hypothesis that structural arteriolar remodeling is the primary adaptation responsible for enhanced flow capacity in mixed-fiber gastrocnemius muscle with interval sprint training.

Arteriolar Adaptation with Interval Sprint Training

The results presented in Figure 1B show that, in comparison to SED control, statistically significant increases in arterioles per vessel order occur in IST muscles among the relatively large-diameter arterioles in the lower vessel orders. Although measurements of structural arteriolar adaptation at intermediate time points were not made, we can infer the growth processes through which IST networks emerged. We've previously reported that new arteriole formation does not occur through sprouting (19, 22, 23) but instead occurs through the investment of capillaries with smooth muscle or "capillary arterialization." Larger-diameter arterioles are known to form via "arteriogenesis" or the enlargement of an arteriole to a larger diameter (8). To illustrate how an IST network could emerge via capillary arterialization and arteriogenesis, an idealized arteriolar tree from a SED network with experimentally derived branching ratios (i.e., total arterioles in order $(N + 1)$ /total arterioles in order N) is shown in Figure 5A. If the arterioles within each generation undergo a uniform luminal expansion, with some 3A and 4A arteriole diameters increasing to the 2A level, these 3A and 4A arterioles will become reclassified as 2A arterioles and the remaining arterioles will also be reclassified to lower orders. Importantly, this remodeling scheme creates IST branching ratios (Figure 5B) and total arterioles per order (Figure 5C) that, in the <6A vessel orders, are in close agreement with experimental results. Furthermore, because arterioles are increasing in diameter at the same time they are being reclassified into lower vessel orders, it is probable that no changes in mean arteriolar diameter per generation would be observed, an outcome that is also consistent with our experimental results (Figure 1C).

Although the scheme proposed in Figure 5 can account for increases in 3A–5A arterioles, it does not accurately predict branching ratios (Figure 5B) and arterioles per order (Figure 5C) above the 6A level because there are too few >6A arterioles to supply the 5A and 6A vessel orders during reclassification. This indicates that higher order arterioles must be generated *de novo* by another means—presumably capillary arterialization. In support of this hypothesis, the 7A/6A branching ratio is <2 (Figure 5B), which indicates that 6A arterioles supply capillaries and that the 6A order is the lowest capable of expansion via capillary arterialization.

In comparison to a previous study from our group, these results are surprising because we have reported that IST does not increase the total arteriolar density of white gastrocnemius muscle (13). In the previous study, data were collected specifically from the deep portion (red) and superficial portion (white) of the gastrocnemius muscle (13). In the present study, we were able to study a larger amount of muscle tissue because the gastrocnemius muscle is primarily of mixed-fiber type composition. Thus, previous results were from relatively smaller amounts of muscle tissue. Although the present analysis likely includes some data from arteries that perfuse the white muscle, the predominance is from mixed-fiber type muscle tissue. We would not necessarily expect the white and mixed-fiber type muscle of the gastrocnemius muscle to exhibit the same adaptations. Thus, it is possible that mixed muscle exhibits an increased arteriolar density in the branch orders (Figure 1), while the white gastrocnemius muscle examined in the previous study does not. On the other hand, if the arteriolar tree in white and mixed gastrocnemius muscle responds to IST similarly, these results suggest that arteriolar sizes redistribute in a manner that causes an increase in larger arterioles that is offset by a decrease in the number of smaller arterioles.

Computational Network Model: Validation and Hemodynamic Predictions

In this study, we used a network modeling approach to estimate resistance changes created by arteriolar remodeling in response IST. Similar modeling approaches have been used to study microvascular remodeling (18,20,21,24,26) and the influence of capillary rarefaction (4) and white blood cell plugging (31) on network resistance. Here, as with many network modeling studies, adjustments to the anatomical data were required to accurately model hemodynamics. Specifically, to account for Microfil shrinkage during polymerization, arteriolar diameters were adjusted to physiological values using an empirical scaling factor (Eq. 1). However, because the gastrocnemius muscle is not amenable to intravital microscopic observation, in vivo arteriolar dimensions are not available. Therefore, derivation of this scaling factor required the assumption that isolated perfused arterioles (17) were representative of the arterioles in vivo, thereby discounting the potential influence of tissue tethering on diameter. In addition, we assumed that the degree of dilation induced by using Locke's/procaine solution in combination with a constant arterial injection pressure of 150 mmHg was homogeneous throughout the arteriolar tree. This permitted us to apply the scaling factor, which was derived from 2A and 3A arterioles, to the higher-order arterioles throughout the remainder of the network.

Given the assumptions needed to derive the scaling factor, it was particularly important to validate the predictive power of the model. To this end, experimentally derived measures of total flow for SED and IST rats (11,15) were compared to model generated values. To match experimental conditions (15) in which muscles were perfused with Tyrode's solution with a driving pressure of 40 mmHg at the abdominal aorta, the model was run with the same reduced driving pressure and a constant viscosity of 1.2 cP. Under these conditions, the model shows excellent agreement with the experimental SED and IST values (Figure 2), thereby supporting the overall approach and suggesting that the diameter scaling factor was appropriately derived.

In vivo, in addition to arteriolar adaptations, alterations in capillarity can potentially serve to reduce hydraulic resistance. Therefore, the flow capacity increase that occurs with IST (15) could be caused by adaptations in the arterioles and/or the capillaries. Because the network model, which only accounts for arteriolar adaptations, predicts that flow capacity will double, arteriolar adaptation alone appears capable of generating increased flow capacity with IST. Finally, under physiological conditions (red blood cells are present and the 2A input pressure is 80 mmHg), the model predicts that flow capacity will increase from 0.7 mL/min in SED to 1.5 mL/min with IST.

Finally, the computational model suggests that arteriolar adaptations cause a shift in the primary site of pressure drop across the network from the 2A and 3A arterioles in SED network to the 5A and 6A arterioles in IST networks. Because our simulations were made for conditions of maximal vasodilation, they do not directly provide information about vascular control. Nonetheless, they do reveal the potential for certain arterioles to significantly impact total flow changes. In particular, the 7A and 8A arterioles are responsible for only a limited percentage of the total pressure drop across the network in the SED networks. However, in response to IST, these 7A and 8A arterioles remodel and are reclassified as 5A and 6A arterioles where they account for almost 50% of the total pressure drop (Figure 4C). This analysis is an important first step. The control of muscle blood flow after training is also influenced by non-uniform changes in neural-humoral control factors, changes in smooth muscle and endothelial cell responsiveness to vasoactive agents (14, 17). Further work is required to allow superimposition of the structural determinants of vascular resistance examined in the current report with these other factors that potentially produce nonuniform changes in control of vascular resistance. Some upregulation of resistance down stream of the larger arterioles is likely required to defend from increases in capillary hydrostatic pressure. It is possible that the adaptations observed in the arteriolar network in white/mixed muscle following IST exercise training is part of the

overall transformation of the muscle tissue phenotype from white to more red, oxidative muscle tissue.

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Figure 1.

Network topology and dimensions of SED and IST gastrocnemius muscles. (A) Photomicrograph of a whole-mount gastrocnemius muscle from an IST-trained animal following Microfil infusion. The mixed-fiber portion of the muscle lies within the region defined by the yellow line. The arrow denotes the 1A arteriole. (B) Number of arterioles per branch order in a defined tissue volume within the mixed portion of the gastrocnemius muscle for the SED and IST groups. (C) Mean arteriolar diameter per branch order in a defined tissue volume within the mixed portion of the gastrocnemius muscle for the SED and IST groups. (D) Mean arteriolar length per branch order in a defined tissue volume within the mixed portion of the gastrocnemius muscle for the SED and IST groups. Values are means $\pm$ SEM.

*Significantly different than SED within same branch order ($p < .05$; $n = 5$ for both SED and IST).

Figure 2.

Results of simulations used to compare model predictions to experimental measurements of total flow in the white gastrocnemius muscle. (A) Model predictions of flow per 2A arteriole assuming a driving pressure at the 2A arteriole of 30 mmHg and a constant viscosity of 1.2 cP. (B) Total number of 2A arterioles in the mixed-fiber portion of the gastrocnemius muscle. (C) Model predicted and experimentally derived total flows in mixed gastrocnemius muscle. Model results were generated by multiplying flow per 2A arteriole (A) with the total number of 2A arterioles per mixed fiber region of gastrocnemius muscle (B). Experimental values were derived from isolated hindlimb studies (11,15) that used Tyrode's solution perfusate and a driving pressure of 40 mmHg at the abdominal aorta. Values are means $\pm$ SEM. *Significantly different than SED ($p < .05$, $n = 10$ networks for both SED and IST).

Figure 3.

(A) Model predictions of flow per 2A arteriole in SED and IST groups, assuming a physiological input pressure of 80 mmHg and the presence of red blood cells. (B) Model predictions of total flow per mixed fiber region of gastrocnemius muscle in SED and IST groups assuming a physiological input pressure of 80 mmHg and the presence of red blood cells. Total flows were derived by scaling flow per 2A arteriole (A) with the total number of 2A arterioles per muscle (Figure 2B). Values are means $\pm$ SEM. *Significantly different than SED control ($p < .05$, $n = 10$ networks for both SED and IST).

Figure 4.

(A) Model predictions of mean intraluminal pressure per branch order for SED and IST networks. (B) Model predictions of mean intraluminal pressure as a function of diameter for SED and IST networks. (C) Percentage of total pressure drop across the entire arteriolar network for each branch order in SED and IST networks. *Significantly different than SED in same branch order or diameter grouping ($p < .05$, $n = 10$ networks for both SED and IST).

Figure 5. Schematic diagram illustrating the proposed process through which arteriolar adaptations occur in response to interval sprint training. (A) At left, a hypothetical SED network with branching ratios chosen to match the experimental data presented in Figure 1 is shown. At right, in response to IST, the network has undergone arteriogenic luminal expansion, but no arteriolar “sprouting.” (B) Experimental and schematic branching ratios for SED and IST networks. (C) Experimental and schematic ratios of IST arterioles per order to SED arterioles per order.