Regulation of Capillary Perfusion by Small Arterioles is Spatially Organized

Mary D.S. Frame, Ingrid H. Sarelius

To explore a mechanism for spatial recruitment of capillaries, this study determined whether the arterioles controlling capillary perfusion, which typically arise as sequential branches along a transverse arteriole, could respond differently from each other in situ in a spatially ordered way. Diameter changes were measured for these arterioles at a known location in the intact microvasculature in the cremaster muscle of anesthetized Golden hamsters (N=67); each arteriole controls separate capillary groups. These arterioles all had the same concentration dependence to locally (by micropipette) applied norepinephrine (NE, \(10^{-8}\) to \(10^{-5}\) mol/L), and \(10^{-8}\) mol/L NE did not induce diameter changes when applied locally to individual vessels. However, \(10^{-8}\) mol/L NE added to the tissue superfused, or 5% added superfusate oxygen (also locally subthreshold), each induced significant diameter changes (both constrictions and dilations), in different branches, that were presumably due to summation of individually subthreshold events that changed the prevailing conditions at the point of observation. These significant diameter changes were related to the maximal diameter or to initial tone of the branches, but these changes occurred in different ways for NE versus oxygen. With NE, the branch arterioles that constricted (versus dilated) were significantly larger (maximal diameter, 22.3±2.6 versus 15.9±2.1 \(\mu m\)) and had higher tone (fractional constriction, 0.53±0.05 versus 0.63±0.05); with oxygen, those that constricted were the same size as those that dilated (maximal diameter, 28.6±1.1 versus 30.5±2.7 \(\mu m\)), but constrictors had lower tone (fractional constriction, 0.49±0.04 versus 0.39±0.06). Both vessel diameter and tone were themselves significantly dependent on the sequential branch position. In addition, the spatial position of the branch along the transverse arteriole modified the extent to which diameter or tone influenced the responses; with NE, the arterioles that were located distally along the transverse arteriole dilated (axial distance versus response, \(y=0.0001x-0.05\); \(F\) test on slope, \(P=0.01\)), yet with oxygen, the distal arterioles constricted (\(y=-0.0001x-0.02\); \(P=0.03\)). Thus, this study shows that the small arterioles that control capillary perfusion are capable of responding differently from each other in a spatially organized way and, further, that the spatial pattern of diameter change is different when prevailing conditions (eg, local pressure/flow) are altered by adrenergic versus metabolic means. (Circulation Research 1993;73:155-163)

KEY WORDS • capillary recruitment • adrenergic reactivity • hamster cremaster muscle

Classically, it is well known that capillaries in striated muscle are arranged anatomically as groups arising from a single terminal arteriole. Recent work has established that these anatomically defined “capillary units” are also the fundamental unit of recruitment, has shown that each complete unit is recruited or derecruited in response to changes in blood flow, and has suggested that recruitment occurs in a spatially ordered way. The arterioles controlling flow into these units in cremaster muscle have been identified.

For recruitment of capillary units to occur, the arterioles controlling flow into each must have the ability to respond differentially to changes in tissue blood flow or metabolism. This ability is implied by the observation that capillary units are recruited and derecruited in a spatially defined sequence and also by our preliminary finding that the arterioles controlling capillary perfusion respond differentially by dilating in some locations and constricting in others when exposed to \(10^{-9}\) mol/L norepinephrine (NE). Further, in spinotrapezius muscle and in cardiac muscle, both arteriolar constrictions and dilations are observed in small arterioles in response to approximately \(10^{-9}\) mol/L NE, which is consistent with our preliminary data. Many studies have shown that different sizes of arterioles have different characteristic responses to adrenergic agonists (eg, see References 8 and 9), but these distinctions are often between broad vessel groupings, eg, vessels larger versus smaller than 50 to 100 \(\mu m\), and such groupings generally include vessels of two to three branch orders (eg, see Reference 8). Information on variability of response is not available for arterioles defined by their function as controllers of capillary recruitment. The primary purpose of the present study was therefore to determine whether these functionally defined arterioles have the capacity to respond differently from each other, in a spatially ordered (ie, nonrandom) way.

The studies of both Marshall7 and Chilian et al.8 as well as our preliminary data, show that, in small arterioles, variable responses as described above are
obtained with concentrations of NE that are widely held from other studies (eg, see Reference 10) to be sub-threshold. These observations imply that the ability of the intact system to respond to small changes in agonist concentrations is different from that expected on the basis of observations in isolated vessels. If confirmed, the observation has important implications about how responses are organized in the intact microvasculature. We therefore chose to examine diameter changes in response to subthreshold concentrations of NE in order to directly explore this phenomenon.

Materials and Methods

Preparation

Adult male Golden hamsters (Lak:LVG(SYR)VAF+ or HSD:Syrr; weight, 132±15 g; N=67 animals) were anesthetized with pentobarbital sodium (70 mg/kg i.p.), tracheostomized, and maintained on constant infusion of pentobarbital sodium in saline (10 mg/mL at 0.56 mL/h) via a left femoral venous catheter. The infusion rate was set to replace respiratory fluid losses; systemic hematocrit was determined before and after the experiment and did not change. Deep body temperature was maintained between 37° and 38°C by a thermostat-regulated heating coil placed under the animal. Mean arterial pressure was monitored via a left femoral arterial catheter and remained constant in each animal.

The right cremaster muscle was prepared for in vivo microcirculatory observations, viewed, and recorded as described previously, except that some recordings were made on a Sony VQ9600 videotape recorder.

Experimental Site

Our test site was a group of arterioles consisting of branches arising in sequence from a common feed vessel; the feed vessel was a transverse arteriole identified as the first branch arising from an arcade located in the lower central region of the preparation, according to previous criteria. The test site could be reproducibly located on each cremaster preparation as a vascular address; previous work has shown that these branch arterioles control perfusion into anatomically distinct groups (units) of capillaries. We have previously characterized spatial differences in arteriolar and capillary function and architecture across this tissue; we thus use the strategy of focusing on one site, as described above, to reduce variability while still retaining our ability to relate the observed behavior to the tissue as a whole. We compared diameter changes of specified branches and diameter changes at the corresponding positions along the transverse arteriole (see Fig 1).

The overall state of each preparation was assessed at the end of a 60-minute stabilization period before starting the experimental protocol. Vasoactive tone was confirmed in three arterioles (two randomly selected and one at the test site) as a brisk dilation in response to local application of 10⁻⁴ mol/L adenosine; oxygen sensitivity was confirmed by observing vasoconstriction in response to transient equilibration of the superfusate with 10% oxygen.

![Fig 1. Diagram of the test site. Observations were made on branch arterioles that arose in sequence from a common transverse arteriole.](http://circres.ahajournals.org/)

**Tissue-Wide Exposure Protocols**

Six or seven animals were observed for each test condition (n=39), in a predetermined sequence, with one test condition per animal. The five test conditions were as follows: (1) control superfusate containing (mmol/L) NaCl, 131.9; KCl, 4.7; CaCl₂, 2.0; MgSO₄, 1.2; and NaHCO₃, 20 (equilibrated with gas containing 5% CO₂–95% N₂; pH 7.4 at 37°C); (2) control superfusate containing NE (10⁻⁹ mol/L plus 100 mg ascorbic acid/L and foil-covered); (3) control superfusate containing phenolamine (10⁻⁶ mol/L; foil-covered, made from a fresh same-day stock solution) (this concentration completely antagonizes maximal constriction with 10⁻⁶ NE in isolated arterioles); (4) control superfusate containing propranolol (10⁻⁶ mol/L) (this is the concentration used to antagonize β contributions to adrenergic vascular responses); and (5) control superfusate equilibrated with gas containing 5% oxygen.

Diameters were videotaped at 0 minutes (control) and after 5 minutes of continuous tissue exposure to the test superfusate (test). The test superfusate was then washed out for 60 minutes and followed by a 5-minute exposure to 10⁻⁴ mol/L adenosine in the superfusate to obtain the maximum (adenosine-dilated) diameters. Preliminary experiments showed that by 5 minutes diameters had reached a steady state and did not change by more than 5% for a further 10 to 15 minutes. The dead-space washout time in our system is approximately 3 minutes; hence, we interpret the 5-minute test diameter as primarily a reflection of the immediate local response to the vascular changes induced by the test condition. In any observation period, all diameters were videotaped within 3 minutes. To control for possible time-dependent changes within the 5-minute taping period, the sequence of videotaping was alternated between preparations to start either at the proximal entrance region or at the distal branches (Fig 1); the responses we report were not related to the sequence of observations. Most steady-state diameter changes in the branches were an average of <5%.

**Local Pharmacology Protocols**

In separate experiments (n=28), NE was applied to the external surface of the branch arterioles using a
micropipette located within ~25 μm of the vessel wall. The pipette filling solution contained control superfusate plus NE (from 10⁻³ to 10⁻¹ mol/L, in log unit increments, prepared as described above). Flow out of the pipette was achieved by raising the driving pressure to 30 cm H₂O. The concentration of NE at the vessel wall was calculated to be twofold less than the concentration in the pipette. This was calculated from the flow rate out of the pipette using Poiseuille’s equation (diameter=8.6±2.5 μm for a tip length=145±60 μm, pressure drop=30 cm H₂O, and viscosity=0.01 poise) and assuming (based on the measured flow-stream diameter from the pipette tip) that the dilution of the pipette contents in the flowing superfusate was 20% to 50% complete at the vessel wall. A tracer concentration of 100 μmol/L fluorescein isothiocyanate-dextran (molecular weight, 4000; Sigma Chemical Co, St Louis, Mo) was added to the pipette solutions, and epifluorescence was used to verify that flow from the pipette was passing directly across the test arteriole. Exposure of arterioles to control superfusate from the pipette produced diameter changes of < 5%.

Arteriolar diameter was recorded continuously for 5 minutes after pipette placement to verify stable baseline diameter and then continuously during a 60-second exposure to NE and for 5 minutes after, to verify vessel recovery. The first, third, and last branch arterioles were tested sequentially in the same preparation, alternating the exposure sequence to start either proximally or distally. Only one concentration of NE was tested per animal. The adenosine-dilated diameters were obtained as before, from the addition of 10⁻⁴ mol/L adenosine to the superfusate after a 60-minute washout.

**Diameter Measurements**

Vessel diameters were measured off-line from the recorded image using a modified image analyzer (model 321, Colorado Video, Inc, Boulder, Colo) and chart recorder (Kipp & Zonen, Bohemia, NY) calibrated with a videotaped stage micrometer. For the tissue-wide exposure protocols, the average diameter over a 10-second period was used for each diameter measurement. For the local pharmacology protocols, the initial diameter was the average diameter during the 60-second interval before NE exposure, and the maximal diameter change achieved during exposure to pipette contents was used for each test response. Measurements were reproducible to within 0.6 μm, which is 1% to 2% of the diameter of these vessels. Subthreshold, for local pharmacology protocols, was defined as the absence of a reproducible diameter change with pipette exposure to NE compared with the diameter change seen with pipette exposure to control solutions.

**Statistics and Calculations**

For the tissue-wide exposure protocol, the diameter change (response) for each test condition was normalized to the maximal diameter and calculated as (test diameter - initial diameter)/maximal diameter. The initial resting tone was determined from the fractional constriction, ie, initial diameter/maximal diameter. The diameter change in the pipette protocols was expressed as the fractional change from the initial diameter, ie, as (test diameter - initial diameter)/initial diameter.

**FIG 2. Bar graphs showing diameters and initial tone of the branch arterioles as a function of sequential position along the transverse arteriole. Panel A: Maximal diameters (mean±SEM, n=32 to 39 for each position) decrease significantly from branch 1 to branch 3. Panel B: Initial fractional constriction (mean±SEM) is significantly lower in branch 3 and usually higher for the last branch, although this was not statistically significant. Thus, initial tone is highest in branch 3 and generally lowest in the last branch. *P<0.05.**

The calculated values were pooled by position and test condition to determine the population mean±SEM, and n is indicated on the figures. Group comparisons were made using t tests or analyses of variance as appropriate. Other nonparametric tests (eg, Kendall’s coefficient of variation) were used as appropriate and are indicated in the text. The significance level for all statistics was evaluated with P=0.05.

**Results**

Our primary aim was to explore a mechanism for spatial recruitment by determining whether sequentially located branch arterioles, each of which perfuse separate groups of capillaries, could respond differently, in a predictable way.

**Arterioles Governing Inflow to Capillary Units Differ in Diameter and Tone in a Spatially Ordered Way**

There was a significant decrease in maximal diameter for the first three branches, from (mean±SEM) 23.1±1.4 μm (first branch) to 19.0±0.9 μm (second branch), and to 17.3±0.9 μm (third branch, which was the smallest of the group); the terminal (last) branch diameter was 18.3±1.2 μm (Fig 2A). The resting tone was significantly greater in the third branch than the others; fractional constriction was 0.54±0.03 (first branch), 0.55±0.04 (second branch), 0.49±0.04 (third
branch), and 0.62±0.04 (last branch) (Fig 2B). Tone in the last branch tended to be lower than in the others, but this was not statistically significant. Thus, in both diameter and resting tone, the branch arterioles were systematically different from each other, with a progressive decline in branch diameter for the three proximal branches and with the lowest tone occurring distally. When all the data were pooled, vessel diameters and tone were related such that large vessels had higher tone and small vessels had lower tone (F test on slope, P=0.0001; n=139 vessels). However, when the data were subdivided by branch position, the mean diameter and fractional constriction in the third branch were always smallest (Fig 2). Thus, spatial position modified the apparent relation between diameter and tone described for the group as a whole.

The transverse arterioles that feed these branches each decreases in diameter along their length but did not vary along their length in resting tone. Thus, the entrance region was significantly larger in maximal diameter (36.7±1.7 μm, n=40) than the distal region (23.1±1.5 μm) of the same vessels; resting tone in the entrance versus distal regions was not different (fractional constriction, 0.65±0.03 versus 0.60±0.04). The average length of these transverse arterioles was 1682±49 μm; length and resting tone were not associated.

All Branches Have the Same Local Responses to NE

To verify that locally applied 10⁻⁹ mol/L NE (ie, a subthreshold concentration) did not induce diameter changes in our preparation, NE was applied to the external surface of individual branch arterioles with a micropipette. Locally applied NE elicited similar concentration-dependent constrictions at all branches (Fig 3). Maximal constriction (to a diameter of 3.0±0.5 μm) was achieved with 10⁻⁴ mol/L NE (pipette concentration; see “Materials and Methods”), and a half-maximal constriction was achieved with approximately 10⁻⁶ mol/L NE (pipette concentration) for each branch (Fig 3). NE less than 10⁻⁸ mol/L (pipette concentration) was subthreshold, as it did not produce significant diameter changes. Thus, all branches respond similarly to locally applied NE.

Subthreshold NE Induces Large Diameter Changes in Branches When Applied to the Entire Tissue

Most (>70%) of the branch arterioles responded to 10⁻⁹ mol/L NE (Fig 4); NE caused both significant constrictions (to −32%) and dilations (to +27%). The branches that constricted (versus dilated) had significantly larger maximal diameters (23.3±2.6 versus 15.9±2.1 μm) (Fig 5) and significantly greater resting tone (fractional constriction, 0.53±0.05 versus 0.63±0.05) (Fig 6). Thus, our data strongly support our hypothesis that these small arterioles are capable of responding differently from each other.

High Concentrations of Adrenergic Antagonists Do Not Elicit the Expected Pharmacological Response in Branches When Applied to the Entire Tissue

Both phentolamine (10⁻⁸ mol/L) and (separately) propranolol (10⁻⁶ mol/L) applied to the tissue via the superfusate induced both constrictions and dilations in the branch arterioles. For phentolamine, 60% of the branches responded, with a maximum constriction of −48% and maximum dilation of +34%. For propranolol, 75% of the branches responded, with a maximum constriction of −31% and maximum dilation of +33%. Thus, when applied to the intact microvasculature, high concentrations of adrenergic antagonists did not elicit the expected pharmacological response in the observed arterioles. Interestingly, for both phentolamine and propranolol, the branches that constricted had signifi-
FIG 5. Panel A: Bar graph showing mean±SEM of the maximal diameter of the branches that constricted (open bars) versus those that dilated (filled bars) with either 10−9 mol/L norepinephrine (NE) or 5% oxygen. For NE, the maximal diameter was significantly (*) greater for constrictors than for dilators. For oxygen, maximal diameters were not different. Thus, the pattern of response was not random and was differently related to maximal diameter for NE and oxygen. Panel B: Plot showing individual data points. A different symbol is used for each branch position. *P<.05.

FIG 6. Panel A: Bar graph showing mean±SEM of the fractional constriction of the branches that constricted (open bars) versus those that dilated (filled bars) with either 10−9 mol/L norepinephrine (NE) or 5% oxygen. For NE, the fractional constriction was significantly (*) lower for constrictors than for dilators; for oxygen, the tone was significantly (*) higher for constrictors than for dilators. Thus, the pattern of response was not random and was differently related to initial tone for NE and oxygen. Panel B: Plot showing individual data points. A different symbol is used for each branch position. *P<.05.

Significantly lower resting tone than did those that dilated (fractional constriction of the branches that constricted versus dilated with phenolamine, 0.72±0.05 versus 0.40±0.04; with propranolol, 0.70±0.06 versus 0.56±0.07), which is opposite the relation between resting tone and response that was seen with NE. In addition, with phenolamine (and not propranolol), constriction occurred in the smaller vessels, and dilation occurred in the larger vessels (maximal diameter of the branches that constricted versus dilated with phenolamine, 16.2±1.8 versus 30.8±2.2 μm; with propranolol, 22.5±2.0 versus 22.1±1.4 μm). With phenolamine, this association between response and vessel size was also opposite that seen with NE.

Spatial Pattern of Diameter Changes Depends on Mechanism of Vascular Perturbation

To determine whether the pattern of diameter changes seen with 10−9 mol/L NE was a characteristic response elicited by low concentrations of vasoconstrictors in general, we tested the response to 5% oxygen (shown by others to be a subthreshold oxygen concentration in the intact tissue; eg. see Reference 14). As with NE, 5% oxygen caused diameter changes in most (70%) of the branches; the maximum constriction was −37%, and the maximum dilation was +30%.

The pattern of diameter changes was quite different with oxygen than with NE. With oxygen, unlike NE, there was no difference between the maximal diameter of the vessels that constricted (18.8±1.6 μm) compared with those that dilated (17.7±2.4 μm) (Fig 5). However, the initial tone was significantly lower for the branches that constricted (versus dilated) with oxygen (fractional constriction, 0.49±0.04 versus 0.39±0.06), which was opposite the response with NE (Fig 6). Thus, with subthreshold oxygen, as with 10−9 mol/L NE, the branch arterioles again responded differently from each other, and again, these diameter changes were nonrandom. Importantly, the pattern of diameter changes was different with oxygen than with NE; ie, there is not a single characteristic pattern of diameter changes induced by tissue exposure to low concentrations of vasoconstrictors.

There was a spatial order to these responses. Overall, our data show that with NE most branches that arose distally from the transverse arteriole dilated (five of seven branches), whereas with oxygen most branches that arose distally constricted (four of six branches).
FIG 7. Panel A: Bar graph showing mean±SEM of the diameter changes for the entrance and distal regions of the transverse arteriole in response to superfuse $10^{-9}$ mol/L norepinephrine (NE) (filled bars, n=7) and, in separate experiments, with 5% oxygen (filled bars, n=7). The entrance and distal regions responded differently with each agonist. With NE, the entrance constricted, whereas the distal region dilated significantly (△); with oxygen, the entrance did not change, whereas the distal region constricted significantly (●). Thus, there was a significant position-dependent difference in the response for the transverse arteriole, and the response was agonist specific. Panel B: Plot showing individual data points with NE (●) and oxygen (○).

These trends were also evident along the transverse (feed) arteriole (Fig 7). With NE, the entrance region of the feed arteriole constricted while the distal region dilated significantly. With oxygen, the entrance region diameter did not change, but the distal region constricted significantly. (The steady-state diameter changes of the feed vessel, ie, without oxygen or NE, were similar in both regions: entrance, $-0.02±0.05$; distal region $-0.02±0.04$; n=7.) To further quantify this spatial pattern of response, we examined the diameter changes of the feed and the branches as a function of axial distance along the feed arteriole. Fig 8 shows that for all responses with NE (Fig 8A) or for all responses with oxygen (Fig 8B) the linear regressions (in the figure legend) are each significantly different from a slope of 0 (in control experiments [not shown], the slope was not different from 0; $P=0.77$). Thus, arteriolar responses were significantly related to the axial position along the feed, and the spatial pattern of response was different with NE than oxygen.

Discussion

This study shows that the small arterioles that control perfusion into separate capillary units have the ability to respond differently from each other in a spatially ordered way. Further, this study shows that the response of small arterioles in the intact microvasculature can be much different from the behavior that has been described for individual arterioles in studies in vitro.

Spatial Differences in Response Cannot Be Explained by Intrinsic (Pharmacological) Responses

The local pharmacology of these arterioles is similar to that in isolated vessels (compare Fig 3 with data in Reference 10). We found that the responsiveness to NE is similar for all branch positions, which is consistent with the widespread view that arterioles of similar size behave similarly to adrenergic stimuli.6,10 In addition, we have determined that $10^{-9}$ mol/L NE is indeed a concentration that is subthreshold for each of these branch arterioles (Fig 3). Arteriolar responsiveness is a function of the initial length-tension relation (transmural pressure load).15-17 Our concentration-response data with local NE (Fig 3) show a similar responsiveness for each branch, which was independent of the initial tone (range of fractional constriction, from 0.23 to 1.32). Thus, our data are consistent with the idea that these arterioles are initially at similar positions on their length-tension curve. Overall, we conclude that these vessels have a similar capacity to respond to NE.

As implied by earlier reports (eg, see References 7 and 8), our data demonstrate that these small arterioles have the ability to respond in situ to tissue-wide exposure to subthreshold NE. These diameter changes were related to the initial tone and arteriolar maximal diameter and were modified by spatial position, whereas local application of NE produced concentration-dependent constrictions that were not related to tone, vessel size, or position. If these arterioles had responded to superfused subthreshold NE as expected from pharmacological studies, then no change in diameter would have been observed. Thus, we know that the observed diameter changes were not related to expected pharmacological responses on the basis of currently understood criteria for vascular reactivity. Instead, we speculate that exposure of the intact system to the agonist must have induced small changes that have integrated in some way to produce a change in the local flow/pressure conditions at our observation site. The responses we observed must in turn be in response to these local changes. It seems likely that these kinds of local differences could occur physiologically, for example, as local changes in flow due to local changes in metabolism.

Spatial Organization of Relative Vascular Resistance

These arterioles belong to the same vascular classification using either Strahler18 or Weideman19 classification schemes, yet they exhibit marked differences in response. The large range of responses for a single classification of arterioles is often described as heterogeneity of response. Our study demonstrates the new finding that this heterogeneity of response is in fact not random but is spatially organized.
We examined the behavior of sequential branch arterioles arising from a common transverse vessel. Both at rest and during maximal dilation, the diameters of the more proximal arterioles were largest, and the third branch was always smallest (Fig 2A). Because vessel diameter is the primary determinant of vascular resistance or conductance, we conclude that the geometric resistance was not equivalent for each of the branches. Resistance was spatially organized, such that it was relatively increased, progressively, in the first three branches. As initial tone was also higher in the third branch, this would further increase the relative resistance at this location. This spatial organization of resistances implies that flow is not equally distributed into each of these branches, and indeed, disproportionately higher cell flow into the first, compared with more distal branches, has been reported. Because these arterioles are known to control perfusion into separate capillary units, a further implication of our study is that the capillary units themselves must differ in a systematic way.

Interactions Between Position-Dependent Responses and Maximal Diameter or Initial Tone

Many studies suggest that vessel tone and size (maximal diameter) each influence the ability of an arteriole to respond to local changes (e.g., see References 7, 9, and 17). In applying these criteria to our data, we found that the diameter changes with NE or oxygen were related to the maximal diameter (Fig 5) or initial tone (Fig 6) in different ways. In addition we found that the spatial position of the branches modified the extent to which diameter or tone influenced the response. All of these interactions (between the responses and maximal diameter, tone, or position) are summarized in the Table. The table shows that no single criterion will by itself explain the responses observed in the intact system, but it usefully summarizes the principal relations and illustrates the influence of spatial position on the responses. For example, in the group as a whole, low tone and smaller diameter are associated with dilation to NE, and the last branches tended to have lower tone than the others and were not the largest (Fig 2). So, as expected, most of this group dilated. Those few of the last branch group that constricted were, as expected from the general relation, those that had larger diameters and higher tone (Table). These three variables (vessel diameter, initial tone, and sequential position) interact in an organized and definable way. Further, the relative importance of each variable in determining the vascular response is different, but predictable,
for hormonal versus metabolic stimuli. Thus, the integrated response of the intact system to changes in prevailing flow is organized and not randomly heterogeneous at the microvascular level.

**Integrated Control of Spatial Recruitment**

In hamster cremaster, like many other muscles, not all capillary units are perfused at rest.4,21,22 A reserve of capillary units can only be achieved if some controlling arterioles behave differently from others. Our data provide strong evidence that this is so. We found that spatially organized changes in relative resistance occur for these controlling arterioles, which implies that flow distribution must differ also in spatially defined ways. Further, our data show that these responses were different from those expected from the known pharmacology of these vessels. Thus, the responses must have occurred via local detection of, for example, pressure and/or flow changes initiated elsewhere in the tissue. This implies that small individually threshold events throughout the system sum to a critical level that can then initiate the pattern of changes we observed.

A further indication that the arteriolar responses we observed were primarily driven by local changes (eg, in pressure or flow) induced by events occurring throughout the system is provided by our observation that high concentrations of adrenergic antagonists in the superfusate did not produce the expected local responses. For phentolamine, we expected dilation via antagonism of the vascular smooth muscle α1-adrenoceptors, which are the prevalent α-adrenergic receptor subtype at this level of the microcirculation.16,23 The expected response to propranolol was constriction via endothelial β-adrenoceptors.23,24 Because neither α- nor β-adrenergic antagonism elicited the expected pharmacological responses, we postulate that changes in prevailing conditions were more important contributors to the responses we observed than were direct pharmacological actions.

Our data also show that the integrated responses of the intact microvasculature were systematically different with NE than with oxygen, which implies that the pattern of selective perfusion of capillary units (ie, spatial recruitment) is different for hormonal versus metabolic stimuli. With the addition of NE to the superfusate, there was a relative decrease in resistance in the distal branches, which would redistribute the blood in the transverse arteriole toward capillaries arising from those distal vessels (Fig 8A). Oxygen produced the opposite effect, ie, a relative increase in distal resistance, with therefore a redistribution of blood flow toward capillary units fed by more proximal arterioles (Fig 8B). Thus, different spatial patterns of local vascular resistance changes, and hence relative flow redistribution, were initiated by two classic vasoconstrictors that act through separate pathways. Clearly, the actual flow redistribution occurring in the intact system will also be affected by changes in the inflow to the feed vessel and in the venous system; our data (eg, see Fig 7) suggest that the inflow to the feed vessel could also vary differently for the different agonists.

**Summary**

In summary, this study shows that the small arterioles that control flow into separate capillary units have the capacity to respond differently from each other in a spatially organized way. Their responses are not just related to maximal diameter and initial tone but also to axial position within the group. Further, we show that small individually subthreshold stimuli, when applied to the intact system, produce large changes in diameter in these arterioles; this mechanism appears to be a more important contributor to the responses we observed than were the direct pharmacological actions. These responses were agonist specific and differently spatially ordered. These responses thus fulfill the functional requirements for a mechanism by which these arterioles control spatial capillary recruitment.

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