SUMMARY This study examined the effect of changing hindlimb metabolic rate on hindlimb blood flow control in anesthetized dogs. The hyperemias induced by graded levels of arterial hypoxia and the degree of steady state autoregulation evoked by changes in blood pressure were measured. Metabolic rate was increased above the resting value by direct electrical stimulation of hindlimb muscles at rates from 0.5 to 1.5 pulses/second, and in three dogs was reduced by cooling. In response to 5 minutes of arterial hypoxia, hindlimb blood flow steadily increased. At rest, and at each level of muscle stimulation, the steepness of the response increased as arterial oxygen saturation (S\text{AO}_2) decreased. At all levels of S\text{AO}_2, the response was steeper at increasing stimulation rates. For S\text{AO}_2 > 50\%, the relationship between the percentage increase in blood flow from control and S\text{AO}_2, however, was unaffected by the degree of muscle activity, suggesting that during mild to moderate hypoxia the dynamics of the response were similar whether the muscles were at rest or exercising. The responses to severe hypoxia (S\text{AO}_2 < 50\%) during stimulation were significantly enhanced compared with those at rest. Autoregulation of blood flow was measured in the steady state by comparing the relative change in blood flow from control with the relative change in blood pressure that produced it. Steady state autoregulation was weak at rest, but improved markedly with increasing muscle stimulation. Conversely, cooling the hindlimb depressed the resting steady state autoregulation. A close correlation was found between the degree of autoregulation and the hindlimb metabolic rate. The results suggest that tissue metabolic rate determines the precision of local blood flow control.

MANY investigators have studied the responsiveness of skeletal muscle microvasculature to arterial hypoxia and to alterations in perfusion pressure. The majority of such studies, however, have been performed on resting muscle preparations, and few studies have attempted to quantify the effect of muscle activity and increased muscle metabolism on these responses. Data presented by Stainsby and Otis\(^1\) showed a marked increase in the skeletal muscle blood flow response to arterial hypoxia in contracting muscles compared with a very modest response in resting muscle. Granger et al.\(^2\) reported that the blood flow response to hypoxia was enhanced when the \(P\text{O}_2\) of the effluent venous blood was lowered by several methods, including muscle stimulation. They showed also that blood flow autoregulation was improved by such maneuvers.\(^2,3\) Data presented by Stainsby\(^4\) revealed enhanced autoregulation of blood flow in contracting skeletal muscle compared with that in resting muscle. Jones and Berne\(^5\) demonstrated that a tendency for resting skeletal muscle to autoregulate consistently improved during muscle stimulation. The results of these studies suggest that the degree of local blood flow control in skeletal muscle may be linked to the level of tissue metabolic activity.

It is well recognized that tissues such as brain and myocardium, having high and relatively constant metabolic rates, exhibit very precise local circulatory control.\(^6,7\) Skeletal muscle, however, is a tissue with variable metabolic activity, depending upon moment-to-moment postural, locomotive, and thermogenetic needs of the animal. In view of this variability in metabolic rate, it seems possible that not only is blood flow controlled in accordance with tissue metabolic requirements, but also the precision of local blood flow control is influenced by the metabolic state of the tissue. This study was designed to examine the local circulatory responses in skeletal muscle of canine hindlimb at different levels of metabolic activity as measured by hindlimb oxygen consumption. The responses studied were the vasodilation produced by arterial hypoxia and the degree of steady state blood flow autoregulation occurring in response to variations of perfusion pressure.

Methods

Twenty-six mongrel dogs ranging in weight from 15 to 34 kg were used in this study. The animals were anesthetized with sodium pentobarbital (30 mg/kg, iv), intubated, and artificially ventilated with room air. Mild hyperventilation ensured arterial oxygen saturations greater than 90\%, while guarding against hypercapnea. End-tidal CO\(_2\) concentrations ranged approximately from 3.5\% to 4.5\% (Beckman Model LB-1 Medical Gas Analyzer).
A lateral extraperitoneal approach exposed the left external iliac artery and vein. Hindlimb blood flow was measured with a cuff electromagnetic flow transducer applied to the external iliac artery above the level of the inguinal ligament. Arterial blood pressure in the hindlimb was measured with a Statham P23AC pressure transducer via a catheter introduced into the deep femoral artery, which branched from the external iliac just distal to the flow transducer. Hindlimb venous blood was sampled continuously via a catheter introduced into the left femoral vein while arterial blood was withdrawn continuously from the right femoral artery. These blood samples were used to monitor hindlimb arteriovenous oxygen difference (Oxford Instrument Company). The blood was returned to the dog through a canula inserted in the right femoral vein. Both carotid arteries were cannulated and connected with 8-mm (i.d.) blood tubing to a reservoir bottle suspended above the dog. Initially this connection was clamped off. To minimize blood flow through cutaneous arteriovenous shunts, the left hindpaw was tied off. A dose of 10,000 U of heparin was given intravenously.

An infusion of Macrodex (Pharmacia), 6% in normal saline, was given intravenously over about 5 minutes. The volume usually was 20–30% of the dog’s estimated blood volume. The hematocrit was used to evaluate hemodilution caused by infusion and was not allowed to fall below 30%. After several minutes of equilibration, a volume of blood equal to the volume of the infusion was drawn off into the reservoir bottle.

To ensure that measured responses were not caused or influenced by neural cardiovascular reflexes, all central nervous system activity was abolished using a modification of a previously described technique. After first withdrawing as much cerebrospinal fluid as possible (usually about 10 ml), 20 ml of absolute ethanol were administered through a cisternal puncture. This caused a profound fall in blood pressure. At this point, the tubing to the blood reservoir bottle was unclamped and, to restore a constant level of vascular tone, an intravenous infusion of norepinephrine bitartrate (NE) was commenced. The infusion rate was adjusted to restore the original blood pressure while keeping the initial volume of blood in the reservoir bottle. Lowering the reservoir to bring the arterial blood pressure to 100 mm Hg usually increased the volume of blood in the bottle by 1.5–2.5 times. The NE infusion rate averaged approximately 3 µg/kg body weight per min (equivalent to 1.5 µg/kg per min of norepinephrine base) and, once set, was not changed during the experiment. Blood alcohol levels measured in five dogs (average weight, 27 kg) at half-hourly intervals following the alcohol injection reached a steady level averaging 39 ± 7 mg/100 ml within the 1st hour. In these concentrations alcohol does not seem to have a significant direct effect on vascular smooth muscle.

Hindlimb deep-muscle temperature was monitored with a needle-tip thermocouple (Ellab) and was maintained at 34–36°C (at rest), using an external heat lamp directed at the limb.

To produce arterial hypoxia, the ventilator inflow was connected to a large spirometer (W.E. Collins, Inc.) in which an hypoxic gas had been prepared by mixing air and nitrogen. Mixtures ranging from 6% to 12% oxygen in nitrogen were used. Arterial oxygen saturation was measured when ventilating with air (control conditions) and with the hypoxic gas mixture (hypoxic test conditions), using a reflectance oximeter (Hemoreflector, Kipp and Zonen). To measure the degree of blood flow autoregulation in the hindlimb, the arterial blood pressure was varied by ± 30–50 mm Hg by raising or lowering the reservoir bottle.

Muscle stimulation in the hindlimb was used to increase hindlimb metabolic rate. Oxygen consumption, calculated as the product of hindlimb arteriovenous oxygen difference and blood flow, provided an index of metabolic rate. Direct muscle stimulation was produced, using stainless steel needle electrodes placed so as to stimulate the entire muscle mass of the thigh. A Grass Model S4C stimulator provided 150-V, 0.1-msec pulses, at rates of 0.5, 1, and 1.5 pulses/sec (p/s). Because of the powerful muscle contraction produced, it was necessary to restrain the hindlimb during stimulation.

In three dogs, hindlimb oxygen consumption was depressed by cooling. The dogs were cooled to approximately 30–32°C, using a controlled temperature water blanket (Gaymar Industries, Inc.), and the left hindlimb was placed in crushed ice.

Left external iliac artery blood flow (pulsatile and mean) and mean arterial blood pressure, left hindlimb arteriovenous oxygen difference, and the heart rate were recorded continuously on a Grass Model 7C Polygraph. Blood flow was measured with a squarewave electromagnetic flowmeter (EMI Aust.). The flow transducers were self-retaining complete-cuff types, made by us for these studies.

The data were analyzed using standard statistical methods.

Results

The control hindlimb blood flows and oxygen uptakes at rest and during muscle stimulation are shown in Figure 1. At rest blood flow averaged 1.93 ± 0.11 (se) (n = 23) ml/min per kg body weight, and oxygen consumption averaged 0.122 ± 0.008 (n = 23) ml/min per kg body weight. Muscle stimulation caused a rapid increase in blood flow and oxygen uptake from their resting levels, and both reached 80% of their final values within the first 2–3 minutes of stimulation. Both blood flow and oxygen uptake increased with increasing stimulation rates. At 1.5 p/s, hindlimb blood flow reached 7.11 ± 0.37 (n = 11) ml/min per kg, an increase of approximately 3.7 times, whereas oxygen uptake averaged 0.786 ± 0.041 (n = 11) ml/min per kg, an increase...
of 6.4 times. The difference in the rates of increase was accounted for by an increase in oxygen extraction during muscle stimulation.

**Hypoxia**

The effects of arterial hypoxia on hindlimb blood flow were measured in 17 dogs: in six with the limb at rest, in six with the limb at rest and during muscle stimulation at 0.5 p/s, and in five at rest and during muscle stimulation at 0.5, 1.0, and 1.5 p/s. The period of hypoxia was limited to approximately 6 minutes for most dogs because severe hypoxia for longer periods produced cardiac arrhythmias. All measurements, therefore, were made 6 minutes from the beginning of arterial desaturation, as indicated by the rapid fall in arteriovenous oxygen difference. The arterial oxygen saturation (SAO₂) fell rapidly after respiration with the hypoxic gas mixture commenced. It reached its minimum value within 2 minutes of the onset of arterial hypoxia. Despite this stepwise change in SAO₂, all experiments the hindlimb blood flow response was a ramp; i.e., the blood flow rose steadily with time. Figure 2 is a typical record made while ventilating a dog with 6% oxygen in nitrogen. In general, it was found that blood flow was still increasing at the end of 6 minutes, and the calculated oxygen uptake was depressed. The slope of the blood flow ramp increased with decreasing SAO₂. In addition, for a given level of SAO₂, the ramp was steeper with increasing muscle activity. Figure 3 shows segments of experimental records from one dog. These records demonstrate the marked change in the flow response to similar levels of hypoxia at rest and during muscle stimulation at 0.5 p/s.

Higher stimulation rates resulted in steeper flow ramps, and therefore increasing values of blood flow at the end of the 6-minute period. Figure 4 shows graphically the data from these experiments. The solid lines are the curvilinear regressions of blood flow (at 6 minutes) on arterial oxygen saturation calculated after logarithmic transformation of the data. The regression analyses revealed a significant linear correlation between log (6-minute blood flow) and log (SAO₂) at each stimulation level. From analysis of covariance, the differences between the regression lines were highly significant. For the data derived during muscle stimulation, these differences were in the intercepts only; the slopes of the lines showed no significant differences. The muscle stimulation lines, however, had a significantly steeper negative slope than the line derived from the resting data (P < 0.01; F-test; df = 1.87). The similarity in slopes of the regressions from the muscle stimulation data suggested that the magnitude of the response might be a function of the control blood flow at each level of muscle activity. Accordingly, the data were converted to percentage change in blood flow from control and plotted as a function of log (SAO₂), shown in Figure 5. In this figure, the data corresponding to muscle stimulation rates of 0.5,

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**Figure 1** Hindlimb blood flow and oxygen uptake at different hindlimb muscle stimulation rates. Blood flow and oxygen uptake are expressed as ml/min per kg body weight, and stimulation rates are in pulses/second (p/s). For 0 p/s, n = 26; 0.5 p/s, n = 17; 1.0 p/s, n = 11; 1.5 p/s, n = 11. Vertical bars represent ± SE.

**Figure 2** Experimental records showing ramp flow response to arterial hypoxia (induced in this case by ventilating with 6% O₂ in N₂, limb at rest). From above down are hindlimb blood flow, mean arterial blood pressure (M.A.P.), hindlimb arteriovenous oxygen difference (ΔA-VO₂), and heart rate (H.R.). The period of hypoxia is indicated by the step depression in ΔA-VO₂.
1.0, and 1.5 p/s (crosses) have been pooled, since there was no significant difference between the regressions computed from the data at the different stimulation frequencies. The filled circles are the resting muscle data points, and the solid line is the corresponding regression line.

The muscle stimulation data show two clearly distinct patterns. Above log (SAO₂) = 1.7, corresponding to SAO₂ of 50%, the data follows a line that, from analysis of covariance, is not significantly different from that of the resting muscle data. For SAO₂ of less than 50%, however, the relative increase in blood flow during muscle stimulation increases greatly as arterial saturation decreases, compared with the resting muscle. The broken lines are the regression lines for the muscle stimulation data, and the difference between slopes below and above 50% arterial saturation is significant (P < 0.01; F-test; 1.49 df).

Despite the enhanced blood flow response to arterial hypoxia during muscle stimulation, hindlimb oxygen consumption was still depressed after 6 minutes of hypoxia, as shown in the lower panel of Figure 4. The relative depression in oxygen uptake during exercise was significantly less than that occurring in resting muscle.

**Steady State Autoregulation**

Blood flow autoregulation in the hindlimb was tested in six dogs at rest and during muscle stimulation at 0.5 p/s, and in six dogs at rest and during muscle stimulation at 0.5, 1.0, and 1.5 p/s.

The ability of the hindlimb tissues to autoregulate was measured by comparing the relative change in blood flow with the relative change in blood pressure, when pressure was changed by raising or lowering the blood reservoir bottle. These measurements were made in the steady state, at least 5 minutes after the blood pressure had reached its new level. The transient changes in flow that are observed when pressure is suddenly changed were not measured in this study. We calculated an index of autoregulation as the ratio of the relative change in blood flow to the relative change in blood pressure, in the steady state.

\[ \text{Index} = \frac{(Q_{\text{max}} - Q_{\text{min}})/Q_c}{(BP_{\text{max}} - BP_{\text{min}})/BP_c} \]

where BP_{max} = blood pressure above control; BP_{min} = blood pressure below control; BP_c = control blood pressure; Q_{max} = flow at BP_{max}; Q_{min} = flow at BP_{min}; Q_c = Control flow (at BP_c).

Blood pressure was varied by ± 30-50 mm Hg from the control value of 100 mm Hg. Table 1 summarizes the results from all the dogs in this group. These data show that, at rest, steady state blood flow autoregulation was poor. The index of 1.07 indicates that variations in blood flow averaged approximately 7% more than the pressure variations. With muscle stimulation there was a striking improvement in autoregulation such that, at the stimulation rate of 1.5 p/s, variations in flow averaged approximately 71% less than the pressure variations (index = 0.29). The alterations in perfusion pressure, however, had relatively little effect on hindlimb oxygen uptake. Except for a 13.9% depression of oxygen uptake during lowered blood pressure at rest (P < 0.05), the averaged percentage changes in oxygen uptake during the blood pressure challenges did not differ significantly from zero (Table 1). Figure 6 illustrates typical recordings from one dog and contrasts the degree of blood flow autoregulation elicited when the limb is at rest with that when the muscles are stimulated at 1 p/s. Whereas a 45% increase in blood pressure resulted in a 59% increase in steady state blood flow (index = 1.3) under basal conditions, during stimulation at 1 p/s, a 33% increase in blood pressure resulted in a blood flow increase of only 7% (index = 0.2). In five dogs, resting hindlimb flow was increased without significantly altering local metabolism, by reducing the NE infusion rate, local intra-arterial infusion of adenosine, or both. The autoregulatory
in blood flow, although small reductions in arteriovenous oxygen difference were noted during the experiments. Autoregulation of blood flow was much weaker in these dogs than in the resting dogs at normal body temperature. The mean value of the autoregulatory index was 1.53 ± 0.09 (n = 6); i.e., the blood flow changes averaged 53% more than the pressure changes.

When autoregulation index was paired with its corresponding control hindlimb oxygen consumption, there was a high degree of correlation throughout the range of metabolic activities studied. In Figure 8, autoregulation index is plotted as a function of oxygen consumption. The open circles are the data from the cooling experiments, the filled circles are the data from the resting dogs at normal temperature, and the crosses refer to muscle stimulation. The solid line is the curvilinear regression line derived by regression analysis after logarithmic transformation of the data. The curve illustrates that, over the range of metabolic activities studied, the degree of blood flow autoregulation exhibited by the hindlimb correlates very closely with the level of hindlimb metabolic oxygen consumption.

**Discussion**

The intact hindlimb preparation used in these studies possesses the advantage of being a simple procedure with minimal surgical interference that leaves muscles intact and allows controlled, pulsatile pressure autoperfusion over a wide pressure range with little trauma to blood. Although some of the ilioc blood flow measured at rest was flow to...
non-muscle tissue, we used hindlimb blood flow as an estimate of blood flow to muscle, an approximation that improved with increasing muscle activity. Throughout the range of metabolic rates studied in these experiments, there was a close correlation between hindlimb blood flow and oxygen consumption (Fig. 9). According to metabolic feedback theories of exercise hyperemia, the vasodilation of muscle exercise (Fig. 1) results from an increase in tissue fluid concentration of vasodilators produced during muscle contraction. On the other hand, the fall in resting blood flow that accompanied depression of tissue oxygen consumption by cold (Fig. 7) suggests that reduced tissue metabolism causes a decrease in the tissue fluid concentration of vasodilator metabolites normally produced at rest.

**Arterial Hypoxia**

A feature of the hypoxic response in all experiments was that it was slow, resulting in significant depression of oxygen uptake during the 6-minute challenge. The steady increase in flow induced by arterial hypoxia suggests that the response depends on a time-dependent accumulation of vasodilators in the interstitial fluid. The experimental data plotted in Figure 5 demonstrate that during mild-to-moderate hypoxia (SAO₂ > 50%) the relative increase in blood flow after 6 minutes of hypoxia is a function of the arterial oxygen saturation, but not of the level of activity (in the range studied). The absolute magnitude of the vasodilator response for a given degree of hypoxia, therefore, depends on the initial flow which, in turn, correlates closely with the prevailing metabolic oxygen consumption (Fig. 9). Thus, it appears that the tissue metabolic rate determines both the control blood flow and the rate of accumulation of vasodilators in tissue fluid in response to mild arterial hypoxia.

A possible explanation for the increased responsiveness to severe hypoxia during muscle stimulation (SAO₂ < 50%, Fig. 5) relates to the increase in turnover of ATP and products of ATP hydrolysis involved in the contractile process. It seems likely that during severe hypoxia the oxygen tension in some contracting muscle cells falls to a level at which resynthesis of ATP following contraction fails, with consequent leakage of substances such as inorganic phosphate, adenine nucleotides, and adenosine from cells which causes an even greater increase in tissue fluid vasodilator concentration. This is in marked contrast to the effect of severe hypoxia in the resting hindlimb, in which the dynamics of the vasodilator response appear similar to those operating during mild hypoxia. Presumably, during rest, the muscle cell requirements for resynthesis of ATP are minimal, and possibly are met, at least partly, by anaerobic metabolism.

**Autoregulation**

Autoregulation has been defined as "the intrinsic tendency of an organ to maintain constant blood flow despite changes in arterial perfusion pressure." Because the microvasculature is disten-

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**TABLE 1 Effect of Muscle Stimulation on Autoregulation and Maintenance of Oxygen Uptake**

<table>
<thead>
<tr>
<th>Stimulation rate</th>
<th>Index</th>
<th>% ΔBP</th>
<th>% ΔO₂ uptake</th>
<th>% ΔBP</th>
<th>% ΔO₂ uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest (n = 12)</td>
<td>1.07 ± 0.07</td>
<td>45.2 ± 1.0</td>
<td>+7.8 ± 5.3</td>
<td>39.9 ± 1.1</td>
<td>-13.9 ± 6.1</td>
</tr>
<tr>
<td>0.5 p/s (n = 12)</td>
<td>0.53 ± 0.06</td>
<td>39.3 ± 0.8</td>
<td>-2.6 ± 2.0</td>
<td>40.5 ± 1.2</td>
<td>-5.7 ± 4.0</td>
</tr>
<tr>
<td>1.0 p/s (n = 6)</td>
<td>0.40 ± 0.05</td>
<td>35.6 ± 0.9</td>
<td>+2.7 ± 1.7</td>
<td>42.4 ± 1.6</td>
<td>-6.7 ± 4.6</td>
</tr>
<tr>
<td>1.5 p/s (n = 6)</td>
<td>0.29 ± 0.05</td>
<td>35.8 ± 1.5</td>
<td>+2.0 ± 1.9</td>
<td>41.5 ± 1.1</td>
<td>-9.8 ± 4.6</td>
</tr>
</tbody>
</table>

Values are mean ± SE. BP = blood pressure.
sible, autoregulation includes the tendency to counteract not only the pressure-induced flow changes of a rigid system, but also pressure-induced resistance changes caused by arteriolar distension or collapse. Several methods have been described to determine the presence and effectiveness of autoregulation in skeletal muscle. Steady state autoregulation has been assessed in terms of the slope of flow-pressure curves and resistance changes induced by changes in perfusion pressure or flow. A flow-pressure curve slope less than that predicted for a rigid system or a change in steady state resistance in the same direction as a change in pressure or flow, were signs that autoregulation was present (or active). Estimates of the degree of autoregulation in resting skeletal muscle obtained by these various methods, however, have not been consistent.

The index of autoregulation that we calculated is a measure of the slope of the flow-pressure curve in the pressure range of 50–150 mm Hg. Perfect autoregulation results in an index of zero. An index between zero and one occurs when flow changes relatively less than pressure, and indicates that there is compensation for both direct pressure- and distensibility-induced alterations of flow. When the autoregulatory response is just sufficient to compensate for distensibility, flow changes are proportional to pressure changes and the index is one. An autoregulatory response too weak to compensate for distensibility results in an index greater than one.

Using this index, the data from the present experiments show that: (1) the degree of steady state autoregulation correlates closely with metabolic oxygen consumption; (2) as muscle metabolic rate increases with increasing activity, the degree of autoregulation greatly improves; and (3) depression of metabolism by cooling is associated with progressively weaker autoregulation.

Because NE was infused in these preparations, it is possible that tissue concentrations of NE varied with local flow, and thus altered a component of arteriolar tone dependent on tissue NE levels. This could have contributed to the resting steady state autoregulation, but if so, its effect appears to have been weak. It was observed that during muscle stimulation there was reduced sensitivity of flow to small fluctuations in NE infusion rate caused by the infusion pump. Thus, apart from ensuring a stable level of basal vascular tone, it appears unlikely that the NE infusion had any significant effect on our measurements of steady state autoregulation.

Decreased autoregulation with hindlimb cooling
could have resulted from depressed microvascular smooth muscle metabolism. Bohr et al.,24 however, reported increasing myogenic tone in perfused vessels from skeletal muscle when the temperature was reduced from 37°C to 15-25°C. From our experiments, temperatures in the range of 20-30°C are associated with an increase in arteriolar tone rather than a decrease from depressed smooth muscle metabolism (Fig. 7). This supports the view that the decreased autoregulation during cooling depends on reduced parenchymal cell metabolism rather than direct cold depression of the resistance vessels.

An important feature of the autoregulation response was that usually 3-4 minutes elapsed between the change in blood pressure and the stabilization of flow at its new level (Fig. 6). This time course of the response, together with the correlation between the degree of autoregulation and metabolic rate, favors the view that steady state autoregulation depends on a feedback mechanism involving metabolically linked vasodilators released from the parenchymal cells.

The influence of local metabolic rate on the degree of autoregulation could be explained on the basis that the level of microvascular tone reflects an equilibrium condition in which intrinsic myogenic activity and extrinsic vasoconstrictor influences (autonomic nerves and blood-borne humoral agents) are balanced by the tissue fluid concentration of locally released vasodilators. At a given metabolic rate, the effective concentration of vasodilator metabolites is inversely related to local flow rate. A pressure-induced change in flow alters this vasomotor equilibrium in such a way as to oppose the flow change, chiefly by resetting the tissue fluid concentration of vasodilator metabolites. At low metabolic rates, turnover rate and tissue concentrations of vasodilators are low and their contribution to the local vasomotor equilibrium is minimal. Under such circumstances, alterations of vasodilator concentration caused by pressure-induced flow changes will be small and consequently relatively ineffective in returning blood flow to its initial level. In contrast, at high metabolic rates the contribution to vasomotor equilibrium made by vasodilator metabolites is much greater. In this situation, alterations in vasodilator concentration resulting from pressure-induced flow changes are larger and more effective in changing arteriolar tone so as to return flow toward its initial value.

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