A Method for Studying Isolated Resistance Vessels from Rabbit Mesentery and Brain and Their Responses to Drugs

By Eiichi Uchida, M.D., David F. Bohr, M.D., and Sibley W. Hoobler, M.D.

ABSTRACT

A technique has been developed for studying the reactivity of single, isolated resistance vessels, 50 to 250 μ o.d., perfused at constant flow rate. The validity of the method is established because responses to a given stimulating agent are reproducible and stable over a reasonable period of time. The magnitude of the response is dependent on the perfusion pressure, being maximal at a physiological pressure level. Resistance vessels from mesentery and brain of normal rabbits were compared with respect to their threshold for response to several vasoconstrictors. The results reaffirmed the individuality of smooth muscle from different vascular beds. Cerebral and mesenteric vessels are alike in the dose required for threshold constrictor response to KCl, angiotensin and plasma, but differ in that cerebral vessels have a higher threshold for response to epinephrine, norepinephrine and serotonin, and a lower threshold for response to vasopressin, than mesenteric vessels. Since the differences in threshold between vessels from the two sources are not the same for all stimulating agents, it seems probable that smooth muscle of the cerebral vessels is not generally less sensitive to all stimuli than that of mesenteric vessels, but that vessels from the two sources differ in the "number of receptors" for the several vasoactive agents.

ADDITIONAL KEY WORDS

vascular smooth muscle
individualities in vascular smooth muscle
pressure/response relationship
tachyphylaxis
plasma constrictor factor
angiotensin II
vasopressin
serotonin
epinephrine
norepinephrine

In the study of the reactivity of isolated vascular smooth muscle, two techniques have been used. One involves direct recording of changes in tension or length of an isolated strip or ring of vascular smooth muscle (1, 2) and the other measures changes in resistance in an isolated perfused blood vessel by recording changes in pressure or flow (3-5). In either case, most of the available data have been obtained with large conduit arteries rather than with small vessels functionally important in the maintenance of vascular resistance. The reactivity of helical strips from arteries (250 μ o.d.) from various vascular beds has been studied (8), but in perfusion experiments, except for a few preparations of small coronary arteries (7), vessels of 550 μ diameter are the smallest that have been studied (8). The reactivity of muscle from cerebral artery has been directly examined only in the pial artery by observation in vivo through a cranial window and indirectly inferred from measurements of cerebral blood flow (9, 10). We have found no publication which describes reactivity of vessels in brain other than the pial artery, or re-
sults of perfusion of isolated cerebral resistance vessels.

The current study describes a method which makes it possible to perfuse a single isolated resistance vessel, 50 to 250 μ o.d. The validity of the method is established because the responses to a given agent are reproducible and the threshold for response is stable over a reasonable period of time. The relationship between responsiveness and perfusion pressure was examined. The technique was used to compare resistance vessels from the mesentery and brain of rabbits.

**Methods**

**Preparation**

The vessels studied were branches of the middle cerebral artery and of mesenteric artery from the mesojejunum. These small branches furnish the effective resistance of the vessel. By leaving them attached at one end to the artery from which they branch, it was possible to perfuse them and study changes in their responsiveness. The method of preparation was as follows: The brain and the mesentery supporting the upper jejunum were removed from 2.0- to 4.0-kg rabbits killed by a blow or by intravenous injection of 1 ml/kg of 1 M potassium chloride. The tissues removed were stored in physiological salt solution (PSS—for composition see section on Solutions and Drugs) at 4°C until used (not more than 4 days). No change in the contractile characteristics of the vessels was associated with length of storage within this period. Under a dissecting microscope (10× and 40×), and with the tissue in PSS, a part of the vascular tree was freed from its surrounding tissue. The section to be perfused was sketched and the diameter and length of each branch was measured and recorded on the sketch. All branches except a selected terminal one were cut so that the blood flow was in the direction from the artery to the capillaries. The ends of the vessels were cannulated with fine glass capillaries and mounted in a muscle bath and connected with a pressure recorder. The perfusate flowing through the vessel fills and overflows the bath chamber and the outflow is measured by a weight recorder. The inflow system just before the cannula consists of a perforated glass tube covered with heavy rubber tubing; this permits the injection of test solutions into the perfusate. Inset at upper right shows transverse section of a perfused mesenteric artery.

**Figure 1**

Diagram showing vessel preparation and perfusion technique. The cannulated vessel segment, with single outflow (shown in detail in central inset), is mounted in a muscle bath and connected with a pressure recorder. The perfusate flowing through the vessel fills and overflows the bath chamber and the outflow is measured by a weight recorder. The inflow system just before the cannula consists of a perforated glass tube covered with heavy rubber tubing; this permits the injection of test solutions into the perfusate. Inset at upper right shows transverse section of a perfused mesenteric artery.
tied off, providing a single outflow from the cannula (Fig. 1, central inset). The terminal branches were 50 to 250 μ o.d. and 0.6 to 8.5 mm in length. A cross section of a terminal branch of a mesenteric artery may be seen in the inset at the upper right of Figure 1. The section of vessel was cannulated at its proximal end (approximately 300 to 400 μ o.d.) and mounted in a 2.5-ml muscle chamber. Preparations that leaked (as identified by microscopic examination during the injection of a small amount of Evans-blue saline solution [1 mg/ml]) were discarded.

Perfusion

The perfusate passed from a reservoir through a cylindrical chamber where it was aerated (95% O2, 5% CO2) and warmed at 37°C (Fig. 1). An alternate aerating chamber was provided so that a change in perfusate could be made by the turn of a stopcock, without interrupting the perfusion. A Sigma Motor pump (Model T8) drove the oxygenated, warmed perfusate through the glass cannula and vessel. The tip of the cannula had a 400-μ o.d., 250-μ i.d., and was 1.5 mm in length. Tygon tubing (5 mm o.d., 1.8 mm i.d.) was used in the pump. A perfusion rate as low as 0.07 ml/min could be maintained. Perfusion passing through the vessel filled and overflowed the muscle chamber.

The outflow from the muscle chamber was collected in a 10-ml glass tube hung just under its orifice. The accumulating volume in the tube was recorded as was increase in tension, by a Grass

![Graphs](image)
force-displacement transducer. Flow rate was represented on the recording paper by a slope of increasing tension with time (Fig. 2). A capillary siphon attached to the tube emptied the tube automatically every 6.5 ml, and thus provided for continuous recording of flow rate.

Perfusion pressure was recorded by a pressure transducer (Statham P 23 AC) through a side arm of the cannula, just proximal to the vessel. Prepared vessels were perfused at constant flow rate by a Sigma motor pump. In experiments in which different levels of perfusion pressure were needed, the rate of pulsation of the pump was readjusted so that another level of constant flow was obtained and recorded along with the new level of perfusion pressure.

The stimulating agents were injected into the perfusate just before the cannula. A microinjector system was used to deliver the drug through a 27-gauge needle inserted through heavy rubber tubing and an underlying perforation in a glass tube forming part of the perfusion path. The volume of the tube between the injection site and the tip of the cannula was 0.25 ml. Injection of 0.002- to 0.02-ml volumes of vasoactive agents gave reproducible responses.

Sample recordings are shown in Figure 2. A terminal branch of a mesenteric arteriole (100 μ o.d. and 5.0 mm long) and a terminal branch of a cerebral arteriole (80 μ and 1.0 mm) were perfused at constant flow rates of 0.27 ml/min and 0.19 ml/min, respectively. Stimulation with norepinephrine produced an increase in perfusion pressure.

**Definitions**

Since perfusion was at constant flow rate, changes in perfusion pressure may be interpreted as reflecting changes in the resistance of the vessel. In this paper, the dose of stimulating agent which elicits the smallest measurable pressure change is referred to, as is customary, as a threshold dose. "Threshold" is also used to describe a quality of the tissue, e.g. a tissue which requires a high concentration of constrictor agent to elicit a response is said to have a high threshold for that agent. "Sensitivity," used in describing a quality of the tissue, is the reciprocal of "threshold"; a high threshold means a low sensitivity. "Responsiveness" of the tissue is measured by the magnitude of its response to a given dose of constrictor agent.

**Results**

**VALIDITY OF METHOD**

**Stability of Preparation**

The isolated minute vessels were perfused for 20 to 30 min at a low flow rate which gave a perfusion pressure below 20 mm Hg. Most preparations showed no change in perfusion pressure during this initial period of constant rate perfusion. A small number of preparations showed a gradual small decrease in pressure within 10 min after the start of perfusion, but, in any case, a stable perfusion pressure was established by the end of the first 10 min.

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The **reproducibility of the responses** and the change of responsiveness to a given agent...
with time were examined in 5 mesenteric vessels. A standard small dose of norepinephrine was injected at 10-min intervals after the initial perfusion period (Fig. 3). A 10-min period was chosen as the interval between injections to allow time for the removal of the stimulating agent from the tissue and the surrounding bath. The contractile response increased gradually over the first 1 to 3 hr of perfusion, remained stable for the next 2 to 3 hr, after which it declined. These changes in magnitude of response with time were relatively small. Responsiveness of the vessel usually persisted for as long as 7 hr of perfusion (Fig. 3). This change in responsiveness with time was also observed in one experiment in which potassium chloride was used as the stimulating agent for a cerebral artery. The period on the plateau of the response was usually longer in larger arteries than in smaller ones and longer in mesenteric than in cerebral.

**Resistance in large and small vessels**

To define the role of the terminal branch in the resistance of the terminal branch and in the resistance of the whole preparation, resistances were compared before and after cutting off the terminal branch. Resistance was calculated from recorded pressure and flow by the formula: 

\[
\text{Resistance} = \frac{\text{Pressure (mm Hg)}}{\text{Flow (ml/min)}}.
\]

An example of the experimental procedure and the results is shown in Figure 4. Using the whole vessel segment, perfusion flow rate was increased and decreased, in steps, at approximately 10-min intervals (Fig. 4, curve 1). The terminal portion (100 \( \mu \) o.d., 3.0 mm long) was then severed under the dissecting microscope, and the same procedure was repeated with the remaining proximal portion (250 \( \mu \) o.d. and 5.5-mm long) alone (curve 2). Finally, the proximal portion was removed and the resistance of the glass cannula alone was studied at several perfusion pressures (curve 3). From these measured values, it was possible to calculate the resistance of the terminal portion (curve 4) by subtracting curve 2 from curve 1, and that of the proximal portion (curve 5) by subtracting curve 3 from curve 2. In 7 experiments of this type, the resistance of the whole vascular segment at a perfusion pressure of 60 mm Hg was 43 to 67% of the total resistance of the system including the cannula and tubing; the resistance of the terminal portion was 45 to 90% of that of the whole vascular segment.

Consistent differences in resistance were observed with changes in perfusion pressure. The total resistance of the system with its vessel (Fig. 4, curve 1) increased with an increase in perfusion pressure. In 25 experiments testing the relation of flow to pressure, this increase in resistance was consistently...
observed. It was seen even when the vessel was perfused with calcium-free PSS containing 3 mM EGTA (ethylene glycol bis-aminoethylether)-N,N'-tetraacetic acid) or when sodium nitrite (1 g/liter) was added to the perfusate. These observations eliminate the possibility that the increase in resistance was due to an active smooth muscle response elicited by the increase in perfusion pressure. That this phenomenon does not depend on physiological properties of the vessel wall is demonstrated by the fact that a similar increase in resistance is seen when the perfusion pressure through the small glass cannula is increased (curve 3). The hydrodynamic basis for this change in resistance is dealt with in the Discussion. The resistance of the proximal portion decreased when perfusion pressure was increased (curve 5) suggesting that the vessel was passively distended. The resistance of the terminal portion (curve 4), however, remained almost constant.

Relationship between response and perfusion pressure

Responses of a mesenteric artery to a standard dose of norepinephrine at several perfusion pressures are shown in Figure 5. Responses increased in magnitude with increased perfusion pressure from 8 to 25 mm Hg remained unchanged in the range of 25 to 60 mm Hg, and then decreased. This pattern of relationship between response and perfusion pressure was essentially the same in 11 experiments with mesenteric arteries and norepinephrine, and in 1 experiment with a cerebral artery and potassium chloride. In a given vessel, responses to small and large doses of a constrictor were increased in the same range of perfusion pressures. At higher pressures, however, when the responses were decreased, the decrease in response to a small dose was apparent at a lower perfusion pressure than that to a large dose. Changes in magnitude of the response occurred in almost the same range of perfusion pressures in vessels of many sizes, but there was no such definite relationship between magnitude of response and flow rate. In three mesenteric vessels, the constrictor response was studied by switching the perfuse from normal PSS to one containing 0.05 to 0.1 µg/ml norepinephrine. In these experiments, the changes in response dependent on perfusion pressure were confirmed by perfusing at 80, 40, and 10 mm Hg. Response to norepinephrine infusion was greatest at 40 mm Hg and least at 10 mm Hg perfusion pressure.

![Figure 5](https://example.com/figure5.png)

**Figure 5**

Effect of perfusion pressure on response of mesenteric vessel (200 µ x 2.0 mm) to norepinephrine (0.2 µg). Pressure increments (first run •, second run ○) and decrements (after second run, △) are at approximately 10-min intervals.
ISOLATED RESISTANCE VESSELS

TABLE 1
Dimensions of the Terminal Segments

<table>
<thead>
<tr>
<th>Terminal segment</th>
<th>Mesenteric vessels</th>
<th>Cerebral vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (o.d.)</td>
<td>80-250 μm</td>
<td>50-240 μm</td>
</tr>
<tr>
<td>Length</td>
<td>0.6-8.5 mm</td>
<td>1.0-8.0 mm</td>
</tr>
</tbody>
</table>

Average diameter and length of 43 mesenteric and 21 cerebral terminal vessel segments tested.

The preparations often showed decreased responsiveness when, after a period of very high perfusion pressure, the pressure was returned to the previous lower level, and in such cases they never regained their former sensitivity.

COMPARISON OF SENSITIVITY OF RESISTANCE VESSELS FROM MESENTERY AND BRAIN

These results are based on a series of 43 experiments with mesenteric and 21 with cerebral vessels from 28 normal rabbits. The similarity of the dimensions of the terminal segments of the vessel preparations is shown in Table 1.

An experimental period starting 1 to 2 hr after perfusion had begun was chosen, and a perfusion pressure between 20 and 60 mm Hg (flow rate 0.14 to 1.29 ml/min) was used. Sensitivity of the preparation was checked at the beginning and end of the experiment, and often during it, by injection of norepinephrine or epinephrine into the mesenteric vessel and potassium chloride into the cerebral vessel. Figure 2A shows the dose-response characteristics of a mesenteric artery to norepinephrine. The minimal effective dose of norepinephrine was 0.03 μg, and this value was considered to be threshold for norepinephrine for this vessel. (In all experiments, the sensitivity of the recording system was fixed at the same gain.) The threshold values for various constrictor agents were compared as indicators of relative responsiveness of mesenteric and cerebral resistance vessels (Table 2). Tachyphylaxis occurred with angiotensin II, vasopressin and serotonin, in preparations from both mesentery and brain, making it necessary in experiments involving these drugs to wait at least 2 hr before repeating an injection of the same agent.

Potassium chloride (6 to 60 μmoles given as 2 to 20 μliters of 3M KCl) produced vasoconstriction in both mesenteric and cerebral vessels (Fig. 6). In a few cerebral vessels perfused at a low flow rate, the response was biphasic, especially after repeated stimulation. This biphasic response consisted of an initial brief, small dilatation followed by a prolonged constriction. No vessel showed only vasodilatation. Threshold doses of KCl for the two vascular beds were in the same range, as shown in Table 2. Generally, constriction of

<table>
<thead>
<tr>
<th>Agent</th>
<th>Threshold for response of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mesenteric vessels</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>6-60 μmoles (12)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.01-0.1 μg (12)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.01-0.5 μg (37)</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>0.1-0.5 μg (12)</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>40-200 milliunits (6)</td>
</tr>
<tr>
<td>Serotonin</td>
<td>0.2-10 μg (10)</td>
</tr>
<tr>
<td>Plasma, rabbit</td>
<td>4-10% (3)</td>
</tr>
<tr>
<td>Plasma, dog</td>
<td>2-20% (3)</td>
</tr>
</tbody>
</table>

Threshold doses of various agents for constriction of mesenteric and cerebral vessels. Mesenteric vessels are more sensitive than cerebral vessels to epinephrine, norepinephrine and serotonin, less sensitive than cerebral vessels to vasopressin, and the two types of vessels are equally sensitive to KCl, angiotensin II and plasma. >, =, and < indicate relative sensitivities of the two types of vessels. The numbers in parentheses indicate number of experiments.

*Four additional preparations failed to respond to 20 μg.
†Six additional preparations failed to respond to 10 μg.

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Response of mesenteric and cerebral resistance vessels to KCl (A) and vasopressin (B). The two vessels are similar in their responsiveness to KCl, but the cerebral vessel responds to a much lower dose of vasopressin (6 mU) than does the mesenteric (60 mU). Tachyphylaxis to vasopressin is apparent in both vessels. The mesenteric vessel was 150 μ × 2.8 mm (flow: (A) 0.18, (B) 0.23 ml/min) and the cerebral vessel was 60 μ × 13 mm (flow: (A) 0.17, (B) 0.13 ml/min).

Cerebral vessels lasted longer than that of mesenteric vessels, even though the flow rate was the same.

Norepinephrine and epinephrine caused vasoconstriction in vessels from mesentery and, usually, brain; however, many cerebral vessels failed to respond, even to doses of 20 μg or more. Mesenteric vessels were much more sensitive to both drugs (Table 2). The magnitude of constriction of cerebral vessels was less and the duration was greater than for mesenteric.

Angiotensin II caused constriction of both mesenteric and cerebral vessels. The minimal effective dose was almost the same for the two vessels. The most characteristic feature of the response to angiotensin II was the strong tachyphylaxis in both preparations, as reported recently (12). After an initial injection of angiotensin II (0.1 to 0.5 μg), there was no response to a second injection 10 or 30 min later, even with higher doses. After a 2-hr recovery period, the response was less than 50% of the initial response. It was, therefore, difficult to evaluate the threshold for angiotensin II correctly. The response of cerebral vessels to angiotensin II was more transient than that to KCl or catecholamines.

Vasopressin caused constriction of both mesenteric and cerebral arterioles. Cerebral vessels were more sensitive to the drug than mesenteric vessels (Fig. 6, Table 2). Tachyphylaxis was observed in response to vasopressin, but was not so marked as to angiotensin II; a second large dose of vasopressin could produce vasoconstriction 10 min after the first small dose. Cross tachyphylaxis between vasopressin and angiotensin II was not found. Both arteries responded to vasopressin with a more gradual increase and decrease in resistance than to any other agent.

Serotonin caused vasoconstriction in both preparations. Mesenteric vessels were a little more sensitive than cerebral vessels (Table 2). The threshold dose of serotonin for a large cerebral vessel from the Circle of Willis was much lower than for small cerebral vessels. A wide divergence in response from one vessel to another from the same site made it difficult to estimate the threshold dose for the vessels. Both mesenteric and cerebral vessels showed tachyphylaxis to serotonin. Serotonin consistently potentiated the action of catecholamines, even after a series of serotonin injections which themselves produced no vasoconstriction. This potentiation lasted 20 to 30 min after the injection of serotonin. It was specific for responses to catecholamines.

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Plasma added to the muscle bath produced
vasoconstriction in both mesenteric and cerebral vessels. The vasoconstrictive action was not blocked by phenoxybenzamine and there was no tachyphylaxis to it. Even in concentrations too low to produce contraction, plasma potentiated the constrictor action of catecholamines and KCl in both mesenteric and cerebral arteries. The potentiating action of plasma disappeared so rapidly with time after mixing in the bath (less than 20 min at most) that the coexistence of stimulant and plasma in the bath seems to be necessary for potentiation. Both vasoconstriction and potentiation of vasoconstriction were produced by protein-free filtrate and by boiled filtrate of plasma as well as by whole nontreated plasma.

Discussion

The method described in this paper was devised in response to a need for information about the reactivity of isolated vascular smooth muscle from resistance vessels, because of their important role in the regulation of circulation. The vessels of 50- to 250-μ o.d. used in the current study are considered to be in this category. These vessels are considerably smaller than the 500-μ vessels catheterized by Haddy et al. (13) in their studies of segmental vascular resistance in the dog. These investigators observed that more than one quarter of the resistance of the vascular tree was proximal to vessels of this size. Beyond this point pressure fell more precipitately. In the case of cerebral resistance vessels, the need for study is reinforced by contradictory reports concerning their reactivity.

The method described may be used in making preparations from any vascular bed. We have applied the technique to cutaneous, skeletal and renal vascular beds, as well as to mesenteric and cerebral, and have found similarities and individualities in response to various vasoactive agents among them. Vessels from mesentery are more readily prepared than those from brain or kidney.

Increase of resistance with increase in perfusion pressure indicates that determinants other than those of the Hagen-Poiseuille equation are applicable in our system. Hinke obtained similar results in a preparation given a constant radius by constriction with norepinephrine (8) and later proposed a modified Poiseuille equation describing the relation of flow and pressure (14). This is a problem in the field of hydrodynamics, and the possible responsible factors are turbulence of flow and lack of steady flow, as pointed out by Hinke. If turbulence is the cause, then resistance should increase greatly at higher pressure. However, in our study, the increase in resistance was less at high pressure (curves 1, 2, and 3 of Fig. 4 appear to be parabolic). This resembles the relationship between resistance and pressure in flow through orifices (15).

In our results with mesenteric vessels, the terminal branch (100-μ o.d.) behaved as a rigid tube, whereas the remaining vessel (250 μ) was distended slightly when perfusion pressure was elevated. In contrast with the stiffness in small vessels, a 556-μ tail artery showed marked distention with increasing pressure (8). This difference is not surprising because the 556-μ group of arteries was not as distensible as the 616-μ group, even though there was a difference in radius of only 60 μ.

Reproducibility and stability of response of the preparations were found adequate for studying the reactivity of vascular smooth muscle. Stable perfusion pressure was established within 10 min after the start of perfusion; this is similar to the time reported by Rogers et al. (16) for an isolated preparation of dog mesenteric artery with small branching resistance vessels. There was no change in perfusion pressure analogous to the gradual (2 hr) relaxation of the aortic helical strip observed by Furchgott and Bhadrakom (1). It is difficult to estimate the role of the terminal branch in the response of the vessel to vasoactive agents because changes in the other response-determining factors are involved. Marked decreases in responsiveness and sensitivity in a segment with its terminal branch removed suggest the important role of this
segment, as does the fact that 45 to 90% of the resistance of the whole vessel is due to the resistance in the terminal branch.

The relationship between response and perfusion pressure is a fundamental problem in the study of any perfused system. There are reports that the magnitude of response decreases with increase of perfusion pressure in the range of 100 mm Hg and higher (17-19). These results, however, are from the isolated hind limb preparation perfused with blood, with or without nervous control, or from the whole animal which has some vascular tone in the control condition. In experiments on isolated perfused vessels, little attention has been given to the effect of perfusion pressure on response to vasoactive agents; most of the experiments have been carried out at perfusion pressures considered physiological, from 60 to 120 mm Hg. Under the conditions of our experiments, in maximally relaxed vessels the magnitude of the response to any agent depends upon the perfusion pressure, increasing with increase in perfusion pressure up to 25 to 30 mm Hg, remaining unchanged from this to about 60 mm Hg, and then decreasing. Henke's results (20), showing flow-pressure relationships in relaxed vessels and in those constricted by norepinephrine, clearly show this same biphasic tendency for responsiveness to change as perfusion pressure is increased.

In our preparation, a 10-mm Hg increase in perfusion pressure increased or decreased the magnitude of the pressor response, depending on whether the starting pressure was below 30 mm Hg or above 60 mm Hg. It is necessary to examine possible mechanisms for both the increase in response in the low pressure range and the decrease in response in the high pressure range.

There are two obvious bases for support of the increase in response in the low pressure range. The first is related to the fact that the response is measured as an absolute pressure change. If a constant flow rate that produces a perfusion pressure of 10 mm Hg is used and a dose of constrictor that doubles vascular resistance is injected, the perfusion pressure doubles and a 10-mm Hg response will be recorded. If a higher constant flow rate that causes a basal perfusion pressure of 20 mm Hg is used and the same dose of constrictor injected (doubling vascular resistance), a 20-mm Hg response will be recorded. Thus, if the constrictor agent is capable of producing the same change in vessel geometry as the perfusion pressure is increased, the magnitude of the absolute pressure response will increase directly as the perfusion pressure increases. A second basis for the increase in response observed with increase in perfusion pressure is the physiological characteristic of all muscle, including vascular smooth muscle (21-23), that its contractility is enhanced by stretch or by an increase in resting tension. This enhanced contractility would be expected to support an increase in pressor response as pressure is increased, at least over the lower pressure range.

Three mechanisms must be considered for the role they might play in causing the observed reduction in response as perfusion pressure is increased above 60 mm Hg. First, since increases in perfusion pressure were effected by increasing flow rate, it seems possible that the higher flow rates would cause a greater dilution of the injected dose of epinephrine and hence reduce the concentration of constrictor agent reaching the tissue. However, there is no relationship between flow rate and response in vessels of different size, but there is a consistent relationship between perfusion pressure and response in vessels of different sizes—so it would seem that the response depends on the pressure, not on the flow rate. This concern was further evaluated by studying the pressor responses produced by infusing a constant concentration of a constrictor agent. These studies confirm the dependence of the pressor response on perfusion pressure, demonstrating that the pressor response to a constant concentration of norepinephrine was decreased when perfusion pressure was increased from 40 to 80 mm Hg. The dilution factor was thus eliminated as a major determinant of the decrease in response.

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A second mechanism which might be responsible for the decrease in response is related to an increase in vessel circumference that might be produced by an increase in perfusion pressure. Assuming that the constrictor agent was able to produce the same absolute shortening of the circumference at a relatively small and a relatively large initial circumference, a given absolute change would have a lesser effect on vascular resistance as the initial, relaxed circumference was greater. Since our studies gave no evidence of an increase in vessel distension with an increase in perfusion pressure (except in the large proximal segment of the vessel, where an increase in perfusion pressure did produce a decrease in resistance), this basis for the decrease in response cannot be supported.

A third mechanism, which must have been responsible for the decrease in responsiveness at higher perfusion pressures, is the decrease in contraction evidenced by all muscle, including vascular smooth muscle (21-23), when it is subjected to very high resting tension. Indirect support for the primacy of this determinant is our observation that when the contractile ability of the muscle is enhanced by subjecting it to a larger dose of constrictor agent, the pressor response is maintained against a higher perfusion pressure.

Comparison of responsiveness to several vasoactive agents showed both similarities and differences between cerebral and mesenteric resistance vessels, and confirmed the individuality of various vascular smooth muscle which has been reported from work with helical strips (6).

The threshold doses of potassium chloride, angiotensin and plasma for the two types of vessels were in the same range. However, the threshold for response to epinephrine, nor-epinephrine and serotonin was higher in cerebral vessels than in mesenteric; mesenteric vessels required a higher concentration of vasopressin for a threshold response than did cerebral vessels. These differences were present consistently. Since the differences in responsiveness of vessels from the two sources are not the same for all stimulating agents, it seems probable that smooth muscle of the cerebral vessels is not generally less sensitive than that of mesenteric vessels to all stimuli, but that vessels from the two sources differ in the number of receptors for the several vasoactive agents.

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References


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