Flow-Induced Constriction and Dilation of Cerebral Resistance Arteries

Jose-Luis Garcia-Roldan and John A. Bevan

Rabbit pial resistance artery segments were cannulated at both ends so they could be perfused with physiological saline solution and were maintained in a tissue bath of the same solution. Both were kept at 37°C and equilibrated with 95% O₂ and 5% CO₂. Perfusion pressure and flow were independently controlled by two servo-controlled pumps, and changes in the diameter of the segment were registered by an automated video technique. In the absence of flow, these segments maintained their diameter when intraluminal pressure was changed over the range 30-90 mm Hg. When intraluminal pressure was low (30 mm Hg), flow at 20 μl/min caused dilation. This is half the rate of flow that causes a maximum flow-induced change under the conditions of these experiments. When pressure was high (90 mm Hg), the same flow rate caused constriction. Both responses usually continued as long as flow was maintained. Thus, flow-induced changes in the diameter of this artery can be initiated and are usually maintained despite the demonstrated capacity of the blood vessel wall to hold its diameter constant when pressure is changed in the absence of flow. The results suggest that these small arteries can independently respond to changes in pressure and flow and that the changes that occur in response to flow are not compensated for by changes in the myogenic response. (Circulation Research 1990;66:1445-1448)

The myogenic response, the contraction of vascular smooth muscle that follows stretch of the blood vessel wall, has been recognized since the turn of the century.¹ This phenomenon has been demonstrated in vivo and in vitro under a variety of circumstances, and many aspects of its cellular mechanism are known.²,³ However, only recently have flow-induced changes in resistance artery and small vein wall tone been observed in vitro.⁴,⁵ These observations were made during the infusion of physiological saline solution (PSS) into myograph-mounted artery segments when wall force was recorded isometrically. It is clear that these in vitro experiments have a number of drawbacks, one of which is that possible interactions between pressure- and flow-induced changes cannot be observed. In vivo, a change in vascular pressure is likely to be associated with concomitant changes in flow and vice versa. Thus, the final state of the blood vessel wall tone after changes of pressure in vivo probably represents the interaction of these two (and possibly other) factors. However, separation of pressure and flow in small blood vessels in the intact organism represents a considerable experimental challenge.

In this paper, we report that flow contraction and flow dilation as well as the myogenic response can be observed in saline-perfused pial artery segments (approximately 200 μm o.d.). These segments were mounted in an apparatus in which changes in segmental diameter can occur and are registered by an automated video monitoring system.⁶ By using two servo-controlled perfusion pumps, pressure and flow through the segments could be controlled independently. The pial artery was chosen because all three phenomena of interest have been demonstrated in segments of that artery with the myographic technique. We have found changes in diameter, both dilation and constriction, associated with flow in this artery segment that cannot be explained by changes in intravascular pressure.

Materials and Methods

Sixteen rabbit pial artery segments (approximately 200 μm o.d. determined at 2 mm Hg intraluminal pressure), each from a different animal, were mounted in the automated video perfusion system of Halpern et al.⁶ The segments were modified in these experiments to allow independent control and registration of pressure and flow. Artery segments were cannulated at both ends to allow perfusion of Krebs' bicarbonate solution equilibrated at 95% O₂-5% CO₂.

Footnotes:
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⁴ Received September 14, 1989; accepted December 7, 1989.
at 37°C. Segments were immersed in an identical solution. Recordings 1) of the pressures inside the proximal and the distal cannulae by pressure transducers and 2) of arterial diameter by the video monitoring system were made on a strip chart recorder.

After an initial equilibration period of 1 hour, responses to standard drug stimuli (histamine $10^{-7}$ M, potassium 9, 17, 33 mM, acetylcholine $10^{-7}$ M) designed to test the reactivity of the artery segment were recorded. Diameter changes were measured in the absence of flow in each segment when intraluminal pressure was set at 30, 60, or 90 mm Hg with a servo-perfusion system connected to the proximal cannula. Flow of preheated preequilibrated Krebs' bicarbonate solution was achieved by using two servo-perfusion systems, one advancing the solution through the proximal cannula and the other withdrawing it through the distal cannula while controlling intraluminal pressure. By changing the proximal/distal pressure gradient by setting proximal and distal pressures in the infusion cannulae with the servo pumps, a specific flow could be achieved at different mean pressures.

Calcium-free PSS contained EGTA (1 mM), but no CaCl$_2$.

**Results**

Pial artery segments (222.6±18 μm o.d.; $n=16$) measured when the intravascular pressure was 2 mm Hg immediately increased their diameter by approximately 50% when the pressure was raised to 60 mm Hg. During the subsequent hour while this intravascular pressure was maintained, segments slowly contracted reaching a new steady-state diameter approximately 30% less than the diameter recorded at this pressure at the beginning of the experiment. This vasoconstriction represented an active increase in tone as it was reversed in calcium-free PSS. Steplike changes in intravascular pressure resulted in a distinctive pattern of diameter change (Figure 1). An increase in pressure caused an immediate increase in diameter followed by a relatively slow contraction, which leveled out at or close to the prepressure increase level. The first but not the second component was observed when pressure was increased in an artery bathed in calcium-free Krebs' bicarbonate solution. When the intraluminal pressure was decreased, there was invariably an immediate decrease in arterial diameter, followed by a slower return to the original level. Again, the first but not the second phase was observed under calcium-free conditions. In a series of experiments, arterial diameters of a segment measured after equilibration, several hours after setup at 30, 60, and 90 mm Hg, were not significantly different from each other (see Table 1).

Intraluminal flow (20 μl/min) caused two types of responses. The one which was invariably observed at 30 mm Hg was dilation, an increase in diameter (Figure 1, Table 1). After flow cessation, although in some instances diameter decreased below the original level, the final diameter was the same as that before flow. At 60 mm Hg, the response to flow was a modest dilation. At 90 mm Hg, the response to flow was constriction. A flow rate of 20 μl/min was half the rate that caused a maximum constriction in these experiments. Although in the majority of instances (>70%) this was maintained as long as flow was continued, on a number of occasions the flow-induced constrictor response diminished while flow was continued. The changes of pressure associated with these flow-induced effects that were needed to achieve the pressure gradient for the

**Figure 1.** Change in diameter of perfused rabbit pial resistance artery to alteration of intraluminal pressure and flow. Top panel: Myogenic response. When there is no flow a decrease in pressure from 60 to 30 mm Hg causes an immediate decrease in diameter followed by a slow return to control levels. Increases in pressure to 90 mm Hg causes an immediate increase in diameter followed by a contraction and transient overshoot and then resumption of the original diameter. Middle and bottom panels: Flow contraction and dilation. Prearterial cannula pressure is represented by the solid line (---) and postarterial cannula pressure by the dashed line (----). The difference between presegmental and postsegmental pressures is necessary to achieve flow (20 μl/min) through the segment. When the control pressure is 90 mm Hg, flow causes constriction, and when the pressure is 30 mm Hg, flow causes dilation.
flow were small and varied between means of 2.1 and 3.0 mm Hg (see Table 1).

**Discussion**

When PSS is infused through an isolated artery segment isometrically mounted in a myograph, constriction and dilation have been observed in rabbit pial resistance arteries, the same vessel used in this study. These arteries also respond to stretch. All of these changes occur after endothelium removal and probably originate from the effects of flow and stretch on the vascular smooth muscle cells. Although techniques centered around the myograph have considerable experimental advantage for some objectives, because all responses are measured isometrically, this approach has its limitations. In vivo, arteries and veins effect their physiological changes primarily through changes in diameter, and changes in diameter do not occur under isometric conditions.

The pial resistance artery mounted in the automated video perfusion system can change its diameter. After equilibration during which the artery develops active tone in the absence of flow, the artery maintains its diameter over the intravascular pressure range of 30–90 mm Hg. The restoration of diameter after pressure change was an active response in that it did not occur under calcium-free conditions.

Two qualitatively different responses to flow were observed. At the lower pressure (30 mm Hg and to a much less extent at 60 mm Hg), flow caused dilation (Figure 1) commonly followed at its cessation by constriction to below perfusion levels to which it subsequently returned. At the higher pressure (90 mm Hg), constriction was observed commonly followed when flow was stopped by dilation, before restoration of the control diameter (Figure 1). The flow rate used was of the same order as that determined in vivo in arteries of similar size in other vascular beds. The infusion of saline through an artery segment from the rabbit ear isometrically mounted in a myograph can, according to the circumstances, cause either constriction or relaxation. These present experiments also show that flow can cause two diametrically opposite changes. In the segments that were mounted in a myograph and that possess little intrinsic (stretch-induced) tone, evidence has been obtained that flow-induced effects are probably the sum of these constrictor and dilator influences and that these together tend to move the level of artery wall tone toward an intermediate level. It may be that the overshoot in diameter seen on flow cessation in these present studies, particularly after flow contraction (see Table 1), reflects the interaction of two such independent flow-induced effects. In parallel to the flow-induced contractions in the myograph experiments, which were abolished by calcium-free conditions (J.A. Bevan and E.H. Joyce, unpublished data, 1989) flow-induced vasoconstriction observed in these experiments had a similar calcium dependence.

These studies show that arterial diameter changes associated with flow were not restored by the myogenic mechanism that was so effective in maintaining arterial diameter when that was changed by pressure. We cannot, however, exclude the possibility that myogenic mechanisms may have modified the effect of flow. Until we know more about the cellular mechanisms involved with these changes in tone, we cannot explain why flow-induced effects are not compensated for by the myogenic response. This observation, however, and the fact that at 30 mm Hg flow causes dilation and pressure myogenic contraction serve to substantiate the claim that the response of these small vessels to pressure and flow are independent.

This pattern of arterial wall response to flow seems an appropriate homeostatic mechanism. When intravascular and thus organ perfusion pressure is low, an increase in intraluminal flow by causing vasodilation would tend to expose the arterial wall to a greater flow or pressure. On the other hand, when intravascular pressure is high and when myogenic tone is considerable, presumably protecting the brain from the consequence of this pressure by maintaining pial diameter, an increase in flow rather than mitigating against this myogenic tone, enforces it.

**References**


### Table 1. Flow-Dependent Changes in Diameter of Rabbit Pial Resistance Arteries at Different Intraluminal Pressures

<table>
<thead>
<tr>
<th>Intraluminal pressure (mm Hg)</th>
<th>Preflow diameter (μm)</th>
<th>Changes in diameter with flow (μm)</th>
<th>Changes in perfusion pressure associated with flow (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>266±13</td>
<td>(−) 22±3</td>
<td>3.0±0.3</td>
</tr>
<tr>
<td>60</td>
<td>258±12*</td>
<td>(−) 2.3±0.5</td>
<td>2.1±0.5</td>
</tr>
<tr>
<td>90</td>
<td>248±15*</td>
<td>(+) 24±3</td>
<td>2.4±0.2</td>
</tr>
</tbody>
</table>

*Values are mean±SEM. Diameter changes with flow (20 µl/min) were studied at the three pressures in each of the 16 animals. +, Constriction; −, dilation.

*Not significantly different from arterial diameter at 30 mm Hg.*


**KEY WORDS** • flow • calcium • constriction • dilation • pial • resistance artery • myogenic tone
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