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Prostaglandins Mediate Arteriolar Dilation to Increased Blood Flow Velocity in Skeletal Muscle Microcirculation

Akos Koller and Gabor Kaley

In cremaster muscle of pentobarbital-anesthetized rats, temporary occlusion of an arteriole increased red blood cell velocity (mean increase, 8.2 ± 1.0 mm/sec from a control velocity of 7.9 ± 0.7 mm/sec) in proximal parallel arteriolar branches (mean control diameter, 19.4 ± 0.6 μm). Increases in flow velocity were consistently followed by proportional delayed (6–15 seconds) increases in arteriolar diameter (5.8 ± 0.7 μm). Administration of N^G -monomethyl-L-arginine (200 μM), an inhibitor of the synthesis of endothelium-derived relaxing factor that blocked the arteriolar responses to acetylcholine (1 μM) but not to arachidonic acid (10 μM), did not affect the dilation (mean increase, 8.9 ± 1.1 μm) due to increases in red blood cell velocity (13.4 ± 1.5 mm/sec). However, the cyclooxygenase inhibitor indomethacin (or meclofenamate), which completely blocked the dilator response to arachidonic acid but did not change the response to acetylcholine, inhibited the arteriolar dilation (mean increase, 0.3 ± 0.2 μm) due to increases in red blood cell velocity (9.3 ± 1.0 mm/sec). Inhibition of prostaglandin synthesis also reduced the increase in calculated blood flow by 57% during occlusion. These results suggest that the arterioles are sensitive to increases in blood flow velocity (wall shear stress), in response to which they release prostaglandins, eliciting vasodilation. The existence of this phenomenon in the skeletal muscle microcirculation suggests a new regulatory mechanism that, by modulation of vascular resistance in the microvascular network, has the role of normalizing wall shear stress and providing for substantial increases in tissue blood flow. (*Circulation Research* 1990;67:529–534)

Recently, we have reported that in skeletal muscle microcirculation, an increase in blood flow velocity elicits dilation of arterioles¹ and that this phenomenon is dependent on vascular endothelium.² The nature of the endothelial mediation, however, has not yet been clarified in the microcirculation in vivo. In large vessels, both endothelium-derived relaxing factor (EDRF)³ and a nonprostaglandin metabolite of arachidonic acid⁴ have been suggested as mediators of a similar “flow-dependent” dilator response. Previously, it was also reported that exposure of cultured endothelial cells^{5,6} to increases in shear stress results in release of vasoactive prostaglandins. In the present experiments, using parallel occlusion¹—a method to elicit an increase in arteriolar blood flow velocity—and inhibitors of prostaglandin

synthesis (indomethacin or meclofenamate), as well as an inhibitor of EDRF production (N^G -monomethyl-L-arginine [NMA]^{7–9}), we demonstrate that in skeletal muscle microcirculation in vivo, the flow velocity (shear stress)–sensitive vasoregulatory mechanism is mediated by prostaglandins.

Methods

Male Wistar rats 5–6 weeks of age were anesthetized with a subcutaneous injection of pentobarbital sodium (35 mg/kg). A constant level of anesthesia was maintained throughout the experiment by subcutaneous injection of supplemental doses (20% of original dose) of the anesthetic agent every 30–45 minutes. The trachea was cannulated to facilitate respiration. Arterial blood pressure was monitored with a Statham P23 D6 transducer (Gould Inc., Oxnard, Calif.) connected to a cannula inserted in the left common carotid artery and recorded on a Sormedics Dynograph recorder (model R511A, Anaheim, Calif.). The left cremaster muscle was surgically exteriorized with effort to maintain an intact blood and nerve supply. Throughout the surgical procedure and during the experiment, the mus-

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cle was superfused with Krebs' solution at a rate of 2 ml/min. The pH of this solution was 7.4; it contained millimolar concentrations of NaCl 154, KCl 5.6, CaCl₂ 2.2, and MgSO₄ 1.2 and was bubbled with 5% CO₂-95% N₂. The temperature of the animal, the superfusion solution, and the supporting Plexiglas platform for the muscle were thermostatically controlled at 37°, 33.5°, and 33.5° C, respectively. These conditions provided for a stable preparation throughout the course of the experiments.

After surgery, 30–40 minutes was allowed to reach a steady state of baseline arteriolar tone. The image of the microvessels was recorded on a videorecorder with a television microscope (Olympus, Lake Success, N.Y.) using a $\times 20$ objective with 0.4 N.A. and transillumination with a tungsten lamp. The resting (control) internal diameter of arterioles and the peak changes in diameter in response to experimental intervention and vasoactive agents were measured with an image-shearing monitor,¹⁰ and red blood cell (RBC) velocity (an indicator of blood flow velocity) was measured with a self-tracking correlator (models 907 and 102B, respectively, IPM, San Diego); the latter was calibrated with a disk coated with dried RBCs rotating in the focal plane.¹¹

Increase in wall shear stress was elicited by an increase in blood flow velocity^{1,2} (wall shear stress = $\mu dV/dr$, where μ is viscosity, V is velocity, and r is radius). This was obtained by occluding (up to 2.5 minutes) an arteriole (40–60 μm in diameter). During this intervention, we followed the events occurring in one of the several parallel arterioles (diameter, 15.7–23.5 μm) branching off proximally (500–2,000 μm) from the occlusion. To avoid confusion with the earlier frequently investigated method of serial occlusion, we named this intervention "parallel occlusion."^{1,2} Because blood flow supply to the region studied is constant, it follows, according to the law of conservation of mass, that occlusion of an arteriole will result in an increase in blood flow (and blood flow velocity) in the several proximal parallel arterioles. Arteriolar blood flow (Q) was calculated by $Q = V_m r^2 \pi$, where V_m (mean velocity) is obtained by V_{rbc}/f , where $f = 1.6 > 15 \mu\text{m} < 1.3$. Arteriolar responses to parallel occlusion were recorded during control conditions and after 30 minutes of superfusion, followed by continuous administration of indomethacin (10 $\mu\text{g/ml}$) or meclofenamate (10 $\mu\text{g/ml}$), or NMA (200 μM) (number of animals, 8, 3, and 7, respectively; 1–3 occlusions were performed in each experimental condition). The microoccluder was fabricated from stainless steel wire and had a tip of approximately 60 μm . The micromanipulator (Narishige U.S.A., Greenvale, N.Y.), used to precisely position the microoccluder, was secured on the animal stage, which allows for free movement of the preparation without interfering with the occlusion.

Basal diameter and peak changes in diameter due to topical acetylcholine (1 μM) and arachidonic acid (10 μM) of the same segments of arterioles used for flow velocity studies were determined before and

during indomethacin, meclofenamate, or NMA administration. Between each application of an agent, about 5 minutes was allowed for the vessel diameter to return to control. All vasoactive substances (80 μl) were administered topically on the arteriole under investigation with a micropipette without interrupting the flow of the superfusion fluid. Appropriate dilution of substances was made with Krebs' solution before administration. Acetylcholine chloride and arachidonic acid were obtained from Sigma Chemical Co., St. Louis. Indomethacin was provided by Merck Sharp & Dohme, Rahway, N.J., and meclofenamate by Parke-Davis Co., Morris Plains, N.J. NMA was obtained from Calbiochem Co., La Jolla, Calif., as the sulfonate salt.

Data reported are mean \pm SEM, with n indicating the number of experimental interventions. Statistical analyses were performed using Student's t test, and regression analysis, as appropriate. A p value less than 0.05 was considered significant.

Results

The mean arterial blood pressure of individual rats did not change over the entire experimental protocol and was within a range of 95–120 mm Hg.

An original recording in Figure 1A depicts the changes in RBC velocity and arteriolar diameter before, during, and after parallel arteriolar occlusion. At the onset of occlusion, RBC velocity started to increase in the arteriole under study, which was then followed (in this case after an approximate 8-second delay) by an increase in arteriolar diameter. First RBC velocity then diameter reached a peak value. On release of the parallel occlusion, RBC velocity decreased, followed by a slower decline in diameter. The increase in RBC velocity always preceded (by 6–15 seconds) the increase in diameter. It is of note that when RBC velocity did not increase during parallel occlusion, there was also no vasodilation.

Next, we investigated the question of whether dilation of the arteriole due to increased blood flow velocity depends on the production of prostaglandins or EDRF in skeletal muscle microcirculation. Original recordings in Figure 1 demonstrate that superfusion of the preparation with indomethacin (panel C) or meclofenamate (panel D) completely eliminates arteriolar dilation despite the sharp increases in RBC velocity. In the later phase of the parallel occlusion, a return of diameter to control or a slight dilation (1–2 μm) was observed. Figure 1 also illustrates that NMA treatment (panel B) did not affect arteriolar dilation due to increased RBC velocity.

Because of the variable structure of the arteriolar subnetworks proximal and distal from the occluder, each arteriole under study exhibited different increases in RBC velocity during occlusion. In Figure 2, the peak increases in RBC velocity during parallel occlusion in control conditions ($n=17$), and after indomethacin ($n=24$), meclofenamate ($n=6$), or NMA ($n=15$) treatment was plotted against the peak changes in arteriolar diameter. Regression analysis of control data

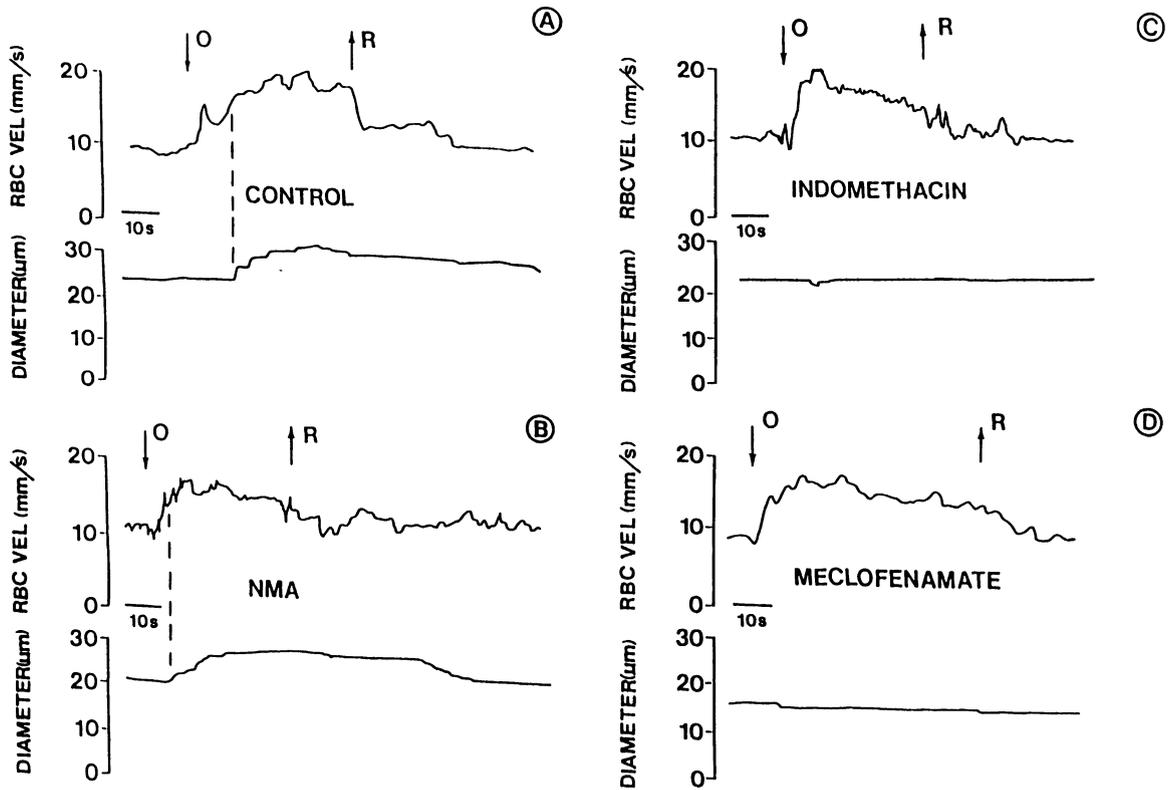


FIGURE 1. Original record of changes in red blood cell (RBC) velocity and diameter of rat cremasteric arterioles during parallel arteriolar branch occlusion (see details in "Methods"). The arteriolar dilation seen in control conditions (panel A) was inhibited by indomethacin (panel C) and meclofenamate (panel D), but not by N^G-monomethyl-L-arginine (NMA) (panel B). O, parallel arteriolar branch occlusion; R, release. The dotted line indicates the onset of diameter increase; note that by this time RBC velocity has already increased.

indicates a positive linear correlation ($r=0.76$, $p<0.05$) between peak increases in RBC velocity (mean increase, 8.2 ± 1.0 mm/sec from a mean of 7.9 ± 0.7 mm/sec, $p<0.05$) and arteriolar diameter (mean increase, 5.8 ± 0.7 μm from a mean of 19.4 ± 0.6 μm , $p<0.05$). However, arteriolar dilation due to

similar increases in RBC velocity (mean increase, 9.3 ± 1.0 mm/sec from a mean of 9.1 ± 0.7 mm/sec, $p<0.05$) was nearly eliminated by indomethacin or meclofenamate, and no correlation was found between velocity and diameter (mean increase in diameter, 0.3 ± 0.2 μm). In contrast, NMA treatment

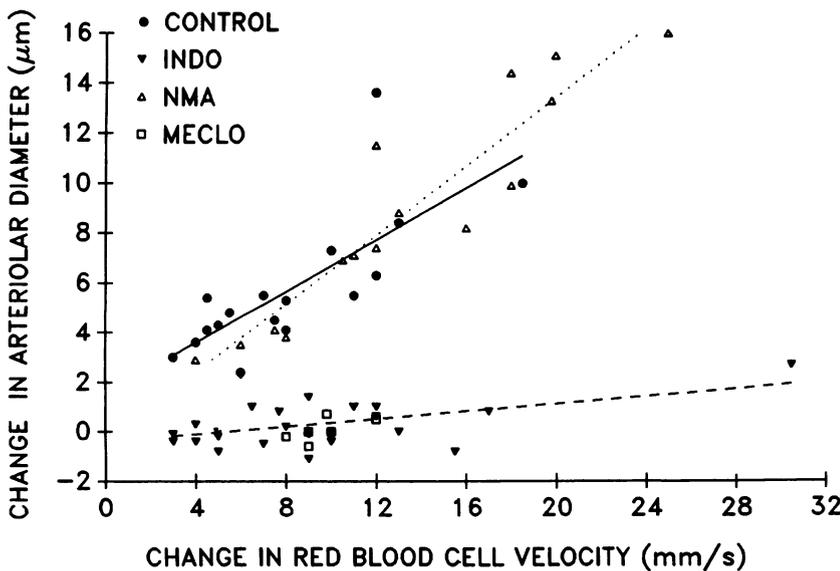


FIGURE 2. Regression analysis of paired data indicates that the peak changes in red blood cell velocity and arteriolar diameter during parallel arteriolar occlusion in control conditions (filled circle, continuous line), and N^G-monomethyl-L-arginine (NMA) treatment (open triangles, dotted line) are linearly correlated ($y=[0.51\pm 0.1]x+1.6$, $r=0.76$; $p<0.05$, and $y=[0.69\pm 0.1]x-0.4$, $r=0.93$; $p<0.05$, respectively). Indomethacin (INDO) (filled triangles) or meclofenamate (MECLO) (open squares) treatment inhibited arteriolar dilation after increases in red blood cell velocity (dashed line is the pooled regression line) ($y=[0.08\pm 0.04]x-0.5$, $r=0.52$; $p>0.05$, $n=15-30$).

TABLE 1. Effect of Indomethacin, Meclofenamate, and N^G -Monomethyl-L-Arginine Treatment on Peak changes in Arteriolar Diameter After Administration of Acetylcholine and Arachidonic Acid

	Change in arteriolar diameter (μm)		
	Control	INDO and MECLO treated	NMA treated
Acetylcholine (1 μM)	5.7 \pm 0.3	6.3 \pm 0.9	1.3 \pm 0.4*
Arachidonic acid (10 μM)	6.0 \pm 0.7	-0.8 \pm 0.4*	7.9 \pm 1.1

Values are mean \pm SEM; $n=7-20$. INDO, indomethacin; MECLO, meclofenamate; NMA, N^G -monomethyl-L-arginine.

* $p<0.05$ vs. control.

had no effect on arteriolar dilation (mean increase, $8.9\pm 1.1 \mu\text{m}$) after increases in RBC velocity (mean increase, $13.4\pm 1.5 \text{ mm/sec}$ from a mean of $5.9\pm 1.0 \text{ mm/sec}$, $p<0.05$) ($r=0.93$, $p<0.05$). Because both velocity and diameter increased, calculated arteriolar blood flow also increased by $260\pm 52\%$ (from a mean of $1.5\pm 0.2 \text{ nl}$) during parallel occlusion in control conditions. After inhibition of prostaglandin synthesis, however, this increase was only $112\pm 27\%$, whereas NMA did not affect the flow increase.

The efficacy of the inhibitors of prostaglandin or EDRF synthesis (indomethacin, meclofenamate, or NMA) was tested immediately before studying their effect, in the same vessel segment, on the blood flow velocity-induced arteriolar dilation. Inhibition of prostaglandin or EDRF synthesis by itself caused a slight but significant decrease in vessel diameter (from 20.1 ± 0.9 to $17.7\pm 0.9 \mu\text{m}$ or from 18.7 ± 0.5 to $15.8\pm 0.8 \mu\text{m}$, respectively). Data summarized in Table 1 demonstrate that arteriolar dilation due to arachidonic acid (10 μM), but not to acetylcholine (1 μM), was completely inhibited by indomethacin or meclofenamate treatment. Data obtained with the two cyclooxygenase blockers were pooled. In contrast, dilation due to acetylcholine, but not to arachidonic acid, was significantly blocked by NMA.

Discussion

In the present study, a significant correlation was found between peak increases in blood flow velocity and arteriolar diameter, providing further evidence that changes in wall shear stress due to increases in blood flow velocity are coupled to changes in vascular resistance. We also demonstrated that this coupling is mediated by prostaglandins in the arterioles of skeletal muscle microcirculation.

Investigation of endothelial cells of large vessel origin in tissue culture,^{5,6} in large conduit arteries,^{3,12} in arcade vessels of mesentery,¹³ and in skeletal muscle microcirculation^{1,2} suggested that the reason for the "flow-dependent" dilation is the increase in shear stress at the surface of endothelial cells, which stimulates the release of mediators, causing relaxation of vascular smooth muscle. Although results of most in vitro studies indicate that the presence of endothelium is necessary for "flow-induced relaxation" to occur,¹² this vascular reaction was observed in isolated resistance arteries even after removal of endothelium.¹⁴

In a variety of studies, several endothelial mediators of this phenomenon were identified. In isolated, Krebs-Ringer-perfused canine femoral and left circumflex coronary arteries, Rubanyi et al³ found that an increase in flow released a nonprostaglandin vasorelaxant mediator similar in nature to EDRF. A similar mediator was suggested to have a role in the control of resistance in the isolated, buffer-perfused rabbit ear preparation.¹⁵ In a blood-perfused canine femoral artery shunt, Kaiser et al⁴ reported that the flow-dependent dilation is mediated by a nonprostaglandin metabolite of arachidonic acid. On the other hand, studies using cultured endothelial cells demonstrated the importance of prostaglandin release^{5,6} or activation of K^+ channels¹⁶ in response to step increases in fluid shear stress. Our previous study² demonstrated the importance of arteriolar endothelium in the mediation of the flow velocity (wall shear stress)-sensitive arteriolar responses in vivo; however, the nature of mediation was not clarified.

In the present experiments, as illustrated by Figures 1 and 2, NMA, a blocker of EDRF production,⁷⁻⁹ did not affect arteriolar dilation after blood flow velocity increased. On the other hand, both indomethacin and meclofenamate, specific, structurally dissimilar inhibitors of prostaglandin synthesis, completely blocked arteriolar dilation due to increases in blood flow velocity. It is believed that the primary source of vasoactive prostaglandins in the vessel wall is the endothelial cell layer.^{17,18} In our previous studies^{19,20} using light/dye treatment to impair the endothelium-associated vasoactive functions in skeletal muscle arterioles,²¹ we found that arteriolar dilation due to arachidonic acid was absent. These findings support the idea that the vasodilator prostaglandins E_2 and I_2 released from arteriolar endothelium are responsible for flow velocity-induced dilation. Furthermore, it is likely that arteriolar dilation due to increased flow velocity during control conditions is neither of myogenic^{1,2} origin nor the result of metabolic factors from skeletal or vascular smooth muscle, because blood flow greatly increases, and pressure, if anything, also increases in the arteriole under study during parallel occlusion. An increase in pressure, if unopposed, would result in a myogenic constriction of the arteriole, the opposite of the observed response. Thus, our findings also suggest that the "flow-sensitive" prostaglandin-mediated dilator mechanism can counteract the pressure-sensitive myogenic constriction. In this context, Hill et al²² recently found that inhibition of

prostaglandin synthesis potentiates myogenic constriction of arterioles. Interestingly, such potentiation of the myogenic response was also observed in the course of our previous study when the "flow sensitivity" of arterioles was abolished by the impairment of arteriolar endothelium.²

It is of note that contrary to our previous experiments in which arteriolar endothelium was impaired by light/dye treatment,^{1,2} a return toward control or even an increase in diameter (1–2 μm) was observed in the later phases of parallel occlusion after prostaglandin synthesis inhibition. This indicates the possible involvement of other endothelial mechanisms or factors, albeit to a much lesser degree than prostaglandins, in the dilation of arterioles during the later phases of parallel occlusion. In our experiments, because blockers of both prostaglandins and EDRF by themselves elicited small but significant decreases in arteriolar diameter (12% and 15%, respectively), we suspect that these mediators are released continuously and that they affect basal vascular tone.^{19,20}

Based on the above, we conclude that in skeletal muscle microcirculation, the increase in arteriolar diameter is induced by vasodilator prostaglandins produced in arteriolar endothelium due to an increase in wall shear stress (increase in flow velocity with fixed diameter), which could be sensed by "rheoreceptors" on the endothelial cell membrane.¹⁶ Once the vasodilation is evoked, it in turn would elicit a decrease in wall shear stress by way of negative feedback because this force is inversely related to vessel diameter. The potency and possible importance of this mechanism is further underscored by the finding that arterioles could dilate near maximally to changes in this flow-related force (a dilation equivalent to that elicited by topical application of 10^{-4} M adenosine¹⁹).

Analysis of our data also revealed the importance of the shear stress-sensitive mechanism in the regulation of blood flow, as inhibition of prostaglandin synthesis resulted in a 57% reduction in flow increase during parallel occlusion. It is interesting to note the previous findings of Messina et al²³ showing that inhibitors of prostaglandin synthesis significantly inhibit arteriolar reactive dilation after serial occlusions (up to 60 seconds) in cremaster muscle. Although in that study the blood flow velocity-sensitive mechanism was not considered as one of the mechanisms eliciting reactive dilation, it is quite conceivable in light of the present work that the sudden increase in blood flow velocity after release of arteriolar occlusion initiates the release of prostaglandins, which, in concert with other mechanisms, participates in the development of reactive hyperemia. It is also of note that EDRF does not seem to be involved in this response because, as we have shown previously, inhibition of EDRF by NMA did not affect the reactive dilation of single arterioles in rat skeletal muscle microcirculation.²⁴

Based on present and previous studies,^{1–6,12–14} it seems reasonable to assume that a wall shear stress-sensitive dilator mechanism is present throughout

the microcirculatory network and that, through secondary changes in diameter, it could provide for a redistribution of resistance and a change in tissue blood flow. If the resistance of distal elements of the network decreases (e.g., during functional or reactive hyperemia, or neurogenically or humorally induced vasodilation), it could evoke an increase in upstream blood flow velocity followed by a secondary dilation of upstream resistance elements (i.e., arteries).²⁵ Dilation of upstream vessels in turn could provide for a substantially increased blood flow in case of increased tissue demand and could at the same time minimize the pressure drop in the network. Such a mechanism could also be important in the development of collateral blood flow,²⁶ in response to changes in blood viscosity,²⁷ and could participate as a modulating factor across the entire network should pressure or resistance change for any reason (e.g., because of constrictor or dilator agents).

In summary, in rat cremaster muscle, increases in blood flow velocity resulted in dilation of arterioles, which was mediated by prostaglandins. The presence of this phenomenon suggests a new, endothelium-dependent, blood flow-regulatory mechanism that has the role of normalizing wall shear stress, and which, by recruitment of upstream vessels, can provide the necessary change in the structure of the microvascular network to provide for a substantial increase in blood supply to the tissue. The impairment of this mechanism in various pathological conditions affecting endothelium and/or prostaglandin synthesis (e.g., atherosclerosis, diabetes, and hypertension) could contribute further to the pathogenesis of these disorders.

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KEY WORDS • wall shear stress • parallel occlusion • blood flow regulation • endothelium-derived relaxing factor