Hemodynamic Consequences of Cerebral Vasospasm on Perforating Arteries
A Phantom Model Study

Jean F. Soustiel, MD; Eli Levy; Roni Bibi; Sergei Lukaschuk, PhD; Dan Manor, PhD

Background and Purpose—Hemodynamics of cerebral vasospasm after subarachnoid hemorrhage remain unclear, and the discrepancy between ultrasonographic or angiographic evidence of arterial narrowing and neurological ischemic deficit is still debated. Most blood flow studies have been involved with large arteries, and thus, very little is known regarding the hemodynamic behavior of small perforating vessels. Patients with symptomatic vasospasm, however, often present with neurological signs suggesting involvement of deep-sited areas of the brain supplied by perforating arteries.

Methods—A pulsatile pump was set to provide an outflow of 350 mL/min through a 10-mm-diameter C-flex tube at a perfusion pressure of 130/80 mm Hg. The perfusion fluid used was prepared to approximate blood viscosity. Perforating arteries were simulated by a 1-mm tube connected to the parent tube at a 90° angle. Cylindrical stenotic devices of decreasing diameters were then introduced into the parent tube at the level of the aperture of the secondary tube and 1.5 diameters upstream of it. Velocity profiles both proximal and distal to the stenosis in the parent tube were obtained with a newly developed ultrasonographic flowmeter that allows for high spatial resolution.

Results—Increasing stenosis resulted in decreased outflow in the main tube, although it was significant only with severe stenosis. Whenever the simulated stenosis was placed upstream of the secondary tube, flow reduction was associated with a progressive change in the velocity profile, which gradually changed from laminar conditions to a jet stream limited to the center of the lumen. Further diameter reduction was responsible for the occurrence of flow separation with retrograde flow velocities in the periphery of the lumen. In the secondary tube, flow reduction was much more pronounced and began at a lesser degree of stenosis. Increasing fluid viscosity and decreasing perfusion pressure enhanced flow separation and prominently affected the outflow in the secondary tube. Conversely, whenever the simulated stenosis involved the branching area of the secondary tube, there was a slightly progressive decrease in the relative flow in the main tube as the stenosis became tighter. When the stenosis equaled the diameter of the secondary tube, the relative contribution of the secondary tube increased markedly at the expense of the main tube outflow.

Conclusions—The present results show that local cerebral vasospasm induces changes in postvasospastic velocity profile affecting the shear rate and may eventually lead to flow separation. This phenomenon may, in turn, result in a venturi-like effect over the aperture of perforating arteries branching out of the postvasospastic portion of the affected parent artery. These alterations of cerebral hemodynamics may account for at least part of the vasospasm symptomatology, especially in the vertebrobasilar system, where vasospasm is commonly focal rather than diffuse. Furthermore, these changes proved to be affected significantly by manipulations of pressure and viscosity, supporting the use of hyperdynamic therapy in the management of cerebral vasospasm. (Stroke. 2001;32:629-635.)

Key Words: blood flow velocity ▪ cerebral blood flow ▪ cerebral vasospasm ▪ ultrasonography

Cerebral vasospasm has emerged as one of the most serious threats after subarachnoid hemorrhage (SAH). The introduction of the transcranial Doppler (TCD) by Aaslid et al1 has transfigured the diagnostic capabilities of neurosurgeons and enabled a broader investigation of this phenomenon. Consequently, numerous studies based on TCD have shown that the actual incidence of vasospasm is higher than previously thought,2,3 especially in traumatic SAH.4,6 Pioneers of aneurysmal surgery have pointed to the importance of perforating vessels for the blood supply of highly eloquent regions of the brain, such as the hypothalamus7 and the brain stem.8 Although these authors have stressed the clinical implications of surgical injury to these vessels, little is known about their hemodynamic response to vasospasm. Given the particular anatomy of perforating arteries, characterized by an abrupt decrease in lumen diameter and a

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From the Department of Neurosurgery (J.F.S.), Rambam (Maimonides) Medical Center, Faculty of Medicine, The Technion–Israel Institute of Technology, Haifa, Israel; and Research Laboratory (E.L., R.B., S.L., D.M.), Biosonix Ltd, Kfar Malal, Israel.
Correspondence to Jean F. Soustiel, MD, Department of Neurosurgery, Rambam Medical Center, PO Box 9602, Haifa 31096, Israel. E-mail jsoustiel@rambam.health.gov.il
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right-angle bifurcation from the parent artery, it seems unlikely that those arteries would behave according to the same hemodynamic rules as for end arteries.

The purpose of the present study was to investigate the impact of cerebral vasospasm on perforating vessels using a phantom model of cerebral vasospasm.

Methods

Phantom Model

A pulsatile pump (Harvard Apparatus) was set to provide a physiological waveform and outflow of 350 mL/min through a 10-mm internal-diameter C-flex tube (Cole Parmer) at a perfusion pressure of 130/80 mm Hg (Figure 1A). Perfusion pressure was continuously monitored by a 25-gauge needle introduced upstream of the stenosis device and connected to a pressure transducer. The perfusion fluid was prepared by mixing glycerol, salt, 20-μm cellulose particles (Sigmacell), and distilled water. In all experiments except that involving manipulation of fluid viscosity, the amount of glycerol used was adjusted to approximate blood viscosity at physiological hematocrit value (2.4 viscosity at 40% hematocrit), according to Holdsworth et al. The C-flex tube was immersed in a water aquarium, the temperature of which was maintained at 30°C. Perforating vessels were simulated by a 1-mm-diameter silicon tube connected to the parent tube at a 90° angle, reproducing thereby the microvascular anatomy of the brain stem both in general architecture and diameter ratio between parent and branching arteries. For each phase of the study, experiments were repeated 3 times and the measured flows averaged for each tube. To improve the reproducibility of flow measurements, digitally time-controlled valves were used for system output. Furthermore, measurement accuracy was double-checked by online monitoring of the system total outflow by electromagnetic flowmeter. Consequently, because the model was based on a steady-state pumping device that was continuously monitored for both flow and pressures upstream of stenosis in the main tube and that used digitally time-controlled valves for time-collected-flows, measurement variations were limited only by reading error (2 to 4 mL). Larger errors indicated improper manipulations, such as incomplete removal of air bubbles after a tube replacement. In such an instance, tubes were cleaned from air and experiments repeated until expected steady results were obtained.

Study Design

Phase 1: Poststenosis Perforating Artery Model

The poststenosis perforating artery model is shown in Figure 1B.

Increasing Stenosis

Cylindrical stenosis devices of 20-mm length and decreasing diameters varying between 1 and 8 mm were introduced into the parent tube 1.5 diameters upstream of the aperture of the secondary tube. Upstream perfusion pressure was maintained at 130/80 mm Hg. Pressure measurements were performed downstream of the stenosis both in the parent and secondary tubes.

Increasing Perfusion Pressure

A 2-mm-diameter stenosis device (80% stenosis) was selected and introduced into the parent tube as previously described. Pump output was then set to produce gradually increasing perfusion pressures from 90/40 to 190/90 mm Hg. Time-collected flows in both parent and secondary tubes were recorded.
Increasing Fluid Viscosity
A 3-mm-diameter stenosis device with a constant perfusion pressure of 130/80 mm Hg was used to raise absolute viscosity of the perfusion fluid from 2.1 to 2.9 by increasing the amount of glycerol in the fluid mixture. These viscosity values were chosen because they reproduce the changes in the blood viscosity due to hematocrit elevation from 30% to 50%. Time-collected flows in both tubes were recorded.

Phase 2: Intrastenosis Perforating Artery Model
In this phase of the study, the secondary tube was connected to the distal part of cylindrical stenosis devices of 40-mm length and decreasing diameters varying between 1 and 8 mm previously introduced into the main tube. As in phase 1, perfusion pressure was maintained at 130/80 mm Hg with a fluid mixture viscosity of 2.4, and time-collected flows in both tubes were recorded. (See Figure 1C.)

Ultrasonographic Assessment
Velocity profiles across the tube cross-sectional area were obtained with the high-resolution FlowGuard Doppler ultrasound flow system (Biosonix Ltd, Israel). The system allows for simultaneous spectrum determination at multiple sample volumes along each ultrasound beam. Both flow velocities and velocity profiles were assessed with the FlowGuard probe 10 parent-tube diameters upstream and 1.5 parent-tube diameters downstream of the stenosis only in the first phase of the study (Figure 1B).

Results
Phase 1: Poststenosis Perforating Model
Arterial Stenosis Simulation
Effect on Velocity Profiles
Increasing stenosis of the parent tube resulted in a progressive change in the poststenotic velocity profile, which gradually turned into a thin jet limited to the center of the lumen (Figure 2). At normal or minimally decreased parent-tube diameter (≅20% stenosis), the distal velocity profile exhibited a smooth parabolic profile indicative of laminar, undisturbed steady-state flow (Figure 2). As stenosis severity increased, a gradual decrease in the poststenotic shear rate was noticed, indicated by flattening of the velocity profile near the walls (ie, decrease in flow velocity at the walls). At 80% stenosis, the velocity profile became completely flat (zero shear rate) in the periphery of the lumen, and no flow could be detected near the tube walls. The poststenotic laminar-like profile was corrupted, and the velocity in the center on the tube lumen began to increase and turned into a sharp velocity jet. Extreme stenosis (90%) eventually caused separation of flow in the periphery of the lumen with a plug flow profile characterized by clear retrograde velocities near the wall boundaries. Surprisingly, these changes in the poststenotic velocity profile, which were clearly noticed even at moderate stenosis levels of 40%, were not coupled with a corresponding effect on the parent-tube flow (Figure 3). It is interesting to note that the laminar proximal velocity profiles became rather flat with increasing stenosis severity. This effect, however, became significant only with stenosis of ≅80% severity.

Effect on Outflow
As expected, increases in stenosis of the parent tube correlated with a gradual decrease in both the parent- and secondary-tube outflows (Figure 3). Unlike changes in velocity profile, however, this decrease in outflow became significant only with stenosis of ≅70%. Quite remarkably, this decrease in outflow was not symmetrical in the parent and secondary tubes, starting at earlier stages of stenosis and being much more emphasized in the secondary tube, whereas it occurred at a 60% reduction in the main-tube diameter (Figure 3). Furthermore, flow reduction was significantly deeper in the secondary tube, reaching an almost 90% flow...
decrease at 90% stenosis, whereas flow reduction was less than half the initial value in the parent tube in the same condition. Such a flow reduction in the secondary tube implies a significant change in flow distribution, where the relative percentage of the flow in the secondary tube compared with total system flow dropped from 18.5% to 4.5%.

**Effect on Intraluminal Pressures**
Stenosis of 70% induced a central lumen pressure drop from 125/80 mm Hg upstream of the stenosis to 80/45 mm Hg at the center of the lumen, 1.5 tube diameters downstream of the stenosis. However, as the recording needle was pulled out from the center of the lumen toward the tube walls, the pressure dropped abruptly to 35/20 mm Hg near the parent-tube wall. Intraluminal pressure recording from within the secondary tube in the same conditions yielded a pressure of 25/20 mm Hg.

**Pump Output and Perfusion Pressure**
Increasing perfusion pressures through an extremely narrowed main tube (80% diameter reduction) induced a gradual increase in the total system outflow. Flow distribution between the parent and secondary tubes, however, was markedly affected by the changes in perfusion pressure (Figure 4). As perfusion pressure was elevated, the relative part of secondary-tube flow compared with total system flow increased progressively from 8% to 14%.

**Fluid Viscosity**

**Effects on Velocity Profile**
Increases in the viscosity of the perfusion mixture from 2.1 to 2.9 were associated with marked changes in velocity profiles that became gradually narrower, with a sharp velocity jet in the center of the tube lumen. With a 70% parent-tube stenosis, even a slight increase in the viscosity of the mixture led to poststenotic flow separation, with notable retrograde flow velocities near the vessel walls at viscosity levels exceeding 2.3 (Figure 5).

**Effects on Volume Flow**
As expected, increased mixture viscosity was responsible for a gradual and significant decrease in the system outflow. This decrease in outflow, however, was much more prominent in the secondary tube, whose relative flow contribution to the
total system flow dropped from 22% at a viscosity level of 2.1 to 15% at a viscosity level of 2.9 (Figure 6).

**Phase 2: Intrastenosis Perforating Artery Model**

At a moderate level of stenosis, there was no significant change in flow distribution between the main and secondary tubes, which was similar to that observed in the same conditions with a poststenosis perforating artery model. Whenever the main tube diameter was reduced beneath 60%, however, there was a progressive although moderate increase in the flow in the secondary tube at the expense of the main tube. At an extreme level of stenosis (90%), although the system outflow was globally reduced, the respective flow in the secondary tube was markedly increased (Figure 7).

**Discussion**

Despite considerable improvement in its understanding and management, cerebral vasospasm after aneurysmal SAH remains a source of etiopathogenic controversies and is still responsible for 10% to 20% of death and disability. One of the most debated controversies is the contribution of arterial narrowing, as demonstrated by TCD or angiographic studies, to delayed neurological morbidity. This may be even more challenging in head injury, where neurological outcome is influenced by multiple factors. In this ongoing debate, most authors have stressed that arterial narrowing, as evidenced by TCD or angiographic studies, is significantly more common than the incidence of delayed brain ischemia and should therefore be distinguished from hemodynamically significant vasospasm. Moreover, the incidence of brain infarction in those patients suffering from symptomatic vasospasm is even lower, ranging from 3% to 17% in different CT studies of SAH patients. A generally accepted assumption for this discrepancy between anatomic and clinical findings is that arterial narrowing does not necessarily result in blood flow reduction below a critical threshold. Clinical and laboratory studies have indeed demonstrated that brain function can be sustained until blood flow remains above a critical threshold of 20 mL/100 g of brain per minute, whereas cell death occurs with blood flow levels <15 mL/100 g of brain per minute. This assumption is well supported by our results showing that flow in the main tube remained almost unaffected by stenosis <70%. Our results are in close accordance with early observations made by Moore and Malone in carotid stenosis and similar to the findings recently reported by Aaslid in a similar phantom model of arterial stenosis. Yet, all those studies, including ours, involved models based on short stenosis, so that the impact of the length of the stenosis was not taken into consideration. This may affect their validity in case of diffuse vasospasm involving large segments of cerebral arteries.

Most of the available information relates to large-vessel vasospasm, and CT scan studies usually refer to hypodense regions in vascular territories of major cerebral arteries. Clinical deterioration due to vasospasm, however, is seldom limited to the motor consequences of anterior or middle cerebral artery constriction. On the contrary, confusion and consciousness impairment most often initiate the clinical picture, whether or not focal deficit eventually develops. These signs suggest the involvement of hypothalamic perforating branches of the anterior cerebral artery. This assumption is in accordance with the anterior location of 85% of all saccular aneurysms and has been supported by pathological studies.

In the present study, a phantom model was designed to simulate the anatomy of the perforating arteries characterized both by a right-angle bifurcation with the parent artery as well as an abrupt decrease in lumen diameter. Although the diameter of the tubes used in the model was significantly larger than that of cerebral arteries, the relative proportions between main cerebral and perforating arteries was respected. As expected, increasing stenosis induced a progressive decrease in the outflow in both tubes. The pattern of this decrease, however, appeared to depend on the relative location of the secondary tube with respect to the stenosis. Whenever the secondary tube emerged from the stenosis itself, its relative contribution to the system outflow increased moderately up to 80% stenosis and then increased abruptly. This phenomenon is likely to be the consequence of the progressive
increase in the main-stem peripheral resistance caused by the stenosis, whereas resistance within the secondary tube remained unchanged. As the stenosis worsens or extends in length, the resistance ratio between the main and secondary tubes further increases, with a subsequent and prominent decrease in the main-tube outflow. This cumulative increase of peripheral resistance is probably responsible for the occurrence of brain infarction in territories supplied by end arteries rather than in deep-sited regions in patients suffering from diffuse spasm involving the branching zone of perforating arteries. This assumption is further supported by relatively higher flow rates in the secondary tube at each level of stenosis compared with the poststenotic model, which used a stenosis device half as long as that used in the intrastenosis model.

Conversely, whenever the secondary tube was connected in the poststenotic portion of the main tube, a decrease in the lumen of the parent tube resulted in a gradual change in the poststenotic velocity profile that progressively turned into a sharp and narrow velocity jet limited to the very center of the lumen. Further increases in the degree of the stenosis proved to be responsible for the occurrence of flow separation, with retrograde flow velocities observed in the periphery of the lumen. Yet, arterial tone of large vessels has proved to be reduced by increased shear rate induced by higher velocities. Therefore, in this situation, a vasodilatory response mediated by the endothelium of the affected artery might have modified the results in vivo. Nevertheless, our results are in close accordance with the findings of Hutchinson, who showed that partial ligation of the common carotid artery in dogs induced significant changes in velocity profile downstream of the carotid stenosis, leading to flow separation. Flow separation, in turn, may produce a venturi-like effect responsible for pressure collapse at the aperture of the secondary tube and partial rerouting of the flow into the main tube. The abrupt decrease in intraluminal pressure from the center of the tube toward its boundaries distally to the stenosis reported here supports this hypothesis. This pressure decrease, secondary to the changes in velocity profiles, most likely accounts for the much more profound reduction in secondary-tube outflow compared with that of the parent tube. Indeed, flow reduction in the secondary tube reached 90% of its initial value in a 90% stenosis model, whereas flow in the parent tube was reduced by only 40% in the same conditions. These results suggest that deep-sited regions of the brain supplied by perforating arteries are particularly vulnerable to changes in velocity profile such as those induced by focal cerebral vasospasm located proximally to such perforating vessels. This assumption is further supported by postmortem studies after SAH showing small brain infarction in cerebral territories supplied by perforating arteries. This clinical situation, however, is more likely to be relevant to the vertebrobasilar system, where vasospasm is most commonly focal and therefore exposes those perforators that branch out of the postvasospastic portion of the parent vessel. These results may also explain the occurrence of severe and prolonged consciousness impairment due to local cerebral vasospasm even in those patients who do not present with motor deficit or crude brain infarction on CT scan. Flow reduction in perforating arteries due to vasospasm has been also advocated to explain upper brain stem ischemia after SAH. More recently, Ritter et al reported on reduced brain stem blood flow in head-injured patients with papillary dilation. They showed that blood flow reduction did not correlate with brain stem lesion on CT scan or with elevated intracranial pressure. Although they did not measure blood flow velocities in the basilar artery, it may be hypothesized that posttraumatic basilar vasospasm may account in part for this blood flow reduction, at least in some of their patients. This hypothesis is supported by the blood supply architecture of the brain stem based mainly on perforating arteries on one hand and on the other hand by recent studies that showed that basilar artery vasospasm was significantly more frequent in posttraumatic hemorrhage than previously thought and could affect neurological outcome.

Interestingly, our results suggest that triple H therapy (hyperdilution, hypervolemia, and hypertension), which is often used in the management of cerebral vasospasm, prominently affects perforating arteries. In the present model, increasing viscosity within physiological limits resulted in significant exacerbation of shear rates and flow separation downstream of a severe stenosis. As viscosity was elevated, thinning of the poststenotic jet wash and subsequent thickening of the turbulent surrounding zone induced a progressive redistribution of the flow at the expense of the secondary tube. This observation suggests that hemocoagulation is therefore more likely to impair flow in perforating vessels. However, several substantial differences between the present model and physiological facts in vivo should be considered, because they might affect the validity of our results. First, the present methodology did not include the complex and dynamic relationships between viscosity, shear rate, and vascular resistance. In large arteries, decreasing viscosity by means of hemodilution has yielded controversial results. As mentioned above, Merkumyants and Balashov showed that the femoral artery of anesthetized cats responds to increase blood flow by endothelium-mediated vasodilatation. Such a vasodilation of large arteries was also speculated by Hudack et al to explain elevation of blood flow secondary to hemodilution despite associated arteriolar constriction. Conversely, Muizelaar et al challenged this hypothesis and proved that hemodilution was in fact accompanied by moderate vasoconstriction of large arteries in vivo, probably acting as a compensatory measure to disproportionate viscosity reduction at the microcirculatory level. They assumed, however, that the vascular bed was not affected by hemodilution and that there was no vascular recruitment. Our results may challenge this assumption by showing that decreased viscosity causes a relative redistribution of the blood flow in favor of perforating arteries, probably by reducing the phenomenon of flow separation. Conversely, increasing viscosity lead to an exacerbation of flow separation that may eventually lead to partial hemodynamic exclusion of at least some of the perforating arteries directly involved by intense negative flow-velocity vectors. This hypothesis, however, is obviously limited by the fact that specific rheological properties of the blood, such as variable erythrocyte aggregation in small vessels, could not be incorporated in the model. In addition, our model could not technically take into consideration
complex physiological vascular properties such as autoregulatory vasodilation that might have otherwise influenced our results. Nevertheless, because changes in viscosity induced by hemodilution and hemocoagulation are more pronounced in the microcirculation, they are even more likely to enhance perturbations induced by changes in velocity profile.

The same limitations exist for the present model of elevation of perfusion pressure. Changes in perfusion pressure in this study had a more significant effect on secondary-tube outflow, probably as a result of an increase in the poststenotic pressure in the periphery of the lumen in the main tube despite further increase in shear stress.

In conclusion, the results of this study suggest that changes in velocity profile induced by cerebral vasospasm may lead to flow separation across the vascular cross-sectional area, resulting in pressure collapse at the aperture of small perforating vessels. These alterations of cerebral hemodynamics may account for at least part of the vasospasm symptomatology. Furthermore, these changes proved to be affected significantly by manipulations of pressure and viscosity, supporting the use of triple H therapy in the management of cerebral vasospasm.

References


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