Role of the Basilar Artery in Regulation of Blood Flow to the Brain Stem in Rats

Kenichiro Fujii, MD; Donald D. Heistad, MD; and Frank M. Farad, PhD

Large arteries contribute to the regulation of cerebral blood flow. The goal of this study was to examine the effects of changes in diameter of the basilar artery on blood flow to the brain stem. We measured blood flow with laser-Doppler flowmetry in anesthetized rats. The topical application of $10^{-6}$ M serotonin, which selectively constricts large arteries, reduced diameter of the basilar artery by $47\pm5\%$ (mean$\pm$SEM, $n=6$) but did not alter blood flow to the ventral brain stem (change in blood flow $-2\pm5\%$). The topical application of $10^{-4}$ M vasopressin, which affects both large and small vessels, decreased blood flow by $33\pm4\%$ ($n=6$). In rats with spontaneous vasomotion, the basilar artery showed rhythmic changes in diameter at a frequency of $4.0\pm0.1$ cycles/min and an amplitude of $20\pm1\%$ of mean diameter ($n=6$). Blood flow to the ventral brain stem cycled at the same frequency as and in phase with changes in diameter of the basilar artery, with an amplitude of $15\pm1\%$. We conclude that constriction of the basilar artery may occur with no change in brain stem perfusion. The distinct changes in blood flow during spontaneous vasomotion suggest that vasomotion occurs in intraparenchymal arterioles as well as in the basilar artery. (Stroke 1991;22:763-767)

Because of anatomic location and technical limitations, the direct and continuous assessment in vivo of diameter of the basilar artery or blood flow to the brain stem has not been readily available. Thus, the role of the basilar artery in regulation of the brain stem circulation has not been well-defined.

We recently developed a method to study blood vessels of the brain stem, including the basilar artery, in vivo. The goal of this study was to evaluate blood flow to the brain stem during changes in diameter of the basilar artery produced by pharmacological interventions and during spontaneous vasomotion. We considered two possibilities. First, blood flow may be constant, despite changes in diameter of the basilar artery, if downstream arterioles fully compensate for changes in basilar artery diameter. Second, blood flow may change if the compensatory responses in arterioles are small or if similar changes in diameter occur in downstream arterioles.

Materials and Methods

Experiments were performed on 16 male Sprague-Dawley rats weighing 350–450 g anesthetized with 50 mg/kg i.p. pentobarbital. The trachea was cannulated and each rat was mechanically ventilated with room air and supplemental oxygen. Skeletal muscles were paralyzed after surgery with 5–10 mg/kg galamine triethiodide. Because the animal was paralyzed, we evaluated it approximately every 30 minutes for adequacy of anesthesia. When pressure to a paw evoked a change in blood pressure or heart rate, additional anesthetic was administered at a rate of approximately 15 mg/kg/hr i.v.

Catheters were placed in both femoral arteries to measure systemic arterial blood pressure and to obtain arterial blood samples. A femoral vein was cannulated for the infusion of drugs. Arterial blood gases were monitored and maintained within normal limits throughout the experiment; $Paco_2$ was $39\pm2$ mm Hg, $Pao_2$ was $151\pm22$ mm Hg, and arterial pH was $7.37\pm0.02$ (mean$\pm$SEM for all). Rectal temperature was monitored and maintained at 37°C with a heating pad.

A craniotomy was prepared over the ventral brain stem as described previously in detail. Briefly, the rat was placed in a head holder in the supine position. The larynx, the esophagus, and the muscle covering the basioccipital bone were retracted later-
ally. A craniotomy 2–3 mm in diameter was made in the bone at the base of the skull between the tympanic bullae using an air-cooled dental drill. The dura was resected with ophthalmic scissors to expose the ventral medulla. The cranial window was suffused with artificial cerebrospinal fluid (CSF) warmed to 37°C and bubbled continuously to produce normal levels of pH and Pco2. In CSF sampled from the craniotomies, Pco2 was 39±3 mm Hg, Po2 was 89±10 mm Hg, and pH was 7.34±0.04. Diameter of the brain vessels was measured using a microscope equipped with a television camera coupled to a video monitor and image-shearing device (model 908, Instrumentation for Physiology and Medicine, Inc., San Diego, Calif.). The images were recorded on videotape for later analysis. In our preparation, the standard deviation of 10 consecutive measurements (one every 10 seconds) of the diameter of a basilar artery without vasomotion and with a diameter of approximately 250 μm was <2.0 μm. The mean vessel diameter and the amplitude and frequency of vasomotion were determined as described previously in detail.3

Blood flow to the ventral medulla was measured by laser-Doppler flowmetry using a BPM Model 403A Laserflo Blood Perfusion Monitor equipped with a 800-μm-diameter needle probe (Thermo-System Inc., St. Paul, Minn.). The probe was positioned with a micromanipulator within the cranial window and advanced into the CSF approximately 0.2 mm from the brain surface. The probe was placed lateral to but near the midpoint of the basilar artery in the rostrocaudal axis, as visualized through the cranial window, and at the midpoint between the basilar artery and the lateral edge of the cranial window. Care was taken to not place the probe over any large vessels. Analog output signals of blood flow were recorded continuously (in volts) using a signal-averaging time of 1 second. Laser-Doppler flowmetry does not provide accurate absolute values for regional cerebral blood flow, but it does accurately reflect changes in this parameter.5 Thus, we regarded laser-Doppler flowmetry outputs as arbitrary units and expressed changes in blood flow as a percentage of the baseline blood flow.

In 10 rats, we examined effects of the topical application of two vasoconstrictor agonists, serotonin (at 10⁻⁶ M) and vasopressin (at 10⁻⁸ M), and a vasodilator, nitroglycerin (at 10⁻⁶ and 10⁻⁵ M). In one group of six rats, we measured diameter of the basilar artery and changes in blood flow to the brain stem. In another group of four rats, we measured diameter of branches of the basilar artery as well as diameter of the basilar artery. In this group, blood flow to the brain stem was not measured because the shadow of the Doppler probe obscured the images of branches of the basilar artery. Concentrations of drugs were chosen so that their effects on diameter of the basilar artery were maximal or near-maximal.3

In six other rats with spontaneous vasomotion, we measured changes in diameter of the basilar artery and blood flow to the ventral brain stem.

All values are expressed as mean±SEM. Student's t test for paired observations or one-way analysis of variance for repeated measurements within each animal was used to compare diameters and blood flows in response to the agonists. A probability value of less than 0.05 was considered to be significant.

Results

The topical application of serotonin decreased diameter of the basilar artery by almost 50% but had no significant effect on blood flow to the brain stem (Figure 1). In contrast, the topical application of vasopressin both constricted the basilar artery and decreased blood flow (Figure 1). Nitroglycerin increased both diameter of the basilar artery and blood flow (Figure 2).

Serotonin did not significantly alter the diameter of small branches of the basilar artery despite producing pronounced constriction of the basilar artery (Table 1). In contrast, vasopressin decreased the diameters of both the basilar artery and its branches. Nitroglycerin increased the diameters of both the basilar artery and its branches.

Changes in diameter of the basilar artery and blood flow to the brain stem during spontaneous vasomotion are illustrated in Figure 3. Blood flow to the brain stem changed in phase with changes in diameter of the basilar artery. There was no detectable time lag between changes in diameter and
changes in blood flow. In these six rats, the baseline diameter of the basilar artery was 278 ± 11 μm. The frequency of vasomotion was 4.0 ± 0.1 cycles/min, and the amplitude was 20 ± 1% of the baseline diameter. The change in blood flow was 15 ± 1%.

Discussion

There are three new findings in this study. First, serotonin produces pronounced constriction of the basilar artery but does not reduce blood flow to the brain stem. Thus, large changes in diameter of the basilar artery may occur without a change in brain stem perfusion. Second, other agonists (vasopressin and nitroglycerin) produce directionally similar changes in diameter of the basilar artery and blood flow. Third, spontaneous vasomotion of the basilar artery is associated with synchronous changes in blood flow to the brain stem.

Laser-Doppler flowmetry measures blood flow through surface vessels and superficial penetrating vessels in small volumes of tissue (approximately 1 mm³). Thus, although we demonstrated that tissue blood flow changes during pharmacological stimulation and vasomotion of the basilar artery, this approach does not allow us to determine whether blood flow to the whole brain stem changes in a similar manner.

Serotonin and vasopressin produced similar contractions of the basilar artery, whereas vasopressin but not serotonin decreased blood flow. It is possible that topically applied serotonin did not reach intraparenchymal vessels due to its inability to penetrate brain tissue and thus did not decrease blood flow. The finding that vasopressin effectively reduced blood flow, however, suggests that topically applied agonists are able to reach smaller arterioles.

It has been shown previously that serotonin and vasopressin produce different responses in different segments of the microcirculation. In some studies, the vascular effects of serotonin have been reported to be size-dependent in that the topical application of serotonin constricts large arteries while having no effect on or producing dilatation of the smaller arterioles. In contrast, the topical application of vasopressin produces constriction of small arteries and arterioles on the cerebrum as well as constriction of large arteries (basilar artery). Findings in the present study (Table 1) are in agreement with these reports. Thus, the different effects of serotonin and vasopressin on blood flow that we observed may be explained by these segmental differences in responsiveness.

Our results indicate that vasoconstriction (up to approximately 50%) that is restricted to the basilar artery (e.g., during the application of serotonin) may not alter blood flow to the brain stem. It is inferred from the results that, when vascular tone is normal in arterioles, the selective constriction of large arteries may have little effect on blood flow. When arterioles are maximally dilated, however, the constriction of large arteries is more likely to produce reductions in blood flow because compensatory dilatation of down-

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<tr>
<td>Serotonin (10⁻⁶ M)</td>
<td>4</td>
<td>277 ± 19</td>
<td>-45 ± 3*</td>
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<td>109 ± 9</td>
<td>-16 ± 6</td>
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<td>Vasopressin (10⁻⁵ M)</td>
<td>3</td>
<td>292 ± 25</td>
<td>-26 ± 5*</td>
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<td>112 ± 10</td>
<td>-37 ± 7*</td>
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<td>72 ± 5</td>
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<td>Nitroglycerin</td>
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Values are mean ± SEM.
*p<0.05 different from 0.
stream vessels cannot occur. Vasopressin and nitroglycerin altered blood flow to the brain stem, probably because they produce responses of both the basilar artery and its branches. These results, however, do not exclude an important contribution of large cerebral arteries to changes in vascular resistance such as those that occur during hypocapnia, hypercapnia, and autoregulation.

Blood flow to the brain stem cycled with changes in diameter of the basilar artery during vasomotion. The results agree with previous studies in the peripheral microcirculation that reported that blood flow cycles in phase with changes in arteriolar diameter. In those studies, the blood flow was estimated from vessel diameter and blood flow velocity and the change in tissue blood flow was not measured independently. Oscillations in laser-Doppler flowmetry signals have been shown in several organs, including human skin and rat cerebrum.

We considered the possibility that cyclic changes in tissue blood flow occur first and that they produce changes in diameter of the basilar artery through flow-mediated mechanisms. Large changes in blood flow are usually required to produce significant changes in the diameter of upstream vessels, and there is a time delay between the onset of a change in blood flow and that in diameter. Thus, based on the magnitude in blood flow (15%) and the time course (flow and diameter changed in phase), it seems unlikely that cyclic changes in diameter of the basilar artery were secondary to changes in tissue blood flow.

In a previous study, we observed that vasomotion occurred in phase in the basilar artery and its branches. Due to obvious technical limitations, we were not able to measure the diameter of vessels within the parenchyma of the brain stem. Thus, we could not determine whether intraparenchymal vessels also manifest vasomotion, and we could not predict whether vasomotion of the basilar artery produces changes in blood flow. Because an approximately 50% reduction in diameter of the basilar artery in response to serotonin did not alter blood flow to the brain stem, the dilatation of downstream arterioles appears to have the potential to compensate fully for constriction of the basilar artery during vasomotion. It is possible that there was not enough time for intraparenchymal arterioles to achieve complete autoregulatory responses during vasomotion of the basilar artery. In that case, however, the phase of changes in tissue blood flow would be expected to shift from that of changes in diameter of the basilar artery. In the present study, changes in blood flow and vessel diameter appeared to be in phase, and we did not observe either variable consistently preceding the other. Thus, oscillation in blood flow to the brain stem suggests that downstream intraparenchymal arterioles also experience vasomotion that occurs in phase with that of the basilar artery. In this setting, changes in diameter of the basilar artery, as well as of downstream arterioles, may play a role in altering tissue blood flow in the same direction.

The incidence of vasomotion in this study was somewhat lower than that in previous studies. We and others have shown previously that vasomotion is sensitive to the depth of anesthesia. In awake rabbits, vasomotion of pial arterioles was observed in all animals, and vasomotion was inhibited by anesthesia. In this study, slightly more pentobarbital was used than in our previous studies. The use of different amounts of anesthetic may explain the somewhat lower incidence of vasomotion in the present compared with previous studies.

The functional role of vasomotion in the microcirculation is not clear. It has been suggested that vasomotion in venules and veins promotes venous
Vasomotion may play a role in regulating local hematocrit, and thus local viscosity. It has also been suggested that vasomotion in arterioles may facilitate fluid exchange between the capillary and interstitial spaces. It has been suggested that oscillations in brain tissue oxygen tension are produced primarily by changes in local blood flow. Our results suggest that vasomotion of the basilar artery and its branches contributes to the local regulation of blood flow to the brain stem. The physiological role of oscillations of blood flow is still to be determined.

Acknowledgment

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