

Intracarotid Nitroprusside Does Not Augment Cerebral Blood Flow in Human Subjects

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Background: The recent resurgence of interest in the cerebrovascular effects of nitroprusside can be attributed to the possibility of using nitric oxide donors in treating cerebrovascular insufficiency. However, limited human data suggest that intracarotid nitroprusside does not directly affect cerebrovascular resistance. In previous studies, physiologic or pharmacologic reactivity of the preparation was not tested at the time of nitroprusside challenge. The authors hypothesized that if nitric oxide is a potent modulator of human cerebral blood flow (CBF), then intracarotid infusion of nitroprusside will augment CBF.

Methods: Cerebral blood flow was measured (intraarterial ^{133}Xe technique) in sedated human subjects undergoing cerebral angiography during sequential infusions of (1) intracarotid saline, (2) intravenous phenylephrine to induce systemic hypertension, (3) intravenous phenylephrine with intracarotid nitroprusside ($0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and (4) intracarotid verapamil ($0.013 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Data (mean \pm SD) were analyzed by repeated-measures analysis of variance and *post hoc* Bonferroni–Dunn test.

Results: Intravenous phenylephrine increased systemic mean arterial pressure (from 83 ± 12 to 98 ± 6 mmHg; $n = 8$; $P < 0.001$), and concurrent infusion of intravenous phenylephrine and intracarotid nitroprusside reversed this effect. However, compared with baseline, CBF did not change with intravenous phenylephrine or with concurrent infusions of intravenous phenylephrine and intracarotid nitroprusside. Intracarotid verapamil increased CBF (43 ± 9 to $65 \pm 11 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$; $P < 0.05$).

Conclusions: The authors conclude that, in humans, intracarotid nitroprusside sufficient to decrease mean arterial pressure during recirculation, does not augment CBF. Failure of intracarotid nitroprusside to augment CBF despite demonstrable autoregulatory vasoconstriction and pharmacologic vasodilation questions the significance of nitric oxide-mediated vasodilation in human cerebral circulation.

IN rodents, intracarotid infusion of sodium nitroprusside, an endothelium-independent nitric oxide (NO) donor, augments cerebral blood flow (CBF) and reduces ischemic cerebral injury.¹ In patients with cerebral va-

sospasm, intrathecal nitroprusside increases CBF and results in angiographic and neurologic improvement.^{2,3} However, despite extensive investigations, the effect of nitroprusside on CBF of resting humans as well as non-human primates remains controversial (tables 1 and 2). As is evident from table 1, most human studies have used intravenous infusion of nitroprusside. Intravenous nitroprusside not only decreases mean arterial pressure (MAP) but can also increase intracranial pressure,^{4,5} impair autoregulation,⁶ and change cardiac output.⁷ Changes in any of these parameters could indirectly affect CBF during intravenous nitroprusside infusion. In contrast to an intravenous infusion, intracarotid infusion of a drug limits the initial volume of distribution to one cerebral hemisphere. Therefore, intracarotid infusions can isolate the regional vascular effects of a drug from their systemic effects. To date, only two studies in humans have investigated the effect of intracarotid infusion of nitroprusside on CBF. These studies were undertaken on awake subjects undergoing angiography for suspected neurologic diseases, and they failed to demonstrate an increase in CBF after nitroprusside infusion.^{8,9} A confounding effect of intracranial pathology on the outcome of these studies cannot be ruled out.

The release of NO from nitroprusside is a one-stage nonenzymatic reaction.¹⁰ Infusion of nitroprusside in coronary and brachial arteries of human subjects increases regional blood flow.^{11–13} Therefore, in noncerebral vessels, it is generally accepted that NO generated from nitroprusside can penetrate the basement layer of the endothelium to reach smooth muscle cells.¹⁴ In the smooth muscle cell, NO activates guanylate cyclase, increases cyclic guanosine monophosphate, and causes vascular relaxation. We hypothesized that, similar to the peripheral circulation, if endothelial NO is a significant modulator of CBF, then NO generated after intracarotid infusion of nitroprusside should be able to diffuse across the blood–brain barrier, relax the vascular smooth muscle cells, and increase CBF.

Our studies were conducted on normal hemispheres of patients undergoing four-vessel cerebral angiography for suspected intracranial vascular pathologies. Because nitroprusside can impair cerebral autoregulation, the drug infusion protocol was designed to avoid hypotension during intracarotid nitroprusside infusion. The protocol also tested physiologic autoregulation and the pharmacologic response to a Ca^{2+} channel blocker, verapamil. In human cerebral circulation, intraarterial verapamil augments CBF; therefore, the drug was used as a positive control.^{9,15}

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Table 1. Effect of Sodium Nitroprusside on Human Cerebral Blood Flow

| Author (Year) | Route | CBF Technique | Experimental State | Outcome: Effect on CBF | Reference No. |
|----------------------------------|-----------|-----------------------------------|---------------------------------|---|---------------|
| Griffiths <i>et al.</i> (1974) | IV | IC ^{133}Xe | During anesthesia | No change | 33 |
| Brown <i>et al.</i> (1977) | IV | IC ^{133}Xe | Awake, neurologic angiography | Decrease in CBF during nitroprusside hypotension | 34 |
| Pinaud <i>et al.</i> (1979) | IV | IC ^{133}Xe | During anesthesia | No change in CBF | 35 |
| Larsen <i>et al.</i> (1982) | IV | Argon washout | During anesthesia | No change in 7 of 9 patients, in 2 increase in CBF associated with increased output | 7 |
| Henriksen <i>et al.</i> (1982) | IV | IC ^{133}Xe | During anesthesia | Decrease in CBF | 36 |
| Henriksen and Paulson (1982) | IV and IA | IC ^{133}Xe | Awake, neurologic patients | No change with IC and a decrease with IV infusion | 8 |
| Henriksen <i>et al.</i> (1983) | IV | IC ^{133}Xe | During anesthesia | No change | 37 |
| Bunemann <i>et al.</i> (1987) | IV | IV ^{133}Xe | During anesthesia | No change | 38 |
| Rogers <i>et al.</i> (1989) | IV | IA ^{133}Xe | During anesthesia | No change in CBF during cardiopulmonary bypass | 39 |
| Pinaud <i>et al.</i> (1989) | IV | IA ^{133}Xe | During anesthesia | No change despite increase in cardiac index | 40 |
| Thomsen <i>et al.</i> (1989) | IV | IV ^{133}Xe | During anesthesia | No change in CBF in 9 of 10, 1 of 10 patient critical decrease in CBF | 41 |
| Bunemann <i>et al.</i> (1991) | IV | IV ^{133}Xe | During anesthesia | Nitroprusside with metoprolol pretreatment, no change in CBF | 42 |
| Rogers <i>et al.</i> (1991) | IV | IA ^{133}Xe | During anesthesia | Decrease in CBF during cardiopulmonary bypass | 43 |
| Joshi <i>et al.</i> (1997) | IA | IA ^{133}Xe | Awake neurologic patients | Decrease in regional CBF | 9 |
| Butterworth <i>et al.</i> (1998) | IV | Single photon emission tomography | Awake patient with acute stroke | Nitroprusside increased CBF and decreased platelet aggregation | 44 |
| Viguera <i>et al.</i> (1998) | IV | Transcranial doppler | Awake | Case report: atenolol pretreatment and nitroprusside did not affect CBF before ECT | 45 |
| Thomas and Rosenwasser (1999) | IT | Transcranial doppler angiography | NA | Case series: increase in CBF in three patients with subarachnoid hemorrhage and vasospasm | 3 |
| Vajkoczy <i>et al.</i> (2000) | IT | Thermal diffusion | NA | Case series: increase in CBF in patients with vasospasm | 2 |

Studies with intraarterial drug infusion are shown in *italics*.

CBF = cerebral blood flow; IV = intravenous; IC = intracarotid; IA = intraarterial (superselective); IT = intrathecal; ECT = electroconvulsive therapy; NA = patients with impaired consciousness.

Materials and Methods

After obtaining approval from the institutional review board of Columbia University (New York, NY), informed consent was obtained from nine neurologically stable patients, American Society of Anesthesiologists status I or II, undergoing four-vessel cerebral angiography, a procedure that requires placement of catheters in normal arterial irrigation for diagnostic purposes. Subjects recruited for the study were without any symptoms of intracranial hemorrhage or increased intracranial pressure. All patients were fasted overnight and 2 h before the procedure were given a 30-mg oral dose of nimodipine. Oral nimodipine was prescribed as a prophylactic measure to minimize the chances of catheter-induced vasospasm during angiography. Patients were sedated with fentanyl, midazolam, and propofol. The level of sedation was adjusted to assure comfort, although the patients were be able to respond to verbal commands. Physiologic parameters that were monitored during angiography included heart rate and rhythm by electrocar-

diography, end-tidal carbon dioxide concentration, arterial oxygen saturation, blood pressure, and urine output.

After infiltrating the skin with 0.25% bupivacaine, a 7.5-French femoral introducer sheath (Chek-Flo; Cook Inc. Bloomington, IN) was placed in the femoral artery. The side-arm of the introducer sheath was transduced to record the systemic arterial pressure and obtain arterial blood gas samples. A 7-French coaxial catheter (Envoy, Cordis Endovascular; Johnson & Johnson Co., Miami Lakes, FL) was placed in the internal carotid artery contralateral to the intracranial pathology *via* the introducer sheath. Propofol infusion was stopped after catheter placement. Two external scintillation detectors (Carolina Medical Co., King, NC) were placed over the middle cerebral artery distribution, with placement confirmed by angiography. Baseline CBF was measured 10 min after stopping the propofol infusion.

Cerebral blood flow was determined by the intraarterial ^{133}Xe injection technique.¹⁶ The technique involved a bolus injection of approximately 1.5 mCi of ^{133}Xe

Table 2. Effect of Nitroprusside on Cerebral Blood Flow of Nonhuman Primates

| Author (Year) | Route (Animal) | Measurement Technique | Outcome | Reference No. |
|--------------------------------|----------------------|---|--|---------------|
| Keany <i>et al.</i> (1973) | Intravenous (baboon) | Intracarotid ^{133}Xe and electromagnetic flowmeters | No change or a decrease | 46 |
| Arfel <i>et al.</i> (1976) | Intravenous (baboon) | Intracarotid ^{133}Xe | No effect at low doses, but at toxic doses, first increased and then decreased CBF | 47 |
| Akerman <i>et al.</i> (1976) | Intravenous (baboon) | Intracarotid ^{133}Xe | Nitroprusside $< 20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ increase ICP, no change in CBF | 48 |
| Crockard <i>et al.</i> (1976) | Intravenous (monkey) | Intracarotid ^{133}Xe | Decrease in CBF | 49 |
| Fitch <i>et al.</i> (1976) | Intravenous (monkey) | Intracarotid ^{133}Xe | No change in CBF | 50 |
| Brown <i>et al.</i> (1978) | Intravenous (monkey) | Intracarotid ^{133}Xe | Decrease in CBF | 51 |
| Candia <i>et al.</i> (1978) | Intravenous (monkey) | Hydrogen clearance | Low dose increased CBF and ICP; High dose decreased CBF and increased ICP | 4 |
| Grubb and Raichle (1982) | Intravenous (baboon) | Intracarotid $^{15}\text{O}_2$ washout | Decrease in CBF | 52 |
| Sivarajan <i>et al.</i> (1985) | Intravenous (monkey) | Radioactive microspheres | No change in CBF | 53 |
| Fitch <i>et al.</i> (1988) | Intravenous (baboon) | Intracarotid ^{133}Xe | Pressure-dependent CBF | 54 |
| Hartmann <i>et al.</i> (1989) | Intravenous (baboon) | Intracarotid ^{133}Xe | Nitroprusside increased CBF and ICP | 6 |
| Rothberg <i>et al.</i> (1979) | Intravenous (monkey) | Intracarotid ^{133}Xe | Nitroprusside and phenylephrine did not increase CBF during experimental vasospasm | 55 |

CBF = cerebral blood flow; ICP = intracranial pressure.

isotope dissolved in saline that was rapidly flushed with a 5–10-ml bolus of normal saline. Bolus intraarterial injection of ^{133}Xe resulted in an instantaneous input function, and thereby avoided the need to determine arterial concentration or deconvolution analysis of the washout curve. The washout of the tracer was recorded over the next 90 s. Blood flow was determined by analyzing the slope of the ^{133}Xe washout curve between 20 and 80 s after tracer injection. The initial slope analysis of ^{133}Xe washout yields a value of CBF that is biased toward the gray matter and is expressed in milliliters per 100 grams per minute. Intracarotid infusions were continued for the next 120 s after bolus injection of ^{133}Xe . Hemodynamic variables (heart rate, MAP, and distal internal carotid artery pressure [P_{ica}]) were recorded at the end of tracer washout. A sample of arterial blood was obtained for each CBF measurement for determining arterial carbon dioxide tension and hematocrit. CBF values obtained from the two detectors were averaged to obtain the mean value. Cerebrovascular resistance (CVR) was calculated by dividing P_{ica} by CBF and was expressed in millimeters of mercury per milliliter per 100 grams per minute.

The study involved four sequential CBF measurements. The first CBF was determined during intracarotid infusion of 0.9% saline at 1 ml/min. The second CBF (intravenous phenylephrine) was determined during systemic hypertension induced by intravenous phenylephrine infusion ($20\text{-}\mu\text{g}$ bolus followed by $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).

Intravenous phenylephrine increased MAP by approximately 10–15%. Intracarotid saline was continued during intravenous phenylephrine infusion. The third CBF (intravenous phenylephrine + intracarotid nitroprusside) was determined during concurrent infusions of intravenous phenylephrine and intracarotid nitroprusside ($0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Based on previous experience, this dose of nitroprusside was sufficient to decrease MAP by 10–15%, so as to reverse the increase in blood pressure and systemic vascular resistance caused by intravenous phenylephrine.⁹ The fourth CBF was determined during intracarotid infusion of verapamil (1 mg/min). This dose was also based on our previous studies with the drug and was sufficient to increase CBF by 35–40%.⁹ Thus, drug sequence was arranged to test for autoregulatory vasoconstriction during induced hypertension, avoid any systemic hypotension during intracarotid nitroprusside infusion, and demonstrate pharmacologic reactivity to verapamil.

To rule out catheter-induced vasospasm, the placement of the internal carotid artery catheter was considered satisfactory if there was free flow of angiographic contrast, an arterial pressure waveform could be observed through the coaxial catheter, and P_{ica} was within 10% of MAP recorded in the femoral artery.

Data Analysis

The data are presented as mean \pm SD. The data were analyzed by repeated-measures analysis of variance, and

Table 3. Effect of Intracarotid Nitroprusside on CBF of Human Subjects (n = 8)

| | Intracarotid Saline | Intravenous Phenylephrine | Intravenous Phenylephrine + Intracarotid Nitroprusside | Intracarotid Verapamil |
|--|---------------------|---------------------------|--|------------------------|
| Hematocrit (%) | 36 ± 3 | 36 ± 2 | 35 ± 3 | 36 ± 4 |
| Paco ₂ (mmHg) | 48 ± 5 | 45 ± 4* | 44 ± 3* | 43 ± 3* |
| Heart rate (beats/min) | 65 ± 11 | 60 ± 11 | 69 ± 16† | 70 ± 15† |
| MAP (mmHg) | 83 ± 12 | 98 ± 6*‡§ | 83 ± 14 | 82 ± 10 |
| Pica (mmHg) | 82 ± 13 | 96 ± 7*‡§ | 83 ± 15 | 80 ± 10 |
| CBF (ml · 100 g ⁻¹ · min ⁻¹) | 53 ± 15 | 45 ± 13 | 43 ± 9 | 65 ± 11*†‡ |
| CVR (mmHg · ml ⁻¹ · 100 g ⁻¹ · min ⁻¹) | 1.7 ± 0.7 | 2.3 ± 0.5* | 2.0 ± 0.7 | 1.2 ± 0.2*†‡ |

Values are expressed as mean ± SD. Significant differences on *post hoc* testing from * intracarotid saline, † intravenous phenylephrine, ‡ intravenous phenylephrine plus intracarotid nitroprusside, and § intracarotid verapamil. See text for details.

Paco₂ = partial pressure of carbon dioxide in arterial blood; MAP = mean arterial pressure; CBF = cerebral blood flow; CVR = cerebrovascular resistance.

post hoc testing for multiple comparisons was conducted using the Bonferroni-Dunn test.

Results

Data are presented from eight of the nine patients who completed the protocol. Data from one patient was lost because of displacement of the detector during the study. Five female and three male patients (mean age, 43 ± 13 yr; weight, 73.6 ± 5.4 kg) had the following diagnoses: cerebral arteriovenous malformations (n = 4), cerebellar arteriovenous malformations (n = 2), and dural arteriovenous fistulae (n = 2). One patient had a history of hypertension, and three were receiving anti-convulsive treatment. Hematocrit did not change significantly during the study. The arterial carbon dioxide tension was higher at baseline than during the rest of the study (table 3).

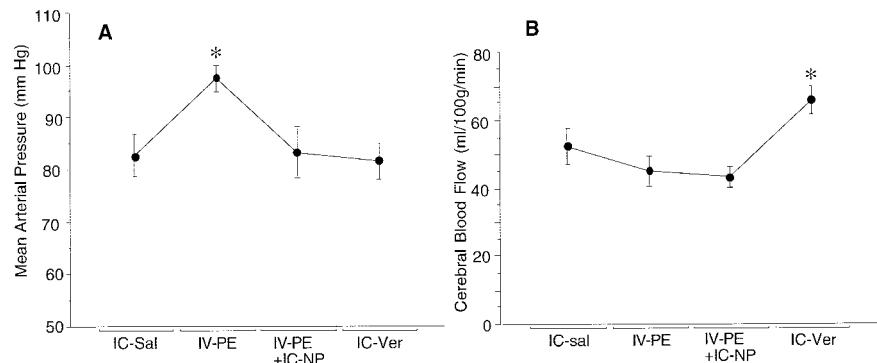
In the eight patients who completed the protocol, MAP increased significantly during the infusion of intravenous phenylephrine infusion compared with intracarotid saline (from 83 ± 12 to 98 ± 6 mmHg; *P* < 0.01; table 3 and fig. 1). However, with concurrent infusion of intravenous phenylephrine + intracarotid nitroprusside, MAP values were comparable to intracarotid saline (83 ± 12 and 83 ± 14 mmHg; nonsignificant). MAP did not change during intracarotid verapamil. A decrease in heart rate and CBF was noted during intravenous phen-

ylephrine infusion that was not significant on *post hoc* testing. Concurrent infusion of intravenous phenylephrine and intracarotid nitroprusside had no significant effect on CBF (45 ± 13 to 43 ± 9 ml · 100 g⁻¹ · min⁻¹; nonsignificant). CBF increased during intracarotid verapamil infusion compared with all other CBF measurements (intracarotid saline, intravenous phenylephrine, and intravenous phenylephrine + intracarotid nitroprusside; table 3 and fig. 1B). Intravenous phenylephrine infusion that significantly increased blood pressure also increased CVR (1.7 ± 0.7 to 2.3 ± 0.5 mmHg · ml⁻¹ · 100 g⁻¹ · min⁻¹; *P* < 0.01). Concurrent infusions of intravenous phenylephrine and intracarotid nitroprusside decreased CVR to levels comparable to baseline (2.3 ± 0.5 *vs.* 2.0 ± 0.7 mmHg · ml⁻¹ · 100 g⁻¹ · min⁻¹). Intracarotid verapamil decreased CVR to 1.2 ± 0.2 mmHg · ml⁻¹ · 100 g⁻¹ · min⁻¹, which was below the baseline value of 1.7 ± 0.7 mmHg · ml⁻¹ · 100 g⁻¹ · min⁻¹; *P* < 0.01).

Discussion

To our knowledge, this is the first study to demonstrate the failure of intracarotid nitroprusside to augment CBF despite the fact that autoregulatory vasoconstriction and pharmacologic response intracarotid verapamil could be demonstrated in human subjects. Our study avoided systemic hypotension during intracarotid nitroprusside infusion. In addition, we ruled out any cerebral

Fig. 1. Changes in mean arterial pressure (A) and cerebral blood flow (B) in eight human subjects at four stages of the experiment: (1) at baseline during intracarotid saline infusion (IC-Sal); (2) during induced hypertension with intravenous phenylephrine (IV-PE); (3) during concurrent infusion of intravenous phenylephrine and intracarotid nitroprusside (IV-PE + IC-NP); and (4) during intracarotid infusion of verapamil (IC-Ver). Error bars represent SE, and asterisks represent significant increases from other stages of the experiment.



arterial spasm caused by endovascular instrumentation. The failure of intracarotid nitroprusside to augment CBF during these circumstances not only questions whether NO plays a major role in regulating human CBF, but also questions the clinical use of intracarotid NO donors to treat cerebrovascular insufficiency.

In contrast to studies in humans, studies in rodents suggest that both intravenous and intracarotid nitroprusside preferentially decrease CVR.^{1,17,18} In goats, intracarotid nitroprusside results in a dose-dependent increase in CBF.¹⁹ In a primate model of experimental vasospasm after subarachnoid hemorrhage, intraarterial NO donors increase CBF.²⁰ Furthermore, there are clinical reports that intrathecal nitroprusside relieves vasospasm after subarachnoid hemorrhage in human subjects.³ These observations would suggest that nitroprusside can augment CBF in some animal species or during vasospasm of human subjects. Thus, the failure of intracarotid nitroprusside to augment CBF in human subjects merits further investigation.

Two previous studies have described the effect of intracarotid nitroprusside on human CBF. Henriksen and Paulson⁸ used a wide dose range of the drug (3–12 $\mu\text{g}/\text{min}$) in patients with neurologic symptoms who were undergoing angiography but did not observe an increase in CBF. The second study⁹ used superselective infusion of nitroprusside. In most instances, the drug was infused in proximity of cerebral arteriovenous malformations. Compared with Henriksen and Paulson,⁸ the latter study used a larger dose of nitroprusside (25–40 $\mu\text{g}/\text{min}$, 0.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) that was sufficient to cause minimum systemic hypotension, but no increase in CBF was evident after intraarterial nitroprusside.⁹ A confounding effect of intracranial pathology on vascular reactivity could not be ruled out in both of these studies. However, these studies provided valuable dose-response and safety data for intracarotid nitroprusside infusion.

Before inferring the physiologic significance of our results, we need to address certain methodologic issues. First, we did not undertake dose-escalation studies with drugs; rather, our doses were based on previous studies.^{9,15} This dose of nitroprusside (0.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was sufficient to result in mild systemic hypotension after intracarotid infusion. Internal carotid artery blood flow is a fraction of the cardiac output. Therefore, it is reasonable to assume that after intracarotid infusion, the concentration of nitroprusside in cerebral artery blood will be at least an order of magnitude greater than systemic arterial concentrations during recirculation of the drug. However, in the current study we failed to observe an increase in CBF after intracarotid nitroprusside. On the other hand, despite dilution, the systemic arterial concentrations of nitroprusside were sufficient to decrease MAP. In closed cranial windows, vasodilator effects of nitroprusside are evident at micromolar drug

concentrations.²¹ Assuming an internal carotid artery bulk blood flow of 200 ml/min, we estimate that during intracarotid infusion, arterial blood concentrations of nitroprusside in the internal carotid artery were in the micromolar range, clearly in the range of effective pharmacologic concentrations.

Second, iohexol, a nonionic contrast agent with low osmolarity, was used for angiography during the study. In the past, unlike iohexol, other radiocontrast agents have been shown to affect endothelial functions.²² However, there is preliminary evidence that preincubation of peripheral vascular rings with iohexol does not affect the cyclic guanosine monophosphate response.²³ Furthermore, in the coronary circulation, NO-mediated vasodilation can be demonstrated during angiography.¹³ Therefore, it seems unlikely that iohexol could have inhibited NO-mediated vasodilation.

The current study suggests that intracarotid nitroprusside fails to augment CBF in humans. It is generally believed that, during physiologic conditions, distal cerebral arteriolar resistance largely determines CBF. Failure of intracarotid nitroprusside to augment CBF raises an intriguing possibility that intracarotid nitroprusside may not relax the cerebral arteriolar bed. The evidence against such an inference, however, comes from studies that demonstrate a dose-dependent increase in intraparenchymal arteriolar diameters after incubation of rodent brain slices in nitroprusside.^{24,25} In rodents, unlike primates, intracarotid nitroprusside increases CBF.¹ Thus, it is possible that there are species-related differences between primates and rodents. However, it should also be noted that brain slice experiments expose both luminal and abluminal surfaces of blood vessels to drugs. Furthermore, brain slice preparation requires precontraction of blood vessels. Such experimental differences could explain why nitroprusside is able to increase parenchymal arteriolar diameters in rodent brain slices, yet in human subjects, intracarotid nitroprusside fails to augment CBF.

There are four converging lines of evidence that suggest that NO affects tone of large intracranial arteries. (1) Direct measurements of vessel diameters demonstrate that inhibition of NO synthase has a more profound effect on the diameters of larger cerebral arterioles compared with small ones.²⁶ (2) There is indirect evidence that nitroglycerine, another NO donor that does not increase CBF, relaxes the middle cerebral artery.²⁷ (3) Intrathecal nitroprusside can reverse vasospasm resistant to medical treatment in patients with subarachnoid hemorrhage.^{2,3} Similarly, intracarotid NO donors can increase CBF during primate vasospasm, which affects angiographically visible large cerebral arteries²⁰ (4) In dogs, intravenous nitroprusside does not increase CBF; however, it increases intracranial pressure, suggesting a greater effect on capacitance than resistance vessels.⁵

As to the question of what role does NO plays in cerebral circulation of higher primates, data from humans and primates suggest that intracarotid or intravenous administration of nonspecific inhibitors of NO synthase decrease CBF 15–20%.^{28–31} These studies suggest that NO plays at least a modest role in regulating resting CVR. However, the nonspecific inhibition of NO synthase does not reveal whether neuronal or endothelial NO affects the resting CVR. In most noncerebral vascular beds of humans, intraarterial nitroprusside is a potent vasodilator.^{12,13,32} This suggests that NO generated from intraarterial nitroprusside can freely penetrate vascular endothelium. Without direct measurements, the effectiveness of NO transfer across the blood-brain barrier of primates can only be speculated. We suspect that if endothelial NO is a major modulator of resting CBF, then physiologically generated NO should be able to freely penetrate the blood-brain barrier because the barrier lies between the endothelium and the vascular smooth muscle cell. Therefore, the failure of endothelially applied NO, by intraarterial injection of nitroprusside, could suggest that, during physiologic conditions, endothelial NO is not a major regulator of CBF of higher primates, or that NO-mediated vasodilation resides on the abluminal surface of the blood vessels beyond the diffusion range of intraarterially generated NO.

In conclusion, in human subjects that demonstrate physiologic autoregulatory vasoconstriction and pharmacologic response to intraarterial verapamil, intracarotid nitroprusside infusions in doses that are sufficient to significantly decrease the MAP during recirculation of the drug do not increase CBF. The failure of intracarotid nitroprusside to augment CBF during these circumstances not only questions whether NO plays a major role in regulating human CBF, but also questions the clinical efficacy of intracarotid NO donors to treat cerebrovascular insufficiency.

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