

Intracarotid Verapamil Decreases both Proximal and Distal Human Cerebrovascular Resistance

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Background: The authors determined the segmental effects of intracarotid verapamil in human subjects by using a novel method of measuring proximal and distal cerebrovascular resistance. Their hypothesis was that intracarotid verapamil, a calcium channel-blocking drug that augments cerebral blood flow and reverses arterial spasm, would decrease both the proximal-conductance and the distal-arteriolar resistance.

Methods: Coaxial catheters were transfemorally floated into internal carotid and middle cerebral arteries during cerebral angiography. Pressures were recorded in the femoral, internal carotid, and middle cerebral arteries. Hemispheric cerebral blood flow was measured by the intracarotid ^{133}Xe injection technique. Cerebrovascular resistance was measured for the proximal and distal arteries. Cerebral blood flow and hemodynamic data were recorded during intracarotid infusion of saline and verapamil (1 mg/min) for 5 min. Transcranial Doppler blood flow velocity in the middle cerebral artery was also recorded.

Results: Intracarotid verapamil increased in ^{133}Xe cerebral blood flow from 43 ± 11 to $59 \pm 11 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ ($P = 0.001$; $n = 9$). The cerebrovascular resistance measured for the proximal and distal arteries decreased from 0.17 ± 0.95 to 0.12 ± 0.75 and from 1.63 ± 0.78 to $1.03 \pm 0.33 \text{ mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ ($P < 0.01$), respectively. The calculated proximal-conductance and distal-arteriolar (pial plus parenchymal) resistances showed a similar decrease. Transcranial Doppler measurements ($n = 5$) underestimated the effects of intracarotid verapamil that were consistent with an increase in middle cerebral artery diameter.

Conclusions: Intracarotid verapamil decreases both the proximal-conductance and the distal-arteriolar resistance. Furthermore, it is feasible to investigate segmental effects of drugs in human subjects by measuring changes in pressure gradients within the cerebral arteries and simultaneous ^{133}Xe cerebral blood flow measurements.

EXPERIMENTS in small animals suggest that the primary site of drug action may differ along the cerebral arterial tree.¹ These observations suggest that the dominant mechanisms regulating vascular tone might be spatially separated in proximal and distal cerebral arteries. There are scant data with regard to segmental effects of drugs

on human cerebral circulation.² In small animals, segmental arterial resistance has been measured using a variety of techniques, all of which require exposure of the surface arteries (table 1).^{3,4} However, the site at which the pressure measurements were made during these experiments frequently lacked anatomic justification. The question arises as to whether observations that are based on such an approach reflect true changes in proximal-conductance and distal-arteriolar resistances or are merely changes observed at the point of pressure measurement.

Advances in microcatheter technology now permit measurement of distal arterial pressures during angiography without the need for operative exposure.⁵ We can assess changes in proximal arterial and distal cerebral arterial resistance at a specific point within the proximal-conductance artery by measuring absolute cerebral blood flow (CBF) with ^{133}Xe washout and by simultaneously measuring the pressure gradients between the internal carotid artery (ICA) and a distal segment of the middle cerebral artery (MCA). Such measurements yield direct values of proximal-conductance arterial resistance that has been sampled between the two points of pressure measurements. However, such measurements do not yield true changes in the distal-arteriolar resistance. To determine the changes in distal arteriolar resistance, we have to either measure or assume the arterial input pressure in the distal-arteriolar bed.⁶ Most studies suggest that in the absence of cerebral vasospasm, the net pressure decrease is approximately 20–25% of the mean arterial pressure (MAP) in proximal-conductance arteries (table 1).⁷ Given this assumption, we can calculate the net changes in the distal-resistance arterial bed even if we measure changes in the resistance of only a portion of the proximal-conductance arteries. Such a modeling-based approach is necessary because when the microcatheter is floated into the distal cerebral arteries, there is an increased likelihood to obstruct the blood flow (fig. 1).

To test our model, we measured changes in the proximal and distal arterial resistances using intraarterial verapamil. We hypothesized that intracarotid infusion of verapamil, a calcium channel-blocking drug that enhances CBF^{8,9} and is also used to treat cerebral vasospasm,^{10,11} would decrease both the proximal-conductance and the distal-arteriolar resistance.

Materials and Methods

After approval from the institutional review board (College of Physicians and Surgeons of Columbia Univer-

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Table 1. Selected Studies on the Contribution of Proximal-Conductance Arteries to the Total Cerebrovascular Resistance

Reference	Animal Model/Technique	Sites of Pressure Gradient Measurements	Proximal-conductance Arterial Resistance, % Total	Rationale for Arterial Pressure Measurement Site
Symon ²⁹ (1967)	Monkeys/direct cannulation	Systemic to 250–400 μm	13	Not stated
Dieckhoff and Kanzow ³⁰ (1969)	Cats, microinjection method	Systemic to pial arteries 30–40 μm	27	Not stated
Shapiro <i>et al.</i> ³¹ (1971)	Cat cranial window/micropipette	Aorta to penetrating arterioles ($\approx 25 \mu\text{m}$)	49	Not applicable
Faraci <i>et al.</i> ³² (1987)	Cats, basilar artery/micropipette	Systemic to 150 μm	31	Not stated
Heistad <i>et al.</i> ³³ (1978)	Dogs	Aorta to 250–400 μm	10	Not stated
Heistad <i>et al.</i> ³⁴ (1987)	Monkeys (normotensive)	Systemic to 300 μm	25	Not stated
Fukasawa ³⁵ (1969)	Human (autopsy)	Short cortical arteries up to 10 μm	18–25	Not applicable
Fein <i>et al.</i> ³⁶ (1983)	Humans (pressure at aneurysm site)	Aorta to 6–16 μm arteries	7	Aneurysm site
Spetzler <i>et al.</i> ³⁷ (1983)	Humans (pressure at aneurysm site)	At aneurysm site	< 5	Aneurysm site
Little <i>et al.</i> ³⁸ (1986)	Humans (pressure at aneurysm site)	Systemic to distal 1.2 mm cerebral arteries	8	Aneurysm site
Handa <i>et al.</i> ³⁹ (1993)	Humans/transfemoral microcatheter	Beyond fourth branch of ICA	15–25	Tumor site
Fogarty-Mack <i>et al.</i> ⁷ (1996)	Humans/transfemoral microcatheter	Beyond fourth branch of ICA	22	Reflects pial arterial pressure

ICA = internal carotid artery.

sity, New York, New York), written informed consent was obtained from neurologically stable patients with American Society of Anesthesiologists physical status I or II who were undergoing four-vessel cerebral angiography. The procedure 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 fasted overnight. Two hours before the procedure, they 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, and the patients were able to respond to verbal commands. Physiologic parameters that were monitored during angiography included heart rate and rhythm by electrocardiography, 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 to obtain arterial blood gas samples. A 6-French coaxial catheter (Envoy; Cordis Endovascular, Johnson & Johnson Co., Miami Lakes, FL) was placed in the ICA contralateral to the intracranial pathology *via* the introducer sheath. The coaxial-guiding catheter in the ICA was used for the injection of ¹³³Xe and for the infusion of drugs. Through this 6-French catheter, a 1.5-French microcatheter (Spin-

maker Elite; Boston Scientific Corp./Target, Fremont, CA) was advanced into the distal cerebral circulation in the M2–3 region of the MCA approximately 10–12 cm beyond the ICA catheter. The microcatheter was used only for distal pressure measurements. Before advancement of the microcatheter, to ensure quality control, pressures were recorded through the three catheters with the microcatheter located just beyond the tip of the coaxial catheter in the ICA. These pressures values generally yield a MAP between 0 and 3 mmHg of each other and are useful in detecting vasospasm. After positioning the catheters, two external scintillation detectors (Carolina Medical Co., King, NC) were placed over the MCA distribution, and the correct placement was confirmed by biplane angiography.

Cerebral blood flow was determined by the intraarterial ¹³³Xe injection technique.¹² The technique involved a bolus injection of approximately 1.5 mCi ¹³³Xe isotope dissolved in saline that was rapidly flushed with a 5- to 10-ml bolus of normal saline through the coaxial guiding catheter in the ICA. Bolus intraarterial injection of ¹³³Xe resulted in an instantaneous input function and thereby avoided the need to determine systemic arterial concentration or deconvolution analysis of the washout curve.¹² The washout of the tracer was recorded over the next 90 s. CBF was determined by analyzing the slope of the ¹³³Xe washout curve between 20 and 80 s after tracer injection. The initial slope analysis of ¹³³Xe washout yields a value of CBF that is biased toward the gray matter and is expressed in $\text{ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$. Intracarotid infusions were continued for the next 90 s after bolus injection of ¹³³Xe. Hemodynamic variables (heart

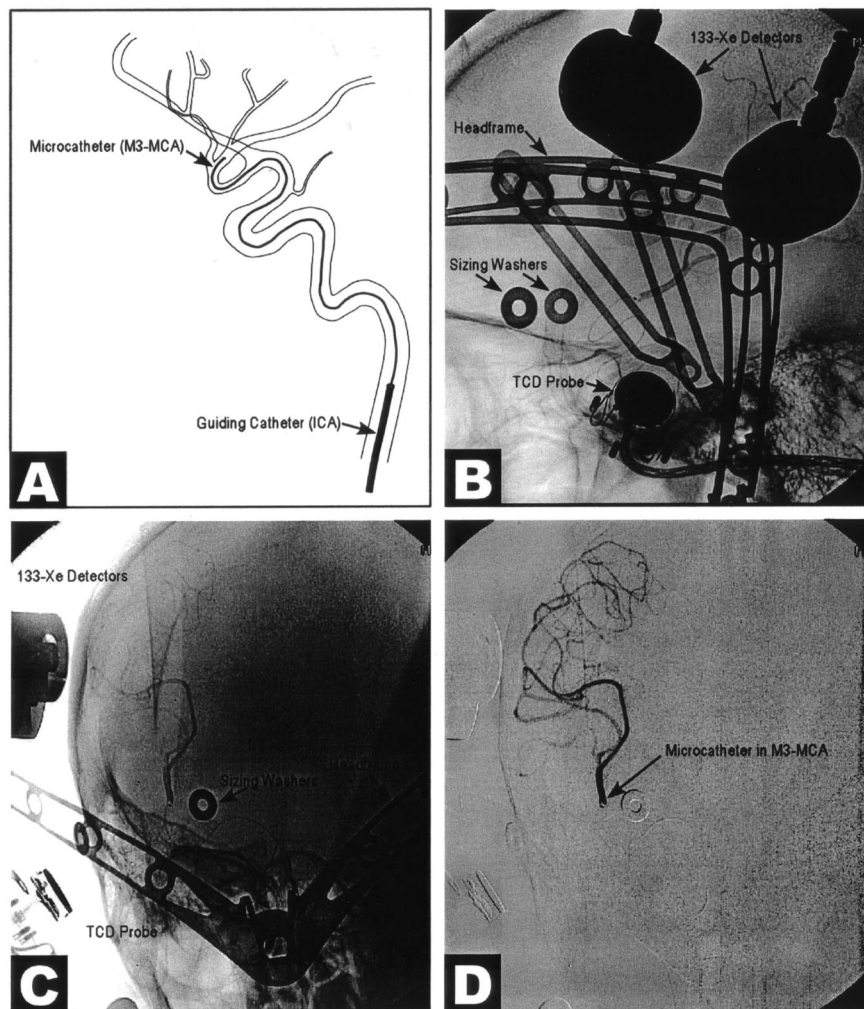


Fig. 1. The panels depict the need for a computational approach to measure proximal-conductance and distal-arteriolar resistances as well as the experimental protocol. (A) The outline shows the isolation of the segment of the conductive artery between the coaxial guiding catheter in the internal carotid artery and microcatheter in the middle cerebral artery (MCA), across which proximal-conductance arterial resistance can be measured without obstructing flow. (B) Lateral view of the ^{133}Xe detectors and transcranial Doppler (TCD) probe placements that monitor total cerebral perfusion and blood flow velocity in the MCA, respectively. (C) Frontal view of the placement of the same detectors. (D) Digital subtraction angiogram showing injection of the dye through the microcatheter shows that segments of proximal-conductance arteries lie distal to the microcatheter. A computational approach enables assessment of the resistance of the segment of the proximal-conductance artery shown in C, across which resistance cannot be measured by advancing the catheter, as it is likely to obstruct flow.

rate, femoral arterial pressure [MAP], ICA pressure (P_{ica}), and microcatheter pressures (P_{micro}) were recorded at the end of tracer washout. All infusions were stopped during pressure measurements. A sample of arterial blood was obtained for each CBF measurement for determining arterial carbon dioxide tension (P_{aCO_2}) and hematocrit. CBF values obtained from the two detectors were averaged to obtain the mean value.

Total cerebrovascular resistance (R_t) was calculated by dividing P_{ica} by ^{133}Xe CBF and was expressed in $\text{mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$. The measured distal cerebrovascular resistance ($mCVR_d$) was calculated by dividing microcatheter (P_{micro}) pressure by ^{133}Xe CBF. The measured proximal CVR ($mCVR_p$) was calculated by dividing $(P_{ica} - P_{micro})$ by ^{133}Xe CBF. Several studies suggest that in the absence of cerebral vasospasm, the net pressure decrease in the proximal-conductance arteries is approximately 20–25% of MAP (table 1).⁷ Given this assumption, we can further compute the net changes in total proximal-conductance (R_c) and total distal-arteriolar (R_r) resistances even if we can only measure changes in the resistance of a portion of these arteries (see appendix for details). In our model, the distal-arterioles are

comprised of the pial, penetrating, and intraparenchymal arterioles. The conductive arteries extend from the ICA to the pial arteries, corresponding to the site of pressure measurements by Fogarty-Mack *et al.*⁷

To rule out catheter-induced vasospasm, the placement of the ICA catheter was considered satisfactory if (1) there was free flow of angiographic contrast, (2) an arterial pressure waveform could be observed through the coaxial catheter, and (3) P_{ica} was not less than 90% of MAP recorded in the femoral artery. After satisfactory placement of the catheter, the microcatheter was gently tugged to rule out any loops that may inadvertently advance the catheter during the study. In addition, to prevent distal migration of the microcatheter, it was secured to the coaxial guiding catheter by an O ring. These precautions were critical to the model because the length of the proximal-conductance arterial segment isolated between the proximal ICA and the distal M2–3 must be the same for saline and drug challenges.

Wherever possible, a transcranial Doppler (TCD) probe was placed over the ipsilateral temporal window to record the MCA blood flow velocity. All TCD measurements were performed using a DWL EZ-Dop (DWL

Table 2. Changes in Measured Systemic and Cerebral Hemodynamic Parameters at Baseline and after Intraarterial Verapamil (n = 9)

	Baseline	Verapamil	P Value
Hematocrit, %	34 ± 3	35 ± 3	NS
ETCO ₂ , mmHg	38 ± 10	38 ± 10	NS
Paco ₂ , mmHg	54 ± 12	52 ± 11	NS
Heart rate, beats/min	66 ± 9	71 ± 11	0.009
MAP, mmHg	74 ± 16	69 ± 15	0.04
Pica, mmHg	73 ± 17	67 ± 15	0.009
Pmicro, mmHg	66 ± 20	61 ± 17	0.04
¹³³ Xe CBF, ml · 100 g ⁻¹ · min ⁻¹	43 ± 11	59 ± 11	0.001
Rt, mmHg · ml ⁻¹ · 100 g ⁻¹ · min ⁻¹	1.80 ± 0.65	1.15 ± 0.28	0.001
mCVR _d , mmHg · ml ⁻¹ · 100 g ⁻¹ · min ⁻¹	1.63 ± 0.68	1.03 ± 0.33	0.002
mCVR _p , mmHg · ml ⁻¹ · 100 g ⁻¹ · min ⁻¹	0.17 ± 0.95	0.12 ± 0.75	0.004
Rc, mmHg · ml ⁻¹ · 100 g ⁻¹ · min ⁻¹	0.45 ± 0.16	0.27 ± 0.06	0.002
Rr, mmHg · ml ⁻¹ · 100 g ⁻¹ · min ⁻¹	1.35 ± 0.49	1.03 ± 0.33	0.002

ETCO₂ = end-tidal carbon dioxide partial pressure; MAP = mean arterial pressure, femoral artery; mCVR_d = measured cerebrovascular resistance in the distal to the microcatheter tip; mCVR_p = measured cerebrovascular resistance in the proximal conductance arteries; NS = not significant; Paco₂ = partial pressure of carbon dioxide in arterial blood; Pica = mean arterial pressure in internal carotid artery; Pmicro = mean arterial pressure in middle cerebral artery; Rc = computed total proximal-conductive arterial resistance; Rr = computed distal-arteriolar resistance; Rt = total cerebrovascular resistance; ¹³³Xe CBF = cerebral blood flow by ¹³³Xe technique.

Elektronische Systeme GmbH, Längerach, Sipplingen, Germany). The position of the TCD probe was fixed using the Lam Rack[®] (DWL Neuroscan), thus ensuring a constant angle of insonation throughout the study period. Figure 1 illustrates the placement of the ¹³³Xe detectors, the TCD probe, and the catheters. To minimize artifact from ¹³³Xe injection, the TCD values were recorded immediately before ¹³³Xe injection. The systolic and mean TCD velocities were recorded for each ¹³³Xe CBF measurement. Changes in MCA diameters were assessed by determining the spasm index, *i.e.*, mean MCA velocity divided by ¹³³Xe CBF.¹³

All measurements were made at baseline during intra-carotid infusion of normal saline and verapamil. Intracarotid infusions were made through the coaxial catheter in the ICA by a mechanized pump. The flow rate was set at 1 ml/min. Verapamil was infused at a rate of 1 mg/min. The dose is based on our previous studies. Such a dose of intraarterial verapamil augments CBF but does not have significant systemic side effects.^{8,9,14} Infusions of saline and verapamil lasted for 5 min. After 3.5 min after the start of infusion, a bolus of ¹³³Xe was injected. Drug and saline infusions were resumed after ¹³³Xe injection for the next 90 s, during which the tracer washout was recorded. Further, to avoid a bolus injection of the drug contained in the dead space of the coaxial catheter, 1 ml blood was withdrawn immediately before ¹³³Xe injection. It was replaced after flushing of the isotope with normal saline. The drug or saline infusion was recommenced after ¹³³Xe injection.

On completion of the study, the position of the catheters was examined by biplane fluoroscopy to ensure that the microcatheter had not migrated distally, and there was no evidence of cerebral vasospasm or vascular injury. The microcatheter was withdrawn under fluoroscopic control. Sedation was stopped, and the well-being of the patient was ensured by a neurologic examination.

Data Analysis

The data are presented as mean ± SD. The data were analyzed by repeated-measures analysis of variance, and *post hoc* testing was performed using the Bonferroni-Dunn test. Differences between proximal-conductance arteries and distal-resistance arterioles were analyzed by factorial analysis of variance. A *P* value less than 0.05 was considered statistically significant.

Results

Nine of the 10 patients recruited for the study completed the protocol. In one patient, the research study was abandoned because of technical difficulties in cannulating the ICA. The patients who completed the protocol had a mean age of 40 ± 16 yr. Seven of the nine patients had cerebral or dural arteriovenous malformations. One patient had a dural arteriovenous fistula, and one patient had an arteriovenous malformation of the internal maxillary artery. There were five men and four women in the study.

Intracarotid verapamil did not affect the hematocrit or Paco₂ (table 2). Compared with baseline values, the mean pressure recorded in the femoral, internal carotid, and middle cerebral arteries decreased after intracarotid verapamil by approximately 10%. There was a mild increase in heart rate (table 3). ¹³³Xe CBF measurements showed a 37% increase in CBF (*P* = 0.001). Rt decreased by 36% (*P* = 0.001), mCVR_p decreased by 29% (*P* = 0.004), and CVR_d decreased by 37% (*P* = 0.002). The computed total proximal vascular resistance (Rc) decreased by 40% (*P* = 0.002), and the computed distal vascular resistance (Rr) also decreased by 24% (*P* < 0.002).

Both ¹³³Xe CBF and TCD measurements were available in five of the nine patients (table 4). Similar trends in the

Table 3. Changes in CBF and TCD Parameters after Intraarterial Verapamil (n = 5)

	Baseline	Verapamil	P Value
Pressures			
MAP, mmHg	71 ± 13	66 ± 14	0.04
P _{ica} , mmHg	70 ± 14	65 ± 13	0.03
P _{micro} , mmHg	63 ± 17	60 ± 14	0.2
¹³³Xe-based			
¹³³ Xe CBF, ml · 100 g ⁻¹ · min ⁻¹	44 ± 16	60 ± 12	0.02
Rt, mmHg · ml ⁻¹ · 100 g ⁻¹ · min ⁻¹	1.75 ± 0.67	1.11 ± 0.24	0.03
mCVR _d , mmHg · ml ⁻¹ · 100 g ⁻¹ · min ⁻¹	1.59 ± 0.69	0.99 ± 0.28	0.04
mCVR _p , mmHg · ml ⁻¹ · 100 g ⁻¹ · min ⁻¹	0.16 ± 0.11	0.12 ± 0.1	0.1
Rc, mmHg · ml ⁻¹ · 100 g ⁻¹ · min ⁻¹	0.44 ± 0.28	0.17 ± 0.07	0.04
Rr, mmHg · ml ⁻¹ · 100 g ⁻¹ · min ⁻¹	1.31 ± 0.5	0.99 ± 0.28	0.06
TCD-based			
Systolic VMCA, cm/s	80 ± 14	103 ± 26	0.03
Mean VMCA, cm/s	50 ± 11	57 ± 17	0.2
MCA spasm index	1.2 ± 0.4	1.0 ± 0.5	0.09

MAP = mean arterial pressure, femoral artery; mCVR_d = measured cerebrovascular resistance in the distal to the microcatheter tip; mCVR_p = measured cerebrovascular resistance in the proximal conductance arteries; mean VMCA = mean blood flow velocity in middle cerebral artery; P_{ica} = mean arterial pressure in internal carotid artery; P_{micro} = mean arterial pressure in middle cerebral artery; Rc = computed total proximal-conductive arterial resistance; Rr = computed distal-arteriolar resistance; Rt = total cerebrovascular resistance; systolic VMCA = systolic blood flow velocity in the middle cerebral artery; ¹³³Xe CBF = cerebral blood flow by ¹³³Xe technique.

hemodynamic variables were evident in these patients. The mean increase in ¹³³Xe CBF was approximately 36% ($P = 0.02$; $n = 5$). The mean increase in systolic blood flow velocity in the MCA was 29% ($P = 0.03$; $n = 5$), although the mean MCA velocity did not show any significant increase. The decrease in MCA spasm index from 1.2 ± 0.4 to 1.0 ± 0.5 was not statistically significant ($P = 0.09$). Figure 2 shows that the percentage of change in systolic and mean MCA blood flow velocities was consistently less than the percentage of change in CBF, although despite the small sample size, the two values seemed to correlate with each other (Percent Change in TCD = $0.6 \times$ Percent Change in CBF; $R = 0.7$, $P = 0.2$; $n = 5$). The ¹³³Xe-CBF increased by 36% after intraarterial verapamil infusion, whereas the systolic and mean blood flow velocities in the MCA increased by 29 and 14%, respectively.

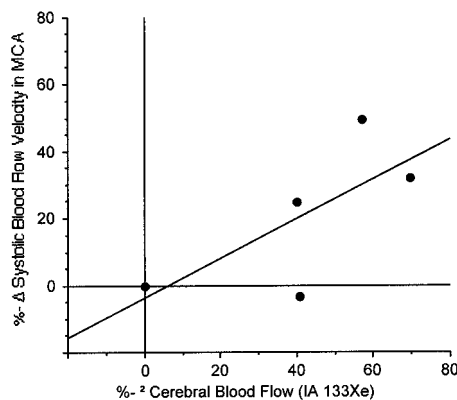


Fig. 2. Bivariate scattergram showing the percentage of change in systolic middle cerebral artery (MCA) velocity (% Δ TCD) and cerebral blood flow (% Δ CBF) values from baseline after intra-carotid infusion of 1 mg/min of verapamil. % Δ TCD = $-3.964 + 0.593 \cdot$ % Δ CBF; $R^2 = 0.494$. IA = intraarterial.

Discussion

There are three significant results of this study. First, the results suggest that intracarotid infusions of verapamil decrease both the proximal-conductance and the distal-arteriolar resistance. Second, in the subset of patients who had both TCD and ¹³³Xe CBF measurements, the increase in CBF after intracarotid verapamil was less evident with TCD than with ¹³³Xe CBF measurements. Third, this study shows that it is feasible to measure proximal-conductive and distal-arteriolar resistances *in vivo* in human cerebral circulation with simultaneous intraarterial pressure and ¹³³Xe CBF measurements.

Before discussing the clinical implications of the study, it is important for us to discuss the features and limitations of our method for measuring proximal and distal cerebrovascular resistance. First, to use our modeling approach, we must make a critical assumption regarding the pressure at which the behavior of the arteries changes from proximal conductance to distal arteriolar, so-called transition pressure. It could be argued that the transition pressure differs considerably between individuals. However, this study was performed in a relatively healthy subject population. Based on published studies summarized in table 1, we believe that the transition pressure assumed in this study is reasonable. It should be noted that the transition pressure is assumed only during saline infusions. No such assumption is required during drug administration. Using our modeling approach, we avoid distal cannulation of the MCA. An alternate method to assess changes in proximal and distal arterial reactivity could be based on direct measurements undertaken in the distal regions of the brain. It is possible to advance the microcatheter as far down as the M5 level of the cerebral arteries.⁷ The disadvantage of this method is

that as the microcatheter is advanced, the likelihood of obstructing the flow increases. Interference with blood flow could alter physiologic or pharmacologic reactivity. Distal catheter placement also carries a greater risk of injury to the vessel.

Second, all research subjects received drugs that were clinically indicated for the procedure, such as fentanyl, midazolam, propofol, oral nimodipine, and heparin. We have conducted several human studies with this background sedation that have revealed a robust response to nitric oxide-independent but not nitric oxide-dependent drugs.^{8,9,14-16} Furthermore, the lack of response to intraarterial nitric oxide donors in our human studies is also reflected by studies in healthy primates under isoflurane anesthesia who did not receive the fentanyl, midazolam, nimodipine, or propofol infusions.¹⁷

Third, intraarterial injection of drugs often results in considerable differences in tissue concentrations due to streaming of the drugs.¹⁸⁻²⁰ Streaming is particularly more significant during distal superselective infusion of drugs than during intracarotid infusions.¹⁹ In this model, the drugs are injected through the outer coaxial catheter that lies in the ICA. Furthermore, the microcatheter lies in the lumen of the coaxial catheter that will enhance drug mixing. We believe that in this model, errors due to streaming of drugs are likely to be minimal.

Our attempt to develop a method to measure proximal and distal arterial resistance is a direct result of our failure to observe any significant effect of intraarterial nitric oxide donors and nitric oxide synthase inhibitors on human CBF. We suspect that nitric oxide plays a significant role in regulating the tone of proximal-conductance arteries because of its ability to relieve cerebral vasospasm when these arterioles are pathologically narrowed.²¹⁻²⁴ It is our bias that distal pial and intraparenchymal cerebral arterioles that are in close proximity to the neurons may have fundamentally different vascular reactivity than the proximal-conductance arteries.²⁵ The distal arterioles are the smart resistors in the cerebral circulation whose tone is directly determined by electrical and metabolic state of the neurons.

There are few practical methods to study the behavior of distal pial and parenchymal arterioles.²⁶ One can measure the changes in the diameter of the parenchymal arterioles in brain slice experiments.²⁷ However, the relevance of studies on brain slices or the harvested penetrating arterioles that have been separated from most of their neuronal connections to the physiologic arteriolar behavior is open to question. Alternatively, the behavior of large and small cerebral arteries has been extensively investigated by direct pressure measurements; however, the rationale for selecting the site of measurement was not always provided (table 1). Because of the ability to advance the microcatheter safely into the distal segments of the cerebral arteries, we can now replicate and even improve on the methods used in

small animal studies. In the current study, we directly measured the changes in resistance of a segment of the conductance artery between the ICA and the M2-3 region of the MCA. We have described this as the measured proximal and distal resistances.

To test the model, we used intracarotid verapamil, a drug that is used routinely during the clinical procedure. In previous human studies, we have observed that intraarterial verapamil increases CBF in angiographically normal cerebral hemispheres in chronically hypotensive vascular beds of patients with cerebral arteriovenous malformations and during acute cerebral hypotension after ICA occlusion. Therefore, the ability of verapamil to decrease the distal-arteriolar resistance and hence augment CBF is consistent with published literature.^{8,9,14} However, our results suggest that intraarterial verapamil also dilated the proximal cerebral arteries. At our institution, intraarterial verapamil is clinically used to treat catheter-induced cerebral vasospasm during angiography and is also used for treating vasospasm after subarachnoid hemorrhage. In both these applications, injection of the drug relaxes the large angiographically visible cerebral conductance arteries. Our results suggest that even in the absence of cerebral vasospasm, verapamil is able to decrease the resistance of the proximal-conductance arteries.

Because of the potential risk of thromboembolism, we limited our total study time to 20 min for each experiment. We were often unable to obtain satisfactory TCD detector placement within the time constraints and were therefore forced to abort TCD measurements. However, we did obtain TCD values in five of the nine subjects. The key data from these subjects are presented separately in table 4. As shown in figure 2, the increase in systolic and mean TCD velocity was significantly less compared with ¹³³Xe CBF measurement and could possibly be attributed to an increase in MCA diameter. The MCA spasm index, which reflects the MCA diameter, decreased by 17% after intracarotid verapamil.

Recently, Oskouian *et al.*²⁸ used multimodality quantification of changes in cerebral hemodynamic parameters to assess the effects of intraarterial papaverine. They measured changes in angiographic diameters, ¹³³Xe CBF, and TCD flow measurements in patients with cerebral vasospasm. Intraarterial papaverine increased CBF from 28 ± 2 to 39 ± 3 ml · 100 g⁻¹ · min⁻¹. The arterial diameters increased approximately 30% on angiography. The MCA velocities decreased from 149 ± 13 cm/s to 111 ± 11 cm/s. The MCA area based on TCD measurements, *i.e.*, the MCA spasm index, decreased by 43%. Because of profound differences in the underlying patient populations, it is difficult to compare the pharmacologic effects of intraarterial verapamil and papaverine. However, the study by Oskouian *et al.* and our own study highlight the significance of multimodality mea-

surements to better understand pharmacologic effects of drugs on the human cerebral circulation.

We conclude that intraarterial verapamil dilates both the proximal-conductance arteries and the distal-arteriolar beds. Because of dilation of the proximal-conductance arteries such as the MCA, TCD measurements might underestimate the effects of intracarotid verapamil. Finally, it is possible to investigate the differential effects of vasoactive drugs on the proximal-conductance and distal-arteriolar resistance beds by simultaneous pressure measurements in the proximal and distal cerebral arteries, combined with intraarterial ^{133}Xe CBF measurements. Such measurement techniques could be useful for investigating the primary site of drug effects and for identifying the location of vascular mechanisms along the arterial tree.

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Appendix

Modeling Assumptions

The model uses the following assumptions:

1. Intracarotid drug has a homogenous effect throughout ICA distribution.
2. There are only two types of vascular behaviors: proximal-conductance and distal-resistance arterioles.
3. Venous outflow pressure and intracranial pressure are negligible.
4. Transition pressure represents the point at which the arterial reactivity changes from proximal-conductance to distal-resistance (pial-parenchymal) type, corresponds to a pressure drop of 25% of P_{ica} in the physiologic state.¹³

Mathematical Determination of Proximal Arterial and Distal Arterial Resistances

We separated the arterial behavior into two theoretical types: (a) proximal-conductance arteries (R_c), and (b) distal arterial beds (R_r). Because these resistances are in series, the total resistance (R_t) is given by the equation:

$$R_t = R_c + R_r \quad (1)$$

or

$$R_c = R_t - R_r \quad (2)$$

Figure 3A illustrates our measured variables during saline infusion. During the saline run, we must establish what fraction of the total proximal resistance (R_t) was measured between the coaxial and the microcatheter; *i.e.*, the measured proximal CVR or $mCVR_p$. This could be presented as a correction factor (X) such that:

$$R_c = mCVR_p \cdot X \quad (3)$$

or

$$X = R_c / mCVR_p \quad (4)$$

During the saline run, we can compute the input pressure into the distal resistance arterioles (Transition Pressure) from the mean ICA

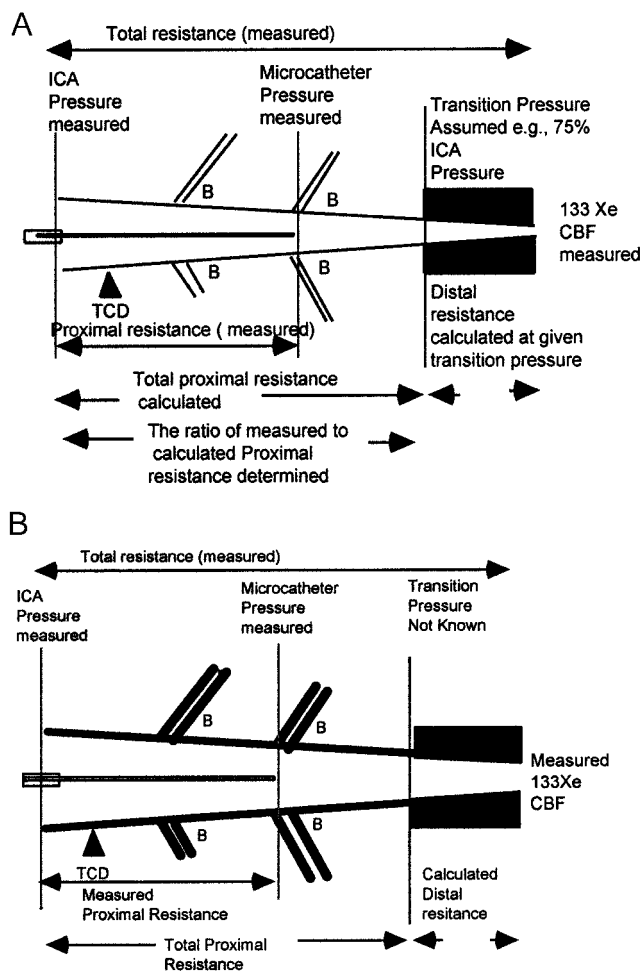


Fig. 3. (A) Method for determining ratio of measured to total proximal-conductive arterial resistance during infusion of saline. (B) Method for determining the effects of drugs on proximal-conductive arterial and distal-arteriolar resistances. Note that during drug infusion, the transition pressure is not assumed; see Appendix for details.

pressure by assuming that the change in vascular reactivity occurs at a 25% pressure drop in the ICA:

$$\text{Transition Pressure (TPsal)} = (75 \cdot P_{ica}) / 100 \quad (5)$$

Furthermore, ^{133}Xe CBF measures the absolute tissue perfusion (in $\text{ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$); therefore, we can apply the same flow anywhere in the ICA irrigation. For example, to deduce the resistance of the arteriolar bed (R_r):

$$R_r \text{ Saline} = \text{TPsal} / \text{CBF} \quad (6)$$

while we can also obtain the values of:

$$R_t = P_{ica} / \text{CBF} \quad (7)$$

After determining R_t and R_r , we can deduce R_c saline by applying equation 2 ($R_c = R_t - R_r$). In addition, we can determine the resistance of the segment of the conductive arteries interposed between the end of the coaxial and microcatheter (proximal R_c) by:

$$\text{MCVR}_p = (P_{ica} - P_{micro}) / \text{CBF} \quad (8)$$

Therefore, from equation 4,

$$X = R_c / mCVR_p = [(P_{ica} / \text{CBF}) - (\text{TPsal} / \text{CBF})] / [(P_{ica} - P_{micro}) / \text{CBF}] \\ = (0.25 P_{ica}) / (P_{ica} - P_{micro}) \quad (9)$$

Determination of X is the critical part of the baseline measurements during intracarotid saline infusion. Intracarotid infusion of drugs may constrict or dilate the conductive arteries. Therefore, the transition pressure cannot be assumed after drug infusion. However, we are directly measuring the change in proximal conductive arterial resistance during drug infusion ($mCVRp$), and we know the proportion of conductive arterial resistance that we are sampling (X). Therefore, we can calculate that the net change is conductive vascular resistance due to drug:

$$Rc\ drug = X * mCVRp\ drug \quad (10)$$

Furthermore, we are also directly measuring the Rt during drug infusion ($Rt\ drug$). Therefore, we can calculate the effect of the drug on the distal arteriolar bed; *i.e.*, $Rr\ drug$:

$$Rr\ drug = Rt\ drug - Rc\ drug \quad (11)$$

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