

Assessment of Cerebral Autoregulation Dynamics From Simultaneous Arterial and Venous Transcranial Doppler Recordings in Humans

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We investigated the validity of transcranial Doppler recordings for the analysis of dynamic responses of cerebral autoregulation. We found no significant differences in percentage changes among maximal (centerline) blood flow velocity, cross-sectional mean blood flow velocity, and signal power—estimated blood flow during 24-mm Hg stepwise changes in arterial blood pressure. We investigated blood flow propagation delays in the cerebral circulation with simultaneous Doppler recordings from the middle cerebral artery and the straight sinus. The time for a stepwise decrease in blood flow to propagate through the cerebral circulation was only 200 msec. Brief (1.37-second) carotid artery compression tests also demonstrated that the volume compliance effects of the cerebral vascular bed were small, only about 2.2% of normal blood flow in 1 second. Furthermore, transients associated with inertial and volume compliance died out after 108 msec. We also investigated the hypothesis that autoregulatory responses are influenced by hyperventilation using the same brief carotid artery compressions. One second after release, the flow index increased by 17% during normocapnia and 36% during hypocapnia. After 5 seconds, the flow index demonstrated a clear oscillatory response during hypocapnia that was not seen during normocapnia. These results suggest that the intact human cerebral circulation in the absence of pharmacological influences does not function as predicted from pial vessel observations in animals. (*Stroke* 1991;22:1148–1154)

Cerebral autoregulation describes the mechanism responsible for changing the cerebral blood flow (CBF) in response to changing cerebral perfusion pressure. Responses of CBF to sudden changes in arterial blood pressure in unanesthetized humans have been found to be extremely rapid, with a latency time (t_L) of <2 seconds.¹ In contrast, a much longer delay was observed in cat pial arteriolar diameters after blood pressure changes.² We address the possibility that errors in the calculation of CBF from transcranial Doppler (TCD) recordings in humans were responsible for this shorter

response time.³ We compared the method used previously for calculating relative flow volume changes, using velocity only, with a method that directly calculates flow volume,⁴ based on the same principle used in laser Doppler measurements of tissue perfusion.⁵ Furthermore, we made simultaneous TCD measurements of arterial inflow and venous outflow during an autoregulatory stimulus to compare the response times. We performed a second set of experiments using brief carotid artery compressions followed by quick release to determine if reflow to the arterial channels due to compliance of the cerebrovascular bed would introduce a significant error into calculation of the autoregulatory response following a sudden decrease in arterial blood pressure. We also measured the response of middle cerebral artery (MCA) blood flow velocity to carotid artery compression and release during normocapnia and hypocapnia to determine if PaCO_2 has a profound influence on the dynamic autoregulatory response.

Subjects and Methods

This study was conducted in 12 healthy volunteer subjects recruited from the hospital staff. Informed

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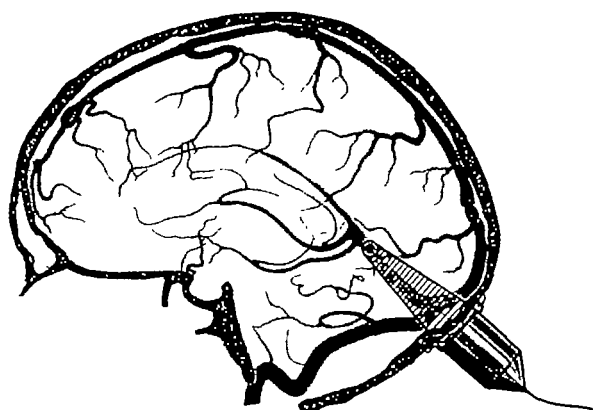


FIGURE 1. Schematic representation of transcranial Doppler measurements from straight sinus. With depth set to about 50 mm, sinus is insonated through occipital window. (Veins redrawn after Reference 7).

consent was obtained prior to the examination. Three subjects were rejected because we did not find adequate occipital windows (see below). The remaining nine subjects included three women and six men with a mean age of 33 years, and none were identical to the subjects employed in an earlier study.¹ The subjects were not on medication. Continuous brachial arterial blood pressure readings and Doppler spectra from the MCA were recorded as described previously.^{1,6} The measurement technique was expanded by using a new prototype TCD instrument that permitted a second channel of recordings to be fast Fourier-transformed (128 points) and visualized in real time simultaneously with the measurement in the MCA. The second TCD channel was used for recordings from the straight sinus. The approach to this vessel is new and will be described in some detail.

The straight sinus was insonated through an occipital window, as shown in Figure 1. This acoustic window was found less frequently than the temporal

window to the basal cerebral arteries,⁶ and we succeeded in only nine of the 12 subjects in whom we attempted it. The search was started with the TCD depth set to 50 mm and the probe directed toward the brain midline. The area around the approximate position of the confluence of the sinuses was searched with the probe for possible intracranial Doppler signals. If arterial signals were found in the region of the calcarine fissure, they usually responded to light/dark stimuli,⁴ indicating their involvement in supplying the visual cortex. Then, the sample volume was directed medially and slightly superiorly to locate the straight sinus signal, which was characterized by a smoother and fuller Doppler sound than arterial signals. The blood flow velocity in the straight sinus was always pulsatile (Figure 2), with pulsatility indexes varying from about 25% to 80% of that in the arterial signals. The flow direction was toward the probe. A venous source of the signal was confirmed by a brief Valsalva maneuver, giving characteristic transients in the venous signal. We always succeeded in finding the straight sinus in subjects in whom arterial signals could be located through an occipital window. In two subjects with very favorable occipital windows, we could scan the straight sinus signal to greater depths, and at approximately 6–7 cm we detected two venous signals separated in the sagittal plane. These signals were probably from the inferior sagittal sinus and Galen's vein.

We used three different methods to estimate flow indexes from the Doppler spectra. First, the spectral outline, V_{max} , corresponding to the centerline blood flow velocity, was determined as described earlier.¹ Second, the cross-sectional average blood flow velocity, V_{mean} , was calculated by the method proposed by Arts and Roelvros.⁸ And third, changes in the theoretical flow volume, F_{mean} , were calculated by a method described earlier,⁴ which is based on the

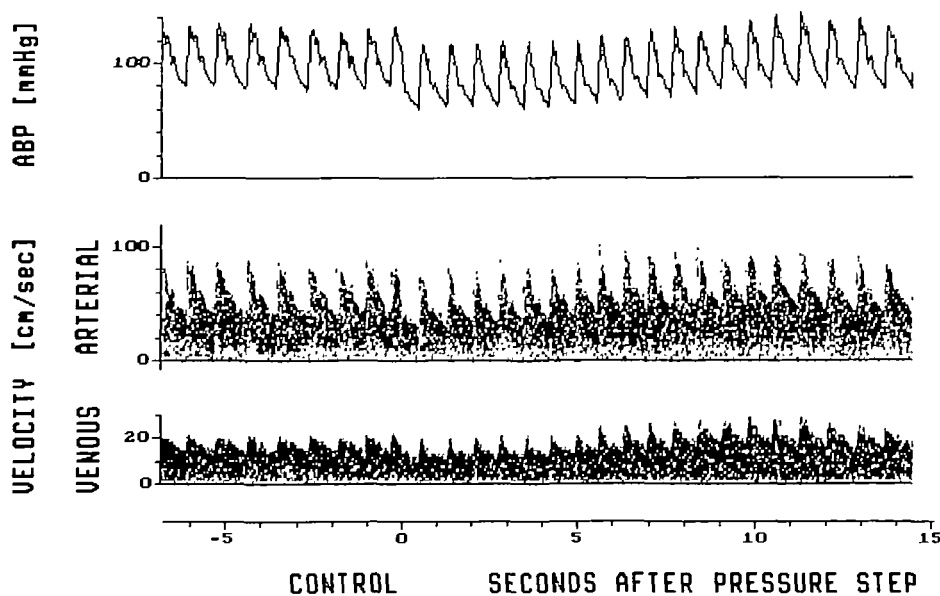


FIGURE 2. Recordings of arterial blood pressure (ABP) and Doppler spectra in middle cerebral artery (arterial) and straight sinus (venous). At time 0, leg cuffs were released and ABP and velocities dropped abruptly.

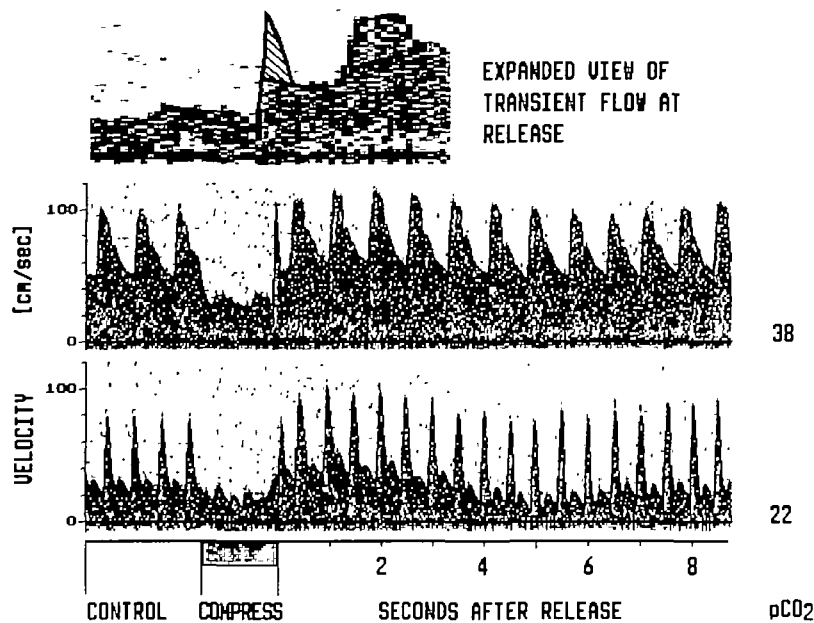


FIGURE 3. Middle cerebral artery Doppler spectra at control, common carotid artery compression, and after release of compression. Upper panel: magnified view of volume compliance transient during normocapnia. Middle panel: normocapnia, $PCO_2=38$ mm Hg. Lower panel: hypocapnia, $PCO_2=22$ mm Hg. Notice augmented response with oscillatory dip in velocity to below control.

same principle as tissue perfusion measurements by laser Doppler methods.⁵ The signal power (proportional to the number of blood cells) of each spectral component was multiplied by the respective Doppler shift, and 60 such products of forward flow were added up, excluding the four lowest spectral components, which are susceptible to arterial wall movement artifacts. Thus, in the situation of blood flow velocity increases due to arterial narrowing with a constant CBF, the signal power would theoretically decrease as much as the velocity increased and the estimate of flow would remain constant. The method requires a good signal-to-noise ratio and stable fixation of the probe during measurement. Such stability was possible during the relatively short time of measurement because the cranium provided a good fixation surface. This method was not used for the venous approach because we employed a hand-held probe for these measurements.

Stepwise decreases in arterial blood pressure were induced as described previously¹ by deflating leg cuffs after a 2-minute supersystolic inflation. V_{max} , V_{mean} , and F_{mean} in the MCA and V_{max} in the straight sinus were calculated from the Doppler spectra and recorded along with the arterial blood pressure. Control values were defined as those during the 2 seconds immediately preceding leg cuff release. These values were used to calculate the percentage changes in the various flow indexes. At least four recordings were made during normocapnia in each subject. There was little variability in arterial blood pressure and TCD responses among recordings, and the results were averaged using leg cuff deflation as the time reference.

Impulse responses were evoked by compressing the ipsilateral common carotid artery for 1–1.5 seconds, as shown in Figure 3. Care was taken not to compress the carotid sinus. Control values were taken from the last 2 seconds before compression. Arterial blood pressure and end-tidal PCO_2 (as mea-

sured by infrared gas analyzer) were recorded along with the Doppler spectra. Four compressions were made during normocapnia, followed by another four during voluntary moderate hyperventilation. Seven subjects were studied with the impulse response protocol.

Student's two-tailed *t* test was used for all determinations of statistical significance. Values are given as mean \pm SEM.

Results

The three flow indexes are compared in Figure 4. Only recordings from the seven subjects with signal-to-noise ratios of >12 dB were included in the flow index comparison. The three flow indexes gave practically identical time courses; the only noticeable difference was that the decrease in flow volume as measured by F_{mean} was slightly (2.2%) larger than that measured by V_{max} . This corresponds to a diameter change of 1.1%, but this value was not significantly different from 0 (for both one-tailed and two-tailed *t* tests). V_{mean} was found to be between F_{mean} and V_{max} .

For the response to stepwise decreases in arterial blood pressure experiments, control blood pressure was 86 ± 3.7 mm Hg and the step was 24 ± 2.1 mm Hg. In Figure 5, averaged tracings of V_{max} in the MCA and the straight sinus are shown. The percentage decrease in the flow index on the venous side was only slightly larger than that on the arterial side. The time lag from the arterial to the venous tracing was 0.2 seconds for abruptly decreasing blood flow. The mean venous blood flow velocity in the straight sinus was 23 ± 3 cm/sec in the nine subjects.

The t_L could be measured as the interval from the blood pressure decrease until the beginning of regulatory action, defined as when the slope of the flow index tracing showed a distinctly more upward deflection than that of the arterial blood pressure tracing (by visual judgement). The t_L was 0.95 sec-

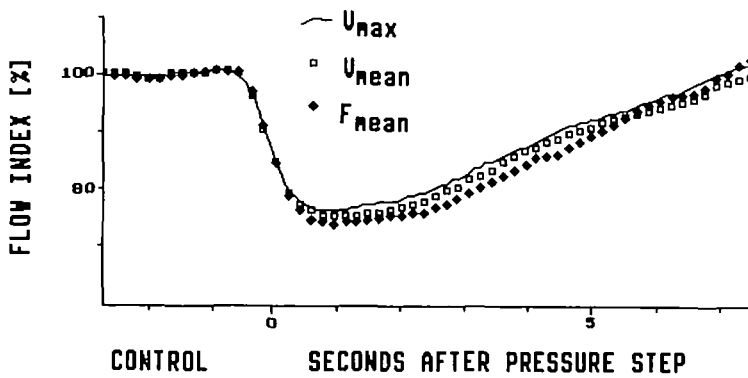


FIGURE 4. Comparison of different flow indexes from seven subjects averaged together. V_{max} , center-line blood velocity; V_{mean} , cross-sectional average velocity; F_{mean} , theoretical flow volume.

onds for arterial recordings and 2.6 seconds for venous recordings. Half-maximal response times (t_{50}) were 3.7 seconds for arterial indexes and 4.6 seconds for venous indexes. Full response times were 6.8 and 6.7 seconds, respectively, for arterial and venous indexes. These results are summarized in Table 1 and compared with findings of other studies.

In the impulse response experiments, blood pressure did not change significantly from control during and after compression. The findings for V_{max} are summarized in Figure 6. During compression, which lasted 1.37 ± 0.06 seconds, V_{max} fell by 37% during normocapnia and by 34% during hypocapnia, but the difference between the two states was not significant. This drop in V_{max} would approximately reflect the transient drop in perfusion pressure of the ipsilateral MCA during the impulse stimulus. After abrupt release of the compression, a very sharp transient increase in V_{max} was found, as illustrated in Figure 3. This transient lasted for an average of 108 msec, and there was no significant change in this time during hypocapnia. The area of the spike, as indicated by hatching in Figure 3, represents approximately the increase in blood flow necessary to fill the compliant arterial bed during the sudden increase in local

perfusion pressure after release of the compression. The area was 2.42% of the area under the normal flow index curve during 1 second. During hypocapnia, the area decreased to 2.04%, but the difference was not significant.

After 200 msec following release of the compression, such flow transients were completely absent. Then, because arterial blood pressure was constant and all inertial and volume compliance effects had settled down, any changes in flow index could have resulted only from autoregulatory action due to the previous transient decrease in CBF. After only 1 second following release of the compression, the flow index was 17% higher than control during normocapnia and 36% higher during hypocapnia. The differences were highly significant ($p < 0.01$). Qualitatively, the flow index followed different time courses in the two states. There was a significant ($p < 0.01$) oscillatory undershoot in the flow index at 4 and 5 seconds during hypocapnia. During normocapnia, however, the flow index settled back to control without such a regulatory transient.

Discussion

Blood flow volume and mean velocity calculated from Doppler spectra are valid only if there are no

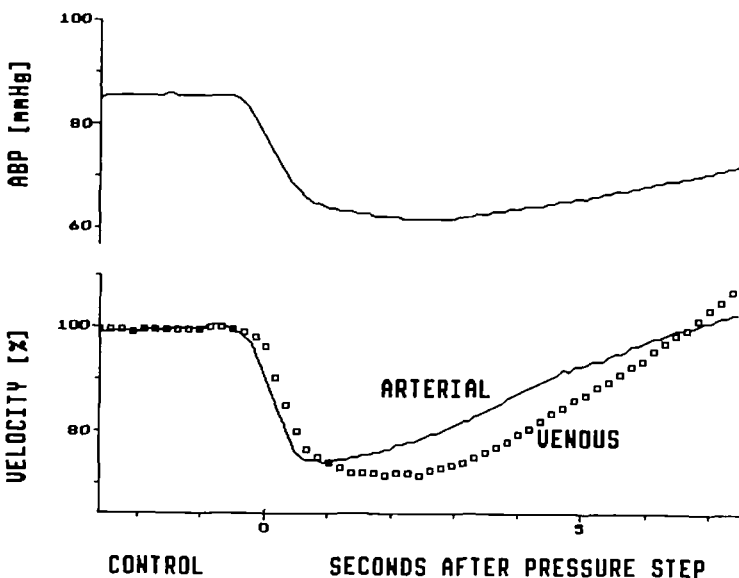


FIGURE 5. Averaged results of step stimulus experiments in nine subjects. Upper panel: response of arterial blood pressure (ABP). Lower panel: responses of middle cerebral artery (—) and straight sinus (□) blood velocity expressed as percent of control.

TABLE 1. Comparison of Dynamic Response Times in Cerebral Circulation

Study	Year	Stimulus	Measurement	Latency time (sec)	Half-maximal response time (sec)	Peak response time (sec)
Symon et al ¹²	1973	ABP increase	Venous blood flow	<1.0	1.9*	...
Kontos et al ²	1978	ABP decrease	Art. diam.	5.2	9–12†	...
Aaslid et al ¹	1989	ABP decrease	MCA velocity	<1.5	3.4	...
Present study		ABP decrease	MCA velocity	0.95	3.7	6.8
			SS velocity	2.6	4.6	6.7
Ngai et al ¹⁴	1988	Sciatic nerve	Art. diam.	1.4	4.5*	7.0
Aaslid ⁴	1987	Visual	PCA velocity	1.05	2.3	5.9

ABP, arterial blood pressure; Art. diam., pial arteriole diameter; MCA, middle cerebral artery; SS, straight sinus; PCA, posterior cerebral artery.

*Estimated from figures in cited paper.

†Phase lag between pressure and diameter recordings.

vessel wall vibrations⁹ or turbulence. This condition was satisfied in our experiments. The excellent agreement between the different velocity calculations in both arteries and veins and the results of the flow calculations based on signal power suggest that changes in MCA diameter do not invalidate the use of velocity measurements for the study of cerebral autoregulation dynamics. These findings are consistent with comparison studies using electromagnetic flowmetry as reference¹⁰ in which a close linear correlation was found between blood flow velocity and volume during moderate changes in arterial blood pressure. It should be emphasized that we have investigated the accuracy of the technique only for stepwise changes in blood pressure. Drugs¹¹ and very large changes in cerebral perfusion pressure may influence artery diameter to an extent that would

make flow index calculations based on V_{max} and V_{mean} invalid.

A change in MCA diameter of 5–10% has been cited³ as a value to be expected during such measurements. However, this assumption was based on measurements in species with basal cerebral artery diameters of <1 mm. The discrepancy between these assumptions³ and our estimate of a very small (1.1%) diameter change may give reason to question the validity of extrapolating data from smaller species to the human anatomy.

The straight sinus has a perfect course for TCD recordings through an occipital acoustic window because its flow is directed toward the probe with small angle errors. Also, the walls of the sinus, being composed of the falx and the tentorium, are very stiff and not subject to direct elastic or vasomotor effects like the walls of arteries. One possible source of a change in cross-sectional area of the sinus could be relative changes in volumes of the supratentorial and infratentorial spaces. Such shifts could possibly lift the tentorium so that the sinus might undergo a partial collapse of its side walls. Compartmental volume changes would have to occur slowly because they would have to be relatively large to affect the entire tentorium. Filling of the intraspinal extradural venous plexuses after leg cuff deflation might have occurred to some degree during the recordings. The effect of this would have been a gradual increase of the infratentorial volume. This could explain why the venous blood flow velocity was 8% higher than control during the late phase of autoregulatory action 7.5 seconds after the stepwise decrease in blood pressure, as shown in Figure 5.

The normal cerebral circulation is a low-resistance, high-flow vascular bed with relatively stiff vessels. This is why it takes only 200 msec for a stepwise change in blood flow on the arterial side to be propagated to the main outflow veins. In this context it is important to distinguish between propagation of flow changes and transport times. In a nonelastic system, stepwise flow changes take place at all locations in parallel, whereas transport of a fluid indicator takes time. For the study of cerebral autoregu-

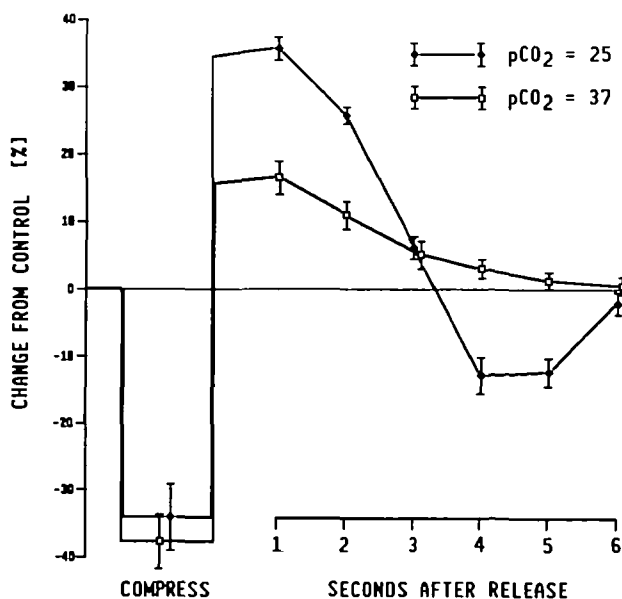


FIGURE 6. Results of impulse response experiments in seven subjects. Compression of ipsilateral common carotid artery lasted 1.37 seconds. □, Middle cerebral artery blood flow velocity during normocapnia; ♦, middle cerebral artery blood flow velocity during hypocapnia. Bars denote SEM.

lation, it is the propagation of flow changes that are important, and these take place almost in parallel on the arterial and venous sides. The extremely swift propagation of flow changes suggests that arterial, capillary, and venous measurements of blood flow are practically equivalent for the analysis of autoregulatory responses.

The slightly longer delay for the autoregulatory response as defined by t_L and t_{50} of the venous recording compared with the arterial recording may have been due to changes in microcirculatory volume during autoregulatory action.³ During vasodilation, the vascular bed expands and outflow must be slightly less than inflow. If this assumption is correct, we could calculate the change in volume of the vascular bed during vasodilation. The area between the arterial and venous curves during regulation (Figure 5) was 0.28% of the total area beneath the arterial curve during 1 minute or 17% of the flow in 1 second. This effect would have introduced an error into the calculations of cerebrovascular resistance and rate of autoregulation during the rapid-change phase, and arterial t_{50} would have been somewhat underestimated.

There is, however, physiological evidence that the simple mathematical concept of cerebrovascular resistance is insufficient for detailed analysis of the brain circulation. It has been shown convincingly that a dynamic pressure-flow plot intercepts the 0 flow axis at an arterial blood pressure much higher than the intracranial pressure.¹² Reanalyzing the recordings from a previous series,¹ we found strong evidence for this phenomenon, particularly during hypocapnia. We are led to conclude that cerebrovascular resistance calculated from pressure and flow must be used with caution in discussion of the cerebral circulation and that physiologically more correct models are needed.

Our present study clearly demonstrated that the fast component of autoregulation is present in both arterial and venous beds. These findings in unanesthetized humans confirm the results of Symon et al¹³ using electromagnetic flowmetry on Labbé's vein in baboons. As shown in Table 1, these authors found even shorter response times than we did. The reason for this could be that they used large stepwise increases in arterial blood pressure, while we used moderate stepwise decreases. Our subjects therefore came closer to the lower limit of autoregulation, where the responses are less effective.

The results should also be discussed in a wider context and compared with response times measured after functional activation by visual⁴ or electrical nerve¹⁴ stimulation, as shown in Table 1. The response times of autoregulatory and functionally induced blood flow changes are very similar, which is compatible with the hypothesis that the fast component of the autoregulatory response is mediated by products of metabolism.¹⁵ From a control systems perspective, it is theoretically inconsistent that a metabolic feedback system regulating CBF after changes in demand (functional stimuli) should react to changes in supply (arterial blood pressure) with

different response delays. Thus, we contend that the tight coupling between metabolism and CBF can also explain the fast autoregulatory response.

The concept of a metabolic feedback loop control system can explain the qualitative as well as the quantitative differences in response between normocapnia and hypocapnia. When the gain in the feedback loop increases with increasing vasomotor tone, the system also changes its dynamic behavior and an oscillatory transient occurs in the response. This was found after an impulse stimulus when blood pressure did not change during the response period. Previously, we found such an oscillation in the dynamic response to step stimuli during hypocapnia.¹ The period for a full oscillation estimated from the previous¹ and present recordings was between 8 and 10 seconds. This period agrees precisely with that of transient oscillations observed in dynamic studies on the coronary autoregulatory mechanism.¹⁶

Why, then, was the dilation of cerebral arterioles in anesthetized cats² so much slower than the autoregulatory responses measured by Symon et al¹² and by us? Two factors could explain this discrepancy. One possibility is that arteriolar diameters as observed by the pial window technique may not represent actual changes in flow in the system. It has been shown recently that tissue perfusion is dissociated from pial arteriolar diameters under dynamically changing blood flow conditions.¹⁷ Another, and perhaps more likely, factor might be that the experimental interventions affected the response of the cerebral autoregulatory mechanism in the cat preparations. We have seen such severe slowing and even complete abolition of the response in patients with ischemic brain damage and head injuries (data to be published). Studies on coronary autoregulation support this view and suggest that differences in anesthesia, sympathetic tone, or circulating humoral agents profoundly influence autoregulatory performance.¹⁶ We therefore contend that the intact normal human without pharmacological intervention remains the only referential standard for the physiology of the cerebral circulation.

References

1. Aaslid R, Lindegaard K-F, Sorteberg W, Nornes H: Cerebral autoregulation dynamics in humans. *Stroke* 1989;20:45-52
2. Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL Jr: Responses of cerebral arteries and arterioles to acute hypotension and hypertension. *Am J Physiol* 1978;234:H371-H383
3. Kontos HA: Validity of cerebral arterial blood flow calculations from velocity measurements. *Stroke* 1989;20:1-3
4. Aaslid R: Visually evoked dynamic blood flow response of the human cerebral circulation. *Stroke* 1987;18:771-775
5. Haberl RL, Heizer ML, Marmarou A, Ellis EF: Laser-Doppler assessment of brain microcirculation: Effect of systemic alterations. *Am J Physiol* 1989;256:H1247-1254
6. Aaslid R, Markwalder T-M, Nornes H: Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg* 1982;57:769-774
7. Huber P: *Zerebrale Angiographie für Klinik und Praxis* (in German). Stuttgart, Thieme Verlag, 1979

8. Arts MGJ, Roelvros JMJJ: On the instantaneous measurement of blood flow by ultrasonic means. *Med Biol Eng* 1972; 10:23-34
9. Aaslid R, Nornes H: Musical murmurs in human cerebral arteries after subarachnoid hemorrhage. *J Neurosurg* 1984;60: 32-36
10. Lindegaard K-F, Lundar T, Wiberg J, Sjøberg D, Aaslid R, Nornes H: Variations in middle cerebral artery blood flow investigated with noninvasive transcranial blood velocity measurements. *Stroke* 1987;18:1025-1030
11. Dahl A, Russell D, Nyberg-Hansen R, Rootwelt K: Effect of nitroglycerin on cerebral circulation measured by transcranial Doppler and SPECT. *Stroke* 1989;20:1733-1736
12. Dewey RC, Pieper HP, Hunt WE: Experimental cerebral hemodynamics: Vasomotor tone, critical closing pressure, and vascular bed resistance. *J Neurosurg* 1974;41:597-606
13. Symon L, Held K, Dorsch NWC: A study of regional autoregulation in the cerebral circulation to increased perfusion in normocapnia and hypercapnia. *Stroke* 1973;4:139-147
14. Ngai AC, Ko KR, Morii S, Winn HR: Effect of sciatic nerve stimulation on pial arterioles in rats. *Am J Physiol* 1988;254: H133-H139
15. Berne RM, Winn HR, Rubio R: The local regulation of cerebral blood flow. *Prog Cardiovasc Dis* 1981;24:243-260
16. Dole WP: Autoregulation of the coronary circulation. *Prog Cardiovasc Dis* 1987;29:293-323
17. Haberl RL, Heizer ML, Ellis EF: Laser-Doppler assessment of brain microcirculation: Effect of local alterations. *Am J Physiol* 1989;256:H1255-H1260

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