

Cerebral Autoregulation Dynamics in Humans

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We studied the response of cerebral blood flow to acute step decreases in arterial blood pressure noninvasively and nonpharmacologically in 10 normal volunteers during normocapnia, hypocapnia, and hypercapnia. The step (approximately 20 mm Hg) was induced by rapidly deflating thigh blood pressure cuffs following a 2-minute inflation above systolic blood pressure. Instantaneous arterial blood pressure was measured by a new servo-cuff method, and cerebral blood flow changes were assessed by transcranial Doppler recording of middle cerebral artery blood flow velocity. In hypocapnia, full restoration of blood flow to the pretest level was seen as early as 4.1 seconds after the step decrease in blood pressure, while the response was slower in normocapnia and hypercapnia. The time course of cerebrovascular resistance was calculated from blood pressure and blood flow recordings, and rate of regulation was determined as the normalized change in cerebrovascular resistance per second during 2.5 seconds just after the step decrease in blood pressure. The reference for normalization was the calculated change in cerebrovascular resistance that would have nullified the effects of the step decrease in arterial blood pressure on cerebral blood flow. The rate of regulation was 0.38, 0.20, and 0.11/sec in hypocapnia, normocapnia, and hypercapnia, respectively. There was a highly significant inverse relation between rate of regulation and PaCO_2 ($p < 0.001$), indicating that the response rate of cerebral autoregulation in awake normal humans is profoundly dependent on vascular tone. (*Stroke* 1989;20:45–52)

Cerebral autoregulation is a homeostatic mechanism that minimizes deviations in cerebral blood flow (CBF) when cerebral perfusion pressure (CPP) changes. Cerebral autoregulation acts through vasomotor effectors that control cerebrovascular resistance (CVR). Previous studies have convincingly documented the ability of this physiologic system to maintain relatively constant CBF when CPP is within the range 50–170 mm Hg.^{1–6} Because this is a very fast-acting homeostatic mechanism,⁷ the method for measuring autoregulatory responses should ideally have good time resolution. Our knowledge about the dynamic response of cerebral autoregulation in humans is limited because most indicator methods permit sampling of regional CBF at intervals of only minutes. Animal experiments^{7–10} indicate that the main autoregulatory response is produced within seconds. Measurement of dynamic response times and response rates to characterize the effectiveness of autoregulation is of interest not only from a physi-

ologic point of view, but perhaps even more so for its clinical implications.

Autoregulation may or may not be impaired in patients with significant disease of the cerebral arteries; moreover, autoregulatory capacity may be partly or completely lost after stroke or subarachnoid hemorrhage. For the diagnosis and management of such patients, it would seem important to know and even monitor the effectiveness of cerebral autoregulation.

To study the dynamics of cerebral autoregulation, it is necessary to introduce a step disturbance (stimulus) in CPP and to record the responses of CBF and CVR continuously before and after this step disturbance. Recent developments in instrumentation now allow such measurements to be made by completely noninvasive means. We have also employed a mechanical noninvasive technique to induce a CPP step disturbance without drugs or changes in the concentration of vasoactive substances in the blood. Our study was designed to determine the response rate of cerebral autoregulation in healthy nonanesthetized humans. Furthermore, the influence of hypercapnia and hypocapnia on these response rates was studied.

Subjects and Methods

Five healthy female and five healthy male subjects aged 20–56 (mean 36) years from the hospital

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staff gave consent to participate in our study after full explanation of the research protocol. No subject had any indications of cerebrovascular disease, and their mean blood pressures were <110 mm Hg. The subjects were investigated in the supine position with the head elevated above the bed by cushions. Step decreases in arterial blood pressure (ABP) were induced by rapid deflation of cuffs around both thighs after a 2-minute inflation. In each subject, six such deflations were performed during normocapnia, three during voluntary hyperventilation, and four while the subject breathed a mixture of 5% CO_2 in air. (Hypercapnia was induced in only six subjects.) We recorded instantaneous values of end-tidal PCO_2 (using an infrared gas analyzer), thigh cuff pressure, ABP in the right brachial artery, and Doppler spectra from the right middle cerebral artery (MCA) sampled with a rate of 25 Hz. After the experiment, the time course of CVR was calculated from these data. The measurements and the calculations used are described in more detail below.

The right MCA was insonated through the temporal bone window using a probe arrangement that could be strapped onto the subject's head and locked in position to permit continuous measurements. The MCA was identified as described previously.^{11,12} The prototype transcranial computer Doppler instrument^{12,13} incorporated a 64-point fast-Fourier transform to analyze the received velocity spectra. The amplitude outputs of four such transforms were averaged over each sample period of 40 msec and stored in memory with ABP, thigh cuff pressure, and end-expiratory PCO_2 values. The data were transferred to disks after each individual experimental run.

Further processing of the Doppler spectra was performed off line. The maximum or outline blood flow velocity, calculated by the standard algorithm of the instrument, corresponds to the blood flow velocity in the center of the MCA. Because the flow is laminar, the mean cross-sectional velocity will be proportional to the maximum velocity (velocity profile does not change significantly with variations in velocity). Previously we have demonstrated a linear correlation between the MCA outline blood flow velocity and blood flow volume measured in the internal carotid artery (ICA) by an electromagnetic flowmeter during similar ABP variations.¹⁴ The finding of a regression line intercept close to the origin in the blood velocity–blood flow volume relation suggested that MCA diameter did not change significantly. Therefore, in the present experiments, CBF was assumed to be proportional to MCA blood velocity. Absolute measurements of blood flow volume were not required for the calculation of the dynamic response, which means that the actual slope of the blood velocity–blood flow volume relation did not have to be known.

As a further precaution to avoid erroneous interpretation of the velocity data in terms of changes in

CBF, we analyzed the Doppler signal power, calculated by squaring each spectral signal amplitude and adding those 32 components with Doppler shifts toward the probe (MCA direction). Signal power is proportional to the number of ultrasound scatterers.¹⁵ Because the sample volume of the Doppler instrument is larger than the artery insonated, the number of such scatterers is proportional to the cross-sectional area of the artery. Therefore, any change in vessel cross-sectional area will be reflected proportionally in the power of the received Doppler-shifted frequency components. Power was determined over the last second before the step decrease in ABP (control) and between seconds 4 and 5 after the decrease, when ABP drop was maximal.

Instantaneous values of ABP are required for the study of autoregulatory dynamics. Conventional noninvasive methods employing slow cuff deflation to record systolic and diastolic blood pressure would miss the fast dynamic components. Therefore, we used a servo-cuff method¹⁶ that is capable of recording the ABP waveform continuously over 1–2 minutes. A normal size arm cuff was connected to a very fast electropneumatic valve, which produced a cuff pressure wave that tracked the ABP wave in real time. The control signal to the servo was derived from an 8-MHz Doppler velocity measurement in the axillary artery 3 cm proximal to the cuff. The control algorithm was designed to maintain low blood flow velocity in the artery throughout the heart cycle. Then, by the flow restriction principle,¹⁶ the artery under the servo-cuff would remain partially collapsed, and the servo-cuff pressure waveform would equal the intra-arterial blood pressure waveform. The servo-cuff pressure waveform was measured by a conventional transducer and filtered by a 10-Hz low-pass filter to eliminate high-frequency artifacts due to the Doppler noise propagating through the servo loop. Such noninvasive ABP recordings have been compared with intra-arterial blood pressures for step decreases in ABP produced by leg cuff deflation (Figure 3 in Reference 16). The servo-cuff method was found to measure these step decreases very accurately.

The servo-cuff was placed on the right arm so that any nerve stimulation from cuff pulsations would be directed to the hemisphere contralateral to the site of CBF measurement. The hydrostatic zero point was assumed to be at the level of the circle of Willis, and the fluid column between this level and the servo-cuff level (approximately 12 mm Hg) was subtracted to give an ABP reading approximating CPP. This assumption was based on the hydrostatic effects of the position used. Because the right atrial blood pressure is lower than the hydrostatic column between the heart and the head, venous sinus pressure and intracranial pressure (ICP) will be close to 0 in a normal subject in the supine position with the head elevated.

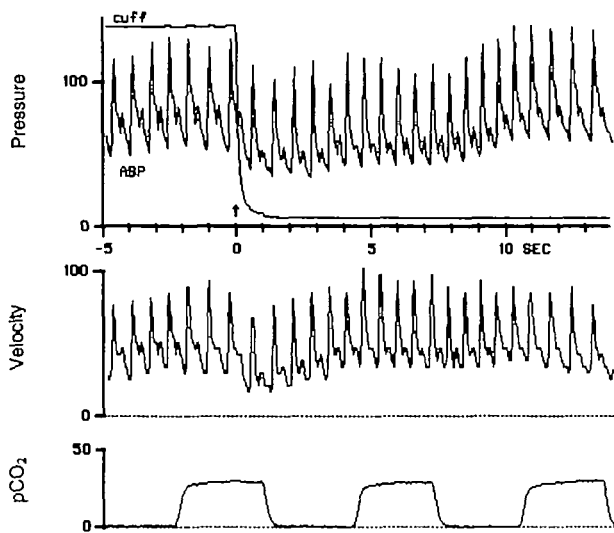


FIGURE 1. Recordings of arterial blood pressure (ABP) and thigh cuff pressure (upper), middle cerebral artery (MCA) velocity (middle), and end-expiratory carbon dioxide partial pressure $p\text{CO}_2$ (lower) from one experiment. Thigh cuffs were released at time 0 (arrow), causing transient drop in ABP and MCA blood velocity. Autoregulatory action is seen from the blood velocity returning to pretest values after only 4 seconds. Absolute units of measure, all pressures in mm Hg and velocity in cm/sec.

Conventional thigh cuffs were modified with larger tubings (5 mm i.d.) and connected with a large-bore Y-piece. The thigh cuffs were wrapped around both thighs and inflated above the systolic blood pressure of the subject. Each subject was maintained in this state for 120 seconds to produce leg hyperemia. Thigh cuff pressure was measured by a transducer connected to the computer system. The thigh cuffs were deflated abruptly by pulling the tube off the Y-piece. Thigh cuff pressure fell below diastolic blood pressure in <200 msec (Figure 1).

Recordings from each subject in each PaCO_2 state were averaged with a common time reference. Time 0 for this averaging algorithm was the abrupt fall in thigh cuff pressure. To determine the overall mean response, all individual recordings were averaged for each PaCO_2 state (Figure 2). MCA velocity and ABP tracings were both smoothed through a digital low-pass filter (-3 dB at 1 Hz and -17 dB at 2 Hz) to dampen harmonics of the pulse wave. Control values of CBF (proportional to velocity) and ABP were defined by their means during the 4 seconds before thigh cuff release. Changes in arterial blood pressure (ΔABP) and cerebral blood flow (ΔCBF) were determined relative to these control values. By this approach, the subject was his own reference. Control values were defined for each PaCO_2 state.

The time course of CVR was determined by dividing ABP by CBF for each time point. The computer then plotted curves as shown in Figure 2,

in which all variables are expressed relative to their respective controls.

In the present experiments, ABP was decreased abruptly and remained low for a limited time, approximately 6–7 seconds; then reflex cardiovascular action gradually restored ABP almost to the control value. Before the onset of the reflex effect, it was possible to equate ΔABP with a step stimulus. The magnitude of the step was calculated by subtracting control ABP from mean ABP during the interval from 1 to 3.5 seconds. This value was then divided by control ABP to obtain the relative step, ΔABP .

During the interval from 1 to 3.5 seconds, CVR changed with time (T) in an approximately linear fashion. A regression line could be fitted to these data (Figure 2, lower). The slope of this regression line ($\Delta\text{CVR}/\Delta\text{T}$) defines the rate at which CVR changes. This rate depends on ΔABP . Full restoration of CBF would theoretically occur if ΔCVR was equal to ΔABP . The rate of regulation (RoR) was therefore defined as $\text{RoR} = (\Delta\text{CVR}/\Delta\text{T}) \div \Delta\text{ABP}$. According to this definition, RoR of 0.2/sec (as in Figure 2, middle) implies a per-second adjustment of 20% of the full CVR change necessary to fully compensate for ΔABP .

Results

Recordings from one representative experiment are displayed in Figure 1. The upper panel shows superimposed tracings of ABP and thigh cuff pressure. The rapid release of the thigh cuffs elicited an abrupt decrease in ABP approximately 200 msec later. This decrease is also seen in the MCA velocity tracing (Figure 1, middle). While ABP remained low for the four or five heart beats, MCA velocity returned to control. After this phase, there was an overshoot in MCA velocity while ABP returned to control.

The averaged and filtered tracings from the entire series are presented in Figure 2 for each PaCO_2 state as listed in Table 1. ΔABP was practically identical across states as seen in Figure 2. A ΔABP of approximately 20%, within the normal physiologic range of blood pressure disturbances, was achieved. Moreover, this ΔABP was sufficient to evoke a marked response of autoregulation (CBF response) as seen in Figure 2.

The CBF response depended on the PaCO_2 state. In hypocapnia (Figure 2, left), autoregulatory action was very rapid; after only 1.9 seconds ΔCBF was reduced to half. After 4.2 seconds CBF was even greater than control. This finding indicated an oscillatory autoregulatory response that was damped at 8 seconds. The autoregulatory response was slower in normocapnia (Figure 2, middle); the time for half-maximal response was 3.4 seconds, and overshoot was seen only when ABP was increasing gradually (8–12 seconds). This type of overshoot was probably not due to an oscillatory autoregulatory response but was more likely to be due to the delay in autoregulatory action compensating for the

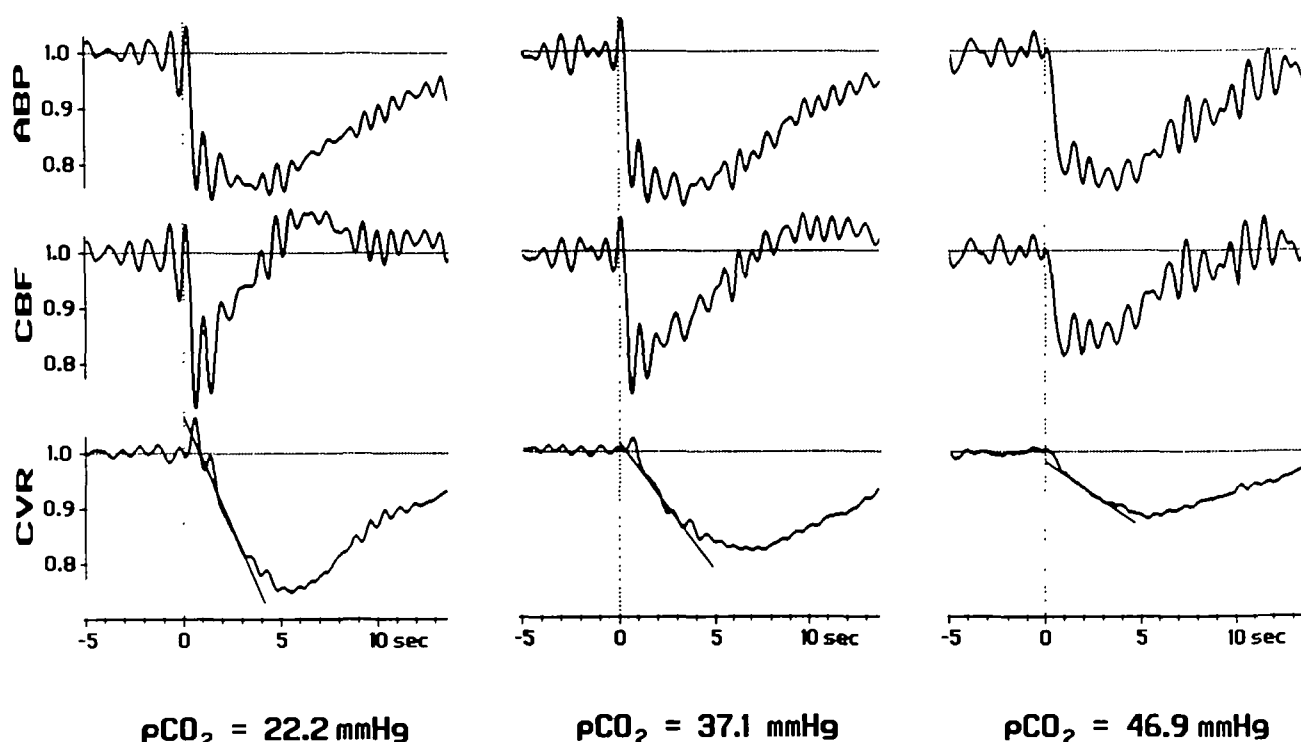


FIGURE 2. Averaged findings of all experiments during hypocapnia (left), normocapnia (middle), and hypercapnia (right). Normalized arterial blood pressure (ABP) (upper) and cerebral blood flow (CBF) (middle) from transcranial Doppler recordings; calculated cerebrovascular resistance (CVR) (lower). Thigh cuffs were released at time 0, causing step decrease in ABP 250 msec later; ABP decrease reached maximum in another 250 msec. Straight lines through CVR curves were determined by regression analysis of data in interval from 1 to 3.5 seconds after thigh cuff release and were used for calculating rate of regulation. All tracings are shown in normalized units relative to control prerelease values during time from -4 to 0 seconds.

rising ABP. Practically no overshoot and a much-delayed half-maximal response (5.2 seconds) was found in hypercapnia (Figure 2, right).

RoR was calculated for each subject for each PaCO_2 state. The results are shown in Figure 3, with lines connecting the findings in each subject. The open squares (not connected) represent the curves shown in Figure 2, in which all responses at each time were averaged before determination of RoR. These averages came very close to the regression line determined by analysis of all the individual responses. There was a highly significant correlation

between RoR and PaCO_2 ($r = -0.72$, $p < 0.001$). RoR almost doubled relative to normocapnia, from 0.20 to 0.38/sec, during hyperventilation. Breathing 5% CO_2 in air caused a 45% reduction in RoR relative to normocapnia, to 0.11/sec. As seen in Figure 3, nine subjects had comparable RoRs, while one subject had a much more rapid response, with an RoR as high as 0.8/sec during hyperventilation. In this subject only 2 seconds were necessary to compensate fully for the step decrease in ABP. This subject had borderline hypertension during the investigation (mean ABP of 109 mm Hg), which was 24

TABLE 1. Parameters Measured in Determining Cerebral Autoregulation Dynamics in Humans

Parameter	PaCO_2 state		
	Hypocapnia (n=10) (22.2 mm Hg)	Normocapnia (n=10) (37.1 mm Hg)	Hypercapnia (n=6) (46.9 mm Hg)
PCO_2 (mm Hg)	22.2±0.6	37.1±0.8	46.9±0.5
Control V_{MCA} (cm/sec)	46.1±3.1	67.4±5.9	89.3±3.4
Control ABP (mm Hg)	84.5±4.1	81.6±4.2	88.2±7.2
Δ ABP (%)	21.9±1.0	24.1±1.1	21.5±2.2
RoR (sec^{-1})	0.38±0.04	0.20±0.30	0.11±0.02
Δ Power (%)	-0.4±1.0	-2.55±1.2	

Data are mean±SEM. PCO_2 , partial pressure of carbon dioxide in expired air; V_{MCA} , blood velocity in middle cerebral artery; ABP, mean arterial blood pressure; Δ ABP, percentage decrease in arterial blood pressure; RoR, rate of regulation; Δ Power, percentage change in power of reflected Doppler signal 4–5 seconds after blood pressure step decrease.

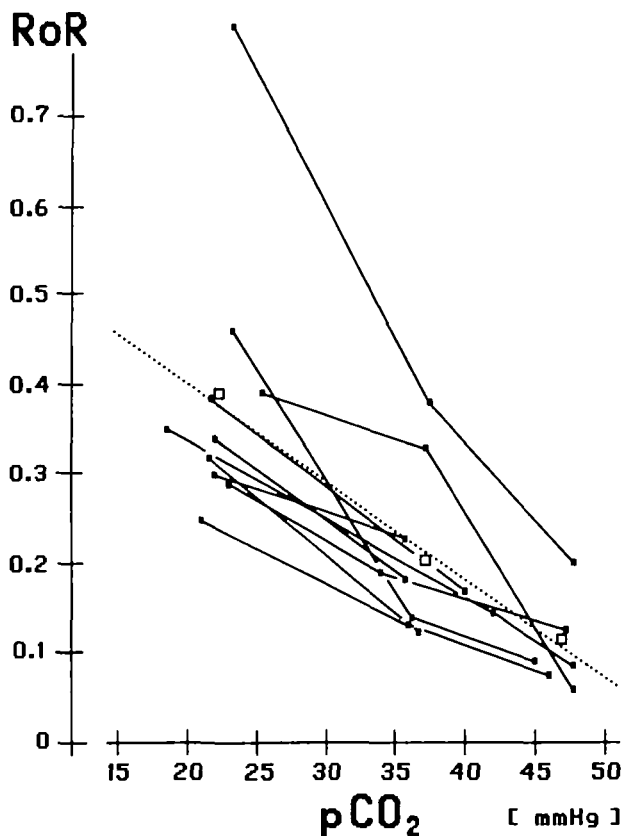


FIGURE 3. Relation between end-expiratory carbon dioxide partial pressure $p\text{CO}_2$ and rate of regulation (RoR) in 10 healthy subjects. Observations in each subject (■) are connected by lines. Dotted line was determined by regression analysis of all data ($y = 0.621 - 0.011x$; $r = -0.717$, $p < 0.001$). □, averages shown in Figure 2, when all individual responses in each $p\text{CO}_2$ state were averaged.

mm Hg higher than the mean of the group and 16 mm Hg higher than the next highest ABP measured. This observation suggested that there could be a possible correlation between ABP and RoR. Regression analysis of the relation between RoR and ABP in normocapnia was therefore performed, and an almost-significant ($r = 0.4$, $p = 0.055$) correlation was found. This result, however, should be viewed from the perspective that our study was not initially designed to correlate autoregulatory dynamics with changes in control ABP and that these findings were not the outcome of a systematic experimental approach.

Analysis of the Doppler-shifted power spectrum during normocapnia demonstrated that the signal power was reduced by $2.55 \pm 1.2\%$ (mean \pm SEM) at 4–5 seconds compared with control. This reduction was not significant ($p > 0.05$) and could possibly be explained by the slight reduction in MCA blood velocity at the time of power calculation. During hypocapnia, when velocity had returned to control at 4 seconds, a reduction in signal power was not seen ($0.4 \pm 1.0\%$). If the MCA had reacted to the step decrease in ABP with compensatory vasodilation, a

marked increase in power would have been expected. Such an effect was not seen in any subject, and the largest increase recorded was only 2.3%.

Discussion

Cerebral autoregulation is an extremely sensitive mechanism, and some attempts to investigate its action have stranded on the experimental design, which induced diminished responsiveness by injuries and lengthy preparations.¹⁷ Investigations in awake, normal humans carry special weight because they are closer to the normal physiologic state than animal experiments. Furthermore, it is necessary to ensure that the interventions used to induce changes in ABP do not have a direct effect upon cerebral vascular smooth muscle.³ A recent review on the cerebral circulation¹⁸ states: "Perhaps the most physiological responses to alterations in perfusion pressure are those induced by changes in posture in unanesthetized humans." Our study was designed to minimize interventions and to study the normal physiologic response to acute reductions in ABP and CPP. Our model might be representative of many situations in daily activity involving posture changes, etc., in which a rapid homeostatic action is necessary to preserve CBF. Because we employed new techniques, we will first discuss the validity of our measurements and the approach we used to evoke the autoregulatory response.

Blood Pressure Step

The ideal stimulus to cerebral autoregulation is an abrupt change in CPP that is maintained during the entire interval in which autoregulatory adjustments take place. In this respect, our method was not entirely ideal in the sense that ABP was lowered in a stepwise fashion for only 5–7 seconds before reflexes started to restore ABP. (The response of these reflexes might be an interesting study in itself.) In normocapnia, and even more so in hypocapnia, this time was sufficient for autoregulation to be observed with almost full restoration of CBF. Therefore, we limited our analysis to a time during which ABP decrease was very close to an ideal step. The first second of the step was also excluded from analysis because CBF during this period might possibly reflect blood flow to and fro in the compliant arterial system. Exclusion of this first second also eliminated transients because of the arterial pulse transmission delays between ABP measured in the arm and CBF measured in the cerebral arteries.

Because our study was performed in normal healthy subjects, we could assume a low ICP that was not influenced significantly by either ABP changes or the cerebral vasodilation necessary to adjust for the decrease in CPP. If the latter effect had been present to any significant degree (such as in subjects with increased ICP and a less compliant intracranial space), this would have meant a secondary decrease in CPP caused by vasodilation,

and compensatory CBF restoration would have been delayed.

Another possible source of error in our experimental design could be the CO₂-rich and hypoxic blood from the legs returning to the circulation and influencing cerebral vascular tone. The transport time from the legs to the cerebral vascular bed through the right heart, the pulmonary circulation, the left heart, the aorta, and the carotid arteries is approximately 15 seconds. The mixed blood from the legs would therefore arrive in the brain long after the data for analysis were collected. The influence of any such PaCO₂ increase even after this period was probably small because no secondary increase in CBF was seen even after 15 seconds.

Cerebral Blood Flow Measurements

The validity of our assumption that CBF (in the MCA territory) is proportional to blood velocity in the MCA depends on the two premises that the cross-sectional area of the MCA does not change significantly and that blood flow in the MCA trunk is not circumvented by collateral networks. The latter premise is almost self-evident in our experiments. Because the measurement site was distal to the circle of Willis, the only collaterals possible were the leptomeningeal anastomoses over the convexities of the cerebrum. This source of collateral blood supply has a high flow resistance. Moreover, perfusion pressure in the anterior and posterior cerebral artery territories changed equally with that in the MCA. Therefore, there could have been no perfusion pressure gradient to drive the blood through peripheral collateral channels connecting these territories.

The first premise was investigated by recording the Doppler signal spectral power before and after the step decrease in ABP. The late period of the step was chosen because blood flow velocity was comparable to that before the step so that reflected power could be compared at similar spectral distributions. The transcranial approach offers an ideal setting for using signal power to investigate changes in the cross-sectional area of arteries. The sample volume of the 2-MHz instrument is slightly larger than the artery studied.¹⁹ The MCA was insonated at an angle of approximately 20° in most subjects. Also, the probe was fixed to the subject's head so that movement artifacts were avoided during the relatively short period of recording. The basal cerebral arteries are anchored so that displacement during the maneuvers is prevented.

According to theories of ultrasonic scattering from blood, any change in artery cross-sectional area would cause a proportional increase in signal power.¹⁵ Even if this relation were not perfect because of inhomogeneities in the ultrasonic beam shape over the artery, we would at least expect that a significant change in area would cause a significant change in power. The change in signal power measured during normocapnia was an order of

magnitude lower than the changes in ABP and CBF; there was no change during hypocapnia. These results strongly suggest that the human MCA cross-sectional area does not change significantly during a 20-mm Hg step decrease in ABP. This conclusion is in agreement with findings of very stiff walls of human cerebral arteries²⁰ and with studies comparing ICA blood flow and MCA blood velocity when ABP changed.¹⁴ Experimental studies^{21–23} have shown that the main autoregulatory action in response to ABP decreases is located in small vessels (diameter of <40 μm) in the brain parenchyma. Arterioles with diameters of 322 μm increased their calibers only minimally when ABP was lowered from 90 to 70 mm Hg.²¹ If this finding is extrapolated to the human MCA, which is larger by an order of magnitude, no significant active regulation of MCA diameter would be expected. In conclusion, the assumption of proportionality between MCA blood velocity and flow in our experimental protocol is supported by the available evidence.

Mechanism of Autoregulation

The response of autoregulation to step increases in ABP was studied in baboons by Symon et al.⁷ They found a very rapid CVR adjustment, with an initial peak at 0.5 seconds and a secondary peak at 3–4 seconds after the step. Since CBF was measured on the outflow side in Labbés vein, it is possible that the initial peak was caused by the delay in the transmission of the flow wave through arterioles, capillaries, and small veins. This delay was clearly seen in one of their other recordings (Figure 9 of Reference 7) when no autoregulation was present due to cerebral ischemia. Therefore, the 3–4-second peak was probably the real autoregulatory response, and it corresponds to our findings of an overshoot at approximately 4.5 seconds (Figure 2, left). It should be noted that step increases were used in the baboon experiments,⁷ whereas we used step decreases. Our data indicate an increase in RoR and overshoot with increasing vasoconstriction, and this could explain the somewhat faster and larger overshoot observed by Symon et al.⁷

Studies on the influence of PaCO₂ on the static CPP–CBF characteristics show that the curve becomes more parallel to the CPP axis during hypocapnia, whereas hypercapnia shifts the curve toward a passive-resistive CPP–CBF relation.^{1,4,18} Interpreted in terms of a feedback system,¹⁸ an error signal (imbalance in blood flow) is necessary to activate changes in vasomotor tone. If the open-loop gain is high, only a small disturbance in CBF is sufficient to cause a large reaction in CVR. This means that hypocapnia would increase feedback gain, whereas hypercapnia would decrease and even abolish the gain.

The changes in RoR could have been mediated through such changes in feedback gain. When gain increases, RoR becomes both more rapid and more

oscillatory. This is a well-known experience in man-made control systems with time constants and delays in the feedback loop. Hypothetically, assuming a potent vasodilator regulator substance involved in a metabolic feedback loop,^{24,25} the overshoot in cerebral autoregulatory response could be explained as follows: Initially there is a step decrease in ABP and an immediate reduction of CBF. Slight hypoxia develops in the neurons and their environment, and (through some unknown pathway) regulator substance is released locally.²⁵ With some delay, the tone of vascular smooth muscle is decreased by the vasodilatory properties of the regulatory substance. Because of these time constants/delays, it could well be that more regulator substance than is required for restoration of normal CBF is released before the vascular smooth muscle has responded to the action of the regulator substance. This situation would cause an overshoot in CBF when the effect of the regulator substance on smooth muscle was fully developed. The CBF overshoot would, in turn, create a slightly hyperoxic environment, reduce production of the regulator substance, and cause smooth muscle to contract again to achieve the desired CBF and metabolic environment. Reasoning along these lines, it is perfectly conceivable that a metabolic feedback system with a high open-loop gain could explain the overshoot of the cerebral autoregulation response seen with a large step increase in ABP⁷ and/or with hypocapnia (this study).

The hypothesis⁷ that the rapid autoregulatory response is produced by a myogenic mechanism is not supported when our results are compared with those from an earlier study in which purely functional stimuli (light on the retina) were used to evoke CBF responses.²⁶ The comparable RoR from the visual evoked CBF study was 0.22/sec for the lights-off response and 0.32/sec for the lights-on response. The half-time responses were also slightly faster than in the present experiments. ABP was higher in the visual evoked CBF study because there was no step decrease in ABP, and this might account for the slightly faster autoregulatory responses. Studies on isolated posterior cerebral arteries of rats²⁷ or pial arteries of monkeys²⁸ showed that the myogenic response developed over a period of 1–10 minutes. This is more than an order of magnitude slower than the autoregulatory response we observed.

Because the time response of CBF to step decreases in ABP was practically identical to that of functional stimuli in normal humans, it seems reasonable to assume that the same feedback loop is involved in both. This is in agreement with studies using venous blood pressure increases to discriminate between the metabolic and the myogenic hypotheses of cerebral autoregulation. This stimulus resulted in arteriolar vasodilation²⁹ and constant CBF,³⁰ whereas vasoconstriction and significantly reduced CBF would have been the result expected from a myogenic mechanism.

In summary, our study lends support to the hypothesis⁶ that the rapid response of the cerebral autoregulation in normal human physiology is mediated by a metabolic mechanism. Furthermore, we have shown that the cerebral autoregulatory actions are significantly faster than those of the baroreceptor reflex regulating ABP.

Clinical Implications

Investigations on physiologic parameters in awake normal humans carry special weight because they more closely represent the normal physiologic state than can be achieved in animal experiments. Our clinically most significant finding is the strong dependence of RoR on cerebral vasomotor tone. Measuring RoR with the present technique is completely noninvasive and nonpharmacologic. Therefore, we envision that it will be possible to obtain clinically relevant information on autoregulatory gain and the cerebral vasomotor state from such noninvasive response studies. This new level of insight may be of value in the day-to-day management of patients under neurointensive care, for diagnostic purposes, and to obtain improved insight into the pathophysiology of many cerebrovascular disorders.

References

1. Harper AM: Autoregulation of cerebral blood flow: Influence of the arterial blood pressure on the blood flow through the cerebral cortex. *J Neurol Neurosurg Psychiatry* 1966; 29:398–403
2. Rapela CE, Green HD: Autoregulation of canine cerebral blood flow. *Circ Res* 1964;14(suppl 1):I-205–I-212
3. Lassen NA: Autoregulation of cerebral blood flow. *Circ Res* 1964;14(suppl 1):I-201–I-204
4. Ekström-Jodal B, Häggendal E, Linder L-E, Nilsson NJ: Cerebral blood flow autoregulation at high arterial pressures and different levels of carbon dioxide tension in dogs. *Eur Neurol* 1971;6:6–10
5. Strandgaard S, MacKenzie ET, Sengupta D, Rowan JO, Lassen NA, Harper AM: Upper limit of autoregulation of cerebral blood flow in the baboon. *Circ Res* 1974;34:435–440
6. Berne RM, Winn HR, Rubio R: The local regulation of cerebral blood flow. *Prog Cardiovasc Dis* 1981;24:243–260
7. Symon L, Held K, Dorsch NWC: A study of regional autoregulation in the cerebral circulation to increased perfusion pressure in normocapnia and hypercapnia. *Stroke* 1973; 4:139–147
8. Lübbers DW, Leiniger-Follert E: Capillary flow in the brain cortex during changes in oxygen supply and state of activation, in *Cerebral Vascular Smooth Muscle and its Control. Ciba Foundation Symposium 56*. Amsterdam/New York, Elsevier/Excerpta Medica/North-Holland, 1978, pp 21–43
9. Silver IA: Cellular microenvironment in relation to local blood flow, in *Cerebral Vascular Smooth Muscle and its Control. Ciba Foundation Symposium 56*. Amsterdam/New York, Elsevier/Excerpta Medica/North-Holland, 1978, pp 49–61
10. Nilsson B, Rehncrona S, Siesjö BK: Coupling of cerebral metabolism and blood flow in epileptic seizures, hypoxia and hypoglycaemia, in *Cerebral Vascular Smooth Muscle and its Control. Ciba Foundation Symposium 56*. Amsterdam/New York, Elsevier/Excerpta Medica/North-Holland, 1978, pp 199–214
11. 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

12. Aaslid R: Transcranial Doppler examination techniques, in Aaslid R: (ed): *Transcranial Doppler Sonography*. Vienna/New York, Springer-Verlag, 1986, pp 39–59
13. Aaslid R: The Doppler principle applied to measurement of blood flow velocity in cerebral arteries, in Aaslid R: (ed): *Transcranial Doppler Sonography*. Vienna/New York, Springer-Verlag, 1986, pp 22–38
14. Lindegaard K-F, Lundar T, Wiberg J, Sjöberg D, Aaslid R, Nornes H: Variations in middle cerebral artery blood flow investigated with noninvasive transcranial blood velocity measurements. *Stroke* 1987;18:1025–1030
15. Arts MGJ, Roelvros JMIG: On the instantaneous measurement of blood flow by ultrasonic means. *Med Biol Eng* 1972; 10:23–30
16. Aaslid R, Brubakk AO: Accuracy of an ultrasound Doppler servo method for noninvasive determination of instantaneous and mean arterial blood pressure. *Circulation* 1981; 64:753–759
17. Sagawa K, Guyton AC: Pressure–flow relationships in isolated canine cerebral circulation. *Am J Physiol* 1961; 200:711–714
18. Heistad DD, Kontos HA: Cerebral circulation, in *Handbook Physiology*, sect 2: *The Cardiovascular System*. Bethesda, Md, American Physiological Society, 1983, vol 3, pp 137–182
19. Grolimund P: Transmission of ultrasound through the temporal bone, in Aaslid R (ed): *Transcranial Doppler Sonography*. Vienna/New York, Springer-Verlag, 1986, pp 10–21
20. Hayashi K, Handa H, Nagasawa S, Okumura A, Moritake K: Stiffness and elastic behavior of human intracranial and extracranial arteries. *Biomed Eng Comput* 1980;13:175–183
21. Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL: Responses of cerebral arteries and arterioles to acute hypotension and hypertension. *Am J Physiol* 1978;234:H371–H383
22. Stromberg DD, Fox JR: Pressures in the pial arterial microcirculation of the cat during changes in systemic arterial blood pressure. *Circ Res* 1972;31:229–239
23. Baumbach GL, Heistad DD: Effects of sympathetic stimulation and changes in arterial pressure on segmental resistance of cerebral vessels in rabbits and cats. *Circ Res* 1983; 52:527–533
24. Winn HR, Rubio R, Berne RM: Brain adenosine production during 60 seconds of ischemia. *Circ Res* 1979;45:486–492
25. Winn HR, Rubio R, Berne RM: The role of adenosine in the regulation of cerebral blood flow. *J Cereb Blood Flow Metab* 1981;1:239–244
26. Aaslid R: Visually evoked dynamic blood flow response of the human cerebral circulation. *Stroke* 1987;18:771–775
27. Halpern W, Osol G: Influence of transmural pressure on myogenic responses of isolated cerebral arteries of the rat. *Ann Biomed Eng* 1985;13:287–294
28. Bevan JA, Hwa JJ: Myogenic tone and cerebral vascular autoregulation: The role of a stretch-dependent mechanism. *Ann Biomed Eng* 1985;13:281–286
29. Wei EP, Kontos HA: Responses of cerebral arterioles to increased venous pressure. *Am J Physiol* 1982;243:H442–H447
30. Wagner E, Traystman RJ: Cerebral venous outflow and arterial microsphere flow with elevated venous pressure. *Am J Physiol* 1983;244:H505–H512

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