Visually Evoked Dynamic Blood Flow Response of the Human Cerebral Circulation

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The dynamics of the metabolic mechanism that regulates cerebral blood flow was studied in 10 normal human subjects using a noninvasive transcranial ultrasonic Doppler method. Flow volume in the posterior cerebral artery, supplying the visual cortex, increased 20.2% in response to light stimulation of the retina, while flow velocity in the same artery increased 16.4%. The regulation of blood flow was very rapid; only 2.3 seconds elapsed from application of the light stimulus to 50% of full response. Full regulation (90% of full response) took 4.6 seconds. The blood flow response adapted slightly after about 10 seconds. Flow velocity in the middle cerebral artery increased significantly, by 3.3%, while flow in the superior cerebellar artery showed no significant change in response to this stimulus. These findings suggest the mechanism of very fast metabolic regulation of cerebral blood flow in humans. (*Stroke* 1987;18:771–775)

Brain blood flow is intimately coupled with brain metabolism and brain function.[1] Previous studies[2,3] using xenon indicator methods have shown a direct relation between specific mental or motor activity and changes in blood flow in regions of the cerebral cortex of human subjects.

The metabolic hypothesis of autoregulation of cerebral blood flow (CBF) maintains that a mediator substance with vasodilator properties is produced by the metabolic processes of the brain[4]; when the metabolic demand increases or the blood flow diminishes, the concentration of vasodilator increases, thereby lowering cerebrovascular resistance and increasing CBF. Previously it has been shown[5] that the autoregulatory response to changes in arterial blood pressure is fast, within seconds. This observation led to speculation that the primary mechanism of regulation was myogenic since it was assumed that a metabolic mechanism would be too slow to account for such a rapid response.[5] However, experimental work[6,7] suggests that adenosine could be the metabolic vasoactive mediator and that the response time of this feedback loop could be very fast.

Xenon indicator and positron emission tomography methods are too slow to study the dynamic blood flow response to changes in brain function. In addition, they can provide only a limited number of sampling points due to the radioactive indicators or the ionizing radiation used. Recently, a transcranial Doppler technique has been developed to measure the instantaneous velocity of the blood flowing in the basal cerebral arteries.[8] Under certain conditions, this method can be used to assess changes in flow volume as well.

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That methodology was used in the present study to determine the response of regional cerebral blood flow (rCBF) to a stimulus that induced changes in function of the visual cortex. Thereby, it became possible to estimate the time constant of the metabolic homeostatic mechanism of CBF regulation.

Subjects and Methods

Ten normal volunteer subjects aged 20–64 were studied. A simple on–off light stimulus to the retina was chosen as evokation because it produced a large response in the main artery supplying the visual cortex. Furthermore, on and off times of this stimulus could be precisely defined, and averaging techniques like those used in evoked potential methodology could be used to extract response from random variations. The retinal stimulus to both eyes was a rectangular bright white surface 20 degrees wide and 30 degrees high alternating with total darkness, each half of the cycle lasting 20 seconds. The light was switched on and off by a signal from a computer. During the light half-cycle, the subjects moved their center of vision from one side of the light surface to the other every second heart beat. In 4 subjects, the same eye movements were also performed during the dark half-cycle.

Transcranial Doppler recordings were taken from the posterior cerebral artery (PCA), which supplies the primary visual cortex as well as the lateral geniculate body and some of the visual association regions. Recordings were made on the left side in 6 subjects and on the right in the remaining 4. Control measurements on the same side and with the same stimulus were also taken from the middle cerebral artery (MCA) and the superior cerebellar artery (SCA). Because of signal-to-noise ratio problems, recordings from the latter artery could be obtained in only 3 subjects. Data from a minimum of 16 cycles were obtained from each artery in each subject. A three-dimensional scanning arm system with computer display was used to identify the arteries.[9,10] After signal identification and adjustments

to maximize the Doppler signal strength, the scanning arm was mechanically locked during the recordings.

The spectral amplitudes of the Doppler signal were calculated by a 64-point fast-Fourier transform (FFT). Eight such transformations were averaged, representing a total time of 70.2 msec. Thus, in each half-cycle of 20 seconds, 280 averaged spectral analyses were stored in memory to be transferred to the hard disk of the prototype transcranial Doppler computer system (Trans-Scan, EME, Ueberlingen, West Germany). Further signal proessing was done after the experiment.

Two different methods were available to process these raw spectral data and to estimate changes in flow velocity (V) and flow volume (F).

Velocity Measurements

The outline or envelope of the velocity spectrum was calculated by the standard algorithm implemented on the instrument. The estimates in the various arteries (V_{PCA}, V_{MCA}, and V_{SCA}) are proportional to changes in velocity and can be used as a substitute for changes in volume only when the cross-sectional area of the artery does not change significantly. It is reasonable to expect that the diameter of a basal cerebral artery will remain constant on a short-term basis if the blood pressure does not change. This assumption has been confirmed by the finding that the CO_2 reactivity of the cerebral vascular bed determined by transcranial Doppler techniques is the same as that determined by rCBF methods.[11] The proportionality between V and F in the MCA is very good even when the blood pressure changes significantly,[12] probably due to the very stiff walls of the basal intracranial arteries.[13] For determining F, these channels can probably be assumed to be rigid tubes whose main function is to conduct blood. This function is different in the largest vessels (the aorta), which act as dynamic elastic volume storage for the intermittent ventricular ejection. Moreover, the function is different from that of the microcirculatory arteries and arterioles, where most of the vascular resistance is encountered. The effects of vasoactive mechanisms at the resistance vessel level are seen as proportional changes in V and F in the conductance channels.

Volume Measurements

The transcranial Doppler method presents a special measurement situation in which a large sample volume (diameter about 3 mm[14]) is used to observe Doppler shifts in a smaller artery (about 2 mm for the PCA). Under such conditions, it also becomes possible to estimate relative changes in F. Arts and Roevros[15] deduced that the power (W_i) of each spectral component (i) is proportional to the partial cross-sectional area of the volume having this particular Doppler shift. If the sample volume is larger than the artery insonated, a change in cross-sectional area is accompanied by a proportional change in W_i of the Doppler signal. The number i ranges from -31 to 32 for a 64-point FFT and is proportional to V by the Doppler equation and the spectral analysis sampling frequency. Multiplying partial flow area by its velocity, we get the partial flow volume contribution of this component. The total flow volume is then given by adding all the partial contributions:

$$F = K \times \sum_{-31}^{32} W_i \times i \qquad (1)$$

The constant K depends on many unknown and only partially known factors, such as the attenuation of ultrasound in bone and brain tissue, the thickness of the ultrasonic window, the hematocrit, the angle of insonation, the gain of the instrument, and the efficiency of the transducer. In the present experimental situation, these physical factors either remain constant during dark/light cycles in each subject or at least they do not vary synchronously with the cycle. Any small variation in probe fixation or aiming is therefore essentially "noise" that will be reduced by averaging the data over many cycles. The absolute value of K is not required for calculation of relative changes in F.

The stored signal amplitude of each spectral component of the FFT was squared to obtain W_i and multiplied by i to obtain the contribution of this ith component to the relative flow.[15] Total relative F was estimated by summing over all spectral components of the signal. To minimize the influence of noise, the negative Doppler shifts were omitted from the calculation. Even then, a good signal-to-noise ratio of the Doppler signal was necessary to avoid errors due to the influence of noise on the weighted average. In 5 subjects in whom the signal-to-noise ratio was >14 dB, the results were evaluated by both the velocity and volume methods to validate the assumption that the cross-sectional area of the conductance artery remained constant. For most purposes, the velocity method is preferred because it gives reproducible results even in cases with relatively poor signal-to-noise ratios.

Two hundred eighty velocity or flow volume samples were calculated from the spectral data for each dark/light half-cycle. All estimates by both methods were normalized relative to their respective mean values during the experiment. The averaging algorithm calculated the arithmetic mean over all cycles for each sample time. The pulsating noise due to heartbeat was eliminated from the recordings by filtering out frequency components of >0.4 Hz (Fourier transform–inverse transform filter). This filter did not introduce any significant phase delays of the main evoked response, which had no significant frequency components above 0.2 Hz in any subject studied.

Results

Figure 1 shows the averaged unfiltered data (noisy thin line curve) from a series of 110 dark/light cycles in 5 different subjects using the flow volume method, estimating F. The flow volume signal calculated from the raw Doppler data had a pulsatile amplitude that was about 80% of the mean[10]; the averaging procedure reduced this pulsatile amplitude to about 8% of the

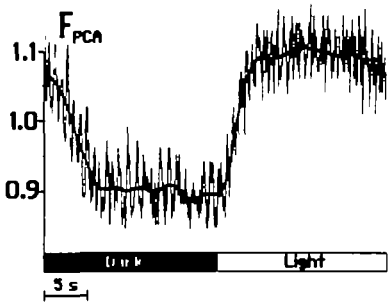

FIGURE 1. *Dark/light response of blood flow volume in the posterior cerebral artery (F_{PCA}) of 5 normal subjects. The ordinate gives relative values with the mean flow volume as reference. The "noisy" thin curve represents the unfiltered averaged data, while the solid line shows the effect of low-pass filtering with a cut-off frequency of 0.4 Hz.*

mean. (This is close to the statistical prediction when averaging the total number of 110 dark/light cycles providing the heartbeat was asynchronous with the light stimulus.) The smooth solid curve of Figure 1 is the output of the filtering algorithm, which effectively eliminated the high-frequency noise while reproducing the response due to the light stimulus. The time to 50% of full response (50% response time) was 2.3 seconds for the light stimulus. This dynamic response can be reconstructed from sine waves of 0.12 Hz and lower. Filtering with 0.4 Hz therefore reproduced frequency components of up to >3 times those of the main components of the immediate response.

The full flow response was 20.2% (Figure 1) compared with 17.1% calculated from the velocity outline recordings (the first method) in the same 5 subjects. The 50% response times were identical for both methods.

Figure 2 shows 4 dark/light cycles in the recording from 1 volunteer using the first method, estimating V. In the V_{PCA} tracing, a clear variation synchronous with the light stimulus can be seen, whereas the V_{MCA} does not show such immediately obvious periodicity with variation in light. Figure 3 shows the computer-averaged responses from this subject: V_{PCA} demonstrates a maximum of 17% increase in response to the light stimulus. The averaged V_{MCA} data show some increase during retinal stimulation (about 3%), but it is much less pronounced than in the PCA. Practically no response was observed in the SCA.

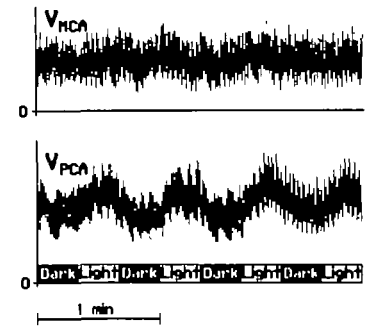

FIGURE 2. *Blood flow velocity in the middle cerebral artery (V_{MCA}) and posterior cerebral artery (V_{PCA}) in response to a stimulus sequence of darkness and light to the retina indicated on the abscissa. The absolute velocities are not calibrated because only relative changes were required for the study. These velocities were calculated from the outlines or envelopes of the Doppler spectral signal analyzed by a 64-point fast-Fourier algorithm.*

The computer-averaged findings in the entire series are shown in Figure 4. Percent difference between the full response in light and darkness was 16.4 ± 1.5% (mean ± SEM) for V_{PCA}. The response to the light stimulus started (10% level) after 1.0 second, reached half of the full response in 2.3 ± 0.3 seconds and 90% in 4.6 seconds. After reaching the maximum, V_{PCA} decreased by 4% during the last 10 seconds of the light half-cycle. This phenomenon was observed in 7 of the subjects studied. The term "adaptation" is traditionally used to describe such leveling of a response. When the light stimulus was removed, V_{PCA} fell to half of the total response in 4.0 ± 0.5 seconds, and to 10% in 5.9 seconds. Eye movement during the dark half-cycle did not produce any noticeable difference in the results, and there was no significant difference between responses in right and left arteries.

In the MCA (Figure 4 *middle*) the difference between the light and dark half-cycles was 3.3 ± 0.8% (mean ± SEM). The relatively small but statistically significant ($p<0.01$) changes induced in this artery were most prominent during the first 8 seconds after the stimulus switched and seemed to adapt after 10–15 seconds. No significant difference (1.2 ± 1.5%) between the light and dark half-cycles was found in the V_{SCA} of 3 subjects (Figure 4 *upper*).

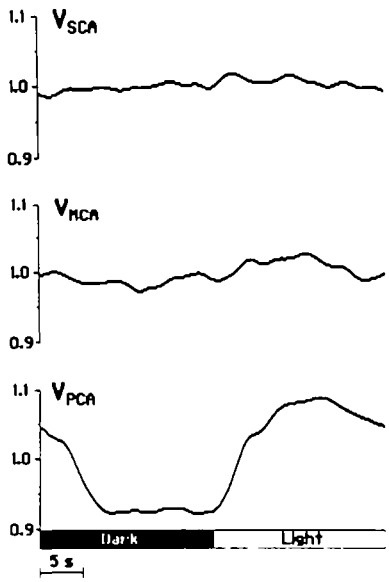

FIGURE 3. *Averaged and filtered blood flow velocities in the superior cerebellar artery (V_{SCA}), middle cerebral artery (V_{MCA}), and posterior cerebral artery (V_{PCA}) in response to a dark/light cycle with a total period of 40 seconds. Same subject as in Figure 2, with a total of 20 cycles averaged for each trace.*

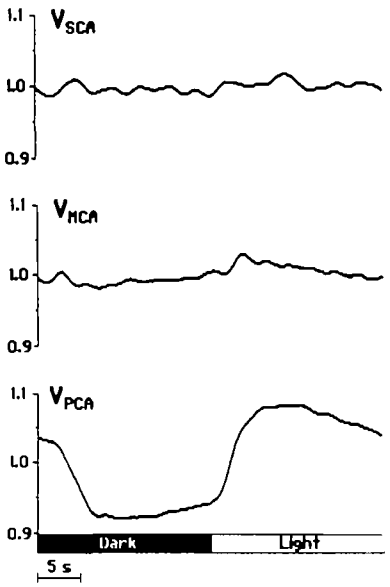

FIGURE 4. *Mean dark/light response in 10 normal subjects with at least 16 cycles for each individual. Averaged and filtered blood flow velocities are shown for posterior cerebral arteries (V_{PCA}), middle cerebral arteries (V_{MCA}), and superior cerebellar arteries (V_{SCA}).*

Discussion

Theoretically, the changes in V during light stimulation could have been caused by a change in the cross-sectional area where the recording was made. This possibility was eliminated by using a calculation method that correctly estimates relative F independent of vessel diameter changes. The difference between the V changes and the calculated F changes was relatively small (3%) and could have been caused by the high-pass (150 Hz) filter used in preprocessing the Doppler signal. It is therefore permissible to substitute changes in V for changes in F in the protocol used.

If recordings had been made only from the PCA, 2 unknown factors would have created uncertainty in the evaluation of the data: 1) the observed response could have been due to a cyclic variation in arterial blood pressure induced by the light stimulus, or 2) it could have been caused by some general mechanism affecting all arteries in the cortex or even the entire brain. A change in blood pressure or a general vasoactive mechanism would have induced similar changes in all brain arteries. Therefore, the findings of practically no response in the SCA and only a small response in the MCA strongly suggest that such effects must have been insignificant in view of the large response of F_{PCA}.

Due to limitations in methodology, previous studies in human subjects have shown only the static response of the metabolic regulatory mechanism. Lassen et al[2] found an approximately 20% increase in blood flow to the visual association region of the cortex when the subject opened the eyes and looked at an object. Meyer et al[3] found a 16.8% higher blood flow to the visual system in persons with open eyes compared with a control group with closed eyes. The present study reports results comparable to these. Additionally, it shows that the blood flow changes occur very rapidly after changes in visual cortical function. With a 50% response time of only 2.3 seconds and a practically full response (90%) in 4.6 seconds, the regulation of blood flow after brain activation is even faster than suggested in a recent review of the cerebral autoregulation[16]: "The rapidity of the autoregulatory response which is initiated within seconds after a change in resistance vessel transmural pressure, and largely completed in 15–30 seconds, suggests a myogenic response." Since the present study used pure functional changes in the brain as stimuli to evoke the regulatory mechanism, the observed change in blood flow could have been produced only by a metabolic or neurogenic control mechanism. Because of the rapidity and magnitude of the response and its localization to specific arteries supplying the activated regions of the brain, a metabolic mechanism provides the most likely explanation. It then follows that the metabolic homeostatic mechanism is more than fast enough to fully explain the rapidity of the cerebral autoregulation response.

There are 2 distinctly different types of provocations for such a homeostatic mechanism: 1) a sudden change in blood flow due to a sudden change in cerebral perfusion pressure, and 2) a sudden change in the metabolic activity of brain tissue. However, for a regulatory mechanism that operates by the metabolic principle, these 2 provocations are functionally equivalent. In both cases, the immediate supply of blood would be different from that desirable; therefore, the concentration of a vasodilator mediator would change very rapidly, and the cerebrovascular resistance would be controlled at a new level to balance blood flow with metabolic activity. The present study does not show what substance mediates the observed response; this study was primarily aimed at inducing a stimulus that in all probability would act by a metabolic pathway and then observing the response of blood flow to this stimulus.

Meyer et al[3] found no significant light stimulus-dependent differences in blood flow in the frontal and temporal cortex supplied by the MCA/ACA. The relatively small but statistically significant change in the MCA blood flow found in the present study could have been detected only with a relatively large number of observations. In our series, the MCA blood flow was based on 172 dark/light cycles. Also, the results show that the MCA response was most prominent 5–10 seconds after application of a light stimulus, after which it adapted. Therefore, the MCA response would have been missed with measurement methods requiring relatively long periods of sampling.

The most likely explanation for the apparant adaptation of the response in the PCA is an adaptation of the cones of the retina to light intensity. The change in sensitivity of cones is known to occur within minutes.[17] It is also possible that adaptive mechanisms exist in the visual cortex.

The slightly slower response to the dark compared with the light stimulus could have been caused by the slower depolarization of cones and rods in the eye

compared with repolarization. However, this observation could also be explained by some similar mechanism in the cortical neuronal network or in the visual pathway itself. For the purpose of determining the response time, the light stimulus is probably closer to an ideal step-response stimulus than the dark stimulus.

The described ultrasonic technique is completely noninvasive. It is therefore well suited for studies in both normal subjects and patients. With further improvement in instrumentation, individual smaller arterial branches may come within reach, improving our ability to study more specific brain territories. However, its main advantage compared with existing methods is the improved resolution in time; evoked blood flow responses can be observed on a short and continuous time scale. Furthermore, recordings over relatively long periods can be made. By using averaging algorithms and statistical techniques, it then becomes possible to detect and quantify small responses in the presence of noise and random fluctuations. This method, therefore, is an interesting future complement to EEG methods to study the relation between brain function and brain blood flow.

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