Visually Evoked Blood Flow Response Assessed by Simultaneous Two-Channel Transcranial Doppler Using Flow Velocity Averaging

Matthias Sturzenegger, MD; David W. Newell, MD; Rune Aaslid, PhD

Background and Purpose We assessed the influence of different visual stimuli and the reproducibility and habituation of evoked flow responses using simultaneous two-channel transcranial Doppler monitoring and flow velocity averaging.

Methods We measured stimulus-related percentage changes in posterior cerebral, basilar, and middle cerebral artery blood flow velocities in 14 normal volunteers using stimulus-triggered velocity averaging. With a two-channel transcranial Doppler system, simultaneous measurements in two arteries (both posterior cerebral arteries and the basilar and middle cerebral artery) were taken using multiple-array light-emitting diodes applying flash stimuli. Both posterior cerebral arteries were monitored to assess reproducibility and habituation of the evoked response with repetitive measurements under unchanged conditions and to analyze the influence of different features of the visual stimulus.

Results There was a distinctive increase in velocities resulting from visual stimuli in both posterior cerebral and the basilar arteries but not in the middle cerebral artery. The responses in both posterior cerebral arteries were larger than in the basilar artery ($P=.0001$). Brightness ($P<.0001$), as well as complexity ($P<.0001$), of the visual stimulus had a significant influence on the response amplitude. There was a trend toward a greater right-sided activation. Amplitudes of the evoked response were very stable during repetitive testing (coefficient of variation of the difference was 0.6). There was a trend toward habituation with monotonous (flash) but not with complex visual stimuli. A "zero" stimulus produced no responses.

Conclusions The use of flow velocity averaging and two-channel simultaneous recording increases the sensitivity of transcranial Doppler monitoring to detect and correlate selective flow changes in the posterior cerebral arteries resulting from cerebral activation produced by visual stimulation. (*Stroke.* 1996;27:2256-2261.)

Key Words • cerebral blood flow • diagnostic imaging • Doppler

Various imaging techniques have been able to demonstrate increases in regional CBF or metabolism during various mental activities, motor tasks, and somatosensory stimulation.[1-3] These techniques are expensive and time consuming and require extensive equipment and that the patient be moved to a special area. Repeated measurement thus can be difficult. These techniques have a relatively high spatial resolution but a low temporal resolution because the measuring periods last for minutes. Therefore, rapid and short-lived hemodynamic changes might be missed.

TCD can be used to evaluate CBF-metabolic coupling by detecting relative blood flow changes in the PCAs in response to visual stimulation.[4] One unique aspect of the TCD method is the ability to provide temporal information about the dynamics of the response.[5] Although absolute BFV cannot be used as an indicator of CBF,[6] changes of BFV have been found in several studies and by various methods to reliably correlate with changes in CBF as long as vessel diameter and perfusion territory remain constant.[4,7-11] Studies reported so far in which TCD was used to analyze task- or stimulus-evoked flow provided variable and partly conflicting results.[12,13] These results are due not only to biological individual variations but also to the vast amount of stimulus- or task-independent influencing factors that are difficult to hold constant during long-lasting and repeated measurements.[14] The high temporal resolution of TCD allows the use of averaging techniques with short-duration recording cycles, and two-channel recording allows direct comparison of different (eg, homologous pairs) vessels.

We report the results of VEFR measurements made using simultaneous recording with a two-channel Doppler system and flow velocity averaging in normal volunteers.

Subjects and Methods

Subjects

Fourteen normal volunteers (7 men, 7 women; mean±SD age, 32±7.1 years [range, 21 to 41 years]) were tested. All were clearly right-handed according to the results of the Edinburgh Inventory[15] testing. They were medication-free, had no active medical disease, and had no history of vascular or neurological disorders. No subject had been drinking caffeine-containing beverages or smoking before the study on the test day. The test results of 2 additional subjects were not included in this study because of (asymptomatic) frequent premature heartbeats that interfered with averaging and introduced enormous variation in the responses.

Testing Conditions

The tests were performed in a quiet room with illumination held constant and the subject in a comfortable chair in a half-supine position with the head supported. Blood pressure and heart rate were continuously monitored using an N-CAT continuous noninvasive blood pressure monitor (model N-500, Nellcor Inc). This system uses a combination of continuous tonometric and

Selected Abbreviations and Acronyms
BA = basilar artery
BFV = blood flow velocity
CBF = cerebral blood flow
MCA = middle cerebral artery
PCA = posterior cerebral artery
PET = positron emission tomography
TCD = transcranial Doppler
VEFR = visual evoked flow response

intermittent oscillometric measurements. Respiration rate and end-tidal P_{CO_2} were obtained at the beginning and at the end of each stimulation trial using a capnograph (DATEX 233 CO_2 monitor, Puritan-Bennett Corp). We aimed to keep these parameters at a constant value. During the visual stimulation trials, we painstakingly avoided any additional stimuli via any sensory modality.

TCD System

We used a commercially available TCD unit (Multi-DOP X/TCD 7, Firma DWL, Elektronische Systeme GmbH). This system has two Doppler channels, allowing simultaneous recording of the signals from two vessels. The outline or envelope of the velocity spectrum and mean maximal BFV were calculated by
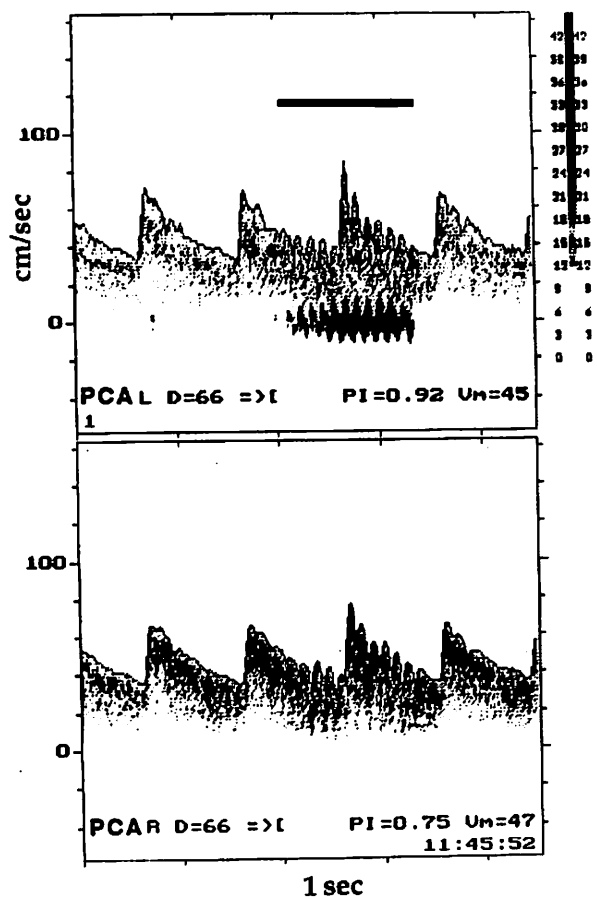

FIG 1.   PCA velocity signals recorded simultaneously in the left (L) and the right (R) P1 segments with a transtemporal approach. Repetitive short oscillations of the vertebral artery applied in the suboccipital region on the atlas loop segment (horizontal bar) evoked a positive response, with transmission of the oscillatory pressure waves into the PCAs. D indicates insonation depth given in millimeters; PI, pulsatility index; and Vm, mean maximal velocity.
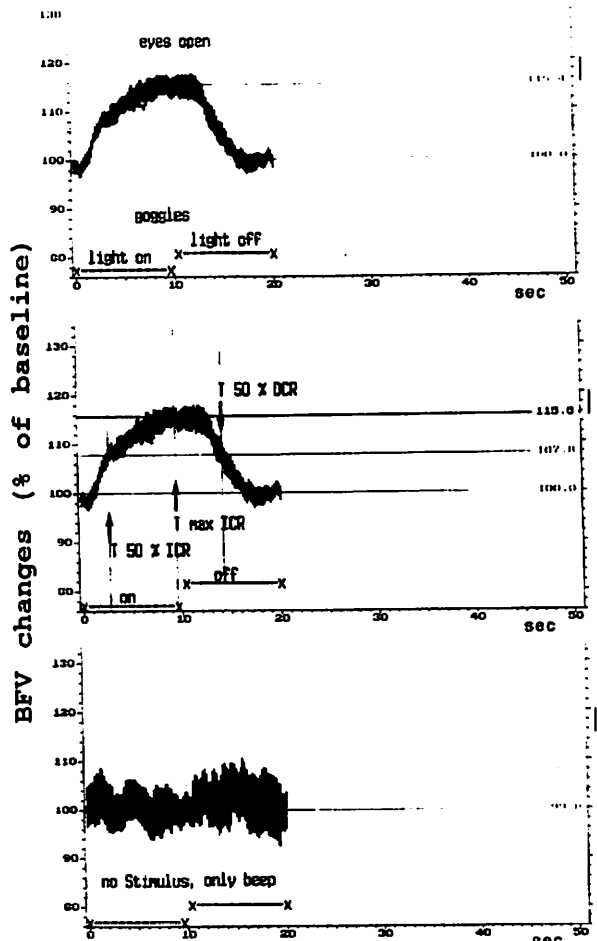

FIG 2.   Changes of BFV, expressed as percentage change of baseline value (VEFR). The upper curve shows the averaged response of 14 cycles with goggle flash stimulation and opened eyes. There is a 15.4% increase (mean value, the shaded areas indicate ±1 SD). The curve in the middle illustrates the analyzed time parameters: T 50% ICR indicates time to 50% of the maximal response; T max ICR, time to maximal response (increase); and T 50% DCR, time to 50% decrease from maximal response. The lower curve illustrates the response to a "zero" stimulus.

the standard algorithm implemented on the instrument using a fast Fourier transform. The special software of this system allows trigger-related BFV averaging during an adjustable time period of "stimulus on" compared with an adjustable time period of "stimulus off" (baseline or rest).

Vessel Identification

The PCAs were identified from the transtemporal approach according to standard criteria such as anatomic landmarks (insonation angle, depth of sample volume, and spatial relationship of the Doppler spectra to those of the MCA, anterior cerebral artery, and the bifurcation of the internal carotid artery), direction of flow, and compression and oscillation maneuvers of the common carotid artery and the vertebral arteries.[16] The transmission of oscillatory pressure waves to both recorded PCA signals was required during rapid suboccipital oscillations of either vertebral artery (Fig 1). Also required to prove PCA insonation was a clear-cut flow velocity increase on both sides during measurement of visual evoked flow during "eyes open" as opposed to "eyes closed" (with the special system software allowing flow velocity averaging) (Fig 2).[4] We were able to insonate the P1 segment of the PCA (flow direction toward the probe) on both sides in all subjects. The MCA was insonated at a depth of 50 mm, with the
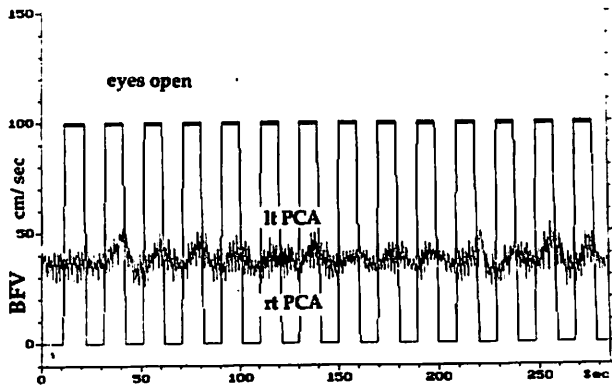
FIG 3.   Continuous recordings of the BFVs simultaneously in the left (lt) and right (rt) PCA during 290 seconds. Mean maximal BFVs were calculated from the outlines or envelopes of the Doppler spectral signal analyzed by a fast Fourier transform algorithm. The responses to a stimulus sequence of eyes open (10 seconds, indicated by the thick horizontal bars above the velocity tracings) followed by eyes closed (10 seconds) are shown; 14 cycles (eyes open, eyes closed) are shown. Opening the eyes induced a regular clear-cut increase of the velocities with a subsequent return to baseline during eyes closed.

signal optimized by adjustment of the probe position ("acoustical window") and insonation angle. The BA was insonated at a depth from 85 to 95 mm in the midsagittal plane.

General Stimulation Procedure

Visual stimulation was provided using goggles with light diodes (NIC-106 LED visual stimulation system with NIC-105 LED goggles). These plastic lightproof goggles had a 5×3 rectilinear dot grid of 15 monochromatic light-emitting diodes for each eye (flash duration, 5 ms; rate, 18/s; flash color, red with a center wavelength of 630 nm). The visual evoked potential stimulator (Nicolet CA-1000 evoked potential system) was driven by a signal from the Doppler unit. Stimulus parameters (flash duration, intensity, and rate) were held constant throughout all measurements. In the case of visual stimulation using room light with the subject's eyes open versus eyes closed as "stimulus off" and when applying a zero stimulus, the command to the subject consisted of a beep tone. Because it has been shown that maximal VEFR is reached within 5 seconds,[4] both "stimulus on" time and "stimulus off" time were set at 10 seconds for all stimulation series.

Signal Averaging

Every stimulation trial comprised 14 stimulus sequences or cycles (10 seconds of stimulus on plus 10 seconds of stimulus off, each cycle) that were averaged (Fig 3). The averaging algorithm calculated the arithmetic mean over all cycles for each sample time. For recording from the PCA and the MCA, the TCD transducers were fixed to the temporal surface with a headband. For BA measurements, the transducer was held manually in the suboccipital position (transforamenal insonation).[17]

Stimulus Paradigms

In all trials, the stimulus paradigms that were used symmetrically covered the subject's whole visual field of both eyes. For recording from both PCAs, the following visual stimulation trials were performed for all subjects: (1) zero stimulus: subjects were instructed to keep their eyes always closed, "doing and thinking nothing," despite the beep tone of the system delivered at a 10-second interval (usually indicating stimulus on and stimulus off, the command to open and close the eyes); (2) room light with eyes open (stimulus on) versus eyes closed (stimulus off) with the subject's gaze fixed to the middle of a white screen (rectangular bright white surface 53 degrees wide and 44 degrees high),

with the patient opening and closing the eyes according to a rhythm determined by the unit providing a beep tone; (3) room light with eyes open (stimulus on) versus eyes closed (stimulus off) with the subject looking around in the room; (4) goggles with light diodes with light on versus light off with the subject keeping the eyes closed; and (5) goggles with light diodes with light on versus light off with the subject keeping the eyes open. For recording from the MCA and BA, we used (6) goggles with light diodes with light on versus light off with the subject keeping the eyes open. To test the reproducibility of the VEFR, trial 5 was repeated in the same 14 subjects after 6 to 8 weeks under exactly the same conditions.

To evaluate for a possible habituation, the VEFR from the first seven stimuli was compared with that from the second seven stimuli, taking the trials with room light stimulation (trials 2 and 3) and the follow-up trials with goggle stimulation (trial 5).

Data for Analysis

For each trial (14 averaged stimulus sequences or cycles), in every patient the mean±SD VEFR was determined separately for the responses in the left and right PCA and the MCA and BA.

The VEFR was expressed as percentage change from baseline (stimulus off) value, using each subject as her or his own control. The criterion for a specific VEFR in a recorded vessel was defined as a percentage increase minus 1 SD >100 (Fig 2).

Statistical Methods

Amplitude and time parameters of the responses among the different stimulation trials and between the different measured vessels (left versus right PCA, MCA versus BA, and BA versus PCA) were compared using the two-tailed paired t test. To evaluate reproducibility and habituation, variance and the coefficient of variation of the difference between two subsequent measurements were calculated also.

Results

The 14 subjects were physiologically stable throughout the testing periods. We did not observe significant changes of blood pressure, heart rate, respiration rate, or end-tidal P_{CO_2} during the different stimulation trials.

In Table 1, the amplitude parameters of the responses to the different visual stimuli recorded in the different vessels are summarized.

For the PCAs, to validate the specificity of the measured responses, we averaged 14 cycles of a "zero stimulus." No subject showed any significant percentage increase in either PCA.

When room light was used as a stimulus, there was a significant VEFR for the group as a whole and for each individual subject on both sides, whether the subject's

TABLE 1.   Summary of Evoked Responses for Different Visual Stimuli (n=14)

Stimulus	Left	Right
PCA response		
Zero stimulus	1.7±3.7	1.4±3.4
Room light (white screen)	10.1±2.9	11.2±3.7
Room light (look around)	15.5±6.8	16±3.0
Goggles with eyes closed	7.8±3.9	8.2±4.4
Goggles with eyes open		
Examination 1	15.5±2.3	17±4.4
Examination 2	14.4±4.6	14.7±2.2
MCA response		
Goggles with eyes open	1.8±2.3	...
BA response		
Goggles with eyes open	9±3.2	...

Values are mean±SD. Response indicates VEFR in percentage increase of flow velocities compared with baseline values.

TABLE 2. Side-to-Side Differences of the Evoked Flow Responses in the PCA (n=14)

	Response	
Stimulus	Difference*	P†
Goggles with eyes closed	−0.65±1.77	.23
Room light (white screen)	−1.18±1.85	.05‡
Room light (look around)	−0.47±7.17	.83
Goggles with eyes open	−0.22±4.52	.87
All stimulus responses taken together	−0.63±4.3	.32

*Left minus right difference.
†Paired *t* test.
‡Trend difference in favor of a larger response on the right side (negative left-right difference). Response indicates VEFR in percentage increase of flow velocities compared with baseline value.

gaze was fixed to a white screen or the subject was allowed to look around. There was no significant side difference for the whole group when allowed to look around, but there was a clear trend toward a larger response on the right side with the gaze fixed to the white screen (Table 2). Analysis revealed 9 individuals with a left-right VEFR ratio that differed from 100% by more than 1 SD and was in favor of the right side in 8 subjects.

When the goggles were used with the eyes of the subjects closed, there was again a significant VEFR on both sides for the whole group. However, when looking at individual responses, a significant increase was recorded only in 8 subjects (7 on the left and 8 on the right side). For the whole group, there was no significant side difference. In the individuals, however, there was a difference in favor of the right side in 3.

With use of the goggles and the eyes opened, there was again a significant bilateral response in all individual subjects and the whole group. No side difference was shown in the group as a whole; however, 8 subjects had a significant side difference in the left-right ratio. The increase was in favor of the right side in 6 and of the left in 2.

There was no difference between the VEFRs to goggle stimulation/eyes open and VEFRs to room light/looking around (*P*=.72), and there was only a weak difference between goggle stimulation/eyes closed and room light/ white screen (*P*=.03). Highly significant differences of the VEFRs were found between (1) goggle stimulation/eyes closed and room light/looking around (*P*<.0001); (2) goggle stimulation/eyes closed and goggle stimulation/eyes open (*P*<.0001); (3) room light/white screen and room light/looking around (*P*=.0002); and (4) room light/white screen and goggle stimulation/eyes open (*P*<.0001).

These differences were the same whether VEFRs were analyzed separately for the left and right PCAs (detailed data not presented) or whether the left and right responses were taken together for every stimulus (Fig 4).

Evaluation of reproducibility showed no significant differences between the amplitude values of the VEFR in the two consecutive trials: absolute difference, 4.3±2.4; variance, 5.8; and coefficient of variation, 0.6.

Testing for habituation revealed no significant differences between the first and second seven averaged stimulus responses with the use of room light (both white screen and looking around): absolute difference, 3.3±3.0; variance, 8.9; and coefficient of variation, 0.9 (*P*=.36, paired two-tailed *t* test for comparison). However, with goggle stimulation there was a tendency to lower amplitude responses in the second period: absolute difference, 4.5±3.1; variance, 9.5; and coefficient of variation, 0.7 (*P*=.13, paired two-tailed *t* test for comparison) (Fig 5).

Recording from the BA and using the same stimulus showed a significant VEFR in the group as a whole, as well as in each individual subject. The response was, however, significantly smaller compared with that in the left (*P*=.0008) and right (*P*=.0001) PCA using the same stimulus (Table 1).

In the MCA, there was no significant VEFR for the group as a whole even with the use of the stimulus, yielding the largest response when recording from the PCAs (goggles/eyes open) (Table 1).

Discussion

Visual stimuli produced clear specific VEFRs in both PCAs but not in the MCA in normal volunteers. The amplitude of the response was significantly influenced by brightness and complexity of the stimulus paradigm used. Reliability of these responses is underscored by the excellent reproducibility and the absence of habituation. These results demonstrate the potential usefulness of the presented technique to evaluate noninvasive vasoneuronal coupling in diseased brain (eg, hypertensive, toxic, or metabolic encephalopathies) or brain influenced by drugs.

Several studies using TCD have already demonstrated increases in BFV during cognitive and visual tasks in the arteries supplying the involved brain.[12,14,18,19] The results are, however, not uniform and show important variations. This may be due in part to the applied methodology involving the use of prolonged stimulation periods susceptible to involvement of stimulus-independent factors and sequential (not simultaneous) measurements of different vessels.
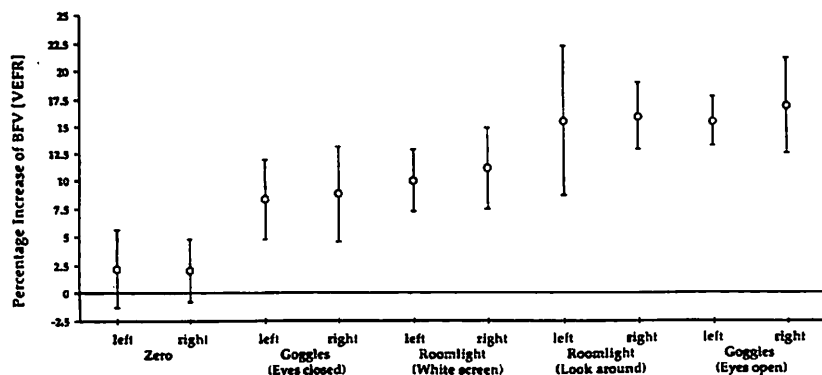

Fig 4. Amplitudes of the VEFR (percentage increase of baseline values) to the different stimuli of the 14 subjects (mean±SD) are plotted separately for the left and right PCAs.
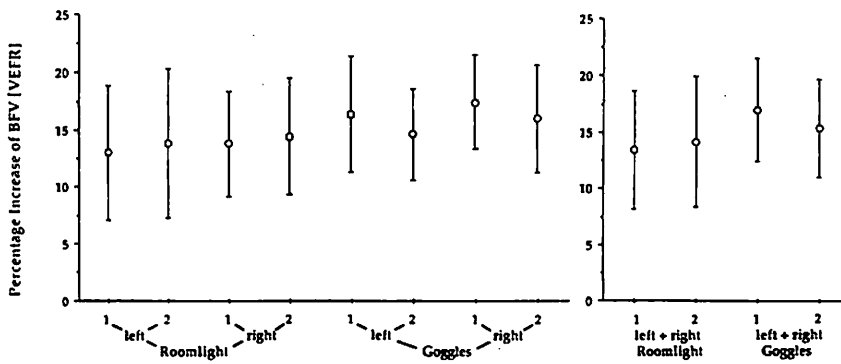
FIG 5.   VEFRs to the first (1) and second (2) seven stimuli of a trial are plotted sequentially for the two stimuli of room light (eyes open, eyes closed) and goggle flash with eyes open. On the left side, the responses in the left and right PCA are separately plotted. The right side of the figure shows the responses in the left and right PCAs taken together. There is a clear trend to habituation for the stimulus with goggle flash only.

Great importance has to be placed on the selection of the activation paradigm (stimulus or task) to produce selective cognitive activation without involving other cortical areas that confound the results.[14] PET studies showing selective topical activation are very helpful in the design of the best study paradigm.[20] With the equipment used in the present study, we have the option of well-defined (duration and intensity) stimuli and of passive stimuli, in which factors such as motivation, anticipation, and attention are less operative. The responses of all cells of the visual system, including striate and extrastriate cortex, follow a highly complex pattern that depends on several attributes of the stimuli, such as spatial and temporal distribution, color, and intensity.[21] PET and TCD studies show impressively corresponding findings with respect to stimulus rate dependency of CBF in the occipital cortex[22] and of PCA BFV.[18] PET studies show increasing glucose metabolic rates in the primary visual cortex and extension of activation into associative visual cortex as the complexity of visual scenes increases.[23] Our results match these findings, with significantly higher responses when subjects look around rather than fix a target. The higher response to flash stimulation with opened eyes opposed to closed eyes demonstrates the dependence of the response on stimulus intensity. It is also important to consider the perfusion territory of the vessel to be monitored. In the MCA, there is a possibility of coactivation of various cortical areas (in both hemispheres) because of its large perfusion territory. Furthermore, there is the possibility that a small increase ensuing from very selective activation may be submerged in the measured overall velocity of the MCA stem. The PCA supplies a smaller territory, with the greater part involved in processing visual tasks. Monitoring the PCA during visual tasks thus will provide more distinct responses.

Conventional TCD may have several shortcomings when used to analyze stimulus-evoked flow velocity responses. (1) Increase in flow in small arterial branches to small cortical areas may not result in a detectable increase in overall velocity in the larger feeding basal artery. (2) A number of factors other than selective activation proved to have an impact on measurements of CBF and BFV: respiratory (coughing, hyperventilation, Valsalva maneuver) and cardiovascular (blood pressure, heart rate, arrhythmia) factors and changes in muscle activation and posture can induce marked short-term changes of BFV, interfering with a stimulus-evoked response; and motivational factors,[24] anxiety and excitement,[25,26] anticipation,[27] pain and strong involvement,[28] handedness, sex,[29] and age[30,31] all

have been reported to influence CBF. Finally, there are normal (physiological) regional asymmetries.[32]

In the present study, we evaluated two improvements in TCD technology with the potential to compensate at least for some of the cited drawbacks: simultaneous two-channel recording and flow response averaging.

Simultaneous recording from homologous vessel pairs may provide more distinctive results in the investigation of hemispheric dominance than the conventional sequential measurements.[14] We did not observe a significant left-right difference for the more elementary visual stimuli applied. However, there was a clear trend toward higher response amplitudes on the right side. This finding is in accordance with PET studies suggesting a general right hemispheric dominance for visual processing.[33,34]

When recording with the second channel from a vessel that is presumably not involved by the applied stimulus, we can recognize a response that is not stimulus related (eg, cyclic changes of respiration rate) or is stimulus related but nonspecific (eg, stimulus-dependent variation of blood pressure) that would affect both vessels. We found no significant response in the MCA with patterned flash stimulation (goggles). A previous study using similar equipment found a small but significant response.[4] The visual stimulus used was, however, much more complex than the flash pattern applied in this study. Several studies[23,24] have shown that with increasing complexity of the visual stimulus, there is an increasing activation of extrastriate associative visual cortical areas that might well be supplied in part by MCA branches.

The use of flow velocity averaging algorithms allows detection and quantification of small responses in the presence of noise and various coexisting random fluctuations. The variations induced by these stimulus-unrelated factors will be reduced by averaging the data over many cycles.

Metabolic and CBF studies show values of activation in the visual cortex similar to the Doppler measurements of velocity changes.[28,35] These closely matching results of PCA velocity changes and reported CBF changes with respect to the influence of various stimulus parameters suggest that the TCD findings are reliable. To evaluate the possibility of a system-inherent stimulus (eg, the beep command to open and close the eyes) triggering the response, we performed trials using a "zero" stimulus that showed no VEFR.

Good reproducibility of the response would also corroborate reliability of the method. Given the strong dependency of the evoked response on various attributes of a visual stimulus, its parameters should be held most con-

stant during repeated testing. Therefore, we chose goggle stimulation, a passive stimulus for which all parameters can be controlled. Furthermore, it does not require much cooperation from the subject, is very easy to perform, and provides a large and clearly discernible response. These features make this setup useful for future studies of VEFR in patients. There was no significant difference between subsequent responses with regard to the amplitudes.

We found a slight short-term habituation for flash stimulation only but not for room light stimulation. The former stimulus is much more monotonous, and habituation is probably due to adaptation of the retinal cones to light intensity. Eye movements create ongoing new visual inputs during the latter stimulus, preventing habituation. With use of prolonged stimulation periods and tasks requiring strong subject cooperation, habituation is an important phenomenon.[12]

In conclusion, the use of multichannel Doppler recordings and a flow velocity averaging algorithm allows quantitative assessment of VEFRs, direct comparison between vessels, and a more precise correlation of these responses to specific tasks.

References

1. Roland PE, Friberg L. Localization of cortical areas activated by thinking. *J Neurophysiol.* 1985;53:1219-1243.
2. Colebatch JG, Cunningham VJ, Deiber M-P, Friston KJ, Frackowiak RSJ, Passingham RE. Regional cerebral blood flow during unilateral arm and hand movements in human volunteers. *J Physiol (Lond).* 1990;423:9P. Abstract.
3. Ginsberg MD, Chang JY, Kelley RE, Yoshii F, Barker WW, Ingenito G, Boothe TE. Increases in both cerebral glucose utilization and blood flow during execution of a somatosensory task. *Ann Neurol.* 1988;23:152-160.
4. Aaslid R. Visually evoked dynamic blood flow response of the human cerebral circulation. *Stroke.* 1987;18:771-775.
5. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebrovascular autoregulation dynamics in humans. *Stroke.* 1989;20:45-52.
6. Bishop CCR. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. *Stroke.* 1986;17: 913-915.
7. Markwalder TM, Grolimund P, Seiler R, Roth F, Aaslid R. Dependency of blood flow velocity in middle cerebral artery on end-tidal carbon dioxide partial pressure: a transcranial Doppler study. *J Cereb Blood Flow Metab.* 1984;4:368-372.
8. Lindegaard K-F, Lundar T, Wiberg J, Sjoberg D, Aaslid R, Nornes H. Variations in middle cerebral artery blood flow investigated with noninvasive transcranial blood velocity measurements. *Stroke.* 1987; 18:1025-1030.
9. Dahl A, Lindegaard K-F, Russell D, Nyberg-Hansen R, Rootwelt K, Sorteberg W, Nornes H. A comparison of transcranial Doppler and cerebral blood flow studies to assess cerebral vasoreactivity. *Stroke.* 1992;23:15-19.
10. Newell DW, Aaslid R, Lam A, Mayberg TS, Winn HR. Comparison of flow and velocity during dynamic autoregulation testing in humans. *Stroke.* 1994;25:793-797.
11. Sorteberg W. Cerebral artery blood velocity and cerebral blood flow. In: Newell DW, Aaslid R, eds. *Transcranial Doppler.* New York, NY: Raven Press Publishers; 1992.
12. Droste DW, Harders AG, Rastogi E. A transcranial Doppler study of blood flow velocity in the middle cerebral arteries performed at rest and during mental activities. *Stroke.* 1989;20:1005-1011.
13. Kelley RE, Chang JY, Scheinmann NJ, Levin BE, Duncan RC, Lee S-C. Transcranial Doppler assessment of cerebral flow velocity during cognitive tasks. *Stroke.* 1992;23:9-14.
14. Markus HS, Boland M. 'Cognitive activity' monitored by non-invasive measurement of cerebral blood flow velocity and its application to the investigation of cerebral dominance. *Cortex.* 1992;28:575-581.
15. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia.* 1971;9:97-113.
16. Buedingen HJ, Staudacher T. Evaluation of vertebrobasilar disease. In: Newell DW, Aaslid R, eds. *Transcranial Doppler.* New York, NY: Raven Press Publishers; 1992.
17. von Reutern G-M, Buedingen HJ. *Ultraschalldiagnostik der hirnversorgenden Arterien.* Stuttgart/New York: Georg Thieme Verlag; 1989:124-139.
18. Gomez SM, Gomez CR, Hall IS. Transcranial Doppler ultrasonographic assessment of intermittent light stimulation at different frequencies. *Stroke.* 1990;21:1746-1748.
19. Conrad B, Klingelhöfer J. Dynamics of regional cerebral blood flow for various visual stimuli. *Exp Brain Res.* 1989;77:437-441.
20. Wise R, Chollet F, Hadar U, Friston K, Hoffner E, Frackowiak R. Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain.* 1991;114:1803-1817.
21. Bartlett JR, Doty RW. Responses of units in striate cortex of squirrel monkeys to visual and electrical stimuli. *J Neurophysiol.* 1974; 37:621-641.
22. Fox PT, Raichle ME. Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission computed tomography. *J Neurophysiol.* 1984;51:1109-1120.
23. Phelps ME, Kuhl DE, Mazziotta JC. Metabolic mapping of the brain's response to visual stimulation: studies in humans. *Science.* 1981;211:1445-1448.
24. Risberg J, Halsey JH, Wills EL, Wilson EM. Hemispheric specialization in normal man studied by bilateral measurements of the regional cerebral blood flow: a study with the 133-Xe inhalation technique. *Brain.* 1975;98:511-524.
25. Gur RC, Gur RE, Skolnick BE. Effects of task difficulty on regional cerebral blood flow: relationships with anxiety and performance. *Psychophysiology.* 1988;25:392-399.
26. Rodriguez G, Cogorno P, Gris A, Marenco S, Mesti C, Nobili F, Rosodini G. Regional cerebral blood flow and anxiety: a correlation study in neurologically normal patients. *J Cereb Blood Flow Metab.* 1989;9:410-416.
27. Reimann EM, Fusselman MJ, Fox PT, Raichle ME. Neuroanatomical correlates of anticipatory anxiety. *Science.* 1989;243:1071-1073.
28. Lassen NA, Ingvar DH, Skinhoj E. Brain function and blood flow. *Sci Am.* 1978;239:62-71.
29. Gur RC, Gur RE, Obrist WD, Hungerbuhler JP, Younkin D, Rosen AD, Skolnick BE, Reivich M. Sex and handedness differences in cerebral blood flow during rest and cognitive activity. *Science.* 1982;217:659-661.
30. Warren LR, Butler RW, Katholi CR, Halsey JH Jr. Age differences in cerebral blood flow during rest and during mental activation measurements with and without monetary incentive. *J Gerontol.* 1985; 40:53-59.
31. Melamed E, Lavy S, Bentin S, Cooper G, Rinot Y. Reduction in regional cerebral blood flow during normal aging in man. *Stroke.* 1980;11:31-35.
32. Perlmutter JS, Powers WJ, Herscovitch P, Fox PT, Raichle ME. Regional asymmetries of cerebral blood flow, blood volume, and oxygen utilization and extraction in normal subjects. *J Cereb Blood Flow Metab.* 1987;7:64-67.
33. Kushner MJ, Rosenquist A, Alavi A, Rosen M, Dann R, Fazekas F, Bosley T, Greenberg J, Reivich M. Cerebral metabolism and patterned visual stimulation: a positron emission tomographic study of the human visual cortex. *Neurology.* 1988;38:89-95.
34. Corbetta M, Miezin FM, Petersen SE. Attentional modulation of neural processing of shape, color, and velocity in humans. *Science.* 1990;248:1556-1559.
35. Phelps ME, Mazziotta JC, Kuhl DE, Nuwer M, Packwood J, Metter J, Engel J. Tomographic mapping of human cerebral metabolism: visual stimulation and deprivation. *Neurology.* 1981;31:517-529.