Age and Stimulus Dependency of Visually Evoked Cerebral Blood Flow Responses

Gyula Panczel, MD; Michael Daffertshofer, MD; Stephan Ries, MD; Dagmar Spiegel; Michael Hennerici, MD

Background and Purpose—During visual stimulation, the increased metabolic demand is coupled with an increase of cerebral blood flow velocity (pCBFV) in the posterior cerebral artery (PCA). Investigation of the visually evoked flow responses (VEFR, expressed as percentage of increase from baseline pCBFV values) was suggested for different conditions of vasoneuronal disorders in the absence of any systematic investigation in healthy subjects.

Methods—We investigated VEFRs from both PCAs to various increasingly complex paradigms (diffuse light, alternating checkerboard patterns, and a color video movie stimulation; 5, 10, 20, and 30-second intervals) in 60 healthy volunteers (mean age, 41.5±14.9 years; range, 24 to 80 years; 28 male, 32 female) at different recording sites (P1 versus P2 segments of PCAs).

Results—With increasing complexity of stimulation, the VEFRs increased significantly (24.3±10.3%, 28.5±13.5%, and 43.4±10.7%, respectively). Twenty-second stimulation intervals yielded maximal responses (41.5±13.2%) compared with 5-, 10-, and 30-second intervals (22.6±14.1%, \( P=0.001 \); 34.4±11.7%, \( P=0.0042 \); and 35.5±9.9%, \( P=0.0032 \), respectively). Significantly higher responses were gained from P2 segments than from P1 segments (42.7±7.2% versus 28.2±7.1%). Although VEFRs tended to decrease in amplitude with age (mean, 41.7±10.5% [20 to 40 years], 35.9±2.2% [40 to 60 years], and 33.9±8.6% [60 to 80 years]); without significant sex-related differences, only the percentage decrement of the pulsatility indices during stimulation were significant (mean, 24±10.7% [20 to 40 years], 20±7.3% [40 to 60 years], and 13±11.2% [60 to 80 years]).

Conclusions—For optimal stimulus conditions for maximum VEFRs, a colored video stimulation of 20-second intervals should be used to combine responses not only from the primary visual projection fields (V1 and V2) but also from temporal lobe areas (V3 through V5) often supplied by the PCA. (Stroke. 1999;30:619-623.)

Key Words: cerebral blood flow ▪ ultrasonography ▪ vasomotor reactivity

Brain function, neuronal metabolism, and local blood perfusion are closely related. During cognitive or motor activities and during sensory stimulation, the regional cerebral blood flow (rCBF) of the involved area increases as metabolic demands become more pronounced. This physiological relationship, called “vasoneuronal coupling,” has been well documented by means of single-photon emission CT (SPECT), positron emission tomography (PET), and MRI.1-3 Since these techniques share a reasonable spatial but poor temporal resolution they fail to assess the dynamic properties of vasoneuronal coupling, which is likely to be impaired in early, mild, or only intermittent stages of cerebrovascular or associated disorders (eg, migraine, epileptic fits).

Transcranial Doppler sonography (TCD) offers the opportunity to evaluate rapid changes of vasomotor reactivity according to metabolic tissue demands during various functional conditions.4 Application was first proposed for an improved identification of arteries tested for obstructive lesions (eg, to separate the posterior cerebral artery (PCA) versus the superior cerebellar artery).4 Because increase in cerebral blood flow velocity in the PCA (pCBFV) to photic stimulation was found to be obligatory, this response was used to measure vasoneuronal regulation qualitatively in humans.5-9 In normal conditions, pCBFV measurements turned out to significantly correlate with rCBF findings, as changes in the diameter of the insolated large cerebral arteries are negligible.10-11

Despite these drawbacks, visually evoked flow response (VEFR) techniques were used for various purposes, including pathological conditions,12-15 although normal values based on a systematic investigation from healthy subjects are still lacking and stimulation and recording conditions so far have not been evaluated.

Subjects and Methods
Sixty healthy volunteers (32 women and 28 men; mean age, 41.5±14.9 years; range, 24 to 80 years) participated in the study.
They had no history of cerebrovascular or cardiovascular diseases or any disorder affecting the visual system, according to clinical and neurological examination, including vascular ultrasound studies. Systemic blood pressure, heart rate, and respiration rate were controlled and remained constant during visual stimulation testing. Subjects were seated in a comfortable chair in a quiet, dark room and were asked to breathe regularly. Measurements started after a 10-minute adaptation period during normocapnic conditions. A 4-channel TCD scanner (DWL Multidop X), with 2-MHz pulsed-wave Doppler transducers affixed to a headband, was used for an online continuous registration of the evoked changes of pCBFV. Doppler spectra of both PCAs were acquired simultaneously through the transtemporal approach. Vessels were identified according to criteria described elsewhere.16

Stimulus presentation was indicated by an acoustic signal (on phase), and stimulus-free intervals (off phase) were initiated by another acoustic signal, with the acoustic beeps serving as a trigger. Each trial comprised at least 10 full on/off cycles. A time-averaged mean flow velocity for each cycle was calculated online by fast-Fourier transformation, and data were stored for further processing. To clearly extract VEFR from random variation, a trigger-related average over all stimulation cycles for each trial (“grand average”) was computed offline. A total of 2400 examination cycles entered the database for statistical analysis. The amplitude of response (VEFR) (Figure 1) was expressed as percentage pCBFV increase from baseline during stimulation:

\[
\text{VEFR} = 100 \times \frac{V_{\text{max}} - V_0}{V_0} \%
\]

Additional parameters calculated included the onset - and offset latency (time elapsed from stimulus onset until 10% increase, and from stimulus offset until 10% decrease of pCBFV, respectively), the off-phenomenon (percent increase of pCBFV after stimulus cessation), and the adaptation (the percent decline of the response at the end of the "stimulus-on" phase relative to the maximal value:

\[
\text{Adaptation} = 100 \times \frac{V_{\text{max}} - V_{\text{off}}}{V_{\text{max}}} \%
\]

The steepness of the increasing slope (\(S_{\text{inc}} = dV_{\text{inc}}/dT_{\text{inc}} \) (cm/s2)) and decreasing slope (\(S_{\text{dec}} = dV_{\text{dec}}/dT_{\text{dec}} \) (cm/s2)), representing mean pCBFV change per second, were also obtained.

Statistical analysis using the Student t test was performed for the left and right side separately as well as for the individual average of both sides. Values are given as mean±SD.

Stimulation Paradigms Applied for the Evaluation of VEFR
The influence of (1) the type of stimulus, (2) the section of PCA insonated, (3) the duration of stimulus, and (4) the aging on VEFR was examined.

Figure 1. "Grand-average" curve and response characteristics of the pCBFV during video stimulation. In the first 20 seconds (x axis), the patients have their eyes open and the video is on. In the next 20 seconds, the patients have their eyes closed and the video is off. The averaged, combined right and left pCBFV is registered on the y axis. is indicates increasing slope; os, overshooting; pl, plateau; off, off-phenomenon; ds, decreasing slope; us, undershooting; V, velocity; T, time; d, difference; inc, increment; and dec, decrement.

Influence of the Type of Stimulus
In 10 subjects (age range, 20 to 40 years) the following 3 types of visual stimuli of different degrees of complexity were applied: (a) white light, (b) checkerboard (black-and-white checkerboard pattern), and (c) color video movie (a color video cartoon). The P2 segments of PCAs were monitored during 20-second “stimulus-on” and 20-second “stimulus-off” phases.

Influence of the Section of PCA Insonated
P2 and P1 segments of the PCAs were insonated in 10 subjects (age range, 20 to 40 years) while the video movie with 20-second stimulation phases was applied.

Influence of the Duration of Stimuli
Each of 4 time intervals of stimulation phases (5-5, 10-10, 20-20, and 30-30 seconds) were applied for 10 cycles of video movie stimulation with the P2 segments insonated in 10 subjects (age range, 20 to 40 years).

Influence of Aging
Ten subjects from 3 age groups (20 to 40, 40 to 60, and 60 to 80 years) were investigated under the paradigm of video movie stimulation with 20-second stimulation phases and with the P2 segments insonated.

Results
Out of 64 healthy volunteers, Doppler signals of satisfactory quality were obtained bilaterally in 60 individuals. A grand-average curve of VEFR is demonstrated in Figure 1.

The characteristics of the responses during video stimulation evaluated in healthy subjects of different age groups are summarized in the Table. VEFR tended to decrease with age, ranging from 41.7±10.5% at 20 to 40 years to 33.9±8.6% at 60 to 80 years. This difference, however, did not reach statistical significance (P=0.093; Figure 2A).

The steepness of increasing and decreasing slopes also decreased with age: 3.04±0.7, 2.69±0.72, and 2.03±0.83 cm/s2 for the increasing slopes and 3.26±1.07, 2.37±0.55, and 1.81±0.94 cm/s2 for the decreasing slopes in the 3 age groups (20 to 40, 40 to 60, and 60 to 80 years), respectively. The difference between the age groups of 20 to 40 and 60 to 80 years was significant (P=0.034 and P=0.0079 for the increasing and decreasing slopes, respectively) (Figure 2B).

The P1 decreased significantly during stimulation (P1d) relative to prestimulation values (P1o) in all age groups (decrease: 0.23±0.11, P=0.00006; 0.2±0.12, P=0.0004; and 0.16±0.11, P=0.0008, respectively). The difference

\[
\frac{V_{\text{max}} - V_0}{V_0} \%
\]
reached a high level of significance when all subjects were considered, regardless of age (PI\text{off}, 0.856±0.28; PI\text{off}, 1.05±0.28; \(P=8.3\times10^{-15}\)).

The PI also showed a clear increase with advancing age in the absence of stimulation (0.94±0.13, 0.97±0.2, and 1.25±0.32 in the 3 age groups; 20 to 40 versus 60 to 80 years, \(P=0.016\)) and in the presence of stimulation (0.71±0.11, 0.77±0.18, and 1.09±0.33, respectively; 20 to 40 versus 60 to 80 years, \(P=0.014\) (Figure 3A). During stimulation, the magnitude of percentage decrease of PI relative to baseline showed an age-dependent significant decrease (24.3±10.8%, 19.7±7.3%, and 12.9±11.2% for the 3 age-groups, respectively; 60 to 80 versus 20 to 40 years, \(P=0.045\)) (Figure 3B).

The response characteristics for different types of stimuli are shown in Figure 4. For diffuse white light, checkerboard, and video movie, the VEFR values were 24.3±10.3%, 28.5±13.5%, and 43.4±10.7%, respectively. The increase of the response with the increasing complexity of stimuli was highly significant (video versus white light, \(P=0.00005\); video versus checkerboard stimuli, \(P=0.0019\)) (Figure 4A). The steepness of increasing slopes did not differ significantly for video and checkerboard stimulation (3.01±1.16 versus 3.11±1.17, \(P=0.43\)); however, a significant decrease was observed for white light relative to the video movie paradigm (2.32±1.07; \(P=0.0016\)). The steepness of decreasing slopes showed a nonsignificant decrease for checkerboard stimulation (2.12±1.01, \(P=0.069\)) and a significant decrease for white-light stimulation (1.85±1.36, \(P=0.047\)) relative to the video movie paradigm (3.05±1.49). The adaptation to stimulation showed a significant decrement with the increasing complexity of paradigm. By the end of the “stimulus-on” phase, the response decreased by 10.6±5.2%, 9±3.2%, and 4.2±2.4% relative to the maximal values for white light, checkerboard, and video paradigms, respectively (video versus checkerboard, \(P=0.00001\); checkerboard versus white light, \(P=0.027\); video versus white light, \(P=0.00008\)).

(Figure 4B) The adaptation was significantly larger in men than in women (women, 5±2.3%, 10±3%, and 13.1±4.4%; men, 2.8±2%, 7.2±2.9%, and 6.2±3.2%; \(P=0.046\), \(P=0.086\), and \(P=0.001\) for video, checkerboard, and white light, respectively). We did not find significant side differences of the adaptation.

The response characteristics for stimulation phases of 5, 10, 20, and 30 seconds were investigated. Maximal response was gained by 20-second stimulation phases (41.5±13.2%), and significant decrement in response was observed in comparison with the 5-second (22.6±14.1%, \(P=0.0001\)), the 10-second (34.4±11.7%, \(P=0.0042\)), and the 30-second (35.5±9.9%, \(P=0.032\)) stimulation phases. The adaptations for the 20-second and 30-second phases did not differ significantly (6.0±3.8% and 5.0±4.1%, respectively; \(P=0.22\)). Overshooting was observed in 70% and off-phenomenon in 50% of individuals for both 20- and 30-second stimulation phases; undershooting was present in 15%, 70%, and 80% of cases for 10-, 20-, and 30-second stimulation phases, respectively.

When comparing response characteristics in the P1 and the P2 segments of the PCA, we found a significantly higher response in the P2 segment (42.7±7.2% versus 28.2±7.1% for P2 and P1 segments; \(P=0.001\)). Neither the steepness of the increasing (2.4±0.56 and 2.82±0.88; \(P=0.22\)) nor the decreasing (2.61±0.83 and 2.98±0.86; \(P=0.15\)) slopes differed significantly between the P1 and P2 segments.

With respect to the side differences, the amplitude of the responses and the steepness of the increasing and decreasing slopes on the right side were significantly larger in amplitude

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>VEFR, %</th>
<th>S\text{inc} \text{cm/s}^2</th>
<th>S\text{dec} \text{cm/s}^2</th>
<th>T\text{on}, s</th>
<th>T\text{off}, s</th>
<th>PI\text{off}</th>
<th>PI\text{on}</th>
<th>dPI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–40</td>
<td>41.7±10.5</td>
<td>3.04±0.70</td>
<td>3.26±1.07</td>
<td>2.6±0.9</td>
<td>3.0±1.3</td>
<td>0.94±0.13</td>
<td>0.77±0.11</td>
<td>24.3±10.8</td>
</tr>
<tr>
<td>40–60</td>
<td>35±9.2</td>
<td>2.69±0.72</td>
<td>2.37±0.55</td>
<td>3.2±0.5</td>
<td>4.1±1.2</td>
<td>0.97±0.26</td>
<td>0.77±0.18</td>
<td>19.7±7.3</td>
</tr>
<tr>
<td>60–80</td>
<td>33.9±8.6</td>
<td>2.03±0.83</td>
<td>1.81±0.94</td>
<td>3.2±0.8</td>
<td>3.8±1.4</td>
<td>1.25±0.32</td>
<td>1.09±0.33</td>
<td>12.9±11.2</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*Video movie stimulation with 20-s on/off phases; P2 segment sonicated.

Figure 2. A. Changes of response characteristics for video stimulation paradigm (20-second stimulation intervals) with age. The response amplitude (VEFR) showed a nonsignificant decrease with age. The x axis represents age groups; the y axis, combined right and left averaged VEFR (%). B. The steepness of increasing slopes (Sinc) and decreasing slopes (Sdec) decreased significantly with age. The x axis represents age groups; the y axis, combined right and left averaged steepness (cm/s²).
compared with those on the left side, when considering all the subjects regardless of age (VEFR: 39.8 ± 10.5% [right] versus 33.9 ± 11.4% [left] (Figure 5), P = 0.0033; Sinc: 2.80 ± 0.93 versus 2.38 ± 0.92, P = 0.005; Sdec: 2.65 ± 1.15 versus 2.31 ± 1.04, P = 0.013). Within the age groups we still found side differences with a nonsignificant tendency toward right-sided dominance. For PIoff and PIon values there were no significant side differences.

Discussion

Visual stimuli evoked remarkable increases of the PCA pCBFV in all individuals included in the study. The increase of pCBFV for visual stimuli corresponds to a decrease of cerebrovascular resistance due to arteriolar dilatation, as evidenced by the highly significant decrease in PI during stimulation.

Several studies have shown an age-related decrease of CBF, pCBFV, and cerebrovascular reactivity. Our results reflect a gradual decrement in pCBFV response with advancing age, in accordance with the concept that the gain of the vasoneuronal coupling decreases with aging. The observed age-dependent decline of VEFR is accompanied by a decrease in the steepness of slopes, reflecting a slower development of the response, by an increased baseline PI, and by a decline in the magnitude of %PI decrease during stimulation. The higher PI refers to an increased vascular resistance, whereas diminished %PI decrease in elderly people corresponds to a decreased capacity of the arteriolar system to dilate during stimulation. Underlying these phenomena, progressing, age-dependent structural changes of the arteriolar system are reported, including hypertrophy and hyalinization of the tunica media; degeneration of the internal elastic lamina; intimal proliferation and atheroma formation, resulting in lumen reduction; loss of elasticity; and increased rigidity of the vessel wall. However, because the applied technique did not measure vasoreactivity but instead the global function of the complex vasoneuronal coupling, the decreasing PI changes with age may also result from age-related changes of the neuronal-metabolic or metabolic-vascular coupling. Particularly, certain biochemical changes in the elderly, such as decrease of CO2 production consequent to the neuronal loss of an aging brain, decreased neurotransmitter synthesis, and alterations in neurotransmitter receptor sites, may contribute to the decrease of the vascular response.

The response of the neuronal pool involved in visual processing follows a complex pattern and is influenced by the characteristics of the visual stimulation paradigms applied. Evoked response became more pronounced with an increasing complexity of the stimuli applied. Based on results of PET studies, the underlying neurophysiological mechanism for this phenomenon is the extended involvement of associative visual cortical areas including selective cell assemblies for more complex paradigms, such as colored, dynamic stimuli compared with unstructured, static white light or black-and-white monochrome checkerboard stimuli.

No data were found to compare VEFR of the P2 and P1 segments of the PCA. In the present study significantly higher levels of VEFR were elicited under similar stimulation paradigms when monitoring the P2 segment. This observation is readily understandable when considering, that the pCBFV in the P2 segment is directly related to the metabolic demand.
of the posterior circulation territory, whereas the pCBFV in the P1 segment is influenced by the extent and direction of the posterior communicating artery blood flow and by the circu-
formation of small branches suppling neuronal structures not involved in visual processing. Therefore, the visually acti-
vated neuronal pool represents a higher proportion of the entire brain tissue supplied by the P2 segment compared with the area supplied by the P1 segment. Consequently, higher level of pCBFV increase reflects the same metabolic demand of the visual cortex in the P2 segment compared with the P1 segment after photic stimulation.

We compared the responses for stimulation phases of 5, 10, 20, and 30 seconds. The 5-second and 10-second stimulation phases did not allow the response to reach the maximal level because stimuli ceased too early, and the 5-second phases were too short to allow the pCBFV to return to baseline prior to the following stimulus. Furthermore, when applying 5-and 10-second stimulus phases, the specific temporal patterns characteristic of responses for stimulation phases of 20 seconds or longer (overshooting, undershooting, off-phenomenon) were missing. Maximal responses were gained by 20-second stimulation phases; 30-second phases yielded larger responses than the 5- and 10-second intervals but smaller responses than the 20-second phases. The most pronounced effect of 20-second stimulation intervals can be attributed to the fact that unlike 5- and 10-second intervals, they are sufficient to allow the responses to reach the maximal values, yet they represent more dynamic stimuli than the 30-second phases.8 The increasing slope of the response curve ended in an overshooting phase in 70% of the cases when 20- or 30-second stimulus phases were applied. A transient increase of response during the offset latency after stimulus cessation (off-phenomenon) appeared in 50% of subjects for both 20- and 30-second stimulation phases, corresponding to neuronal off-effects in the visual cortex. Undershooting was observed in 80% and 70% for 20-second and 30-second stimulation phases, respectively, representing an underbalanced downregulation of CBF.

For optimal stimulus conditions for maximum VEFRS, a color video movie should be presented at 20-second intervals to recruit primary and secondary visual projection areas, all supplied by the PCA.

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References


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