A Transcranial Doppler Study of Blood Flow Velocity in the Middle Cerebral Arteries Performed at Rest and During Mental Activities

D.W. Droste, A.G. Harders, MD, and E. Rastogi

While changes in blood velocity in the middle cerebral artery relative to rest were assessed by transcranial Doppler sonography, 70 volunteers with no sign of cerebrovascular disease performed two (left and right middle cerebral artery) series of six cognitive tasks. The tasks are assumed to be processed predominantly by either the left (verbal and mathematical tests performed aloud) or the right hemisphere (dot/distance estimation, spatial perception, and face recognition performed silently). All tasks were shown to increase middle cerebral artery blood flow velocity on both sides, by 1.6–10.6%. After an initial maximum at approximately 8 seconds, velocity decreased then increased again. A steady state was reached after approximately 24–42 seconds. The initial minimum during the following rest phase was reached some seconds later, followed by a slow increase to the reference rest steady state. A difference according to side could be determined only during the three right-hemispheric tasks (right>left, 2.5–2.9%). Left-handedness/ambidexterity, familial sinistrality, and profession seemed to have no influence on the results. The middle cerebral artery blood flow velocity increase on both sides was higher in women than in men during the dot/distance estimation and was also higher bilaterally in older than in younger subjects during the dot/distance and the spatial perception tasks. Habituation in performing the tasks was an important factor associated with a decrease of blood flow velocity, especially in the right middle cerebral artery. The habituation more pronounced on the right side possibly reflects the role of the right hemisphere in attention and arousal. The absolute blood velocities at rest decreased bilaterally with age. (Stroke 1989;20:1005–1011)

The first to report a connection between brain activity and cerebral blood flow was Fulton in 1928. He described an increased blood flow murmur over a patient’s occipital angioma while the patient was reading. Brain activity, metabolism, and blood flow have been found to be closely related. The xenon-133 injection technique, the xenon-133 inhalation technique, single-photon emission computed tomography, and positron emission tomography (PET) have been used to compare regional cerebral blood flow/metabolism during various mental activities such as speech and reading and during rest. These four techniques have the advantage of high spatial resolution; their common drawback is their low temporal resolution. The three xenon techniques measure during periods of from a few minutes down to approximately 40 seconds. With PET, the signals of approximately 40 minutes are summed. It is assumed that cerebral blood flow is regulated by changes in the diameter of the small resistance vessels, while the large basal arteries remain constant in diameter. Thus, changes in brain perfusion should result in velocity changes in the large cerebral arteries.

In 1982, Aaslid et al introduced transcranial Doppler sonography (TCD). For the first time it was possible to measure blood flow velocity continuously in the large basal arteries. TCD is a useful tool for describing changes in cerebral blood flow, not absolute values. Using TCD, Aaslid found blood flow velocity changes between darkness and light stimulation in the posterior and middle cerebral arteries (MCAs). One aim of our study is to use TCD to measure cerebral blood flow velocity in both MCAs during the performance of various cognitive activities since the MCAs supply much of...
the brain area involved in the processing of these tasks.\textsuperscript{5-15} We paid special attention to the time course of changes in V\textsubscript{MCA}, caused by cerebral blood flow regulation as a response to a new state of brain activity.

Corresponding to cerebral dominance, the performance of special tasks (e.g., verbal and spatial) lead to left–right differences in cerebral blood flow.\textsuperscript{23-26} Less pronounced hemispheric specialization and reversed laterality have been observed in a certain percentage of left-handed/ambidextrous (LH) people.\textsuperscript{27-29} This also seems to apply to persons with a LH mother, father, or sibling (familial sinistrality).\textsuperscript{28-33} Sex differences in lateralization are controversial.\textsuperscript{34-37} Since hemispheric dominance is especially a function of brain areas supplied by the MCAs, the second aim of our study is to detect left–right differences of V\textsubscript{MCA} during the performance of “left-hemispheric” and “right-hemispheric” tasks, paying special attention to handedness, familial sinistrality, and sex.

Subjects and Methods

After giving informed consent, 70 subjects with no clinical signs of cerebrovascular disease participated in our study. Thirty-seven were right-handed (RH) without familial sinistrality, nine were RH with familial sinistrality, 16 were LH without familial sinistrality, and eight were LH with familial sinistrality. Considered LH were those subjects who performed at least one of the following activities with their left hand as well as or better than with their right hand: drawing, erasing, dealing cards, throwing a ball, using scissors, and using a hammer.\textsuperscript{33} Familial sinistrality was present when at least one parent or one sibling was LH. Further, we assessed age (ranging from 16 to 63 years), 37 subjects were \textless 30 years old while 33 were \textgreater 30 years old), sex (29 women, 41 men), and profession (29 academic, 41 nonacademic). Of 91 original volunteers, 21 were excluded for various reasons: 10 because at least one MCA could not be detected, seven because the TCD signals were too weak, three because we were not sure about the identity of the perceived signal, and one because of cardiac arrhythmia.

We used the TC2-64 transcranial Doppler device (EME GmbH, Uberlingen, FRG). The highest V\textsubscript{MCA} signal was sought at a depth of 45 or 50 mm; in a very few subjects a 55-mm signal was accepted. Ultrasound intensity was 100 mW/cm\textsuperscript{2}. By hand we noted the time-averaged peak frequencies (mean) calculated by the machine every 3 seconds in centimeters per second. Continuous measurement was made possible by securing the probe in a head ribbon.

The subjects performed six 90-second tasks and had seven 42-second rest phases. They started with a rest phase and performed a task and a rest phase alternately. The tasks were 1) reading abstract four-syllable nouns aloud,\textsuperscript{40-44} 2) assigning dot clusters to a point on a distance scale without speaking,\textsuperscript{35,45-48} 3) finding nouns that begin with a certain letter aloud,\textsuperscript{23,24,49,50} 4) spatial perception test of finding the three-dimensional equivalent of unfolded geometric shapes without speaking,\textsuperscript{50-52} 5) multiplication aloud,\textsuperscript{40,49} and 6) face recognition without speaking; for Task 6 the subjects were shown a display of 80 pictures of faces and had to pick out the faces that appeared more than once.\textsuperscript{53,54} Tasks 1, 3, and 5 are generally assumed to be processed predominantly by the left hemisphere; Tasks 2, 4, and 6 by the right hemisphere.

During the entire procedure the subjects sat comfortably at a table. The tasks were explained to the subjects, who were instructed to perform them quickly and to move as little as possible. The subjects were allowed to perform some sample tasks for practice. The tasks (except Task 3) were presented on sheets of paper that were placed on a music stand. During rest phases, the eyes were closed and the subjects were told to relax; during the tasks the eyes were open. Each subject performed the complete series of six tasks and seven rest phases twice (similar items with comparable degrees of difficulty) to measure left V\textsubscript{MCA} and right V\textsubscript{MCA}. In 36 subjects right V\textsubscript{MCA} was measured first and left V\textsubscript{MCA} was measured second. In 34 subjects the order was reversed. Each task was preceded by the sentence “And now open your eyes and (e.g.) read aloud” and finished by the sentence “And now close your eyes again.” These two sentences were included in the first task V\textsubscript{MCA} values and rest V\textsubscript{MCA} values, respectively.

Results

The first rest phase of each series was considered a standardized buffer and was not used because of substantial fluctuation. During approximately the last 9 seconds of each rest phase, we found a steady state. For each series and side, we averaged raw V\textsubscript{MCA} values of the last six rest steady states and used this value as a reference (V\textsubscript{MCA}\textsubscript{ref}). All further imaging and calculation was done with the ratio V\textsubscript{MCA}/V\textsubscript{MCA}\textsubscript{ref}. Thus, a ratio of 1.00 means no change in V\textsubscript{MCA} above or below the reference. We paid particular attention to the grouping according to the order of measurement, for it appeared to be an important factor influencing our results (see below). Figures 1–3 and Table 1 pertain to 68 subjects counterbalanced with regard to order. The time course of the measurement illustrated in Figures 1–3 shows V\textsubscript{MCA} during a task immediately followed by a rest phase. We show the time courses of only Tasks 1–3 as Tasks 2, 4, and 6 on one hand and Tasks 1 and 5 on the other hand had similar curves. However, the height of the curves in general was lower for Tasks 4–6 performed later. In all tasks a maximum was reached after approximately 8 seconds, followed by a decrease (marked in Task 3) to a minimum, and an increase to a steady state. The task steady state values continued for approxi-
Figure 1. Time course of blood flow velocity changes ($V_{MCA}/V_{MCA_{ref}}$) in right (hatched) and left (black) middle cerebral artery (MCA) while reading aloud (Task 1, $n=68$). No left-right difference. Initially during task, velocity increases by approximately 15% after approximately 8 seconds, followed by decrease and second increase to steady state of approximately 110%. Initially during rest, steady state velocities are maintained for approximately 6 seconds, and maximum decrease of velocity is reached approximately 8 seconds later. Maximum decrease is followed by slow increase to rest steady state.

Figure 2. Time course of blood flow velocity changes ($V_{MCA}/V_{MCA_{ref}}$) in right (hatched) and left (black) middle cerebral artery (MCA) during dot cluster and distance estimation, Task 2, $n=68$). In this right hemispheric task there is significant left-right difference during steady state. Velocity in right MCA increases more than in left. Initial peak during task is less pronounced than in Figure 1, and rest phase minimum is reached a little bit later. There is small peak before decrease during rest phase, which is present in most tasks (especially those tasks performed silently).

Figure 3. Time course of blood flow velocity changes ($V_{MCA}/V_{MCA_{ref}}$) in right (hatched) and left (black) middle cerebral artery (MCA) while finding nouns aloud (Task 3, $n=68$). Unusual initial time course with brief increase in velocity of approximately 15% followed by rapid decrease of approximately 6% below normal reference value and reaching steady state after approximately 42 seconds may represent Valsalva's maneuver. No significant left-right difference.

by handedness, familial handedness, profession, order, sex, or age.

The steady state during the task began after approximately 24–42 seconds, Task 3 having the longest adaptation phase. All of the following calculations of relative increase were done with the values of the last 48 seconds. All of the work values for the group of 68 and subgroups were different from 1.00 (two-tailed $t$ tests, $p=0.0000$). It was statistically impossible to perform a seven-way analysis of variance (ANOVA) including handedness, familial handedness, sex, profession, age ($\leq$30 vs. $>30$ years), order, and side (left vs. right). Handedness and familial handedness were the two least important variables (no difference in two-tailed $t$ tests with matched subgroups; in lower-way ANOVAs interactions with other variables only from the third-order level up). Thus, these two variables were excluded from the following calculations. The $p$ values in Tables 1–4 are from five-way ANOVAs (sex, profession, age, order, and side) performed separately for each task. We present only main effects and second-order interactions since the higher-order interactions are hardly interpretable.

The results of individual subjects lack consistency due to the side-order interaction. In some subjects and for some tasks, this effect is more pronounced than in others. Increases in $V_{MCA}$ may be higher on the left during a right-hemispheric task if the left side was measured first. On the other hand, there was also considerable variability in the unexpected direction.

In older subjects the mean $V_{MCA_{ref}}$ rest values were lower on both the left ($p<0.01$) and on the right ($p<0.05$) than in younger subjects (correlation
TABLE 1. Side Differences Affecting Blood Flow Velocity Changes in Middle Cerebral Artery of 68 Subjects Performing Six Tasks

<table>
<thead>
<tr>
<th>Task</th>
<th>Left</th>
<th>Right</th>
<th>Difference</th>
<th>t test</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading aloud</td>
<td>1.1055</td>
<td>1.0988</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Dot/distance estimation</td>
<td>1.0564</td>
<td>1.0854</td>
<td>-0.0290</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>Noun finding</td>
<td>1.0382</td>
<td>1.0182</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Spatial perception</td>
<td>1.0426</td>
<td>1.0682</td>
<td>-0.0256</td>
<td>0.0002</td>
<td>0.0004</td>
</tr>
<tr>
<td>Multiplication</td>
<td>1.0321</td>
<td>1.0155</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Face recognition</td>
<td>1.0256</td>
<td>1.0508</td>
<td>-0.0252</td>
<td>0.0003</td>
<td>0.0042</td>
</tr>
</tbody>
</table>

ANOVA, analysis of variance (side effect), n=70; NS, not significant (p>0.05).

Discussion

Several factors such as the brain activity/blood flow relation, excitement (see the remarks below on habituation), and cardiovascular and respiratory factors may be included in the time course of \( V_{\text{MCA}} \) changes at the beginning of a task: increase, peak after approximately 8 seconds, decrease, and increase again until the steady state is reached after approximately 24-42 seconds. Aaslid\textsuperscript{22} found a \( V_{\text{MCA}} \) increase of 3.3% following light stimulation, most prominent during the first 8 seconds after the stimulus switched and adapting after 10-15 seconds. Unlike during our Tasks 1 and 5 (for Task 5 the subjects first read the problem aloud and then performed the intermediate calculations aloud), the subjects did not speak at the beginning of Task 3, and our subjective impression was that they performed Valsalva's maneuver. This may explain the characteristic time course of Task 3.

Before they decreased, the task steady-state \( V_{\text{MCA}} \) values continued for approximately 6 seconds at the beginning of the rest phase. In Aaslid's study\textsuperscript{22} also, the decrease of blood flow velocity in the posterior cerebral artery took slightly longer than its increase. Reasons for the prolonged decrease may include persisting elevated brain activity or persisting elevated brain metabolism due to previous task-related brain activity.

When considering the speed of cerebral blood flow adjustment, it is important to keep in mind that the brain metabolism/blood flow relation and autoregulation of cerebral blood flow in response to changes in transmural vessel pressure are two different processes with the same effect and that their detailed mechanisms are not yet well understood.\textsuperscript{55} Tada,\textsuperscript{56} for example, found that the time factor of the autoregulatory response to arterial blood pressure changes measured by Doppler flowmetry was 10 seconds for an increase and 16 seconds for a decrease. This is consistent with our 8-second peak and the delayed decrease. Tada\textsuperscript{56} attributes the delayed decrease to the method of changing the blood pressure (intra-aortic balloon). Further studies should pay attention not only to the speed of blood flow increase but also to that of blood flow decrease.

The initial phase of our curves resembles the curves of brain adenosine concentration following acute ischemia. Adenosine, a potent vasodilator, is claimed to have a role in autoregulation.\textsuperscript{57} All six tasks increased \( V_{\text{MCA}} \) on both sides, indicating the participation of both hemispheres in cognitive activities. There are at least four bilateral xenon-133 inhalation studies comparing regional cerebral blood flow during rest and during the performance of verbal and spatial tasks. Results of three\textsuperscript{23,25,26} show higher regional cerebral blood flow on the left side during the verbal task and on the right side during the spatial task. In the fourth

TABLE 2. Sex Effect and Side x Sex Interaction Affecting Changes in Blood Flow Velocity in Middle Cerebral Artery of 70 Subjects Performing Six Tasks

<table>
<thead>
<tr>
<th>Task</th>
<th>Women Left</th>
<th>Women Right</th>
<th>Men Left</th>
<th>Men Right</th>
<th>Sex effect</th>
<th>Side x sex interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading aloud</td>
<td>1.1124</td>
<td>1.1029</td>
<td>1.0951</td>
<td>1.0908</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Dot/distance estimation</td>
<td>1.0787</td>
<td>1.0911</td>
<td>1.0387</td>
<td>1.0777</td>
<td>0.0015</td>
<td>0.0104</td>
</tr>
<tr>
<td>Noun finding</td>
<td>1.0528</td>
<td>1.0331</td>
<td>1.0273</td>
<td>1.0070</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Spatial perception</td>
<td>1.0579</td>
<td>1.0717</td>
<td>1.0298</td>
<td>1.0620</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Multiplication</td>
<td>1.0443</td>
<td>1.0084</td>
<td>1.0202</td>
<td>1.0160</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Face recognition</td>
<td>1.0360</td>
<td>1.0602</td>
<td>1.0167</td>
<td>1.0414</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant (p>0.05).
The decreases of cerebral blood flow and Doppler signal with age have frequently been published. The absolute capacity of the brain vessels to react to higher brain activity is reported to remain unaffected. Because we measured relative changes, this could explain the higher values found in older subjects during Tasks 2 and 4. We are not certain how to interpret the side x age interactions.

Habituation/loss of motivation seems to have a major effect on VMCA. VMCA values are mostly higher on the side measured first (Table 4). Factors entering into this connection might also be rapid speaking and breathing, as motivated subjects will try to finish the task quickly. This is evident in Tasks 1, 3, and 5 (performed aloud, with their results heard by the examiner). The effect of familiarity with the task is stronger at the beginning. This effect was particularly pronounced in Task 1 and was present only in the first of the tasks performed silently (2, 4, and 6). Gur et al. found a low anxiety state to be associated with increased cerebral blood flow. Pain and strong involvement in a task have the same effect. Risberg et al. described a reduction of the left-hemispheric blood flow increase in the frontal areas during habituation to a reasoning test. In our study the side x order interaction is mostly due to a difference in the right MCA, possibly reflecting the role of the right hemisphere in attention and arousal. In our study, habituation took place between the tasks but not during the tasks (the steady state did not decrease gradually).

With TCD, changes of the brain activity in the area supplied by the MCA can be measured indirectly with high temporal resolution. The next steps would be bilateral simultaneous TCD measurements using computer registration and measurements in more distal MCA branches.

<table>
<thead>
<tr>
<th>Task</th>
<th>≤30 years</th>
<th>&gt;30 years</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>1 Reading aloud</td>
<td>1.1060</td>
<td>1.1254</td>
<td>1.0981</td>
</tr>
<tr>
<td>2 Dot/distance estimation</td>
<td>1.0423</td>
<td>1.0602</td>
<td>1.0698</td>
</tr>
<tr>
<td>3 Noun finding</td>
<td>1.0601</td>
<td>1.0424</td>
<td>1.0129</td>
</tr>
<tr>
<td>4 Spatial perception</td>
<td>1.0322</td>
<td>1.0475</td>
<td>1.0518</td>
</tr>
<tr>
<td>5 Multiplication</td>
<td>1.0631</td>
<td>1.0302</td>
<td>0.9932</td>
</tr>
<tr>
<td>6 Face recognition</td>
<td>1.0176</td>
<td>1.0415</td>
<td>1.0326</td>
</tr>
</tbody>
</table>

NS, not significant (p>0.05).

<table>
<thead>
<tr>
<th>Task</th>
<th>First left</th>
<th>First right</th>
<th>Side x order interaction (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>1 Reading aloud</td>
<td>1.1238</td>
<td>1.0463</td>
<td>1.0819</td>
</tr>
<tr>
<td>2 Dot/distance estimation</td>
<td>1.0600</td>
<td>1.0761</td>
<td>1.0508</td>
</tr>
<tr>
<td>3 Noun finding</td>
<td>1.0425</td>
<td>0.9914</td>
<td>1.0335</td>
</tr>
<tr>
<td>4 Spatial perception</td>
<td>1.0397</td>
<td>1.0663</td>
<td>1.0431</td>
</tr>
<tr>
<td>5 Multiplication</td>
<td>1.0386</td>
<td>0.9798</td>
<td>1.0222</td>
</tr>
<tr>
<td>6 Face recognition</td>
<td>1.0304</td>
<td>1.0487</td>
<td>1.0192</td>
</tr>
</tbody>
</table>

NS, not significant (p>0.05).
Acknowledgments

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