Noninvasive Determination of Language Lateralization by Functional Transcranial Doppler Sonography

A Comparison With the Wada Test

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Background and Purpose—Functional transcranial Doppler ultrasonography (fTCD) can assess event-related changes in cerebral blood flow velocities and, by comparison between sides, can provide a measure of hemispheric perfusional lateralization. It is easily applicable, insensitive to movement artifacts, and can be used in patients with less than perfect cooperation. In the present study we investigated the validity of fTCD in determining the hemispheric dominance for language by direct comparison of fTCD with intracarotid amobarbital anesthesia (Wada test).

Methods—fTCD and the Wada test were performed in 19 patients evaluated for epilepsy surgery. By the Wada test, 13 patients were classified as left-hemisphere dominant and 6 as right-hemisphere dominant for language. fTCD was based on the continuous bilateral measurements of blood flow velocities in the middle cerebral arteries and event-related averaging during a cued word generation task previously shown to activate lateralized language areas in normal adults.

Results—In 4 patients fTCD assessment was not possible because of lack of an acoustic temporal bone window. In the remaining 15 candidates, determination of language dominance was concordant with the Wada test in every case. Moreover, the correlation of the lateralization measures from both procedures was highly significant ($r = .92, P < .0001$).

Conclusions—This strong correlation validates fTCD as a noninvasive and practical tool for the determination of language lateralization that can be applied for clinical and investigative purposes. (Stroke. 1998;29:82-86.)

Key Words: cerebral dominance • laterality • ultrasonography, Doppler • Wada test

In most epilepsy surgery programs, hemispheric dominance for language is assessed by intra-arterial administration of amobarbital by means of a transfemoral catheter placed into the cerebral arteries (Wada test). Although of proven value in predicting the potential risk of language impairment after resective surgery, the Wada test has several inherent limitations, most importantly its invasiveness. Recently, fMRI has been used to measure cerebral perfusional changes noninvasively during language tasks in patients capable of avoiding movement artifacts during MRI scanning. The technique has been found to correlate closely with the outcome of the Wada test.

The changes in cerebral perfusion during cognitive tasks that underlie fMRI result in corresponding alterations of blood flow velocities in the feeding basal arteries. These alterations can be noninvasively and conveniently assessed by fTCD. The technique involves the continuous bilateral measurement of blood flow velocities in both MCAs during repeated performance of a task. Successive, event-related changes of blood flow in both arteries relative to the respective pre-event baseline are averaged, and averages from each hemisphere are then subtracted from each other. The calculation of mean relative blood flow differences makes the technique very robust, even allowing for intermittent moving and speaking. Moreover, it renders fTCD insensitive to global changes of perfusion due to modulations in PCO$_2$ or PO$_2$ that affect blood flow velocities in both insonated arteries equally. Thus, fTCD can even be applied in patients unsuitable for examinations by fMRI and can easily be repeated for follow-up. Its only limitation is that some subjects lack an acoustic temporal bone window for insonation of the MCA. In a previous study we demonstrated that fTCD during cued word generation in healthy right-handed subjects was associated with a significantly higher blood flow increase to the left relative to the right hemisphere in every subject. In the present study we directly compared fTCD with the Wada test in patients evaluated for epilepsy surgery to test the validity of fTCD as a tool for determination of language dominance.

Subjects and Methods

Subjects

We studied 19 patients (12 males, 7 females) aged 17 to 45 years (mean age, 29 years) who underwent comprehensive evaluation for surgical treatment of medically intractable epilepsy at our department in...
Selected Abbreviations and Acronyms

CBFV = cerebral blood flow velocity
fMRI = functional magnetic resonance imaging
fTCD = functional transcranial Doppler ultrasonography
LI = laterality index
MCA = middle cerebral artery
TCD = transcranial Doppler ultrasonography

Münster and the Epilepsie-Zentrum Bethel (Germany). The assessment included neurological examination, ictal semiology, video monitoring with continuous interictal and ictal electrophysiological recording, MRI, neuropsychological evaluation, fTCD, and the Wada test. Subjects gave informed consent to participate in the study. All were native German speakers. Thirteen were right handed and six left handed by the Edinburgh Handedness Inventory (Table). Wada and fTCD evaluations were performed by two different examiners blinded to the results obtained with either technique.

Functional TCD

Determination of hemispheric language dominance by fTCD was performed as previously described by our group. Subjects were seated in front of a computer screen where, 5 seconds after a cueing tone, a letter was presented for 2.5 seconds (Fig 1). Subjects silently had to find as many German words as possible starting with the displayed letter. To control the performance of the task, subjects were instructed to report the words after a second auditory signal 15 seconds after presentation of the letter. All words had to be reported within a 5-second time period. Afterward, a relaxation period of 60 seconds after presentation of the letter. To control the performance of the task, subjects were instructed to report the words after a second auditory signal 15 seconds after presentation of the letter. All words had to be reported within a 5-second time period. Afterward, a relaxation period of 60 seconds was given. Then the next letter was presented in the same way. Letters were presented in random order. Q, X, and Y were excluded because very few German words have these letters as initials. No letter was displayed more than once.

To measure CBFV changes in the basal arteries as an indicator of a downstream increase of regional metabolic activity during the language task, a commercially available dual TCD device (Multi-Dop T, DWL) was used. The MCAs were insonated at a depth of 50 mm with two 2-MHz transducer probes attached to a headband and placed at the temporal skull windows bilaterally (Fig 1). Details of the insonation technique, particularly the correct identification of the MCA, have been published elsewhere. The angles of insonation were adjusted to obtain the maximal signal intensity at the predetermined insonation depth. The spectral envelope curves of the Doppler signal were recorded with a rate of 28 sample points per second and stored for off-line analysis with custom-tailored software that had been programmed by one of the authors (M.D.). Artifacts like those elicited by probe displacement were automatically detected by comparison of the number of pulses per time unit of the entire recording session with the frequency of peaks in a given segment. Frames of recordings were rejected when these frequencies differed by more than one third. Additionally, epochs containing CBFV values outside the range of 30% to 200% of the mean flow velocity were rejected. The remaining data were integrated over the corresponding cardiac cycles, segmented into epochs that related to the cueing tone, and were then averaged. The epochs were set to begin 15 seconds before and to end 35 seconds after the cueing tone. The mean velocity in the 15-second precueing interval (t\text{mean}) was taken as the baseline value. The relative CBFV changes (\text{dV}) during cerebral activation were calculated by the formula

\[
\text{dV} = \frac{V(t) - V_{\text{pre.mean}}}{V_{\text{pre.mean}}} \times 100
\]

where \(V(t)\) is the CBFV over time. Relative CBFV changes from repeated presentations of letters (on the average 20 runs) were averaged time-locked to the cueing tone. Differences in the velocity changes in the two MCAs in every patient were statistically evaluated by the Wilcoxon test for each time point. This nonparametric test is less sensitive to outliers when only a limited number of epochs can be averaged. The number of repetitions was less than 22 because no letter was presented more than once during the word generation task. An LI\text{fTCD} was calculated by the following formula (the integral was substituted by the corresponding sum over the sampled data points representing the velocity curve):

\[
LI_{\text{fTCD}} = \frac{1}{T_{\text{int}}} \int_{t_{\text{left}}}^{t_{\text{left}} + 0.5s} \frac{dV}{dt} dt
\]

where \(\Delta V(t) = dV(t)_{\text{left}} - dV(t)_{\text{right}}\) is the difference between the relative velocity changes of the left and right MCAs. \(\Delta V(t)_{\text{left}}\) represents the latency of the absolute maximum of \(\Delta V(t)\) during an interval of 7 to 27 seconds after cueing, i.e., during verbal processing. For integration a time period of \(T_{\text{int}} = 2\) seconds was chosen. The test-retest reproducibility of this procedure in determining hemispheric language lateralization based on the Pearson product moment correlation coefficient was \(r = .95, P < .0001\) (S.K. et al., unpublished data, 1997). Results of the language lateralization by fTCD LI\text{fTCD} and Wada test LI\text{WADA} were compared by linear regression of the respective LIs.

Wada Method

The Wada procedure corresponded to the one described by Jokeit et al. Briefly, angiography was performed by a transfemoral approach with patients in a supine position. A single bolus of 150 mg amobarbital was injected over a 4-second interval into the internal carotid artery under study. First the side of suspected seizure focus and, 30 minutes later, the contralateral side were assessed. Immediately after injection, numerical ratings were performed for the following language tasks. Following simple commands such as “Lift your arm” (maximal score, 4); reporting his/her first and second names (maximal score, 2); naming the days of the week (maximal score, 8; 1 point per day listed with an additional point for the correct sequence); reading simple words (maximal score, 15); reading complex words (maximal score, 10); naming colors, objects, and numbers presented visually (maximal score, 10 each); repeating sentences (maximal score, 10); describing concrete drawings (maximal score, 15); and explaining the meaning of words (maximal score, 10). The performance in tasks having maximal scores of 10 or 15 points was rated with the use of a scale between 0 and 5 for each of two or three items: 0 indicated no response, 1 meant that the response was unintelligible, 2 indicated that the response was incorrect, 3 that only repetition of an answer spoken aloud was possible, 4 that a correct response was possible only after verbal priming, and 5 that a correct answer was given spontaneously.

A Wada LI (LI Wada) was calculated by the formula: LI Wada = (P\text{left} - P\text{right}), where P is the language score after left and right internal carotid artery injection, respectively. This formula yields Wada indices between −104 for strong left-hemispheric language dominance and +104 for strong right-hemispheric language dominance.

Figure 1. Experimental setup of language dominance assessment by fTCD. Displayed data represent the averaged results from 20 letter presentations in a single subject. Note the delay of approximately 4 to 7 seconds before the maximal hemispheric difference is reached. \text{dV} indicates relative CBFV changes.
Results

Of 19 patients who underwent successful Wada testing, fTCD could be performed in 15 patients. In the remaining 4 candidates no adequate acoustic temporal bone window for insonation of the MCAs could be found. There were no dropouts due to distress, movement artifacts, or lack of cooperation. The Table presents details of the patients, duration of epilepsy, handedness, and results on the Wada test and the fTCD.

Functional TCD

During the examined task, 8% (mean; range, 0% to 20%) of the recorded CBFV epochs were rejected because of artifacts. Mean CBFV data from the remaining epochs showed a bilateral biphasic CBFV augmentation. A first CBFV increase was seen approximately 1 second after the cueing tone but before letter presentation. This increase peaked on average at the time when the letter was expected, ie, 5 to 7 seconds later.

A second CBFV augmentation began during letter presentation and, on average, peaked 4 seconds later. During actual word generation, ie, from letter presentation to the second tone, a significant ($P=.05$, Wilcoxon test) relative predominance of CBFV increase in the left hemisphere was seen in 11 patients and in the right hemisphere in 4 patients. The extent of relative hemispheric CBFV predominance, ie, the difference between the mean CBFV increase from the baseline in one hemisphere relative to the other, varied from 1.3% to 6.3% (median, 3.2%; quartile, 2.6% to 4.0%) (left greater than right) in patients with left-hemisphere language dominance, and it varied from 1.3% to 5.7% (median, 3.6%; quartile, 2.2% to 4.9%) (right greater than left) in patients with right-hemisphere language dominance. In every case the determination of language lateralization by fTCD was concordant with the Wada test.

While attending the screen for an upcoming letter, ie, after the first cueing tone and before the actual display of a letter on the screen occurred, patients with left-hemisphere language dominance often showed a relative right-hemispheric CBFV increase. Patients with right-hemisphere language dominance showed either a relative CBFV increase in the right hemisphere or, in one case, in the left hemisphere. In most cases, however, these attention-related activations did not reach significance.

The LIs for language determined with the Wada test (LI Wada) revealed a highly significant correlation with the LIs measured by fTCD (LI fTCD) ($r=.92, P<.0001$) (Fig 2).

Discussion

The main finding of this study was that determination of hemispheric language dominance by fTCD was concordant with the result of the Wada test in every case. Moreover, even the quantitative measure of lateralization assessed by both techniques correlated closely ($r=.92, P<.0001$). Obviously, the activated cerebral areas during the employed word generation task, which led to a lateralization on fTCD, correspond closely to those areas underlying the hemispheric dominance as assessed by the Wada test. Unlike the Wada test, however, fTCD is without any risk or inconvenience to the patient. The statistical technique of averaging relative blood flow differences provides a very reliable indicator of the language lateralization and the extent of this lateralization in individual patients. The findings in the present study, obtained on this basis, corroborate...
rate the suggestion that language lateralization occurs along a graded continuum.\textsuperscript{5}

The Wada test, although a proven standard for determination of language dominance, has several substantial disadvantages.\textsuperscript{3,4,23} The required intracarotid angiography necessitates hospitalization, is distressing to the patients, and has a morbidity risk reported as high as 5%.\textsuperscript{24} Obtundation after injection of amobarbital can make the distinction between attention-related and language-related deficits difficult. Results can be influenced by cross flow of anesthetic from the injected internal carotid artery to the contralateral hemisphere via the circle of Willis\textsuperscript{25} or by carryover effects from the first to the second injection when both carotid arteries are injected on the same day.\textsuperscript{26} The very restricted time for testing after amobarbital injection and the unavailability of test-retest reliability data constitute further limitations.

Because of the risks and shortcomings associated with the Wada test, various attempts have been made to find alternatives to this technique. Speech localization has been performed with the use of repetitive transcranial magnetic stimulation.\textsuperscript{27} Repetitive magnetic stimulation of the brain, however, carries a small but definite risk for seizures, particularly in epileptic patients.\textsuperscript{28} Moreover, it can induce facial and laryngeal muscle contractions interfering with speech performance. Positron emission tomography is another technique that allows localization of cerebral language functions\textsuperscript{29–32} but is in itself invasive because of radiation exposure.

Functional MRI offers another noninvasive alternative for the determination of hemispheric language dominance.\textsuperscript{5,6} In patients with refractory epilepsy, however, fMRI can be difficult to perform. It requires maximal cooperation because the technique is very sensitive to movement artifacts.\textsuperscript{33} It cannot be used in patients with claustrophobia, gross obesity, metallic implants near to or in the head, or cardiac pacemakers. Here fTCD holds promise as a complementary technique, since the perfusional changes assessed by fTCD are similar to those detected by fMRI but without the above restrictions.\textsuperscript{12}

The physiological information obtained by either fTCD or the Wada test depends on the arterial distribution under study. While the amobarbital injection during the Wada test impairs cerebral function within the territory of the internal carotid artery, fTCD operates more selectively by pinpointing the distribution of a specific pial artery, eg, the MCA. Functional TCD imposes no time or space restraints and is associated with no distress and little to no inconvenience to the patient. Furthermore, TCD is a mobile and comparatively inexpensive technique, available in most neurological departments. It can be performed on an outpatient basis and may easily be repeated for follow-up purposes. It allows control regarding patient cooperation during every task without jeopardizing the recording in toto due to movement artifact, as is sometimes the case in fMRI studies. This makes it a practical tool for the determination of language dominance in the clinical setting. Functional TCD is, however, dependent on its ability to acoustically penetrate the temporal bone. In our series this was not always feasible because 4 of 19 patients lacked a "window." In these patients, determination of language dominance by fTCD was not possible with our technology. However, auxiliary techniques are now becoming available that allow TCD assessment even in the presence of thicker bones.\textsuperscript{34}

Full use of the potential of fTCD has in the past been hampered by the fact that the CBFV signal displays large fluctuations of the mean in the range of \(\pm 30\%\) due to heart rate or changes in P\textsubscript{CO\textsubscript{2}}. This makes detection of small functional changes on the order of 2% to 5% difficult. During cognitive tasks, triphasic modulations of heart rate and cardiac ejection fraction add to fluctuations of CBFV.\textsuperscript{35,36} It was not before the introduction of bilateral simultaneous TCD that mean lateralized increases of the CBFV relative to these global fluctuations could be assessed by comparison between sides. This comparison between sides also allows for detection of bilateral language representation characterized by CBFV increases in both MCAs with small differences, ie, a low LI. In some series the reported incidence of bilateral language function determined by multiple language tasks applied during Wada testing is almost 20%.\textsuperscript{37} In our series only one patient\textsuperscript{27} had a low LI by both the Wada test and fTCD. Given the limited sample size, this study does not lend itself to establish a representative incidence of hemispheric language dominance. Although patients had not been specifically selected for the purpose of our study, the 20% incidence of right-hemispheric dominance was far higher than in amobarbital studies based on several hundred patients.\textsuperscript{38}

The word generation task during fTCD corresponds to paradigms used in other studies involving functional imaging.\textsuperscript{39–41} Conversely, the Wada test, as used in the present study, assesses a wider variety of language functions. Time restraints during the intracarotid amobarbital procedure did not allow us to perform an additional word generation task identical to the one used for fTCD. Thus, there were not only methodological differences between fTCD (involving activation) and the Wada test (involving anesthesia) but also differences in the behavioral task. In the literature, impairments in word generation capabilities are linked to damage in the left frontal lobe but can also be seen in nonfrontal lobe lesions.\textsuperscript{42,43} Activation studies indicate that lexical retrieval involves multiple regions of one hemisphere, many of which are located outside the classic language areas.\textsuperscript{44} Moreover, many of the patients in this study had long-standing cerebral lesions. Thus,

![Figure 2. Correlation between lateralization by the Wada test and the fTCD (\(r=.92045, P<.0001\)) (Wada = −1.594 + 16.892fTCD). Dashed lines indicate 95% confidence intervals; individual patients with right- or left-hemispheric dominance for language.](http://stroke.ahajournals.org/)

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**Figure 2.** Correlation between lateralization by the Wada test and the fTCD (\(r=.92045, P<.0001\)) (Wada = −1.594 + 16.892fTCD). Dashed lines indicate 95% confidence intervals; individual patients with right- or left-hemispheric dominance for language.
there was an increased likelihood of functional reorganization of language areas and involvement of atypical anatomic locations. However, the strong correlation between the results from fTCD based on the word generation task and from the Wada test based on multiple language tasks indicates that there was a substantial overlap of brain regions involved in the respective behavioral tasks. Nevertheless, further fTCD studies involving different activation paradigms and direct comparison with postoperative language performance should be performed to better delineate the potential role of this new technique in epilepsy surgery and in other investigational fields of language lateralization.

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