Transcranial Doppler Versus Angiography in Patients With Vasospasm due to a Ruptured Cerebral Aneurysm
A Systematic Review

Christopher Lysakowski, MD; Bernhard Walder, MD; Michael C. Costanza, PhD; Martin R. Tramèr, MD, DPhil

Background and Purpose—Transcranial Doppler (TCD) is used for diagnosis of vasospasm in patients with subarachnoid hemorrhage due to a ruptured aneurysm. Our aim was to evaluate both the accuracy of TCD compared with angiography and its usefulness as a screening method in this setting.

Methods—A search (MEDLINE, EMBASE, Cochrane Library, bibliographies, hand searching, any language, through January 31, 2001) was performed for studies comparing TCD with angiography. Data were critically appraised using a modified published 10-point score and were combined using a random-effects model.

Results—Twenty-six reports compared TCD with angiography. Median validity score was 4.5 (range 1 to 8). Meta-analyses could be performed with data from 7 trials. For the middle cerebral artery (5 trials, 317 tests), sensitivity was 67% (95% CI 48% to 87%), specificity was 99% (98% to 100%), positive predictive value (PPV) was 97% (95% to 98%), and negative predictive value (NPV) was 78% (65% to 91%). For the anterior cerebral artery (3 trials, 171 tests), sensitivity was 42% (11% to 72%), specificity was 76% (53% to 100%), PPV was 56% (27% to 84%), and NPV was 69% (43% to 95%). Three of these 7 studies reported on the same patients, each on another artery, and for 4, data recycling could not be disproved. Other arteries were tested in only 1 trial each.

Conclusions—For the middle cerebral artery, TCD is not likely to indicate a spasm when angiography does not show one (high specificity), and TCD may be used to identify patients with a spasm (high PPV). For all other situations and arteries, there is either lack of evidence of accuracy or of any usefulness of TCD. Most of these data are of low methodological quality, bias cannot not be ruled out, and data reporting is often uncritical. (Stroke. 2001;32:2292-2298.)

Key Words: angiography ■ diagnostic imaging ■ meta-analysis

Spasm of cerebral vessels due to aneurysmal subarachnoid hemorrhage carries a 15% to 20% risk of stroke or death. Angiography of the nutritional vessels of the brain may be considered the gold standard diagnostic test in this setting. However, this procedure is invasive, expensive, not always available, and not without risk; cerebral embolus, dissection, or rupture of cerebral arteries and hemorrhage have been described. Almost 20 years ago, transcranial Doppler (TCD) was proposed for the diagnosis of cerebral vasospasm. The diagnosis of a spasm with a TCD device is based on the hemodynamic principle that the velocity of blood flow in an artery is inversely related to the area of the lumen of that artery. In theory, TCD may serve as a relatively simple screening method of cerebral vasospasm, and some investigators have advocated the replacement of angiography by TCD. Indeed, TCD has been implemented by many neurosurgical units. This, however, is contentious, because some authors were unable to find any correlation between TCD and angiographic results in patients with cerebral vasospasm.

The aim of this systematic review was, first, to test the accuracy of TCD compared with angiography for the diagnosis of cerebral vasospasm after subarachnoid hemorrhage due to a ruptured aneurysm; second, to test the usefulness of TCD as a screening method in this setting; and third, to evaluate the validity of the published data.

Methods

Inclusion Criteria
Included studies were full reports of trials comparing TCD with cerebral angiography in adults with subarachnoid hemorrhage due to a ruptured aneurysm. Angiography and TCD had to be performed no more than 24 hours apart. Only studies that used conventional TCD devices were included (ie, power color TCD was not considered).

Search Strategy
Electronic searches were carried out using MEDLINE (Data Star, PubMed, and KnowledgeFinder 4.19, from 1966 through January 31, 2001; final revision received June 26, 2001; accepted June 28, 2001.
From the Divisions of Anesthesiology, Neuroanesthesia Unit (C.L., M.R.T.), and Surgical Intensive Care (B.W.), Department APSIC, and the Division of Clinical Epidemiology (M.C.C.), Geneva University Hospitals, Geneva, Switzerland.
Correspondence to Christopher Lysakowski, MD, Neuroanesthesia Unit, Division of Anesthesiology, Department APSIC, Rue Micheli –du –Crest 24, CH–1211 Geneva 14, Switzerland. E-mail christopher.lysakowski@hcuge.ch
© 2001 American Heart Association, Inc.
Stroke is available at http://www.strokeaha.org
TABLE 1. Validity Score for Diagnostic Tests

<table>
<thead>
<tr>
<th>Criterion*</th>
<th>1 Point</th>
<th>0 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study design</td>
<td>Comparative</td>
<td>Case control</td>
</tr>
<tr>
<td>2. Patient selection</td>
<td>Consecutive</td>
<td>Not consecutive</td>
</tr>
<tr>
<td>3. Data collection</td>
<td>Prospective</td>
<td>Retrospective</td>
</tr>
<tr>
<td>4. Observer blinding</td>
<td>Details on both tests are sufficiently described (sufficient details to allow replication and validation of tests, description of devices)</td>
<td>Observer not blinded</td>
</tr>
<tr>
<td>5. Description of tests</td>
<td>Insufficient description of one or both tests</td>
<td></td>
</tr>
<tr>
<td>6. Complete verification of both tests</td>
<td>Both tests done in all patients</td>
<td>One test only done in all patients</td>
</tr>
<tr>
<td>7. Data reporting</td>
<td>The numbers of true positives and true negatives and false-positives and false-negatives are reported</td>
<td>The numbers of true positives and true negatives and false-positives and false-negatives are not reported</td>
</tr>
<tr>
<td>8. Details on study population</td>
<td>Patients are sufficiently described (at least age and gender ratio)</td>
<td>Patients are not sufficiently described</td>
</tr>
<tr>
<td>9. Homogeneity of study population</td>
<td>All patients have the same pathology</td>
<td>Patients have different pathologies</td>
</tr>
<tr>
<td>10. Reporting of long-term outcome</td>
<td>Morbidity/disability and mortality data are reported</td>
<td>No morbidity/disability or mortality data are reported</td>
</tr>
</tbody>
</table>

*Criteria 1 through 8 are from Lijmer et al.16 Maximum score of an included study is 10; minimum score is 0.

2001, EMBASE (from 1984 through January 31, 2001), and the Central Trials Register of the Cochrane Library (issue 1, 2001). Key words used were “subarachnoid hemorrhage,” “intracranial aneurysm,” “cerebral vasospasm,” “cerebral angiography,” “transcranial Doppler,” and “blood flow velocity.” Reference lists of retrieved reports and of relevant review articles8,12–15 were checked. No language restriction was applied. Data from abstracts, letters, and animal studies were not considered, manufacturers were not contacted, and unpublished data were not searched. Authors were contacted when there was ambiguity about the reported data.

Study Selection, Validity Assessment, and Data Extraction

Two authors (C.L., B.W.) screened all retrieved reports. Papers that did not clearly meet inclusion criteria were excluded at this stage. Three authors (C.L., B.W., M.R.T.) then read independently the remaining papers and scored them for methodological quality, using an 8-point validity score for diagnostic tests (Table 1).16 We added 2 further criteria for the purpose of this study, homogeneity of the study population and reporting of clinical outcome (Table 1). For each fulfilled criterion, 1 point was given. If the criterion was not fulfilled or if the answer was unclear, no point was given. Thus, the lowest possible score for an included study was 0, and the highest score was 10. All authors entered the results of their individual validity assessment into a standardized working sheet. Authors then met to agree on consensus; disagreements were resolved by discussion.

One author (C.L.) extracted separately for different arteries dichotomous diagnostic data (ie, true- and false-positives, and true- and false-negatives) to create conventional 2×2 cross-classification tables (Figure 1). This was done only for trials that compared both tests in all patients. Two other authors (B.W., M.R.T.) cross-checked the data. Disagreement was resolved by discussion. Definitions of “positive” TCD (increasing of flow velocity) and “positive” angiography (narrowing of arteries) were taken as reported in the original studies.

There was a pre hoc decision to test the accuracy of TCD as a diagnostic tool compared with angiography. Thus, TCD would be regarded as a useful diagnostic tool if it proved to detect most patients who had a positive angiography (high sensitivity), and if it proved to exclude most patients without a positive angiography (high specificity).17 There was also a pre hoc decision to assess the potential usefulness of TCD as a screening method in patients who

Figure 1. 2×2 table for diagnostic tests. Angio indicates angiography (gold standard test).

Figure 2. Flow chart of retrieved, excluded, and included trials.
may have a vasospasm. This was done in 2 ways. First, TCD would be regarded as a useful screening method if a positive TCD usually indicated that an angiographic vasospasm was present (positive predictive value [PPV]), and a negative TCD indicated that there was none (negative predictive value [NPV]). These latter measures need to be interpreted with some caution however, because the samples of patients in the various studies under review most probably were not representative of the relevant target patient populations at large. And second, we calculated the likelihood ratio for a positive test (ie, the ratio that indicates how much more likely a positive TCD is found in a patient with a vasospasm than in a patient without it), and the likelihood ratio for a negative test (ie, the ratio that indicates how much more likely a negative TCD is found in a patient without a vasospasm than in a patient with it).

Meta-Analyses

Quantitative meta-analyses were done only when there was evidence of complete verification of both tests in a trial (ie, all patients who had a TCD measurement of an artery also had an angiography of that artery, and vice versa). When combined data on different arteries were reported and the data could not be separated, we did not further analyze those data. Sensitivity, specificity, PPVs, NPVs, and likelihood ratios were calculated for each valid study, together with 95% CIs. A random-effects model that takes into account both within- and between-study variation was used to generate summary measures. Random-effects models produce conservatively wider CIs than fixed effect models which do not account for between-study variation. When one of the cells in a 2×2 table was zero, 0.5 was added to all cells before computing the summary measure.

Results

Included and Excluded Trials

Eighty-one reports were retrieved; 54 were subsequently excluded for different reasons (Figure 2). One additional report was a duplicate of a previously published full report; the original report only was considered by us. We eventually analyzed data from 26 studies. An exact quantification of the number of included patients and the number of tests performed was impossible, because there was inconsistency in reporting these numbers in the original studies. We contacted the main authors of 2 studies by letter to clarify queries about the reported data, but we did not receive any answer. Two trials were in Japanese; one was in French; all others were in English.
Validity Assessment

None of the included reports fulfilled all ten methodological criteria (Table 2). The median score was 4.5 (range 1 to 8); one trial scored 1, four scored 2, three scored 3, five scored 4, five scored 5, two scored 6, five scored 7, and one scored 8. Study design was comparative in 24 trials (92%), patient selection was consecutive in 15 (58%), data collection was prospective in 3 (12%), observers were blinded in 8 (31%), sufficient details on both TCD and angiography were reported in 8 (31%), complete verification of both diagnostic tests was done in ten (38%), data reporting on diagnostic performance was adequate in 9 (35%), details of the study population were described in 19 (73%), study populations were homogenous in 14 (54%), and long-term outcomes were reported in 8 (31%). Three studies reported on the same patients, each on another artery.\textsuperscript{21,35,40} Data recycling (ie, reuse of some already published data in subsequent studies) could not be disproved for 4 studies.\textsuperscript{10,11,23,28}

Diagnostic Performance

Dichotomous diagnostic data for 2×2 tables could be extracted from 9 trials.\textsuperscript{4,11,21,27–29,34,35,40} In 2 of those, however, verification of tests was incomplete.\textsuperscript{4,11} Of the remaining 7, 2 reported on data per artery,\textsuperscript{21,29} and in 1 trial, several tests were performed in all patients but only one result was reported.\textsuperscript{27} In 2 trials, there were some inconsistencies in the reporting of data.\textsuperscript{21,35} Often it was unclear on what grounds patients had been excluded from the analysis. For instance, in 3 trials false-negatives were reported to be due to operator inexperience or technical failures of the TCD, but these data seemed to have been included in the analyses.\textsuperscript{21,34,40} In 2 studies, some patients were excluded by the original trialists when there were unfavorable anatomic conditions to perform the TCD.\textsuperscript{29,35} Often, we had to assume that patients were recruited only when their angiography was positive. In 5 trials, for instance, there were no or only very few false-positives.\textsuperscript{21,27–29,34}

The cut off for a positive TCD was defined as a flow velocity in the middle cerebral artery of 120 cm/s in 5 studies,\textsuperscript{21,27,34,35,40} of 130 cm/sec in 1,\textsuperscript{28} and of 140 cm/s in 1.\textsuperscript{29} The cut off for a positive angiography was defined as a lumen reduction in any artery of at least 25% in 5 studies,\textsuperscript{21,27,28,35,40} of at least 30% in 1,\textsuperscript{34} and no definition was provided in 1 study.\textsuperscript{29} Five trials (198 patients, 317 tests)
reported on the middle cerebral artery, and dichotomous diagnostic data could be extracted and combined (Table 3). Three trials (108 patients, 171 tests) reported on the anterior cerebral artery, and dichotomous diagnostic data could be extracted and combined (Table 3). The internal carotid artery, posterior cerebral artery, basilar cerebral artery, and vertebral artery were tested in only 1 trial each, with a limited number of patients.

**Discussion**

The optimal diagnostic tool should be easy to use, should identify most patients with the disease, should allow to follow the effect of a treatment in these patients, and thus should have an impact on outcome. The data from these trials suggest that when angiography does not show a spasm of the middle cerebral artery, TCD is not likely to refute this (high specificity). However, if angiography of the middle cerebral artery indicates a spasm, TCD is of no use to confirm this (low sensitivity). For the anterior cerebral artery, data from only 3 trials could be analyzed, and both sensitivity and specificity were low. Thus, compared with angiography, TCD’s diagnostic accuracy for spasms of the anterior cerebral artery is low. For all the other arteries, data came from no more than 1 trial each; no conclusions could be drawn.

Because sensitivity and specificity do not inform us on the usefulness of a test as a screening method among patients in the general population, we calculated PPVs, NPVs, and likelihood ratios. For the middle cerebral artery, these measures suggested that most patients in whom TCD indicated a spasm did have an angiographic spasm, and that TCD was actually 17 times more likely to indicate the presence of a spasm in a patient who had a spasm than in a patient who had none. However, in patients in whom TCD does not indicate a spasm of the middle cerebral artery, one cannot be sure that there is none (low NPV and low likelihood ratio for a negative test). For the anterior cerebral artery, the data from 3 trials that could be analyzed suggested that TCD is of no use as a screening method. For all the other arteries, again the data came from no more than a single trial each.

This meta-analysis has several limitations. First, patient samples were small, and were from a limited number of analyzable published studies. Thus, even if all the studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>True Positive</th>
<th>False Positive</th>
<th>True Negative</th>
<th>False Negative</th>
<th>No. Patients/No. Tests</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Middle cerebral artery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burch21</td>
<td>15</td>
<td>3</td>
<td>45</td>
<td>24</td>
<td>49/87</td>
<td>38%</td>
<td>94%</td>
<td>83%</td>
<td>65%</td>
<td>6.2</td>
</tr>
<tr>
<td>Kyoi27</td>
<td>10</td>
<td>0</td>
<td>7</td>
<td>1</td>
<td>18/18</td>
<td>91%</td>
<td>100%</td>
<td>100%</td>
<td>88%</td>
<td>14.0</td>
</tr>
<tr>
<td>Langlois28</td>
<td>11</td>
<td>0</td>
<td>97</td>
<td>4</td>
<td>56/112</td>
<td>73%</td>
<td>100%</td>
<td>100%</td>
<td>96%</td>
<td>140.9</td>
</tr>
<tr>
<td>Lennihan29</td>
<td>6</td>
<td>1</td>
<td>58</td>
<td>1</td>
<td>41/66</td>
<td>86%</td>
<td>98%</td>
<td>86%</td>
<td>98%</td>
<td>50.6</td>
</tr>
<tr>
<td>Sloan34</td>
<td>17</td>
<td>0</td>
<td>5</td>
<td>12</td>
<td>34/34</td>
<td>59%</td>
<td>100%</td>
<td>100%</td>
<td>29%</td>
<td>7.0</td>
</tr>
<tr>
<td><strong>Anterior cerebral artery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyoi Kikuo27</td>
<td>9</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>18/18</td>
<td>82%</td>
<td>71%</td>
<td>82%</td>
<td>71%</td>
<td>2.9</td>
</tr>
<tr>
<td>Lennihan29</td>
<td>2</td>
<td>0</td>
<td>51</td>
<td>13</td>
<td>41/66</td>
<td>13%</td>
<td>100%</td>
<td>100%</td>
<td>80%</td>
<td>16.3</td>
</tr>
<tr>
<td>Wozniak40</td>
<td>9</td>
<td>13</td>
<td>24</td>
<td>41</td>
<td>49/87</td>
<td>18%</td>
<td>65%</td>
<td>41%</td>
<td>37%</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Internal carotid artery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burch21</td>
<td>11</td>
<td>4</td>
<td>42</td>
<td>33</td>
<td>84/90</td>
<td>25%</td>
<td>91%</td>
<td>73%</td>
<td>56%</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Posterior cerebral artery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wozniak40</td>
<td>11</td>
<td>19</td>
<td>42</td>
<td>12</td>
<td>47/84</td>
<td>48%</td>
<td>69%</td>
<td>37%</td>
<td>78%</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Basilar cerebral artery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sloan35</td>
<td>10</td>
<td>6</td>
<td>23</td>
<td>3</td>
<td>42/43</td>
<td>76.9%</td>
<td>79%</td>
<td>63%</td>
<td>88%</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>Vertebral cerebral arteries</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sloan35</td>
<td>7</td>
<td>6</td>
<td>42</td>
<td>9</td>
<td>42/64</td>
<td>43.8%</td>
<td>88%</td>
<td>54%</td>
<td>82%</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Angio indicates angiography, the gold standard; TCD is the diagnostic test.
were of high methodological quality, the problem of low statistical power for validating null results remains. In fact, the majority of these studies were of low methodological quality, several biases could not be ruled out, and data reporting was often uncritical. None of the reports fulfilled all 10 criteria of the validity score; only one achieved 8 points, and 50% of all studies had a score of <5. In one third of trials only, the observers were blinded to the results of the angiography or the TCD, respectively. In some trials, there were very few false-positives (1% of all tests for the middle cerebral artery). It cannot be ruled out that, in the absence of adequate blinding, the observers may have consciously or subconsciously influenced the TCD results in patients who had a positive angiography, or that patients were recruited only when their angiography was positive. This is known as expectation bias. Second, the representativeness of some of the patient samples was (at best) doubtful. For instance, in many trials, most patients were among true negatives (67% of all tests for the middle cerebral artery). This suggests that these trials investigated low-risk populations. False-negatives were reported to be caused by operator inexperience or technical failures of the TCD, and sometimes patients were excluded when there were unfavorable anatomic conditions to perform the TCD. Thus, operators’ skills and experience with the TCD devices may have influenced the results. Third, often it was difficult to identify original data in these studies. There was duplication of data, some trials reported on the same patients, and for some, data recycling could not be ruled out. Finally, we had to rely on the original authors’ definitions of vasospasm (ie, in most trials a flow velocity of >120 cm/s and an angiographic narrowing of an artery of >25%21,27,28,34,35,40). These, however, may not necessarily be correlated with important endpoints, for instance, delayed ischemia. It has also been suggested that by coupling the patient’s vital neurological data with trends of blood flow velocity, a health care provider could anticipate the onset or patient’s vital neurological data with trends of blood flow ischemia. It has also been suggested that by coupling the patient’s vital neurological data with trends of blood flow velocity, a health care provider could anticipate the onset or worsening of vasospasm. Thus, in future trials, correlation coefficients rather than 2×2 tables based on arbitrary cutoffs would be more useful, and long-term outcomes should be studied.

If these data from the literature are valid, and we assume that the results from an angiography are always correct in this setting, we may draw three conclusions. First, if TCD of the middle cerebral artery in a patient who may have a spasm of that artery indicates the presence of a spasm, it is indeed likely that this patient has a spasm. Second, if in the same patient, TCD does not suggest a spasm of that artery, the operator does not know for sure that there is none. Finally, there is no evidence for any usefulness of TCD as a diagnostic tool for spasms of other cerebral arteries. Thus, at best it can be said that, based on the evidence (or lack thereof) today, TCD cannot be recommended as a screening method in patients with possible cerebral vasospasm due to ruptured aneurysms.

Acknowledgments

Supported in part by the PROSPER fund (No. 3200-59752.97) from the Swiss National Research Foundation (M.R.T.). We are grateful to Mr Daniel Haake from the Library of the Geneva Medical School for his help in searching electronic databases and to Dr Tanaka Norimitsu, Department of Neuroradiology, Geneva University Hospitals, who translated Japanese reports.

References

Transcranial Doppler Versus Angiography in Patients With Vasospasm due to a Ruptured Cerebral Aneurysm: A Systematic Review

Christopher Lysakowski, Bernhard Walder, Michael C. Costanza and Martin R. Tramer

Stroke. 2001;32:2292-2298
doi: 10.1161/hs1001.097108

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/10/2292

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/