Association of Intraoperative Transcranial Doppler Monitoring Variables With Stroke From Carotid Endarterectomy

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Background and Purpose—The outcomes of carotid endarterectomy (CEA) are, in addition to patient baseline characteristics, highly dependent on the safety of the surgical procedure. During the successive stages of the operation, transcranial Doppler (TCD) monitoring of the middle cerebral artery (MCA) was used to assess the association of cerebral microembolism and hemodynamic changes with stroke and stroke-related death.

Methods—By use of data pooled from 2 hospitals in the United States and the Netherlands, including 1058 patients who underwent CEA, the association of various TCD emboli and velocity variables with operative stroke and stroke-related death was evaluated by univariable and multivariable logistic regression analyses in combination with receiver operating characteristic (ROC) curve analyses. The impact of basic patient characteristics, such as age, sex, preoperative cerebral symptoms, and ipsilateral and contralateral internal carotid artery stenosis, on the prediction of operative stroke was also evaluated.

Results—We observed 31 patients with ischemic and 8 patients with hemorrhagic operative strokes. Four of these patients died. Emboli during dissection (odds ratio [OR] 1.5, 95% CI 0.8 to 2.9) and wound closure (OR 2.3, 95% CI 1.2 to 4.4) as well as ≥90% decrease of MCA peak systolic velocity at cross-clamping (OR 3.3, 95% CI 1.3 to 8.5) and ≥100% increase of the pulsatility index of the Doppler signal at clamp release (OR 7.1, 95% CI 1.4 to 35.7) were independently associated with stroke. The ROC area of this model was 0.69. Of the patient characteristics, only preoperative cerebral ischemia (OR 1.9, 95% CI 1.0 to 3.7) and ≥70% ipsilateral internal carotid artery stenosis (OR 0.5, 95% CI 0.2 to 0.9) were associated with stroke. Adding these patient characteristics to the model, the area under the ROC curve increased to 0.73.

Conclusions—In CEA, TCD-detected microemboli during dissection and wound closure, ≥90% MCA velocity decrease at cross-clamping, and ≥100% pulsatility index increase at clamp release are associated with operative stroke. In combination with the presence of preoperative cerebral symptoms and ≥70% ipsilateral internal carotid artery stenosis, these 4 TCD monitoring variables reasonably discriminate between patients with and without operative stroke. This supports the use of TCD as a potential intraoperative monitoring modality to alter the surgical technique by enhancing a decrease of the risk of stroke during or immediately after the operation. (Stroke. 2000;31:1817-1823.)

Key Words: carotid endarterectomy ■ monitoring, intraoperative ■ stroke ■ surgery ■ ultrasonography, Doppler, transcranial

The beneficial effects of carotid endarterectomy (CEA) in symptomatic and asymptomatic patients with high-grade carotid artery stenosis have been published in detail in 3 previous studies.1-3 However, the risk of carotid surgery must be set against its benefits, and unfortunately, the risks are not negligible. In all 3 studies, a small percent (3% to 5%) of the patients who underwent surgery had disabling or nondisabling strokes or died during or just after surgery. Therefore, the safety of the surgical procedure is of paramount importance, and it is essential to place emphasis on the prevention of neurological complications. Many techniques of quality control during CEA have been used to warn the surgeon of the possibility of an adverse outcome. Intraoperative transcranial Doppler (TCD) monitoring provides online surveillance of both hemodynamic changes and cerebral microembolism in the middle cerebral artery (MCA) on the side of surgery.4-9

We have previously reported on our separate experience with TCD monitoring and its usefulness with regard to microemboli detection in CEA.4,5 However, these studies were primarily designed to examine the suitability of intra-
operative TCD monitoring. Because there were low complication rates and because the clinical relevance of cerebral embolism during CEA still requires further foundation, we performed a pooled data analysis on 2 studies executed in Seattle, Wash, and Nieuwegein, the Netherlands, to increase the number of patients.

In the present study, we analyzed whether intraoperative cerebral embolism as detected by TCD during different stages of CEA was associated with the occurrence of operative stroke (ischemic and hemorrhagic) and stroke-related death within 7 days after surgery. Additionally, we evaluated the association of intraoperative TCD velocity variables with outcome. The identification of emboli and velocity variables as predictors of stroke by TCD monitoring may be useful in stratifying patients during surgery according to their risk of operative stroke and can help the surgeon to improve his or her technique.

**Subjects and Methods**

**Patients**
The present study is based on individual patient data pooled from the data sets of 2 former studies involving intraoperative TCD monitoring in CEA from 2 major institutes: Spencer Technologies, Seattle, Wash, and St. Antonius Hospital, Nieuwegein, the Netherlands. The methods of both studies are described elsewhere.6–9 In brief, the Dutch data concern the period from April 1990 until January 1996 and include 602 patients; the American data concern the period between October 1985 and July 1994 and include 456 patients. Only patients with reliable TCD monitoring throughout the entire operation entered the study. No patients who underwent endarterectomy of only the external carotid artery were included, and none had other concurrent surgical procedures. In patients who underwent a second CEA (ipsilaterally or contralaterally), only the first operation was analyzed in the present study. Special efforts were made to conform the definitions of all documented variables used in both countries.

**Carotid Endarterectomy**
In the vast majority of patients, the operation was performed by general anesthesia with the use of nitrous oxide and halothane or isoflurane. In the American study, in 20 cases, surgery was performed in conscious patients with local-regional anesthetic techniques. In both countries, surgery was executed by an experienced vascular surgeon or by a specialist vascular trainee, and there were no significant differences with respect to specific qualities in the performance of CEA. Before cross-clamping, an intravenous injection of heparin (5000 IU) was administered; protamine reversal was continuously recorded on video or digital audiotape. In each stage of the operation, microemboli were counted. The identification and counting of microemboli were performed without the use of automatic emboli detection software. On the basis of previous experience,6,11 the following TCD emboli and TCD velocity variables that were thought to be associated with adverse outcome were analyzed in the present study.

**TCD Emboli Variables**
Emboli occurred during (1) dissection (skin preparation to carotid clamping), (2) shunt manipulation (shunt introduction to removal of shunt), (3) clamp release (the first 10 seconds at restoration of flow through the carotid arteries), and (4) wound closure (termination of manipulation to the end of recording, ~30 minutes after final restoration of flow). In patients who were not shunted, emboli that occurred during clamping were considered absent. Additionally, a new variable of the number of stages or periods during which emboli occurred was evaluated. This number varied from 0 (no emboli detected) to 4 (emboli occurred during each of the above 4 stages or periods). The possible impact of microemboli during the postoperative stage on clinical outcome was not analyzed.

**TCD Velocity Variables**
TCD velocity variables were as follows: (1) decrease of peak systolic velocity (PSV) at cross-clamping, (2) increase of PSV, and (3) increase of the Gosling pulsatility index (PI) of the Doppler signal at declamping at the end of the endarterectomy. All 3 velocity variables were computed from the envelope of the Doppler spectrum by the TCD equipment and calculated as the proportional change compared with intraoperative preclamp values.

**Preoperative Patient Characteristics**
Age, sex, preoperative cerebral symptoms, and ipsilateral and contralateral internal carotid artery stenosis assessed by duplex ultrasonography and digital arteriography were also documented.

**Outcome**
In both centers, a complete hospital chart review was performed to obtain information about clinical outcome. In patients with possible postoperative cerebral deficit, a neurological consultation was executed by a neurologist. New cerebral deficits persisting for >24 hours were regarded as stroke. Operative stroke was defined per patient and not per operation. In the analyses, we focused on the prediction of ischemic and hemorrhagic stroke and stroke-related death within 7 days after surgery.

**Data Analysis**
First, within each country, the association between the occurrence of stroke and stroke-related death and each of all above-mentioned TCD variables and preoperative patient characteristics was quantified by use of univariable logistic regression analysis. The odds ratio (OR) and 95% CI were used as measures of association. A variable with a 95% CI that does not include the value 1 can be considered statistically significantly associated with a value of \( P < 0.05 \). If a test for homogeneity showed no major heterogeneity (\( P > 0.10 \)) of the associations, the ORs were pooled by use of the Mantel-Haenszel method. Continuous variables were initially included without categorization as long as a linear relation was plausible, but various cutoff values and transformations (eg, square root and log) were assessed as well.12 Age showed a linear relation with outcome, but the 3 TCD velocity variables did not. The latter were dichotomized at clinically relevant thresholds on the basis of previous results13 or marked differences in actual stroke incidence. Hence, decrease of PSV at cross-clamping was dichotomized at 90%, and increases of PSV and Gosling PI at clamp release were dichotomized at 100%.

Our aim was not to develop a prediction model primarily based on preoperative clinical and angiographic characteristics but to assess whether and which TCD emboli and velocity variables were associated with adverse outcome. Accordingly, we first estimated which
of the 4 TCD emboli variables was independently associated with outcome by use of multivariable logistic regression modeling. Because the aim of these analyses is the prediction of stroke, all variables contributing prognostic information should be included in the model. Therefore, as is common in prediction research, we defined an independent association if the OR had a value of \( P \leq 0.10\). Starting with a model including all 4 TCD emboli variables, the nonsignificant \( (P>0.10)\) ones were excluded. This model was extended with the univariate significant \( (P \leq 0.10)\) TCD velocity variables, and the same method of model reduction then was performed. Finally, this last model was extended with the documented preoperative patient characteristics that were significant in the univariate analyses to evaluate whether they additionally contributed to the TCD variables in the prediction of complications, resulting in the final model. Of each model, the ability to discriminate between patients with and without complications was estimated by using the area under the receiver operating characteristic (ROC) curve. The ROC area is a suitable parameter to summarize the predictive or discriminative ability of a model and can range from 0.5 (useless model, such as a coin flip) to 1.0 (perfect discrimination). A value \( >0.7\) can be interpreted as reasonable, and a value \( >0.8\) can be interpreted as good. Differences in discriminative value between models were estimated by differences in ROC area with 95% CI taking into account the correlation between the models because they were based on the same cases.

Of all 1058 cases, 108 had missing values on \( \geq 1 \) variable (but not on the outcome or TCD emboli variables). To decrease bias and increase statistical efficiency, these missing values were filled in (imputed) by using the expectation maximization method. Such imputation is based on the correlation between each variable with missing values and all other variables. These correlations were estimated from the 950 complete cases. The results of the analyses based on the complete subject data and on all subject data after imputation were compared. Because this yielded no different results (ie, the same independent predictors were selected with similar regression coefficients), only the latter (imputed) approach is presented.

### Results

Table 1 shows the distribution of patient characteristics, outcome, and the TCD emboli and velocity variables for both countries separately and in the pooled data set. In all stages of surgery, the number of microemboli assessed by TCD was higher in Seattle than in Nieuwegein. Differences across the countries were also present for the shunt ratio, proportional PSV and PI increase at clamp release, preoperative cerebral ischemia, and \( \geq 70\%\) ipsilateral internal carotid artery stenosis. However, the ORs for all variables with the outcome (stroke), except for sex \( (OR 2.7 \text{ and } 95\% \text{ CI } 0.6 \text{ to } 12.1 \text{ for the United States versus } OR 0.4 \text{ and } 95\% \text{ CI } 0.2 \text{ to } 0.8 \text{ for the Netherlands}), and \( \geq 70\%\) contralateral internal carotid artery stenosis \( (OR 0.4 \text{ and } 95\% \text{ CI } 0.1 \text{ to } 1.9 \text{ for the United States versus } OR 1.9 \text{ and } 95\% \text{ CI } 0.8 \text{ to } 4.3 \text{ for the Netherlands})\), were reasonably homogeneous between the 2 countries. In the pooled data set, in 39 (3.7%) of 1058 CEAs, surgery resulted in a stroke. Thirty-one patients developed an ischemic stroke, and 8 patients developed a hemorrhagic stroke. Four patients died from their strokes.

As shown in Table 2, only emboli during dissection \( (P=0.03)\) and wound closure \( (P=0.002)\) showed a statistically significant association with outcome. Emboli during shunting were also associated with outcome, although only...
borderline significance ($P=0.12$) was reached. We also analyzed the impact of the number of embolic periods per operation. Table 2 delineates that patients with no or only 1 embolic period per operation were less often suffering from stroke than those with $\geq 2$ embolic periods. After dichotomization, the TCD emboli variable $\geq 2$ embolic periods showed a significant association with stroke ($P=0.01$). All 3 TCD velocity variables also showed a statistically significant association with outcome. Of the preoperative patient characteristics, only preoperative cerebral ischemia (excluding amaurosis fugax [AFx]) was associated with an increased risk of stroke. For $\geq 70\%$ ipsilateral stenosis, the association was inverse. Age (whether analyzed as a continuous or as a dichotomous variable with a cutoff of 75 years), sex, and $\geq 70\%$ contralateral internal carotid artery stenosis were not statistically significant.

After including all 4 TCD emboli variables (dissection, clamp release, wound closure, and shunting) in a multivariable logistic regression model, emboli during dissection and wound closure were independently associated with outcome, whereas emboli during shunting (OR 1.2, 95% CI 0.6 to 2.5) and during clamp release (OR 0.9, 95% CI 0.4 to 1.7) were far from significant. The model including only emboli during dissection and wound closure is given in Table 3 (model 1). The ROC area of this model was 0.66. The association was weaker for emboli during dissection ($P=0.12$) than for emboli during wound closure ($P=0.007$). Inclusion of the number of embolic periods, as 4 indicator variables or dichotomized at a value of $\geq 2$ embolic periods, did not improve the model. After adding the 3 TCD velocity variables to model 1, $90\%$ decrease of PSV at cross-clamping ($P=0.02$) and $100\%$ PI increase at clamp release ($P=0.02$) as well as both embolic variables were associated with outcome (model 2, Table 3). However, emboli during dissection became less significant ($P=0.18$). The ROC area increased to 0.69. Subsequently, model 2 was extended with the 2 univariably significant preoperative patient characteristics. This resulted in an ROC area of 0.73 (model 3, Table 3). Of this latter model, all variables were associated with outcome; only emboli during dissection again became less significant ($P=0.20$).

We also performed the analyses without the 20 patients from the American study who underwent CEA with local-regional anesthesia. However, no differences in the results (ie, the same independent predictors with the same ORs) were found.
The present study evaluated which intraoperative TCD emboli and velocity variables were independently associated with operative stroke and stroke-related death from CEA. We found that microemboli that occurred during dissection and wound closure were associated with stroke, whereas microemboli that occurred at clamp release and during shunting were clinically irrelevant. These associations remained after taking into account the TCD velocity variables and various preoperative patient characteristics. Of the TCD velocity variables, ≥90% PSV decrease at cross-clamping and ≥100% PI increase at clamp release were associated with outcome, independent from the TCD emboli variables and preoperative patient characteristics. The independent patient characteristics were preoperative cerebral ischemia (excluding AFx) and ≥70% ipsilateral internal carotid artery stenosis. These results suggest that intraoperative TCD monitoring can be useful in providing an early warning of postoperative complications in patients undergoing CEA.

The results of the present study are consistent with the literature. Previous studies involving cerebral microembolism during CEA have shown that microemboli that occur at clamp release are predominantly gaseous and are not associated with the development of postoperative cerebral deficits.24 During shunting, microemboli are mostly a mixture of air and particulate and are sometimes associated with perioperative complications.4 On the contrary, microemboli that are noticed during dissection and wound closure are particulate and are associated with new mostly transient operative cerebral complications and psychometric deterioration.21,22 Moreover, Jansen et al23 demonstrated an association between multiple microembolism during dissection and new white matter lesions on MRI of the brain made after surgery. However, in the majority of these patients, the new MRI lesions were clinically silent. This finding demonstrates that during CEA the incidence of TCD-detected microemboli far exceeds the morbidity and mortality rates for the operation. However, this does not mean that these phenomena are not clinically important. Strokes that occur during the dissection stage of CEA were reported before the introduction of TCD monitoring, but this was previously thought to be due to the development of one large embolus. Although occlusion of the MCA mainstem by a macroembolus sometimes occurs,24 most research work involving intraoperative TCD monitoring in CEA suggests that multiple microembolization is the more likely mechanism. Microemboli that occur at the end of the operation are possibly a precursor of the well-known phenomenon of postoperative platelet aggregation and thrombus formation at the endarterectomy and clamping sites. This supports the hypothesis that multiple microembolization may result in sustaining postoperative embolization and occlusion.25–29 The latter could not be verified in the present study because postoperative TCD monitoring was not performed in the majority of our patients. The associations we have found between ≥90% PSV decrease at cross-clamping and ≥100% PI increase at clamp release with postoperative stroke are also supported by earlier evidence.6,13,30–32 In a multicenter study of CEA with intraoperative TCD monitoring, Halsey30 showed that severe persisting ischemia without shunting often results in an operative stroke. With respect to a postoperative hyperperfusion syndrome, Dalman et al13 demonstrated that TCD monitoring is a practical and sensitive method to identify intraoperatively the patients who are at risk for this serious postoperative complication. The association of ≥70% ipsilateral internal carotid artery stenosis with outcome was inverse, as described previously.33 Although this seems paradoxical, it can be explained from a hemodynamic point of view: cross-clamping of a severely stenosed artery will have less influence on cerebral blood flow than cross-clamping of an artery with a lesser degree of stenosis. It was not our intention to develop a prediction model primarily based on preoperative clinical and angiographic predictors of stroke from CEA, as described elsewhere.34–36 Nevertheless, we did evaluate such a model, including all available preop-

### Table 3. Results of Multivariable Logistic Regression Analyses

<table>
<thead>
<tr>
<th>Determinants</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>TCD emboli variables</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Emboli during dissection</td>
<td>1.7 (0.9–3.2)</td>
<td>1.6 (0.8–3.1)</td>
<td>1.5 (0.8–2.9)</td>
</tr>
<tr>
<td>Emboli during wound closure</td>
<td>2.5 (1.3–4.8)</td>
<td>2.3 (1.2–4.6)</td>
<td>2.3 (1.2–4.4)</td>
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<tr>
<td>TCD velocity variables</td>
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<tr>
<td>≥90% PSV decrease at cross-clamping, cm/s</td>
<td>⋯</td>
<td>3.0 (1.2–7.7)</td>
<td>3.3 (1.3–8.5)</td>
</tr>
<tr>
<td>≥100% PI increase at clamp release</td>
<td>⋯</td>
<td>6.0 (1.3–31.5)</td>
<td>7.1 (1.4–35.7)</td>
</tr>
<tr>
<td>Preoperative characteristics</td>
<td></td>
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<tr>
<td>Preoperative cerebral ischemia (~AFx)</td>
<td>⋯</td>
<td>⋯</td>
<td>1.9 (1.0–3.7)</td>
</tr>
<tr>
<td>≥70% ipsilateral stenosis</td>
<td>⋯</td>
<td>⋯</td>
<td>0.5 (0.2–0.9)</td>
</tr>
<tr>
<td>ROC area</td>
<td>0.66 (0.57–0.75)</td>
<td>0.69 (0.60–0.78)</td>
<td>0.73 (0.66–0.80)</td>
</tr>
</tbody>
</table>
erative patient characteristics. Again, only preoperative cerebellar ischemia (excluding AFx) and ≥70% ipsilateral internal carotid artery stenosis were associated with outcome with a ROC area of 0.67. Besides preoperative cerebellar symptoms, Rothwell et al\textsuperscript{34} also found age, female sex, hypertension, and peripheral vascular disease as predictors of stroke from CEA. In the present study, age was not associated with outcome. Female sex was very heterogeneously distributed over the 2 countries and could not be analyzed properly, whereas the other 2 variables were not available for our patients. Also, if we repeated the analysis of our data starting with the preoperative patient characteristics, the final model would be the same as model 3 presented in Table 3.

Given all available evidence, we believe that intraoperative TCD monitoring is useful for early detection of postoperative complications in patients undergoing CEA. If the Doppler signal is made audible in the operating theater, the acoustic feedback to the surgeon can assist in a more careful dissection of the artery and facilitate an early distal clamping of the internal carotid artery. Sustained embolization during wound closure is probably an indication of a residual luminal thrombus and impending postoperative occlusion. In these cases, quality control with intraoperative duplex\textsuperscript{37} and completion angiography\textsuperscript{38} can modify the surgical technique and reduce the number of cerebral complications. Although it can be argued that the majority of microemboli during shunting and clamp release are microbubbles and are clinically less important, one must not overlook the fact that lengthy showers of presumed gaseous emboli can contain particular emboli as well. Therefore, it is preferable to minimize embolization at times of shunt opening and flow restoration. With respect to hemodynamic causes of stroke from CEA, TCD monitoring is a very useful modality for the selective use of a shunt and a sensitive tool for the prediction of postoperative hyperperfusion. When a serious event happens despite all these precautions, the best medical treatment and clamp release are microbubbles and are clinically less important, one must not overlook the fact that lengthy showers of presumed gaseous emboli can contain particular emboli as well. Therefore, it is preferable to minimize embolization at times of shunt opening and flow restoration. With respect to hemodynamic causes of stroke from CEA, TCD monitoring is a very useful modality for the selective use of a shunt and a sensitive tool for the prediction of postoperative hyperperfusion. When a serious event happens despite all these precautions, the best medical treatment and hyperperfusion. When a serious event happens despite all these precautions, the best medical treatment and could not be analyzed properly, whereas the other 2 variables were not available for our patients. Also, if we repeated the analysis of our data starting with the preoperative patient characteristics, the final model would be the same as model 3 presented in Table 3.

To appreciate the present results, a few aspects need to be discussed. First, because we have performed a pooled data analysis over 2 countries, differences in definitions and, therefore, in distributions may have occurred. This was likely for emboli during dissection, clamp release, and shunting, as well as for PI increase at clamp release. This could have biased our findings, although the associations of the investigated factors were not heterogeneous across the countries. Moreover, in daily practice, similar differences between countries and medical institutions will be present, and risk estimates should be sufficiently robust to overcome any heterogeneity. Second, in contrast to other studies\textsuperscript{35–37} that evaluated the association of preoperative patient characteristics with stroke from CEA, we evaluated whether clinically relevant intraoperative TCD emboli and velocity variables were associated with outcome, taking into account some always available basic patient characteristics. Third, in both countries, the data are from the first years of carotid surgery with TCD monitoring; thus, the presence of a learning effect will be likely. Particularly with respect to emboli detection, surgeons developed, in the course of time, an understanding of and reliance on the TCD data.

In conclusion, we have determined that TCD-detected microembolism during dissection and especially during wound closure as well as ≥90% MCA velocity decrease at cross-clamping and ≥100% PI increase at clamp release were associated with operative stroke and stroke-related death from CEA. To our knowledge, the association with stroke has not been demonstrated before, certainly not by using a multivariable approach that takes into account some basic preoperative patient characteristics. We believe that TCD monitoring is most useful in providing an early warning of unpredictable phenomena. It should be used as a quality control assessment for early detection of microemboli and MCA velocity changes during surgery to modify the surgical technique. This would reduce the number of cerebral complications.

References


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