Time Period Required for Transcranial Doppler Monitoring of Embolic Signals to Predict Recurrent Risk of Embolic Transient Ischemic Attack and Stroke From Arterial Stenosis

Till Blaser, MD; Wenzel Glanz; Stephan Krueger, MD; Claus-Werner Wallesch, MD; Siegfried Kropf, PhD; Michael Goertler, MD

Background and Purpose—We aimed to investigate whether the time period of transcranial Doppler monitoring for embolic signals can be reduced without loss of clinical yield compared with routinely performed 1-hour monitoring.

Methods—Investigations on the basis of a post hoc analysis of a previously published cohort of 86 patients (55 men, 31 women; mean age 60.6 years) with a nondisabling arterioembolic ischemic event in the anterior circulation within the last 30 days (mean 7.3) and an ipsilateral medium-grade or high-grade stenosis of the carotid or middle cerebral artery. Patients underwent 1-hour monitoring for embolic signals and were followed up prospectively for 6 weeks to evaluate the relationship between embolic signals and risk of an early ischemic recurrence. Risk was also calculated after fictitious reduction of the monitoring period from 60 minutes to 50, 40, 30, 20, and 10 minutes, respectively, and compared with the results obtained from the 1-hour period.

Results—The number of patients positive for embolic signals decreased with the decreasing monitoring period. By this, the odds ratio of embolic signals for an early ischemic recurrence “decreased” from 40 (derived from the 1-hour monitoring) to 10 when the monitoring lasted ≤30 minutes. The relationship between the rate of embolic signals per hour and risk of a recurrent stroke is described by an S-shaped curve. As a consequence, risk estimated from reduced monitoring periods can differ considerably from that derived from the 1-hour monitoring if the signal frequency lies within a medium range (eg, between 3 and 15 signals in 30 minutes).

Conclusions—The time period of monitoring for embolic signals may be reduced without loss of clinical relevant information when signal frequency is low or already high during the reduced monitoring period, but it should be prolonged to maximally an hour at signal numbers within a medium range. However, our results need to be externally validated on an independent cohort of patients or confirmed by a prospective study before this modification can be recommended in general. (Stroke. 2004;34:2155-2159.)

Key Words: carotid stenosis ▪ cerebral embolism ▪ stroke, ischemic ▪ ultrasonography, Doppler, transcranial
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For the purpose of this study, the time period of the 1-hour monitoring that preceded the follow-up period was fictitiously reduced from 60 minutes to 50, 40, 30, 20, and 10 minutes, respectively. Embolic signals that had appeared between the start of the monitoring and the end of a period were counted for that period. Periods with ≥1 signal were considered embolic signal positive. The risk of a recurrent stroke or TIA in relation to the presence or absence of embolic signals was analyzed by Cox regression for each of the 5 fictitious monitoring periods and compared with that calculated from the 1-hour monitoring. Covariates were expected to be associated with recurrent TIA and stroke and included in the analysis of the 1-hour period. The estimated probability $S(t)$ to be event free up to time $t$ can be calculated by means of Cox regression analysis according to the equation: $S(t) = \exp[-H_d(t) \exp(P_I)]$, where $H_d(t)$ is the baseline-integrated hazard at time $t$ and $P_I$ is prognostic index. The estimated probability to be event free up to time $t$ (ie, at 6 weeks) were calculated. Because measured and calculated 1-hour frequency may differ in an individual patient, calculated probabilities for the absence of a recurrent event will also differ in this patient. This difference was plotted against the number of embolic signals counted during the reduced monitoring period. Therefore, a single plot shows the deviation in the estimated stroke risk for each patient that occurred as a consequence of the reduced monitoring period in relation to counted embolic signals within this reduced monitoring period. Five of these plots were created, 1 for each reduced period. For statistical analysis, we used SPSS version 10.0, with significance set at $P<0.05$.

Results

The number of patients in whom embolic signals ipsilateral to the symptomatic stenosis could be detected decreased along with the decreasing monitoring period (Table 1). This also applied to the 7 patients with recurrent TIA or stroke during follow-up, of whom 4 were negative for embolic signals at the shortest monitoring time (10 minutes) in contrast to only 1 patient at the 1-hour monitoring. As a consequence, the adjusted odds ratio of the presence of embolic signals (without consideration of their number) for a recurrent ischemic event was 10 at monitoring periods lasting ≤30 minutes, in contrast to 40, when the presence or absence of embolic signals was assessed by 1-hour monitoring (Table 1).

Table 2 shows results of Cox regression analysis when signal presence/absence at 1-hour monitoring was replaced by the 1-hour signal frequency. On the basis of the coefficients derived from this Cox regression analysis, the risk of a subsequent embolic ischemic event within 6 weeks (ie, $1 - S(t)$, with $t = 42$ days; see above) was calculated in relation to the number of embolic signals detected at the 1-hour monitoring. Calculation revealed a relationship that is described by an S-shaped curve (Figure 1). An alteration of the signal frequency within a range from 10 to 25 signals per hour was associated with a remarkable risk increase/decrease per signal of 5%. In contrast, risk was only slightly or not influenced when the frequency of embolic signals altered within the range of 0 to 5 or >30 per hour, respectively. When the monitoring period was reduced stepwise and the 1-hour frequency was subsequently calculated (instead of measured), the following calculation of the estimated risk of a subsequent ischemic event (according to the above-mentioned equation)
revealed substantial differences for numerous patients compared with the risk derived from the 1-hour measurement. For each of the 5 reduced monitoring periods, these differences were plotted against the number of embolic signals detected in the corresponding monitoring period (Figure 2). Plots suggest for each of the reduced periods a medium range of frequencies associated with a considerable deviation that is maximal for the shortest monitoring period and decreases with prolongation of the monitoring.

**Discussion**

Our study demonstrates that in patients with recently symptomatic arterial stenosis, the combination of the length of the monitoring period and the number of embolic signals counted within this period has major impact on the reliability of estimated recurrent ischemic risk derived from presence and frequency of embolic signals.

Varying monitoring periods may be responsible primarily for the diverging odds of the presence of embolic signals on an early ischemic recurrence. In patients with recent cerebral ischemia and a corresponding arterial embolic source, Valton et al described a 10-fold higher risk for an early recurrent ischemic event if embolic signals were detected during a 20-minute transcranial Doppler monitoring. In the cohort of our patients with recently symptomatic carotid or middle cerebral artery stenosis and 1-hour transcranial Doppler monitoring, former evaluation has found an even 40-fold higher risk of an early ischemic recurrence in the presence of embolic signals when compared with patients without detectable signals. The higher risk in our patients might be explained by the smaller time window since the index event, the noninclusion of patients with arterial lesions at other localizations than carotid or middle cerebral artery, and that we used an alteration of the antithrombotic medication since the last monitoring as an end point of follow-up. However, the present investigation on the same cohort of patients suggests that this difference also might be caused solely by the different monitoring periods. Shortening of the monitoring period from 60 to 20 minutes in our patients resulted in a pseudoreduction of risk in patients positive for embolic signals from 40-fold to 10-fold of that in patients without detectable embolic signals. Although the largest “decline” of risk was between 50 and 40 minutes, conclusions about the relationship between shortening of the monitoring period and “reduction” of risk cannot be drawn reliably on the basis of our data. For that, the number of patients investigated and the number of outcome events were too low, resulting in rather wide CIs. However, it seems obvious that with shorter monitoring periods, a larger number of patients is classified as negative for embolic signals compared with the 1-hour assessment. This might lead to an ignorance of an increased ischemic risk in these patients if the risk is predicted solely on the basis of presence or absence of embolic signals.

**TABLE 1. Effect of the Time Period of Transcranial Doppler Monitoring on the No. of Patients Positive for Embolic Signals, No. of Recurrent Ischemic Events in “Positive” and “Negative” Patients, and Adjusted Odds Ratio for a Recurrent Ischemic Event in the Presence of ESs From Cox Regressions**

<table>
<thead>
<tr>
<th>Time Period of TCD Monitoring</th>
<th>ES-Negative Patients</th>
<th>ES-Positive Patients</th>
<th>Recurrent Ischemic Events in ES-Negative Patients</th>
<th>Recurrent Ischemic Events in ES-Positive Patients</th>
<th>OR 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 minutes</td>
<td>61</td>
<td>25</td>
<td>1</td>
<td>6</td>
<td>37.037</td>
<td>3.534–333.448</td>
</tr>
<tr>
<td>50 minutes</td>
<td>61</td>
<td>25</td>
<td>1</td>
<td>6</td>
<td>37.037</td>
<td>3.534–333.448</td>
</tr>
<tr>
<td>40 minutes</td>
<td>63</td>
<td>23</td>
<td>2</td>
<td>5</td>
<td>13.587</td>
<td>2.200–83.905</td>
</tr>
<tr>
<td>30 minutes</td>
<td>64</td>
<td>22</td>
<td>3</td>
<td>4</td>
<td>10.846</td>
<td>1.779–66.109</td>
</tr>
<tr>
<td>20 minutes</td>
<td>64</td>
<td>22</td>
<td>3</td>
<td>4</td>
<td>10.846</td>
<td>1.779–66.109</td>
</tr>
<tr>
<td>10 minutes</td>
<td>70</td>
<td>16</td>
<td>4</td>
<td>3</td>
<td>8.838</td>
<td>1.290–60.534</td>
</tr>
</tbody>
</table>

These regressions include presence of embolic signals (ESs), age, type of initial event (persistent vs transient), multiple initial events, time since the initial event, and degree and localization (extracranial vs intracranial) of the stenosis.

Only the odds ratio (OR) of the presence vs absence of ESs is presented from each of the 6 regression analyses.

**TABLE 2. Interaction Between Risk Factors and Early Recurrent TIA or Stroke in 86 Patients With Recently Symptomatic Arterial Stenosis**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>b</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.010</td>
<td>1.010</td>
<td>0.933–1.094</td>
<td>0.800</td>
</tr>
<tr>
<td>Time since initial ischemic event (days)</td>
<td>−0.200</td>
<td>0.818</td>
<td>0.613–1.093</td>
<td>0.175</td>
</tr>
<tr>
<td>Stroke as initial ischemic event</td>
<td>−1.037</td>
<td>0.354</td>
<td>0.047–2.691</td>
<td>0.316</td>
</tr>
<tr>
<td>Recurrent initial ischemic event</td>
<td>0.134</td>
<td>1.143</td>
<td>0.158–8.254</td>
<td>0.894</td>
</tr>
<tr>
<td>Extracranial (nonintracranial) stenosis</td>
<td>0.697</td>
<td>2.008</td>
<td>0.199–20.300</td>
<td>0.555</td>
</tr>
<tr>
<td>High-grade (nonmedium grade) stenosis</td>
<td>0.503</td>
<td>1.654</td>
<td>0.236–11.580</td>
<td>0.612</td>
</tr>
<tr>
<td>ESs during 1-hour monitoring (number)</td>
<td>0.177</td>
<td>1.194</td>
<td>1.052–3.355</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Regression coefficient (b) and odds ratio (OR) derived from Cox regression analysis.
Recommendation for 1-hour monitoring is derived from long-term monitoring periods that had demonstrated only very few gaps without embolic signals lasting ≥1 hour in patients in whom signals could be detected at all. Nevertheless, depending on a patient’s individual signal frequency and signal variability over time, embolic signals might be detected only after prolonged or repetitive monitoring. In contrast, studies on acute stroke patients suggest that even 1-hour monitoring may neither be tolerated by a substantial number of patients nor be applicable in the setting of acute stroke management. However, with respect to a patient’s ischemic risk, less the presence of embolic signals in general (especially as a single signal), their specific relevance at distinct constellations seems to be clinically important. In our patients with recent embolic TIA or stroke caused by carotid or middle cerebral artery stenosis, detection of a single or even several embolic signals at 1-hour monitoring was not associated with a relevant risk increase for an early ischemic recurrence. Prolonged monitoring for embolic signals may not be necessary in this situation. Moreover, because of the S-shaped relationship between the 1-hour frequency of embolic signals and the predicted risk of a subsequent ischemic event, risk may be estimated without clinically relevant deviation by means of reduced monitoring periods if a single or several embolic signals occur during these periods (eg, ≤2 signals within 20 minutes or ≤3 signals within 30 minutes). This also may hold true for already high numbers of signals at reduced monitoring periods (eg, ≥10 signals within 20 minutes or ≥15 signals within 30 minutes). Stroke risk predicted from embolic signals was already maximal at 30 signals per hour without further increase at increasing signal frequency.

It should be emphasized that our findings must not be transferred to situations other than recently symptomatic arterial stenosis. In patients with asymptomatic stenoses, the rate of embolic signals is much lower, and a relationship between the occurrence of signals and the risk of a subsequent ischemic event has not been evaluated yet. In contrast to symptomatic patients, a considerable number of patients with asymptomatic stenosis may be without an antithrombotic medication during monitoring as well as follow-up. This also holds true for patients with a potential cardiac source of embolism, in whom the variability of embolic signals over time is also considerably high compared with that in patients with an arterial stenosis.
But also in patients with recently symptomatic carotid or middle cerebral artery stenosis, the encouraging results of our study must be interpreted with caution. If tolerance for and applicability of 1-hour transcranial Doppler monitoring for embolic signals is limited, monitoring may be stopped after 20 to 30 minutes without loss of clinically relevant information if no more than $\sim 2$ signals in 20 minutes or 3 signals in 30 minutes have been detected or if their number already exceeds $\sim 10$ signals in 20 minutes or 15 signals in 30 minutes. Otherwise, patients should be encouraged to tolerate ongoing monitoring for a maximum of 1 hour. However, this cannot be recommended in general until our results (assessed by post hoc analysis of data from a previously published cohort of patients) have been externally validated on an independent cohort of patients or confirmed by a larger prospective study.

**Acknowledgments**

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**References**


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