Rapid Decline of Cerebral Microemboli of Arterial Origin After Intravenous Acetylsalicylic Acid

Michael Goertler, MD; Matthias Baeumer, MD; Regina Kross, MD; Till Blaser, MD; Gerd Lutze, MD; Stefan Jost, MD; Claus-Werner Wallesch, MD

Background and Purpose—The present study investigated the influence of the antiplatelet agent acetylsalicylic acid (ASA) on cerebral microembolism as detected by transcranial Doppler sonography (TCD).

Methods—Nine patients with recent transient ischemic attack or minor stroke of arterial origin were investigated. Eight had not received an antiplatelet or anticoagulant medication before TCD, and in 1 patient a preexisting ASA medication (100 mg/d) had not been changed since the onset of stroke symptoms. An initial 1-hour TCD monitoring was extended for an additional 2.5 hours after an intravenous bolus injection of 500 mg ASA and was repeated for 1 hour on the following day.

Results—Microembolic signals (MES) were detected in all patients only on the symptomatic side. After the ASA bolus injection, a significant drop of the MES rate was found in 7 patients, all without previous medication, starting 30 minutes after the application (mean per hour=25.1 [range, 6 to 66] versus mean per hour=6.4 [range, 0 to 14]). In 3 of these patients, platelet aggregation tests were performed that demonstrated normal aggregation before bolus injection and inhibited aggregability as early as 30 minutes after bolus injection. The rate of MES remained unchanged in 1 patient without antiplatelet medication. The ninth patient, who had suffered an ischemic event on ASA, showed only a transient decrease of MES frequency.

Conclusions—In patients with recent stroke of arterial origin, intravenous ASA can rapidly reduce cerebral microemboli as detected by TCD. Microemboli might be a useful parameter to monitor early effects of antiplatelet therapy. (Stroke. 1999;30:66-69.)

Key Words: antiplatelet agents • carotid artery stenosis • cerebral embolism • stroke • ultrasonography, Doppler
Oral and extent of absorption, especially with respect to potential ASA (Aspisol, Bayer AG) was injected into an antecubital vein. Intravenous performed for 3.5 hours. After the initial 1 hour, a bolus of 500 mg ASA administration (300 mg/d) was started the day after the bolus injection, and MES recording (1 hour) was repeated within 2 days of the administration of ASA (end of initial 1-hour recording) and again 30 minutes after ASA injection. Platelet-rich and platelet-poor plasma were obtained from blood samples (9 mL, anticoagulated with 1 mL trisodium citrate solution, 0.105 mmol/L) by differential centrifugation. Platelet concentration in platelet-rich plasma was adjusted with platelet-poor plasma to 3 × 10^11/L. Aggregation in stirred platelet-rich plasma was induced by bovine collagen (Impfstoffwerke Dessau), and the response, measured optically by increasing light transmission, was recorded for 7 minutes (PAP-4C aggregometer, Bio Data Corp, Wellcome Laboratories). Maximal intensity and maximal slope of the aggregation were assessed and compared with corresponding laboratory references from control subjects (lower limit of intensity, 75%; lower limit of slope, 33).

Statistical analysis was performed with the use of SPSS software, version 6.1.3. For each patient, polynomial curves were fit to the scatterplots of (cumulative) MES counts and the time of events to evaluate the best regression model. Curves were fit separately for the preinjection and postinjection periods. For group analysis, the continuous 3.5-hour monitoring was divided into three 1-hour periods (−60 to 0, 30 to 90, 90 to 150 minutes; time was measured relative to ASA injection at 0 minutes). Frequency of MES in these periods and in the additional 1-hour recording 1 to 2 days after the bolus injection were compared by nonparametric tests for related samples (Friedman 2-way ANOVA, Wilcoxon matched-pair signed rank test). The relative decrease of MES after ASA compared with the corresponding baseline measurement was analyzed by t tests for paired samples. A P value of <0.05 was considered significant.

Results

During a cumulative monitoring time of 40.5 hours, a total of 521 MES ipsilateral to the symptomatic stenoses were detected. No signals were observed in contralateral MCAs. For the 1-hour preinjection periods, scatterplots of the cumulative MES count and the time of MES appearance were best fit by linear regression models, indicating a constant incidence of MES over time (Figure 2). In 7 patients, the frequency of MES decreased after the application of ASA (patients 1 to 7) (Table). Two of them, who had presented 6 and 18 MES/h before medication, showed no additional signal during continuous 2.5-hour postinjection monitoring. In 5 patients (initial MES rates 13 to 66/h), the incidence started to decrease ~30 minutes after intravenous ASA, indicated by a declining slope of the regression curve (Figure 2, patient 2). In 1 patient, MES frequency did not respond to ASA (Table and Figure 2, patient 8). In the 1 patient who at stroke onset received a preexisting ASA medication of 100 mg/d since former cardiac bypass surgery, only a minor and transient effect could be demonstrated (Table and Figure 2, patient 9). MES frequencies for each of the 9 patients, as well as mean values of those who showed a decrease after ASA, are presented in the Table. In patients who responded to ASA (patients 1 to 7), the mean MES rate continuously decreased after ASA and was significantly lower than before the 500-mg bolus injection; this was already observed in the 1-hour monitoring period starting 30 minutes after ASA. In 3 of the 7 patients with decreasing MES frequency after ASA,
blood samples were drawn for platelet aggregation tests immediately before and 30 minutes after ASA injection. Samples of these patients exhibited normal collagen-induced platelet aggregation before and inhibited aggregability after ASA application (intensity and slope below the lower limit of normal range).

**Discussion**

There is strong evidence that MES detected in our patients correspond to cerebral microemboli of arterial origin. Embolic signals were only observed in the territory of the symptomatic arterial stenosis, which itself was the only pathological finding detected as a potential source of cerebral microemboli during clinical workup. Criteria for identification of MES and differentiation from artifacts were recently summarized in a consensus statement on cerebral microembolism. Of particular concern was the evaluation of a threshold value between MES and artifacts for the dual-gated time lag of signal appearance, since axial gate distances of <10 mm and insonation angels of ≥20 degrees (due to the individual course of the MCA and distal placement of sample volumes in case of MCA stenosis) were necessary in a substantial number of our patients.13,17

The homogeneous, rapid decline of MES in 7 of our patients may be considered exclusively induced by ASA independently of other potential causes. Clinical setting and technical parameters remained constant during the examinations, which in the 3.5-hour monitoring periods, after the 500-mg bolus injection of ASA, revealed a decline of the mean MES rate in these patients to 12.9% of the preinjection count. A causative relation is also suggested by the strong temporal correspondence between initiation of MES decrease and inhibited platelet aggregation as early as 30 minutes after ASA injection. Because they are undetermined and of minor extent, spontaneous temporal variations of MES frequency in prolonged18 or recurrent19 monitoring periods may be considered irrelevant.

With respect to the known rapid effect of ASA on platelet inhibition and the rapid decline of MES observed in 7 patients after ASA, one might assume that MES in these cases mainly corresponded to platelet-rich emboli. However, until now the discrimination of particulate embolic material on the basis of a given Doppler signal has not been possible. Therefore, the lack of effect or only minor effect of ASA on MES frequency in 2 other patients has not necessarily been caused by a lack of response of platelet aggregation to ASA. In particular, because platelet aggregability was not investigated in these 2 patients, arterial emboli composed of atheromatous debris, fat, or coagulated erythrocytes, which are not expected to be influenced by antiplatelet agents, must be considered alternative causes.

Comparable experience regarding the effect of medical therapy on MES is limited. Follow-up examinations in a patient with symptomatic 70% carotid artery stenosis failed to show a relation between signal count and intensity of anticoagulation.20

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Scatterplots of cumulative counts of MES and time of appearance, measured relative to an intravenous ASA injection of 500 mg at 0 minutes. Patients 2 and 8 had not been treated with ASA before the monitoring; patient 9 had received 100 mg/d. Linear regression curves assessed from the preinjection periods are shown. Incidence of MES decreased ∼30 minutes after ASA injection in patient 2, whereas the other patients showed no response (patient 8) or only transient response (patient 9).

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>No. (%) of MES per 1-h Period</th>
<th>Cerebrovascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 min Before ASA 30 min After ASA 90 min After ASA 1–2 d After ASA</td>
<td>Within 1 mo Before ASA Within 3 mo After ASA</td>
</tr>
<tr>
<td>1</td>
<td>6 (100) 0 (0) 0 (0) 0 (0) 3 0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>23 (100) 10 (44) 4 (18) 2 (9) 2 0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>32 (100) 14 (43) 7 (22) 4 (13) 5 0*</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>66 (100) 11 (17) 8 (12) 8 (12) 1 0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>13 (100) 5 (38) 5 (38) 0 (0) 2 0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>18 (100) 5 (28) 0 (0) 0 (0) 1 0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>18 (100) 0 (0) 0 (0) 0 (0) 2 0</td>
<td></td>
</tr>
<tr>
<td>Mean pts 1–7</td>
<td>25.1 (100) 6.4 (24.3) 3.4 (12.9) 2.0 (4.9) 2.3 0</td>
<td>3 0†</td>
</tr>
<tr>
<td>8</td>
<td>8 (100) 9 (113) 8 (100) 6 (75) 3 0†</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>58 (100) 32 (55) 57 (98) 52 (89) 3 0†</td>
<td></td>
</tr>
</tbody>
</table>

In patients (Pts) 1 to 7, MES frequency decreased after ASA; in patients 8 and 9, there was no response or only a transient response.

*Carotid endarterectomy 3 days after TCD monitoring.
†Ticlopidine medication 4 days after TCD monitoring.
In a patient presenting with recurrent amaurosis fugax despite anticoagulation with warfarin (international normalized ratio, 2.4), MES were detected in repeated monitoring periods, probably caused by embolism from carotid artery plaque. After ASA (300 mg/d) was started, amaurosis fugax events and MES stopped within 24 hours. In 2 patients with symptomatic intracranial stenoses receiving intravenous heparin (activated partial thromboplastin time >2-fold that of baseline level), high MES rates dropped to ≈20% of the baseline count 6 hours after an intravenous bolus of 800 mg ASA. In contrast, embolic signals detected in symptomatic patients with atrial fibrillation were abolished by anticoagulation and reappeared after discontinuation of medication in a reported single case. No drug effect on the frequency of MES was observed in patients with prosthetic cardiac valves, who were symptomatic despite sufficient anticoagulation by warfarin and additional heparin or intravenous ASA.

In patients with prosthetic valves, MES might be caused, at least to some extent, by gaseous emboli that cannot be discerned from solid particles and cannot be expected to respond to antithrombotic treatment. In other conditions, the detection of MES as a parameter for cerebral emboli could be useful to monitor early effects of anticoagulants and antiplatelet agents. This might enable determination of appropriate individual medication, eg, by early diagnosis of an insufficient response of cerebral embolism to an antiplatelet agent, as presumed in 2 of our patients, as well as appropriate antithrombotic medication in patients with different sources of cerebral embolism.

In the 7 patients in whom MES frequency responded to ASA, no ischemic event was observed within a 90-day follow-up after the initiation of ASA prevention compared with 2.3 events in the month before. However, therapeutic regimens were inhomogeneous (additional endarterectomy was performed in 1 patient), and the number of investigated patients is far too small to draw conclusions about an association of MES and cerebral ischemia on the basis of our data. Nevertheless, further evaluation of a correspondence of TCD-detected microemboli with future ischemic events, as suggested recently, might enable new insights in pathophysiology and prevention of cerebral ischemia.

In summary, in patients with recent stroke from large-arterial-vessel disease, intravenous ASA can rapidly reduce cerebral microemboli of arterial origin, as detected by TCD. The onset of or change in an ASA medication should be considered when a potential correlation between the incidence and frequency of TCD-detected microemboli and the risk of future ischemic events is investigated.

Acknowledgments

We thank Jane Heisinger for technical assistance.

References

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Stroke. 1999;30:66-69
doi: 10.1161/01.STR.30.1.66

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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