Microembolic Signal Monitoring after Coiling of Unruptured Cerebral Aneurysms: An Observational Analysis of 123 Cases

BACKGROUND AND PURPOSE: Thromboembolic events after aneurysm coiling are common, but the optimal algorithm for embolism prevention remains unclear. MESs correlate with the occurrence of impending ischemic events and may be used for management guidance. This study reports the use of MES monitoring with regard to aneurysm characteristics and coiling technique after a specific anticoagulation protocol.

MATERIALS AND METHODS: We analyzed 123 consecutive, elective endovascular procedures. Patients received intraprocedural and continuous heparin if feasible. Demographic data, aneurysm size, type of intervention/complication, medication, imaging, and clinical outcome were analyzed. MES monitoring was performed in all patients both immediately after as well as >12 hours after the procedure.

RESULTS: Heparinization within the first 12 hours was associated with lower numbers of MESs early after coiling (3.4 versus 18.8 MESs/hr). When on heparin, larger aneurysm size, stent-assisted procedures, or incomplete occlusion did not lead to a significant increase in MESs. If the initial MES count on heparin was >10 MESs/hr, it was always safe to discontinue heparin. Inability to initiate early, continuous heparinization was associated with new neurologic deficits. Additional administration of antiplatelet agents showed lower MES counts initially, but the difference was not significant.

CONCLUSIONS: MES monitoring is a powerful adjunct to monitor efficacy of treatment algorithms for embolism prevention after coiling. In our series, early heparinization was associated with a lower incidence of MESs. This is of particular importance in larger aneurysms, stent-assisted procedures, and incomplete occlusions, in which the thromboembolic risk is greatest early on and antiplatelet treatment alone may not suffice.

Received October 11, 2010; accepted after revision December 16.

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http://dx.doi.org/10.3174/ajnr.A2507

ABBREVIATIONS: ACA = anterior cerebral artery; ACT = activated clotting time; BA/VA = basilar/vertebral artery; ICA = internal carotid artery; MCA = middle cerebral artery; MES = microembolic signal; PcomA = posterior communicating artery; TCD = transcranial Doppler; TEE = thromboembolic event.
ated and established as a useful adjunct during and after open carotid endarterectomy and aneurysm surgery,\textsuperscript{11} as well as after cardiac valve replacements.\textsuperscript{12} The presence and frequency of MESs have contributed to the management of stroke patients and have been established as useful predictors for the occurrence of future strokes for both symptomatic and asymptomatic carotid stenosis,\textsuperscript{13,14} but they also have been used to monitor treatment efficacy, i.e., the administration of aspirin or other antiplatelet agents.\textsuperscript{11,15}

Only limited data are available regarding the use of MES monitoring after coiling procedures, but such monitoring was found to be positive in up to 31\% of cases in a smaller series.\textsuperscript{16} The exact role of MESs, however, and the correlation between MESs and aneurysm characteristics, coiling technique (with and without stent), result (grade of occlusion), and anticoagulation disorders are not well defined.

This retrospective analysis aims to illustrate the use of MES monitoring after embolization of unruptured cerebral aneurysms when following a standardized anticoagulation protocol. The purpose of this analysis is to prove the validity and safety of our treatment concept as well as to illustrate the effect of aneurysm characteristics and coiling technique on emboli monitoring.

Materials and Methods

For this study, we reviewed all coiling procedures from May 2007 until June 2010 ($n = 244$) that were performed at our institution by J.E. To maximize the homogeneity of our study group, we excluded all patients with evidence of recent hemorrhage and previously treated patients with evidence of recanalization, pseudoaneurysm, or significant comorbidities such as fibromuscular dysplasia or profound coagulation disorders. Of the remaining $128$ patients, $5$ patients were excluded due to the absence of adequate cranial windows for emboli monitoring ($3.9\%$).

Since its implementation at our institution in 2007, the electronic patient record allows complete and retrospective analysis of all pertinent patient data in an anonymous manner, including $1$ patient demographics (sex, age at time of intervention); $2$ aneurysm, including location, size ($<10 \text{ mm}$, $\geq 10 \text{ mm}$), technique of embolization (coiling with and without stent), degree of occlusion achieved (complete; near complete, $>90\%$; incomplete, $<90\%$), and intra procedural complications (permanent coil protrusion, rupture, distal/adjacent stenosis/occlusion/thrombosis, device-related/fracture, need for access site revision); $3$ medications administered throughout hospitalization (including heparin, aspirin, and clopidogrel); and $4$ diagnostic tests performed during hospitalization and on follow-up (MES count on TCD, CT postoperatively, and at time of follow-up; neurologic assessment on admission, at time of discharge, and upon follow-up).

Our periprocedural treatment protocol was observed in all patients. Previous medications, including antiplatelet agents, were continued; only warfarin (Coumadin) was stopped in time to allow for normalization of international normalized ratio. Patients may have received additional doses of clopidogrel either before or immediately after the procedure upon the surgeon’s discretion ($n = 95$). All patients were given an initial heparin bolus of $7000–10000$ international units according to body weight upon completion of the preceding, diagnostic arteriogram. ACT was determined 5 minutes after bolus injection; additional boluses were given as needed to maintain an ACT $>300$ throughout the procedure. All procedures were completed under general anesthesia, after which a heparin drip was started. The drip was adapted to achieve a goal partial thromboplastin time of $60–90$ seconds. A CT scan was obtained $4–6$ hours after the procedure, after which the first MES monitoring (MES-1) was performed.

Emboli monitoring in the Transcranial Power M-mode transcranial Doppler system (PMD 100 or ST3; Spencer Technologies, Seattle, Washington) used a $2$-MHz digital Doppler with $33$ sample gates arranged in an M-mode display with Doppler signal intensity power color-coded for flow directionality. The sonography beam was aligned along the vessel axis showing blood flow from multiple depths and vessels at the same time.\textsuperscript{17} Microemboli were visible moving through the M-mode display as high intensity, slanting tracks and were frequently seen simultaneously in the spectral waveform from a single user-selected depth. All examinations were performed by registered vascular sonographers specializing in neurovascular sonography, using a head frame to stabilize the Doppler transducer (Marc 600 Headframe; Spencer Technologies). The examination was focused on the arterial segment distal to the coiled aneurysm and was performed continuously for at least $20$ minutes.

If the MES-1 showed $<10$ MESs/hr, heparin was discontinued at $6$ AM the following morning, and the MES-2 monitoring was performed no sooner than $4$ hours after discontinuation of the drip to allow for adequate wear-off according to the half-life of heparin. If the first scan showed $>9$ MESs/hr, heparin was continued until the next monitoring, and the decision for discontinuation was based upon the MES count of the second scan on heparin. If the MES count had decreased, heparinization was stopped and the MESs repeated to verify absence of persistent emboli. All patients were discharged home on either $1$ or $2$ antiplatelet agents (aspirin, clopidogrel, or both) that either had been continued from preoperatively or had been started the day of the procedure.

Statistics

Values are presented as means ± SDs. Student $t$ test for quantitative and Fisher exact test for qualitative, dichotomized parameters were used as indicated, with the $P$ value for significance being set at $<.05$ (significant), $<.01$ (highly significant), and $<.001$ (extremely significant), respectively.

Results

In total, $123$ consecutive cases were included for analysis ($72\%$ women, $28\%$ men; mean age, $57.7 \pm 11.9$ years). Table 1 illustrates location, size, and percentage of stent placement for all aneurysms treated. All patients were adequately heparinized during the procedure.

Intraprocedural complications were noted in $11$ patients ($8.9\%$). We observed a trend toward a higher overall compli-

| Table 1: More than 50\% of aneurysms were originating from the ICA, followed by ACA, MCA, and BA/VA |  |
|---|---|---|---|
| Aneurysm Location | $n$ (%) | Aneurysm Diameter ± SD (mm) | Stent (%) |
| All | 123 (100) | 6.58 ± 3.7 | 26.8 |
| ICA | 62 (50.4) | 6.91 ± 4.35 | 41.9 |
| ACA | 22 (17.9) | 4.93 ± 1.70 | 0 |
| MCA | 14 (11.4) | 5.21 ± 1.27 | 0 |
| PcomA | 11 (8.9) | 8.58 ± 4.36 | 18.2 |
| BA/VA | 14 (11.4) | 7.48 ± 3.02 | 35.7 |

Note:—Less than 10\% of aneurysms originated from PcomA. Average diameter was 6.58 mm, and 26.8\% of aneurysms required concomitant stent placement.
Table 2: Incidence of MES on MES-1 and MES-2 scans is listed according to the following variables: modality of treatment, heparin, clopidogrel, heparin ± clopidogrel, extent of occlusion ± heparin, and size of aneurysm ± heparin

| Variable | MES-1 Scan | | MES-2 Scan | | New Infarct | | New Symptom at Discharge |
|---|---|---|---|---|---|---|---|
| | n (% of Total) | MES (Mean (SD)) | t Test | n (% of Total) | MES (Mean (SD)) | t Test | n (% of Group) | n (% of Group) |
| Total | 123 (100) | 3.9 (12.4) | | 123 (100) | 0.8 (2.8) | | 2 (1.6) | 1 (0.8) |
| With stent | 33 (26.8) | 6.8 (18.2) | | 33 (26.8) | 1.6 (4.4) | | 2 (6.1) | 1 (3.0) |
| Heparin | 103 (91.2%) | 3.4 (10.9) | | 10 (8.1) | 6.7 (2.2) | | 1 (0.9) | 0 (0) |
| On heparin | 119 (96.7) | 3.4 (10.9) | P < .05 | 113 (91.9) | 0.4 (1.3) | | 1 (25) | 1 (25) |
| Off heparin | 4 (3.3) | 18.8 (35.5) | | 0 (0) | 0 (0) | | 0 (0) | 0 (0) |
| Clopidogrel | 94 (76.4) | 3.5 (11.8) | NS | 105 (85.4) | 0.9 (3.0) | NS | 2 (2.1) | 1 (1.1) |
| On clopidogrel | 28 (22.7) | 5.3 (14.4) | | 18 (14.6) | 0.3 (1.4) | | 0 (0) | 0 (0) |
| Off clopidogrel | 93 (76.5) | 2.8 (9.5) | NS | 10 (8.1) | 6.7 (2.2) | | 1 (1.1) | 0 (0) |
| Heparin ± clopidogrel | 26 (21.1) | 5.6 (14.9) | NS | 0 (0) | 0 (0) | | 0 (0) | 0 (0) |
| On heparin, on clopidogrel | 91 (74.0) | 3.4 (11.0) | NS | 85 (69.1) | 0.4 (1.4) | NS | 1 (0.8) | 0 (0) |
| On heparin, off clopidogrel | 24 (19.5) | 25 (20.3) | | 1 (0.8) | 0 (0) | | 1 (20) | 1 (20) |
| Extent of occlusion | 4 (3.3) | 1.5 (3) | | 3 (2.4) | 0 (0) | | 1 (20) | 1 (20) |
| Complete (100%) | 97 (79.9) | 3.0 (9.4) | NS | 91 (74.0) | 0.3 (1.0) | NS | 0 (0) | 0 (0) |
| Near complete (>93%) | 22 (17.9) | 5.1 (16.0) | | 22 (17.9) | 0.7 (3.3) | | 2 (8.3) | 1 (4.2) |
| Incomplete (<93%) | 2 (1.6) | 29 (23.6) | | 29 (23.6) | 0.3 (1.2) | | 2 (6.1) | 1 (3.0) |
| Size of aneurysm | 87 (70.7) | 2.9 (9.4) | | 84 (68.3) | 0.4 (1.4) | | 0 (0) | 0 (0) |
| <10 mm | 97 (78.9) | 3.0 (9.4) | NS | 91 (74.0) | 0.3 (1.0) | NS | 0 (0) | 0 (0) |
| ≥10 mm | 22 (17.9) | 5.1 (16.0) | | 22 (17.9) | 0.7 (3.3) | | 2 (8.3) | 1 (4.2) |
| Stent-assisted | 32 (26.0) | 4.8 (14.2) | NS | 29 (23.6) | 0.3 (1.2) | NS | 2 (6.1) | 1 (3.0) |
| With stent | 87 (70.7) | 2.9 (9.4) | | 84 (68.3) | 0.4 (1.4) | | 0 (0) | 0 (0) |
| Without stent | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | | 0 (0) | 0 (0) |

Note:—Total number of patients and relative percentage of total are given. Significance of differences for the absolute number of occurrences is calculated by a Student t test. Total number of new infarcts or new symptoms at the time of discharge is shown, with relative percentage of respective group.

- All patients underwent MES monitoring both within 12 and 24 hours after the intervention. A summary of MES data stratified by type of intervention, medication, and grade of occlusion is given in Table 2.
- In total, 119 patients (96.7%) were on a heparin drip during the MES-1 scan. Among those patients, the total number of MESs observed was lower than in cases where heparin was not continued (3.4 versus 18.8 MESs/hr). Of those 4 cases, where a heparin drip was not initiated after the procedure, 2 patients had evidence of contrast extravasation on the post-procedural CT scan, 1 patient had evidence of a hemodynamically relevant retroperitoneal hematoma, and 1 patient had refused treatment with heparin (Fig 1, case illustration).
- One hundred patients (81.3%) had received antiplatelet agents (aspirin, clopidogrel, or both) before the MES-1 scan. If patients had received either aspirin, clopidogrel, or both in addition to heparin before the first monitoring session, MES-1 was less likely to be positive, and the total number of MESs observed was lower, but the difference was not significant.
- In 113 of the patients on heparin (91.9%), we were able to stop the heparin drip the next day off heparin (MES-2, 0.4 ± 1.4). One patient underwent a stent-assisted procedure, could not get started on a heparin drip, and was found to be higher (31.8 versus 1.4 MESs/hr). All of these patients were on heparin and on anticoagulants at the time of the MES-2 scan, and mean MESs had significantly decreased to 6 MESs/hr (P < .05), so the heparin drip could be stopped with the MES-3 scan being negative in all cases.
- Grade of Obliteration
- Size of Aneurysm
- Stent-Assisted Procedures

In patients on heparin early after the procedure, more emboli were observed after stent-assisted interventions (MES-1, 4.8 ± 14.2 versus 2.9 ± 9.4), but the difference was not significant. Heparin could be stopped in most cases, and no difference in MESs was observed the next day off heparin (MES-2, 0.4 ± 1.4 versus 0.3 ± 1.2). One patient underwent a stent-assisted procedure, could not get started on a heparin drip, and was found...
to have 72 MESs/hr early after the treatment (Fig 1, case illustration).

CT scans were performed within our timeframe of 4–6 hours after the procedure in 117 of 123 patients, and newly infarcted areas were identified in 2 cases (1.7%). Three patients developed a new neurologic deficit after the procedure (2.4%), one of which was found to be permanent on follow-up (0.8%).

When dichotomized for heparin (yes/no), clopidogrel (yes/no), heparin + clopidogrel (yes/no), heparin + any anticoagulant (yes/no), stent (yes/no), size (<10 mm, ≥10 mm), or grade of occlusion (complete and nearly complete/incomplete), no significant influence could be detected on whether emboli monitoring was positive (≥1 MESs/hr) or negative.

Follow-up examinations were available in 79 cases (64%; mean, 5.5 months since procedure). One patient had persistent postembolization symptoms (1.3%), which had been present since the time of discharge. Twenty-nine patients were available for follow-up emboli monitoring, all of which were negative.

**Discussion**

TEE, although fortunately seldom clinically apparent, are commonly found on MR imaging scans after endovascular procedures and are thought to develop more readily if the aneurysm is large, incompletely coiled due to a greater volume of turbulent flow and possible clot formation, or both. Stent-assisted coiling, in contrast, is thought to contribute significantly to the increase in embolic risk because of the increase in thrombogenic surface (similar to that of a protruding coil segment) as well as vessel wall manipulation. No standardized risk stratification has been identified, and no clear consensus has been reached as to what may represent the “ideal” prophylaxis situation.
Heparin is probably the most commonly used intraprocedural medication, thought to minimize the risk of clot formation during the intervention, though its treatment effect has not yet been quantified. The duration of administration and the addition of further antiaggregational therapy also remain a matter of debate.

Detection of microemboli via TCD has recently emerged as a powerful, noninvasive monitoring tool that can be applied in a variety of cerebrovascular diseases. A decrease in MES as a result of antithrombotic treatment has been related to a reduced risk of overall recurrent ischemic attacks in cerebral steno-occlusive disease. Furthermore, MES very recently has been found to facilitate risk stratification for patients with asymptomatic carotid stenosis, allowing for more individualized treatment recommendations. In a smaller series looking at patients undergoing coiling procedures, MESs were found to be higher in clinically symptomatic patients. Another study also found TEE to be common after coiling (MR imaging positive in 57%) but fortunately largely silent (National Institutes of Health Stroke Scale score unchanged in 93%). In our series of 123 procedures, we found an overall inaprocedural complication and occlusion rate comparable with that of other studies. In another investigation, hep-arin was stopped immediately after the procedure, and the incidence of long-term neurologic deficit was only 0.27%. The study did, however, only include smaller aneurysms (≤7 mm in diameter), and the risk profile for early discontinuation of heparin may indeed be distinctly different in larger aneurysms in which clot fragments can form more easily, particularly if occlusion is incomplete.

In our experience, early and continuous administration of heparin was associated with a low occurrence of MESs, which correlates with the incidence of ischemic sequelae. Although the comparative group where heparin could not be given was very small, MESs were found to be higher without heparin. If patients were on heparin, additional antiaggregational treatment did lower the incidence of MES, but the difference was not significant. Under the current regimen, use of stents did not increase MESs significantly, which is of importance because stent placement is known to significantly increase the rate of not only inaprocedural complications but also of delayed ischemia. Size and configuration of aneurysms also are associated with an increase in thromboembolic events detected by diffusion-weighted imaging. Our analysis indicates that concomitant treatment with heparin may be able to ameliorate the inherent, immediate risk for thromboembolic events in larger and/or incompletely occluded aneurysms due to manipulation and clot dislocation, because no significant change in MESs was observed for either size or grade of occlusion. Clot formation in or adjacent to the aneurysm or to the stent seems to occur mostly within the first 6–12 hours after the coiling, which is indirectly demonstrated by higher numbers of MESs. During early heparinization, fewer occurrences of emboli were noted. Consolidation of the thrombus should be confirmed by a decrease or absence of MESs before prophylaxis with antiplatelet agents alone is deemed sufficient. The risk persists later after the treatment (>12 hours) but probably does not reach clinical relevance, because we demonstrate that the total amount of MESs is then already very low, and new adverse events were not observed at that time.

We routinely stopped the heparin drip in patients where MES-1 showed <10 MESs/hr. Despite discontinuation of heparin, MESs were highly significantly decreased on follow-up examination the next morning. If MES-1 count was elevated, continuation of the heparin drip in addition to anticoagulants led to a significant decrease of embolic signals on MES-2. Once a patient qualified for discontinuation of the drip, the next monitoring scan was negative in most cases and never exceeded our critical threshold of 9 MESs/hr. A secondary increase was not observed.

Within our treatment algorithm, no patient required hepar-arin for >24 hours, and emboli monitoring was negative in all patients who were available for follow-up (n = 29). This helps to illustrate the need for continuous heparinization early after the intervention, when formation is an immediate, though probably transient risk.

We found that the total number of MESs per hour was more sensitive to detect treatment effects, because differences were less apparent when dichotomizing for presence or absence of MES only. We use an empirical limit of 10 MESs/hr in our algorithm, and discontinuation of heparin was safe in all cases in which this critical threshold was not exceeded. Incidentally, this threshold corroborates findings observed for ipsilateral stroke/transient ischemic attack after carotid endarterectomy.
known to determine the specific need for anticoagulation because they correlate with occurrence of ischemic complications. Through quantification of microemboli, we are now able to indirectly assess the risk for thromboembolic complications that in turn allows for a more individualized, safer approach to each patient.

Conclusions
MES monitoring is a powerful adjunct to monitor efficacy of treatment algorithms aimed at the prevention of embolic complications after coiling. In our observational analysis of 123 consecutive endovascular procedures, early heparinization was associated with a low incidence of MESs. This is of particular importance in larger aneurysms, stent-assisted procedures, and incomplete occlusions in which the thromboembolic risk is greatest early on and antplatelet treatment alone may not suffice. In our experience, it was always safe to discontinue heparinization if TCD showed <10 MESs/hr.

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