Occurrence and Clinical Impact of Microembolic Signals During or After Cardiosurgical Procedures

Ralf Dittrich, MD; E. Bernd Ringelstein, MD

Background and Purpose—Microembolic signals (MESs) are detectable within the transcranial Doppler frequency spectrum downstream from vascular atherothrombotic or cardiothrombotic lesions. A frequent occurrence of MESs has also been shown during bypass surgery or after mechanical valve implantation. We sought to compile the knowledge on MES prevalence, the clinical impact of these cardiogenic MESs, and microemboli composition.

Summary of Review—We performed a systematic MEDLINE search and summarized the currently available literature about MESs during or after cardiosurgical procedures for this state-of-the-art report.

Conclusions—The nature of cardiogenic MESs is heterogeneous, and their prevalence is highly variable, reflecting their different origin from a broad spectrum of cardiosurgical conditions. The occurrence and number of MESs during cardiac catheterization and percutaneous coronary angioplasty seem to have a clinical impact but need to be explored further. In patients with prosthetic heart valves, in those with left ventricular assist devices, and during cardiac surgery, the occurrence of MESs has an important clinical impact, and MES monitoring has proven its reliability. Although the data encourage intensifying MES detection in cardiac disorders, their heterogeneous nature does not yet allow the use of MESs as a general surrogate parameter for neuronal damage or cardial thromboembolic risk. (Stroke. 2008;39:503-511.)

Key Words: cardiac embolism ■ cardiac surgery ■ cognitive impairment ■ tcd ■ transcranial Doppler ■ ultrasound

In the late 1960s, decompression bubbles in divers were described by means of diagnostic ultrasound, as well as arterial aeroembolism during cardiac surgery. These clinically silent signals, preferably called microembolic signals (MESs), are detectable within the transcranial Doppler frequency spectrum (TCD). Because of the detection of MESs in patients with artificial heart valves, it became evident that MESs can also originate from the heart itself. Their clinical impact depends on the presence of thromboembolic diseases within the heart or other cardiogenic embolic sources, eg, during or after cardiosurgical procedures. Despite the widespread use of TCD monitoring in patients with cardiac sources of embolism, a systematic overview, in particular with respect to cardiac surgical procedures, about this topic is missing. Thus, the goal of the following review is to summarize the present state of knowledge about the cardiosurgical conditions leading to MESs, their prevalence, clinical impact, and microemboli composition.

Methods

We performed a systematic MEDLINE search limited to the English language containing the search terms “microembolic signals,” “microemboli,” or “high-intensity transient signals.” These search terms were combined with the different topics of the review: “heart valves,” “prosthetic heart valves,” “artificial heart valves,” “assist device,” “cardiac surgery,” “bypass surgery,” “coronary angioplasty,” and “cardiac catheterization.” Comments, reviews, letters, case reports, animal studies, and in vitro studies were not considered. The inclusion criteria were systematic TCD monitoring in homogeneous patient groups providing new findings and scientifically relevant results in the aforementioned topics. We screened and extracted the articles and decided by consensus about their inclusion.

MESs in Prosthetic Heart Valves

In patients with mechanic heart valves (MHVs), the frequency of MESs4–6 depends on the type of valve installed, whereas the prevalence of MESs is much lower with bioprostheses (see Table 1). The majority of MESs, particularly in MHV carriers, reflect gaseous microemboli due to cavitation at the rim of the MHV18,19 and not to the shedding of thromboembolic material. This hypothesis is supported by the stable number of MESs found during repeated investigations and the lack of patients’ clinical deterioration over time. Also, the rate of cardioembolic stroke in these patients does not appear to be correlated with the number of MESs detected. No correlation could be identified between the patient’s hemostaseology and either the number of MESs or the type and extent of antithrombotic treatment. Similarly, neurologic deficits based on the number of MESs detected in MHV carriers could not be predicted.

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<table>
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<tr>
<th>Study Reference No.</th>
<th>No. of Patients</th>
<th>Type of Heart Valve</th>
<th>Study Reference No.</th>
<th>No. of Patients</th>
<th>Type of Heart Valve</th>
<th>No. of MES, Median/h</th>
<th>TCD Device</th>
<th>Recording Duration</th>
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<td>85</td>
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<td>56</td>
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<td>TC-2000</td>
<td>30 min</td>
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<td>38</td>
<td>53</td>
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<td>92</td>
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<td>6–41 per patient</td>
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<td>50</td>
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<td>1 (standard)</td>
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<td>15</td>
<td>18</td>
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<td>5</td>
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<td>14 (mean)</td>
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<td>30 min</td>
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<td>133</td>
<td>DWL Multi-Dop X</td>
<td>30 min</td>
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</table>
be demonstrated in MESs between symptomatic and asymptomatic MHV carriers.23 The gaseous MESs associated with MHVs are characterized by a higher relative intensity increase over the background speckle as opposed to solid MESs. There is, however, considerable overlap of the “loudness” of these various types of MESs, thereby not allowing a clear differentiation between the 2.23 This is why inhalation of concentrated oxygen has been used to suppress cavitation formation to distinguish solid thromboembolic from gaseous material.14,24,25 Because the solubility of oxygen in blood is 5 times greater than that of nitrogen, the blood is preferably saturated with oxygen instead of nitrogen. Oxygen cavitation is short-lived, which means that many oxygen bubbles do not reach the brain at all. Most of the oxygen cavitation bubbles have a diameter of 3 to 5 μm, allowing them to easily pass capillaries without doing harm to brain tissue. In patients with MHVs, the number of MESs could significantly be reduced by inhaling oxygen compared with a period without oxygen inhalation.18 Similarly, no effect on the MES rate was seen in patients with solid microemboli derived from atherothrombotic arterial sources during oxygen inhalation.26

Quite contrary, a higher number of MESs per hour in MHV carriers with a medical history suggestive for stroke60 compared with asymptomatic MHV carriers61 was reported.5 In other studies, impaired working memory could be demonstrated in patients having received MHVs, presumably caused by continuous “showers” of cerebral microembolism.27,28 Also, increased levels of platelet-derived microparticles, an increased procoagulant activity, and an increased rate of MESs were found in MHV carriers symptomatic with cerebrovascular events.29 In 30 patients with bileaflet valves, a reduction of MESs by 16% to 41% after administration of acetylsalicylic acid of 81 to 531 MESs/h was demonstrated.25 Furthermore, a higher number of MESs was found in patients with valve obstruction.30 Successful thrombolysis led to a marked decrease of MESs, whereas the number of MESs remained almost stable after unsuccessful thrombolysis. The fact that successful thrombolysis may lead to a higher number of gaseous MESs due to better leaflet mobility and that the authors used a nonvalidated threshold of 400 Hz to differentiate solid from gaseous MESs are limitations of that study. However, the described results indicate that microemboli in MHV carriers are at least in part composed of solid material.

In conclusion, the potential harm due to chronic MESs, particularly in patients with MHVs, seems to be low or negligible because the majority of these microemboli are gaseous and generated by microcavitation. However, owing to their mixed gaseous and solid origin, they cannot be used as an indicator of a thromboembolic threat or event.

**MESs in LVADs**

In patients with left ventricular assist devices (LVADs), thromboembolism is 1 of the most frequent complications requiring effective anticoagulation.31 Depending on the device implanted, the MES prevalence ranges from 20% to 100%.32–40 A higher amount of MESs corresponds to thromboembolic events in patients with the Novacor N100 LVAD,32,34,37 but not in patients with a DeBakey device.38,40 Patients with the Novacor N100 device and antithrombotic therapy in addition to anticoagulation (eg, antiplatelet agents) had significantly fewer MESs and thromboembolic events.37 Again, this phenomenon could not be demonstrated in patients with a DeBakey device.38 MESs in DeBakey LVAD carriers could be abolished in part by oxygen inhalation, indicating that a substantial number of these MESs are gaseous in origin38,39 (see also Table 2). However, the use of time domain analysis to differentiate the mixed composition of gaseous and solid emboli was unsuccessful.39

A “hidden” procoagulable state is presumably the reason for the higher number of solid MESs in the patients who experience thromboembolic events. In conclusion, the MES load, MES composition, and the relation to thromboembolic events depend strongly on the device installed, the individual thromboembolic risk, and the extent of antithrombotic treatment. The heterogeneity of influencing factors does not allow us to draw a final conclusion about the predictive value of MES monitoring, but it might be possible for each individual type of LVAD.

**Monitoring of MESs During Cardiac Surgery**

The number of MESs during open-heart surgery is high, and often showers of MESs are recorded, particularly during clamp placement and removal in cardiopulmonary bypass grafting (CABG).41–46 Also, residual air in the venous cannula increases the number of MESs at the beginning of CABG.47 These intraoperative MESs can cause cognitive

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Table 1. Continued

<table>
<thead>
<tr>
<th>Study Reference No.</th>
<th>Type of Heart Valve</th>
<th>No. of Patients</th>
<th>MES Prevalence, %</th>
<th>No. of MES, Median/h</th>
<th>TCD Device</th>
<th>Recording Duration</th>
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<tbody>
<tr>
<td>14</td>
<td>Sorin Bicarbon, n=31; Carbomedics, n=9</td>
<td>40</td>
<td>55–83</td>
<td>All valve types recording 1: mean=0.22/min; recording 2: mean=0.24/min; recording 3: mean=0.25/min</td>
<td>DWL Multi-Dop</td>
<td>30 min (3 recordings)</td>
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<tr>
<td>29</td>
<td>Biological (Carpentier-Edwards, n=1; Perimount-Baxter pericardial, n=4; Hancock II porcine, n=15; Mosaic porcine, n=7; Toronto, n=2)</td>
<td>0–20</td>
<td></td>
<td></td>
<td>LMDX-TCD 7</td>
<td>30 min (3 recordings)</td>
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<tr>
<td>10</td>
<td>Homograft valve</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td>30 min (3 recordings)</td>
</tr>
</tbody>
</table>

NS indicates not specified.
Table 2. No. of Patients, Type of LVAD, MES Prevalence, MES Number, TCD Device, Recording Duration, and Association With Different Clinical Parameters in Patients With an LVAD

<table>
<thead>
<tr>
<th>Study Reference No.</th>
<th>No. of Patients</th>
<th>Type of LVAD</th>
<th>MES Prevalence, %</th>
<th>No. of MESs</th>
<th>TCD Device</th>
<th>Recording Duration, h</th>
<th>Association Between Thromboembolic Events and MESs</th>
<th>Association With Hemostatic Parameters/Inflammation Markers/Pump Dynamics/Oxygen Inhalation and MESs</th>
<th>Association With Treatment and MESs</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>6</td>
<td>Novacor N100</td>
<td>55–100 per patient</td>
<td>Median 1.5–40 per recording</td>
<td>EME/Nicolet Pioneer TC-4040</td>
<td>0.5/d; minimum 24 recordings</td>
<td>Yes; 18.5 median (embolism) vs 4 median (event-free) P&lt;0.001</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>33</td>
<td>14</td>
<td>Thermo-Cardiosystems Hartmate (intraperitoneal)</td>
<td>36</td>
<td>Total MESs 0–6 per patient (0.016–0.03/min)</td>
<td>EME/Nicolet TC-2020</td>
<td>0.5 (up to 7 recordings per patient; up to 305 postoperative days)</td>
<td>NS</td>
<td>NS</td>
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<td>34</td>
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<td>38–100 per patient</td>
<td>Median 6–40 per recording</td>
<td>EME/Nicolet Pioneer TC-4040</td>
<td>0.5/d; minimum 30 recordings</td>
<td>Yes; 8 median (embolism) vs 4 median (event-free) P&gt;0.001</td>
<td>NS</td>
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<tr>
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<td>12</td>
<td>Novacor</td>
<td>50</td>
<td>0.17/min</td>
<td>Medasonics Transpect-2000</td>
<td>Nine recordings 10–15 min (up to 60 postoperative days)</td>
<td>No; 85% of patients had MESs (mean 11/min) with embolic events; 73% of patients had MESs (mean 4/min) without embolic events P=0.066</td>
<td>Yes; elevated prothrombin fragment F1.2 (&gt;1.4 nmol/mL) was associated with MES showers</td>
<td>NS</td>
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<td>5</td>
<td>Nonpulsatile DeBakey</td>
<td>20 (MESs in 1 patient in 50% of recordings)</td>
<td>0.2/min</td>
<td>DWL Multi-Dop X4</td>
<td>Nine recordings 1 hour (up to 10 postoperative weeks)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>37</td>
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<td>Novacor N100</td>
<td>35.3</td>
<td>Mean 2.3 per recording</td>
<td>EME/Nicolet Pioneer TC-4040</td>
<td>0.5/wk (range, 5–34)</td>
<td>Yes 38.5% of patients had MESs (mean 2.94/30 min) with embolic events; 25.7% of patients had MESs (mean 0.53/30 min) without embolic events P=0.02</td>
<td>ns</td>
<td>Yes; 18.3% of patients had MESs (mean 0.9/30 min) and thromboembolism (0.7%); with additional antiplatelet therapy 65.4% of patients had MESs (mean 4.7/30 min, P&lt;0.001) and thromboembolism (2.5%, P=0.001) without additional antplatelet therapy</td>
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<td>38</td>
<td>23</td>
<td>DeBakey (6 patients with Carmeda)</td>
<td>87</td>
<td>Mean 81.2/h</td>
<td>EME/Nicolet Pioneer TC-4040</td>
<td>40 min (20 min with O2 6 L/min)–2 wk; mean 22 recordings per patient</td>
<td>No; MES prevalence 26.5% in patients with thromboembolic events; MES prevalence 33.5% in patients without thromboembolic events P&gt;0.5</td>
<td>Yes; MESs decline during O2 inhalation (MES prevalence 25% with O2 and 34% without O2, P=0.01); absolute MES 46.5 vs 104 P&lt;0.01</td>
<td>No (Reduction of thromboembolism and additional ASA therapy P&gt;0.9; Reduction of thromboembolism and additional dipyridamole+ASA P&gt;0.6)</td>
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(Continued)
impairment. In patients having <200 MESs during their CABG procedure, 8.6% showed postoperative neuropsychological deficits, but this proportion rose to 43% in patients having >1000 MESs. Moreover, a higher occurrence of postoperative neurologic complications in patients with a high number of MESs (>60) during CABG was demonstrated. In another study, a reduction in postoperative cerebral glucose metabolism was found, correlating with the number of MESs recorded (r = −0.46, P < 0.05). Although neuropsychological impairment occurred after the surgical procedure, its correlation with the number of MESs or the decrease in cerebral glucose metabolism could not be proven. Lee et al demonstrated that a higher number of intraoperative MESs corresponded with an impairment in an auditory verbal learning test 2 weeks and 1 year after CABG (P ≤ 0.05). Interestingly, a specific verbal memory decline in patients with predominantly left-sided MESs was observed, whereas a higher number of right-sided MESs was associated with a nonverbal memory deficit after open-heart surgery. The correlation of a high number of MESs, particularly during on-pump cardiac surgery, with a relative reduction of prefrontal activation during functional magnetic resonance imaging while performing verbal memory tasks 4 weeks postoperatively could also be demonstrated. There are additional reports on cognitive impairment and delayed recovery after CABG due to intraoperative MESs.

The nature of these MESs, either solid or gaseous, is not fully understood. An increased number of MESs during aortal manipulation, especially in the case of severe aortal atherosclerosis, indicated the predominantly solid nature of MESs. In another study, the higher number of MESs in patients with valve replacement or CABG was associated with postoperative neu-
ropsychological impairment. A much higher number of MESs (mean, 2083 per case during operation) in patients with valve replacement compared with those with CABG (mean, 50 MESs per case during operation, \( P \leq 0.05 \)) was found. Interestingly, both conditions led to similar severe neuropsychological impairment. The authors concluded that this observation reflected the primarily gaseous nature of the MESs during valve replacement as opposed to the predominantly solid MESs during bypass surgery.\(^{64}\) Similar conclusions were drawn in a larger study with a more simple detection technique despite a lower number of MES detected.\(^{58}\)

A considerable proportion of MESs during cardiac surgery appear to be gaseous. These gas bubbles are much larger than the cavitation-induced bubbles and may do harm to the brain. With respect to various surgical steps during CABG, the occurrence of MESs was analyzed.\(^{69}\) During the aortic clamp placement and its removal, more solid MESs were seen (mean MES increase, 1.5±1.5/min). By contrast, during perfusion interventions (eg, blood sampling, drug administration), more gaseous MESs could be registered (mean MES increase, 6.9±4.5/min). The number of MESs was significantly higher during perfusion interventions. Similarly, a higher number of MESs and more severe neuropsychological deficits were found when ≥10 perfusion interventions became necessary during the entire course of the operation compared with patients with fewer interventions.\(^{60}\) Reduced purging and the use of continuous infusions instead of bolus injections significantly decreased the number of MESs during the surgical procedure.\(^{61}\) Also, when a large-bore syringe was used, the rate of MESs was significantly lower compared with that seen with a small-bore syringe.\(^{62}\) Moreover, it could be demonstrated that CO\(_2\) insufflation in the cardiothoracic wound during open-heart valve surgery reduced the number of gaseous MESs.\(^{63}\)

Finally, a dramatic and significant reduction of MESs was achieved with off-pump CABG.\(^{50,64–70}\) Another study group\(^{71}\) not only confirmed the higher number of MESs during on-pump (mean, 335.1) compared with off-pump (mean, 144.7) surgery but also found a significantly lower 6-month postoperative “cognitive impairment-index” in the off-pump patient group, as assessed by counting the number of impaired test performances for each patient in 7 tests. A limitation of these results is the fact that a significant cognitive decline was not related to the number of MESs during operation. Others observed the same phenomenon, but the amount of MESs was not correlated with the S100 protein level, a marker of diffuse cerebral injury.\(^{66}\) In contrast, a significantly higher level of S100 protein in patients undergoing on-pump surgery and a higher intraoperative number of MESs in patients with retinal microvascular damage were reported.\(^{70}\)

Further refinement of surgical techniques, like avoidance of aortic side clamping and the use of clampless devices, also reduces the number of solid MESs.\(^{56}\) In that study, automatic software had been used to discriminate between solid and gaseous MES, which could be a potential source of error. The additional use of a sutureless proximal aortic device led to a decrease of MESs during the surgical procedure.\(^{72}\) Arterial filters, in particular leukocyte-depleting filters, fat-removal filters, or an air bubble trap in the arterial line, could also considerably reduce the number of MESs.\(^{73–79}\) Because the number of MESs is higher in cases of longer-duration CABG procedures, shorter operation times may prevent harm due to MESs.\(^{80}\) In left heart valve replacement, the application of a new “dual-vent” de-airing technique could significantly reduce the number of carotid MESs.\(^{81}\) Furthermore, cannulation of the distal aortic arch led to a decrease of MESs compared with conventional cannulation of the ascending aorta.\(^{82,83}\) The use of a straight or curved aortic cannula, or cannulas of different diameters, had no influence on the number of MESs.\(^{84}\) However, optimized positioning in the aorta descended was not associated with better performance in postoperative cognitive tests.\(^{85}\) The number of MESs again depends on the type of oxygenator device used, even when modern versions are used. The mean number of MES during the whole procedure was 309 for the DIDEKO oxygenator but only 143 for the COBE oxygenator (\( P < 0.00001 \)).\(^{86}\)

Not all protective efforts lead to a significant decline in MESs during cardiac surgery. A surface-modifying additive during conventional cardiopulmonary bypass surgery did not reduce the number of MESs.\(^{87}\) In addition, there was no difference in MES number when a minimally invasive versus a conventional mitral valve operation was performed.\(^{88}\) Finally, an asymmetry connector system, to avoid partial clamping, was followed by an increased number of MESs, presumably due to gaseous microemboli.\(^{89}\)

Another point of interest is the hemispheric distribution of MESs during cardiac surgery, but the results are ambiguous so far. Whereas some study groups described a preponderance of left-sided MESs,\(^{50,60}\) others either reported an equal distribution of MESs\(^{91}\) or found a preference for the right hemisphere.\(^{49,51}\) In conclusion, MESs are a common phenomenon during cardiac surgery. The composition of the microemboli is heterogeneous and reflects solid and gaseous particles. So far, it remains controversial which composition of MES represents the majority during cardiosurgical procedures. However, it is indisputable that a large number of MESs during cardiosurgical procedures leads at least to temporary if not permanent neuropsychological deficits due to neuronal damage. The type and degree of the resulting deficit depends on the hemisphere to which the higher number of MESs are channelled. Thus, MES monitoring by TCD is a reliable, easily accessible, noninvasive tool to guide and improve surgical techniques.

Monitoring of MESs During Cardiac Catheterization and Percutaneous Coronary Angioplasty

Asymptomatic MESs were detected in >50% of patients during left atrial catheterization.\(^{22,93}\) The same phenomenon was discovered during percutaneous transluminal coronary angioplasty.\(^{94}\) The majority (70%) of the 679 MESs occurred after injection of solutions; hence, the authors concluded that these MES were predominately gaseous. Other authors confirmed this finding and detected MESs primarily during contrast agent injection.\(^{95}\) Further evidence for the primarily gaseous origin was the reduction in the number of MESs by using solutions with a low gas content.\(^{96}\) In all of the aforementioned studies, clinically apparent neurologic deficits did not occur after the procedure. The use of a guidewire and different catheter types also influenced the number of MESs.\(^{97}\) In a recent more
sophisticated study, the authors verified the primarily gaseous origin of MESs in 47 patients during left heart catheterization by automated software (92.1% gaseous vs 7.9% solid MESs).98 Interestingly, 3 (6.4%) patients had transient neurologic deficits immediately after the procedure, and 7 (16.7%) patients had cognitive impairment as detected by neuropsychological tests 24 hours after the procedure. Five (15.2%) patients had new cerebral lesions detected by diffusion-weighted magnetic resonance imaging 24 hours after catheterization. This finding coincided with a higher number of solid MESs ($P=0.016$). These results suggest that the procedural occurrence of MESs during catheterization is potentially harmful; it can damage the brain parenchyma and cause at least transient neurologic symptoms. However, in another study, only 1 of 46 patients developed a new diffusion-weighted imaging lesion after the procedure.99 In conclusion, the clinical impact of MESs during left heart catheterization appears to be clinically relevant but needs to be investigated further with standardized study protocols.

**Limitations of MES Monitoring**

Unfortunately, MES monitoring by TCD has general major limitations. Studies conducted so far have used different monitoring times, ultrasound devices, and monitoring protocols, thus hampering the comparability of results. In addition, the overlapping physical properties of the microemboli do not let us unequivocally differentiate gaseous from solid MESs, despite promising technical progress, like multifrequency TCD,100 a longer sample volume length for gaseous microemboli,101 and Doppler time domain analysis.102 Finally, there is a lack of large, prospective and long-term, follow-up studies in all fields of cardiosurgical procedures. These limitations are the major drawbacks for the validity of MESs as a surrogate parameter that could replace clinical outcome events.

**Summary**

The prevalence and number of cardiogenic MESs during all types of cardiac interventions is high but depends strongly on the underlying cardiosurgical condition. The clinical impact is as heterogeneous as the number of settings in which MESs occur. MESs in patients with MHVs are mainly cavitation-based, gaseous in nature, and usually harmless to the brain. Quite contrary, the differing load of solid particles in various cardioembolic disorders allows us to define a hierarchy of embolic risk related to the various diseases and procedures. Showers of solid or large gaseous MESs during cardiac surgery, cardiac catheterization, or percutaneous coronary angioplasty are harmful but are partly preventable by both better technical equipment and improved and meticulous surgical technique. MESs can provide clues to successfully modify surgical interventions, and they may serve as a guide to the choice of timing and technical guidelines of a given intervention. However, MESs during or after cardiosurgical procedures are not yet an accepted surrogate parameter for the prediction of thromboembolic risk or neuronal damage with cognitive decline.

**Disclosures**

None.


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MES During or After Cardiosurgical Procedures


Occurrence and Clinical Impact of Microembolic Signals During or After Cardiosurgical Procedures
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