

## Review Article

# Microembolus Detection by Transcranial Doppler Sonography: Review of the Literature

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Transcranial Doppler can detect microembolic signals which are characterized by unidirectional high intensity increase, short duration, random occurrence, and a "whistling" sound. Microembolic signals have been detected in a number of clinical settings: carotid artery stenosis, aortic arch plaques, atrial fibrillation, myocardial infarction, prosthetic heart valves, patent foramen ovale, valvular stenosis, during invasive procedures (angiography, percutaneous transluminal angioplasty), surgery (carotid, cardiopulmonary bypass, orthopedic), and in certain systemic diseases. Microembolic signals are frequent in large artery disease, less commonly detected in cardioembolic stroke, and infrequent in lacunar stroke. This article provides an overview about the current state of technical and clinical aspects of microembolus detection.

## 1. Introduction

*1.1. Clinical Aspects.* Acute stroke is one of the leading cause of morbidity and mortality worldwide. In developed countries, stroke ranks as either second or third most common cause of death and embolization is the cause of ischemic stroke in 40%–80% of cases [1]. TCD is a sensitive technique for real-time detection of microembolic signals (MESs). In the last 20 years, a substantial number of studies dealing with emboli detection have been carried out, showing that MES are proven to represent emboli passing within cerebral circulation. MES have been detected in a number of clinical conditions: carotid artery stenosis, aortic arch plaques, atrial fibrillation, myocardial infarction, prosthetic heart valves, patent foramen ovale, valvular stenosis, during carotid surgery, surgery on open heart, stent implantation, percutaneous transluminal angioplasty and angiography, and in patients with migraine and patent foramen ovale (PFO). Patients who have detectable MES, especially in larger number, should be considered as high-risk patients for stroke. MES detection may help in localization of embolic source, identification of patients with high stroke risk, monitoring during invasive procedures and surgery, and monitoring of the effectiveness of therapy.

Consensus on MES detection by TCD has been established [2]; MES can be identified as short lasting (<0.01–0.03 s), unidirectional intensity increase, and intensity increase (>3 dB) within the Doppler frequency spectrum; intensity increase is focused around 1 frequency. MESs appear randomly within the cardiac cycle and produce a "whistle," "chirping," or "clicking" sound when passing through the sample volume.

*1.2. Technical Aspects.* TCD is a very convenient tool to monitor intracranial circulation, however, the thick temporal bone window is an obstacle in certain patients. A new transcranial modality, power M-mode Doppler (PMD), has been developed to overcome the difficulties in location and insolation through transcranial ultrasound windows. PMD has 33 sample gates placed with 2 mm spacing for display of Doppler signal power, colored red and blue for directionality, in an M-mode format. The spectrogram from a user-selected depth is displayed simultaneously. PMD facilitates window location and alignment of the ultrasound beam to view blood flow from multiple vessels simultaneously, without sound or spectral clues. MES appear as characteristic sloping high-power tracks in the PMD image [3, 4].

The optimal time of monitoring depends on the clinical entity. In patients with implanted artificial heart valves in whom MES can be detected in large proportion, monitoring during 30 minutes will be sufficient. In patients with carotid artery stenosis, atrial fibrillation, or other cardiac disease, frequency of MES is usually low, 1-2 MES over 60 minutes. Extended monitoring up to 8 hours, or repetitive monitoring over a couple of days in succession, is in relation with the percentage of MES positive patients [5, 6]. The embolic activity is highest in the first couple of hours after stroke; however, MES may be detectable days and weeks after cerebrovascular incidents which means that those patients are under higher risk for stroke [7–11].

Although technological improvement in the area of MES detection has recently developed, it is still impossible to reliably distinguish the composition of emboli (particles of fat, platelet aggregates, or particles of atheroma). Differentiation between solid and gaseous microemboli is based on the principle that solid emboli reflect more ultrasound at higher frequency, whereas the opposite is the case for gaseous emboli. This principle is used in multifrequency TCD instrumentation where the vessels are insonated simultaneously with 2.5 and 2.0 MHz and can be used for the differentiation between gaseous and solid emboli [12]. A recent study has shown that there is a significant relationship between low- and high-intensity MES, indicating that many MESs routinely rejected because of their low intensity are real and may predict future occurrence of high-intensity MES [13].

## 2. Clinical Condition in Which MES May Be Detected

### 2.1. Atherosclerotic Disease

**2.1.1. Carotid Stenosis.** Carotid artery stenosis is a well-known source of cerebral MES [7, 8, 14–19]. Systematic review of the literature showed that MES can be detected in 43% of patients with symptomatic and in 10% with asymptomatic carotid stenosis; presence of one MES indicated an increased risk of future events (OR 7.5, 95% confidence interval (CI): 3.6–15.4,  $P < 0.0001$  for symptomatic and OR 13.4, 95% CI: 6.5–27.4,  $P < 0.0001$  for asymptomatic disease) [20]. A meta-analysis of the literature revealed that MESs are most frequent in large artery disease, less frequent in cardioembolic stroke, and infrequent in lacunar stroke. For symptomatic carotid stenosis, ES predicted stroke alone (OR, 9.57;  $P = 0.02$ ) and stroke/TIA (OR, 6.36;  $P < 0.00001$ ). For asymptomatic carotid stenosis, ES predicted stroke alone (OR, 7.46;  $P = 0.001$ ) and stroke/TIA (OR, 12.00;  $P = 0.002$ ) but with heterogeneity ( $P = 0.004$ ). In acute stroke, ES predicted stroke alone (OR, 2.44;  $P = 0.02$ ) and stroke/TIA (OR, 3.71;  $P = 0.002$ ). A high frequency of ES immediately after carotid endarterectomy predicted stroke alone (OR, 24.54;  $P < 0.00001$ ) and stroke/TIA (OR, 32.04;  $P < 0.00001$ ). The meta-analysis suggests that MES predict stroke risk in acute stroke, symptomatic carotid stenosis, and postoperatively after carotid endarterectomy; however, in asymptomatic carotid stenosis, the predictive value of MES is less clear [21].

In the asymptomatic carotid emboli study (ACES), a prospective observational study, patients with asymptomatic carotid stenosis of at least 70% were monitored by TCD; the results showed that the hazard ratio for the risk of ipsilateral stroke and transient ischaemic attack from baseline to 2 years in patients with MES compared with those without was 2.54 (95% CI 1.20–5.36;  $P = 0.015$ ). For ipsilateral stroke alone, the hazard ratio was 5.57 (1.61–19.32;  $P = 0.007$ ). The absolute annual risk of ipsilateral stroke or transient ischaemic attack between baseline and 2 years was 7.13% in patients with MES and 3.04% in those without, and for ipsilateral stroke was 3.62% in patients with MES and 0.70% in those without [22].

Studies have shown that intraluminal thrombosis, irregular plaque surface, and ulceration are in relation with emboli frequency [23–25]. Carotid plaque inflammation is associated with cerebral microembolism in patients with recent transient ischemic attack or stroke [26].

Despite optimum standard antiplatelet therapy, cerebral microembolisation occurs in 30% of patients with symptomatic carotid artery disease [27]. Patients with symptomatic high-grade ICA stenosis and who were on antiplatelet treatment underwent bilateral MES monitoring for 30 minutes. The study has shown that the presence of MES is independent of intrastenotic blood flow disturbances and gray-scale ultrasound plaque characteristics. The authors concluded that the presence of MES is an indicator of an unstable plaque [27].

Carotid plaques in patients with severe unilateral carotid restenosis at least one year after surgery are similar to patients with primary severe stenosis in their embolic potential and ultrasonic characteristics [28].

Dissection of carotid arteries is an embolic source and MES in those patients can be detected in a high proportion [29]. Among patients with cervical artery dissection presenting with TIA or stroke, 50% had MES compared with 13% of patients with local symptoms ( $P = 0.006$ ) [20].

**2.1.2. Aortic Arch Atheroma.** Aortic arch atheroma has long been underestimated as an embolic source. Studies have shown that severe atheroma of the aortic arch has now been established as an important and independent risk factor for stroke. The prevalence of severe arch atheroma among patients presenting with acute ischaemic stroke is approximately 20%.

The odds ratio for stroke or peripheral embolism in patients with severe arch atheroma (>4 mm) is greater than four, and for mobile atheroma it is greater than twelve, particularly in patients with other stroke risk factors. Patients found to have severe atheroma are at high risk of recurrent events (14.2% per year) and may, therefore, need an aggressive secondary prevention strategy [19, 20].

**2.1.3. Intracranial Stenosis.** Intracranial stenosis is a significant source of cerebral emboli, although in most studies not appreciated as important as carotid stenosis. A recent study has shown that MESs were reported in 25% of 220 patients with symptomatic versus 0% of 86 patients with asymptomatic intracranial stenosis ( $P < 0.0001$ ) [20].

**2.1.4. Thrombolysis and MES Occurrence.** Thrombolysis is a well-established therapy in acute stroke. TCD has proven to serve as an enhancement tool in clot dissolution. MES detected by TCD at the site of arterial obstruction can indicate clot dissolution and recanalization of intracranial arteries, and therefore serve as a predictor for outcome [30].

**2.1.5. Carotid Endarterectomy (CEA), Carotid Artery Stenting (CAS), and Percutaneous Transluminal Angioplasty (PTA).** After carotid endarterectomy, MESs disappear or the frequency is significantly lower [31, 32]. However, patients with clinically significant postoperative microembolism have an approximately 15 times higher risk of ipsilateral stroke or TIA [33]. Efficacy of CEA largely depends on postoperative results, that is, perisurgical complications. Intraoperative monitoring of hemodynamic changes and detection of MES may significantly influence postsurgical outcome [34]. Different antiplatelet regimens (combination of dipyridamole, aspirin and clopidogrel) following CEA does not show a significant influence on postoperative TCD embolization [35]. However, administration of dual antiplatelet therapy (clopidogrel 75 mg plus aspirin 75 mg) prior to CEA reduces postoperative embolisation and thromboembolic events [36].

Meta-analysis of trials to date shows that symptomatic and asymptomatic CAS patients had significantly higher 30-day postprocedure incidence of death/stroke/MI when compared with CEA patients [37, 38].

Experimental studies have shown that during PTA, the majority of MESs are gaseous in origin, while MESs detected during balloon inflation are probably attributable to solid particles [39].

The use of cerebral protection devices appears to reduce thromboembolic complications during PTA and stenting. The combined stroke and death rate within 30 days in patients treated with cerebral protection devices was 1.8% compared with 5.5% in patients without [40].

**2.1.6. Angiography.** MESs detected during angiography are attributable to gas bubbles, contrast injection, clot formation in catheter, and disrupted atheromatous material [41, 42]. Magnetic resonance studies have shown increased number of brain parenchymal lesions after angiography, although the majority of patients had no neurological deficit [43]. However, angiography of the aortic arch is associated with 1% risk for stroke with permanent deficit, and in 3% mild-to-moderate stroke or TIA [41, 42]. In a study with 24 patients undergoing angiography, all had detectable MES, approximately 51 per patient. The majority of MES had the characteristics of gas bubbles. The number of detected MESs correlated with the volume of injected contrast and all patients except one who had stroke were asymptomatic [42].

**2.2. Cardiac Sources.** Approximately 15–30% of strokes are caused by cardiac diseases [44]. Prospective studies have shown that recurrent stroke or systemic embolization in that group of patients is high, approximately 20% [7, 45].

**2.2.1. Atrial Fibrillation.** Atrial fibrillation (AF) is present in 1.7% of population aged 60–64 years, and in 6% of

population older than 75 years [46]. Incidence of stroke in patients with AF is 4.5% per year [47]. In cases when AF is associated with mitral valve stenosis, risk of stroke is 17 times higher [48]. Majority of strokes in patients with AF are embolic in origin; MES can be detected in 15–30% [49, 50].

**2.2.2. Patent Foramen Ovale.** The prevalence of patent foramen ovale (PFO) in common population is 22–34.4% [51, 52]. In patients with cryptogenic stroke, especially younger patients, a high prevalence of PFO has been found [53, 54]. The rate of recurrent stroke or TIA is 9.9% [55]. A multicentric study has shown that stroke risk over 4 years is 5.6% in patients with isolated PFO and 19.2% in patients with PFO and atrial septal aneurysm (ASA) [56]. However, a prospective population-based study has established that PFO is not an independent risk factor for stroke when age and comorbidity are considered [57].

A connection between migraine (especially migraine with aura), stroke, and PFO has been established [58–63]. Studies have shown that the prevalence of PFO in patients with migraine is about 2.5 times greater in comparison with patients who do not suffer from migraine [64, 65]. Patients with migraine with aura have twice as high risk for stroke. Patients with probable migraine are 1, 5 times higher risk. If female patients with migraine smoke and take oral contraceptives, the risk increases up to seven times compared to those who do not have migraine [66–68].

According to one of the proposed hypothesis, paradoxical embolization causes segmental hypoperfusion and vasodilatation, that is, PFO enables vasoactive substances (hypothetically serotonin) and microemboli from venous circulation to pass the pulmonary filter (normally they would be stopped in lungs), and entering the brain they can induce cortical spreading depression which characterizes migrainous attack [69]. This hypothesis could explain the decrease of migraine prevalence and intensity after PFO closure (in most studies). In favor of microembolization as a provoking factor speaks the MRI study in which a 13.7 times higher incidence of white matter lesions has been found in patients with migraine with aura compared to brains of controls [70–72]. Furthermore, most TCD studies have shown that most paradoxical MES can be detected in posterior brain circulation [70], which is interesting because in these patients PFO and migraine are more frequently present. However, up to now, there is no definite evidence for proposed theories regarding migraine onset caused by circulating microemboli.

**2.2.3. Prosthetic Heart Valves.** Thromboembolism is a significant complication in patients with prosthetic heart valves (PHV). MES can be detectable in cerebral circulation ranging from 50 to 90% [73–75]. The majority of HITS in patients with PHV correspond to gaseous, for example, due to cavitations at mechanical heart valves [76].

**2.2.4. Myocardial Infarction.** Approximately 2.5% of patients with acute myocardial infarction (MI) will have stroke within 2–4 months [77]. In a prospective study in patients with anterior wall MI, MES could be detected in 21% [78].

**2.2.5. Infective Myocarditis.** The prevalence of stroke in patients with infective myocarditis is 15–20% [79]. The size of vegetations has a predictive value: risk for embolization is higher in patients with vegetations larger than 10 mm, in patients with endocarditis of the mitral valve and mobile vegetations [79].

**2.2.6. Dilatative Congestive Myocardiopathy.** Incidence of embolic complications in patients with cardiomyopathy is 4% per year [78]. MESs are detectable in one third of patients with dilatative congestive myocardiopathy [44].

**2.2.7. Mitral Valve Prolapse.** Prevalence of mitral valve prolapse (MVP) in common population is 1–15% [80]. Isolated MVP is not considered as a significant risk factor for stroke in older patients, but in younger patients myxomatous change of mitral valves is considered to be in relationship with cerebrovascular incidents [80].

**2.2.8. Cardiac Tumors.** Although rare, atrial myxoma is the most frequent primary cardiac tumor, usually present in the left atrium. Due to its fragile nature, myxoma has a high potential for embolization to the brain as well as to other organs [81].

**2.2.9. Systemic Diseases.** MESs in cerebral circulation are detectable in primary antiphospholipid syndrome, Sneddon's syndrome, systemic lupus, Behcet's disease, and Takayasu's arteritis and are in temporal relation with cerebrovascular incidents in those patients [82–85].

**2.2.10. Coagulation.** Clinical studies have shown that hyperfibrinogenemia is in a positive correlation with cardiovascular and cerebrovascular diseases [86–88]. Patients with progressive atherosclerosis have higher levels of fibrinogen compared with those with nonprogressive disease [89].

### 3. Monitoring of Therapeutic Efficacy

Monitoring of therapeutic effect has shown that after CEA, MESs disappear or decrease in frequency, this finding is consistent through studies [31, 32]. Studies that investigated the efficacy of anticoagulant and antiaggregation therapy and frequency of MES have shown various results. Although some studies have shown decrease in MES frequency after aspirin or heparin administration, consistent correlation has not been found [90].

The first multicenter, randomized, double-blind trial that used MES detection as an endpoint to evaluate antiplatelet therapy, the Clopidogrel (CARESS and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis) trial, has shown that clopidogrel plus aspirin is superior to aspirin alone in reducing the frequency of MES in patients with recent symptomatic carotid stenosis [91]. Glycoprotein IIb/IIIa receptor antagonist tirofiban is a highly selective platelet aggregation inhibitor. Administration of tirofiban resulted in microembolic rate drop down to zero in patients with severe carotid artery stenosis in two studies. However, the inhibitory effect of tirofiban is reversible [92, 93].

### 4. Clinical Significance of Emboli Detection

It is important to emphasize that the vast majority of MESs do not produce immediate symptoms. MESs in cerebral circulation indicate asymptomatic patients with increased stroke risk. Nevertheless, correlation of cerebral microemboli with clinical symptoms (stroke or TIA ipsilateral to carotid stenosis, higher incidence of stroke in patients with cardiac diseases, neurological complications after angiography, postoperative neurological complications after CEA, in patients after CABG) in a number of studies has been shown. In symptomatic patients, the etiology of neurological deficit may be elucidated and adequate therapy may be introduced.

Patients with cerebral microembolism have higher cognitive deficits; cumulative effect of embolism is thought to be the cause. Even minor neuropsychological impairment should not be underestimated, the presence of an embolic source should be regarded as the possible cause for cognitive decline. Imaging techniques (CT scan, MRI, DWI-MRI) can show “silent” areas of cerebral ischemia. These small and multiple areas of acute or subacute brain infarction may occasionally present with clinical features atypical for brain embolism or will not produce any apparent symptoms [94].

Despite disputable clinical significance in certain conditions, the potential benefit of TCD detection of MES remains substantial.

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