Is the Measurement of Cerebral Microembolic Signals a Good Surrogate Marker for Evaluating the Efficacy of Antiplatelet Agents in the Prevention of Stroke?

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Key Words

Antiplatelet therapy · Atherothrombosis · Cerebral microembolic signals · Clopidogrel · Stroke

Abstract

Stroke is difficult to treat with few treatment options. Until such time as appropriate therapeutic regimens are established, prevention, both in the primary and in the secondary setting, is of paramount importance. Evaluation of pharmacological agents for the prevention of stroke in conventional clinical studies has the advantage that the outcome parameter is a direct measure of efficacy, and the disadvantage that many patients must be recruited and many evaluations performed over an extended period to provide adequate statistical power, making such studies lengthy and costly. Measurement of cerebral microembolic signals (MES) using transcranial Doppler ultrasonography has been proposed as a useful surrogate end point to investigate new antiplatelet agents and to evaluate further the benefits of existing antiplatelet therapies. MES measurements may provide a means of more directly evaluating the pharmacological activity of an antiplatelet agent. However, does measurement of MES accurately predict efficacy in stroke prevention? This review evaluates recent studies where the relationship between MES and cerebral ischaemic events has been explored and studies where the effects of antiplatelet agents on MES rates have been investigated.

Overall, there is a growing body of evidence to suggest that MES may be used as a surrogate marker for cerebral infarction and clinical events, thus allowing quick appraisal of the efficacy of antiplatelet agents. Studies currently in progress should provide further insight into the value of the measurement of MES in clinical studies in stroke prevention.

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Introduction

Stroke is a major cause of death and disability in the world. However, despite a relentless search over the last few years for efficacious treatments, stroke remains difficult to treat and frequently results in long-term disability with attendant social and economic implications [1]. Currently the only approved treatment for acute strokes is tissue plasminogen activator (tPA). The vast majority of stroke sufferers are not, however, suitable for tPA treatment as tPA must be administered within 3 h of the onset of symptoms and this condition is often not met. Clearly, until such time as appropriate therapeutic regimens are established, prevention, both in the primary and in the secondary setting, is of paramount importance.

Most strokes are ischaemic in nature and are a consequence of underlying atherothrombotic disease. Evidence that antiplatelet agents can reduce the risk of stroke has emerged from a number of clinical studies. The Anti-

thrombotic Trialists' Collaboration [2] summarized the evidence for the efficacy of antiplatelet therapy in reducing the risk of stroke in high-risk patients. This evidence included the results of two large well-controlled trials: the European Stroke Prevention Study 2 (ESPS2) [3] and Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) [4]. ESPS2 demonstrated that both acetylsalicylic acid (ASA) and sustained-release dipyridamole produce a significant risk reduction in stroke and transient ischaemic attack (TIA) compared with placebo in patients who had already survived a stroke or TIA, while the two treatments combined have an additive effect. The CAPRIE study [4] showed that clopidogrel treatment of patients with atherothrombosis is more effective than treatment with ASA in reducing the combined risk of ischaemic stroke, myocardial infarction or vascular death. Subsequent studies such as the Clopidogrel in Unstable Angina to prevent Recurrent Events [5] trial and the Clopidogrel for Reduction of Events During Observation [6] trial have provided convincing evidence of the additive effects of treatment with clopidogrel in addition to ASA.

Evaluation of pharmacological agents for the prevention of stroke in conventional clinical studies, such as ESPS2 and CAPRIE, has the great advantage that the outcome parameter is a direct measure of efficacy. However, clinical trials of this kind are not without their disadvantages. Studies need to recruit many patients, and evaluations need to be performed over an extended period to provide adequate statistical power, resulting in studies that are costly to perform and take many years to accomplish. Furthermore, studies with cardiovascular and cerebrovascular end points as efficacy outcome parameters do not permit the evaluation of the direct pharmacological activity of the therapy.

Measurement of microembolic signals (MES) using transcranial Doppler ultrasonography (TCD) has been proposed as a useful (simple, rapid) technique for determining the presence of microemboli moving through cerebral arteries, and therefore as a surrogate end point to investigate the value of new antiplatelet agents in the treatment of stroke and to evaluate further the benefits of existing antiplatelet therapies. MES can be a consequence of artery-to-artery embolism in patients with large artery disease (carotid or middle cerebral artery stenosis) and drugs that reduce MES may prevent stroke by preventing artery-to-artery embolism. Consequently, measurement of MES may provide a means of more directly evaluating the pharmacological activity of an antiplatelet agent.

This review will evaluate recent studies, where the relationship between MES and cerebral ischaemic events

has been explored and studies where the effects of antiplatelet agents on MES rates have been investigated.

Microemboli and MES

Microemboli in the cerebral circulation can have a number of origins, including sources such as atherothrombotic lesions of the carotid arteries and cardiac sources such as severe ventricular dysfunction, atrial fibrillation and valvular disease [7]. Microemboli also appear to be commonly seen during interventional procedures such as cerebral and coronary angiography, carotid angioplasty, carotid endarterectomy and cardiopulmonary bypass [8]. Microemboli can be caused by platelet aggregation consequent to atherosclerotic plaque rupture, or may result from shear stress due to vessel narrowing by vascular stenosis [9, 10].

The detection of arterial emboli using TCD is a well-established technique, which is simple, non-invasive, inexpensive, sensitive and specific. Circulating cerebral microemboli – which may be of thrombus, platelet, atheroma or air bubble origin depending on the clinical situation – passing through the sample volume of an ultrasound probe cause a unidirectional intensity increase within the Doppler frequency spectrum (fig. 1), which can be acoustically identified by the operator [8, 11–14]. Recordings of the signal of at least 30 min to 1 h are usually assessed by an independent observer, blinded to the patient history.

One of the major drawbacks of TCD is that trained personnel are required to carry out the procedure and interpret the results. Furthermore, many old patients may have poor acoustic bone window, and patients need to be monitored for prolonged periods of time. Recently, Mackinnon et al. [15] have published a paper describing a device that permits ambulatory monitoring. Technical improvements of this kind will significantly increase the utility of the technique.

Another major problem of TCD is that many microemboli are gaseous, rather than solid, in nature and are produced by cavitation at mechanical heart valves or other processes. These two types of microemboli produce very similar signals during TCD, which has historically made them very difficult to differentiate [14]. As the clinical implications of the presence of the two types are quite different, some physicians have disputed the ability of MES to predict recurrent ischaemic events. This problem will hopefully soon be solved with the ongoing development of better equipment and automated analysis, which

Fig. 1. An example of microembolic signal detected in the middle cerebral artery. There is a change in the frequency detected by TCD, which produces a color change on the signal.

already achieves better than 80% sensitivity and specificity for solid emboli [16].

Relationship between MES and the Risk of Stroke

The association between the presence of MES and the risk of ischaemic cerebral events has been studied by a number of researchers. Table 1 lists the studies discussed in this article, together with details of the study design, etc. Since all of the patients enrolled had proven atherosclerosis, it is reasonable to assume that most MES detected would have been caused by solid emboli from vascular lesions.

Siebler et al. [17] were amongst the first groups to investigate the relationship. They measured MES frequency in 64 patients with unilateral 70–90% internal carotid artery stenosis and no history of retinal or cerebral ischaemic symptoms. Five patients developed ischaemic symptoms during the follow-up period (mean duration 72 weeks). A microembolic rate of ≥ 2 per hour in the ipsilateral middle cerebral artery was associated with a sig-

nificantly increased risk of developing cerebral ischaemia [odds ratio (OR) = 31, 95% confidence interval (CI) = 3–302, $p = 0.005$].

The relationship between MES frequency and risk of cerebral ischaemia in patients undergoing carotid endarterectomy was studied by Levi et al. [18]. They measured MES in 59 patients intra- and post-operatively. MES were detectable in 69% of patients during the first postoperative hour with a mean frequency of 19 counts per hour [standard error of the mean (SEM) ± 4.5]. There was a clear association between MES counts >50 per hour (7 cases) and the development of ischaemic stroke (3 cases) and TIA (two cases) in the territory of the insonated middle cerebral artery during the monitoring period ($\chi^2 = 45.9$, $p < 0.0001$). The positive predictive value for cerebral ischaemia of counts >50 per hour was 0.71.

Valton et al. [19] investigated the incidence of early ischaemic recurrence (EIR) in 73 patients with strokes or TIAs that were considered to be of carotid origin on the basis of symptomatic presentation and lack of confounding co-morbid conditions. Patients were monitored for MES within 7 days of the onset of symptoms and followed-up for the duration of their hospital stay [mean $\pm$

Table 1. Summary of studies showing association between MES and risk of ischaemic events

Study	Study design	Condition	Study end points	Outcome
Siebler et al., 1995 [17]	prospective, blinded off-line assessment, n = 64	asymptomatic carotid stenosis	ischaemic symptom (stroke/TIA)	MES $\geq 2/h \rightarrow$ OR = 31 (95% CI = 3–302, $p = 0.005$)
Levi et al., 1997 [18]	prospective, blinded off-line assessment, n = 65	carotid endarterectomy	any focal ischaemic neurological deficit and/or death ≤ 30 days after operation	MES $>50/h \rightarrow$ greater risk of stroke/TIA ($p < 0.0001$)
Valton et al., 1998 [19]	prospective, blinded off-line assessment, n = 73	symptomatic carotid stenosis	EIR (stroke/TIA)	presence of MES $\rightarrow$ RR = 8.7 (95% CI = 2–38.2, $p = 0.015$)
Molloy and Markus, 1999 [20]	prospective, blinded off-line assessment, n = 111	carotid stenosis	stroke, TIA, death, carotid endarterectomy or angioplasty	MES predictive of stroke/TIA in symptomatic ($p = 0.02$) and asymptomatic ($p = 0.007$) patients
Babikian et al., 1997 [21]	retrospective, unblinded, n = 302	carotid stenosis	new or recurrent cerebral ischaemic event	more EIRs observed in MES-positive arteries (9 of 10)
Wong et al., 2002 [22]	prospective, blinded off-line assessment, n = 30	middle cerebral carotid artery stenosis	acute cerebral infarct	MES predicts acute infarcts on DWI ($R^2 = 0.475$, $p < 0.001$)
Gao et al., 2004 [23]	prospective, blinded off-line assessment, n = 114	middle cerebral carotid artery stenosis	further ischaemic event (stroke/TIA)	presence of MES $\rightarrow$ OR = 8.45 (95% CI = 1.69–42.22, $p = 0.01$)

MES = Microembolic signals; TIA = transient ischaemic attack; EIR = early ischaemic recurrence; OR = odds ratio; RR = relative risk.

standard deviation (SD) follow-up = 10 ± 8 days]. Eight patients had an EIR during the follow-up period (two strokes and six TIAs) – 5 occurred in the 15 patients with MES (33%), but only 3 in the 58 patients without MES (5%, $p = 0.008$). Further analysis showed that the presence of MES is a significant independent predictor of EIR in patients with carotid stroke or TIA (relative risk = 8.7, 95% CI = 2–38.2, $p = 0.015$).

Molloy and Markus [20] looked at the correlation between the frequency of MES and subsequent incidence of stroke or TIA in 111 patients with $>60\%$ carotid stenosis (measured by Duplex ultrasound) and no obvious source of cardiac emboli. Just over a third of the patients were asymptomatic and the remainder had had symptoms in the territory of the stenosed artery within the previous 12 months. MES were detected in 41 subjects. The presence of MES was predictive of TIA and stroke risk during follow-up in both symptomatic ($p = 0.02$) and asymptomatic patients ($p = 0.007$), while MES were more common in subjects with plaque ulceration with a relative risk of 4.94 (95% CI = 1.23–19.84, $p = 0.025$).

In a retrospective study, Babikian et al. [21] examined the relationship between the presence of MES along the internal carotid or basilar artery territories and the risk of experiencing a recurrent cerebral or retinal ischaemic event. Out of 229 patients with cerebrovascular disease,

but no cardiac embolic sources, MES were detected in 61 out of 310 affected arteries and were observed significantly more often in symptomatic (28.6%) compared with asymptomatic (12.4%) vessels (relative risk = 2.3, 95% CI = 1.4–3.7, $p < 0.001$). Out of 10 recurrent ischaemic events that occurred during a median follow-up of 8 days after MES measurement, 9 occurred in the territories of MES-positive arteries, but only 1 in the territory of an MES-negative artery. Furthermore, MES were seen significantly more frequently in arteries with lesions causing more than 70% stenosis or occlusion than in those with a degree of stenosis $<70\%$ ($p = 0.016$).

In a study to examine the mechanism of acute cerebral infarction in patients with middle cerebral artery stenosis, we found that MES frequency predicted the number of acute cerebral infarcts as measured by diffusion weighted imaging (DWI) [22]. Of the 30 patients who entered the study, 15 had single and 15 multiple infarcts. MES were detected in 10 patients; 9 with multiple infarcts and 1 with a single infarct. The number of MES predicted the number of acute infarcts on DWI (linear regression, adjusted $R^2 = 0.475$, $p < 0.001$). A follow-up study involving an additional 114 patients found that MES was more common in patients with severe stenosis (48%) than in those with mild-to-moderate stenosis (15%, $p = 0.02$, Pearson χ^2). In addition, MES was a predictor for further

ischaemic stroke or TIA (adjusted OR = 8.45, 95% CI = 1.69–42.22, $p = 0.01$) [23].

Overall, these studies provide a wealth of data to support the premise that MES are a surrogate marker for stroke and TIA risk. The presence of MES also appears to correlate with the presence and degree of severity of the arterial stenotic lesion. It should be noted that the confidence limits of the results reported above are very wide, demonstrating the need for larger, better powered studies.

Use of MES Measurements in Evaluating Antiplatelet Therapies for Stroke Prevention

A number of relatively small studies have investigated the relationship between antiplatelet therapy and MES frequency. These are summarized in table 2, together with details of the study design and endpoints. Most studies have looked at the effects of ASA on MES frequency, although recent studies have investigated the effects of the glycoprotein IIb/IIIa receptor antagonist tirofiban, and of the adenosine diphosphate (ADP) receptor antagonist clopidogrel. Studies have also been carried out on the investigational products *L*-arginine and *S*-nitrosoglutathione (GSNO). Both substances have been proposed as having antiplatelet activity; *L*-arginine on the basis that it reduces platelet aggregation and adhesion in vitro and GSNO on the basis that it is a physiological nitric oxide donor.

Goertler et al. [24] investigated the effects of intravenous ASA treatment on MES in 9 patients who had had a recent stroke or TIA, considered to be middle cerebral arterioembolic in origin, within the previous 12 days. The frequency of MES detection decreased significantly in 7 of 9 patients following the administration of ASA, from a mean signal rate per hour of 25.1 to a mean value of 6.4, 30 min after drug administration. One patient did not respond to treatment and only a minor and transient effect was seen in another, although this latter patient was already receiving ASA at the time of study entry. Interestingly, MES were only detected ipsilateral to the symptomatic stenoses with no signals detected in the contralateral middle cerebral arteries.

Another study from this group published in 2001 [25] investigated the frequency of MES in 74 patients with amaurosis fugax, TIA or minor stroke attributable to the territory of the middle cerebral artery and without evidence of cardiac involvement. MES were detected in 19 of 26 (73%) patients who did not receive antiplatelet med-

ication, 9 of 23 (39%) who received ASA since experiencing the ischaemic event and 10 of 25 (40%) who were already receiving ASA before experiencing the ischaemic event. Multivariate analysis indicated an association between the absence of medication with ASA and the occurrence of MES (OR = 7.1, 95% CI = 1.6–31.4, $p = 0.01$).

Goertler et al. [26] further studied this relationship in 86 patients with a non-disabling arterioembolic ischaemic event in the anterior circulation within the previous 30 days and a medium- or high-grade stenosis ($\geq 50\%$) of the ipsilateral carotid or middle cerebral artery. Patients underwent TCD monitoring on admission and antithrombotic treatment commenced. Patients in whom embolic signals were detected underwent a second monitoring within 4 days and were then followed up for 6 weeks. MES were detected at admission in 44 patients, while only 25 were MES positive at the second monitoring. During follow-up, 6 ischaemic events (2 strokes, 3 TIAs, 1 amaurosis fugax) occurred in the 25 patients with persisting MES, compared with none in the 19 patients in whom signals had ceased by the second monitoring. The decrease in MES was found to be significantly associated with the administration of antiplatelet agents ($p < 0.001$).

The effect of tirofiban in reducing MES has been studied in 24 patients with recent cerebral or retinal embolism of arterial origin and without obvious source of cardiac emboli [27]. In this study, patients who had an MES rate of >6 per hour received tirofiban by infusion at a dose of $0.4 \mu\text{g/kg}$ body weight for 30 min followed by continuous infusion at a dose of $0.1 \mu\text{g/kg}$ body weight together with intravenous unfractionated heparin. Within 24 h of initiation of the tirofiban infusion, the MES frequency decreased from a median of 38 (range 9–324) per hour to 0 in all patients. The inhibitory effect of tirofiban on MES rate was reversible; on cessation of therapy, the rate of MES increased significantly to a median value of 13.5 (range 0–35).

The effects of clopidogrel treatment on top of ASA in reducing MES has been investigated in 8 patients (5 with acute ischaemic stroke and 3 with TIA) with extracranial stenosis diagnosed by duplex ultrasound or intracranial artery stenosis identified by TCD [28]. All patients were receiving ASA therapy at the time of study entry, with 1 patient also receiving dipyridole. After study entry, patients received clopidogrel 75 mg daily on top of their ASA. The median number of MES at baseline was 8 (range 3–51). MES measurements carried out on days 3–7 of dual therapy showed a significant reduction in sig-

Table 2. Summary of design and endpoints of studies evaluating effect of anti-platelet therapy on MES

Study	Study design	Condition	Study arms	Assessment	Outcome
Goertler et al., 1999 [24]	single arm, n = 9	symptomatic carotid stenosis; symptoms 0–12 days prior to initiation	bolus ASA 500 mg i.v.; oral ASA 300 mg/day next day onwards	TCD 2.5 h after bolus; additional assessment (1 h) within 2 days	MES reduced from 25.1 to 6.4 per hour
Goertler et al., 2001 [25]	unblinded, dual arm, n = 74	symptomatic carotid stenosis	ASA or no antiplatelet therapy during TCD	1-hour TCD immediately after patient admission/presentation	detection of MES reduced from 73 to 40% of patients
Goertler et al., 2002 [26]	single arm, n = 86	arterioembolic stroke, with $\geq 50\%$ carotid stenosis	antithrombotic therapy initiated after 1 h TCD after admission	1-hour TCD within 4 days; occurrence of cerebral ischaemic events after 6 weeks	MES decreased significantly by antiplatelets ($p < 0.001$)
Junghans and Siebler, 2003 [27]	single-arm, blinded off-line MES assessment, n = 24	recent symptoms of ischaemic event	bolus tirofiban 0.4 $\mu\text{g}/\text{kg}/\text{min}$ for 30 min, followed by 0.1 $\mu\text{g}/\text{kg}/\text{min}$ cont. inf.	20–30 min TCD before tirofiban, at end of cont. inf., and ≥ 2 h after infusion	MES frequency reduced from median 38 (9–324) to 0 in all patients
Esagunde et al., in press [28]	single arm, n = 8	symptomatic carotid stenosis	75 mg clopidogrel added to ongoing ASA therapy	Repeat TCD between days 3–7 and after 2 months	MES reduced from median 8 (3–51) to median 0.5 (0–12) after 7 days ($p = 0.012$); no emboli observed at 2 months
Payne et al., 2004 [29]	dual-arm, double-blinded, randomized, placebo-controlled, independent MES assessment, n = 100	carotid endarterectomy	75 mg clopidogrel or placebo night before surgery; all patients on long-term ASA 150 mg	TCD ≤ 3 h after surgery	MES decreased by clopidogrel over placebo (OR = 10.23, 95% CI = 1.3–83.3, $p = 0.01$)
Kaposzta et al., 2001 [30]	double-blind, randomized, placebo-controlled, blinded off-line MES assessment, n = 42	carotid endarterectomy	GSNO 2.2–4.4 nmol/kg/min i.v. or <i>L</i> -arginine 30 g i.v. or saline i.v. given 30 min after surgery; all patients given ASA and heparin	TCD for 1 h ≤ 24 h before surgery, for 4 h 30 min after surgery, and for 1 h 6 and 24 h after surgery	MES reduced by both active agents at 4 and 24 h ($p < 0.001$)
Kaposzta et al., 2002 [31]	double-blind, randomized, placebo-controlled, blinded off-line MES assessment, n = 16	angioplasty/carotid artery stenting	GSNO 2.2–4.4 nmol/kg/min i.v. or saline i.v. given 30 min after surgery; all patients given ASA	TCD for 1 h before treatment, for 3 h on initiation of therapy, and 1 h 6 and 24 h after initiation	MES reduced by GSNO at 3 h (95%, $p = 0.007$) and 6 h (100%, $p = 0.01$)
Kaposzta et al., 2002 [32]	double-blind, randomized, placebo-controlled, blinded off-line MES assessment, n = 20	symptomatic carotid stenosis	GSNO 2.2–4.4 nmol/kg/min i.v. or saline i.v. given 30 min after surgery; all patients given ASA	TCD for 1 h before treatment, for 3 h on initiation of therapy, and 1 h 6 and 24 h after initiation	MES reduced by GSNO at 3 h (84%, $p < 0.0001$), 6 h (95%, $p = 0.003$) and 24 h (100%, $p < 0.0001$)
Markus and Ringelstein, 2004 [33]	multicenter, randomized, double-blind, two-parallel groups, blinded off-line MES assessment, n = 107	symptomatic carotid stenosis/TIA/minor stroke	clopidogrel (300 mg d1, 75 mg d2–7) or placebo; all patients given ASA 75 mg d2–7	1 h TCD on days 0, 1 and 7	MES decreased by clopidogrel/ASA over ASA from 72.5 to 45% (RR = 37.7%, $p = 0.01$)

MES = Microembolic signals; ASA = acetylsalicylic acid; TCD = transcranial Doppler ultrasonography.

nal frequency [median = 0.5 (range 0–12), $p = 0.012$] with a complete cessation of MES in 4 patients. Another study assessed the effect of clopidogrel combined with aspirin on platelet response to ADP and postoperative MES in carotid endarterectomy (CEA) patients. The number of emboli detected by TCD within 3 h of CEA were independently quantified and the results displayed a significant decrease in MES for clopidogrel over placebo (OR = 10.23, 95% CI = 1.3–83.3, $p = 0.01$). Clopidogrel also significantly reduced platelet ADP response compared with placebo (8.8%, $p < 0.05$) [29].

Recently, a number of studies have used the measurement of MES as an experimental tool to assess the potential efficacy of *L*-arginine and GSNO in stroke prevention. In the first study [30], 42 patients undergoing CEA were treated postoperatively with intravenous *L*-arginine, GSNO or placebo for 90 min, and MES measurements were made. MES were significantly reduced in the *L*-arginine and GSNO groups compared with the placebo group ($p < 0.001$ in both cases) at 4 h and 24 h after treatment. In a second study [31] in 16 patients undergoing carotid angioplasty and stenting for symptomatic $\geq 70\%$ internal carotid artery stenosis, GSNO treatment resulted in a rapid reduction in the frequency of embolic signals of 95% at 3 h and 100% at 6 h ($p = 0.007$ and $p = 0.01$ vs. placebo, respectively). In a third study [32] involving 20 patients with $\geq 50\%$ internal carotid artery stenosis and with ≥ 3 embolic signals detected during a half-hour screening, MES were measured following treatment with either GSNO (4.4 mmol/kg per min) or placebo for 90 min. GSNO resulted in a rapid reduction in the frequency of embolic signals of 84% at 3 h, 95% at 6 h and 100% at 24 h ($p < 0.0001$, $p = 0.003$ and $p < 0.0001$ vs. placebo, respectively).

The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis study was designed to investigate the effects of clopidogrel in addition to ASA compared with the effects of ASA alone on the incidence of cerebral MES in patients with symptomatic (TIA or stroke within past 3 months) carotid artery stenosis ($>50\%$). Platelet aggregation, activation and platelet-dependent thrombin generation were also investigated. Initial results have shown that the incidence of MES was reduced from 72.5% in the placebo group to 45% in the clopidogrel group (relative risk reduction = 37.7%, $p = 0.01$). Furthermore, the mean rate of embolization (expressed as a percentage of baseline) was reduced compared with placebo at day 1 from 59.3 to 22.1% ($p < 0.001$) and at day 7 from 37.1 to 14.4% ($p = 0.001$) [33].

Some of the above studies were not placebo controlled. This is important as MES in acutely symptomatic pa-

tients is known to fall in the days after an event; recordings compared between day 1 and some days later may therefore show a significant reduction by chance. However, equivalent reductions in MES following antiplatelet therapy have also been observed in a number of randomized, double-blind, placebo-controlled studies, which strongly suggests that this effect is real. Taken together, these studies provide a sound basis for suggesting that measuring MES frequency might be a good surrogate marker for evaluating the efficacy of antiplatelet agents in the prevention of stroke.

The Future

While there are now compelling data showing an association of MES with the combined end point of stroke and TIA, equivalent data are not yet available for the end point of stroke alone. For MES to be confirmed as a surrogate marker for stroke, positive results from such studies will be required.

The Clopidogrel plus Aspirin for Infarct Reduction in acute stroke/TIA patients with large artery stenosis and microembolic signal (CLAIR) study will evaluate the effects of clopidogrel in addition to ASA compared with the effects of ASA alone on the incidence of cerebral MES. CLAIR will also look at the correlation between MES and numbers of acute infarct as measured by DWI. This latter investigation has the potential to correlate MES and clinical events using the imaging data.

Together these studies should help to clarify whether cerebral microemboli are sensitive to antiplatelet therapy and whether MES measurements are a reliable surrogate marker of efficacy for evaluation of antiplatelet regimens. CLAIR and other large, ongoing trials will in addition also greatly expand the total patient sample, which is to date still limited.

Conclusions

From the results of studies to date, there is good evidence to suggest that measurement of MES may be a suitable surrogate marker for evaluating the efficacy of antiplatelet agents in the prevention of stroke, particularly as methods for discriminating between solid and gaseous MES are continually being improved. Studies currently in progress should provide further insight into the value of the measurement of MES in clinical studies in stroke prevention.

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