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Microemboli Monitoring in Ischemic Stroke

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1. Introduction

Circulating microemboli in the arterial system were detected using ultrasound as early as 1969 (Spencer, Lawrence et al. 1969) (Fig 1). Microemboli to brain can be detected with high sensitivity using trancranial Doppler by insonating the middle cerebral arteries.

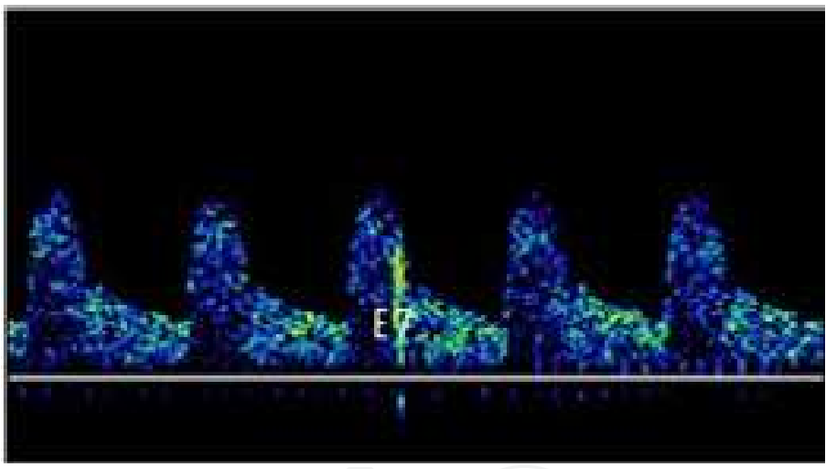

Fig. 1. Microemboli from middle cerebral artery detected by TCD.

The detection is made possible because of the acoustic impedance between microemboli and blood, which increases the ultrasound intensity. Microemboli are transient (<100ms), high intensity (> 3dB) and unidirectional signal which are accompanied by a characteristic click or chirp sound (Ringelstein, Droste et al. 1998). The origin of microemboli are usually from an atheromatous plaque in the carotid artery or the aorta, from the heart chambers in patients with atrial fibrillation, or from prosthetic heart valves.

2. Characteristics of microemboli

The detected signals are either of gaseous or solid embolic material (Russell, Madden et al. 1991). Solid microemboli consist of platelet aggregates, thrombus or whole blood (Markus and Brown 1993). Platelet aggregates are usually ruptured off an atheromatous plaque because of the shear stress on vessel wall (Kessler 1992). Postmortem studies have shown

that solid microemboli contain lipids in addition to small birefrigent particles (Brown, Moody et al. 1996). The gaseous microemboli usually originates from a prosthetic heart valve. It is created by mechanically induced cavitations. A reliable differentiation between gaseous and solid microemboli is not possible with single frequency probe that are being currently used in most centers (Dittrich, Ritter et al. 2002). Newly available dual frequency probes can reliably differentiate between solid and gaseous microemboli. However, such differentiation is not of much significance in most patient subgroups.

3. Impact of microemboli on brain

Solid microemboli are much bigger than gaseous microemboli, having an approximate diameter of 100 μm and 4μm respectively. The larger size of solid microemboli compared to capillaries (diameter 7-10 μm) can cause blockade of microcirculation. Solid microemboli, which predominantly arises from atheromatous plaque, can cause injury to the brain, which may manifest as cognitive impairement. Histological studies have shown that such microemboli leads to loss of enzymatic activities of endothelial cells leading to degeneration of capillaries (Brown, Moody et al. 1996). These microemboli usually disappear from brain within two weeks, but can persist there for up to 6 months. In contrast gaseous microemboli, predominantly seen in patients with prosthetic valve, have no deleterious effect on brain (Kaps, Hansen et al. 1997).

4. Prevalence

Prevalence of microemboli varies in different patient sub-groups. An estimated prevalence of 1-5% is estimated in the general population based on small control groups from different studies(Daffertshofer, Ries et al. 1996) (Georgiadis, Lindner et al. 1997). The prevalence is higher in high-risk patients who are vulnerable to thromboembolic events.

4.1 Prevalence in acute ischemic stroke

A large proportion of ischemic stroke is of embolic etiology. Therefore, assessing the prevalence of microemboli following ischemic stroke is of great interest. Very few studies have assessed the prevalence of microemboli in the acute phase of stroke because of the technical difficulties. The available studies in the acute phase of stroke (<24 hours) have shown the prevalence of microemboli to be between 19-49% (Sliwka, Lingnau et al. 1997; Delcker, Schnell et al. 2000; Iguchi, Kimura et al. 2008; Idicula, Naess et al. 2010). However monitoring beyond the first 24 hours after stroke shows a lower prevalence ranging from 6 to 32% (Tong and Albers 1995; Del Sette, Angeli et al. 1997; Koennecke, Mast et al. 1998; Valton, Larrue et al. 1998; Kaposzta, Young et al. 1999; Lund, Rygh et al. 2000; Serena, Segura et al. 2000; Gucuyener, Uzuner et al. 2001; Poppert, Sadikovic et al. 2006). The prevalence of microemboli in the largest of those studies (n=653) was less than 6% (Poppert, Sadikovic et al. 2006). It seems like there is an inverse relationship between timing of monitoring and the prevalence of microemboli following acute ischemic stroke. Table 1 shows the prevalence of microemboli following ischemic stroke in various studies.

Author	Monitoring	n	Prevalence(%)
Iguchi	< 24 hrs	125	49
Delcker	< 24 hrs	61	43
Sliwka	< 24 hrs	100	19
Idicula	< 24 hrs	40	25
Del Sette	> 24 hrs	75	12
Gucuyener	> 24 hrs	359	32
Koennecke	> 24 hrs	145	24
Lund	> 24 hrs	83	27
Poppert	> 24 hrs	653	6
Serena	> 24 hrs	182	9
Tong	> 24 hrs	38	11
Valton	> 24 hrs	73	21

Table 1. The prevalence of microemboli in various studies performed before and after 24 hours of stroke onset in various studies.

4.2 Prevalence in atherosclerotic carotid artery disease

The prevalence of microemboli is high in patients with large artery disease as in carotid artery stenosis. Table 2 shows a review of all studies in which prevalence of microemboli was assessed in symptomatic and asymptomatic carotid stenosis (Babikian, Hyde et al. 1994; Siebler, Kleinschmidt et al. 1994; Markus and Harrison 1995; Daffertshofer, Ries et al. 1996; Georgiadis, Lindner et al. 1997; Markus and MacKinnon 2005; Spence, Tamayo et al. 2005; Zuromskis, Wetterholm et al. 2008).

Author	**n**	**Symptomatic(%)**	**Asymptomatic(%)**
Zuromskis	197	32	4.5
Georgiadis	500	52	7
Siebler	89	82	
Babikian	75	28	
Daffertshofer	280	9	
Markus	38	34	3.5
Markus	230	48	
Spence	319		10

Table 2. Shows the prevalence of microemboli in symptomatic and asymptomatic carotid artery disease.

While the prevalence of microemboli in patients with carotid stenosis ranged from 20-90%, most of the studies showed a prevalence of more than 30% in symptomatic carotid stenosis (Markus and Harrison 1995). The large variation in the prevalence of microemboli in different studies may be attributed to differences in the timing of study, use of antiplatelet agents at the time of monitoring and the sample population itself. However the studies, which compared prevalence of microemboli in symptomatic and asymptomatic side, clearly shows a higher prevalence in the symptomatic side. A recent pooled analysis of microemboli in patients with symptomatic and asymptomatic carotid stenosis showed a prevalence of 42% and 8% respectively (Ritter, Dittrich et al. 2008).

4.3 Prevalence in intracranial stenosis

The prevalence microemboli in intracranial stenosis is less well studied compared to carotid stenosis. A review of those studies is given in table 3.

Author	n	Symptomatic	Asymptomatic
Wong	60	15	0
Nabavi	14	14	7
Gao	114	22	
Wong	30	33	
Droste	33	15	
Segura	29	36	

Table 3. Shows the prevalence of microemboli in the symptomatic and asymptomatic intracranial stenosis in various studies.

The available data shows that the prevalence of microemboli in intracranial stenosis to be between 7-33% (Nabavi, Georgiadis et al. 1996; Segura, Serena et al. 2001; Wong, Gao et al. 2001; Droste, Junker et al. 2002; Wong, Gao et al. 2002; Gao, Wong et al. 2004). The prevalence of microemboli in the largest of those studies (n=114) was 22%. The prevalence of microemboli in asymptomatic stenosis were between 0-7% (Nabavi, Georgiadis et al. 1996; Wong, Gao et al. 2001). A pooled analysis of patients with intracranial stenosis shows the prevalence of microemboli in the symptomatic and asymptomatic side to be 25% and 0% respectively (Ritter, Dittrich et al. 2008). Overall, the prevalence of microemboli in intracranial stenosis is lower compared to carotid artery stenosis. Lower prevalence of microemboli in intracranial stenosis may be because of the technical difficulty in performing microemboli monitoring in the presence of intracranial stenosis as well as the difference in plaque morphology.

4.4 Prevalence in various cardiac diseases

Microemboli from the heart originate either from the heart chambers itself or from prosthetic heart valves. Parallel to the known risk factors for cardioembolic stroke, microemboli are often observed in atrial fibrillation, prosthetic heart valves, patent foramen ovale, acute myocardial infarction and left ventricular dysfunction. The highest prevalence of microemboli is seen in patients with prosthetic heart valves, about 60% with mechanical prosthetic heart valves and about 10% with biological prosthetic heart valves (Eicke, Barth et al. 1996). In patients with atrial fibrillation, the prevalence of microemboli seems to be higher in symptomatic atrial fibrillation (29%) as opposed to asymptomatic atrial fibrillation (10%) (Kumral, Balkir et al. 2001). Similarly, there is a higher prevalence of microemboli in valvular atrial fibrillation as opposed to non-valvular atrial fibrillation corresponding to a higher risk for thromboembolic events (Kumral, Balkir et al. 2001). Except for mechanical prosthetic heart valves, the overall prevalence of microemboli in various heart conditions seems to be lesser than in carotid artery disease.

5. Application of microemboli monitoring

5.1 Application of microemboli monitoring in acute stroke

It is optimal to perform microemboli monitoring closer to the onset of symptoms because of the inverse relationship between timing of monitoring and the prevalence of microemboli

(Forteza, Babikian et al. 1996). The technical difficulty and the need for manpower make it difficult to perform monitoring within the first 24 hours after stroke onset. However, it may still be adequate to perform monitoring after the first 24 hours. Identification of microemboli will help us understand the etiology, predict outcome and assess the effectiveness of secondary prophylaxis.

5.1.1 Assessing the etiology of stroke

TOAST is one of the commonly used classifications to define stroke etiology. However, this classification fails to clearly define etiology in more than one third of the patients (Kolominsky-Rabas, Weber et al. 2001). More tools are needed to determine stroke etiology reliably. Microemboli are generally found in patients with embolic etiologies, both of arterial and of cardiac origin. A review of studies conducted in ischemic stroke patients shows that microemboli are mostly present when an embolic source is present (Del Sette, Angeli et al. 1997; Sliwka, Lingnau et al. 1997; Koennecke, Mast et al. 1998; Kaposzta, Young et al. 1999; Lund, Rygh et al. 2000; Serena, Segura et al. 2000; Poppert, Sadikovic et al. 2006; Iguchi, Kimura et al. 2008; Idicula, Naess et al. 2010). Some studies have, however, shown the presence of microemboli in lacunar stroke, even though less frequent than in other etiologies (Koennecke, Mast et al. 1998; Lund, Rygh et al. 2000; Iguchi, Kimura et al. 2008). Microemboli were absent in all lacunar stroke patients in most other studies including the largest of them (Poppert, Sadikovic et al. 2006). Even though the specificity of microemboli in determining an embolic etiology is not fully known, the presence of microemboli strongly suggests the possibility of an embolic source. Further differentiation between large-artery and cardioembolic stroke can also be made based on characteristics of microemboli. Bilateral microemboli may suggest microemboli from heart or arch of aorta (Kaposzta, Young et al. 1999), whereas unilateral microemboli suggest carotid artery stenosis or intracranial artery stenosis. This can especially be relevant when two potential embolic sources are simultaneously present as in carotid stenosis along with atrial fibrillation. Specificity of bilateral microemboli in determining cardiac source of embolism can further be improved by recording both the proximal carotid arteries and both middle cerebral arteries simultaneously.

5.1.2 Predicting outcome after stroke

The value of microemboli in predicting outcome and future vascular events following an ischemic stroke is known only to a limited extent due to the lack of sufficient studies. A review of all studies involving 602 patients reveals an interesting finding. All except one study showed that microemboli is an independent predictor of future vascular events with an odds ratio of 4 or above (Valton, Larrue et al. 1998; Censori, Partziguian et al. 2000; Gao, Wong et al. 2004; Markus and MacKinnon 2005; Iguchi, Kimura et al. 2008; Idicula, Naess et al. 2010). It infers that microemboli monitoring may be of value in predicting recurrence following acute ischemic stroke.

The functional outcome or disability after stroke is, however, less well predicted by the presence or absence of microemboli. Two studies in which data on functional outcome was available failed to observe any association between microemboli and functional outcome (Delcker, Schnell et al. 2000; Idicula, Naess et al. 2010). One of the studies showed a trend towards higher mortality among patients with microemboli, but the association was not significant after adjusting for confounding factors (Idicula, Naess et al. 2010). Thus, there is a paucity of evidence to suggest that microemboli predict poor functional outcome after ischemic stroke.

5.1.3 Assessing efficacy of secondary prophylaxis

Many platelet inhibitors are approved for secondary prophylaxis after ischemic stroke. It is difficult to predict which of the approved agents would be a better alternative in an individual patient. Microembolic mostly consist of platelet aggregates. Therefore, their measurement may be used as a surrogate marker for evaluating anti-platelet effect (Wong 2005). Glycoprotein IIb/IIIa receptor antagonist such as tirofiban infusion has shown to reduce the rate of microemboli and the effect was reversible with the cessation of infusion (Junghans and Siebler 2003). Administration of intravenous and oral acetylsalicyclic acid (ASA) has shown to reduce the frequency of microemboli rapidly (Goertler, Baeumer et al. 1999; Goertler, Blaser et al. 2001). Several small studies have shown that dual antiplatelet therapy might lead to rapid decline in microembolic frequency (Esagunde, Wong et al. 2006). The studies were not double blinded randomized studies. However, they showed that the frequency of microemboli was significantly reduced after administering antiplatelet agents. It indicates the potential of measuring microemboli as a surrogate marker of anti-platelet effect. This is particularly important in patients with recent symptomatic carotid stenosis.

In CARESS trial, a randomized double-blind study, patients with symptomatic carotid stenosis were randomized to either aspirin alone or aspirin and clopidogrel. Patients who received dual anti-platelet therapy with aspirin and clopidogrel had significantly lower microemboli compared to patients who received aspirin alone (Markus, Droste et al. 2005). Subsequently, fewer recurrent ischemic events were observed in patients who received dual antiplatelet therapy (Mackinnon, Aaslid et al. 2005). Dual antiplatelet therapy with aspirin and clopidogrel may be an optimal choice at least in a subgroup of high-risk stroke patients who can be identified with the help of microemboli monitoring. However, the long-term outcome or the optimal duration of dual antiplatelet therapy is not known yet. On the contrary, the effect of anticoagulation on microemboli is highly uncertain. Except for some anecdotal reports, there is no evidence that anticoagulation would abort microemboli (Poppert, Sadikovic et al. 2006).

5.2 Application of microemboli monitoring in carotid artery and intracranial artery stenosis

Microemboli from an unstable carotid plaque often represent inflammation within the plaque (Jander, Sitzer et al. 1998). Studies with FDG-PET in patients with carotid plaque have shown that patients with microemboli are more likely to have inflammation within the plaque (Moustafa, Izquierdo-Garcia et al. 2010). Plaque specimens in patients undergoing endarterectomy have shown that presence of microemboli is strongly associated with plaque fissuring and luminal thrombosis (Sitzer, Siebler et al. 1995). In patients with symptomatic carotid stenosis, microemboli is an indicator of plaque instability (Siebler, Kleinschmidt et al. 1994). Carotid endarterectomy results in drastic reduction or disappearance of microemboli (Orlandi, Parenti et al. 1997). Similarly, patients with asymptomatic carotid stenosis microemboli have proven to be a known marker of future vascular events as shown in several studies (Siebler, Nachtmann et al. 1995; Molloy and Markus 1999). Thus, the presence of microemboli might help choose the right therapeutic option including endarterectomy especially in patients with asymptomatic stenosis. Microemboli monitoring is also important in patients with intracranial artery disease as well. Even though there are technical difficulties in performing microemboli monitoring in the presence of intracranial stenosis, the presence of microemboli provides valuable information to choose appropriate

management. The frequency of microemboli in the presence of intracranial artery stenosis has shown to be associated with the number of infarcts on imaging (Wong, Gao et al. 2002). In patients with frequent microemboli, dual antiplatelet agents has shown to reduce the frequency of microemboli from intracranial stenosis as in carotid artery stenosis (Sebastian, Derksen et al. 2011), arguing in favour of using it in those patients.

5.3 Application of microemboli monitoring in heart diseases

The clinical and prognostic significance of microemboli in patients with atrial fibrillation and prosthetic valves is unclear. Only few studies have shown that anticoagulation may reduce microembolic frequency in patients with atrial fibrillation (Tinkler, Cullinane et al. 2002). It is difficult to choose between anticoagulation versus anti-platelet agents based on the presence or absence of microemboli. However, the presence of microemboli may prompt the use either anticoagulation or anti-platelet agents in patients with atrial fibrillation regardless of any thromboembolic events.

5.4 Application of microemboli monitoring in special situations

5.4.1 Arterial dissection

As in embolic stroke, microemboli are often seen in patients with dissection. More microemboli are present in patients who present with stroke symptoms as opposed to local symptoms (Ritter, Dittrich et al. 2008). Presence of microemboli seems to be a predictor of stroke recurrence (Molina, Alvarez-Sabin et al. 2000). Microemboli are seen both in dissection of carotid and vertebral arteries, and possibly predict thromboembolic events (Droste, Junker et al. 2001). Presence of microemboli may be a determining factor in choosing the right medication, favoring anticoagulation over antiplatelet agents (Engelter, Brandt et al. 2007).

5.4.2 Monitoring during and after carotid endarterectomy

Presence of microemboli during carotid endarterectomy is an indicator of new ischemic events (Ackerstaff, Moons et al. 2000) (Ackerstaff, Jansen et al. 1995). Presence of microemboli should alert the physician to change the surgical technique. Ongoing microemboli after endarterectomy indicates other sources of emboli, which prompt reassessment of the operated carotid as well as searching for other sources.

6. Uncertainties and future directives

Microembolic signals have been identified in a number of clinical neurovascular settings with a variety of embolic sources, but predominantly in patients with large vessel atherosclerosis. In these patients microembolic signals may be an independent predictor of future stroke or TIA, but the association between microembolic signals and long-term clinical outcome has not always been found (Lund, Rygh et al. 2000; Abbott, Chambers et al. 2005). Research has mainly focused on quantity, i.e. presence or frequency of microemboli, but less on quality, i.e. size or constituents of microemboli due to technical limitations. After years of studies, the relevance of microemboli in the individual patient with acute stroke remains elusive and uncertainty prevails. There may be several reasons for this, of which the timing of assessment may be of great relevance. Studies have been performed within 24 hours, 48 hours, 72 hours, or even 7 days. The implications of microemboli in the early hours after stroke may be different from those at later stages. The number of microemboli seems to

be inversely associated with the time from stroke onset. Early microemboli may reflect an ongoing acute vascular process, which might be satisfactorily controlled with adequate antithrombotic and statin treatment. Late microemboli persisting in spite of adequate treatment may reflect a true malignant vascular process with a high risk of future stroke. And in between, there is a transition time zone with microemboli of possibly varying long-term clinical relevance. Embolization is, however, not a continuous or a random process. Embolization occurs with temporal clustering and may occur outside the microemboli monitoring time window. Strength of TCD monitoring is it's time resolution. It is conceivable that repeated microemboli monitoring over time will yield more information than what a short glimpse at one single time-point does. The temporal variability of embolization underlines the need for repeated long-lasting microemboli monitoring to improve estimation of true embolic load and pattern of embolization (Mackinnon, Aaslid et al. 2005).

The size of an embolus is of obvious relevance. Although embolic signals become more intense with increasing thrombus size, there is currently no method for estimating size (Martin, Chung et al. 2009). Low-intensity signals are routinely rejected in standard monitoring set-up, but there may be many real microemboli among these low-intensity microemboli signals, and the presence of low-intensity microemboli signals significantly increases the chance of finding high-intensity microemboli signals (Telman, Sprecher et al. 2011). Therefore, low-intensity microemboli signals need increased attention as a possible marker of clinically significant embolization. Quality of microemboli may be further analyzed using transcranial power M-mode Doppler and an energy signature. This approach may define a subgroup of patients with malignant microemboli, who have larger baseline infarcts, and worse clinical outcome (Choi, Saqqur et al. 2010). In general, careful assessment of diffusion-weighted MRI may give indirect evidence of the size of microemboli (Droste, Knapp et al. 2007).

Microemboli are markers of disease activity, not the disease itself. Microemboli have been associated with carotid plaque inflammation (Moustafa, Izquierdo-Garcia et al. 2010), coagulopathies (Seok, Kim et al. 2010) and platelet activation markers (Ritter, Jurk et al. 2009). Adding information on basic disease mechanisms may improve our understanding of the complex pathophysiology of acute embolic stroke as defined by MES monitoring.

7. Conclusion

The assessment of microemboli in acute stroke needs to move from quantity to quality, taking into account the natural variability in embolization rates and the temporal clustering of embolization. There is need to establish optimal monitoring protocols with extensive time windows. The emboli as such need to be understood within the complex framework of acute stroke, including vessel wall or cardiac pathology, inflammation and coagulation, as well as end-organ damage. Multimodal approach, including transcranial microemboli monitoring, is a prerequisite for future advances in embolic stroke.

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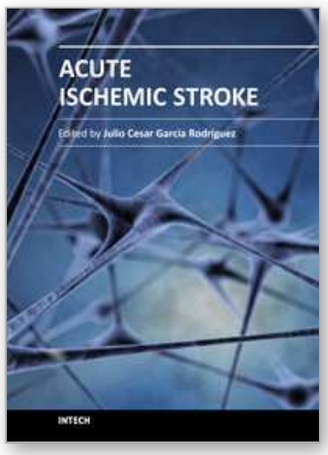

Acute Ischemic Stroke

Edited by Prof. Julio Cesar Garcia Rodriguez

ISBN 978-953-307-983-7
Hard cover, 236 pages
Publisher InTech
Published online 18, January, 2012
Published in print edition January, 2012

Despite significant technological advances in recent years, their impact on our overall health and social, well-being is not always clear to see. Perhaps, one of the best examples of this can be highlighted by the fact that mortality rates as a result of cerebrovascular diseases have hardly changed, if at all. This places cerebrovascular diseases as one of the most prominent causes of both disability and death. In Cuba, for instance, a total of 22,000 cases of cerebrovascular diseases are reported each year in a country where life expectancy should increase to 80 years in the near future. In such a situation, to have a book that includes in a clear and summarized way, a group of topics directly related to the preclinical investigations advances and the therapeutic procedures for the cerebrovascular disease in its acute phase constitutes a useful tool for the wide range of the contributors to this affection's problems solution. In this group is included students, professors, researchers, and health policy makers whose work represents one of the greatest social and human impact challenges of the XXI century basic and clinical neurosciences.

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