Prevalence and frequency of microembolic signals in 105 patients with extracranial carotid artery occlusive disease

Dirk W Droste, Ralf Dittrich, Vendel Kemény, Gernot Schulte-Altedorneburg, E Bernd Ringelstein

Abstract
Besides the established factors “presence of symptoms” and “degree of stenosis”, plaque echolucency is considered to be associated with increased risk of stroke in patients with carotid artery disease. An evaluation was carried out as to whether the prevalence and number of microembolic signals (MES) detected by transcranial Doppler ultrasound were higher in patients with echolucent carotid plaques.

One hundred and five patients with carotid artery stenosis from 20%-99% or occlusion underwent clinical investigations, duplex ultrasound of the carotid arteries, and a 1 hour recording from the middle cerebral artery downstream to the carotid artery pathology using the four gate technique. The presence of MES was more frequent and the number greater in symptomatic patients (21 out of 64 patients (33%); mean number of MES in all 64 patients 3.1) than in asymptomatic patients (four out of 41 patients (10%); mean number of MES in all 41 patients 0.3) (p=0.007, and p=0.006, respectively). Echogenicity of the lesions did not affect either number or presence of MES. Positivity for MES and the number of MES increased with increasing degree of stenosis (both p<0.002). Four out of 12 patients with carotid artery occlusion showed MES. No MES could be detected in carotid artery stenosis below 80%. There was a decline in positivity of MES and of the number of MES with the time after the ischaemic event. After 80 days or more after the index event, only one patient showed MES.

In conclusion, increasing degree of stenosis and presence of symptoms similarly affect macroembolic and microembolic risk. Thus MES may be a surrogate parameter for risk of stroke. The presence of MES in a few asymptomatic patients suggests that clinically silent circulating microemboli may give additional information on the pending embolic potential of carotid artery stenoses. Echolucency of the plaque was not related to an increased number of MES.

Keywords: ultrasonics; carotid artery disease; embolism

In extracranial carotid artery stenosis, besides the presence of symptoms and the degree of stenosis, low plaque echogenicity has been claimed to be also associated with future stroke risk.1–6 Clinically silent circulating cerebral microemboli can be detected as high pitched signals within the transcranial Doppler (TCD) frequency spectrum.7 8 The presence of such microembolic signals (MES) proves ongoing embolisation into the cerebral arteries, gives information on the frequency of embolisation, and helps to localise the embolic source.

In this study we evaluated the clinical and the ultrasonic features of patients with different degrees of extracranial carotid artery occlusive disease in relation to the presence and frequency of circulating microemboli in the dependent middle cerebral artery (MCA) using the four gate technique.9 In particular, we wanted to show that the above established risk factors for macroembolisation (presence of symptoms and degree of stenosis) and the debated risk factor “echolucency” are also risk factors for microembolisation.

Patients and methods
One hundred and five patients, aged from 29 to 86 years, were investigated (mean age 62 (SD 11 years) There were 27 women and 78 men. They were inpatients and outpatients of our department and underwent routine clinical investigations. All of them had extracranial carotid artery stenosis ≥20% or internal carotid artery (ICA) occlusion on ultrasound. Sixty four of them had presented at least one transient or permanent ipsilateral ocular or cerebral ischaemic event in the carotid artery territory under investigation. The time between the recording and the last event varied from 0 to 3474 days. Five patients were in atrial fibrillation during the recording. Thirty two patients were taking intravenous heparin, one...
Relation between the number of MES and the degree of stenosis. There is an increasing number of MES and of MES positive patients with increasing degree of stenosis and a peak at 90%-99% stenosis.

### Results

The distribution of degrees of stenosis and presence of symptoms is given in the figure. Thirty plaques were uniformly echoluent, 34 plaques were predominantly echoluent, 37 plaques were predominantly echogenic, and four were uniformly echogenic. In 46 patients a cross flow via the anterior communicating artery was present. Contralateral carotid artery high grade stenosis was present in nine patients, 12 patients had a contralateral ICA occlusion. No intracranial ICA or MCA stenoses were detected. Out of the 40 patients with either oral or intravenous anticoagulation, all but two had a stenosis ≥50%.

The total number of MES was 212, ranging from 0–38 in the individual patients. Twenty-one out of 64 symptomatic patients (33%) and four out of 41 asymptomatic patients (10%) showed MES. Symptomatic patients were more likely to have emboli (p=0.007) than asymptomatic patients. The number of MES was higher in the symptomatic patients (mean 3.1 (SD 7.7)) compared with the asymptomatic patients (mean 0.3 (SD 1.0); p=0.006). These values refer to the whole groups of patients, not only those embolus positive.

### Analysis and Statistics

The number of MES as well as the number of embolus positive patients in symptomatic patients and asymptomatic carotid artery disease were compared using the non-parametric Mann-Whitney U test. The number and presence of MES were investigated in the four echogenicity categories by a Kruskal-Wallis one way analysis of variance (ANOVA). The impact of the degree of stenosis on the number of MES and on embolus positivity was also evaluated using a Kruskal-Wallis one way ANOVA. For these analyses, the 12 patients with ICA occlusion were excluded. Significance was assumed at a value of p<0.05.

### Patient Characteristics

Patient subcutaneous heparin, eight oral antithrombotics, and 72 patients were taking aspirin or ticlopidine (some were on two drugs or switched, the previous drug still being active).
ischaemic event; only one patient showed MES more than 80 days after the index event.

Echogenicity of the lesion did not affect either the number or presence of MES (p=0.56 and p=0.49, respectively). Eight patients out of 30 with plaques uniformly echolucent had MES (mean number of MES for the whole group of 30 patients 0.97 (SD 2.82)), 10 patients out of 34 with plaques predominantly echolucent showed MES (mean number of MES 1.91 (SD 4.11)), seven out of 37 patients with predominantly echogenic plaques showed MES (mean number of MES 3.19 (SD 9.21)), and none of the four patients with uniformly echogenic plaques.

Out of the 25 patients with MES, four had possibly competing embolic sources. Two of these patients were in atrial fibrillation and two patients had a cross flow via the anterior communicating artery with a high grade carotid artery on the contralateral side.

Discussion
The degree of stenosis and the presence of ocular or cerebral ischaemic events were associated with a higher number and with a higher presence of MES in the present study.

Therefore, our study suggests that the presence and number of clinically silent circulating MES may be surrogate parameters for macroembolic (stroke) risk. Van't Hoff et al described a non-significant trend towards a higher number of MES with increasing degree of stenosis.13 Babikian et al described a higher prevalence of MES in patients with a stenosis of more than 50% compared with patients with ≤50% stenosis.14 The table gives a summary of the studies performed so far in this field.

Our finding that echogenicity of the plaque is not related to an increased number of MES reflects the debated role of echolucency as a risk factor for stroke.14-16 The decline of the MES number with time has also been reported by other authors.17-29 The low number of MES after about 80 days may indicate the time needed for plaque healing after disruption.20-22

The presence of MES in a few asymptomatic patients suggests that clinically silent circulating microemboli may give additional information on the impending embolic potential of carotid artery stenoses not covered by the patient's history. At present, there is still insufficient evidence to operate on clinically asymptomatic stenoses only relying on the presence of MES. So far no large study has unequivocally shown MES to be a risk factor for stroke, as the number of patients is high and the observation time needed is long.22 Our study indirectly further supports this possible relation of microembolic events and macroembolic risk. We showed an increase in microembolic risk with increasing degree of stenosis and presence of symptoms, a relation which is well known for macroembolic risk from clinical endarterectomy trials.24-27

The fissure of Rolando

The gyri of the brain are thought to have been first named “coils” by Praxagoras of Cos c300 BC and by Erasistratus c260 BC. Vesalius amplified the description. Thomas Willis believed that: “movement is initiated in the cerebrum . . .”

Vicq d’Azyr described the convolutions in 1786 noting the differences in morphology in different animals. Magendie similarly had noticed that: “The number, the volume, the disposition of the circumconvolutions are variable . . .”

The attachment of eponyms to cerebral fissures started with the fissure of Sylvius in 1663, though it had been clearly noted by Casper Bartholin (1585–1629), an anatomist in Denmark. The second structure to be so dignified was the fissure of Rolando in 1839.

Rolando observed the precentral and postcentral gyri on either side of the great central fissure. He referred to the convolutions as enteroid processes, a term not very different from fissure. He referred to the convolutions as central gyri on either side of the great central fissure. He returned to Turin as Professor of Experimental Anatomy. He was also responsible for demonstrating the primitive local damage that he knew he had caused, he was reluctant to draw firm conclusions about the relation of function to the anatomical areas examined.

“I rarely obtained a constant effect since it is extremely difficult to recognize what bundles of fibres have been lacerated . . . it is not possible to determine the consequences clearly and distinctly . . .”

Indeed many of his experiments were directed not at the cortex but at the cerebellum, striatum, thalamus, and quadrigeminal bodies. Rolando found the largest motor responses by stimulation of the cerebellum and stressed the importance of this structure in determining movement.

Pierre Flourens (1794–1867) in refuting much of Rolando’s work was accused of plagiarism; he therefore gave an annotated French translation to disprove these charges. Flourens experimented mainly on birds. He believed that the cerebrum was not divided functionally, but that intelligence and special senses were diffusely distributed throughout the brain: an early landmark of the holistic hypotheses of brain function.

It fell to Francois Leuret to give credit to Rolando: “Between these two convolutions of the brain: an early landmark of the holistic hypotheses of brain function.

Rolando: “Between these two convolutions exists a furrow that separates them . . .; it is as constant as the Sylvian fissure. I have called this furrow the fissure of Rolando, because it was this anatomist who first described it in man, in whom it is still more developed than in the monkey.”

Vicq d’Azyr had illustrated the central sulcus in 1786, but attached no special importance to it, so Rolando deserves the credit for its demonstration, despite the experimental difficulties he honestly recorded.

Luigi Rolando was born in Turin. After completing his medical studies he soon concentrated on experimental anatomy. He studied in Florence and became physician to the King of Savoy in Turin. The invasion of Italy by Napoleon drove him into exile in Sardinia for 12 years, where he became Professor of “Theoricopractical” Medicine at Sassari. He returned to Turin as Professor of Anatomy.

Rolando worked extensively on the cerebellum. He observed minor damage to cause staggering, but complete destruction caused total locomotor paralysis in his animals. He therefore regarded the cerebellum as of major importance in determining not only the regulation but also the strength of movement. Although an inaccurate view, this was a great step forwards from the prevailing notions of the cerebellum as controller of intellect, sensation, or vital forces.

He was also responsible for demonstrating in unstained tissue, “a particular grey matter in the posterior third of the posterior horns”, which he noticed was, “more gelatinous . . . of a different colour.”

The substantia gelatiosa was subsequently named after this remarkable anatomist. An original engraving of Luigi Rolando is found in the Biblioteque de l’Academie Nationale de Medecine, Paris.

J M S PEARCE
304 Berkeley Road, Aulaby, Hull HU10 7BG, UK

HISTORICAL NOTE

The fissure of Rolando

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