Persistent Microembolic Signals in the Cerebral Circulation on Transcranial Doppler after Intravenous Sulfur Hexafluoride Microbubble Infusion

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ABSTRACT

BACKGROUND AND PURPOSE: **Microembolic signals (MES) are detectable by transcranial Doppler monitoring and associated with increased risk of first or recurrent ischemic stroke. MES detection can also illuminate stroke etiology and the effect of prophylactic treatment. MES detection cannot accurately distinguish between stroke-related microemboli and ultrasound contrast agents. These agents contain microbubbles and are frequently used in neuro- and cardiovascular diagnostics. We aimed to assess how long after contrast infusion microbubbles are detectable by transcranial Doppler monitoring.**

METHODS: **Ten healthy volunteers received an intravenous infusion of stabilized sulfur hexafluoride microbubbles (SonoVue®) for 30 minutes. The infusion was followed by continuous unilateral Doppler monitoring (TCD-X, Atys Medical, Soucieu-en-Jarrest, France) for 3.5 hours.**

RESULTS: **MES persisted for 12 to 77 minutes (median 40.5 minutes), and the frequency tended to decrease gradually until cessation.**

CONCLUSIONS: **None of the subjects had detectable MES for more than 77 minutes after ultrasound contrast infusion. MES detection with the intent to detect stroke-related microemboli should wait for at least this long after completed infusion.**

Keywords: Microemboli, SF6 microbubbles, transcranial Doppler, ultrasound contrast agent.

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Introduction

Cerebral microemboli are clinically silent but detectable by transcranial Doppler monitoring as high-intensity transient signals. The presence of microembolic signals (MES) is an independent risk factor for future ischemic stroke in large-vessel atherosclerosis and a frequent finding in other embolic causes of stroke.[1–6] MES detection can be used to clarify the cause of stroke, discover circulating emboli in the acute phase of stroke or during interventions, and assess the effect of antithrombotic treatment.[7–12]

MES detection cannot precisely differentiate between stroke-related microemboli and ultrasound contrast agents (UCAs) containing microbubbles.[13] These agents enhance 2-dimensional B-mode images and flow-mediated Doppler signals, providing the opportunity of detailed morphological and quantitative information.[14] UCAs are potentially necessary for about 20% of transcranial Doppler examinations due to poor insonation.[15] Stabilized sulfur hexafluoride (SF6) microbubbles are a frequently used UCA in neuro- and cardiovascular diagnostics.[15,16] It has also been used in contrast-enhanced sonothrombolysis in acute ischemic stroke.[17–19] SF6 is administered intravenously and provides a clinically useful Doppler signal enhancement for 2-9 minutes. The elimination half-life is approximately 6 minutes, and more than 80% of the administered SF6 is exhaled after 11 minutes. The elimination of SF6 is entirely pulmonary.[20,21]

Contrast enhancement is not necessary for MES detection, but it may be required for vascular examinations that are relevant in stroke diagnostics. If MES detection is performed after these examinations, it is important to know how long MES persist after UCA infusion, to avoid confusing microbubbles and stroke-related microemboli. Although the Doppler signal enhancement ceases minutes after completed UCA infusion, we have observed that MES may persist for a longer time. To our knowledge, the persistence of MES after SF6 infusion has not previously been investigated. An ambulatory transcranial Doppler system allows for continuous monitoring for up to several hours with minimal discomfort.[22,23] We aimed to assess the persistence of MES after UCA infusion to determine how soon after infusion, it is feasible to search for microemboli in stroke diagnostics.

Methods

We recruited healthy volunteers as subjects to limit the risk of stroke-related MES confounding the results. Ten research group members (60% females, age range 25-71, no history of arterial disease) received a 30-minute intravenous infusion of SF6 microbubbles (10 mL SonoVue® 8 microliters/mL) via a VueJect infusion pump (Bracco Imaging, Milan, Italy). Continuous infusion was chosen because it is the preferred way of administering SF6 for neurovascular examinations in our department. Compared to bolus injection, it provides a constant level of contrast enhancement with less initial blooming artifacts and an extended diagnostic window.[15,24] In addition, contrast-induced variations in velocity measurements are reduced.[25] Continuous infusion is also the preferred method of administration for contrast-enhanced sonothrombolysis.[19] After completed infusion, the subjects underwent continuous ambulatory Doppler monitoring for 3.5 hours. The left middle cerebral artery was insonated through the temporal bone window at a depth between 47 and 55 mm with a transcranial robotized 1.5 MHz Doppler probe (TCD-X, Atys Medical, Soucieu-en-Jarrest, France). Fast Fourier transform (FFT) settings were, as recommended by the manufacturer, 128-point FFT with Blackman filter and sample frequency of 400 Hz. The detection threshold was set to 9 dB, high-pass filter at 150 Hz, sample volume at 9.9 mm, and gain at the lowest level that preserved a flow signal in the spectrogram. The software algorithms applied for MES detection and artifact rejection are previously described.[26,27] MES were automatically registered and subsequently verified by three experienced observers in consensus. MES criteria were defined by the International Consensus Committee, ie, unidirectional signals lasting less than 300 milliseconds, with an amplitude at least 3 dB above the background blood flow intensity and accompanied by a characteristic "snap," "chirp," or "moan" on the audible output.[28,29] Predisposing conditions potentially related to interpersonal variations in MES persistence, such as patent foramen ovale (PFO) or pulmonary shunts, were not investigated in this study.

MES persistence, defined as the time between completed UCA infusion and the last detected MES, was presented as median (interquartile range). Statistical analyses were performed using STATA 15.1 (StataCorp, College Station, TX, USA). As the study design was descriptive, power calculations were not performed.

The study received prior approval by the regional local ethics committee (REK Vest) as a substudy of NORMASS (The Norwegian Microemboli in Acute Stroke Study, Clinical.Trials.gov-ID NCT03543319). Informed consent was obtained from all individual participants included in the study. The study was carried out in accordance with the declaration of Helsinki.

Results

Median MES persistence after SF6 infusion was 40.5 minutes (minimum 12 minutes, maximum 77 minutes, interquartile range 16-51 minutes). Individual MES persistence is presented in Table 1, and the temporal distribution is shown in Figure 1. In 9 of 10 subjects, MES ceased after less than 1 hour, and we observed a gradual decrease in frequency until cessation. In one subject, we observed a cessation of MES, followed by a second, spontaneous increase. Emboli detection was performed for 3.5 hours after complete infusion in all 10 subjects. None of the subjects had detectable MES after 77 minutes, and all 10 monitoring sequences thereby contain at least 2 hours of MES-free data after MES cessation. There were no adverse events during any of the monitoring sequences.

Table 1. Persistence of Microembolic Signals after Sulfur Hexafluoride Infusion

Subject	MES Persistence (MM:SS)
1	51:06
2	16:09
3	12:12
4	13:24
5	49:16
6	76:38
7	39:34
8	36:24
9	41:46
10	57:25

MM = minutes; SS = seconds.

Discussion

This study shows that after UCA infusion, MES persist for a longer time than the observable Doppler signal enhancement. In our study sample, none of the subjects had detectable MES for more than 77 minutes after completed infusion. The search for stroke-related microemboli should therefore wait for at least this long. We are not aware of previous studies assessing the persistence of MES after UCA infusion, and we thereby have no basis for result comparison.

Figure 1 shows a gradual increase in recorded MES during the first 5 minutes. This gradual increase does not reflect the actual temporal distribution of MES. The actual MES frequency is at its peak during and right after infusion, which can be seen as a continuous shower of emboli in the spectrogram. The MES detection software is, however, not able to register all MES during a shower of emboli, which leads to underestimating of MES during the first 5 minutes.

This study is novel, it increases our understanding of UCAs, and it has potential clinical implications for stroke diagnostics and treatment. Presence of MES in stroke patients implies an embolic stroke etiology, and cessation of MES may suggest effect of antithrombotic treatment. This effect can be seen as early as during the first hour.[30] Confusing microbubbles and stroke-related microemboli may mislead diagnostics and treatment choices. Knowledge of the persistence of MES after UCA infusion is therefore important.

However, this study also has limitations. The sample size is small, and the subjects are healthy volunteers. We chose not to include patients admitted to our stroke unit in the study, as these are more likely to have stroke-related microemboli, which are not possible to differentiate from MES caused by microbubbles. Published data on the pharmacokinetics of SF6 in patients with organ dysfunction are limited, but rapid, pulmonary elimination in healthy volunteers suggests a similar rate of elimination in such patients.[31] Still, the presence of a right-to-left shunt (for example, a PFO) could decrease the elimination of SF6, as this elimination is entirely pulmonary. PFO has a prevalence of about 25% in the general population, and it is possible that the presence of an asymptomatic right-to-left shunt in some of our

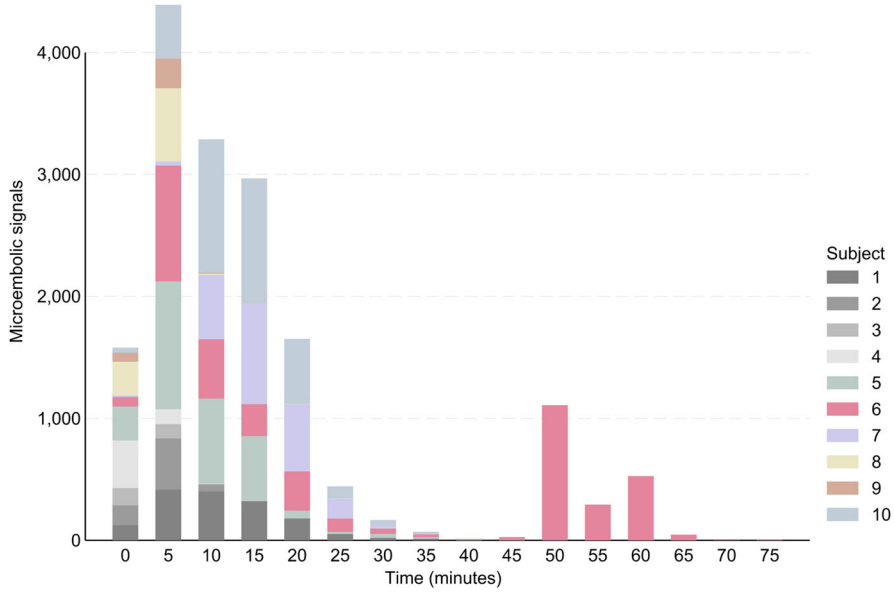

Fig 1. Time distribution of microembolic signals after sulfur hexafluoride infusion.

subjects can explain some of the variations in MES persistence. This could explain the second increase in MES frequency observed in one of the subjects, but this matter was not further investigated.

Technical factors in MES detection influence the results and need consideration. Ultrasound waves cause forced expansion and compression of microbubbles, leading to bubble disruption.[32] It is thus possible that the MES persistence would be longer without continuous ultrasound insonation. This influence is, however, unavoidable, as ultrasound is the only way of monitoring circulating microbubbles in vivo. MES detection is dependent on the ultrasound transmission frequency, and our results with a 1.5 MHz probe may not be comparable to other clinically used frequencies of 1 or 2 MHz.[33] However, 1.5 MHz is currently the only available frequency for an ambulatory Doppler system, which was considered necessary when performing a study with several hours of transcranial monitoring.

The interpretation of the data from the MES detection software is challenging. Despite recent advances in automatic embolus detection, human experts are still considered the gold standard for MES detection.[34,35] Assessment by one individual expert would limit the reproducibility of the result, but we addressed this by requiring consensus between three experienced observers.

This study provides new knowledge of microbubble behavior and MES persistence after SF6 infusion. UCAs are frequently used to improve vascular diagnostics in stroke patients, and MES detection is a pathophysiological adjunct to vascular imaging. A better understanding of the persistence of MES after UCA infusion may avoid misinterpreting microbubbles as stroke-related emboli, which may lead to improved diagnostics and treatment of stroke patients.

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