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.

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.

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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 (Braconn 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.26 After completed infusion, the subjects underwent continuous ambulatory Doppler monitoring for 3.5 hours. The left middle cerebral artery was imaged 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 6 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.

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
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. 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. 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. 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.

References
1. Gao S, Wong KS, Hansberg T, et al. Microembolic signal predicts recurrent cerebral ischemic events in acute stroke patients with middle cerebral artery stenosis. Stroke 2004;35:2832-6.
2. Markus HS, MacKinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. Stroke 2005;36:971-5.
3. Markus HS, King A, Shipley M, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol 2010;9:663-71.
4. Ritter MA, Dittrich R, Thoenissen N, et al. Prevalence and prognostic impact of microembolic signals in arterial sources of embolism. A systematic review of the literature. J Neurol 2008;255:953-61.
5. King A, Markus HS. Doppler embolic signals in cerebrovascular disease and prediction of stroke risk: a systematic review and meta-analysis. Stroke 2009;40:3711-7.
6. Best LM, Webb AC, Gurusamy KS, et al. Transthoracic Doppler ultrasound detection of microemboli as a predictor of cerebral events in patients with symptomatic and asymptomatic carotid disease: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2016;52:565-80.
7. Poppert H, Sadikovic S, Sander K, et al. Embolic signals in unselected stroke patients: prevalence and diagnostic benefit. Stroke 2006;37:2039-43.
8. Sliwka U, Lingnau A, Stohmann WD, et al. Prevalence and time course of microembolic signals in patients with acute stroke. A prospective study. Stroke 1997;28:358-63.
9. Spencer MP. Transthoracic Doppler monitoring and causes of stroke from carotid endarterectomy. Stroke 1997;28:685-91.
10. Dittrich R, Ringelstein EB. Occurrence and clinical impact of microembolic signals during or after cardiosurgical procedures. Stroke 2008;39:503-11.
11. Markus HS, Droste DW, Kaps M, et al. Dual antplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation 2005;111:2233-40.
12. Wong KS, Chen C, Fu J, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. Lancet Neurol 2010;9:489-97.
13. Markus HS, Punter M. Can transcranial Doppler discriminate between solid and gaseous microemboli? Assessment of a dual-frequency transducer system. Stroke 2003;36:1731-4.
14. Blomley MJ, Cooke JC, Unger EC, et al. Microbubble contrast agents: a new era in ultrasound. BMJ 2001;322:1222-5.
15. Droste DW. Clinical utility of contrast-enhanced ultrasound in neurosonology. Eur Neurul 2008;59:2-8.
16. Senior R, Becher H, Monaghan M, et al. Clinical practice of contrast echocardiography: recommendation by the European Association of Cardiovascular Imaging (EACVI) 2017. Eur Heart J Cardiovasc Imaging 2017;18:1205-af.
17. Perren F, Louidi J, Poglia D, et al. Microbubble potentiated transcranial duplex ultrasound enhances IV thrombolysis in acute stroke. J Thromb Thrombolysis 2008;25:219-23.
18. Rubiera M, Ribo M, Delgado-Mederos R, et al. Do bubble characteristics affect recanalization in stroke patients treated with microbubble-enhanced sonothrombolysis? Ultrasound Med Biol 2008;34:1573-7.
19. Nacu A, Kvistad CE, Naess H, et al. NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study): randomized controlled contrast-enhanced sonothrombolysis in an unselected acute ischemic stroke population. Stroke 2017;48:335-41.
20. Schneider M. Characteristics of SonoVue trade mark. Echocardiography 1999;16:743-6.
21. Kaps M, Legemate DA, Ries F, et al. SonoVue in transcranial Doppler investigations of the cerebral arteries. J Neuroimaging 2001;11:261-7.
22. Mackinnon AD, Aaslid R, Markus HS. Long-term ambulatory monitoring for cerebral emboli using transcranial Doppler ultrasound. Stroke 2004;35:73-8.
23. Mackinnon AD, Aaslid R, Markus HS. Ambulatory transcranial Doppler cerebral embolic signal detection in symptomatic and asymptomatic carotid stenosis. Stroke 2005;36:1726-30.
24. Schminke U, Motsch L, Bleiss A, et al. Continuous administration of contrast medium for transcranial colour-coded sonography. Neuroradiology 2001;43:24-8.
25. Logallo N, Fromm A, Waje-Andreassen U, et al. Effect of microbubble contrast on intracranial blood flow velocity assessed by transcranial Doppler. J Ultrasound 2014;17:21-6.
26. Guepie BK, Sciolla B, Milliz F, et al. Discrimination between emboli and artifacts for outpatient transcranial Doppler ultrasound data. Med Biol Eng Comput 2017;55:1787-97.
27. Guepie BK, Martin M, Lacrosaz V, et al. Sequential emboli detection from ultrasound outpatient data. IEEE J Biomed Health Inform 2019;23:334-41.
28. Basic identification criteria of Doppler microembolic signals. Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium. Stroke 1995;26:1123.
29. Ringelstein EB, Droste DW, Babikian VL, et al. Consensus on microembolus detection by TCD. International Consensus Group on Microembolus Detection. Stroke 1998;29:725-9.
30. Goertler M, Baumer M, Kross R, et al. Rapid decline of cerebral microemboli of arterial origin after intravenous acetylsalicylic acid. Stroke 1999;30:66-9.
31. Morel DR, Schwieger I, Hohn L, et al. Human pharmacokinetics and safety evaluation of SonoVue, a new contrast agent for ultrasound imaging. Invest Radiol 2000;35:80-5.
32. Dijkmans PA, Juffermans LJ, Musters RJ, et al. Microbubbles and ultrasound: from diagnosis to therapy. Eur J Echocardiogr 2004;5:245-56.
33. Droste DW, Lerner T, Dittrich R, et al. Comparison of a 1-MHz and a 2-MHz probe for microembolus detection using transcranial Doppler ultrasound. Neurul Res 2005;27:471-6.
34. Fan L, Evans DH, Naylor AR, et al. Real-time identification and archiving of micro-embolic Doppler signals using a knowledge-based DSP system. Med Biol Eng Comput 2004;42:193-200.
35. Geryes M, Menigot S, Hassan W, et al. Detection of Doppler microembolic signals using high order statistics. Comput Math Methods Med 2016;2016:3243290.