A Combined Power M-mode and Single Gate Transcranial Doppler Ultrasound Microemboli Signal Criteria for Improving Emboli Detection and Reliability

Youngbin Choi, MD, Maher Saqqur, MD, Talip Asil, MD, Albert Jin, MD, Eileen Stewart, RN, Caroline Stephenson, RN, Mohamad Ibrahim, MD, Jayanta Roy, MD, Jean-Martin Boulanger, MD, Shelagh Coutts, MD, Firosh Khan, MD, Andrew M. Demchuk, MD, FRCPC

From the Department of Neurology, Catholic University of Korea, Seoul, South Korea (YC); Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada (YC, TA, ES, CS, JR, JMB, SC, FK, AMD); Department of Neurology, University of Alberta, Edmonton, Alberta, Canada (MS, MI); Department of Neurology and Psychiatry, Saint Louis University, St. Louis, Missouri (YC); Department of Medicine (Neurology), Queen's University, Kingston, Ontario, Canada (AJ); Department of Neurology, Amala Institute of Medical Sciences, Thrissur, Kerala, India (FK).

ABSTRACT

BACKGROUND AND PURPOSE

Single gate transcranial Doppler spectrogram (sgTCD) has a high variability in the detection of microembolic signals (MES), Adding Power M-mode Doppler (PMD) information may improve MES detection. Our study's aim is to derive combined PMD/sgTCD microemboli criteria to overcome this limitation.

METHODS

Patients with symptomatic carotid disease were prospectively enrolled within 24 h of symptom onset underwent 1 hour TCD emboli monitoring. We reviewed disparity between PMD MES criteria and sgTCD MES criteria. We compared combined PMD/sgTCD criteria to sgTCD alone criteria by measuring the intraclass correlation coefficient (ICC).

RESULTS

Of 92 patients, 28 patients had evidence of MES on sgTCD or PMD. Total MES count was 269 based on sgTCD criteria, and 326 based on combined PMD/sgTCD criteria ($P = 0.005$). Combined PMD/sgTCD criteria revealed 17 MESs (4.8%) based on sgTCD criteria to represent artifacts and 57 MESs (17.5%) not to be detected by sgTCD criteria. Overall ICC based on sgTCD criteria was 0.67 [95% confidence interval (CI): 0.58–0.74]; however, introducing combined PMD/sgTCD criteria resulted in a significant increase in the ICC, 0.91 (95% CI: 0.88–0.93).

CONCLUSION

Our combined PMD/sgTCD criteria for MES appeared to improve the yield of MES detection. Reliability in MES detection interpretation was improved when combined PMD/sgTCD criteria was applied.

Keywords: microemboli, transcranial doppler, power M-mode, diagnostic criteria.

Acceptance: Received November 24, 2008, and in revised form August 18, 2009. Accepted for publication September 12, 2009.

Correspondence: Address correspondence to Talip Asil, M.D., Department of Clinical Neurosciences, University of Calgary, Foothills Medical Centre, Room 1162, Calgary, AB T2N 2T9. E-mail: talip_asil@yahoo.com.

J Neuroimaging 2010;20:359-367.
DOI: 10.1111/j.1552-6569.2009.00446.x

Introduction

Transcranial Doppler (TCD) emboli monitoring has the ability to detect high intensity transient signals (HITS), otherwise referred to as microembolic signals (MES), which represent emboli traversing through the major intracranial vessels. These MES correspond to true emboli in animal models[1] and are frequently seen following an acute stroke.[2] MES are more frequently identified in the setting of large vessel atherosclerotic disease such as carotid stenosis.[3] They represent an independent predictor of early ischemic recurrence when the cause appears related to carotid or middle cerebral artery stenosis.[4,5]

The main barriers to the widespread clinical use of TCD emboli monitoring is a lack of an automated method of detection and confirmation of an MES and difficulties with interpretation of MES over artifacts. In spite of the available current criteria of single gate TCD (sgTCD) based on the Consensus Committee of the 9th International Cerebral Haemodynamic Symposium,[6] the high variability in the detection of microemboli in different studies is problematic, such as difficulty in finding ultrasound windows, differentiating real MES from artifacts, and differentiating gaseous from solid MES.[7] The use of higher-decibel threshold (>6-7 dB above background) has been suggested in order to improve the reproducibility and interobserver agreement for the detection of MES.[8] However, there is still possibility of not detecting small and low-intensity MES by sgTCD spectrogram alone.[7]

Transcranial power M-mode Doppler (PMD) is now available with digital TCD that simultaneously samples 33 gates over 60 mm of intracranial space.[9] Specific flow signatures are seen with PMD which provides simpler identification of the insonated artery, artifact rejection, and specific signatures of stenosis and occlusion.[10] In addition, using novel PMD–MES criteria may enhance the detection of MES and microbubble signals during TCD bubble studies.[11] The MES on PMD display represent a unique signature or track in the image, which defines them as representing emboli. In contrast, artifacts are suppressed from the PMD image.[9,10] PMD also has automated algorithm for MES detection which avoids the

impractical need for recording of the entire 1-hour monitoring period for review. Given the potential advantages of PMD for MES detection and artifact discrimination, we sought to derive combined PMD/Spectrogram TCD microemboli criteria in a microemboli-positive population with carotid disease, then validate our developed criteria.

Methods

We prospectively collected TCD emboli monitoring data from patients who participated in either TASC (Transcranial Doppler And Symptomatic Carotid disease study) or VISION (Vascular Imaging of acute Stroke for Identifying predictors of clinical Outcome and recurrent ischemic events) studies at a single academic center between May 1, 2002, and December 31, 2006. Both research studies were approved by our institutional ethics committee, and all participants were prospectively enrolled and provided written informed consent.

TASC study was a TCD study of transient ischemic attack (TIA) or acute ischemic stroke patients (within 48 hours) who were accompanied with carotid stenosis (>50%), occlusion, or unstable plaque. VISION study was a prospective cohort study investigating three neurovascular imaging methods: magnetic resonance imaging, computed tomography, and TCD to determine which combination of imaging modalities should be used in various clinical situations allowing for the most optimal outcome. Patients presenting with stroke or TIA consisting of hemiparesis or aphasia lasting more than 5 minutes within 24 hours of last seen well were enrolled. The patients who had carotid disease (stenosis > 50%), occlusion, or ulcerated/very irregular plaque in the VISION study were collected for this analysis. In both studies, the patients underwent bilateral hemisphere TCD emboli monitoring for 1 hour within 48 hours of their presentation. The TCD monitoring for MES was performed by a technician and an expert neurosonologist. PMD 100 machine (Spencer Technologies, Inc., Seattle, WA) was used. This technology collects: (1) 2-MHz spectral single-gate TCD information at a specific depth, and (2) PMD information from 33 sample volumes placed at 2-mm intervals from 24- to 88-mm depth of insonation.[9] The PMD was configured with red or blue colors for directionality, and with brightness of colors to reflect Doppler signal intensity. A 2-MHz pulsed-wave transducer was used to generate simultaneous PMD and sgTCD displays. The PMD equipment used an emitting transducer surface 13 mm in diameter. The pulse repetition scale settings were 5 kHz, gain of 40 dB, and minimum dynamic range of 80 dB. Algorithms for signal intensity measurement utilized power (in decibels) of the Fourier transform coefficients; acquisition and processing parameters included a 6-mm axial sample volume length, 128 points Hanning window data taper, 128 points fast Fourier transform (FFT) (15 ms), 50% FFT overlap, 2-MHz carrier frequency, 200-Hz high-pass filter (7c m/s), and 1-minute recording time. An appropriate temporal window was identified prior to the procedure with a standard handheld technique. Probe fixation using Marc 500 head frame (Spencer Technologies) was used for monitoring. One proximal middle cerebral artery (MCA) segment was insonated and, when possible, ipsilateral anterior cerebral artery (ACA) or internal carotid artery (ICA) for PMD. The insonation depths for spectrogram recording were between 45 and 65 mm for the ipsilateral MCA, 60 and 75 for the ipsilateral ACA, and 60 and 75 for the ipsilateral ICA. In suspected posterior circulation events, the posterior cerebral artery (PCA) was insonated on either side at a depth of 60–75 mm. Semi-automated algorithm counted every possible signal as MES to the hard disc for 1-hour period. Whole 1-hour recordings were reviewed to confirm the presence of MES, which might not be detected or might be an artifact. The MES were reviewed by an experienced neurosonologist blinded to all clinical and imaging information.

Derivation of Combined PMD/sgTCD Criteria

Two stroke neurologists who were blind to clinical data and imaging data reviewed the PMD results together by consensus for MES using sgTCD criteria and modified PMD criteria.[11] Based on the disparity in emboli counts between sgTCD and modified PMD criteria, we derived combined PMD/sgTCD criteria which was defined as the followings: (1) high signal intensity that meet either the sgTCD or modified PMD criteria, and (2) no evidence of artifact on sgTCD or modified PMD criteria (Supporting Table). We defined artifact on PMD as an increase in power occurring in multidepth simultaneously (Fig 1A-B) or increase in power occurring at not random pattern within the cardiac cycle (Fig 1C).

Yield of New Combined sgTCD/PMD Criteria

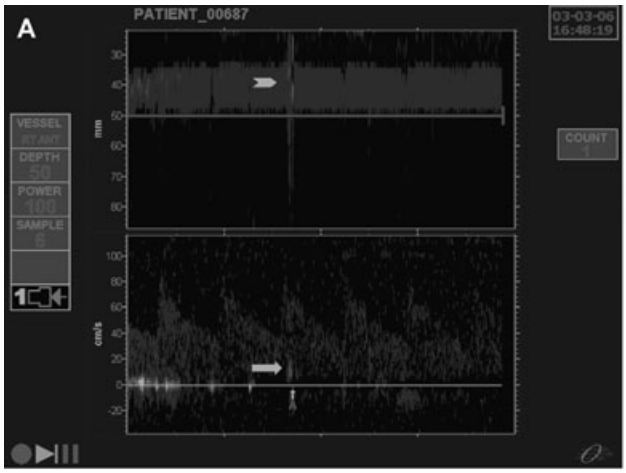
The recordings of TCD emboli monitoring from 92 patients were reviewed in a random fashion by two expert stroke neurologists using sgTCD criteria alone with blindness to the PMD display. At a separate session, the same recordings were reviewed by the same readers using our newly developed combined PMD/sgTCD criteria. The comparisons in the MES counts were made based on the derived criteria mentioned above.

Comparison of Reliability (Intraclass Correlation Coefficient, ICC) between sgTCD Alone Criteria and Combined PMD/sgTCD Criteria among 6 Readers

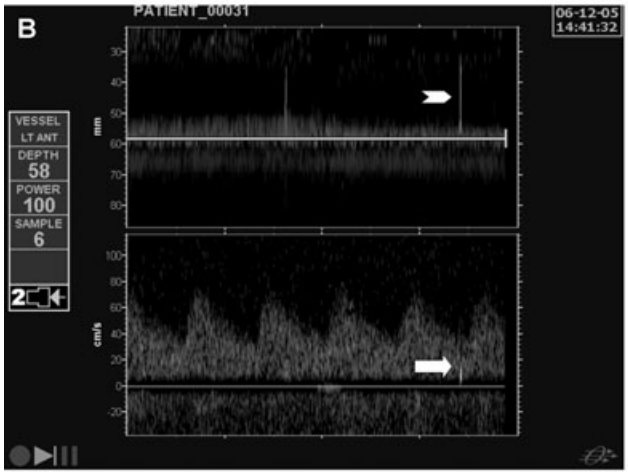
One hundred recordings of 8-second-duration TCD display were selected for ICC analysis based on two expert readers' consensus, which consisted of 79 recordings with more than one MES, 13 recordings without MES, and 8 recordings with artifacts. The recordings were read by 6 readers independently (4 stroke neurologists and 2 sonographers). Each reader reviewed spectrogram display only by using sgTCD alone criteria, then reviewed randomly rearranged PMD/sgTCD display together by using combined PMD/sgTCD criteria at a separate session. Each reader reported the presence and number of MES, or artifact.

Statistical Analysis

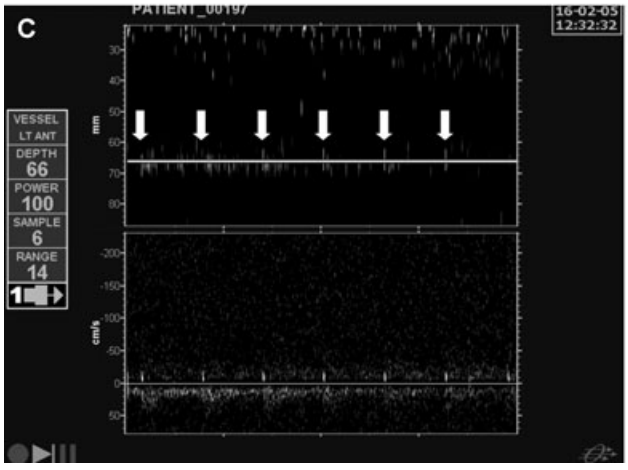
Demographics of study population and MES counts were reported using descriptive statistics. Paired sample *t*-test was used to evaluate the statistical difference of emboli count based on each method. ICC was used to calculate a correlation among 6 readers. Two-way mixed model was applied as the rater factor was treated as a fixed factor. *P* value less than 0.05 were



Even though embolus is shown in high signal at a depth of 50 mm in the SPECT display (arrow), high signal transit appears simultaneously from a depth of 80 mm to 20 mm without slope on PMD display(arrow head)



One embolus shown at a depth of 58 mm in the SPECT (arrow) demonstrates multidepth simultaneous high signal transit from 60 mm to 30 mm without slope on PMD (arrow head).



Increase in power occurring at not random pattern within the cardiac cycle is considered to be artifacts.

Fig 1. (A) Even though embolus is shown in high signal at a depth of 50 mm in the sgTCD display (arrow), high signal transit appears simultaneously from a depth of 80-20 mm without slope on PMD display (arrow head). (B) One embolus shown at a depth of 58 mm in the sgTCD (arrow) demonstrates multidepth simultaneous high signal transit from 60 mm to 30 mm without slope on PMD (arrow head). (C) Increase in power occurring at not random pattern within the cardiac cycle is considered to be artifacts. sgTCD = single gate transcranial Doppler; PMD = power M-mode.

considered to be significant. SPSS 11.5 was used for statistical analysis (SPSS Inc., Chicago, IL).

Results

Ninety-two TIA/stroke patients with carotid disease performed emboli monitoring by using PMD 100 within 48 hours of the symptom's onset. Mean age was 67.7 ± 13.1 years and 69 patients (75.0%) were men. Median baseline National Institutes of Health Stroke Scale is 2 (IQR: 0 - 4). Twenty-nine patients (31.5%) had TIA and 63 (68.5%) patients had stroke. The mean time from symptoms onset to evaluation was 12.8 ± 6.4 hours. The TCD monitoring for MES was performed at median 16.4 hours [intraquartile range (IQR); 2.5-47 h] from symptom onset. Twenty-eight patients (male 71.5% and mean age 63.4 ± 17.3 years) had a positive MES on either sgTCD or PMD.

Using sgTCD criteria alone, TCD emboli monitoring was positive in 26 patients (26/92, 28.3%) patients (total 269 MES, mean MES count 2.88 ± SD 8.6, median 0, IQR: 0-1), whereas with using combined PMD/sgTCD criteria, 28 patients had positive MES on their monitoring (28/92, 30.4%)(total 326 MES, mean MES count is 3.55 ± SD 10.6, median 0, IQR: 0-1) [P = 0.005, 95% confidence interval (CI): 0.21-1.13; paired sample t-test]. Disparity between two criteria suggested 57 MES were not detected by sgTCD alone criteria, but detected by combined PMD/sgTCD criteria. The MESs, which were not detected by sgTCD alone, were characterized on PMD display as followings: 15 MES were shown as traveling through ACA, 10 MES traveling into branchs, 5 MES in ICA only, 7 MES only in distal MCA, 8 MES arterial curvature, and 12 MES suboptimally targeted (Fig 2). Thirteen MES on sgTCD display (13/269 = 4.8%) were considered to be artifacts on PMD display (Fig 1–C, Fig 2). Two MES on sgTCD display were considered not to be detected by PMD display alone.

ICC for overall MES of sgTCD alone criteria was 0.67 (95% CI: 0.58-0.74), whereas ICC for overall MES of combined PMD/sgTCD criteria was 0.91 (95% CI: 0.88-0.93). According to the subgroup analysis based on the type of MES, ICC for identifying real MES and artifact based on combined PMD/sgTCD criteria was 0.93 (95% CI: 0.91 – 0.95) and 0.73 (95% CI: 0.48 – 0.92), respectively, whereas, ICC for real MES based on sgTCD alone criteria was 0.60 (95% CI: 0.50-0.70) and artifact 0.60 (95% CI: 0.32-0.88) (Table 1).

There are several potential explanations why the MES may not be detected by sgTCD alone criteria, but detected by combined PMD/sgTCD criteria (see Fig 3).

1. **Suboptimal targeting of the spectrogram**: Figure 3A and 3B shows the evidence that the sgTCD placed at the depths of 50 mm (Fig 3A) and 44 mm (Fig 3B) in the MCA does not show the embolic signatures seen on the PMD display. Despite the entering of the emboli into the MCA, they do not traverse to a gate depth of spectrogram;
2. **Dynamic range sampling limitation of spectrogram**: Figure 3C shows that embolic signature seen on the PMD display represents embolus passing through the ipsilateral ACA and is not detected by spectrogram. The detection of ACA emboli is not easily possible with single-gate TCD;
3. **Embolus passing curved artery**: Figure 3D showed the embolus passing through the curved MCA artery is not seen on sgTCD despite with proper depth of targeting; and

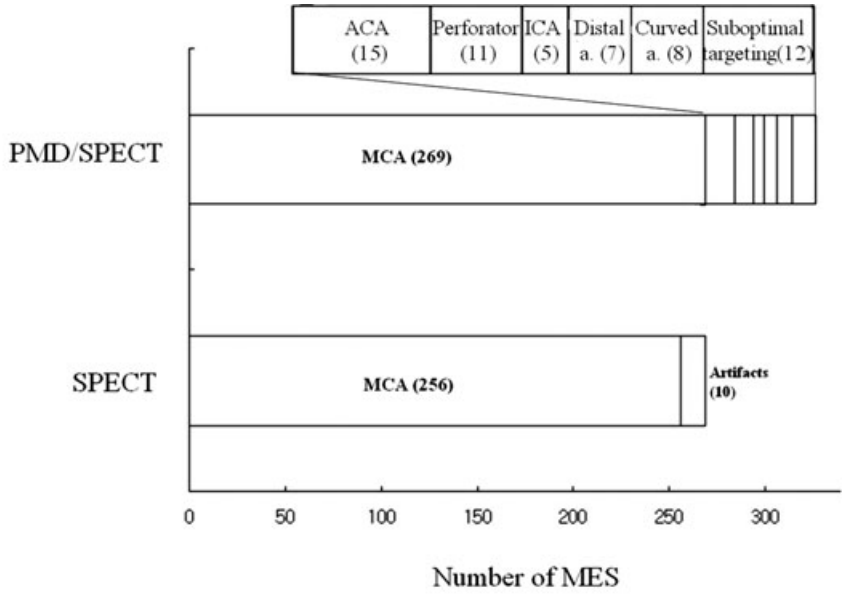


Fig 2. Bar graph comparing the number of MES based on the combined PMD/sgTCD criteria and sgTCD alone criteria: The bar graph reveals that the combined PMD/sgTCD criteria shows higher number of MES than sgTCD alone criteria. In addition, various types of MES based on combined PMD/sgTCD criteria were missed by sgTCD alone criteria. MES = microembolic signal; sgTCD = Spectrogram alone criteria for MES; PMD/sgTCD = combined power M-mode/spectrogram criteria for MES.

Table 1. Comparisons of Intraclass Correlation Coefficient of sgTCD Alone Criteria and Combined PMD/sgTCD Criteria According to the Type of Emboli

	sgTCD Total Cases	ICC	95%CI	PMD/sgTCD ICC	95%CI
Overall	100	.67	.58-.74	.91	.88-.93
Embolus	79	.6	.50-.70	.93	.91-.95
Artifact	8	.6	.32-.88	.73	.48-.92

sgTCD = Single gate TCD alone criteria for MES; PMD/sgTCD = combined power M-mode/single gate TCD criteria for MES; ICC = Intraclass correlation coefficient; CI = confidence interval.

4. **Embolus entering the branch artery**: Figure 3E showed variable movement of embolus suggesting entering branch artery shown in the PMD display from a depth of 58 mm to a depth of 48 mm, which is not detected by sgTCD.

Figure 4 suggests schematic illustration showing imagined spatial arrangement of the vessels and the sampling volume of sgTCD and PMD. It shows several patterns explaining the reasons for the disparity between the two techniques. Several emboli apparently enter the distal segment of ICA, but none of them traverse the gate depth of 50 mm and appears in the sgTCD.

Discussion

Our study showed that our combined PMD/sgTCD criteria increased the yield of detecting MES and differentiated an artifact from real emboli compared to sgTCD alone criteria. Combined

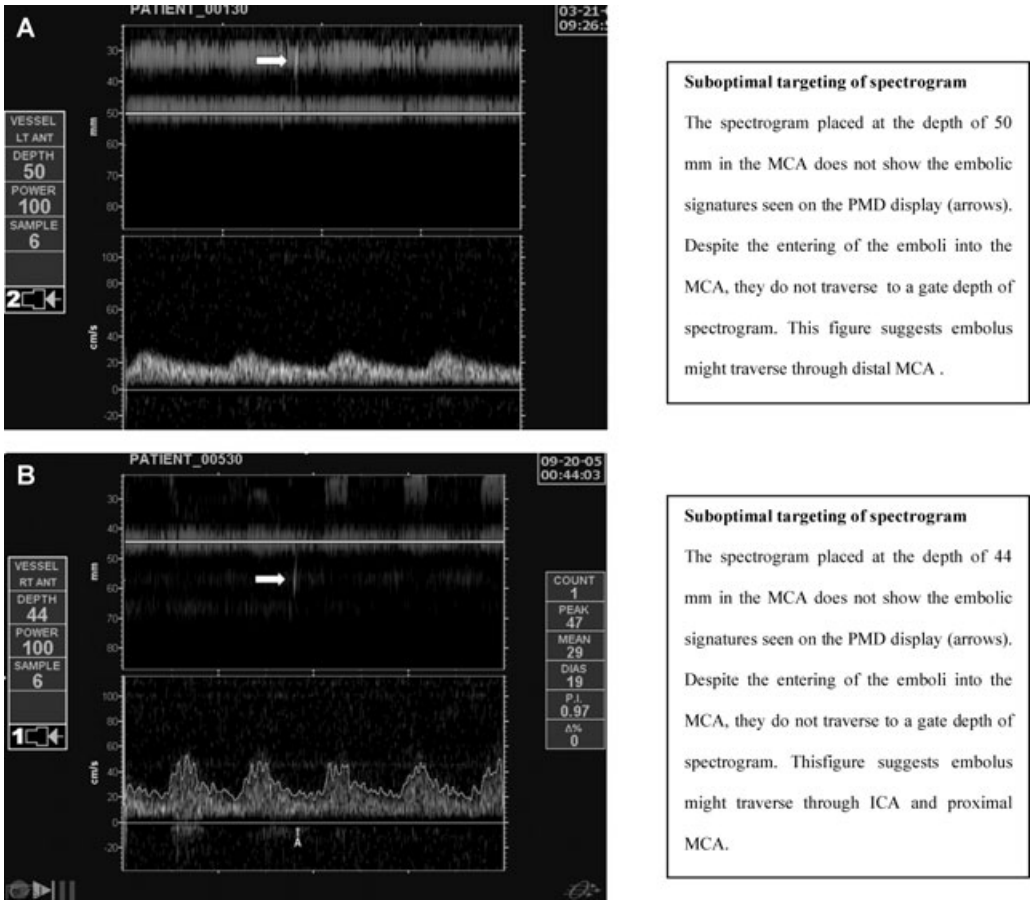


Fig 3. A and B. The evidences of suboptimal targeting of spectrogram: The spectrogram placed at the depths of 50 mm (A) and 44 mm (B) in the MCA does not show the embolic signatures seen on the PMD display (arrows). Despite the entering of the emboli into the MCA, they do not traverse to a gate depth of spectrogram. Figure A suggested embolus might traverse through distal MCA and Figure B suggested embolus might traverse through ICA and proximal MCA. (C) The evidence of dynamic range sampling limitation of spectrogram: Embolic signature seen on the PMD display represents embolus passing through the ipsilateral ACA (arrow) and not detected by spectrogram. (D) The embolus passing through the curved MCA artery (arrows) not seen on spectrogram despite proper depth of targeting. (E) The evidence of variable movement of emboli shown in the PMD: the emboli moved from a depth of 58 mm to a depth of 48 mm (arrow), then disappeared and was not detected by sgTCD. This picture suggested the course of emboli into the branch artery.

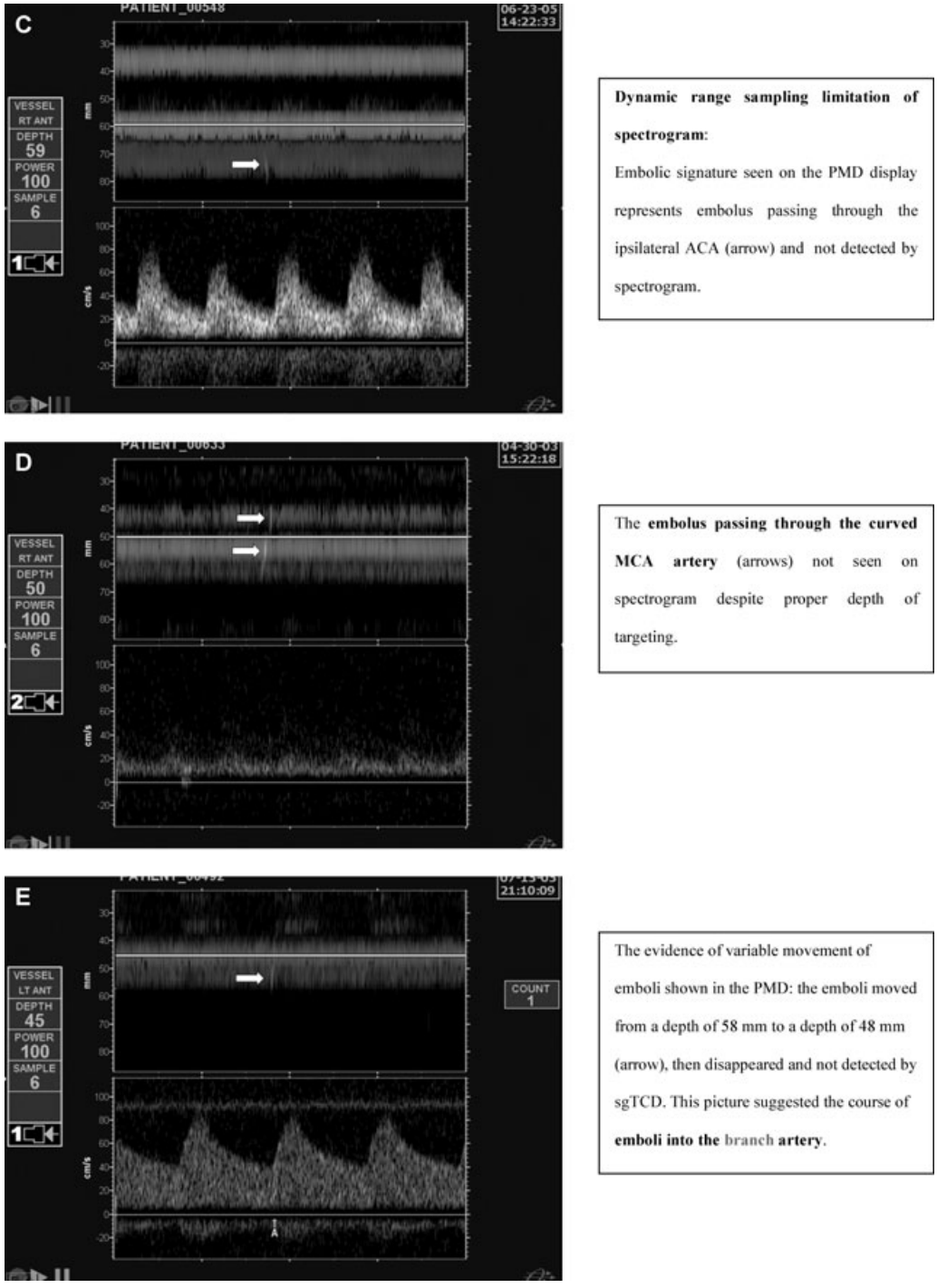


Fig 3. continued.

PMD/sgTCD criteria also proved to be more accurate with better interrater reliability than sgTCD alone criteria. By applying our combined PMD/sgTCD criteria in TCD emboli monitoring, emboli detection measurement is likely to be more accurate and reproducible.

Although the sgTCD is considered the established method of detecting microemboli, our study suggests there are significant limitations with this approach. The sample volume for sgTCD covers a small part of the travel path of an embolus, since it monitors the velocity and ultrasound echo amplitude at one sample volume (millimeters in size). We think that a single sample volume is not enough to evaluate the complex behavior of microembolus. In addition, artifacts from subtle probe movement result in high-intensity signals that make differentiation of real emboli from artifact problematic for Spectrogram. The low yield of sgTCD can be explained by several factors such as suboptimal targeting, dynamic range sampling limitations, and anatomical variance of artery and variable movement

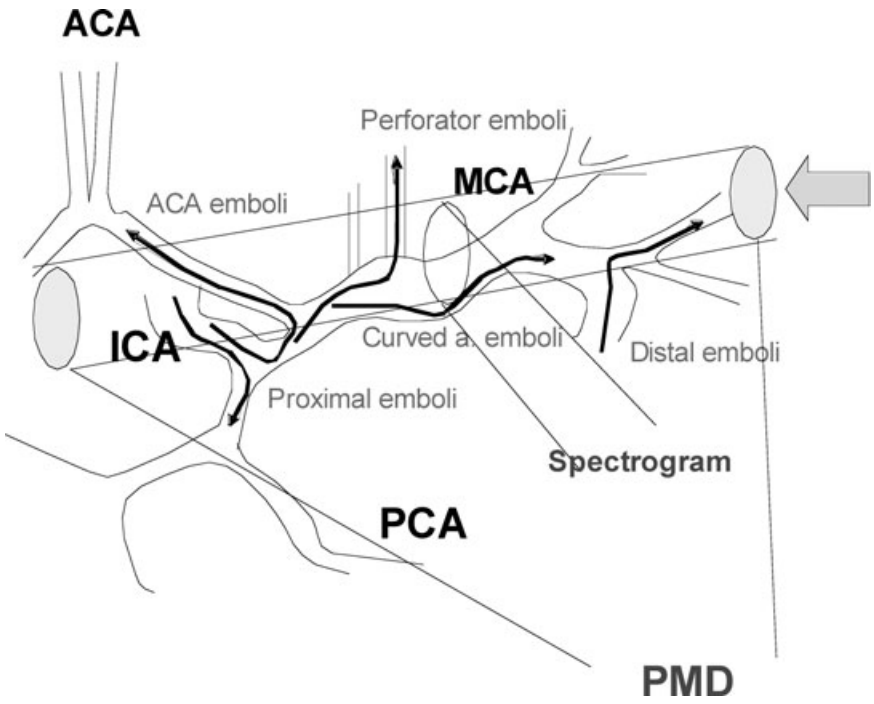


Fig 4. Imaginary spatial arrangement of the vessels and the sampling volume of sgTCD and PMD: it shows several patterns explaining the reasons for the disparity between two techniques. Several emboli apparently enter the distal segment of ICA, but none of them traverse the gate depth of 50 mm and appears in the sgTCD. sgTCD = single gate spectrogram; PMD = power M-mode.

of microembolus. This is supported by previous work which has demonstrated false negative studies using spectrogram criteria at a single gate.[12,13] We observed that major limitation of sgTCD criteria alone was the sound criteria which was not heard on many occasions but demonstrated classic MES features based on PMD criteria. However, applying PMD criteria alone can be also problematic as the probability of missing MES based on PMD is still present, which may be detectable based on sgTCD alone. Our result also demonstrated 2 MESs were not detected by PMD, but by sgTCD. This disparity could be explained by problem of automatic MES detection algorithm. Combining PMD and sgTCD criteria for MES can overcome these problems.

Distinguishing of MES from spontaneous speckling in the background signals and artifacts is extremely important. Artifacts are usually bidirectional and are maximal at low frequencies on spectrogram display, but they are suppressed from the PMD display.[9,10] In addition, subtle probe movement might result in high-intensity signals on sgTCD which could be read as emboli whereas PMD had the advantage of distinguishing this type of artifact from real emboli by the shape of long track without slope on PMD display. Furthermore, artifact may also occasionally produce typical embolic signals on sgTCD with incorrect instrumentation settings. Those artifacts can be differentiated by the combined PMD/sgTCD criteria because all those signals showed increase in power occurring in multidepth simultaneously with no slope[12,14] or increase in power occurring at not random pattern within the cardiac cycle.

Recently, several small phase-2 clinical trials had adopted MES as a surrogate outcome for treatment effect. Anticoagulant treatment for atrial fibrillation[2,15] antiplatelet agents in patients with carotid atherosclerosis[16] and intracranial artery disease[17] had demonstrated MES count reduction with treatment.[18,19] MES had been also used to evaluate treatments such as dextran,[20] tirofiban,[21] S-nitrosoglutathione,[22] and aspirin with clopidogrel[16] to limit thrombotic complications of carotid endarterectomy peri and postoperatively. Larger phase-3 clinical trials have been planned based on these findings. Our study would suggest caution when extrapolating MES count reduction into large efficacy trials, especially given the significant limitations with sgTCD alone criteria. Considering artifacts as an MES or missed MES could have a substantial impact on estimating treatment effect and sample size calculation for a phase-3 trial. We think that applying our combined PMD/sgTCD criteria will overcome these limits of sgTCD alone criteria in future clinical trials where MES is to be surrogate marker. Also, the PMD display has been shown to be more sensitive for the detection of embolic flow signatures than the single-gate spectral display in posterior circulation, because it allows simultaneous display of flow over long arterial segments as well as more than one vessel.[23] In one series, the authors noted PMD embolic tracks in the cerebellar arteries (depicted as red bands on PMD display over different depths), when their sample volume interrogation was set in depths corresponding to VA or BA. Because the cerebellar arteries are not routinely insonated during the assessment of posterior circulation vessels with single-gate TCD, the presence of embolization distal to an extracranial or intracranial stenoocclusive arterial lesion in the VA may have not been identified without PMD-TCD.[23]

This study has several limitations. First, any comparison of MES criteria suffers from lacking a true gold standard for comparison. We tried to provide examples of artifacts misinterpreted by sgTCD or MES missed by sgTCD in order to overcome this limitation. Second, the possibility of missing true emboli should be considered, as the automated embolus detection system for artifacts removal present in the PMD 100 system was used, which might influence our results. The PMD system may overcome this limitation by adopting the full hour of monitoring to maximize MES detection for clinical trial purposes.[24] Third, more advanced techniques than sgTCD have been developed. Multi-gated TCD have been introduced with good sensitivity and specificity to detect MES.[25] Also, multifrequency TCD had been shown to be able to differentiate between solid and gaseous emboli.[26,27] However, those techniques had not been considered to be the current standard for MES detection.

In conclusion, even though optimizing MES detection criteria is challenging due to an absence of gold standard, our combined PMD/sgTCD criteria improved the yield of detecting MES and distinguished a significant number of artifacts that could result in false positive MES counting based on sgTCD alone criteria. The combined PMD/sgTCD criteria were also more reliable among a wide range of TCD readers than sgTCD alone criteria. Future clinical trials adopting MES as a surrogate outcome should consider the adoption of our combined PMD/sgTCD criteria in order to overcome the limitations of standard sgTCD alone criteria.

The study was supported by funding from the Alberta Heritage Foundation for Medical Research, Canadian Institutes for Health Research and Heart and Stroke Foundation of Alberta, NWT, and Nunavut.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Combined PMD/sgTCD MES criteria

1. High signal intensity that meet either the sgTCD or modified PMD criteria.
2. No evidence of artifact on sgTCD or modified PMD criteria.

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