Feasibility of simultaneous pre- and postfilter transcranial Doppler monitoring during carotid artery stenting

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Objective: **Carotid artery stenting (CAS) is emerging as an acceptable treatment alternative to surgery for patients with carotid artery stenosis. The major risk of CAS is cerebral embolization of plaque and thrombus causing stroke or asymptomatic brain infarction. Use of embolic protection devices (EPD) to trap emboli before they reach the brain is now standard practice in CAS. The pore size of the currently available filters is >100 microns and emboli smaller than the EPD pores can still reach the brain. While the use of EPD is widespread, little evidence exists of their in vivo efficacy in preventing distal embolization. Our aim was to quantify the number of emboli reaching the brain with the device in place. Therefore, the expected value of this report is in its description of a novel application of transcranial Doppler (TCD). Due to the limited number of cases, it is not intended to support the use of one EPD over another.**

Methods: **Six patients were monitored with ipsilateral simultaneous dual probe TCD during CAS. Two types of cerebral protection systems were evaluated: FilterWire EZ System (FW; Boston Scientific, Santa Clara, Calif) and GORE Neuro Protection System (NPS; W.L. Gore and Associates, Flagstaff, Ariz). By placing TCD probes both proximal and distal to the filterwire EPD, we quantified the microembolic signals before the EPD as well as those, which reached the intracranial circulation after the EPD. One probe was placed submandibularly to monitor the ICA (SICA), while another was placed transtemporally to monitor the middle and anterior cerebral artery (MCA + ACA). We compare the number of extracranial emboli prior to the EPD with the number of intracranial emboli after the EPD.**

Results: **Dual probe monitoring was successful during the five stages of the CAS: lesion crossing (LC), predilatation (PreD), stent placement (SP), postdilatation (PostD), and filter/device removal (FR/DR). Using FW during LC by probe 1 (SICA)/probe 2 (MCA + ACA): (18 [range, 15-22]/15 [range, 11-20]), PreD (111 [range, 101-121]/ 101 [range, 90-111]), SP (68 [range, 60-76]/42 [range, 30-53]), PostD (27 [range, 25-30]/24 [range, 22-27]), FR (0.3 [range, 0-1]/0.7 [range, 0-1]) average number of microembolic signals were detected. Using NPS during LC (1.7 [range, 0-3]/1 [range, 0-2]), PreD (0/1.7 [range, 0-4]), SP (0/0), PostD (0/0), DR (18 [range, 0-18]/6.7 [range, 1-13]) average number of microembolic signals were detected.**

Conclusion: **EPD significantly reduces but does not eliminate the number of microemboli reaching the brain during carotid artery angioplasty and stenting. We propose monitoring of CAS with submandibular and transtemporal TCD probes to further evaluate the practice of distal embolization protection. Although our study is not powered to make any recommendations about EPDs, we believe that sequential dual probe TCD monitoring is a worthy tool with the potential to give vital information to assess the various devices and the techniques of utilization. (J Vasc Surg 2009;49:340-5.)**

Carotid endarterectomy (CEA) is a procedure that has withstood the test of time. It has been performed with great success and safety over approximately 50 years, supported by multiple multicenter randomized trials.[1,2] Carotid artery stenting (CAS) has now been performed for nearly 10 years, with the addition of embolic protection devices (EPD) since the year 2000. Gray et al showed that the predictors of poor outcome, by multivariate analysis, were predilatation without EPD, symptomatic carotid lesions, age, and the use of multiple stents per procedure.[3] It was also noted by transcranial Doppler (TCD) that showers of microemboli noted during postdilatation have a significant association with adverse cerebral outcome.[4]

The benefits of using EPDs seem evident. In the case of filters, their design has to be such that it not only allows adequate cerebral perfusion, but that its pore size is appropriate to prevent major embolization. Evidence has shown that deployment of a filter device reduces cerebral blood flow by 10% to 30%.[5] Pore size for the available EPDs varies from 110 μm to 150 μm, but has generally been shown to be able to eliminate up to 96% of embolic particles.[6] Protection with carotid flow reversal has also been shown to produce a remarkably low incidence of intraprocedural cerebral embolization.[7,8] Despite this fact, several studies have shown that new intracranial lesions are detected by magnetic resonance (MR) diffusion-weighted imaging

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(DWI).[6,9-11] Hammer et al found that postprocedural DWI detected new focal ischemic lesions in 40% of patients.[12] It is our goal to describe maneuvers during CAS, which prompt embolization, as well as determining by TCD sequential dual probe monitoring, the ability of the EPD to prevent emboli from reaching the cerebral circulation. The use of EPDs is almost universally applied during CAS procedures and so this approach to dual monitoring during the procedure should be a successful way of describing the performance measures of EPDs.

The value of this report is in its description of a novel application of TCD. Due to the limited number of cases, it is not intended to support the use of one EPD over another.

PATIENTS AND METHODS

The six patients included in this analysis were evaluated and treated in the period between May 2007 and February 2008. These were consecutive patients on whom sequential dual probe TCD technique was used. They all met criteria for being poor surgical candidates to have a carotid endarterectomy.[13] Comorbidities were recorded. All procedures were performed by a single experienced vascular surgeon (A.B.L.).

TCD monitoring protocol and interpretation

Probe/head frame placement. A commercially available probe-holding head frame system (Marc 600 series; Spencer Technologies, Seattle, Wash) is used to affix probes just anterior to the ear at the posterior temporal bone windows and second probe was placed for submandibular insonation at the angle of jaw (Fig 1).[14]

TCD machine and software settings. Doppler parameters for our PMD100 (Spencer Technologies, Seattle, Wash) are: transducer = 2 MHz, 13 mm circular probe surface; pulse repetition frequency = 8 kHz; fast Fourier transformation = 128 points, overlap = 66%; sample volume axial length = 9 mm; output power = 80% to 100% (<700 mW/cm^2 spatial peak temporal average intensity); filter = 125-175 Hz; noise 0-3 dB; range 30 dB; Doppler volume = 4 dB; M-mode range = 30 dB; and sweep period = 4-16 seconds.

We identified the proximal middle cerebral artery (MCA) and anterior cerebral artery (ACA), as well as the submandibular internal carotid artery (SICA) before the start of the procedure and selected the appropriate gate for spectral display. The M-mode screen enables visualization of intracranial flow signals from depths of between 25 and 85 mm from the ultrasound probe (Fig 2, online only), making it easier for the sonographer to localize the blood flow in the target vessel.

The spectral waveform above the zero line represents the MCA flow, traveling towards the probe, and corresponds with the red-labeled signal on the PMD display. The spectral waveform below the zero line represents ACA flow, traveling away from the probe and is displayed by a blue-labeled signal on the PMD. PMD-TCD signal was continuously recorded, while postprocedural analysis of the recording was completed for quantification of microembolic signals (MES).

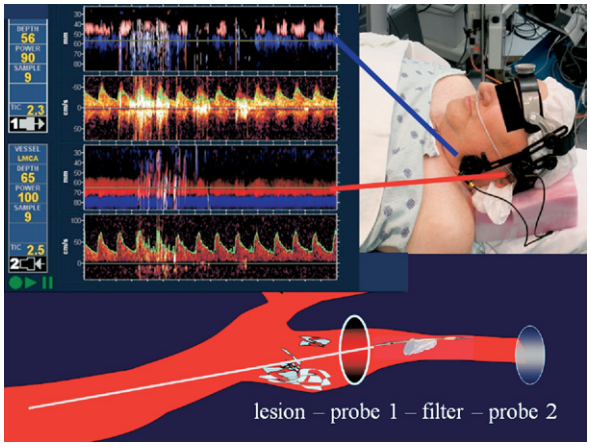

Fig 1. Dual probe transcranial Doppler monitor setup as seen on the patient and as it relates to the carotid artery embolic protection device.

Microembolus signal detection. The intensity of the Doppler signal for an embolus traveling in blood depends on the size and acoustic impedance. Air has much lower acoustic impedance than blood and, therefore, reflects sound waves to a greater extent.

Based on Consensus Committee guidelines, certain technical criteria must be met to qualify as microembolic signals (MES) by TCD.[15]

A microembolic signal recorded on the PMD screen can be tracked as it moves through the intracerebral circulation (Fig 3, online only). An embolus traveling up the middle cerebral artery (MCA) would first appear in the proximal portion of the artery on PMD at 60-mm and then travels distally in the MCA at 40-mm. MCA embolic signal has a slight tilt or forward slash-shaped signal ("/") in PMD that indicates direction. An ACA or SICA MES signature on PMD screen has a backslash-shaped signal ("\"). Calculating the MCA and ACA total MES count on the PMD screen permits direct comparison between the two TCD probes because almost all the ICA flow volume/MES would be delivered into these arteries.

Extraneous activity such as muscle movement, skin scrubbing, cough or tap against the head frame, and electric artifacts appears at various depths on PMD at the same time and removed from the PMD display and would not be counted by the automatic embolus detection.

Air emboli during contrast injection were not included in our analysis. The emboli counting was performed without the use of the automatic emboli detection software. To evaluate the embolic potential of the various steps of the procedure, we divided it into five parts: lesion crossing, predilatation, stent placement, postdilatation, and filter/device removal. The MES counts from the PMD screen were entered into the database for respective parts of the procedure.

Carotid artery stenting

Extracranial and intracranial angiography was performed bilaterally at the time of the intervention to confirm

preoperative evaluation prior to proceeding with the procedure. We never compromised our visualization due to the TCD probes. An optimal view allowing proper identification of the culprit lesion and the filter was always assured prior to proceeding. Once the severity of the lesion had been verified and the anatomy deemed to be suitable for CAS, the procedure was performed. The CAS technique involved use of either FilterWire EZ System (Boston Scientific, Santa Clara, Calif) or GORE Neuro Protection System (W.L. Gore and Associates, Flagstaff, Ariz), a reversal of flow mechanism. After placement of the wire and EPD in the appropriate vessel, as per standard CAS technique, predilatation with a 3.0-5.0-mm balloon was performed. The preferred stent in all cases treated in this series of patients was the NexStent Carotid Stent (Boston Scientific, Santa Clara, Calif). This stent has a closed stent configuration, with self-sizing capability so that tapered and nontapered vessels can be treated. Stent deployment was followed by postdilatation in all cases. Technical success was considered to be a residual stenosis in the stented arterial segment of ≤30%. Postprocedural intracranial angiography was also performed.

All patients were given bivalirudin, as per standard protocol, after having gained secure access via the femoral artery, which consisted of a bolus dose of 0.75 mg/kg followed by a constant infusion of 1.75 mg/kg/hr for the duration of the procedure. Activated clotting times were followed and all remained in the therapeutic range thereby not requiring additional boluses. Patients who had no contraindication were given both aspirin 81 mg and Plavix 75 mg postoperatively.

RESULTS

A total of 6 patients were interrogated using dual probe TCD monitoring during CAS. Three of these had cerebral embolic protection with the FilterWire EZ System (FW), while the other three with the GORE Neuro Protection System (NPS). Procedural success was 100% for CAS as it was for dual probe TCD monitoring. Only one stent was used for each of the cases. No patient suffered a periprocedural neurological event, defined as a period from initiation of procedure to a 2-week follow-up.

Dual probe monitoring was successful during the five stages of the CAS: lesion crossing (LC), predilatation (PreD), stent placement (SP), postdilatation (PostD), and filter/device removal (FR/DR). Using FW during LC by probe 1 (SICA)/probe 2 (MCA + ACA): (18 [range, 15-22]/15 [range, 11-20]), PreD (111 [101-121]/101[range, 90-111]), SP (68 [range, 60-76]/42 [range, 30-53]), PostD (27 [range, 25-30]/24 [range, 22-27]), and FR (0.3 [range, 0-1]/0.7 [range, 0-1]), average number of microembolic signals were detected. Using NPS during LC (1.7 [range, 0-3]/1 [range, 0-2]), PreD (0/1.7 [range, 0-4]), SP (0/0), PostD (0/0), and DR (18 [range, 0-18]/6.7 [range, 1-13]), average number of microembolic signals were detected.

The median age of the patients was 72 years. Five of 6 (83%) patients had hypertension and coronary artery disease, all patients had a history of hyperlipidemia, 4 of 6 (67%) had a history of tobacco use, while only 2 patients were diabetic. Of the 6 patients, three were for symptomatic cerebrovascular disease. All were on antiplatelet therapy except one who was intolerant of aspirin and clopidogrel.

Embolic signals identified during contrast injection were easily identifiable and were excluded from the final embolic counts (Fig 4, online only). Emboli detected at the level of the ICA, which also traveled into the MCA were observed to do so after a one to two heart beat delay (Fig 5, online only). Interestingly, in 1 patient, an embolus was identified in the SICA and traveled into the ACA and, on the same 8-second screen, a second SICA embolus instead traveled into the MCA (Fig 3, online only).

As we had expected, the only MES noted on TCD when using the reversal of flow system, were found to occur after and during removal of the (Fig 6) NPS. For the patients with the FilterWire EZ System, the results were very different (Fig 7). The greatest number of emboli were seen during predilatation (Fig 8), where an average of 111 emboli were seen at the level of the SICA, and 101 in the MCA. This accounts for a filter capture rate of 9% during this segment of the procedure. During stent deployment, a significant number of emboli were appreciated at the level of the SICA with 38% being captured by the filter and therefore not reaching the MCA. Overall 20% fewer emboli were identified at the level of the MCA, relative to the SICA.

Eight total emboli were detected during the procedure at the level of the MCA with flow reversal vs 547 with the distal filter device. During device removal, the trend was reversed so that 20 emboli were seen for reversal of flow and only two with the filter device. Therefore, removal of the device accounted for 71% of all emboli measured in the MCA with the reversal of flow system.

DISCUSSION

The treatment of carotid stenosis has the goal of preventing embolic events, but treating the culprit lesion itself carries a risk of embolization. The evolution of the management of carotid artery disease has meant that CAS is now a formidable counterpart to CEA. One of the major developments in CAS has been the creation of EPDs. Rosenkranz et al showed that most cerebral microemboli that occur during CAS are gaseous, while only <15% of microemboli are actually solid. Interestingly, they noted no relationship between the number of solid emboli and new ischemic lesions as detected by MR DWI.[16] On the other hand, it has previously been shown that particulate matter visible to the naked eye can be found in EPDs after CAS in 19% to 63% of cases.[17-19]

Furthermore, microscopic analysis revealed that 50% to 80% of EPDs contain debris. Coggia et al showed that most emboli originating from carotid bifurcations during balloon angioplasty were actually less than 60 μm.[20] These emboli would therefore have the potential of traversing the pores of the filter devices. By dual TCD

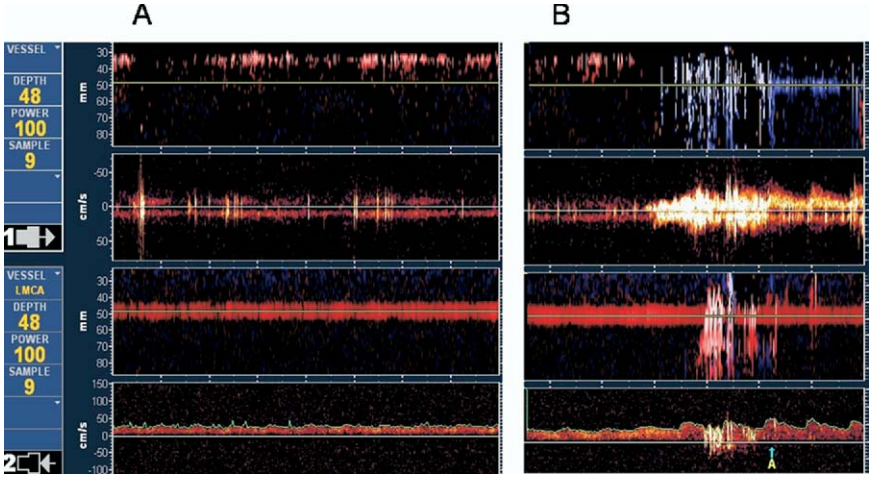

Fig 6. Using the GORE Neuro Protection System (W.L. Gore and Associates, Flagstaff, Ariz), (**A**) no microembolic signals (MES) were identified during stent placement (**B**) deflation of carotid balloon provokes MES.

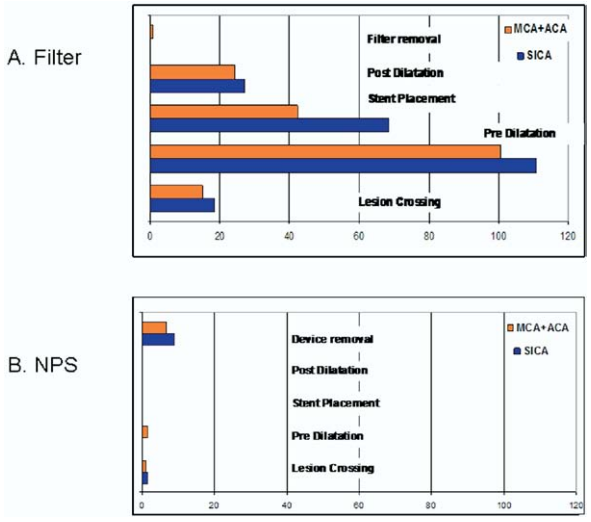

Fig 7. Graphic display of average microemboli count during stenting with filter protection (**A**) and GORE Neuro Protection System (W.L. Gore and Associates, Flagstaff, Ariz) (**B**).

monitoring, we were able to identify embolic signals in the ICA proximal to the filter as well as distal to the filter in the MCA. Overall, only 20% of the emboli detected in the submandibular position were not identified by the temporal TCD probe, and therefore the presumption is that the remainder of the particles are ending up in the cerebral circulation.

Although, TCD remains the only method to detect cerebral embolization, and this has been well documented for both CEA and CAS, not all of the MES seen on M-mode will be represented and detected on the spectral screen. Spencer et al reported 40% higher MES count on M-mode vs single channel TCD with spectral screen only.[21] One of the limitations of TCD remains its operator/interpretation dependence as well as the occasional suboptimal temporal bone windows, reportedly an issue in approximately 16% of cases.[4] Additionally, an ultrasound signal tested by using dual frequency TCD probes is unable to characterize the consistency of the embolus. Differentiating gas from particulate matter with a high level of sensitivity has been reported and would help determine the embolic source. The minimum detectable diameter of gaseous emboli has been reported at 10 microns while particulate emboli can be detected from 40 microns.[22] Again then, pore size becomes vital to cerebral protection as pore size determines which emboli have the ability to travel to MCA from the working areas. The major limitation of filter pore size is that decreasing the pore size also decreases flow.

The greatest number of emboli identified in our series was during the predilatation phase of the CAS procedure, which is not consistent with a great deal of the literature which has identified stent deployment as the most "embologenic" aspect of CAS.[16,23,24] There is inconsistency in the actual effects of microemboli , with showers of microemboli at postdilatation being strongly associated with adverse cerebral outcome.[4] We have no explanation for the preponderance of emboli during predilatation, but this step is not one that is uniformly practiced by all practitioners of CAS and this may be an area that requires further evaluation.

The major achievement of this report is to identify a novel way of using dual level TCD monitoring to evaluate EPDs. It has been described that a significant number of emboli are identified in vascular territories independent of the stented ICA,[6] which can be monitored using additional TCD systems.

In conclusion, our approach to CAS monitoring has identified a useful way to evaluate EPDs, but the analysis is limited in number and therefore is unlikely to modify practice patterns. It does though raise some important

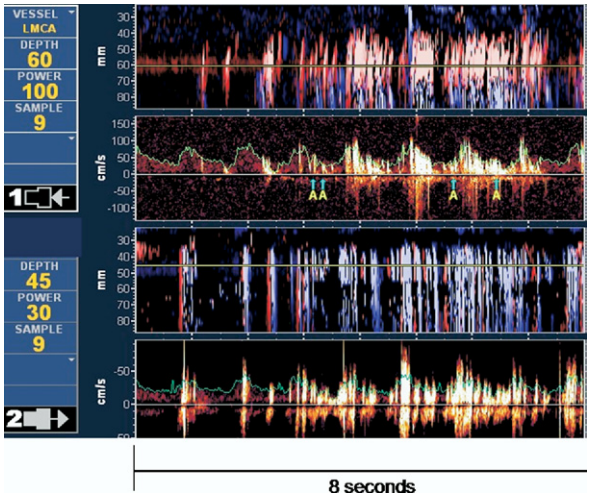

Fig 8. Predilatation with filter protection (shower of microembolic signals [MES] recorded on both channels).

questions and will serve as a future platform for potential modification of CAS as well as better prediction of particular events leading to ischemic cerebral lesions.

AUTHOR CONTRIBUTIONS

Conception and design: ZG, AL
Analysis and interpretation: ZG, JB, AL
Data collection: ZG, JB
Writing the article: ZG, EP, KC-O, JB
Critical revision of the article: ZG, JB, MD, AL
Final approval of the article: AL, MD
Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: ZG, AL

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DISCUSSION

Dr Brajesh Lal (*Newark, NJ*). I think this is an important area of research, and we need to do this kind of research if we want to improve the outcome of carotid stenting. With filter pore sizes ranging from 80 to 150 microns, it is no surprise that some microparticles will escape capture during carotid stenting. Our group and several others have been reporting on this phenomenon for at least the past 4 years.

The key assumption of your study is that transcranial Doppler (TCD)-detected emboli are a faithful and accurate marker for risk for stroke. You are using TCD-detected microemboli as a surrogate marker for risk for stroke. And because of that assumption, there are several questions that need to be addressed before we can accept that at face value. The true significance of these microemboli still remains elusive. Some studies have shown a correlation between the number of emboli and the extent of microinfarction, but others have not. Furthermore, some studies have shown a correlation between the extent of microinfarction and the incidence of stroke, while others have not. There are studies that have tried to address this issue with completely conflicting results. I am sure you are aware of that. So how do you try to reconcile your results with what is in the literature in terms of the value of TCD-detected microemboli and magnetic resonance (MR)-detected microinfarctions with clinical outcomes?

The second question is along similar lines. The Pittsburgh group has reported on perhaps the only randomized trial of carotid stenting with and without a filter that showed no difference in stroke rates or computed tomography (CT)-measured microinfarcts in the two groups. In fact, the infarct numbers were higher in the elderly patients with a filter compared with patients that did not have a filter. How do you reconcile that with your findings?

Third question, if the microemboli do not serve as markers for risk for stroke, then can they be predictors or markers for something else? We are very interested in cognitive function and we are currently in the process of completing an American Heart Association (AHA) -sponsored study, looking at cognitive outcomes and microemboli counts. So I would like your comments on that, too.

Fourth, a question on methodology. How practical do you think TCD monitoring is for every carotid stenting case, especially with the submandibular probe, which can, as I have observed, get in the way of good imaging. It is a fairly crowded, small field. Would you recommend this for all procedures, or limit it to an investigative tool where you could assess the performance of one filter versus the other?

Dr Jean Bismuth. We had a discussion earlier about diffusion-weighted images (DWI) and its importance. I think, as you mentioned, the literature varies quite a bit on what exactly the significance of these lesions is. We did not use DWI in our patients. But there is one study that I briefly mentioned in the beginning, which is just out, and it does show that a lot of these lesions out approximately a month do reverse. I think with stents what happens is you have a cumulative effect, and I think that what is going to be important is that you have continued microembolization, and possibly TCD could play a role in evaluating these patients and seeing whether patients with these stents, long term, have continued microembolization. And that may give you the potential to predict poor outcome a little bit better.

Simultaneous pre- and postfilter TCD monitoring is a good tool to evaluate our protection devices and see what works and should primarily be used in that role. I think TCD has a role during stenting, not only for embolization, but changes in flow patterns due to complications are almost immediate, thereby allowing you to react a little sooner than you can possibly with electroencephalogram (EEG).

Dr Alipour I just want to make one comment. I would strongly urge you to review some of the literature on especially the two most recent randomized trials in cardiothoracic surgery where aortic filters were used and TCD-detected microemboli were virtually eliminated, but the incidence of cognitive dysfunction did not change. So there is a lot more we need to understand about these three things before we can come to some clinical conclusion.

Dr Bismuth. For your first comment, there are actually several studies out showing that the plaque characteristics do not necessarily predict outcome. One would expect poorer outcomes when treating vulnerable plaques, but that is not really the case.

Dr Alipour. Not the outcome, but the shower of emboli is more common.

Dr Bismuth. Sure.

Dr Wei Zhou (*Stanford, Calif*). It appears that TCD is an excellent method examining real-time microemboli during carotid stenting. We have also evaluated microembolic phenomenon using DW-magnetic resonance imaging (MRI) over the last several years. Studies have shown that microemboli may occur 48 hours after the stenting procedures. Have you or are you planning to perform postprocedural TCD? Although we do not know the cognitive effects of microemboli yet, it will be important to know what percentage of microemboli occurs after stenting.

Dr Bismuth. We have not looked at that data, so I would not be able to tell you. I can tell you that we are now, as a standard, preoperatively doing TCD and, obviously, carotid duplex, and following that postoperatively. So hopefully in the next year or so, we should be able to give you some numbers on that.

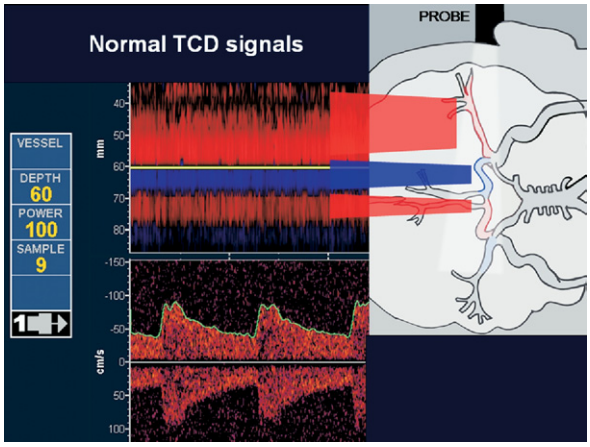

Fig 2, online only. Schematic representation of normal transcranial Doppler (TCD) signals from a transtemporal probe placement. Middle cerebral artery (MCA) (red: 40-60 mm), anterior cerebral artery (ACA) (blue: 60-70 mm), and contralateral ACA (red: 70-80 mm) (Schematic drawing courtesy of Debra Liles Canter.)

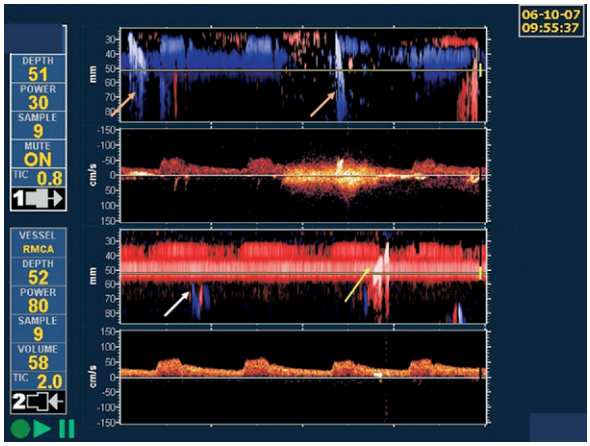

Fig 3, online only. Channel 1: Submandibular internal carotid artery (SICA) recording two microembolic signals (MES) (*orange arrows*). First one on the channel 2 power M-mode Doppler screen (recoding middle and anterior cerebral artery [MCA + ACA]) traveled to ACA (*white arrow*). Second MES from SICA traveled to MCA (*yellow arrow*).

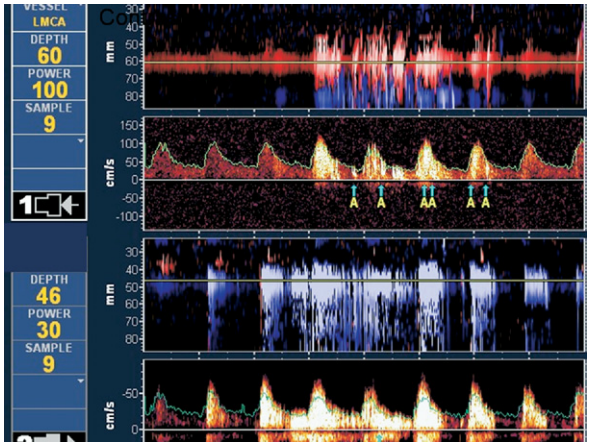

Fig 4, online only. Contrast injection is shown as hyperintense signals on the PMD-TCD screen channel 1, in the middle anterior cerebral artery (MCA), during four cardiac cycles and channel 2, in the submandibular internal carotid artery (SICA), during seven cardiac cycles.

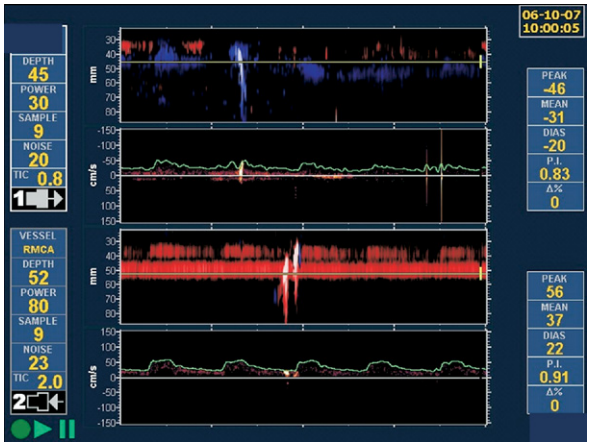

Fig 5, online only. On transcranial Doppler (TCD) monitor a microembolic signals (MES) recorded on channel 1 in the submandibular internal carotid artery (SICA) is seen after a delay of a single heartbeat in the middle anterior cerebral artery (MCA) by transtemporal transcranial Doppler (TCD) probe on the lower channel 2.