Eur J Vasc Endovasc Surg **25**, 262–266 (2003)
doi:10.1053/ejvs.2002.1805, available online at http://www.sciencedirect.com on SCIENCE DIRECT

Feasibility and Reliability of On-line Automated Microemboli Detection after Carotid Endarterectomy. A Transcranial Doppler Study

A. G. Munts[1], W. H. Mess[3], E. F. Bruggemans[4], L. Walda[3] and R. G. A. Ackerstaff*[2]

[1]*Department of Neurology, Atrium Medical Center, Heerlen,* [2]*Department of Clinical Neurophysiology, St. Antonius Hospital, Nieuwegein (Utrecht),* [3]*Department of Clinical Neurophysiology, University Hospital Maastricht, Maastricht and* [4]*Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands*

Objectives: *recently, a new algorithm for transcranial Doppler (TCD) ultrasound detection of microembolic signals (MES) was developed. In the present study, we investigated its on-line performance in TCD monitoring after carotid endarterectomy (CEA) and assessed off-line its accuracy in detecting MES.*
Materials and Methods: *first, the feasibility of MES detection in TCD monitoring after CEA in a routine clinical setting was evaluated in 50 patients. Second, to test the reliability of the software a 2-h digital audio study tape was made and analysed by the algorithm and five human experts. The "gold standard" was defined as the agreement between human experts: a MES was considered to be present if at least three human observers agreed.*
Results: *TCD monitoring for emboli detection after CEA was well tolerated by the patients and could be performed reliably. In the study tape, the human gold standard detected 107 MES, with 93 MES having an intensity of $\geq$7 dB. The software detected 81 and 77 MES, respectively. Using the 7 dB intensity threshold, the software had no false positives and 16 false negatives. The κ value between the human gold standard and the software was 0.91, the proportion of specific agreement was 0.83.*
Conclusions: *the tested algorithm provides a reliable method for automated on-line microemboli detection after CEA. This makes monitoring of the effectiveness of antiplatelet agents in the prevention of stroke after CEA more practicable.*

Key Words: Cerebral embolism; Ultrasonography; Automated emboli detection; Interobserver agreement.

Introduction

Transcranial Doppler (TCD) ultrasonography enables to detect cerebral microemboli during and after carotid endarterectomy (CEA). These microembolic signals (MES) seem to be a predictor of stroke.[1–3] The large number of patients who are candidates for this examination has led to the development of systems aimed at detecting MES automatically with rejection of artifacts. Recently, a new algorithm for on-line MES detection has been developed.[4] A first evaluation of this system by its development group in a limited number of patients ($n=9$) who underwent CEA showed satisfactory results.[5] The purpose of the present study was to evaluate the clinical feasibility of TCD monitoring shortly after CEA in a routine clinical setting and to test the reliability of the algorithm for automated emboli detection.

Materials and Methods

Since January 2000, in the St. Antonius Hospital postoperative TCD monitoring for emboli detection has been routinely performed after CEA, beginning 45–60 min after skin closure and with a duration of 1 h. The Doppler spectra are observed in the recovery room by an experienced sonographer and made audible by ear-phones. Besides changes in middle cerebral artery blood flow velocity, special interest is focused on MES and the number and time of occurrence of MES are documented. Simultaneously, the Doppler signal is analysed by recently developed software (FS1, EME-Nicolet, Madison, WI, U.S.A.) using a novel signal analysis approach.[4,5] For the current

* Please address all correspondence to: R. G. A. Ackerstaff, Department of Clinical Neurophysiology, St. Antonius Hospital, Post-box 2500, 3430 CM Nieuwegein (Utrecht), The Netherlands.

study, the raw Doppler signals from 50 consecutive patients with an adequate acoustic temporal window were continuously recorded on digital audio tape (DAT). All patients were symptomatic with a 70–90% ipsilateral internal carotid artery stenosis. CEA was performed in a standardised way and executed by an experienced vascular surgeon or by a specialist vascular trainee under supervision. Data tapes were reanalysed off-line by the algorithm and the results of this analysis were compared with (1) the judgement by one of the authors (R.A.) and (2) the results of the on-line analysis made by the algorithm. Finally, from six patients with at least 5 MES in a 20-min period, a 2-h study tape was composed by another co-worker (A.M.). This study tape was independently analysed by five human observers from three centres throughout The Netherlands and again by the algorithm. Each human observer was blinded to both the results of the software and the results of the other human observers. Human observers registered all MES by writing down the exact moment in time at which a MES occurred. Standard criteria for MES detection were used.[6] In all automated analyses, the embolus probability threshold for MES detection was set at 65%. The artifact threshold was switched off. All analyses were done with a Nicolet-EME TCD apparatus (Pioneer TC 4040). Statistical calculations were made with and without an embolus intensity threshold of 7 dB. Intensity was measured using the colour coded intensity scale of the fast Fourier transform and comparing the colour of the MES with the colour of the Doppler spectrum at a similar location in the preceding or next cardiac cycle.

Statistical Analysis

Statistical analysis was performed in two ways. Firstly, Cohen's kappa (κ) values were calculated, as in an earlier study.[7] For this analysis, the running time of the study tape was subdivided in periods of 1 s. In a former study,[8] we found that for κ values above 0.5, altering the duration of this time period had a negligible effect on the results. In the current analysis, the "gold standard" was defined as the agreement between human experts: a MES was considered to be present if at least three observers agreed.

Secondly, to compare our results with the results of the international panel in the original study,[5] we used their method that is based on the proportion of specific agreement.[9] This analysis method is independent of the number of observations in which two observers would not detect a MES and we took into account that there were more than two observers. Thus, the probability was calculated that a specific human observer or the algorithm would identify a MES under the condition of one or more of the other observers would detect the MES.

Results

Postoperative TCD monitoring was well tolerated and in all patients it was possible to perform one hour of continuous monitoring without significant interruptions. During the on-line analysis in the recovery room, the algorithm for MES detection was insensitive for artifacts (e.g., speaking, snoring, vomiting). With the artifact threshold switched off, such artifacts were never falsely interpreted as MES. During on-line analysis, in only two patients with a high number of MES of low amplitude (<7 dB) and low velocity (<30 cm/s), there was a noticeable discrepancy between the results of the sonographer and those of the software. Off-line analysis of the 50 digital audio tapes usually resulted in the same numbers and times of occurrence of MES as reported during the on-line analysis.

The number of MES in the study tape detected by the five human observers and by the algorithm are shown in Table 1. The κ values for agreement between the human observers ranged between 0.84 and 0.91 (Table 2a). One hundred and seven MES were detected by the human gold standard (defined as agreement between at least three human observers). Of these 107 MES, the software system detected 78 MES (true positives). Sensitivity was 0.73, with 3 MES being false positives and 29 false negatives. The κ value (SE) for agreement between the gold standard and the software system was 0.83 (0.030). Using an intensity threshold of 7 dB, the number of MES detected by the human observers decreased (Table 1) and the κ values increased to values ranging from 0.93 to 0.98 (Table 2b). With the 7 dB threshold, the sensitivity of the software system was 0.83, as no false positives and 16 false negatives were detected, and

Table 1. Numbers of MES detected by the human observers and by the software system.

	MES	MES ≥ 7 dB
1	103	91
2	124	94
3	99	90
4	112	90
5	105	87
Gold standard	107	93
Algorithm	81	77

Table 2. **κ values (SE) between the human observers.**

	1	2	3	4	5
(a) All MES					
1	–	0.85 (0.025)	0.89 (0.023)	0.86 (0.025)	0.84 (0.027)
2		–	0.88 (0.023)	0.91 (0.020)	0.89 (0.022)
3			–	0.91 (0.021)	0.87 (0.025)
4				–	0.89 (0.022)
5					–
(b) Only MES $\geq 7\,dB$					
1	–	0.95 (0.016)	0.94 (0.019)	0.94 (0.019)	0.93 (0.020)
2		–	0.98 (0.011)	0.98 (0.011)	0.96 (0.015)
3			–	0.98 (0.011)	0.94 (0.019)
4				–	0.95 (0.017)
5					–

SE = standard error.

Table 3. **Probability of detecting a MES by a second observer.**

	1	2	3	4	5	Mean
(a) All MES						
Second observer						
1	x	0.78	0.91	0.83	0.84	0.84
2	0.94	x	0.99	0.96	0.97	0.96
3	0.87	0.79	x	0.86	0.85	0.84
4	0.90	0.86	0.97	x	0.92	0.91
5	0.85	0.82	0.90	0.87	x	0.86
Algorithm	0.73	0.65	0.77	0.68	0.70	0.70
(b) Only MES $\geq 7\,dB$						
Second observer						
1	x	0.94	0.94	0.94	0.95	0.94
2	0.97	x	1.0	1.0	1.0	0.99
3	0.93	0.96	x	0.98	0.95	0.96
4	0.93	0.96	0.98	x	0.97	0.96
5	0.91	0.93	0.92	0.93	x	0.92
Algorithm	0.80	0.82	0.84	0.83	0.83	0.83

the κ value (SE) was 0.91 (0.024). In the latter analysis, signals with an intensity of less than 7 dB were not regarded as MES, neither by the human observers nor by the algorithm.

The results of the second analysis based on the proportion of specific agreement are shown in the Table 3a and b. The mean probability of agreement averaged for the five human observers was 0.88 for all MES, and 0.95 for MES with a threshold of 7 dB. The mean values for the software system were 0.70 and 0.83, respectively.

Discussion

The present study has demonstrated that early postoperative TCD monitoring after CEA can be performed with excellent patient acceptance. With all κ values for interobserver agreement between the human observers lying above 0.80, a high level of reproducibility for emboli detection was found and, therefore, a reliable human gold standard was obtained. Compared with this gold standard, the algorithm performed well in detecting emboli with an intensity of ≥7 dB, with a κ value of 0.91, a sensitivity of 0.83, and no false positives. In the original study on the use of this algorithm,[5] the mean probability of agreement averaged for the six human observers was 0.88 and for the computer algorithm 0.87. In our study, we replicated these promising results finding a mean probability of agreement for human observers of 0.95 and for the algorithm of 0.83. Use of an intensity threshold for MES detection has been shown to increase both interobserver agreement and sensitivity, and was recommended in recent consensus criteria.[6] Whether only microemboli of high intensity have a clinical impact in the early postoperative hours after CEA is still unknown and subject to future studies.

Patients undergo CEA in the hope that it will protect them against stroke. However, the most devastating complication of this operation is stroke. The efficacy of CEA is determined by the minimisation of perioperative stroke rates. Therefore, we have placed emphasis on a better understanding of the mechanisms of perioperative stroke from CEA. A recent analysis of these mechanisms in our institution[10] showed that most perioperative strokes were due to thrombus formation at the endarterectomy and clamping sites, resulting in cerebral emboli and carotid artery occlusion. Removal of plaque and intima expose subendothelial matrix which provides a thrombogenic surface supporting the formation of platelet thrombi. Technical errors such as clamp injuries, intimal flaps, and unusually rough endarterectomy surfaces contribute to the risk of thrombosis and embolism, but even after a technically perfect procedure thrombosis and embolism can still occur.

Systematic TCD evaluation of patients following CEA has demonstrated a significant association between frequent cerebral microemboli detected early in the postoperative period and the development of new postoperative cerebral deficits. For example, Levi *et al*.[11] found that more than 50 microemboli per hour detected postoperatively significantly increased the risk of subsequent TIA and stroke, with a positive predictive value of 0.71. Cantelmo *et al*.[3] later reported that multiple cerebral microemboli detected while in the recovery room were associated with new ischaemic lesions on MRI of the head made after surgery. These studies suggest that postoperative microemboli detection by TCD may play a role in the identification of patients at high risk of stroke in the setting of CEA. Moreover, based on this assumption microemboli may be used as a surrogate endpoint for stroke to test therapies that might be useful in reducing the risk of embolic stroke in the early postoperative period.[12–14]

Unfortunately, microemboli detection by TCD is a time-consuming and mentally strenuous procedure. Moreover, this technique is still characterised by technical and methodological problems that have to be solved in the future. The major technical impediment to its widespread use is the lack of a reliable automated method of embolic signal detection. In the current study, we tested a recently developed signal processing approach that describes the characteristics of MES compared with episodes of random Doppler speckle and artifacts.[5]

There are, however, caveats pertaining to the present study. First, we have only validated the use of the algorithm during postoperative monitoring after carotid surgery. In this setting, embolic signals probably represent platelet aggregates and are in general of a relatively high intensity. Table 1 shows that, on average, only 17% of all analysed microemboli had an intensity of less than 7 dB. This is likely the reason for the good performance of both the human observers and the software in this group of patients. Second, the software does not work well during CEA. During surgery a proportion of the microemboli are believed to arise from air bubbles and to result in MES of much higher intensity. This can lead to receiver overload and aliasing. The latter makes it appear as a bidirectional intensity increase in the Doppler spectrum and this again will lead to mistaken identification of the MES as an artifact by the algorithm. A solution might be to devote one extra receiver channel with much lower front end gain to the gaseous emboli.

In conclusion, the automated system provides a sufficiently reliable method for emboli detection after CEA. This makes it very useful for both scientific and clinical studies. Although our study showed a better performance of the human observers compared to the automated detection software, with a κ value of 0.91 the algorithm proved to be a reliable system. This finding means a better feasibility of future studies on TCD emboli detection after carotid surgery. In our opinion, for a reliable performance in this particular clinical setting there is no need anymore to record, safe, and review all raw Doppler signals for time consuming off-line analysis. Longer measurements and studies with larger populations become a possibility if a human observer is no longer needed.

References

1 Jansen C, Ackerstaff RGA. Microembolism and hemodynamic changes in the brain during carotid endarterectomy. *Stroke* 1994; **25**: 2504–2505.
2 Ackerstaff RGA, Moons KGM, Vlasakker CJWVD, Moll FL, Vermeulen FEE, Algra A *et al*. Association of intraoperative transcranial Doppler monitoring variables with stroke from carotid endarterectomy. *Stroke* 2000; **31**: 1817–1823.
3 Cantelmo NL, Babikian VL, Samaraweera RN, Gordon JK, Pochay VE, Winter MR. Cerebral microembolism and ischemic changes associated with carotid endarterectomy. *J Vasc Surg* 1998; **27**: 1024–1031.
4 Markus H, Cullinane M, Reid G. Improved automated detection of embolic signals using a novel frequency filtering approach. *Stroke* 1999; **30**: 1610–1615.
5 Cullinane M, Reid G, Dittrich R, Kaposzta Z, Ackerstaff R, Babikian V *et al*. Evaluation of new online automated embolic signal detection algorithm, including comparison with panel of international experts. *Stroke* 2000; **31**: 1335–1341.
6 Ringelstein EB, Droste DW, Babikian VL, Evans DH, Grosset DG, Kaps M *et al*. Consensus on Microembolism Detection by TCD. International Consensus Group on Microembolus Detection. *Stroke* 1998; **29**: 725–729.
7 Zuilen EVV, Mess WH, Jansen C, Tweel IVD, Gijn JV, Ackerstaff RGA. Automatic embolus detection compared with human experts. A Doppler ultrasound study. *Stroke* 1996; **27**: 1840–1843.

8 Ackerstaff RGA, Mess WH, Zuilen EVV, Tweel IVD. Reliability in the identification of Doppler embolic transient signals: A statistical problem? *Stroke* 1997; **28**: 876.

9 Markus HS, Ackerstaff R, Babikian V, Bladin C, Droste D, Grosset D *et al*. Intercenter agreement in reading Doppler embolic signals. A multicenter international study. *Stroke* 1997; **28**: 1307–1310.

10 Borst GJD, Moll FL, Pavoordt HDWMVD, Mauser HW, Kelder JC, Ackerstaff RGA. Stroke from carotid endarterectomy: when and how to reduce perioperative stroke rate? *Eur J Vasc Endovasc Surg* 2001; **21**: 484–489.

11 Levi CR, O'Malley HMO, Fell G, Roberts AK, Hoare MC, Royle JP *et al*. Transcranial Doppler detected cerebral microembolism following carotid endarterectomy. High microembolic signal loads predict postoperative cerebral ischaemia. *Brain* 1997; **120**: 621–629.

12 Lennard N, Smith J, Dumville J, Abbott R, Evans DH, London NJM *et al*. Prevention of postoperative thrombotic stroke after carotid endarterectomy: The role of transcranial Doppler ultrasound. *J Vasc Surg* 1997; **26**: 579–584.

13 Kaposzta Z, Baskerville PA, Madge D, Fraser S, Martin JF, Markus H. L-Arginine and S-nitrosoglutathione reduce embolization in humans. *Circulation* 2001; **103**: 2371–2375.

14 Levi CR, Stork JL, Chambers BR, Abbott AL, Cameron HM, Peeters A *et al*. Dextran reduces embolic signals after carotid endarterectomy. *Ann Neurol* 2001; **50**: 544–547.

Accepted 15 October 2002