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Introduction of an embolus detection system based on analysis of the transcranial Doppler audio-signal

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A new embolus detection system (EDS) is presented, built with the intention of detecting ongoing cerebral embolization in patients at risk of transient ischaemic attacks or stroke. It is based on the analysis of the audio-Doppler signal of a transcranial Doppler machine. The algorithm of the EDS estimates the intensity, duration and zero-crossing dynamics of the audio signal. The EDS has a multi-layer neural network which classifies events into micro-emboli signals (MES) or artefacts. The decision-making component of the software has been validated against human experts. Data from patients in the post-operative phase of carotid surgery were used for the validation process. The results showed agreement in MES and artefact classification of $> 93\%$. Apart from a monitoring display, the monitoring system includes a verification unit that allows the user to listen and to look at all data of individual MES and artefacts. Moreover, the system allows the user to record, store and re-calculate all data files. Data are stored using European Data Format, which allows data transportation over the Internet. The EDS may have a potential in stroke risk stratification, evaluating the effect of novel anti-thrombotic therapies, and in peri-operative and remote monitoring of carotid endarterectomy.

Keywords: Transcranial Doppler ultrasound; Micro-embolic signal; Monitoring

1. Introduction

Cerebral embolization underlies the pathogenesis of transient ischaemic attacks (TIA) and strokes. The presence of asymptomatic micro-embolic signals (MES) is recognized as an important factor associated with increased stroke risk [1 – 4]. Ongoing MES are a medical emergency, requiring rapid determination of the embolic source and urgent treatment to prevent further embolization. The only modality capable of detecting ongoing cerebral embolization with high temporal resolution is transcranial Doppler (TCD) [5]. However, TCD embolus detection can be tedious and time-consuming, due to clustering of signals and low rates of embolization. To overcome these drawbacks automatic embolus detection systems have been developed [6, –9]. Recent publications claim that automatic detection systems can reach a high level of accuracy in discrimination of artefacts and emboli compared to human experts [10,11].

MES are the result of corpuscular and/or gaseous emboli in the blood stream. Both solid and gaseous emboli are characterized by a short increase in intensity within the Doppler waveform spectrum and typically have a characteristic musical murmur. In 1995, an international

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meeting of TCD experts (known as the 'Consensus Committee') reached agreement on the definition of an embolus [12]. The main criteria were: durations of less than 300 ms, an intensity increase of more than 3 dB from the normal background, a unidirectional flow pattern, and an audio signal containing musical characteristics. These initial criteria were not completely satisfying and two years later the committee discussed the problems with embolus detection and determined guidelines for its proper use in clinical practice, as well as in scientific investigations [13].

The aim of our research was to develop a new embolus detection system, which can be used to detect ongoing cerebral embolization in patients admitted to the stroke unit, emergency room, or intensive care. Under these clinical circumstances the software should be able to detect and discriminate both discrete cerebral embolization as well as artefacts related to patient and/or probe movements. We did not intend to detect embolic events observed during cardiac surgery or intravascular procedures. During surgery—and especially during cardiac surgery—more complex types of embolic events and artefacts are observed. Examples include continuous embolic flows (known as 'embolic showers') and more or less periodic artefacts with a relatively long duration as observed during diathermia. These complex embolic events and artefacts will require a more sophisticated algorithm design. The current software has been written for a well-defined clinical situation: detection of discrete cerebral emboli in a conscious patient in whom artefacts are mainly related to movements. To validate the software we used TCD recordings obtained during the first few hours following carotid surgery. This is a good source of discrete cerebral embolization and movement artefacts. Based on consensus committee guidelines a relatively simple 'audio-based' algorithm has been developed which uses the audio signal of a transcranial Doppler machine. This paper describes the algorithm and neural network, and the display of the embolus detection system. We also perform a preliminary validation of the software for embolus/artefact discrimination.

2. Methods

2.1. The algorithm

To detect MES from TCD ultrasound data, an algorithm should be able to quantify the duration, intensity and the 'musical' characteristics of the signal. Based on these parameters the algorithm should also be able to distinguish MES from artefacts. Although duration and intensity can be measured more or less straightforwardly by estimating the time in ms and intensity in dB, numerous possibilities are available to classify the musical aspects of a MES. The current algorithm uses the information given by the zero-crossing frequency of the audio Doppler signal. Classification of candidate signals as MES or artefacts was performed using a multi-layered neural network. The input of the neural network consists of parameters related to duration, intensity, and zero-crossing characteristics. The value of the output 'neuron' (or node) is related to the MES or artefact classification.

2.2. Calculus of intensity and time

The algorithm performs a real-time calculation of the intensity or power (P) of the discrete incoming audio signal ($x[n]$) over a certain interval (of N samples) of approximately 1 s:

$$P_{\text{neighbour}} = \sqrt{\frac{1}{N}\sum_{n=0}^{N-1} x[n]^2} \tag{1}$$

The same procedure is applied for a smaller time interval of approximately 10 ms to detect short duration (MES or artefact) transient signals:

$$P_{\text{current}} = \sqrt{\frac{1}{N}\sum_{n=0}^{N-1} x[n]^2} \tag{2}$$

Then the relative intensity of the current event (which can be either an embolus or an artefact) and its neighbourhood (which is the normal Doppler speckle around the MES or artefact) is calculated according to the equation:

$$P_{\text{ratio}} = \frac{P_{\text{current}}}{P_{\text{neighbour}}} \tag{3}$$

The intensity is expressed in dB:

$$P_{\text{dB}} = 10\log_{10}(P_{\text{ratio}}) \tag{4}$$

The duration of the signal is the time between periods where the intensity increases above 3 dB and subsequently decreases below 3 dB. The duration is expressed in milliseconds.

2.3. Calculus of the zero-crossing dynamics

The zero-crossing spectrum of the MES is reconstructed from the audio time series, as seen in figure 1. This spectrum shows the duration of consecutive zero-crossing intervals or 'period time' (on the y-axis) versus time (on the x-axis). It also shows the changes that take place when a MES is detected. Compared to the surrounding normal Doppler speckle, which exhibits large variations of consecutive zero-crossing intervals, a MES is characterized by relatively small changes in consecutive zero-crossing intervals.

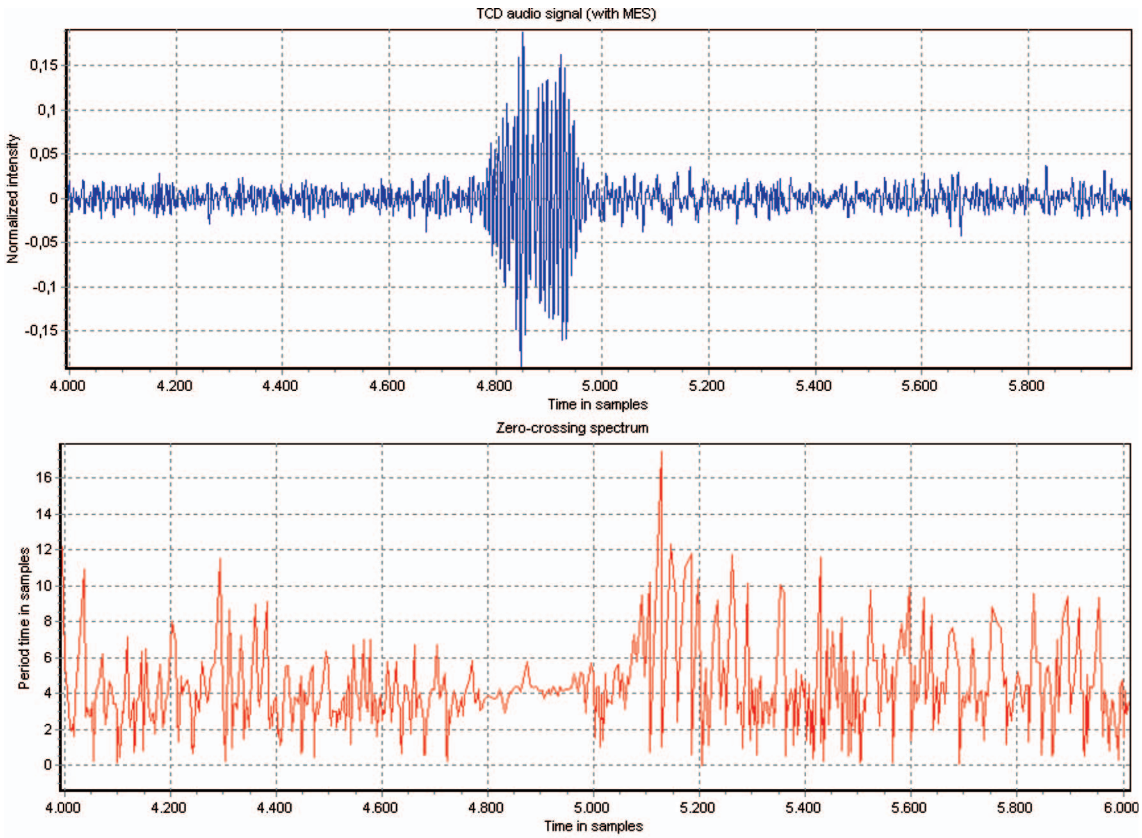

Figure 1. Top: MES of a TCD audio-signal; bottom: the zero-crossing spectrum, which shows changes in consecutive zero-crossing values over time. Note that compared to the surrounding Doppler signal the MES exhibits a spectrum with a relatively fixed level around sample numbers 4800 – 5000, indicating that the consecutive zero-crossing intervals of the MES itself show very gradual changes over time. This is in contrast to the more variable zero-crossing values of the regular Doppler speckle.

To quantify these changes of the zero-crossing spectrum the zero-crossing index (ZCI) is estimated. The ZCI is a value related to changes over time in the zero-crossing spectrum over time. The time between two consecutive zero-crossings is called a period (Period[n]). The ZCI is defined by the following equation:

$$ZCI = \sum_{n=0}^{N-1} (\mathrm{Period}[n] - \mathrm{FilteredPeriod}[n])^2 \qquad (5)$$

The FilteredPeriod[n] is the result of applying a moving average filter on the periods within the time-window studied. The ZCI has no dimension and varies between 0 and infinity. Zero means that only one frequency is observed in the time-series.

To gain familiarity with the ZCI trend curve, figure 2 shows the ZCI curve of a healthy individual who has undergone an artefact-free TCD examination of the middle cerebral artery (MCA) without micro-emboli. The figure is representative for a normal ZCI curve and shows a time-interval of two consecutive heart beats. The mean ZCI value lies between 100 and 300. During systole the ZCI tends to decrease, while during the diastole the ZCI tends to go up.

Figure 3 shows the variations in ZCI when a MES has been detected. Note the sharp decrease in ZCI compared to the ZCI of the surrounding normal Doppler speckle.

2.4. The neural network

The neural network was constructed using Matlab (version 70.0.19920 The Mathworks, Inc., Natick, MA, USA). It has an input layer with 15 nodes, five nodes in the hidden layer and one output node. Each input node is connected to all hidden nodes and all hidden nodes are connected to the output node. The weights of each individual connection may exhibit both negative and positive values. Seven parameters are used for the input of the neural network: mean duration, mean intensity, maximum intensity, mean ZCI, minimum ZCI, the number of zero-crossings and the number of zero-crossings per ms. To train the neural

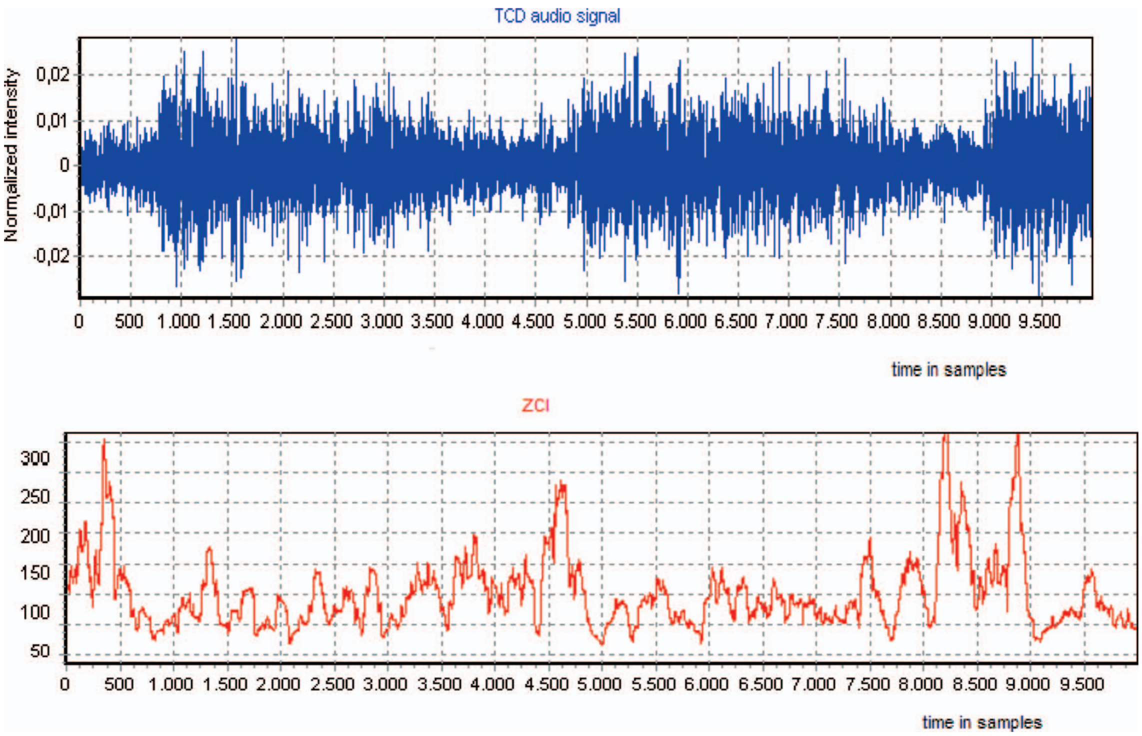

Figure 2. Top: the Doppler audio-signal of a healthy individual who has an artefact-free TCD examination of the middle cerebral artery over a time-interval of two consecutive heart beats. Bottom: the ZCI curve, which is a histogram of consecutive ZCI values. The ZCI values vary between approximately 100 and 250. During systole the ZCI tends to decrease while during diastole the ZCI tends to increase.

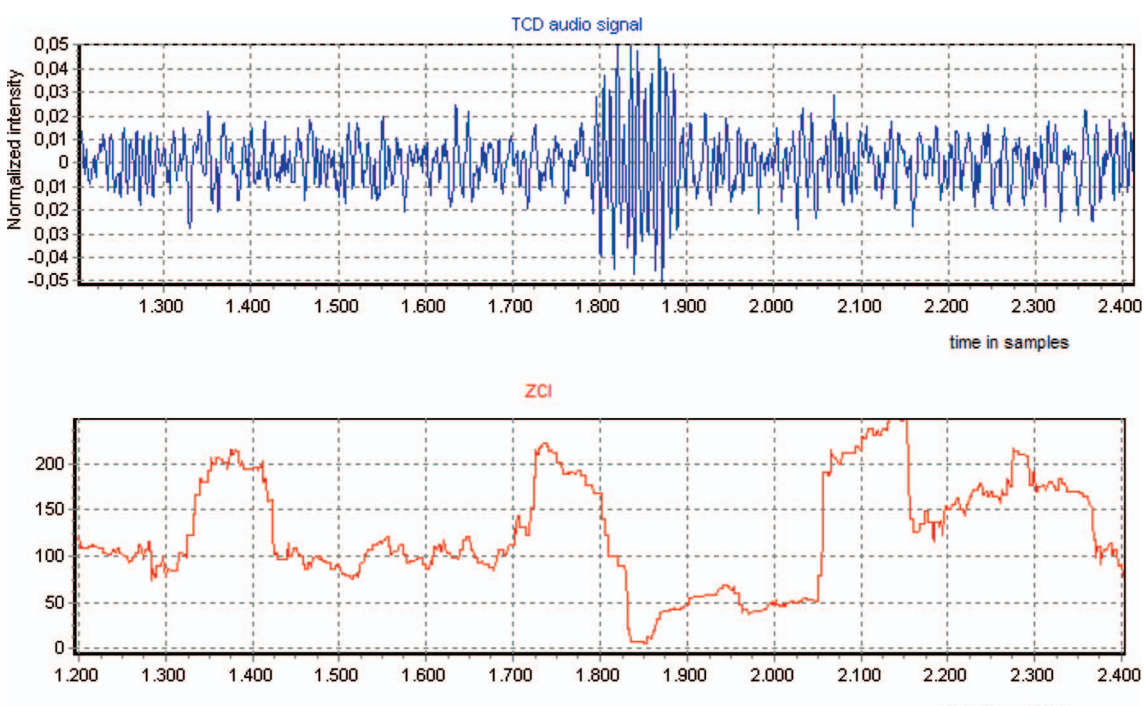

Figure 3. Top: the Doppler audio-signal of a MES. Bottom: the ZCI curve. The MES is characterized by a sharp decrease of the ZCI value compared to the ZCI values of the surrounding Doppler signal.

network for reliable discrimination between emboli and artefacts, the back-propagation method was used.

The teaching file consisted of 142 MES and 259 artefacts. The MES selected for the teaching file were chosen after pre-analysis of the intensity, duration and ZCI of MES profiles that are regularly seen in the postoperative phase of carotid surgery. After analysis of 500 embolic events under these circumstances we noticed that most emboli exhibited both a low intensity (3–6 dB) and a short duration (10–20 ms) while MES with longer durations (>20 ms) and higher intensities (>6 dB) were a minority compared to the former group. Therefore the neural network was trained with a diversity of emboli that matched the observed MES profile. The same procedure was applied to the selection of artefacts that were included for the teaching file. Pre-analysis of 500 artefacts in the post-operative phase of carotid surgery showed that artefacts were mainly related to probe and patient movements (including speech); however, short transient signals associated with to electronic artefacts were also seen. Details of the teaching file are given in table 1.

2.5. *Outline of the monitoring system*

In the present work, we used a Nicolet Pioneer TC 2000 (Nicolet Instruments, Madison, WI, USA) equipped with a 2 MHz TCD transducer and notebook Acer, Aspire 1800 Series (Acer Inc., Taiwan, China). A special headband was used to hold a ball-shaped 2 MHz transducer, which allowed hands-off monitoring. Firm fixation of the headband prevented lateral probe movements (MARC500, Spencer Technologies, Seattle, WA, USA). TCD was performed with standard settings in accordance with the consensus guidelines mentioned in the introduction. The insonated artery was the middle cerebral artery at its origin, just lateral of the terminal internal carotid artery, on the ipsilateral side of the carotid surgery. Insonation depth varied between 45 mm and 55 mm. Minimal intensity and gain setting were used for achieving an optimal embolus to Doppler speckle ratio.

From the audio output of the TCD machine, the signal was sampled in the notebook (sample frequency 6 kHz; filter type: 4th order IIR Butterworth filter; filter settings 60 Hz and 5940 Hz). Then the algorithm calculated in real time the intensity, duration and zero-crossing characteristics. These parameters were fed into the neural network. Both emboli and artefacts were displayed in real time, and during the monitoring session a FFT-based velocity spectrum was displayed. Apart from the monitoring display, the system includes a verification unit, which allows the user to see all data from individual MES and artefacts. Moreover the system allows recording, storage and re-examination of patients' data files.

Table 1. Characteristics of the teaching file.

Transients (n)	Emboli (142)	Artefacts (259)
Duration (ms)	22.6 ± 20.3	36.4 ± 32.5
Mean intensity (dB)	5.0 ± 1.6	4.8 ± 2.0
Maximum intensity (dB)	6.1 ± 2.4	5.8 ± 2.8
Mean ZCI	42.7 ± 31.0	338.0 ± 391.0
Minimum ZCI	9.3 ± 13.0	118.7 ± 109.3
Number of zero-crossings	50.1 ± 26.0	22.2 ± 22.1
Zero-crossing (ms)	2680 ± 994	745 ± 675

2.6. *Outline of the interface*

The interface of the system outlined in figure 4 shows a Windows format, which allows the technician or clinician to navigate between different menus. In the upper bar four main menus are seen: File, Monitoring, Verification and Instruction mode. The display shows four graphs and one event log. The upper two displays represent the monitoring unit, which show the velocity spectrum (left) and the MES/artefact histogram versus time (right). This histogram shows MES as positive orange bars while artefacts are presented as negative blue bars. During the monitoring session all events above 3 dB are listed in an embolus or artefact file. For each event, the time of detection, duration, intensity and ZCI are stored. By clicking on an individual MES or artefact in the event log, the signal can be observed in the verification unit shown in the lower two displays; verification velocity display on the left, and verification audio-time series on the right. Clicking on the audio button enables the technologist to listen to the actual event. A user input in the event-log allows the user to annotate the file during the monitoring period. The system also permits recording, storage and re-examination of patient data. All data are stored in European Data Format (EDF), which can be transmitted over the hospital network or internet. This facility would make it possible to check the system remotely, or to obtain a second opinion from a remote colleague or expert.

2.7. *Validation procedure*

To validate the system, MES and artefacts from both healthy controls and patients in the post-operative phase of carotid surgery were used. For validation we used no 'hand-picked' data but the whole dataset acquired during the post-operative monitoring setting. Only patients who showed more that 50 emboli were included in the validation procedure. In each person the middle cerebral artery was examined. The goal of the current validation procedure was to answer the question whether human experts (R.A & R.K.) agree on the discrimination capacity of the software to classify events > 3 dB into emboli or artefacts. Therefore humans were given all details of transient signals, such as duration, intensity, ZCI, the actual velocity display, the graphical data of the audio-signal, and the actual sound of the event. The EDS allows the user to change the colour

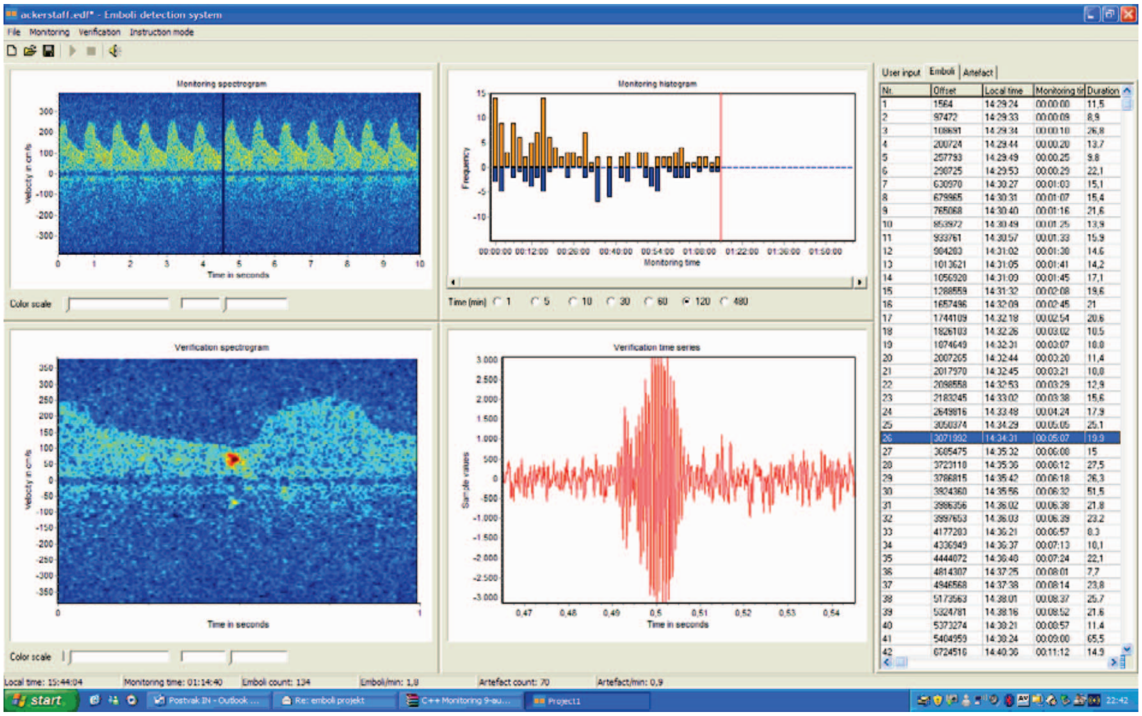

Figure 4. The display of the embolus detection system. The display shows four graphs and one event log. The upper two displays show the velocity spectrum (left) and the MES/artefact histogram versus time (right). The velocity spectrogram and the Doppler audio-signal of the individual events (MES or artefacts) are shown in the lower two displays: on the left the verification velocity display, on the right the verification audio-signal. The histogram nicely shows the gradual decay of MES (the positive orange bars), which is often observed in the postoperative period of carotid surgery.

scales of the velocity display, thus the human expert can highlight events by changing these scales. Within the display of the audio-signal a zoom function has been implemented which also enables the human expert to see all details of events at different time scales.

The validation protocol, outlined in figure 5, consists of three consecutive steps: data extraction, data classification and statistical data analysis. Human experts were blinded to the result of the neural network classification. For classification of micro-emboli the experts used established criteria (typical sound, unidirectional appearance in the FFT display, amplitude of at least 3 dB and duration of less than 300 ms). The final classification of MES and artefacts, both by the human experts and the neural network are presented in a 2×2 matrix. Data analysis included estimation of the overall accuracy of discrimination between MES and artefacts for all signals > 3 dB.

2.8. Ethical aspects

The standard procedure in the Antonius Hospital is that all patients are informed and give consent for combined TCD & electro-encephalographic monitoring during the surgical procedure. Patients were informed that TCD monitoring was used both as a surrogate marker of the cerebral blood flow and as a marker of embolic load during and shortly after the carotid endarterectomy. The patients presented in this study gave consent for off-line use of their dataset for testing new algorithms and anonymous publication of these data analyses.

3. Results

3.1. Normal volunteers

During 10 minutes of TCD examination in six healthy volunteers only artefacts were observed. Most were related to gradual movements and none of these artefacts were classified by the EDS as MES. Changes in intensity or gain of the TCD equipment did not induce additional artefacts or MES. Firm transducer fixation is crucial for prevention of sudden lateral probe movements. Sudden movements may induce very ‘periodic’ artefacts which could lead to a ‘false’ MES classification.

3.2. Micro-embolic signals

For validation of MES, data of four patients were used. These patients were chosen, out of a cohort of 25 patients, because they showed more than 50 emboli during the

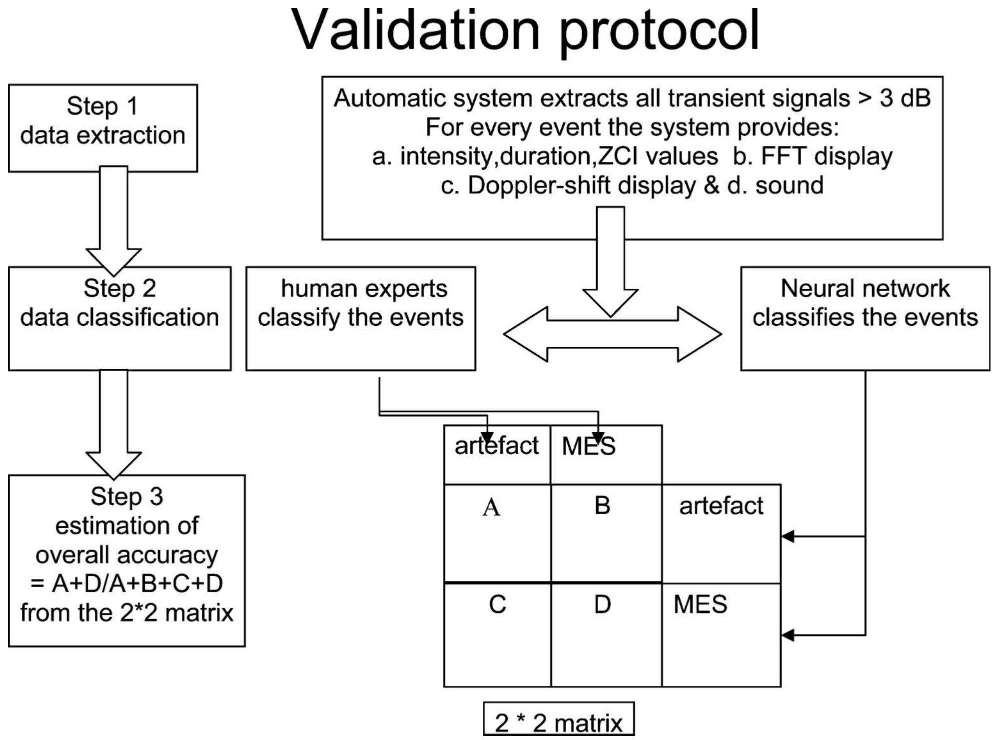

Figure 5. The validation protocol.

post-operative monitoring procedure. The mean monitoring time was 1 hour and 7 minutes (range 42 min to 1 hour and 14 min). A total amount of 789 post-operative events were analysed using the method summarized in figure 5. Humans classified 312 signals as MES and 477 as artefacts. The EDS classified 327 signals as embolic and 462 as artefacts. Due to the fact that only patients with a high embolic load were included for analysis, the emboli count outweighs the artefact count in this small cohort of patients.

The classification results are provided in the matrix shown in table 2.

Given that the EDS had detected a transient signal over 3 dB in intensity, human experts agreed with the EDS classification for 98% of signals classified as emboli, and 95% of signals classified as artefacts. Adopting the human experts' decision as a gold standard, the EDS had a 93% probability of correctly classifying emboli and a 98% probability for correctly classifying artefacts. The system was estimated to possess an overall accuracy of 96%. Mean values for duration, intensity, and ZCI of MES and artefacts are presented in table 3.

Only a minority (2.2%) of emboli detected by the algorithm were not classified as emboli by the human experts (seven out of 312). Disagreement between experts and the EDS were mainly observed in the category of artefacts. Human experts classified 4.6% of the 'EDS artefacts' as MES (22 out of 477). These MES were characterized by a relatively short duration, low intensity (<4 dB) and an intermediate ZCI value. An explanation for the EDS incorrectly classifying MES with very short durations and very low intensities lies in the fact that the neural network is trained by a large number of emboli which have a somewhat longer duration and higher intensity. Data from the 'misclassified' MES, 305 MES on which humans and EDS agreed, and 142 training MES are given in table 4.

Table 2. Classification of events.

	Human experts		
	Artefact	MES	Total
EDS			
Artefact	455	22	477
MES	7	305	312
Total	462	327	789

Table 3. Duration, intensity and ZCI of MES and artefacts.

Event	Number	Duration	Intensity	ZCI value
MES	305	16.8 ± 8.2 ms	5.6 ± 1.9 dB	12.3 ± 11.3
Artefact	455	30.2 ± 25.3 ms	5.3 ± 2.5 dB	347.6 ± 198.5

Table 4. Data of the 'misclassified' MES, the MES on which humans and EDS agreed and the training MES.

Event	Number	Duration	Intensity	ZCI value
Misclassified MES	22	14.3 ms	3.9 dB	40.1
MES	305	16.8 ms	5.6 dB	12.3
Training MES	142	22.6 ms	5.0 dB	42.7

4. Discussion

Although the sensitivity of detection of embolic signals was not explicitly compared to that of human experts in a double-blind analysis, our initial experience with the new algorithm suggests that it is capable of detecting discrete cerebral embolization in patients, and can discriminate between emboli and movement artefacts to a level which is similar to human experts. This makes the algorithm a good candidate for peri-operative monitoring or risk-stratification. Whether this algorithm can differentiate between gaseous and solid emboli has to be explored in future studies. Based on a limited number of observations in patients with artificial heart valves we noted that the current system has a potential to detect MES from discrete gaseous emboli and that there were differences in the ZCI value of discrete solid and gaseous emboli.

Although human experts are currently considered the gold standard for embolus detection, they also have limitations when relying on their own human capacity to listen to emboli or artefacts and to look for transient intensity increases in the Doppler velocity display [14,15]. Low intensity emboli are particularly difficult to discriminate from the normal Doppler speckle and low velocity emboli might easily be confused with low frequency movement artefacts of short duration. Given doubts as to the reliability of the human expert as a gold standard we chose not to assess the EDS against the human expert for the initial detection of signals . Rather, we gave the experts all the information calculated by the software. The EDS was used to provide the human experts with additional information with which to judge the nature transient signals.

The present ZCI based algorithm has differences compared to commercially available algorithms. Most of these algorithms detect emboli after subjecting the raw Doppler shift to a fast Fourier transform (FFT) [9,10]. However, FFT procedures have limitations in detecting MES, especially when the MES has a short duration. Another potential drawback of the FFT is that it removes phase information which may be used for determining the periodicity of a MES. The ZCI is not the only algorithm used for emboli detection based on the raw Doppler shift. Other examples include the temporal and spatial resolution method [16,17], wavelet transform [18,19], and analysis of the TCD signal by nonlinear dynamics [20]. Nonlinear analysis was initially implemented in the system to detect periodicity of MES but the ZCI proved to be more robust in MES signals of short duration. Moreover, compared to nonlinear analysis and complicated FFT-based algorithms, analysis of the ZCI is a much faster procedure and allows real-time processing of the periodicity of the signal.

The current system has several limitations. The software has not been designed for the detection of embolic showers. Showers are characterized by longstanding increases in intensity, and because the algorithm is built to detect short duration transient increases, it fails properly to classify showers. The same holds true for diathermia artefacts which are 'musical' artefacts of relatively long duration. Future goals will focus on algorithm designs that are capable of better classification of embolic showers and diathermia artefacts. It is important to know that reliable embolus detection is only possible in patients who are cooperative during TCD examinations. Firm transducer fixation by a headband is crucial to prevent the occurrence of 'false' MES induced by sudden lateral probe movements.

Apart from patient data files, the present system features a monitoring unit and a verification unit. A FFT display of the velocity waveform is included in the monitoring screen, which permits online visual control of the monitoring procedure.

The verification unit allows the evaluation of each single event that has been classified as an artefact or embolus. This is a great benefit compared to systems that do not give the raw data of the artefact or embolus calculus. Instead of being subjected to a 'black box' classification system, the current EDS provides transparency and gives the user the opportunity to judge whether or not an artefact or embolus has been properly classified. The log shows the exact time of the events and enables the user to make annotations. The software facilitates off-line calculations from a stored TCD time-series with different parameter settings of ZCI, duration or intensity. Although the ZCI algorithm seems to have promising clinical potential, it has not been fully tested on typical consecutive patients. Studies are underway to provide these necessary data that could prove the clinical relevance of the current system for monitoring of stroke patients.

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