Microemboli Detection by
Transcranial Doppler Ultrasound

Mikroembólia-detektálás
transcranialis Doppler módszerrel

Ph.D. thesis

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BACKGROUND

Cerebral embolism is the main cause of ischemic stroke. Consequently, the detection and prevention of embolic events is critical to reducing the burden of stroke. Emboli may cause either large disabling strokes or small subclinical events, depending on the size and eventual location of the embolus. Emboli generated from the chambers or valves of the heart or from atherosclerotic plaques in the arteries of the neck are variable in their size and consistency. Embolus detection using transcranial Doppler ultrasound (TCD) allows for the identification of active embolic sources in stroke-prone individuals and the selection of high-risk patients for appropriate treatment. The large number of patients at risk and the time and manpower needed for TCD-based embolus detection led to the development of various systems for semi-automatic or automatic microembolic signal (MES) evaluation. Cerebral embolus monitoring systems suitable for routine clinical use must have the ability to automatically recognize high intensity transient signals and differentiate between artifacts and emboli. Additional information is needed about MES, mainly on their size, composition and nature (solid or gaseous). Without an automated embolic signal detection system that is as effective as the human expert in terms of sensitivity and specificity, embolus detection remains a time-consuming process, restricted to research studies and unsuitable for clinical practice.

AIMS OF THESE THESES

Microembolus detection by TCD is time consuming and challenging issue, additionally more information is needed about MES's occurrence and on their nature (solid or gaseous). In this thesis, the technical background and possibilities of semi-automated and automated methods for identifying true embolic signals and approaches established for solid-gas differentiation were studied.

-Firstly, we wanted to answer the question, how reliable are some of the "on market" automated/ semiautomated TCD systems on MES evaluations?

-Secondly, we built up and tested our automated off-line TCD system, and we assed its capability for differentiate artifacts and true MES.

-The third issue of this thesis is solid-gas differentiation. We wanted to answer the question, whether our new TCD system is capable also to differentiate solid MES and gaseous MES? Additionally we wanted to determine, if oxygen inhalation is capable to define the composition of MES in different circumstances? We also wanted to demonstrate, that the majority of MES in patients with prosthetic heart valve are gaseous in nature.

To answer and investigate these questions series of research works were planned and performed with the help of the neurosonological research teams in Münster/ Germany and in Lausanne/ Switzerland.

METHODS AND MATERIALS

Controls and patients

In these works control persons (n=53) and patients (n=158) were investigated. The healthy subjects served as negative controls and also for testing the provoked artifacts. None of the overall 53 controls had neither atherosclerosis nor any potential source of cardiogenic emboli.

A total of 158 patients with potential source of embolism was investigated. Thirty-four patients with mechanical prosthetic valve participated in these studies. The subjects with mechanical prosthetic valves serve as a good model for studying micro-embolization, since most of them are "embolus positive". Additionally overall 120 patients with arterial source of emboli were studied. The majority of them had carotid territory atherosclerosis (occlusive disease), however, a few patients underwent MES detection over PCAs with pathologies on their vertebral, basilar or posterior cerebral arteries. Additionally 4 patients with previously diagnosed patent foramen ovale were investigated. These patients underwent the so-called contrast TCD test for producing surly gaseous microemboli. In all studies the collective of the patients were separated in terms of source of embolization (i.e. the patients with prosthetic heart valve had no significant carotid atherosclerosis). All controls and patient had given informed consent.

Ultrasound investigations

All subjects received a full color duplex or/and a continuous wave Doppler ultrasound investigation of their neck arteries and a continuous wave Doppler examination of the periorbital arteries. The majority of the controls and patients were also investigated by TCD and/or by TCCD (transcranial color coded duplex) including the intracranial segments of the ICAs, the MCAs, the ACAs and the PCAs and the basilar artery. In patients with occlusive diseases the collateral pathways were also as far as possible clarified.

For MES detection by TCD in all patients two MHz probes were mounted on their skull with different head-frames. The monitorings were performed uni- or bilateral over MCAs or PCAs (P1 segments). For the microemboli monitoring three different type of TCD devices were used, namely TC4040 (EME), Neuro-Guard (CDS/

Medasonics) and Multi-Dop X4 (DWL). The duration of detections lasted 60 minutes in the majority of the monitorings. During the evaluation of neural network for controls only 20 minutes monitoring were performed additionally to the series of provoked artifacts. In the study testing our new system controls were investigated during the period of provoking artifacts.

The settings of the machines were maintained possible unchanged throughout the recordings.

Documentation, data analysis and applied statistics

In the first part of the work the different algorithms for detecting and analyzing signals were tested. For that purpose the signals with the above detailed characteristics were saved either automatically or/and continuously as raw Doppler shift data onto digital audiotapes. The recording on DAT has the opportunity to reload the whole detection to the same TCD device for complete off-line evaluation. In the case of automated recording to the TCD device the data are already pre-selected data. During the first part of the study the detection threshold for that device and settings was determined and later this level was used in all studies with the same machine (EME TC4040). In the study for testing the neural network the automatic recordings of events were compared to the as "gold standard" accepted experienced human observers decisions. He based his results on off-line analysis of data played back from digital audio tapes. The neural network was installed and adjusted for that TCD device (Neuro-Guard CDS/ Medasonics), we used its given settings for MES detection. In the study performed by our research group in Lausanne we used the raw data of signals, which were by the TCD (Multi-Dop X4, DWL) pre-selected. The TCD settings were adjusted and validated according to the criteria recommended in the International Consensus Group on Microembolus Detection. The MES classification algorithms analyzed off-line these data.

For the solid-gaseous MES discrimination by oxygen inhalation the audio-signals recorded on digital audiotapes were used, the evaluation was performed by an off-line, blinded experienced analysis of MES'.

Generally, the experienced observer's analysis of MES consisted of (1) on-line analysis during the recording; (2) visual and acoustic off-line verification of the events pre-selected by the algorithm, and (3) blinded off-line analysis of the tape-recorded signals re-introduced into the FFT processor. Conflicting results were re-evaluated. MES were identified according to their previously documented characteristics.

We used the non-parametric Mann-Whitney U-test (1) for comparing the relative intensity increase of MES, (2) to compare the duration of MES. Linear regression was used (1) for the analysis for the relative intensity increases of MES and artifact signals, (2) for the relationship between the MES' relative intensity increase and duration, (3) for the relationship between the lowest relative intensity increase of given MES in one of the channels and its range of relative intensity increases within all four channels, and (4) for the relationship between the time delay of MES from one channel to others and the spatial distance between the sample volumes. For evaluating the neural network the sensitivity, and positive predictive values for MES detection by this algorithm in comparison to investigator's decisions were assessed. To assess our new MES analyzing system the data were divided into 2 sets. The first data set was used as learning set and the second was used as validation set. The κ values were determined to measure the level of agreement between the human experts and the automated Doppler system. Additionally, the sensitivities, the positive and negative values were determined . The nonparametric Wilcoxon test was used to compare the numbers of MES as well as the systolic and end-diastolic blood flow velocity and the heart rate with or without oxygen inhalation. Statistical significance was declared at the 0.05 level.

RESULTS

Semi-automated detection of microemboli by four-gated transcranial Doppler ultrasound

By the premonitoring TCCD investigations the maximum separation of the first and fourth sample volumes of 10 mm could be achieved in all subjects. The mean insonation depth for the target vessel segment ranged from 45.5 to 55.4 mm. During the monitorings by TCD at least a faint signal could be obtained in the four channels, the quality of signal was qualified as “poor” only in 19 out of 4x42=168 recordings.

In this and all later studies performed with the same TCD instrument (EME TC4040) a detection threshold of ≥ 5 dB was used taking into account that only 2.1% of the natural fluctuations of the Doppler spectrum occurred in this range. The software detected 767 by the investigator confirmed MES in the 22 patients. No MES were detected in controls. As the MES were detected in four channels these MES corresponded to 238 single embolic events. Figure 3 gives the distribution of the relative intensity increases of these signals with respect to their origin. MES in patients with prosthetic heart valves had higher intensity increases (14.7 ± 4.3 dB) and longer duration (21.5 ± 12.8 ms) than MES in patients with carotid occlusive disease (7.2 ± 2.2 dB, $p<0.001$ and 11.1 ± 3.9 ms, $p<0.001$).

MES corresponding to the same embolus detected in all four channels showed a varying relative intensity increase in different channels. The detectability of MES in as many channels as possible clearly depended on the relative intensity increase, i.e. weaker signals were detected in fewer channels. The time delays of MES in adjacent channels were either zero or greater. In most cases artifact signals did not produce a measurable time delay, but they could also provide small positive or negative time delays.

For the calculations of the sensitivity and observer-software agreement the term “embolic event” refers to one underlying embolus. With the detection threshold of ≥ 5 dB, the software recorded in the patients a total of 3092 events (2021 in patients with mechanical valves and 1071 in patients with carotid artery disease). Of these embolic events 238 (158 in patients with mechanical valves and 80 in patients with carotid artery disease) were confirmed as true embolic by the experienced investigator. Fourteen additional events, unnoted by the software, were found by the investigator in the valve group and 23 in the carotid artery disease group. Thus the software had a sensitivity of 91.9% and an observer –software agreement on MES of 7.8% in the valve patients, and 77.7% and 7.5%, respectively, in carotid artery disease. Overall sensitivity was 86.5% and the agreement on MES was 7.7%.

Automated microembolus detection by a neural network

During the off-line analysis, the blinded investigator detected no embolic signal on normal subjects. The software detected 238 events during the entire period and 216 events from the 1342 provoked artifacts were recorded as embolic signals. Thus the artifacts rejection rate was 85%. Most of the artifacts, detected by the software as emboli, had an energy increase of more than 10 dB above background (16.5 ± 5 dB).

The automatic embolus detection system detected 282 events in both groups of patients, ranging from 1 to 95 MES per individual. Among these events, 122 signals originated from artifacts. During the offline analysis, the blinded investigator identified a total number of 218 MES. The software did not identify 58 additional MES detected by the investigator (cf. Table 1). The neural network achieved an overall sensitivity of 73.4% and a positive predictive value of 56.7% in comparison to the experienced human investigator. MES from patients with artificial heart valves had a spectral power of 6.4 ± 2.1 dB; however, in patients with other sources of emboli, MES had an averaged energy reflection of 2.7 ± 0.9 dB.

Table 1

MES Detection in All Patients

	Investigator's Decision		
Neural Network	MES yes	MES no	Total Network
MES yes	160	122	282
MES no	58		
Total Investigator	218		

Automated MES identification and classification by a Wavelet representation combined with dual-gate TCD

A combination of the peak frequency of detected signals and the time delay makes it possible to separate artifacts from emboli. In general, artifacts have a lower frequency than emboli; however, there is a zone of overlap. In this zone, the time delay was used to distinguish between artifacts and emboli. A pair of signals with a time delay <4 ms was classified as an artifact, otherwise as an embolus. Above 500 Hz, the signals were declared to be emboli, and below 250 Hz they were declared to be artifacts. On the validation set 98% of artifacts were recognized as artifacts, which means that the specificity was 98%. The sensitivity was 194/200 =97%. The positive predictive value (PPV) yielded 194/196=99%, where positive referred to the emboli, and the negative predictive value (NPV) was 98/104=94%.

In general, gaseous emboli tend to have a higher relative power and a higher frequency than solid ones. Thus the plane defined by the peak frequency and the relative power was divided into 3 regions. The high-frequency (>1600 Hz) or high-relative-power (>18 dB) region was associated with gaseous emboli, and the low-frequency (<1600 Hz) and low-relative-power (<14 dB) region was associated with solid emboli. The nature of points falling into the third region was decided as follows. If the envelope asymmetry was high (>2%), the corresponding point was classified as belonging to a gaseous embolus, whereas if the asymmetry was low (<1%), it was classified as belonging to a solid embolus; points with an intermediate symmetry were classified as undefined. On the validation set the sensitivity achieved 89% and the specificity 86%. Conditional on their being classified as emboli, the predictive value for solid emboli (PPV) was 89% and the predictive value for gaseous emboli (NPV) was 89%. See table 2. The κ values for the entire table are 0.84 with 89% agreement (*P*<0.0001).

Table 2

Cross-tabulation of detected events classification into artifacts or gaseous or solid emboli by the automated Doppler system and human experts (validation set)

	Human experts			
Automated Doppler system	Artifacts	Gaseous emboli	Solid emboli	Total
Artifacts	98	4	2	104
Gaseous emboli	0	83	10	93
Solid emboli	2	11	87	100
Undefined	0	2	1	3
Total	100	100	100	300

Agreement: 89.33%, κ: 0.8408, Standard error: 0.0404, p=0.0001

Differentiation of gaseous from nongaseous MES with oxygen inhalation

In this study, which was performed to prove that microemboli in patients with mechanical prosthetic valve are predominantly gaseous a significant decline of MES under oxygen inhalation was found in valve patients (144 MES without versus 63 MES with oxygen, p= 0.002). There was no significant decline of MES number in patients with arterial source of emboli (145 MES without oxygen versus 135 MES with oxygen inhalation, p=ns), 12 patients had more MES without oxygen and 9 had more with oxygen. One patient had the same amount of MES under the two conditions. None of the control subjects showed any MES. There were no significant differences between the heart rates and blood flow velocities with or without oxygen inhalation neither in patients nor in controls.

DISCUSSIONS

Transcranial Doppler ultrasound is capable of detecting gaseous and solid microemboli within the pentagon of Willis. In general, these microemboli are clinically silent, however, they could indicate an increased risk of stroke. The time and manpower needed to evaluate the recordings led to the development of various semi-automatic/ automatic detection systems. The differentiation of artifacts and MES from the normal spectrum and the differentiation of MES from artifacts are challenges also for experienced human observers and not only for these systems. Although inter-observer agreement can be high within centers, previous studies demonstrated that different centers might disagree in the interpretation of MES especially in MES with small intensity increases. For improving semiautomatic or automatic detection techniques the knowledge about the basics of Doppler method, the good quality of signal is relevant.

The assessment of the anatomy of intracranial arteries prior microemboli monitoring can improve the signal-quality by adequate localizing the sample volume. It is crucial issue especially for multi-gated TCD technique, since e.g. four-gate TCD requires both the sample volume and the beam width to cover the vessel section under investigation. A longer distance between the sample volumes would result in a greater time delay making MES easier to identify. The results of our study demonstrated, that a target vessel segment of 1 cm length was sufficient for MES detection in MCA. According to the findings of this study, a potential overlap of sample volumes did not affect the multi-gate technique.

Other relevant issue for MES discriminating is the detection threshold. The detection of microembolic particles within the streaming blood is based on the measurement of backscatter from the emboli. The diffuse backscatter of the ultrasound from the normal flowing blood is usually much lower than the backscatter from emboli. It has been recommended by several authors to take into account the device-specific and setting-specific spontaneous fluctuations of Doppler spectrum for determining the threshold. In our study we found, that only 2.1% of 5040 normal background speckles reached the 5 dB, therefore this threshold was used in all study performed with the same device (EME 4040). The neural network used a different calculation for the energy of background signal. Most of the recorded provoked artifacts, detected by the software as events had an energy increase of more than 10 dB above background, as the MES form patients with artificial cardiac valves and other source of emboli had lower averaged energy reflections. For DWL TCD instrument used in our third study the intensity detection threshold of 9 dB was selected according to the validation performed in each participating centers and to recommendation of previously published guidelines. The relevant differences could be explained by the different device characteristics and variable algorithms used for embolus detection.

The discrimination of true MES from artifacts, e.g. produced by probe displacement, is crucial important. There are several attempts to solve this question. Multi-gate TCD using sampling from different depths of the same artery simultaneously is a promising step in this direction. The software traces the embolus at two or more different depths, and uses the time delays of signals, which are produced by a moving embolus. This is contrary to an artifact, which affects the signals in all depths simultaneously. The relatively new commercial software using the four-gate TCD technique yielded a good sensitivity, although observer-software agreement on MES was poor. A high sensitivity is mandatory for reliable pre-selection of the raw data, which should be re-evaluated by an experienced investigator afterwards. Using this technique, a 1-h recording can be assessed in a few minutes using the by the software recorded sounds and spectra ("SoundTrak®"). Other way of automatic MES detection is the use of trained neural network software. In general, the neural network is capable of classifying patterns in given categories after learning typical examples. In a previous study of Georgiadis et al the neural network achieved a sensitivity of 93% for detection in patients with mechanical prosthetic hear valves as compared with human observers. However, this study had the methodological limitation, that only the overall number of detected MES had been compared and not their actual position on the tape on an event-by-event basis. Van Zuilen et al found a network's overall sensitivity to be 62% in patients with arterial sources of embolism. In that study the individual MES were identified for comparison rather than their absolute number. In our research work also the signal-by-signal approach was chosen to ensure agreement in the corresponding identification of distinct signals. We found, that the EMBotec® software correctly rejected 85% of the provoked artifacts, although this software version was not trained for signals with a >10 dB power. The network in this study achieved an overall positive predictive value of 56.7% and overall sensitivity of 73.4% for the identification of MES. The present study showed, that the neural network could not reject all strong artifacts (over 10 dB). On the other hand, a variety of normal spectra in healthy subjects and patients demonstrated patterns similar to embolic signals. This reflects the neural network technique: all patterns, which have not yet been trained to the network and provide extreme features, pose problems for it. Thus, the network requires a good signal-to-noise ratio and embolic signals between 1 and 10 dB. The network's decisions probably could be improved by a combination of a threshold algorithm and another training set of abnormal and „normal" signals.

To go further in the direction of combined MES detections systems, we used the multi-gate technique with another signal analyzing method. The rational for our approach was based on increasing evidence that fast Fourier transform, universally used in Doppler devices for spectral analysis, has notable drawbacks, especially in terms of its poor time-frequency resolution. Lately, Cullinane et al had shown that the use of frequency-filtering approach improves the differentiation of artifacts from emboli and that the performance of their on-line automated system is only slightly below the mean performance of that of a panel of human experts. Based on these increasing evidences that new time-frequency techniques are necessary and on a pilot study of our team, we developed a new off-line automated system. This approach uses the matching pursuit signal analyzing method in combination with multi-gated (bi-gated) TCD. With only four characteristic features – peak frequency and time delay, relative power and envelope asymmetry index (the two later for gas-solid discrimination) – the classification model was fairly efficient. The results of our work showed a high level of agreement between the human experts and the off-line automated classification of signals. To distinguish between artifacts and emboli, this system uses only two characteristic features – the peak frequency and the time delay – and achieved an excellent correct classification rate of 98% compared with investigators. With a sensitivity of 97 % and a specificity of 98% for emboli, the level of artifact rejection obtained is on the order of that required if automatic system is to replace the experienced human observer in the detection of embolic signals.

There are increasing evidences that microemboli detected in patients with mechanical prosthetic heart valves are dominantly gaseous in nature. The characteristics of these MES differ from those detected in patients with other cardiac or arterial source of emboli. We found, that MES in patients with prosthetic cardiac valves had a longer duration and higher intensity than MES in carotid diseases. A higher relative intensity increase made the embolus more detectable: the sensitivity of the method was 91.9% and observer-software agreement on MES was 7.8% in the valve patients, and 77.7% and 7.5% in the carotid artery disease patients, respectively. Even the neural network yielded better results in the subgroup of valve patients. MES from patients with prosthetic heart valve had higher energy reflections than MES in patients with other source of emboli (6.4 ± 2.1 dB and 2.7 ± 0.9 dB, respectively). The sensitivity for identification of real MES achieved 70.7 % and the positive predictive value was 75.9 %, both higher than the values in the patients with thromboembolic sources of emboli (76.5% and 44.8%, respectively).

In our further study, we wanted to validate these findings and to demonstrate, that microemboli detected in patients with mechanical prosthetic cardiac valves are mainly gaseous. Cavitation, i.e. formation of bubbles from gas dissolved in the blood, in patients with mechanical prosthetic valves is a known phenomenon. It was found that cavitation is generated primarily by the deceleration of the closing body of the valve. Some of these bubbles can persist and can be washed out into cerebral circulation where they can be detected by TCD. Oxygen can inhibit the cavitation process of mechanical valves or can speed up the redissolution of gas bubbles generated by cavitation. We found that only 44% of the MES persist under oxygen inhalation (144 MES without versus 63 MES with oxygen, p= 0.002) in patients with mechanical prosthetic cardiac valves. Moreover, our data demonstrated that microemboli in patients with arterial thromboembolic source are predominantly nongaseous, since the oxygen inhalation had no effect on the number of detected MES in this group of patients (145 MES without oxygen versus 135 MES with oxygen inhalation, p=ns). This simple method of application of oxygen for discriminating gaseous microemboli from solids may be used in patients with other thromboembolic sources, however it doesn’t allow the postmonitoring signal assessment. Additionally, in certain clinical situations it is not possible to apply pure oxygen or disconnect the patient from oxygen inhalation (e.g. during surgical interventions, monitorings in intensive care unit etc). To overcome these limitations other approaches are needed for solid-gas discrimination. Therefore we developed a sophisticated signal processing technique based on our new time-frequency domain in combination with dual gate TCD and we evaluated this system for gaseous-solid differentiation. The system resulted in the validation set a sensitivity of 89% and a specificity of 86%, where the sensitivity was the probability that a solid embolus was declared as such. To achieve these results, our automatic off-line system used three features: the peak frequency, the relative power of MES and the symmetry of the signal envelope. Given the large variability of the TCD signals, it was clear that a combination of features was necessary, and this was all the more true for the distinction between gaseous and solid emboli. Although these results are promising, this performance in discriminating between solid and gaseous emboli should still be improved, but it seems evident that this task is more difficult and challenging than the separation of emboli from artifacts.

CONCLUSIONS

In these theses I reported about series of researches performed on MES detection by means of transcranial Doppler. The aims of these research works were to assess and improve the detectability and discrimination of MES of different origin and composition.

According to the findings of our researches, the four-gated technique revealed to be a relevant step forwards to semi-automated MES detection. The software investigated yielded a good sensitivity, and so in combination with the provided "SoundTrak®" the investigator can assess the 1-h recordings off-line in a few minutes. Automatic MES detection using the neural network revealed that the verification of the signals by the investigator is still mandatory. We suggested that the combination of the multi-gated TCD technique in combination with other sophisticated signal analyzing methods could improve the automated MES detection. Based on these ideas we built up, evaluated and tested a new approach for MES detection and MES discrimination. We concluded, that our new off-line automatic system combining a time frequency technique and dual-gate TCD using two characteristic features achieved an excellent correct classification rate for artifact rejection and MES identification. Although the results of solid-gaseous discrimination are also promising, this performance should still be improved, but it seems evident, that this task is much more difficult than the separation of emboli from artifacts.

However, in distinct patients, as in patients with mechanical prosthetic cardiac valves the solid-gas discrimination was quite successful by inhalation of pure oxygen. Our study demonstrated, that the oxygen breathing could inhibit the cavitation process of mechanical valves yielding in significant decrease of detected MES. We can conclude that the majority of clinically silent cerebral microemboli in patients with mechanical prosthetic heart valves are gaseous in nature. We can also suggest that microemboli in arterial thromboembolic sources are predominantly nongaseous.

BIBLIOGRAPHY

ORIGINAL PUBLICATIONS in close relation with PhD theses:

I. Droste DW, Dittrich R, Hermes S, Kemény V, Schulte-Altedorneburg G, Hansberg T, Ringelstein EB. Four-gated transcranial Doppler ultrasound in the detection of circulating microemboli. Eur J Ultrasound 1999;9:117-125.

II. Kemény V, Droste DW, Hermes S; Nabavi DG, Schulte-Altedorneburg G, Siebler M, Ringelstein EB. Automatic embolus detection by a neural network. Stroke 1999;30:807-810.

III. Devuyst G, Darbellay GA, Vesin J-M, Kemény V, Ritter M, Droste DW, Molina C, Serena J, Sztajzel R, Ruchat P, Lucchesi C, Dietler G, Ringelstein EB, Despland P-A, Bogousslavsky J. Automatic classification of HITS into artifacts or solid or gaseous emboli by a wavelet representation combined with dual-gate TCD. Stroke 2001;32:2803-2809.

IV. Droste DW, Hansberg T, Kemény V, Schulte-Altedorneburg G, Ritter M, Nabavi DG, Ringelstein EB. Oxygen inhalation can differentiate gaseous from non-gaseous microemboli detected by transcranial Doppler ultrasound. Stroke 1997;28:2453-2456.

ORIGINAL PUBLICATIONS concerning embolus detection:

V. Nabavi DG, Allroggen A, Reinecke H, Kemény V, Droste DW, Breithardt G, Ringelstein EB. Absence of circulating microemboli in patients with atrial fibrillation undergoing electric cardioversion. Cerebrovasc Dis 2001;11:95-99.

VI. Droste DW, Ritter M, Kemény V, Schulte-Altedorneburg G, Ringelstein EB. Microembolus detection at follow-up in 19 patients with acute stroke. Correlation with stroke etiology and antithrombotic treatment. Cerebrovasc Dis 2000;10:272-277.

VII. Droste DW, Kemény V, Tietje R, Kaps M, Ringelstein EB. Microembolus detection by transcranial Doppler ultrasound. Funct Neurol 2000;15:7-18.

VIII. Droste DW, Dittrich R, Kemény V, Schulte-Altedorneburg G, Ringelstein EB. Prevalence and frequency of microembolic signals in 105 patients with extracranial carotid artery occlusive disease. J Neurol Neurosurg Psychiatry 1999;67:525-528.

IX. Droste DW, Kaps M, Nabavi DG, Kemény V, Dittrich R, Schulte-Altedorneburg, Ringelstein EB. [Detection of microemboli with transcranial Doppler ultrasound]. German. Dt Aerztebl 1999;96:A-478-482.

X. Nabavi DG, Arato S, Droste DW, Schulte-Altedorneburg G, Kemény V, Reinecke H, Borggrefe M, Breithardt G, Ringelstein EB. Microembolic load in asymptomatic patients with cardiac aneurysm, severe ventricular dysfunction, and atrial fibrillation. Clinical and hemorheological correlates. Cerebrovasc Dis 1998;8:214-221.

PUBLICATIONS:

Articles:

Devuyst G, Piechowski-Jozwiak B, Karapanayiotides T, Fitting JW, Kemény V, Hirt L, Urbano LA, Arnold P, van Melle G, Despland PA, Bogousslavsky J. Controlled contrast transcranial Doppler and arterial blood gas analysis to quantify shunt through patent foramen ovale. Stroke 2004;35:859-63.

Kemény V. Antiatherogenic effect of ACE-inhibitors. Agyérbetegségek 2003;9 (1 suppl.): 7-10.

Kemény V, Jung DK Devuyst G. Ultrasound Characteristics of Adherent Thrombi in the Common Carotid Artery. Circulation 2001;104:e24-25 (correspondence).

Droste DW, Silling K, Stypmann J, Grude M, Kemény V, Wichter T, Kuhne K, Ringelstein EB. Contrast transcranial Doppler ultrasound in the detection of right-to-left shunts: Time window and threshold in microbubble numbers. Stroke 2000;31:1640-1645.

Schulte-Altedorneburg G, Droste DW, Haas N, Kemény V, Nabavi DG, Fuzesi L, Ringelstein EB. Preoperative B-mode ultrasound plaque appearance compared with carotid endarterectomy specimen histology. Acta Neurol Scand. 2000;101:188-94.

Kemény V, Droste DW, Ringelstein EB. Carotisendarterectomia-mûtétek indikációi. Agyérbetegségek 1999;5(2):2-6.

Droste DW, Ritter MA, Mönnig G, Kemény V, Breithardt G, Ringelstein EB. Abdudance of microembolic signals detected by transcranial Doppler ultrasound in a patient with Eisenmenger's syndrome. Cerebrovasc Dis 1999;9:334-336.

Droste DW, Lüdemann P, Anders F, Kemény V, Thomas M, Krauss JK, Ringelstein EB. Middle cerebral artery blood flow velocity, end-tidal pCO2 and blood pressure in patients with obstructive sleep apnea and in healthy subjects during continuous positive airway pressure breathing. Neurol Res. 1999;21:737-41.

Brilla R, Nabavi DG, Schulte-Altedorneburg G, Kemény V, Reichelt D, Evers S, Schiemann U, Husstedt IW. Cerebral vasculopathy in HIV infection revealed by transcranial Doppler. Stroke 1999;30:811-813.

Droste DW, Reisener M, Kemény V, Dittrich R, Schulte-Altedorneburg G, Stypmann J, Wichter T, Ringelstein EB. Contrast transcranial Doppler ultrasound in the detection of right-to-left shunts: reproducibility, comparison of two agents, and distribution of microemboli. Stroke 1999;30:1014-1018.

Nabavi DG, Droste DW, Schulte-Altedorneburg G, Kemény V, Panzica M, Weber S, Ringelstein EB. Diagnostic benefit of echocontrast enhancement for the insufficient transtemporal bone window. J Neuroimaging 1999;9:102-107.

Happe S, Kemény V, Evers S. Functional Doppler sonography in a patient with global aphasia but sustained song recognition. Neurol Rehabil 1999;5:216-217.

Kemény V, Droste DW, Nabavi DG, Schulte-Altedorneburg G, Schuierer G, Ringelstein EB. Collateralization of an occluded internal carotid artery via a vas vasorum. Stroke 1998;29:521-523.

Nabavi DG, Kemény V, EB Ringelstein. [Clinical significance of echocontrast enhancement in neurovascular diagnosis. Review of experience following a year of use]. Fortschr Neurol Psychiatr 1998;66:466-473.

Nabavi DG, Droste DW, Kemény V, Schulte-Altedorneburg G, Weber S, Ringelstein EB. Potential and limitations of echocontrast-enhanced ultrasonography in acute stroke patients: a pilot study. Stroke 1998;29(5):949-954

Droste DW, Nabavi DG, Kemény V, Schulte-Altedorneburg G, Ritter M, Weber S, Ringelstein EB. Echocontrast enhanced transcranial colour-coded duplex offers improved visualization of the vertebrobasilar system. Acta Neurol Scand 1998;98:193-199.

Kemény V, Droste DW, Hansberg T, Schulte-Altedorneburg G, Ritter M, Hermes S, Nabavi DG, Ringelstein EB. Oxigéninhaláció hatása a transcranialis Doppler- vizsgálattal detektálható microemboliákra. Agyérbetegségek 1997;3(4):2-5.

Book-chapters:

Devuyst G, Kemény V, Despland PA. New Trends in Neurosonology. In Fisher M, J. Bogousslavsky (editors): Current Review of Cerebrovascular Disease. Philadelphia, Current Medicine Inc. 2001;71-85.

Droste DW, Lüdemann P, Nabavi D, Schulte-Altedorneburg G, Kemény V, Ritter MA, Ringelstein EB. Indikationen zur Karotisdesobliteration aus der Sicht des Neurologen. In Sulkowski U, Dinse P (editors): Aktuelle Karotischirurgie. München, Hans Marseille Verlag GmbH., 1999;43-51.

Kemény V, Droste DW, Ringelstein EB. Kollateralisation eines Arteria carotis interna Verschlusses über eine Vas Vasorum. in Aktuelle Neurologie, Sonderband. Thieme, 1998;M1.1-4.

Nabavi DG, Brilla R, Kemény V, Schulte-Altedorneburg G, Evers S, Riedasch M, Husstedt IW. HIV- assoziirte zerebrale Vaskulopathie- Eine Entität?. In: AIDS Neue Perspektiven, Therapeutische Erwartungen, Die Realität. Jäger.1997;179-181.

Droste DW, Lüdemann P, Kemény V, Nabavi DG, Schulte-Altedorneburg G, Ringelstein EB. Therapie von Erkrankungen hirnzufürender Arterien. In: Aktuelle Entwiklungen in der Behandlung mit Antikoagulanzien und Thrombozytenfunktionshemmern. Schattauer-Verlag. 1997.

Droste DW, Nabavi D, Hansberg T, Ritter M, Kemény V, Ringelstein EB. Detection of clinically silent circulating emboli by transcranial Doppler ultrasound: technical and clinical aspects; in Klingelhöfer J, Bartels E, Ringelstein EB (editors): New Trends in Cerebral Hemodynamics and Neurosonology. Amsterdam, Elsevier Science B. V., 1997;393-397.

Abstracts:

Greber C, Karapanayiotides T, Ruchat P, Kemény V, Piechowski-Jozwiak B, Despland PA, Bogousslavsky J, Devuyst G. The cognitive impact of carotid endarterectomy: benefit and for whom? Cerebrovasc Dis 2003;16(suppl 4):42.

Karapanayiotides T, Ruchat P, Darbellay G, Kemény V, Piechowski-Jozwiak B, Vesin JM, Despland PA, Bogousslavsky J, Devuyst G. What is the nature and clinical importance of microembolic signals in carotid endarterectomy? Cerebrovasc Dis 2003;16(suppl 4):54.

Lucchesi C, Darbellay G, Kemény V, Vesin JM, Devuyst G, Dietler G. On the variability of micro-embolic signal features for repeated same-embolus measurements, and on background speckles variance. Cerebrovasc Dis 2002;13(suppl 4):45.

Piechowski-Jozwiak B, Karapanayiotides T, Kemény V, Fitting J, Bogousslavsky J, Despland PA, Devuyst G. Shunt quantification with contrast-transcranial Doppler and arterial oxygen desaturation in stroke patients with PFO: which is the optimal type of valsalva maneuver? Cerebrovasc Dis 2003;16(suppl 2):36.

Darbellay GA, Ruchat P, Kemény V, Karapanayiotides T, Vesin JM, Lucchesi C, Bogousslavsky J, Despland PA, Devuyst G. Patients with prosthetic heart valves may have both solid or gaseous microemboli depending on the number of microemboli. Cerebrovasc Dis 2002;13(suppl 4):31.

Darbellay G, Vesin JM, Ruchat P, Kemény V, Despland PA, Bogousslavsky J, Devuyst G. Classification of HITS into Artefacts or Solid or Gaseous Emboli by a Panel of Signal Processing Methods combined with the dual-gate TCD: Results and Whereabouts. Cerebrovasc Dis 2002;13(suppl 3):25.

Pánczél G, Kemény V, Bönöczk P, Nagy Z. Is ultrasound safe when applied parallel with thrombolysis? Cerebrovasc Dis 2002;13(suppl 4):42.

Devuyst G, Urbano LA, Kemény V, Jonasson L, Ruchat P, Cuisenaire O, Thiran JP, Despland PA, Bogousslavsky J. Is the thickness of the "cap cover" associated with "unstable" carotid atheromatous plaque? Cerebrovasc Dis 2002;13(suppl 3):25.

Devuyst G, Cuisenaire O, Thiran J-Ph, Kemény V, Jung DK, Karapanayiotides T, Despland PA, Bogousslavsky J. Is the thickness of the fibrous cap associated with carotid atheromatous plaque activity? A controlled pilot study. Cerebrovasc Dis 2001;11(suppl 3):6.

Ruchat P, Kemény V, Devuyst G, Bogousslavsky J, von Segesser LK. Détection de microemboles par Doppler transcânien lors de chirurgie carotidienne. Ont-ils une signification clinique ? Kardiovaskuläre Medizin 2001;4:(Suppl. 3):63.

Ruchat P, Kemény V, Devuyst G, Despland P-A, von Segesser LK. Validation de la différenciation automatique des signaux Doppler transcrânien pour la chirurgie cardiovasculaire. Kardiovaskuläre Medizin 2001;4:(Suppl. 3):63.

Kemény V, Lucchesi C, Krayenbuehl J, Ponard J, Gloor S, Darbellay G, Dietler G, Devuyst G. Validation of an in-vitro MCA model for emboli detection and comparison to human subjects. Cerebrovasc Dis 2001;11(suppl 3):25.

Devuyst G, Darbellay G, Kemény V, Afsar N, Bogousslavsky J. Discrimination of microembolic signals in patients with prosthetic heart valves. Cerebrovasc Dis 2001;11(suppl 3):15.

Kemény V, Droste DW, Hermes S, Nabavi DG, Schulte-Altedorneburg G, Siebler M, Ringelstein EB. Computer-Assisted detection of microemboli using a neural network. Cerebrovasc Dis 1999;9(suppl 2):36.

Droste DW, Ritter M, Kemény V, Schulte-Altedorneburg G, Ringelstein EB. Microembolus detection in 19 patients with very acute stroke: follow-up and correlation with stroke etiology and antithrombotic treatment. Cerebrovasc Dis 1999;9(suppl 2):25.

Allroggen A, Nabavi DG, Reinecke H, Kemény V, Droste DW, Breithardt G, Ringelstein EB. Absence of cerebral microemboli after cardioversion of atrial fibrillation. Cerebrovasc Dis 1999;9(suppl 2):34.

Kemény V, Nabavi DG, Droste DW, Schulte-Altedorneburg G, Panczica M, Weber S, Ringelstein EB. Contrast-enhanced transcranial color-coded duplex ultrasonography in patients with insufficient temporal window. Cerebrovasc Dis 1998;8(suppl 3):15.

Droste DW, Kemény V, Nabavi DG, Schulte-Altedorneburg G, Ritter M, Weber S, Ringelstein EB. Echocontrast enhanced transcranial colour-coded duplex offers improved visualization of the vertebrobasilar system. Cerebrovasc Dis 1998;8(suppl 3):19.

Happe S, Kemény V, Evers S. Funktionelle Dopplersonographie bei einer Patientin mit globaler Aphasie und erhaltener Liederkennung. Akt Neurol 1998;25(Suppl 3):111

Schulte-Altedorneburg G, Droste DW, Haas N, Kemény V, Nabavi DG, Ringelstein EB. Comparison of pre-operative B-mode ultrasound appearance with carotid endarterectomy specimen pathology. European Journal of Ultrasound 1997;5:13.

Nabavi DG, Kemény V, Schulte-Altedorneburg G, Droste DW, Ringelstein EB. Potential and limitations of echocontrast-enhanced ultrasound in acute stroke patients. European Journal of Ultrasound 1997;5:46.

Ritter M, Droste DW, Hansberg T, Kemény V, Schulte-Altedorneburg G, Nabavi DG, Hermes S, Ringelstein EB. Variability of circulating microemboli in follow-up transcranial Doppler recordings. European Journal of Ultrasound 1997;5:39.

Droste DW, Hansberg T, Kemény V, Hammel D, Schulte-Altedorneburg G, Nabavi DG, Kaps M, Scheld HH, Ringelstein EB. Circulating microemboli in patients with mechanical prosthetic cardiac valves are predominantly gaseous in contrast to microemboli from other cardiac and atherothrombotic sources. European Journal of Ultrasound 1997;5:41.

Hansberg T, Droste DW, Ritter M, Hermes S, Hammel D, Kemény V, Schulte-Altedorneburg G, Nabavi DG, Scheld HH, Ringelstein EB. Technical and anatomical background of four-gate microembolus detection by transcranial Doppler ultrasound. European Journal of Ultrasound 1997;5:42.

Droste DW, Hansberg T, Kemény V, Hammel D, Schulte-Altedorneburg G, Nabavi DG, Kaps M, Scheld HH, Ringelstein EB. Oxygen inhalation can differentiate gaseous from non-gaseous microemboli detected by transcranial Doppler ultrasound. Cerebrovasc Dis 1997;7(suppl 4):13.

Droste DW, Hansberg T, Kemény V, Hammel D, Schulte-Altedorneburg G, Nabavi DG, Kaps M, Scheld HH, Ringelstein EB. Oxygen inhalation can differentiate gaseous from non-gaseous microemboli detected by transcranial Doppler ultrasound. Journal of the Neurological Sciences 1997;150 (suppl 1):S10.

Hansberg T, Droste DW, Kemény V, Hammel D, Schulte-Altedorneburg G, Nabavi DG, Kaps M, Scheld HH, Ringelstein EB. Differenzierung von gasförmigen und nichtgasförmigen Mikroembolien mittels Sauerstoffinhalation. Ultraschall in der Medizin 1997;18(suppl1):60.

Nabavi DG, Junker R, Lüdemann P, Evers S, Doherty C, Droste DW, Schulte-Altedorneburg G, Kemény V, Kessler C, Ringelstein EB. Factor-V gene mutation is a risk factor for cryptogenic stroke of the young. Results of a case-control study on 225 patients. Cerebrovasc Dis 1997;7(suppl 4):16.

Nabavi DG, Stockmann J, Georgiadis D, Schmid C, Deng M, Droste DW, Kemény V, Schulte-Altedorneburg G, Scheld HH, Ringelstein EB. Factor-V gene mutation is a risk factor for cryptogenic stroke of the young. Results of a case-control study on 225 patients. Cerebrovasc Dis 1997;7(suppl 4):34.

Kemény V, Nabavi DG, Droste DW, Schulte-Altedorneburg G, Ringelstein EB. Validity of echocontrast-enhanced ultrasound diagnostics in acute stroke. Cerebrovasc Dis 1997;7(suppl 4):62.

Ritter MA, Hansberg T, Droste DW, Kemény V, Hermes S, Nabavi DG, Ringelstein EB. Auftreten und zeitliche Verteilung von Mikroembolien bei akuten Schlaganfallpatienten. Ultraschall in der Medizin 1997;18(suppl1),60-61.