Differentiation Between Gaseous and Formed Embolic Materials In Vivo

Application in Prosthetic Heart Valve Patients

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Background and Purpose
Doppler emboli detection is an established technique, but the nature of the underlying embolic material remains unclear. The intensity and spectral distribution of emboli signals could help to distinguish between signals arising from formed and gaseous emboli. We undertook this study to develop and evaluate a differentiation algorithm based on the spectral characteristics of emboli signals. Subsequently the algorithm was applied to patients with mechanical prosthetic cardiac valves.

Methods
Emboli signals detected in patients with carotid disease, acute stroke, and atrial fibrillation were used as formed emboli data, and signals detected in patients undergoing cardiac catheterization studies were used as gaseous emboli data. For each embolus signal, the maximal amplitude, the sum of amplitudes, and the spectral intensity distribution were calculated. Two hundred emboli signals from each category were used to develop a differentiation algorithm, which was subsequently evaluated on 501 additional solid and 995 gaseous emboli signals. The same algorithm was used to analyze 5958 emboli signals detected in 60 patients with mechanical prosthetic valves.

Results
The best results were obtained with an algorithm based on both the maximal amplitude and the sum of amplitudes (sensitivity, 99%; specificity, 96.5%). On subsequent evaluation, the sensitivity and specificity of the algorithm were 99.6% and 89.8%, respectively. Of the 5958 emboli signals detected in prosthetic valve patients, 92.4% were classified as gaseous.

Conclusions
Differentiation between gaseous and formed emboli signals, as detected by transcranial Doppler in vivo, is feasible by means of spectral analysis. Application of the differentiation algorithm in prosthetic valve patients suggests that the embolic material in these patients is gaseous. The possibility of distinguishing between different formed embolic materials with this technique remains to be evaluated.

Key Words
- embolism
- heart valve prosthesis
- ultrasonics

Embolic materials are a major cause of stroke. Current therapeutic approaches depend on the embolic source. However, as Caplan1 pointed out in a recent review, the nature of the embolic material is more important, particularly in deciding the appropriate antithrombotic treatment.

Transcranial Doppler ultrasonography (TCD) can be used to detect intra-arterial emboli in several patient groups.6 The reflected signal amplitude depends on both the size and density of the scattering particles.7,8 Several in vitro9,10 and animal7,8,11,12 studies have used amplitude of reflected Doppler signal in an attempt to distinguish between embolic materials. A recent study suggested that emboli signals arising from patients with carotid stenosis and patients with prosthetic valves can be differentiated on the basis of power of reflected Doppler signal.13

This study was undertaken to develop and evaluate an algorithm to differentiate formed and gaseous emboli signals as detected by TCD in vivo. For this purpose emboli signals from patients with carotid disease, acute stroke, and atrial fibrillation, which are presumed to be caused by solid emboli, were analyzed and compared with emboli signals from patients undergoing cardiac catheterization studies, caused primarily by gaseous emboli. Subsequently, the differentiation technique was applied to emboli signals from patients with mechanical prosthetic cardiac valves in an attempt to identify the embolic material in these patients.

Subjects and Methods
All emboli signals were detected during TCD monitoring with a pulsed ultrasound Doppler machine (EME TC-2000) with a 2-MHz probe. Monitoring was performed over the middle cerebral artery (MCA), using an elasticated band to stabilize the probe. The monitoring time varied between 0.5 and 3 hours per patient. The machine settings were kept constant in all studied patients (power, 58%; sweep speed, 6 seconds; depth of insonation, 46 to 56 mm; sample volume, 9 mm). After identifying the MCA and adjusting the probe, the gain was reduced to produce a homogeneous background signal, with an intensity of 4 dB. Standard criteria were used to differentiate between emboli signals and artifact both during the recording14 and in off-line analysis15 of digital data stored to hard disk, as defined in detail elsewhere.3

The following patients were examined. Group 1 included 58 patients (age, 28 to 82 years; median, 66 years) with carotid disease, which was unilateral in 36 and bilateral in 22 cases. Eight patients had a unilateral carotid occlusion and a contralateral severe (>70%, n=5) or moderate (50% to 70%, n=3) stenosis. Of the remaining 50 patients, 38 had a severe (>70%) occlusion and 12 had a moderate (>50%) stenosis. Group 2 comprised 995 patients (age, 28 to 82 years; median, 66 years) with mechanical prosthetic cardiac valve patients.
stenois, 11 a moderate (30% to 70%) stenosis, and 1 a non–hemodynamically significant plaque. In 24 patients additional cardiac abnormalities were diagnosed (atrial fibrillation n = 14), valvular lesion n = 5, and dilated cardiomyopathy n = 1). Fifty-two patients were receiving aspirin (75 to 300 mg), 1 warfarin, and 5 were on no antithrombotic treatment. All subjects were output at the time of examination. Monitoring time in these patients was 30 minutes over each MCA. Group 2 included 20 patients with atrial fibrillation (age, 61 to 70 years; median, 66 years) who were recruited from the anticoagulant clinic and were stabilized on warfarin at the time of the study (international normalized ratio, 2.0 to 3.0). Monitoring time for these patients was 30 minutes. Group 3 included patients presenting with acute ischemic stroke (n = 33) or transient ischemic attack (n = 8) (age, 32 to 76 years; median, 67 years). All of these patients were hospitalized at the time of TCD study. None of them had an arterial line, but 21 had a venous line. No intravenous injections were performed during TCD monitoring, which was performed for 30 minutes over each MCA. Group 4 included 32 patients undergoing cardiac catheterization studies for ischemic heart disease (n = 30) or valvular lesions (n = 2) (age, 32 to 68 years; median, 58 years). Only emboli signals that were associated with the introduction of gas in the left heart or in the aorta (emboli signals detected 5 to 20 seconds after contrast or saline injection in the ventricle or supra-aortic region, during ventriculography, and during flushing of the catheter) were analyzed. Emboli signals detected during catheter insertion or manipulation were not further evaluated in this study. Monitoring time in these patients varied between 20 and 80 minutes, depending on the duration of the procedure.

The screen display of the TCD consists of 512 spectral lines in the x axis and 128 lines in the y axis. The amplitude of each of the 128 points along each vertical line (a1, a2, a3, ... a128) containing an embolus signal was calculated using software developed in our department. The 128 amplitudes were then compressed to 64 by addition of consecutive amplitude pairs (a∗1 = a1 + a2/2, a∗2 = a3 + a4/2, ... a∗64 = a127 + a128/2). For emboli signals extending over more than one spectral line, the average amplitude was calculated at each of the 64 points of the y axis (sum of amplitudes [a∗1 + b∗1, a∗2 + b∗2, ... a∗64 + b∗64]). The number of spectral lines containing the embolus (Fig 1). All subsequent data manipulations were based on these average values. The maximal amplitude and the sum of amplitudes of each embolus signal were then calculated. Only unidirectional emboli signals arising from emboli in the MCA were studied.

Emboli signals detected in patients with carotid disease, atrial fibrillation, and acute stroke were unidirectional, forming the group of solid emboli signals. Emboli signals detected during cardiac catheterization formed the group of air emboli signals.

Two hundred emboli signals detected in patients with carotid disease (n = 102 emboli), atrial fibrillation (n = 15 emboli), and acute stroke (n = 83 emboli) and 200 emboli detected during coronary angiography were randomly selected and used as training data. Ideal cutoff limits based on the maximal amplitude or the sum of amplitudes were calculated using receiver operating characteristic (ROC) curves. Based on statistical decision theory,12 these curves were developed in the context of electronic signal detection and have been applied to decision making in diagnostic systems in clinical medicine.13,14 The ROC curve shows the various trade-offs existing between proportions of true-positive and false-positive responses, as the decision criterion is systematically varied, for a given capacity to discriminate between positive and negative cases. Each point of the curve represents the detection values of true positives, depending on the decision criteria. The calculated cutoff limits were then explored to determine sensitivity and specificity in differentiating gaseous from formed emboli signals. Afterward a combination of the cutoff values of maximal amplitude and sum of amplitudes was used in the same way. This algorithm was then evaluated on a test set of 501 formed (carotid disease patients, n = 281 emboli; atrial fibrillation patients, n = 24 emboli; acute stroke patients, n = 196 emboli) and 995 gaseous emboli signals.

The same algorithm was applied to 5958 emboli signals detected in 60 patients (age, 30 to 74 years; median, 59 years) with mechanical prosthetic heart valves (Bjork-Shiley monstrut, n = 38 patients, 5777 emboli; Medtronic-Hall, n = 22 patients, 181 emboli) (duration since valve insertion, 21 ± 5 months). The monitoring time in this group was 30 minutes, but some of the patients underwent prolonged monitoring (up to 3 hours).

Results

Emboli signals were detected in 94% of carotid disease patients, 71% of acute stroke patients, and 40% of atrial fibrillation patients. The detailed results of the emboli signal counts in the acute stroke and carotid disease patients have been described elsewhere.19,20

Training data consisting of 200 solid and 200 gaseous emboli signals were used to develop the algorithm. According to the ROC curves, the best cutoff values were a maximal amplitude of 110 (Fig 2) and a sum of amplitudes of 600 (Fig 3). Use of the maximal amplitude provided a sensitivity of 85% and a specificity of 95.5% in differentiating gaseous from solid emboli; use of the sum of amplitudes provided a sensitivity of 97.5% and a specificity of 91.5%. A combination of these two cutoff values (emboli signals were classified as gaseous if their maximal amplitude was >110 and their sum of amplitudes >600) provided a sensitivity of 83.5% and a specificity of 90.5%.

A two-step combination was then used. Emboli signals were classified as gaseous when their maximal amplitude was greater than 110. Remaining signals with a smaller value were categorized depending on sum of their amplitudes to be either gaseous, if this exceeded 600, or formed, if it did not. The sensitivity of this algorithm was 99% and the specificity 96.5%.

On evaluating the algorithm, 991 of 995 gaseous emboli signals and 449 of 501 solid emboli signals were correctly identified (specificity, 89.8%; sensitivity, 99.6%).

The distribution of amplitudes, based on the combined test and evaluation data sets of gaseous and formed emboli signals, is displayed in Fig 4. The spectral distribution of gaseous emboli signals is highly variable. Gaseous emboli had significantly higher maximal amplitudes (median, 234 [95% nonparametric confidence interval [95% CI], 228 to 250] versus 66 [95% CI, 62 to 70]; P < .0001, Mann-Whitney). The sum of amplitudes was also significantly higher in gaseous than in formed emboli signals (median, 2162 [95% CI, 1848 to 2355] versus 308 [95% CI, 287 to 333]; P < .0001, Mann-Whitney). Subsequent application of the algorithm to the prosthetic valve patients resulted in 92.4% of emboli signals (5503 of 5958) being classified as gaseous. The spectral distribution of the amplitudes of this group is displayed in Fig 4.

Discussion

The detection of emboli signals by TCD has been widely reported, but the constitution and clinical significance of the underlying embolic substances have not always been apparent. The potential exists to distin-
Fig 1. A (top), Embolus signal in patient with mechanical prosthetic cardiac valve. A (bottom), Spectral analysis reveals that this embolus signal is contained in six spectral lines (103 through 108). B, Detail of spectral line 107, which consists of 128 points. The amplitude of each point is calculated (a₁, a₂, ..., a₁₂₈). Subsequently the 128 amplitudes are compressed to 64 (for example, \(a^*_n = a_{2n} + a_{2n+1}/2\)). The embolus signal in panel A extends over 6 spectral lines. The average amplitude for each of the 64 points is therefore calculated from \(\frac{a^*_n + a^*_{n+1} + a^*_{n+2} + a^*_{n+3} + a^*_{n+4} + a^*_{n+5}}{6}\) (n=1 to 64). The maximal amplitude in this example is \(a_{17}\) (continuous line).
guish between different embolus types on the basis of the reflected Doppler signal. Furthermore, the vast difference in density between gaseous and formed emboli suggests that these two emboli categories may be particularly susceptible to differentiation by ultrasound. To date, no definitive guidelines have been developed to distinguish between emboli signals caused by gaseous and formed embolic materials.

Earlier attempts to distinguish between emboli types, by means of Doppler spectral analysis applied to in vitro and animal models, have been unsuccessful. This may in part be attributable to the use of embolic material of sizes incomparable to the in vivo situation. Sizes of biological formed emboli, prepared using microscopical dissection and studied with TCD in previous studies, were 0.4 to 1.5 mm (Russel et al7) and 1 to 5 mm (Markus and Brown10). Pugsley21 was unable to distinguish between emboli signals produced by 30- to 90-um microspheres and air emboli. Stump et al11 compared the emboli signals produced by three sizes of microsphere (50, 100, and 200 um) to air and biological emboli signals. They suggested that differentiation between gaseous and formed emboli may be possible. Albin et al22 reached the same conclusion. They compared the emboli signals produced by bubbles of various sizes (0.8 to 100 mm^3) and aggregates of 1- and 25-mm^3 microspheres, diluted in 0.1 mL of blood in an animal model, and assumed that simple pattern recognition techniques could be used to differentiate between gaseous and solid emboli signals. Microemboli signals detected by TCD in asymptomatic patients are probably generated by smaller particles than the biological material used in the above studies, as suggested by studies performed with a canine model by Moody et al.23 After as many as 25×10^6 15-um microspheres were introduced into the left circulation the dogs appeared grossly intact, while a much smaller number of 50-um microspheres produced neurological injury.23

Methods previously used to analyze the intensity of emboli signals have lacked sensitivity. Markus and Brown10 used the maximal amplitude to differentiate various formed embolic materials. However, the maximal amplitude has only a finite range of values (0 . . . 346), which could explain the reported absence of a further rise in amplitude when emboli with a maximum dimension of 2 mm or more were introduced.10 Furthermore, this analysis method does not take the embolus signal spectral distribution into account. In particular, air emboli signals, which cause an intensity increase over a wide range of frequencies,12 cannot be adequately characterized by this method (Fig 4). Russell et al13 used the color scale of the Doppler display to estimate the intensity increase in decibels. Spencer14 determined the relative amplitude of embolic signals by estimating the noise threshold level required to suppress the background and emboli signals. The combined sum of intensities and maximal intensity technique developed in this study provides a more reliable means of characterizing emboli signals, since it takes both the magnitude and spectral distribution of the intensity increase into account.

Our results suggest that differentiation between emboli signals arising from formed and gaseous emboli, as detected by TCD in vivo, is possible. It is unclear if discrimination among various types of formed emboli is feasible using the same method. Since the constitution of formed emboli is not apparent in any clinical group, further in vitro and animal studies are required. However, the generation of sufficiently small emboli still proves difficult. Cerebral embolization models, based on endogenous emboli generation, were recently described.24,25 Such models combined with TCD monitoring may prove better than in vitro models, since the generated microemboli correspond to the clinical situation.
The fact that the vast majority of emboli signals detected in patients with mechanical prosthetic heart valves correspond to the criteria set for gaseous emboli lends further support to the hypothesis that the embolic material in these patients is gaseous. The proportion of emboli signals classified as solid is explicable by the specificity of the algorithm of 85% to 90%. In recent years, previously unrecognized phenomena, such as the formation of cavitation microbubbles, and fibrin "strands" were described in normally functioning prosthetic valves. Although the cavitation potential of prosthetic valves has been documented, it was assumed that such cavitation bubbles have a very short life span and cannot be detected far from the site of creation. However, three different types of cavitation bubbles were described in a recent study of prosthetic valve function, one of which is larger and has a longer life span than previously assumed. The exact mechanism of the microemboli generation associated with the valve implant remains to be determined.

References
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