The Effect of Velocity on the Appearance of Embolic Signals Studied in Transcranial Doppler Models

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Background and Purpose Transcranial Doppler ultrasound can be used to detect circulating cerebral emboli. Recent studies have demonstrated that embolus size is significantly related to both the relative intensity increase and duration of an embolic signal. This may allow information about embolus size to be obtained by analysis of Doppler embolic signals. However, theoretically duration will be inversely related to velocity, and therefore velocity may need to be accounted for if information on embolus size is to be derived from the duration of Doppler embolic signals.

Methods The relation between velocity and both relative intensity increase and duration of embolic signal was investigated in an in vitro flow model, a sheep carotid artery model, and in patients with prosthetic heart valves. The same standard transcranial Doppler ultrasound machine was used for all studies. Embolic signals resulting from 99 glass microspheres (size, 210 to 250 μm) were studied in the in vitro model, as were those from 64 glass microspheres (size, 105 to 150 μm) in the sheep model. Embolic signals recorded from the six middle cerebral arteries of three patients with prosthetic cardiac valves were also studied.

Results There was a significant ($P<.001$) inverse relation between velocity and duration of high-intensity signal (in vitro model, $r=-.82$; sheep model, $r=-.43$); the exact relations were described using best-fit equations. Correlation coefficients for this relation in patients varied between $-.30$ and $-.55$. There was also an unexpected significant positive relation between velocity and intensity in the sheep model ($r=.44$, $P<.001$) but not in the in vitro model ($P>.05$). This relation was also seen in some, but not all, patients.

Conclusions When the duration of embolic signals is used to provide information about the relative size of an embolus, the velocity of the embolic signal should be taken into account. A relation between velocity and relative intensity increase was found in the sheep model and in some patient recordings. It is suggested this relation may result from greater power being supplied to emboli traveling at higher velocities in the center of the vessel; this may occur under certain recording conditions. (***Stroke*. 1994;25:986-991.**)

Key Words • blood flow velocity • cerebral embolism and thrombosis • ultrasonics

Solid emboli such as thrombus and atheroma originating from carotid and aortic plaques and from the heart are major causes of cerebral ischemic events in humans. Recently the detection of asymptomatic circulating solid cerebral emboli using transcranial Doppler ultrasound has been described. The initial report was in patients undergoing carotid endarterectomy,[1] but such embolic signals have also been noted in subjects with carotid stenosis,[2] prosthetic cardiac valves,[3] and atrial fibrillation with recent stroke.[4] This technique is likely to be an important advance both in the determination of the embolic site in individual patients with stroke and in the identification of subjects at particularly high risk of subsequent stroke in whom appropriate preventive treatment can then be started. Cerebral emboli produce a visible and audible short-duration high-intensity signal in the Doppler flow spectrum.[1] Both in vivo[5,6] and in vitro[7] models have demonstrated that signals identical to those recorded in patients can be produced by atheroma, platelet, and thrombus emboli. Furthermore, in these models it was found that signal parameters provided information on the size of the embolus. There was a significant positive relation between embolus size and both the intensity[6-8] and duration[6,7] of the embolic signal. Although exact estimation of embolus size is not currently possible because the nature of the embolic material in individual patients is unknown, an estimation of the relative size may be obtained using these signal parameters.

Practical application of this technique will require computerized programs to automatically detect these embolic signals. Automatic embolus detectors have been developed,[9] and these are able to analyze the intensity and duration of individual signals. However, the duration and possibly the intensity of the embolic signal will depend on the velocity of the embolus. Theoretically one would expect the duration of a signal produced by an embolus to depend on embolus velocity; ie, if flow is laminar, emboli traveling centrally will have highest velocity and therefore will pass through the ultrasound beam faster and result in signals of shorter duration. Therefore, one might expect emboli of the same size to have different duration depending on their position in the Doppler spectrum. Furthermore, there is experimental evidence suggesting that the intensity of embolic signals may also depend on the velocity and therefore on the position in the Doppler spectrum. Hills and Grulke[10] reported that the audible detection of

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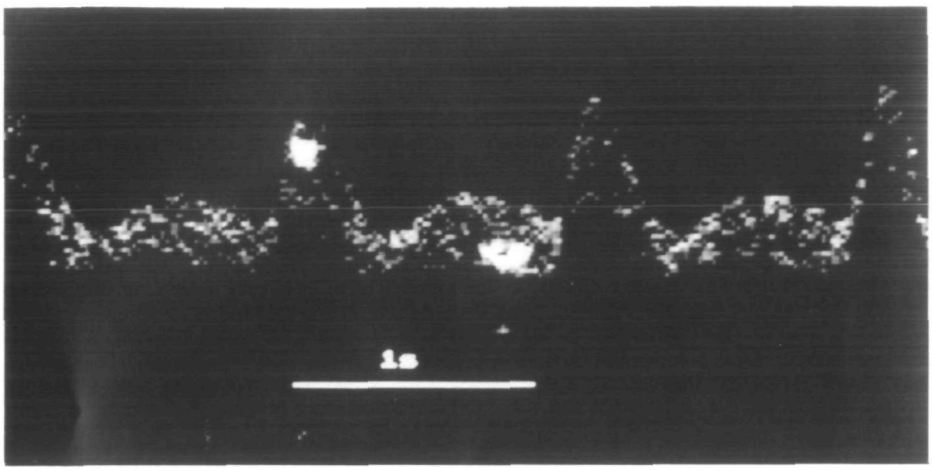

FIG 1. Doppler recording from the in vitro model. The flow pattern approximated that of the human middle cerebral artery. Two high-intensity embolic signals due to 250-μm glass microspheres are seen. The effect of velocity on duration of high-intensity signal can be seen, with the lower velocity signal having a longer duration. Intensity is coded on a gray scale, with white indicating high intensity.

bubbles by ultrasound varied markedly with bubble velocity. Only larger bubbles were detectable at a low velocity, whereas at a higher velocity smaller bubbles were also detectable. This might be due to emboli having different reflection properties at different velocities. To determine the actual relation between velocity and signal parameters, we investigated the effect of velocity on the duration and intensity of embolic signals associated with emboli of known size in both an in vitro flow model and a sheep model. We also studied the relation in patients with prosthetic cardiac valves in whom multiple embolic signals were recorded from the middle cerebral artery.

Methods

The same transcranial pulsed-Doppler ultrasound machine (TC2000 S, Eden Medizinische Elektronik GmbH) was used for all studies. It uses a 128-point fast Fourier transform and uses a graded color scale to display the intensity of the received Doppler signal. The Doppler signal was recorded onto an IBM-compatible microcomputer that allowed subsequent off-line analysis with specially designed software (EME Ltd). This allows each time frame of the Fourier transform to be analyzed; for each frame relative power amplitude (RPA) appears plotted against velocity. The software allows RPA at each velocity to be obtained. Maximum RPA was recorded for each embolic signal. Background RPA in the absence of an embolic signal was measured from the Doppler spectrum of the previous or next cardiac cycle, at the same point in the cycle and at the same velocity. The relative intensity increase (in decibels) of each embolic signal was calculated using the following equation:

$$\text{Relative Intensity Increase} = 10 \log \left(\frac{\text{Maximum RPA of Embolic Signal}}{\text{RPA in Absence of Embolic Signal}}\right)$$

The duration of high-intensity signal (in milliseconds) was calculated from the number of time frames over which it persisted, including all frames in which RPA was greater than an arbitrary one third of maximum RPA for that embolic signal. Each time frame represents a 20-millisecond time interval. For each embolic signal the velocity (in centimeters per second) at peak RPA was recorded. Embolic signals were identified according to their previously documented characteristics[1]: short-duration unidirectional high-intensity signals visible in the Doppler spectrum. In the patients, recordings were analyzed blinded to the diagnosis and interspersed with recordings from patients with other potential embolic sources and normal control subjects.

In Vitro Model

An extracorporeal flow circuit was used. A pulsatile flow pattern was superimposed on constant flow by the use of a valve controlled by a solenoid opening and closing, resulting in a pulse frequency of 50 cycles per minute. The closure was not complete, thereby allowing diastolic flow. A flow pattern similar to the human middle cerebral artery was obtained (Fig 1). The circuit was filled with a starch solution in water. Polyoxyethylenesorbitan (Tween, a surfactant) was added to the solution to prevent microsphere aggregation. A polyethylene tube with a luminal diameter of 2.5 mm was positioned in a human skull in the position of right carotid artery and its continuation into the middle cerebral artery. The internal diameter of this tube is similar to the luminal diameter of the human middle cerebral artery.[11] Flow in the tube at a depth of 46 mm was insonated via the transtemporal window using a 2-MHz probe fixed in position with an insonation angle of 15°. The skull and probe tip were immersed in water. Glass microspheres (Polysciences Ltd, Park Scientific Ltd) with mean size of 230 μm (range, 210 to 250 μm) were introduced into the circuit. A power of 4% (corresponding to an intensity of 22 mW/cm^2 spatial peak-temporal average) and sample volume of 8 mm were used. Pulse repetition frequency was 3 kHz, and a 60-Hz high-pass filter was used.

In Vivo Model

One sheep was studied during terminal anesthesia after a separate study of extracranial vascular grafting. In sheep a single carotid artery on each side supplies cerebral territories equivalent to those of the internal and external carotid arteries in humans. Carotid angiography was performed before the experiment to confirm the individual anatomy. Insonation of a major carotid branch was performed via the transorbital approach at a depth of 36 mm with a sample volume of 9 mm and a power of 3%. The angle of insonation was approximately 55° to 60°. The angiographically determined luminal diameter at this point was 5 mm. The high-pass filter was set at 80 Hz. Pulse repetition frequency was 3 kHz. An indwelling cannula was placed in the proximal extracranial carotid artery on the same side as the insonated marginal artery. Glass microspheres with a mean size of 230 μm (range, 210 to 250 μm) resulted in overloading of the dynamic range of the receiver in this system,[6] and therefore glass microspheres (Polysciences Ltd) with a mean size of 127.5 μm (range, 105 to150 μm) were studied. These were suspended in a saline/Tween solution, disaggregated using a rotamix, and introduced through the proximal carotid cannula. The Doppler signal was recorded for later off-line analysis.

Patient Study

Recordings were analyzed from six middle cerebral arteries in three patients with prosthetic cardiac valves. These were

selected from a group of patients in whom recordings were made from each middle cerebral artery for 20 minutes using the same 2-Mhz probe fixed in position with a head strap. Recordings were made at a depth of 48 to 54 mm using a sample volume of 9 mm. The three patients were selected for this analysis because they showed the most embolic signals. Each artery was analyzed separately because the recording parameters, such as amount of power reaching the artery, the angle of insonation, and the local anatomy, are likely to differ, making comparisons across arteries difficult. Two patients were in atrial fibrillation, and the maximum systolic velocity varied considerably between individual cardiac cycles. Therefore, when calculating correlation coefficients, each velocity was corrected for the individual cardiac cycle by dividing by the maximum systolic velocity for that cardiac cycle. The data from the artery of one patient in whom 60 embolic signals were detected are presented in detail, including graphs of the relations. The data from the other arteries in which embolic signals were less frequent are presented in summary form. The degree of spectral broadening for each patient artery recording was graded from 1 (nil) to 3 (no systolic acoustic window).

The theoretically expected relation between velocity and duration is as follows:

$$\text{Duration} = \text{Sample Volume}/\text{Velocity}$$

This expected inverse relation was sought; a fixed constant of 20 milliseconds was included in the equation because the temporal resolution of the system is limited, and the lowest duration the system is able to record is 20 milliseconds The correlation coefficient for this relation was calculated; adjusted correlation coefficients are given in the results. A linear relation was investigated between velocity and intensity increase. The difference in the relative intensity increase of embolic signals in systole and diastole was also determined. Significance was declared at the $P<.05$ level.

Results

In Vitro Model

Maximum systolic flow velocity was 48 cm/s (angle-corrected velocity, 49.7 cm/s), and end-diastolic flow velocity was 14 cm/s (angle-corrected velocity, 14.5 cm/s). The flow pattern was constant throughout the study. Short-duration high-intensity signals identical to those reported previously were detected.[1] Control infusions without microspheres did not produce embolic signals. Embolic signals were seen during both systole and diastole and at velocities between 3 and 44 cm/s, although more frequently at higher velocities adjacent to the envelope curve. Ninety-nine embolic signals were recorded for later off-line analysis. For the embolic signals, mean (±SD) relative intensity increase was 5.82±1.41 dB, mean velocity was 21.53±10.17 cm/s, and mean duration was 136.94±63.79 milliseconds. There was a significant inverse relation between velocity and duration ($r=-.82$, $P<.001$; Fig 2, top panel) There was no relation between velocity and intensity increase ($r=.17$, $P=.072$ [NS]; Fig 3, top panel) Embolic signals were more intense during systole than during diastole; the mean (±SD) relative intensity increase during systole was 6.38±1.54 dB and during diastole was 5.42±1.96 dB ($P<.004$).

In Vivo Model

Maximum systolic flow velocity was 31 cm/s (angle-corrected velocity, 57.7 cm/s), and end-diastolic flow velocity was 15 cm/s (angle corrected velocity, 27.9 cm/s). Sixty-four embolic signals were analyzed. Embolic signals had a mean (±SD) relative intensity increase of 10.39±2.03 dB, mean velocity of 14.13±6.02 cm/s, and mean duration of 55.63±19.99 milliseconds. There was a significant inverse relation between velocity and duration ($r=-.43$, $P<.001$; Fig 2, middle panel). There was a significant positive linear correlation between velocity and intensity ($r=.44$, $P<.001$; Fig 3, middle panel). Embolic signals were more intense during systole than during diastole, but the difference was not significant; mean (±SD) relative intensity increase during systole was 10.60±2.14 dB and during diastole was 10.01±1.78 dB ($P=.1$).

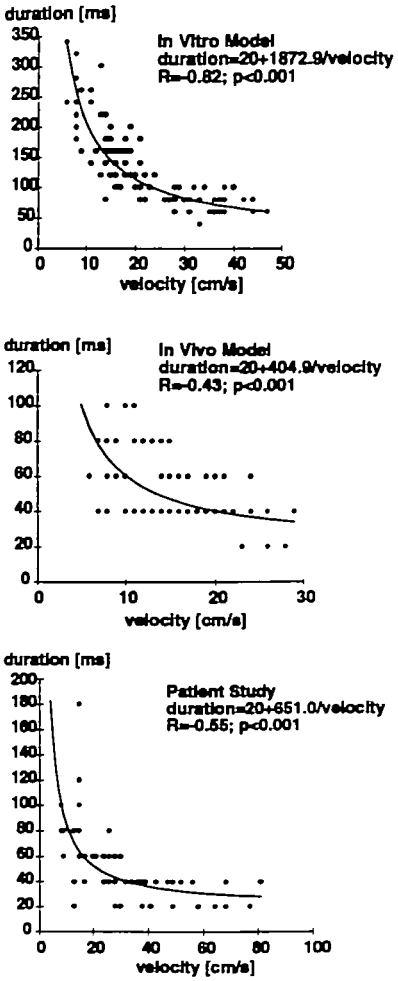

FIG 2. Scatterplots show the relation between duration of embolic signals and their velocity for 210- to 250-μm glass microspheres in the in vitro model (top panel), 105- to 150-μm glass microspheres in the sheep model (middle panel), and embolic signals in a patient with a prosthetic cardiac valve (patient 2, left middle cerebral artery) (bottom panel). The curves represent the best fit of the following relation: duration=20+a/velocity, where a is a constant.

Patient Study

The values of the correlation coefficients for the six middle cerebral arteries of three patients are given in the Table. In one patient (patient 1, left side) 60 embolic signals were analyzed; the data from this patient are illustrated in Figs 2 and 3. For this artery embolic signals had a mean (±SD) relative intensity increase of 7.13±1.00 dB, mean velocity of 32.47±17.65 cm/s, and mean duration of 50.0±27.43 milliseconds.

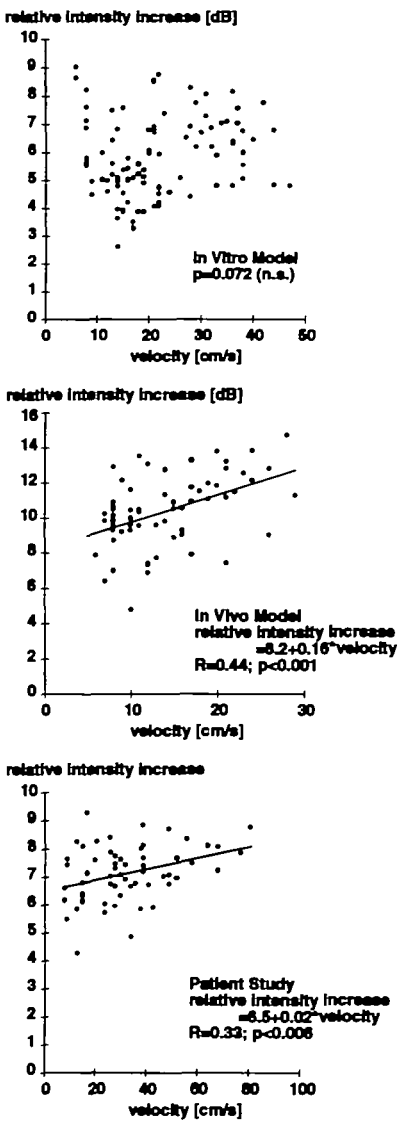

FIG 3. Scatterplots show the relation between duration of embolic signals and their relative intensity increase for 210- to 250-μm glass microspheres in the in vitro model (top panel), 105- to 150-μm glass microspheres in the sheep model (middle panel), and embolic signals in a patient with a prosthetic cardiac valve (patient 2, left middle cerebral artery) (bottom panel). The lines represent the best-fit linear regression.

There was a significant inverse relation between velocity and duration ($r=-.55$, $P<.001$; Fig 2, bottom panel). There was a significant positive linear correlation between velocity and intensity ($r=.33$, $P<.006$; Fig 3, bottom panel). Embolic signals were more intense during systole than during diastole; mean±SD relative intensity increase during systole was 7.76±0.63 dB and during diastole was 6.85±1.01 dB ($P<.0004$). There were fewer embolic signals detected in the other arteries; the smaller numbers did not provide sufficient power to determine whether significant relations were present between velocity and intensity increase and duration. However, for all arteries the correlation coefficient between velocity and duration was between −.30 and −.55. In contrast, there was a variable relation between velocity and intensity increase with correlation coefficients between .05 and .35. There was a significant negative correlation between the degree of spectral broadening and the strength of the relation between velocity and intensity increase (Kendall's correlation coefficient corrected for ties, $P<.05$).

Discussion

In our idealized in vitro model we found a significant inverse relation between velocity and duration of embolic signal. This is illustrated in Fig 1, where an embolus traveling at low velocity can be seen to have a longer duration than a similarly sized embolus traveling at a higher velocity. In a sheep model and in our patient recordings we found a similar relation, although the correlation was not as strong. Nonlaminar flow, forward and backward flow of the embolus at the transition zones of systole and diastole, spin of the embolus, and adhesion of the embolus to the vessel wall may be factors that make this relation more complex and reduce the correlation in vivo. In the models the emboli were of known size; this was not the case in the human recordings. Although for each analysis all embolic signals were from the same artery, they may have resulted from emboli of differing size. Nevertheless, a relation was found in the patients that was similar to that in the models. Our results demonstrate that when using duration of embolic signal to provide information on their relative size, velocity must be taken into account. Automatic emboli detectors being developed need to account for velocity when measuring duration of signal. However, it should be pointed out that in the models and patients only 10% to 60% of the variance in duration is accounted for by velocity, and other factors such as embolus size are likely to be of equal or greater importance; in a recent study in the same sheep model embolus size accounted for approximately 50% of the variance in duration of embolic signal.[6]

In the in vitro model the angle of insonation was 15°. Therefore, the sample volume or gate of 8 mm, rather than the beam width, determined the effective sample volume. The fact that the effective sample volume found was 18.7 mm (see equation in Fig 2, top panel), which is greater than 8 mm, is likely to be explained by the shape of the sample volume. Studies in our laboratory using a flow phantom (unpublished data) and manufacturers' information (EME Ltd) demonstrate that the shape of the sample volume is not a square wave, but rather there is a gradual increase and decrease in delivered and received ultrasound power at both ends of the sample volume. Therefore, some ultrasound power is delivered to and received from points well outside the 8-mm sample volume. Because of the small angle of 15°, these regions of lesser power at either end of the sample volume will be delivered to the region of the insonated vessel. Emboli have a high reflectivity and may be detected when they are in this borderline area outside the given sample volume. With a beam width of 5.4 mm and an insonation angle of 15°, the maximum length of vessel exposed to the ultrasound beam is 20.9 mm, and this is only slightly greater than the 18.7-mm sample volume found in the sheep model. In the sheep model the angle of insonation was 55° to 60°, making the beam width of approximately 5.4 mm rather than the sample volume the factor determining the effective sample volume of 4.0 mm (Fig 2, middle panel). In patients the angle of insonation of the middle cerebral artery is

Relation Between Velocity and Intensity Increase and Duration of Embolic Signals in Middle Cerebral Arteries of Three Patients in Whom Multiple Embolic Signals Were Detected

Patient No.	Side	No. of Emboli	Spectral Broadening	Relation Between Velocity and	
				Duration	Intensity
1	R	30	3	−.303	.212
1	L	60	2	−.550	.330
2	R	14	3	−.486	.279
2	L	20	3	−.403	.032
3	R	7	1	−.293	.346
3	L	11	3	−.403	.194

Pearson's correlation coefficients are shown. R indicates right; L, left. The degree of spectral broadening is represented on a scale from 1 (marked systolic acoustic window) to 3 (no systolic acoustic window).

likely to be between 10° and 30°, and this is consistent with the effective sample volume found of 6.5 mm (Fig 2, bottom panel). The smaller sample volume found in the detailed patient study compared with the in vitro model, which had a similar angle of insonation, may reflect the characteristics of the ultrasound beam described above. Glass is likely to be more echogenic than embolic materials in patients, and the microspheres with a mean diameter of 230 μm are likely to be larger than the asymptomatic emboli detected in humans. Because they are more echogenic, the microspheres will be detected in the model on the borders of the sample volume, whereas in the patient less echogenic emboli in a similar position in the sample volume might not be detected.

In our in vitro model we found no relation between velocity and intensity increase of embolic signals. However, in the sheep model and in the largest patient study of 60 embolic signals we found a significant positive relation between velocity and intensity of embolic signals. A correlate of this is the observation that embolic signals were more intense during systole when velocities are on average higher. A significant difference between systole and diastole was seen in the in vitro model and in the patient; a nonsignificant difference was found in the sheep model. In the other patients the correlation coefficient for this relation varied widely between .05 and .35, although the numbers of embolic signals were too small in each group to identify significant correlations. The variance in intensity increase resulting from velocity is therefore likely to be not greater than 20%. The relation between velocity and relative intensity may be partly due to the ultrasound beam not supplying equal power over the cross section of the insonated artery. The ultrasound beam produced by the system we used has highest power centrally, and power decreases toward the periphery with the −6-dB radius being 0.27 cm (information supplied by EME Ltd). This results in emboli in the center of the beam receiving higher power and therefore resulting in signals of greater intensity. Assuming the beam is centered on the vessel and assuming predominantly laminar flow, the emboli in the center of the beam are those at highest velocity, and therefore this would account for the relation between intensity and duration. However, in the sheep model the greater angle of insonation results in the beam cutting across the artery. If this were the only explanation one would expect a lesser relation in this model, which was not the case in our study. If this explanation is correct one might expect an inverse relation between the degree of spectral broadening and the strength of the correlation between velocity and intensity increase. Assuming laminar flow in the center of the middle cerebral artery, a systolic acoustic window without spectral broadening will be seen if most ultrasound power is supplied to the center of the vessel, while the periphery of the vessel receives much less power. In such cases one would expect emboli in the center of the vessel traveling at higher velocities to receive more ultrasound power and therefore result in a greater relative intensity increase. In contrast, in cases in which the ultrasound beam covers the whole vessel no acoustic window will be detected, and all parts of the vessel will receive a similar amount of ultrasound. Comparing the six patient arteries, an inverse relation between degree of spectral broadening and the correlation coefficient between embolus velocity and intensity was found. This is consistent with our hypothesis; however, only six arteries were studied, and flow may not have been laminar in all the middle cerebral arteries. Therefore, this explanation is not proven. However, it may explain the inconsistent nature of the relation betwen velocity and intensity increase among the different models and patients depending on the extent to which the ultrasound beam covers the insonated vessel, which would depend in turn on the angle of insonation, the beam width at the depth of insonation, and the vessel diameter.

Our results are directly applicable to Doppler emboli recordings made using the EME TC2000 transcranial Doppler system, a system which has been used in many of the publications on emboli recordings to date. They are also likely to apply in principle to other systems, although intermanufacturer variation in ultrasound beam characteristics may result in minor differences. A number of studies have confirmed a highly significant relation between embolus size and both intensity[6-8] and duration[6,7] of embolic signal. However, even in these studies some unexplained variance occurred. The demonstration of a relation between velocity and duration of high-intensity signals and in some cases a weaker relation with intensity in the in vivo situation may explain some of this variance. These relations are important if signal parameters are to be used to derive information on the relative size of emboli in humans,

and they need to be incorporated into programs currently being developed that are designed to detect and characterize emboli in patients.

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