Carotid Artery Intraplaque Hemorrhage and Stenotic Velocity

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Background and Purpose: One of the proposed mechanisms for sudden expansion of a carotid bifurcation plaque is hemorrhage within the lesion. It has been postulated that the sudden increase in plaque size will acutely reduce blood flow to the ipsilateral hemisphere and induce either a transient ischemic attack or a stroke. In this study, the relation between peak systolic velocity at the site of narrowing and its potential role in the development of intraplaque hemorrhage were investigated.

Methods: Ten patients who had carotid endarterectomy were examined by duplex Doppler sonography before surgery to determine the peak systolic velocity at the site of maximal narrowing. The excised carotid plaques were sectioned at 1-mm intervals and examined for histological evidence of intraplaque hemorrhage. The recorded peak systolic velocities in patients with intraplaque hemorrhage were compared with the velocities in cases in which no hemorrhage was identified.

Results: Five of the ten patients had intraplaque hemorrhage. Four of the five patients with intraplaque hemorrhage had a peak systolic velocity of >420 cm/sec and diastolic velocities of >160 cm/sec; none of the patients without intraplaque hemorrhage had such high values.

Conclusions: Peak systolic velocity is significantly higher in patients with intraplaque hemorrhage. The specificity and sensitivity of a peak systolic velocity of >420 cm/sec in predicting intraplaque hemorrhage remains to be determined. (Stroke 1993;24:314–319)

KEY WORDS • carotid artery diseases • carotid endarterectomy • ultrasonics

The relation between intraplaque hemorrhage and the development of symptoms of cerebral ischemia is not clear. Some authors have found intraplaque hemorrhage in a significantly higher percentage of plaques from symptomatic patients than from asymptomatic patients,1–9 while others have found no relation.10–12 The studies reported to date have been either pathological examinations of plaques removed at the time of operation,1–4,7,12 ultrasound studies of plaque morphology with later comparison with removed plaques,5,6,13–15 or direct comparisons between pathological and angiographic findings.16 Regardless of the role of intraplaque hemorrhage on the course of clinical events, there is interest in how the process occurs.

Intraplaque hemorrhage in carotid artery plaques is much more common when a stenosis exceeding 70% diameter reduction is present.2,16 The majority of hemorrhagic plaques have a smooth surface on angiography,16 even though they are associated with neurological symptoms.

Texon17 suggested that intraplaque hemorrhage may result from the hydraulic forces of blood flow, which “tend to draw the plaque toward the center of the lumen.” These forces may lead to subintimal hemorrhage.18 The forces are due to a pressure depression in the stenosis and are proportional to the square of the blood velocity according to the Bernoulli effect.19,20 To test this hypothesis, we compared the presence of intraplaque hemorrhage with peak systolic velocity in the narrowest region of the stenosis using ultrasonic Duplex scanning.

Materials and Methods

Each patient scheduled for carotid endarterectomy at University of Washington Medical Center and at Seattle Veterans Affairs Hospital was asked to participate in the study. Each volunteer provided informed consent for the study according to the conditions set by the University of Washington Human Subjects Institutional Review Board.

Each recruited patient was examined using ultrasonic duplex scanning with single-gate pulsed Doppler.21 All Doppler measurements were taken using an examination angle of 60° between the direction of the ultrasound beam and the visualized artery axis. Measurements were made in kilohertz, and the velocity was computed using the Doppler equation22,23 as $V = \frac{1}{2}C_x^2 \times \frac{1}{\cos \theta}$, where $V =$ blood velocity, $f =$ Doppler frequency measured by ultrasound device, $F =$ transmitted ultrasound frequency, $C =$ speed of ultrasound in tissue, and $\theta =$ angle between artery axis and ultrasound beam.

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The plaque removed at endarterectomy was fixed, decalcified, and embedded in paraffin, and 6-μm-thick cross-sections were obtained every millimeter over the entire length of the plaque, with additional sections obtained every 0.5 mm in the region of the carotid bifurcation. The resulting histological sections were mounted on glass slides, stained with hematoxylin and eosin, and examined microscopically for intraplaque hemorrhage.

Hemorrhage was identified by the presence of hemosiderin plus fibrin or platelet aggregates. Hemorrhage was classified into five categories according to the age of the hemorrhage (Figure 1). If completely formed erythrocytes were present, the hemorrhage was considered to have occurred during surgery (H1); if erythrocyte ghosts were present, the hemorrhage was considered recent but to have occurred before surgery (H2); the oldest hemorrhage was “glassy” (H5). Intraplaque hemorrhage was defined as hemorrhage in the plaque that did not communicate with the lumen. Plaques were also examined for other features including neovascularization and the presence of vasa vasorum penetrating into the plaque.

Annotated tracings of each histological section were made on transparent film placed on printed images of the histological sections. The examiner outlined areas of hemorrhage by examining the histological slide through a microscope while drawing the area of hemorrhage on the tracing. Such tracings included fiducial marks for alignment. The tracings were digitized into a three-dimensional computer imaging program to form a three-dimensional rendition of the plaque. Volumes of hemorrhage, indicated by the outlined area multiplied by section spacing, were computed for each plaque.

**Results**

Preoperative Doppler data and plaque histological data were available from 10 cases; five had regions of intraplaque hemorrhage, and five did not (Table 1). Peak systolic velocity from the five cases with hemorrhage was significantly higher than that from the cases with no hemorrhage (Mann-Whitney U test, p=0.016). The majority of cases with hemorrhage had a peak systolic velocity of >420 cm/sec, equivalent to a Bernoulli pressure depression of 70 mm Hg.

One patient (B) had a peak systolic velocity of 720 cm/sec. Such velocities are surprising according to the assumptions at the basis of the Bernoulli equation, that total mechanical energy is the sum of kinetic energy (associated with velocity) and potential energy (associated with pressure). According to Bernoulli, a velocity of 720 cm/sec requires a minimum stump pressure of at least 207 mm Hg. This patient had severe hypertension (270/110 mm Hg). A static pressure of 270 mm Hg represents a potential energy equivalent to the kinetic energy associated with a velocity of 820 cm/sec.

Another patient (R) had a ventricular arrhythmia so that peak systolic velocity was seen on only one of eight cardiac cycles, after an increased R-R interval. Even occasional peak systolic velocities exceeding the critical velocity are expected to permit intraplaque hemorrhage.

**Discussion**

Ultrasound duplex scanning is now the standard method of classifying the severity of arterial stenoses. Duplex scanning obtains two complementary kinds of information: information about the ultrasonic echogenicity of tissue in the image plane (B-mode imaging) and information about the velocity of blood flowing through vessels in the image plane (pulsed Doppler with spectral analysis). Patients with a carotid stenosis of >80% diameter reduction can be identified on the basis of an end-diastolic velocity of >140 cm/sec. Approximately one half of patients with a stenosis of >80% diameter reduction are likely to have a clinical event in 2 years compared with 2% of patients with lesser grades of narrowing. The risk of an event is even greater in patients with an end-diastolic velocity of >200 cm/sec. Of the patients with end-diastolic velocities between 140 and 200 cm/sec, 30% had an event in 2 years; of those with end-diastolic velocities of >200 cm/sec, 68% had an event during the same period. Half of the events were transient ischemic attacks and half were completed strokes and/or internal carotid artery occlusions.

Cerebral ischemic events may be prevented by surgical excision of the carotid lesions. In the 4 years (1983–1986) after the finding of an association between neurological symptoms and ipsilateral carotid stenoses of >80% diameter reduction at our institution, patients with high end-diastolic velocities were encouraged to have prophylactic endarterectomies. Of 56 patients who elected to have an endarterectomy based on that recommendation, 5% had cerebral events over the 2-year follow-up period by life table analysis. In comparison, of the 73 patients who elected to not have an endarterectomy, 50% had a cerebral event in a similar time. In each group, 16% died during the follow-up period. These findings are similar to those of the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial.

The factors that result in intraplaque hemorrhage are unknown. Patterson et al suggested that both chronic and transient hypertension might result in intraplaque hemorrhage. This suggestion was supported by Fryer et al, who found that 73% of hypertensive cases had severe intraplaque hemorrhage compared with 58% of normotensive cases. The relation of chronic hypertension and risk of stroke is well known. In addition, short-term control of blood pressure will reduce the chance of stroke in the short term. Atherosclerotic plaques from the carotid artery contain networks of vasa vasorum that originate from branches of the external carotid artery or internal carotid artery distal to the location of the plaque. Pressure in the vasa vasorum is lower than intraluminal arterial pressure since blood flow through the vasa vasorum can be occluded by a soft collar applied around the artery. Thus, for intraplaque hemorrhage to occur from the vasa vasorum, a pressure reduction must be applied to the plaque through the Bernoulli effect, as suggested by Texon. The pressure depression effect is enhanced by increased intrastenotic velocities (see Appendix) that result from increasing degrees of stenosis and increasing peak systolic blood pressure.

Although one line of logic suggests that the volume of intraplaque hemorrhage might be related to the peak systolic velocity, other factors are also important. The volume of intraplaque hemorrhage should also be related to the duration of high velocity. We have no information on this subject. The volume of intraplaque hemorrhage may be related to the mechanical strength of the plaque.

materials. In the plaques that we studied, the regions of intraplaque hemorrhage were not of uniform “age” according to histological analysis. Therefore, more than one hemorrhage event probably occurred.

While the results of this study are preliminary, the data suggest that peak systolic velocity may be an important factor related to the development of intraplaque hemorrhage. Peak systolic velocity measurement may aid in the quest to “define which groups of patients will be helped by [endarterectomy].” In the interim, “eliminating...stressful influences that cause transient and severe elevations in blood pressure” can help break the “chain of events” that lead to stroke.36 Peak systolic velocity is easily measured using ultrasonic duplex scanning. We plan further studies on a larger number of patients to confirm this hypothesis.

Appendix

Bernoulli Effect

According to conservation of energy, the total mechanical energy density in the blood is the sum of potential energy density (which can be determined by measuring the blood pressure) and kinetic energy density (which can be determined by measuring the blood velocity). These can be expressed as:

\[
E = \rho g h + \frac{1}{2} \rho v^2
\]

where \( \rho \) = density of fluid, \( g \) = acceleration of gravity, \( h \) = height of fluid column, and \( v \) = fluid velocity. Mechanical energy can be freely exchanged between the two forms, kinetic and potential. In a Venturi tube,46 flow is always laminar and no boundary layer separation occurs in the poststenotic region (Figure 2, panel A). Pressure at the distal end of the tube is nearly equal to that at the proximal end. The transmural pressure exerted on the wall in the stenosis is lower than either the proximal or the distal pressure. This is because the potential energy density (pressure energy) in the proximal region, where velocity is low, must be converted into kinetic energy density (velocity energy) in the stenosis, where velocity is high.

If, distal to the stenosis, the tube is shaped so that the flow is streamlined, then kinetic energy is converted back to potential energy in the poststenotic region according to the principle of conservation of energy. Alternatively, if distal to the stenosis there is a sharp expansion of the stenosis (Figure 2, panel B), flow separation and turbulence result. If the flow separation is minor, the effect of fluid viscosity in the high shear rates of the turbulence converts some of the kinetic energy into heat. The remainder of the kinetic energy is converted back into pressure (potential energy density). If the flow separation and turbulence are severe, such as distal to an aortic valve stenosis, all of the kinetic energy is converted to heat. Then the pressure drop across the stenosis is equal to the pressure depression in the stenosis (Figure 2, panel B).

When very high velocities are involved, a Venturi tube can be used to create a vacuum. Venturi devices are used to create vacuums in industrial applications and in the power siphon in the laboratory sink. A vacuum of more than half an atmosphere is easily attained.

Within an arterial stenosis, where kinetic energy is high, the hydrostatic pressure exerted on the walls (transmural pressure) is low (Figure 2, panel C). The transmural pressure depression in a high-velocity steno-

| Table 1. Blood Flow Velocity and Intraplaque Hemorrhage in Carotid Artery |
|-----------------|-----------------|-----------------|-----------------|
| Patient | Hemorrhage volume (cm³) | Diastolic | Systolic | Bernoulli “pressure”22 (mm Hg) |
| With hemorrhage | | | | |
| Z | 179.7 | 185 | 462 | 85 |
| R | 97.8 | 110 | 365 | 53* |
| B | 24.8 | 340 | 720 | 207† |
| M | 2.5 | 185 | 462 | 85 |
| D | 0.9 | 169 | 431 | 74 |
| Without hemorrhage | | | | |
| A | 0 | 123 | 400 | 64 |
| h | 0 | 46 | 185 | 14 |
| H | 0 | 154 | 370 | 55 |
| N | 0 | 123 | 339 | 46 |
| W | 0 | 46 | 185 | 14 |

Mann-Whitney U test17 p=0.028 p=0.016

*Patient with arrhythmia.
†Patient with systolic hypertension 270/110 mm Hg.
The Bernoulli hypothesis raises an intriguing pathophysiological consequence. If the intrastenotic velocity is 350 cm/sec systolic and 150 cm/sec diastolic, then the intrastenotic Bernoulli pressure depression is 49 mm Hg systolic and 9 mm Hg diastolic, and if the aortic blood pressure is 120 mm Hg systolic and 80 mm Hg diastolic, then the intrastenotic blood pressure is aortic minus depression or 71 mm Hg systolic and 71 mm Hg diastolic. In the stenosis, systolic pressure is equal to diastolic pressure, so there is no pressure pulsation in the stenosis. If the intrastenotic systolic velocity was higher (450 cm/sec systolic and 150 cm/sec diastolic), then the intrastenotic Bernoulli pressure depression is 81 mm Hg systolic and 9 mm Hg diastolic and the intrastenotic blood pressure is 39 mm Hg systolic and 71 mm Hg diastolic. The pulsations in the stenotic region are paradoxical: large diameter during diastole, small diameter during systole. In real-time imaging, the stenotic entrance will rock with each cardiac cycle.

The loss of pressure oscillations or the paradoxical pressure pulsations caused by the Bernoulli effect invalidate conventional arterial compliance measurement that depend on indirect measurements of systolic and diastolic pressure.

The Bernoulli hypothesis also suggests an alteration in the conventional method of carotid Doppler examination. In patients with arrhythmia, an extended R-R interval will manifest higher systolic blood pressure and a higher peak systolic velocity, which may induce intraplaque hemorrhage. Thus, the highest peak systolic velocity from an irregular beat should be noted for the purpose of predicting intraplaque hemorrhage. In addition, systolic blood pressure should be measured and considered when classifying intraplaque hemorrhage. In addition, systolic blood pressure should be measured and considered when classifying intraplaque hemorrhage. In addition, systolic blood pressure should be measured and considered when classifying intraplaque hemorrhage.

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