Detection of Mitral Valve Abnormalities by Carotid Doppler Flow Study: Implications for the Management of Patients with Cerebrovascular Disease

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SUMMARY Patients with symptoms of cerebral ischemia are often evaluated with non-invasive carotid artery testing. An abnormal carotid Doppler ultrasound frequency shift pattern of early systolic flutter (ESF) was demonstrated by auscultation and velocity wave form analysis in patients with normal carotid bifurcations. Ten of these patients were studied with echocardiography (echo) and eight had mitral valve prolapse (MVP). To evaluate the association between ESF and MVP, a prospective blinded study was performed, recording carotid Doppler frequency shift in 50 patients referred for routine echocardiography. A total of 18 patients had ESF: 9/12 patients with MVP by echocardiography had ESF. Nine additional patients without MVP had ESF (two with mitral regurgitation and two with redundant mitral valves). The association of ESF with MVP was significant (p < 0.001). The findings of ESF with a normal carotid artery by non-invasive testing suggests a possible mitral valve origin for symptoms of cerebrovascular disease.

Materials and Methods

Patients Fifty consecutive patients referred for echocardiography were examined with carotid Doppler study, blinded to the cardiac diagnosis. This study design was specifically chosen to eliminate any bias in performing and interpreting both the carotid and echocardiographic examinations. The mean age of the patients was 51.5 years, with a range from 15 to 83 years. There were 15 males and 35 females. The referring diagnosis and echocardiographic findings were not known to the investigator performing the carotid Doppler studies. The reason for referral of the 50 patients were: rule out mitral valve prolapse 15, midysstolic murmur 2, syncope 1, onset of atrial fibrillation 2, mitral valve regurgitation 2, mitral stenosis 1, rule out bacterial endocarditis 7, pericarditis 3, aortic stenosis 4, hypertrophic cardiomyopathy (idiopathic sub-hypertrophic aortic stenosis) 1, evaluate left ventricular wall motion and rule out mural thrombus 6, evaluate atrial septal defect repair 1, unknown source of emboli 1, rule out cardiac source of cerebrovascular disease 4.

The four patients with symptoms of cerebrovascular disease had also been referred independently for a non-invasive carotid test battery consisting of pneumo-oculoplethysmography, Supraorbital Doppler, Direct Carotid Flow Study and Real Time B-Mode ultrasonography. None of these four patients had any evidence of carotid artery disease.

Carotid Doppler Studies Carotid Doppler examination was performed with a 9.5 MHz probe (Parks 806) by the velocity wave form method of Rutherford. Four of the patients who were referred independently for carotid studies because of symptoms of cerebrovascular disease were also studied with a 4 MHz Doppler probe (Sonomed) attached to a spectral frequency analyzer (Angioscan). Doppler studies were performed immediately before or following the echocardiograms. Early systolic flutter (ESF) was detected by auditory assessment of the Doppler shift signal in the common and internal carotid arteries. A fluttering or bubbling sound was detected in early systole, followed by a midysstolic low pitched beat, which could be plotted as a midysstolic downward deflection in the velocity wave form. The fluttering sound sometimes continued throughout systole. Spectral analysis (4 cases) and linear plotting (50 cases) of the wave form both revealed a deep midysstolic deflection (fig. 1). There was no spread of frequencies, as seen with obstruction to flow in the carotid bifurcation.

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FIGURE 1. Velocity wave form recorded over the common carotid artery of a patient with mitral valve prolapse on Echocardiography. The recording was performed with a 4 MHz Doppler probe (Sonomed) attached to a spectral frequency analyzer (Angioscan). Similar patterns were recorded with the 9.5 MHz Doppler probe attached to a linear plotter which demonstrated the average wave form without revealing the full spectrum of recorded frequencies. There is a pronounced mid-systolic deflection (arrow) and slight irregularities on the surface of the systolic wave compared to the normal velocity wave form.

The mid-systolic downward deflection was much more pronounced than the late systolic downward deflection often seen in the normal common carotid artery (fig. 2), and which is exacerbated by aortic valve disease. The presence of both the auditory detection of flutter and the mid-systolic downward deflection on velocity wave form were required to make the diagnosis of ESF.

Echocardiography

M-mode and two-dimensional echocardiograms were performed with either an ATL Mark IV or Irex System III using a 2.25 or 3 MHz transducer with the patient in a left lateral decubitus position. Echocardiograms were analyzed independent of carotid Doppler findings. Mitral valve prolapse was defined as systolic hammocking of 2 mm or more below the C-D line on M-mode echocardiography. In addition, mitral valve prolapse was diagnosed by 2-D echocardiography in the parasternal long axis view by drawing an arbitrary line between the aortic root and the atroventricular junction. If either the anterior or posterior mitral leaflet passes behind this line, the diagnosis of MVP is confirmed.

Data were analyzed employing the Chi-square goodness of fit test to determine the association between mitral valve abnormalities and ESF.

Results

Early systolic flutter was identified in 18 of the 50 patients who had echocardiography. Among these 18 patients, 13 had mitral valve abnormalities. Nine were found to have mitral valve prolapse on 2-D echocardiography. Two patients had redundant mitral valves without prolapse. Two additional patients had mitral regurgitation by auscultation, with normal echocardiograms.

Only 5 patients with ESF did not have mitral valve abnormalities. Three patients with MVP on echocardiography were not found to have ESF, though one had a mid-systolic deflection. Of the remaining twenty-nine patients with no mitral valve abnormalities on echocardiography, 28 had normal carotid Doppler wave form. One additional patient without mitral valve disease also had a mid-systolic deflection in the velocity wave form, but no flutter. This patient was found to have hypertrophic cardiomyopathy with ventricular outflow obstruction murmur (idiopathic sub-hypertrophic aortic stenosis) on echocardiography. Overall, 9 of the 12 patients with MVP had ESF (75%) whereas only 9 of 38 patients without MVP had ESF (24%), (p < 0.001). The sensitivity for diagnosing MVP by carotid Doppler ultrasound was 75% and the specificity 76%. This indicates that the finding of ESF by carotid Doppler is related to mitral valve dysfunction, though it is not necessarily diagnostic of mitral valve prolapse. The results are summarized in table 1.

**Table 1** Correlation of Carotid Doppler Flow with Echocardiography in the Diagnosis of Mitral Valve Prolapse

<table>
<thead>
<tr>
<th>Doppler</th>
<th>Mitral valve prolapse</th>
<th>No mitral valve prolapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESF</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>(2 mitral regurgitation)</td>
<td>(2 redundant mitral valve)</td>
</tr>
<tr>
<td>No ESF</td>
<td>3</td>
<td>29</td>
</tr>
</tbody>
</table>

The results of carotid Doppler study in 50 patients referred for echocardiography are shown. Early systolic flutter (ESF) was found in 18 patients. The results of the echocardiogram were not known at the time of the Doppler study, nor were the results of the Doppler study known at the time of interpretation of the echocardiogram. The association of ESF with mitral valve prolapse was significant (p < 0.001).

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Discussion

Patients with mitral valve dysfunction, particularly mitral valve prolapse, can experience symptoms of cerebrovascular disease. Mitral valve prolapse is a common entity. Estimates of the incidence in the young normal population ranges from 0.5% to 5% in men and up to 6% in women. Patients with mitral valve prolapse typically present with atypical chest pains, dizziness, syncope, cardiac arrhythmias or auscultation of a mid-systolic click and late systolic murmur on routine physical examination. The incidence of stroke is not increased in patients with mitral valve prolapse. However, there is a significantly higher incidence of mitral valve prolapse in patients with stroke than in the general population. This is particularly true in young patients under age 45 and in patients without other risk factors for stroke.

Recognition of flow abnormalities originating from the mitral valve in patients being studied by non-invasive carotid testing enhances the diagnostic value of these procedures by suggesting a possible cardiac source of cerebrovascular symptoms. The abnormal flow pattern detected by Doppler consistently begins in early systole, prior to a mid-systolic deflection. The murmur of mitral valve prolapse is typically heard in late systole, following a midsystolic click. However, phonocardiographic and echocardiographic analyses of the murmur of mitral valve prolapse have shown that abnormalities begin most commonly in early systole, in association with pan-systolic bowing of the posterior leaflet of the mitral valve. During systole, with the aortic valve open and an incompetent mitral valve, the entire column of blood from the left atrium to the carotid artery may demonstrate the reverberation of turbulence in the left atrium due to MVP or mitral regurgitation. This reverberation of turbulence from the left atrium may account for the detection of audible ESF on carotid Doppler examination. An alternative explanation is that the posterior wall of the aortic root and the anterior wall of the left atrium are contiguous and sudden left atrial pressure changes can be transmitted directly to the aortic root and thence to the carotids.

The association of early systolic flutter with echocardiographic evidence of mitral valve prolapse was statistically significant (p < 0.001). Nevertheless, none of the patients with ESF did not have demonstrable prolapse on the echocardiogram. Four patients had other abnormalities of the mitral valve associated with mitral regurgitation. Patients with typical click-murmur findings of mitral valve prolapse may not always have prolapse on echo. Three neurologically symptomatic patients in this study who had mitral valve prolapse on echocardiography had had normal echocardiograms previously. In another series, 11 patients with cerebrovascular symptoms that were thought to be of cardiac origin had normal echocardiograms and were found to have mitral valve prolapse by cardiac catheterization. Thus, the absence of echocardiographic visualization of prolapse in patients with ESF does not exclude these patients from having prolapse. Also, patients with flow abnormalities at the mitral valve may be at risk for having embolic events even though there is no demonstrable prolapse.

It is important to identify mitral valve prolapse in patients with symptoms of transient ischemic attack or stroke. Cerebrovascular symptoms in patients with mitral valve prolapse are thought to be due to emboli arising from the mitral valve. It is not clear what factors predispose some patients with mitral valve prolapse to have stroke. Stroke does not correlate with the degree of prolapse or mitral regurgitation. There is evidence that there are co-existing platelet abnormalities in some patients with mitral valve prolapse that give rise to a hyperaggregable state, resulting in the formation of thrombus on the mitral valve. The carotid Doppler finding of ESF appears to originate from the mitral valve, and is significantly associated with mitral valve prolapse. The examiner should be aware of the possible association between ESF and mitral valve abnormalities to distinguish flow abnormalities transmitted from the mitral valve from bruits due to carotid stenosis. Detecting ESF in patients referred for non-invasive carotid artery studies can alert the examiner that the neurologic symptoms may be of cardiac origin, so that appropriate cardiologic investigations can be pursued.

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References

Effects of Estradiol On Platelet Aggregation In Cerebral Microvessels of Mice

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SUMMARY Mice were implanted subcutaneously with a pellet containing 0.5 mg estradiol or with a placebo. Eight to 12 days later platelet aggregation was produced in pial arterioles by injuring their endothelium in vivo with a noxious light/dye stimulus. The time between the onset of the noxious stimulus and the appearance of platelet aggregates was significantly shortened (p < .02) by estradiol treatment in young (2 month old) mice. The same treatment had the opposite effect in 4–6 month old mice and significantly delayed the onset of aggregation (p = .01). When platelet rich plasma (PRP) was prepared, aggregation by sodium arachidonate was always inhibited in PRP from estradiol treated mice, irrespective of age. Estradiol treatment had no effect on aggregation induced ex vivo by ADP. Thus the enhanced aggregation observed in pial arterioles of young estradiol treated mice may not reflect direct effects of estradiol on the platelet itself. The data are discussed in light of the literature suggesting enhancement of ischemic vascular disease, including strokes, in patients receiving estrogens, and especially high doses of estrogens.

IN SPITE OF great interest in the possible adverse effects of estrogen on blood clotting or hemostatic mechanisms in humans,1–6 few pertinent in vivo experimental studies have been reported. Most studies have been in vitro or ex vivo investigations. A single in vivo report indicated that estradiol and related estrogens enhanced platelet aggregation in injured mesenteric microvessels of female mice.7 Others8 have shown that estradiol inhibits the ability of arachidonate to induce platelet thrombi in mouse pulmonary vessels. This difference in the platelet response within different vascular beds may indicate that platelet aggregation in vivo is a complex function of drug or hormone action directly on the platelet itself and indirectly on the platelet via drug effects on the metabolism of the vessel wall and/ or adjacent tissue. Indeed we have shown that a drug tested in exactly the same way in 2 different microvascular beds in the same species, can produce opposite effects on platelet aggregation in one bed as opposed to the other.9,10 Therefore, in order to draw conclusions concerning estradiol’s action on aggregation in cerebral vessels it is necessary to use the cerebral vasculature in an appropriate study. In view of the absence of any published experimental work concerning estradiol’s action on platelet aggregation in cerebral vessels, and in view of suggestions that estrogens may be a factor enhancing ischemic stroke2–3 we performed the investigation described below.

Methods

Platelet Aggregation in Vivo

Our methods have been published in great detail.9–13 Endothelial injury13 is produced by exposing the vessels in a microscopic field to filtered light from a mercury lamp via epillumination and Leitz Ultropak objectives.9,11,13 The filtered light is innocuous unless sodium fluorescein (0.8 ml of a 2% solution per 100g body weight) is intravenously injected. It is probable that the endothelial injury13 is initiated by free radicals generated when the dye is excited.14 We measure, in seconds, the latent period between application of light and dye, and the onset of the first recognizable adherent platelet aggregate in an arteriole in the microscopic field. The vessel is preselected arbitrarily from arterioles 30–60 μm in internal diameter, at the site of craniotomy.15 With our method of inducing aggregation it is easy to monitor aggregation because the aggregates fluoresce when appropriate barrier filters are used.9,11 The method has enabled us to detect a variety of drug effects on platelet aggregation in cerebral surface vessels (pial vessels). Some of these effects are the anti-aggregatory action of cyclooxygenase inhibitors,9,16
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