Cerebrovascular Complications Associated with Idiopathic Hypertrophic Subaortic Stenosis

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SUMMARY One hundred fifty patients with idiopathic hypertrophic subaortic stenosis (IHSS) were followed-up for an average of 5.5 years. There were 95 males and 55 females with a mean age of 51 years. Patients usually presented with cardiac symptoms or syncope; no patient presented with stroke. Eight patients (5%) died during follow-up, all from cardiac causes. Eleven patients (7%) developed cerebrovascular complications; 5 (3%) had a stroke and 6 (4%) had TIA only. Patients with IHSS and atrial fibrillation have a much greater stroke risk. Mitral annulus calcification may also increase stroke risk in IHSS. However, stroke is almost never the presenting manifestation of IHSS, and the long-term risk of stroke for most patients with known IHSS is low.

THE LINK between mitral valve prolapse and stroke has keyed interest in other cardiac conditions not previously thought to increase stroke risk. In two recent studies of the role of echocardiography in the evaluation of stroke, 1, 2 no cases of asymmetric septal hypertrophy (ASH) or more severe forms of idiopathic hypertrophic subaortic stenosis (IHSS) were discovered. Nonetheless, we recently saw a patient with unexplained stroke in whom two-dimensional echocardiography revealed unexpected IHSS, and the question arose whether this was the cause of the event or a coincidental finding. Since the hemodynamic and myocardial changes associated with IHSS create potential conditions for cerebrovascular complications, we undertook this study to assess the risk of stroke in patients with this disorder.

Methods

Between 1967 and 1981, 180 patients with IHSS confirmed by cardiac catheterization were seen at the Cleveland Clinic. The catheterization criteria for diagnosis were: left ventricular hypertrophy; systolic anterior motion of the mitral valve; asymmetric septal hypertrophy; small left ventricular cavity; vigorous contraction of all wall segments. The presence of a ventricular outflow tract gradient at rest and after stimulation with isoproterenol or amyl nitrite was also recorded.

Follow-up dated from the time of cardiac catheterization and was accomplished using available medical records, telephone interviews and standardized questionnaires addressed to the patient and/or referring physician.

Results

An average follow-up of 5.5 years was achieved in 150 patients (83%). There were 95 males and 55 females with a mean age of 51 years (range, 7 months to 77 years). The clinical presentation included syncope or near syncope in 32 patients (21%), non-specific dizziness and/or lightheadedness in 31 patients (21%) and palpitations in 37 patients (25%). Two patients had a remote history of transient ischemic attacks and no patient presented with a stroke. A list of associated conditions is given in table 1. None of the patients had mural thrombus, including those with left atrial enlargement.
The IHSS subtypes were: obstructive, 135 patients (90%); nonobstructive, 13 patients (9%); simple ASH, 2 patients (1%).

Eight patients (5%) died during followup after an average interval of 3.8 years. All of the deaths were cardiac related (myocardial infarction, 4; congestive heart failure, 3; sudden death, 1). Eleven patients (7%) developed cerebrovascular complications during follow-up. Five patients (3%; 593/100,000 person years; 0.6%/year) had a stroke and 6 (4%) had transient ischemic attacks only. All of the stroke victims were men with a mean age of 49 years. It was difficult to assess other potential causes for stroke in this patient population, but a list of possible contributing factors is given in table 2.

Discussion

IHSS is a distinct form of non-dilated hypertrophic cardiomyopathy. It is characterized by disproportionate and asymmetric septal hypertrophy compared to the left ventricular free wall, systolic anterior motion of the mitral valve and myofibril disarray in the interventricular septum and ventricular wall. The hemodynamic features of IHSS include dynamic and variable left ventricular outflow tract obstruction which produces a systolic pressure gradient across the left ventricular outflow. The term asymmetric septal hypertrophy usually refers to the most benign end of the IHSS spectrum, although there are other cardiac conditions associated with an abnormal septal to left ventricular wall ratio. Autosomal dominant and sporadic forms of IHSS have been described, and there is no consistent sex predilection.

IHSS is usually diagnosed before the age of 40, although it may be more common in older age groups than previously believed. Patients usually present with a heart murmur, dyspnea, angina, palpitations, or syncope. Syncope is the predominant "neurologic" complication of IHSS, and reflects ventricular outflow tract obstruction resulting in global brain hypoperfusion. Focal brain infarction is not mentioned as a presenting manifestation of IHSS in any of the larger series, and none of our patients presented with stroke. Embolism is the probable mechanism of stroke in most patients with IHSS.

The natural history of IHSS has been incompletely studied, Hardarson et al estimated a mortality rate of 15% at 5 years and 35% at 10 years. Death was most often sudden, although one patient died from a subarachnoid hemorrhage due to a ruptured mycotic aneurysm secondary to bacterial endocarditis, and another died from cerebral embolism. We found a mortality rate of only 5% and there were no stroke-related deaths. Our 3% stroke rate agrees closely with the 2.4% rate reported by Glancy et al. Hardarson et al found a 9.2% frequency of systemic or pulmonary embolism but they did not report a separate rate for brain embolism.

Atrial fibrillation occurs in 5–10% of patients with IHSS and is associated not only with cardiac deterioration but also a markedly increased risk of stroke. Atrial fibrillation tends to develop late in the course of IHSS and is often associated with left atrial enlargement. One of our stroke victims had mitral valve annulus calcification in addition to atrial fibrillation. Tajik et al have reported a relation between mitral annulus calcification and IHSS, and a relation between isolated mitral annulus calcification and stroke has been suggested.

The available data suggests that echocardiographic evidence of isolated ASH should be viewed as a coincidental finding in patients with unexplained stroke, and that stroke is almost never the presenting manifestation of IHSS. Such patients should be monitored for unsuspected atrial fibrillation, but other etiologies for stroke should be avidly sought. The long-term stroke risk in most patients with known IHSS is low. However, consideration should be given to prophylactic antiplatelet or anticoagulant therapy in the IHSS subgroup with atrial fibrillation, left atrial enlargement and/or mitral annulus calcification since their stroke risk is much greater.

References

Effects of Calcium Channel Blockers on Pial Vascular Responses to Receptor Mediated Constrictors

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Summary

Published studies have seldom examined the in vivo effect of calcium channel blockers on the contractile response of cerebral vessels to receptor mediated constrictors, and have had little success in demonstrating any effect of a single systemic dose of the channel blockers in contrast to the effects of continuous infusions. The present study examines the effect of topical norepinephrine, prostaglandin F$_2$o and serotonin on pial arterioles of the mouse, in the presence of locally applied channel blockers and also 15 and 30 minutes after a single i.p. injection of the blockers. Verapamil, nisoldipine and nimodipine were all effective inhibitors of constriction by either route of administration, and in doses having little or no dilating action. The data not only indicate that single systemic doses can effectively alter contractile behavior of cerebral arterioles, but also demonstrate the importance of testing these drugs against receptor mediated constrictors whose effects, alone or in combination, may be important during initiation or maintenance of cerebral vasospasm.

FOR SEVERAL YEARS there has been particular interest in the actions of calcium channel blockers (CCB) on cerebral vessels, because of experimental evidence suggesting that cerebral vessels were especially sensitive to such agents.\(^1\)\(^-\)\(^5\) This sensitivity might permit CCB to improve cerebral blood flow and/or relieve cerebral vasospasm without altering circulation in other vascular beds. Some experimental studies published thus far use direct application of CCB to the cerebral vessels in vivo.\(^6\)\(^-\)\(^8\) Other studies utilize a continuous intravascular infusion of CCB.\(^6\)\(^-\)\(^11\) Studies of the effects of a single systemic dose on subsequent behavior of cerebral vessels appear rare, and in two such studies of which we are aware\(^1\)\(^-\)\(^3\)\(^-\)\(^8\) CCB failed to alter cerebral blood flow (CBF). It would seem important to investigate further, the action of single doses of systemically administered CCB on cerebral circulation. Moreover, in many vessels and species, in vitro, CCB may fail to influence resting vascular tone yet may markedly inhibit vasoconstriction.\(^1\)\(^-\)\(^3\)\(^-\)\(^8\) Therefore it is important to test the effect of CCB on constriction rather than simply test the effect on diameter or resting flow. The in vitro anticontractile effects of CCB on cerebral vessels appear particularly marked where receptor mediated agonists are the contractile agents.\(^1\)\(^-\)\(^2\)

Yet studies of cerebral circulation which report no effect of CCB on resting diameter\(^9\) or flow\(^3\)\(^-\)\(^8\) have not investigated the effects of CCB on receptor mediated constriction. Rather than agonists like serotonin, prostaglandin F$_2$o, or norepinephrine, hypocapnia or BaCl$_2$ have been used as the contractile stimulus.\(^3\)\(^-\)\(^6\) It seems advisable to study the effects of CCB on the contractile response to directly applied receptor mediated agonists. The following report describes such experiments, employing 3 different receptor mediated agonists, and 3 different CCB, each of the latter administered both directly to the pial vasculature and also given in a single intraperitoneal injection 15 and 30 minutes prior to testing the contractile response.

Methods

Male mice (Institute for Cancer Research Strain, Flow laboratories) weighing 22–35 g were anesthetized with urethan and subjected to tracheotomy and craniotomy as previously described.\(^13\)\(^-\)\(^14\) The dura was stripped as previously described\(^13\)\(^-\)\(^14\) and the cerebral surface (pial) vessels in the subarachnoid space between the transparent arachnoid and the brain were observed through a Leitz Ultrapak microscope.\(^13\)\(^-\)\(^14\) A TV camera and monitor were employed together with an image splitter and strip-chart recorder for measurement of diameter and diameter changes as described by Baez.\(^15\) In each mouse a single arteriole was arbitrarily selected for monitoring. The mice were maintained at 37°C, and the surface of the brain was irrigated with an artificial cerebrospinal fluid (CSF) flowing at 2 ml/min\(^3\) at 37°C and pH of 7.35 ± 0.03 (SD), as measured in the fluid passing across the craniotomy


\(^12\) DeBono DP, Warlow CP: Mitral-annulus calcification and cerebral or retinal ischemia. Lancet 2: 383–385, 1979


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