Ischemic Cerebrovascular Complications and Risk Factors in Idiopathic Hypertrophic Subaortic Stenosis

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To determine the risk and time to cerebrovascular complications with idiopathic hypertrophic subaortic stenosis, we studied 119 patients (66 men and 53 women) with evidence of this disease based on strict echocardiographic criteria and followed them up for a mean ± SEM of 6.5 ± 0.6 years. Cerebral ischemic events occurred in 26 patients (22%), and in five patients stroke was the initial presenting event. Men had cardiac symptoms at a younger age than women, but there was no significant difference in age at the time of stroke. Cardioembolic cerebrovascular events were associated with atrial fibrillation and left atrial enlargement, whereas atheroembolic events were associated with hypertension. An increased risk of stroke was associated with female sex, mitral anulus calcification, hypertension, and atrioventricular conduction delay. Unlike most previous series, this study shows that patients with idiopathic hypertrophic subaortic stenosis may present with stroke. (Stroke 1991;22:1143–1147)

Idiopathic hypertrophic subaortic stenosis (IHSS) is a cardiac disorder characterized by hypertrophy of the ventricular septum and anterolateral free wall of the heart and has diverse etiologies, including congenital causes and hypertension. Since the first published description of IHSS, the cardiovascular complications of the disorder have been well described. Despite the coexistence of many known risk factors for stroke, such as atrial fibrillation, left atrial enlargement, and mitral anulus calcification, the association between IHSS and stroke has only recently been appreciated. Furthermore, stroke has been described as an infrequent complication and presenting event in IHSS. Our experience suggested that in this disorder transient ischemic attacks (TIAs) and strokes were far more common than had previously been appreciated and that stroke may be the initial manifestation of IHSS. We therefore undertook this study to determine the types and incidence of ischemic cerebrovascular events and possible mechanisms for stroke in patients with IHSS.

Subjects and Methods

We analyzed the computer records for all patients undergoing echocardiograms at the University of Iowa Hospitals and Clinics over the previous 10 years and found 119 patients who met strict echocardiographic criteria for IHSS. The clinical courses of these patients between 1966 and 1990 were obtained from their hospital records. When possible, we used standardized telephone interviews with either the patient or a referring physician for those patients no longer followed up at this hospital. Age at the onset of cardiac symptoms, age at the time of the cerebrovascular event, and time from the diagnosis of IHSS to the cerebrovascular event were recorded. All patients were seen by a cardiologist, and their echocardiograms were reviewed. We determined the type of cerebrovascular complication based on clinical criteria developed for the Harvard Cooperative Stroke Registry and on diagnostic studies, including cranial computed tomography, magnetic resonance imaging of the brain, and carotid duplex ultrasonography. Electrocardiogram results were obtained from the hospital record, and the presence of high serum cholesterol concentrations, diabetes mellitus, and smoking history were noted.

Transthoracic two-dimensional (2-D) echocardiography was performed at the time of clinical pre-
sentation in 99 patients. Twenty patients with IHSS were diagnosed clinically, with M-mode echocardiography or with cardiac catheterization prior to the routine availability of 2-D echocardiography, and the diagnosis was confirmed later with this modality. The echocardiographic diagnosis of IHSS was based on established criteria.\textsuperscript{12,24} IHSS was diagnosed if any two of the following criteria were present: 1) septal-to-posterobasal ventricular free wall ratio of $>1.5$, 2) systolic anterior motion of the mitral valve, and 3) left ventricular outflow tract obstruction on Doppler echocardiogram at rest or with provocative testing.

If the echocardiogram showed symmetrical concentric hypertrophy of the left ventricle but no systolic anterior motion of the mitral valve or outflow tract obstruction, then the patient was excluded from our study population. By echocardiographic criteria, there was no abnormal wall motion to indicate ischemic heart disease or intrinsic valvular disease. Echocardiography was also used to determine the presence of intraventricular or intra-atrial thrombus, aortic or mitral valve calcification, and to measure left atrial size. Left atrial enlargement was defined as a left atrial diameter of $>4$ cm on an echocardiogram.

Data for time to stroke were analyzed by Cox's proportional hazards regression.\textsuperscript{25} This procedure was used to assess each variable as a risk factor for stroke. The regression method produces an estimate of the hazard ratio or relative risk between two groups of having a cerebral ischemic event (e.g., ratio of the male hazard to the female hazard of having a stroke). The two-sided Cox score test was used to determine whether the hazard ratio was equal to 1, and 95\% confidence intervals for the hazard ratio were computed. This analysis did not include the five patients who presented with stroke or one patient whose stroke occurred immediately following the diagnosis of IHSS. No multiple regression analysis was performed because of the small number of patients with cerebral ischemic events not presenting with stroke ($n=21$). The two-sample $t$ test was used to compare the ages at stroke and at cardiac presentation for different groups.

Fisher's exact two-tailed test was used to compare all dichotomous risk factor variables such as atrial fibrillation, left atrial enlargement, mitral anulus calcification, etc. Where multiple comparisons were made between groups, $p<0.025$ was required to attain significance.

**Results**

The group of 119 patients comprised 66 men and 53 women. Mean±SEM duration of follow-up for all patients was $6.5±0.6$ years, and that for the 26 patients with cerebral ischemic events was $7.3±1.3$ years. Follow-up was complete for 82 patients (duration $7.6±0.7$ years) and incomplete for 37 patients ($4.2±0.8$ years). Of the 26 patients with cerebral ischemic events, 17 had complete ($8.8±1.7$ years) and nine had incomplete ($4.6±1.7$ years) follow-up.

There were 93 patients with IHSS but without cerebral ischemic events, of whom 65 had complete ($7.3±0.8$ years) and 28 had incomplete ($4.0±0.9$ years) follow-up. There was no significant difference in duration of follow-up between patients with complete ($p=0.40$) and incomplete ($p=0.74$) follow-up in either the stroke or the nonstroke group. The mean±SEM age at cardiac presentation in men was $40.6±2.1$ years, and that in women was $54.2±2.5$ years. Presenting symptoms included angina in 33 patients (28\%), dyspnea in 31 (26\%), palpitations in 18 (15\%), syncope or presyncope in 14 (12\%), and sudden cardiac death in one (1\%). Five patients (4\%) presented with stroke, and 17 (14\%) were asymptomatic. Left atrial enlargement was found in 14 (54\%) of the 26 patients with cerebral ischemic events compared with 61 (66\%) of the 93 patients without strokes. Eight patients with cerebral ischemic events (31\%) and 14 patients without neurological symptoms (15\%) had atrial fibrillation.

Of the 119 patients, 26 (22\%) had ischemic cerebral events: 18 (15\%) had strokes, seven (6\%) had only TIA's, and one (1\%) had transient global amnesia. Presumptive etiology of the cerebral ischemic event was cardioembolic in nine patients (8\%) (four had stroke and five had TIA), atheroembolic in 11 (9\%) (10 had stroke and one had TIA), atherothrombotic stroke in two (2\%), lacunar stroke in two (2\%), TIA of undetermined cause in one (1\%), and transient global amnesia in one (1\%). Of the five patients presenting with stroke, one had a lacunar and four had atheroembolic events.

Mean±SEM time from the cardiac diagnosis to onset of the cerebrovascular ischemic event was $4.8±0.9$ years. Increased risk of stroke (Table 1), calculated for the 49 women and 64 men who did not have an initial stroke (6 patients), was significantly ($p<0.05$) associated with female sex, mitral anulus calcification, hypertension, and an atrioventricular
conduction delay of >20 msec. In particular, the
hazard ratio for hypertension was 3.0, meaning that
hypertensive patients were three times as likely to
have a stroke as their nonhypertensive counterparts,
and men had only one third the risk of stroke that
women did. Risk of a cerebrovascular ischemic event
for all patients not presenting with a stroke was not
significantly associated with atrial fibrillation, left
atrial enlargement, increased gradient across the left
ventricular aortic outflow tract, history of smoking,
diabetes (not shown), or hypercholesterolemia. No
patient with ischemic cerebrovascular events had diabetes, and only two had hypercholester-
olemia (not shown).

There were several differences between men and
women with IHSS (Table 3). Age at presentation

had chronic and two had acute-onset atrial fibrillation
at the time of the cerebrovascular event. Hypertension
was more common in the atheroembolic than in the
cardioembolic group (p<0.05). There were no signif-
icant differences among stroke etiology groups in
the incidences of left ventricular outflow obstruction, atrio-
ventricular conduction delay of >20 msec, or history of
smoking. No patient with ischemic cerebrovascular
events had diabetes, and only two had hypercholester-
olemia (not shown).

There were several differences between men and
women with IHSS (Table 3). Age at presentation

TABLE 2. Characteristics of Patients With Cerebrovascular Ischemic Events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AE (n=11)</th>
<th>CE (n=9)</th>
<th>Lacunar (n=2)</th>
<th>AT (n=2)</th>
<th>Other (n=2)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at stroke (mean yr)</td>
<td>68</td>
<td>59</td>
<td>66</td>
<td>70</td>
<td>58</td>
<td>0.146*</td>
</tr>
<tr>
<td>Age at cardiac presentation (mean yr)</td>
<td>66</td>
<td>43</td>
<td>59</td>
<td>64</td>
<td>51</td>
<td>&lt;0.001*</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0.16</td>
<td>0.608</td>
</tr>
<tr>
<td>Women</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0.001</td>
<td>0.011</td>
</tr>
<tr>
<td>Left atrial enlargement</td>
<td>3</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>0.004</td>
<td>0.007</td>
</tr>
<tr>
<td>Mitral anulus calcification</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0.017</td>
<td>0.119</td>
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<tr>
<td>Calcification of aortic/mitral valve</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.617</td>
<td>0.604</td>
</tr>
<tr>
<td>Left ventricular outflow obstruction</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0.608</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0.004</td>
<td>0.007</td>
</tr>
<tr>
<td>Atrioventricular conduction delay</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0.608</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Smoking</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0.001</td>
<td>0.004</td>
</tr>
</tbody>
</table>

AE, atheroembolic; CE, cardioembolic; AT, atherothrombotic; other, transient ischemic attack of undetermined cause (one) and transient global amnesia (one).

*p Probability assessed using two-tailed t test; p<0.025 is required to obtain significance due to multiple comparisons. Two-tailed Fisher's exact test used for other assessments of probability.

TABLE 3. Characteristics of Patients With Idiopathic Hypertrophic Subaortic Stenosis According to Sex

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th>Women</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial cardiac symptom (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SEM yr</td>
<td>n=56</td>
<td>n=46</td>
<td></td>
</tr>
<tr>
<td>40.64±2.14</td>
<td>54.24±2.47</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Left atrial enlargement</td>
<td>50</td>
<td>25</td>
<td>0.002</td>
</tr>
<tr>
<td>Mitral anulus calcification</td>
<td>5</td>
<td>16</td>
<td>0.002</td>
</tr>
<tr>
<td>Calcification of aortic/mitral valve</td>
<td>9</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Left ventricular outflow obstruction</td>
<td>41</td>
<td>26</td>
<td>0.194</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16</td>
<td>6</td>
<td>0.096</td>
</tr>
<tr>
<td>Atrioventricular conduction delay</td>
<td>2</td>
<td>6</td>
<td>0.137</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19</td>
<td>28</td>
<td>0.009</td>
</tr>
<tr>
<td>Smoking</td>
<td>30</td>
<td>17</td>
<td>0.128</td>
</tr>
</tbody>
</table>

*p Probability assessed using two-tailed t test. Two-tailed Fisher's exact test used for other assessments of probability.
with initial cardiac symptoms was available in 102 of the 119 patients; ages in women and men differed significantly \((p<0.001)\). Other parameters were calculated for all 119 patients. Left atrial enlargement \((p<0.01)\) was more common in men; hypertension \((p<0.05)\) and mitral anulus calcification \((p<0.01)\) were more common in women. There were no significant sex differences in the incidences of atrial fibrillation, aortic/mitral valve calcification, left ventricular outflow obstruction, atrophicventricular conduction delay of >20 msec, but not in those with left atrial enlargement, smoking history.

The overall crude stroke rate for patients without an initial stroke was 29.3/1,000 person-years; that for those with IHSS and chronic atrial fibrillation was 312.5/1,000 person-years. Stroke rates were 17.7/1,000 person-years in men and 50.0/1,000 person-years in women. No significant difference in age at time of stroke was found between the sexes. Death was due to cardiovascular causes in four patients and stroke in two patients (one cardioembolic and one atheroembolic). Stroke did not occur in any patient dying of cardiac causes.

**Discussion**

The incidence of stroke in this study (22%) is higher than that in other series.\(^9\) Moreover, the rate for all cerebrovascular ischemic events and the stroke rate for patients with IHSS and chronic atrial fibrillation were greater than those recorded in the Framingham Study\(^26\) for patients of similar ages. Men with IHSS usually become symptomatic earlier than women.\(^6\) In this study, men presented with cardiac symptoms on average 14 years earlier than women. This sex difference in age at presentation occurs in both the familial and sporadic forms of IHSS.\(^7\)

The association between cardioembolic ischemic events and atrial fibrillation may be related to the coexistence of left atrial enlargement. Patients with chronic atrial fibrillation were more likely to have cardioembolic strokes, an association that has been noted in IHSS\(^19\) and other cardiac disorders.\(^12,13\)

Atheroembolic cerebrovascular ischemic events were associated with hypertension but not diabetes, hypercholesterolemia, or a history of smoking. IHSS may be acquired after a prolonged period of hypertension,\(^27\) and this form predominates in elderly women.\(^8,28\) Mitral anulus calcification was as common in both the familial and sporadic forms of IHSS.\(^7\)

The risk of stroke was increased in women and in patients with mitral anulus calcification, hypertension, and an atrophicventricular conduction delay of >20 msec but not in those with left atrial enlargement, atrial fibrillation, left ventricular outflow obstruction, history of smoking, diabetes, or hypercholesterolemia. These differences in risk factors for all patients compared with only those suffering cerebrovascular ischemic events may reflect the relatively small size of the stroke group, the heterogeneous etiology of the cerebrovascular events, and the need to continue follow-up for a longer period. The increased risk of a cerebrovascular event in women may be related to the larger number of atheroembolic and other cerebrovascular ischemic events compared with cardioembolic events and to the larger number of women in these groups.

Most large clinical series\(^24,30\) of IHSS patients did not observe stroke as the initial symptom; however, five patients in our series presented with stroke. Although cardiac disease was a more common cause of death, two patients died of stroke.

In summary, cerebrovascular ischemic events occur more frequently in patients with IHSS than has previously been appreciated. Cardioembolic and atheroembolic events occur in patients with different characteristics, which may in part reflect the heterogeneous etiology of the disease. The high incidence of cardioembolic events in those with atrial fibrillation suggests the need for antiarrhythmic therapy and the use of anticoagulant or platelet antaggregant medication in this group. Hypertension, as the major risk factor for the atheroembolic group, should be carefully controlled. A larger prospective study would delineate more clearly which patients would benefit from prophylactic therapy.

**References**


KEY WORDS • cardiomyopathy, hypertrophic • cerebral ischemia
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