Investigation of a Hemodynamic Basis for Syncope in Hypertrophic Cardiomyopathy
Use of a Head-Up Tilt Test

David M. Gilligan, MB, MRCPI; Petros Nihoyannopoulos, MD; Wan L. Chan, MD; and Celia M. Oakley, MD, FACC

Background. Syncope and sudden death in hypertrophic cardiomyopathy may have a hemodynamic basis. The presence of a small ventricular cavity with high intracavity pressures may activate left ventricular baroreceptors and cause reflex hypotension as described in other populations with syncope.

Methods and Results. To investigate this potential mechanism of syncope in hypertrophic cardiomyopathy, we studied 17 patients with a history of syncope (syncopal), 19 without syncope (nonsyncopal), and nine normal control subjects by using a head-up tilt test. Head-up tilt at 60° for 45 minutes was followed by 10-minute tilts during incremental doses of isoprenaline. Heart rate, blood pressure, and two-dimensional and Doppler echocardiography were monitored throughout. On tilting, hypertrophic cardiomyopathy patients showed a decline in mean arterial pressure of −5±6 mm Hg (p<0.001) compared with no change in control subjects (0.2±6 mm Hg, p=0.9). Left ventricular outflow tract velocity decreased on tilting in control subjects (−8±6 cm/sec, p=0.004) but increased in the syncopal and nonsyncopal patients (20±50 cm/sec, p=0.05). Reflex hypotension with or without bradycardia, associated with syncope or presyncope, was induced in seven syncopal patients, two nonsyncopal patients, and two control subjects (p=0.05). The early response to tilt in these subjects was characterized by maintenance of blood pressure but a greater increase in left ventricular fractional shortening than in the other subjects (19±8% versus 1±1%, p=0.002). The onset of hypotension was associated with a trend toward further decreases in left ventricular diameters, outflow tract velocity, and transmitral flow velocities. In the remaining patients who had a negative test, transient hypotension (systolic pressure <100 mm Hg) occurred in seven syncopal patients and three nonsyncopal patients compared with none of the control subjects (p=0.01). In total, hypotension was demonstrated in 82% of syncopal patients compared with 26% of nonsyncopal patients and 22% of control subjects (p=0.001).

Conclusions. Patients with hypertrophic cardiomyopathy and a history of syncope frequently display hypotension during head-up tilt. In some cases, sudden hypotension occurs and is usually associated with bradycardia and a reduced cavity size, findings compatible with activation of a ventricular baroreflex. In other cases, transient hypotension occurs and could be explained by an impairment of baroreceptor function. These mechanisms may contribute to the occurrence of syncope in daily life. (Circulation 1992;85:2140–2148)

KEY WORDS • upright tilt • baroreceptors • isoprenaline • vasovagal action

Syncope is common in hypertrophic cardiomyopathy and is associated with an increased risk of sudden death.¹ Both events may result from the same mechanism(s). The precise pathophysiological substrate(s) that predispose to and the sequence of events that lead to cardiovascular collapse in hypertrophic cardiomyopathy remain controversial.² Although arrhythmia may be the cause of such episodes,³ a primary hemodynamic mechanism may be responsible on some occasions. This hypothesis is based on the observation of syncope during sinus rhythm,⁴,⁵ the presence of an abnormal blood pressure response to exercise in one third of patients,⁶ and the absence of arrhythmia on Holter monitoring in children,⁷ despite the high risk of sudden death in this group.⁸ Although myocardial ischemia, diastolic dysfunction, or outflow tract obstruction are all potential hemodynamic mechanisms of syncope in hypertrophic cardiomyopathy, it has been proposed that activation of left ventricular baroreceptors could be the cause of exercise hypotension and hemodynamic collapse in this condition.⁹

Activation of left ventricular mechanoreceptors, when left ventricular volume decreases and vigorous contraction continues, is known to produce reflex hypotension and bradycardia in animals and has been suggested to play a role in a number of clinical settings such as acute blood loss, head-up tilt, and aortic stenosis.⁹,¹⁰ We hypothesized that this reflex would be facilitated in hypertrophic cardiomyopathy in which a small hypercontractile left ventricle already exists. The hemodynamic changes resulting from head-up tilt appear to
induce this reflex in a clinical setting, and in recent years, head-up tilt testing has been found to reproduce syncpe in approximately 60% of patients with a history of otherwise unexplained syncpe.11 This response to head-up tilt has been termed “neurally mediated bradycardia/hypotension”12 or “malignant vasovagal syndrome.”13 The administration of isoprenaline during tilt has been reported to increase the rate of syncpe to 80% in these patients, possibly by mimicking the normal rise in catecholamines before syncpe.12 We therefore considered that head-up tilt would be a valuable method of investigating whether patients with hypertrophic cardiomyopathy were vulnerable to a reflex bradycardia/hypotension syndrome. To obtain more detailed information regarding ventricular changes during head-up tilt and the mechanism of tilt-induced syncpe, we performed two-dimensional and Doppler echocardiography during the tests.

Methods

Patients

The diagnosis of hypertrophic cardiomyopathy was based on the presence of typical clinical and electrocardiographic findings in association with a hypertrophied, nondilated left ventricle on two-dimensional echocardiography in the absence of hypertension, valvular disease, or any other systemic cause of hypertrophy. Eighteen patients were selected on the basis of a history of syncpe (defined as a sudden episode of loss of consciousness with spontaneous recovery) within the preceding 5 years. One of these patients declined to proceed to the tilt plus isoprenaline phase of the study and was excluded from analysis. The remaining 17 patients formed the syncopal group. Five patients had only one episode of syncpe, seven patients had two to five episodes, and five patients had more than five episodes. The circumstances of syncpe were at rest or on ordinary effort in nine, on strenuous effort in five, with change of posture in two, and vasovagal (precipitated by fear of injections, etc.) in one. Nineteen age- and sex-matched patients without syncpe in the preceding 5 years were selected to form the nonsyncopal group. Patient exclusion criteria were 1) age <18 or >70 years, 2) overt heart failure, 3) uncontrolled cardiac arrhythmia, 4) severe mitral regurgitation or technically difficult echocardiographic subject for any reason, 5) when withdrawal of medication was considered unacceptable, 6) history of coronary artery disease or myocardial infarction, 7) other major systemic disease. All patients had a complete echocardiographic study and 48-hour Holter monitoring with the methodology and definitions previously described for our institution14 within the 6-month period preceding the current study. The results of these investigations, clinical features, and drug therapy of the patients are shown in Table 1 (these data are also used in describing individual patients in Table 5). All drugs were stopped for at least 5 half-lives before the study except for amiodarone, which was continued in seven patients: four in the syncopal group and three in the nonsyncopal group. Nine age- and sex-matched normal control patients were also studied: five men and four women with a mean age of 45±10 years and a range of 33 to 63 years. Normal subjects had no history of cardiovascular disease or syncpe and normal physical examination, electrocardiogram, and echocardiography.

Study Protocol

The study was approved by the research ethics committee of the Royal Postgraduate Medical School and Hammersmith and Queen Charlotte’s Special Health Authority in 1989. All subjects gave written informed consent. Subjects fasted after their usual breakfast on the day of study. In the afternoon, subjects came to the tilt table laboratory. During studies, a constant ambient temperature was maintained in the laboratory; the lighting was dimmed and the room was quiet.

Head-Up Tilt Protocol

An electrically operated tilt table was used. Restraining belts were placed at waist and knee levels. After 30 minutes of supine rest, subjects were tilted head-up at an angle of 30° to the horizontal for 2 minutes and then tilted to 60° for a further 45 minutes.13 A positive test was defined as the occurrence of a progressive fall in blood pressure to <90 mm Hg systolic associated with impairment of consciousness with or without bradycardia. If this occurred, the subject was immediately returned to the supine position, and the test was terminated. If the test was negative after 45 minutes, the subject was returned to the supine position and rested for 15 minutes. Baseline measurements were repeated. An 18-gauge butterfly needle was inserted into an arm vein and an intravenous infusion of isoprenaline was begun at 1 μg/min. The subject remained supine for 5 minutes, at which time hemodynamic and echocardiographic measurements were repeated. The subject was tilted again, to 30° for 30 seconds and to 60° for 10 minutes. If negative, two further 10-minute tilts were performed at isoprenaline infusions of 2 and 4 μg/min with 5-minute periods of supine rest between each tilt.12 Indications for termination of the test during the tilt plus isoprenaline phase were 1) a positive test as described above, 2) heart rate of >150 beats per minute, 3) frequent or complex ventricular extrasystoles, 4) chest pain or other discomfort, 5) when a heart rate >120 beats per minute was achieved during a stage, that stage was completed, but the subject did not proceed to the next isoprenaline dose.

Hemodynamic Measurements

A single-lead electrocardiogram (lead I or lead II) was monitored continuously during the test. Blood pressure was measured by an automatic oscillometric device (Critikon Dinamap TM Vital Signs Monitor 1846). Heart rate and systolic, diastolic, and mean blood pressures were recorded on three occasions 5 minutes apart at supine rest every minute for the first 7 minutes of tilt and every second minute thereafter or more frequently when symptoms occurred. During isoprenaline infusion, supine hemodynamics were measured before and 5 minutes after each isoprenaline dose and every minute during the 10-minute tilts.

Two-Dimensional Echocardiography and Doppler

All echocardiographic studies were performed by one experienced operator. A General Electric Pass C echocardiography machine was used for all studies with a
3.3-MHz phased-array probe. Left ventricular end-systolic and end-diastolic dimensions were measured from the parasternal long-axis view at the level of the mitral leaflet tips. This was found to be the optimum view for assessing dimensions during tilt, and dimensions could be reliably obtained at the same level during tilt. Fractional shortening was derived. Pulsed Doppler recordings of transmural flow velocities were obtained from the apical four-chamber view with the sample volume positioned just proximal to the mitral leaflet tips. The maximum early flow velocity (E) and the maximum late flow velocity (A) were measured, and the E/A ratio was derived. From the apical five-chamber view, the sample volume was placed immediately under the aortic valve. When turbulent flow with high velocity was present, continuous-wave Doppler was used to measure velocity. In either case, the optimum signal was obtained, and the outflow tract velocity was taken as the maximum value measured. All two-dimensional and Doppler measurements were made at supine rest, at 5 minutes of 60° tilt, and every 10 minutes thereafter. When there was a hemodynamic change or the patient developed symptoms, the measurements were repeated in the following order of priority: ventricular diameters, outflow tract velocity, and transmural inflow velocities.

Statistical Analysis

Data were tested for normality of distribution using Shapiro and Francia's W2 test. All data were normally distributed and analyzed using the two-tailed Student's t test for paired and unpaired data as appropriate. Proportions were compared using the Fisher exact test. The relation between blood pressure change and the degree of hypertrophy was assessed by linear regression analysis. All group data are expressed as mean±SD. Error bars on the figures represent 1 SEM. A probability value of 0.05 or less was considered statistically significant.

Results

Initial Hemodynamic Response to Head-Up Tilt

The initial hemodynamic response to 30° tilt and 60° tilt of all hypertrophic cardiomyopathy patients was compared with that of control subjects (Table 2). There were no significant changes in heart rate or blood pressure in normal subjects at 30° tilt for 2 minutes. However, in patients with hypertrophic cardiomyopathy, systolic blood pressure fell by −5±8 mm Hg at 30° tilt (p=0.04). After 5 minutes of 60° tilt, hypertrophic cardiomyopathy patients and control subjects showed similar increases in heart rate. However, hypertrophic cardiomyopathy patients had falls in systolic, diastolic, and mean arterial pressures (Figure 1) in contrast to normal subjects who maintained blood pressure unchanged. These differences persisted when the seven patients receiving amiodarone were excluded from the analysis. There was no correlation between the fall in

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Syncope patients</th>
<th>Nonsyncope patients</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>7</td>
<td>9</td>
<td>16 (44%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50±13</td>
<td>46±14</td>
<td>48±14</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>26–70</td>
<td>18–68</td>
<td>18–70</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>7±8</td>
<td>8±8</td>
<td>7±8</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>I 6</td>
<td>II 6</td>
<td>II 5</td>
</tr>
<tr>
<td></td>
<td>II 6</td>
<td>II 10</td>
<td>II 16 (44%)</td>
</tr>
<tr>
<td></td>
<td>III 5</td>
<td>III 4</td>
<td>III 9 (25%)</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pattern of hypertrophy</td>
<td>ASH 15</td>
<td>Concentric 2</td>
<td>32 (89%)</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>20±6</td>
<td>20±6</td>
<td>20±6</td>
</tr>
<tr>
<td>PW (mm)</td>
<td>13±2</td>
<td>13±3</td>
<td>13±3</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>38±8</td>
<td>43±11</td>
<td>41±10</td>
</tr>
<tr>
<td>LVOT gradient &gt;30 mm Hg</td>
<td>8</td>
<td>7</td>
<td>15 (42%)</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; ASH, asymmetric septal hypertrophy; IVS, intraventricular septum; PW, posterior wall; LA, left atrium; LVOT, left ventricular outflow tract.

TABLE 1. Details of 36 Hypertrophic Cardiomyopathy Patients Studied
TABLE 2. Hemodynamic Response to Tilt Alone and Tilt Plus Isoprenaline

<table>
<thead>
<tr>
<th></th>
<th>Heart rate</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>Mean BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC</td>
<td>Control</td>
<td>HC</td>
<td>Control</td>
</tr>
<tr>
<td><strong>Tilt alone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine 60°</td>
<td>69±13</td>
<td>73±11</td>
<td>130±20</td>
<td>137±13</td>
</tr>
<tr>
<td>2 Minutes at 30°</td>
<td>70±13</td>
<td>74±10</td>
<td>126±21*</td>
<td>136±16</td>
</tr>
<tr>
<td>5 Minutes at 60°</td>
<td>76±13*</td>
<td>79±13</td>
<td>122±16*</td>
<td>133±13</td>
</tr>
<tr>
<td><strong>Tilt plus isoprenaline‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine before isoprenaline</td>
<td>72±16</td>
<td>67±11</td>
<td>130±19</td>
<td>130±11</td>
</tr>
<tr>
<td>Supine 5 minutes after isoprenaline</td>
<td>97±15*</td>
<td>90±8*</td>
<td>129±21</td>
<td>131±21</td>
</tr>
<tr>
<td>10 Minutes at 60°</td>
<td>115±19*</td>
<td>112±8*</td>
<td>121±15</td>
<td>134±14</td>
</tr>
</tbody>
</table>

BP, blood pressure; HC, hypertrophic cardiomyopathy group.

*p<0.05 compared with supine value.

†p<0.05 patients compared with control.

‡Results for highest dose of isoprenaline achieved in each subject.

mean arterial pressure on tilting and intraventricular septal thickness (p=0.4) or posterior wall thickness (p=0.9). There were no significant differences in the initial hemodynamic responses to head-up tilt between syncopal and nonsyncopal patient groups.

Echocardiographic Changes During Head-Up Tilt

At supine rest, left ventricular end-diastolic diameter was similar in hypertrophic cardiomyopathy patients and control subjects, but left ventricular end-systolic diameter was smaller, and thus, fractional shortening was greater in hypertrophic cardiomyopathy. (See Table 3.) On tilting, there were similar decreases averaging 3 mm in each diameter in both groups (Figure 2) with no significant change in fractional shortening. The left ventricular outflow tract velocity was higher in hypertrophic cardiomyopathy patients than in control subjects in the supine position. On tilting, the mean outflow tract velocity decreased in control subjects but increased in the hypertrophic cardiomyopathy patients (Figure 3). The average transmural flow velocities were similar in both groups at supine rest. On tilting, the E wave decreased by approximately 25% in hypertrophic cardiomyopathy patients and control subjects. In control subjects, the A wave tended to decrease (−7±1 cm/sec, p=0.09), but the A wave did not change in hypertrophic cardiomyopathy patients on tilting (−3±15 cm/sec, p=0.95). These echocardiographic and Doppler changes, apparent at 5 minutes of tilt, remained unchanged throughout the 45-minute tilt in the majority of subjects. There were no significant differences in two-dimensional or Doppler measurements at rest or during tilt between the syncopal and nonsyncopal patient groups.

Hypotension During 45-Minute Head-Up Tilt

A positive test with syncope or presyncope occurred in seven subjects: four syncopal, two nonsyncopal, and one normal subject (p=0.3). The clinical features of these subjects are shown in Table 5. In these subjects, systolic blood pressure was maintained in the early part of tilt (124±13 mm Hg supine versus 121±16 mm Hg at 5 minutes of tilt, p=0.6) and subsequently fell abruptly and progressively to 81±9 mm Hg (p=0.002). The concomitant heart rate changes are shown in Figure 4. Case 1 developed bradycardia and prolonged asystole at 5 minutes of tilt. Cases 2, 3, 5, and 6 had a variable fall in heart rate before return to the supine position, whereas heart rate increased in cases 5 and 8. In all cases, bradycardia, occurred in the first minute on return to the supine position and often persisted for a number of minutes, even though blood pressure recovered rapidly. Case 8 was atypical in that she developed chest pain and presyncope associated with tachycardia, progressive hypotension, and increased end-systolic diameter, which suggested that myocardial ischemia had occurred. In this case, bradycardia occurred on return to supine position, and hypotension with tachycardia progressing to bradycardia (without chest pain) was induced on a repeat test. In subjects with a positive test (compared with subjects who had a negative test), the early response to tilt was characterized by a greater fall in left ventricular end-systolic diameter (−5±6 mm versus −2±3 mm, p=0.02) and a greater increase in

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Blood pressure changes at 2 minutes of 30° tilt and 5 minutes of 60° tilt. In both patient groups, systolic pressure fell at 30° (p<0.05) and systolic and diastolic pressures fell at 60° (p<0.01) compared with no significant change in control subjects.
Fractional shortening (10±8% versus 1±1%, respectively, p=0.002). In these positive cases, the onset of hypotension was associated with a trend toward further decreases in left ventricular diameters (Figure 2), a decrease in outflow tract velocity (Figure 3), and a decrease in transmval flow velocities; however, transmval flow velocities were obtained only in three subjects at the time of hypotension. Thirteen syncopal, 17 nonsyncopal, and eight control subjects had a negative 45-minute head-up tilt test. In these subjects, transient hypotension (systolic pressure <100 mm Hg) occurred on one or more occasions in six syncopal patients and three nonsyncopal patients but in none of the control subjects (p=0.11). These episodes were symptomatic in four of the nine cases. However, the blood pressure fall was nonprogressive, bradycardia did not occur, and symptoms were transient; therefore, the tilt test was continued.

### Head-Up Tilt Plus Isoprenaline

All patients with a negative 45-minute tilt proceeded to 10-minute tilts with increasing doses of isoprenaline. For simplicity, only the values obtained at the highest dose of isoprenaline are shown in each case (Table 2). The increase in heart rate induced by isoprenaline was similar in hypertrophic cardiomyopathy patients and control subjects. In both groups, isoprenaline caused an average decrease of 4 mm Hg in mean arterial blood pressure in the supine position. Tilt plus isoprenaline caused changes in hemodynamic and echocardiographic parameters similar to those with head-up tilt alone (Table 3). These hemodynamic, two-dimensional, and Doppler echocardiographic changes were similar in the syncopal and nonsyncopal patient groups. The end points of tilt plus isoprenaline were as follows: Six subjects completed the full protocol, 18 achieved a heart rate of ≥120 beats per minute and did not proceed to a higher dose of isoprenaline, the test was stopped during an isoprenaline stage because of a positive result in four (see below), a heart rate of ≥150 beats per minute in two, chest pain in two, palpitation in two, and frequent ventricular extrasystoles in two. These end points were evenly distributed among the three groups.

#### Hypotension During Tilt Plus Isoprenaline

Three syncopal patients and one normal subject had a positive response to tilt with isoprenaline. In the three patients, hypotension occurred with continuing tachycardia, whereas in the normal subject, hypotension was associated with a sudden decrease in heart rate from 110 to 90 beats per minute. Echocardiographic measurements showed that these episodes were associated with reductions in end-diastolic and end-systolic diameters. In two patients, left ventricular outflow tract velocities were measurable at the time of hypotension and markedly elevated in contrast to the positive cases during tilt alone (Figure 5). Transient hypotension occurred in one additional syncopal patient who was normotensive during tilt alone.

#### Complete Tilt Test

A positive tilt test was more frequent in syncopal patients (seven of 17, 41%) compared with nonsyncopal patients (two of 19, 11%, p=0.05) but not compared with normal subjects (two of nine, 22%, p=0.38). Transient hypotension was observed only in patients with hypertrophic cardiomyopathy and was more common in syncopal patients (seven of 10, 70%) compared with...
nonsyncopal patients (three of 17, 18%, \( p=0.01 \)). The total prevalence of hypotension, i.e., positive cases and transient hypotension, was much higher in syncopal patients (14 of 17, 83%) compared with both nonsyncopal patients (five of 19, 26%) and control subjects (two of nine, 22%, \( p=0.001 \)).

Reproducibility of a Positive Tilt Test

Of the nine hypertrophic cardiomyopathy patients with a positive test, eight underwent a repeat test on a second occasion. Of five patients with an initial positive response to tilt alone, this was reproducible in four with tilt alone and in the fifth with tilt plus isoprenaline (Table 5). In case 1, a positive response with profound bradycardia was reproducible and could be prevented by pretreatment with 2 mg atropine orally 45 minutes before tilt. A positive test with tilt plus isoprenaline was reproducible only in one of three cases.

**Discussion**

**Hemodynamic Response to Head-Up Tilt**

The major hemodynamic consequence of head-up tilt is venous pooling in the lower limbs and a reduction in central blood volume.\(^15\) These changes are sensed by high- and low-pressure baroreceptors that initiate compensatory reflexes.\(^16,17\) Low-pressure cardiopulmonary baroreceptors are sensitive to slight falls in preload such as occur with 30° tilt and cause a compensatory rise in peripheral vascular tone.\(^17\) High-pressure baroreceptors in the carotid sinuses and aortic arch are activated when preload change is sufficient to affect systemic arterial pressure such as occurs with 60° tilt, and these receptors mediate increases in heart rate in addition to vascular tone.\(^17\) Therefore, the early responses to 30° and 60° tilts were examined in detail in this study. At 30° tilt in normal subjects, there was no significant change in heart rate or blood pressure, although diastolic pressure tended to increase. This observation supports the assertion that only low-pressure receptors are stimulated at this degree of tilt.\(^18\) In contrast, hypertrophic cardiomyopathy patients had a fall in systolic blood pressure at 30°, suggesting an impairment of cardiopulmonary baroreceptors. At 60° tilt in normal control subjects, the baroreceptor mechanism again acted appropriately to maintain mean arterial pressure.\(^18\) However, in hypertrophic cardiomyopathy patients, arterial pressure fell, and there was not a correspondingly greater rise in heart rate. This response is abnormal, as even patients after heart-lung transplantation, who lack cardiopulmonary afferents, maintain mean arterial pressure at 60° tilt.\(^19\) Therefore, our findings can be interpreted as indicating impairment of overall baroreceptor function in patients with hypertrophic cardiomyopathy. Further, more sensitive tests of baroreceptor function are necessary to confirm this hypothesis.

The initial fall in blood pressure was insufficient to produce symptoms, but as tilt was maintained, several patients had transient hypotension (sometimes symptomatic) without an appropriate increase in heart rate.
The impairment of cardiopulmonary baroreceptors may be reversed by the regression of hypertensive left ventricular hypertrophy, suggesting that the impairment is due to the local effects of hypertrophy on cardiac baroreceptors; clearly, this could be the case in hypertrophic cardiomyopathy. The apparent impairment of baroreceptor function demonstrated by our patients may explain why the incidence of a hypotension/bradycardia reflex on tilting was relatively low despite the presence of a small cavity with vigorous systolic function in hypertrophic cardiomyopathy, the ideal substrate to elicit this reflex. It is of interest that the patients who did have a positive test initially maintained blood pressure with upright tilt, suggesting that their baroreceptor function was intact. These findings would agree with the hypothesis that a hypotension/bradycardia reflex may be due to a highly sensitive or exaggerated left ventricular baroreceptor reflex.10

Syncope During Head-Up Tilt

Studies in patients with a history of recurrent syncope but without evidence of structural cardiac disease or electrophysiological abnormality have found that a head-up tilt test may reproduce symptoms in 60–80% of cases. In our patients with hypertrophic cardiomyopathy, the tilt test protocol that we used reproduced syncope/presyncope in 41% of patients with a history of syncope significantly more often than in nonsyncopal patients (11%, p = 0.05). However, there was a significant false-positive rate (two of 19 nonsyncopal patients and two of nine normal subjects) in our study, and this is comparable to the false-positive rate reported in other studies. It is likely that the vasodepressor reflex mediating a positive tilt test is present in all individuals and that a positive tilt test usually occurs in the context of an exaggerated reflex or an abnormal hemodynamic response to tilt. Despite these limitations, there is increasing evidence that a head-up tilt test can be used to reproduce typical symptoms and test prophylactic therapy in selected patients with syncope.

This phenomenon occurred more frequently in syncopal (70%) than in nonsyncopal patients (18%) and was not observed in normal subjects. The episodes were mild, transient, and not associated with heart rate or echocardiographic changes and were therefore not typical of a vasodepressor reflex (see below). They are more likely explained on the basis of baroreceptor impairment. Such an impairment of baroreceptor function could be a factor in the occurrence of syncope in hypertrophic cardiomyopathy, as these patients when subjected to a hemodynamic stress, e.g., tachyarrhythmia, may be less able to maintain blood pressure and therefore more likely to develop syncope.

An impairment of baroreceptor function has been documented in patients with congestive heart failure, hypertension associated with hypertrophy, and athletes with hypertrophy. This impairment may reflect either inherent disease of the actual peripheral receptors or resetting of baroreceptor control caused by hemodynamic impairment. It has been reported that

### Table 5. Clinical Features of 11 Subjects With Positive Head-Up Tilt Test

<table>
<thead>
<tr>
<th>Case</th>
<th>Study group</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Number of episodes</th>
<th>Circumstances</th>
<th>Type of LVH, IVS/mm</th>
<th>LVOTG (mm Hg)</th>
<th>VT on Holter</th>
<th>Time to positive result*</th>
<th>Repeat test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HC syncopal</td>
<td>45</td>
<td>M</td>
<td>&gt;10</td>
<td>Vasovagal</td>
<td>ASH/16 &lt;30</td>
<td>-</td>
<td>2 Minutes</td>
<td>Positive at 7 minutes</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>HC nonsyncopal</td>
<td>41</td>
<td>M</td>
<td>0</td>
<td>-</td>
<td>ASH/18 &lt;30</td>
<td>-</td>
<td>9 Minutes</td>
<td>Positive at 9 minutes</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>HC syncopal</td>
<td>57</td>
<td>F</td>
<td>1</td>
<td>Walking</td>
<td>CONC/14 &lt;30</td>
<td>+</td>
<td>11 Minutes</td>
<td>Positive at 4 µg</td>
<td>isoprenaline</td>
</tr>
<tr>
<td>4</td>
<td>HC nonsyncopal</td>
<td>24</td>
<td>M</td>
<td>0</td>
<td>-</td>
<td>ASH/27 36</td>
<td>-</td>
<td>16 Minutes</td>
<td>Positive at 20 minutes</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Control</td>
<td>33</td>
<td>M</td>
<td>0</td>
<td>-</td>
<td>ASH/27 36</td>
<td>-</td>
<td>17 Minutes</td>
<td>Not done</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>HC syncopal</td>
<td>32</td>
<td>F</td>
<td>3</td>
<td>Change of posture</td>
<td>ASH/20 72</td>
<td>-</td>
<td>35 Minutes</td>
<td>Not done</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>HC syncopal</td>
<td>52</td>
<td>F</td>
<td>3</td>
<td>Standing</td>
<td>ASH/26 &lt;30</td>
<td>+</td>
<td>39 Minutes</td>
<td>Positive at 45 minutes</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>HC syncopal</td>
<td>70</td>
<td>F</td>
<td>&gt;20</td>
<td>Ordinary effort</td>
<td>ASH/16 36</td>
<td>+</td>
<td>2 µg/min</td>
<td>Positive at 1 µg</td>
<td>isoprenaline</td>
</tr>
<tr>
<td>9</td>
<td>HC syncopal</td>
<td>57</td>
<td>F</td>
<td>2</td>
<td>Standing</td>
<td>ASH/18 &lt;30</td>
<td>-</td>
<td>2 µg/min</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>HC syncopal</td>
<td>47</td>
<td>F</td>
<td>7</td>
<td>Strenuous effort</td>
<td>ASH/23 &lt;30</td>
<td>+</td>
<td>4 µg/min</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Control</td>
<td>50</td>
<td>M</td>
<td>0</td>
<td>-</td>
<td>ASH/26 &lt;30</td>
<td>-</td>
<td>4 µg/min</td>
<td>Not done</td>
<td></td>
</tr>
</tbody>
</table>

IVS, intraventricular septum; LVH, left ventricular hypertrophy; LVOTG, left ventricular outflow tract pressure gradient; VT, ventricular tachycardia; HC, hypertrophic cardiomyopathy; M, male; F, female; ASH, asymmetric septal hypertrophy; CONC, concentric.

*Duration of 45-minute tilt or dose of isoprenaline at which a positive response occurred.
cope. In this study, we believe that the occurrence of a positive tilt test (approximately four times more frequently in syncopal compared with nonsyncopal patients) provides a new insight into the potential mechanisms of syncope in hypertrophic cardiomyopathy.

Syncope in hypertrophic cardiomyopathy is almost certainly due to different mechanisms in different patients. Thus, tachyarrhythmia, bradyarrhythmia, myocardial ischemia, outflow tract obstruction, and diastolic dysfunction may each be the primary cause of syncope, and there may be more than one mechanism of syncope in an individual patient. Our study suggests that in some patients with hypertrophic cardiomyopathy, reflex hypotension with or without bradycardia inducible by head-up tilt is an additional cause of syncope. In a clinical setting, we suggest that a head-up tilt test may be of value when used selectively in patients with hypertrophic cardiomyopathy and syncope, according to the history and other clinical features. Inclusion of a head-up tilt test in the workup of a patient with syncope associated with vasovagal circumstances (typified by case 1) or syncope unrelated to strenuous effort (only one of five cases positive) may be worthwhile. Further studies are necessary to determine whether patients with tilt-induced syncope have a better prognosis than those with negative tests whose syncope may have a more serious arrhythmic basis. Studies in young patients with hypertrophic cardiomyopathy are also needed, because a left ventricular baroreceptor reflex may be relatively preserved or more powerful at a younger age.

**Mechanism of a Positive Tilt Test Response**

In this study, we had an opportunity to examine the events occurring at the ventricular level before and at the onset of tilt-induced syncope. We found that subjects who went on to develop syncope initially responded to 60° tilt with a greater fall in left ventricular end-systolic diameter and a greater increase in fractional shortening than subjects with negative tests. This observation would support the view that reflex hypotension/bradycardia during head-up tilt results from excessive stimulation of ventricular baroreceptors by vigorous contraction on a small end-systolic cavity. Frenneaux et al have also proposed activation of ventricular baroreceptors to explain their findings of exercise hypotension and excessive peripheral vasodilation in hypertrophic cardiomyopathy. Our study provides further and more direct evidence for operation of a ventricular baroreceptor reflex in hypertrophic cardiomyopathy by documenting sudden, progressive, symptomatic hypotension, variable bradycardia, and decreasing cavity size—features typical of this reflex.

The usual pattern of a positive response to tilt in our study was similar to that previously described, namely, initial tachycardia and mild hypotension progressing rapidly to profound hypotension with or without bradycardia. We observed that the development of hypotension was associated with a further decrease in ventricular diameters, and where filling patterns were measured, these also decreased. Importantly, patients with hypertrophic cardiomyopathy had a fall in left ventricular outflow tract velocities at the onset of hypotension. Therefore, outflow tract obstruction was not the cause of these episodes; rather, a reduction in filling pressures, cavity dimensions, and a secondary reduction in cardiac output appeared to occur. The mechanism whereby isoprenaline and tilt induced a positive test in patients with hypertrophic cardiomyopathy may be different from tilt alone. Episodes of hypotension during isoprenaline were associated with continuing tachycardia and high outflow tract gradients. These observations suggest that isoprenaline may have caused syncope in these patients by inducing outflow tract obstruction or direct vasodilation rather than initiation of a left ventricular baroreceptor reflex. In Cases 8 and 9, β-blockers had been withdrawn acutely before the study; therefore, adrenergic hypersensitivity may have been a factor in the response to isoprenaline.

**Decrease in Ventricular Filling With Head-Up Tilt**

We observed a decrease in the early transmural flow velocity on tilting in hypertrophic cardiomyopathy patients and control subjects that would be expected to accompany a fall in filling pressure. In normal subjects, the A wave also tended to decrease at 60° tilt, and this effect has been reported in other normal populations. In hypertrophic cardiomyopathy patients, however, the A wave did not change on tilting, and the relative contribution of the atrial component to filling increased. This may reflect an increased dependence on atrial filling in these patients or higher left ventricular filling pressures at supine rest that have “normalized” an abnormal filling profile.

Consequent upon decreased filling pressure and transmural flow velocities, the reduction in ventricular dimensions on tilting were to be expected and were similar in both hypertrophic cardiomyopathy patients and normal subjects. However, the behavior of the left ventricular outflow tract velocity was significantly different between the two groups. In normal subjects, left ventricular outflow tract velocity declined, which is compatible with a reduced stroke volume. In hypertrophic cardiomyopathy patients, the outflow tract velocity increased, presumably secondary to the reduced left ventricular cavity and outflow tract size in the upright position. In some patients, the increase in
outflow tract pressure gradient on moving from the supine to 60° tilt position was substantial (Figure 3).

Conclusions

The hemodynamic response of patients with hypertrophic cardiomyopathy to head-up tilt as characterized by noninvasive methods differs from normal subjects in a number of respects. Most importantly, patients with a history of syncope frequently display hypotension, suggesting that head-up tilt may yield information about the mechanisms of syncope. The data suggest that, in some patients, hypotension is due to activation of a ventricular baroreflex, whereas in others, impairment of baroreceptor function may be responsible.

References

Investigation of a hemodynamic basis for syncope in hypertrophic cardiomyopathy. Use of a head-up tilt test.
D M Gilligan, P Nihoyannopoulos, W L Chan and C M Oakley

Circulation. 1992;85:2140-2148
doi: 10.1161/01.CIR.85.6.2140

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/85/6/2140