The Science of Uncertainty and the Art of Probability
Syncope and Its Consequences in Hypertrophic Cardiomyopathy

Perry Elliott, MD; William McKenna, MD

Medicine is a science of uncertainty and an art of probability.
—William Osler (1849–1919)

In this edition of Circulation, Spirito and coworkers present a retrospective study of a large cohort of patients with hypertrophic cardiomyopathy in which they compare the prognostic significance of neurally mediated (vasovagal) faints and unexplained syncope. Although neither symptom was significantly associated with sudden-death risk, subgroup analysis revealed that unexplained syncope was associated with a higher mortality in patients who had experienced their symptom within 6 months of their initial evaluation and in those aged <18 years. The authors conclude that recent unexplained syncope in all age groups “may justify consideration for prophylactic implantation of a cardioverter-defibrillator.” The challenge for clinicians is the translation of this message into everyday clinical management.

Table 1. Causes of Syncope in Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Arhythmia</th>
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<tr>
<td>Paroxysmal atrial fibrillation/supraventricular tachycardia</td>
</tr>
<tr>
<td>Complete heart block/sinus node dysfunction</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
</tr>
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</table>

Primary hemodynamic mechanism

| Left ventricular outflow tract obstruction |
| Abnormal vascular control mechanisms leading to episodes of hypotension due to inappropriate vasodilatation |
| Hypotension due to impaired filling when preload is reduced in the setting of diastolic dysfunction |

Data from Williams and Frenneaux.

The first and most important step is a careful history. For example, syncope that occurs after prolonged standing in a hot crowded environment or during the postprandial absorptive state or that is associated with nausea and vomiting is suggestive of neurally mediated (reflex) syncope. In contrast, syncope during exertion or preceded by palpitation or chest pain is more suggestive of a cardiac origin. Physical examination is also important to exclude postural changes in blood pressure and signs suggestive of provokable left ventricular outflow tract obstruction.

All patients with suspected cardiac syncope should undergo noninvasive investigations. Twelve-lead electrocardiography and prolonged ambulatory ECG monitoring may show various degrees of atrioventricular block or sinus node dysfunction that suggest a bradyarrhythmic mechanism. Sustained ventricular tachycardia can occasionally precipitate syncope, but documented sustained ventricular arrhythmias are remarkably uncommon. In contrast, atrial arrhythmias such as atrial fibrillation are very frequent, and although they typically present with palpitations, dyspnea, and reduced exercise tolerance, they can occasionally precipitate syncope, particularly in individuals with preserved atrial function and high filling pressures. In patients with recurrent episodes of syncope, implantation of a loop recorder can help to confirm or refute a cardiovascular mechanism.

Left ventricular outflow tract obstruction caused by systolic anterior motion of the mitral valve leaflets may be the most common cause of effort syncope in patients with hypertrophic cardiomyopathy. Outflow obstruction can be detected on 2-dimensional and Doppler echocardiography under resting conditions in ~25% of patients and in another 20% to 30% is present during maneuvers that alter ventricular loading conditions or increase myocardial contractility. Provokable obstruction should always be suspected when patients experience recurrent effort syncope in the same or similar circumstances—for example, when hurrying upstairs or when straining—and should be excluded by performing echocardiography during upright exercise testing.

The role of exercise testing in the assessment of patients with syncope is mainly to detect poor augmentation of systolic blood pressure during exercise. In some individuals, this phenomenon is caused by an inability to increase cardiac output because of chronotropic incompetence, diastolic dysfunction, left ventricular outflow tract obstruction, or myocardial ischemia. In other patients, the dominant mechanism is an exaggerated fall in systemic vascular resistance. The mechanism for this latter phenomenon remains speculative, but abnormal blood pressure responses during exercise are strongly associated with inappropriate vasodilatation or a failure of vasoconstriction in nonexercising vascular beds.
Table 2. Major and Possible Risk Factors for Sudden Death in Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>“Conventional”</th>
<th>“Possible” in Individual Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior cardiac arrest</td>
<td>Left ventricular outflow tract obstruction</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>Extreme late gadolinium enhancement on magnetic resonance imaging</td>
</tr>
<tr>
<td>Family history of premature sudden cardiac death</td>
<td>Myocardial ischemia</td>
</tr>
<tr>
<td>Left ventricular wall thickness ≥30 mm</td>
<td>Specific mutations (eg, Troponin T and I)</td>
</tr>
<tr>
<td>Abnormal blood pressure response to exercise</td>
<td>Intense physical exertion (in individual patients)</td>
</tr>
<tr>
<td>Nonsustained spontaneous ventricular tachycardia</td>
<td>Atrial fibrillation</td>
</tr>
</tbody>
</table>

Data from Zipes et al.14

Most data point to abnormal left ventricular mechanoreceptor behavior as the underlying mechanism, perhaps caused by inhomogeneous myocardial strain associated with myocyte disarray and fibrosis. The recent demonstration of recurrent abrupt spontaneous episodes of hypotension during daily activities associated with a fall in systemic vascular resistance suggests that abnormal vascular control mechanisms may also explain some episodes of non–exercise-related syncope.15

Data on tilt testing in patients with hypertrophic cardiomyopathy and syncope are relatively scant. In a small study, head-up tilt at 60° for 45 minutes resulted in a fall in mean arterial pressure and reflex hypotension in 82% of syncopal patients compared with 26% of nonsyncopal patients and 22% of control subjects.12 In some cases, hypotension was sudden and associated with bradycardia and a reduced cavity size, compatible with activation of a ventricular baroreflex. In a more recent study, significant hypotension or syncope during orthostatic stress in patients with a history of syncope was associated with an early decrease in cardiac output that occurred before the onset of symptoms and was felt to be secondary to diastolic dysfunction.13 Whatever the mechanism, the high rate of positive tests in patients without a history of syncope indicates that tilt testing is not useful in routine assessment.

Syncope and Sudden Cardiac Death

The fact that sudden cardiac death can occur without warning in young and often mildly symptomatic people provides a powerful argument to preemptively identify individuals who are at high risk. The current approach to risk prediction (recommended in American College of Cardiology/American Heart Association/European Society of Cardiology guidelines) is based on a simple model that uses a small number of clinical surrogates of disease severity to identify individuals with a relatively high probability of sudden cardiac death (Table 2).14 The highest risk is seen in patients who have survived an episode of sustained tachycardia or ventricular fibrillation.15 Patients with no history of aborted sudden death and multiple risk markers have an annual sudden-death risk of ≈3%; the presence of any single risk factor alone is associated with an annual risk of ≈1%.16

Many studies have examined the relation between syncope and outcomes. Although the findings vary, the relative risk of sudden cardiac death for syncope alone is on average 2 fold.17 However, the fact that most patients who experience a syncopal episode do not die suddenly emphasizes the need for individualized risk assessment. If a treatable mechanism for the syncopal episode is identified, it should, if possible, be remedied. For example, if an atrial arrhythmia or bradycardia is the cause, drug therapy, ablation, or a pacemaker may be appropriate. Similarly, patients with syncope caused by moderate to severe left ventricular outflow tract obstruction should receive pharmacological therapy followed, if symptoms persist, by invasive strategies to reduce the outflow gradient. In the minority of patients in whom abnormal vascular responses are the major mechanism, options are more limited. We have recently demonstrated in a randomized double-blind placebo-controlled study that exercise blood pressure responses can be attenuated or normalized by propanolol, clonidine, and paroxetine.18 Whether these drugs reduce the number or the severity of hypotensive episodes or improve prognosis in patients with syncope remains to be determined.

In our view, implantable cardioverter-defibrillators should be reserved for patients in whom a treatable (or avoidable) cause of syncope cannot be elucidated after extensive clinical evaluation. The decision to implant a cardioverter-defibrillator should take into account the age of the patient and the presence of other clinical risk factors. It is also important to consider the risks of intervention, ensuring that patients have sufficient time and access to appropriate resources in order to make informed decisions.

Disclosures

None.

References


**KEY WORDS:** Editorials ■ cardiomyopathy, hypertrophic ■ syncope ■ sudden death
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