Hypertrophic cardiomyopathy (HCM) is an inherited disease with marked phenotypic variability that includes the extent of hypertrophy, the presence and severity of symptoms, and the natural history of the disease. Symptoms of impaired consciousness (syncope and pre-syncope) occur in approximately 15–25% of the patients with HCM. In young patients, a history of recurrent syncope is associated with an increased risk of sudden death. Detailed investigations identify a probable mechanism in a minority of these, usually paroxysmal atrial fibrillation or ventricular tachycardia. In the majority, however, no likely mechanism is found despite extensive investigation. Although this may be the case, it is still of vital importance to exclude potentially treatable causes of syncope.

**Introduction**

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**Principal causes of syncope in hypertrophic cardiomyopathy**

The principal causes of syncope in patients with HCM can be broadly divided into two underlying mechanisms: arrhythmia and a primary haemodynamic mechanism (Table 1).

**Arrhythmias**

Syncope in HCM may be related to atrial or ventricular tachyarrhythmias or bradyarrhythmias, heart block, or sinus node dysfunction.

**Supraventricular arrhythmias**

Atrial fibrillation is the most common sustained arrhythmia in HCM. Clinical cohort studies show that AF is reasonably well tolerated by about one-third of patients and is not an independent predictor of sudden cardiac death (SCD). However, paroxysmal episodes of AF may be responsible for acute clinical deterioration, resulting in syncope or heart failure that resulted from reduced diastolic filling and cardiac output—as a consequence of increased ventricular rate and loss of atrial contraction (and its contribution to atrial filling) in an already hypertrophied left ventricle with pre-existing impaired relaxation and compliance. Other supraventricular arrhythmias may result in syncope.
via similar mechanisms. In a study by Schiavone et al.,\textsuperscript{15} 24-hour Holter monitoring and electrophysiology studies (EPS) were performed on 26 patients with HCM, some with an evidence of LV outflow tract obstruction and some with a history of syncope, in order to predict their vulnerability to syncope and to potentially malignant arrhythmias. Holter monitoring demonstrated supraventricular tachycardia (SVT) in 9/26 patients, whereas atrial programmed electrical stimulation (PES) induced SVT in 17/26 patients. Of the 17 patients, nine had symptomatic hypotension with SVT while lying supine. The authors concluded that atrial PES-induced SVT with hypotension best predicted a history of syncope in these patients.\textsuperscript{15}

Fananapazir et al. performed EPS in 155 patients with HCM. Indications for EPS were cardiac arrest in 22 patients, syncope in 55 patients, pre-syncope in 37 patients, asymptomatic VT in 24 patients, palpitations in 10 patients, and a strong family history of SCD in 7 patients. Electrophysiology abnormalities were present in 126 (81%) patients. A high prevalence of abnormal sinus-node function (66%) and His-Purkinje (HV) conduction (30%) was noted. The most commonly induced supraventricular arrhythmias were atrial re-entrant tachycardia and AF (10 and 11% of patients, respectively). Accessory atroventricular (AV) pathways were present in seven (5%) patients.\textsuperscript{16}

**Ventricular arrhythmias**

Non-sustained ventricular tachycardia (NSVT) is common in HCM, but is not usually associated with symptoms. Indeed, typically episodes occur most commonly during sleep.\textsuperscript{17-19} In a study by Nienaber et al.,\textsuperscript{8} NSVT proved to be non-specific as a predictor for syncope. The authors studied 27 patients with HCM and stratified them into two groups: those with witnessed documented syncope and those without syncope. The incidence of premature ventricular beats, complex ventricular ectopic activity, and NSVT was similar in patients with or without syncope.\textsuperscript{8} This is indirectly supported by previous data\textsuperscript{17,18,20,21} confirming that NSVT in HCM is usually slow and short-lasting, thus not itself the cause of syncope. In contrast, sustained VT is relatively uncommon in HCM, but can be a cause of syncope. It can arise from a distal aneurysm in patients with mid-cavity obstruction.\textsuperscript{22} Programmed electrical stimulation studies appear unhelpful in identifying whether ventricular arrhythmia is the cause of syncope in patients with HCM. Kuck et al. performed PES in 54 consecutive patients with HCM. The type and incidence of induced ventricular arrhythmias did not differ between the ‘symptomatic (syncope)’ and ‘asymptomatic (no syncope)’ groups. They concluded that PES induced the same type of ventricular arrhythmia in ‘symptomatic’ and ‘asymptomatic’, with no causal relation between induction of arrhythmias and the incidence of syncope.\textsuperscript{23}

### Primary haemodynamic mechanisms for syncope

Various triggers may potentially precipitate syncope and SCD in patients with HCM. However, there is a growing body of evidence demonstrating that disturbed reflex control of the vasculature is a frequent abnormality in patients with HCM. This abnormal control may result in sudden inappropriate vasodilatation, resulting in episodes of hypotension, which may in turn lead to recurrent syncope and act as a trigger for sudden death. Almost 50% of SCD’s in HCM patients occur during or soon after exercise.\textsuperscript{24} A small study of beta-blocker therapy published in 1970 noted exercise hypotension in some patients,\textsuperscript{25} but the significance of this observation was largely ignored initially. It is now apparent that abnormal blood pressure responses (ABPRs) on exercise are seen in a substantial proportion of patients and confer an increased risk of SCD.\textsuperscript{26,27}

**Abnormal blood pressure responses during exercise in hypertrophic cardiomyopathy patients**

It is now clear that a significant proportion of patients have ABPRs during maximal treadmill exercise. This was first described by Edwards et al.\textsuperscript{25} in 1970 in a small study and was subsequently confirmed by us in a consecutive series of 129 patients attending a tertiary referral centre.\textsuperscript{26} An ABPR is defined as either a failure of systolic BP to rise by at least 20 mmHg during maximal treadmill exercise, or as a fall of >20 mmHg at peak exercise compared with pre-exercise levels or a reading obtained earlier in exercise. According to these criteria, we found that approximately one-third of patients had an ABPR on exercise. In a subsequent study of 126 patients attending a community-based hospital, this ABPR was observed in 22%.\textsuperscript{28}

**Left ventricular outflow tract obstruction in hypertrophic cardiomyopathy**

Outflow tract obstruction was initially thought to be the usual cause of syncope and hypotension on exertion. Although no association between ABPR and resting LV outflow tract obstruction (LVOTO) has been found, this does not exclude dynamic LVOTO as an important mechanism, and in our clinical experience, we have certainly encountered some patients in whom cardiac output limitation was the dominant mechanism of ABPR during exercise. Indeed, recent studies have reported a normalization of ABPR following alcohol septal ablation for LVOTO.\textsuperscript{29} In a subsequent review of 65 patients who had undergone septal myectomy between 1986 and 1992, significant improvement was observed in 86% of patients with pre-syncope pre-procedure and in 100% of patients with syncope.\textsuperscript{30} However, in our experience, an exaggerated fall in systemic vascular resistance appears to be a major component in a substantial proportion of patients.

**Abnormal vascular control mechanisms in hypertrophic cardiomyopathy**

We performed invasive haemodynamic studies in 14 patients with HCM and a normal blood pressure response and 14 with
HCM and an ABPR. In this highly selected study population, the increase in cardiac output was marginally (but signifi-
cantly) higher in the ABPR group, and by implication, ABPR
was due to an exaggerated fall in systemic vascular resist-
ance during exercise.24 In a subsequent study of 103 con-
secutive patients with HCM, we examined the vascular
responses in a non-exercising vascular bed during supine
cycle exercise and the blood pressure response during
maximal treadmill exercise. Forearm vascular resistance
(FVR) was measured using strain gauge plethysmography.
In normal controls, there is an increase in FVR during leg
exercise (vasoconstriction in the non-exercising muscle
bed). In contrast, in one-third of the patients with HCM,
FVR failed to increase or paradoxically decreased during
exercise. This abnormal pattern was strongly associated
with ABPR during maximal treadmill exercise.31 These
data indicate that ABPR may, in most cases, be at least in part
due to an exaggerated fall in systemic vascular resistance
related to inappropriate vasodilatation or a failure of vaso-
constriction in non-exercising vascular beds. This does not
exclude an abnormal cardiac output response as the domi-
nant mechanism or as a contributory mechanism in some
patients. A normal ventricle might be expected to increase
cardiac output to a greater extent in the face of a fall in sys-
temic vascular resistance than was seen in HCM patients.
Consistent with this, we have shown that patients with
vasovagal syncope frequently demonstrate an abnormal
fall in FVR during cycle exercise, yet ABPR was relatively
uncommon in these patients who have normal ventricles.32
Several factors may contribute to the inability to
increase cardiac output appropriately in the face of an exag-
gerated fall in systemic vascular resistance. As mentioned
earlier, dynamic outflow tract obstruction cannot be
excluded as an important mechanism. However, other
mechanisms may contribute. The normal increase in stroke
volume on exercise results in part from an increase in
pre-load (end-diastolic volume). We have shown that
patients with HCM frequently exhibit a failure of splenic
venoconstriction during exercise (presumably via a
mechanism similar to that responsible for the failure of
resistance vessel constriction).33 This, together with the
diastolic dysfunction, which characterizes HCM, may
markedly limit the ability to augment cardiac output in
some patients.

We recently reported that paroxetine ameliorated both
ABPR and abnormal forearm vascular responses during
lower body negative pressure (LBNP) and that clonidine
and propanolol ameliorated the latter but not the
former.34 Paroxetine is a highly selective serotonin (5-HT)
reuptake inhibitor and has been reported to provide func-
tional improvement in patients with vasovagal syncope.
We assessed the frequency of abnormal forearm vasodilator
responses to LBNP in 21 non-obstructive HCM patients
with an ABPR during exercise testing and the effects of three
drugs used to treat vasovagal syncope (propanolol, cloni-
dine, and paroxetine) in a double-blind crossover study.
By reversing or attenuating the ABPR during exercise, and
their abnormal vascular response during abrupt reductions
in central blood volume, Paroxetine may potentially
reduce the number or severity of hypotensive episodes
and/or syncope in patients with HCM and ABPR, and might
conceivably reduce the risk of SCD, but this remains to be
evaluated.

Potential mechanisms for abnormal vascular control:
abnormal baroreflex sensitivity
In healthy subjects during exercise, central command and
skeletal muscle metaboreceptor inputs increase vasocon-
strictor sympathetic outflow from the brainstem, and this
is responsible for vasoconstriction in non-exercising vascular
beds. Vasodilatation in exercising vascular beds appears to
be mediated by metabolic products of exercise.35 In the
1970’s, Mark et al. reported that exercise syncope in
patients with aortic stenosis was associated with an abnor-
mal fall in FVR during leg exercise (similar to that seen in
HCM patients) and that this reverted to a normal response
after aortic valve replacement.36 In another study in anaes-
ethetized dogs, this group showed that inflation of a balloon
in the left ventricle resulted in a fall in skeletal muscle vas-
cular resistance, whereas balloon inflation in the left atrium
had no effect.37 They concluded that the abnormal exercise
vascular response seen in patients with aortic stenosis was
most likely the result of enhanced activation of stretch-
sensitive LV mechanoreceptors due to increased LV wall
stresses (which could be attributed to increased intracavi-
tary pressures resulting from the aortic stenosis). Activation of these mechanoreceptors, which relay to the
brainstem via non-myelinated afferents, has an inhibitory
effect on sympathetic outflow from the brainstem, and
this may overcome the input from central command and
skeletal metaboreceptors, leading to inappropriate
vasodilatation.

These findings parallel those in HCM patients, but the role
of LV mechanoreceptors in generating abnormal vascular
responses is inferred rather than proven. Increased LV wall
stresses might be expected to occur in HCM for three
reasons:

(i) the presence of LVOTO;
(ii) the presence of patchy myocyte disarray and/or fibro-
sis causing localized areas of increased wall stress;
(iii) the presence of subendocardial ischaemia.38

There is, however, further evidence pointing to the dys-
function of the LV mechanoreceptors in HCM. Central
blood volume unloading, which occurs on assuming an
upright posture (as a result of pooling of blood in the
pelvic and lower limb veins), normally causes reflex com-
ponsatory adjustments that result in an increase in systemic
vascular resistance, vasoconstriction, and a modest
increase in the heart rate in order to maintain cardiac
output and blood pressure. In health, these adjustments
ensure that the fall in blood pressure is small and brief.
The initial fall in cardiac chamber size and blood pressure
results in reduced afferent input from cardiopulmonary
and arterial baroreceptors, respectively, which results in
increased sympathetic outflow from the brainstem. Lesser
degrees of central blood volume unloading, which are insuf-
icient to reduce blood pressure, can be achieved by the
application of LBNP. A marked increase in FVR is seen,
despite the absence of any fall in blood pressure. Available
evidence suggests that this response is predominantly
mediated via inactivation of LV mechanoreceptors.39 The
reflex is absent in the denervated transplanted heart.40
We showed that during application of LBNP, in approximately
one-third of patients, there was paradoxical forearm vasodi-
latation. There was no evidence of an abnormality of central
or efferent mechanisms. Furthermore, the function of
carotid baroreceptors was assessed and was shown to be normal.\textsuperscript{41} We considered that the most likely explanation for these observations was a failure of the normal inactivation (and in some cases, paradoxical activation) of LV mechanoreceptors during central blood volume unloading in these patients. The mechanism of this abnormality is unclear, but heterogeneous strain changes associated with the patchy myocyte disarray and fibrosis may provide a substrate.

Abnormal vascular control: episodic hypotension and recurrent syncope
As noted above, multiple mechanisms may be responsible for recurrent syncope in patients with HCM, including arrhythmia and dynamic LVOTO, yet despite extensive investigation, the cause is not identified in the majority of patients.\textsuperscript{4,12} We recently assessed a highly selected series of 18 HCM patients with recurrent pre-syncope and/or syncope for which no cause had been identified despite extensive investigation. This group was compared with 11 HCM patients without such a history. Beat-by-beat blood pressure waveforms were recorded using a Portapres system for a period of 24 h. Recurrent abrupt spontaneous episodes of hypotension without an associated reflex tachycardia were observed in eight of the patients with a history of syncope, but in none of those without such a history. Sixty per cent of these episodes were associated with a period of impaired consciousness. Using a validated transfer function, we were able to show that systemic vascular resistance fell markedly during these episodes, whereas stroke volume and cardiac output did not change during these episodes, and by implication, the hypotension was due to vasodilatation. Consistent with the proposed neurally mediated mechanism, there was no reflex increase in the heart rate during these episodes, indicating an abnormal baroreflex response.

Investigation of recurrent syncope in hypertrophic cardiomyopathy
Symptoms of impaired consciousness occur in 15–25\% of the patients with HCM. In young patients, a history of recurrent syncope is associated with an increased risk of SCD. Syncope usually occurs without warning or prior symptoms suggestive of the cause. Detailed investigations identify a probable mechanism in a minority of these, usually paroxysmal AF or VT. In the majority of cases, however, no likely mechanism is found despite repeated 24-h ambulatory ECG or patient-activated monitoring, exercise testing, and invasive electrophysiological testing. Although this may be the case, it is still of vital importance to exclude the potentially treatable causes of syncope. Investigations can be divided into those for arrhythmia causes and those assessing primary haemodynamic mechanisms.

Arrhythmic causes
A resting ECG should be performed to exclude the evidence of conduction disease, and all patients should undergo ambulatory ECG monitoring for a period of 48 h. In rare cases, an implantable recorder may be useful for identifying an arrhythmic basis. Electrophysiology studies are not routinely performed, but may be necessary to identify the mechanism of supraventricular arrhythmias. As noted above, PES is usually unhelpful.

Primary haemodynamic mechanisms
It is important to exclude dynamic LVOTO as a cause of syncope. This is best achieved by means of exercise echocardiography. All patients should undergo cardiopulmonary exercise testing with an assessment of the blood pressure to exercise. Although not routinely available, beat-by-beat ambulatory blood pressure monitoring (e.g. by Portapres) can demonstrate inappropriate vasodilatation and its relation to clinical symptoms.

Management of syncope in hypertrophic cardiomyopathy
The following principles of management should be adhered to all patients with HCM. It is vital to try and establish the mechanism of syncope, although as mentioned earlier, in the majority of cases, no cause can be identified. Where possible, treatment should be based on the identified mechanism. Empiric treatment with amiodarone, a pacemaker, or an ICD is commonly employed, but is often unsuccessful in relieving symptoms. However, there are some target-specific treatments available in patients in whom the mechanism underlying symptoms has been identified.

Supraventricular arrhythmias
Most symptomatic arrhythmias are supraventricular, which develop in association with atrial dilatation. Amiodarone is the most effective agent for reducing the occurrence of paroxysmal AF and for maintaining sinus rhythm following cardioversion in patients with new-onset AF. In patients with established atrial fibrillation, rate control can usually be achieved with verapamil or a beta-blocker. Occasionally, AV nodal ablation with permanent pacemaker implantation is required. Unless a contra-indication exists, patients with established or paroxysmal AF should receive anticoagulation.

Ventricular tachycardia
Sustained VT, although rare in patients with HCM, should be treated with amiodarone or an implantable cardioverter–defibrillator. Non-sustained ventricular tachycardia is not usually a cause of syncope but is one risk factor for SCD. In the absence of other risk factors, treatment with amiodarone is appropriate, but when NSVT occurs in combination with one or more other risk factors for SCD (as listed below), an ICD is the most appropriate therapy.

Conduction disturbances
Premature conduction disease and chronotropic incompetence may cause exercise limitation and symptoms of impaired consciousness in patients with HCM. Any kind of bradyarrhythmia or conduction disturbance that is considered to cause haemodynamic decompensation should be considered for pacemaker implantation according to current guidelines.\textsuperscript{42}
Relief of left ventricular outflow tract obstruction

Initial treatment of symptomatic patients with outflow tract obstruction is pharmacological, with beta-blockade and, if necessary, addition of Disopyramide. The negative inotropic effects of this combination are usually effective at reducing the gradient and symptoms if high doses of disopyramide can be maintained. The anticholinergic side effects are often well tolerated in young patients, whereas this pharmacological approach is usually not practical in older males because of urinary retention. If medical therapy fails, then surgical myectomy is effective (>80% success), and, in experienced centres, pre-operative mortality rates during the past decade have been below 2% (~1% in high volume centres). Surgery has also been shown to reduce the symptoms of presyncope and syncope. Alcohol septal ablation has also been reported to reduce syncopal symptoms in selected patients but mortality is no lower than surgery, the risk of procedure-related complications is no lower than surgery, the risk of procedure-related complete heart block higher, and there have been fatalities. The selection of patients for myectomy vs. alcohol septal ablation therefore remains controversial. Recent studies have reported a normalization of ABPR following alcohol septal ablation for outflow tract obstruction.

Initial reports suggested that short AV delay right ventricular pacing could relieve the symptoms in patients with obstructive HCM, but subsequently two large studies reported that much of this was a ‘placebo’ effect. Nevertheless, there are clear ‘responders’. Clinically, older patients with syncope seem most likely to be responders.

Abnormal vascular responses

As mentioned earlier, we have recently demonstrated in a randomized double-blind placebo-controlled study that exercise blood pressure responses were improved by perhexiline therapy and that abnormal forearm vascular responses during the application of LBNP were attenuated or normalized by propanolol, clonidine, and paroxetine. By reversing or attenuating the ABPR during exercise, and the abnormal vascular response during abrupt reduction in central blood volume, paroxetine may potentially reduce the number or the severity of hypotensive episodes and/or syncope in patients with HCM and ABPR and might conceivably reduce the risk of SCD, but this remains to be elucidated.

Risk stratification and syncope as a risk factor in hypertrophic cardiomyopathy

HCM is an important cause of SCD. Many of these SCDs occur in patients with minimal or no symptoms. With the development of the ICD, effective preventive therapy is now available. The challenge is to distinguish high-risk from low-risk patients in order to target prophylactic therapy to those at risk.

Several risk factors have been shown to be associated with an increased risk of sudden death in patients with HCM. The predictive accuracy of each of these risk factors is generally low during medium-term follow-up. Consequently, the use of single risk factors to guide risk factor stratification is unhelpful. Elliott et al. have argued persuasively that the risk factor profile of patients with HCM is much more accurately assessed in terms of their total burden of risk factors. The following algorithm for risk stratification should be applied to individual patients.

(i) Patients with a prior cardiac arrest or spontaneous sustained VT are at high risk and should be considered for prophylactic therapy with an ICD.

(ii) In the absence of such a history, risk is probably best assessed in terms of the total number of the following risk factors:

(a) maximum wall thickness > 30 mm;

(b) systolic blood pressure response measured at one-minute interval during maximal upright exercise in patients, 40 years of age (ABPR = failure to increase by >25 mmHg or a fall from peak values during continued exercise of >15 mmHg);

(c) non-sustained VT during 48-h ambulatory ECG monitoring;

(d) a history of at least one SCD in a relative before the age of 45 years, together with a history of syncope;

(e) a resting peak instantaneous LV outflow tract gradient of >30 mmHg.

Patients with no risk factors can be strongly reassured. Those with two or more risk factors are at high risk and should be considered for prophylactic therapy with an ICD and/or amiodarone. Those with a single risk factor are at intermediate risk.

Summary

Symptoms of impaired consciousness (syncope and presyncope) occur in ~15–25% of patients with HCM, and in young patients with a history of recurrent syncope are associated with an increased risk of SCD. Detailed investigations identify a probable mechanism in a minority of these, usually paroxysmal AF or VT. In the majority of cases, however, no likely mechanism is found despite extensive investigation. Although this may be the case, it is still of vital importance to exclude the potentially treatable causes of syncope.

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