Sudden death in hypertrophic cardiomyopathy: potential importance of altered autonomic control of vasculature

Donald Teare’s original pathological description of hypertrophic cardiomyopathy (HCM) was based on eight young adults, seven of whom died suddenly.1 Almost 40 years later, the identification of individuals at risk for sudden death and its effective prevention remains the major therapeutic challenge in this disorder. While HCM is, in most series, the most common cause of sudden death in asymptomatic young adults, adolescents and athletes,2 the annual risk of sudden death for patients with HCM is not certain. Annual incidences of 1–2% in adults and 4–6% in children and adolescents have been reported from tertiary centres.2 Recent natural history studies from non-referral centres however indicate a better prognosis.3 This in part reflects referral bias as well as increased recognition of the disease. HCM has been considered a rare disease with adverse prognosis; however, emerging data from a number of studies indicate that it is a common disease (< 1 in 500; estimated 150 000 sufferers in the UK),4 with relatively good prognosis. The challenge therefore remains to identify the small group who are at risk of major complications particularly sudden death.

Mechanism of sudden death: structural basis
It is likely that sudden death in HCM can be initiated by several different triggers and the underlying propensity to ventricular fibrillation is on the basis of an electrophysiological substrate. Histologically, myocyte disarray is the hallmark of the disorder. The combination of myocyte disarray, myocardial fibrosis,5 and the recently reported presence of abnormal cardiac desmosome and connexin disposition, particularly in areas of severe myocyte disarray,6 set the scene for inhomogeneous electrical conduction that is important in the genesis of micro re-entrance arrhythmias. Inhomogeneity of electrical conduction has been demonstrated by Saumarez, using paced electrogram fractionation.7 Survivors of out of hospital ventricular fibrillation demonstrated the greatest degree of fractionation, with individuals clinically at low risk demonstrating much less fractionation. Thus, inhomogeneous conduction, in the setting of an appropriate trigger, may result in ventricular fibrillation and hence sudden death. The observation of extensive myocyte disarray without hypertrophy in individuals dying suddenly lends further support to the potential importance of myocyte disarray as a determinant of the electrical substrate.8

Triggers for sudden death
The potential triggers for sudden death include ventricular arrhythmia,9 atrioventricular conduction disease, atrial fibrillation with fast ventricular response,10 myocardial ischaemia,11 abnormal vascular control,12 and autonomic dysfunction. Although the terminal event in most patients with HCM who die suddenly is probably ventricular fibrillation, the antecedent events are rarely documented. The potential mechanism and the relative importance or prevalence of these triggers in not known. Goodwin and Krikler13 were the first to hypothesise that sudden death may be arrhythmic and this was supported by two studies that showed that ventricular arrhythmia on ambulatory ECG recordings was associated with increased risk of sudden death.14 Anecdotal reports with fortuitous ambulatory ECG recordings in patients dying suddenly have demonstrated ischaemia and ventricular tachycardia at the time of the event.15 However, tolerance to arrhythmias (whether supraventricular or ventricular) is variable and appears to be modulated by other factors. It is well recognised that some patients tolerate atrial fibrillation16 while others do not,17 independent of the ventricular rate. Anecdotal reports’ suggest that accompanying hypotension may be an important determinant of outcome. We have observed severe haemodynamic collapse associated with slow atrial fibrillation in several patients with mild hypertrophy but who had been demonstrated to show abnormal forearm vasodilator responses during dynamic leg exercise; conversely, other patients with severe hypertrophy but normal vascular response tolerate fast atrial fibrillation well (Prasad K, Frenneaux MP, McKenna WJ, unpublished data, 1996). Brignole et al found that a history of syncope during paroxysmal atrial fibrillation in patients who did not have HCM strongly correlated with a positive tilt test18 and lower systolic blood pressure at the onset of symptoms. This highlights the importance of vascular behaviour as a modulator of response to arrhythmias.

ABNORMAL CONTROL OF VASCULAR TONE
In a recent prospective study of 161 consecutive patients with HCM aged 8–40 years, we demonstrated that an abnormal blood pressure response during treadmill exercise identified a high risk cohort for sudden death. Abnormal blood pressure response had a sensitivity of 75%, specificity of 66%, and negative predictive accuracy of 97% for sudden death over a mean (SD) follow up of 44 (20) months.19 Malignant ventricular arrhythmias were not encountered during exercise in this study, suggesting that abnormal vascular response may in fact be an independent trigger for sudden death. Approximately one third of patients with HCM demonstrate an abnormal blood pressure response during exercise with either a flat response or development of hypotension.20 This hypotension is due to an exaggerated fall in systemic vascular resistance, and such patients demonstrate inappropriate vasodilatation rather than vasoconstriction in the forearm vessels during dynamic leg exercise.21 A failure of constriction or pathological dilatation of venous capacitance vessels is also seen in these patients and may contribute to the hypotension.22 Similar abnormal responses during exercise have been associated with hypotension in patients with ischaemic heart disease23 and aortic stenosis.24 In both these settings, exercise hypotension has adverse prognostic significance underscoring the potential role of hypotension as a trigger in the appropriate setting. Patients with vasovagal syncope also demonstrate abnormal vascular responses during exercise,25 occasionally resulting in exercise syncope.26 However, the risk of sudden death in subjects with vasovagal syncope is exceptionally low, emphasising the importance of substrate as well as trigger in the aetiology of sudden death.
ALTERATIONS IN AUTONOMIC FUNCTION

Autonomic dysfunction is associated with poor prognosis in patients with ischaemic heart disease. Is there a role for such dysfunction in the genesis of sudden death in HCM? Gilligan et al reported a high rate of positive tilt table tests in patients with HCM, especially in those with history of syncope, whereas in the study by Sneddon et al, tilt table positivity was not associated with clinical history of syncope. A recent study reported abnormal vasodilator responses during application of lower body negative pressure in patients with HCM, suggesting paradoxical activation of left ventricular mechanoreceptors during central blood volume unloading. These observations suggest the potential for neurally mediated hypotension in hypertrophic cardiomyopathy in situations other than exercise. The mechanism of this abnormal reflex vascular control in HCM is unproven, but it most likely represents abnormal activation of left ventricular mechanoreceptors as a result of abnormal local left ventricular wall strain perhaps related to the patchy nature of myocyte disarray and to abnormal desmosome disposition. Approximately 50% of episodes of sudden death occur during or soon after exercise. A recent study using continuous ambulatory monitoring during daily activities showed an association between syncope and episodic hypotension. Importantly, this ambulatory study demonstrated occurrence of spontaneous, inappropriate, episodic hypotension frequently during ordinary daily life, both at rest and during activity. Hypotension may act as a trigger for sudden death leading to ischaemia, ventricular tachycardia, or both, but baroreflex dysfunction may also modulate the threshold for arrhythmia. Disturbances in autonomic function reflected by alterations in heart rate variability and baroreflex sensitivity have prognostic significance in patients with heart failure and myocardial infarction. Assessment of heart rate variability in patients with HCM has yielded disparate results; some studies have shown reduced parasympathetic tone in symptomatic patients, while one study found no difference between survivors of cardiac arrest and others. However, as pointed out by Malik and Camm, changes in components of heart rate variability may not be a direct measure of the activities of the parasympathetic and sympathetic systems, rather modulations of these two and the sympathovagal balance. The overall heart rate variability indices were reduced in all of the aforementioned studies suggesting alterations in sympathovagal balance in patients with HCM.

MYOCARDIAL ISCHAEMIA

Myocardial ischaemia is common in patients with HCM. Left ventricular hypertrophy imposes an increased demand for oxygen. Coronary flow reserve is limited by reduced transcoronary pressure gradient, by structural changes in small vessels, and by endothelial dysfunction. Diliszian et al reported objective evidence of reversible ischaemia (thallium) in 15 young patients with history of syncope or cardiac arrest compared with only three of eight young patients without such history. Although not commented on by the authors, the patients with evidence of ischaemia had significantly lower peak exercise blood pressure (calculated), raising the question of whether this may have been contributory. Ischaemia may be a trigger for sudden death by increasing inhomogeneity of conduction and repolarisation; however, sudden death occurs in 1% of HCM patients despite the use of high dose ischaemic agents (β blockers and calcium channel blockers), indeed there is no evidence that these drugs improve prognosis.

Summary

Current evidence suggests that alterations in the autonomic function and abnormal vascular control play a significant role either as isolated factors or in combination with other factors in the aetiology of arrhythmias in HCM patients. Autonomic dysfunction and ischaemia are therefore likely to act as triggers for sudden death. The relative contribution of each of these factors needs further detailed study.

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