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Risk management in hypertrophic cardiomyopathy

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Management of patients with hypertrophic cardiomyopathy (HCM) is implicitly based on their estimated risk of sudden cardiac death due to ventricular arrhythmias.[1,2] Currently, risk cannot be defined with absolute accuracy but several important generalisations can be made. First, the bulk of outcome data is derived from tertiary referral centres and is biased towards high-risk patients.[1] By contrast, data derived from population-based studies of unselected patients suggest that the rate of sudden cardiac death is much lower and, in some studies, approaches that of matched controls, which underlines the fact that most patients with HCM do well.[3–5] Second, patients who present with sustained ventricular tachycardia or ventricular fibrillation, and also some who have a strong family history of sudden cardiac death, have already declared themselves at high risk and should be given an implantable defibrillator (ICD).[2,6] This view is supported by recent studies showing a likelihood of up to 11% of appropriate ICD discharges per year in these patients.[2] Third, for most patients uncertainties in the assessment of risk may be coming to an end with recent studies indicating that a low-risk group can be defined.[7,8] There remain, however, considerable difficulties in identifying which patients warrant prophylactic implantation of a defibrillator.

To enable a systematic approach to the assessment of risk of arrhythmic sudden cardiac death presented by HCM, a model can be constructed on the basis of triggers for arrhythmias and the electrophysiological substrate on which they are thought to act. The substrate includes readily observable features such as the increase in ventricular muscle mass and more subtle changes such as myocyte hypertrophy and disarray.[9] Possession of both the triggers and the substrate indicates a risk of sudden cardiac death. Hence current practice is to apply readily available tests to detect both the triggers and the substrate, to generate a risk profile and a framework for treatment. In the assessment of triggers exercise testing has become routine—a follow-on of the idea that disordered autonomic responses contribute to exercise-induced hypotension, which may in turn lead to myocardial ischaemia and arrhythmias.[10] Accordingly, the 60–80% of HCM patients with a normal physiological increase in blood pressure on exercise have been found to have low risk at follow-up.[7,11,12] Caveats must be applied when interpreting results that will be valid only if obtained under carefully controlled conditions by experienced personnel in patients younger than 40–50 years of age.[11] Ambulatory electrocardiography is also important, most specifically in the assessment of ventricular arrhythmias.[1] However, although frequent, repetitive, or lengthy runs of ventricular premature beats or non-sustained ventricular tachyarrhythmias adversely influence prognosis, they have low positive predictive value (PPV) and do not, in themselves, justify aggressive management.[1,13,14] The real worth is in a high negative predictive value, so an ambulatory tape showing only brief, infrequent episodes of ventricular arrhythmias in a symptom-free patient over 20 years of age, when taken together with other tests suggesting low risk and a family history free of tragedy, presages a favourable prognosis.[7,14]

The anatomical substrate, defined most readily by echocardiography, has until recently not been seen as a key independent determinant of risk of sudden cardiac death in most patients with HCM.[1] In today's *Lancet* Perry Elliott and colleagues have investigated the influence of this substrate by assessing the capacity of echocardiographically defined indices of ventricular hypertrophy to predict sudden cardiac death. This study of 630 patients was prompted, in part, by an earlier report that suggested that the degree of ventricular hypertrophy was an independent predictor of sudden cardiac death.[8] It confirms the relation between maximum left-ventricular-wall thickness and the risk of sudden cardiac death, but the conclusions of the two papers differ in two important respects. First, the PPV of ventricular hypertrophy for sudden cardiac death is low in Elliott and colleagues' study, and patients would not be recommended an ICD on the basis of their findings. Second, Elliott and colleagues found that a proportion of patients with mild hypertrophy are also at risk and cannot be reassured on the basis of echocardiographic findings. The results of the two studies can, however, be reconciled because each strongly indicates that symptoms, investigations other than echocardiography, and family history should also be taken into account before deciding management. Therefore the extent of hypertrophy should now be factored into the planning of interventions to reduce the risk of sudden cardiac death.

By contrast, the direct, conventional evaluation of the electrophysiological substrate has in general, and rather surprisingly, been disappointing in the identification of patients at risk of sudden cardiac death. Programmed

electrical stimulation, although advocated by some clinicians,[15] has a low PPV in the prediction of future arrhythmic events.[1,16-18] One electrophysiological technique that may improve PPV is paced electrogram fractionation analysis (PEFA), which directly examines myocardial conduction and the potential for slowed conduction, the substrate for arrhythmias.[16,17] The value of this technique in predicting the risk of sudden cardiac death is being examined in a prospective clinical trial with sudden cardiac death and appropriate ICD discharge as combined endpoints. A preliminary analysis suggests that it has a PPV of 0·30 (95% CI, 0·15–0·45), consistent with three out of every ten patients identified at high risk by this test developing ventricular fibrillation.[18]

The recent studies, when taken together, serve to support the intuitive notion that the greater the number of risk factors, the greater the risk of sudden cardiac death (refs 7,8, and that reported today). This evidence is important since it increases the confidence with which the clinician can describe to patients a graded risk profile, so that informed choices can be made. Accordingly, in all patients, key initial investigations should include an echocardiogram, an ambulatory electrocardiogram, and an exercise test. The symptom-free patient with a left-ventricular-wall thickness of less than 20–25 mm, only occasional ventricular arrhythmias on an ambulatory electrocardiogram, and a normal rise in systolic blood pressure during a rigorously conducted exercise test can be reassured. The only precaution that patients may need to take is against participation in contact or high-intensity sports.[1,7,19] If one or more of the results are abnormal, or if there is a family history of sudden cardiac death, patients should be referred to a centre with a specific interest in HCM for further assessment and advice on management.[1] Further procedures may include genetic testing, and in certain European centres inclusion in the trial prospectively examining the value of PEFA.[18] Assessment will identify a group of patients in whom risk reduction will be considered necessary. β-blockers and calcium-channel antagonists do not protect against sudden cardiac death, and most anti-arrhythmic agents are likely to increase risk.[1] Amiodarone has been used, but it is a difficult drug and there are, as yet, no rigorously controlled data supporting its efficacy in risk reduction. Indeed a consistent finding of recent data is that patients taking amiodarone continue to be at risk of sudden cardiac death (refs 2, 5, 6 ,8, and Elliott and colleagues).

Against this background, the decision to implant a defibrillator in patients perceived to be at risk is likely to become more common. The threshold of risk at which ICDs are used already varies between countries and will doubtless fall, prompted in part by advanced device specification. Although the technology will continue to improve, it will remain preferable not to put ICDs in patients at low risk. Research efforts should therefore continue to develop potentially novel approaches with greater PPV to identify patients likely to benefit from ICDs. Such advances are imperative to help in difficult decisions not only for patients with HCM but also for other large groups with non-coronary heart disease.

*Andrew A Grace, Peter A Brady, Leonard M Shapiro
Cardiac Unit, Papworth Hospital, Cambridge CB3 8RE, UK
(e-mail: ag@mole.bio.cam.ac.uk)

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Targeting voracious appetite of malaria-infected red-blood cell

The malarial parasite has a complex life-cycle that requires invertebrate (mosquito) and mammalian (man) hosts, but the part responsible for the 250 million clinical cases of malaria (and up to 2 million deaths) every year is infection of the red-blood cell. Apart from *Babesia* and *Bartonella* spp few, if any, infectious agents other than plasmodia invade the human red cell. Moreover the infected cell is neither a red blood cell nor a parasite but acquires attributes that are distinctive because the parasite rapidly modifies the cell to satisfy its own need to multiply, and that includes the insertion of parasite-derived molecules into the surface of the red cell. Left unchecked *Plasmodium falciparum* will increase in numbers sufficient to be life-threatening. To satisfy its voracious appetite, the parasite needs to acquire nutrients and ions and rid itself of damaging metabolites across the three major membranes (figure). Nutrients and ions entering the cell have first to cross the red-cell membrane; the second hurdle is the parasitophorous vacuolar membrane, which was originally continuous with