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EDITORIAL

Non-invasive risk stratification in hypertrophic cardiomyopathy: don't throw out the baby with the bathwater

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This editorial refers to 'Paced ventricular electrogram fractionation predicts sudden cardiac death in hypertrophic cardiomyopathy'† by R.C. Saumarez *et al.*, on page 1653

Although historical accounts consistent with sudden cardiac death (SCD) date back to ancient times, only in the past quarter of a century has prevention of these events become possible. Growing understanding of underlying disease states, development of effective anti-arrhythmic therapy, and the advent of the implantable cardioverter-defibrillators (ICDs) have all contributed to realization of this goal. Nevertheless, prophylactic ICD placement in the inherited cardiovascular disease population to some extent represents a double-edged sword. On the one hand, averting SCD in individuals without debilitating symptoms or co-morbidities may yield an exceptional number of quality-adjusted life years. Conversely, the present knowledge gap regarding the consequences of extended device therapy is of particular relevance in young patients in whom the aim is to achieve normal life expectancy. Increasing awareness that ICDs are not a trouble-free panacea for all patients with SCD syndromes[1,2] has underscored the importance of reliable risk prediction.

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disorder, with an estimated prevalence of 1 in 500 in the adult population. Morbidity may result from diastolic dysfunction, left ventricular outflow tract obstruction (LVOTO), atrial fibrillation, myocardial ischaemia, systemic thromboembolism, mitral regurgitation, and left ventricular systolic impairment. In community-based cohorts, the annual mortality from HCM may be $\leq$1%, implying a stable clinical course in the majority.[3] Nevertheless, most of the deaths that do occur are sudden and arrhythmic, with myocyte disarray and fibrosis serving as the substrate, while purported precipitants include myocardial ischaemia, LVOTO, abnormal vascular responses, conduction disease, paroxysmal atrial fibrillation, supraventricular tachycardia with accessory pathway conduction, and non-sustained ventricular tachycardia (VT).[4]

The risk predictors hitherto identified in HCM (*Table 1*) each correspond to one or more of these factors, although their interplay in any instance of SCD is undoubtedly complex. A family history of premature SCD signifies the presence of genetically determined high-risk substrate; flat or depressed blood pressure response to exercise indicates vascular instability and/or low cardiac output; non-sustained VT is both a pointer to arrhythmogenic substrate and a potential trigger of ventricular fibrillation, as confirmed on analysis of intracardiac electrograms from appropriate ICD firing.[4] Syncope may be related to abnormal vascular responses, LVOTO, or transient haemodynamic compromise at the onset of supraventricular arrhythmia, but not usually non-sustained VT, which seldom causes symptoms in HCM patients.[5] Sustained VT, in contrast, may cause syncope, but is uncommon in HCM and raises suspicion of left ventricular apical aneurysm. The magnitude of left ventricular hypertrophy (LVH) may be an indirect guide to the extent of substrate and predisposition to ischaemia.

Among a cohort of 368 HCM patients followed for a mean of 3.6 years, there were only four instances of SCD without any of the five primary predictors.[6] In each case, one of the secondary indicators could be implicated, namely co-existing coronary disease in two, resting LVOTO in one, and microvascular ischaemia in the fourth. This latter phenomenon is recognized in clinical practice by deep ST depression on exercise testing or reversible defects on perfusion scanning, in the absence of obstructive coronary disease. Current guidelines for risk stratification in HCM therefore rely on non-invasive evaluation comprising clinical and family history, two-dimensional echocardiography, ambulatory ECG monitoring, and maximal upright exercise testing.[3] The appeals of this protocol are its simplicity, ready applicability to asymptomatic relatives without potential for harm, repeatability at

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Table 1 Non-invasive predictors of sudden cardiac death risk in hypertrophic cardiomopathy[3,4,6–10,12]

Primary risk factors	Secondary and putative risk factors
(Prior cardiac arrest)	Co-existing obstructive coronary artery disease
(Spontaneous sustained VT)	Resting LV outflow tract obstruction
Family history of one or more instances of SCD	Microvascular ischaemia
Non-sustained VT (≥3 consecutive beats at ≥120 bpm)	(Prior alcohol septal ablation)
Failure of systolic BP to rise by ≥25 mmHg during maximal upright exercise testing	('Burnt out' disease)
Unexplained syncope	(Diffuse late gadolinium enhancement on CMR)
Maximum LV wall thickness ≥30 mm	(High-risk mutation)

BP, blood pressure; CMR, cardiovascular magnetic resonance; LV, left ventricular; SCD, sudden cardiac death; VT, ventricular tachycardia.

appropriate intervals, and feasibility in any centre with basic cardiac diagnostic facilities.

Where clinical expertise becomes requisite is in the contextual interpretation of prognostic indicators and development of composite risk profiles. For example, non-exertional syncope has low positive predictive value (PPV) for arrhythmic events in HCM because it is commonly vasovagal, as in the general population; when combined with a family history of SCD, however, the risk ratio increases manifold.[6] Similarly, an abnormal blood pressure response to exercise occurs in 22–37% of HCM patients and in isolation has low PPV.[7,8] In the setting of a troponin T mutation, however, it is a harbinger of SCD and potential indication for ICD placement. Troponin T mutations may be associated with SCD in the absence of significant LVH and arrhythmic findings. In small nuclear families, genetic predisposition to SCD may not be apparent, suggesting a possible, albeit limited role for genotyping in risk stratification.

In children with HCM, the psychological repercussions of device placement and possible lead stretch during somatic growth influence decision making, as does the prominence of syndromic and metabolic phenocopies with clinical courses distinct from sarcomeric disease.[9] Older HCM patients may also pose a challenge. Three out of five primary risk factors (non-sustained VT, abnormal exercise blood pressure, and marked LVH) have demonstrably higher predictive potential in younger patients than the over-50 age group,[7,10,11] and a family history of SCD[12] is also considered less relevant with advancing years. Although survival beyond middle age *per se* suggests favourable prognosis, an important minority of older patients have delayed-onset HCM, with concomitant risk of events in later life and consequent need for tailored prognostication.

Saumarez *et al.* have compared the utility of paced electrogram fractionation analysis (PEFA) and conventional risk stratification in predicting events in 179 patients with HCM.[13] The area under the receiver operating characteristic (ROC) curve was an impressive 0.88 for PEFA, compared with 0.71 for non-invasive evaluation. The interest in PEFA reflects the ongoing search for the elusive Holy Grail of definitive risk stratification in HCM, a response to the 2-fold limitations of the current algorithm. The more practical of these shortcomings is the consistent finding of a single risk factor in a sizeable subset of HCM patients (20–30%), the majority of whom will not experience an event, and should not, in an ideal world, be subject to the hazards of prophylactic ICD placement. Although follow-up of 506 HCM patients with ICDs found no association between the number of risk factors and appropriate intervention rates, this study was limited by absence of Holter recordings in a significant proportion and omission of one primary predictor, abnormal exercise blood pressure, as well as secondary indicators such as LVOTO and ischaemia.[14,15] The relevance of multivariate analysis in such a selected cohort is also questionable. Earlier work supported the intuitive expectation that the impact of adverse prognostic indicators would be cumulative, and existing consensus guidelines advise tailoring prognostic assessment on a case-by-case basis for individuals with a single risk factor.[3,6]

It is the laudable goal of avoiding unnecessary implants that underpins the authors' choice of PPV as the primary study variable. Here indeed conventional prognostication falls short, since the PPV of ≥2 primary risk factors for SCD was only 10.6%, with a lower confidence limit of 2%, approaching the expected mortality in an unselected cohort of HCM patients. Conversely, PEFA attained a PPV of 38% (17–59%), perhaps because it represents the closest clinical surrogate of the underlying histological substrate of myocyte disarray.[13]

The other drawback of conventional risk prediction is less utilitarian but far more emotive. Most clinicians who have provided care for a substantial HCM population over an extended period will attest to having lost at least one patient to SCD in the absence of conventional risk factors. The reassurance afforded by a normal assessment is reflected in the negative predictive value (NPV), which exceeds 95% for the five primary risk factors in HCM, and might be higher still if secondary markers were incorporated. In the cohort presented by Saumarez *et al.*, not a single HCM patient suffered SCD during follow-up without risk factors, underscoring the relative rarity of these events. Nevertheless, unexpected preventable deaths are so devastating that the cardiovascular community will continue to pursue absolute assurance, with NPV approaching 100%. Achieving this gold standard may entail inclusion of novel prognostic indicators, such as late gadolinium enhancement on cardiovascular magnetic resonance (CMR), which is associated with increased myocardial collagen content, and more prevalent among patients with ≥2 conventional risk factors.[16] The predictive potential of gadolinium-enhanced CMR in HCM remains to be determined, although it is liable to be of most value as an adjunct to, rather than a substitute for, the current risk stratification protocol.

In contrast, Saumarez *et al.* propose PEFA as a stand-alone replacement for conventional risk stratification.[13] Although PEFA has the capacity to identify at-risk HCM patients who lack other clinical markers, and its NPV during a 4-year follow-up period was a respectable 95%, it was outperformed in this respect by non-

invasive risk assessment. There were three events in the PEFA-negative group, but none among patients without primary risk factors.[13] Another downside is the four-electrode electrophysiology protocol which, while safe in experienced hands and complication-free in this study, is ill-suited to assessment of asymptomatic relatives, who represent a growing proportion of the HCM population. Nor does any invasive technique easily lend itself to periodic repetition, recommended in HCM as in all inherited cardiovascular diseases, owing to dynamic risk profiles. PEFA warrants further investigation as a predictor of SCD in HCM, not least because of its unparalleled PPV. However, the ultimate aim should be to refine the existing risk stratification protocol through judicious integration of complementary indicators such as delayed-enhancement CMR, mutation analysis, and PEFA, not to throw out the proverbial baby with the bathwater.

Conflict of interest: none declared.

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