Exercise-induced ventricular dysfunction in hypertrophic cardiomyopathy: stunning by any other name?

Houman Ashrafian, Hugh Watkins

Hypertrophic cardiomyopathy (HCM) is a common cardiac genetic disorder with a prevalence of 1/500 and is caused principally by mutations in genes encoding proteins of the cardiac sarcomere (eg, β-cardiac myosin heavy chain and cardiac troponin T).[1] Although of substantial scientific importance, HCM is best recognised for being the most common cause of sudden cardiac death (SCD) in the young, especially in young athletes, accounting for up to one-third of all such deaths in the US.[2] HCM might be expected to impair exercise capacity, for example through left ventricular hypertrophy (LVH) and diastolic ventricular dysfunction; however, some HCM patients not only tolerate exercise well, but indeed excel athletically. This is surprising given that even HCM patients without LVH exhibit subtle systolic and diastolic abnormalities. Additionally, approximately one-third of HCM patients exhibit abnormal blood pressure (bp) responses during maximal treadmill exercise (ie, a flat blood pressure response, or a fall in blood pressure), which portends a poor prognosis.[3 4] Ultimately, exercise in HCM is a matter of considerable concern, as many of the cases of SCD in HCM are associated with exertion.[2] Exercise-induced SCD thus represents the rationale, albeit controversially, for preparticipation cardiac screening and exclusion of affected athletes from sporting activity.[5]

WHAT THEN IS THE IMPACT OF EXERCISE IN HCM?

Sakata *et al* address this question in this issue of (***see page 1282***) by proposing that exercise-induced LV systolic dysfunction (LVSD) occurs more frequently in HCM patients with cardiac troponin gene mutations than in those without troponin mutations.[6] While this observation is potentially of great interest, it is not without methodological limitations. First, there are marked differences between the two patient groups other than, but potentially not independent of, their genetics. These include marked differences in: number of patients recruited (10 vs 42), age (43.6 vs 53.4 years old), family history of HCM (100% vs 23.8%) and family history of SCD (100% vs 16.7%) in troponin and non-troponin mutation respectively. Ascertainment bias is a well-recognised confounding feature of HCM genetic studies[1]; additionally, differences in the age and family history of patients recruited in each group are pertinent confounders to this study. However, the greatest limitation of this work is apparent in Sakata *et al*'s fig 2, which suggests that, while overall differences exist between the two groups, a proportion of non-troponin mutation patients also exhibit exercise-induced LVSD. This can be interpreted to mean that a subgroup of non-troponin mutation patients also exhibit a physiology akin to that of troponin mutation patients. It is striking that so many in the non-troponin mutation group are older and do not have known familial HCM, suggesting a mixed group of "phenocopies" as well as some true sarcomeric HCM. Thus the data are compatible with a different interpretation – that exercise-induced LVSD is characteristic of typical familial sarcomeric HCM per se. Rather like an abnormal bp response, exercise-induced LVSD may more likely be a manifestation of aberrant HCM physiology than a manifestation of any given gene mutation. Subgroups with sarcomeric HCM in the non-troponin mutant group would be statistically subsumed by the greater mass of patients with no change in their LV function. While the consequences of confounders are ill-defined, they may nevertheless limit the generalisability of these findings.

Another limitation of this study is the use of supine ergometer exercise and radionuclide ventricular function monitoring with a cadmium telluride detector (VEST). Since abnormal bp responses during exercise represent a prognostic indicator in HCM,[4] there has been extensive interest in the haemodynamic determinants of this phenomenon. Pertinent to the present study, some investigators suggest that abnormal bp responses are due to a profound impairment of cardiac output augmentation (ie, systolic function) on exercise.[7] Other investigators have disputed this finding[8] by suggesting that abnormal bp responses are due to an exaggerated fall in systemic vascular resistance due to vasodilation in non-exercising vascular beds instead of the "normal" vasoconstrictor response.[9 10] Both these aberrations would incur abnormal bp responses, though through different mechanisms. These discrepancies may relate, in part, to limitations of VEST.[8] While VEST has been used in numerous studies, there are potential methodological difficulties (eg, not being able to ensure that the detector faithfully follows the ventricle during exercise despite visual adjustment pre and post-exercise); it has not been validated against invasive studies.[8] These limitations may have been further complicated by the use of VEST to determine supine exercise haemodynamics. These limitations notwithstanding, previous VEST studies in HCM attest to the common physiology of HCM patients, which is similar even in obstructive and non-obstructive disease.[7 11 12] This common physiology of HCM reinforces the proposal that at least some of the non-troponin mutation group with seemingly different physiology may not have had sarcomeric HCM but may instead have been phenocopies.

WHAT ARE THE CLINICAL CONSEQUENCES OF THIS STUDY?

There is a significant clinical need for better surrogate markers for HCM prognosis, since identifying high-risk HCM patients for aggressive prophylactic therapy (eg, implantable cardioverter defibrillators) is at present imprecise.[4] While this study suggests that a subgroup of HCM patients exhibit severe physiological aberrations, at least at present it does not support exercise-induced LVSD as a clinical test for prognostication. In a prospective exercise echocardiographic study of 35 HCM patients, exercise-induced LVSD at baseline was associated with clinical deterioration (eg, by deteriorating resting LV function) and worse clinical outcome at 6.4 years' follow-up (fig 1). Do the

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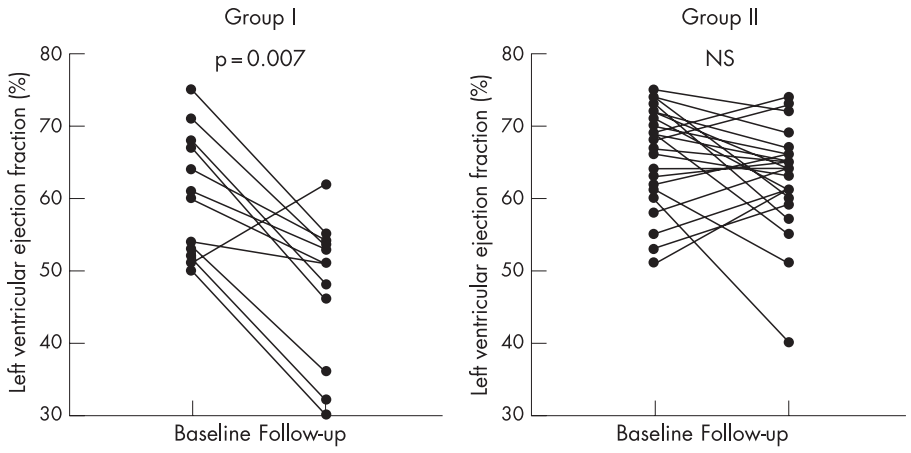

Figure 1 Left ventricular ejection fraction at baseline and at last follow-up evaluation in patients of group I (EILVSD) and group II (Non-EILVSD). This study demonstrates that patients with exercise-induced left ventricular systolic dysfunction (EILVSD) show a markedly increased potential for deteriorating ventricular systolic function at 6.4 years' follow-up. While this study was not powered for formal clinical endpoints (eg, mortality or sudden cardiac death), intriguingly, though not conclusively, these events appeared to be increased in Group I.[13] Reprinted with permission from International Journal of Cardiology, vol 1, Francesco Pelliccia, Cumulative exercise-induced left ventricular systolic and diastolic dysfunction in hypertrophic cardiomyopathy, pp 1–2, copyright Elsevier (2008).

patients identified by Pelliccia *et al*[13] in their Group 1, with exercise-induced LVSD and a poorer prognosis, overlap with the troponin mutation patients identified with exercise-induced LVSD by Sakata *et al*? While both studies are of great interest, bearing in mind the limitations of study size, power and methodology, Sakata *et al*, to their credit, are circumspect about the mechanistic and clinical applicability of their study pending much larger studies.

WHAT ARE THE MECHANISTIC CONSEQUENCES OF THIS STUDY?

Whether or not the specificity of these findings for troponin mutations is confirmed or extended to a broader group of other sarcomeric HCM patients with aberrant physiology, the study by Sakata *et al* raises a number of as yet unexplored novel mechanistic questions. There is extensive precedent for episodes of exercise-induced contractile dysfunction in ischaemic heart disease; this has broadly been termed myocardial stunning.[14] This persisting contractile dysfunction resulting from ischaemia has been attributed to energy deficiency as manifested by the decreasing myocardial adenine nucleotide pool (ie, [ATP+ADP+AMP]) and the ensuing alterations in oxygen radicals and calcium homeostasis.[15] We and others have proposed, with substantial supporting evidence, that HCM is a disease of energy deficiency.[1] In HCM, could sarcomeric rather than ischaemic energy deficiency be exacerbated during exercise sufficiently to cause systolic dysfunction? If so, are mechanisms similar to that enacted during ischaemic stunning pertinent to HCM-induced exercise-induced LVSD (HCM-induced "stunning")? It is plausible that some HCM patients, as identified by Sakata *et al*, experience particularly extreme energy deficiency as their mutations appear to be especially energetically profligate.[16 17] Furthermore, there are also other similarities between ischaemia and HCM. Severe microvascular dysfunction is found in HCM, manifesting as impaired coronary flow reserve in hypertrophied segments, and this may mediate ischaemia during exercise, especially in the subendocardium.[18] Coronary microvascular flow impairment is a potent long-term predictor of adverse LV remodelling and systolic dysfunction, which may exacerbate energy deficiency.[19] To test the HCM-induced "stunning" hypothesis, exacerbation of energy deficiency during exercise should be formally demonstrated in HCM patients. Moreover, a comparison should be made between the cellular consequences of exercise-induced energy deficiency and ischaemic stunning. If these two conditions prove mechanistically similar, HCM animals may prove particularly tractable models in which to study the complexities of stunning[14] and the sizeable stunning literature may be reciprocally informative regarding the pathogenesis of HCM.[15]

Repetitive episodes of fatigue-inducing exercise in HCM may induce contractile dysfunction, which is associated[13] with long term ventricular dysfunction and may portend ominous outcomes. There is, however, little evidence at this stage that symptom-limited echocardiographic or radionuclide exercise testing is warranted in identifying high-risk patients as a genetic surrogate or for clinical prognostication purposes. Nevertheless, these studies provide a good rationale to investigate the role of exercise-induced exacerbation of energy deficiency and stunning in HCM. They also provide another rationale to warn HCM patients to be wary of extreme recreational or professional exercise.

Competing interests: None declared.

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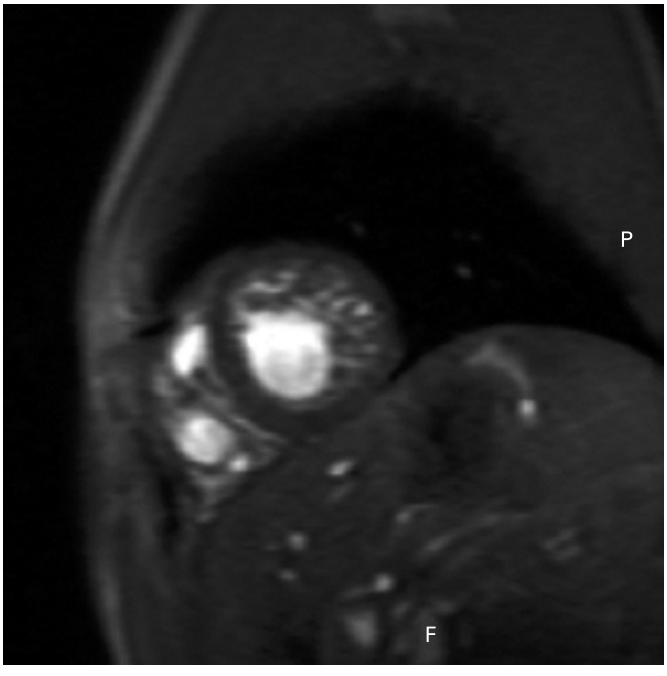
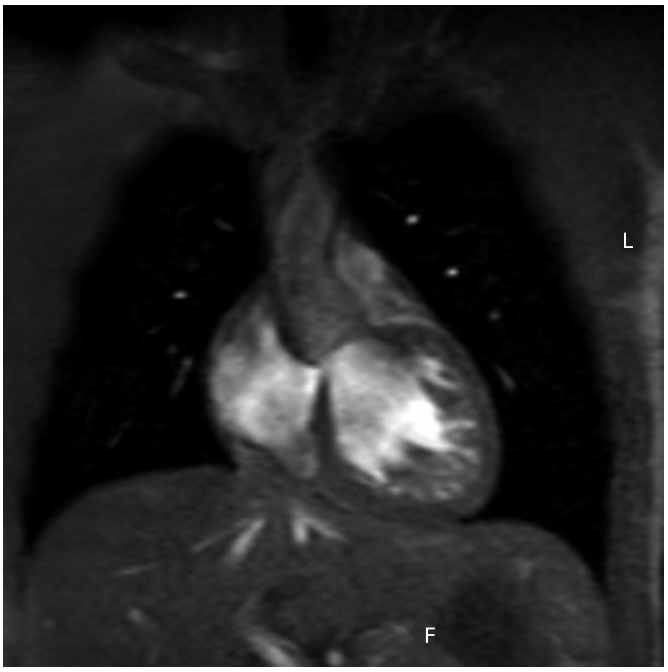
Images in cardiology

Apical hypertrophic cardiomyopathy and left ventricular non-compaction: two faces of the same disease

A 15-year-old male came to our clinic because his father had died suddenly with a previous diagnosis of apical hypertrophic cardiomyopathy at age 38. His father's records said he had congestive heart failure, a maximal left ventricular wall thickness of 28 mm, biventricular systolic dysfunction and left atrial hypertrophy on echocardiography. A female cousin of the father had had a heart transplant because of restrictive hypertrophic cardiomyopathy with severe heart failure (the explanted heart showed hypertrophy, myocyte disarray and fibrosis). At 18 years of age, our patient was asymptomatic on normal physical examination. The ECG demonstrated sinus rhythm with biventricular hypertrophy. The echocardiogram showed a normal wall thickness in the basal and mid-left ventricular segments and prominent trabeculations in the apical posterior, inferior and lateral walls. The diagnosis of left ventricular non-compaction was confirmed on cardiac magnetic resonance imaging (panels A and B). Holter monitoring was normal. Exercise echocardiography demonstrated an increase in ejection fraction (from 60% to 68%) and a rise in systolic blood pressure (from 120 mm Hg to 170 mm Hg). Genetic testing demonstrated a heterozygous mutation from guanine to adenine at nucleotide 2263 of the *ACTC* gene that causes a change from glutamic acid to lysine at the amino acid 101 of the protein (E101K). An association of this mutation with non-compaction and septal defects has been subsequently confirmed in six families from Galicia, Spain, and two from Switzerland-Germany. These and other cases demonstrate the association between mutations in cardiac sarcomeric protein genes and left ventricular non-compaction.



Panel A



Panel B

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