OPINION

Myocardial energy depletion and dynamic systolic dysfunction in hypertrophic cardiomyopathy

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Abstract | Evidence indicates that anatomical and physiological phenotypes of hypertrophic cardiomyopathy (HCM) stem from genetically-mediated, inefficient cardiomyocyte energy utilization, and subsequent cellular energy depletion. However, HCM often presents clinically with normal left ventricular (LV) systolic function or hyperkinesia. If energy inefficiency is a feature of HCM, why is it not manifest as resting LV systolic dysfunction? In this Perspectives article, we focus on an idiosyncratic form of reversible systolic dysfunction provoked by LV obstruction that we have previously termed the 'lobster claw abnormality' — a mid-systolic drop in LV Doppler ejection velocities. In obstructive HCM it explains the mid-systolic closure of the aortic valve, the bifid aortic pulse, and why patients cannot increase stroke volume with exercise. This phenomenon is characteristic of a broader phenomenon in HCM that we have termed dynamic systolic dysfunction. It underlies the development of apical aneurysms, and rare occurrence of cardiogenic shock after obstruction. We posit that dynamic systolic dysfunction is a manifestation of inefficient cardiomyocyte energy utilization. Systolic dysfunction is clinically inapparent at rest. However, it becomes overt through the mechanism of afterload mismatch when LV outflow obstruction is imposed Energetic insufficiency is also present in nonobstructive HCM. This paradigm suggests new therapies. Other pathways that might be central to HCM, such as myofilament Ca^{2+} hypersensitivity, and enhanced late Na^{+} current, are discussed.

Hypertrophic cardiomyopathy (HCM) is a common inherited heart disease with a prevalence of at least 1 in 500. Presentation is highly variable even within families, and although the majority of affected individuals lead a normal life, some develop severe, progressive heart failure symptoms, angina, or arrhythmia, and others die suddenly, either with or without previous symptoms. Left ventricular outflow tract (LVOT) obstruction occurs in two-thirds of patients either at rest or after provocation and can be improved by negatively inotropic drugs, surgical septal myectomy, or alcohol septal ablation[1]. Patients judged to be at high risk of sudden death (SCD) from ventricular fibrillation can be treated with an implanted defibrillator, most often as primary prevention, or for secondary prevention after surviving a potentially lethal ventricular arrhythmia[2,3].

A crucial advance in our understanding of HCM was made in 1990 with the first report of a disease-associated mutation[4]. Subsequently, multiple disease-associated mutations have been discovered, most coding for sarcomeric proteins[5]. Mutations in multiple genes, encoding sarcomeric or nonsarcomeric proteins, lead to similar clinical manifestations; this observation gives hope that understanding the final common pathways that link known disparate mutations might lead to new and widely applicable therapies. Most of the mutations act as dominant negatives; they produce poisoned peptides, in which the mutant polypeptide produced disrupts the activity of the wild-type gene. An exception is the truncation mutations in *MYBPC3* in which haploinsufficiency (a reduction in protein production) has been shown. In myectomy specimens from patients with an *MYBPC3* truncation mutation, protein content was reduced by 24–33% compared with transplant donor, or non-*MYBPC3* myectomy specimens[6,7].

In vitro experiments on preparations from mutant HCM cardiomyocytes have produced strikingly contrasting results; both gain and loss of contractile function have variously been demonstrated[8]. See, for example, the compilation of disparate results

published just for the R403Q mutation in *MYH7*, which encodes myosin-7 the cardiac β-myosin heavy chain[9]. Force generation with exposure to Ca^{2+} and the degree of leftward displacement (in most mutations) of force–Ca^{2+} curves is the method of determination. The difference between experiments might depend on intrinsic differences in the mutations, but also on the wide variety of experimental models used. Early experiments with the myosin heavy chain mutant R403Q showed loss of function, leading to the hypothesis that hypertrophy was a compensation for decreased force generation; others have shown increased sensitivity. Subsequent work with thin filament mutations showed increased Ca^{2+} sensitivity of force generation.

Despite the bewildering array of differing functional results, two pathophysiological pathways from sarcomeric mutations to a HCM phenotype have been consistently experimentally validated: first, inefficient energy utilization (energy wasting for tension development) and, second, increased myofilament Ca^{2+} sensitivity. In this Perspectives article, we focus primarily on the energy depletion hypothesis, but we also summarize the evidence for Ca^{2+} sensitization, and discuss how the two theories overlap. Increasing evidence indicates that energy depletion has an important role in the development of hypertrophy and in the wider pathophysiology of HCM[9-15]. We summarize this evidence, and then discuss the phenotypic manifestations of energy depletion in three realms of cardiac function: diastolic dysfunction, dynamic systolic dysfunction (especially against imposed afterload), and arrhythmogenesis. In particular, we show how patients with HCM experience a highly idiosyncratic form of systolic dysfunction, which we posit is best explained by inefficient utilization of energy.

Energy Depletion, HCM and Diastole

The theory that the failing heart is running out of fuel is a longstanding one, going back to the early twentieth century[11]. The energy turnover of the normal heart can only be described as extravagant. The daily cardiac turnover of ATP, an astonishing 6 kg, is very many times the mass of the heart itself, and its myocardial ATP pool[16]. In <10–15 s, the total amount of ATP present within a myocyte is consumed by myocardial work and requires constant replenishment[17]. High energy needs make the myocardium sensitive to genetic and acquired perturbations in energy supply, and to inefficiency in its utilization, which result in the HCM phenotype in some patients[12,13]. The rationale for inefficient energy utilization as a cause of the HCM phenotype rests on several lines of evidence.

First, high-energy phosphate metabolism can be assessed *in vivo* in the heart using ^{31}P-magnetic resonance (MR) spectroscopy. Investigators compared the cardiac phosphocreatine (PCr) to ATP ratio in 31 patients harbouring mutations in the genes for either β-myosin heavy chain, cardiac troponin T, or myosin-binding protein C, and in 24 control individuals. The PCr/ATP ratio was reduced in the patients with HCM by 30% relative to controls, and the reduction was of a similar magnitude in all three disease-gene groups, and not related to the degree or presence of hypertrophy[13,17]. ATP is produced in the mitochondria, but is used elsewhere, mainly by sarcomeric proteins and ion transporters. PCr, the most abundant high-energy phosphate in the heart, acts as an energy shuttle and as an energetic reserve, moving high-energy phosphate from the mitochondria to sites of utilization. In heart failure, cytosolic levels of ATP are generally zealously maintained, whereas PCr levels fall[18,19].

Second, PET scanning using clearance of ^{11}C-acetate as a semiquantitative measure of myocardial oxygen consumption has shown reduced consumption in patients with HCM as well as genetic carriers[17,21,22]. However, myocardial stroke work was reduced to an even greater extent than oxygen consumption; myocardial efficiency (the ratio of stroke work to

myocardial oxygen consumption) was, therefore, decreased. A combined *in vitro* and *in vivo* study using tissue of genotype-positive patients with HCM, and PET and cardiac MR scans, revealed an increase in energy tension–cost based on an imbalance between force-generating capacity and ATPase activity[9,14].

Third, HCM phenocopies, caused by nonsarcomeric protein mutations can develop hypertrophy that resembles HCM, and also have similar flaws in cellular energetics. Examples are a mutation in the γ_2 subunit of 5′ AMP-activated protein kinase (AMPK; known as the 'cellular thermostat' because of its central role in energy sensing and regulation) that was found to cause an HCM-like familial syndrome[23,24]. Similarly, maternally-inherited HCM owing to mutations in mitochondrial tRNA have been described[25], with demonstrated defects in oxidative metabolism; all three respiratory chain complexes tested showed reduced activity. Abnormal mitochondrial electron microscopic morphology with disordered function have been described in HCM[26,27]. Patients with Friedreich ataxia, an autosomal recessive neurological disorder, also develop a syndrome of otherwise unexplained left ventricular hypertrophy. Mutations in the frataxin gene (*FXN*) result in reduced protein levels, leading to insufficient biosynthesis of iron–sulphur clusters that are required for mitochondrial electron transport and, therefore, ATP generation[28]. Moreover, two groups have shown impaired myocardial energetics with MR spectroscopy in patients with Friedreich ataxia associated with hypertrophic heart disease[29,30].

Fourth, energy depletion is hypothesized to allow an increase in cytosolic Ca^{2+} that might mediate an upregulation of transcriptional processes that result in hypertrophy[12]. MR spectroscopy has shown that the observed levels of energetic depletion in HCM could compromise sarco/endoplasmic reticulum calcium ATPase (SERCA), that transports Ca^{2+} from the cytosol into the sarcoplasmic reticulum, because of the very high obligate energy requirements of this ion transporter[8]. Dysregulation of Ca^{2+} cycling and elevation of

intracellular Ca^{2+} has been shown in HCM cardiomyocytes derived from induced pluripotent stem cells (iPSCs). Sustained elevation of Ca^{2+} is a known trigger for activation of calcineurin, which is an effector of hypertrophy. In iPSC-derived HCM myocytes, inhibition of calcineurin, and also of cellular Ca^{2+} inflow by verapamil, reduced hypertrophy[32].

Multiple converging, genetically-mediated metabolic pathways that are associated with an increased energetic cost of tension development, therefore, lead to the hypertrophic phenotype: classic autosomal dominant HCM sarcomeric mutations, defective cellular energy-sensing machinery, autosomal recessive Friedreich ataxia, and genetic morphologically and functionally disordered mitochondria.

Passive viscoelastic properties of human HCM cardiomyocytes are similar to those of normal hearts and so cannot account for increased stiffness of HCM hearts[38]. Diastolic relaxation is a highly energy-dependent process; diastolic dysfunction owing to impaired relaxation is the most common phenotypic physiological abnormality in patients with HCM[33], and diastolic dysfunction has been associated with abnormal energetics in experimental models of HCM[9,34,35]. The additional demonstration of diastolic dysfunction in HCM phenocopies and in Friedreich ataxia[36,37] has driven development and acceptance of the theory that energetic impairment, hypertrophy, and diastolic dysfunction are causally linked[23].

An alternate explanation is that mutant myofilament Ca^{2+} sensitivity directly causes diastolic dysfunction, and desensitization has been shown to improve it[31]. Studies in phosphorylation-deficient *MYBPC3* mice suggest an important role for protein kinase A-mediated phosphorylation of this protein to enhance lusitropy[39]. The enhanced late Na^{+} current observed in HCM increases cytosolic Ca^{2+}, which increases cross-bridging and directly slows diastolic relaxation[40].

[H1]Systolic dysfunction

[H2] At rest

If energy insufficiency is a feature of HCM, why is it not manifest as resting systolic dysfunction on echocardiography? Ejection fraction is normal or hyperdynamic in HCM, except infrequently in the 2% of patients who develop transformation into LV hypokinesia owing to diffuse fibrosis.[61] A disparity often exists between the macroscopic assessment of global ejection fraction in patients with HCM who have decreased diastolic volumes, and the more granular assessment of decreased systolic strain even at rest. Reduced systolic strain is commonly detected both with echocardiographic speckle-tracking and using cardiac MR in patients with HCM, and correlates with the extent of exercise impairment even in nonobstructed patients[41]. van Dijk *et al*. found normal global systolic function in patients with impaired cardiomyocyte peak force generation and blunted length-dependent activation (Frank–Starling mechanism) in patients with *MYBPC3* mutations[7]. Hypokinetic sarcomeres were found in these patients with normal macroscopic LV systolic function, irrespective of the four different mutations studied[7]. Thus, subclinical systolic LV dysfunction at rest is common in HCM; the underlying substrate for load-induced dynamic systolic dysfunction is present even when there is normal global function at rest.

[H2] After exercise

Further evidence of latent dynamic systolic dysfunction can be elicited in some patients with HCM after exercise. During exercise, regional and global systolic wall-motion abnormalities can occur in patients with either obstructive or nonobstructive HCM, in the absence of epicardial coronary disease[42-44]. The question of whether exercise-induced wall-motion abnormalities occur because of energy depletion from inefficient utilization or owing to

microvascular ischaemic disease leading to impaired ATP generation is controversial, and is discussed in detail below. Until recently, *in vivo* assessment of high-energy phosphate stores were performed at rest for technical reasons. Dass *et al*. studied 35 patients with HCM (of varying genotypes) with a resting outflow gradient <30 mmHg and matched controls, performing MR spectroscopy before and during leg-raise exercise inside the scanner[45]. As expected, the PCr/ATP ratio was lower at rest in patients with HCM. With exercise, the ratio dropped a further 8 ± 17% in patients, but not in controls. The resting energetic impairment did not correlate with the extent of hypertrophy, and only weakly with late gadolinium enhancement.

[H2] With imposition of afterload

Three phenomena, with features unique to HCM, illustrate the vulnerability of the energy inefficient myocardium to the imposition of obstruction and afterload: the mid-systolic drop in LV ejection velocities, apical aneurysm formation in mid-cavity obstruction, and rarely, profound systolic hypokinesia, or in extreme cases, cardiogenic shock when latent obstruction becomes persistent and severe.

[H3] The 'lobster claw abnormality'

In patients with HCM and a LVOT gradient ≥60 mmHg, an abnormal Doppler ejection velocity pattern occurs in the left ventricle, just below the tips of the mitral valve leaflets and also, therefore, below the site of LVOT obstruction. This phenomenon has been termed the 'lobster claw abnormality' because of its characteristic appearance[46] (FIG. 1). Early in systole, when the left ventricle is unimpeded, LV ejection velocities are normal (FIG. 2a). Simultaneously with mitral–septal contact, an abrupt reduction in ejection velocities occurs because of the sudden imposition of afterload (FIG. 2b). The mid-systolic reduction in

ejection velocities is reversed when outflow obstruction is alleviated or abolished[47,48]. The drop in velocities explains some of the well-recognised clinical features of HCM, for example the biphasic carotid pulse and mid-systolic closure of the aortic valve[49]. Conklin and colleagues extended this observation by measuring flow in the proximal descending aorta by Doppler echocardiography and showed an exacerbation of the reduction in flow after administration of dobutamine[50]. The appearance of the mid-systolic drop in velocities can vary between patients and from hour to hour depending on the severity of the outflow gradient, and the capacity of the left ventricle to overcome the obstruction[48]. However, the timing of the nadir always moves precisely in synchrony with timing of the peak velocity of the continuous-wave Doppler in the outflow tract and, therefore, with peak afterload[46]. Breithardt *et al*. used tissue Doppler imaging to record a similar drop in systolic myocardial velocities with obstruction[51]. This observation demonstrates that the lobster claw abnormality is not merely a flow phenomenon, but is caused by myocardial dysfunction (FIG. 3). Barac and colleagues also showed premature termination of septal contraction with obstruction that was reversed by abolition of obstruction[47].

Ross explained the concept of afterload mismatch as the inability of the left ventricle to "…maintain a normal stroke volume against the prevailing systolic load on the left ventricle, and it generally occurs in the setting of limited preload reserve."[52]. Afterload mismatch was Ross's term to explain the rapid recovery of poorly contracting myocardium after relief of outflow obstruction in aortic stenosis[52]. At the time, the actual mechanics of this phenomenon at the myocardial level were unknown. Increasing evidence now shows that aortic stenosis can cause severe energetic insufficiency that is mediated by increased afterload and is normalized after aortic valve replacement. Subclinical LV impairment can be demonstrated during stress, and this impairment responds to surgical correction[53-56]. Ross contrasted afterload mismatch in aortic stenosis to patients with irreversibly depressed

myocardial contractility, whose true (low) ejection fraction is unmasked by correction of the (usually mitral) regurgitation.

In HCM, LV performance can be doubly affected by energy inefficiency. Energy depletion can impair diastolic relaxation, which is nearly ubiquitous in HCM, and the effect of the acute imposition of afterload on an energy-depleted left ventricle reduces systolic flow. Together, diastolic and systolic dysfunction contribute to the observed inability to increase stroke volume with exercise, and thereby to symptoms of exercise intolerance and heart failure[57]. Energetic insufficiency can be genetic (HCM) or acquired (aortic stenosis), or be from a combination of both (obstructive HCM).

[H3] Energy inefficiency or ischaemia?

Is the mid-systolic drop in ejection velocities and flow simply due to ischaemia from microvascular disease, or to ischeamia from oxygen supply–demand mismatch? We argue that it is not due to either ischaemic cause. First, there is the important clinical observation that angina at rest is uncommon in obstructive HCM. Secondly, substantial evidence indicates that resting ischaemia does not occur in patients with resting obstruction, as assessed using various techniques.

Cannon and colleagues assessed myocardial lactate consumption in the coronary veins. Myocardial lactate consumption at rest was normal, even in the presence of high resting gradients[58,59]. Lactate production did not occur until atrial pacing commenced[58,59]. Moreover, resting perfusion defects are not visualized on thallium scintigraphy in the great majority of patients[60]. Only 24% of patients had resting perfusion defects, and these patients had reduced resting systolic function owing to myocardial fibrosis in the end-stage phase of the disease[61]. Additionally, overall resting myocardial blood flow (assessed using PET and ^{13}N-labelled ammonia) did not differ between patients with HCM and controls (although the

vasodilator ‘reserve’, assessed using dipyridamole, was blunted)[62]. Accordingly, Crilley *et al*. showed that the myocardial perfusion reserve index in these patients did not correlate with energy impairment[13]. Carriers of the HCM-associated *MYBPC3* mutation have reduced myocardial efficiency in the absence of hypertrophy and microvascular dysfunction[63]. Together with other findings[17], Timmer and Knaapen concluded that “these results imply that impaired energetics are, at least in part, the direct result of ATP-wastage by mutated sarcomeres, and may precede coronary microvascular dysfunction in the pathophysiological cascade”[22].

From this evidence, we believe that the mid-systolic reduction in LV Doppler ejection velocities, which is routinely and universally observed in patients with LVOT gradients of ≥60 mmHg, is not caused by ischaemia, but by another phenomenon. We posit that inefficient utilization of energy in HCM is the cause. When ischaemia is superimposed on top of energetic impairment, the effects on systolic function and diastolic function are adversely synergistic, especially after exercise.

[H3] Resting wall motion abnormalities

Afterload-induced systolic dysfunction can trigger the occurrence of apical akinetic aneurysm in severe mid-LV obstruction, and heart failure and cardiogenic shock in the most extreme cases. In HCM with mid-LV obstruction, the LV apex can be subjected to very high impedance to ejection, which can lead to an apical akinetic aneurysm[64]. The same mid-systolic drop in LV ejection velocities is seen just before the obstructing segment of the left ventricle (FIG. 4). The phenotype can be severe, with intrusive heart failure symptoms[65,66], and ventricular arrhythmias can occasionally cause sudden death. The apical aneurysm increased the risk of thrombus formation and subsequent stroke or other systemic embolism[66]. These patients are difficult to manage, because symptoms are often refractory to

therapy, and they have a significantly worse prognosis than those with isolated apical hypertrophy. In mid-LV obstruction, though afterload mismatch begins the process of apical aneurysm formation, ischaemia owing to supply–demand mismatch and fibrosis can make dyssynergy irreversible. An interesting corollary might be seen in Takotsubo cardiomyopathy; evidence now shows that patients with this (in some ways phenotypically similar) syndrome have severe energetic impairment at presentation, as measured using ^{31}P-MR spectroscopy, and that metabolic abnormalities persist at 4-month follow-up[67,68].

When patients with latent LVOT obstruction suddenly develop persistent severe obstruction, systolic wall-motion abnormalities can occur in segments that previously had normal wall motion. Resolution of LVOT obstruction precedes resolution of severe wall-motion abnormalities. Cardiogenic shock is a rare complication of obstructive HCM and usually occurs in the context of reduced preload owing to dehydration. In patients with latent obstruction who suddenly develop a persistently high resting gradient, we have observed progressive LV systolic dysfunction and cardiogenic shock. Although some patients can be rescued with volume loading and negative inotropes[69], we have seen several individuals in whom this spiral could be arrested only by surgical relief of obstruction[70]. These patients had systolic dysfunction that was disproportionate to the degree of ischaemia manifest on the electrocardiogram, and disproportionate to the minimal rise in cardiac biomarkers. Their syndrome reversed within minutes of surgical relief of LVOT obstruction (FIGS 5,6). Although we cannot exclude additional factors (such as catecholamine or other neurohumoral effects), we believe their dramatic presentation was caused by acute myocardial energy depletion — a concept supported by the rapid reversal after relief of obstruction.

[H3] Normal and impaired responses to afterload

Is it possible that the mid-systolic drop in LV ejection velocities and flow is caused by obstruction alone, without HCM impaired energetics? Would normal individuals with normal left ventricles have the same degree of mid-systolic drop in the event of severe outflow obstruction? We cannot exclude this possibility. However, previous experiments argue in favour of intrinsic latent myocardial dysfunction having a role in the mid-systolic drop. Experiments in dogs with normal left ventricles showed that, after chronic aortic constriction, stroke volume returned towards normal.[98,99] Moreover, after angiotensin administration to patients with a spectrum of LV dysfunction, stroke volume fell or remained constant only in those with compromised LV function[96]. In patients with normal left ventricles stroke volume and stroke work increased. In another study of 12 control patients given low dose intravenous angiotensin there was no change in tissue Doppler echocardiographic velocities[97]. In contrast, 21 non-obstructive HCM patients had a fall in tissue Doppler velocities even with small increases in afterload, including a drop in velocities in the non-hypertrophied posterior wall. "Systolic LV function is easily impaired by slight increases in afterload in patients with HCM".[97] These experimental observations are qualitatively similar to those observed by Barac and Breithardt in the course of gradient rise and fall.[47,51]

Compensation to afterload in the normal left ventricle is accomplished first by an increase in preload, dilatation of the left ventricle, and a Frank–Starling-mediated increase in contractility; this initial response is followed during the chronic phase by a compensated period marked by LV hypertrophy[71]. In HCM, the capacity of the left ventricle to use preload as compensation can be compromised acutely and chronically because of impaired diastolic function, which could contribute to the observed instantaneous fall in LV stroke volume seen during the mid-systolic drop[50]. Abnormalities from sarcomeric mutations have been shown to affect LV contractile reserve. When isoproterenol was administered to mouse hearts with troponin T mutation-I79N an impaired responsiveness to inotropic stimulation was

demonstrated, along with worsening of diastolic function compared with normal controls[72], and compared with a control troponin mutation with no effect on myofilament sensitivity. The investigators reviewed similar results with other models of sarcomeric HCM, and discussed how the findings could be explained by altered Ca^{2+} kinetics, including decreased energetics. In an earlier study using this mouse model of I79N mice, systolic function was increased relative to controls; however, the inotropic response to isoproterenol was impaired. The increase in LV fractional shortening was 9% vs 26% in controls [73]. Also, four out of 13 of the mice developed global hypokinesia and died. The investigators hypothesized that with increased Ca^{2+} sensitivity, the fibres might already be operating at the flat part of the force–pCa relationship[73]. Energetic depletion could also explain this phenomenon.

The integrity of the Frank–Starling mechanism was evaluated in preparations from myectomy specimens of patients with five different HCM-related mutations of either thick or thin filaments. These experiments involved force measurements from single cardiomyocytes. Ca^{2+} sensitivity was demonstrated in all 38 patient samples and every mutation. Length-dependent activation was lower in all HCM samples compared with donor samples. This impairment of the Frank–Starling mechanism was normalized when mutant troponin proteins were replaced with wild-type protein. Protein kinase A also increased phosphorylation of myosin-binding protein C and troponin I, and normalized length-dependent activation in the donors with sarcomere-negative HCM and truncating *MYBPC3* mutations, but not in HCM caused by missense mutations[74]. The process of phosphorylation by protein kinase A requires ATP for catalysis and, therefore, might depend on energetic state.

In summary, though macroscopic LV systolic function may appear normal or even increased in HCM at rest, multiple imaging modalities, pulsed Doppler, tissue Doppler, strain echocardiography and CMR strain have shown subclinical systolic abnormalities at rest in non-obstructive HCM. Imposition of afterload in the form of LVOT obstruction (or in

experimental preparations by angiotensin) exacerbates dynamic systolic dysfunction. In light of the ample evidence of energetic depletion in HCM, even in non-obstructive disease, we have argued that spectrum of dynamic dysfunction- the mid-systolic drop in LV ejection velocities, the nascent onset of aneurysms in mid-LV obstruction, and rarely shock are due to exacerbations of chronic energy depletion.

[H1] Ventricular tachyarrhythmias

Fractionation of paced ventricular electrocardiograms has been observed in patients with HCM who survive ventricular fibrillation, but not in those without ventricular fibrillation[75]. Clinically important ventricular arrhythmias can now be studied in patients with HCM using data from implanted cardioverter–defibrillators of patients who have had therapeutic discharges. In 230 recipients of implantable cardioverter–defibrillators, O'Mahony *et al*. analysed 56 ventricular arrhythmias from 29 patients[76]. The arrhythmia was monomorphic ventricular tachycardia in 86% of cases, ventricular fibrillation in 9%, and polymorphic ventricular tachycardia in 5%. Younger patients had shorter cycle length ventricular tachycardia, in keeping with the peak incidence of sudden cardiac death in younger patients and suggesting a genetic modifier of the re-entry circuit. The majority of ventricular tachycardia was monomorphic, and 67% was terminated by antitachycardia pacing[76]. In nine patients with sustained ventricular arrhythmia, Cha *et al*. found that more than half had monomorphic ventricular tachycardia, which frequently could be terminated (in 94% of patients) by pacing that interrupted re-entrant pathways[77].

Sustained ventricular arrhythmias originate from two mechanisms. First, they originate from micro and macro re-entry. Second, they originate from abnormal automaticity, including triggered activity from early and late afterdepolarizations, and from enhanced pacemakers.

[H2] Re-entry

Fibrosis is a common finding in HCM hearts, especially in patients who have died suddenly. Volumetric cardiac MR delayed hyperenhancement (expressed as a percentage of the LV mass) has been associated with sudden cardiac death or aborted sudden death events[78]. The relationship with fibrosis would seem to validate the re-entry mechanism as a cause for monomorphic ventricular arrhythmias in HCM. However, although fibrosis is fairly common in HCM hearts (occurring in 50%), sudden cardiac death is rare, occurring in only 1% per year[2,3]. Even in patients with a level of fibrosis of 15% of LV mass have a rate of sudden cardiac death or aborted sudden death of barely more than 1% per year. [78]

[H2] Abnormal automaticity

Ventricular fibrillation or polymorphic ventricular tachycardia occurred in 14–44% of patients analysed after discharge from an implantable cardioverter–defibrillator[76,77]. These arrhythmias, especially if they occur without preceding premature ventricular contractions are likely to depend on abnormal automaticity. Cha *et al*. found clusters of ventricular arrhythmia in three patients with repeated, sustained ventricular arrhythmia, between four and 25 repeated episodes in 5–120 min[77]. O'Mahony *et al*. observed clustered activity in four patients, between two and five episodes within 24 h[76]. These clusters might indicate that a trigger is acting on top of the underlying substrate, even in patients with re-entry.

Sinus tachycardia or atrial fibrillation have been observed immediately before the sustained ventricular arrhythmia in the majority of patients, suggesting a sympathetic drive to ventricular arrhythmia; tachycardia would also foster cytosolic Ca^{2+} accumulation and ATP depletion that would drive sustained ventricular arrhythmia[77]. Primary ventricular fibrillation, clustered ventricular tachycardia, and the ventricular fibrillation episodes, as well as

tachycardia before episodes, suggest that an enhanced automaticity trigger is acting on top of existing substrate. In HCM, potential triggers for ventricular arrhythmia are a change in the intracellular environment, either depletion of cytosolic energy stores, increased myofilament Ca^{2+} sensitivity, or cytosolic Ca^{2+} overload.

[H3] Depletion of cytosolic energy stores

Impairment of resting energetics, exacerbated during exercise, reduces the ATP available for energy-intensive processes elsewhere in the cell. The sarco/endoplasmic reticulum calcium ATPase (SERCA) hydrolyses ATP to transport Ca^{2+} from the cytosol into the sarcoplasmic reticulum. MR spectroscopy has shown that the levels of energetic depletion can compromise SERCA because of its extreme energy requirements[8]. Impaired function of this pump leads to increased cytosolic Ca^{2+} levels, which results in further Ca^{2+}-induced Ca^{2+} release via activation of ryanodine receptors, potentially leading to malignant arrhythmias. By analogy, catecholaminergic polymorphic ventricular tachycardia is caused by a gain-of-function mutation in the ryanodine receptor gene. A 33% increase in calcium antagonist binding sites are demonstrated in the right atrial appendage of myectomy patients; these receptors were components of voltage-sensitive calcium channels; they are increased in parallel with increases in calcium flux.[79] Increased catecholamine responsiveness has been reported[80].

[H3] Increased myofilament Ca^{2+} sensitivity

Enhanced myofilament Ca^{2+} sensitivity is demonstrated by a left shift of the force–Ca^{2+} relationship. Ca^{2+} sensitization causes susceptibility to arrhythmias without remodelling, that is, without fibrosis or hypertrophy[81]. In mouse papillary muscles, myofibril Ca^{2+} sensitivity changes the shape of ventricular action potentials, induces greater beat-to-beat variability in action potential durations, and increases dispersion of conduction velocities at fast heart rates,

providing an arrhythmogenic substrate[82]. This enhanced arrhythmogenicity was blocked by blebbistatin, a myosin inhibitor that selectively reduces Ca^{2+} sensitivity. Linkage of the energy depletion and the Ca^{2+}-sensitivity mechanisms was shown by Huke and colleagues[83]. Using a mouse model of troponin T I79N HCM, they showed that focal energy deprivation underlies ventricular arrhythmia susceptibility in mice with Ca^{2+}-sensitized myofilaments. In this model, they found dephosphorylation (loss) of connexin-43 (gap junction α1 protein) that normally promotes gap-junction coupling[85], with consequent focal slowing of conduction and a proarrhythmic state. ATP depletion was the mechanism for rapid connexin-43 dephosphorylation. In this model, therefore, the two proposed pathophysiological effects — increased myofilament Ca^{2+} sensitivity and energy depletion — were linked. Sudden cardiac death in athletes during competition can reasonably be understood as an 'energy crisis' in this context[12,84,83].

In a mouse models, desensitization to calcium as a result of gain-of-function mutations in myofilaments prevents development of the HCM phenotype[31]. The diastolic dysfunction and hypertrophy induced by the tropomyosin mutation, E180G (Tm180), with increased Ca^{2+} sensitivity, was reversed by desensitization. The investigators created a double transgenic mouse line, crossing Tm180 mice with mice expressing a pseudophosphorylated cardiac troponin I (S23D and S24D (TnI-PP); with reduced calcium sensitivity. Pathological hypertrophy did not occur in mice expressing both Tm180 and TnI-PP and LV performance was improved . A small-molecule inhibitor of sarcomeric contractility (MYK-461) prevents HCM development in mice with a gain-of-function mutation in myosin[92].

[H3] Enhanced late Na^+ current

Investigators from Florence, Italy have highlighted abnormalities of cardiomyocytes from surgical specimens from patients undergoing myectomy. HCM cardiomyocytes showed

prolonged action potential duration owing to increased late Na^+ and Ca^{2+} currents, and decreased repolarizing K^+ current[37]. These abnormalities led to increased, prolonged Ca^{2+} transients, higher diastolic Ca^{2+} concentration, early and delayed afterdepolarizations, and arrhythmogenicity. The investigators found increased activity of calmodulin, a calcium-binding messenger protein, that underlies increased phosphorylation of the L-type calcium channel, phospholamban, the ryanodine receptor, and the late Na^+ channel in the HCM specimens. Sustained activation of calmodulin is driven by increased cytosolic Ca^{2+} concentration[37].

Ranolazine partially reversed the increase in the late Na^+ current, shortened action potential duration, and decreased the frequency of afterdepolarizations[37]. A novel late Na^+ channel-inhibiting agent Eleclazine is currently under investigation in a multicentre trial[86,94]. Although its capacity to increase exercise oxygen consumption through a lusitropic effect is the primary end point, an important secondary end point is the effect of this drug on ventricular arrhythmias assessed using a 30-day monitor[82].

Ventricular arrhythmias are the cause of SCD in HCM, and the prevention of SCD has assumed a central role in HCM clinical care[1-3]. At this time the widely applied method for SCD prevention is the implanted defibrillator; but current risk stratification guidelines have low sensitivity and specificity [2,3]. This may lead to sudden deaths in patients who have not been implanted, and implantation of ICDs in patients who never have appropriate discharges. In addition, sudden deaths are rare, as well, in patients who have had successful myectomy[1] but such patients constitute a minority of patients with high risk profiles. It is hoped that an understanding of the basic pathways leading to ventricular arrhythmias will lead to biological treatments to prevent such deaths, and someday preclude the need for ICDs in many patients. A summary of the known pathophysiological mechanisms underlying development of the HCM phenotype is shown in FIG. 7.

[H1] Treatment of energy depletion

In the modern era, specific pathophysiological HCM derangements have been targeted in the preclinical realm, and trials are beginning in patients[15,87,88]. Targeting cellular energetic impairment is a promising paradigm in HCM. If substrate utilization can be made more efficient and save more energy, then improved contractile reserve results from the same conditions. Various therapeutic agents affect myocardial metabolic pathways[87] and might prove useful in HCM. Therapeutic efforts in this area are in their infancy, but a positive clinical trial has been published[89].

A total of 46 patients with symptomatic, nonobstructive HCM were randomly assigned in a double-blind manner to perhexiline (a metabolic modulator or placebo[89]. Perhexiline has pleiotropic actions including inhibition of long chain fatty acid uptake into the mitochondria by inhibition of carnitine O-palmitoyltransferase 1. In a mouse model of HCM, perhexiline therapy resulted in a metabolic shift from fatty acids to glucose[90]. Energy obtained during glucose oxidation requires less oxygen consumption than fatty acid metabolism, enhancing cardiomyocyte energy efficiency. Despite the lack of LV outflow gradient, patients with HCM had a markedly reduced exercise capacity (peak VO_2) compared with matched healthy controls, and also had impaired diastolic function measured using tissue Doppler imaging. Participants were followed up for a mean of 16 weeks of therapy. The perhexiline group showed a significant increase in peak VO_2 (the primary end point), and in functional class and quality of life. The heart-rate-normalized time to peak filling (nTTPF), a sensitive marker of early LV filling, was measured using radionuclide ventriculography at rest and during exercise. Whereas healthy controls showed a shortening of nTTPF on exercise, patients with HCM showed an abnormal lengthening, which indicates a profound impairment of (energy-dependent) LV active relaxation on exercise. This abnormal response

was almost normalized with perhexiline, which was associated (presumably causally) with a significant improvement in the cardiac energetic impairment (an increase in PCr/ATP ratio).

Other metabolic agents are being investigated in HCM, although these studies are in an early phase. Trimetazidine is being evaluated in a phase IIb clinical trial[91] of symptomatic patients with nonobstructive HCM, to assess a primary end point of peak VO_2.

A small-molecule inhibitor of sarcomeric contractility (MYK-461) suppresses HCM development in mice with a gain-of-function mutation in myosin, in parallel with reductions in fractional shortening and ATPase activity[92]. The investigators compared gene expression of proteins localized to the mitochondria and found dysregulated gene expression in 20% of genes in R403Q mice and 29% of genes in R453C mice compared with wild type.Early treatment of these mice with MYK-461 reduced the percentage of dysregulated mitochondrial genes to 4% and 8%, respectively. These data demonstrated that correction of gain of function at the myofilament level resulted in a normalized cellular metabolic state. This improvement might stem from more efficient energy utilization and less substrate depletion, or directly from correction of the myofilament gain of function.

[H2] Inhibition of the late Na^+ current

Ranolazine has pleiotropic effects, including inhibition of the late Na^+ current. A study of its use in cardiomyocytes obtained from myectomy showed beneficial effects on the contraction–relaxation cycle, which were attributed to improvements in Ca^{2+} signalling rather than a metabolic effect[40,93]. The novel agent GS-6615, which inhibits the late Na^+ current, is currently under investigation in the multicentre LIBERTY-HCM trial[86,94]. A pilot trial investigated whether oral diltiazem attenuated disease progression in patients with preclinical HCM and an identified genetic mutation. [95]. LV end-diastolic diameter improved towards normal in the diltiazem group but decreased further in controls

[H2] Potential future applications

The mid-systolic drop reflects a 'tug-of-war' between the contractile force of the left ventricle and the afterload imposed by obstruction. Its extent, the percent drop to the nadir, and the absolute velocity of the nadir, might be used to assess the inotropic state of the left ventricle to any given magnitude of gradient, longitudinally, and in response to therapy. The mid-systolic drop could act as a biomarker of contractile reserve. Currently, clinical application of metabolic resonance spectroscopy is limited by long acquisition times and low applicability of the technique for individual patients. Improved and shorter protocols, as well as developments allowing measurement of abnormal metabolic flux (rather than steady state levels of metabolites) might increase the clinical relevance of this technique. In the future, the magnitude of energetic impairment might provide prognostic information in both heart failure and sudden death. Otherwise MR spectroscopy might be used to identify which patients with mid-LV obstruction are at highest risk for future apical aneurysm, or inform counselling of individual patients about intense exercise, which is a challenging area with limited evidence. Finally, the concept of energetic insufficiency as a central mechanism in the pathophysiology of obstructive and nonobstructive HCM opens up new areas for potential pharmacological intervention, particularly for patients with nonobstructive disease, for whom current therapeutic options for relief of severe symptoms are very limited.

[H1] Conclusions

Energetic insufficiency can be genetic (HCM) or acquired (aortic stenosis) or result from a combination of both (obstructive HCM). Energy depletion in HCM, and in its phenocopies, explains a wide variety of phenotypic abnormalities. In nonobstructive HCM, preliminary evidence from a clinical trial indicates that improving myocardial energetics improves

rigorously-measured exercise tolerance and also symptoms. In obstructive HCM, energy depletion might best explain the echocardiographic mid-systolic drop in LV ejection velocities and flow. This abnormality is characteristic of underlying, clinically inapparent LV impairment at rest that is exacerbated by exercise, and especially by afterload.

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Author contributions

All the authors researched data for the article, discussed its content, wrote the manuscript, and reviewed and edited it before submission.

Competing interests statement

M.P.F. is the inventor of method of use patents for perhexiline in heart muscle diseases; these patents are owned by Heart Metabolics Ltd in which he has no financial interest. M.V.S. has provided protocol consultation to Heart Metabolics LLC. J.O.M.O. declares no competing interests.

Figure 1 | **Mid-systolic drop in ejection velocities. a** | The 'lobster claw abnormality' is the mid-systolic drop in left ventricular ejection velocities, seen with pulsed Doppler echocardiography at the entrance to the left ventricular outflow tract (LVOT) in a patient with a 90 mmHg LVOT systolic gradient owing to mitral–septal contact. The mid-systolic drop (white arrow) is caused by the sudden imposition of afterload from mitral–septal contact in patients with hypertrophic cardiomyopathy and a LVOT gradient ≥60 mmHg. The feature is direct evidence of the effect of gradient in obstructive HCM; we posit that it is caused by afterload mismatch caused by myocardial energy depletion. **b** | The same patient after disopyramide and abolition of the gradient. Note that the mid-systolic drop in ejection velocities is no longer present.

Figure 2 | LV Ejection velocities in early systole and mid-systole in obstructive HCM. **a** | Early systole before mitral–septal contact. Pulsed Doppler at entrance of left ventricular outflow tract. Mid and late systole is shaded on the second trace. Early systolic unobstructed flow occurs before mitral–septal contact (arrows). **b** | Before mitral–septal contact, flow

courses around the septum and catches the anteriorly displaced mitral valve and sweeps it into the septum. The chordae and papillary muscles act to posteriorly restrain the mitral valve. **c** | After mitral–septal contact. Early systole is shaded on the second trace. The beginning of the mid-systolic drop occurs at the onset of mitral–septal contact, and the abrupt increase in afterload. The nadir of the drop occurs simultaneously with the peak of the continuous wave Doppler gradient and peak afterload (arrow)[46,48]. **d** | The mid-systolic drop is caused by afterload mismatch between the impedance of obstruction and left ventricular contractility.

Figure 3 | **ECG, invasively-measured LVOT pressure gradient, and TDI velocity trace from the basal septum.** Note the simultaneous development of the left ventricular outflow tract (LVOT) gradient (open arrow) and the mid-systolic septal deceleration notch (solid arrow). ECG electrocardiogram; LV left ventricular; TDI tissue Doppler imaging. Reprinted from Breithardt, O.-A. *et al.* Mid systolic septal deceleration in hypertrophic cardiomyopathy: clinical value and insights into the pathophysiology of outflow tract obstruction by tissue Doppler echocardiography. *Heart* **91** (3), 379–380 (2005), with permission from BMJ Publishing Group Ltd.

Figure 4 | **Apical aneurysm in mid-LV obstruction. a** | Pulsed Doppler at the entrance of the obstructing neck of mid-left ventricular (LV) obstruction showing the mid-systolic drop in LV ejection velocities. Trapped blood escapes only from the aneurysm in early diastole. Thin arrow points to the nadir of the mid-systolic drop, and thicker arrow indicates the onset of virtually complete mid-LV obstruction. **b** | Systolic frame from LV cineangiogram of a patient with severe mid-LV obstruction (arrows). There were high resting mid-LV systolic pressure gradients and an apical akinetic aneurysm. We propose that afterload mismatch

initiates aneurysm formation; then ischemia and afterload mismatch act in concert to increase its size. Panel **a** reprinted from Sherrid, M. V. *et al*. Reflections of inflections in hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **54** (3), 212–219 (2009), with permission from Elsevier. Panel **b** reprinted from Po, J. R. F. *et al.* Doppler systolic signal void in hypertrophic cardiomyopathy: apical aneurysm, and severe obstruction without elevated intraventricular velocities. *J. Am. Soc. Echocardiogr.* **28** (12), 1462–1473 © (2015), with permission from Elsevier.

Figure 5 | **Acute heart failure and shock.** 2D echocardiograms performed on admission to the emergency department in a patient with previously diagnosed hypertrophic cardiomyopathy and latent obstruction. Patient had developed refractory cardiogenic shock after a diarrhoeal illness. Hypotension did not respond to copious fluids, intravenous β-blockade, and phenylephrine. **a** | Parasternal long-axis frames showing the septal bulge (wide arrow), mitral–septal contact (thin arrow), and systolic septal dyskinesia (arrowheads). **b** | Mid-left ventricular short-axis frames showing diffuse akinesia with mid-anterior septal and anterior dyskinesia. **c** | Apical four-chamber frames showing the septal bulge (wide arrow) and mitral–septal contact (thin arrow). There is apical and mid-left ventricular dilatation, and severe hypokinesia of the apical and mid-left ventricular segments, but preservation of basilar wall motion. Doppler left ventricular outflow gradient was 90 mmHg. **d** | Cardiac catheterization shows peak-to-peak systolic gradient of 70 mmHg. Coronary arteries were normal. Reprinted from Sherrid, M. V. *et al.* Reversal of acute systolic dysfunction and cardiogenic shock in hypertrophic cardiomyopathy by surgical relief of obstruction. *Echocardiography* **28** (9), E174–E179 (2011), with permission from XXX.

Figure 6 | **Postoperative echocardiogram performed 4 months later.** The format is the same as in FIG. 5. A bioprosthetic mitral valve is now present and myectomy has been performed to thin the septum. **a** | Parasternal long-axis frames showing no left ventricular outflow tract obstruction. The septum is thinned and there is normalization of septal and posterior wall motion. **b** | Mid-left ventricular short-axis frames showing normal wall motion. **c** | Apical four-chamber frames showing normalization of the left ventricular dilatation and normalization of wall motion in the apical and mid-left ventricular segments. Doppler showed no left ventricular outflow gradient. Reprinted from Sherrid, M. V. *et al.* Reversal of acute systolic dysfunction and cardiogenic shock in hypertrophic cardiomyopathy by surgical relief of obstruction. *Echocardiography* **28** (9), E174–E179 (2011), with permission from XXX.

Figure 7 | **Three proposed central pathophysiological pathways for development of hypertrophic cardiomyopathy phenotype in genetic hypertrophic heart disease.** Inefficient utilization of energy by mutant myofilaments leads to energy depletion (detected in patients as a decreased phosphocreatine [PCr]/ATP ratio). Energy depletion is also observed in phenocopies: 5′-AMP-activated protein kinase (AMPK) mutations, Friedreich ataxia, and mitochondrial mutations. Energy depletion pathway (**shown with black arrows**) results in impaired function of sarco/endoplasmic reticulum calcium ATPase (SERCA, because of its high obligate energy requirements) leading to decreased diastolic uptake of Ca^{2+} and cytosolic Ca^{2+} overload. In an adverse feedback loop, elevated Ca^{2+} level impairs the ryanodine receptor leading to even higher diastolic Ca^{2+} levels and ventricular arrhythmias. Energy depletion results in latent global left ventricular dynamic systolic dysfunction, of which the characteristic abnormality is the mid-systolic drop in ejection velocities when obstruction afterload is interposed, although exercise can provoke a

hypokinetic response even in nonobstructed patients. Increased cytosolic Ca^{2+} can lead to ventricular arrhythmias regardless of the mechanism. Diastolic function is highly energy-dependent and energy depletion is associated with impaired relaxation in sarcomeric hypertrophic cardiomyopathy and the phenocopies. Myofilament Ca^{2+} sensitivity (**green arrows)** directly causes inefficient energy utilization and depletion, directly impairs diastolic function, and is arrhythmogenic. Increased cytosolic Ca^{2+} can signal upregulated transcription through mediators of calmodulin (calcium/calmodulin-dependent protein kinase II; CaMKII) or calcineurin. Ca^{2+} overload acting through calmodulin (**red arrows**) enhances late Na^{+} channel and cytosolic Na^{+}, which — through the reciprocal exchange pumps in the sarcoplasmic reticulum and cell membrane — results in Ca^{2+} overload.

Author biographies

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