As described in earlier reviews in this series on the molecular basis of hypertrophic cardiomyopathy (HCM), HCM is one of the archetypal monogenic cardiovascular disorders to be understood at the molecular level. Twenty years after the discovery of the first HCM disease gene, genetic studies still confirm that HCM is principally a disease of the sarcomere. At the biophysical level, myofilament mutations generally enhance Ca\textsuperscript{2+} sensitivity, maximal force production, and ATPase activity. These defects ultimately appear to converge on energy deficiency and altered Ca\textsuperscript{2+} handling as major common paths leading to the anatomic (hypertrophy, myofiber disarray, and fibrosis) and functional features (pathological signaling and diastolic dysfunction) characteristic of HCM. In this review, we provide an account of the consequences of HCM mutations and describe how specifically targeting these molecular features has already yielded early promise for novel therapies for HCM. Although substantial efforts are still required to understand the molecular link between HCM mutations and their clinical consequences, HCM endures as an exemplar of how novel insights derived from molecular characterization of Mendelian disorders can inform the understanding of biological processes and translate into rational therapies. (Circ Res. 2011;109:86-96.)

Key Words: hypertrophic cardiomyopathy □ calcium □ energetics □ translational

Progress in the genetic delineation of Mendelian disorders has afforded us insights into their biology and fuelled expectations that understanding their pathogenesis may yield novel strategies for treatment.\textsuperscript{1} HCM represents an exemplar for such an approach, because its monogenic nature implies that discrete pathways are sufficient to cause disease. By inference, it may reasonably be surmised that modification of these pathways may alter or even prevent disease. HCM patients exhibit variable, often age-related, penetrance and variable disease expression. These observations suggest that the HCM mutations do not inevitably result in disease but that their effects are modifiable by genetic and environmental context. Optimistically, it may follow that interventions modifying these stimuli, or their consequences, may protect or rescue HCM hearts.
Although HCM is characterized by unexplained left ventricular hypertrophy (LVH), LV outflow obstruction (LVOTO), heart failure, and potentially lethal arrhythmias,² treating these phenotypes per se may not influence the biology of HCM. For example, though regression of LVH may be regarded as a beneficial attribute of an HCM therapy,³,⁴ in other contexts, regression of LVH may represent a detrimental prelude to ventricular dilatation.⁵ Moreover, existing treatments for HCM are often applied without robust evidence, being based on underpowered studies with end-points that do not reflect the biology of the disease. Even though some therapies such as high-dose β-blockers have supporting evidence in specific patient subgroups,⁶ they often accrue side effects without changes in the natural history of the disease.⁷ For example, though implantable cardioverter-defibrillators (ICDs) may virtually obviate the risk of sudden death, this assertion is not based on randomized controlled trials but on retrospective observational registries with all their limitations.⁸,⁹ Bearing in mind the significant lifelong risk of complications of ICDs (eg, inappropriate discharge, device infection, and lead fracture), identifying those who may or may not benefit from ICD implantation and timing of intervention (eg, during a hot phase of disease) remains challenging when our understanding of the mechanisms of arrhythmogenesis is limited. We focus herein on pathways implicated in HCM through experimental, often reductionist, approaches, including myofilament biology, calcium handling,¹⁰ myocardial metabolism,¹¹,¹² signaling,¹³ microvascular changes,¹⁴ fibrosis,¹⁵,¹⁶ and organ physiology¹⁷ are rational therapeutic targets.

**Myofilament Biology**

Over a thousand private mutations in at least 9 genes encoding components of the cardiac sarcomere cause disease in >50% of HCM patients. These include β-myosin heavy chain (MYH7), cardiac myosin-binding protein C-MYBP-C (MYBPC3), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), cardiac troponin C (TNNC1), cardiac α-actin (ACTC1), α-tropomyosin (TPM1), essential myosin light chain (MYL3), and regulatory myosin light chain (MYL2). Many of the remaining cases of HCM remain unexplained, with less robust associations having been made between HCM and mutations in genes coding for other sarcomere and Z-disc-related genes (eg, titin, muscle LIM protein, LIM domain binding 3, α-actinin 2, myozoen 2, and cardiac ankyrin repeat protein).

The majority of these mutations are missense alleles (encoding single amino acid substitutions) that result in dominant negative mutant (“poison”) peptides, which become incorporated into, and adversely affect, sarcomere function. The exceptions to this poison peptide basis for HCM are those MYBPC3 mutations that reduce the amount of full-length protein, resulting in insufficient protein for normal function (haploinsufficiency).¹⁸ A substantial body of evidence indicates that HCM mutations in

<table>
<thead>
<tr>
<th>Non-standard Abbreviations and Acronyms</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE-I</td>
<td>angiotensin-converting enzyme inhibitors</td>
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<tr>
<td>ACTC1</td>
<td>cardiac α-actin</td>
</tr>
<tr>
<td>Akt-Akt/PKB</td>
<td>a serine/threonine protein kinase</td>
</tr>
<tr>
<td>AMPK</td>
<td>5′ adenosine monophosphate–activated protein kinase</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker (antagonist)</td>
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<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
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<tr>
<td>β-AR</td>
<td>beta-adrenoceptor</td>
</tr>
<tr>
<td>BMP-7</td>
<td>bone morphogenetic protein 7</td>
</tr>
<tr>
<td>BIVP</td>
<td>biventricular pacing</td>
</tr>
<tr>
<td>CAMKKII</td>
<td>Ca2+/calmodulin-dependent protein kinase II</td>
</tr>
<tr>
<td>MyBP-C</td>
<td>cardiac myosin-binding protein C</td>
</tr>
<tr>
<td>CPT1/2</td>
<td>carnitine palmitoyltransferase 1/2</td>
</tr>
<tr>
<td>CRT</td>
<td>cardiac resynchronization therapy</td>
</tr>
<tr>
<td>DCM</td>
<td>dilated cardiomyopathy</td>
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<tr>
<td>FFA</td>
<td>free fatty acid</td>
</tr>
<tr>
<td>Gαq</td>
<td>a guanine nucleotide-binding protein of the of G-alpha proteins family</td>
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<tr>
<td>GPCR</td>
<td>G-protein-coupled receptors</td>
</tr>
<tr>
<td>GSK3</td>
<td>glycogen synthase kinase 3</td>
</tr>
<tr>
<td>GRK</td>
<td>G-protein-coupled receptor kinase</td>
</tr>
<tr>
<td>HIF-1α</td>
<td>hypoxia-inducible factor 1, alpha subunit</td>
</tr>
<tr>
<td>HCM</td>
<td>hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>ICD</td>
<td>implantable cardioverter–defibrillator</td>
</tr>
<tr>
<td>IGF1</td>
<td>insulin-like growth factor 1</td>
</tr>
<tr>
<td>iPS</td>
<td>induced pluripotent stem cells</td>
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<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
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<tr>
<td>LVOTO</td>
<td>left ventricular outflow tract obstruction</td>
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<tr>
<td>MAPK</td>
<td>mitogen-activated protein kinase</td>
</tr>
<tr>
<td>MMP</td>
<td>matrix metalloproteinase</td>
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<tr>
<td>mTOR</td>
<td>mammalian target of rapamycin</td>
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<tr>
<td>MYBPC3</td>
<td>cardiac myosin-binding protein C</td>
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<tr>
<td>MYH7</td>
<td>beta-myosin heavy chain cardiac</td>
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<tr>
<td>MYL2</td>
<td>regulatory myosin light chain</td>
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<tr>
<td>MYL3</td>
<td>essential myosin light chain</td>
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<tr>
<td>Na+/K+ ATP-ase</td>
<td>sodium–potassium adenosine triphosphatase, or the Na+/K+ pump, sodium–potassium pump</td>
</tr>
<tr>
<td>NCX</td>
<td>sodium–calcium exchanger</td>
</tr>
<tr>
<td>NFAT</td>
<td>nuclear factor of activated T cells</td>
</tr>
<tr>
<td>P3K[π110α]</td>
<td>phosphatidylinositol 3-kinase</td>
</tr>
<tr>
<td>PHD</td>
<td>prolyl hydroxylase domain–containing protein</td>
</tr>
<tr>
<td>PLN</td>
<td>phospholamban</td>
</tr>
<tr>
<td>PPARγ</td>
<td>peroxisome proliferator-activated receptor gamma</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin–angiotensin–aldosterone system</td>
</tr>
<tr>
<td>RAS</td>
<td>RAT sarcoma</td>
</tr>
<tr>
<td>SAM</td>
<td>systolic anterior motion of the mitral valve</td>
</tr>
<tr>
<td>SERCA</td>
<td>sarco/endoplasmic reticulum Ca2+/ATPase</td>
</tr>
<tr>
<td>SHP2</td>
<td>a protein phosphatase encoded by PTPN11</td>
</tr>
<tr>
<td>TGFβ</td>
<td>transforming growth factor beta</td>
</tr>
<tr>
<td>TNNC1</td>
<td>cardiac troponin C</td>
</tr>
<tr>
<td>TNNI3</td>
<td>cardiac troponin I</td>
</tr>
<tr>
<td>TNNT2</td>
<td>troponin T</td>
</tr>
<tr>
<td>TPM1</td>
<td>alpha-tropomyosin</td>
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myofilament proteins generally increase Ca\(^{2+}\) sensitivity and Ca\(^{2+}\) affinity, and thereby actin-dependent ATPase activity.\(^{19}\) These changes in Ca\(^{2+}\) sensitivity and the consequent defects in Ca\(^{2+}\) homeostasis (ie, in intracellular Ca\(^{2+}\) cycling, sarcoplasmic reticulum [SR] Ca\(^{2+}\) re-uptake and CaMKII-mediated phosphorylation of proteins, including phospholamban)\(^{20}\) likely contribute to many aspects of HCM. In a transgenic troponin T model of HCM, the burden of ventricular arrhythmias correlated with the degree of Ca\(^{2+}\) sensitization resulting from the mutation. This association was reinforced by the observation that the myofilament Ca\(^{2+}\)-sensitizer EMD 57033, mimicking thin-filament mutations, exacerbated arrhythmias. Conversely, reversing Ca\(^{2+}\) sensitization using blebbistatin almost entirely eliminated these arrhythmias, supporting the proposal of a causal relation between Ca\(^{2+}\) sensitization and arrhythmogenesis in HCM.\(^{21}\)

One potential approach to directly mitigating the consequences of myofilament mutations is the application of gene therapy, which has emerged as a therapeutic strategy in rare Mendelian metabolic disorders (eg, lentiviral-mediated therapy of stem cells in adrenoleukodystrophy).\(^{22}\) Although this success has motivated attempts to eliminate, compensate for,\(^{23}\) or quantitatively overwhelm native mutant proteins, several obstacles limit the applicability of gene therapy to dominant monogenic muscle disorders such as HCM for the foreseeable future. These include the challenges of gene delivery with respect to the practicality/potency/safety of vectors (eg, adeno-associated virus 1 and other vectors),\(^{24}\) the receptivity of muscle to gene transduction; achievement of adequate, spatially uniform and sustained stable expression of exogenous genes; the avoidance of a dose-limiting or tissue-damaging immune response; and the risk of tumorigenesis. Although short oligonucleotide strategies are being investigated in HCM (eg, siRNA/microRNA mediated mutant mRNA degradation or antisense mediated “exon-skipping” splicing) and may be relevant to a minority of HCM mutations (eg, those leading to aberrant splicing of MyBP-C),\(^{25}\) achieving sufficient intracellular oligonucleotide levels to chronically suppress each private HCM missense mutation throughout the myocardium is substantially more challenging than replacing absent proteins in hemopoietic stem cells.

Because heightened myofilament Ca\(^{2+}\) sensitivity is common in HCM mutations, another therapeutic approach might be to recalibrate myofilament Ca\(^{2+}\) sensitivity. In dilated cardiomyopathy (DCM), in contrast to HCM, a decreased myofilament Ca\(^{2+}\) sensitivity has been observed.\(^{26}\) Pharmacological myofilament Ca\(^{2+}\) sensitization by agents such as levsimendan and cardiac myosin activators (omecamtiv mecarbil) hold promise for DCM and heart failure.\(^{27}\) Although no corresponding clinical myofilament desensitizers are available, the protective effects of blebbistatin noted above justify the search for a new class of drug decreasing Ca\(^{2+}\) sensitivity, which may be beneficial in HCM.\(^{28}\) Because posttranslational modification of TnI by phosphorylation at serine residues S23/ S24 is recognized as decreasing myofilament Ca\(^{2+}\) sensitivity, mimicking this change may also represent an attractive molecular target.\(^{29}\) One concern about such approaches relates to the precision with which myofilament sensitivity can be modified (we are mindful of the potential for converting HCM to DCM by excessive myofilament desensitization). Addressing these concerns and supporting the myofilament recalibration strategy, albeit in artificial cellular or transgenic models, the crossing of sarcomeric HCM mutants with mutants exhibiting decreased sarcomeric Ca\(^{2+}\) sensitivity normalizes overall Ca\(^{2+}\) sensitivity and prevents cardiac deterioration.\(^{23,29}\) However, although it is natural to assume that each cell in the myocardium behaves uniformly, fiber-to-fiber variation in force generation has been reported in HCM caused by β-myosin mutations.\(^{30}\) Although the generalizability of this cellular heterogeneity observation remains to be established, fiber-to-fiber variation in HCM nevertheless has clear implications for agents intended to modify presumed uniform myofilament properties such as those described above.

**Calcium Handling**

Another strategy to alter the biophysical consequences of myofilament mutations is to target intracellular Ca\(^{2+}\) ([Ca\(^{2+}\)]) flux. Myocyte excitation–contraction coupling is stringently regulated, in part, through the modulation of Ca\(^{2+}\) influx/release and removal/sequestration and is dysfunctional in many myocardial diseases (Figure 1). Influx of Ca\(^{2+}\) is regulated by sarcolemmal voltage-dependent L-type calcium channels, which in turn triggers Ca\(^{2+}\) release from the sarcoplasmic reticulum (SR) by the ryanodine receptor. Ca\(^{2+}\) reuptake by the SR Ca\(^{2+}\)-ATPase (SERCA) is modulated by phospholamban (PLN). The sarcolemmal Na\(^+/\)Ca\(^{2+}\) exchanger (NCX), the sarcolemmal Ca\(^{2+}\)-ATPase, and the mitochondrial Ca\(^{2+}\) uniporter further contribute to Ca\(^{2+}\) cycling. Finally, sarcomeres also powerfully sequester Ca\(^{2+}\) (100:1 bound:free ratio).\(^{31}\) The latter is especially pertinent to HCM because through increased calcium affinity, HCM mutations may increase “Ca\(^{2+}\) trapping,” and through altered on–off kinetics may lead to altered Ca\(^{2+}\) signaling and arrhythmogenesis. Thus although uncertainty remains about how sarcomeric Ca\(^{2+}\) handling relates to Ca\(^{2+}\) in other spatially/temporally isolated microdomains, the regulation of Ca\(^{2+}\)-sensitive signaling, such as Ca\(^{2+}\)-calmodulin–dependent protein kinase, calcineurin, and PKC is considered to contribute to HCM.\(^{31}\)

In mouse models of HCM, including an α cardiac myosin heavy-chain Arg403Gln missense mutant mouse (αMHC403) and a transgenic mouse model expressing cardiac troponin T (179N) mutation, inhibition of plasma membrane L-type Ca\(^{2+}\) channels by diltiazem-normalized aberrant levels of Ca\(^{2+}\) storage protein (calsequestrin, junction, and triadin) and prevented fibrosis and cardiac dysfunction.\(^{10,32}\) These observations have motivated an ongoing trial of genotype-positive hypertrophy-negative HCM patients who are being treated “prophylactically” with diltiazem (NCT00319982).
Additionally, cardiac troponin T (cTnT) mutant mouse models of HCM have further refined our understanding of the consequences of specific mutation on calcium handling in HCM, including alterations in the SERCA2a-to-PLN ratio, the degree of S16 and T17 phosphorylation of PLN, SR Ca^{2+} uptake, and increased NCX protein levels. Moreover, studies in HCM patients with severe hypertrophy and impaired contractile reserve emphasize the putative role of SERCA2a mRNA downregulation, potentially altering Ca^{2+} handling. A logical extension of such observations is the targeting of SERCA2a, PLN, and related proteins in HCM. For example, adenoviral delivery of a dose of SERCA2a in 1-day-old Tm180 mouse model of HCM improved the response to β-adrenergic stimulation, prevented hypertrophy, and improved global cardiac function. Similarly, transgenic overexpression of parvalbumin (a calcium buffer) in an α-tropomyosin mutant (E180G) mouse model of HCM corrected impaired relaxation.

These studies support the proposal that modification of calcium handling proteins (eg, SERCA2a and PLN) is promising in HCM, especially if applied prophylactically in genotype-positive hypertrophy-negative individuals or early in disease. However, although PLN elimination (effected by a cross with PLN knockout mice) appears to improve cardiac function and morphology, including LVH and fibrosis, for up to 1 year in the Tm180 mouse model of HCM, it failed to rescue the cardiomyopathic phenotype of MyBP-C mutations. This discordance parallels the divergence between PLN elimination in mice (beneficial) and in humans (with DCM). These observations, reflecting 65 million years of divergent evolution and the lack of equivalency between artificially induced null alleles (mice) and natural missense mutations (human), remind us that therapies developed in model organisms need careful consideration in humans.

**Myocardial Metabolism and Energetics**

A consequence of increased sarcomeric Ca^{2+} sensitivity is increased cross-bridge turnover and higher actin-activated ATPase activity. HCM mutations were therefore predicted to generate higher-energy costs to produce a given tension ("tension cost"). Consistent with the interpretation of these biophysical observations, a number of studies have demonstrated mitochondrial abnormalities and impaired myocardial energy metabolism in HCM. In transgenic models of HCM expressing a variety of mutant sarcomeric proteins, impaired energetics precede cardiac pathology. Similarly, HCM patients, irrespective of the presence or absence of hypertrophy, exhibit a 30% reduction in the phosphocreatine-to-ATP ratio, an established marker of cellular energy status. A reduction in cellular energy charge would be expected to compromise the regulation of membrane potentials and ion currents (regulated by energy-requiring transporters such as Na+/K+ ATPase and SERCA) and activate cellular energy sensors such as the AMP-activated protein kinase (AMPK) (Figure 2). It has been proposed that defects in cellular energetics may contribute to the arrhythmogenesis and the LV dysfunction of HCM.

Although energy deficiency is now a well-recognized feature of HCM, invoking energetics as a causative determinant (rather than an association) of HCM demands a greater burden of proof. The most compelling proof would derive from the capacity of energy augmentation to prevent or attenuate HCM disease development. Although in principle a number of strategies exist to enhance cellular energetics, in practice modification of myocardial substrate utilization in HCM is perhaps the most clinically applicable.
To mitigate the well-documented adverse consequences of FFA oxidation and to augment myocardial energetics, we have assessed the influence of perhexiline in HCM. Perhexiline is a piperazine-derived racemate with an established role in heart failure diverting myocardial substrate utilization from FFAs to carbohydrates by inhibiting carnitine palmitoyl transferase (CPT-1/2), which is involved in mitochondrial uptake of long-chain fatty acids. Patients with symptomatic HCM were randomized to perhexiline or placebo for 4 to 6 months. Perhexiline corrected resting cardiac energetics, normalized exercise diastolic dysfunction characteristic of HCM, and increased exercise capacity. Moreover, consistent with extensive biochemical and clinical experience, through simple drug-level monitoring, acute and chronic side effects were negligible. Not only does this study support the hypothesis that energy deficiency causatively contributes to HCM, but it provides a rationale for the application of metabolic therapies in HCM. Substrate utilization is an especially attractive target for clinical trials, because agents such as perhexiline are available for routine practice. As with any pharmacological agent, a number of questions arise from this study including the following: What is perhexiline’s principal target (e.g., carnitine palmitoyl transferase 1 resulting in inhibition of fatty acid metabolism)? Which of perhexiline’s metabolites are clinically relevant? Do systemic effects (including augmentation of insulin sensitivity) or cardiac effects of perhexiline predominate? Can the same effect be achieved with other metabolic modulators (e.g., trimetazidine or ranolazine)? Although perhexiline improved myocardial energetics and symptoms over 4.6±1.8 months, will perhexiline have a more enduring effect, in a larger, more diverse set of HCM patients (e.g., those with LVOTO)? Finally, importantly, will perhexiline reduce or prevent disease development and arrhythmogenesis?

Conclusions

Despite the multiple complex, context-dependant, and redundant pathways underlying cardiac hypertrophy, modification of signaling is a promising target in LVH. The distinction between physiological (e.g., athletic) and pathological hypertrophy (e.g., HCM), albeit imperfect, provides a framework within which to conceptualize aspects of LVH biology. Supported by observations such as those by McMullen et al., that exercise-related/genetic augmentation of PI3K(p110α) can ameliorate pathological LVH, the [IGF1–(PI3K,[p110α])–Akt–GSK3–mTOR] and [GPCR—Goq—CAMKII—MAPKs and nuclear factor of activated T cells (NFAT)] signaling pathways appear to contribute to physiological and pathological hypertrophy, respectively. The relevance of these convergent signaling pathways (e.g., ERK/MAPK) to HCM has been affirmed by the identification of gain of function mutations in SHP2, a protein phosphatase encoded by PTEN, in Noonan syndrome (NS), whose cardiac phenotype is a close phenocopy of HCM, including left ventricular hypertrophy and myocyte disarray.

Examples of the potential for GPCR signaling inhibition to ameliorate myocyte hypertrophy, interstitial fibrosis, and cell death (apoptosis) are evident in the success of angiotensin-converting–enzyme inhibitors (ACE-I), angiotensin-receptor blockers (ARBs), aldosterone antagonists, and β-blockers in heart failure. Although there is a paucity of evidence that such agents may be germane to HCM, one study has demonstrated that myocardial aldosterone and aldosterone synthase mRNA levels were elevated by 4- to 6-fold in HCM patients in comparison with controls. Thus, neurohormonal antagonism using the above, natriuretic peptide mimetics, or even modulation of G protein–coupled receptor kinases (GRKs) that desensitize βARs, represent candidates for HCM therapy. Neurohormonal antagonism potentially has pleiotropic benefits including suppression of: tissue/systemic neuroendocrine activation, electrolyte defects (K+ and Mg2+), fibroblast activity with collagen deposition (e.g., via BMP-7/TGF-β1) and mitigation of microvasculopathy, which may have pathophysiological and prognostic benefits in HCM. In mouse, feline, and human studies, RAAS inhibition in HCM using ACE-I/ARBs/spironolactone, diminished mi-
crovasculopathy, fibrosis, cardiac dysfunction, and adverse symptoms.467–73 Other pharmacological approaches to mitigating LVH include rapamycin (inhibiting the mammalian target of rapamycin -mTOR), which exhibits antihypertrophic properties in rodents.74 In practice, derivatives or substitutes of such agents will likely be required because of their immunosuppressive effects.

Nonpharmacological strategies to modify pathological signaling also include exercise. Although vigorous exercise, as experienced by athletes, has been discouraged in HCM, moderate exercise has been shown to benefit a mouse model of HCM expressing a mutant β-MHC.75 NFAT suppression in this model suggests that in addition to a host of other effects,76 moderate exercise activates the Akt/mTOR pathway and suppresses the influences of sustained Ca2+ signaling. Suppression of calcineurin (a Ca2+/calmodulin-dependent phosphatase) mediated dephosphorylation and nuclear translocation NFATc3 (coupled with reduced GATA-4 activity) may mitigate pathological LVH.77 There is therefore a mandate to assess the impact of moderate exercise regimens on symptoms, myocardial anatomy, and outcomes (eg, arrhythmias and sudden death) in HCM.

Finally, resonating with the lessons learned from Noonan syndrome, statins (3-hydroxy-3-methylglutarylcoenzyme A reductase inhibitors) putatively acting through reducing mias and sudden death) in HCM. This correlated with reduced oxidative stress, myocardial properties attributed to statins may have contributed to these observations, including reduced oxidative stress, myocardial lipid peroxides, and oxidized mitochondrial DNA. Similarly, the antioxidant N-acetylcysteine reduced markers of oxidative stress in the rabbit β-MyHC-R403Q TG and the mouse cTnT-Q92 models of HCM. This correlated with reduced expression of phospho-p38, pERK44/42, and ERK1/2 activation, reduced cardiac hypertrophy and fibrosis in a β-MyHC-R403Q TG rabbit model of HCM.78,79 A number of beneficial properties attributed to statins may have contributed to these observations, including reduced oxidative stress, myocardial lipid peroxides, and oxidized mitochondrial DNA. Similarly, the antioxidant N-acetylcysteine reduced markers of oxidative stress in the rabbit β-MyHC-R403Q TG and the mouse cTnT-Q92 models of HCM. This correlated with reduced expression of phospho-p38, pERK44/42, and the active, dephosphorylated form of NFATC1.80,81 Although these animal studies are hypothesis generating, the disappointing results of preliminary human HCM statin studies82,83 remind us of the need to test specific inhibitors (which powerfully and in a sustained manner target the intended molecular pathways)84 in appropriately powered trials for this heterogeneous population.

Organ-Level Physiology

Although LVH, impaired LV diastolic function, and LV outflow tract obstruction (LVOTO) are central features of HCM, their physiological basis remains obscure. Their importance is confirmed by their statistical relationship with prognosis85–88; however, the limited predictive value of LVH or LVOTO for clinical outcomes in any given patient attests to the incompleteness of our existing account of HCM physiology. To address this, the use of tissue Doppler strain and speckle tracking echocardiography have recently demonstrated reduced strain and delayed untwist as indicators of early diastolic and ensuing systolic LV dysfunction in HCM.89–91 These surrogates for impaired dynamic early diastolic filling17 likely correspond, at least in part, directly to the biophysical consequences of sarcomeric mutations, including increased calcium sensitivity and energy deficiency.89

Systolic dysfunction, previously considered to be generally normal in HCM, appears to occur earlier and more commonly than previously thought in the course of disease, and is related to the degree of LVH and fibrosis.89,92 Even gene carriers with normal wall thickness exhibit increased LV torsion with respect to controls as a possible manifestation of subendocardial myocardial dysfunction.93 In aggregate, these studies reinforce the often arbitrary nature of the distinction made between systolic and diastolic function in heart disease generally, and in HCM in particular, especially when a more nuanced perspective on myofiber architecture and hence contractile tissue is adopted.94 In HCM, tissue deformation studies (eg, detailed interrogation of longitudinal and circumferential strain) more accurately reflect myocardial dysfunction than do traditional measures of systolic function and should be considered in future studies. As a corollary in HCM, regional systolic asynchrony is associated with impaired global LV relaxation.95–97

There is also increasing recognition that the nonmyocyte compartment is concomitantly affected in HCM. Although there is a paucity of data in human HCM, the aberrant turnover of the extracellular matrix characterized by the upregulation of MMPs and inadequate inhibition by TIMPs apparent in heart failure are also likely to promote the proliferation of fibroblasts resulting in fibrosis.15 In HCM, the intramural coronary arteries exhibit thickened walls and narrowed lumens,98 resulting in myocardial ischemia.14,62–64 With progression of disease, there is even an indication that the endocardial vasculature can develop into a highly interconnected vascular plexus communicating with the ventricular cavity as an adaptation to severe chronic ischemia.99 There is also a body of emerging evidence that in HCM, testing and dynamic geometric abnormalities exist in the mitral valve. Elongated mitral leaflet surface area, septal displacement of papillary muscle insertion, and an abnormal coaptation point in systole appear to be key determinants of SAM, LVOTO, and mitral regurgitation in HCM.100,101

Addressing these defects, existing therapies (eg, metabolic agents)99 already modify HCM physiology. To progress further, several trials have promoted the benefits of cardiac resynchronization (CRT) by biventricular pacing (BiVP) in delaying or even preventing advanced heart failure in those with asynchronous LV contraction.102 The detection of asynchrony in HCM noted above, combined with the recognition that CRT can reverse heterogeneous ventricular segmental peak myocardial strain, raises the potential for BiVP in HCM. An existing study of end-stage HCM, in which BiVP promoted LV reverse-remodeling, and improved symptoms provide a rationale for further studies that are ongoing (NCT00504647).103

The Future

Pathogenic mutations remain elusive in 30% to 40% of even stringently investigated HCM patients. This may be explained by the limitations of genotyping strategies with
respect to yet-to-be discovered genes with different patterns of inheritance (eg, nonautosomal dominant or indeed non-Mendelian), phenocopies caused by recognized but incompletely investigated genetic abnormalities (Fabry’s disease, Noonan Syndrome, Friedreich’s Ataxia, mitochondrial mutations), the possibility of nongenetic/complex genetic causes of HCM (eg, mosaicism), and the challenges of interpreting variants of unknown significance in individuals or small families undergoing state-of-the-art whole-genome/exome sequencing.104–106 Intensive recruitment of probands and their families (not just from large centers with select referral patterns) with comprehensive genotyping, modifier mapping and the application of novel biomarkers (identified from an –omics discovery program), and imaging combined with natural history studies will provide a basic framework guiding future diagnostic/therapeutic studies. Novel targets emerging from such studies should be tested in appropriate models. For example, patient-derived pluripotent stem cells (iPS) differentiated into cardiomyocytes may represent an ideal model with which to test electrophysiological responses to new agents.107 However, to provide substantial insights into HCM pathogenesis and therapeutics, these iPS cells will, through tissue engineering approaches, need to be integrated into a matrix in which contraction under load can be examined.

Modifying intermediary metabolism with customized derivatives of existing metabolic agents synergistically combined with calcium modifying agents108 or amelioration of microvascular disease (and ischemia) may represent effective strategies to augment the central etiologic feature of altered energetics. The latter may be achieved by stabilizing the transcription factor HIF-1α by manipulation of HIF-1α 4-hydroxylases (PHDs). A novel orally active HIF-PHD inhibitor, GSK360A, has been shown to improve LV function, remodeling, and vascularity in a rat model of myocardial infarction.109 However, and of concern, the HIF-1α -PPARγ axis is already active and responsible for many of the metabolic changes in LVH, and chronic HIF-1α activation contributes to the adverse features of heart failure.110

As noted earlier, myocardial fibrosis represents an early and important marker of prognosis in HCM.15,65.66 Although conventional RAAS inhibition appears capable of preventing fibrosis when given prophylactically, it appears less effective in reversing established fibrosis.16 Accordingly, BMP-7/ TGF-β signaling and its downstream mediators (which may have less off-target consequences) have been proposed as novel pharmacological targets.16 Not only might such targeting improve lusiotropy and ventricular arhythmias in HCM, but it may also serendipitously improve the burden of atrial fibrillation and ventricular arrhythmias in HCM, but it may also serendipitously improve lusiotropy and ventricular arrhythmias in HCM, (and indeed LVH) will substantially inform the biology of HCM by establishing the chronology and reversibility of these phenomena. Moreover, to prospectively map the evolving trajectory of HCM, these techniques should be applied to genetically defined genotype-positive HCM patients prior to the expression of LVH. Because HCM often progresses slowly with few clinical events per annum, relating clinical surrogates (eg, fibrosis) to the underlying biology of HCM will be of utility in assessing the impact of such novel interventions.

The substantial progress made in understanding the pathophysiology of HCM inspires confidence in the prospect of identifying successful therapies in the not-too-distant future.7 A clear-sighted vision will be required to formulate the basic science and clinical observations into a coherent synthesis, guiding both diagnosis and therapy. Cross-fertilization among the maturing fields of sequencing, gene therapy, stem cell biology, medicinal chemistry, targeted drug discovery, and epidemiology will not only hasten the rate of therapeutic discovery but, using this pure cardiomyopathy as an exemplar (eg, for impaired energetics and fibrosis), will, one hopes, pay dividends in more common diseases with more complex contributions from both genetic and environmental influences.

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Disclosures

Dr. Ashrafian reports holding a European method-of-use patent for perhexiline in systolic heart failure and having patents pending for its use in diastolic heart failure and hypertrophic cardiomyopathy and for its use in systolic heart failure in countries outside Europe.

References


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