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SPOTLIGHT REVIEW

Targets for therapy in sarcomeric cardiomyopathies

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To date, no compounds or interventions exist that treat or prevent sarcomeric cardiomyopathies. Established therapies currently improve the outcome, but novel therapies may be able to more fundamentally affect the disease process and course. Investigations of the pathomechanisms are generating molecular insights that can be useful for the design of novel specific drugs suitable for clinical use. As perturbations in the heart are stage-specific, proper timing of drug treatment is essential to prevent initiation and progression of cardiac disease in mutation carrier individuals. In this review, we emphasize potential novel therapies which may prevent, delay, or even reverse hypertrophic cardiomyopathy caused by sarcomeric gene mutations. These include corrections of genetic defects, altered sarcomere function, perturbations in intracellular ion homeostasis, and impaired myocardial energetics.

Keywords Hypertrophic cardiomyopathy • Dilated cardiomyopathy • Gene therapy • Ion channels • Energetics and microvasculature

This article is part of the Spotlight Issue on Sarcomeric cardiomyopathies: from bedside to bench and back.

1. Current state of therapeutic approaches in sarcomeric cardiomyopathies

Prior to the landmark discoveries that hypertrophic cardiomyopathy [HCM; and later dilated cardiomyopathy (DCM)] was caused by mutations in components of the cardiac sarcomere, clinical management was entirely symptom-based. In fact, the current AHA/ACC HCM guidelines released in 2011 still clearly state that direct therapeutic intervention should be focused on symptom relief, not the diagnosis *per se*.[1] Likewise, the recently published 2014 ESC guidelines on HCM management describe drug therapies to manage symptoms and complications.[2] Although this is a well-supported approach that decreases patient morbidity, it is, by nature, palliative in that it does not alter the natural history of the progressive cardiovascular remodelling that defines HCM/DCM. Beta-blockers, calcium channel blockers, and disopyramide are used to optimize haemodynamics by modulating the effects of existing left ventricular (LV) dysfunction in HCM, whereas patients with inherited DCM are managed with standard heart failure regimens. Prior to the 'genetic era', this was a reasonable approach because patients were not identified before the onset of symptoms, symptoms that were directly caused by significant pathogenic LV remodelling. Due to the widespread use of modern DNA sequencing techniques to perform mutational screening among the relatives of cardiomyopathy patients, the cohorts of genotype-positive individuals (mutation carriers) without disease expression have dramatically increased in recent years.[3] The growing cohorts of mutation carriers who do not yet show cardiac remodelling have changed our view of the clinical syndrome from a disease of 'thick or thin hearts' to one of a complex longitudinal process that is often defined by both a distinct preclinical phase and a later stage of remodelling. This modern view of sarcomeric cardiomyopathies coupled with our advanced understanding of the molecular and cellular mechanisms that underlie disease pathogenesis sets the stage for advanced, targeted therapeutics to alter the natural history of sarcomeric cardiomyopathies, before end-stage irreversible remodelling occurs. Thus, in the following section, novel and specific approaches are addressed to the management of sarcomeric cardiomyopathies, with an emphasis on HCM (*Table 1*). Novel therapies to prevent onset and progression of sarcomeric cardiomyopathies may target the disease-causing gene directly or intervene with cellular pathomechanims that play a role in the (early) progression of cardiomyopathy, such as alterations of myofilament Ca^{2+} sensitivity, ion channel remodelling, perturbations in energetics, and microvascular dysfunction.

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Table 1 Therapies investigated in preclinical and clinical studies

Defect	Potential target	Potential therapies
Sarcomeric proteins		
Myofilament Ca^{2+} sensitivity	Thin filament (troponin C)	Ca^{2+} desensitizers Blebbistatin[6] Calmodulin antagonists[7–9] Green tea[10] β-blocker (nebivolol)[a17]
	Actin–myosin interaction	Actin–myosin interaction inhibitors Blebbistatin, 2,3-butanedione monoxime[6]
Myosin activity	Myosin heavy chain	Small molecules Myosin inhibitors Myosin activators (omecamtiv mecarbil)[28]
Gene mutation	Mutant genes	Gene therapy Trans-splicing[54] mRNA silencing[29,30] Gene replacement[31]
Ion channels		
LVOT obstruction Cardiac remodelling	Ca^{2+}/CaMKII	CaMKII inhibition Small molecules—CaMKII inhibitors[88] L-type Ca^{2+} channel blocker (diltiazem),[91,103] ongoing clinical trial in preclinical HCM[104] I_{NaL} inhibition (ranolazine)
	Na^+ channel	Sodium channel blocker (disopyramide)[a70–74]
	Ca^{2+} channel	Ca^{2+} channel blockers (verapamil and diltiazem)[a75–77]
Arrhythmias	K^+ channel Late Na^+ current	Class III antiarrhythmic agent (amiodarone)[a1,79] I_{NaL} inhibitor (ranolazine),[60] ongoing clinical trial: ESTYLE-HCM; EUDRA-CT 2011-004507-20
Diastolic dysfunction	Late Na^+ current	I_{NaL} inhibitor (ranolazine)[60]
Energy deficiency		
Vascular dysfunction	LVOT obstruction and regional perfusion defects	β-Blockers and Ca^{2+} channel blocker (verapamil)[a148] Ca^{2+} desensitizers (see above)
Disturbed energetics	Metabolic substrate modification	Metabolic therapy (perhexiline)[151]

[a]Already used in clinic.

2. Targeting sarcomeric proteins

2.1 Modulation of myofilament Ca^{2+} sensitivity via the thin filament

HCM-associated mutations in myofilament proteins have been associated with increased myofilament Ca^{2+} sensitivity, whereas DCM-associated mutations have been proposed to underlie reduced sensitivity of myofilaments to Ca^{2+}.[4,5] Although the direct effect of sarcomeric mutations on myofilament Ca^{2+} sensitivity changes is under discussion, increased Ca^{2+} sensitivity seems to be a common factor in HCM due to secondary myofilament remodelling (e.g. due to altered disease-related phosphorylation patterns). The increases in the myofilament response to Ca^{2+} may contribute to impaired relaxation and diastolic dysfunction. Although the mechanisms responsible for increased myofilament Ca^{2+} sensitivity remain unclear, the use of Ca^{2+}-desensitizing interventions (*Table 1*) may be an attractive alternative for the treatment of sarcomeric cardiomyopathies and alleviation of the disease-related symptoms (*Figure 1*). Ideally, Ca^{2+} desensitizers, by targeting specifically myofilament molecules involved in muscle contraction rather than the membrane-bound Ca^{2+}-handling molecules, would avoid altering cytosolic Ca^{2+} homeostasis which would perturb the regulation of other Ca^{2+}-based signalling pathways. Ca^{2+} desensitizers may also have the potential ability to prevent arrhythmias in HCM patients. This therapeutic advantage of compounds that target sarcomere Ca^{2+} sensitivity was first demonstrated in mouse models characterized by myofilament hypersensitivity to Ca^{2+} caused by troponin mutations or by the Ca^{2+}-sensitizing agent EMD 57033.[6] *In vitro* cardiac muscle from these animal models exhibited significant arrhythmia susceptibility that was prevented by the myosin inhibitor blebbistatin.[6] The protective effect of blebbistatin provided the first direct evidence that myofilament Ca^{2+} desensitization is antiarrhythmic and may be beneficial in the treatment of HCM. The use of Ca^{2+}-desensitizing compounds for the treatment of diastolic dysfunction is practically a novel idea. So far, the number of Ca^{2+}-desensitizing interventions available for research, medical trials, or therapeutic use is very limited. Most of them are at present unsuitable for therapeutic use and can be only tested in animal models and in *in vitro* experiments as 'proofs of concept'. Investigations of the mechanisms of Ca^{2+}-desensitizing interventions are generating molecular insights into structural features that can be useful for the design of novel specific Ca^{2+}-desensitizing drugs.

Due to its central role as the Ca^{2+} sensor for cardiac muscle contraction, cardiac troponin C (cTnC) stands out as the obvious target to modulate cardiac muscle Ca^{2+} sensitivity (*Figure 1*). Unfortunately,

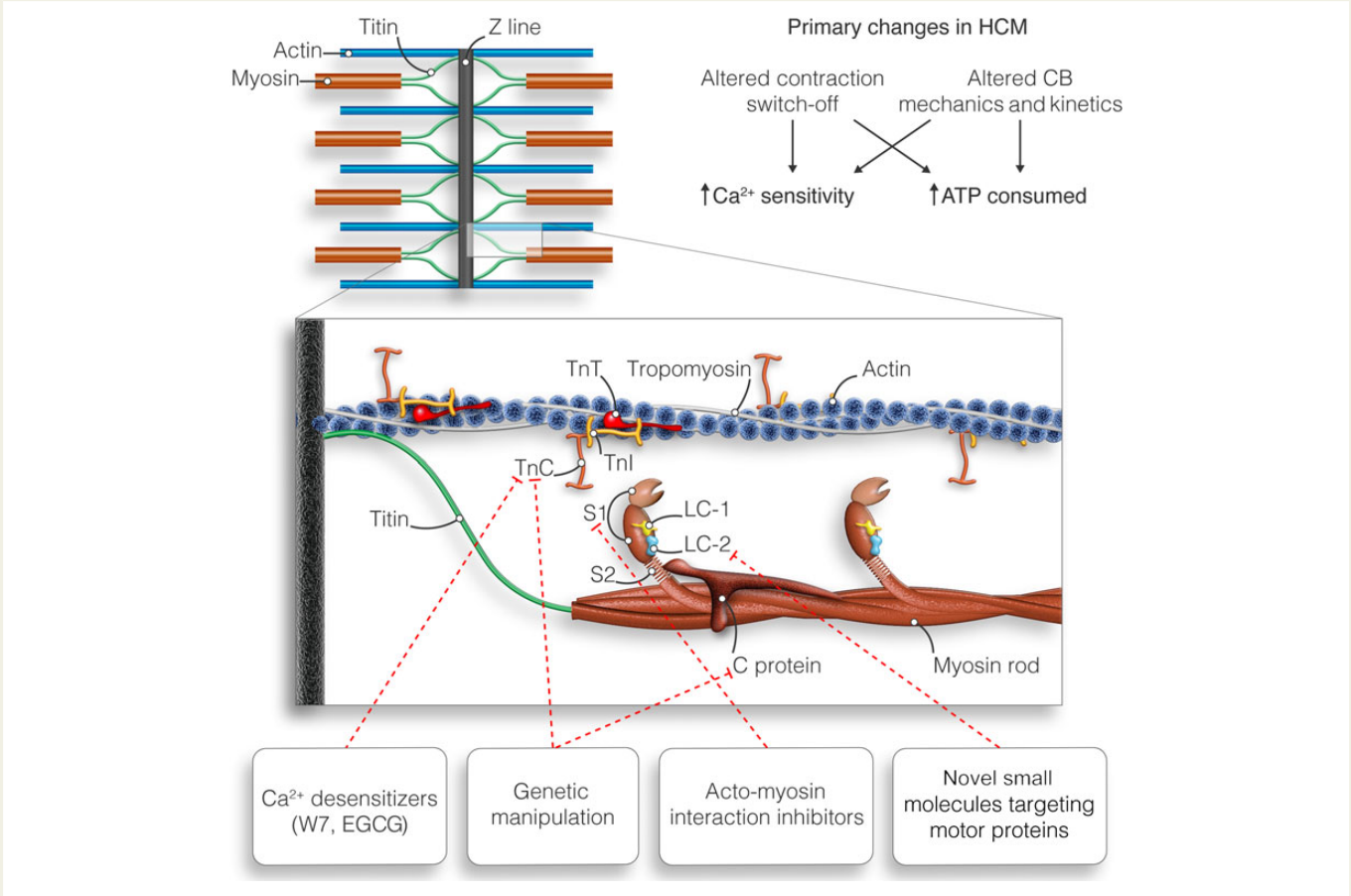

Figure 1 Several myofilament proteins may be target of treatment to reverse primary functional changes of the sarcomeres. CB, cross-bridge; TnC, troponin C; TnI, troponin I; TnT, troponin T; LC, light chain; C protein, myosin-binding protein C. Modified from Ferrantini *et al.*[154]

there are only a few compounds that only target cTnC to decrease sarcomere Ca^{2+} sensitivity. An alternative approach is to use cTnC as a target of genetic manipulation. The intrinsic Ca^{2+}-binding properties of cTnC can be finely or grossly tuned to design cTnC mutant constructs, which behave as Ca^{2+} desensitizers in solution systems and in isolated muscle models. Compounds have been identified that elicit their activity through binding either the N-terminal regulatory domain or the C-terminal structural domain of cTnC. Both groups of compounds likely interfere with the Ca^{2+}-dependent interaction between cTnC and cardiac troponin I (cTnI) that is crucial in the signalling of muscle contraction. Because of the structural homology between cTnC and calmodulin (CaM), CaM-binding compounds originally developed as inhibitors of CaM function may also interact with cTnC and be candidates as modulators of cardiac myofilament Ca^{2+} sensitivity (*Table 1*). Early studies have shown that some hydrophobic CaM antagonists (calmidazolium, bepridil, trifluoperazine, chlorpromazine, and pimozide) stimulate myofibrillar ATPase activity, whereas others (W7, haloperidol, and mastoparan) inhibit ATPase activity.[7] Among the compounds of the latter group, W7 has been studied more extensively as a potential Ca^{2+} desensitizer of striated muscle myofilaments. W7 [*N*-(6-aminohexyl)-5-chloro-1-naphthalenesulfinamide] was designed as a specific inhibitor of CaM function.[8] It binds to both the N- and C-terminal hydrophobic substrate-binding sites of CaM, inhibiting binding of CaM to its myosin light-chain kinase target protein.[9] W7 has been used to explore a wide range of physiological processes involving Ca^{2+} signalling in cardiomyocytes. Previous studies in rabbit skeletal and mouse cardiac muscles established that W7 inhibits force and ATPase during Ca^{2+} activation in both muscle types by reducing the ability of Ca^{2+} to activate thin filaments.[10] The W7 inhibition is most likely mediated via specific interactions between W7 and cTnC. This notion is supported by the observation that W7 binds specifically to cTnC and not to tropomyosin, actin, or myosin.[8] In addition, the possibility that W7 interferes directly with the actin–myosin interaction is unlikely as W7 has no effect on *in vitro* skeletal acto-myosin ATPase activity over the range of [W7] required for Ca^{2+}-activated ATPase and force inhibition (M. Regnier, personal communication).

A number of studies suggest that consumption of green tea decreases the risk of several pathological conditions. Green tea (*Camellia sinensis*) contains catechins as biologically active polyphenols. Major catechins in green tea are (−)-epicatechin (EC), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epigallocatechin-3-gallate (EGCG). ECG and EGCG have been shown to be particularly effective against cardiovascular diseases.[11] Epicatechin derivatives were found to significantly decrease pCa_{50} of force–pCa relationships in skinned ventricular trabeculae from rabbit hearts in a concentration-dependent manner.[12] EC and EGC had no significant effects on cardiac myofilament Ca^{2+} sensitivity, indicating that the galloyl group in ECG and EGCG has a critical role in the Ca^{2+}-desensitizing effects. NMR spectroscopy studies provided strong evidence that cTnC is one of the primary targets for EGCG in the myofilaments.[13] The therapeutic effect of

EGCG as a Ca^{2+} desensitizer was analysed in a transgenic mouse model of HCM expressing the *TNNT2* ΔE160 deletion mutation.[12] The mouse ΔE160 cTnT myocardium exhibited increased myofilament Ca^{2+}-sensitivity. EGCG (30 μM) fully reversed the effects of increased myofilament Ca^{2+} sensitivity of the isolated HCM myocardium. Lower concentrations of EGCG were enough to improve the diastolic function of working hearts of ΔE160cTnT-Tg mice and increase their cardiac output. EGCG also restored the Ca^{2+} transient parameters without changing myocardial contractility and improved the diastolic dysfunction without changing the cardiomyocyte resting Ca^{2+} level. These results suggest that EGCG restores the impaired cardiac pump function due to diastolic dysfunction by reversing the increased myofilament Ca^{2+} sensitivity. EGCG is the first chemical compound that could ameliorate diastolic dysfunction of HCM, at least partially, through its direct Ca^{2+}-desensitizing effects on cardiac myofilament. The use of EGCG as a therapeutic alternative for cardiac dysfunction is particularly interesting because it is attributed to have several benefits including antioxidative,[11] anti-inflammatory,[14] and vasorelaxant effects[15] on the cardiovascular system. Its cardioprotective effects against ischaemia/reperfusion injury have been demonstrated as well.[16] The use of transgenic animals will allow determining its relevance for the treatment of HCM and the overall effects of Ca^{2+} desensitization on diastolic dysfunction.

Among β-blockers that are commonly used in clinical pharmacotherapy of cardiovascular diseases, nebivolol has been reported to desensitize cardiac myofilaments.[17] In both rabbit and human skinned cardiac trabeculae, nebivolol depressed maximal tension and displaced the Ca^{2+}-tension relation to the right, whereas neither propranolol nor carvedilol had an effect. Experiments with intact trabeculae confirmed depressed contractility: when all β-adrenoceptors were blocked by propranolol, subsequent addition of nebivolol reduced developed twitch force. The Ca^{2+}-desensitizing effect of nebivolol was related to the beneficial effects on myocardial function reported in situations of oxidative stress associated with intracellular Ca^{2+} overload. This preservation of contractile function by nebivolol might be due to compensation of the intracellular calcium overload through a shift of the force–Ca^{2+} relationship into a range where contraction is maintained. The mechanism of the Ca^{2+}-desensitizing effect of nebivolol, however, remains unaddressed.

2.2 Modulation of thick filament function

The actin–myosin interface is also a potential site of action for Ca^{2+}-desensitizing drugs (*Figure 1* and *Table 1*). Myosin ATPase inhibitors such as blebbistatin[18] and 2,3-butanedione monoxime have been used as desensitizing compounds *in vitro* and as excitation–contraction uncouplers for electrophysiological and mechanical studies both *in vitro* and *ex vivo* due to their ability to inhibit acto-myosin force-generating cross-bridge formation.[6,19,20] As stated above, first evidence of the protective effect of Ca^{2+} desensitization on arrhythmia susceptibility associated with increased Ca^{2+} sensitivity has been given with actin–myosin interaction inhibitors.[6] However, these compounds characterized by strong negative inotropic effects and cardiac toxicities are at present unsuitable for use in intact animals. There are also accessory proteins in the thick filaments that modify the actin–myosin interaction, but have not been explicitly investigated as targets of Ca^{2+}-desensitizing agents. These include the essential and regulatory light chains of myosin and cardiac myosin-binding protein C. Both groups of proteins likely regulate cross-bridge kinetics, and modifications of their protein–protein interactions may be an additional route to alter Ca^{2+} sensitivity of force generation.

Studies of systems containing some HCM-mutant myosins imply that the mutant proteins have increased mechanical performance.[21–24] Although the precise impact of specific HCM mutations on the maximal force-generating capacity of human cardiac sarcomeres *in vivo* remains somewhat controversial,[25–27] advances in screening methods have enhanced the development of small molecules acting like cardiac myosin inhibitors that could become a resource for developing treatments for diseases involving myosin overactivity. These compounds, as well as other mutation-specific sarcomeric allosteric modulators, could rebalance contractility in HCM, therefore potentially reversing the course of disease.

Myosin activators, on the other hand, are small molecule drugs that bind to the myosin head, and stimulate its activity without increasing the cytosolic Ca^{2+} concentration. As a result, the systolic ejection time is lengthened. The first molecule omecamtiv mecarbil has been shown to ameliorate cardiac function by increasing the duration of ejection without changing the rates of contraction. Therefore, cardiac myosin activation may provide a new therapeutic approach for sarcomeric cardiomyopathies leading to DCM with systolic dysfunction.[11]

2.3 Targeting the genetic cause of sarcomeric cardiomyopathy by gene therapy

Another obvious therapy for inherited sarcomeric cardiomyopathy would be to target directly the cause of the disease by gene therapy (*Figure 1* and *Table 1*). In theory, this could be done by removing the mutation at the mRNA level or by replacing endogenous mutant proteins by functional ones. Gene therapy to prevent or rescue the disease phenotype in cardiomyopathy mouse models has emerged in the recent years,[29–33] and therefore paved the way for a causal therapy of sarcomeric cardiomyopathy in patients. Gene therapy is of particular interest for the severe forms of the disease which result in systolic heart failure and premature death, for which no treatments except heart transplantation are available. A growing body of evidence indicates that severe cardiomyopathies are due to the presence of double heterozygous, compound heterozygous, or homozygous mutations in sarcomeric genes.[34–47] Specifically, all infants with truncating bi-allelic *MYBPC3* mutations (expected to result in low level or the absence of cMyBP-C in the cardiac sarcomere) present at birth with neonatal cardiomyopathy (HCM, DCM, or LV non-compaction), which rapidly evolves into systolic heart failure and death within the first year of life.[34–41,43,48]

Gene therapy, a concept introduced as early as 1947,[49] has been rediscovered in the last decade with the development of adeno-associated viral vectors (AAVs) exhibiting high-efficiency and long-lasting cardiac gene expression following a single administration. This has accelerated the field of gene therapy for heart failure, targeting proteins involved in calcium handling such as phospholamban[50] and S100A1.[51] The successful completion of Phase II trials of SERCA2a gene therapy demonstrated the feasibility and safety of AAV1-mediated gene transfer as well as the improvement of the symptoms and exercise capacity of patients with advanced heart failure.[52] Using a combination of cardiac AAV serotype and cardiomyocyte-specific promoter, it is now possible to specifically target the heart after systemic administration.[53]

Different approaches have been evaluated in the context of HCM. The first strategies target the endogenous mutant sarcomeric pre-mRNA or RNA such as exon skipping, spliceosome-mediated RNA *trans*-splicing (SMaRT), or RNA silencing.[29–31,54] In SMaRT, two independently transcribed RNA molecules, a target mutant pre-mRNA and a therapeutic pre-*trans*-splicing molecule (delivered by AAV), are spliced together (for a detailed review, see Wally *et al.*[55]). As a result,

a full-length repaired mRNA is formed. *Trans*-splicing has the potential to treat autosomal-dominant diseases by repairing a mutant pre-mRNA. A recent proof-of-concept study demonstrated that 5′-*trans*-splicing repaired *Mybpc3* mRNA in cardiac myocytes and *in vivo* in homozygous *Mybpc3*-targeted knock-in (*Mybpc3*-KI) mice, even if the efficiency was not sufficient to prevent the disease phenotype.[54] An alternative approach is the in-frame skipping of mutated exons by antisense oligonucleotides (AONs), which mask *exonic splicing enhancer* motifs and therefore prevent the binding of regulatory splicing proteins that mediate exons inclusion into the mature mRNA.[56,57] The resulting proteins, which are internally deleted of a small part, should remain functional. This strategy has been recently evaluated in *Mybpc3*-KI mice, using two AONs that were expected to produce an in-frame deletion of two exons. AONs were introduced in tandem into U7 small nuclear RNA and packaged in AAV9. A single systemic administration of AAV9 in newborn *Mybpc3*-KI mice produced a stable functional protein and transiently prevented the cardiac disease phenotype.[30] More recently, allele-specific silencing of mutant *Myh6* mRNA by AAV-mediated RNAi delivery delayed the expression of the disease phenotype (induced by cyclosporine) in heterozygous *Myh6*-KI mice.[29]

The alternative strategy consists of adding a functional sarcomeric protein in place in the sarcomere. Although this has been widely used to create transgenic animals,[58] only two groups have envisioned this approach for sarcomeric cardiomyopathies in mouse models.[31,32] The sarcomere is indeed a tightly regulated system in which the stoichiometry of all components is preserved. Therefore, additional expression of any sarcomeric protein is expected to replace in part or completely the endogenous protein level in the sarcomere. This approach is particularly attractive for *MYBPC3* mutations that result in low level or the absence of mutant proteins. A very recent study has evaluated whether replacement of endogenous mutant cMyBP-C by exogenous wild-type cMyBP-C could prevent the cardiac phenotype in homozygous *Mybpc3*-KI mice, which genetically mimic the situation of the severe forms in patients.[31] A single systemic injection of AAV9 encoding cMyBP-C under the control of human cardiac troponin T promoter in neonatal mice, which do not exhibit a disease phenotype at this stage, was sufficient to enable a long-term prevention (until 34 weeks) of the disease phenotype, including LV hypertrophy, diastolic, and systolic dysfunction. Importantly, these data show that endogenous mutant cMyBP-C proteins are almost fully replaced by exogenous functional cMyBP-C. These data paved the way for a causal therapy of severe neonatal sarcomeric cardiomyopathy due to bi-allelic *MYBPC3* mutations.

3. Targeting ion channels in HCM

Drugs targeting ion channels are an important component of pharmacological therapy for many HCM patients (*Table 1*).[59] To better understand how drugs affect the pathophysiological determinants of symptoms and arrhythmias in HCM patients, it is useful to know how this disease alters excitation–contraction coupling (ECC) in adult ventricular cardiomyocytes. A recent study characterized the abnormalities of ECC occurring in the human HCM myocardium as concomitant determinants of diastolic dysfunction and arrhythmias in this disease.[60] Myocardial specimens from the interventricular septum of obstructive patients undergoing surgical myectomy were compared with non-failing non-hypertrophic surgical patients. Action potential duration (APD) was markedly prolonged in HCM cardiomyocytes compared with controls and was associated with prolonged QTc in patients from the HCM group, a common feature in patients with this disease.[61] APD prolongation in HCM cardiomyocytes led to the increased risk of arrhythmogenic early after depolarizations (EADs) and was caused by an imbalance between inward and outward currents: repolarizing K^+ currents were reduced and depolarizing L-type Ca^{2+} current and late Na^+ current (I_{NaL}) were increased. HCM cardiomyocytes also displayed several abnormalities of intracellular Ca^{2+} cycling: while the amplitude of Ca^{2+} transients was preserved, the kinetics of Ca^{2+} rise and decay were markedly slower and diastolic Ca^{2+} concentration was increased, resulting in a higher rate of Ca^{2+} waves and delayed after depolarizations (DADs). Among the determinants of intracellular Ca^{2+} overload, a reduced Ca^{2+} extrusion through the Na^+/Ca^{2+} exchanger (NCX) played a major role. NCX functional abnormalities were attributed to intracellular Na^+ accumulation due to excessive Na^+ entry via an increase in the late Na^+ current. The abnormalities of ECC observed in single cells resulted in slower relaxation and increased diastolic tension in intact trabeculae isolated from the same samples, suggesting that alterations of Ca^{2+} cycling contribute to diastolic dysfunction in HCM myocardium. On the other hand, systolic function was preserved, with a slower rate of force development and prolonged twitches. Increased activity of Ca^{2+}/CaM-dependent kinase II (CaMKII) appeared to underlie several of the observed functional abnormalities: increased phosphorylation of Na^+ channels and enhanced Na^+ current (I_{NaL}),[62,63] increased ryanodine receptor phosphorylation caused Ca^{2+} waves and DADs,[64] and increased phosphorylation of Ca^{2+} channels slowed Ca^{2+} current inactivation. Notably, all those changes ultimately lead to increased intracellular Ca^{2+} concentration, which is a main driver for CaMKII activation, thus creating a vicious cycle. Indeed, this type of positive feedback from Na–Ca–CaMKII back to higher $[Na]_i$ and more spontaneous sarcoplasmic reticulum (SR) Ca^{2+} release may be important in this pathological effect.[65] Pharmacological intervention should therefore be aimed at impeding intracellular Ca^{2+} overload, by inhibiting either CaMKII or one of the other pathways of Ca^{2+} entry and cytosolic accumulation. The features of maladaptive remodelling in HCM cardiomyocytes, including electrical anomalies, Ca^{2+} handling abnormalities, and alterations of CaMKII signalling, are similar to other forms of pathological hypertrophy,[66,67] and thus represent a potential common pathway of disease, eventually driving the common pathophysiological features occurring in patients with cardiac hypertrophy, namely arrhythmias and diastolic dysfunction. Alterations of ion channels are central in this process, thus drugs targeting ion channels directly (or indirectly via CaMKII inhibition) may play a crucial role in treating hypertrophic remodelling and, in particular, HCM (*Figure 2*).

3.1 Targeting ion channels to prevent detrimental effect of LV outflow tract obstruction

A principal determinant of symptoms in overt HCM is obstruction of the LV outflow tract (LVOT), which occurs at rest in approximately one-third of all patients (rest obstruction). The number of patients with LVOT increases during exercise (inducible obstruction) to two-thirds of all patients.[68] The generation of a pathological gradient in the LVOT during systole (>30 mmHg) is determined by the increased systolic thickening of the upper septum and systolic motion of the (often elongated) anterior mitral valve leaflet towards the septum. When obstruction is present at rest, LVOT gradients lead to a reduction of cardiac output and congestive symptoms (e.g. dyspnoea). In patients with inducible obstruction, the generation of gradients during exertion limits exercise capacity. In symptomatic HCM individuals without obstruction,

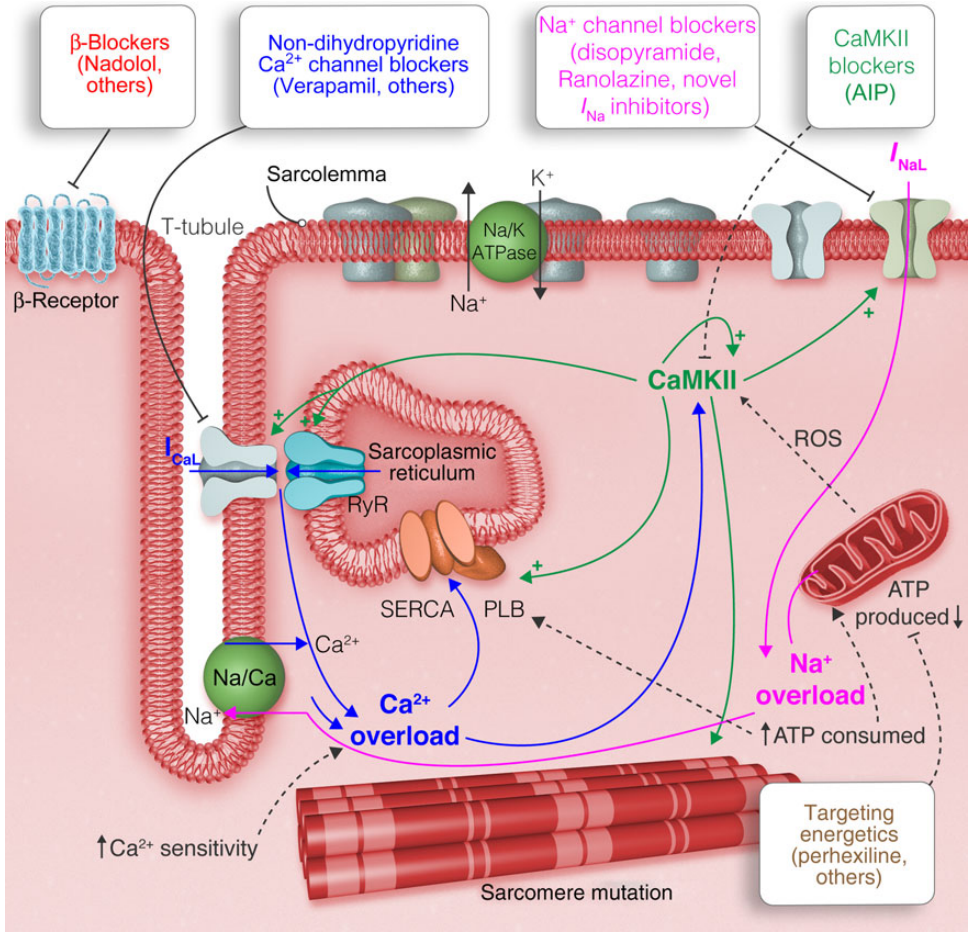

Figure 2 Treatment of sarcomeric cardiomyopathies may be directed at non-sarcomeric targets such as ion channels, β-adrenergic receptors, and Ca^{2+}/CaMKII. In addition, metabolic therapy, such as perhexiline, may be targeted at the mitochondria to improve the energetic status of the heart. Modified from Coppini *et al.*[60]

diastolic dysfunction and myocardial perfusion abnormalities determine reduced exercise capacity and angina.[69] Besides β-blockers, disopyramide, a Class Ia sodium channel blocker, has been used largely as a first-line therapy for obstruction for more than 30 years[70] and received a Class IIa recommendation in the latest HCM guidelines.[1] Disopyramide was shown to reduce LVOT gradients and ameliorate obstructive symptoms in two-thirds of treated patients, with a significant benefit on survival and no apparent pro-arrhythmic effects when used properly.[71] However, a significant number of patients cannot tolerate the drug due to its anti-cholinergic effects and the significant reduction of cardiac contractility, leading to a decreased ejection fraction (10% on average).[72] Cellular mechanisms underlying the negative inotropic effect of disopyramide are poorly understood at present. At therapeutic concentrations (5–10 μM), disopyramide is known to reduce the upstroke velocity and the amplitude of action potentials,[73] and may thus diminish or delay ECC and slowing septal contraction. Moreover, the reduction of intracellular Na^+ is likely to limit Ca^{2+} levels and contractility via enhancement of Ca^{2+} extrusion and reduction of Ca^{2+} entry through the NCX. In HCM patients, these effects may result in a slower and reduced force generation by the septum, lower blood flow acceleration in the LVOT, diminished hydrodynamic pull on the mitral leaflet, and reduced mitral–septal contact, eventually leading to reduced outflow gradients.[74]

Non-dihydropyridine Ca^{2+} channel blockers such as verapamil and diltiazem are also commonly employed in symptomatic patients with non-obstructive HCM. On the contrary, HCM guidelines stand against the use of Ca^{2+} channel blockers in patients with LVOT obstruction and high gradients at rest,[1] due to the risk of severe hypotension, bradycardia, and syncope mediated by the mild systemic vasodilation. Nonetheless, these drugs may be indicated in combination with β-blockers for patients with inducible obstruction and mild gradients. Verapamil is the most studied agent in HCM patients, despite a lack of definitive evidence that Ca^{2+} channel blockers ameliorate exercise capacity in non-obstructive symptomatic patients.[1] Verapamil and diltiazem exert their beneficial effects on HCM-related symptoms in part through their negative inotropic and chronotropic effects and in part via improvement of myocardial diastolic function. Reduction of heart rate is mediated by a direct effect on Ca^{2+} current in sinoatrial cells and leads to prolongation of relaxation time. Reduced Ca^{2+} entry into ventricular myocytes determines a reduction in peak force with no effect on the speed of force generation, eventually causing a negative inotropic effect, that may be effective against obstruction.[75] In addition, relaxation

time of ventricular myocardium is reduced by Ca^{2+} channel blockers with a significant increase of LV early filling rates.[76] The latter is likely to be a consequence of the decreased intracellular diastolic Ca^{2+}, leading to reduced diastolic tension. Since coronary perfusion occurs predominantly during diastole, the reduction of diastolic tension after Ca^{2+} channel blocker administration leads to increased myocardial blood flow,[77] preventing exercise-induced myocardial ischaemia, a common occurrence in HCM patients.

3.2 Targeting ion channels to prevent arrhythmias

While the presence of LVOT strongly affects the symptomatic state of HCM patients with a largely 'stable' phenotype, atrial and ventricular arrhythmias are the main determinant of the outcome and need to be addressed by aggressive preventive strategies, which to date are both insufficient and difficult to administer.[78] Amiodarone is the most used antiarrhythmic agent to prevent ventricular tachycardia and fibrillation in high-risk HCM patients.[1,79] As a Class III antiarrhythmic agent, the principal mode of action is the inhibition of rapid and slow delayed rectifier potassium channels (I_{Kr}), leading to delayed repolarization. This could represent a potential risk in HCM patients, who already suffer from a prolonged QT interval due to APD prolongation.[60,61] However, amiodarone exerts a number of additional effects, including block of L-type Ca^{2+} current, peak and late Na^{+} currents; counteracting the AP prolonging effect of the compound and effectively antagonizing the pathological arrhythmogenic changes occurring in HCM myocytes, making it a potentially effective agent to prevent arrhythmias in this disorder. Nonetheless, clinical evidence suggests that amiodarone used for primary prevention does not exert a significant benefit in terms of survival,[80] and is to be used only in patients with frequent symptomatic ventricular arrhythmias or to decrease the frequency of effective shocks in patients with implantable cardioverter/defibrillators.[1] On the other hand, amiodarone is the most commonly used antiarrhythmic drug to maintain sinus rhythm in HCM patients with paroxysmal atrial fibrillation.

The previous observations emphasize the lack of effective pharmacological agents capable of ameliorating diastolic dysfunction and reducing ventricular arrhythmogenesis in HCM. The inhibitors of I_{NaL} may fill this gap. The first drug of this category, ranolazine, is the only commercially available I_{NaL} inhibitor, currently in use for the treatment of angina. The molecular effects of ranolazine were recently evaluated in surgical myocardial samples from HCM patients.[60] Consistent with inhibition of the depolarizing I_{NaL}, ranolazine significantly reduced the prolonged APD in HCM myocytes, thus nearly abolishing the occurrence of EADs. This effect was paralleled by a marked acceleration of Ca^{2+} transients and a reduction of diastolic Ca^{2+} concentration, the latter more evident at high frequency of stimulation. Reduced intracellular Na^{+} accumulation leading to increased Ca^{2+} extrusion through the NCX underlie the beneficial effects of ranolazine on Ca^{2+} handling in HCM cardiomyocytes. In addition, normalization of Ca^{2+} cycling properties with ranolazine causes a mild reduction of systolic force, an acceleration of twitch force generation and relaxation, as well as a reduction of diastolic tension in HCM trabeculae, supporting a potential improvement of diastolic function. Taken together, these observations suggest that inhibition of I_{NaL} may exert a number of significant beneficial effects in HCM patients, by reducing both the arrhythmogenic potential and the intrinsic impairment of diastolic function at the cellular level. These features strongly support the use of I_{NaL} inhibitors to treat symptomatic HCM patients without obstruction. Of note, a clinical trial is ongoing, evaluating the effect of ranolazine on exercise capacity in this class of patients (RESTYLE-HCM; EUDRA-CT 2011-004507-20). A small proof-of-concept placebo-controlled clinical trial in patients with severe diastolic heart failure (RALI-DHF) recently suggested that filling pressures (LVEDP), pulmonary artery pressures, and wedge pressures could be reduced by ranolazine.[81] Additionally, the slight negative inotropic effect of ranolazine, far from representing a concern for clinical use, may provide a safe option aimed at reducing septal hypercontractility and thus may relieve obstruction in HCM patients. Finally, by improving diastolic function, I_{NaL} inhibition has the potential to increase myocardial perfusion, thus addressing myocardial ischaemia in HCM. Recently, novel highly selective I_{NaL} inhibitors[82,83] are in early clinical stages of development and may represent a valid alternative for HCM treatment in the near future.

3.3 Targeting ion channels to prevent adverse remodelling in manifest HCM

Studies on several models of hypertrophy highlighted alterations of intracellular Ca^{2+} handling, leading to intracellular Ca^{2+} overload as central determinants of pathological cardiomyocyte remodelling, acting via a number of signalling pathways, among which the CaMKII-dependent cascade plays a central role.[84] CaMKII hyperactivation during disease is associated with activation of hypertrophic gene expression programme, changes in ion channel or SR protein levels, and may play a role in enhancing fibroblast growth and extracellular matrix expansion.[85,86] With these mechanisms, CaMKII hyperactivation is likely to play a crucial role in driving progression of cardiac hypertrophy to heart failure.[87] Sustained activation of CaMKII-dependent pathways play a central role in determining electro-mechanical myocardial dysfunction in human HCM,[60] and may therefore be a highly relevant target for progression. Direct inhibition of cardiac CaMKII with small molecules is still in early preclinical development;[88] therefore, the best option to date is to indirectly reduce CaMKII activity by lowering intracellular Ca^{2+} levels. Inhibition of Ca^{2+} current appears to be the most straightforward way of reducing intracellular Ca^{2+}, as the amount of Ca^{2+} entering the cytosol via the L-type Ca^{2+} channels directly modulates CaMKII activity.[89] Early reports on the use of L-type Ca^{2+} channel blockers in HCM patients showed a reduction of cardiac mass upon long-term administration.[90] Treatment with diltiazem prevented worsening of diastolic dysfunction and limited progression to diastolic heart failure in HCM *Tnnt2* mutant transgenic mice.[91] At present, there is no evidence on whether treatment with L-type Ca^{2+} channel blockers is able to reduce CaMKII activation and alter cardiomyocyte remodelling in HCM.

A clinically relevant therapeutic option to address intracellular Ca^{2+} overload and reduce CaMKII activity in HCM is pharmacological inhibition of I_{NaL}. In pathological settings, there is continuous interplay among CaMKII, intracellular Ca^{2+}, and I_{NaL}. On the one hand, enhanced CaMKII activity due to increased intracellular Ca^{2+} or oxidative stress increases I_{NaL} via specific phosphorylation of cardiac Na^{+} channel $Na_v1.5$;[63,92,93] on the other hand, increased I_{NaL} determines elevated intracellular Ca^{2+} and thus activates CaMKII.[94] Such complex interplay is relevant for the progression of diastolic dysfunction in cardiac disease and may play a role in favouring decompensation of stable hypertrophy.[95] I_{NaL} inhibition may therefore be a viable option for interrupting the CaMKII-dependent remodelling pathway in HCM. In support of this hypothesis, acute treatment with ranolazine led to a reduction of

diastolic Ca^{2+} levels in human HCM cardiomyocytes.[60] Over time, this effect may lead to overall lower CaMKII activity, eventually affecting the functional and structural remodelling of HCM myocardium, with possible implications for disease progression.[96] In keeping with this observation, ranolazine administration has been shown to reduce the degree of myocyte hypertrophy and interstitial fibrosis in experimental models with moderate heart failure.[97] In principle, I_{NaL} inhibition is a promising therapeutic strategy for HCM patients, with a wide range of potentially positive actions, which may critically impact on acute symptoms as well as on the natural history of the disease.

3.4 Targeting ion channels to prevent disease progression in mutation carriers

During the so-called pre-hypertrophic phase of HCM, periodic non-invasive cardiac screening is performed to identify early markers of disease, such as mitral valve abnormalities or a mild impairment of diastolic function.[98,99] However, no clinical strategy exists to prevent disease progression in mutation carriers. While the primary disease cause is the gene mutation of a sarcomeric protein, alterations in intracellular Ca^{2+} handling are among the earliest secondary changes occurring in HCM myocardium, as confirmed by studies in transgenic or targeted mouse models.[100–102] Intracellular Ca^{2+} overload may be present in the pre-hypertrophic phase of the disease. Thus, reducing intracellular Ca^{2+} in this critical phase is likely to affect phenotype presentation. This hypothesis has been tested by treating transgenic mice carrying the R403Q myosin heavy-chain mutation with diltiazem since birth.[103] Ca^{2+} channel block, by diminishing intracellular Ca^{2+} overload, was able to reduce the development of hypertrophy, intramyocardial fibrosis, and myocyte disarray, to prevent pathological changes of SR protein expression, and to limit the extent of diastolic and systolic dysfunction in the adult mice. Such changes may well be mediated by alteration of CaMKII-mediated signalling. Following this intriguing preclinical evidence, an ongoing study is testing the hypothesis that diltiazem may prevent the development of the HCM phenotype in mutation carriers.[104]

In the presence of increased CaMKII activity, I_{NaL} is increased by CaMKII-dependent phosphorylation. An increase of I_{NaL} may also be an early change in the preclinical phase. Similar to diltiazem, I_{NaL} inhibitors such as ranolazine may lead to a sustained reduction of intracellular Ca^{2+}, thus impacting on the signalling pathway leading to hypertrophy, tissue remodelling, and, eventually, electrical and mechanical dysfunction of affected myocardium. Whether I_{NaL} inhibition is able to prevent or significantly delay the onset of phenotype in mutation carriers remains to be assessed and deserves preclinical investigation. This is of particular interest since ranolazine has an improved profile when compared with diltiazem and may therefore become an important therapeutic option to prevent disease development in young individuals carrying high-risk mutations.

4. Targeting vascular dysfunction and energetics

Cellular 'energy deficiency' is a prominent feature of HCM,[105] but how sarcomeric mutations cause this deficiency at the whole organ level is not clearly understood. Increased energy demand and decreased energy supply both likely contribute to the energy deprivation. Many HCM mutations increase 'tension cost',[106,107] meaning the amount of ATP necessary for a unit of work is elevated, thus directly increasing energy demand. There is also evidence that energy supply may be compromised due to changes in substrate utilization or mitochondrial dysfunction.[108] At the cardiac level, insufficient coronary perfusion, whether related to epicardial or microvascular abnormalities (i.e. vessels of <400 μm), will limit oxygen supply and exacerbate the primary cellular energy privation related to sarcomeric mutations.

4.1 Causes and consequences of primary energy deficiency in HCM

Energy deficiency, specifically resulting from inefficient generation of contractile force (e.g. requiring more ATP per pN of force generated), remains an enduring primary biophysical consequence of HCM sarcomeric mutations.[5] Sophisticated techniques interrogating human HCM samples have confirmed this observation for the R403Q mutation in *MYH7*.[106] Moreover, many forms of LV hypertrophy (LVH), whether inherited or acquired, are increasingly recognized to exhibit impaired myocardial perfusion reserve and oxygenation that are likely to contribute to the derangement in myocardial energetics.[109] In HCM, the biophysically driven cellular energy deficiency is a primary feature of disease rather than the consequence of hypertrophy,[110] as deduced from the observation that energy deficiency is manifest very early in the course of disease.[111] The cumulative consequence of adaptations, ranging from those at the cellular level through the level of the myocardium (e.g. myocardial remodelling including the vasculature) to the level of systemic response (e.g. the autonomic response), is likely to extenuate this primary energy deficiency.

The immediate consequences of increased ATP demand are likely to be on intermediary metabolism and Ca^{2+} kinetics. Increased energy demand has a direct influence on metabolic pathway fluxes. Normally, energy supply and its influence on intermediary metabolism is exquisitely spatially regulated via the creatinine kinase (CK) system, reducing the temporal delays resulting from compartmentalization of cellular activities, and globally via AMP-activated protein kinase (AMPK). Threatened energy deficiency (i.e. increased ADP) is transmitted by the CK system, activating AMPK, the cellular energy gauge, increasing ATP production, and mitigating energy-consuming activities. These systems are sufficiently robust to ensure that even in advanced heart failure, myocardial ATP levels rarely fall below 75% of the levels seen in normal hearts. As a corollary, mutations in the γ2 subunit of AMPK, which mimic an energy deficiency signal, are a cause for HCM.[112] Energy deprivation triggers cellular hypertrophy, cell death, and replacement fibrosis, which likely contributes to the microvascular remodelling described below. Delineating the contribution of these processes on overall energy deficiency and HCM progression remains an active research goal.[113] The mechanisms culminating in LVH in HCM remain obscure. While it seems intuitive to attribute LVH to the consequences of energy deficiency on Ca^{2+} kinetics, perhaps via the calcineurin pathway, there is little to support this hypothesis.

Hypertrophy *per se* is characterized by changes in myocardial metabolism including a switch from fatty acid to carbohydrate utilization. Although this substrate shift is generally considered to be beneficial by virtue of the oxygen sparing effects of carbohydrate metabolism, there is an increasing recognition that increased carbohydrate metabolism is accompanied by a shift towards anaplerotic flux which contributes to a less energy-efficient myocardium. This substrate shift is driven by activation of the HIF1α–PPARγ axis.[114] This intrinsic feature of hypertrophy is compounded by vascular consequences of HCM, including

chronic HIF1α activation, perpetuating substrate shifts, and driving changes in Ca^{2+} handling that are likely to be detrimental.[115,116]

4.2 Evidence for vascular dysfunction and ischaemia in HCM patients

The occurrence of ischaemia in HCM is a well-recognized clinical phenomenon.[117] HCM patients often experience chest pain and dyspnoea, and have an elevated arrhythmia risk, all typical of myocardial ischaemia. Circulating levels of markers of acute ischaemic damage were found to be elevated in some studies.[118,119] Histological examinations report infarct-like areas in different stages of healing. Unlike in patients with isolated coronary artery stenosis, the spatial arrangement of scarring is not consistent with perfusion territories of larger coronary arteries, but is patchy with principal involvement of the mid-myocardium.[120,121] Several functional studies have observed a diminished coronary flow reserve despite normal epicardial coronary arteries, proposing microvascular dysfunction as an explanation.[122,123] The vascular dysfunction was found independent of the structural HCM subtype and occurs in asymmetrical sepal as well as apical hypertrophy.[124] Further evidence for ischaemia arises from studies demonstrating hypoperfused myocardial regions during exercise in >50% of patients.[125,126] Stress-induced reversible perfusion defects are found most frequently in hypertrophic regions in patients with normal or enhanced LV function.[125] However, decreased perfusion is pathological only if tissue oxygenation is compromised; a blunted tissue oxygenation response was recently directly measured during vasodilator stress in HCM mutation carriers.[127] The timing of the onset of vascular dysfunction during the disease process is currently unclear. The prevailing notion is that cardiac structural remodelling precedes vascular dysfunction, although no study has demonstrated a clear sequence. Microvascular dysfunction is often spatially associated with tissue remodelling, but it is also found adjacent to patchy fibrosis.[47,127] Repeated bouts of ischaemia can induce hypertrophy,[128] and fibrosis replaces terminally damaged cardiomyocytes. Thus, it should not be ruled out that vascular dysfunction is an early consequence of the genetic defect, precedes or even promotes hypertrophy and fibrosis, and contributes to the eventual development of ventricular dysfunction.

4.3 Causes for vascular dysfunction in HCM

Although some DCM gene mutations may affect vascular structure and function directly,[129] in case of HCM the mutant proteins are almost exclusively expressed in cardiomyocyte. In HCM patients, the capillary density is decreased,[130] at least in hypertrophic parts, and the arteriolar lumen of the intramural coronary arteries normalized to wall area is lower,[131] partially due to thickening of the medial and intimal layers.[132] What promotes this remodelling is currently unclear. In pulmonary arterial hypertension, endothelial cell dysfunction leads to similar remodelling of the pulmonary vasculature,[133,134] but there is no obvious link yet found between HCM causing mutations and endothelial cell function.

Diastolic dysfunction during stress is a frequent observation in HCM and is a potentially early consequence of the genetic defect in patient and mouse models.[91,102,104] Impaired LV relaxation and the resulting increased filling pressure impinge on diastolic coronary perfusion particularly at faster heart rates as a result of increased extravascular compression.[135] Myocardial filling pressures may be further elevated in the presence of LVOT, aggravating extravascular compression particularly in the subendocardial layer. Consistent with this notion, surgical correction of LVOT improves myocardial blood flow reserve.[136] Impaired relaxation of the ventricle may also diminish a critical 'suction wave' that is generated during normal relaxation, which is a critical driver of diastolic coronary blood flow.[137] Other causes for vascular dysfunction in HCM are less frequently discussed, but additional mechanisms likely exist. Sarcomere mutation carriers are characterized by more severe microvascular dysfunction and increased prevalence of myocardial fibrosis when compared with sarcomere non-carriers, suggesting a direct link between sarcomere dysfunction and vascular dysfunction that is not yet understood.[138] Anatomical causes that may contribute to ischaemia and angina symptoms include myocardial bridging, which has an increased incidence in HCM[139] and coronary vasospasm, which also has been reported in HCM patients. It is conceivable that the metabolic and energetic changes in HCM disturb metabolic coronary flow regulation and manifest in regional vascular dysfunction, which is largely unexplored. It is intriguing that the mechanism whereby the matching of local oxygen demand with supply is continuously maintained is poorly understood.[140]

To fully understand all factors that contribute to vascular dysfunction in HCM, it will be critical to longitudinally evaluate the time of onset and progression of vascular dysfunction in relation to other manifestations starting in young HCM mutation carriers. It would be also valuable to generate or identify animal models that reproduce the vascular dysfunction and display, e.g. regional perfusion defects. Myosin heavy-chain mutant HCM mice develop focal replacement fibrosis[141] and we have recently shown that *Tnnt2* mutant HCM mice develop focal energy deprivation during stress, which was linked to increased myofilament Ca^{2+} sensitivity mediated by the mutation.[142] Investigating the underlying causes would be informative.

4.4 Vascular dysfunction and energy deprivation in HCM and prognosis

Vascular dysfunction or the diminished ability to respond to hypoxia appears to contribute to a worse prognosis in HCM mutation carriers. Patients who have concomitant HCM and significant coronary artery disease are at a substantially increased risk of death than comparable patients without HCM.[116] A substantial number of HCM patients have increased high-sensitivity cardiac troponin T marker serum concentrations, a circulating marker for ischaemic damage, and the level may predict the adverse outcome.[143] HCM patients with certain common variants in hypoxia response genes, which affect the expression of hypoxia-inducible signalling molecules, had more severe hypertrophy and diastolic dysfunction.[144] Vascular dysfunction is currently not utilized as a factor to determine risk for lethal arrhythmias, with the exception of an inappropriate drop of systemic blood pressure during exercise.[145]

To date, there is no evidence relating the degree of energy deficiency to prognosis. Notwithstanding the most parsimonious explanation that the degree of energy deficiency, as a continuous variable, does not contribute to outcomes, a number of other explanations may contribute to this lack of prognostic value. The most compelling is the relative lack of granularity afforded by the most readily available measure of energy deficiency, the PCr/ATP ratio. On an individual patient basis, this parameter, typically measured at rest, is a relatively noisy and insensitive measure even in the best MRI laboratories. The PCr/ATP ratio can be refined either through dynamic measurement[146] and/or through the measurement of flux.[147] Nevertheless, the confounding effect of cellular adaptation, maintaining the cellular energy charge to maintain the Gibbs free energy of ATP hydrolysis that is so critical to general cellular

function, reduces the dynamic range and hence discriminating the value of energy parameters.

4.5 Vascular dysfunction and disturbed energetics as therapeutic targets in HCM

Vascular dysfunction represents a promising potential target for novel HCM therapies. Current pharmacological treatments to relieve LVOT and angina symptoms, β-blockers and Ca^{2+} channel antagonists, are thought to be largely effective because of the negative chronotropic and inotropic effects, increasing diastolic perfusion time, and reducing extravascular compression. In addition, verapamil has also been demonstrated to prevent regional perfusion defects in a considerable fraction of asymptomatic HCM patients.[148] Despite this, current treatment has not been shown to alter the natural history of the disease.[149] While this will need to be confirmed in clinical trials, this is intriguing and indicates that either the drugs are given too late and disease has progressed irreversibly, or we still lack fundamental understanding about the disease process. Other strategies to enhance relaxation, e.g. myofilament Ca^{2+} desensitization (discussed above), may exhibit a more attractive therapeutic profile.[150] We know that the coronary microvascular dysfunction importantly contributes, as it is inversely related to death from cardiovascular causes in HCM patients as well as adverse LV remodelling and systolic dysfunction.[69] Efforts are underway to test drugs that have benefits in patients with diastolic dysfunction unrelated to HCM. Typically, these drugs also influence vascular causes and consequences, e.g. ranolazine, ACE inhibitors etc., and it is quite possible that these studies will correct the underlying defect or at least point us into the direction we need to investigate.

An alternative strategy might be to target metabolic substrate modification with a goal of altering the state of myocardial oxygenation to augment any primary vascular therapeutic strategies. The advantage of a metabolic approach is that it addresses a common yet proximal cause of myocardial remodelling in HCM. The primary effect of shifting fatty acid to carbohydrate metabolism is the benefit related to oxygen sparing. This is especially germane to a myocardium with compromised perfusion. The benefits of this strategy have been exemplified by success of perhexiline (*Figure 2*), a partial fatty oxidation inhibitor, in the treatment of symptomatic HCM as well as patients with angina.[151] A more nuanced perspective of re-balancing cardiac metabolism (i.e. other than fatty acid vs. carbohydrate) would confer additional benefits. It has been observed that, in LVH, glucose oxidation-derived carbon flux is shifted away from pyruvate dehydrogenase (PDH)-derived acetyl coenzyme A production towards anaplerosis (i.e. the use of glucose-derived carbons to contribute to the backbones of metabolic intermediates). Increased carboxylation of pyruvate via cytosolic malic enzyme generates malate, which ultimately feeds into the citric acid cycle (TCA). It has been argued that this shift away from direct glucose oxidation by PDH is profligate and may represent an excellent therapeutic target.[152] While from a stoichiometric perspective increased anaplerosis may appear profligate, increased TCA intermediates may have additional benefits that have hitherto not been considered. We have recently demonstrated that, by stabilizing the transcriptional regulator Nrf2, the TCA intermediate fumarate up-regulates protective antioxidant response element genes.[153] These additional consequences of metabolic modification may have profound influences beyond intermediary metabolism pertinent to the consequences of vascular privation.

Finally, it is worth bearing in mind that as well as pharmacological therapies, diverse cardiac interventions such as device therapy (e.g. cardiac resynchronization therapy) may also have an influence on HCM through their impact on intermediary metabolism. Importantly, as with other aspects of HCM as an archetypal cardiac disease, insights derived from metabolic modulation in HCM may, when applied with care, provide valuable lessons for the management of other forms of LVH.

5. Conclusions and future directions

For a not uncommon disorder for which the pharmacological treatment has not appreciably changed in 50 years, the preceding sections represent an exciting look into the future of the management of sarcomeric cardiomyopathies. The ability to identify patients at risk of developing a cardiomyopathy via genetic testing and eventually develop a tailored, mechanistic approach to altering the natural history of the disease process at the molecular level holds profound promise. For example, it is important to note that some subsets of patients eventually require cardiac transplantation, often at a young age. Even the ability to delay the need for transplant for 10–20 years by initiation of targeted therapies in the preclinical stage would represent a significant advance. Moreover, the ability to directly reduce the risk of sudden cardiac death or the onset of atrial fibrillation by mitigating ion channel remodelling would alter the burden of these complex cardiomypathies. While the eventual goal of developing genotype-specific risk assessments and fully targeted therapies still requires a more advanced understanding of early (preclinical) disease pathogenesis, it is clear that our growing ability to subdivide the process of LV remodelling into separate molecular and cellular bins will provide a framework for developing specific treatment regimens that can eventually be applied to specific genetic cohorts and finally alter the natural history of these common disorders as opposed to simply mitigating symptoms.

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