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Review

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Metabolic alterations in human hypertrophic cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is a highly common cardiomyopathy and is characterized by left ventricular hypertrophy and diastolic dysfunction. In half of the cases, HCM is associated with mutations in genes encoding sarcomere proteins, while the remaining cases occur without identifiable genetic mutations. Disrupted bioenergetic homeostasis has increasingly been recognized as a key feature of HCM pathophysiology. In this review, we summarize and critically evaluate studies addressing cardiometabolic alterations in HCM, with a particular focus on human-based research. These include non-invasive imaging studies, blood-based analyses, and molecular and functional assays of myocardial tissue. We also explore the therapeutic potential of targeting metabolic pathways in HCM and highlight promising directions for future studies.

Keywords: Hypertrophic cardiomyopathy, cardiac metabolism, mitochondrial function, metabolic therapy

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most frequently inherited cardiomyopathy, with a prevalence of 1 to 3 out of 500 individuals[1]. HCM is clinically characterized by diastolic dysfunction and hypertrophy

of the left ventricle (LV; typically within the interventricular septum) that cannot be attributed to abnormal loading conditions such as hypertension or arterial disease[2,3]. A common complication in HCM is obstruction of the LV outflow tract (LVOT) caused by hypertrophy of the interventricular septum and systolic anterior motion of the mitral valve[4]. This obstruction increases afterload, leading to elevated LV systolic pressure and wall stress, while exacerbating diastolic dysfunction, promoting hyperdynamic contraction, and increasing the risk of heart failure and sudden cardiac death[5]. These patients with LVOT obstruction are classified as obstructive HCM (oHCM)[5].

Approximately 50% of all patients with HCM harbor a heterozygous pathogenic or likely pathogenic (P/LP) mutation in sarcomere protein-encoding genes, most frequently in thick filament genes (e.g., *MYH7, MYBPC3*) and less often in thin filament genes (e.g., *TNNT2, TNNI3*)[6-8]. These patients are termed genotype-positive (G+). The other half of patients do not test positive for any causative gene variant (including gene variants associated with HCM phenocopies such as Noonan syndrome, Fabry disease, and Barth syndrome[9]) and are commonly referred to as genotype-negative (G-)[6]. Despite expanded diagnostic testing, most newly diagnosed HCM patients are now G-[10,11]. Some studies, particularly in Asian HCM cohorts, have reported mutations in mitochondrial DNA and mitochondrial-related nuclear genes associated with supercomplex proteins, transfer RNA, and ribosomal RNA, but the clinical significance of these findings remains poorly understood[12].

In recent years, it has become increasingly evident that impaired bioenergetic homeostasis is a central hallmark of HCM pathophysiology, irrespective of the presence of sarcomere pathogenic variants. Here, we summarize and critically evaluate studies on cardiac metabolism in human HCM. Additionally, we explore the therapeutic potential of metabolic therapy in HCM and highlight avenues for future research.

PERTURBED MYOFILAMENT FUNCTION RAISING ENERGETIC DEMAND IN HCM

HCM is characterized by multiple functional alterations at the myofilament level that result in sarcomere inefficiency and hypercontractility, elevating adenosine triphosphate (ATP) consumption [Figure 1]. This imposes dramatic consequences on energetic demand, which is thought to be an important upstream driver of metabolic and cardiac remodeling. In brief, sarcomere inefficiency and hypercontractility lead to a state of chronically elevated mitochondrial workload and oxidative stress, rewiring cardiac metabolism and promoting cardiac remodeling via activation of hypertrophic and fibrotic pathways[13,14].

A key component underlying high ATP consumption is increased Ca^{2+} sensitivity of the myofilaments[15-19]. High Ca^{2+} sensitivity activates the myofilaments at comparatively low diastolic Ca^{2+} levels and slows the dissociation of Ca^{2+} from cardiac troponin C, prolonging cross-bridge activation and impairing relaxation. In G+ patients, high myofilament Ca^{2+} sensitivity may be caused directly by P/LP variants in sarcomere genes, particularly *MYH7* and *TNNT2*[15,18,19]. Additionally, reduced phosphorylation of myofilament proteins, most notably troponin I, due to β-adrenergic desensitization is a major driver of elevated myofilament Ca^{2+} sensitivity in both G+ and G- patients[16,18]. Posttranslational modifications such as S-glutathionylation, resulting from oxidative stress that is apparent in HCM[20-22], additionally impact myofilament contractility[23,24]. Impaired capacity to buffer adenosine diphosphate (ADP) levels[25] may lead to further sensitization of the myofilaments to Ca^{2+}[26]. Finally, cardiomyocytes from patients with HCM display a blunted increase in Ca^{2+} sensitivity and maximal force generation in response to sarcomere lengthening[18], further underpinning inefficient sarcomere function.

Disruption of the super-relaxed (SRX) state of myosin is a well-recognized defect in G+ HCM[27,28]. In the SRX state, the myosin heads are in the OFF state and folded back onto the filament backbone, during which

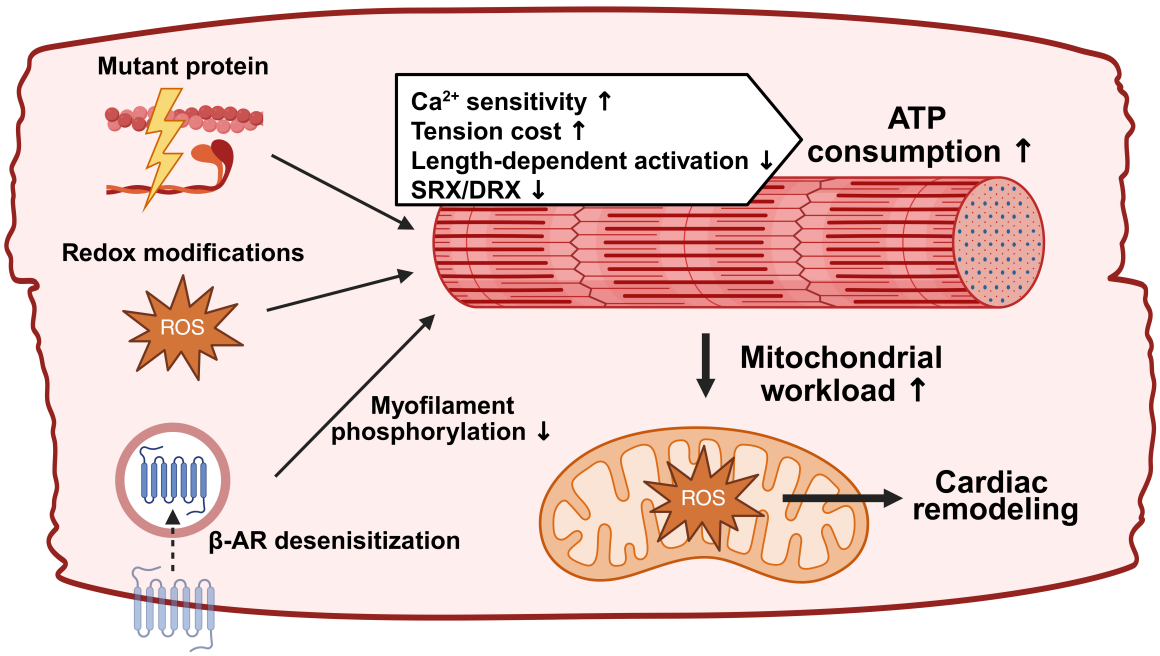

Figure 1. Hypercontractility is central to the pathophysiology of hypertrophic cardiomyopathy. Sarcomere proteins are affected by mutations, redox modifications, and hypophosphorylation, imposing a multitude of functional consequences on the myofilaments. These lead to hypercontractility, increasing adenosine triphosphate (ATP) consumption and raising mitochondrial workload. Sustained elevated mitochondrial workload causes oxidative stress, inducing activation of hypertrophic and fibrotic pathways. Created in BioRender. Nollet E. (2025) https://BioRender.com/ntotvnr. SRX: Super-relaxed myosin; DRX: disordered-relaxed myosin; β-AR: β-adrenergic receptor; ROS: reactive oxygen species.

ATP consumption is low, thereby conserving energy [Figure 2][29]. In HCM, myosin heads disproportionally favor the disordered relaxed state (DRX)[27,28,30,31], during which myosin heads are in an unstable energy-consuming state, leading to an increase in ATP consumption as ATP turnover is 10-fold higher when myosin heads are in the DRX state compared to the SRX state[32]. This imposes a significant burden on the energetic demand in HCM. The implications of disruption of the SRX state have mostly been described in the context of thick filament mutations[30,31]. Its involvement in patients harboring thin filament mutations has only been shown for the HCM-associated cTnT-Ile79Asn mutation[33]. In a small set of G- patient tissue (N = 3), no changes in the myosin SRX state were reported[27]. However, these findings were obtained under tightly controlled permeabilized conditions, where elevated ADP levels or afterload-dependent mechanical strain, both potential drivers of DRX mobilization[34], are not adequately represented. Thus, further study is warranted to gain more insight into the implications of disruption of the SRX state of myosin in HCM linked to thin filament mutations and G- HCM.

A final aspect of inefficient sarcomere function entails lower cross-bridge force-generating capacity caused by P/LP sarcomere gene variants, which is associated with an increased detachment rate of myosin heads and a coincident higher ATP utilization[35-37]. Thus, more ATP is consumed to generate the force needed for contraction, increasing the energetic cost of cardiac work. This is also apparent from imaging studies showing reduced myocardial external efficiency in phenotype-negative carriers of pathogenic mutations in thin and thick filament proteins[38-40].

Taken together, elevated energetic demand in HCM stems from inefficient sarcomere function, which is the combined result of myofilament Ca^{2+} sensitization, perturbed myosin super-relaxation, and altered

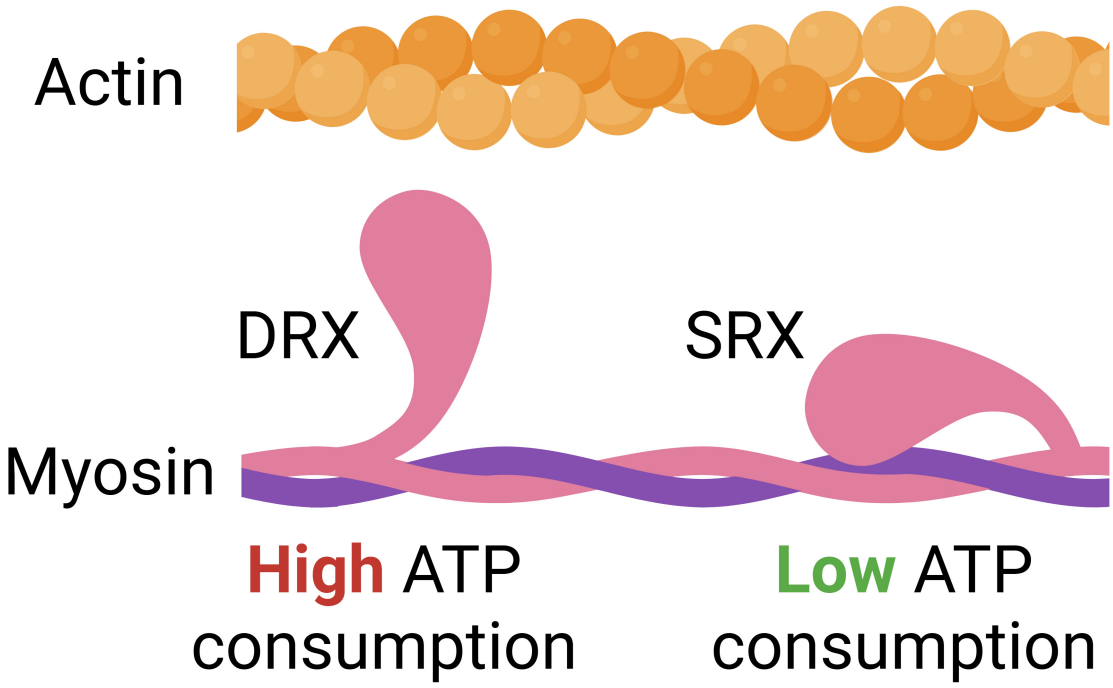

Figure 2. Conformational states of relaxed myosin. In the disordered relaxed state (DRX), myosin heads are in a high adenosine triphosphate (ATP)-consuming unstable state. In the super-relaxed state (SRX), myosin heads are folded onto the myosin backbone and consume tenfold lower amounts of ATP. Created in BioRender. Nollet E (2025) https://BioRender.com/p5fg70j.

cross-bridging kinetics.

ENERGY METABOLISM IN THE HEART

Because of its relentless activity, the heart has a high metabolic demand and requires a continuous supply of energy in the form of ATP to fuel the cardiac cycle. In healthy hearts, this is achieved by the uptake and oxidation of energy substrates, of which fatty acids are the main source[41]. To a lesser extent, the heart uses glucose and lactate, and it can also use ketones and amino acids as fuel[42]. The heart demonstrates remarkable metabolic flexibility and may change substrate use based on local availability or abrupt changes in cardiac demand[43].

A schematic overview of energy metabolism in the normal heart is shown in Figure 3. The vast majority of cardiac ATP is produced via mitochondrial oxidative phosphorylation (OXPHOS)[44]. Production of ATP via OXPHOS relies on a proton gradient across the mitochondrial inner membrane that is used by complex V to regenerate ATP from ADP. The proton gradient is established via proton pumping by the proteins of the electron transferring system (ETS), which requires electron input via the reducing equivalents nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$). NADH enters the ETS via complex I and is generated during glycolysis, fatty acid β-oxidation and by the Krebs cycle dehydrogenase enzymes. The latter are predominantly fueled by acetyl-CoA input from fatty acid oxidation and glycolysis- and lactate-derived pyruvate, but also by anaplerotic enzymes that use amino acids as substrate. $FADH_2$ produced by succinate dehydrogenase enters the ETS at complex II, while $FADH_2$ derived from fatty acid oxidation feeds electrons into the ETS via electron transfer flavoprotein (ETF) and ETF dehydrogenase[45].

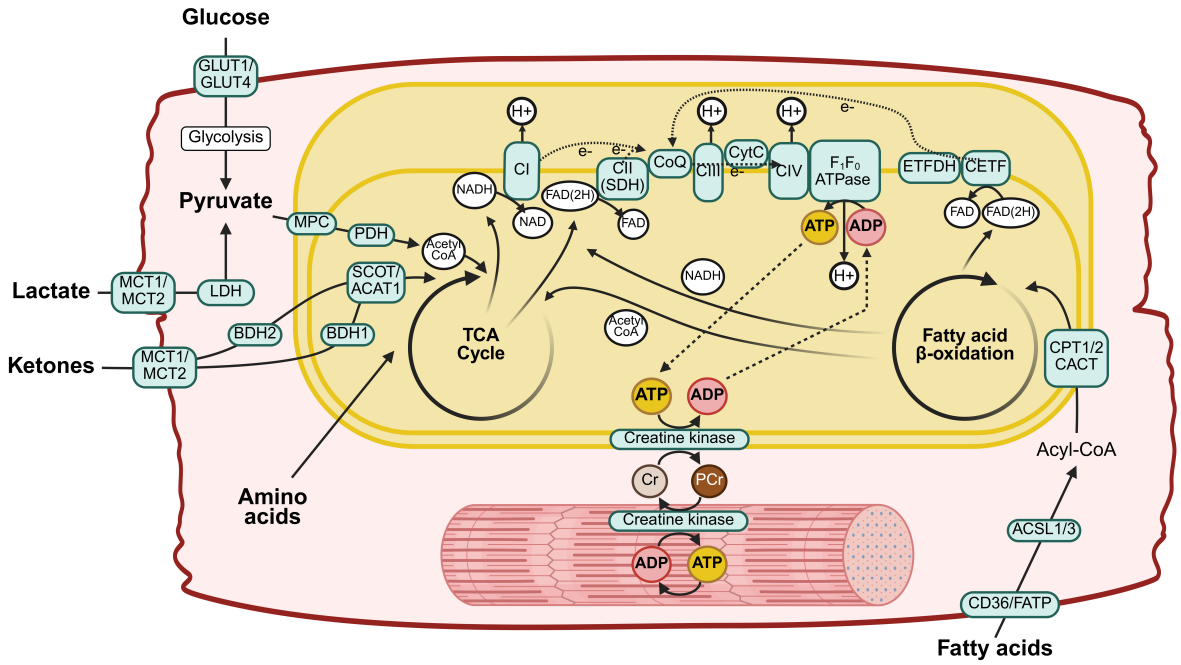

Figure 3. Cardiac energy metabolism. Glucose and fatty acids are the main substrates for mitochondrial energy production in the heart. Substrates are catabolized in order to enter mitochondria and subsequent input into cyclic pathways [tricarboxylic acid cycle (TCA); fatty acid β-oxidation], yielding nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$). NADH and $FADH_2$ feed electrons into the electron transfer system, generating a proton gradient across the inner mitochondrial membrane. This proton gradient enables the regeneration of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) at the $F-_1F_0$ATPase complex. The creatine kinase shuttle facilitates the rapid exchange of ATP and ADP between the myofilaments and mitochondria. Created in BioRender. Nollet E (2025) https://BioRender.com/5j35tv9. LDH: Lactate dehydrogenase; MPC: mitochondrial pyruvate carrier; PDH: pyruvate dehydrogenase; FAD: flavin adenine dinucleotide; NAD: nicotinamide adenine dinucleotide; SDH: succinate dehydrogenase; CI: complex I; CII: complex II; CIII: complex III; CIV: complex IV; ETFDH: electron-transferring-flavoprotein dehydrogenase; CETF: electron transfer flavoprotein complex.

A final crucial aspect of myocardial energy homeostasis is the creatine kinase (CK)/phosphocreatine (PCr) shuttle. Mitochondrial CK uses ATP from mitochondrial OXPHOS to phosphorylate creatine, generating PCr, which is, in turn, used by muscle CK at the sarcomere to locally phosphorylate ADP into ATP[46].

In healthy hearts, mitochondrial ATP production is tightly coupled to acute changes in cardiac workload. Increased ADP delivery via the CK shuttle directly stimulates ATP regeneration at complex V, which requires a proportional increase in electron input into the ETS (so-called "pull" condition)[47,48]. This *per se* causes oxidation of mitochondrial NADH and $FADH_2$, which is rebalanced by raising levels of mitochondrial Ca^{2+}, boosting the activity of mitochondrial dehydrogenases to match NADH and $FADH_2$ formation to the elevated demand (so-called "push" condition)[49].

In the following sections, we describe alterations in substrate utilization that have been reported in human HCM [Figure 4]. Subsequently, we discuss mitochondrial defects that have been described in myocardial samples from patients with HCM.

ALTERED SUBSTRATE UTILIZATION IN HCM

Fatty acids

Lipid metabolism relies on a delicate balance between fatty acid synthesis, uptake, and oxidation. In patients with HCM, the reduced usage of fatty acids as an energy substrate is well-established. This has been

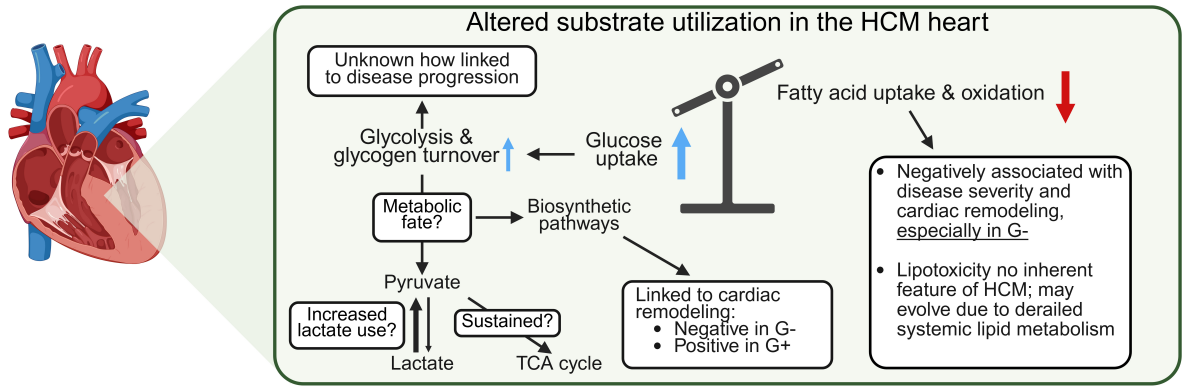

Figure 4. Altered substrate utilization in the hypertrophic cardiomyopathy (HCM) heart. Metabolism in the HCM heart is characterized by a shift away from fatty acid uptake and oxidation toward increased glucose uptake. Fatty acid uptake and oxidation become increasingly impaired as cardiac remodeling and disease severity worsen, which is especially prominent in genotype-negative (G-) patients. Based on current literature, lipotoxicity does not appear to be an inherent feature of HCM, despite lowered fatty acid use. Glycolysis and glycogen turnover are elevated in HCM, although it is unknown how this may change throughout the disease. The preferred metabolic fate of glucose is incompletely understood. Multiomics studies suggest no increase in anaerobic lactate production and sustained input into the TCA. Glucose input into biosynthetic pathways such as the pentose phosphate pathway may be altered in a genotype-specific manner. Created in BioRender. Nollet E (2025) https://BioRender.com/53r16kv. TCA: Tricarboxylic acid cycle.

demonstrated in multiple studies using radiolabeled substrates. A positron emission tomography (PET) study using C11 palmitate was the first to observe reduced fatty acid uptake in the interventricular septum in mildly symptomatic non-obstructive patients with HCM[50]. Later studies performed in Japanese cohorts of patients with HCM using ^{123}I-BMIPP (β-methyl-P-iodophenyl-pentadecanoic acid) and single-photon emission computed tomography consistently reported impairment of fatty acid metabolism[51-61]. ^{123}I-BMIPP is a methyl branched-chain fatty acid that is resistant to fatty acid β-oxidation and is thus metabolically trapped in myocardial triglyceride pools[62]. Hence, its uptake in the myocardium is a reflection of myocardial fatty acid uptake and activation[63], and is a more indirect evaluation of global myocardial fatty acid metabolism compared to C11 palmitate PET. One study found that ^{123}I-BMIPP uptake was most severely reduced in the interventricular septum[56]. Impaired ^{123}I-BMIPP was moreover observed to occur in the absence of other metabolic abnormalities[55], indicating that decreased fatty acid metabolism is one of the first metabolic alterations in HCM. Uptake of ^{123}I-BMIPP was furthermore reported to be negatively associated with LV ejection fraction[51], fractional shortening[53], and maximal wall thickness[59]. A study using proton magnetic resonance spectroscopy also found a negative correlation between myocardial triglyceride content and LV mass[64]. Altogether, these findings support the notion that fatty acid metabolism defects are most prominent in the hypertrophied regions of the HCM heart, and that the severity of these defects worsens alongside disease progression. Accordingly, the severity of lowered ^{123}I-BMIPP uptake was in several studies also linked to a worse prognosis in terms of cardiac function decline and overall mortality[53,57,61].

A major limitation of the imaging reports cited here is that the patients who were studied mostly did not undergo genetic screening; thus, it is not certain whether these patients are all true patients with HCM or suffer from conditions that are a phenocopy of HCM. Furthermore, no distinctions were made between G- and G+ patients, or with respect to the type of gene variant patients may express. Mitochondrial function analyses in fresh myectomy tissue samples from patients with HCM revealed a more pronounced negative association between the capacity to oxidize C8:0-carnitine and septal hypertrophy in G- compared to G+ HCM[65]. In addition, metabolomics in HCM myectomy samples revealed strong negative correlation patterns between numerous acylcarnitines on the one hand and pathological cardiac remodeling and

diastolic dysfunction on the other hand in G- HCM, while in G+, such correlations were only observed for two acylcarnitine species[21]. Thus, the association between altered fatty acid metabolism and cardiac remodeling is different between G+ and G- HCM. In G- HCM, deterioration of fatty acid metabolism throughout disease progression appears to be strongly tied to progressive impairment of fatty acid oxidation capacity[21]. Within G+ HCM, the relation between fatty acid metabolism alterations and cardiac remodeling may be specific to the genotype. This is exemplified by a PET study using 14-fluoro-6-thiaheptadecanoic acid to evaluate fatty acid metabolism in patients with HCM carrying the pathogenic Asp175Asn variant in alpha-tropomyosin, which found that, compared to control subjects, these patients displayed increased fatty acid metabolism, which regressed with the development of LV hypertrophy[66].

Another constraint of using modified fatty acids such as ^{123}I-BMIPP is the inability to distinguish between fatty acid uptake and fatty acid oxidation, making the specific nature of the observed impairment in fatty acid metabolism unclear. If the impairment predominantly lies in a lowered capacity to oxidize fatty acids, a mismatch is expected between fatty acid uptake and oxidation, leading to the accumulation of toxic lipid intermediates (i.e., lipotoxicity)[67]. Kinetics of C11 palmitate metabolism in mildly symptomatic patients with HCM were not found to be altered[50], suggesting that at early disease stages, lowered fatty acid metabolism in HCM is due to downregulation of myocardial fatty acid uptake rather than defects downstream in mitochondrial fatty acid β-oxidation capacity. Of note, this would be in contrast with the observation of increased fatty acid oxidation in early-stage HCM in Asp175Asn variant carriers[66]. However, these patients displayed elevated fasting serum free fatty acid levels compared to healthy controls, highlighting the importance of reporting basal metabolic parameters in study populations. Proteomic studies using myectomy samples from patients with oHCM consistently reported a lowered abundance of key enzymes of mitochondrial fatty acid β-oxidation while fatty acid uptake proteins were mostly unchanged[21,68-71], indicating a mismatch between fatty acid uptake and oxidation capacity to be expected at a more advanced disease stage. Two lipidomic studies in HCM myectomy samples indeed report elevated levels of lipotoxic species such as free fatty acids, ceramides, and diglycerides[71,72]. A recent study, however, found that these lipids were less abundant or unchanged in HCM compared to non-failing control hearts, and were negatively correlated with cardiac remodeling especially in G+ patients[21]. A key difference is that in this report, the average body mass index of patients was comparatively low and well matched to non-failing controls, in contrast to the two former studies. Thus, lipotoxicity is not an inherent feature of HCM and may rather be driven by the presence of comorbidities associated with elevated body weight. Impaired capacity to oxidize fatty acids appears to be accompanied by downregulation of fatty acid uptake. Whether this is regulated by changes in the localization and posttranslational modification of fatty acid transport protein CD36 should be a subject of future study[73].

Glucose

While imaging studies generally agree that fatty acid metabolism is impaired in patients with HCM, less consensus exists among PET imaging studies using F-18 fluorodeoxyglucose (18-FDG) to assess alterations in myocardial glucose metabolism. Uptake of 18-FDG was found to be reduced in mildly symptomatic patients with HCM compared to healthy controls[50], although it should be noted that it is unknown how well these patients were matched to controls in terms of age, sex, and comorbidities. In contrast, another study concluded that glucose uptake was elevated in symptomatic patients with HCM, based on the observation of normal 18-FDG uptake but reduced blood flow in hypertrophied segments of HCM hearts[74]. Other studies later reported that 18-FDG uptake was lower in hypertrophied compared to non-hypertrophied regions in the hearts of patients with HCM[75-77]. Under fasting conditions, HCM hearts demonstrated higher 18-FDG uptake than hearts in people with hypertension[78].

More recently, it was reported that 18-FDG uptake was highest in the hypertrophied septal segments in patients with non-obstructive HCM[79]. In patients with oHCM, elevated 18F-FDG uptake was observed in non-hypertrophied regions, particularly in the lateral and posterior wall segments, extending beyond the hypertrophied myocardium[79]. Importantly, after septal reduction therapy in patients with oHCM, 18-FDG uptake was significantly lowered by 47% in the non-hypertrophied regions of the heart[79]. Thus, glucose uptake in non-hypertrophied segments of the HCM heart may be drastically elevated in response to increased cardiac workload resulting from augmented afterload due to LVOT obstruction. This may explain earlier findings of higher glucose uptake in non-hypertrophied versus hypertrophied regions in HCM hearts[75-77]. Notably, similar findings were observed in non-obstructive patients with HCM; however, 18-FDG uptake in these patients was measured following a 75 g oral glucose load[76], while patients in the aforementioned study underwent 24 h of carbohydrate restriction[79]. Consequently, subsequent cardiac 18-FDG uptake predominantly reflects insulin sensitivity, which may be different in hypertrophied and non-hypertrophied myocardium.

Overall, these reports suggest that HCM is characterized by increased glucose uptake both in hypertrophied and non-hypertrophied regions of the heart. In non-hypertrophied regions, high glucose uptake appears to be a consequence of elevated cardiac workload, whereas in hypertrophied myocardium, increased glucose uptake seems linked to cardiac hypertrophy. However, similar to the imaging studies into fatty acid metabolism discussed in the previous section, it is not known whether patients with HCM phenocopies were included in the studies cited here. Thus, comprehensive studies comparing clinically well-characterized patients with HCM to non-failing controls and studies addressing patient genotype-specific alterations are lacking. Additionally, understanding the impact of comorbidities and disease severity on glucose metabolism in HCM warrants further study.

Furthermore, it remains unclear what fate glucose undergoes in the HCM heart. Glucose may be stored as glycogen or enter glycolysis, resulting in pyruvate production, which can be directed toward the mitochondria for aerobic ATP production, or can be converted into lactate for anaerobic ATP production. In addition, glucose serves as input for metabolic pathways that facilitate cardiac hypertrophy, such as the pentose phosphate pathway and the hexosamine biosynthetic pathway[80,81].

Multiple studies provide insight into the metabolic fates of glucose via proteomic and metabolomic analyses of myectomy samples from patients with HCM[21,68-72]. At the protein level, several studies report no uniform increase or decrease in the abundance of glycolytic enzymes in HCM myocardium[68-70], while other papers found these enzymes to be mostly more abundant[21,71]. However, it should be noted that alterations in abundance do not necessarily reflect differences in enzymatic activity. Metabolomic findings are also inconsistent, with global depletion of glycolytic metabolites in one paper[72], while other studies report bidirectional changes[21] or accumulation of downstream glycolytic intermediates[71]. These discrepancies may be explained by cohort differences, such as symptomatic status and genotypic make-up, as well as variations in factors like age, sex, and the presence of comorbidities (e.g., hyperlipidemia and diabetes). These variables must be properly matched to controls to avoid introducing bias[21]. Nevertheless, while imaging studies seem to favor elevated glucose uptake in HCM, none of the studies cited here suggest this is associated with an overall increased abundance of glycolytic metabolites. Thus, caution is warranted when relying on metabolomic data to evaluate glycolytic pathway flux alterations in human myocardium.

Another pressing issue concerns whether pyruvate, the end-product of glycolysis, is preferably routed toward the mitochondria to sustain oxidative ATP production, or is anaerobically converted to lactate to maintain cellular ATP levels. In healthy hearts, lactate is a major source of pyruvate production both at rest

and during increased workload[42,67]. Lactate consumption has also been reported to be elevated in human heart failure[82]. Early studies in patients with HCM demonstrated that at rest, the HCM heart is a net consumer of lactate[83-85]. Following an acute increase in workload, lactate consumption in the HCM heart decreases, or the HCM heart may even release lactate[84-86]. This phenomenon is diminished after septal reduction therapy[86], suggesting that anaerobic conversion of pyruvate to lactate in the HCM heart occurs only under extreme conditions. Intriguingly, most studies report lowered levels of lactate in HCM myectomy samples[21,71,72], possibly indicating elevated lactate consumption in HCM to sustain pyruvate levels.

With respect to glucose entry into biosynthetic pathways, one study observed an apparent increased input from glucose[71], while others found the opposite[72]. Another study suggested that the abundance of biosynthetic intermediates depends on both genotype and severity of cardiac remodeling[21]; in G+ patients, biosynthetic metabolites were positively associated with septal hypertrophy and diastolic dysfunction, while these relationships were inverted in G- patients.

Increased storage of glucose as glycogen is to be expected should the uptake of glucose exceed its usage for ATP production and input into anabolic pathways. One study reported increased glycogen deposition on transmission electron microscopy images of myocardium from three exercise-intolerant patients with HCM without known genotype[87], suggesting glycogen accumulation in advanced HCM. Another research, however, found that, compared to non-failing donors, glycogen content was not elevated in myectomy samples from patients with HCM and even appeared to be lowered in cardiac tissue from patients with end-stage HCM[21], suggesting glycogen accumulation is not an inherent feature of HCM. In contrast, in glycogen storage diseases that mimic HCM[9], myocardial glycogen levels are elevated due to the inability to catabolize glycogen, leading to metabolic inflexibility and activation of pro-hypertrophic signaling[88].

Last, an understudied aspect of altered glucose metabolism in the HCM heart concerns the potential impact of myocardial insulin resistance. Hypertrophied hearts from non-diabetic patients with aortic stenosis were found to display lower glucose uptake during euglycemic-hyperinsulinemic clamp[89], indicating cardiac insulin resistance is an inherent feature of cardiac hypertrophy. Phosphoproteomic analyses in HCM myectomy samples revealed activation of the insulin-like growth factor 1 pathway[90], suggesting altered insulin signaling also occurs in HCM. Myocardial insulin resistance in the HCM heart may seem counterintuitive in the context of a metabolic shift toward glucose. A potential explanation underlying such a paradox may be a shift toward increased expression of the insulin-independent glucose transporter GLUT1, which has been reported to occur in various settings of heart failure[91]. The consequences of myocardial insulin resistance may particularly apply to episodes of elevated cardiac workload, during which the inability to increase cardiac glucose uptake may lead to failure to meet energetic demand.

Insights from blood-based metabolomic analyses

In recent years, multiple groups aimed to gain insight into metabolic changes in HCM by defining the metabolomic and lipidomic signature in plasma or serum samples from patients with HCM.

Altered levels of metabolites and lipids involved in fatty acid metabolism are frequently reported in studies. Finnish HCM patients carrying the *MYBPC3*-Gln1061X mutation displayed elevated plasma levels of multiple triglycerides, (ether)phospholipid species and branched-chain amino acids[92]. A subset of triglycerides and phospholipids were positively associated with septal thickness and diastolic dysfunction. Others observed that stearic acid, a relatively common fatty acid in human blood, and glutarylcarnitine were elevated in plasma samples from patients with HCM compared to carriers of P/LP variants not displaying

an HCM phenotype and healthy controls[93]. It was also found that a set of metabolites distinguished the groups, demonstrating the potential of serum metabolomics for the development of biomarker panels. In patients with HCM carrying founder mutations in *MYBPC3*, several acylcarnitines species were also elevated[94]. Moreover, in a follow-up study on these samples using targeted acylcarnitine metabolomics, multiple acylcarnitines were found to be positively associated with indicators of disease severity[95]. Another report compared the metabolomic plasma signature in oHCM and non-obstructive HCM and found that the latter group displayed higher plasma levels of branched-chain amino acids and two fatty acid species (arachidonic acid and palmitoleic acid)[96]. However, it should be noted that these patients also had a higher average body weight; thus, it is unclear if the findings in that study are truly related to disease severity or reflect comorbidity-related differences between the patient groups. Another study evaluated the plasma metabolome before and three months after myectomy in patients with oHCM and found that multiple acylcarnitine species were lowered after septal reduction therapy[97]. The most significantly altered metabolites were related to improved liver and kidney function, demonstrating the positive systemic impact of septal reduction therapy. A recent study reported that in a large cohort of patients with HCM (n = 420), total free fatty acid levels in plasma were negatively associated with LV ejection fraction, and positively associated with atrial dilatation and brain natriuretic peptide levels[98].

Taken together, the reports cited here consistently demonstrate that symptomatic HCM is associated with distinct circulatory metabolic signatures. The exact alterations that are reported differ substantially between studies, which may be due to the specific method used (e.g., targeted versus untargeted metabolomics), patient cohort differences, and sub-optimal matching to control groups in terms of sex and body mass index. Overall, these studies suggest symptomatic HCM is associated with systemic elevations of fatty acids, acylcarnitines, and branched-chain amino acids. However, it cannot be excluded that these differences are in part related to overall metabolic health status rather than cardiac disease.

Potential of arteriovenous sampling in patients with HCM

Due to the observational nature of the blood metabolomics studies cited above, it cannot be inferred whether plasma metabolite levels are due to reduced uptake or increased release by the heart. A powerful approach to overcome this is invasive arteriovenous blood sampling followed by metabolite analysis[99]. Such studies were performed in patients with HCM in the 1980s[83-86]; however, these studies were limited by small cohort sizes, lack of control subjects, limited throughput of metabolites and mainly addressed alterations induced by pacing, medication, or septal reduction therapy. Aided by high-throughput metabolomics and lipidomics analysis, enabling quantitative evaluation at the level of individual metabolites, arteriovenous sampling has made a comeback in recent years[82,99,100].

Recently, a study performed arteriovenous sampling and metabolomics in patients with HCM and compared these to controls, i.e., people with no LV hypertrophy and patients with severe aortic stenosis[101]. Arteriovenous metabolite gradients in patients with HCM did not clearly differ from controls and patients with aortic stenosis on clustering analysis, suggesting only modest differences in cardiac uptake and release of metabolites between groups. Hearts of patients with HCM displayed reduced extraction of pyruvate, glutamate, and branched-chain amino acid breakdown products compared to control hearts, which may be indicative of reduced entry into the tricarboxylic acid cycle (TCA) cycle of these metabolites[101]. It was not reported whether arteriovenous gradients of glucose and lactate differed between HCM and controls. While fatty acid uptake and release were not measured, no apparent acylcarnitine release by the HCM heart was reported[101]. These findings suggest that elevated plasma acylcarnitine levels in HCM are not caused by cardiac acylcarnitine efflux and are in line with the absence of evidence for a mismatch between fatty acid uptake and oxidation capacity in HCM[21]. Additionally, it was assessed whether the HCM heart relies more on ketones as an alternative fuel, which has been reported to occur in various settings of cardiac

disease[82,100,102,103]. Remarkably, however, a net elution of β-hydroxybutyrate was reported, which is in disagreement with early findings of net uptake of β-hydroxybutyrate in the HCM heart[83]. As pointed out by the authors, differences in blood flow between the aortic root and coronary sinus could not be taken into account, which diminished the accuracy of arteriovenous metabolite gradients[99]. The study was additionally constrained by the presence of mild LV hypertrophy in control subjects, possibly obscuring metabolic alterations in HCM hearts. Nevertheless, the study discussed here demonstrates the potential of measuring arteriovenous metabolite gradients in patients with HCM. Further research is warranted in clinically well-characterized patient cohorts, including local blood flow measurements and using mass spectrometry platforms that detect a wide range of metabolites and lipids.

MITOCHONDRIAL DEFECTS IN HCM

Bioenergetic impairment is a well-recognized feature in patients with HCM. This is evident from 31-phosphorus magnetic resonance spectroscopy imaging studies showing the ratio of PCr over ATP or the ratio of PCr over inorganic phosphate is lowered in the hearts of patients with HCM[25,104-107]. This imbalance worsens during exercise[108]. Moreover, symptomatic HCM is characterized by lowered myocardial oxygen (O_2) consumption[38,39], thus suggesting mitochondrial impairment is a key factor underlying disrupted bioenergetic homeostasis. As outlined in section 3, mitochondrial O_2 consumption is the combined action of substrate uptake and subsequent catabolism in mitochondria, enabling electron input via NADH and $FADH_2$, channeling of electrons by the ETS, and ATP regeneration from ADP by complex V. The latter largely depends on the proper functioning of the CK shuttle. Defects anywhere in this multilayered process may contribute to reduced O_2 consumption in HCM myocardium. Part of the observed impairment in O_2 consumption may thus be related to impaired (i.e., less flexible) substrate use, as described in section 4. In this section, we discuss mitochondrial alterations that have been described in human HCM, which are schematically depicted in Figure 5.

High-resolution respirometry represents a powerful tool to evaluate mitochondrial function. This method relies on sequential titration of substrates, uncouplers, and inhibitors to provide insight into the functioning of total OXPHOS and its individual components[109]. By reconstituting the TCA cycle and supplying saturating levels of ADP, this method bypasses O_2 consumption limitations by upstream substrate catabolism and the functioning of the CK shuttle. However, a drawback of this technique is its requirement for fresh myocardial tissue, which has restricted its application to just two studies involving myocardial samples from patients with HCM[65,72]. The first of these studies reported lower O_2 consumption in isolated mitochondria following stimulation of NADH-dependent complex I respiration with glutamate, malate, and ADP in a small number of myectomy samples (n = 5) relative to non-failing donor samples[72]. The later study applied a more extensive experimental protocol in a large number of HCM myectomy samples (n = 59)[65]. In G- HCM patients, mitochondrial dysfunction - particularly impaired NADH-linked complex I respiration and octanoylcarnitine oxidation - was tightly linked to septal hypertrophy. This demonstrated that the involvement of mitochondrial dysfunction in cardiac pathophysiology is different in G- and G+ HCM.

Mitochondrial respiratory impairment was closely related to disruption of mitochondrial organization as evaluated via transmission electron microscopy, presenting as abnormal mitochondrial clusters or misaligned to sarcomere structures[65]. Such organizational perturbations can also be appreciated in early electron microscopy studies[110,111]. In a Japanese cohort of patients with HCM, impaired contractile reserve was linked to abnormal mitochondrial organization[87], suggesting proper mitochondrial organization is required to adequately respond to elevated workload. Mitochondria require proximity to the myofilaments for efficient energy recycling[112], which is likely affected by mitochondrial disorganization in HCM. In

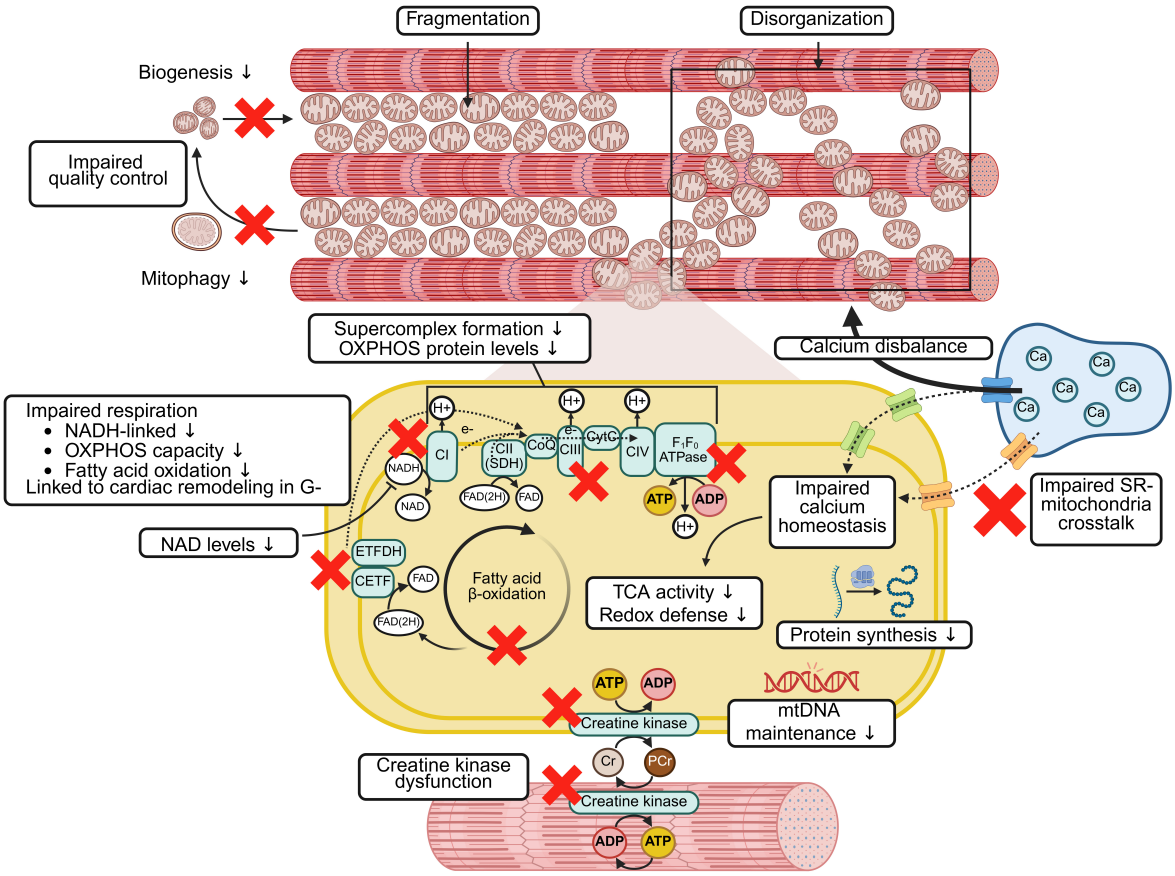

Figure 5. Mitochondrial defects in the hypertrophic cardiomyopathy (HCM) heart. Mitochondrial ultrastructure in the HCM heart is characterized by fragmentation and disorganization relative to the myofilaments. Dampening of mitophagy and mitochondrial biogenesis underlie impaired mitochondrial quality control. Functionally, mitochondria in HCM exhibit defects in fatty acid oxidation capacity, total oxidative phosphorylation (OXPHOS) capacity, and nicotinamide adenine dinucleotide (NADH)-linked respiration, which are strongly linked to cardiac remodeling in genotype-negative (G-) patient tissue. Respiratory impairment may be caused by NAD depletion, impaired supercomplex formation, and lower levels of OXPHOS proteins. Impaired Ca^{2+} homeostasis due to perturbed crosstalk between the sarcoplasmic reticulum (SR) and mitochondria and disproportional loading of Ca^{2+} to the mitochondria relative to the myofilaments further affect mitochondrial respiration and redox defense. Reduced mitochondrial protein synthesis and impaired maintenance of mitochondrial DNA (mtDNA) may additionally impact overall mitochondrial homeostasis. Dysfunction of the creatine kinase shuttle thwarts efficient energy provision to the myofilaments and compromises ADP buffering capacity. Created in BioRender. Nollet E (2025) https://BioRender.com/cnpuycj. TCA: Tricarboxylic acid cycle; ADP: adenosine diphosphate; ATP: adenosine triphosphate; FAD: flavin adenine dinucleotide; NAD: nicotinamide adenine dinucleotide; SDH: succinate dehydrogenase; CI: complex I; CII: complex II; CIII: complex III; CIV: complex IV; ETFDH: electron-transferring-flavoprotein dehydrogenase; CETF: electron transfer flavoprotein complex.

addition, mitochondrial activity and antioxidant defense are regulated by Ca^{2+} levels[49], which are mediated by crosstalk between mitochondria and the sarcoplasmic reticulum[113]. Thus, disrupted mitochondrial organization may perturb mitochondrial Ca^{2+} homeostasis and cause bioenergetic and oxidative stress. This may be worsened further by high myofilament Ca^{2+} sensitivity in HCM, causing a disproportional amount of cytosolic Ca^{2+} to be directed toward the myofilaments instead of toward the mitochondria[13,114]. As a result, mitochondrial energy production and antioxidative capacity are insufficiently stimulated to meet the elevated ATP demand caused by hypercontractility linked to heightened Ca^{2+} sensitivity[14]. In fact, it was recently observed that this energetic mismatch induces oxidative stress, which in turn triggers ventricular arrhythmias in HCM mice[114]. It is important to note that these alterations occur before any dysfunction of mitochondria *per se* occurs, indicating that the defective mitochondrial function observed in more advanced human oHCM samples may be secondary, but potentially related to the oxidative stress induced by the

energetic mismatch[114]. Furthermore, a recent study reported changes in the expression of the mitochondrial Ca^{2+} uniporter complex and related proteins in HCM myectomy samples[115], representing an additional factor potentially contributing to impaired mitochondrial Ca^{2+} uptake.

Ultrastructural alterations other than disrupted organization of mitochondria have also been reported in myectomy samples from patients with HCM. Other studies reported a decrease in average mitochondrial size[65,72], indicative of a disbalance between mitochondrial fusion and fission. This may be linked to failure to upregulate mitochondrial biogenesis and mitochondrial clearance via mitophagy[72,116]. Mitochondrial size was not related to overall mitochondrial respiratory function[65]; however, it is possible that other mitochondrial processes essential for cardiac homeostasis are perturbed by abnormal fusion and fission, e.g., mtDNA maintenance and regulation of apoptosis[117], both of which have been found to be affected in HCM[72,116,118]. Disrupted cristae formation is associated with mitochondrial respiratory impairment[119] and has been observed in electron microscopy images of HCM myocardium[72]. However, another paper found no indications for this in electron microscopic and proteomic analyses of HCM myectomy samples[65]. A recent study in myocardial biopsies from patients with heart failure with preserved ejection fraction (HFpEF) reported that aberrant cristae structure was most frequently seen in obese patients[120]. Thus, cristae disruption in HCM myocardium may be associated with the presence of comorbidities and is not an inherent feature of HCM. Of note, total mitochondrial abundance was reported to be unchanged in HCM hearts compared to non-failing hearts and was not related to mitochondrial respiratory function[65,72,116], further substantiating the concept that mitochondrial quality rather than quantity underlies respiratory capacity.

Proteomic analyses have also provided significant insight into mitochondrial defects in HCM. All proteomic studies observed a lowered abundance of OXPHOS protein subunits in HCM myocardium[21,68-71]. The notion that this negatively affects mitochondrial function is apparent from the observation that total OXPHOS capacity was positively associated with the abundance of a subset of OXPHOS protein subunits[65]. Another common finding among proteomic studies concerns lowered levels of key enzymes in fatty acid oxidation, which may likewise contribute to impairment of fatty acid oxidation capacity in HCM myocardium[21,68-71]. Recently, high-coverage proteomics revealed that levels of mitochondrial ribosomal subunits were widely lowered in HCM myectomy samples[21], implicating an overall impairment of mitochondrial protein synthesis in HCM. This may, in part, explain the lowered abundance of particularly complex I subunits and derailed NADH-linked complex I respiration in HCM[121].

Defects in the CK shuttle system have also been implicated in the bioenergetic derailment observed in HCM. Imaging studies have shown that the reductions in PCr/ATP are related to depressed energy transfer (i.e., flux through the CK shuttle)[122,123]. Part of this impairment may be explained by a lowered abundance of CK subunits, a finding consistently reported in proteomics studies[21,68-70]. In addition, CK activity may be further dampened by redox-linked modifications due to its susceptibility to oxidative stress[124].

TARGETING METABOLISM AS A THERAPEUTIC STRATEGY IN HCM

Conventional treatment of HCM comprises standard heart failure medication, i.e., β-blockers, Ca^{2+} channel blockers, diuretics, and blood pressure-lowering agents. Patients with persistent oHCM may undergo invasive septal reduction therapy via myectomy surgery, or via alcohol septal ablation[2,3]. While the benefit of these treatment options is substantial, they are centered around symptom relief and therapeutic strategies targeting the driving mechanisms of disease in HCM are thus direly needed. As discussed, metabolic and mitochondrial derailment are central hallmarks of disease and are tightly linked to cardiac remodeling in HCM. Thus, treatment aimed at correcting metabolic abnormalities and improving mitochondrial function

may hold the potential to halt and reverse disease. In this section, we discuss current therapeutic strategies that may confer bioenergetic benefits in HCM hearts, which are summarized in Figure 6.

Modifying substrate utilization

As outlined in previous sections, energy metabolism in HCM hearts is characterized by a shift away from fatty acid oxidation to increased glucose utilization. Since glucose oxidation is more efficient than fatty acid oxidation in terms of ATP yield per unit of O_2 consumed, such a shift has been proposed to be beneficial during episodes of elevated cardiac workload and stress[125]. Past and ongoing efforts aimed at boosting this shift using drugs that inhibit fatty acid oxidation have yielded mixed outcomes. Perhexiline, an antianginal agent that dampens mitochondrial fatty acid oxidation by inhibiting the transfer of fatty acids into mitochondria[126], improved myocardial energetics and exercise capacity in patients with non-obstructive HCM[127]. However, a clinical trial with trimetazidine, which inhibits the last enzyme (3-ketoacyl-CoA thiolase) in mitochondrial fatty acid β-oxidation[128], reported no therapeutic benefit in symptomatic patients with non-obstructive HCM[129]. Additionally, in asymptomatic carriers of a pathogenic mutation in *MYH7* or *MYBPC3*, trimetazidine did not improve myocardial efficiency[130]. More recently, a phase 2 trial testing the safety and efficacy of ninerafaxstat, which, similarly to trimetazidine, is a 3-ketoacyl-CoA thiolase inhibitor, found a positive effect on ventilatory efficiency and quality of life in patients with non-obstructive HCM[131]. The beneficial effects of perhexiline have been proposed to be predominantly mechanisms other than fatty acid oxidation inhibition, such as increased antioxidant enzyme activity and modification of membrane ion channel function[132,133]. Whether the differential effects of trimetazidine and ninerafaxstat are similarly mediated by yet undescribed off-target actions is unknown and warrants further investigation. Additionally, the therapeutic benefit of fatty acid oxidation inhibition may depend on overall metabolic health and disease severity. Patients treated with perhexiline displayed lowered circulating free fatty acid and glucose levels and a non-significant improvement in insulin sensitivity[127]; thus, its beneficial effects may be mediated by amelioration of peripheral metabolism. Although information on blood lipid and glucose levels and the presence of diabetes in patients in the ninerafaxstat trial is not provided, patients had an average body mass index (BMI) of 32, suggesting the presence of (pre-)diabetes in a significant part of the study population[131]. The therapeutic action of ninerafaxstat may thus be similarly mediated by its antidiabetic actions[134], i.e., whole body improvement of glucose metabolism. In the first trimetazidine trial, patients were not obese and were relatively symptomatic; a subset had already undergone septal reduction therapy, and smoking prevalence was high[129]. These factors are associated with severe impairment of mitochondrial function[65,135], which may limit the capacity to upregulate pyruvate entry into mitochondria to fuel oxidative ATP production. Taken together, the efficacy of fatty acid inhibition therapy likely depends largely on individual patient characteristics.

An unforeseen consequence of inhibiting cardiac fatty acid oxidation might be evoking a mismatch between cardiac fatty acid uptake and catabolism, inducing lipotoxicity[67]. An alternative strategy might, therefore, be restoring rather than inhibiting fatty acid utilization. In patients with heart failure with reduced ejection fraction, it was recently reported that cardiac energetics and contractility were improved following intralipid infusion, forcing a metabolic shift away from glucose toward fatty acids[136]. Therapy aimed at improving myocardial delivery of fatty acids may thus be effective as well in patients with HCM. As cardiac-specific fatty acid oxidation agonists are not available, further research using preclinical models of HCM is warranted to address the potential of fatty acid oxidation stimulation via genetic manipulation.

Improving mitochondrial respiration

A key component of proper mitochondrial OXPHOS functioning in the myocardium is the efficient transfer of electrons through the ETS. This is facilitated by the configuration of ETS complex proteins into respiratory supercomplexes, which is supported by the mitochondrial membrane-specific phospholipid

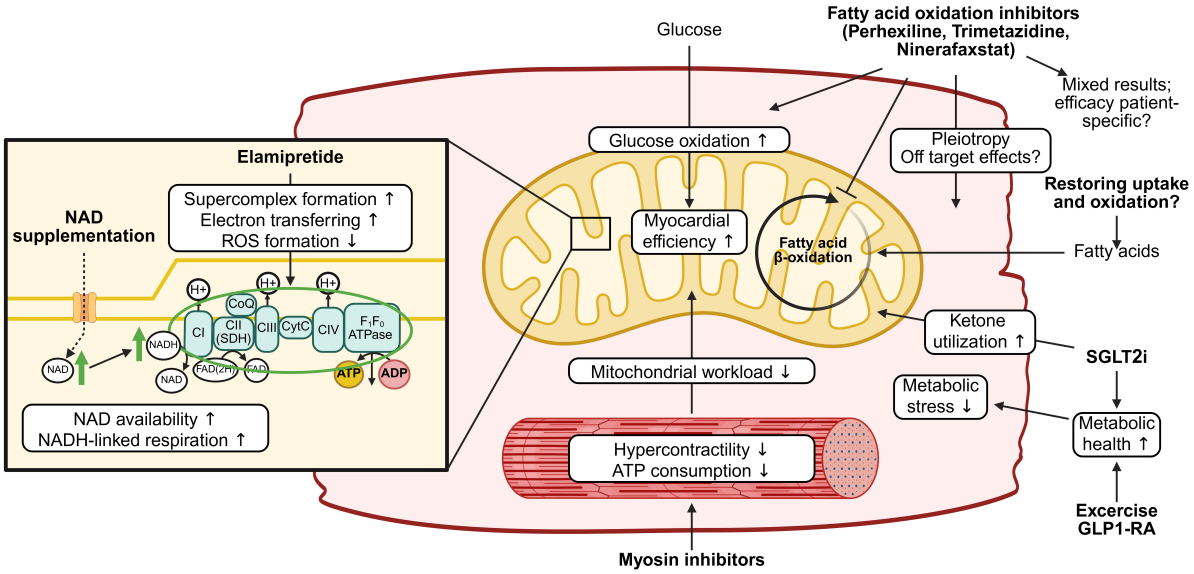

Figure 6. Metabolic therapy strategies in hypertrophic cardiomyopathy. NAD supplementation may boost mitochondrial function by increasing mitochondrial NAD availability and NADH-linked respiration. Elamipretide may ameliorate mitochondrial dysfunction by increasing the formation of respiratory supercomplexes, facilitating efficient electron transferring throughout the electron transport system and lowering reactive oxygen species (ROS) formation. Fatty acid oxidation inhibitors may improve myocardial efficiency by enhancing the metabolic shift away from fatty acids to glucose, which is typical in HCM hearts. However, results have been variable and may depend on patient-specific characteristics. Additionally, beneficial effects may be mediated by pleiotropy and off-target effects. The therapeutic potential of restoring the uptake and oxidation of fatty acids warrants investigation. Myosin inhibitors may confer metabolic benefits via relief of hypercontractility and concomitant lowered ATP consumption. Moreover, safeguarding whole-body metabolic health via exercise and antidiabetic drugs such as glucagon-like peptide 1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) is vital to minimize metabolic stress in the HCM heart. The latter drug class potentially provides the additional benefit of increased ketone utilization. Created in BioRender. Nollet E (2025) https://BioRender.com/3uniy0h. HCM: Hypertrophic cardiomyopathy; ADP: adenosine diphosphate; ATP: adenosine triphosphate; NADH: nicotinamide adenine dinucleotide; FAD: flavin adenine dinucleotide; NAD: nicotinamide adenine dinucleotide; SDH: succinate dehydrogenase; CI: complex I; CII: complex II; CIII: complex III; CIV: complex IV.

cardiolipin[137]. However, it should be noted that under non-pathological conditions in mouse hearts, OXPHOS efficiency does not require stable structurally defined supercomplexes, but rather appears to depend on tight proximity between ETS complex proteins[138]. Cardiolipin is highly sensitive to oxidative stress-induced peroxidation[139], which has been reported to occur in HCM hearts[72,140]. As a result, the efficiency of electron flow and ATP regeneration are disrupted, while electron leak and reactive oxygen species (ROS) formation are promoted[137]. The latter has been demonstrated in feline HCM, in which mitochondrial OXPHOS dysfunction occurred alongside increased mitochondrial ROS formation[141]. Elamipretide is a mitochondria-targeted drug that stabilizes cardiolipin, thereby promoting respiratory supercomplex assembly and dampening mitochondrial ROS production[142]. In fresh myectomy samples from patients with HCM, *ex vivo* incubation with a high concentration of elamipretide resulted in amelioration of NADH-dependent complex I respiration[65]. This was associated with increased incorporation of complex I into respiratory supercomplexes.

Altered NAD^+ homeostasis is another component that may underlie mitochondrial impairment in HCM. This is apparent from proteomic findings indicating major alterations in NAD^+ synthesis and salvage pathways[69]. This may reduce the availability of NAD^+ for conversion to NADH, which could contribute to impaired NADH-linked respiration via complex I. Stimulation with a high concentration of NAD^+ in fresh HCM myectomy samples led to a major increase in NADH-linked respiration, especially in samples in which baseline NADH-linked respiration was most severely affected[65].

These *ex vivo* observations in human myocardial samples are supported by in vivo data in mice, where treatment with elamipretide, but also the mitochondria-targeted coenzyme Q (Mito-Q), which scavenges superoxide radicals, prevented the slowing of electrical conduction and ventricular arrhythmias during β-adrenergic stimulation[114]. Collectively, these findings demonstrated that mitochondria in HCM are responsive to treatment strategies that acutely improve mitochondrial respiration, despite severe cardiac remodeling, supporting further study into the efficacy of mitochondria-targeted strategies as a treatment in HCM.

Lowering energetic burden by targeting hypercontractility

Hypercontractility lies upstream of cardiac remodeling in HCM, particularly in G+ patients, and thus represents an attractive therapeutic target. In HCM caused by P/LP variants, this may be achieved via gene therapy, correcting the primary mutation-induced myofilament defects underlying hypercontractility. While approaches using genome editing, gene replacement, and allele-specific silencing have shown promise in preclinical models, the translation of gene therapy to clinical applications is still in the early phases of development[143].

Mavacamten and aficamten represent a novel class of drugs that inhibit the myosin ATPase and thereby mitigate hypercontractility[144-146]. Mechanistically, mavacamten promotes the folding of myosin heads back onto the filament backbone into the SRX state, while aficamten stabilizes myosin in a weak-actin binding conformational state. In both cases, this results in lowered myosin ATPase activity, reducing mitochondrial workload[147]. In clinical trials in patients with oHCM, mavacamten and aficamten have been demonstrated to alleviate LVOT obstruction and improve cardiac structure, symptoms, functional capacity, and exercise tolerance[148-153]. The beneficial effect of myosin inhibition on myocardial energetics has so far been demonstrated only in preclinical models of HCM[28]. It would be valuable to investigate whether similar effects occur in humans with HCM. Such an effect is expected secondary to the unloading effect of reduced LVOT obstruction[86], but may also be a direct consequence of dampened hypercontractility. A potential constraint of myosin inhibition is that clinical responsiveness may vary based on the genotypic status of patients. In a retrospective clinical study, it was reported that both G- patients and G+ patients with mutations in *MYH7* and *MYBPC3* responded to mavacamten treatment, although the effect was more pronounced in G+ patients[154]. Further study is needed to define clinical responsiveness in varying patient groups and which mechanisms underpin such differences. These findings also underscore the need for the development of diverse treatment strategies that target different components of disease.

Mitigating the impact of cardiovascular comorbidities

Penetrance of disease and severity of clinical course in HCM are adversely associated with cardiovascular risk factors and comorbidities such as hypertension, aging, diabetes, hyperlipidemia, and obesity[155-165]. The presence of one or more of these factors can sensitize P/LP variant-related pathogenicity in G+ HCM[160,166]. Moreover, G- HCM may be particularly driven by cardiovascular comorbidities, given their exceptionally high prevalence in this patient population[10,11,164,165,167,168]. Proper management of these conditions is recommended[169] as this may prevent or ameliorate the clinical course of disease in a substantial portion of patients with HCM. Exercise is generally safe in patients with HCM and should be encouraged[170]. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists are effective in promoting weight loss, improving glycemic control, and enhancing clinical course in patients with HFpEF[171,172]. These drugs are currently recommended in patients with HCM and diabetes type II or obesity[169], although their efficacy has not been established. The benefit of these drugs may also apply to patients with HCM with pre-diabetes or mildly elevated body weight, given the linear association between metabolic health and HCM risk and severity[156,157,159]. The beneficial effects of SGLT2i in HFpEF are seen in both diabetic and non-diabetic individuals[171] and extend beyond positive impacts related to weight loss,

improved glycemic control and renal function[173]. SGLT2i increase plasma ketone levels[174], which may serve as an alternative fuel in the metabolically inflexible HCM heart. A study using a real-world dataset reported better survival, lower hospitalization rate, and improved cardiovascular symptoms in patients with HCM using SGLT2i[175]. A preclinical study in stem cell-derived heart models carrying HCM-related *MYH7* and *TNNT2* variants showed improvement in relaxation upon treatment with SGLT2i[176]. Further study is warranted to evaluate whether the therapeutic benefit is seen across patient groups and is not solely related to improved management of diabetes.

CONCLUSION

Metabolism in the HCM heart is characterized by a shift away from fatty acids as the energy substrate, which progresses with cardiac remodeling and disease severity. Reduced fatty acid utilization in HCM is not necessarily met with lipotoxicity, but this may develop in the presence of obesity-related comorbidities. Glucose uptake is generally elevated in HCM; however, further study is warranted to assess how glucose uptake and metabolic fate are modified by genotype, disease severity, and the presence of comorbidities. Blood-based metabolomic analyses can yield significant insight into metabolic alterations and disease mechanisms in HCM, particularly when applied to arteriovenous blood samples. This will also uncover the possible involvement of altered ketone and amino acid metabolism in HCM. Furthermore, substrate flux analyses in isolated animal hearts may be useful in assessing cardiac substrate use and metabolic flexibility. Lastly, while the number of induced pluripotent stem cell-based models of HCM is growing rapidly, their usefulness in studying metabolic alterations is currently limited due to metabolic immaturity[177].

The therapeutic benefit of metabolic therapy may be specific to individual patient characteristics. Boosting glucose oxidation seems beneficial in patients who suffer from cardiovascular comorbidities. Further study is warranted to address the patient group-specific potential of correcting fatty acid oxidation in HCM. Mitigating the impact of cardiovascular comorbidities is vital in preventing and ameliorating disease.

Disrupted mitochondrial organization appears to be the most prominent known factor underlying mitochondrial impairment in HCM. Nonetheless, mitochondria are responsive to therapies aimed at improving NADH-linked respiration, encouraging follow-up studies into the potential of mitochondrial therapy as a treatment strategy. This might be particularly beneficial in G- patients, as mitochondrial impairment is tightly linked to cardiac remodeling in these patients. Myosin inhibitors may be effective in dampening hypercontractility and lowering cardiac energetic burden especially in G+ patients.

Cardiac metabolism in HCM is modified by genotype, disease severity, and the presence of cardiovascular comorbidities and risk factors; thus, information on these characteristics should be provided in studies into metabolic alterations in HCM. Integrating patient characteristics with multiomics, structural and functional analyses is a powerful approach to identify patient group-specific metabolic disease mechanisms in HCM.

DECLARATIONS

Author's contributions

Writing the first version of the manuscript: Nollet EE
Commenting on all versions of the manuscript: Nollet EE, Sequeira V, Maack C, Ochala J, van der Velden J
Approving the final version of the manuscript: Nollet EE, Sequeira V, Maack C, Ochala J, van der Velden J

Availability of data and materials

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Conflicts of interest

Maack C is an advisory board member for Bristol Myers Squibb, Boehringer Ingelheim, AstraZeneca, Servier, Amgen, Novo Nordisk, Bayer, Novartis, Edwards, and Berlin-Chemie. Sequeira V received research funding from Bristol Myers Squibb. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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