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The development of familial hypertrophic cardiomyopathy; from mutation to bedside

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Abstract

Hypertrophic cardiomyopathy (HCM) is a familial disorder characterized by left ventricular hypertrophy in the absence of other cardiac or systemic disease likely to cause this hypertrophy. HCM is considered a disease of the sarcomere as most causal mutations are identified in genes encoding sarcomeric proteins, although several other disorders have also been linked to the HCM phenotype. The clinical course of HCM is characterized by a large inter- and intrafamilial variability, ranging from severe symptomatic HCM to asymptomatic individuals. The general picture emerges that the underlying pathophysiology of HCM is complex and still scarcely clarified. Recent findings indicated that both functional and morphological (macroscopic and microscopic) changes of the HCM muscle are present before the occurrence of HCM phenotype.

This review aims to provide an overview of the myocardial alterations that occur during the gradual process of wall thickening in HCM on a myofilament level, as well as the structural and functional abnormalities that can be observed in genetically affected individuals prior to the development of HCM with state of the art imaging techniques, such as tissue Doppler echocardiography and cardiovascular magnetic resonance imaging (CMR). Additionally, present and future therapeutic options will be briefly discussed.
Early changes in human HCM mutation carriers

Background

Hypertrophic cardiomyopathy is a genetic heart disease characterized by asymmetric left ventricular (LV) hypertrophy which most frequently involves the interventricular septum, although wall thickening may occur throughout the entire left ventricle [1]. Over 900 gene mutations have been linked to HCM, which predominantly encode for proteins of the thick filament of the sarcomere, such as cardiac myosin-binding protein C (MYBPC3) and beta-myosin heavy chain (MYH7) [2]. The main targets of the thin filament are troponin T (TNNT2) and troponin I (TNNI3), both accounting for ~6% of HCM-causing mutations (Human Gene Mutation Database (HGMD) Cardiff; http://www.hgmd.cf.ac.uk/ac/index.php). Next to sarcomeric mutations as a cause for HCM, several metabolic disorders are linked to the HCM phenotype, such as the glycogen storage diseases Fabry (an X-linked lysosomal hydrolase α-galactosidase A deficiency), Danon (an X-linked lysosome-associated membrane protein gene [LAMP2] deficiency) and Pompe (a lysosomal acid α-1,4-glucosidase [GAA] deficiency with a recessive pattern of inheritance) [3-5]. Besides, mutations in the AMP-activated protein kinase γ2 (PRKAG2 gene) result in dysregulation of cardiac energy metabolism and may mimic hypertrophic cardiomyopathy [6]. The morphological features associated with cardiac amyloidosis may also be difficult to distinguish from sarcomeric HCM [7]. Finally, genetic abnormalities in mitochondrial DNA are linked to HCM phenotype, following a maternal pattern of inheritance [8].

Inasmuch sarcomeric HCM displays an autosomal dominant pattern of inheritance, first-degree relatives of genotyped index patients have a 50% a-priori chance of carrier status. Unfortunately, genetic testing fails to identify causal mutations in an
important subset of index patients (30-40%) [9]. Therefore, alternative diagnostic strategies have been applied that aimed to identify morphological and functional markers of the disease, before the development of (regional) hypertrophy [10-16].

**Morphological alterations in pre-hypertrophic HCM mutation carriers**

Recently, it was shown that morphological abnormalities in HCM are not confined to patients with overt hypertrophy, but are also present in HCM mutation carriers without signs of wall thickening. These morphological abnormalities described as crypts were allocated at the inferoseptum (see Figure 1) and were best visualized with cardiovascular magnetic resonance imaging (CMR) in end-diastole [10]. Although variable in extent, these crypts were visualized in approximately 70% of HCM mutation carriers, of which the majority carried a MYBPC3 founder mutation. The histological background of these crypts is unclear. They have been hypothesized to be the macroscopic manifestation of myocardial disarray, which is typically known to be excessively present at the interventricular junctions in HCM patients [17,18]. The exact diagnostic value of crypts and its potential to serve as a predictor of disease progression is still under investigation [19]. Unravelling the exact histological basis of crypts might be important, since it has been postulated that areas of myocardial disarray may serve as pathological substrates for arrhythmias and sudden cardiac death (SCD), irrespective to the extent of LV hypertrophy [20].
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\textit{Functional alterations in pre-symptomatic HCM mutation carriers}

Detailed in-vivo assessment of myocardial function can be assessed with echocardiography, CMR, angiography and computed tomography (CT). The latter two imaging modalities are rarely applied, due to the ionizing radiation necessary for this purpose. With Tissue Doppler Imaging (TDI), which allows to measure myocardial tissue velocities in the direction of the ultrasound beam [21], subtle alterations in early diastolic (Ea) and systolic (Sa) LV function can be detected in genotyped HCM carriers with otherwise normal LV morphology [11-15]. Recently, a more sensitive functional imaging technique, CMR tissue tagging, was used to confirm the presence of functional abnormalities in 28 genotyped carriers with normal LV wall thickness [16]. With CMR tissue tagging, intramyocardial deformation (strain) can be visually assessed, since 'tags' deform during the cardiac cycle (Figure 2). Using CMR tissue tagging, Germans et al. revealed that mainly the

Figure 1. Image A shows a modified two-chamber image through the inferoseptum of an asymptomatic HCM mutation carrier demonstrating intramyocardial crypts (indicated by the white arrows) at the inferior LV wall. On the right (image B) a short-axis image, depicting the exact (inferoseptal) location of the crypts (again indicated by a white arrow). LV= Left ventricle, LA= Left atrium, RV= Right ventricle

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myocardium of the basal LV segments displayed a reduced peak diastolic circumferential strain rate (peak DCSR), reflecting impaired diastolic function [16]. The exact mechanism(s) responsible for the changes in diastolic function are still unknown and merit further investigation, although Ho et al. [22] recently reported increased myocardial collagen synthesis in a large group of genotyped carriers without overt disease. Apparently, a concomitant profibrotic response occurs early in the process of hypertrophic remodelling in asymptomatic carriers, which was also seen in an animal study [23]. It is likely that a global deposition of interstitial fibrosis is, at least in part, responsible for diastolic impairment in carriers.

In all above mentioned functional studies, assessment of myocardial dysfunction alone was demonstrated to be insufficient to serve as a sole diagnostic criterion to identify HCM mutation carriers within asymptomatic family members of HCM patients, since there was considerable overlap in Ea velocities and peak DCSR between HCM mutation carriers and controls [13,16]. However, a combination of LV ejection fraction ≥ 68% with Ea velocity < 15 cm/s proved to be 100% specific and 44% sensitive in predicting affected genotype [13]. Also, a combination of peak DCSR <105 %/s with CMR derived septal to lateral wall ratio > 1.2 discriminated well between HCM mutation carriers and unaffected family members (with a sensitivity of 45% and specificity of 100% [16]). These results were confirmed in a more recent paper by Gandjbakhch et al., in which the diagnostic accuracy of TDI in combination with standard (2D) echocardiography was evaluated in a large HCM mutation carrier population [15]. In this study, a combination of TDI derived velocities with LV remodelling (echo) parameters improved identification of carriers (i.e. receiver operator characteristic (ROC) analysis showed a 67% sensitivity and 96% specificity). In conclusion, results seem promising for diagnosing HCM in a pre-
hypertrophic state with advanced imaging techniques, although larger future studies are needed, perhaps with additive or different parameters, since sensitivity of previous studies was still rather low.

Figure 2. Image A depicts a LV end-diastolic short-axis image of a healthy volunteer with a (horizontally applied) sinusoidal tagging pattern. Figure B is the corresponding short-axis image at the end-systolic phase, showing deformed taglines during maximal cardiac contraction. The right image (C) represents a typical result of (circumferential) strain analysis, in which negative values represent the amount of contraction. Determination of the slope (Δ strain/Δ T) of the red tangential line reveals the peak diastolic circumferential strain rate (peak DCSR). LV= Left ventricle, RV= Right ventricle

Pathogenesis of wall thickening

The mechanism by which mutations in genes encoding for sarcomeric proteins lead to dysfunctional sarcomeres are various. A commonly affected gene, the MYBPC3 gene, is generally associated with age-related penetrance of disease [24,25], although
childhood-onset hypertrophy may also occur [26], which is often accompanied with severe clinical symptoms and high mortality rates [27]. In adult-onset hypertrophy, an apparent (slow) pathophysiological hypertrophic response is triggered by mutations in MYBPC3 genes. As most mutations are heterozygous, both the mutant (i.e. poison peptide) and normal protein, encoded by the unaffected allele, can be expressed in the diseased heart. Mutations may give rise to stable mutant proteins which are incorporated in the sarcomere and affect its function, which is referred to as dominant negative effect of the mutant (i.e. poison) peptide. Most MYBPC3 mutations associated with slow progression of disease, involve nonsense or frameshift mutations which encode truncated proteins. Interestingly, previous studies [28,29] were unable to detect truncated cMyBP-C protein in myocardium from patients with a MYBPC3 mutation. Recently, we have provided evidence that the truncated mutant cMyBP-C protein is absent in myectomy samples from patients with manifest HCM harbouring founder mutations in MYBPC3, while expression of the normal full-length protein was significantly lower compared to non-failing donor myocardium [30]. This indicates that MYBPC3 mutations cause haploinsufficiency rather than a dominant negative effect via incorporation of a poison (mutant) peptide; this observation has been confirmed by Marston et al. [31]. Thus, dysfunctional myofilaments in HCM carriers may either involve haploinsufficiency or incorporation of poison peptides into the sarcomere.

Subsequently, on a sarcomeric level, two concepts exist that link dysfunction of mutant myofilaments to cardiac hypertrophy and failure. One concept favours altered Ca^{2+}-sensitivity of the sarcomeres as a trigger for hypertrophy. Studies using recombinant mutant proteins or transgenic animals harbouring a mutant sarcomeric protein indicate that Ca^{2+}-sensitivity of the myofilaments is increased in HCM
As the myofilaments represent the major dynamic buffer of Ca$^{2+}$ within the cell, it is likely that an increase in myofilament Ca$^{2+}$-sensitivity will prolong the cellular Ca$^{2+}$-transient. The subsequent disturbances in intracellular Ca$^{2+}$ are thought to activate hypertrophy-signalling pathways [2,34].

Alternatively, it has been proposed that HCM mutations lead to inefficient ATP-utilization of the sarcomeres, which will increase energy demand [35]. The increased sarcomeric ATP-utilization causes oxidative metabolism to be increased relative to cardiac work rendering the heart less efficient. In support of this, Crilley et al. [36] showed that phosphocreatin/ATP levels are reduced, irrespective of LV wall thickness in HCM patients. A mismatch between energy generation and energy demand will compromise other ATP consuming mechanisms, in particular re-uptake of Ca$^{2+}$ by the sarcoplasmic reticulum (SR) Ca$^{2+}$-ATPase pump (SERCA2a). Inefficient re-uptake of Ca$^{2+}$ into the SR again will prolong cytosolic Ca$^{2+}$ transients, which may stimulate hypertrophic signalling pathways.

Intense research has emphasized on unmasking the intracellular molecular pathways associated with cardiac hypertrophy [37], which may also apply to HCM. Studies in animals revealed a variety of signalling circuits associated with physiological and pathological (due to pressure overload) hypertrophy, such as the phosphoinositide 3-kinase (PI3K)-Akt pathway, the calcineurin-nuclear factor of activated T cells (NFAT) and cyclic guanosine monophosphate (GMP)-PKG-1 pathways, and signalling pathways associated with the cardiac Na$^+$/H$^+$-exchanger (NHE) and G-protein-coupled receptors, which bind factors such as angiotensin. The hypertrophic response, often initiated by biomechanical and stretch-sensitive mechanisms, appeared highly complex with many parallel and interdependent routes [38]. Various transgenic mouse models have also established a role for the
calcineurin pathway in the pathogenesis of hypertrophy in HCM [39-41]. Nevertheless, calcineurin inhibitory drugs, which were used in these preclinical studies, have not (yet) been explored in human HCM patients due to the conflicting results of preclinical studies. Notably, in one mouse model of HCM, the drug even augmented left ventricular hypertrophy [41]) and hazardous side-effects in transplant patients have been described [42].

Recently, both animal and human studies reported on the influence of oxidative stress on the hypertrophic response in HCM [43,44]. Serum plasma levels of specific markers of oxidative stress were significantly elevated in HCM patients (especially in those with left ventricular outflow tract (LVOT) obstruction and systolic dysfunction) [44,45]. Interestingly, the anti-oxidant agent N-acetylcysteine was able to reverse established hypertrophy and fibrosis in animals [43,46], suggesting a potential applicability for anti-oxidants in humans (Figure 3).

Manifest HCM

Unlike preclinical HCM, the variety of LV morphological changes, together with the functional abnormalities and clinical consequences, have been extensively reported in manifest HCM after the original description by Teare in 1958 [47].

Morphology

Typically, the majority of manifest HCM patients display areas of hypertrophy mainly localized at the anterior region of the ventricular septum [1]. However, isolated apical as well as concentric hypertrophy have also been described in large cohorts of HCM patients [48]. The apical form of HCM is a typical finding in Japanese HCM patients, although this morphology is also regularly seen in Western HCM
populations [49,50]. Symmetric wall thickening might be difficult to distinguish from LV hypertrophy in athletes, although contemporary imaging techniques enable clinicians to discriminate between pathological and non-pathological types of hypertrophy by assessment of LV systolic and diastolic function and with the use of geometric indices [51,52]. Rickers et al. [53] demonstrated that CMR should be the first-choice imaging modality to establish diagnosis, since CMR is able to detect areas of wall thickening in the anterolateral free wall, which were otherwise unidentified with standard (2D) echocardiographic examination.

Marian et al. hypothesized that not only hypertrophy, but also HCM-associated histological hallmarks such as intramyocardial fibrosis, myocardial disarray and medial thickening of intramural coronary arteries might be the ultimate result of perturbations of the cardiac sarcomere [54]. Histogenesis of fibrosis however might not only be explained by direct stimulation of fibroblasts by certain (intracellular) hypertrophic signalling molecules (such as the mineralocorticoid aldosterone [55]), but also by the presumed pathophysiological relation between ischemia and myocyte death and secondary deposition of fibrosis. A post-mortem study performed by Basso et al. provided histological evidence of ischemic injury at different stages, ranging from an acute-subacute phase towards a chronic phase characterized by post-necrotic replacement fibrosis [56]. Most likely, myocardial ischemia is the result of morphological alterations in small intramural arterioles, resulting in microvascular dysfunction with subsequent blunting of the myocardial blood flow, especially during periods of increased oxygen demand such as stress or exercise [57]. In line with abovementioned findings, Kwon et al. [58] found a strong association between the degree of small intramural coronary arteriole dysplasia and the amount of myocardial fibrosis/scarring assessed with Late Gadolinium
Enhancement (LGE) CMR imaging in HCM patients (Figure 4). LGE uses gadolinium chelate as a contrast agent, which tends to accumulate in myocardial regions with increased extracellular space, such as fibrotic tissue [59]. However, Knaapen et al. used both Positron Emission Tomography (PET) and MRI imaging and suggested that LGE in HCM might not solely represent fibrosis, but also oedema [60].

**Symptomatology**

*Heart failure*

The clinical course of this complex disease is highly variable and disease manifestation may occur at any time point during life. Fortunately, most patients show a benign course [61], in contrast to a small subset of HCM patients, who experience heart failure (HF) or ventricular arrhythmias and subsequent SCD. Signs of HF, such as dyspnoea or impaired exercise tolerance, are most commonly accompanied with preserved or even supranormal LV ejection fraction, but reduced stroke volume. In these patients, HF symptoms are most likely caused by diastolic dysfunction, which is defined as increased left ventricular filling pressures necessary to obtain adequate LV stroke volume. Diastolic dysfunction is the net result of reduced LV compliance, increased LV mass, deposition of interstitial fibrosis and/or the presence of ischemia [62]. In addition, clinical impairment might be a direct effect of local hypertrophy of the septum with narrowing of the LVOT. This in turn results in increased afterload and augmentation of LV hypertrophy and worsens during exercise or sudden relief of preload (e.g. by administration of amyl nitrate or with Valsalva manoeuvre). LVOT obstruction may also be caused or aggravated by systolic anterior movement (SAM) of the mitral valve, leading to impaired coaptation of the mitral leaflets with mitral regurgitation as a result [62]. Other HCM associated
malformations of the mitral valve apparatus, such as elongation of mitral leaflets [63], and direct insertion of the papillary muscles into the mitral valve leaflet, can further aggravate the development of SAM [64]. Importantly, LVOT obstruction is an independent determinant of mortality in HCM patients [65].

A minority of the general HCM population (less then 5%) makes a gradual transition towards end-stage heart failure, characterized by systolic dysfunction (ejection fraction ≤50%) and morphological alterations such as cavity dilatation and wall thinning. Prognosis of these patients is poor; Harris et al. [66] calculated annual mortality rates of 11% for end-stage heart failure patients, which is 11-fold higher than for the general HCM population. Recently, Maron et al. found apical aneurysm formation in 2% of a large cohort of HCM patients (1299 patients), which was also accompanied with an increased cardiovascular mortality and morbidity [67]. An important subset of these patients developed systolic LV impairment, suggesting that similar pathophysiological processes might be responsible for deterioration of function in patients with apical aneurysms and end-stage HCM.

*Atrial fibrillation*

Atrial fibrillation (AF) is a common rhythm disorder in HCM, affecting over 20% of the general HCM population [68], and is associated with increased incidence of stroke, HCM-related death and progression to heart failure, especially in the elderly [69]. Signs of heart failure are frequently aggravated during disease progression by the occurrence of atrial fibrillation [70], resulting in decreased diastolic filling and a reduction of cardiac output. Since diastolic filling of a left ventricle with reduced compliance highly depends on the contribution of atrial contraction, the sudden abolition of the atrial kick occurring with onset of atrial fibrillation can result in
nearly instant deterioration of exercise capacity. The strongest determinants of AF in HCM are left atrial size and age [71,72]. Restoration to sinus rhythm is warranted, since AF in HCM importantly affects exercise capacity and is related to increased, mainly stroke related, mortality [69]. If medical treatment fails to prevent recurrences of AF, pulmonary vein radio-frequency catheter ablation may be indicated [73].

**Sudden cardiac death**

Sudden cardiac death has an annual incidence of 1% in the general HCM population, while higher rates (2-4%) are found at tertiary referral centers [74]. The exact pathophysiology of SCD needs to be determined, but it is proposed that either areas of fibrotic tissue and/or myocardial disarray [75] serve as unstable electrophysiological substrates for lethal re-entrant (ventricular) tachycardias, or that secondary phenomena such as ischemia, systemic hypotension, diastolic dysfunction and/or LVOT obstruction contribute to SCD. In order to prevent these catastrophic events, the search for new clinical parameters predicting the risk of SCD will be continued to optimize risk stratification algorithm and to improve patient selection for implantable cardioverter defibrillator (ICD) therapy, which is the current standard prophylactic treatment for high-risk patients. Several risk factors have been found to help identify those patients: 1. a documented episode of sustained ventricular tachycardia (lasting over 30 seconds with a heart rate over 120 beats per minute) or a previous cardiac arrest with a registration of ventricular fibrillation; 2. extreme LV hypertrophy with maximal LV wall thickness ≥ 3 cm (note that the risk of SCD is directly related to the extent of LV wall thickness) [76,77]; 3. non-sustained ventricular tachycardia (ns-VT) lasting <30 seconds; 4. abnormal
blood pressure response during upright exercise using (modified) Bruce protocol; 5. a family history of SCD; 6. unexplained syncope. Gene mutations in TNNT2, MYH7 and TPM1 (alpha-tropomyosin) have also been linked to SCD [78,79]. However, large demographical variability in arrhythmogeneity of these mutations has been observed and as a consequence, the exact value of genetic testing to estimate the risk of SCD remains to be determined. Recently, CMR-LGE imaging showed a positive correlation between LGE (representing areas of fibrosis) and the occurrence of nsv-TVs [80], but future (prospective) studies are needed to verify if LGE serves as an independent risk factor [81].

Controversy remains about the amount of risk factors necessary to justify ICD-implantation, although Maron et al. [82] found that the likelihood for appropriate ICD-discharges was similar in patients with 1, 2 or 3 risk factors. Appropriate ICD-shocks (by virtue of a successful termination of ventricular tachycardia/fibrillation), were administered in 20% of patients and intervention rates were 3.6% per year for primary intervention, and 10.6% per year for secondary prevention in this high-risk HCM cohort of patients. Nevertheless, inappropriate discharges also occurred in up to 27% of all patients after a mean follow-up of 3.7 years, underscoring the necessity to optimize risk calculation of SCD in HCM patients.

Current therapeutic options

Medication

When patients exhibit signs and symptoms of HF, several pharmacological agents are used in clinical practice as first-line treatment [83]. Preferably, beta-adrenergic receptor antagonists, like propranolol or metoprolol, are prescribed to abolish (provocative) gradients. These agents cause a relief of symptoms by decreasing
microvascular ischemia, since negative chronotropic properties of beta-blockers lengthen the diastolic phase and thereby improve microvascular perfusion, next to negative inotropic effects which reduce energy demand of the heart muscle.

Calcium antagonists, such as verapamil, have been shown to improve diastolic function [84,85]. Also, verapamil reduced the amount of silent ischemia in patients with exercise induced reversible perfusion defects, underscoring its potential to reduce anginal complaints and ischemia-based ventricular arrhythmias [86]. Verapamil should be administered with caution when severe heart failure and signs of outflow tract obstruction dominate the clinical findings, since it is reported that hemodynamic deterioration might be induced [87]. In case of resting LVOT obstruction (gradient ≥30 mmHg), class Ia anti-arrhythmic drug disopyramide is preferably prescribed since it has shown to ameliorate symptoms in two-thirds of HCM patients at long term follow-up, and does not seem increase mortality [88]. Nevertheless, HCM patients using disopyramide should be closely monitored for QT-prolongation, and the subsequent occurrence of ventricular tachycardias after initiation of treatment [89].

**Interventional options**

If obstructive HCM patients remain symptomatic despite optimal drug treatment, ultimate clinical improvement may be achieved by invasive procedures like myectomy (Morrow-procedure) or alcohol septal ablation (ASA). Myectomy is the surgical resection of a portion of hypertrophied septum and usually causes an immediate decrease of outflow tract gradient. This intervention appears to be relatively safe with low complication and mortality rates [90] and is still considered to be the cornerstone of therapy. ASA, which was first performed in 1994 by Sigwart
and colleagues [91], creates a (controlled) septal infarction by the infusion of a small amount of ethanol in the first perforating branch of the left anterior descending (LAD) artery. Currently, there is ongoing debate regarding the potential pro-arrhythmogeneity of septal scar created with ASA. Results of a recent study by ten Cate et al. [92] suggested that myectomy is the recommended treatment in symptomatic HCM patients, since ASA patients showed a 5-fold increase in the estimated annual primary end point rate (cardiac death or aborted SCD, 4.4% versus 0.9%).

**Future therapeutic options in HCM**

**Therapy aimed at myocardial remodelling**

Due to the established role of the renin-angiotensin-aldosterone-system (RAAS) in the development of cardiac hypertrophy [93], pharmacologic studies aimed to influence HCM phenotype by blocking an angiotensin receptor. Results of these few studies showed a reversal of interstitial fibrosis and/or LV hypertrophy in animals [94] and humans [95-97]. If replicated in larger clinical settings, the use of angiotensin receptor blockers (ARB’s) may become a promising treatment option in HCM. Strikingly, the mineralocorticoid-antagonist spironolacton attenuated myocyte disarray extensively in troponin T transgenic mice, besides reversing the amount of interstitial fibrosis [55]. Patel et al. [98] used statins in a preclinical study in transgenic HCM rabbits with a MYH7 mutation (Q403), and was able to reduce both hypertrophy and fibrosis and improve LV function, suggesting a potential applicability for statins in humans (Figure 3). As outlined in section 2.4, new therapeutic applications might also be reserved for anti-oxidants, of which N-acetylcysteine proved to possess prominent anti-fibrotic effects [43] (Figure 3).
**Therapy aimed at sarcomeric dysfunction**

Therapeutic strategies aimed at restoring sarcomeric dysfunction and Ca\(^{2+}\)-homeostasis might theoretically prevent or slow the (presumed) hypertrophic response in HCM patients. Treatment of genetically engineered HCM mice with the L-type Ca\(^{2+}\) inhibitor diltiazem already showed that early restoration of sarcoplasmatic reticulum Ca\(^{2+}\)-homeostasis resulted in a decrease of the hypertrophic and fibrotic response to a sarcomeric gene mutation [99]. Besides, lowering the Ca\(^{2+}\)-sensitivity of cardiac myofilaments, which is consistently increased in both in-vitro and rodent studies, might even prevent arrhythmic events, especially in patients with troponin T mutations [100]. A potential applicability for agents affecting cardiac energy metabolism seems plausible in HCM; drugs that shift the preferred fatty acid oxidation towards carbohydrate metabolism (e.g. Trimetazidin [101]) might increase ATP supply in the heart muscle and restore reduced efficiency of contraction (which is impaired in HCM patients [102]) and thereby inhibit intracellular processes which stimulate the hypertrophic response (Figure 3).
Therapeutic strategies aimed at restoring sarcomeric dysfunction and Ca²⁺-homeostasis might theoretically prevent or slow the (presumed) hypertrophic response in HCM patients. Treatment of genetically engineered HCM mice with the L-type Ca²⁺-inhibitor diltiazem already showed that early restoration of sarcoplasmatic reticulum Ca²⁺-homeostasis resulted in a decrease of the hypertrophic and fibrotic response to a sarcomeric gene mutation [99]. Besides, lowering the Ca²⁺-sensitivity of cardiac myofilaments, which is consistently increased in both in-vitro and rodent studies, might even prevent arrhythmic events, especially in patients with troponin T mutations [100]. A potential applicability for agents affecting cardiac energy metabolism seems plausible in HCM; drugs that shift the preferred fatty acid oxidation towards carbohydrate metabolism (e.g. Trimetazidin [101]) might increase ATP supply in the heart muscle and restore reduced efficiency of contraction (which is impaired in HCM patients [102]) and thereby inhibit intracellular processes which stimulate the hypertrophic response (Figure 3).

Figure 3. Overview of current concepts leading to development of LV hypertrophy in HCM patients affected with MYBPC3 gene mutations. The time point at which current therapeutic interventions are performed is outlined at the right, besides the possibilities for early (future) therapeutic interventions.
Figure 4. Late Gadolinium enhancement (LGE) two chamber image showing extensive scarring in a patient with manifest HCM. The bright, contrast enhanced areas indicate myocardium with extensive fibrosis, the dark areas of myocardium, indicated by the white arrows is myocardium with no or little fibrosis, LA= left atrium, LV= left ventricle.

**Summary**

In conclusion, both clinical and preclinical studies reveal (global and microscopic) functional alterations of the HCM heart muscle even before the development of hypertrophy. Apparently, myocardial and sarcomeric dysfunction precede (or even initiate) a complex, and yet incompletely unravelled process of wall thickening. Therefore, future longitudinal (animal) studies are needed to elucidate molecular pathways that promote regional (septal) hypertrophy. Besides, extension of knowledge regarding physiological properties of human HCM tissue is wanted, since data on (human) sarcomeric function is scarce. As current treatment in HCM is strictly symptomatic, early targeted drug treatment (aimed at slowing the hypertrophic response by reducing Ca$^{2+}$-sensitivity of myofilaments or restoring energy metabolism), may have important clinical implications, but future animal studies (and subsequent clinical trials) are needed to confirm this hypothesis.
Summary
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