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Muscle dysfunction in hypertrophic cardiomyopathy: What is needed to move to translation?

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Abstract

Hypertrophic cardiomyopathy (HCM) is caused by mutations in sarcomere genes. As such, HCM provides remarkable opportunities to study how changes to the heart's molecular motor apparatus may influence cardiac structure and function. Although the genetic basis of HCM is well-described, there is much more limited understanding of the precise consequences of sarcomere mutations—how they remodel the heart, and how these changes lead to the dramatic clinical consequences associated with HCM. More precise characterization of the mechanisms leading from sarcomere mutation to altered cardiac muscle function is critical to gain insight into fundamental disease biology and phenotypic evolution. Such knowledge will help foster development of novel treatment strategies aimed at correcting and preventing disease development in HCM.

Keywords

Cardiac muscle mechanics; Thin filament; Thick filament; Myofilament calcium sensitivity; Excitation contraction coupling; Cardiac muscle energetics

Background and Introduction

Hypertrophic cardiomyopathy (HCM) is a primary disorder of the myocardium. Traditionally, it has been characterized by the presence of unexplained left ventricular hypertrophy (LVH)—increased LV wall thickness which occurs in the absence of other causes, such as pressure overload (systemic hypertension, aortic stenosis) or other multisystem illness (storage or infiltrative diseases). Pathognomonic histological features of HCM are myocyte disarray and interstitial fibrosis (Fig. 1).

HCM is often familial with autosomal dominant inheritance. Genome-wide linkage studies in the 1980s led to the discovery of pathogenic mutations in genes that encode different components of the contractile apparatus. This discovery established the paradigm that HCM is a disease of the sarcomere. Disease-causing (pathogenic) mutations have been identified in the genes encoding cardiac β -myosin heavy chain (*MYH7*), cardiac myosin binding protein C (*MYBPC3*), cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), α -tropomyosin (*TPM1*), essential and regulatory myosin light chains, and cardiac actin (Seidman and Seidman 2001; Richard et al. 2006). Sarcomere mutations can be identified in ~60 % of individuals with familial HCM and in ~20–30 % of patients with HCM who do not have a family history (Richard et al. 2006). The *MYH7* and *MYBPC3* genes are most commonly involved. As the prevalence of unexplained LVH is estimated at 1 in 500 to 1000 (Maron et al. 1995) HCM is the most common monogenic cardiovascular disorder.

HCM is highly complex and heterogeneous. There is substantial variation in clinical manifestations, cardiac morphology, symptom burden, and prognosis (Gersh et al. 2011). Although most patients with HCM have a normal life expectancy, symptoms of pulmonary congestion, chest pain, and exercise intolerance result in substantial limitations despite medical or surgical therapy. HCM can also result in striking events, including the development of end stage heart failure leading to death or cardiac transplantation, or a high risk of sudden cardiac death.

The clinical diagnosis of HCM has traditionally relied on identifying unexplained LVH. However this strategy has important limitations. Although the gene mutation responsible for causing HCM is present before birth, the development of LVH is highly age-dependent and LV wall thickness is usually normal during childhood. LVH commonly emerges in adolescence or early adulthood, although for some individuals, clinically overt disease may not be detectable for decades more (Niimura et al. 1998; Maron et al. 2004). Very little is known about how disease develops or the mechanisms that drive cardiac remodelling. With gene-based testing, at-risk sarcomere mutation carriers (G+) can be identified before they can be clinically diagnosed with HCM (LVH-). By studying this unique G+/LVH- population, the full spectrum of biophysical, morphologic, and functional changes associated with sarcomere gene mutations can be described, prior to the diagnosis of overt HCM. Furthermore, laboratory-based research has the power to describe the specific molecular mechanisms of disease with great precision and detail. Collectively, collaborative basic science and clinical translational investigation has great potential to transform the practice of medicine by defining mechanistic pathways, identifying novel therapeutic targets, and directing preventive, disease-modifying treatment to genetically susceptible individuals early in disease course, before irreversible changes in cardiac structure and function are established.

Basic mechanisms of muscle dysfunction in HCM and potential therapeutic targets

Most HCM mutations appear to act in a dominant negative fashion, and the mutant proteins are incorporated into the sarcomere where they affect contractile performance (e.g. Cuda et al. 1993; Bottinelli et al. 1998). An exception to this perspective may be truncation

mutations in *MYBPC3* for which evidence of haploinsufficiency has been generated (van Dijk et al. 2009; Marston et al. 2009).

Previously developed techniques to measure altered contractility in HCM have largely used recombinant proteins (either studied in vitro or exchanged into demembranated muscle preparations) or engineered mouse models. Although early studies showed that HCM mutations depressed cardiac contractility, most of the biophysical and biochemical studies with recombinant proteins and mouse models of HCM suggest that HCM mutations increase contractility, either by enhancing motor function (Palmiter et al. 2000; Lowey 2002) or increasing the intrinsic force of the motor (Seeböhm et al. 2009; Sommesse et al. 2013) (*MYH7* mutations; see also “Decreased/increased force generating capacity” section), or by elevating myofilament Ca^{2+} -sensitivity (Elliott et al. 2000; Hernandez et al. 2001; Marston 2011) (thin filament mutations; see also “Increased myofilament calcium sensitivity” section). To reconcile these apparent inconsistencies regarding contractile function in HCM, it has been proposed that HCM sarcomere mutations may lead to increased energy cost of force production through inefficient or excessive ATP usage (see also “Increased energy cost of tension generation” section), and that this ultimately results in an energy deficiency that contributes to the pathogenesis of the disease (Ashrafian et al. 2003; Ashrafian and Watkins 2007). One of the predicted consequences of energetic defect in HCM is that reuptake of Ca^{2+} into the sarcoplasmic reticulum will be compromised because of the extreme energy requirements of the sarcoplasmic reticulum SERCA pump. In support of this notion, magnetic resonance studies of mouse models of HCM have shown that the G of ATP hydrolysis is reduced to a level at which SERCA function will be compromised (Javadpour et al. 2003; Spindler et al. 1998). Disruption of cardiomyocyte Ca^{2+} homeostasis and excitation–contraction coupling has been shown to be an important early event in the pathogenesis of HCM (Semsarian et al. 2002). Increased $[\text{Ca}^{2+}]$ in specific microdomains can also alter intracellular signalling pathways leading to adverse cardiac muscle remodelling (see also “Excitation-contraction coupling adverse remodelling” section and Fig. 2).

In spite of many studies of mutations in experimental models of HCM, there have been few reports to date that actually directly document the functional abnormalities present in human HCM heart muscle. The most significant reason for this has been the limited availability of both affected tissue and of suitable control human myocardium. An important advancement for the definition of the structural and functional changes present in human HCM tissue is the recent creation of a large bank of affected and control tissue by the European BIG Heart Consortium (www.big-heart.eu). In addition, recent technical advances have been made in the biophysical analysis of human heart muscle. Single skinned cardiac myocytes (Borbely et al. 2005) and single myofibrils (Piroddi et al. 2007) can be easily obtained in large amounts from small human cardiac biopsies. Methods to measure ATPase activity during isometric contraction have been successfully applied to chemically demembranated human ventricular muscle strips (Narolska et al. 2005). Techniques that allow separation of intact viable myocytes from samples of human ventricular myocardium have been improved (Coppini et al. 2013). One main advance over previous techniques is provided by a custom-

made digestion device which delivers gentle mechanical stirring of tissue specimens, allowing single cell separation without excessive damage.

Decreased/increased force generating capacity

Since the discovery of the first HCM-associated mutation in *MYH7* (Geisterfer-Lowrance et al. 1990), a large number of studies have been published on the impact of HCM mutations on the force generating capacity of the sarcomere. Early studies of systems containing the R403Q mutant myosin (Cuda et al. 1993; Sweeney et al. 1998; Lankford et al. 1995; Sata and Ikebe 1996; Fujita et al. 1997; Roopnarine and Leinwand 1998) showed severely diminished function, whatever sources of mutant protein were used (biopsies from slow skeletal muscle of HCM patients or recombinant proteins from different expression systems) and whatever assays were performed (in vitro motility assays and acto-myosin ATPase in isolated proteins, force and shortening velocity in slow skeletal skinned muscle fibres). On the basis of these results, it was hypothesized that HCM is caused by altered acto-myosin interactions and that the accompanying loss of sarcomere force drives the hypertrophy of the left ventricle (Cuda et al. 1993; Marian 2001).

Although intuitively appealing, the “compensatory hypertrophy hypothesis” for HCM, has been challenged by more recent work on the R403Q and other *MYH7* mutations and by a number of studies on HCM mutations in sarcomeric proteins other than β -myosin heavy chain. Studies of systems containing the R403Q and other HCM-mutant myosins imply that the mutant proteins have increased mechanical performance rather than diminished function (e.g. Tyska et al. 2000; Miller et al. 2003; Seebohm et al. 2009; Sommesse et al. 2013). Evidence of enhanced motor activity has been also reported for HCM mutations in thin filament proteins and cardiac myosin binding protein C (e.g. Homsher et al. 2000; Stelzer et al. 2006).

The precise impact of specific HCM mutations on the maximal force generating capacity of human cardiac sarcomeres in vivo remains somewhat controversial. The myosin R403Q mutation that increased maximal tension in skinned preparations from a mouse model of HCM (Palmer et al. 2008) significantly depressed maximal tension of cardiac myofibrils from a young HCM patient, in spite of an apparent gain in the protein motor function (the observed increase in cross-bridge turn-over rate was mostly due to increased detachment rate of force generating actomyosin complexes; Belus et al. 2008). The R723G mutation in *MYH7* that had been reported to significantly increase maximal tension of human soleus fibres from HCM patients compared to controls (Seebohm et al. 2009) actually depressed maximal tension of left ventricular cardiomyocytes from HCM patients carrying the same mutation (Kraft et al. 2013). Recent work in skinned cardiomyocyte and single myofibril preparations from several HCM patients carrying mutations in different myofilament proteins has shown that the disease is usually associated with some impairment of the sarcomere maximal tension generating ability (Witjas-Paalberends et al. 2013). In most cases this can be related to reduced myofibril density and secondary hypertrophy remodelling rather than to a primary defect of the mutation. Furthermore, the force generating ability of the human cardiac sarcomere in HCM may be influenced by the specific gene mutation (especially *MYH7*). Work, still in progress, suggests that impairment

of maximal tension is more severe in sarcomeres from HCM patients with complex genotype.

Advances in screening and computational methods have enhanced the development of small-molecules such as cardiac myosin activators or inhibitors. Omecamtiv mecarbil, a direct activator of cardiac myosin that stabilizes an actin-bound conformation of myosin, has been shown to increase cardiac function in animal models of systolic heart failure (Malik et al. 2011). Potent and selective myosin inhibitors are not only tools for understanding myosin function, but can also become a resource for developing treatments for diseases involving myosin over-activity (Bond et al. 2013). These compounds, as well as other mutation-specific sarcomeric allosteric modulators, could rebalance contractility in HCM, therefore potentially stopping and reversing the course of disease. Further understanding of the precise consequences of the mutation on in vivo force generation, post-translational modification of myofilament proteins, and their relationship to disease development will be necessary for such treatment strategies to come to fruition.

Increased myofilament calcium sensitivity

Increased myofilament Ca^{2+} -sensitivity has been reported as a common dysfunction in experimental models of HCM and has been proposed as a trigger of disease pathogenesis (e.g. Marston 2011). Besides detrimental effects on cardiac myocyte relaxation and energetics, increased Ca^{2+} -sensitivity may contribute to electrical remodeling and increased risk of arrhythmias (Baudenbacher et al. 2008; see also “Excitation-contraction coupling adverse remodelling” section). Myofilament Ca^{2+} -sensitization has been recently reported to directly determine arrhythmogenic changes in cardiomyocyte Ca^{2+} homeostasis by increasing cytosolic Ca^{2+} buffering (Schober et al. 2012).

Recent work in cardiac samples from HCM patients has shown that high myofilament Ca^{2+} -sensitivity is a common characteristic of human HCM that seems independent of the exact mutation and sarcomeric protein involved. The high myofilament Ca^{2+} -sensitivity found in human HCM samples partly reflects hypo-phosphorylation of PKA-targets compared to non-failing donors rather than a primary effect of sarcomeric protein mutations (Sequeira et al. 2013).

Although the mechanisms responsible for increased myofilament Ca^{2+} -sensitivity in HCM remain unclear, restoring the impaired relaxation and diastolic dysfunction and reducing the arrhythmogenic substrate by targeting the myofilament Ca^{2+} sensitivity is a promising alternative for treatment of HCM and alleviation of the disease-related symptoms. Ideally, Ca^{2+} desensitizers, would specifically target molecules involved in muscle contraction rather than the cardiomyocyte Ca^{2+} -handling system. This strategy would avoid altering cytosolic Ca^{2+} homeostasis which would perturb the regulation of other Ca^{2+} -based signalling pathways. Ca^{2+} -desensitizers may also have the potential ability to prevent arrhythmia in HCM patients. This therapeutic advantage of compounds that target sarcomere Ca^{2+} -sensitivity was first demonstrated in mouse models characterized by myofilament hypersensitivity to Ca^{2+} caused by troponin mutations or by the Ca^{2+} sensitizing agent EMD57033. Isolated hearts from these animal models exhibited significant arrhythmia susceptibility that was prevented by the myosin inhibitor blebbistatin (Baudenbacher et al.

2008). The protective effect of blebbistatin provided the first direct evidence that Ca^{2+} -desensitization in myofilaments is antiarrhythmic and may be beneficial in the treatment of HCM.

The use of Ca^{2+} -desensitizing compounds for the treatment of diastolic dysfunction is a novel concept. So far, the number of Ca^{2+} -desensitizing interventions available for basic research or clinical trials is very limited. Most of them are at present unsuitable for therapeutic use and can be only tested in animal models and in in vitro experiments as “proof of concept”. Investigations of the mechanisms of Ca^{2+} -desensitizing interventions are generating molecular insights into structural features that can be useful for the design of novel specific Ca^{2+} -desensitizing drugs.

Myofilament Ca^{2+} -desensitization may attract future clinical interest as an alternative approach to treat HCM—both to address symptoms and potentially to modify the underlying disease process. The mechanisms by which Ca^{2+} -desensitization can be achieved vary widely from direct inhibition of Ca^{2+} -binding to cTnC and associated downstream consequences, to direct inhibition of myosin motors. To date, no ideal drugs or interventions exist because of the lack of knowledge of how most of these interventions may affect whole heart and whole organism physiology. Nonetheless, some of the findings reported in the recent literature (e.g. Robertson et al. 2009; Oleszczuk et al. 2010; Li et al. 2010; Liu et al. 2012) look convincing and encourage further investigation to identify suitable interventions for clinical testing.

Increased energy cost of tension generation

The pathogenesis of sarcomeric HCM has been variously attributed to increased sarcomeric Ca^{2+} sensitivity, increased ATPase activity/force, aberrant cross-bridge dynamics leading to complications such as oxidative stress (e.g. Lombardi et al. 2009), and altered sarcomeric phosphorylation (e.g. van Dijk et al. 2009). However, a common feature of many studies on HCM disease mechanisms is the excessive energetic cost of tension generation by sarcomeric mutations (e.g. Chandra et al. 2005; Frey et al. 2006; Ferrantini et al. 2009). Evidence that HCM sarcomere mutations may increase the energy cost of force production through inefficient or excessive ATP usage has led to the proposal of the “energy depletion hypothesis” for HCM. It has been shown, using nuclear magnetic resonance (31P NMR) spectroscopy, that the cardiac phosphocreatine (PCr) to ATP ratio (PCr/ATP), a measure of energy status, is significantly reduced in HCM patient hearts and animal models compared with controls (Jung et al. 1998; Crilley et al. 2003; Javadpour et al. 2003; He et al. 2007; Luedde et al. 2009). In HCM patients the PCr/ATP ratio was reduced in mutation carriers both with and without left ventricular hypertrophy, and was even compromised in asymptomatic HCM. Collectively, these studies suggest that energy deficiency is a primary consequence of the underlying mutation rather than a secondary consequence of cardiac remodelling (either LV hypertrophy or heart failure). The resulting final common path of energy deficiency, rather than sarcomeric mutations per se, may specifically contribute to the HCM phenotype, as observed in other primary disorders of myocardial energy deficiency (Ashrafian et al. 2003).

Strategies designed to increase the energetic efficiency of contraction and/or improve cardiomyocyte energetics may be able to rescue the HCM phenotype. This hypothesis has been recently tested in HCM mouse models by genetically remodelling the sarcomere by substituting the α myosin normally expressed in the mouse ventricle with the slower β isoform that is more efficient at force generation (He et al. 2012). The intervention normalized the increased cost of cardiac contraction, rescuing both contractile dysfunction and energetic abnormalities of R92Q cTnT mutant hearts, while wild-type hearts were unaffected. There is evidence that agents modifying substrate use (e.g. perhexiline) enhance myocardial energetics and are efficacious in the energy-starved state of heart failure (Ashrafian et al. 2007). Although the mechanisms of action of perhexiline are likely to be complex, its capacity to divert myocardial metabolism toward carbohydrates, especially in the context of microvascular dysfunction limiting myocardial oxygen delivery is expected to enhance the efficiency of myocardial energy generation. Consistent with this idea, in symptomatic non-obstructive HCM patients, perhexiline augmented myocardial PCr/ATP ratio, improved diastolic dysfunction and increased exercise capacity (Abozguia et al. 2010). The proof of concept studies reported above, besides supporting the idea that impaired energetics is central to the HCM disease process, provide a rationale for further consideration of energy sparing and metabolic therapies in HCM. Widespread use of perhexiline is limited due to associated liver toxicity, but other agents are being evaluated.

Excitation–contraction coupling adverse remodelling

In the intact myocardium, compromised energetics may impair relaxation and diastole by altering the Ca^{2+} transport function needed for intracellular $[\text{Ca}^{2+}]$ to fall. Elevated diastolic intracellular $[\text{Ca}^{2+}]$ and altered function of other ion transporters needed for normal electrophysiological activity may also render the myocardium vulnerable to the arrhythmias that underlie sudden cardiac death in HCM. In mouse models of HCM dysfunction of membrane bound macromolecules responsible for cardiac excitation–contraction coupling occurs in advance of changes in cardiac histology or morphology (e.g. Semsarian et al. 2002) suggesting that therapeutic interventions targeting membrane transport mechanisms and their regulation could prevent the onset and progression of HCM.

The electromechanical profile of cardiomyocytes from HCM patients undergoing myectomy has been recently assessed and compared with that of cardiomyocytes from non-hypertrophic non-failing surgical patients by performing patch-clamp and intracellular Ca^{2+} studies (Coppini et al. 2013). Compared with controls, HCM cardiomyocytes showed prolonged action potential related to increased late Na^+ (I_{NaL}) and Ca^{2+} (I_{CaL}) currents and decreased repolarizing K^+ currents; increased occurrence of cellular arrhythmias; prolonged Ca^{2+} -transients; and higher diastolic Ca^{2+} . Such changes were related to enhanced Ca^{2+} /calmodulin kinase II (CaMKII) activity and increased phosphorylation of its targets. Ranolazine at therapeutic concentrations partially reversed the HCM-related cellular abnormalities via I_{NaL} inhibition. There were negligible effects in controls. By shortening the action potential duration in HCM cardiomyocytes, ranolazine reduced the occurrence of early and delayed after-depolarisations. Finally, as a result of the faster kinetics of Ca^{2+} -transients and the lower diastolic Ca^{2+} , ranolazine accelerated the contraction-relaxation cycle of HCM trabeculae, ameliorating diastolic function (Fig. 2).

A specific set of functional changes in human HCM myocardium stem from a complex remodelling process involving alterations of CaMKII-dependent signalling, rather than being a direct consequence of the causal sarcomeric mutations. Among the several ion channel and Ca^{2+} -handling proteins changes identified, an enhanced I_{NaL} seems to be a major contributor to the electrophysiological and Ca^{2+} dynamic abnormalities of ventricular myocytes and trabeculae from patients with HCM, suggesting potential therapeutic implications of I_{NaL} and CaMKII inhibition.

Additional mechanisms underlying HCM cardiomyocyte adverse remodelling are under investigation. Among them there is a marked reduction of t-tubular density and function (Ferrantini et al. 2013). T-tubules are transverse invaginations of the surface sarcolemma that occur in mammalian heart ventricles at each Z-line and ensure rapid and homogeneous propagation of the action potential into the cell interior, eventually inducing synchronous Ca^{2+} release from the SR and myofibril contraction. In septal myocytes from myectomy samples of non-failing HCM patients with obstructive hypertrophy, it has been recently observed that T-tubules are almost completely lost, indicating that T-tubule remodeling likely precedes the endstage of the disease. Decreased T-tubule density likely contributes to abnormal amplitude and kinetics of Ca^{2+} -transients and twitches of HCM myocytes due to impaired and asynchronous Ca^{2+} release from the SR. In the absence of T-tubules, increased myofilament Ca^{2+} sensitivity, as commonly found in HCM, could further contribute to impair the spread of propagated Ca^{2+} -induced Ca^{2+} -release from the surface sarcolemma to the cell core. One could speculate that myofilament Ca^{2+} desensitizers, besides ameliorating diastolic function, may be effective in enhancing SR Ca^{2+} release propagation in HCM myocardium rescuing abnormalities related to T-tubule loss.

Translating mechanism-based therapy to clinical medicine

As described above, fundamental research strives to identify key mechanistic pathways and agents that may effectively target them. Once promising agents are identified, clinical trials are then needed to assess safety and efficacy in human populations. Additionally, for such trials to be successful, we need to identify patients who are most likely to benefit from disease-modifying treatment; and we need to be able to detect treatment response. There are several considerations to identifying the optimal target population. Trials on animal models of HCM suggest that disease-modifying therapy is most effective when administered early to genetically-susceptible mice, prior to the development of overt HCM. Treatment initiated after animals developed LVH failed to show clear benefit (Semsarian et al. 2002). As such, disease-modifying agents may not be able to reverse pathology in patients with long-established HCM. Developing clinical trials to test novel treatment strategies in populations with early disease, as well as patients with late-stage disease, may be most productive.

Using genetic testing, we can identify an at-risk human population comprised of sarcomere mutation carriers without clinical HCM. This population is an appealing target for early treatment intended to modify or prevent disease. However, detecting treatment response will be a major challenge in this generally young and healthy cohort. More dynamic and informative surrogate endpoints are needed. Studies on sarcomere mutation carriers have helped to characterize early phenotypes that are present prior to the emergence of clinically

overt disease. Impaired relaxation (Fig. 3, Ho et al. 2002, 2009), altered myocardial energetics (Crilly et al. 2003), ECG abnormalities (Lakdawala et al. 2011), and evidence of a profibrotic state (Fig. 4, Semsarian et al. 2002; Kim et al. 2007), can be identified even if LV wall thickness is normal. These changes help to differentiate preclinical mutation carriers from normal controls, and tend to become more marked as clinically overt disease develops. As such, early phenotypes may be viable surrogate endpoints to monitor disease progression and treatment response. Disease-modifying therapy would strive to make preclinical mutation carriers appear “more normal”. However, current methods to detect early phenotypes are limited by their relatively low resolution and sensitivity. Identifying more robust and quantitative novel early phenotypes will critically facilitate development of robust trials to change the natural history of disease.

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Fig. 1.
HCM is characterized by LVH, myocyte disarray, and myocardial fibrosis

Fig. 2.

Electro-mechanical remodeling in human HCM cardiomyocytes. Sarcomeric mutations may cause a primary sustained increase of intracellular Ca^{2+} with multiple mechanisms: (i) increased sarcomeric ATP consumption that may lead to SERCA (and mitochondria) dysfunction and impaired Ca^{2+} removal; (ii) increased myofilament Ca^{2+} sensitivity that slows Ca^{2+} dissociation from the myofilaments and contributes to increased Ca^{2+} levels during diastole. Intracellular Ca^{2+} overload (in combination with increased production of reactive oxygen species) leads to sustained activation of CaMKII: increased phosphorylation of its downstream targets (Ca^{2+} channels, Ryanodine Receptors, phospholamban, Na^+ channel) is responsible for the abnormalities observed in HCM cardiomyocytes, including increased I_{NaL} . Overall, these changes aggravate intracellular Ca^{2+} overload. The enhanced I_{NaL} is responsible for intracellular Na^+ overload, which favors reverse over forward NCX mode. The latter contributes to cytosolic Ca^{2+} overload, further promoting CaMKII activation, thus setting up a vicious circle. Modified from Coppini et al. (2013)

Fig. 3.

Evidence for impaired relaxation as an early phenotype of sarcomere mutations. Averaged early myocardial relaxation velocity (Ea) is significantly lower in G+/LVH- subjects than normal controls. Ea velocities are further reduced in subjects with overt HCM (G+/LVH+). * $p < 0.0001$ compared with controls. † $p < 0.0001$ compared with G+/LVH+ (Adapted with permission from Ho et al. 2002)

Fig. 4.

Evidence that profibrotic pathways are activated early as a consequence of sarcomere mutations. **a** serum levels of the C-terminal propeptide of procollagen type 1 (PICP), a biomarker of collagen synthesis, are elevated in sarcomere mutation carriers both with and without left ventricular hypertrophy. (Adapted with permission from Ho et al. 2010). **b** myocardial extracellular volume, as assessed by T1 mapping, is significantly increased not only in sarcomere mutation carriers with clinically overt HCM, but also in preclinical mutation carriers with normal LV wall thickness. (Adapted with permission from Ho et al. 2013)