Published in final edited form as:
J Mol Cell Cardiol. 2010 November ; 49(5): 715–718. doi:10.1016/j.yjmcc.2010.07.016.

Static and Dynamic Properties of the HCM Myocardium

Shannamar Dewey, **Qian Xu**, and **Aldrin Gomes***
Department of Neurobiology, Physiology and Behavior, University of Cailfornia, Davis, Davis, CA 95616

Hypertrophic cardiomyopathy (HCM) is a complex and relatively common genetic cardiac disease associated with significant genotypic and phenotypic heterogeneity and affects about one in 500 individuals of the general population [1-2]. HCM is typically associated with a portion of the myocardium being hypertrophied - usually of the left ventricle in the absence of loading conditions such as hypertension [3]. While the occurrence of HCM is a significant cause of unexpected (sudden) cardiac death in all age groups, it is best known as a leading cause of sudden cardiac death in young athletes [4]. HCM is associated with more than 550 mutations in 10 genes that code for cardiac sarcomeric proteins [5]. Five genes account for greater than 90% of the HCM mutations so far discovered [5]. These genes include β-myosin heavy chain (β-MyHC, encoded by the MYH7 gene), β-myosin binding protein C (MyBP-C encoded by the MYBPC3 gene), cardiac troponin T (cTnT, encoded by the TNNT2 gene), cardiac troponin I (cTnI, encoded by the TNNI3 gene), and α-tropomyosin (α-Tm, encoded by the TPM1 gene).

The clinical course of HCM is highly variable with some patients being asymptomatic or mildly symptomatic while others undergo dyspnea, syncope, and even sudden cardiac death. This dyspnea has been suggested to be largely due to increased stiffness of the left ventricle (LV), which impairs ventricular filling resulting in elevated pressures in the left atrium and left ventricle. Myocyte hypertrophy, disarray and interstitial fibrosis have also been proposed as main contributors to HCM induced diastolic and systolic dysfunction [6]. However, the link between the sarcomeric mutations as well as the actual molecular mechanism of pathological progression remain unclear. The paper by Hoskins et al. in this issue of *Journal of Molecular and Cellular Cardiology* investigated the steady-state and dynamic characteristics of passive stiffness and active force production in the myocytes from HCM and non-diseased hearts to determine the extent to which dysfunction at the myocyte level contributes to impairment of cardiac performance [7]. Myocytes from heart samples of patients with mutations in the two main sarcomeric proteins associated with HCM, β-MyHC (R719Q) and MyBP-C (R502W and T2604A + C deletion at 2605), as well as HCM hearts not associated with any mutations (three patients) were compared with myocytes from non-diseased hearts [7]. Although the number of HCM samples from patients with sarcomeric mutations were small (two patients with *MYBPC3* mutations and one with a *MYH7* mutation) it is important to be aware of the difficulty in getting these types of samples. All of the HCM samples were compared against four non-

*Corresponding author: avgomes@ucdavis.edu .

Disclosure Statement

The authors do not have any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the work submitted that could inappropriately influence (bias) our work.

diseased donor hearts. Under pathogenic conditions, like HCM, the heart shows increased myocardial stiffness compared to non-diseased hearts [6]. Hoskins et al. investigated two types of passive force of myocytes: elastic (time-independent) and viscoelastic (time-dependent). Interestingly, and perhaps unexpectedly, Hoskins et al. found that the passive elastic and viscous properties of the myocytes were similar between HCM patients and were not significantly different from those of donor myocytes, suggesting that the increased wall stiffness was not due to changes in myocyte passive stiffness. While the peak force showed a trend to be higher for HCM myocytes it was not significantly different from the donor myocytes [7]. These results provide the first evidence that diastolic dysfunction in at least some HCM myocytes do not originate from the stiffness of the sarcomere.

Measurement of passive viscoelasticity in cardiac muscle started 28 years ago when Noble measured the force of cat papillary muscle during diastole at different stretch velocities [8]. Five years later, Chiu et al. observed viscous resistance to both stretch and active shortening in cat papillary muscle [9-10]. Viscoelasticity, which manifests itself in stress relaxation (force decay at constant length) following a stretch and in force hysteresis during a stretch-release cycle [11], is thought to reflect passive stiffness of the myocardium, and thus is an important measurement of diastolic function. Cardiac muscle behaves as a viscoelastic material, resulting in the filling of the ventricle which generates a resisting force (stress) when myocardial length is increased (strain). Changes in myocardial stiffness can be assessed by examination of the myocardial stress, strain, and strain-rate relationships during diastole [12].

Titin (also known as connectin) is known to be the main factor involved in determining both elasticity and viscoelasticity of myofibrils [13]. Titin is the largest known protein and extends from the Z-line to M-line regions of the sarcomere [14]. While part of titin is inextensible (Z line and A-band regions), the majority of the I-band region of titin functions as a molecular spring that develops passive force [15]. Cardiac titin exists in two main isoforms termed N2B and N2BA, and its isoform expression and relative phosphorylation has been shown to be altered in human heart failure (HF) myocytes when compared to donor myocytes. In heart failure myocytes, the N2BA titin (compliant isoform) increases relative to the N2B (stiff isoform) and the total phosphorylation of the stiff N2B titin isoform is significantly lower in HF resulting in raised passive force of human HF cardiomyocytes [16]. Hoskins et al. investigated titin and found that, unlike what was found in a previous animal model of overload hypertrophy [17], no differences in titin isoform content, amount, or extent of degradation was seen between the groups [7]. Measurement of titin phosphorylation is currently impractical since phosphorylation by PKCα increases stiffness [18] while phosphorylation by PKA or PKG decreases stiffness [19]; furthermore, these phosphorylation sites are not yet fully characterized. Considering that the passive viscoelastic properties of titin largely define the properties of the entire sarcomere, no change in the ratio of N2B to N2BA as well as no change in overall amount of N2B correlates with the results of the mechanical fiber experiments [7] which suggest that the stiffness of the sarcomere is not changed in the HCM hearts investigated.

While titin is the main protein involved in the viscosity of cardiac muscle [13], changes in viscous properties have been attributed to increased microtubule density in pressure-overload cardiac hypertrophy [20-21], suggesting that other factors may also contribute to the viscoelasticity of muscle. Other studies also suggest that Ca^{2+} [13,22], collagen [23], and interstitial fibrosis [24] may be associated with passive myocardial tension. Two other proteins, merosin and alpha7-integrin (which both occur in cardiac muscle), have been suggested to be involved in passive skeletal muscle tension [25-26]. Collagen is the main structural component of connective tissue in the heart and experiments using a furazolidone-induced model of DCM in turkey poults trabecular muscle suggest that the increase in passive myocardial stiffness observed was primarily collagen-based [23]. It may be that collagen is partly involved in passive force in HCM myocytes since collagen IV fibers in HCM myocytes were more

abundant and less associated with costamere structures than donor myocytes [7]. However, more detailed experiments on collagen in HCM hearts is needed out as some experimental data suggest that the higher diastolic stiffness in the failing myocardium may not be related to increased interstitial collagen [27].

The paper by Hoskins et al. is one of only two papers that have significantly investigated the contractile properties of myocytes from HCM patients with known sarcomeric mutations. A previous study by Van Dijk et al. compared myocyte force measurements in human samples from two MyBP-C truncation-mutation carriers (c.2373dupG, n=7 and c.2864_2865delCT, n=4) to myoctes from nonfailing donors (n=13) [28]. This group observed decreased maximal force of myocyte contraction (Table 1) and a non-significant trend of increased force in mutant fibers during passive measurements. To build on these findings, Hoskins et al. investigated several related aspects of myocyte performance besides passive force measurements: Ca^{2+} sensitivity of force, myocyte structure, collagen localization, contractile protein and phosphoprotein expression, maximum Ca^{2+} activated force, and cross-bridge cycling kinetics [7]. Hoskins et al. also found that skinned cardiac myocytes showed a large decrease in maximal force per cross-sectional area of the myocytes in samples from HCM hearts (irrespective of the mutation) relative to donor hearts (Table 1). This decreased maximum force is consistent with a transgenic mouse model of the thick filament protein myosin light chain 2 (MLC2) [29] (Table 1). This impaired maximal force production links systolic dysfunction to deficiency at the level of the sarcomere. The possibility of impaired force production due to myocyte structural deficiencies was examined by staining for myofibrillar components and videomicroscopy inspection [7]. While there was no difference in quantity of myofibrils there did seem to be structural implications which could be contributing to systolic impairment and warrant further investigation. Cross-bridge analysis revealed that a faster rate of cross-bridge detachment is a likely contributor to the force development deficiency [7]. The cross-bridge cycling kinetics during maximal Ca^{2+}-activation as indexed by k_{tr} (rate constant of force redevelopment) was about 10% faster in HCM myocytes [7].

Several functional studies using both human recombinant proteins in reconstituted porcine fibers and skinned fibers from animal models have indicated increased Ca^{2+} sensitivity of contraction and variable maximal force production (but mainly decreased) for many sarcomeric protein mutations were associated with HCM [30-31]. Similar increases in sensitivity to Ca^{2+} were observed in both recent human HCM studies [7,28] (Table 1). This increased Ca^{2+} sensitivity observed in HCM myocytes has also been found in myocytes from end-stage failing human myocardium (idiopathic dilated cardiomyopathy) [32]. To elucidate the source of the increase in Ca^{2+} sensitivity, Hoskins et al. determined the level of phosphorylation of both cTnI (at ser-23/24) and MyBP-C (at ser-282) [7]. Their results suggest that impairment of PKA regulated sarcomere phosphorylation may be at least partly responsible for the increased sensitivity to Ca^{2+}. These results were in part corroborated by van Dijk et al., who also found decreased phosphorylation of cTnI, but that group showed no difference in MyBP-C phosphorylation [28]. Reduced cTnI and MyBP-C phosphorylations have been observed in animal models of cardiac hypertrophy and failure and in humans with end-stage idiopathic and ischemic cardiomyopathy [33-34]. Furthermore, a HCM mutation in cTnI (R21C) has been shown to directly affect the rate of phosphorylation of ser-23/24 on cTnI [35]. The differences observed between the two human HCM studies may be due to differences in how MyBP-C phosphorylation is determined. To further help understand the role of phosphorylation and sarcomeric protein levels in cardiac dysfunction we have to be careful not to rely solely on antibodies. Studies have shown that some phosphoantibodies do not accurately report the phosphorylation levels [36]. Both van Dijk et al. and Hoskins et al. base a significant amount of their conclusions on the phosphorylation status of cTnI and MyBP-C. While the cTnI phosphoantibody has been extensively validated and was obtained from Cell Signaling

Technology for both studies, the anti phosphoMyBP-C was obtained from different non-commercial sources and has not been widely tested.

Van Dijk et al. showed that although the truncated MyBP-C that should be expressed by these mutant carriers were not detected by western blots, the total protein expression of MyBP-C was significantly reduced in hearts from mutant carriers by 33±5% [28]. They further observed reduced phosphorylation of desmin, cTnT, and MLC2 in *MYBPC3* mutant carriers when compared with donor samples [28]. Treatment with exogenous protein kinase A (PKA, which mimics β-adrenergic stimulation) eliminated the increase in Ca^{2+} sensitivity between the MyBP-C mutant and donor samples [28]. These results suggest that enhanced Ca^{2+} sensitivity in MyBP-C mutant carriers is due to hypophosphorylation of cTnI secondary to mutation-induced dysfunction [28]. The decrease in Ca^{2+} sensitivity to levels similar to donor myocytes observed in HCM myocytes after PKA treatment is interesting since it would be expected that the 33% decrease in MyBP-C (independent of phosphorylation) would result in increased Ca^{2+} sensitivity [37-38]. Removal of ~30% to 70% of MyBP-C from rat cardiomyocytes has previously been shown to increase Ca^{2+} sensitivity [37-38]. Hoskins et al. found that treatment of unrestrained skinned myocytes with PKA decreased myofibrillar Ca^{2+} sensitivity but only to levels in-between the original HCM myocyte and the donor Ca^{2+} sensitivity [7]. The increased Ca^{2+} sensitivity observed in HCM myocytes (relative to donor myocytes) after PKA treatment may be due to the influence of the primary mutation or changes in the non-PKA dependent phosphorylation of other proteins. In both van Dijk et al. and Hoskins et al. studies, PKA treatment of MyBP-C mutant samples did not correct the reduced maximal force [7,28].

As the number of investigated heart samples of known mutations increase, the unknown role of differences in medications, age, and gender on the biophysical parameters measured could be better determined. It is also important to determine if there are differences in the muscle parameters measured in tissue from LV versus the septum from the same heart. In both studies by Hoskins et al. and van Dijk et al. HCM tissue was obtained from septal tissue while donor tissue was obtained from the LV free wall [7] [28]. It is not known if the amount, isoform pattern and phosphorylation status of titin in different regions of the same heart are the same. Besides possible differences between the septum and the LV, another concern is the nonuniformity of the normal adult LV [39]. Stretch-dependent Ca^{2+} sensitization of skinned rat myocytes increases from sub-epicardium to sub-endocardium and correlates with an increase in passive tension. This increase in passive tension is not associated with changes in titin isoforms, changes in cTnI levels, changes in titin or cTnI phosphorylation levels but could be associated with phosphorylation of ventricular MLC2 isoform (VLC2b) in the sub-endocardium [39]. However, MLC-2 (RLC) phosphorylation level was not significantly different between human HCM and donor myocardium [7]. HCM is associated with marked regional differences in wall thickness and is characterized by regions of local fiber disarray which vary in size and are typically localized within hypertrophic regions [40-42]. In a study to investigate the regional and global LV function and wall thickness in patients with HCM using deformation imaging it was found that the heterogeneity of regional LV systolic function was partly attributable to the heterogeneity of LV hypertrophy. This suggests a link to impaired global LV relaxation in HCM [43]. Other studies also suggest a regional nature of myocardial involvement in HCM [42,44]. Hence, the location of the tissue studied in the heart may be more important than we currently realize.

The experiments by Hoskins et al. provide evidence against the passive properties of the sarcomere as a cause of diastolic dysfunction. These studies also suggest that while the mutations as well as phosphorylation of cTnI and MyBP-C are important in HCM, other unknown factors are also involved [7]. Understanding the molecular mechanism(s) behind the decreased maximal force production of HCM myofibrils will lead to a better understanding of the pathogenesis of systolic dysfunction. The data regarding the contractile protein

phosphorylation status as well as the impact of PKA strongly suggest higher activation of PKA in the donor samples than in HCM samples. Determination of PKA activity in HCM and donor samples will help to better define the role of PKA in HCM.

In summary, while the Hoskins et al. paper advances our knowledge about the passive properties of HCM myocytes [7], we are still in the infant stage of understanding the passive properties of HCM muscle. Although titin is a major contributor to passive tension, recent results suggest that it is unlikely that titin can account for all the features of the resting tension response in cardiac muscle. The observations by Hoskins et al. and van Dijk et al. suggest that HCM pathogenesis is associated with increased Ca^{2+} sensitivity (diastolic impairment) and decreased maximal force of contraction (systolic impairment). The increase in Ca^{2+} sensitivity is a sarcomeric contribution to diastolic dysfunction and the occurrence of these functional changes which were independent of the gene mutation suggests that they are secondary consequences of the underlying genetic differences between patients. As more laboratories gain access to human HCM hearts the dissection of the signaling pathways and components of active and passive tension will proceed at a significant rate.

Acknowledgments

The author's work is supported by grants from NIH HL096819 and the American Heart Association #0835335N.

References

[1]. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270–6. [PubMed: 17916581]

[2]. Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. Lancet 2004;363:1881–91. [PubMed: 15183628]

[3]. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002;287:1308–20. [PubMed: 11886323]

[4]. Maron BJ, Thompson PD, Puffer JC, McGrew CA, Strong WB, Douglas PS, et al. Cardiovascular preparticipation screening of competitive athletes. A statement for health professionals from the Sudden Death Committee (clinical cardiology) and Congenital Cardiac Defects Committee (cardiovascular disease in the young), American Heart Association. Circulation 1996;94:850–6. [PubMed: 8772711]

[5]. Xu Q, Dewey S, Nguyen S, Gomes AV. Malignant and benign mutations in familial cardiomyopathies: insights into mutations linked to complex cardiovascular phenotypes. J Mol Cell Cardiol 2010;48:899–909. [PubMed: 20298698]

[6]. Maron BJ, Sato N, Roberts WC, Edwards JE, Chandra RS. Quantitative analysis of cardiac muscle cell disorganization in the ventricular septum. Comparison of fetuses and infants with and without congenital heart disease and patients with hypertrophic cardiomyopathy. Circulation 1979;60:685–96. [PubMed: 572271]

[7]. Hoskins AC, Jacques A, Bardswell SC, McKenna W, Tsang V, Dos Remedios CG, et al. Normal passive viscoelasticity but abnormal myofibrillar force generation in human hypertrophic cardiomyopathy. J Mol Cell Cardiol. 2010 in press.

[8]. Noble MI. The diastolic viscous properties of cat papillary muscle. Circ Res 1977;40:288–92. [PubMed: 837476]

[9]. Chiu YL, Ballou EW, Ford LE. Internal viscoelastic loading in cat papillary muscle. Biophys J 1982;40:109–20. [PubMed: 7171707]

[10]. Chiu YL, Ballou EW, Ford LE. Velocity transients and viscoelastic resistance to active shortening in cat papillary muscle. Biophys J 1982;40:121–8. [PubMed: 7171708]

[11]. Minajeva A, Kulke M, Fernandez JM, Linke WA. Unfolding of titin domains explains the viscoelastic behavior of skeletal myofibrils. Biophys J 2001;80:1442–51. [PubMed: 11222304]

[12]. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation 2002;105:1387–93. [PubMed: 11901053]

[13]. Stuyvers BD, Miura M, ter Keurs HE. Dynamics of viscoelastic properties of rat cardiac sarcomeres during the diastolic interval: involvement of Ca2+ J Physiol 1997;502(Pt 3):661–77. [PubMed: 9279816]

[14]. LeWinter MM, Wu Y, Labeit S, Granzier H. Cardiac titin: structure, functions and role in disease. Clin Chim Acta 2007;375:1–9. [PubMed: 16904093]

[15]. Labeit S, Kolmerer B, Linke WA. The giant protein titin. Emerging roles in physiology and pathophysiology. Circ Res 1997;80:290–4. [PubMed: 9012751]

[16]. Borbely A, Falcao-Pires I, van Heerebeek L, Hamdani N, Edes I, Gavina C, et al. Hypophosphorylation of the Stiff N2B titin isoform raises cardiomyocyte resting tension in failing human myocardium. Circ Res 2009;104:780–6. [PubMed: 19179657]

[17]. Wang X, Li F, Campbell SE, Gerdes AM. Chronic pressure overload cardiac hypertrophy and failure in guinea pigs: II. Cytoskeletal remodeling. J Mol Cell Cardiol 1999;31:319–31. [PubMed: 10093045]

[18]. Hidalgo C, Hudson B, Bogomolovas J, Zhu Y, Anderson B, Greaser M, et al. PKC phosphorylation of titin's PEVK element: a novel and conserved pathway for modulating myocardial stiffness. Circ Res 2009;105:631–8. 17 p following 8. [PubMed: 19679839]

[19]. Kruger M, Linke WA. Titin-based mechanical signalling in normal and failing myocardium. J Mol Cell Cardiol 2009;46:490–8. [PubMed: 19639676]

[20]. Tagawa H, Wang N, Narishige T, Ingber DE, Zile MR, Cooper Gt. Cytoskeletal mechanics in pressure-overload cardiac hypertrophy. Circ Res 1997;80:281–9. [PubMed: 9012750]

[21]. Yamamoto S, Tsutsui H, Takahashi M, Ishibashi Y, Tagawa H, Imanaka-Yoshida K, et al. Role of microtubules in the viscoelastic properties of isolated cardiac muscle. J Mol Cell Cardiol 1998;30:1841–53. [PubMed: 9769239]

[22]. Fujita H, Labeit D, Gerull B, Labeit S, Granzier HL. Titin isoform-dependent effect of calcium on passive myocardial tension. Am J Physiol Heart Circ Physiol 2004;287:H2528–34. [PubMed: 15548726]

[23]. Wu Y, Tobias AH, Bell K, Barry W, Helmes M, Trombitas K, et al. Cellular and molecular mechanisms of systolic and diastolic dysfunction in an avian model of dilated cardiomyopathy. J Mol Cell Cardiol 2004;37:111–9. [PubMed: 15242741]

[24]. Thai HM, Van HT, Gaballa MA, Goldman S, Raya TE. Effects of AT1 receptor blockade after myocardial infarct on myocardial fibrosis, stiffness, and contractility. Am J Physiol 1999;276:H873–80. [PubMed: 10070070]

[25]. Lopez MA, Mayer U, Hwang W, Taylor T, Hashmi MA, Jannapureddy SR, et al. Force transmission, compliance, and viscoelasticity are altered in the alpha7-integrin-null mouse diaphragm. Am J Physiol Cell Physiol 2005;288:C282–9. [PubMed: 15643051]

[26]. Jannapureddy SR, Patel ND, Hwang W, Boriek AM. Genetic Models in Applied Physiology. Merosin deficiency leads to alterations in passive and active skeletal muscle mechanics. J Appl Physiol 2003;94:2524–33. discussion 3. [PubMed: 12736195]

[27]. Bronzwaer JG, Paulus WJ. Matrix, cytoskeleton, or myofilaments: which one to blame for diastolic left ventricular dysfunction? Prog Cardiovasc Dis 2005;47:276–84. [PubMed: 15991155]

[28]. van Dijk SJ, Dooijes D, dos Remedios C, Michels M, Lamers JM, Winegrad S, et al. Cardiac myosin-binding protein C mutations and hypertrophic cardiomyopathy: haploinsufficiency, deranged phosphorylation, and cardiomyocyte dysfunction. Circulation 2009;119:1473–83. [PubMed: 19273718]

[29]. Kerrick WG, Kazmierczak K, Xu Y, Wang Y, Szczesna-Cordary D. Malignant familial hypertrophic cardiomyopathy D166V mutation in the ventricular myosin regulatory light chain causes profound effects in skinned and intact papillary muscle fibers from transgenic mice. FASEB J 2009;23:855–65. [PubMed: 18987303]

[30]. Gomes AV, Potter JD. Molecular and cellular aspects of troponin cardiomyopathies. Ann N Y Acad Sci 2004;1015:214–24. [PubMed: 15201162]

[31]. Morimoto S. Sarcomeric proteins and inherited cardiomyopathies. Cardiovasc Res 2008;77:659–66. [PubMed: 18056765]

[32]. van der Velden J, Papp Z, Zaremba R, Boontje NM, de Jong JW, Owen VJ, et al. Increased Ca2+-sensitivity of the contractile apparatus in end-stage human heart failure results from altered phosphorylation of contractile proteins. Cardiovasc Res 2003;57:37–47. [PubMed: 12504812]

[33]. Hamdani N, Kooij V, van Dijk S, Merkus D, Paulus WJ, Remedios CD, et al. Sarcomeric dysfunction in heart failure. Cardiovasc Res 2008;77:649–58. [PubMed: 18055579]

[34]. El-Armouche A, Pohlmann L, Schlossarek S, Starbatty J, Yeh YH, Nattel S, et al. Decreased phosphorylation levels of cardiac myosin-binding protein-C in human and experimental heart failure. J Mol Cell Cardiol 2007;43:223–9. [PubMed: 17560599]

[35]. Gomes AV, Harada K, Potter JD. A mutation in the N-terminus of troponin I that is associated with hypertrophic cardiomyopathy affects the Ca(2+)-sensitivity, phosphorylation kinetics and proteolytic susceptibility of troponin. J Mol Cell Cardiol 2005;39:754–65. [PubMed: 16005017]

[36]. Huke S, Bers DM. Ryanodine receptor phosphorylation at Serine 2030, 2808 and 2814 in rat cardiomyocytes. Biochem Biophys Res Commun 2008;376:80–5. [PubMed: 18755143]

[37]. Hofmann PA, Hartzell HC, Moss RL. Alterations in Ca2+ sensitive tension due to partial extraction of C-protein from rat skinned cardiac myocytes and rabbit skeletal muscle fibers. J Gen Physiol 1991;97:1141–63. [PubMed: 1678777]

[38]. Kulikovskaya I, McClellan G, Levine R, Winegrad S. Effect of extraction of myosin binding protein C on contractility of rat heart. Am J Physiol Heart Circ Physiol 2003;285:H857–65. [PubMed: 12860568]

[39]. Cazorla O, Szilagyi S, Le Guennec JY, Vassort G, Lacampagne A. Transmural stretch-dependent regulation of contractile properties in rat heart and its alteration after myocardial infarction. FASEB J 2005;19:88–90. [PubMed: 15498894]

[40]. Maron BJ, Anan TJ, Roberts WC. Quantitative analysis of the distribution of cardiac muscle cell disorganization in the left ventricular wall of patients with hypertrophic cardiomyopathy. Circulation 1981;63:882–94. [PubMed: 7193536]

[41]. Sengupta PP, Mehta V, Arora R, Mohan JC, Khandheria BK. Quantification of regional nonuniformity and paradoxical intramural mechanics in hypertrophic cardiomyopathy by high frame rate ultrasound myocardial strain mapping. J Am Soc Echocardiogr 2005;18:737–42. [PubMed: 16003271]

[42]. Ganame J, Mertens L, Eidem BW, Claus P, D'Hooge J, Havemann LM, et al. Regional myocardial deformation in children with hypertrophic cardiomyopathy: morphological and clinical correlations. Eur Heart J 2007;28:2886–94. [PubMed: 17971400]

[43]. Kato TS, Izawa H, Komamura K, Noda A, Asano H, Nagata K, et al. Heterogeneity of regional systolic function detected by tissue Doppler imaging is linked to impaired global left ventricular relaxation in hypertrophic cardiomyopathy. Heart 2008;94:1302–6. [PubMed: 18198205]

[44]. Dong SJ, MacGregor JH, Crawley AP, McVeigh E, Belenkie I, Smith ER, et al. Left ventricular wall thickness and regional systolic function in patients with hypertrophic cardiomyopathy. A three-dimensional tagged magnetic resonance imaging study. Circulation 1994;90:1200–9. [PubMed: 8087929]

Table 1

Effect of HCM on Ca^{2+} sensitivity, Maximal Force and Myofibrillar protein Changes

Parameter	HCM	Donor (control) heart	Significance	Ref.
Ca^{2+} sensitivity of force development (pCa_{50})	6.4±0.05 (human) 5.62±0.04 (human) 5.30±0.04 (mouse MLC2 D166V Tg)	6.09±0.02 (human) 5.54±0.02 (human) 5.02±0.03 (mouse MLC2 D166V Tg)	P<0.01 P<0.05 P<0.01	[7] [28] [29]
Maximal Ca^{2+} activated force	14±1 kN/m^2(human) 20.2±2.7 kN/m^2(human) 61.9±3.0 kN/m^2 (mouse MLC2 D166V Tg)	23±3 kN/m^2 (human) 34.5±1.1 kN/m^2(human) 42.2±2.8 kN/m^2 (mouse MLC2 D166V Tg)	P<0.001 P<0.001 P<0.001	[7] [28] [29]
cTnI Ser23/24 phosphorylation (relative to donor heart)	Decreased Decreased by 84±5%	–	NL P<0.0001	[7] [28]
MyBPC Ser282 Phosphorylation (relative to donor heart)	Decreased No change*	–	NL NS	[7] [28]
Titin isoform ratio (relative to donor heart)	No change	–	NS	[7]
Titin protein level (relative to donor heart)	No change	–	NS	[7]
Resting SL	1.73±0.01μM	1.78±0.01μM	P<0.001	[7]
nH	3.73±0.56	2.95±0.12	NS	[7]

NS, not significant; NL, not listed; n_H, hill coefficient; SL, sarcomere length.

*Phosphorylation of MyBP-C normalized to its own protein level was similar between MyBP-C mutant and donor myocardium but phosphorylation of MyBP-C normalized to α-actinin was reduced by 47±7% in the MyBP-C mutant compared with donor myocardium (P<0.0001).