Chapter 4

Positive correlation between contractile dysfunction of the sarcomere and regional systolic strain in hypertrophic cardiomyopathy

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Abstract

Aims

Recent studies showed reduced maximal force generating capacity of cardiomyocytes from hypertrophic cardiomyopathy (HCM) patients with normal systolic function. In the present study we investigated if reduced maximal force generating capacity at cellular level is associated with local systolic dysfunction in HCM patients.

Methods and results

A total of 46 HCM patients (age 51 ±10 years, 64% male) underwent pre-operative transthoracic echocardiography, and additionally, segmental systolic strain and strain-rate were measured from apical 4-, 2-, and 3-chamber views. Echocardiographic data were compared with age- and sex-matched controls. Maximal force development was measured in membrane-permeabilized cardiomyocytes isolated from tissue obtained via myectomy surgery from 30 of these patients. Non-failing donors (N=10) served as control group. Ejection fraction of HCM patients was in the normal range. Peak systolic strain and strain rate were markedly lower in the septal wall of HCM patients compared with controls. A significantly lower maximal force generating capacity was found in cells from the HCM patients compared with non-failing donor hearts and correlated with the reduction in systolic strain. In addition, systolic strain correlated negatively with septal wall thickness.

Conclusion

Systolic function in HCM patients is reduced at a regional level despite normal ejection fraction. Impairment of regional systolic function, demonstrated by strain and strain rate analysis, may be explained by a reduction in maximal force generating capacity at the level of the sarcomeres. This could result in the development of asymmetric hypertrophy.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most prevalent inheritable myocardial disease, and is defined by the presence of left ventricular hypertrophy (LVH) of ≥15 mm, in absence of abnormal loading conditions.[1] Genotyping studies have identified a pathogenic mutation in ± 70% of all patients with HCM.[2,3] In total, >1300 mutations have been found in 13 genes, mostly coding for the sarcomeric proteins.[2] There is both genetic and clinical heterogeneity in HCM.[4] Even when patients harbor the same mutation, the phenotype varies widely. The complex genotype-phenotype relationship remains unclear.

Recent studies[5–8] showed that, regardless of the disease-causing mutation, the force generating capacity of the cardiomyocyte was reduced. Interestingly, this reduced force generating capacity was found in patients with normal global systolic function.[7–9] On the other hand, there is increasing evidence that regional myocardial dysfunction is present in HCM patients based on systolic strain analysis.[10–13] However it is unclear if there is a correlation between this regional myocardial dysfunction and the reduced force generating capacity at sarcomere level of HCM cardiomyocytes.

In the present study we therefore investigated whether reduced maximal force generating capacity at single cardiomyocyte level is associated with regional systolic dysfunction in HCM patients with and without sarcomeric gene mutations. *In vitro* force measurements were performed in single cardiomyocytes isolated from septal tissue obtained during myectomy surgery from HCM patients. These measurements were combined with the *in vivo* systolic function of these patients which was assessed before surgery.

Methods

Study design and patient population

The initial study population consisted of 46 HCM patients who underwent surgical myectomy at the Thorax center, Erasmus Medical Center, Rotterdam, The Netherlands. Each patient had an established diagnosis of HCM, based on unexplained LVH of ≥15 mm, assessed by echocardiography. Patients with HCM linked to Noonan's syndrome, Fabry's disease, mitochondrial disease or congenital heart defects were excluded. All patients were accepted for surgical myectomy or alcohol septal ablation (ASA) based on the presence of symptoms despite maximal medical therapy and LVOT (left ventricular outflow tract) gradients > 50 mmHg. In these patients tissue from the interventricular (IVS) septum was obtained directly during surgery, or a IVS biopsy prior to the ablation procedure.

Genetic testing was performed in all patients; the following genes were screened: cardiac myosin binding protein C (*MYBPC3*), β-cardiac myosin heavy chain (*MYH7*), myosin regulatory light chain (*MYL2*), cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), cardiac troponin C (*TNNC1*), α-actin (*ACTC1*), and α-tropomyosin (*TPM1*). Next-generation sequencing was not systematically performed in all patients. Patients were divided in 2 groups: sarcomere mutation-positive HCM (HCM_{MUT}) and sarcomere mutation-negative HCM (HCM_{SMN}). Echocardiographic control values were obtained from age- and gender matched healthy subjects. Donors (N=10, age 36±5, 80% male) with no history of cardiac abnormalities, normal ECG and normal ventricular function on echocardiography within 24 hours of heart transplantation served as controls for the myocardial samples.

The study conforms to the principles of the Helsinki Declaration. Informed consent of each patient was obtained in addition to local institutional review board approval.

Myocyte measurements

The septal tissue obtained during myectomy surgery was used for single cardiomyocyte force measurements using a previously described method.[7,14] In short, single cardiomyocytes were mechanically isolated and treated with 0.5% Triton X-100 to permeabilize the membranes providing us with the opportunity to asses force generating capacity of the sarcomeres without interference of Ca^{2+}-handling proteins. A single cardiomyocyte was mounted between a force transducer and a piezoelectric motor and stretched to a sarcomere length of 2.2 µm (Figure 1A). In an activating solution with a [Ca^{2+}] of 31.6 µmol/L (pCa 4.5), the cardiomyocyte started to generate force. After reaching the steady state force level the cardiomyocyte was mechanically shortened by 30% to determine total force development (F_{total}). Subsequently, the cardiomyocyte was transferred to relaxing solution with a [Ca^{2+}] of 10^{-6} µmol/L (pCa 9.0) to measure passive force development (F_{pas}). Maximal force generating capacity (F_{max}) was calculated by subtracting F_{pas} from F_{total}. Force values were normalized to cross-sectional area (CSA), to obtain the tension, of the preparations calculated on the basis of cardiomyocyte width and depth determined in the experimental set-ups (i.e. CSA = width x depth x π/4). Force signals were analyzed using Labview version 9.0 (National Instruments Corporation, Austin, TX).

Echocardiography

All patients underwent comprehensive echocardiography using commercially available ultrasound machines (Philips Healthcare, Eindhoven, The Netherlands en Siemens Healthcare, Erlangen, Germany). All echocardiographic analyses were blinded from clinical characteristics. The following data were acquired: end-diastolic IVS and posterior wall thickness, end-diastolic and end-systolic diameters, left atrial dimensions, and LV ejection fraction, all according to current guidelines.[15] The severity of the mitral valve regurgitation (MR) was graded on a 0 to 4 scale by color flow Doppler echocardiography.[16] The severity of the systolic anterior motion (SAM) of the anterior mitral valve leaflet was determined from the 2D images and was graded on a scale from 0 to 3 depending on the mitral-septal distance (grade 0 indicating no SAM and grade 3 indicating prolonged contact between mitral valve and septum).[17] Peak LVOT gradient was estimated with continuous wave Doppler echocardiography by the modified Bernoulli equation (P = 4v2), where P is the pressure gradient and v is Doppler-determined blood velocity.

Speckle tracking echocardiography (STE) was performed as previously described,[12,18] to measure peak systolic longitudinal strain, peak systolic longitudinal strain rate (SR), and early diastolic SR in apical 4-chamber, 2-chamber and 3-chamber views (TomTEC Imaging Systems, Unterschleissheim, Germany). After manual tracing of the endocardial borders at end-systole, tracking was done automatically by the software. When necessary, manual readjustment of the tracking was performed. For each segment longitudinal strain and SR curves were generated and peak values were documented.

Statistical Analysis

Regarding the clinical data SPSS version 20 (IBM, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) were used for statistical analyses. Categorical variables were summarized as percentages. Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data are expressed as median (interquartile range). To compare continuous variables (such as ejection fraction, LV wall thickness, left ventricular outflow tract gradient, segmental systolic strain values) Student t test, ANOVA-tests or Mann-Whitney U-test were used, and to compare categorical variables the χ^2-test was used. Correlation was determined using Spearman's ρ.

Regarding the cardiomyocyte force measurements data analysis and statistics were performed using Prism version 4.0 (Graphpad Software, Inc., La Jolla, CA). A One-way ANOVA was used to gain insight in the differences in force development of the cardiomyocytes among the patient groups (HCM_{MUT}, HCM_{SMN} and Donor). All tests were 2-sided and a *P*-value <0.05 was considered statistically significant.

Results

Clinical characteristics

Cardiomyocyte force measurements could not be performed in 13 of 46 patients due to lack of tissue availability and/or genetic data, and these were excluded from further analysis. The clinical and echocardiographic characteristics of the remaining 33 patients (51 ± 13 years old, 12 (36%) female) are listed in Table 1. Myectomy surgery was performed in 27 patients (81%), and alcohol septal ablation (ASA) in 6 (18%). In 21 patients a pathogenic mutation was found: *MYBPC3* in 15 (71%), *MYH7* in 3 (14%), *TNNI3* in 2 (10%) and *TPM1* in 1 patient (5%). The *MYBPC3* mutations are all truncating mutations and the mutations in the other genes are missense mutations. In 12 patients genetic screening revealed no pathogenic mutation. These patients were older (57 ± 10 years) than patients with a mutation (48 ± 15, *P*=0.05). Other clinical and echocardiographic characteristics did not differ significantly between the two groups: septal wall thickness was 23±5 mm in HCM_{MUT} and 21±3 in HCM_{SMN} (*P*=0.2); maximal LVOT gradient (either resting or after provocation) was 83±25 mmHg in HCM_{MUT} and 96±33 in HCM_{SMN} (*P*=0.7); and LVEF was 63±6 % in HCM_{MUT} and 65±8 % in HCM_{SMN} (*P*=0.5) (Figure 2A).

Table 1. Clinical and echocardiographic characteristics of 33 HCM patients at the time of surgery.

	Mutation	Age	Sex	NYHA	LVWT	LVOTG	LVEF
Truncating mutations							
MYBPC3							
1	c.2373dupG	69	M	3	19	60	61
2	c.2373dupG	32	M	2	23	85	69
3	c.2373dupG	60	M	3	26	77	70
4	c.2827C>T	24	F	3	24	80	58
5	c.2827C>T	34	M	3	39	60	67
6	c.2827C>T	50	M	3	20	80	56
7	c.2864_2865delCT	62	F	3	19	110	61
8	c.927-2A>G	37	M	3	20	60	66
9	c.927-2A>G	58	F	3	25	75	63
10	c.927-2A>G	21	M	3	32	70	49
11	c.1790G>A	47	F	2	20	85	55
12	c.2783C>T	71	M	3	22	75	66
13	c.3029delA	45	F	3	23	125	56
14	c.3407_3409del	55	M	3	19	95	68
15	c.772G>A	36	M	2	30	10	63
Mean±SD		47±16			24±6	76±26	62±6
Missense mutations							
MYH7							
1	c.1291G>C	35	M	3	20	93	65
2	c.1816G>A	48	F	3	25	80	71
3	c.4130C>T	43	M	3	24	120	53
TNNI3							
1	c.433C>T	46	M	2	20	100	74
2	c.433C>T	66	M	2	20	100	65

TPM1							
1	c.850A>T	65	M	3	20	100	60
Mean±SD		51±12			22±2	99±13	65±8
HCM_{smn}							
1	-	74	F	3	21	137	61
2	-	58	M	3	26	115	51
3	-	73	F	3	24	90	62
4	-	49	M	3	18	60	63
5	-	65	F	2	17	85	78
6	-	52	M	3	22	170	72
7	-	44	M	2	20	85	64
8	-	60	M	2	20	100	64
9	-	46	F	3	20	90	66
10	-	56	F	2	15	75	76
11	-	52	M	3	17	45	55
12	-	60	F	2	17	100	59
		57±10			20±3	96±33	64±8

LVEF: left ventricular ejection fraction in %; LVOTG: maximal left ventricular outflow tract gradient in mmHgt; LVWT: maximal left ventricular wall thickness in mm; NYHA: New York Heart Association functional class.

Force measurements

Single cardiomyocyte force measurements were performed at sarcomere length of 2.2 µm to gain insight in F_{max}. Figure 1A shows a representative image of a single cardiomyocyte mounted in the experimental set-up. An example force recording is provided in Figure 1B of a HCM_{MUT} cardiomyocyte. Tension was significantly lower (P=0.002) in the HCM_{MUT} compared to donor cardiomyocytes (Figure 2D).

There was no significant difference in tension between cardiomyocytes with truncating (*MYBPC3*) and missense (*MYH7*, *TNNI3* and *TPM1*) mutations. However, cardiomyocytes with missense mutations showed clearly a lower tension compared with cardiomyocytes from HCM_{SMN} patients (Table 2).

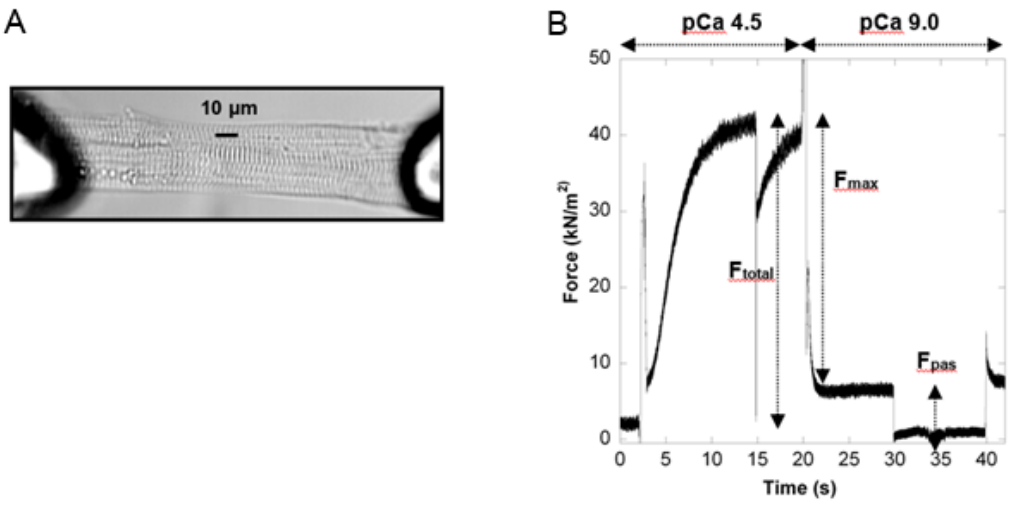

Figure 1. Functional measurements of single cardiomyocytes. A. Single cardiomyocyte at a sarcomere length of 2.2 µm in the experimental setup. **B.** Force recording of a cardiomyocyte.

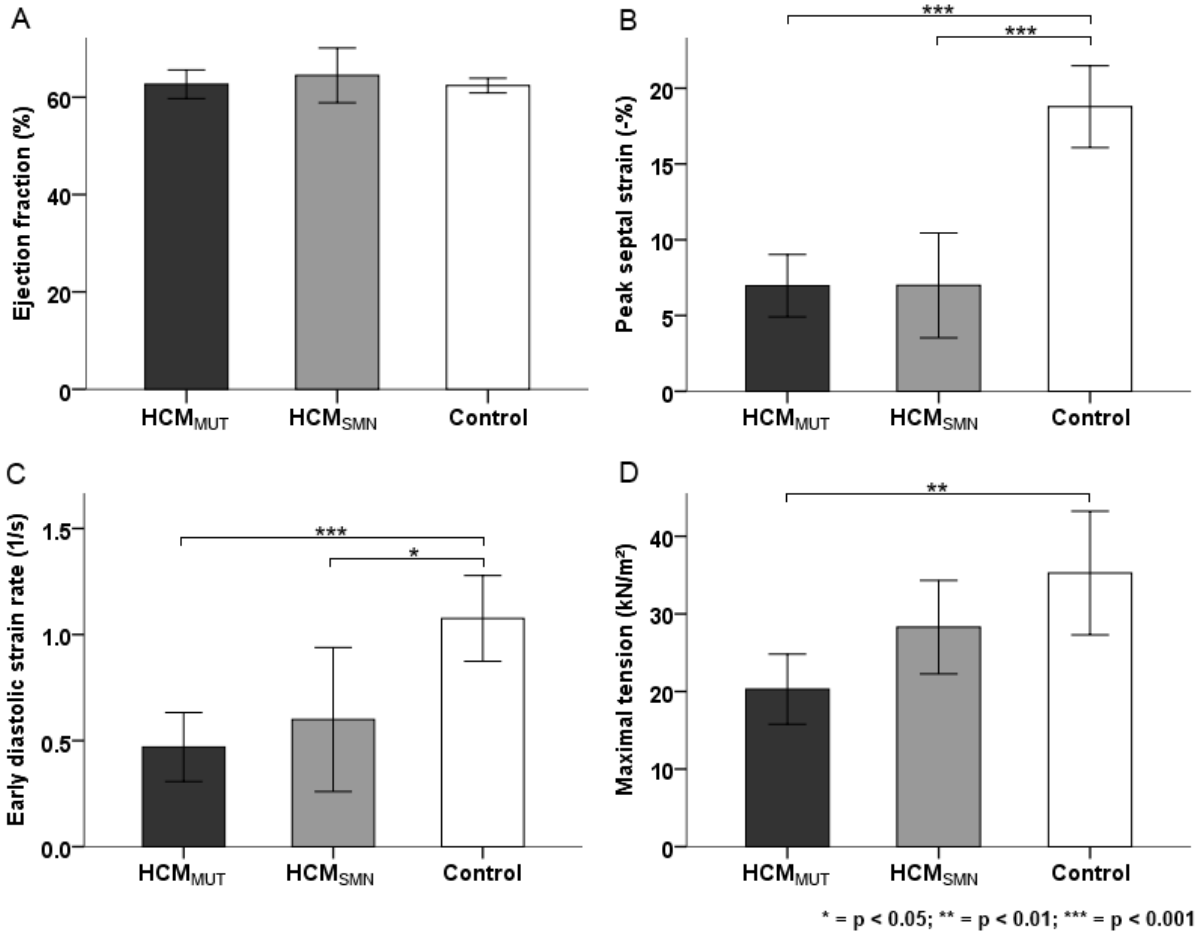

Figure 2. *In vivo* and *in vitro* contractile dysfunction. Despite a normal ejection fraction **A.** in the 3 groups (Control, HCM_{MUT}, HCM_{SMN}) there is reduced peak systolic septal strain **B.,** reduced early diastolic septal strain rate **C.**, and reduced cardiomyocyte maximal tension development at 2.2 µm sarcomere length **D.** in HCM patients.

Table 2. Myocardial and cardiac mechanics of the basal septum in HCM patients with truncating and missense mutations.

	HCM_{MYBPC3}		**$HCM_{Missense}$**		**HCM_{SMN}**	
		P vs. HCM_{SMN}		*P* vs. *MYBPC3*		*P* vs. missense
Tension at 2.2µm (kN/m²)	22.9 ± 10.4	0.4	13.7 ± 4.1	0.1	28.3 ± 9.5	**0.01**
Septal systolic strain, (%)	-7.5 ± 3.8	1.0	-5.7 ± 5.4	1.0	-7.0 ± 4.8	1.0
Septal systolic SR (1/s)	-0.60 ± 0.29	1.0	-0.73 ± 1.01	1.0	-0.62 ± 0.39	1.0
Septal early diastolic SR (1/s)	0.56 ± 0.30	1.0	0.29 ± 0.32	0.5	0.60 ± 0.48	0.4

SR: longitudinal strain rate. *P* values calculated with One-way ANOVA.

Regional function and wall thickness

Ejection fraction was in the normal range in both the HCM_{MUT} (63 ± 6%) and HCM_{SMN} patients (65 ± 8%), and was similar to controls (63 ± 4%, *P*=1.0 and *P*=0.9 respectively, Figure 2A). An overview of segmental strain per group is shown in Figure 3. Global strain was reduced in both HCM_{MUT} (-16.0 ± 3.2%) and HCM_{SMN} (-15.1 ± 3.1%) compared with controls (-21.0 ± 3.2%, p<0.001 and *P*<0.001 respectively). The biggest reduction in regional strain, compared with controls, was at basal segments of the anterior and inferior septum, both in HCM_{MUT} and HCM_{SMN} patients (Table 3 and Figures 2&3). Decrease in septal strain was similar in HCM_{MUT} and HCM_{SMN}, and no differences were found between truncating and missense mutations (Tables 2&3). Apical levels of strain were normal or slightly increased compared with controls. Peak septal systolic SR and early diastolic SR were clearly decreased compared with controls (Figure 2C), but no difference was found between truncating and missense mutations (Tables 2&3)

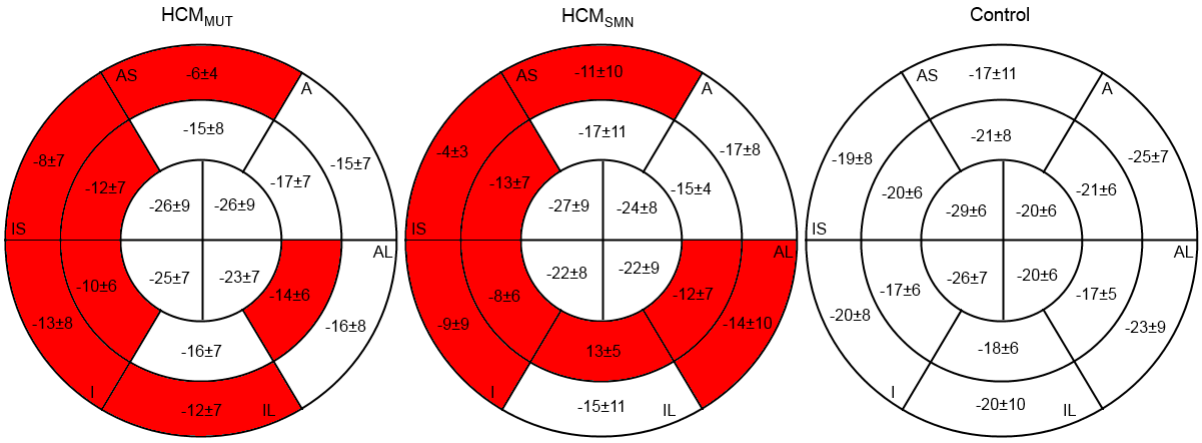

Figure 3. Peak systolic longitudinal strain per segment in HCM_{MUT} group, HCM_{SMN} group, and control group. A: anterior; AL: anterolateral; AS: anteroseptal; I: inferior; IL: inferolateral; IS: inferoseptal. Red segments have peak systolic strain < -15%.

Table 3. Myocardial and cardiac mechanics of the basal septum in HCM_{MUT} patients, HCM_{SMN} patients and healthy controls.

	HCM_{MUT}		HCM_{SMN}		Control	
		P vs. *Control*		*P* vs. HCM_{MUT}		*P* vs. HCM_{SMN}
F_{max} at 2.2µm (kN/m^2)	20.3 ± 9.9	**0.002**	28.3 ± 9.5	0.09	35.3 ± 10.4	0.4
Septal systolic strain (%)	-7.0 ± 4.3	**<0.001**	-7.0 ± 4.8	1.0	-18.8 ± 7.4	**<0.001**
Septal systolic SR (1/s)	-0.64 ± 0.58	**0.007**	-0.62 ± 0.39	1.0	-1.19 ± 0.64	**0.03**
Septal early diastolic SR (1/s)	0.47 ± 0.33	**<0.001**	0.60 ± 0.48	1.0	1.08 ± 0.54	**0.02**

SR: longitudinal strain rate. *P*-values calculated with One-way ANOVA

Although the maximal wall thickness was similar between the groups (see above), basal anterior wall thickness was increased in HCM_{MUT} patients (22 ± 5 mm) compared with HCM_{SMN} patients (18 ± 6 mm; *P*=0.02). Hypertrophy was most pronounced in the septal wall, with exception of the apical area (Figure 4).

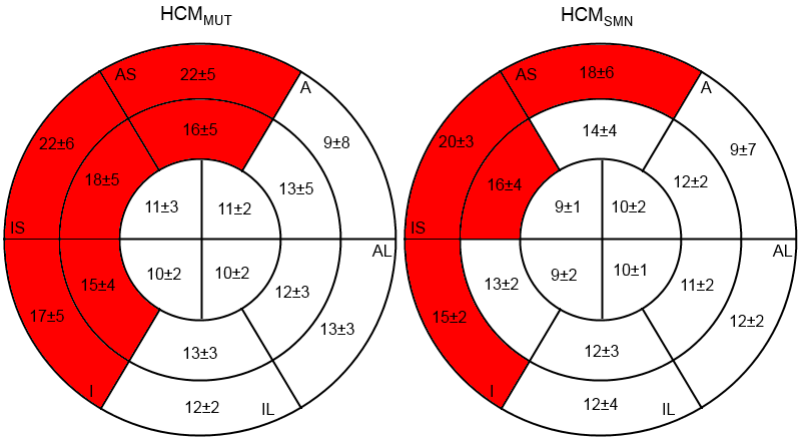

Figure 4. Maximal wall thickness per segment in HCM_{MUT} and HCM_{SMN} groups. A: anterior; AL: anterolateral; AS: anteroseptal; I: inferior; IL: inferolateral; IS: inferoseptal. Red segments have wall thickness ≥ 15 mm.

Basal septal peak longitudinal strain was plotted as a function of F_{max} (Figure 5A) and septal wall thickness (Figure 5B) revealing a modest correlation with maximal force development (Spearman's ρ 0.46, *P*= 0.01) and a negative correlation with hypertrophy (Spearman's ρ -0.38; *P*= 0.04).

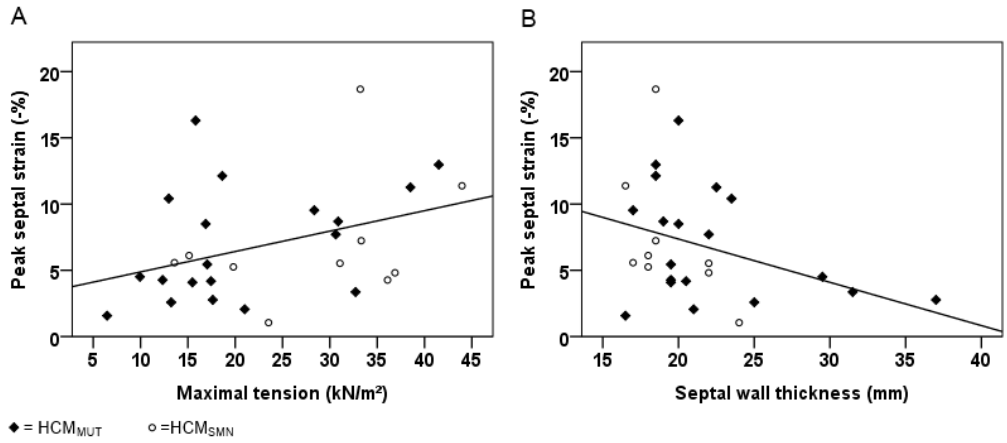

Figure 5. Correlations. A. Correlation between septal peak longitudinal strain and maximal tension development at 2.2µm sarcomere length. **B.** Septal peak longitudinal strain and maximal segmental wall thickness.

Discussion

This is the first study comparing myocardial function on regional with cellular level. The most important finding of this study is that there is an correlation between the reduced maximal force development of the cardiomyocyte and impaired regional systolic function, especially of the septal wall, in patients with HCM.

Reduced force generating capacity at single cardiomyocyte level

A lower maximal force generating capacity was measured in HCM cardiomyocytes compared with non-failing donor cardiomyocytes (Figure 2C), and this was in line with previous studies.[5-8] This drop in cellular performance can be explained by a combination of structural cellular remodeling and mutation-induced intrinsic sarcomeric defects.

Cellular remodeling exists of cardiomyocyte hypertrophy and a reduction in myofibrillar density. Previously we revealed a negative correlation between myofibrillar density and cardiomyocyte area. Interestingly, cellular remodeling and dysfunction was more evident in patients with a sarcomeric gene mutation compared to HCM patients without an identified mutation, suggesting a clear difference in genotype-positive and genotype-negative HCM disease.[7] In addition, in the present study maximal force generating capacity was less decreased in HCM_{SMN} patients (Figure 2C).

Depending on the type of mutation reduced force generating capacity is caused by the mutant protein itself or results from cellular remodeling. Most included patients harbored a truncating mutation in *MYBPC3* (N=15) and the remainder carry missense mutations in *MYH7*, *TNNI3* and *TPM1* (N=6). Truncated proteins are not incorporated in the sarcomere, hence only the healthy protein is incorporated[5,19,20], albeit to a lesser extent. Missense mutations, however, potentially lead to poison peptides incorporated in the sarcomere.[21,22] Previously, when maximal tension was corrected for myofibrillar density[7], maximal tension was normalized to donor level in the absence of a mutation (HCM_{SMN}) or in the presence of a truncating mutation in *MYBPC3* or missense mutation in *TNNI3*. This was not the case when a missense mutation in *MYH7* or *TPM1* was present. Indeed, the present results confirm this previous observation as cardiomyocytes harboring missense mutations revealed even a lower tension compared with cardiomyocytes with *MYBPC3* mutations and reached significance compared with HCM_{SMN} cardiomyocytes (Table 2). This suggests a clear mutation-induced sarcomere defect leading to the reduction in tension in addition to cellular remodeling.

Regional systolic impairment and hypertrophy

Leaving the specific type of sarcomeric gene mutation out of the equation, the observed reduction in maximal force generating capacity is typical for HCM, as in patients with idiopathic dilated cardiomyopathy and ischemic cardiomyopathy this reduction in force is not present.[23] This suggests the possibility that underlying HCM mutations trigger a common pathway of impaired contraction of the cardiomyocytes, and that this hypocontractility leads to regional dysfunction and asymmetrical hypertrophy. Classic echocardiographic assessment of HCM patients usually describes a hypercontractile heart, with normal or

increased ejection fraction. However using deformation and strain analysis, it has become clear that there is regional systolic and diastolic dysfunction in HCM, especially in the basal septal wall.[11,13] Indeed, in the present study the lower force generating capacity of the cardiomyocytes in HCM patients is accompanied with regional systolic and diastolic dysfunction, demonstrated by strain and SR analysis, and regional hypertrophy (Figures 3&4, Table 3).

Impaired cardiac mechanics appear to be an expression of the HCM phenotype: apical and classic HCM have different strain patterns.[24] Recently, it was demonstrated that strain was similarly reduced in HCM patients with and without pathogenic mutations.[11] In our study likewise no significant differences in regional strain values were found between HCM_{MUT} and HCM_{SMN} patients (Figure 3 and Table 3). On the other hand, there was a relationship between wall thickness and impaired regional function.

The reduced strain and SR (both systolic and diastolic) can be ascribed to several aspects of the myocardium of HCM patients. First, the presence of fibrosis is associated with reduced strain. Using cardiac magnetic resonance (CMR) imaging, Popovic *et al.*[25] demonstrated that the presence of myocardial fibrosis on CMR was correlated with reduced systolic strain, and Kobayashi *et al.*[13] showed that both systolic and diastolic septal SR were more decreased if more interstitial fibrosis was present on a cellular level. But both studies also demonstrated that the presence of hypertrophy was an independent predictor of reduced strain and strain rate. This is also confirmed by the negative correlation found in this study between wall thickness and septal strain (Figure 5B).

Not only in patients with HCM is strain reduced. In patients with LVH caused by severe valvular aortic stenosis, longitudinal systolic strain was also reduced. However, after aortic valve replacement, strain would improve to normal values.[26–28] Strain analysis after surgical myectomy[29] and septal ablation[30] showed that despite improved NYHA class and reduced LVOT gradient and septal wall thickness, longitudinal strain remained impaired. This suggests that the impaired cardiac mechanics in HCM also appear to be related to the intrinsic myocardial dysfunction, and not only to the loading conditions and LVH.

Disease progression in HCM.

The mechanisms involved in the progression from preclinical HCM to the classic phenotype are largely unknown[31], and it has been suggested that diastolic dysfunction precedes the development of hypertrophy. The findings in this study combined with other literature may hint at an alternative hypothesis for the development of HCM which is pointed out below.

Patients with preclinical HCM appear to have a normal heart, but at a certain point remodeling of the cardiomyocyte starts. Several intrinsic and external factors could lead to cardiomyocyte remodeling: impaired contractility (related to structural cellular remodeling and mutation-induced intrinsic sarcomeric defects, see above), microvascular dysfunction and energy depletion. Coronary microvascular dysfunction may lead to local ischemia, replacement fibrosis[31], and together with increased energetic costs of contraction[32], possibly increased oxidative stress of the cardiomyocyte. In combination with a reduction in myofilament protein phosphorylation and higher Ca^{2+}-sensitivity, contractility might be further hampered leading to impairment of cardiomyocyte relaxation.[5] The remodeling of the hypocontractile cardiomyocyte may then lead to compensatory hypertrophy of the

myocardium - initially locally - and more regional as disease progresses. This might present itself as initial diastolic dysfunction and later also clear (regional) systolic impairment. Further studies that focus on the development of hypertrophy and the digression of systolic and diastolic function during follow-up of preclinical HCM patients could provide further support for this hypothesis.

Clinical limitations and implications

The number of included patients with both strain and SR analysis echocardiography and myocardial tissue analysis was relatively small. In addition, the study was performed in a referral center for patients with HCM, therefore selection and referral bias may have influenced the study results. All patients included were severely symptomatic due to important LVOT obstruction requiring surgical septal reduction therapy. This is only a subset of the disease-spectrum of HCM. Nevertheless, to improve our understanding of the development of HCM, a longitudinal prospective study assessing strain and SR in a large cohort of HCM mutation carriers and overt HCM patients would be of interest to investigate the development of the HCM phenotype over time. In addition, further research is required to reveal possible therapy targets at cellular contractile level to possibly delay or even reverse the progression from pre-hypertrophic HCM to manifest HCM disease.

In conclusion, despite the preserved ejection fraction of the HCM patients, regional systolic strain and strain rate was reduced. This correlated with the reduction in maximal force generating capacity at the cellular level and with septal wall thickness. Therefore, contractile dysfunction at the sarcomere might lead to regional systolic dysfunction and eventually asymmetrical hypertrophy.

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Disclosures

None**.**

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