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ORIGINAL PAPER

Could two-dimensional radial strain be considered as a novel tool to identify pre-clinical hypertrophic cardiomyopathy mutation carriers?

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Abstract
Treatment of overt form of hypertrophic cardiomyopathy (HCM) is often unsuccessful. Efforts are focused on a possible early identification in order to prevent or delaying the development of hypertrophy. Our aim was to find an echocardiographic marker able to distinguish mutation carriers without left ventricular hypertrophy (LVH) from healthy subjects. We evaluated 28 patients, members of eight families. Three types of mutation were recognized: MYBPC3 (five families), MYH7 (two families) and TNNT2 (one family). According to genetic (G) and phenotypic (Ph) features, patients were divided in three groups: Group A (10 patients), mutation carriers with LVH (G+/Ph+); Group B (9 patients), mutation carriers without LVH (G+/Ph−); Group C (9 patients), healthy subjects (G−/Ph−). Echocardiography examination was performed acquiring standard 2D, DTI and 2D-strain imaging. Global longitudinal strain (GLS) and global radial strain (GRS) at basal and mid-level were measured. GRS was significantly different between group B and C at basal level (32.18% ± 9.6 vs. 44.59% ± 12.67 respectively; p-value < 0.0001). In basal posterior and basal inferior segments this difference was particularly evident. ROC curves showed for both the involved segments good AUCs (0.931 and 0.861 for basal posterior and inferior GRS respectively) with the best predictive cut-off for basal posterior GRS at 43.65%, while it was 38.4% for basal inferior GRS. Conversely, GLS values were similar in the three group. 2D longitudinal strain is a valid technique to study HCM. Radial strain and particularly basal posterior and inferior segmental reduction could be able to identify mutation carriers in a pre-clinical phase of disease.

Keywords Hypertrophic cardiomyopathy · Sarcomeric mutations · Strain · Echocardiography

Introduction

Hypertrophic cardiomyopathy (HCM) is an inherited disease, caused by mutations in sarcomeric genes, characterized by an unexplained hypertrophy in absence of condition able to cause a pathological increase of the left ventricular wall thickness.

Many years have passed since Donald Teare published the first modern description of HCM defining the disease as a"muscular hamartoma… with a picture of bizarre arrangement of muscle bundles" [1] and even since genetic studies have described the molecular basis of this disease. Notwithstanding, therapy of overt HCM is often unsuccessful, trying just to alleviate symptoms and to prevent sudden cardiac death [2]. In this context, the early identification of phenotype-negative mutation carriers in the pre-clinical stage of disease is therefore, of primary importance, in order to begin, at the earliest, the therapy capable to prevent or to delay the increase of wall thickness, and to plan a closer follow-up. In fact, some drugs have been already tested with this purpose [3]. Genetic tests commercially available permit to diagnose mutations in

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about 70% of patients affected by HCM; the remaining 30% is lacking genetic diagnosis with an obvious negative effect in the pre-clinical stage [4]. Further and alternative diagnostic examination have a growing interest in the challenging identification of the healthy mutation carriers. For example, cardiac magnetic resonance, shows "crypts", described as a deep disruption of normal compacted profile of myocardium in the pre-clinical phase of disease [5, 6]. Likewise, echocardiography examination recognizes some typical features in free-hypertrophy mutation carriers such as mitral leaflets elongation, papillary muscles malposition and their direct insertion into anterior mitral leaflet [7]. Furthermore Global Longitudinal Strain (GLS), a recent echocardiography technique able to detect systolic dysfunction prior to the alteration of ejection [8], has been proposed as a tool able to identify mutation carriers without Left Ventricular Hypertrophy (LVH) particulalry when we consider segmental alterations [9–11]. Fewer data are present for Global Radial Strain that has also been found to be impaired in overt HCM disease [10–13]. Finally, other two points need to be mentioned: (1) more than global longitudinal strain, segmental one [9] and (2) mechanical dispersion, i.e. a strain sign of heterogeneous myocardial contraction due to disarray and fibrosis, seem to be more important to precociously identify mutation carriers [14].

The aim of our study is to verify the role of echocardiography as a possible tool for an earlier identification of pre-clinical mutation carriers, particularly referring to 2D longitudinal and radial strain. To do this we evaluated 28 subjects, members of eight families, dividing them accordingly to genetic (G) and phenotypic (Ph) features into three groups: Group A (10 patients), mutation carriers with LVH (G+/Ph+); Group B (9 patients), mutation carriers without LVH (G+/Ph−); Group C (9 patients), healthy subjects (G−/Ph−).

Methods

Study population

This study recruited 28 subjects (age 16–72 years), members of 8 families, referred for HCM at Niguarda Hospital. HCM was defined, according to 2014 ESC Guidelines, as the presence of a wall thickness ≥ 15 mm in one or more left ventricular myocardial segments that is not explained solely by loading conditions [15].

The presence of condition contributing to hypertrophy (uncontrolled hypertension, moderate or severe aortic stenosis), previous septal alcoholization or myectomy, arrhythmia, ischemic cardiomyopathy and clinical instability represented exclusion criteria.

All individuals were genotyped and mutations were recognized in three sarcomeric genes: MYBPC3 (five families), MYH7 (two families) and TNTT2 (one family).

According to genetic (G) and phenotypic (Ph) features patients were divided in three groups: Group A (n = 10, age: 48 ± 18 years; 6 male), mutation carriers with left ventricular hypertrophy (G+/Ph+); Group B (n = 9, age: 34 ± 12 years; 3 male), mutation carriers without LVH (G+/Ph−); Group C (n = 9, age: 30 ± 11 years; 5 male), healthy control subjects (G−/Ph−).

The local ethical committee approved the study and all patients gave their consent.

Abnormal electrocardiographic (ECG) findings were considered as the presence of Q wave, T wave inversion and/or ST-segment depression. Body surface area (m^2) through the DuBois formula: 0.007184 * (Altezza (cm)$^{0.725}$ * Peso (kg)$^{0.425}$).

Echocardiographic protocol

Standard 2D echocardiographic examination and Doppler Tissue Image (DTI) were performed in all patients using a Vivid E9 ultrasound System (GE Medical System, Horten, Norway). We measured left ventricular volumes, ejection fraction, and left atrial volumes using Simpson biplane method, indexing left atrial volume by body surface area [16]. We also measured diastolic function parameters accordingly to current guidelines [17]. Myocardial systolic and diastolic velocities were measured at lateral and septal level of mitral annulus in the apical 4-chamber view by DTI (Sa and Ea). The mean value (lateral and septal) was calculated for systolic and diastolic velocity, respectively Sam and Eam. Specific acquisitions in 2D grey-scale, with maximized frame rate, were recorded in 4-, 2- and 3- chamber views for longitudinal strain and in parasternal short axis at basal and mid-level for radial strain analysis, both on the basis of the speckle-tracking approach by EchoPac SWO 113 (General Electric, Boston, Massachusetts). Global longitudinal strain (GLS) has to be considered the average segmental value measured in 4, 2 and 3 chamber view (LSCH4, LSCH2 and LSCH3, respectively). Global radial strain (GRS) means the average value from 6 basal and 6 middle segments; mean values were also computed, separately, from 6 basal (GRS bas) and 6 mid-ventricular (GRS mid) segments.

In our laboratory the intra-session within- and between-operator variability of GLS amounts respectively to a coefficient of variation of the mean value of 1.5% and to 3%, the corresponding value for the inter-session within-operator variability being 2%. The same figures for GRS were respectively 2.5, 4 and 3%. Same results were found when analysis was repeated for the basal inferior and posterior segment specifically.

The time to maximal myocardial shortening was measured from the electrocardiographic onset Q/onset R wave in the 6 basal segment of the left ventricle. As previously described, the SD of the time intervals to maximal myocardial shortening was used to quantify left ventricle mechanical dispersion [14].

The intra-session within- and between-operator variability of GRS mechanical dispersion amounts respectively to a coefficient of variation of the mean value of 2% and to 5%, the corresponding value for the inter-session within-operator variability being 4%.

The software used for the radial strain analysis identifies, in short axis view, 6 segments of left ventricle: antero-septal, infero-septal, inferior, posterior, lateral and anterior. In order to this specific segmentation we prefer to not rename the walls accordingly to the 2015 version of the Cardiac Chamber Quantification [16].

Statistical analysis

Patient's characteristics were analyzed by descriptive statistics. For continuous variables, means and standard deviations were calculated, while for categorical variables, numbers and percentages in each category were recorded. The characteristics of the groups were compared using ANOVA with Bonferroni corrections for continuous variables and Fisher's exact test for categorical variables.

Results were adjusted for age and family relations (with clustering to adjust for the influence of relationships between family members). Further corrections were introduced regarding GRS of the basal posterior and inferior segments in order to test if significant difference remains. We add to the model all the variables that showed significant correlation with the GRS of those two segments, that are the respective thickness and body surface area (BSA).

Receiver-operating characteristic (ROC) curve was constructed to evaluate the ability of GRS of the basal posterior and inferior segment to discriminate patients in group B from patients in group C. Area under the curve (AUC) was calculated and Youden Index was used to choose the best cut point that optimize sensibility and specificity.

p value was considered significant when < 0.05. All computations were carried out using ASA, version 9.4 (SAS Institute, Cary, North Carolina).

Results

Population characteristics

We studied 28 patients from 8 families. Subjects were divided into three groups according to genetic and echocardiographic features: A: (G+/Ph+); B: (G+/Ph−); C (G−/Ph−). Demographic, clinical, genetic, ECG and echocardiographic characteristics are summarized in Table 1. Pre-clinical subjects and control group were younger than group A subjects while blood pressure and heart rate values were similar between groups. As expected abnormal ECG findings were showed in a greater proportion of group A subjects in comparison to group B. No subjects in group C showed ECG alterations.

All healthy relatives (Group C) and pre-clinical patients (Group B) were not taking drugs (except only one using a low dose of ACE-inhibitor and diuretic for mild hypertension) and were asymptomatic. Patients with overt HCM (Group A) were taking beta-blockers, associated in some cases with amiodarone and showed mild to moderate symptoms (prevalent NYHA Class II).

Cardiac dimensions and systolic function were within the normal range in all groups. Septal thickness was higher in group A (19.5 ± 5.9 mm) than in group B and C (8.2 ± 1.3; 8.6 ± 1.4 mm, respectively) and left indexed atrial volume was significantly larger (43.6 ± 16.3; 26.9 ± 4; 26.7 ± 5.8 ml, respectively in group A, B and C).

Diastolic function and DTI

Mitral inflow pulsed wave (PW) parameters showed impaired relaxation in A group; LV end-diastolic pressures were not likely to be defined as normal in all patients of group A; on the contrary, standard diastolic function and E/Eam ratio were normal in asymptomatic and control subjects.

Lateral, septal and mean S peak annular values were decreased in group A respect to pre-clinical and healthy relatives with a statistically significant difference between septal and mean S peak in group A and C (Septal Sa: 0.067 m/s ± 0.029 vs. 0.098 ± 0.018; Sam: 0.072 m/s ± 0.028 vs. 0.107 ± 0.02; Table 2).

Myocardial septal diastolic velocities were significantly reduced in group A compared to B and C; while this was not the case for lateral velocities in which, despite different values, the statistical significance was not reached (Table 2).

2-D longitudinal and radial strain

The evaluation of 2-D longitudinal strain yielded superimposable results, referring to global and segmental longitudinal strain in phenotype-negative mutation carriers and controls (Table 2). Differently, longitudinal strain was reduced in almost all segments in manifest disease, more seriously at basal infero-septal and basal antero-septal level ($-6.81\% \pm 6.4$; $-9.15\% \pm 8.15$, respectively).

Furthermore, we analyzed radial strain at basal and mid-ventricular level, dividing short axis view in 6 segments, as previously described. The global analysis at mid-ventricular segments (GRS mid) showed no significant

Table 1 Demographic, clinical, genetic and standard echocardiographic characteristics of the population

	Group A (G+/Ph+)	Group B (G+/Ph−)	Group C (G−/Ph−)	p-value		
				A versus B	A versus C	B versus C
Number	10	9	9	–	–	–
Age (years)	48.5 ± 18.7	34.4 ± 12.1	30.3 ± 11.0	0.01	< 0.0001	0.99
Male gender	6 (60%)	3 (33%)	5 (56%)	0.73	0.99	0.99
BSA (m^2)	1.83 ± 0.1	1.73 ± 0.2	1.80 ± 0.2	0.34	0.99	0.99
Systolic BP (mmHg)	113.1 ± 12.5	110.2 ± 14.1	110.0 ± 14.1	0.99	0.99	0.99
Diastolic BP (mmHg)	71.9 ± 7.5	71.4 ± 9.4	66.9 ± 14.3	0.11	0.99	0.12
Heart Rate (bpm)	69.3 ± 7.6	75.5 ± 13.1	71.7 ± 5.4	0.23	0.43	0.47
Abnormal ECG findings (%)	44	25	0	0.02	–	–
MYBPC3 mutation carriers	6	7	0	–	–	–
MYH7 mutation carriers	3	1	0	–	–	–
TNNT mutation carriers	1	1	0	–	–	–
LVEF (%)	60. 2 ± 6.9	65.6 ± 5.4	61.8 ± 4.8	0.03	0.99	0.15
LVEDV (ml)	90.8 ± 15.4	75.9 ± 16.6	89.2 ± 20.0	0.006	0.99	0.24
IVS thickness (mm)	19.5 ± 5.9	8.2 ± 1.3	8.6 ± 1.4	< 0.001	< 0.001	0.99
Deceleration time (ms)	209.7 ± 55.8	168.4 ± 19.0	170.1 ± 32.9	0.68	0.99	0.99
E-peak (m/sec)	0.65 ± 0.2	0.94 ± 0.2	0.93 ± 0.2	0.06	0.16	0.99
E/Eam	10.1 ± 3.5	7.7 ± 2.2	6.4 ± 1.5	0.43	< 0.001	0.72
LA volume indexed (ml/m^2)	43.6 ± 16.3	26.9 ± 4.0	26.7 ± 5.8	< 0.001	< 0.001	0.99

Data are expressed as mean ± standard deviation or number and percentage

BSA body surface area, *BP* blood pressure, *ECG* Electrocardiography, *LVEF* left ventricular ejection fraction, *LVEDV* eft ventricular end diastolic volume, *IVS* inter-ventricular septum, *Eam* Diastolic annular mean velocity, *LA* left atrium

Table 2 Tissue doppler imaging (TDI) and 2D STRAIN ANALYSIS

	Group A (G+/Ph+)	Group B (G+/Ph−)	Group C (G−/Ph−)	p-value		
				A versus B	A versus C	B versus C
Lateral Sa (m/s)	0.077 ± 0.027	0.112 ± 0.024	0.117 ± 0.027	0.244	0.054	0.999
Septal Sa (m/s)	0.067 ± 0.029	0.091 ± 0.015	0.098 ± 0.018	0.233	0.032	0.999
Sam (m/s)	0.072 ± 0.028	0.102 ± 0.016	0.107 ± 0.020	0.193	0.034	0.529
Lateral Ea (m/s)	0.091 ± 0.058	0.148 ± 0.032	0.167 ± 0.033	0.727	0.330	0.044
Septal Ea (m/s)	0.053 ± 0.034	0.120 ± 0.033	0.132 ± 0.036	0.001	0.0015	0.477
Eam (m/s)	0.072 ± 0.045	0.118 ± 0.049	0.149 ± 0.033	0.709	0.012	0.345
GLS (%)	− 15.68 ± 3.87	− 21.21 ± 2.86	− 20.32 ± 3.01	< 0.001	0.028	0.246
GRS basal (%)	35.28 ± 8.45	32.18 ± 9.06	44.6 ± 12.67	0.397	0.228	< 0.001
GRS basal mechanical dispersion (ms)	21.08 ± 20.07	17.81 ± 20.47	17.16 ± 15.77	0.736	0.657	0.945
GRS mid (%)	30.95 ± 19.35	37.53 ± 16.7	34.65 ± 12.06	0.999	0.999	0.999
GRS basal posterior (%)	39.98 ± 11.37	33.58 ± 9.50	51.17 ± 13.41	0.264	0.181	< 0.001
GRS basal inferior (%)	38.11 ± 11.67	32.91 ± 8.38	49.07 ± 13.5	0.436	0.431	< 0.001
Posterior basal segment thickness (mm)	9.21 ± 2.1	7.94 ± 0.34	7.96 ± 0.57	0.102	0.114	0.922
Inferior basal segment thickness (mm)	7.99 ± 1.61	7.33 ± 0.53	6.71 ± 0.65	0.259	0.038	0.041

All values are expressed as mean ± standard deviation, p-values are adjusted for age and family relations

Sa systolic annular velocity, *Sam* systolic annular mean velocity, *Ea* diastolic annular velocity, *Eam* diastolic annular mean velocity, *GLS* global longitudinal strain, *GRS* global radial strain

differences between the three groups. At the basal level (GRS basal) no differences were seen between group A and B group while impaired strain values were founded when group B was compared with controls (32.18% ± 9.06 vs. 44.59% ± 12.67; p value < 0.0001) (Fig. 1; Table 2). These results appeared more evident for two specific

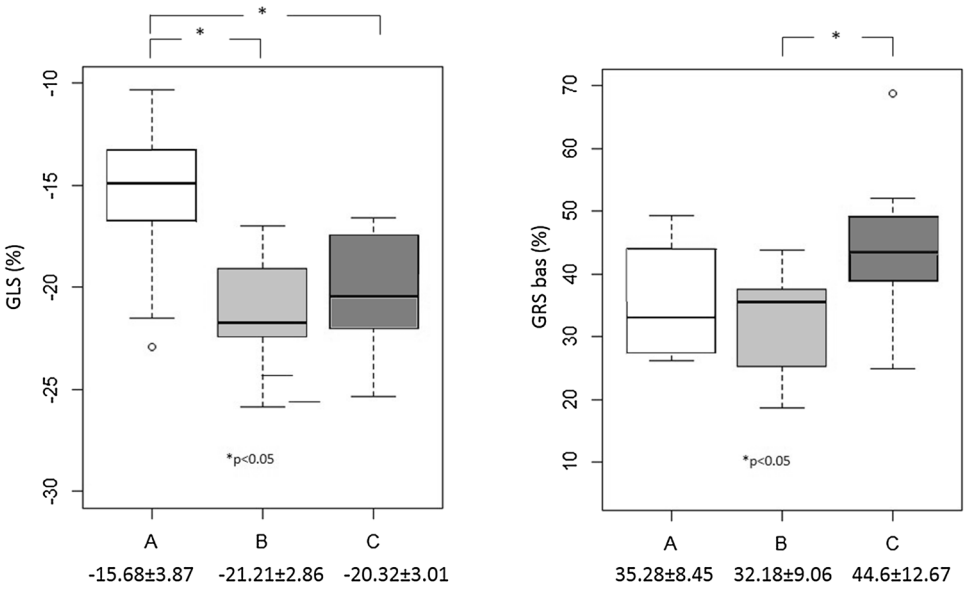

Fig. 1 Global longitudinal strain and global basal radial strain in the three group. *GLS* global lateral strain, *GRS bas* basal global radial strain

basal segments: the inferior one (32.91% ± 8.38 vs. 49.07% ± 13.49; p value < 0.0001) and the posterior one (33.57% ± 9.5 vs. 51.17 ± 13.41; p value < 0.0001) (Fig. 2; Table 2). No significant differences in terms of mechanical dispersion were seen between the three group (Table 2).

Table 2 reports also the thickness of these two segment with no significant difference for the posterior one. On the contrary a thicker inferior basal segment was showed in group B when compared to group C (7.33 ± 0.53 vs. 6.71 ± 0.65 mm, p = 0.04).

No changes in terms of p-value regarding GRS at the basal segment of the inferior and posterior wall were seen when statistical test were also adjusted for segment thickness and BSA (that correlate with both).

Finally, ROC curves (Fig. 3) were performed showing, for both the involved segment, good AUCs (0.931 and 0.861 for basal posterior and inferior GRS respectively). The best predictive cut-off for basal posterior GRS, based on highest Youden index, was 43.65% (with 100% sensitivity and 87.5% specificity), while it was 38.4% (with 88.9% sensitivity and 87.5% specificity) for basal inferior GRS.

Figure 4 shows an example of normal basal radial strain in a group C subject while Fig. 5 shows an example of the regional reduction in basal posterior and inferior segments in a pre-clinical patient.

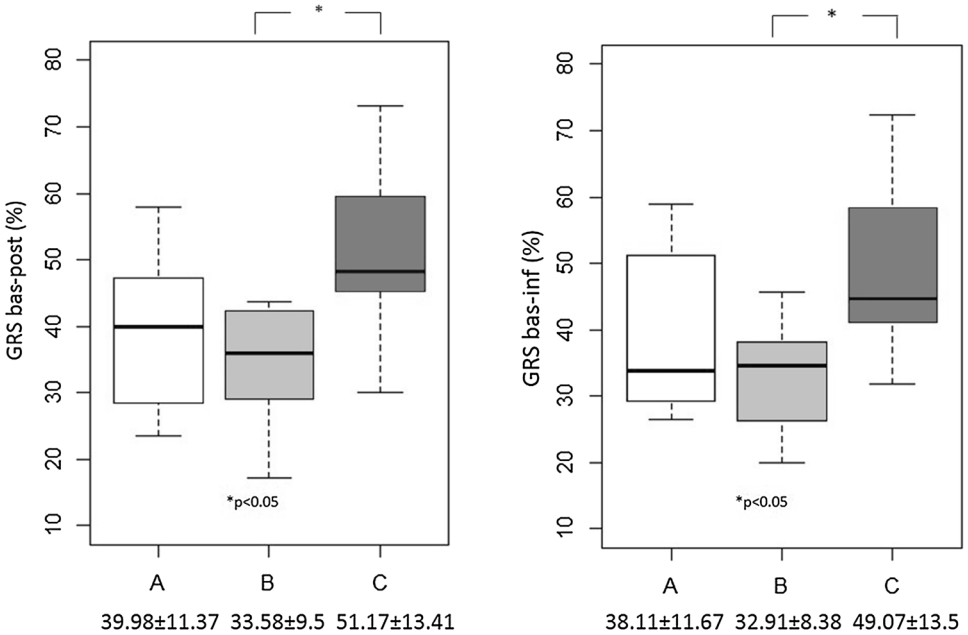

Fig. 2 Basal-posterior and basal-inferior GRS in the three group. *GRS bas-post* basal-posterior global radial strain, *GRS bas-inf* basal-inferior global radial strain

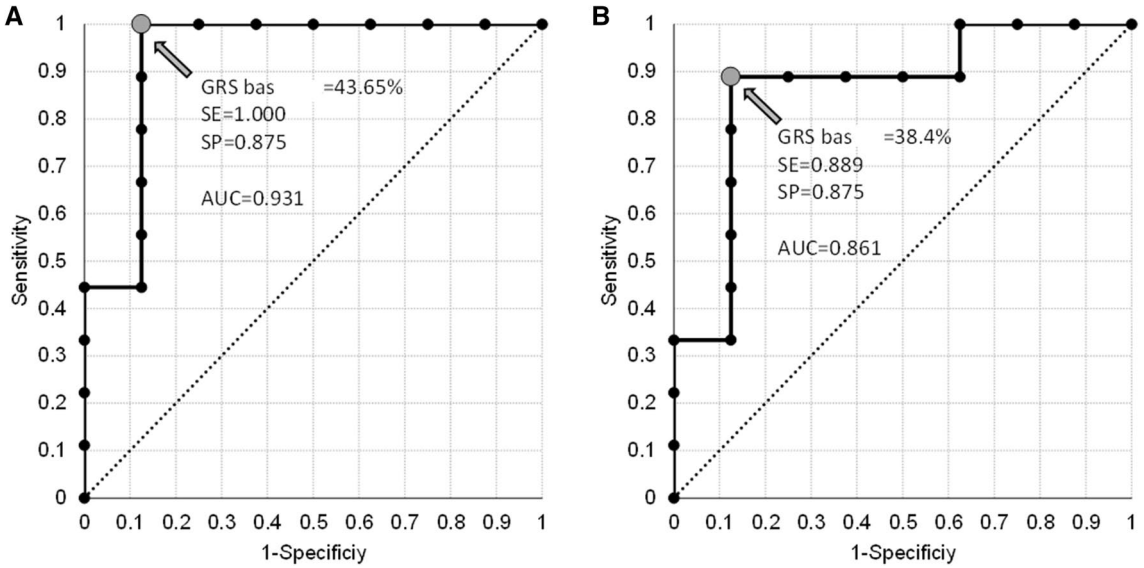

Fig. 3 ROC curves for basal posterior (panel A) and inferior (panel B) GRS. *GRS* global radial strain, *AUC* area under the curve, *SE* sensitivity, *SP* specificity

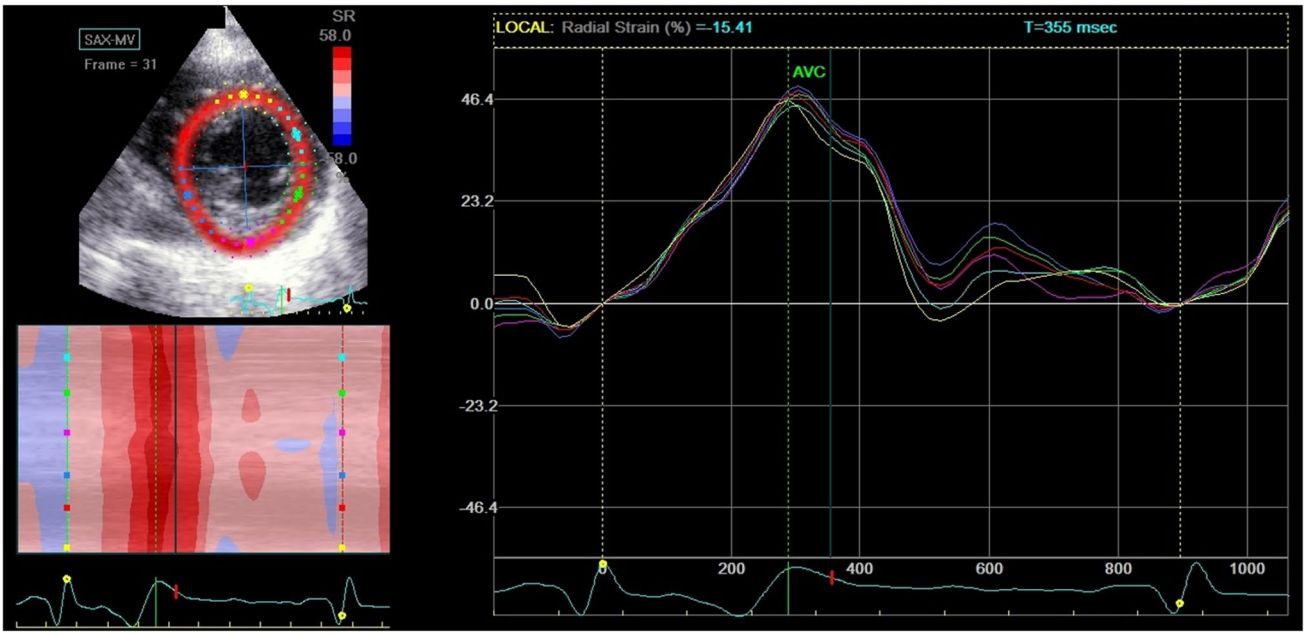

Fig. 4 Example of normal radial strain at basal level in a subject of group C

Discussion

In our study, we analyzed global and segmental longitudinal and radial strain with the aim to identify specific abnormalities able to distinguish pre-clinical patients from healthy subjects in the same family. We found a significant decrease in GLS in patients with manifest LVH compared with group B and C, even though ejection fraction was normal in all groups; no difference was found between mutation carriers and healthy controls. However, the main finding of our study is related to the radial strain analysis. In fact, we found a significant difference in global radial strain at the level of basal segments between group B and C, while mutation carriers showed similar values of overt HCM subjects. When we analyzed separately the basal

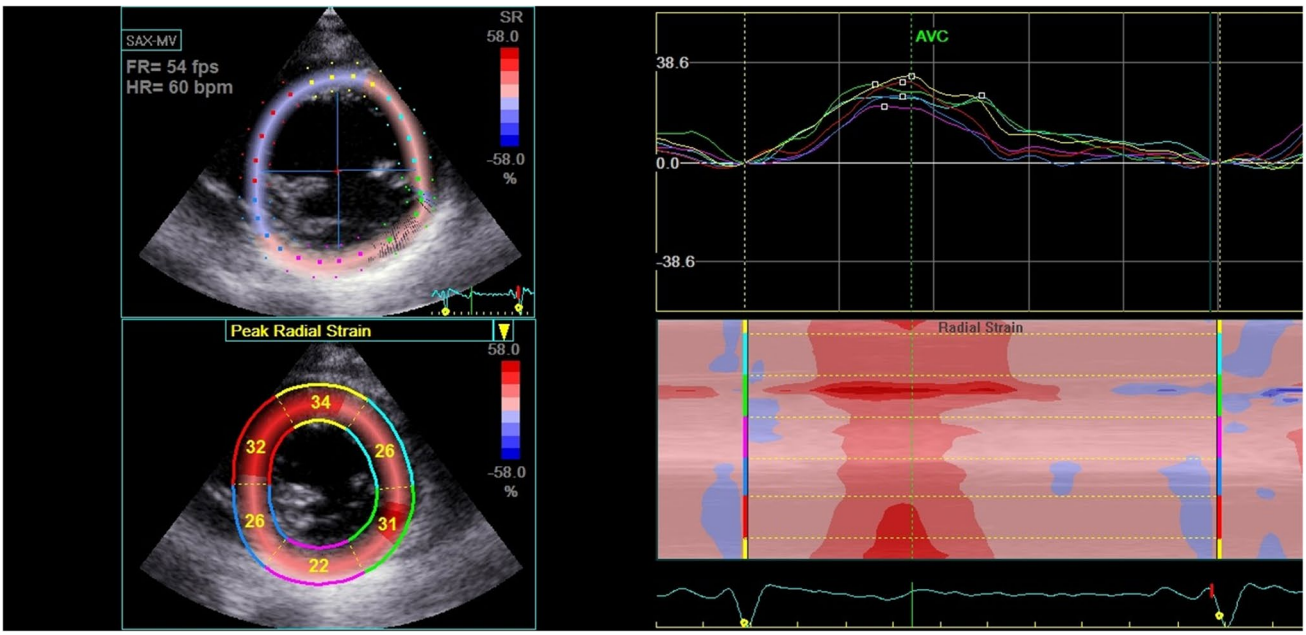

Fig. 5 Example of basal radial strain reduction in a pre-clinical mutation carrier subject. Basal posterior and basal inferior reduction are particularly evident (violet and blue curve)

segments, those, in which we observed the most significant impairment were the inferior and posterior one.

Previous studies showed impairment of radial strain in HCM patients compared to controls [10–13], while none of these presented data on mutation carriers. In this latter group only five focused previous studies were published [9, 18–21]. Among these, all found similar values between mutation carriers and controls in the global longitudinal strain while four of them found regional longitudinal strain impairment. These latter four studies found alterations in different segments but principally in the basal segment of the septum [9, 18–20].

Concerning this, we think that is attractive the role of segmental strain abnormalities, as a typical feature of disease, respect to the global strain reduction. Some Authors have described significant longitudinal strain reduction of basal LV segments strain in Anderson–Fabry disease [22]; likewise, the so called "apical sparing" seems to be specific for the diagnosis of amyloidosis [23]. Similarly, Authors described severe reduction of longitudinal strain in the septal and apical segments, in sarcoidosis [24].

Our paper is the first one describing radial strain analysis in mutation carriers with the finding of a basal impairment particularly at the level of the inferior and posterior wall. This difference remains significant also when further correction for thickness and BSA were inserted into the model excluding their influences on the final results.

Finally, ROC curves also confirm the capacity of the GRS, at these two segments level, to discriminate mutation carriers from healthy relatives, with good AUC, sensibility and specificity.

One could speculate why these segments should present an impaired radial contraction in comparison with the others. Reduction in septal strain has been associated to more pronounced histological alterations such as myocyte hypertrophy, disarray, and interstitial fibrosis. The strain alterations could also reflect an energetic metabolism dysfunction before hystological disarray begins [25]. A further hypothesis could be that the impaired segments could be contiguous to crypts' areas. In fact, those have been identified in Cardiac Magnetic Resonance as disruption of the normal compacted ventricular profile and observed at basal infero-septal level in phenotype-negative mutation carriers [5, 6].

Finally, mechanical dispersion is a parameter took into account as a predictor of ventricular arrhythmias and appropriate defibrillator therapy in hypertrophic cardiomyopathy [26, 27]. Moreover, one recently published study [14] found that, despite a similar GLS, mechanical dispersion, could help to distinguish athletes with HCM from healthy athletes. In our study we checked if mechanical dispersion in GRS could help to distinguish mutation carriers from healthy subjects. We didn't find any difference regarding this parameter but, it could be possible that studies with more patients are needed on this specific point.

The most important limitation of our study is the low number of patients that could limit our power to detect findings and associations.

Comparing radial strain analysis with cardiac magnetic resonance sequences for crypts research could be valuable.

Conclusions

2D longitudinal strain is a valid technique to study HCM patients and their relatives. Radial strain and particularly basal inferior and posterior segmental reduction could be able to identify mutation carriers in pre-clinical phase of disease.

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Compliance with ethical standards

Conflict of interest The authors report no specific funding in relation to this research and no conflicts of interest to disclose.

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