CMR feature tracking strain patterns and their association with circulating cardiac biomarkers in patients with hypertrophic cardiomyopathy

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Abstract

Aims CMR feature tracking strain (CMR-FT) provides prognostic information. However, there is a paucity of data in hypertrophic cardiomyopathy (HCM). We sought to analyze global CMR-FT parameters in all four cardiac chambers and to assess associations with NT-proBNP and cardiac troponin T (hsTnT) in patients with HCM.

Methods This retrospective study included 144 HCM patients and 16 healthy controls with CMR at 1.5 T. Analyses were performed on standard steady-state free precession cine (SSFP) CMR data using a commercially available software. Global left ventricular (LV) strain was assessed as longitudinal (LV_{LAX}-GLS), circumferential (LV_{LAX}-GCS) and radial strain (LV_{LAX}-GRS) on long-axis (LAX) and as LV_{SAX}-GCS and LV_{SAX}-GRS on short-axis (SAX). Right ventricular (RV-GLS), left atrial (LA-GLS) and right atrial (RA-GLS) strain were assessed on LAX.

Results We found LV_{LAX}-GLS [-18.9 (−22.0, −16.0), −18.9 (−22.0, −16.0), p = 0.0001), LV_{SAX}-GRS [86.8 (65.9–115.5), 86.8 (65.9–115.5), 119.6 (91.3–143.7) %, p = 0.0001] and LA_{LAX}-GLS [LA_{2CH}-GLS 29.2 (19.1–37.7), LA_{2CH}-GLS 38.2 (34.3–47.1) %, p = 0.0036; LA_{4CH}-GLS 22.4 (14.6–30.7) vs. LA_{4CH}-GLS 33.4 (28.4–37.3) %, p = 0.0033] to be impaired in HCM compared to healthy controls despite normal LVEF. Furthermore, LV and LA strain parameters were impaired in HCM with elevated NT-proBNP and/or hsTnT, despite preserved LVEF compared to HCM with normal biomarker levels. There was a moderate correlation of LV and LA CMR-FT with levels of NT-proBNP and hsTnT.

Conclusion CMR-FT reveals LV and LA dysfunction in HCM despite normal LVEF. The association between impaired LV strain and elevated NT-proBNP and hsTnT indicates a link between unapparent functional abnormalities and disease severity in HCM.
**Background**

Hypertrophic cardiomyopathy (HCM) is characterized by inappropriate and mostly asymmetric left ventricular (LV) hypertrophy, resulting from disarrays of fibers and fascicles, dysmorphic myocytes and accumulation of myocardial fibrosis [1]. It represents the most frequent cause of sudden cardiac death in young people, thus early diagnosis and initiation of therapy can prevent life-threatening events [2]. Nevertheless, assessing myocardial function in HCM by cardiac imaging is challenging since conventional parameters, i.e. left ventricular ejection fraction (LVEF), are often preserved or supernormal in HCM patients despite clinical heart failure symptoms [2]. In the past, echocardiography-based strain analyses (speckle tracking imaging (STI)) were able to detect regional and global myocardial dysfunction in patients with HCM with a superior prognostic value for major adverse cardiac events compared to LVEF assessment [3]. In particular, impaired global longitudinal strain (LVLAXGLS), was associated with major cardiovascular events in HCM [4]. CMR feature tracking strain (CMR-FT) has the ability to assess early changes in myocardial mechanics more sensitive compared to echocardiography due to the excellent image quality across the complete left and right ventricle of steady-state free precession (SSFP) cine CMR [5]. CMR-FT has been used to assess LV strain in several studies in recent years, indicating incremental prognostic information in different cardiac diseases such as dilatative cardiomyopathy, ischemic cardiomyopathy, and HCM [6]. However, most available study populations were small and a comprehensive approach in HCM including all cardiac...
chambers is missing. The aim of our retrospective study was to analyze global CMR-FT strain parameters in all four cardiac chambers of HCM patients. Furthermore, we aimed to assess potential associations with well-established cardiac biomarkers such as NT-proBNP and troponin T (hsTnT).

Methods

Patients and controls

This retrospective study included 144 consecutive patients with HCM and 16 healthy subjects as controls. HCM patients were outpatients, in stable health condition and underwent clinically indicated CMR between Jun 2006 and Nov 2017. HCM was defined by a wall thickness ≥ 15 mm in one or more LV myocardial segments according to current guidelines of the ESC [2]. Exclusion criteria included coronary artery disease, relevant valvular dysfunction, post-operative status (myectomy, alcohol septal ablation), glomerular filtration rate (GFR) < 30 ml/min/1.73 m². The control group consisted of recently published healthy individuals [7]. Diastolic dysfunction (DD) was assessed and categorized by echocardiography in agreement with current guidelines [8]. Blood samples of all participants were obtained routinely ± 3 days before/after CMR. Troponin T was measured by a high-sensitive assay and an established cutoff was applied with ≥ 14 pg/mL using the 99th percentile for defining abnormal values [9]. The NT-proBNP cutoff was set at 125 pg/mL according to the current guidelines [10]. The study followed the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee. All patients and controls gave their written informed consent to use CMR information for research purposes.

CMR protocol

Clinically indicated CMR was performed on a 1.5-T scanner (Achieva, Philips Medical Systems, Best, the Netherlands). For the assessment of LV volumes and function, standard retrospectively gated SSFP cine CMR was performed in short- and in long-axis [two-chamber (2CH), three-chamber (3CH), four-chamber view (4CH)]. Typical imaging parameters were: voxel size 1.36 × 1.36 × 6 mm³, echo time = 1.67 ms, time to repetition = 3.34 ms, flip angle = 60°, parallel acquisition technique = SENSE. Late gadolinium enhancement (LGE) images were acquired using a phase-sensitive inversion recovery (PSIR) sequence at least ten minutes after bolus injection of contrast media, 0.075 mmol/kg Gd-BOPTA (MultiHance®). Imaging parameters were as follows: voxel size 1.36 × 1.36 × 8 mm³, echo time = 2.40 ms, time to repetition = 5.50 ms, flip angle = 15°. Since T1 mapping was routinely introduced not until 2011 in our institution, we did not include T1 mapping in this analysis.

CMR data analysis

CMR data analysis was performed by two trained observers who were blinded to all clinical information. Commercially available post-processing software (Medis Suite MR, QMass ver. 8.1.74.2, QStrain ver. 2.0.70.2, Leiden, The Netherlands) was used to assess volumes and function of all cardiac chambers. LV and RV volumes, as well as LV mass and LV maximal wall thickness, were obtained from cine SAX. LA and RA volumetry were obtained from cine LAX as recommended [11].

CMR-FT measurements were performed using the QStrain application of Medis Suite MR [12]. To generate the most accurate tracing points, endo- and epicardial contours were manually traced in QMass and then copied to QStrain. In agreement with current recommendations LV strain was based on endo- and epicardial contours in short- and long axis, whereas RV, LA and RA contours were tracked from endocardium in LAX [5], [13–16]. Global CMR-FT was assessed as longitudinal (GLS), radial (GRS) and circumferential strain (GCS) in LV; in LA, RA and RV GLS were assessed. Negative values represent shortening of myocardium and positive values represent thickening referred to the direction of the deformation process (longitudinal, radial, circumferential). LA/RA maximum was defined at end-systole and LA/RA minimum at end-diastole. LGE was assessed semiquantitatively as recommended for clinical indications [11] on PSIR images according to the 17-segment model of the AHA [17].

Statistical analysis

Statistical analysis was performed using MedCalc for Windows, version 12.7.7.0 (MedCalc Software, Ostend, Belgium). Continuous data are presented as median and IQR. Categorical data are presented as numbers and percentage. Inter-observer agreement was assessed by intra-class correlation coefficients (ICC) and ICC values indicated poor (< 0.5), moderate (0.5–0.75), good (0.75–0.9) or excellent (> 0.9) reliability [18]. Continuous data were compared using the Mann–Whitney test. Categorical data were analyzed using the chi-quadrat test or Fisher exact test, where appropriate. Correlations between continuous parameters were analyzed by spearman’s correlation coefficient (rho). Statistical significance was set to p < 0.05 without correction for multiple testing.
Results

**Inter-observer agreement CMR-FT strain**

Inter-observer agreement of CMR-FT strain parameters was as follows: ICC for LVLAX-GLS was 0.95 (0.93, 0.96), LVLAX-GCS 0.89 (0.85, 0.92), LVLAX-GRS 0.89 (0.78, 0.89), LVLAX-GRS 0.66 (0.53, 0.76), LVSAX-GRS 0.97 (0.96, 0.98), LA2CH-GLS 0.97 (0.95, 0.98), LA4CH-GLS 0.94 (0.92, 0.96), and RA-GLS 0.94 (0.91, 0.95).

**HCM patients and controls**

LV Mass index (LVMi), maximal LV wall thickness (LVWT) and median LA volumes were significantly higher in HCM patients compared to controls (Table 1). Eighty-seven (91.6%) of 95 HCM patients with sufficient echocardiography had diastolic dysfunction ≥ II (Table 1). Median LVLAX-GLS of HCM patients was significantly lower compared to controls [−18.9 (−22.0, −16.0), −23.5 (−25.5, −22.0) %, \( p = 0.0001 \); Table 1, Fig. 1]. Furthermore, median LVSAX-GRS, LA2CH-GLS and LA4CH-GLS were significantly lower in the HCM group compared to controls (Table 1, Fig. 1). In contrast, median RV-GLS was significantly higher in HCM compared to controls [−38.0 (−43.6, −33.9), −31.4 (−34.3, −28.3) %, \( p = 0.0002 \); Table 1).

**NT-proBNP**

104 (84%) HCM patients had elevated NT-proBNP levels. There were no significant differences in major clinical and conventional CMR characteristics between HCM patients with and without elevated NT-proBNP levels (Table 2). HCM patients with elevated NT-proBNP had a significantly higher extent of LGE, LVLAX-GLS, LVLAX-GCS, LVGRS-GRS, LVGRS-GCS, LVGRS-GRS and global longitudinal LA strain were all significantly lower in the group of HCM patients with elevated NT-proBNP (Table 1, Fig. 1). Median LVLAX-GLS was significantly lower in HCM compared to controls [−18.9 (−22.0, −16.0), −23.5 (−25.5, −22.0) %, \( p = 0.0001 \); Table 1, Fig. 1]. Furthermore, median LVSAX-GRS, LA2CH-GLS and LA4CH-GLS were significantly lower in the HCM group compared to controls (Table 1, Fig. 1). In contrast, median RV-GLS was significantly higher in HCM compared to controls [−38.0 (−43.6, −33.9), −31.4 (−34.3, −28.3) %, \( p = 0.0002 \); Table 1].

**Discussion**

This study analyzed global myocardial strain patterns in all four cardiac chambers in patients with HCM by CMR-FT strain. The major findings were the following: first, we found LVLAX-GLS, LVSAX-GRS and LALAX-GLS to be impaired in HCM patients compared to healthy controls despite normal LVEF in both groups (Table 1, Fig. 1). Second, all global LV and LA strain parameters were impaired in HCM patients with elevated NT-proBNP and hsTnT levels, despite preserved LVEF and a similar degree of diastolic dysfunction (Tables 2, 3). Third, we found significant but modest correlations of LV and LA CMR-FT strain with NT-proBNP and hsTnT levels (Fig. 2).

**LV and RV strain in HCM**

We found significantly decreased median LVLAX-GLS and LVSAX-GRS despite preserved LVEF in HCM patients compared to healthy controls. Although LVEF is by far the most important clinical measure of LV function [19], it tends to overestimate LV systolic function in hypertrophied ventricles [2]. Therefore, more advanced approaches to assess myocardial function in HCM are desirable. CMR-FT offers many different advantages; it traces the cardiac deformation process precisely and reflects local forces (Fig. 3: arrows show direction and proportion of motion), displays disproportional LV thickening (note the reduced amplitude of voxel motion in CMR-FT strain in Fig. 4a–h), is well validated, and has been used in a variety of cardiovascular diseases [20]. Moreover, LVLAX-GLS and LVSAX-GRS provide incremental prognostic information to LVEF in ischemic and non-ischemic cardiac disease [3, 21] and are associated with an increased risk of mortality and poor cardiovascular outcome in HCM [6]. We suspect that the association of strain with myocardial fibrosis [22] and scaring [23] could explain this observation.

In contrast, we found RV-GLS to be higher in HCM compared to controls (Table 1). RV function was neglected in
Hypothetically, the “supra-normal” RV-GLS we found could indicate a compensatory reaction to increased LV filling pressure and requires

### Table 1 Clinical characteristics

| Parameter, unit | Controls (n = 16) | HCM (n = 144) | p value |
|-----------------|-------------------|---------------|---------|
| Age, years      | 51 (46–58)        | 55 (43–64)    | 0.2191  |
| Male, n, (%)    | 8 (50)            | 88 (61)       | 0.4277  |
| Heart rate, bpm | 61 (57–76)        | 65 (59–73)    | 0.6327  |
| Height, m       | 1.73 (1.63–1.76)  | 1.74 (1.66–1.82) | 0.5636 |
| Weight, kg      | 78 (70–88)        | 82 (71–90)    | 0.4110  |
| Creatinine, mg/dL | 0.79 (0.66–0.90) | 0.9 (0.80–1.10) | **0.0220** |
| GFR, mL/min     | 97 (91–109)       | 78 (70–88)    | **0.0037** |
| Creatine kinase, U/L | 127 (65–184) | 115 (79.5–171) | 0.8737 |
| hsTroponin T, pg/mL | 3 (3–4) | 12 (7–21.5) | **<0.0001** |
| NT-proBNP, pg/mL | 46 (32–97) | 581 (227–1542) | **<0.0001** |

**Volumes and functions**

| Parameter, unit | Controls (n = 16) | HCM (n = 144) | p value |
|-----------------|-------------------|---------------|---------|
| LVEF, %         | 65 (59–68)        | 64 (58–71)    | 1.0000  |
| LVEDVi, mL/m²   | 85 (79–90)        | 88 (78–99)    | 0.6842  |
| LVESVi, mL/m²   | 29 (26–38)        | 30 (24–40)    | 0.9410  |
| LV mass index, g/m² | 45 (36–58) | 76 (57–95) | **<0.0001** |
| Maximal LVWT, mm | 8.9 (8.2–9.9) | 17.9 (15.6–21.4) | **<0.0001** |
| RVEF, %         | 62 (57–65)        | 64 (58–68)    | 0.5153  |
| RVEDVi, mL/m²   | 80 (67–89)        | 73 (64–88)    | 0.4712  |
| RVESVi, mL/m²   | 29 (23–35)        | 27 (21–35)    | 0.5832  |
| LAEDVi, mL/m²   | 14 (12–17)        | 36 (22–56)    | **<0.0001** |
| LAESVi, mL/m²   | 39 (31–41)        | 54 (41–73)    | **0.0002** |
| RAEDVi, mL/m²   | 22 (16–25)        | 22 (16–32)    | 0.4050  |
| RAESVi, mL/m²   | 40 (28–43)        | 38 (27–48)    | 1.0000  |
| LGE presence, n, (%) | 0/16 (0) | 104/143 (73) | **<0.0001** |
| LGE extent, n (amount of LGE segments in %) | 0/272 (0) | 308/2448 (12.6) | **<0.0001** |
| Atrial fibrillation, n, (%) | 0 | 7(4.9) | **<0.0001** |
| HCM-SCD-score, % | 0 | 3.3 (2.2–5.5) | **<0.0001** |

**Strain parameters, %**

| Parameter, unit | Controls (n = 16) | HCM (n = 144) | p value |
|-----------------|-------------------|---------------|---------|
| LV_LAX-GLS      | −23.5 (−25.5, −22.0) | −18.9 (−22.0, −16.0) | **0.0001** |
| LV_LAX-GCS      | −25.0 (−26.9, −23.2) | −22.9 (−26.4, −20.0) | 0.0848 |
| LV_LAX-GRS      | 96.4 (75.4–114.1)  | 87.5 (68.9–107.4) | 0.3113 |
| LV_SAX-GCS      | −23.3 (−27.9, −21.1) | 22.1 (−24.8, −18.3) | 0.1696 |
| LV_SAX-GRS      | 119.6 (91.3–143.7) | 86.8 (65.9–115.5) | **0.0014** |
| LA2CH-GLS       | 38.2 (34.3–47.1)   | 29.2 (19.1–37.7) | **0.0036** |
| LA4CH-GLS       | 33.4 (28.4–37.3)   | 22.4 (14.6–30.7) | **0.0033** |
| RV-GLS          | −31.4 (−34.3, −28.3) | −38.0 (−43.6, −33.9) | **0.0002** |
| RA-GLS          | 29.8 (24.1–35.1)   | 31.1 (23.5–39.2) | 0.6959 |

Statistical significance was defined as p < 0.05. Significant results are highlighted in bold.

Values are median [first (Q1) and third (Q3) quartiles] for continuous and n (% of total column number) for categorical data. HCM indicates hypertrophic cardiomyopathy, bpm, beats per minute, hs high-sensitive, NT N-terminal, LV left ventricular, RV right ventricular, LA left atrial, RA right atrial, EF ejection fraction, EDVi end-diastolic volume index, ESVi end-systolic volume index, LVWT left ventricular wall thickness, LGE late gadolinium enhancement, SCD-Score sudden cardiac death score, LAX longitudinal axis, SAX short axis, GLS global longitudinal strain, GCS global circumferential strain, GRS global radial strain, 2CH two-chamber view, 4CH four-chamber view

*a hsTnT was available in n = 119

*b NT-proBNP was available in n = 124

most cardiac diseases for a long time, but in recent years, the awareness is increasing [24, 25]. Hypothetically, the
Table 2  Clinical and CMR characteristics of HCM patients with and without elevated NT-proBNP

| Parameter, unit | NT-proBNP < 125 pg/mL (n = 20) | NT-proBNP ≥ 125 pg/mL (n = 104) | p value |
|----------------|--------------------------------|---------------------------------|---------|
| Age, years     | 49 (38–57)                     | 57 (45–65)                      | 0.0631  |
| Male, n, (%)   | 18 (90)                        | 60 (57.7)                       | 0.0054  |
| Heart rate, bpm| 65 (57–72)                     | 66 (59–73)                      | 0.4713  |
| Height, m      | 1.79 (1.72–1.84)               | 1.73 (1.65–1.82)                | 0.0616  |
| Weight, kg     | 88 (81–92)                     | 82 (73–90)                      | 0.1065  |
| Creatinine, mg/dL | 1.0 (0.9–1.2)   | 0.9 (0.8–1.1)                  | 0.0268  |
| GFR, mL/min    | 79 (66–97)                     | 80 (68–100)                     | 0.5543  |
| hsTroponin T, pg/mL | 138 (118–170) | 108 (73–169)                  | 0.1108  |
| Normal diastolic Function, n, (%)  | 0/12 (0) | 1/83 (1.2)                  | 1.0000  |
| DD I°, n, (%)  | 0/12 (0)                       | 7/83 (8.4)                      | 0.5901  |
| DD II°, n, (%) | 11/1292 (92)                   | 61/83 (73.5)                    | 0.2821  |
| DD III°, n, (%)| 1/12 (8)                      | 14/83                           | 0.6837  |
| NYHA I, n, (%) | 12/12 (100)                    | 75/83 (90.3)                    | 0.5901  |
| NYHA II, n, (%)| 7/20 (35)                      | 32/99 (32.3)                    | 0.7996  |
| NYHA III, n, (%) | 11/20 (55) | 45/99 (45.5)                  | 0.4703  |
| NYHA IV, n, (%) | 2/20 (10) | 22/99 (22.2)                  | 0.3587  |
| LGE presence, n, (%) | 11/20 (55) | 78/104 (75)                  | 0.1013  |
| LGE extent, n (amount of LGE segments in %) | 19/340 (5.6) | 233/1768 (13.2) | <0.0001 |
| Atrial fibrillation, n, (%) | 0 (0) | 4 (3.8)                       | 1.0000  |
| HCM-SCD-Score, % | 2.6 (1.8–6.1) | 3.5 (2.2–5.0) | 0.3939  |
| LVOT obstruction, n, (%) | 4 (20) | 39 (37.5)                     | 0.1990  |

Statistical significance was defined as p < 0.05. Significant results are highlighted in bold

Values are median [first (Q1) and third (Q3) quartiles] for continuous and n (% of total column number) for categorical data

HCM indicates hypertrophic cardiomyopathy, bpm beats per minute, hs high-sensitive, NT N-terminal, LV left ventricular, RV right ventricular, LA left atrial, RA right atrial, EF ejection fraction, EDVi end-diastolic volume index, ESVi end-systolic volume index, LVWT left ventricular wall thickness, DD diastolic
further investigation. Taken together, our findings suggest that CMR-FT identifies LV and RV functional changes in HCM independent from conventional parameters. CMR-FT contributes to a better understanding of pathophysiology and could potentially improve risk stratification in HCM.

**Atrial strain in HCM**

We found that LA_{2CH}-GLS and LA_{4CH}-GLS were significantly lower in patients with HCM compared to controls. Quantification of LA Strain is a sensitive marker of LV diastolic dysfunction independent of LVEF [26]. In our

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**Table 2 (continued)**

dysfunction, NYHA New York Heart Association, LGE late gadolinium enhancement, SCD-Score sudden cardiac death score, LAX longitudinal axis, SAX short axis, GLS global longitudinal strain, GCS global circumferential strain, GRS global radial strain, 2CH two-chamber view, 4CH four-chamber view

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**Fig. 1** Distribution of LV and LA strain. Box-Whisker plots of median LV_{LAX}-GLS and LA_{2CH}-GLS in controls and HCM (a, b) and in HCM with negative (<125 pg/mL) NT-proBNP blood levels compared to HCM with elevated (positive) NT-proBNP levels (c, d) as well as in HCM with negative hsTnT (<14 pg/mL) or elevated (positive) hsTnT (e, f)
study, the majority of HCM patients (92%) had advanced diastolic dysfunction (Table 2). Interestingly, Habibi et al. demonstrated that deteriorations in LA-GLS precede the development of HF [27]. It is also known, that LA-GLS is predictive of worsening HF in patients with HCM [28]. Taking these results into account, LA2CH-GLS and LA4CH-GLS may not only reflect diastolic LV dysfunction in HCM but could also serve as an early predictor of HF and atrial fibrillation risk in HCM patients. Longitudinal studies are necessary in this context. However, we did not find significant difference in RA-GLS between HCM and controls (Table 1). Median RA-GLS was similar to previously described reference values [29]. We assume that the role of RA function in the pathophysiology of HCM is marginal.
Table 3  Clinical and CMR characteristics of HCM patients with and without elevated hsTnT

| Parameter, unit | HCM with hsTnT < 14 pg/mL (n=75) | HCM with hsTnT ≥ 14 pg/mL (n=44) | p value |
|-----------------|----------------------------------|----------------------------------|---------|
| Age, years      | 53 (41–63)                       | 59 (53–67)                       | 0.0471  |
| Male, n, (%)    | 48/75 (64%)                      | 26/44 (59%)                      | 0.6958  |
| Heart rate, bpm  | 65 (60–72)                       | 66 (58–76)                       | 0.7557  |
| Height, m       | 1.74 (1.66–1.82)                 | 1.75 (1.65–1.83)                 | 0.7809  |
| Weight, kg      | 82 (74–92)                       | 84 (75–92)                       | 0.9079  |
| Creatinine, mg/dL | 0.9 (0.75–1.09)              | 1.0 (0.80–1.16)                  | 0.1255  |
| GFR, mL/min     | 85 (68–101)                      | 74 (62–99)                       | 0.0375  |
| Creatine kinase, U/L | 113 (79–169)           | 115 (84–174)                     | 0.6362  |
| NT-proBNP, pg/mL | 421 (136–961)                  | 1228 (459–2451)                  | <0.0001 |
| Volumes and functions |
| LVEF, %         | 66 (58–72)                       | 62 (57–66)                       | 0.0138  |
| LVEDV, mL/m²     | 85 (76–96)                       | 92 (81–106)                      | 0.0445  |
| LVESV, mL/m²     | 28 (24–35)                       | 36 (28–46)                       | 0.0016  |
| LV Mass Index, g/m² | 71 (55–86)                   | 83 (70–109)                      | 0.0013  |
| Maximal LVWT, mm | 17.3 (15.3–20.7)               | 19.1 (15.9–21.4)                 | 0.1831  |
| RVEF, %         | 64 (58–68)                       | 64 (53–70)                       | 0.8017  |
| RV EDVi, mL/m²   | 72 (64–87)                       | 74 (65–91)                       | 0.5244  |
| RV ESVi, mL/m²   | 26 (23–34)                       | 29 (22–37)                       | 0.4360  |
| LA EDVi, mL/m²   | 27 (20–43)                       | 45 (28–65)                       | **0.0011** |
| LA ESVi, mL/m²   | 50 (42–63)                       | 64 (48–90)                       | **0.0115** |
| RA EDVi, mL/m²   | 20 (16–27)                       | 24 (18–39)                       | 0.0582  |
| RA ESVi, mL/m²   | 38 (28–47)                       | 36 (26–58)                       | 0.5691  |
| Normal diastolic function, n, (%) | 0/57 (0) | 1/32 (3.1) | 0.3596  |
| DD I°, n, (%)    | 2/57 (3.5)                       | 5/32 (15.6)                      | 0.0930  |
| DD II°, n, (%)   | 46/57 (80.7)                     | 21/32 (65.6)                     | 0.1308  |
| DD III°, n, (%)  | 9/57 (15.8)                      | 5/32 (15.6)                      | 1.0000  |
| Diastol dysfunction ≥ II°, n, (%) | 55/57 (96.5) | 26/32 (81.3) | **0.0233** |
| NYHA I, n, (%)   | 26/73 (35.6)                     | 13/40 (32.5)                     | 0.8371  |
| NYHA II, n, (%)  | 33/73 (45.2)                     | 19/40 (47.5)                     | 0.8456  |
| NYHA III, n, (%) | 14/73 (19.2)                     | 8/40 (20)                        | 0.4335  |
| NYHA IV, n, (%)  | 0/73 (0)                         | 0/40 (0)                         | 1.0000  |
| LGE presence, n, (%) | 51/74 (69)           | 35/44 (80)                       | 0.2847  |
| LGE extent, n (amount of LGE segments in %) | 129/1258 (10) | 118/748 (16) | **0.0003** |
| Atrial fibrillation, n, (%) | 2/75 (2.7) | 5/44 (11.4) | 0.1117  |
| HCM-SCD-Score, % | 2.9 (2.1–5.1)                   | 3.3 (2.2–5.3)                    | 0.3997  |
| LVOT obstruction, n, (%) | 26/75 (34.7) | 15/44 (34.1) | 1.0000  |
| Strain parameters, % |
| LV LAX-GLS       | −20.8 (−23.4, −19.0)            | −18.0 (−19.7, −13.8)             | **0.0001** |
| LV LAX-GCS       | −24.7 (−26.9, −22.0)            | −20.5 (−24.3, −17.1)             | **0.0001** |
| LV LAX-GRS       | 91.2 (76.4–115.1)               | 79.8 (58.9–96.4)                 | **0.0230** |
| LV SAX-GCS       | −22.2 (−25.5, −19.7)            | −21.0 (−23.8, −16.4)             | **0.0217** |
| LV SXX-GRS       | 93.5 (70.0–119.7)               | 72.0 (53.3–97.0)                 | **0.0020** |
| LA2CH-GLS        | 31.8 (26.5–43.7)                | 21.8 (11.9–32.0)                 | **0.0001** |
| LA4CH-GLS        | 25.3 (18.4–31.6)                | 16.4 (12.6–26.1)                 | **0.0021** |
| RV-GLS           | −38.3 (−44.1, −33.7)            | −38.3 (−43.9, −34.2)             | 0.9015  |
| RA-GLS           | 33.9 (26.4–43.1)                | 26.5 (22.0–32.1)                 | **0.0011** |

Statistical significance was defined as p < 0.05. Significant results are highlighted in bold.

Values are median [first (Q1) and third (Q3) quartiles] for continuous and n (% of total column number) for categorical data.

HCM indicates hypertrophic cardiomyopathy, bpm beats per minute, hs high-sensitivity, NT N-terminal, LV left ventricular, RV right ventricular, LA left atrial, RA right atrial, EF ejection fraction, EDVi end-diastolic volume index, ESVi end-systolic volume index, LVWT left ventricular wall thickness, DD diastolic dysfunction, NYHA New York Heart Association, LGE late gadolinium enhancement, SCD-Score sudden cardiac death, LA2CH left atrial volume index, LA4CH left atrial volume index, RV right ventricle, RA right atrium.
Myocardial strain and the association with cardiac biomarkers

NT-proBNP is a major cardiac biomarker, that is not only used to diagnose HF [10] but also as a powerful prognostic factor in different cardiomyopathies [30]. Cardiac hsTnT is a crucial marker of myocardial injury and is linked to poor outcome in ischemic as well as non-ischemic cardiomyopathies [31, 32]. We found that all global CMR-FT parameters of the LV, but not conventional LVEF and diastolic function, were significantly impaired in HCM patients with elevated biomarker concentrations (Tables 2, 3). Furthermore, we found a significant correlation of biomarker levels with CMR-FT (Fig. 2). These findings are in line with recent STI and CMR-FT studies, in which reduced GLS, GCS and GRS in HCM were independent predictors of poor cardiac outcome, particularly HF [6, 33]. Furthermore, in a recent CMR-FT study Tanacli et al. demonstrated that LV GLS and GCS drop with the severity of HF [34]. Our findings indicate that LV CMR-FT strain reveals occult systolic dysfunction in HCM. Furthermore, diastolic dysfunction is very common in HCM (Table 2) and LA-GLS seems to be a suitable strain parameter to evaluate diastolic dysfunction [26]. In conclusion, alterations in myocardial strain and elevated biomarkers seem to depict patients with more severe disease, independent from conventional assessment such as LVEF, NYHA classification, LVOT obstruction or the SCD risk score. Future studies are necessary to assess the potential prognostic implications of these findings.

Limitations

This study is a retrospective study with its inherent limitations, such as missing values of cardiac biomarkers in some patients. Furthermore, this study did not include longitudinal, follow-up data and is, therefore, not designed to address a potential incremental value of CMR-FT strain over conventional imaging. Future longitudinal studies are needed to assess a potential incremental prognostic value of CMR-FT over conventional imaging such as the assessment of cardiac death score, LAX longitudinal axis, SAX short axis, GLS global longitudinal strain, GCS global circumferential strain, GRS global radial strain, 2CH two-chamber view, 4CH four-chamber view.
diastolic dysfunction by echocardiography. To date, CMR-FT strain is often used in addition to conventional imaging parameters since there is currently no clinical application with immediate individual benefit for patients. In particular, there is a substantial overlap in some strain parameters between HCM patients and controls. However, strain reflects the myocardial deformation process much more accurately compared to conventional imaging and may therefore contribute to a better understanding of subclinical pathophysiological myocardial alterations. In addition, T1-mapping/ECV imaging was not available before 2011 in this study population. Therefore, we were not able to systematically address potential associations between strain parameters and quantitative tissue characterization in this study. Long-axis-based GLS is currently perceived as the most robust and reproducible CMR-FT parameter, but the reproducibility of other strain parameters can differ significantly [12, 35]. We found that LV_{LAX}-GRS and LV_{SAX}-GCS were affected by a poor and moderate inter-observer agreement in our study population, respectively. However, there were good to excellent inter-observer agreements for all other CMR-FT-derived measurements in this study population, which supports the reliability of the major findings of this work.

**Conclusion**

CMR-FT reveals LV and LA dysfunction in HCM patients despite normal LVEF. The association between impaired LV strain and elevated NT-proBNP and hsTnT levels indicates a link between unapparent functional abnormalities and disease severity in HCM.

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**Declarations**

**Conflict of interest** None.

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**Fig. 4** Typical LV-strain findings in HCM in comparison to a control. a–d Short-axis (SAX) left midventricular (LV) cine images of a control (a, b) and a HCM patient in end-diastole and end-systole (c, d). Note, the typical asymmetric septal LV hypertrophy (c, d). e–h Long-axis (LAX) LV strain of the same control (e, f) and the same HCM patient (g, h). Note, red dots follow green lines and display myocardial deformation within one heart cycle. Septal deformation is lower than i.e., lateral deformation, shown by shorter green lines.
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