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# The association between cardiac MR feature tracking strain and myocardial late gadolinium enhancement in patients with hypertrophic cardiomyopathy

*Aim*

Hypertrophic cardiomyopathy (HCM) is a relatively common, heritable cardiomyopathy, and cardiac magnetic resonance (CMR) studies have been performed previously to evaluate different aspects of the disease. However, a comprehensive study, including all four cardiac chambers and analysis of left atrial (LA) function, is missing in the literature. The aim of this retrospective study was to analyze CMR-feature tracking (CMR-FT) strain parameters and atrial function of HCM patients and to investigate the association of these parameters with the amount of myocardial late gadolinium enhancement (LGE).

*Material and Methods*

In this retrospective, cross-sectional study, we analyzed the CMR images (CMRI) of 58 consecutive patients, who from February 2020 to September 2022 were diagnosed with HCM at our tertiary cardiovascular center. Patients who were younger than 18 yrs or who had moderate or severe valvular heart disease, significant coronary artery disease, previous myocardial infarction, suboptimal image quality, or with contraindication to CMR were excluded. CMRI was performed at 1.5 T with a scanner, and all scans were assessed by an experienced cardiologist and then re-assessed by an experienced radiologist. SSFP 2-, 3- and 4-chamber, short axis views were obtained and left ventricular (LV) end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), and mass were measured. LGE images were obtained using a PSIR sequence. Native T1 and T2 mapping and post-contrast T1 map sequences were performed and each patient's myocardial extracellular volume (ECV) was calculated. LA volume index (LAVI), LA ejection fraction (LAEF), LA coupling index (LACI) were calculated. The complete CMR analysis of each patient was performed with CVI 42 software (Circle CVi, Calgary, Canada), off-line.

*Results*

The patients were divided into two groups, HCM with LGE (n=37, 64%) and HCM without LGE (n=21, 36%). The average patient age in the HCM patients with LGE was 50.8±14 yrs and 47±12.9 yrs in the HCM patients without LGE. Maximum LV wall thickness and basal antero-septum thickness were significantly higher in the HCM with LGE group compared to the HCM without LGE group (14.8±3.5 mm vs 20.3±6.5 mm (p<0.001), 14.2±3.2 mm vs 17.3±6.1 mm (p=0.015), respectively). LGE was 21.9±31.7 g and 15.7±13.4% in the HCM with LGE group. LA area (22.2±6.1 vs 28.8±11.2 $cm^2$; p=0.015) and LAVI (28.9±10.2 vs 45.6±23.1; p-0.004) were significantly higher in the HCM with LGE group. LACI was doubled in the HCM with LGE group (0.2±0.1 vs 0.4±0.2; p<0.001). LA strain (30.4±13.2 vs 21.3±16.2; p-0.04) and LV strain (15.2±3 vs 12.2±4.5; p=0.012) were significantly decreased in the HCM with LGE group.

*Conclusion*

This study sheds light on the CMR-FT differences between HCM with and without LGE. We found a greater burden of LA volume but significantly lower LA and LV strain in the LGE patients. These findings highlight further the LA and LV remodeling in HCM. Impaired LA function appears to have physiological significance, being associated with greater LGE. While our CMR-FT findings support the progressive nature of HCM, beginning with sarcomere dysfunction to eventual fibrosis, further studies are needed to validate these results in larger cohorts and to evaluate their clinical relevance.

*Keywords*

Cardiac MR imaging; hypertrophic cardiomyopathy; left atrium; late gadolinium enhancement

*For citations*

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## Introduction

Hypertrophic cardiomyopathy (HCM) is a relatively common, heritable cardiomyopathy with a prevalence of 1:200–1:500 [1]. HCM has a complex phenotypic and genetic expression and is characterized by left ventricular (LV) hypertrophy in the absence of loading conditions [1, 2]. Myocardial fibrosis in HCM results in arrhythmias and even sudden cardiac death [3], and HCM consists of interstitial and replacement subtypes [4, 5].

Recently, cardiac magnetic resonance (CMR) feature-tracking (CMR-FT) imaging, i.e., quantifying myocardial deformation by utilization of standard CINE sequences without a need for tagged images [6, 7], has emerged as a novel method for the diagnostic and prognostic evaluation of a wide range of cardiac diseases. Several studies have shown that evaluation of LV myocardial strain with CMR-FT is a sensitive predictor of preclinical LV dysfunction [8, 9]. The role of right ventricle (RV) strain in HCM has also been investigated, yet data on RV deformation assessed by CMR-FT in adult HCM are very limited [10].

In addition to quantifying systolic ventricular function, CMR-FT has been utilized for analyzing global, longitudinal left atrial (LA) strain and strain rate. A significant correlation between impaired LA function and replacement and diffuse myocardial fibrosis has been shown in previous studies with late gadolinium enhancement (LGE) [11]. However, a comprehensive study including all four cardiac chambers and LA function analysis is absent in the literature. Thus, the purpose of this retrospective study was to analyze CMR-FT strain parameters and atrial function of HCM patients and to investigate the association of these parameters with the amount of LV LGE.

## Material and Methods

In this retrospective, cross-sectional study, we analyzed the cardiac magnetic resonance images (CMRI) of 58 consecutive patients who were diagnosed with HCM from February 2020 to September 2022 at our tertiary cardiovascular center. The study protocol was approved by the local ethics committee. We excluded patients who were younger than 18 yrs, or had moderate or severe valvular heart diseases, significant coronary artery disease, or previous myocardial infarction. Also, excluded were patients with suboptimal image quality resulting in unreliable LGE assessment. Patients with CMR-associated contraindications (pacemaker, ICD, claustrophobia, GFR<35 ml/min/1.73 $m^2$) were also excluded.

### *Cardiac Magnetic Resonance assessment*

CMRI was performed with a 1.5 T scanner (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany). All CMR scans were assessed by an experienced cardiologist and re-assessed by an experienced radiologist. Steady-state free-precession (SSFP) 2-,3-, and 4-chamber, short axis views were obtained, and end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), and LV mass were measured by the analysis of short axis cine images. LGE images were obtained using a phase-sensitive inversion recovery (PSIR) sequence. We included native T1 and T2 mapping and postcontrast T1 map sequences as well, and we calculated each patient's LV myocardial extracellular volume (ECV). The CMR analysis of each patient was performed off-line with CVI 42 software (Circle CVi, Calgary Canada).

### *Feature-tracking cardiac magnetic resonance*

LV, LA, and RA average longitudinal strain analysis was performed with an automatic measurement option of the CVI 42 software using four chamber and two chamber CINE images, off-line. The automatic measurements were checked and corrected manually if the borders in the systolic and diastolic phases are not satisfactory. Only the RV strain analysis was not performed automatically. This was performed by manually defining the RV endocardial and epicardial borders. Image contrast was adjusted to provide the highest contrast between blood and endocardium.

### *Late gadolinium enhancement*

10 min after the intravenous administration of 0.1 mmol/kg of the gadolinium agent, LGE sequences were obtained in a stack of short-axis, four chamber, three chamber, and two chamber projections to cover the whole LV. The normal myocardial inversion time was determined with the scout sequence. The presence and definition of LGE was determined in these images. Papillary muscles were not included in the LV myocardial mass calculation. Subsequently, the enhancement mass, expressed as a percentage and as grams, was quantified with an automatic method by the definition of endocardial and epicardial borders in all stacks and by marking the enhanced myocardium as a reference region of interest to determine the global fibrosis in the entire LV myocardium.

### *Assessment of LA volume index (LAVI), LA EF (LAEF), and LA coupling index (LACI)*

The LACI was defined by the ratio between the LA end-diastolic volume and the LV end-diastolic volume. The LA

end-diastolic volume was obtained from short axis cine images by defining the endocardial borders of the LA in the end-diastolic phase. The LA end-diastolic volume was calculated automatically, but it was examined after each calculation to check if the endocardial borders were accurately delineated. The volume was corrected manually if necessary. Both LAEF and LAVI were calculated with the same automatic method and examined afterwards. Adjustments were performed manually in case of inaccurate delineation by the automatic program.

### *Statistics*

Continuous variables are presented as mean±standard deviation (SD), and categorical data are presented as number and percentages or frequencies. Continuous variables were examined by Kolmogorov–Smirnov test to check for normality of distribution, and all passed the test. Student t-tests and Mann Whitney U tests were used to compare parametric and nonparametric continuous variables, respectively. Categorical variables were compared by Chi-square ($\chi^2$) test. Univariate linear regression analysis with conventional clinical variables, i.e., age, and factors with significant correlations were entered in a multiple linear regression model. Possible collinearity was checked by examining tolerance and variance inflation factor. Variables with a tolerance of less than 0.10, a variance inflation factor of 10, and above were withdrawn from the multivariate linear regression model. A two-tailed p-value of <0.05 was considered as statistically significant. All data were analyzed with SPSS v23.0 (IBM Corp, Armonk, NY, USA).

## Results

The study included 58 patients with HCM diagnosis. The patients were divided into two groups: HCM with LGE (n=37, 64%) and HCM without LGE (n=21, 36%). The average age of the HCM patients with LGE was 50.8±14 yrs and 47±12.9 yrs in HCM patients without LGE. Women comprised 24% (n=9) of the HCM with LGE group and 19% (n=4) of the HCM without LGE group. Complaints, BSA, and BMA of the patients are given in Table 1, and they were similar in both groups.

All the CMR derived measurements were recorded and compared with LGE presence. Maximum LV wall thickness and basal antero-septum thickness were significantly higher in the HCM with LGE group compared to the HCM without LGE group (14.8±3.5 mm vs 20.3±6.5 mm (p<0.001), 14.2±3.2 mm vs 17.3±6.1 mm (p=0.015), respectively). The mean LGE amount was 21.9±31.7 g and 15.7±13.4% in the HCM with LGE group.

Left atrial area (LAA) was 22.2±6.1 vs 28.8±11.2 $cm^2$ (p=0.015) and LAVI (28.9±10.2 vs 45.6±23.1 $ml/m^2$ (p=0.004) were significantly higher in the HCM with LGE group compared to the group without LGE. LACI was doubled in the HCM with LGE group compared to the other group (0.2±0.1 vs 0.4±0.2 (p<0.001). Left atrial strain (30.4±13.2 vs 21.3±16.2%, p=0.04) and LV strain (15.2±3 vs 12.2±4.5%, p=0.012) were significantly decreased in the HCM with LGE group, while RA and RV strain was comparable in both groups (Table 2).

As shown in Table 3, the multivariate linear regression analysis revealed that the LACI, LA strain, T1 map, maximal wall thickness, extracellular volume, LV end-diastolic volume index, LV mass, LVEF were the independent variables associated with the LGE expressed in grams.

## Discussion

In the present study, we investigated whether the CMR-FT assessments of cardiac chambers differed between HCM patients with and without LV LGE. The main findings of this study are: 1) Patients with HCM and LV LGE exhibited higher CMR-derived measures of LA volume (LAVI and LACI), but they had significantly lower LA and LV strain compared to patients without LGE 2) RA and RV ventricular strain patterns were comparable between the groups.

CMR has emerged as an indispensable imaging modality in HCM, with its high spatial resolution and tomographic capability [12]. Moreover, CMR provides clinically relevant tissue characterization. LGE is a highly accurate marker of myocardial fibrosis, and it has been shown to have prognostic implications [13]. Roughly half of HCM patients exhibit LGE with a diverse pattern and location [14]. In the present study, we allocated HCM patients into two groups according to the presence of LGE in the LV myocardium.

LA enlargement is an established marker of disease severity and prognosis in patients with HCM [15, 16]. However, novel methods, such as speckle tracking echocardiography (STE), can provide additional information on LA function

**Table 1.** General features of the study population

| | HCM without LGE (n=21) | HCM with LGE (n=37) | p |
|---|---|---|---|
| Female, n (%) | 4 (19) | 9 (24) | 0.751 |
| Complaints | | | |
| SOB | 18 (86) | 23 (62) | 0.126 |
| Fatigue | 0 (0) | 1 (2.7) | |
| Palpitation feeling | 2 (1) | 9 (24) | |
| Chest pain | 0 (0) | 4 (11) | |
| Syncope | 1 (4.8) | 0 (0) | |
| Age, yrs | 47±12.9 | 50.8±14 | 0.317 |
| BSA ($m^2$) | 2±0.2 | 2±0.2 | 0.906 |
| BMI ($kg/m^2$) | 28.5±3.5 | 28.3±4.9 | 0.896 |

Data are n (%) or mean±SD. BSA, body surface area; BMI, body mass index; SOB, shortness of breath.



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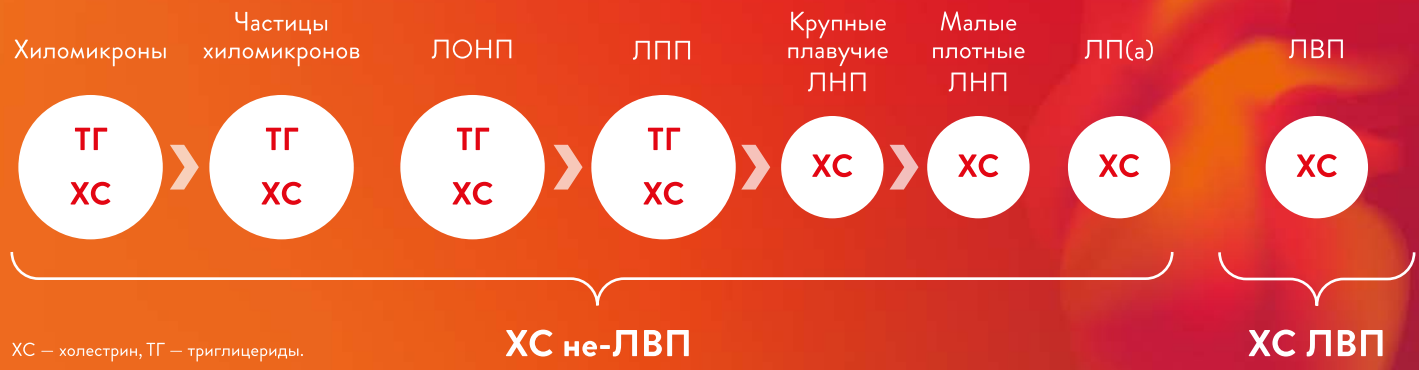
# НЕ-ЛВП ХОЛЕСТЕРИН — МИШЕНЬ ДЛЯ СНИЖЕНИЯ СЕРДЕЧНО-СОСУДИСТОГО РИСКА[1]

## ХС не-ЛВП включает в себя все атерогенные классы липопротеинов[1]




ХС — холестрин, ТГ — триглицериды.

ДЛЯ СНИЖЕНИЯ УРОВНЯ НЕ-ЛВП ТРЕБУЕТСЯ КОНТРОЛЬ ВСЕХ АТЕРОГЕННЫХ ЧАСТИЦ

## Целевые значения ХС не-ЛВП для пациентов с различным уровнем сердечно-сосудистого риска

Основа SCORE-2

| ХС неЛВП | | |
|---|---|---|
| < 2,6 ммоль/л | < 2,2 ммоль/л | < 1,8 ммоль/л |
| желателен для лиц с высоким риском | у лиц с очень высоким риском | для лиц с экстремально высоким риском |

Оценка ХС не-ЛВП не требует дополнительных затрат

Формула определения не-ЛВП

Не-ЛВП холестерин = ОХ - ЛВП

## ХС не-ЛВП — достоверный индикатор сердечно-сосудистой смертности у пациентов:

- с ожирением и метаболическим синдромом
- с ССЗ (ИБС, перенесенный инфаркт миокарда)
- с СД 2-го типа
- с гипертриглицеридемией
- с низким уровнем ЛНП


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**Table 2.** CMR measurements of 'HCM with and without LGE' groups

| | HCM without LGE (n=21) | HCM with LGE (n=37) | p |
|---|---|---|---|
| LVEDD (mm) | 47±5.1 | 48.7±6.6 | 0.312 |
| LVESD (mm) | 21±0 | 22.4±3.7 | 0.025 |
| Maximum wall thickness (mm) | 14.8±3.5 | 20.3±6.5 | <0.001 |
| Anteroseptum basal wall thickness(mm) | 14.2±3.2 | 17.3±6.1 | 0.015 |
| Inferolateral wall basal thickness(mm) | 7.4±1.8 | 8±2.7 | 0.329 |
| LVEDVI (ml/m²) | 70.9±12 | 74.5±17.1 | 0.400 |
| LVESVI (ml/m²) | 26±9.7 | 27.5±13.8 | 0.650 |
| LVSVI (ml/m²) | 44.3±6.8 | 46.1±8.2 | 0.400 |
| LV mass index (gr/m²) | 69.5±17.6 | 80.3±27.6 | 0.115 |
| RVEDVI (ml/m²) | 67.4±13.9 | 67.2±12.5 | 0.953 |
| RVESVI (ml/m²) | 26.8±8.7 | 25.3±7.5 | 0.509 |
| LVEF (%) | 64.2±8.9 | 64.1±8.6 | 0.954 |
| RVEF (%) | 62.3±6.1 | 63.1±7 | 0.645 |
| LGE (g) | 0±0 | 21.9±31.7 | 0.003 |
| LGE (%) | 0±0 | 15.7±13.4 | <0.001 |
| LAA area (cm²) | 22.2±6.1 | 28.8±11.2 | 0.015 |
| RAA (cm²) | 19.3±4.7 | 22±5.8 | 0.077 |
| MAPSE (mm) | 11.8±2.3 | 10.8±3.4 | 0.231 |
| TAPSE (mm) | 19.5±3.2 | 20.6±4.5 | 0.309 |
| LAVI (ml/m²) | 28.9±10.2 | 45.6±23.1 | 0.004 |
| LACI | 0.2±0.1 | 0.4±0.2 | <0.001 |
| LA strain (%) | 30.4±13.2 | 21.3±16.2 | 0.040 |
| LV strain (%) | 15.2±3 | 12.2±4.5 | 0.012 |
| RA strain (%) | 37±13.3 | 34.4±15.1 | 0.524 |
| RV strain (%) | 25.3±2.8 | 23.5±5.2 | 0.162 |
| LAEF (%) | 62.3±8 | 44.1±14.3 | <0.001 |
| T1map (msec) | 1010.9±53.1 | 1015.3±119.5 | 0.889 |
| ECV (%) | 23.8±2.6 | 39.3±61 | 0.350 |

Data are mean±SD. ECV, extracellular volume; LAA, left atrial area; LACI, left atrial coupling index; LAEF, left atrial ejection fraction; LA strain, left atrial strain; LAVI, left atrial volume index; LV strain, left ventricle strain; LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter LVEDVI, left ventricle end-diastolic volume index; LVESVI, left ventricle end-systolic volume index; LVESVI, left ventricle end-systolic volume index; LVSVI, left ventricle stroke volume index; LV mass index, left ventricle mass index; MAPSE, mitral annular plane systolic excursion; LVEF, left ventricle ejection fraction; RVEF, right ventricle ejection fraction; RAA, right atrial area; RVEDVI, right ventricle end-diastolic volume index; RVESVI, right ventricle end-systolic volume index; RA strain, right atrial strain; RV strain, right ventricular strain; TAPSE, tricuspid annular plane systolic excursion.

**Table 3.** Determinants of LGE expressed in grams as determined by univariate and multivariate linear regression analysis

| Variables | Univariate | | Multivariate | |
|---|---|---|---|---|
| | r | p | R2 | p |
| MAPSE (mm) | -0.117 | 0.279 | – | – |
| LAVI (ml/m²) | -0.033 | 0.836 | – | – |
| Maximum wall thickness (mm) | 0.001 | 0.992 | – | – |
| LV strain (%) | -0.056 | 0.732 | – | – |
| LVESVI (ml/m²) | 0.122 | 0.837 | – | – |
| LAEF (%) | -0.173 | 0.340 | – | – |
| LVEDD (mm) | 0.134 | 0.321 | – | – |
| LVESD (mm) | 0.007 | 0.935 | – | – |
| Age | -0.194 | 0.046 | 0.847 | 0.006 |
| LV myocardial ECV (%) | 0.323 | 0.015 | | <0.001 |
| LVEDVI (ml/m²) | -0.492 | 0.189 | | <0.001 |
| T1 map (msec) | 0.477 | 0.000 | | <0.001 |
| LV mass index (gr/m²) | 0.277 | 0.056 | | 0.002 |
| LVEF (%) | -0.208 | 0.555 | | 0.001 |
| LA strain (%) | 0.301 | 0.043 | | 0.013 |
| LACI | 0.404 | 0.153 | | <0.001 |

ECV, extracellular volume; LAVI, left atrial volume index; LV strain, left ventricle strain; LVESVI, left ventricle end-systolic volume index; LAEF, left atrial ejection fraction; LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; LVEDVI, left ventricle end-diastolic volume index; LV mass index, left ventricle mass index; LVEF, left ventricle ejection fraction; LA strain, left atrial strain; LACI, left atrial coupling index; MAPSE, mitral annular plane systolic excursion.

beyond diameter assessment. An example of this is the study of Debonnaire et al., in which both LA volume and echocardiography derived LA strain improved AF prediction in patients with normal LA size, although LA diameter, volume, and strain all relate to new-onset atrial fibrillation in HCM patients [17]. Kim et al. evaluated LA function with STE and the LV function with CMR, and they found that HCM patients had increased LAVI, impaired reservoir function, and decreased LA strain compared to the control subjects [18]. That study also suggested that the determinant of LA remodeling and dysfunction was the LV mass index rather than LV myocardial fibrosis, as indicated by LGE [18]. Nevertheless, STE has its limitations, including high interobserver variability and the challenge of tracking the thin-walled LA, particularly in patients with poor acoustic windows [19, 20].

CMR-FT, on the other hand, is the STE equivalent in CMR, and it offers high tracking quality in comparison to echocardiography [19]. Hinojar et al. explored the prognostic role of LA function measured with CMR-FT in HCM patients [21]. These investigators found that longitudinal LA strain was impaired even in patients with normal LA volume. Moreover, impaired global longitudinal strain was associated with higher all-cause mortality and with higher combined endpoints of hospital admission related to heart failure, lethal


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ventricular arrhythmias, LAV, or cardiovascular death [21]. Previous studies alluded to LA function changes preceding changes in LA size, perhaps owing to altered myocardial tissue properties [22].

In the current study, we demonstrated that HCM patients with LV myocardial LGE had higher LAVI and LACI, while their LA-strain was significantly reduced. Our findings are corroborated by previous CMR studies showing marked reduction in LA function in those patients in which HCM exhibited the greatest amount of LGE [22]. Fibrotic changes in the ventricular myocardium may predispose it to a decline in LA function, in addition to concomitant primary atrial myopathy. Such findings are clinically important, given the association of LA function with adverse outcomes in HCM, such as new onset AF [15, 17]. While LA strain has been associated with the patients' symptomatic status [23], there is sparse and conflicting data with the relationship of LA strain to LV structure. In patients with HCM, LA strain has been previously related to LV GLS, LV filling pressure, and elastic recoil, whereas those with LV systolic deformation had larger LA strain. However, this was not related to the LGE burden or LV mass [24]. In contrast, our study showed significantly reduced LA strain in those with LGE compared to those with HCM and no LGE. One possible explanation arises from the complex interplay between the LA and LV; when LA contractility is normal, LA relaxation is preserved, leading to lower LA pressure in early systole, increased LA systolic filling, and, thus, higher LA reservoir strain. This explains the direct relation between LA reservoir and indices of LA systolic function observed in this study.

One of the determinants of LA strain is LA afterload. An increase in LV afterload leads to lowering of the LV GLS. At the same time, LA strain is decreased and the worsening obstruction is often accompanied with an increase in LA pressure. Furthermore, LA strain is dependent on LA stiffness, and, given the positive association between LA stiffness and LA pressure, there is a negative association between LA strain and LV filling pressures [24]. In fact, those with LGE, as in our study, had reduced LAEF compared to those with no reduction. This, again, demonstrated poor LA contractility, ejection of blood, and reduced reservoir strain in such patients.

Although HCM is mainly considered a disease of the LV, functional and/or structural alterations might occur in the right heart chambers. RV dysfunction has been shown to predict worse adverse outcomes in several cardiovascular diseases, such as dilated cardiomyopathy [25]. However, while assessment of the right heart with 2D-echocardiography is challenging due to its complex anatomy and high load dependency, CMR-FT could provide a comprehensive high-resolution assessment [26]. Li et al. enrolled 82 HCM patients and 32 age- and sex-matched healthy controls and assessed RV strain using 3.0 Tesla CMR [27]. They found significantly lower RV global and regional strain in HCM patients compared to controls. Despite their findings of lower global and regional RV train in HCM patients with RVH compared to those in HCM patients without RVH and in patients with RV–LGE, they found no significant differences in RV strain between HCM patients with LV outflow tract obstruction (LVOTO) and those without LVOTO. These results indicate that CMR-derived strain could detect subclinical RV deformation even prior to the impairment in RVEF [27]. In the current study, we did not enroll a healthy control group. However, we found no differences between HCM patients with or without LGE with respect to RA and RV strain. Our results may indicate that right heart involvement may not be associated with LV fibrosis. Such findings contribute to the growing data on RV involvement in the prognostication and risk stratification of HCM.

## Study limitations

The limitations of this study include its retrospective, single center, cross-sectional analysis design, which might have led to selection bias. As the patients were referred for CMR studies, comparison with detailed echocardiography was not possible. Given the naturally progressive course of HCM, follow up CMR studies would have been useful to examine differences in chamber parameters over time and to support the findings of this study. We have described a small study group, with no control group, and with no LA LGE assessment. Larger studies with adequate follow up to evaluate clinical outcomes and longitudinal disease evolution and with comparisons of multi-modality assessments are needed.

## Conclusion

In conclusion, this study sheds light on the CMR-FT differences between HCM with and without LGE. We found a greater burden of LA volume but significantly lower LA and LV strain in the LGE patients, despite comparable RA and RV strain patterns. These findings further highlight LA and LV remodeling in HCM. The impaired LA function appears to have physiological significance, being associated with a greater extent of LGE. While our CMR-FT findings support the progressive nature of HCM, beginning with sarcomere dysfunction to eventual fibrosis, further studies are needed to validate these results in larger cohorts and to evaluate their clinical relevance.

*No conflict of interest is reported.*

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