Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2022;47(2):811-819
DOI: 10.17826/cumj.1086581

ARAŞTIRMA / RESEARCH

Role of cardiac magnetic resonance imaging in predicting atrial fibrillation in patients with hypertrophic cardiomyopathy

Hipertrofik kardiyomiyopati hastalarında atriyal fibrilasyon gelişimini öngörmede kardiyak manyetik rezonans görüntülemenin rolü

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Cukurova Medical Journal 2022;47(2):811-819

Abstract

Purpose: The present study sought to investigate the association between Cardiac magnetic resonance (CMR) imaging parameters including late gadolinium enhancement (LGE), total left ventricular mass (TLVM), mitral regurgitation, and left atrial (LA) volume, with atrial fibrillation (AF) in hypertrophic cardiomyopathy (HCM). patients.
Materials and Methods: Consecutive 122 patients with the diagnosis of HCM and together with having 48-hour Holter monitoring were included in the present work. Two experienced observers evaluated all CMR images. The correlation between AF and CMR parameters including TLVM, LA volume, the presence and extent of LGE, mitral regurgitation, and the maximum left ventricular thickness were evaluated.
Results: Between the LA volume and AF, a significant correlation was observed. Additionally, TLVM was also associated with AF. The logistic multivariate analysis assessing TLVM, LA volume, and the extent of LGE revealed that only the left atrial volume was the independent predictor. Significant correlations were observed between the existence and extent of LGE, TLVM, mitral regurgitation and LA volume.
Conclusion: The presence of LGE was positively correlated with LA volume. LA volume appears to be the most important independent predictor of AF in HCM patients.

Keywords: Atrial Fibrillation, Atrial volume, CMR; Hypertrophic cardiomyopathy

Öz

Amaç:, Bu çalışmada Hipertrofik kardiyomiyopati (HKMP) hastalarında geç kontrast tututulmu (GKT), toplam sol ventrikül kütlesi (TSVK), mitral yetersizlik ve sol atriyum (SA) hacmi dahil olmak üzere Kardiyak manyetik rezonans (KMR) görüntüleme parametreleri ile atriyal fibrilasyon (AF) arasındaki ilişkiyi araştırmayı amaçladık.
Gereç ve Yöntem: Bu çalışmaya HKMP tanısı alan, KMR çekimi yapılmış ve 48 saatlik Holter monitorizasyonu olan ardışık 122 hasta dahil edilmiştir. KMR tecrübesine sahip Radyoloji ve Kardiyoloji uzman hekimleri tarafından KMR görüntüleri değerlendirilmiştir. TSVK, SA hacmi, GKT varlığı ve yaygınlığı, mitral yetersizliği ve maksimum sol ventrikül kalınlığını içeren KMR parametreleri ile AF arasındaki korelasyon değerlendirilmiştir.
Bulgular: SA hacmi ve AF arasında anlamlı bir korelasyon gözlendi. Ek olarak TSVK, AF ile ilişkili bulundu. TSVK, SA hacmi ve GKT'nin kapsamını değerlendiren lojistik çok değişkenli analiz, yalnızca sol atriyal hacmin bağımsız öngörücü olduğunu ortaya koydu. GKT, TSVK, mitral yetersizlik ve SA hacminin varlığı ve yaygınlığı arasında anlamlı korelasyonlar gözlendi.
Sonuç: GKT'nin varlığı, SA hacmi ile pozitif korelasyon gösterdi. SA hacmi, HKMP hastalarında AF'nin en önemli bağımsız belirleyicisi gibi görünmektedir.

Anahtar kelimeler: Atriyal fibrilasyon, sol atriyum hacmi, kardiyak MR, hipertrofik kardiyomiyopati

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Geliş tarihi/Received: 13.03.2022 Kabul tarihi/Accepted: 24.05.2022

INTRODUCTION

Hypertrophic cardiomyopathy is a genetic disease characterized by thickening of the myocardium and caused by sarcomere mutations[1-4]. Histological and pathological variances of the HCM are generated by replacement of fibrosis due to a microvascular obstruction, myofibrillary disorder resulting from mutations in genes encoding sarcomere, and enhanced extracellular collagen amount[5-7]. For a very long time, the echocardiography had been the main method to evaluate HCM; however, the improvements in cardiac magnetic resonance imaging (CMR) have significantly transformed our diagnostic approach to HCM[8-10]. With its higher spatial resolution and multi-planar imaging capacity, CMR could readily determine the disease phenotypes. Also, CMR's capability in management of HCM by identifying the presence of fibrosis in the myocardium using delayed contrast-enhancement [Late Gadolinium Enhancement (LGE)] sequence[11,12] has brought significant improvements. Although it is impossible to differentiate the exact underlying cause of LGE based solely on CMR, numerous clinical studies have documented that LGE is connected with the enhanced risk of sudden cardiac death, ventricular arrhythmias, and heart failure[13-15]. In HCM patients, the negative effect of myocardial fibrosis is particularly related to its being a triggering substrate for arrhythmias.

Among the patients with HCM, one of the most common arrhythmia types is atrial fibrillation (AF) and AF is intimately linked to adverse outcomes and poor prognosis[16-19]. The etiology of AF is rather complicated and controversial, and many pathophysiological and anatomical factors are considered that its affects the occurrence of AF in HCM patients[20,21]. Among the proposed factors, left ventricular fibrosis has been a favoured topic in recent years. Hence, we pursued to research the association between CMR parameters including LGE, total left ventricular mass (TLVM), mitral regurgitation, and left atrial (LA) volume, with atrial fibrillation (AF) in HCM patients.

MATERIALS AND METHODS

Study population

This study was performed at Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital between January 2017 and December 2020. The HCM patients were retrospectively evaluated by using our hospital database. The clinical and demographic information of the patients were obtained by scanning the archive files of the hospital electronic medical record system. The data will be stored in a locked cabinet and will not be accessible to anyone other than the researchers specified in the study. Anonymous data of the patients were used in the analysis of the study. The patients were diagnosed in accordance with the European Society of Cardiology HCM guideline[22]. The criteria of inclusion were: (1) diagnosis of HCM in accordance with current guidelines, (2) having cardiac MRI, (3) having 48-h Holter monitoring. The criteria of exclusion were: (1) history of myocardial infarction or coronary artery disease, (2) presence of concomitant significant (moderate to severe) valvular disease rather than mitral valvular disease, (3) history of any autoimmune or storage disorder, (4) existence of hypertension, and (5) patients with insufficient data. Our article was approved by the Clinical Research Ethics Committee of Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital with the number 2019-13 on 19/02/2019. The study is also in compliance with the principles outlined in the Declaration of Helsinki.

Atrial fibrillation screening

AF screening of the patients was performed within one month before or after CMR. 12-lead basal ECG and 48-hours Holter monitoring were used for screening. 48-h Holter evaluation was performed by 2 experienced cardiologists (A.G, A.A.S). However, interobserver variability in assessing Holter monitoring findings of HCM patients have not been determined. According to the current guidelines, a recorded episode of absolutely irregular RR intervals and no discernible, distinct P waves on an electrocardiogram (ECG) for at least 30 sec. was diagnosis of AF.

CMR acquisition

All MRI studies with a 1.5 T scanner (Aera, Siemens Medical Systems, Enlargen, Germany) were obtained. By using phased-array body coils, all CMR acquisitions were performed. Our CMR protocol includes breath-hold black-axis blood spin echoes (SE), multiple breath-hold long-axis four-chamber, long-axis two-chamber, and 9-12 stacks of short-axis cine images breath-hold using balanced steady-state free precession imaging (SSFP), and LGE sequences in four-chamber, two-chamber, and short-axis views, each covering the entire myocardium of the left ventricle. LGE sequences were procured for approximately 12 minutes (range 10-15 minutes) following to administer 0.10-0.12 mmol/kg gadolinium-DTPA (Magnevist, Schering AG, Berlin, Germany). The parameters of the SSFP film image are TR/TE = 3.8/1-3 ms, slice thickness = 5 mm, interslice gap is 5 mm, time resolution = 35 m, and LGE sequence parameters are TR/TE = 9/3 ms, slice thickness = 5 mm, reversal time = 200-300 ms, adjust according to the patient to eliminate the standard myocardial signal.

Image analysis

CMR images of the patients were taken from our hospital image archiving system (PACS, Extremepacs system Ankara/Turkey). Two physicians, one cardiologist and one radiologist, (B.U., S.A.) having a broad expertise in CMR have evaluated the CMR images. Initially, the observers have calculated the left ventricular functions, including ejection fraction (EF), end-systolic volume (ESV), end-diastolic volume (EDV), stroke volume (SV), cardiac index (CI), cardiac output (CO), and TLVM using the modified Simpson's method on short-axis cine images by the software (ARGUS, Siemens, Erlangen/Germany). Maximal wall thickness was measured according to the American Heart Association segmentation model[23]. The myocardium has been divided into 16 segments mainly basal, midventricular and apical levels with six, six and four areas, respectively.

The maximal wall thickness was perpendicularly measured on short-axis cine images using digital clippers during end-diastole. The study has not focused on free muscle bundles in measuring. The left atrium volume using the biplane method during the end-systole (volume = (0.85 × four-chamber area × two-chamber area) / length of the perpendicular axis) was calculated and then were adjusted to body surface area (BSA) (Figure 1).

Respectively, we explored the left ventricular myocardium LGE using short-axis images from base to apex. The long-axis images were used as an adjunct if needed. The LGE was defined as the areas with signal intensity higher than the mean signal intensity plus two standard deviations (SD) higher than the signal intensity of the normal myocardium. The extent of LGE was automatically determined by viability prototype software (Siemens Medical Solutions, Erlangen, Germany) using 2 SD above viable myocardium as the cut-off value on short-axis images.

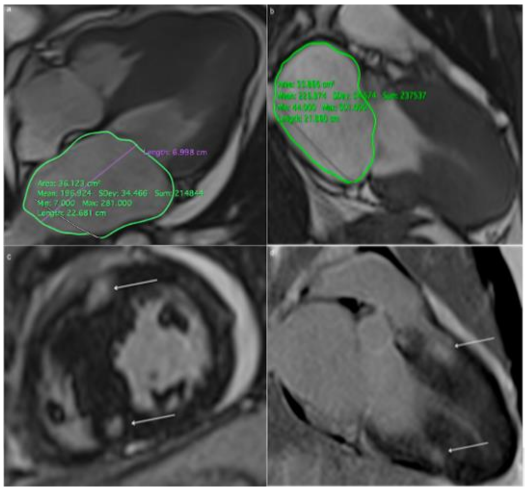

Figure 1. A 53-year-old male patient with asymmetrical septal HCM.

Four-chamber (a) cine image show dilated LA, and biplanar volumetric measurement of LA calculated as 72 mL/m². Short-axis LGE image (b) and corresponding two-chamber LGE image (c) show focal hyperintensities (arrows) in anterior and posterior septum at basal level representing fibrosis (d).

Statistical analysis

The SPSS software version 21 (SPSS Inc., Chicago, Illinois, USA) is used for for statistical analyses. The Kolmogorov-Smirnov test was used to examine the variables to determine whether or not they were correctly distributed. Normally distributed continuous variables including ESV, EDV, SV, CI, and age were compared using the Student's t-test between LGE (+) and LGE (-) patients; the Mann-Whitney U test was used to compare non-normally distributed continuous variables such as LA volume, and TLVM, and ordinary variable as NYHA class, between two groups. The Chi-square test was used to compare proportions of mitral regurgitation and gender between two groups. The associations between AF and CMR parameters were assessed using the Spearman correlation test. For multivariate analysis, the selected factors identified with univariate analyses were further entered into the logistic regression analyses to determine independent predictors of AF. The Hosmer-Lemeshow fit statistic was used to evaluate model fit. In addition, a multiple linear regression model was used to identify the independent predictors of LA volume. Model fit was assessed using appropriate residual and goodness-of-fit statistics. A P value of less than 0.05 was used to conclude statistical significance. Papavassiliu et al. detected AF in 42% of 87 HCM patients. In the study of Tani et al., AF was found in 22% of 141 HCM patients. As a result of these data, the sample size was calculated as 120 with a margin of error of 0.05 and a power of 80% in our study.

RESULTS

In our study, a total of 186 patients who underwent CMR due to HCM were screened, 64 of these patients were not included in the study due to exclusion criteria. 38 patients were excluded from the study because of hypertension, 20 patients with a history of myocardial infarction or coronary artery disease, 1 patient with autoimmune disease (rheumatoid arthritis) and 5 patients with aortic stenosis. Finally, a sum of 122 patients with HCM, 78 males (63.9%), with a mean age of 50.63 ± 13.05 years, were enrolled in the final study cohort. Table 1 shows patients' demographics, clinical and CMR findings in detail.

Atrial fibrillation was observed in 28 of 122 patients (22%). The majority of the patients (66.4%) had HCM subtype of asymmetrical septal hypertrophy and among all the patients, 40 (32.8%) of them had systolic anterior motion and 94 (77%) of them had AF. 80 (65.6%) patients had LGE (+) in the CMR and 42 (34.4%) patients did not have LGE (-) in the CMR.

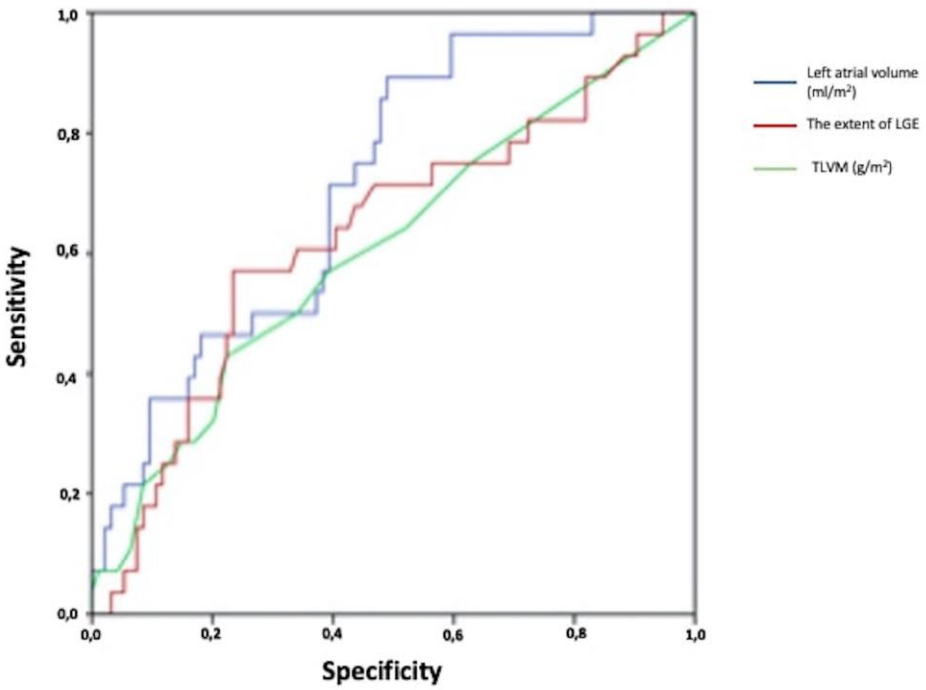

Figure 2. ROC curves of TLVM, the extent of LGE, and LA volume as a predictor of AF. For TLVM: AUC= 0.63, P= 0.035, 95% CI= 0.50 to 0.75, for the extent of LGE: AUC= 0.60, P =0.084, 95% CI= 0.48 to 0.73, and for LA volume AUC=0.71, P= 0.001, 95% CI= 0.61 to 0.81.

Table 1. Demographic, clinical and cardiac magnetic resonance findings of the patients

Variables	**Findings**
Age (years)	50.63 ± 13.05
Male Gender, n (%)	78 (63.9%)
NYHA class, n (%)	
• I	53 (43.4%)
• II	47 (38.5%)
• III	17 (13.9%)
• IV	5 (4.1%)
HCM subtype, n (%)	
• Asymmetrical septal	81 (66.4%)
• Symmetrical septal	9 (7.4%)
• Diffuse concentric	20 (16.4%)
• Asymmetrical concentric	7 (5.8%)
• Midventricular obstructive	3 (1.4%)
• Apical	2 (1.6%)
End systolic volume (mL/m2)	17.82 ± 13.81
End diastolic volume (mL/m2)	65.84 ± 18.61
Stroke volume (mL/m2)	50.03 ± 13.81
Cardiac index (L/min/m2)	3.3 ± 0.92
Cardiac output (L/min)	6.24 ± 1.8
Ejection fraction (%)	73.72 ± 9.88
Maximal left ventricular wall thickness (mm)	20.69 ± 3.85
Myocardial Mass (g/m2)	118.51 ± 47.32
Presence of Atrial Fibrillation, n (%)	94 (77%)
Presence of Mitral Regurgitation, n (%)	85 (69.7%)
Presence of Systolic Anterior Motion of Mitral Valve, n (%)	40 (32.8%)
Late Gadolinium Enhancement, n (%)	80 (65.6%)

HCM: Hypertrophic Cardiomyopathy, NYHA: New York Heart Association *All variables are expressed as mean ± standard deviations unless otherwise specified.

Table 2. Comparison of clinical and cardiac magnetic resonance findings of the LGE (+) and LGE (-) patients.

	LGE (+) patients	**LGE (-) patients**	**P value**
Age (years)	49.36 ± 13.15	53.07 ± 12.67	0.13
Presence of atrial fibrillation	21/80 (26.3%)	7/42 (16.7%)	0.23
Maximal wall thickness (mm)	19.86 ± 4.80	20.84 ± 4.08	0.30
Mitral regurgitation	30/80 (37.5%)	7/42 (16.7%)	**0.018**
Myocardial mass (g/m2)	132.30 ± 49.62	92.24 ± 28.02	**0.0001**
Ejection Fraction (%)	72.33 ± 10.72	76.36 ± 7.45	0.27
End systolic volume (mL/m2)	19.01 ± 11.21	15.62 ± 9.15	0.089
End diastolic volume (mL/m2)	66.04 ± 18.52	65.47 ± 19.01	0.87
Cardiac index (L/min/m2)	3.41 ± 0.94	3.31 ± 0.9	0.57
Stroke volume (mL/m2)	50.34 ± 14.83	49.23 ± 11.7	0.73
Left atrial volume (mL/m2)	70.56 ± 29.39	55.92 ± 24.22	**0.007**

LGE: Late Gadolinium Enhancement * All variables are expressed as mean ± standard deviations

Table 3. Correlation between the presence of atrial fibrillation and selected cardiac magnetic resonance imaging findings.

	r value	P value
Presence of LGE	0.10	0.23
Extent of LGE	0.16	0.077
Presence of mitral regurgitation	0.10	0.24
Presence of SAM of the mitral valve	0.03	0.71
Left atrial volume (mL/m^2)	0.31	<0.0001
Total left ventricular mass (g/m^2)	0.19	0.03
Maximum left ventricular thickness (mm)	0.04	0.63

LGE: Late Gadolinium Enhancement, SAM: Systolic anterior motion * All variables are expressed as mean ± standard deviations

Table 4. Correlation between the presence of the left atrial volume and selected cardiac magnetic resonance imaging findings

	r value	P value
Presence of LGE	0.25	0.004
Extent of LGE	0.28	0.001
Presence of mitral regurgitation	0.29	0.001
Presence of SAM of the mitral valve	0.24	0.007
Total Left Ventricular Mass (g/m^2)	0.23	0.003
Maximum Left Ventricular Thickness (mm)	0.19	0.051

LGE: Late Gadolinium Enhancement, SAM: Systolic anterior motion
* All variables are expressed as mean ± standard deviations

The detailed comparisons between LGE (+) and LGE (-) regarding clinical and CMR findings are shown in table 2. No statistical differences were observed between LGE (+) and LGE (-) patients in terms of EF, EDV, ESV, SV, CI, and CO (P > 0.05). Furthermore, there was no difference between groups due to gender, family history, and NYHA class (P > 0.05, details not shown). The median total myocardial mass in LGE (+) patients was higher than in LGE (-) patients [132.30 (57.9) g/m2 vs. 92.24 (38.3) g/m2, P <0.0001]. Additionally, the median left atrium volume of the LGE (+) patients were found increased when compared to LGE (-) patients, [70.56 mL/m2 vs. 55.92 mL/m2, P= 0.004] and presence of mitral regurgitation was determined as increased in patients with LGE (+) [30 (37.5%) vs. 7 (16.7%), p=0.018). Despite the fact that the frequency of AF was higher in LGE (+) patients (26.3%) compared to LGE (-) patients (16.7%), it is identified that no statistical difference appeared between the two groups (P=0.23).

The correlation between the presence of AF and selected CMR findings is provided in Table 3. We identified no correlation between the presence of LGE and AF in our study cohort (r=0.10, P=0.23). Moreover, no correlation was observed between the extent of LGE and AF (r = 0.16 P = 0.077).

A significant correlation was observed between left atrial volume and the presence of AF (r=0.66, P<0.0001). Additionally, TLVM was found to correlate with AF (r=0.44, P=0.035). Figure 2 shows characteristic (ROC) curve analysis of TLVM [area under the curve (AUC)= 0.63, P= 0.035, 95% CI= 0.50 to 0.75], extent of LGE (AUC= 0.60, P =0.084, 95% CI= 0.48 to 0.73), and LA volume (AUC=0.71, P= 0.001, 95% CI= 0.61 to 0.81) as predictors of AF. The cutoff value for LA volume was 59.3 mL/m2, which had a predictive power of AF with a sensitivity of 82.1% and a specificity of 53% (Figure 2). Logistic multivariate analyses assessing TLVM, LA volume, and the extent of LGE revealed that only the LA volume was the independent predictor of AF (P=0.0001, OR= 2.85, 95% CI 1.011 – 4.55).

While there was no correlation between the presence of AF and the extent of LGE, moderate to strong correlations were observed between the presence of LGE, the extent of LGE, TLVM, mitral regurgitation, and LA volume (P<0.05). The correlations between the left atrial volume and CMR parameters are shown in table 4.

DISCUSSION

The present study assessed the presence of AF in HCM patients. The study demonstrated that TLVM and LA volume were associated with AF in these patients, yet only LA volume remained an independent predictor of AF in multivariate analysis. Any correlation between the presence or extent of LGE and AF has not been determined. The extent of LGE, in addition to mitral regurgitation, the presence of LGE and TLVM, were positively associated with the increased LA volume.

The prevalence of AF was 23% in the study cohort, parallel to the literature[20]. In line with our results, studies by Pujadas et al.[24] and Papavassiliu et al.[25] demonstrated that the frequency of AF was not associated with the presence of LGE in the left ventricular wall. On the other hand, both studies observed a relationship between the extent of LGE and AF.

Contrary to these researches, the current study identified no association between the extent of LGE and AF. There are several possible reasons for these inconsistencies. First, Pujadas et al.[24] did not perform a multivariate analysis to identify whether the extent of LGE was an independent predictor of AF. For instance, despite the extent of LGE being associated with AF in univariate analysis, only LA volume remained an independent predictor in Papavassiliu's research[25]. We suggested that the extent of left ventricular fibrosis might indirectly contribute to the risk of AF by reducing ventricular compilation and diastolic filling, hence increasing left ventricular pressure and sequentially atrial pressure, which eventually leads to an increase in atrial strain and AF. Furthermore, a more recent study by Maron et al.[26] underlyned that the extent of LGE was not linked with AF occurrence, which supported the findings of our study.

LA volume was the main independent predictor of AF in our study. The impact of the LA volume on the occurrence of AF has been demonstrated in many CMR and echocardiographic studies[25-30]. In the present work, the optimal cut-off LA volume was 59.3 mL/m2 to predict AF with 82.1% sensitivity and 53% specificity. The CMR study of Papavassilu[25] identified a cut-off value of 50 ml/m2 in predicting AF with a sensitivity of 80.8% and specificity of 64.1%. Maron et al.[26] determined the cut-off value of LA volume as 118 ml, yielding the optimal diagnostic accuracy to predict AF. Besides CMR, many different cut-off values have been reported using different measurement methods and modalities[20]. Although it is not likely to compare these cut-off values, ample evidence indicates that LA volume is one of the significant predictors of AF in HCM patients. The we asserted that LA volume in HCM patients should be carefully evaluated and interpreted.

In the present work, TLVM also predicted the occurrence of AF in univariate analysis, yet the association did not reach significance in our multivariate model. There is conflict in evidence regarding the impact of TLVM on the occurrence of AF[31,32]. TLVM was found positively associated with the LA volume, as this connection has also been determined in several other articles[31,32]. Furthermore, in the present work, TLVM was also associated with the extent and the presence of left ventricular fibrosis concordant with the results of Maron et al.'s study[26].

Mitral regurgitation is a recognized and common entity in HCM, exacerbating atrial wall stress by increasing volume load[16,33]. In our study cohort, 30.3% of patients had mitral regurgitation, and the existence of the regurgitation was positively correlated with LA volume. However, no association has been observed between mitral regurgitation and AF concordant with the findings of the CMR studies by Pujadas et al.[24] and Papavassiliu et al.[25] while Maron et al.[26] revealed a significant correlation between the mitral regurgitation and AF. On the other hand, these studies had not included mitral regurgitation as a parameter in multivariate analysis.

We assume that TLVM, mitral regurgitation, and the presence or extent of LGE do not directly impact the development of AF. These pathological alterations exacerbated atrial stretch and pressure, which eventually ends in atrial remodelling and myopathy whichis led by atrial fibrosis. This pathological remodeling substantially shortens the effective atrial refractory interval and primes the ectopic triggers to prompt and sustain AF[19].

Several limitations need to be acknowledged. First and foremost, the we did not obtain histopathological samples from the LGE positive areas; hence, using LGE as a surrogate marker for myocardial fibrosis mainly was based on assumptions drawing on the previous histological reports[5-7]. Second, the we did not evaluate LV diastolic dysfunction impact on AF given the inadequate temporal resolution of CMR, which is a well-known predictor of AF. Finally, we did not evaluate interobserver variability in assessing CMR findings of HCM patients. Notwithstanding, CMR measurements have excellent reproducibility rates, as demonstrated in previous reports[34].

In conclusion, the extent and the presence of LGE were positively correlated with LA volume, yet no association was observed between AF and the extent of LGE in HCM patients. LA volume seems to be the important independent predictor of AF in HCM patients. If there is a high left atrial volume in the CMR evaluation of HCM patients, it may be important to perform AF screening more carefully. Also we need more data and large cohorts for evaluation of CMR tools for predicting AF in HCM patients.

Yazar Katkıları: Çalışma konsepti/Tasarımı: AG, AAŞ, ME; Veri toplama: SA, SUU; Veri analizi ve yorumlama: AAŞ, ME; Yazı taslağı: AG, BU, SUU; İçeriğin eleştirel incelenmesi: ME, ÖÇ; Son onay ve sorumluluk: AG, AAŞ, SUU, SA, BU, ÖÇ, ME; Teknik ve malzeme desteği: -; Süpervizyon: ÖÇ, BU, SA; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Sağlık Bilimleri Üniversitesi Istanbul Mehmet Akif Ersoy Göğüs, Kalp ve Damar Cerrahisi Eğtim ve Araştırma Hastanesi Kminik Araştırmalar Etik Kurulundan 19.02.2019 tarih ve 2019-13 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek almadıklarını beyan etmişlerdir.
Author Contributions: Concept/Design : AG, AAŞ, ME; Data acquisition: : SA, SUU; Data analysis and interpretation: AAŞ, ME; Drafting manuscript: AG, BU, SUU; Critical revision of manuscript: ME, ÖÇ; Final approval and accountability: AG, AAŞ, SUU, SA, BU, ÖÇ, ME; Technical or material support: -; Supervision: ÖÇ, BU, SA; Securing funding (if available): n/a.
Ethical Approval: For this study, ethical approval was obtained from the Ethics Committee of the University of Health Sciences Istanbul Mehmet Akif Ersoy Thoracic, Cardiovascular Surgery Training and Research Hospital Clinical Research dated 19.02.2019 and numbered 2019-13.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: The authors have stated that they have not received financial support.

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