Art. 1.12382-PM 28261

European Review for Medical and Pharmacological Sciences 2023; 27: 199-207

The frontal planar QRS/T angle in patients with non-ischemic type late gadolinium enhancement on cardiac magnetic resonance

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Abstract. – OBJECTIVE: Evaluation of myocardial fibrosis may offer an insight into underlying pathological mechanisms of ventricular arrhythmias. We intended to investigate the possible association between the presence and extent of myocardial fibrosis and ventricular repolarization heterogeneity based on frontal planar QRS/T angle.

PATIENTS AND METHODS: We retrospectively investigated patients in whom gadolinium-based contrast agent cardiac magnetic resonance imaging was performed due to the suspicion of any myocardial disease. Patients with non-ischemic type late gadolinium enhancement (LGE) were enrolled into this study. The association between presence and extent of myocardial LGE and frontal planar QRS/T angle defined as the absolute difference between QRS wave axis and T-wave axis on a resting 12-lead surface ECG was evaluated.

RESULTS: The frontal planar QRS/T angle was significantly higher in patients with myocardial fibrosis indicated by LGE compared to those without LGE (61.67 ± 40.70 *vs.* 37.27 ± 32.35, $p < 0.001$). LGE extent score assessed by visual 17-segment model was the only independent variable, which had a significant effect on frontal planar QRS/T angle [Unstandardized Coefficients B = 4.052, 95% CI [(2.025) – (6.079), $p < 0.001$].

CONCLUSIONS: In conclusion, this study showed that inhomogeneous areas of myocardium due to varying degrees of myocardial fibrosis might affect the electrical activity of the left ventricle, even with normal left ventricular dimensions and function.

Key Words:

Cardiac magnetic resonance imaging, Non-ischemic type late gadolinium enhancement, Myocarditis, Frontal planar QRS/T angle.

Introduction

Myocardial fibrosis, as evidenced by LGE, may offer an insight into underlying pathological mechanisms of ventricular arrhythmias, and can identify a subgroup of patients who are at higher risk for life-threatening ventricular arrhythmias. Despite a long list of possible causes, the most common etiology remains myocarditis characterized by inflammation of the myocardium with or without cardiac dysfunction[1]. Nevertheless, myocarditis appears to be one of the frequent causes of sudden cardiac death due to lethal ventricular arrhythmias in individuals below 40 years of age, especially in acute phase[2]. However, the identification of patients at high risk for malignant arrhythmias remains as a challenging problem.

Endomyocardial biopsy is still considered as the gold standard for the diagnosis of myocardial fibrosis. However, it has inherent limitations. Patchy involvement of the myocardium either would derive false negative results or require additional sampling at the cost of increased complication rates. In the recent years, cardiac magnetic resonance (CMR) imaging has emerged as an exclusive diagnostic tool, due to its high spatial resolution and multiplanar capability that allow comprehensive visualization of all cardiac structures (myocardium, valves, pericardium, great vessels) and tissue characterization, overcoming the well-known limitations of echocardiographic imaging[3-5]. Furthermore, contrast enhancement imaging with the use of gadolinium has improved the diagnostic yield of CMR[6].

The QRS axis reflects the main orientation of the electrical activity of the heart during ventricular depolarization, whereas the T axis reflects it during ventricular repolarization. The frontal planar QRS/T angle simply describes the angle between main electrical axes of ventricular depolarization and repolarization in the 12-lead electrocardiogram (ECG)[7]. Abnormalities in ventricular depolarization and repolarization are well known predictors of life-threatening ventricular arrhythmias[8]. Similarly, the myocardial fibrosis

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or scar, as evidenced by late gadolinium enhancement (LGE), appears to be a strong predictor for both spontaneous and inducible ventricular tachycardia[9,10]. However, there is not enough data supporting the predictive role of LGE for ventricular repolarization heterogeneity in patients with varying degrees of myocardial fibrosis. In this study we investigated the possible association between the presence and extent of myocardial fibrosis diagnosed by LGE on CMR and ventricular repolarization heterogeneity based on frontal planar QRS/T angle.

Patients and Methods

Study Population

We retrospectively investigated patients, who were referred to our institute for further evaluation of chest pain. Patients' data, including detailed clinical evaluation, 12-lead electrocardiogram (ECG), 2-dimensional transthoracic echocardiography, and coronary angiography (if performed) were revealed from medical charts. Patients with LGE on CMR located in mid-myocardial and/or sub-epicardial layer of myocardial wall indicating non-ischemic myocardial injury were enrolled into this study (Figure 1A and 1B). Exclusion criteria were as follows: acute myocarditis, ischemic-type LGE which involves the sub-endocardium, with varying degrees of transmural extension corresponding to the distribution of coronary arteries, dilated cardiomyopathy either ischemic or non-ischemic, atrial fibrillation, inadequate or incomplete ECG data, hypertrophic cardiomyopathy, restrictive cardiomyopathy, suspected infiltrative heart disease or other specific cardiomyopathies, valvular heart disease, congenital heart disease, contraindication to CMR (claustrophobia, heart valve prostheses, pacemaker, ICD, and metallic clips) and chronic renal failure with an estimated glomerular filtration rate of < 30 mL/min. A total of 153 CMR images were analyzed. 35 patients who met the above criteria were excluded. 118 patients were enrolled in the study. The Ethics Committee of the Gulhane Training and Research Hospital approved the study protocol.

Measurement of Frontal Planar QRS/T Angle

Resting 12-lead surface ECG with a paper speed of 25 mm/s and a signal size of 10 mm/mV was assessed for each patient. The QRS wave axis and T-wave axis were obtained from automated ECG reports. The absolute difference between them was defined as frontal planar QRS/T angle. If such a difference exceeded 180 degrees, the difference was calculated by subtracting from 180 degrees[11].

CMR Protocol and Image Analysis

CMR imaging was performed with a 1.5T scanner (Symphony; Siemens, Erlangen, Germany) using 6-channel body-array coil as a receiver. Breath-hold cine CMR images were obtained using retrospectively electrocardiographically gated segmented true fast imaging with steady-state free-precession (SSFP). Cine CMR images were acquired in vertical, horizontal long-axis and short-axis planes covering the whole left ventricle. Typical imaging parameters were TR/TE 3.05/1.3 ms, flip angle 80 degrees, 192 × 192 matrix and 240-340 mm field of view. Slice thickness was 8 mm and interslice gap 20% (2 mm). Eight to ten minutes after intravenous injection of 0.1 mmol/kg 0.5M gadolinium-based contrast agent LGE imaging was performed. LGE images were acquired in the same views as for cine images, using phase sensitive inversion-recovery (PSIR) sequence. Typical imaging parameters were TR/TE 28/4.8 ms, flip angle 25 degrees,

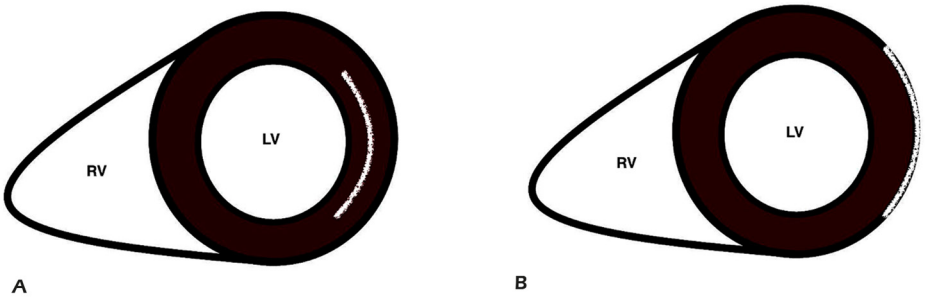

Figure 1. Illustration shows mid-myocardial (**A**), and sub-epicardial localization of LGE in the myocardial wall (**B**).

256 × 256 matrix, and 240-340 mm field of view. Slice thickness was 8 mm and interslice gap 20% (2 mm). Inversion times were optimized to null the signal intensity of normal myocardium in the TI scout images (200-330 ms).

CMR images were analyzed for left ventricular myocardial LGE by an experienced cardiovascular radiologist. LGE presence was evaluated visually and LGE in the myocardium was determined as mid-myocardial and/or sub-epicardial localization (Figure 2A and 2B). Visual scoring method based on the standard 17-segment model was used to estimate the global extent of LGE in the left ventricle. This method has been shown to be rapid and accurate in estimating LGE both in ischemic and non-ischemic cardiomyopathies[12-14]. The extent of LGE was expressed as the sum of the scores of each segment involved. Left ventricular functional parameters (EF, EDV, ESV) were calculated with standard software (ARGUS, Siemens Healthcare, Erlangen, Germany) on workstation.

Statistical Analysis

The data were tested for normal distributions using the Kolmogorov-Smirnov test. Continuous variables were described as mean ± standard deviation (SD) and categorical variables as percentages. Chi-square test was used to compare categorical data. An independent sample *t* test was used to compare quantitative data with normal distribution between groups, while Mann-Whitney U test was used for data without normal distribution. Spearman's and Pearson's correlation coefficients were used to perform univariate correlation with frontal planar QRS/T angle. Following univariate correlations, a multivariate linear regression model with backward selection process using the variables, which were significant at univariate analysis, together with risk factors, was applied to identify independent predictors of frontal planar QRS/T angle. Differences were considered statistically significant when the *p*-value was < 0.05. The Statistical Package for Social Sciences version 20 (IBM Corp., Armonk, NY, USA) was used for all calculations and statistical analyses.

Results

A total of 118 patients (mean age 28.00 ± 7.22 years) were enrolled in this study. The study group consisted of 78 patients with LGE on CMR, which was located in mid-myocardial and/or sup-epicardial layer of myocardial wall, were considered as non-ischemic type of myocardial injury. 40 patients without LGE on CMR were accepted as control group. Since our institute is a military hospital, the study population was consisted of solely adult males, and 55 of the patients (46.6%) were smokers.

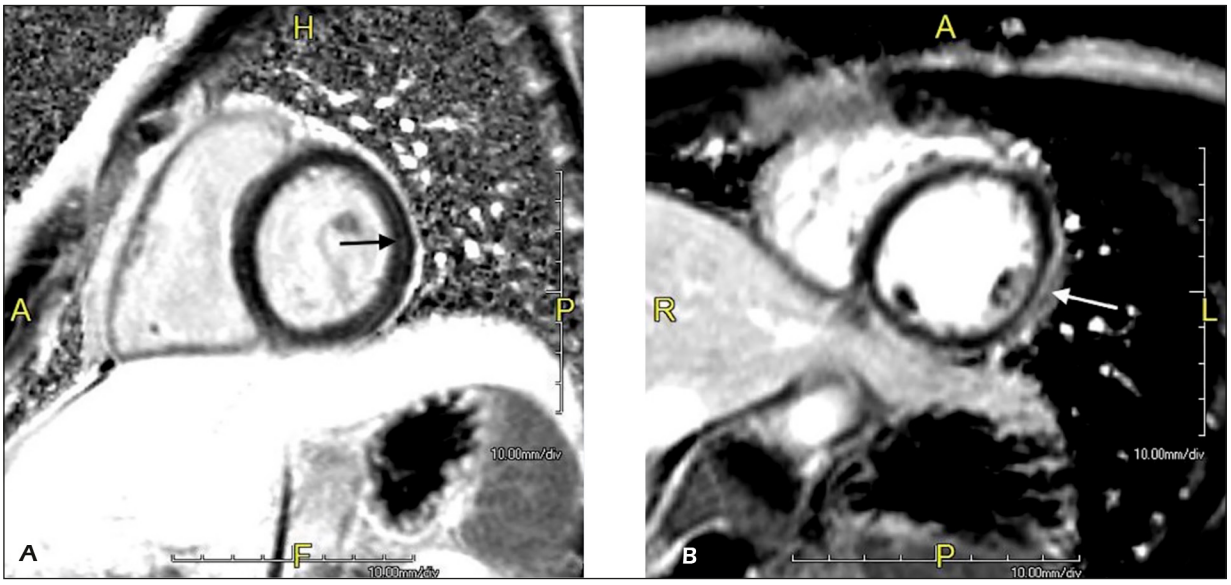

Figure 2. Cardiac magnetic resonance images showing mid-myocardial (**A**), and sub-epicardial localization of LGE in two different patients (**B**).

Table I. Results of the study group.

	LGE (-) (n = 40)	LGE (+) (n = 78)	*p*-value
Age, years	29.10 ± 8.98	27.43 ± 6.11	0.135*
Smoke, n (%)	21 (52.5)	34 (43)	0.196
White blood cell, (10^3/μL)	8.12 ± 1.99	9.33 ± 4.24	0.450*
Hemoglobin, (g/dL)	15.57 ± 0.98	15.24 ± 1.30	0.195*
Hematocrit, (%)	45.57 ± 2.32	45.07 ± 3.78	0.322*
Red cell distribution width (%)	13.45 ± 1.20	13.85 ± 1.89	0.469*
Platelet count, (10^3/μL)	243.17 ± 38.06	241.84 ± 52.71	0.536*
Neutrophil / Lymphocyte ratio	2.13 ± 0.89	3.03 ± 3.17	0.573*
ECG Findings			
QRS duration, (msn)	95.92 ± 12.03	100.43 ± 17.07	0.098*
QTc, (msn)	398.17 ± 23.34	409.33 ± 34.50	0.068
Frontal planar QRS/T angle, (o)	37.27 ± 32.35	61.67 ± 40.70	< 0.001
Echocardiography Findings			
IVSd, (mm)	8.60 ± 1.35	8.79 ± 1.13	0.209*
LVIDd, (mm)	45.12 ± 2.76	47.20 ± 4.35	0.014*
LVEF, (%)	61.17 ± 6.23	58.55 ± 8.50	0.180*
Ao ann, (mm)	22.37 ± 2.84	21.79 ± 2.50	0.398*
LA, (mm)	32.00 ± 7.11	31.37 ± 5.09	0.557*
CMR findings			
LVEF, (%)	56.27 ± 8.36	54.82 ± 7.59	0.225*
LV EDV, (ml)	112.39 ± 48.35	135.60 ± 31.80	0.046*
LV ESV, (ml)	50.54 ± 24.15	61.30 ± 21.14	0.122*
LGE involvement type, n (%)			
None	40 (100)		< 0.001
Sub-epicardial		8 (10.3)	
Mid-myocardial		28 (35.9)	
Mixed		42 (53.8)	
LGE extent score	NA	5.28 ± 2.78	NA

LGE was located in mid-myocardial (28 patients), sub-epicardial (8 patients) layer of myocardial wall and 42 patients had mixed type LGE. LGE extent score assessed by visual 17-segment models was 5.28 ± 2.78. Furthermore, our data demonstrate that patients with myocardial fibrosis have larger left ventricle end-diastolic internal diameter and higher CMR end-diastolic volume compared to those without myocardial fibrosis (Table I). However, left ventricular ejection fraction (LVEF) measured either by echo or CMR did not differ significantly between the two groups.

The frontal planar QRS/T angle was significantly wider in patients with myocardial fibrosis indicated by LGE compared to those without LGE (61.67 ± 40.70 *vs.* 37.27 ± 32.35, $p < 0.001$). Afterwards, we compared the frontal planar QRS/T angle between different LGE types. The frontal planar QRS/T angle was 56.53 ± 35.92 for mid-myocardial involvement, 58.87 ± 27.29 for sub-epicardial involvement, and 65.64 ± 45.81 for mixed type involvement. According to the result of one-way ANOVA test, there was no statistically significant difference for frontal planar QRS/T angle between different LGE types (p=0.649) (Figure 3). Corrected QT Interval (QTc), which also represent the electrocardiographic correlate of ventricular depolarization and repolarization, was also higher in patients LGE on CMR in our study. However, the difference was not statistically significant possibly due to the small sample size of our study (p=0.068).

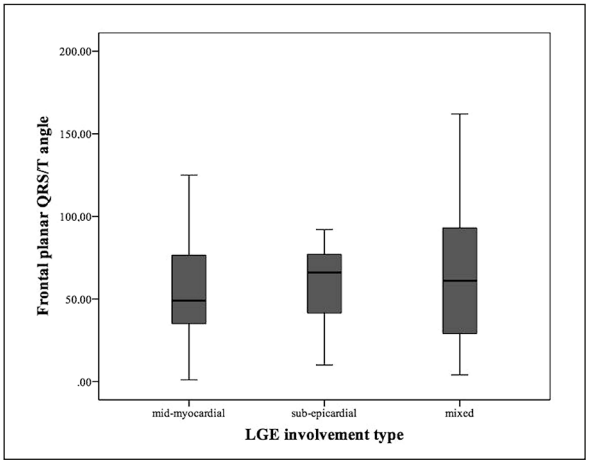

Figure 3. Comparison of frontal planar QRS/T angle for different LGE types (One-Way ANOVA shows p=0.649).

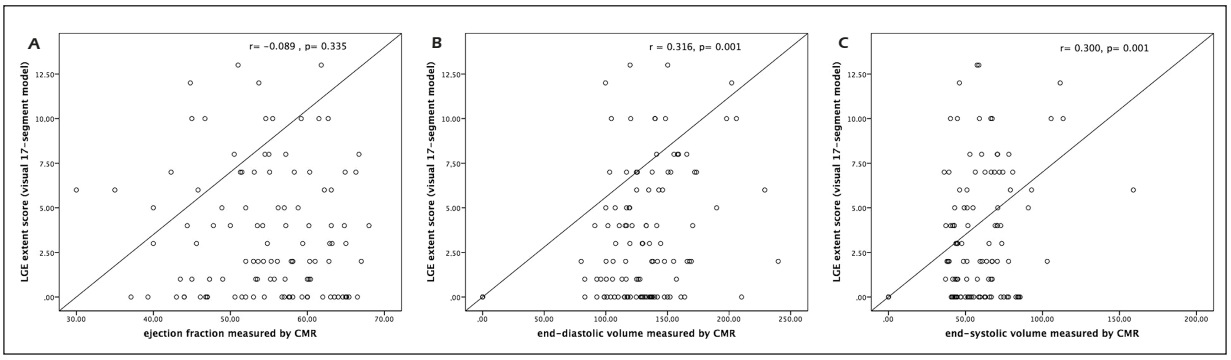

Figure 4. Correlations between CMR parameters (**A)** ejection fraction, (**B)** end-diastolic volume, (**C)** end-systolic volume] and LGE extent score.

In univariate correlation analysis, there were significant correlations with LGE extent score and CMR end-diastolic and end-systolic volumes. However, probably due to small size of study population, there was no significant correlation between LGE extent score and LVEF measured by CMR (Figure 4). Left ventricle end-diastolic internal diameter (r=0.185, p=0.045), LGE involvement type (r=0.288, p=0.002) and LGE extent score assessed by visual 17-segment model (r=0.345, $p < 0.001$) were significantly correlated with frontal planar QRS/T angle. Furthermore, a backward stepwise multivariate linear regression analysis revealed that LGE extent score assessed by visual 17-segment model was the only independent variable, which had a significant effect on frontal planar QRS/T angle [Unstandardized Coefficients B = 4.052, 95% CI [(2.025) – (6.079), $p < 0.001$] (Table II).

Discussion

In our study, we found that the presence and the extent of non-ischemic type LGE was independently associated with frontal planar QRS/T angle, which is a simple indicator of ventricular repolarization heterogeneity.

LGE-CMR is a noninvasive tool in discriminating regions of fibrosis (scar), necrosis, or inflammation from the normal tissue. After intravenous injection of gadolinium-contrast, it is washed out rapidly in healthy myocardium, whereas retention of gadolinium prolongs in damaged myocardial tissue[15]. The proposed mechanism underlying contrast enhancement is the replacement of necrotic myocytes by fibrous tissue during the chronic healing phase of myocardial inflammation. In clinical practice, the question often arises as to whether this myocardial fibrosis is ischemic or non-ischemic. On LGE-CMR, focal myocardial injury located in the mid-myocardium and sub-epicardium of LV, unrelated with the distribution of coronary arteries, is indicative of probable viral myocarditis and/or non-ischemic cardiomyopathy[16,17]. In myocarditis, the subendocardial tissue is spared, in contrast to what occurs in myocardial infarction. Recently, it has also been described that the two patterns of LGE in

Table II. Univariate and Multivariate analysis based on various variables likely to affect the frontal planar QRS/T angle.

Variable	Univariate analysis		Multivariate analysis	
	r	*p*-value	Unstandardized coefficients B (95% CI)	*p*-value
LVIDd	0.185	0.045	1.163 [(-0.582)-(2.907)]	0.189
LVEF, (echo)	-0.151	0.102	-0.503 [(-1.381)-(0.375)]	0.258
QTc	0.117	0.207	0.078 [(-0.142)-(0.299)]	0.485
LGE Involvement type	0.288	0.002	1.100 [(-6.997)-(9.197)]	0.788
LGE extent score	0.345	< 0.001	4.052 [(2.025)-(6.079)]	< 0.001

LVIDd: left ventricle diastolic internal diameter; LVEF: left ventricular ejection fraction; QTc: corrected QT Interval; CMR: cardiac magnetic resonance; LGE: late gadolinium enhancement. * = p value at the last step, which the independent variables remained in model.

myocarditis patients are associated with different types of viral infection. The hyperenhancement of the subepicardial layer of the LV lateral wall was often due to parvovirus B19 infection, while mid-myocardial hyperenhancement was more often associated with herpes virus 6 or infection of both viruses[18,19]. In addition, post-mortem evaluations reported the epicardial layers of the lateral wall as the most common location of myocardial necrosis in myocarditis patients who died suddenly[20]. With relatively small sample size of our study, the LGE pattern was mainly mixed type, which includes mid-myocardial and sub-epicardial layers, while only 12 patients had sole sub-epicardial LGE.

There is a lack of consensus on the best method of LGE detection and quantification. Visual analysis based on a threshold of 2SD above that of the remote myocardium was often proposed to determine the presence of LGE in clinical studies[21,22]. Nonetheless, LGE extent is also variably described in studies as a percentage of left ventricular mass or scar volume[21,23,24]. However, these methods are time-consuming, comprehensive and difficult to use in routine daily practice. In this study, the visual scoring technique through the standard 17-segment model was used to assess the overall extent of LGE in the left ventricle, as used in echocardiography for the evaluation of wall motion abnormalities. This has been shown to be a rapid, accurate and reproducible method to estimate the extent of LGE[12-14].

To date, several studies[21,25-30] have demonstrated that LGE-CMR not only improve the detection of myocardial fibrosis, but also indicate increased risk of adverse cardiovascular events including heart failure related hospitalization, all-cause mortality and poor responses to standard medical and interventional therapies, independent of traditional risk factors. The reason why LGE pattern was related to poor prognosis has not been fully elucidated. Two important possibilities are worsening of diastolic functions and heart failure symptoms due to increased pulmonary capillary wedge pressure and development of scar-related ventricular arrhythmia[31].

The frontal planar QRS-T angle has evolved as a quick, safe, and non-invasive tool for assessing abnormalities in ventricular repolarization and depolarization. The frontal planar QRS-T angle has been found to carry prognostic value for the prediction of malignant ventricular arrhythmias, cardiac and/or all-cause mortality in general population and different patients' groups[11,32-35]. The direction of the ventricular depolarization and repolarization axes is in parallel, as a consequence of the balanced regulation of electric activation. Therefore, narrow frontal planar QRS/T angle is indicative of a predominantly concordant ECG, while wider frontal planar QRS/T angle likely represent as a discordant ECG[36]. This angle is inherently associated with structural and functional myocardial changes.

Despite many studies[32-36] about this new parameter on several cardiac disorders, to our knowledge, our study is the first to report on the predictive value of the frontal QRS-T angle in in patients with LGE on CMR. In our study, we found that frontal planar QRS/T angle is wider (but still in the normal range) in patients with myocardial fibrosis, as evidenced by non-ischemic type LGE on CMR, compared to those without myocardial fibrosis. The distortion of electrical forces through sub-epicardial or mid-myocardial fibrosis regions and/or electrical instability of these damaged myocardium segments *via* re-entrant circuits might be the possible pathophysiological mechanisms underlying the increased heterogeneity of ventricular repolarization demonstrated by wider frontal planar QRS/T angle.

Previous studies[30,37,38] reported that the arrhythmic risk is increased proportionally with the increasing percentage of myocardial fibrosis (scar). In this regard, Gulati et al[26] showed that the LGE size was an independent predictor of malignant arrhythmic events with an HR of 1.08 per 1% increase in patients with non-ischemic cardiomyopathy. Klem et al[39] found a significant increase in the risk of malignant arrhythmia when the LGE size exceeded 5% of left ventricle mass. In accordance with previous studies[30,37-39], our study showed a positively significant correlation between frontal planar QRS/T angle and the extent of LGE by visual 17-segment model assessment, and thereby, we proposed that a greater extent of LGE might confer a higher arrhythmic risk. In contrast, it should be remembered that the absence of LGE does not guarantee an uneventful arrhythmic outcome.

Limitations

This was a retrospective analysis with a relatively small number of patients. The present study was performed in a military hospital; therefore, all the study population was male. For this reason, it may be difficult to generalize our results to general community. Since endomyocardial biopsy was not performed, ei-

ther infiltrative or storage myocardial disease could not be excluded definitively. However, no patients had a CMR pattern consistent with these diseases. The lack of long-term prognostic data and quantitative analysis of LGE are other limitations. Although there is no consensus on the strategy how to exactly define the extent of LGE, we calculated the extent of LGE by visual assessment based on 17-segment model and did not perform a quantitative analysis. Finally, we did not measure the spatial QRS-T angle, which has better prognostic value for cardiac risk prediction[40]. Despite these limitations, we believe that our study can give inspiration for further larger sample size prospective studies.

Conclusions

Our study showed that inhomogeneous areas of myocardium due to varying degrees of myocardial fibrosis might affect the electrical activity of the left ventricle demonstrated by frontal planar QRS/T angle, even with normal left ventricular dimensions and preserved LVEF. We believe that our study provides an arrhythmic insight into the pathophysiological consequences of myocardial fibrosis. Subjects with non-ischemic type LGE on CMR and wider frontal planar QRS/T angle may require closer follow-up for arrhythmic events.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Ethical Approval
All procedures in this study were in accordance with the ethical standards of the institutional local Ethics Committee of the Gulhane Training and Research Hospital and with the regulations of Declaration of Helsinki.

Informed Consent
Not required.

Funding
There is currently no funding source related with this study.

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