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Association of ECG markers with myocardial fibrosis as assessed by CMR in different clinical settings

ECG and CMR fibrosis

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Abstract

BACKGROUND

Cardiac magnetic resonance (CMR) is a unique tool for non-invasive tissue characterization, especially for identifying fibrosis.

AIM

This study aims to present the existing data regarding the association of electrocardiographic (ECG) markers with myocardial fibrosis identified by CMR- late gadolinium enhancement (LGE).

METHODS

A systematic search in Medline and Cochrane databases through February 2021 was performed.

RESULTS

A total of 32 studies were included. In hypertrophic cardiomyopathy (HCM), Fragmented QRS (fQRS) is related to the presence and extent of myocardial fibrosis. fQRS and abnormal Q waves are associated with LGE in ischemic cardiomyopathy patients, while fQRS has also been related to fibrosis in myocarditis. Selvester score, abnormal Q waves, and notched QRS have also been associated with LGE. Repolarization abnormalities as reflected by increased Tp-Te, negative T-waves, and higher QT dispersion are related to myocardial fibrosis in HCM patients. In patients with Duchenne muscular dystrophy, a significant correlation between fQRS and the amount of myocardial fibrosis as assessed by LGE-CMR was observed. In atrial fibrillation patients, advanced inter-atrial block is defined as P-wave duration ≥ 120 ms, and biphasic morphology in inferior leads is related to left atrial fibrosis.

CONCLUSION

Myocardial fibrosis, a reliable marker of prognosis in a broad spectrum of cardiovascular diseases, can be easily understood with an easily applicable ECG. However, more data is needed on a specific disease basis to study the association of ECG markers and myocardial fibrosis as depicted by CMR.

Key Words: Myocardial fibrosis; Late gadolinium enhancement; Electrocardiogram; Cardiac magnetic resonance

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Core Tip: Myocardial fibrosis, a reliable marker of prognosis in a broad spectrum of cardiovascular diseases, can be easily understood with an easily applicable electrocardiogram (ECG). However, more data is needed on a specific disease basis to study the association of ECG markers and myocardial fibrosis as depicted by cardiac magnetic resonance.

INTRODUCTION

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Cardiac magnetic resonance (CMR) is a useful non-invasive and radiation-free imaging modality that is the gold standard for estimating left ventricular volumes and ejection function [1]. Furthermore, CMR is a unique tool for non-invasive tissue characterization, especially for identifying edema, infarction, scar, and fibrosis. Tissue characterization can provide useful data not only for diagnostic purposes but also for the risk stratification of patients in different clinical settings [2-6]. In this setting, late gadolinium enhancement (LGE) is a commonly used CMR technique to identify myocardial fibrosis. However, CMR is not a widely available imaging modality, and also the high cost limits its widespread use in clinical practice.

On the other hand, an electrocardiogram (ECG) is a well-established, easily obtained, low-cost diagnostic tool that is the cornerstone of cardiological evaluation. ECG markers have been associated with the presence of myocardial fibrosis, as depicted from CMR evaluation. This systematic review aims to present the existing data regarding the association of ECG markers with myocardial fibrosis identified by CMR-LGE.

MATERIALS AND METHODS

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement) [7]. PROSPERO ID: CRD42021225119.

Search strategy

This study aimed to identify all relevant studies that provided data about the association of ECG markers with myocardial fibrosis as depicted in CMR. Two independent investigators searched Medline and Cochrane databases systematically through February 2021. The reference lists of all included studies, relevant review studies, systematic reviews, and meta-analyses were manually searched. The following keywords were used in the search strategy: “(CMR OR cardiac magnetic resonance) AND (LGE OR late gadolinium enhancement) AND (ECG OR electroc*)” without any limitations. We first screened the titles and abstracts of each retrieved study, and in case of considering a study relevant, we studied the full text.

Inclusion/exclusion criteria

We included studies that provided data regarding the association of any ECG markers with myocardial fibrosis as depicted in CMR in different clinical settings. We excluded studies that did not provide data about the studied outcome, studies that provided data about the association of endocardial electrograms with fibrosis, or data about the association of atrial LGE with atrial fibrillation, as well as review studies, case reports/series, and experimental studies.

Data extraction

The data extraction was performed independently by two authors. The following data were extracted: First author, year of publication, journal, type of study (single or multicenter), number of patients, gender, age, clinical setting, ECG markers that were studied as well as the major outcomes reported in each study. The Newcastle–Ottawa Quality Assessment Scale (NOS) was used for the quality assessment of the observational studies [8].

RESULTS

Study search

Of the 616 studies, 534 studies were excluded at the title/abstract level and 50 studies were excluded at the full-text level. Finally, 32 studies [9–40] were included in the systematic review. The search strategy is shown in figure 1.

Study characteristics

The baseline characteristics and the main findings of the included studies are presented in Tables 1 and 2. Our search strategy identified 15 studies in hypertrophic cardiomyopathy patients [9–23], two studies with ventricular arrhythmias patients [24, 25], two studies with non-ischemic cardiomyopathy patients [26, 27], one study with drug refractory AF patients [32], two studies with myotonic dystrophy patients [28, 29], two studies with myocardial infarction patients [30, 31], two studies about myocarditis [33, 34], two studies included general population [35, 36], one study with arrhythmogenic cardiomyopathy patients [37], one study with patients with preserved ejection fraction [38], one study in cardiac sarcoidosis patients [39], one study in patients with LBBB [40]. The quality assessment of the included studies is summarized in Tables S1 and S2 (supplementary file). Overall, the included studies were classified as high-quality studies.

Association of ECG markers with LGE in different clinical settings

Hypertrophic cardiomyopathy

Fragmented QRS (fQRS) is defined as additional notches in the QRS complex. FQRS has been found to be related to more extensive myocardial fibrosis in HCM patients (figure 2A) [9]. A recent study showed that quantitative fQRS, defined as the total amount of deflections in the QRS complex in all 12 routine ECG leads together, was an independent predictor of myocardial fibrosis and showed a good performance in identifying patients with a higher fibrotic burden [9]. Dohy Z *et al* showed that fQRS and the strain pattern predicted more fibrosis, while the Cornell index was a negative predictor of myocardial fibrosis [13]. The number of fQRS leads has been significantly correlated to %LGE, average ECV, and T2, while more than one lead with fQRS could predict >5% of LGE mass with 58% sensitivity and 63% specificity [20]. Suwa K *et al* showed that the presence of fQRS was associated with apical LGE [22]. On the other hand, Tangwiwat C *et al* showed that fQRS was not associated with LGE [23]. Chen S *et al* studied the role of Selvester QRS scoring criteria in diagnosing myocardial scar in HCM patients [11]. The authors found that the Selvester score³¹ showed a better performance in predicting LGE presence. Also, the same study showed a positive association between the Selvester score and the extent of LGE [11]. Abnormal Q waves are more prevalent in patients with LGE, but no correlation between the location of Q waves on ECG and territory of LGE on CMR was revealed (figure 2B) [15]. Interestingly, quantitative analysis of LGE was not related to the presence of abnormal Q waves [15]. However, findings of another study showed that abnormal Q waves were associated with more ventricular segments with extensive LGE [10]. In a cohort study, LGE was associated with notched QRS, leftward QRS axis, and prolonged QRS duration, but not with abnormal Q waves, R-wave amplitude, or ST-T changes [17]. fQRS has been found to have higher diagnostic accuracy for detecting myocardial fibrosis compared to abnormal Q waves in HCM patients [18]. A cut-off of the number of leads with notched QRS ≥ 2 was found to predict the presence or absence of myocardial fibrosis, with a sensitivity of 70% and a specificity of 81% [17]. Interestingly the same study showed that

³ the number of notched QRS leads was positively correlated with LGE volume, while a correlation between the lead distribution of notched QRS and the location of LGE was revealed [17]. Although giant negative T waves have been associated with apical HCM, no significant association was demonstrated with apical LGE [10]. On the other hand, in another observational study, repolarization disturbances, including negative T waves in lateral and anterior leads, have been correlated with “parietal” LGE scores, while QT dispersion has been associated with “global” LGE score [14]. Tp-Te has also been found to be an independent predictor of LGE, while a cut-off value of 99.4 ms can detect the LGE with a sensitivity of 64.3% and a specificity of 84.2% [12]. In a small cohort of the pediatric population, the presence of LGE was associated with significantly decreased voltages in SV1, RV6, and SV1+RV6 despite increased septal dimensions [16]. Furthermore, the slopes of the QTe/RR and QTa /RR have been found to be significantly steeper in the LGE positive patients, while both slopes have been significantly correlated with the total LGE scores [24]. The association of late potentials with myocardial fibrosis has also been studied in HCM patients. However, ventricular late potentials were not found to be a reliable marker for the detection of myocardial fibrosis as assessed by LGE on CMR [19].

Ischemic and non-ischemic cardiomyopathy

Two studies were identified through the search strategy regarding the association of ECG markers with fibrosis as identified by CMR. Nadour W *et al* studied the comparative efficacy of Q waves and CMR-LGE to predict prior myocardial infarction [30]. Interestingly, the authors found that ECG-defined scars had a lower sensitivity compared to CMR-LGE-defined scars. Specifically, it was found that a significant number of pathological Q waves had absent infarct etiology, indicating high false positivity [30]. Chew DS *et al* showed that in myocardial infarction patients, fQRS has been found to be significantly associated with the peri-infarct zone but not with core infarct volume [31]. In the setting of non-ischemic cardiomyopathy, two studies were identified. Specifically, Piers SRD *et al* found that prolongation of the paced QRS duration after premature stimulation was related to long, thick strands of fibrosis but

not to focal LGE-CMR [26]. CMR has been reported to have a complementary role to ECG findings in dilated cardiomyopathy patients [27]. Specifically, it has been found that while QRS-prolongation and septal mid-wall LGE are often co-existed, no significant correlation between these markers was revealed [27].

Myocarditis

Two studies that provided data about ECG markers with CMR fibrosis were identified. In myocarditis patients, fQRS has been correlated with the distribution of LGE (figure 2C) [33]. Interestingly, fQRS was also associated with ongoing inflammation and poor prognosis in terms of ventricular function and fatal arrhythmias [33]. Fischer K *et al* studied the association of ECG parameters with LGE-CMR in patients with clinical suspicion of acute or subacute myocarditis [34]. In this population, a wide QRS-T angle, low voltage, and fQRS were found to be significantly associated with LGE-CMR [34].

Myotonic dystrophy

Two studies were found to provide data about ECG markers and myocardial fibrosis in patients with muscular dystrophy. Specifically, in patients with Duchenne muscular dystrophy, a significant correlation between fQRS and the amount of myocardial fibrosis as assessed by LGE-CMR was observed [29]. On the other hand, in patients with myotonic muscular dystrophy type 1, PR, QRS, and QTc duration, frontal QRS-T angle, absolute Cornell voltage, LVH-Cornell, LBBB, RBBB, fascicular block, bifascicular block, AH interval, and HV interval were not significantly different between LGE positive and LGE negative patients [28].

Other clinical settings

Ciuffo L *et al* studied the association between the interatrial block and atrial fibrosis using CMR imaging in patients with drug-refractory AF [32]. It was found that advanced inter-atrial block, defined as P-wave duration ≥ 120 ms and biphasic morphology in inferior leads, was significantly associated with left atrial fibrosis [32]. Furthermore, P-

wave duration was also independently associated with left atrial fibrosis in this clinical scenario [32]. Mewton N *et al* studied the association of ECG markers in patients with preserved ejection fraction [38]. A significant independent and positive association between T-wave alternans value and total scar was revealed [38]. Furthermore, patients with a myocardial ischemic scar had significantly greater QRS duration as compared with patients with nonischemic scar and patients without a myocardial scar. On the other hand, QRS-T angle was not associated with total myocardial scar size, core of scar, and gray zone size in grams by LGE-CMR [38]. In the clinical setting of PVC, the presence of an RBBB pattern as the clinically dominant PVC morphology presence of LGE-defined fibrosis or the presence of multiple PVC morphologies were significantly correlated with the presence of LGE-defined fibrosis [25]. On the other hand, in patients with VT or VF, the slopes of the QTe/RR (QT measured at the apex of the T waves) and QTa /RR (QT measured at the end of T waves) were significantly steeper in the LGE positive patients while both slopes were significantly correlated with the total LGE scores [24]. Interestingly, the QTe day/night and QTa day/night ratios were significantly greater in LGE positive patients than those in the LGE negative patients making clear the correlation between fibrosis and QT dynamicity [24]. In the setting of cardiac sarcoidosis, QRS estimated scar using Selvester QRS score was significantly correlated with CMR-LGE scar while it was related with life-threatening arrhythmic events [39]. However, the Selvester QRS score intended for use in the presence of conduction abnormalities was not found to predict CMR-defined LV scar in a general population of suspected cardiovascular disease [36]. Similarly, the LBBB Selvester QRS score showed poor accuracy in the detection and quantification of myocardial scar in LBBB patients [40]. In ARVC patients, ϵ wave and terminal activation duration >55 ms were not associated with either right or left ventricular LGE [37]. On the other hand, the presence of low QRS voltages in limb leads was associated with the presence of left ventricular LGE but not with right ventricular LGE (figure 2E) [37]. In addition, the presence and extent of right precordial T-wave inversions were associated with the presence of right ventricular but not with left ventricular LGE [37]. Finally, in a prospective cross-sectional

study that included individuals free of prior coronary heart disease, QRS Cornell voltage, QRS duration, and QTc were significantly associated with LGE presence, while QRS Sokolow-Lyon voltage was not shown a significant correlation with LGE-CMR (figure 2D) [35].

DISCUSSION

In our systematic review, we examined in detail studies that have reported associations between ECG markers and CMR-reported myocardial fibrosis. In the literature, studies have reported controversial results regarding the association between pathological Q wave presence in ECG and LGE-CMR at first glance [10, 17]. Moreover, another controversy on the association between fQRS and LGE in apical hypertrophic cardiomyopathy was reported [22, 23]. These findings should be evaluated with caution because the study population, study design, ECG parameters used, and statistical approach have been heterogeneous among the included studies. Considering all included data, fQRS, QRS duration, Selvester QRS score, and ventricular repolarization variables have been detected to have a great prediction value of myocardial fibrosis, which is validated by LGE-CMR in various cardiovascular diseases. The studies examining the association between ECG markers and CMR have been first evaluated in patients with HCM and ischemic cardiomyopathy. HCM has always been attracted attention due to its heterogeneous electrocardiographic presentations, and it is rational to assess the fibrosis markers of ECG in HCM with the validation of CMR [41]. Since myocardial fibrosis has been associated with the arrhythmia burden in patients with HCM, early detection of myocardial fibrosis using 12-lead ECG has the potential to rapidly change management strategy in these patients [42, 43]. LGE-CMR has been proposed as one of the predictors of clinical prognosis in patients with HCM [44]. Thus in the next step, ECG parameters correlated with LGE-CMR may be investigated in the risk scores of HCM in addition to other well-known risk factors to provide more precise prediction in the follow-up of these patients. As the use of CMR is limited due to its

high cost, ECG parameters found to represent myocardial fibrosis according to LGE-CMR may easily be used for the risk assessment.

In the evaluation of myocardial scar in patients with ischemic and non-ischemic cardiomyopathy, there appears to be a clear performance difference between CMR and ECG. The highly promising ECG parameters such as fQRS and pathological Q waves have not satisfied the expected performance compared to LGE-CMR [30]. The pathophysiological occurrence of myocardial scar in infarction may play an important role while explaining the poor performance of pathological Q waves predicting myocardial fibrosis of LGE-CMR. Since Q waves symbolize a loss of electrical activity, not purely myocardial fibrosis, pathological Q waves without evident LGE-CMR may be explained for this reason [45]. However, fQRS, which has not been correlated with core infarct volume, has been associated with peri-infarct volume [31]. In myocarditis, fQRS has been demonstrated to have a good LGE-CMR prediction performance, similar to its significance in patients with HCM [33, 34]. Since ECG variables, including fQRS, change dynamically during the disease course of myocarditis, more investigations are warranted to determine the time of obtained ECG, which should be examined to correlate LGE-CMR. On the other hand, ECG parameters regarding atrial tissue fibrosis have been closely related to LGE-CMR because there have been several investigations defending the association between p wave duration and morphology and left atrial fibrosis. Therefore, p wave duration and inter-atrial block have a great potential to present left atrial fibrosis, which has been validated with CMR [32].

CONCLUSION

Myocardial fibrosis, which is a reliable marker of prognosis in a wide spectrum of cardiovascular diseases, can be easily understood with an easily applicable ECG. More investigations are needed on a specific disease basis to fill the gap of evidence regarding the association of ECG markers and CMR, which may practically change our daily clinical practice.

ARTICLE HIGHLIGHTS

Research background

Electrocardiogram (ECG) is a well-established, easily obtained, low-cost diagnostic tool that is the cornerstone of cardiological evaluation. ECG markers have been associated with the presence of myocardial fibrosis, as depicted from cardiac magnetic resonance (CMR) evaluation.

Research motivation

ECG can be a valuable tool for the risk stratification of sudden cardiac death (SCD) in different clinical settings.

Research objectives

More research studies are needed to elucidate the association of ECG markers with CMR-late gadolinium enhancement (LGE) in different clinical settings.

Research methods

Methodology of ¹¹Systematic reviews in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement).

Research results

Our results summarize the existing evidence about the association of ECG markers with fibrosis as identified by CMR. Existing data show that fragmented QRS (fQRS), Q waves and repolarization abnormalities are some of the ECG indices that are associated with myocardial fibrosis.

Research conclusions

Myocardial fibrosis, a marker of prognosis in a wide spectrum of clinical settings, can be easily identified by ECG indices.

Research perspectives

Future research should be focused on the identification of ECG markers that are reliably associated with myocardial fibrosis in different clinical settings. Furthermore, the association of ECG markers with all-cause mortality and arrhythmic events is of great importance.

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