fQRS as a marker of granulomatous disease in patients presenting with ventricular tachycardia and normal left ventricular ejection fraction

Henri Roukoza, Mandar Shah, Lawrence Jesuraj Masilamanib, Ajit Thachil, Prem K. Jayakumar, David G. Benditt, Calambur Narasimhan

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Background: Granulomatous myocarditis may present with sustained monomorphic ventricular tachycardia (SMVT) in the presence of normal left ventricular ejection fraction (LVEF), and could be mistaken for idiopathic ventricular tachycardia (IVT). The use of cardiac imaging for diagnosis can be limited by availability and high cost. ECG is readily available and inexpensive. Fragmented QRS (fQRS) on ECG has been found to be associated with myocardial scar. We hypothesized that fQRS could be useful in the diagnosis of granulomatous VT (GVT).

Methods: We compared the 12-lead ECG of 16 patients with GVT and 42 patients with IVT who presented with SMVT.

Results: The presence of fQRS was significantly higher in the GVT group compared to the IVT group (75% versus 19.1%, \( p < 0.001 \)). The location of fQRS correlated with delayed enhancement cardiac magnetic resonance imaging (DE-CMR) in the same segment in 4/16 patients in the GVT group. It correlated with an affected segment on either DE-CMR or 18FDG positron emission computed tomography in 4/11 patients in the GVT group who had both imaging modalities. Whenever fQRS was present in contiguous leads other than the inferior leads, it always corresponded to an affected segment on imaging.

Conclusions: In patients presenting with SMVT and no structural heart disease, the presence of fQRS is strongly associated with granulomatous myocarditis. fQRS on the surface ECG is a helpful tool the presence of which should prompt a CMR for a definitive diagnosis.

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1. Introduction

Sustained monomorphic ventricular tachycardia (SMVT) of left ventricular origin in patients with normal left ventricular ejection fraction (EF) is most often referred as idiopathic VT which has a good response to antiarrhythmic or ablation therapy. However, granulomatous myocarditis having a more worrisome prognosis, can also present with SMVT and normal EF and readily mistaken for idiopathic VT. Ventricular tachycardia of granulomatous origin, including cardiac sarcoidosis, is relatively infrequent cause of SMVT and is most definitively diagnosed by cardiac magnetic resonance (CMR) and/or ¹⁸FDG positron emission computed tomography (¹⁸F-FDG PET CT). However, use of these imaging modalities is limited by the restricted availability and the high cost involved. Inexpensive pre-screening of such cases for myocardial scar consistent with granulomatous disease would be desirable.

Fragmented QRS (fQRS) on surface electrocardiogram (ECG) has been linked to the presence of myocardial scar in coronary artery disease. ECG is a readily available and a low-cost tool. fQRS on ECG has been found to be a marker of cardiac involvement in patients with systemic sarcoidosis. As myocardial scar is a distinguishing feature between granulomatous myocarditis and idiopathic VT, we hypothesized that the fQRS would be a useful screening tool for preliminary evaluation of SMVT patients without evident structural heart disease.

2. Methods

2.1. Patient selection

We screened retrospectively all patients referred for a DE-CMR after presentation for SMVT between January 2008 and December 2011. DE-CMR was requested based on physician discretion at the time of presentation. Patients with history or evidence of structural heart disease including coronary artery disease (CAD), myocardial infarction, dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy or EF < 50% were excluded.

Recognition of granulomatous myocarditis was based on presence of both patchy scar on DE-CMR that did not correspond to a vascular distribution and subsequent histopathological confirmation of granulomatous involvement from sampled paracardiac lymph nodes. These patients formed the study group. GVT patients were further classified as having cardiac sarcoidosis if M.Tuberculosis IS6110 Polymerase Chain Reaction and mycobacterial culture on all histopathologic samples were negative. Control patients comprised those with SMVT and normal DE-CMR examination.

2.2. ECG criteria for fQRS

We defined fQRS on the standard 12-lead ECG recording (high pass filter 0.15–0.5 Hz, Low pass filter 100–150 Hz, AC filter 50 Hz, paper speed 25 mm/s, voltage 10 mm/mV) based on previous published work. If QRS < 120 ms, fQRS was defined as an additional R wave (R'), notching in the nadir of the S wave, or the presence of >1 R' in at least two contiguous ECG leads. fQRS in presence of bundle branch block (QRS > 120 ms) was defined by the presence of >2 R' or >2 notches in the R wave or >2 notches in the nadir of S wave in at least two contiguous leads. We excluded an RSR’ pattern in V1-V2 in the presence of complete or incomplete right bundle branch block and an RSR’ pattern in V5-V6 in the presence of complete left bundle branch block.

fQRS patterns present in 2 or more anatomically contiguous leads were assigned as follows: anterior leads (V1 to V5) — to anterior myocardial segment, lateral leads (I, aVL, V5, and V6) to lateral myocardial segment, and those in inferior leads (II, III, and aVF) to inferior segment. If V1 was included in any of the above lead combinations, we considered the septum affected. All ECGs were reviewed by 2 independent experienced readers blinded to CMR results. The agreement between readers was 81% on the presence of notching in any single lead and 90% on the presence of fQRS criteria. Examples of fragmented QRS are presented in Fig. 1.

2.3. Imaging

CMR was performed using a 1.5 T scanner (Siemens, Erlangen, Germany). Steady-state free-processing sequence and Gradient Echo cine images were obtained in the two and four chamber views and in the short axis every 10 mm from base to apex. Volumes and global function were derived. Delayed enhancement (DE-CMR) was acquired starting 10 min after gadolinium contrast administration using segmented inversion recovery fast gradient echo, constantly adjusting inversion time for optimum nulling of the normal myocardium. The fasting and resting ¹⁸F-FDG PET CT was performed in patients with granulomatous myocarditis by employing a standard protocol previously described.

2.4. Statistical analysis

Continuous variables were expressed as mean ± SD and were compared using Student t-test. Categorical variables were expressed as percentages and compared using chi-square test or Fisher exact test as appropriate. All P values were 2-tailed, with statistical significance set at 0.05 and confidence intervals calculated at the 95% level. All analyses were performed using JMP software version 7.0 (SAS Institute Inc., Cary, NC, USA).

<table>
<thead>
<tr>
<th>RSR'</th>
<th>Notched R</th>
<th>Notched S</th>
<th>Fragmented QRS</th>
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Fig. 1 – The figure shows different morphologies of fragmented QRS as explained in the text.
3. Results

3.1. Patient population

Sixteen patients with evidence of granulomatous myocarditis formed the GVT group. Forty-seven patients with SMVT and a normal CMR exam were identified as having idiopathic VT. In five of 47 patients the baseline ECG was not available. Therefore, these patients were not included in the study. The remaining 42 patients served as the Control group.

All patients presented with SMVT and were without evident structural heart disease on preliminary evaluation. All had LVEF of 50% or more. Each was referred for CMR based on physician discretion. Of the 16 patients in the GVT group, 12 had confirmed cardiac sarcoid with completely negative evaluation for tuberculosis. Four patients had confirmed tuberculosis on PCR or culture. Demographic and electrocardiographic characteristics are presented in Table 1.

3.2. Electrocardiogram and fQRS

Notching or RSR’ pattern in any single lead was present in 81.2% in the GVT group and 50% in the Control group (p = 0.03). The presence of fQRS was significantly more frequent in the GVT group (GVT, 75% versus Control, 19.1%, p < 0.001). Three out of 4 patients (75%) with tuberculous myocarditis and 9 out of 12 patients (75%) with cardiac sarcoid had fQRS.

3.3. Correlation of fQRS with imaging

Whenever fQRS was present in contiguous leads other than the inferior leads, it always corresponded to an affected segment on imaging (Table 2).

The location of a solitary lead fQRS correlated with CMR-DE in the same segment in only 4/16(25%) patients in the GVT group. Similarly solitary lead fQRS correlated with an affected segment on either DE or PET in 4/11 (36.3%) patients in the GVT group who had both imaging modality.

The location of fQRS, DE on CMR and inflammation on 18FDG PET CT in the different segments of LV in GVT group is shown in Table 2. Among the 8 patients with fQRS in the Control group, 7 had fQRS in the inferior leads and 1 in the lateral leads.

4. Discussion

This study assessed the potential for fQRS on surface ECG to play a role as a preliminary screening tool for identifying the possibility that SMVT patients with apparently normal hearts may be due to granulomatous myocarditis VT. The principal finding was that fQRS was present in 75% of patients in whom both imaging and histopathology confirmed the presence of granulomatous myocarditis. The fQRS was more frequent in GVT patients than in Controls (75% versus 19.1%. p < 0.001). Finally, when fQRS was present in a location other than the inferior leads, and was present in adjacent leads, there was closer concordance with the affected myocardial segment on imaging. On the other hand, the location of fQRS on a solitary ECG lead did not correlate well with the location of scar or inflammation on imaging studies.

Granulomatous myocarditis includes primarily cardiac sarcoidosis and cardiac tuberculosis and can present with SMVT and a preserved EF. Early stages of cardiac sarcoidosis may not be detected or show non-specific findings on echocardiography. Moreover, SMVT can be the primary presentation of both sarcoidosis and tuberculosis. Hence, granulomatous myocarditis related VT can be easily mistaken with idiopathic VT especially if no extracardiac manifestations of sarcoidosis are present.

SMVT has been found to be an independent risk factor for mortality in patients with cardiac sarcoidosis. Therefore, the early identification of this entity might have an important impact on patient risk stratification and management. Furthermore, disease specific therapy initiated early in the course of the disease has been shown to decrease VT recurrence. Consequently, patients with SMVT and normal left ventricular EF on echocardiography, and fQRS on ECG should be investigated further to rule out granulomatous myocarditis, especially in countries with higher prevalence of this disease.

Cardiac MR and 18FDG PET CT have been increasingly used for the diagnosis and prognostic evaluation of granulomatous myocarditis. However, their use is limited by availability and cost, especially in countries with limited resources. Electrocardiogram is a readily available tool with low cost, and fQRS is known to be a marker of myocardial scar, mortality and cardiac events in patients with coronary artery disease. It is also associated with increased mortality and arrhythmic events in non-ischemic cardiomyopathy and more prevalent in arrhythmogenic right ventricular cardiomyopathy (ARVC) patients. In one study, fQRS was associated with cardiac involvement in patients with sarcoidosis. Our report shows that fQRS is also associated with granulomatous myocarditis in patients with SMVT and no apparent structural heart disease.

In our study, unlike the one by Howmset al, we did not find a correlation between solitary leads with fQRS and the sites of myocardial involvement. This, we speculate, is because of involvement of multiple regions of the myocardium as seen in the majority of our cases as opposed to less diffuse myocardial

| Table 1 – Demographic and electrocardiographic characteristics of patients in both groups. |
|----------------------------------------------|-------------|-------------|----------------|
| Age (years)                                | GVT group   | IVT group   | p value    |
|                                             | (n = 16)    | (n = 42)    |             |
| 43.9 ± 8.9                                 | 43.5 ± 11.1 | 0.91        |
| Male gender, n (%                           | 9 (56.2)    | 23 (54.8)   | 0.92        |
| EF (%)                                      | 58.4 ± 8.3  | 63.7 ± 5.9  | 0.01        |
| PR interval (ms)                            | 163 ± 27    | 150 ± 16    | 0.07        |
| PR interval > 200 ms, n (%)                 | 2 (12.5)    | 0 (0)       | 0.07        |
| QRS interval (ms)                           | 99 ± 16     | 94 ± 11     | 0.19        |
| Abnormal QRS axis, n (%)                    | 2 (12.5)    | 4 (9.5)     | 0.66        |
| QRS > 120 ms, n (%)                         | 2 (12.5)    | 0 (0)       | 0.07        |
| Presence of notching, n (%)                 | 13 (81.2)   | 21 (50)     | 0.03        |
| Presence of fQRS, n (%)                     | 12 (75)     | 8 (19.1)    | <0.001      |

EF = ejection fraction; fQRS = fragmented QRS; GVT = granulomatous myocarditis related ventricular tachycardia; IVT = idiopathic ventricular tachycardia.
scar seen in the aforementioned study. The affected regions of the myocardium could overlap leading to fQRS reflections in leads not corresponding to the specific areas of myocardial involvement. Another study of patients with CAD showed an increase in sensitivity of fQRS for detection of scar when analyzed independent of regional correlation.21 This means that fQRS predicted the presence of scar on imaging, but not necessarily in the same regional distribution.

4.1. Limitations

Our study has several limitations. First, it is a single center retrospective study with a small number of patients. However, it is one of the largest series with granulomatous myocarditis presenting with SMVT in a seemingly normal heart on pre-liminary evaluation. Second, the ratio of patients in the GVT group compared to the idiopathic VT patients in our study overestimates the prevalence of granulomatous myocarditis. This is due to the fact that only a small proportion of patients with suspected idiopathic VT are referred for CMR, as it is often considered unnecessary. Physicians will have a much lower threshold to investigate a patient with history of tuberculosis, exposure to tuberculosis, lymphadenopathy or elevated inflammatory markers.

5. Conclusion

In patients presenting with SMVT and no evident structural heart disease on initial evaluation, the presence of fQRS on ECG is strongly associated with underlying granulomatous myocarditis, particularly cardiac sarcoid. Consequently, the presence of fQRS on the surface ECG in such patients provides a helpful screening tool that should prompt a CMR and other necessary investigations for a definitive diagnosis.

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Conflicts of interest

All authors have none to declare.

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