QRS fragmentation as a possible electrocardiographic diagnostic marker in patients with acute myocarditis: preliminary histopathological validation

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Abstract

**Aims** We aim to assess the reproducibility of QRS fragmentation (fQRS) on a multi-centre dataset of patients with acute myocarditis (AM), including a histopathological validation in a subgroup with biopsy-proven disease. Electrocardiogram (ECG) in patients with myocarditis is usually considered aspecific. ST changes and conduction anomalies have been commonly reported so far. We have previously described fQRS in patients with AM.

**Methods and results** Patients admitted between 2008 and 2019 in two centres with a diagnosis of AM were included. Standard ECG, echocardiography, and cardiac magnetic resonance (CMR) findings were recorded at baseline and at follow-up (FU). Eighty patients were analysed, 66 men (82%), with median age of 34 (26–43) years. Twenty-two patients had biopsy-proven AM. At presentation, 61 patients (76%) displayed fQRS. Median ejection fraction (EF) was 55% (43–60). Seventy-two patients (90%) underwent CMR and displayed late gadolinium enhancement (LGE). ECG leads showed that fQRS was present in 72 patients (82%). Median FU was 419 days (224–956). Complete FU was available for 64 patients (80%), and 33 patients (52%) displayed persistence of fQRS. Median EF was 60% (57–64). Eleven patients underwent a repeated biopsy at FU, eight of whom had persistent inflammation and fQRS. Fifteen patients (23%) had ventricular tachycardia, 14 of whom still showed fQRS.

**Conclusions** In this cohort fQRS was confirmed as an additional useful ECG sign. Persistence of fQRS was associated with ongoing inflammation and with a poorer outcome in terms of ventricular function and occurrence of arrhythmias.

Keywords QRS fragmentation; Myocarditis; Diagnosis

Received: 10 March 2020; Revised: 17 May 2020; Accepted: 20 May 2020

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Introduction

Diagnosis of acute myocarditis (AM) is based on a multi-parametric assessment including clinical presentation, electrocardiogram (ECG), non-invasive cardiac imaging, serum biomarkers of myocardial damage, and endomyocardial biopsy (EMB). Although EMB represents the diagnostic gold standard and provides valuable information to guide specific treatments with immunosuppressive medications, ECG is still the first-line assessment, along with clinical profile and increase of serum biomarkers, in patients presenting with suspected AM, particularly those with symptoms overlapping with acute coronary syndromes.1–3 On the other hand, ECG is usually considered a blunt diagnostic tool as changes are deemed to be aspecific and transient. Clinical prognostic variables are also still poorly defined. Persistence of inflammation in EMBs is recognized as a risk factor.4 Additional new ECG features, expression of structural changes within the myocardium, might be particularly useful in the clinical practice to support diagnosis and clinical follow-up.

Fragmentation of QRS (fQRS) is one of the most promising diagnostic and prognostic indexes described in a wide range of myocardial heart diseases characterized by the presence of infiltrates and/or of myocardial fibrosis.5 Different patterns
of fragmentation have been described; the common characteristics are the presence of discernible multiple notches in either the R or S component of the QRS. fQRS has been extensively studied in ischaemic heart disease and has been shown to be correlated with ventricular function and cardiac events at follow-up, irrespective of the presence of Q wave and extension of myocardial necrosis. Although some of the histopathological features described in ischaemic and non-ischaemic cardiomyopathies overlap with those typical of AM, fQRS has never been described in patients with this particular disease.

We hypothesize that pathological changes observed in patient with AM, similarly to other model of disease, might affect the local electrical activation leading to anisotropic conduction expressed as fQRS in one or more leads.

We have previously described the association of fQRS with late gadolinium enhancement (LGE) at cardiac magnetic resonance (CMR) in patients with AM referred to a single centre.

This study aims to validate the observation of fQRS as additional electrocardiographic diagnostic sign on a larger cohort of patients with AM, including a subgroup with biopsy-proven disease. We also sought to investigate if persistence of fQRS might predict ongoing structural changes at biopsy or CMR at follow-up.

**Methods**

Patients admitted between 2008 and 2019, in two centres, with acute onset of symptoms were retrospectively assessed. Diagnosis was based on a consistent clinical presentation with acute onset of symptoms were retrospectively assessed.

Methods were presented as counts and percentages and compared by Student t-test or Wilkinson rank sum test, as appropriate. Normality of continuous variables was assessed by visually inspecting the distribution histograms. Categorical variables were presented as counts and percentages and compared by $\chi^2$ or Fisher exact test.

A $P$ value of 0.05 was assumed as cut-off for statistical significance. Analysis was performed with STATA 11.0 by Stata Corp.

**Statistical methods**

Continuous variables were reported as median ± standard deviation or median and inter-quartile ranges and compared by Student $t$-test or Wilkinson rank sum test, as appropriate. Normality of continuous variables was assessed by visually inspecting the distribution histograms. Categorical variables were presented as counts and percentages and compared by $\chi^2$ or Fisher exact test.

A $P$ value of 0.05 was assumed as cut-off for statistical significance. Analysis was performed with STATA 11.0 by Stata Corp.

**Results**

**Clinical presentation and in-hospital management**

Eighty patients were included in the analysis (66 male, 82%), 68 (85%) Caucasian. Median age was 34 years (26–43). In 22 (27%) patients, the diagnosis was biopsy proven; in 14 (17%) patients, both biopsy and CMR were positive; and in the remaining, only CMR was performed (Figure 1). Biopsy showed lymphocytic, eosinophilic, and giant cell myocarditis in 19 (86%), 2 (9%), and 1 (5%) patients, respectively.

Seventy-three patients (91%) reported typical prodromal symptoms, in particular flu-like and gastrointestinal syndrome, in 61 (76%) and 12 (15%), respectively. The most common symptom at presentation was chest pain in 66 (82%). Seven patients (9%) presented with cardiac arrest and 10 (12%) with cardiogenic shock or low cardiac output syndrome. ECG was pathologic in 76 (95%); 24 (30%) were aspecific, and 45 (56%) showed transient ST-T changes. fQRS was visible in 61 (76%) patients. At first examination, there was agreement on fQRS diagnosis in all cases but three, giving an inter-observer variability $K$ coefficient of 0.93 (95% CI 0.86–1). ECG leads involved roughly matched the distribution of LGE at CMR (Figure 2).

In patients with ST-T changes, a significantly higher normalized release of troponin was observed: 414 (98–761) vs.
Figure 1  Diagram summarizing prevalence of QRS fragmentation in different categories of patients. fQRS, fragmented QRS; CMR, cardiac magnetic resonance.

Figure 2  Illustration of correlation between LGE distribution and ECG leads displaying fragmentation. ECG, electrocardiogram; fQRS, fragmented QRS; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement. (A) CMR long-axis view. Blue arrows indicate LGE. (B) ECG showing fQRS in the peripheral leads (black arrows). (C) ECG showing fQRS in precordial leads (black arrows). (D) CMR short axis view. Blue arrows indicate LGE.
83 (20–182), P = 0.003. Ventricular arrhythmias, either sustained or not sustained, occurred in 25 (31%) patients. fQRS was not associated with occurrence of ventricular arrhythmias in the acute phase. Median echocardiographic ejection fraction (EF) at admission was 55% (43–60). Seventy patients (87%) underwent CMR during the acute phase, which showed anterior/septal, inferior/lateral, and spot LGE in 14 (19%), 37 (51%), and 21 (29%) patients, respectively. Ischaemic heart disease was excluded by coronary angiography in 44 (55%) patients who had a medium-high probability of coronary artery disease.

Median troponin peak at presentation was 191 (29–642) times the upper limit of the normal institutional range, while C-reactive protein was 5.9 (3.4–13.6) times. Median BNP peak was 293 (66–980) pg/mL.

No correlation between troponin, C-reactive protein, and BNP levels were observed. Furthermore, levels of troponin, C-reactive protein, and BNP did not significantly differ patients displaying fQRS: 200 (29–635) vs. 171 (50–642), P = 0.9; 5.9 (3.3–13.5) vs. 6.6 (3.7–16.9), P = 0.5; and 304 (69–990) vs. 293 (56–741), P = 0.9, respectively.

C-reactive protein was significantly lower in patients presenting with gastrointestinal symptoms 4.6 (1.6–6) vs. 6.6 (3.5–14.2), P = 0.03, and in patients with chest pain, 5.6 (3.4–11.5) vs. 15 (5.3–26) P = 0.03. On the other hand, chest pain was not associated with a significantly different level of troponin.

Early inotropic support and mechanical circulatory support at admission were needed in 14 patients (17%) and 6 patients (7%), respectively. This latter group included four patients who underwent extracorporeal membrane oxygenator (ECMO) and two Impella. All patients received conventional heart failure medications, while 15 patients (19%) were treated with different combinations of immunosuppressive therapy (Tables 1 and 2).

One patient who presented with cardiogenic shock and needed ECMO support died in hospital.

Follow-up

Complete follow-up was available in 64 (80%) patients with a median of 419 days (224–956). CMR was available in 54 (67%) patients, showing persistence of LGE in 40 (74%). fQRS was present at follow-up in 33 (51%) patients. Inter-observer variability K coefficient at follow-up was 0.91 95% CI (0.83–0.9).

There was a significant association between persistence of fQRS and both LGE and biopsy positivity at follow-up: 25 patients out of 40 with LGE persistence displayed also fQRS (P < 0.01); likewise, all the eight patients have persistently positive biopsies (Figures 3 and 4).

Significant arrhythmias were recorded at follow-up in 15 (21%) patients, six of whom underwent implantable cardioverter defibrillator implantation (Table 2). All patients but one with significant arrhythmic burden showed persistence of fQRS.

Ten patients had relapses of AM (14%). At last follow-up, median EF was 60% (55–63) and was found to be lower in patients with persisting fQRS: 56 ± 7% vs. 61 ± 6% P = 0.002. Thirteen (17%) patients displayed incomplete recovery of systolic function, which was associated with persistence of fQRS: 11 out of 33 with fQRS vs. 2 out of 31 without fQRS. On the other hand, of 51 patients who had complete recovery at follow-up, 22 (43%) still displayed fQRS (P = 0.03).

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| Table 1 | General demographics and clinical characteristics of the population |
|---------|---------------------------------------------------------------|
|         | n = 80                                                          |
| Age (years), median (IQR) | 34 (26–43) |
| Male, n (%) | 66 (82) |
| Caucasian ethnicity | 68 (85) |
| Prodromal symptoms, n (%) | 73 (91) |
| Flu-like syndrome, n (%) | 61 (76) |
| Gastrointestinal disorders | 12 (15) |
| Clinical presentation/in-hospital course |
| Chest pain, n (%) | 66 (82) |
| Cardiac arrest, n (%) | 7 (9) |
| Shock/LCO, n (%) | 10 (12) |
| Inotropic support, n (%) | 14 (17) |
| Mechanical circulatory support, n (%) | 6 (7) |

| Laboratory findings |
| C-reactive protein ratio (peak), median (IQR) | 5.9 (3.4–13.6) |
| Troponin ratio (peak), median (IQR) | 191 (29–642) |
| BNP peak (pg/mL), median (IQR) | 293 (66–980) |
| EMB performed, n (%) | 22 (27) |
| Coronary angiography performed | 44 (55) |
| Immunosuppressive therapy, n (%) | 15 (19) |
| Recurrence of AM, n (%) | 11 (14) |

AM, acute myocarditis; BNP, brain natriuretic peptide; EMB, endomyocardial biopsy; IQR, inter-quartile range; LCO, low cardiac output.

| Table 2 | Electrocardiographic, echocardiographic, and cardiac magnetic resonance findings at admission and follow-up |
|---------|--------------------------------------------------------------------------------------------------|
|         | Admission | Follow-up |
| ECG, n (%) | 80 (100) | 64 (80) |
| QRs fragmentation, n (%) | 61 (76) | 33 (51) |
| Rhythm identification, n (%) | 80 (100) | 71 (88) |
| Ventricular arrhythmia, n (%) | 25 (31) | 15 (21) |
| Echocardiography, n (%) | 80 (100) | 64 (80) |
| EDD (mm), median (IQR) | 49 (47–52) | 48 (45–51) |
| Pericardial effusion, n (%) | 16 (20) | 0 |
| LVEF, median (IQR) | 55 (43–60) | 60 (55–63) |
| CMR, n (%) | 70 (87) | 54 (67) |
| LVEDVi (mL/m²), median (IQR) | 78 (70–92) | 79 (69–88) |
| LVEF, median (IQR) | 59 (53–64) | 60 (57–64) |
| LGE, n (%) | 70 (100) | 40 (74) |
| Antero-septal LGE, n (%) | 14 (19) | 9 (17) |
| Infero-lateral LGE, n (%) | 37 (51) | 22 (41) |
| Other-pattern LGE, n (%) | 21 (29) | 9 (17) |

ECG, electrocardiographic; EDD, end-diastolic diameter; IQR, inter-quartile range; LGE, late gadolinium enhancement; LVEDVi, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction.
Discussion

ECG is strongly recommended in patients with suspected AM presenting with typical or atypical chest pain or rhythm disturbances. In the literature statements, the most common findings discussed are ST changes, helping to identify AM mimicking acute coronary syndromes. However, these signs, as well as bundle branch blocks, are aspecific and may be only occasionally and transiently present. fQRS has been previously described in different cardiac conditions such as ischemic, congenital, and arrhythmogenic cardiomyopathy, in which it has also a prognostic role. This electrocardiographic feature is deemed to be the expression of a local slowing of electrical conduction across the myocardial muscle due to structural changes.

This feature has never been systematically reported in patients with AM, although the documentation of oedema and fibrosis in this disease represents a putative substrate for the development of fQRS. In a series of patients in previously published data, we observed that fQRS consistently mirrored the evidence and persistence of LGE on the CMR. In that preliminary report, diagnosis of AM was based on clinical finding and CMR. In the present analysis, we included a group of patients with biopsy-proven myocarditis from another centre in which the observation of fQRS in both the acute phase and at follow-up was confirmed. Interestingly, the presence of fQRS in the acute phase was not associated with higher troponin nor with BNP levels. In a proportion of patients, fQRS disappeared at follow-up. This finding seems to be associated with a better prognosis in terms of mechanical function. On the other hand, a non-negligible proportion of patients whose ventricular function normalized had fQRS at follow-up. Hence, we can speculate that despite a tight association between fQRS and LGE, ECG is a sensitive but not specific predictor of incomplete EF recovery. Persistence of fQRS, but not its presence at admission, seems to be associated with a higher arrhythmic burden at follow-up. This is in agreement with a similar observation in ischemic and non-ischemic cardiomyopathy in which fQRS was associated with a higher risk of arrhythmic events.

This observation is particularly intriguing, as criteria for stratification of arrhythmic risk in patients with myocarditis are still poorly defined despite that many potential arrhythmic trigger have been recognized. In the subset of patients who had undergone CMR, similarly to ischemic and non-ischemic cardiomyopathy, fQRS and LGE distribution appeared correlated, confirming our preliminary observation.

Interestingly, persistence of fQRS was also significantly correlated with evidence of ongoing disease at biopsy, supporting the pathophysiologic link between histological...
and electrical changes in this particular model of structural disease. If confirmed on larger samples, fQRS might be used as a simple clinical bedside tool to support the initial suspect of AM and to predict histological persistence of disease, which has been recognized as a detrimental prognostic factor.4

Limitations

A major limitation of this study is the retrospective design, suggesting caution about reproducibility of fQRS diagnosis in the general population. Furthermore, the histopathological feature in AM may change overtime; therefore, a variable latency in fQRS appearance may be supposed. On the other hand, given the dynamic healing process of myocarditis, the heterogeneity of the follow-up might have affected the rate of ventricular function recovery and ECG normalization. Owing to the retrospective design of the study, some follow-up ECGs were missing, potentially causing an underestimation of fQRS persistence. Finally, the limited number of events at follow-up does not allow to draw conclusions about the prognostic significance of fQRS.

Acknowledgement

We acknowledge Ms. Monika Willner for collecting and co-ordinating the follow-up of these patients.

Conflict of interest

None declared.
Funding

None.

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