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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Diagnostic value of fragmented QRS complex in myocardial scar detection: systematic review and meta-analysis of the literature

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Abstract

Background and aim: The present study aimed to investigate the diagnostic value of fragmented QRS complex (fQRS) on 12-lead electrocardiogram (ECG) for myocardial scar detection, and presented the results in a systematic review and meta-analysis format.

Methods: Medline, SCOPUS, and ISI Web of Knowledge were searched electronically with "Fragmented QRS" or "fQRS" as key words. All related studies that had evaluated the accuracy of fQRS for myocardial scar diagnosis were included.

Results: Eight studies (2560 patients) were finally included in the systematic review. Specificity assessment could be evaluated only by five out of these eight articles. Overall pooled sensitivity of fQRS, Q wave, and mixed Q-fQRS was 68% (65–71), 51% (47–55), and 74% (69–79) and the pooled specificity was 80% (79–81), 97% (97–98) and 92% (91–93), respectively.

Conclusions: Fragmented QRS is a novel ECG marker with more sensitivity and less specificity than Q wave. A combination of fQRS with Q wave in a 12-lead ECG results in up to 74% sensitivity and 92% specificity. Additional studies are needed to assess the significance of this ECG parameter for regional myocardial scar detection.

Key words: fragmented QRS, fQRS, myocardial scar, myocardial infarction, meta-analysis

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INTRODUCTION

Accurate diagnosis of myocardial infarction (MI), which is the most serious complication of coronary artery disease (CAD) is highly sought after. Diagnosis of a previous MI helps the cardiologist to accurately determine how a patient should be managed and the expected outcome. On the other hand, high global incidence of CAD necessitates easily available tools for MI detection.

Electrocardiogram (ECG) is an invaluable, simple, accessible and cost–effective diagnostic modality for this purpose, and pathologic Q wave presenting on a 12-lead ECG is the best known marker of this entity. However, this parameter has some serious limitations in myocardial scar detection which strongly affects its accuracy and makes it unhelpful in defining myocardial scar in two thirds of documented MI [1, 2].

Some studies have suggested that post-MI changes in Purkinje fibres and myocardial fibrosis may alter the QRS complex morphology [3], producing fragmentation in QRS complex. As this new parameter (fragmented QRS [fQRS]) is an easily evaluated ECG sign, it has attracted much attention as a potentially diagnostic and/or prognostic tool for myocardial scar identification in recent years. This novel marker includes various RSR′ patterns, and based on the complex duration has been sub classified into two major groups: fQRS complex (< 120 ms duration) and fragmented wide complex (f-wQRS) [4]. Fragmented QRS as defined by Das et al. [5] includes only the narrow complexes with the presence of initial R wave followed by an S wave and a terminal positive deflection (R′) on a resting 12-lead ECG. The presence of ST segment elevation with or without RSR′ pattern or fragmentation was also included. Figure 1 shows different patterns of QRS complex which met the fQRS criteria.

Thus far, there have been some studies that have evaluated the diagnostic significance of fQRS in patients with MI. In the current study we reviewed the available literature on this topic and presented the results in a systematic review and meta-analysis format.

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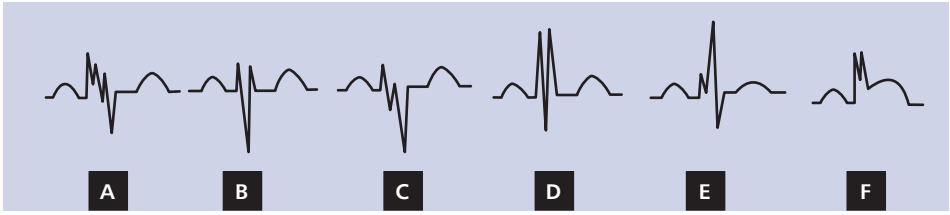

Figure 1. Six different patterns of QRS complex that categorised as fragmented QRS; **A**. Fragmented QRS; **B**. rSŕ; **C**. Notched S; **D**. RSŔ; **E**. Notched R; **F**. RsŔ with ST elevation

METHODS

Search strategy

Medline, SCOPUS, and ISI Web of Knowledge were searched with "Fragmented QRS" or "fQRS" as key words by two authors independently (last search on April 2014) with no language or time limit. The reference lists of the retrieved studies were searched for possible relevant citation.

Inclusion criteria

All studies evaluating the diagnostic significance of fQRS complex in myocardial scar detection were included. Case reports, correspondence, and narrative review articles were excluded. Meeting abstracts were not excluded. We excluded articles on the significance of wide QRS complexes. Two authors reviewed the retrieved articles independently, and discrepancies were resolved by a third author's opinion. The duplicate studies were discussed, and only the most recent publication of each group was included.

Data abstraction

Data abstraction was done in duplicate by two authors independently, and data on authors, publication year, gold standard, patient data, study quality, and sensitivity and/or specificity (if possible based on patients' spectrum) were extracted. The Oxford Centre for Evidence-Based Medicine checklist for diagnostic studies was used to assign a level of evidence to each included study.

Statistical analysis

The PRISMA statement was followed while performing the statistical analyses. The random-effects model was used for statistical pooling of diagnostic accuracy indices. The Cochrane Q test was used for heterogeneity evaluation ($p < 0.05$ was considered statistically significant). The Cochrane Q test measures the statistical excess variability among the included studies. To quantify the heterogeneity, the I^2 index was used. The I^2 index is the amount of heterogeneity among the studies that is real and cannot be attributed to the sampling errors. The effect of positivity cutoff point on sensitivity and specificity was evaluated using correlation between sensitivity and specificity. In case of any threshold effect, we would expect a high reverse correlation between specificity and sensitivity. Overall accuracy was also reported by summary receiver operating characteristic (SROC) curve fitting, area under the curve (AUC) calculation, and Q* value. The SROC curve represents overall performance of the test. AUC is the area under the SROC curve, and the higher values of AUC (closer to one) mean better performance of the test. Q* is the point on the SROC curve at which the sensitivity and specificity are equal. Higher values of Q* also show better performance of the test.

For publication bias evaluation, funnel plots and regression intercept of Egger were used. The Funnel plot is a graphical representation of the possible publication bias. Any asymmetry in the plot can be due to publication bias. Egger's regression is the statistical counterpart of this asymmetry.

Statistical analyses were performed using Meta-DiSc (version 1.4) and Comprehensive Meta-Analysis (CMA version 2) software.

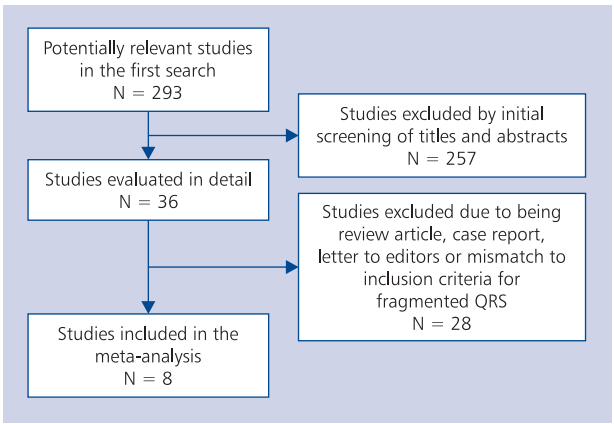

Figure 2. Flowchart of the literature search

RESULTS

Figure 2 shows the results of the literature search. The first search yielded 293 potential studies. However, 257 studies were excluded after viewing the titles and abstracts. The full texts of the remaining 36 articles were evaluated in detail. Twenty-five studies were excluded as they were letters to editors, case reports, or narrative review articles. Two studies [6, 7] were excluded because they had worked on wide fragmented complexes that were excluded according to Das criteria [5].

Table 1. Characteristics of the included studies

First author	Year	No. of patients	Mean age [years]	Spectrum of the patients	Study design (retrospective/prospective)	Used modality	Criterion standard	Consecutive recruitment	Blindness	Enough explanation of the tests
Das MK	2006	479	58.2	Known or suspected for CAD	Prospective	ECG	MPI	Yes	Yes	Yes
Ozdemir S	2013	261	61.0	Known cases of CAD	Retrospective	ECG	MPI	N/A	N/A	Yes
Mahenthiran J	2007	409	57.6	Known or suspected for CAD	Prospective	ECG	MPI	Yes	Yes	Yes
Wang DD	2010	462	N/A	Known or suspected for CAD	Retrospective	ECG	MPI	Yes	Yes	Yes
Ahn MS	2013	190	58.5	Patients with acute MI	Retrospective	ECG	Cardiac MRI	N/A	No	Yes
Guo R	2012	183	62.0	NSTEMI patients	Retrospective	ECG	Coronary angiography	Yes	Yes	Yes
Erdem FH	2013	100	54.6	Acute STEMI patients	Retrospective	ECG	Coronary angiography	N/A	No	Yes
Dabbagh Kakhki VR	2014	476	57.0	Known or suspected for CAD	Prospective	ECG	MPI	Yes	Yes	Yes

CAD — coronary artery disease; ECG — electrocardiogram; MI — myocardial infarction; MPI — myocardial perfusion imaging; MRI — magnetic resonance imaging; N/A — not available; NSTEMI — non-ST elevation myocardial infarction

And one study was excluded because the researchers assessed the correlation between fQRS and left ventricular aneurysm instead of myocardial scar [8]. Eight studies (2560 patients) were finally included in the systematic review [5, 9–15]. Table 1 shows the characteristics of the included studies.

Different standard modalities were used for MI detection among studies (Fig. 3). Fortunately, five out of eight articles used myocardial perfusion single-photon emission *computed* tomography (SPECT), which is a highly accurate tool for scar detection. However, one study used cardiac-magnetic resonance imaging (c-MRI), and in two other studies coronary angiography images were analysed to identify myocardial scar by using Thrombolysis in Myocardial Infarction (TIMI) grade and TIMI myocardial perfusion grade of infarct-related artery. Because all three of these techniques are considered valid for myocardial scar detection we decided to include all of them for diagnostic value assessment of fQRS.

Figure 3 shows the forest plots of sensitivity and specificity pooling for fQRS as well as the SROC curve. Overall pooled sensitivity was 68% (65–71; Cochrane Q = 106; $p < 0.00001$; $I^2 = 93.4\%$), and pooled specificity was 81% (79–82; Cochrane Q = 176; $p < 0.00001$; $I^2 = 97.7\%$).

The correlation coefficient between logit (true positive rate) and logit (false positive rate) was 0.2; $p = 0.74$ denotes the minimal threshold effect. SROC analysis showed AUC of 0.78 and Q* of 0.71.

Figure 4 shows the funnel plots of fQRS sensitivity and specificity pooling. Egger's regression intercepts for sensitivity and specificity funnel plots were 0.83 ($p = 0.88$) and –0.4 ($p = 0.95$), respectively, which shows that publication bias is not a major concern in our systematic review.

Table 2 shows the pooled diagnostic accuracy indices of fQRS, Q-wave, and mixed Q-fQRS for myocardial scar detection.

DISCUSSION

Alteration in QRS complex morphology is a readily detectable sign on a 12-lead ECG. To date, many applications have been suggested for this novel marker as a clue to variable ischaemic and non-ischaemic cardiac diseases [16]. The diagnostic and prognostic significance of fQRS as well as the suitability for risk stratification have been studied by several researches. Among the suggested applications for this electrocardiographic index, it has been shown that fQRS is an invaluable tool for myocardial scar detection; however, some conjecture remains in this regard.

Fragmented QRS vs. f-w-QRS complexes

The RSR' patterns are sub-classified into fQRS complexes and fragmented wide complexes based on QRS duration [4]. A classic fQRS is only a narrow complex with duration less than 120 ms [16]. According to this definition, we did not include in our systematic review the diagnostic studies that

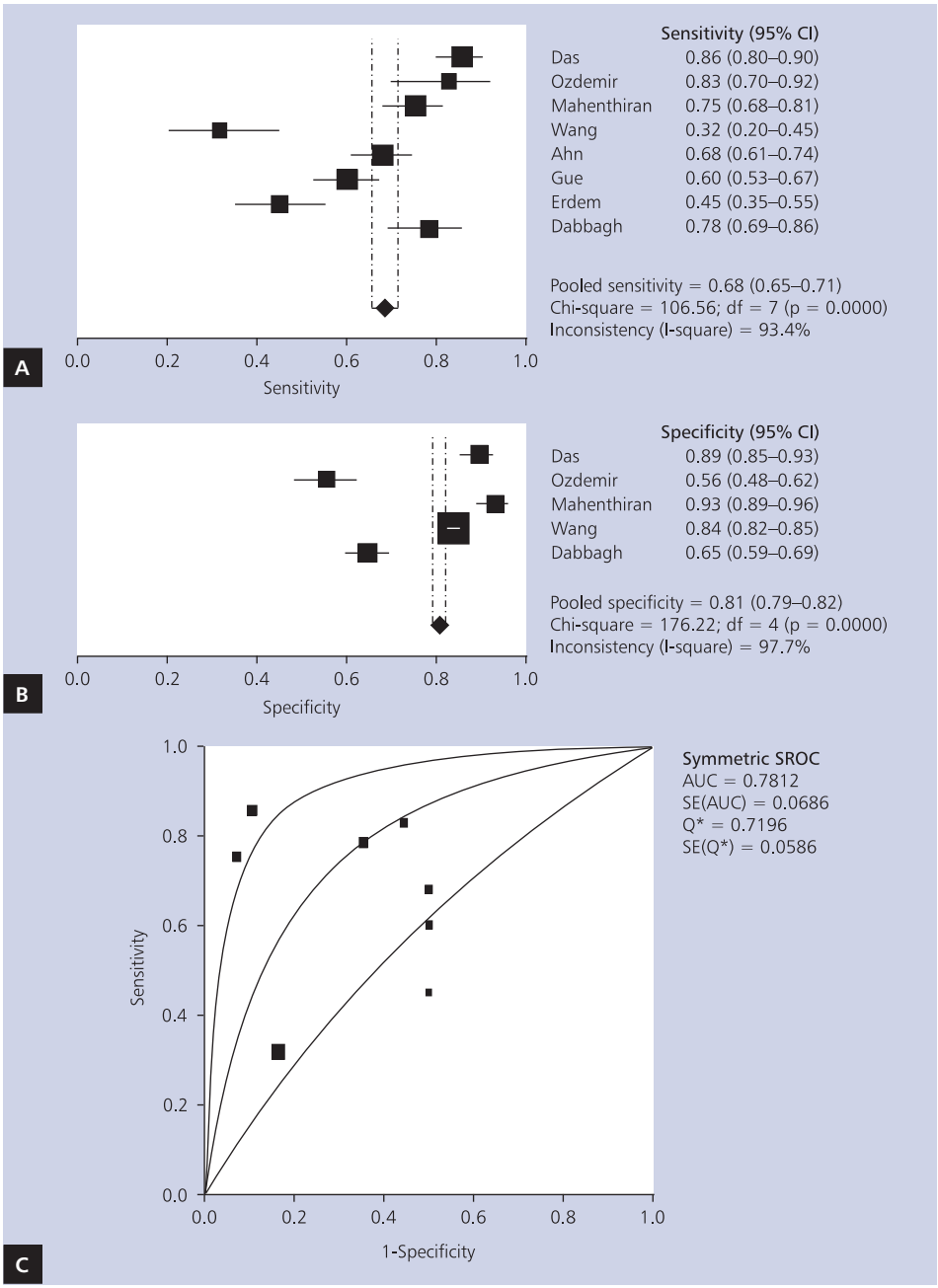

Figure 3. Forest plots of sensitivity (**A**) and specificity (**B**) pooling as well as summary receiver operating characteristic (SROC; **C**) of the study; CI — confidence interval

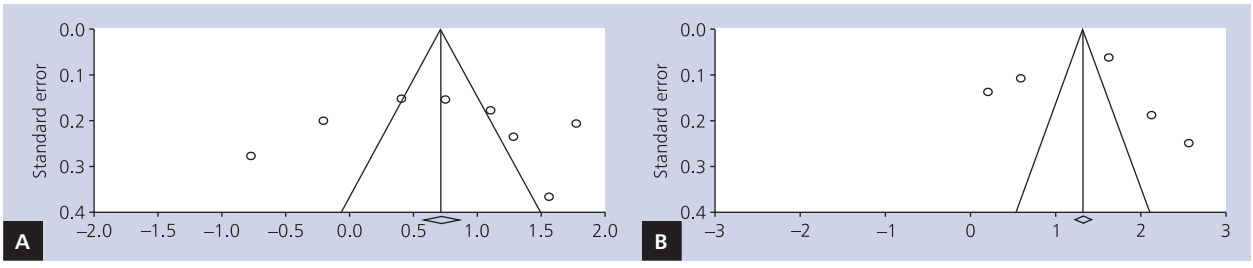

Figure 4. Funnel plots of sensitivity (**A**) and specificity (**B**) pooling

Table 2. Diagnostic indices of fragmented QRS (fQRS), Q wave, and Q-fQRS for myocardial scar detection

	Sensitivity [%]	Specificity [%]	LR+	LR–	DOR
fQRS	68.4	80.5	3.63	0.32	11.32
	(65.5–71.2)	(79–81.9)	(1.78–7.4)	(0.15–0.69)	(3.45–37)
Q wave	51.2	97.7	13.4	0.61	23.9
	(47.2–55.1)	(97–98.2)	(6.8–26.2)	(0.43–0.87)	(10.21–56)
Q-fQRS	74.8	92.1	3.48	0.27	13.8
	(69.9–79.2)	(91–93.2)	(0.9–13.4)	(0–958)	(2–91)

LR — likelihood ratio; DOR — diagnostic odds ratio

consisted of wide fragmented complexes [6, 7]. It seems that specific studies to evaluate the wide fragmented complexes as a surrogate of MI are needed.

Fragmented QRS sensitivity

Our study showed that fQRS has higher sensitivity than Q wave in myocardial scar detection. Pooled data showed that the combination of these two markers (fQRS and Q wave) significantly improves the sensitivity of ECG for MI diagnosis. Among the eight related studies the reported sensitivity varied in a wide range: 32% [11] to 86% [5]. Two studies reported a sensitivity below 50% for fQRS [11, 14], and the sensitivity of fQRS in another six studies was higher than 60%. In the research by Wang et al. [11] the patients' ECGs were performed within three months of the myocardial perfusion imaging (MPI) studies (not at the same time as the MPI). This method naturally results in non-homogeneity in ECG performing protocol and ECG tools as they had been performed in different centres. In addition, although Wang et al. [11] declared that they used Das criteria, they only accepted fragmentation when it had more than 50% frequency in the beats of a specific field. This can result in less fragmentation detection and lower sensitivity. Also, there is a problematic difference between Wang et al. [11] and most other studies on the combination of fQRS and Q wave. Despite the authors describing the mixed morphology assessment as the significance of "fQRS and/or Q wave", their results showed that they only considered an ECG positive when both markers existed concurrently. It can be expected that this criterion would result in lower sensitivity as compared to the assessment of each marker separately. Achieving a lower sensitivity for Q wave than the expected amount reported in the past literature is another sign that there is a potential error or restriction in ECG marker detection. Another study with discordance results was conducted in Turkey [14]. The authors aimed to evaluate the ability of fQRS as a marker of reperfusion. Their studied population was quite different from the other seven studies because they assessed the fQRS significance on the patients who had recent acute MI for the first time and were administered thrombolytic therapy before performing ECG. Because thrombolytic therapy for ST elevation MI results in reperfusion to the damaged myocardium, it can be expected to reduce the frequency of fQRS among the population, with resulting lower sensitivity. The adverse effect of reperfusion interventions (such as thrombolytic therapy) on Q wave has been proven previously in the literature [2, 17]. We performed a sensitivity analysis by excluding the two mentioned discordant studies. The resulting pooled sensitivity improved to 73.5% (70.5–76.4).

A brief review of Table 2 showed that five out of eight studies used myocardial perfusion SPECT as the reference standard for MI diagnosis. Among the other three researches, Ahn et al. [12] assessed fQRS as an index of myocardial injury detected by c-MRI in patients with documented acute MI. The authors mentioned that delayed enhancement in c-MRI might not accurately reflect myocardial scar tissue; however, the reported sensitivity of this study was similar to those using MPI.

Fragmented QRS specificity

Three studies (out of eight) assessed fQRS markers in patients with documented MI (Table 2). These studies have been included only for pooling fQRS sensitivity. Five studies remained at hand for specificity assessment.

The pooled specificity of fQRS for MI detection was 81%, which is less than Q wave (97%). This means that fQRS is not as specific as Q wave for myocardial scar.

Five out of eight studies used myocardial perfusion SPECT as the reference standard for MI diagnosis (Table 2). This limitation results in non-homogeneity of included studies. Including only studies with MPI gold standard showed the following pooled indices: pooled sensitivity = 75.3% (71.5–78.7) and pooled specificity = 80.5% (79–81.9).

There are several reports that show correlation between fQRS and other cardiac diseases [16] such as ventricular arrhythmias and idiopathic ventricular fibrillation [18], Brugada and acquired long QT syndromes [19], and a variety of structural heart diseases such as idiopathic dilated and hypertrophic cardiomyopathies [20], Chagas' cardiomyopathy [21], and miscellaneous diseases such as Behcet's disease [22] and sarcoidosis [23]. Also, some studies reported fQRS as a normal

variant in the elderly population [24], who are a significant part of suspected CAD patients.

CONCLUSIONS

Fragmented QRS is a novel ECG marker with greater sensitivity and lower specificity than Q wave for regional myocardial scar detection. Combination of fQRS with Q wave in a 12-lead ECG results in up to 74% sensitivity and 92% specificity. Additional studies are needed to assess the significance of this ECG parameter for regional myocardial scar detection.

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Conflict of interest: *none declared*

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Wartość diagnostyczna fragmentacji zespołu QRS w wykrywaniu blizn mięśnia sercowego: przegląd systematyczny z metaanalizą danych literaturowych

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Streszczenie

Wstęp i cel: Celem niniejszego badania była analiza wartości diagnostycznej fragmentacji zespołu QRS (fQRS) w 12-odprowadzeniowym elektrokardiogramie (EKG) w wykrywaniu blizn mięśnia sercowego oraz przedstawienie wyników w formie przeglądu systematycznego z metaanalizą.

Metody: Przeszukano elektroniczne bazy Medline, SCOPUS i ISI Web of Knowledge, wpisując jako słowa kluczowe terminy „fragmented QRS" lub „fQRS". Do analizy włączono wszystkie badania, w których oceniano dokładność diagnozowania blizn mięśnia sercowego na podstawie obecności fQRS.

Wyniki: Ostatecznie do przeglądu systematycznego włączono 8 badań (2560 chorych). Ocena swoistości była możliwa tylko w przypadku 5 z 8 prac. Czułość wskaźnika fQRS, załamka Q oraz skojarzenia Q-fQRS wynosiła odpowiednio 68% (65–71), 51% (47–55) i 74% (69–79), natomiast swoistość — 80% (79–81), 97% (97–98) i 92% (91–93).

Wnioski: Fragmentacja zespołu QRS jest nowym wskaźnikiem w badaniu EKG charakteryzującym się większą czułością i mniejszą swoistością niż załamek Q. Czułość i swoistość w przypadku skojarzenia fQRS i załamka Q w 12-odprowadzeniowym EKG wynosiła odpowiednio 74% i 92%. Należy przeprowadzić dalsze badania w celu oceny znaczenia tego parametru EKG w wykrywaniu regionalnych blizn mięśnia sercowego.

Słowa kluczowe: fragmentacja QRS, fQRS, blizna mięśnia sercowego, zawał serca, metaanaliza

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