Fragmented QRS on hospital presentation is independently associated with no-reflow in patients with first anterior ST-elevation myocardial infarction

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Abstract
Aim: No-reflow, that is the absence of sufficient myocardial perfusion after stent implantation, is associated with increased mortality in patients with ST-elevation myocardial infarction (STEMI). There is no definitive treatment, although there are some preventive approaches. Therefore, it is important to predict the patients at risk of no-reflow. Fragmented QRS (fQRS) is the presence of different RSR' patterns without a bundle branch on electrocardiography. Both fQRS and no-reflow share similar pathophysiological mechanisms. Thus, we thought that the presence of fQRS on admission to hospital may reflect an increased risk for no-reflow. The aim of the study was to assess the possible relationship between fQRS on admission and the development of no-reflow.

Materials and Methods: The study included patients with first anterior STEMI who underwent primary percutaneous intervention. fQRS was evaluated at the time of admission to the hospital. No-reflow was diagnosed by thrombolysis in myocardial infarction flow grade (< 3) after stent implantation. A multivariable model was created to determine factors independently associated with no-reflow.

Results: The study included 259 patients, including 56 (20.3%) with no-reflow and 203 (73.6%) without no-reflow. fQRS was more frequent in patients with no-reflow than in those without (71.4% vs 42.4%, p<0.001). In the multivariable model, fQRS (OR: 3.731, 95% CI: 1.912-7.279, p<0.001) and male gender (OR: 2.351, 95% CI: 1.025-5.391, p=0.043) were independently associated with the development of no-reflow.

Discussion: The presence of fQRS on admission is independently associated with no-reflow in these patients. It can be used as a simple and non-invasive tool to predict the patients at risk for no-reflow.

Keywords
Fragmented QRS, No-reflow, Myocardial infarction
Introduction
No-reflow is defined as the presence of inadequate myocardial perfusion after successful opening of the infarct-related artery by percutaneous coronary intervention (PCI). The incidence varies widely and has been reported in the literature to range usually from 5% to 30% [1-3]. It reflects high-risk patients because it is associated with severe left ventricular (LV) dysfunction, LV remodeling, and increased short- and long-term mortality [1-3].

There is no definitive treatment for no-reflow because it is caused by different combinations of the four pathophysiological mechanisms of distal thrombus embolization, ischemia-induced injury, reperfusion injury, and individual susceptibility [4]. Some preventive techniques, including thrombus aspiration, primary stenting, avoidance of high-pressure stent implantation, and the use of GP IIb/IIIa inhibitor may reduce the degree of no-reflow and its adverse effects in patients at risk for no-reflow [5,6]. Therefore, although some clinical and angiographic parameters have already been defined, there remains a need for indicators that reflect the patients at risk for developing no-reflow [6].

Fragmented QRS (fQRS) is defined as the presence of the RSR' fragment or all of its variants in 2 contiguous leads associated with a major coronary artery territory without bundle branch on electrocardiography (ECG) [7]. It reflects impaired homogeneity of myocardial depolarization because of scar tissue and/or fibrosis [7]. The presence and effects over time of fQRS in patients with acute coronary syndrome, including ST-elevation (STEMI) and non-ST-elevation (NSTEMI) myocardial infarction, have been evaluated in previous studies. In early studies, it was reported that the fQRS developed within 48 hours of hospital admission and was associated with increased mortality and major adverse cardiovascular events in both patients with STEMI who underwent primary PCI and those with NSTEMI [8,9].

Later, the presence of fQRS on admission to hospital was shown to be independently associated with increased WMSI and decreased EF in patients with STEMI who underwent primary PCI [10]. However, the possible mechanisms of the adverse effects of fQRS have not been fully revealed in that population. As it was thought that the fQRS on admission might be caused by ischaemic injury and microvascular dysfunction, which are also pathophysiological mechanisms of no-reflow, the hypothesis of this study was that the presence of fQRS at the time of admission may suggest an increased risk for the development of no-reflow in patients with STEMI. Therefore, the aim of this study was to assess the relationship between fQRS on admission and the development of no-reflow in patients with anterior STEMI.

Material and Methods
Patient Selection
The study population consisted of consecutive patients with first anterior acute myocardial infarction (AMI) who underwent primary PCI. Anterior STEMI was diagnosed based on the presence of anginal chest pain and ST segment elevation in at least two contiguous precordial (≥ 2 mm) or extremity derivations (≥1 mm) on ECG. Patients were excluded from the study if they had a complete or incomplete bundle branch, atrial flutter or fibrillation, cardiac pacing, known heart failure (heart failure or left ventricular ejection fraction <50%), known valvular heart disease, known coronary artery disease (previous myocardial infarction, PCI or coronary by-pass) or chronic renal disease.

The use of antihypertensive and antidiabetic drugs (or insulin) was accepted for the diagnosis of hypertension (HT) and diabetes mellitus (DM), respectively. Complete demographic data, biochemical blood tests and electrocardiography were obtained from all study participants. The study was conducted in accordance with the guidelines of the Declaration of Helsinki. The Local Ethics Committee approved the study protocol. The written informed consent was obtained from all study participants.

Assessment of fragmented QRS
The fQRS was assessed on an ECG obtained upon admission to the hospital. It was defined as the presence of an additional R wave (R'), notching of R or S wave, or the presence of fragmentation of more than one R' in 2 contiguous ECG leads without bundle branch (filter range, 0.15-100 Hz, 25 mm/s, 10 mm/mV) (Figure 1) [7].

Coronary angiography, revascularization and assessment of no-reflow
Selective coronary angiography (CA) was performed using the Judkins technique on the right or left femoral artery. Before primary PCI, 600 mg clopidogrel or 180 mg ticagrelor and 300 mg acetylsalicylic acid were given to all patients. During primary PCI, intracoronary unfractionated heparin was routinely used, and GpIIb/IIIa inhibitors were used as bail-out therapy if necessary. All angiographic records during PCI were assessed by two experienced interventional cardiologists who were blinded to the patient’s ECG data. In case of disagreement, the final decision was obtained by consensus with a third cardiologist’s assessment.

The presence of thrombolysis in myocardial infarction (TIMI) 3 flow grade and <30% residual lesion in the left anterior descending artery was accepted as successful PCI [11]. The TIMI flow grades of 0, 1, or 2 in the target vessel after stent implantation was considered a no-reflow phenomenon. The study population was then separated into two groups: patients with no-reflow (Group 1) and those without no-reflow (Group 2).
Results Baseline demographic and electrocardiographic parameters of both groups are presented in Table 1. A total of 259 patients were included in the study. No-reflow developed in 56 (20.3%) patients (Group 1) and did not develop in 203 (73.6%) (Group 2). FQRS was more frequent in Group 1 than in Group 2 (71.4% vs 42.4%, p<0.001). Age and pain duration were higher in Group 1 than in Group 2 (age: 64.4±13.6 years vs 60.2±12.6 years, p=0.002; pain: 5.5±5.1 vs 4.2±4.2, p=0.003, respectively). The presence of diabetes mellitus, hypertension, and smoking was comparable between the two groups. Results of univariate and multivariate analysis are shown in Table 2. In univariate analysis, age, gender (male), fQRS and pain duration were associated with no-reflow. In multivariate analysis, only fQRS (OR:3.731, 95% CI:1.912-7.279, p<0.001) and gender (OR:2.351, 95% CI:1.025-5.391, p=0.043) were independently associated with no-reflow.

Table 1. Baseline features of study population

|                          | Patients with no-reflow (n=56) | Patients without no-reflow (n=203) | p     |
|--------------------------|--------------------------------|-----------------------------------|-------|
| Age, years               | 64.4±13.6                      | 60.2±12.6                         | 0.02  |
| Gender (male), n (%)     | 42 (75%)                       | 178 (87.7%)                       | 0.02  |
| Diabetes mellitus, n (%) | 15 (26.8%)                     | 40 (19.8%)                        | 0.26  |
| Hypertension, n (%)      | 25 (44.6%)                     | 95 (46.8%)                        | 0.78  |
| Smoking, n (%)           | 26 (46.4%)                     | 113 (55.7%)                       | 0.22  |
| Pain duration (hour)     | 5.5±5.1                        | 4.2±4.2                           | 0.03  |
| FQRS, n (%)              | 40 (71.4%)                     | 86 (42.4%)                        | <0.001|

Table 2. The results of univariate and multivariate analysis between no-reflow and other variables

|                          | Univariate analysis | Multivariable analysis |
|--------------------------|---------------------|------------------------|
|                          | OR 95% CI           | p                      | OR 95% CI           | p     |
| Age                      | 1.025 1.002 1.049   | 0.035 1.013 0.988 1.039 | 0.501 |
| Gender                   | 2.373 1.137 4.952   | 0.021 2.351 1.025 5.391 | 0.043 |
| FQRS                     | 3.401 1.788 6.471   | <0.001 3.731 1.912 7.279 | <0.001 |
| Pain duration            | 1.063 1.001 1.129   | 0.046 1.061 0.995 1.133 | 0.07  |

Figure 1. There were fragmented QRS between derivations from V2 to V4 on electrocardiography obtained at the time of admission to hospital.

Discussion The results of this study demonstrated that the presence of fQRS at the time of admission to hospital is independently associated with the development of no-reflow in patients with first anterior STEMI who underwent primary PCI. No-reflow is a disappointing complication of primary PCI in patients with STEMI because of the high incidence (generally, 5-30%, but up to 60%) and associated high morbidity and mortality rates [1-3]. Unfortunately, there is still no definitive treatment, because the pathophysiological mechanism is still not fully understood, although some mechanisms have been proposed [4]. Therefore, it is important to identify patients at risk and use preventive techniques in current medical practice. Performing thrombus aspiration in patients with high thrombus load, primary stenting, avoidance of high pressure stent implantation, and the use of GP IIb/IIIa inhibitor during primary PCI have been proposed as preventive techniques in patients at risk for developing no-reflow [5,6]. Therefore, the identification of patients with an increased risk of the development of no-reflow is an essential part of STEMI management to reduce associated morbidity and mortality. Some clinical and angiographic parameters, such as hyperglycemia, hypertension, hypercholesterolemia, renal insufficiency, plaque composition and thrombus burden, have already been defined as risk features for no-reflow [6]. Recently, P- and R-wave peak times have been reported as an ECG finding of the increased risk of no-reflow in this population [12,13]. However, a more practical and easy ECG finding is needed, because the assessment of P- and R-wave peak times is not practical during hospital admission of patients with STEMI. FQRS is a relatively novel ECG finding, which reflects impaired homogeneity of electrical activation waves during myocardial depolarization [7]. In an early study, it was reported that fQRS was caused by a chronic impairment of myocardium such as the development of scar or fibrotic tissue [7]. It was later defined in patients with acute coronary syndrome, including STEMI and NSTEMI, in whom it was associated with adverse effects such as decreased ejection fraction and increased mortality rate in the STEMI population [8-10]. However, the mechanism of the negative effect of fQRS has not yet been documented. Therefore, the aim of this study was to examine the relationship between fQRS and no-reflow as a possible mechanism of these adverse effects. To date, only one study has investigated the relationship between fQRS and no-reflow [14]. In that study, Lorgis et al. evaluated the relationship between fQRS and infarct size, peri-infarct zone and microvascular obstruction using cardiac magnetic resonance on average on the 6th day after hospital admission in patients with acute coronary syndrome, including STEMI and NSTEMI. It was reported that the fQRS was associated with the extent of microvascular obstruction, although it was significantly less in patients with isolated fQRS than in those with Q waves. However, there are important differences between that study and the current study. First, Lorgis et al. actually evaluated microvascular obstruction after myocardial infarction, not no-reflow, which developed during PCI. Second, they retrospectively evaluated the presence of fQRS by ECG on MR day (on average on the 6th day after admission), but in the current study, ECG was evaluated at the time of admission.

Fragmented QRS is associated with no-reflow
to the hospital according to the study hypothesis. Third, the previous study included both STEMI (any type) and NSTEMI, but the current research included only patients with first anterior STEMI. Therefore, the previous study is significantly different and does not reflect the current study hypothesis. A mechanism, which can be proposed to explain the relationship between fQRS and no-reflow is that they both develop with a similar pathophysiological mechanism. It should be noted first that no-reflow is caused by different and individual combinations of the four pathophysiological mechanisms of distal thrombus embolization, ischemia-induced injury, reperfusion injury and individual susceptibility [4]. The presence of myocardial damage caused by ischemia-induced injury and individual susceptibility may also play a role in the development of fQRS by three possible mechanisms. First, permanent cell damage begins to develop when the duration of ischemia exceeds 20-30 minutes during myocardial infarction. This structural impairment may change electrical propagation along the myocardium, which in turn causes fQRS fragmentation, especially if there are non-homogenous infarction areas within the myocardium. Second, impaired electrical homogeneity between infarcted and peri-infarcted tissue may cause fQRS. Third, Purkinje fibers and other small conduction pathways may be affected, and then lead to fragmentation of QRS because of disrupted electrical activity. Based on the current study, some suggestions can be made that can make important contributions to the literature; Patients with first anterior STEMI should be assessed for the presence of fQRS on ECG on admission to hospital. Patients with fQRS on admission have an increased risk for developing no-reflow. Therefore, in these patients, preventative techniques including thrombus aspiration, primary stenting and avoidance of high pressure stent implantation, should be applied to prevent the development of no-reflow and to protect the myocardium during primary PCI. The primary use of gllb/lll inhibitors may even be considered in patients with high thrombus load after initial coronary angiography. These patients will also have decreased EF and increased mortality rates compared to those without fQRS in the follow-up. Thus, they should be followed and managed more closely. Study limitations First, the long-term course of patients with fQRS on admission could not be assessed because of the absence of longitudinal data in the study. Therefore, further studies are needed to evaluate the long-term effects of the presence of fQRS at the time of admission to hospital. Second, some interventional predictors, such as balloon predilatation and stent implantation at high pressure, were not evaluated in the study. However, the primary aim of the study was to evaluate the effectiveness of fQRS as a non-invasive and simple tool that may show the risk of no-reflow at the time of admission to hospital. Conclusion The results of this study demonstrated that the presence of fQRS at the time of admission to hospital is independently associated with the development of no-reflow in patients with first anterior STEMI. It can be used as a simple and non-invasive tool to predict the patients who are at increased risk for the developing no-reflow.

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