ORIGINAL ARTICLE

High-Frequency QRS Analysis in Patients with Acute Myocardial Infarction: A Preliminary Study

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Background: The 12-lead electrocardiogram (ECG) is a primary tool in the evaluation and risk stratification of patients with suspected acute myocardial infarction (AMI), even though the initial ECG of these patients is often normal or nondiagnostic. Myocardial ischemia induces depolarization changes that can be quantified by analysis of high-frequency QRS (HFQRS) components. We aimed to demonstrate the potential usefulness of HFQRS analysis in diagnosing myocardial ischemia by characterizing the morphological patterns of the HFQRS signals in patients with AMI before and following reperfusion.

Methods: Five-minute high-resolution ECG was acquired from 30 patients with AMI (age 55 ± 11 years, 26 men) upon their admission to the intensive coronary care unit (ICCU). Serial ECGs were acquired following coronary revascularization and after additional 24 hours (24h). High-frequency morphology index (HFMI), quantifying the extent of ischemic patterns was computed by a custom software, and its values were compared between the serial ECG measurements.

Results: HFMI values were significantly higher on the admission ECG as compared to the post intervention ECG ($4.6 \pm 2.9\%$ vs $3.4 \pm 2.3\%$, $P < 0.05$) and to the 24h ECG ($4.6 \pm 2.9\%$ vs $2.8 \pm 2.1\%$, $P < 0.01$). In 79% of the patients who were successfully revascularized HFMI value decreased from admission ECG to 24h ECG.

Conclusions: Analysis of HFQRS morphology in patients with AMI provides information about the existence and severity of myocardial ischemia. HFQRS analysis may aid in risk stratification of patients with suspected myocardial ischemia, complementarily to conventional ECG.

Ann Noninvasive Electrocardiol 2013;18(2):149–156

high-frequency ECG; acute coronary syndrome; myocardial ischemia; acute myocardial infarction; electrocardiography; chest pain

Electrocardiography remains a primary cornerstone in the triage, evaluation, and management of patients with acute myocardial infarction (AMI). However, initial electrocardiogram (ECG) findings have been reported to be diagnostic of acute injury or ischemia in only 40–65% of patients with AMI.¹ A pattern of intermittent reperfusion, manifested as dynamic ST-segment changes in the early hours of acute MI is observed in 34–40% of ST-elevation

myocardial infarctions (STEMI),² decreasing the diagnostic value of the initial resting ECG. ST-segment resolution after percutaneous coronary intervention (PCI) is associated with favorable prognosis in STEMI.³

While ST-T indications of myocardial ischemia reflect repolarization abnormalities, ischemia also affects the depolarization phase of the electrical cardiac cycle.⁴ Depolarization abnormalities can

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Disclosure information: Travel grant (BSP Ltd): Ori Galante (Modest)

Employee (BSP Ltd): Guy Amit, Linda Davrath, Oded Luria (Significant)

Consultancy (BSP Ltd.): Shimon Abboud (Significant)

Clinical Trial Registration: <http://www.clinicaltrials.gov>. Unique identifier: NCT01150825

be detected and quantified using analysis of the high-frequency components of the QRS complex (HFQRS). HFQRS analysis, typically performed in a frequency band above 100 Hz, quantifies the subtle changes in the propagation of the electrical activation wave front throughout the myocardium. Myocardial ischemia reduces the myocyte-to-myocyte conduction velocity, causing reduced intensity and altered morphology of the HFQRS components.⁵⁻⁷ HFQRS has been studied in animal models⁸⁻¹⁰ and in humans undergoing PCI^{11,12} or exercise testing.^{13,14} These studies showed that HFQRS morphology is modified following coronary occlusion, exhibiting an ischemic pattern named "reduced amplitude zones" (RAZ).^{15,16} We aimed to study and quantitatively characterize the morphological patterns of the HFQRS signals in patients with AMI and to describe the trend of these patterns following reperfusion.

METHODS

The study included patients with AMI admitted to the intensive coronary care unit (ICCU) of Soroka Medical Center, a large tertiary university hospital. The study protocol was approved by the Institutional Review Board and all patients provided informed consent. Patients were included if they were >40 years old, had elevated serum biomarkers, and their ischemic symptoms started ≤ 12 hours prior to their ICCU admission. Patients with prior MI, prior coronary artery bypass graft, atrial fibrillation, sustained ventricular arrhythmia, QRS duration ≥ 120 ms, left-ventricular hypertrophy, or paced rhythm were excluded. High-resolution 12-lead resting ECG recordings (HyperQ system, BSP Ltd., Tel-Aviv, Israel) were acquired for 5 minutes: (1) at ICCU admission, (2) following angiography, and (3) 24 hours after angiography (Fig. 1).

HFQRS analysis was performed using offline custom software (HyperQ, BSP Ltd.). The analysis algorithm (Fig. 2) first used template-based correlation to identify valid QRS complexes and exclude noisy or ectopic beats. Accurate subsample beat alignment, followed by beat averaging was used to obtain high signal-to-noise ratio. The level of noise in the HFQRS signal was calculated as the root-mean-square of high-frequency components in the ST segment. Beat averaging was applied to each of the leads until the level of noise was $\leq 1 \mu\text{V}$.

Figure 1. Flowchart of the study protocol. AMI = acute myocardial infarction; ICCU = intensive coronary care unit; PCI = percutaneous coronary intervention; HFQRS = high-frequency QRS.

Averaged beats with higher noise level, or with low intensity of the HFQRS signal (root-mean-square intensity $< 2.75 \mu\text{V}$) were removed. Each valid average QRS complex was filtered by a band-pass digital filter in the frequency band of 140–250 Hz. The time-domain envelope of the HFQRS complex was then calculated using Hilbert transform,¹⁷ and a new index, named high-frequency morphology index (HFMI), was introduced to quantify the extent of RAZ morphology in the HFQRS envelope. HFMI value, measuring the relative area of the basins in the HFQRS envelope (in %), was calculated for each average HFQRS complex, and the median index of all valid complexes in a lead was determined as the HFMI value of the lead. HFMI value per patient was defined as the average of the six leads with maximal index value. Patients who had less than six leads with valid HFMI were excluded from the analysis.

Conventional ECG recordings were interpreted by an expert cardiologist who was blinded to all other data. Myocardial ischemia or infarction was diagnosed based on the universal definition of myocardial infarction (MI)¹⁸ independent of the HFQRS data.

HFMI values at admission, post angiography, and 24-hours were compared. Continuous values are presented by mean $\pm$ SD. Comparisons between groups were performed by post hoc tests using either *t*-test, chi-square test, or Fisher's exact test, as appropriate. *P* value < 0.05 was considered statistically significant.

Figure 2. Principles of high-frequency QRS (HFQRS) analysis. (A) QRS complexes are detected while rejecting arrhythmias and noisy complexes. (B) The detected QRS complexes are aligned and averaged to suppress noise. (C) Filtering in the 140–250 Hz frequency band produces the HFQRS signal. (D) HFQRS signal envelope is calculated and reduced area zones (RAZ) are detected and quantified. (E) An index of ischemia is calculated based on RAZ quantification in all 12 leads (E).

RESULTS

Of 32 patients who met the criteria for study inclusion and had a complete set of three ECG recordings, HFQRS analysis was available in 30 patients (age 55 ± 11 years, 26 men). The remaining two patients, whose signal quality did not facilitate reliable interpretation, were excluded from the analysis. The baseline characteristics of patients are summarized in Table 1. Most patients (97%) did not have previously diagnosed coronary artery

Table 1. Baseline Characteristics of Study Patients

	Analysis Group
N	30
Age (years)	55 ± 11
Male	26 (87%)
BMI	27.7 ± 4
Diabetes mellitus	3 (10%)
Hypertension ^a	13 (43%)
Hyperlipidemia ^a	20 (67%)
Smoking	18 (60%)
Family history of CAD	10 (33%)
History of coronary artery disease ^b	1 (3%)
Prior PCI	1 (3%)
Prior CVA	1 (3%)

^aPatients diagnosed by the referring physician and treated medically; ^bPatients had documented myocardial infarction, prior percutaneous coronary intervention or coronary bypass surgery.

disease (CAD). Fifteen patients (50%) had three or more coronary risk factors.

The majority of patients (26 patients, 87%) had ST-elevation MI. Of these patients, 17 were urgently reperfused, with a door-to-balloon time of 87 ± 23 minutes. In eight STEMI patients, ST-segment changes were already resolved by the time of ICCU admission, indicating that spontaneous reperfusion occurred prior to angiography. One patient had a recent STEMI. In all patients except one, angiography indicated significant CAD ($\geq 70\%$ stenosis in a major coronary artery, or $\geq 50\%$ stenosis in the left-main artery). Successful revascularization by angioplasty was achieved in 24 patients (80%). Of the patients with no revascularization, four were referred for coronary artery bypass graft (CABG), one had failed PCI, and one had insignificant CAD. These patients were included in the analysis, although their serial ECG recordings were acquired before intervention. The clinical characteristics of the patients are given in Table 2. The TIMI risk score for STEMI,¹⁹ calculated for 26 STEMI patients, was 2.2 ± 1.8 (mean $\pm$ SD). The average time between onset of symptoms and acquisition of first high-resolution ECG at the ICCU was 5.8 ± 6 hours. Post revascularization ECG was acquired 0.7 ± 0.8 hours after angiography, and 24-hour (24h) ECG was acquired 26.1 ± 15 hours following angiography.

The ECG at ICCU admission was interpreted by the blinded observer as "ischemic" in 19 patients (63%), "nonischemic" in nine patients (30%), and "inconclusive" in two patients (7%). ECG was non-ischemic in six STEMI patients with spontaneous

Table 2. Clinical Characteristics

	Analysis Group	STEMI	Urgent. reperfusion (STEMI)	Spont. reperfusion (STEMI)	P value
N	30	26	17	8	
Positive first Troponin-T	25 (83%)	21 (81%)	14 (82%)	6 (75%)	1.00
Heart rate at ICCU admission (bpm)	71 ± 15	72 ± 16	74 ± 18	70 ± 9	0.63
Systolic blood pressure (mmHg)	130 ± 23	127 ± 23	127 ± 26	127 ± 16	0.99
Diastolic blood pressure (mmHg)	77 ± 12	77 ± 12	78 ± 14	78 ± 7	0.99
TIMI risk score (STEMI)	-	2.2 ± 1.7	2.4 ± 2	1.6 ± 0.9	0.3
Time from symptoms onset to ICCU admission (hours)	3.7 ± 5	3.8 ± 5	3.1 ± 5	4.4 ± 5	0.57
Time from ICCU admission to revascularization (hours)	7.7 ± 11	7.3 ± 11	1.5 ± 0.4	21.4 ± 13	<0.001
Time from ICCU admission to first ECG recording (hours)	2.1 ± 3	1.5 ± 1.7	1.2 ± 1.3	1.9 ± 2.2	0.35
Chest pain during first ECG recording	16 (53%)	15 (58%)	11 (65%)	4 (50%)	0.67
Time from revascularization to second ECG recording (hours)	0.7 ± 0.8	0.6 ± 0.8	0.75 ± 0.9	0.3 ± 0.6	0.22
Time from revascularization to third ECG recording (hours)	26.1 ± 15	25.9 ± 16	29.9 ± 17	16.5 ± 7	0.06
Significant CAD on angiography	29 (97%)	26 (100%)	17 (100%)	8 (100%)	-
Single-vessel disease	13 (43%)	12 (46%)	9 (53%)	3 (38%)	0.67
Dual-vessel disease	9 (30%)	8 (31%)	5 (29%)	2 (25%)	1.00
Multivessel disease	8 (27%)	6 (23%)	3 (18%)	3 (38%)	0.34
Successful revascularization	24 (80%)	23 (88%)	16 (94%)	7 (88%)	1.00
ICCU admission ECG					
Ischemic ECG	19 (63%)	17 (65%)	15 (88%)	2 (25%)	0.004
Nonischemic ECG	9 (30%)	7 (27%)	1 (6%)	6 (75%)	0.001
Inconclusive ECG	2 (7%)	2 (8%)	1 (6%)	0 (0%)	1.00
Post angiography ECG					
Ischemic ECG	14 (47%)	12 (46%)	10 (59%)	2 (25%)	0.2
Nonischemic ECG	10 (33%)	8 (31%)	4 (24%)	4 (50%)	0.36
Inconclusive ECG	5 (17%)	5 (19%)	3 (18%)	1 (13%)	1.00
24h ECG					
Ischemic ECG	18 (60%)	16 (62%)	11 (67%)	4 (50%)	0.67
Nonischemic ECG	6 (20%)	4 (15%)	2 (12%)	2 (25%)	0.57
Inconclusive ECG	6 (20%)	6 (23%)	4 (24%)	2 (25%)	1.00
HFMI					
ICCU admission value (%)	4.6 ± 2.9	4.7 ± 2.8	5.2 ± 2.9	4.2 ± 2.6	0.21
Post angiography value (%)	3.4 ± 2.3	3.4 ± 2.5	4.0 ± 2.4	2.3 ± 2.3	0.08
24h value (%)	2.8 ± 2.1	2.8 ± 2.1	3.2 ± 2.3	1.8 ± 1.1	0.11

P values refer to the comparison between urgent reperfusion and spontaneous reperfusion columns. Bold type indicates statistical significance

reperfusion and two non-ST-elevation MI (NSTEMI) patients. After 24h, 32% of the patients with ischemic admission ECG had nonischemic or inconclusive ECG, and 45% of the patients with nonischemic or inconclusive admission ECG had indications of ischemia or infarction.

A typical example of HFQRS analysis results is given in Figure 3, for a 41-year-old male patient with STEMI. The patient, without history of CAD, was diagnosed with acute anterior STEMI in the emergency department before being admitted to

the ICCU. Admission ECG, acquired 2.25 hours after onset of symptoms, showed spontaneous ST resolution, although chest pain persisted. HFQRS exhibited significant ischemic morphology (RAZ pattern) in multiple leads, with HFMI = 15% in a typical lead (V₄). Urgent angiography, performed 2 hours after admission, revealed two-vessel disease with total occlusion of the mid-LAD and critical occlusion of a first marginal branch. Both vessels were successfully dilated. Post revascularization ECG was normal, and HFQRS signal exhibited

Figure 3. ECG and HFQRS signals acquired at admission, post revascularization, and after 24 hours from a 41-year-old male with ST-elevation MI. Note the profound change in the HFQRS signal morphology, showing a significant reduced amplitude zone (RAZ) during admission, which is resolved after 24 hours. Conventional ECG does not exhibit ischemic pattern.

Figure 4. Comparison of average HFMI values at ICCU admission, post angiography, and after 24 hours. Error bar represent standard error of the mean. HFMI = high-frequency morphology index; angio. = angiography; STEMI = ST elevation myocardial infarction; Urgent reperf. = urgent reperfusion; Spont reperf. = spontaneous reperfusion.

partial resolution of RAZ morphology, with HFMI = 7%. At 24h, both conventional ECG and HFQRS morphology did not indicate ongoing ischemia.

The values of HFMI per patient were higher on the admission ECG than on the post angiography ECG ($4.6 \pm 2.9\%$ vs $3.4 \pm 2.3\%$, $P < 0.05$) and the 24h ECG ($4.6 \pm 2.9\%$ vs $2.8 \pm 2.1\%$, $P < 0.01$), as shown in Figure 4. The number of leads with HFMI value $>3\%$, was higher on the admission ECG, compared to post angiography ECG (3.4 ± 2.7 vs 2.1 ± 2 , $P < 0.03$) and 24h ECG (3.4 ± 2.7

vs 2.1 ± 1.8 , $P < 0.02$). The trend of decrease in average HFMI values, following angiography and after 24h was also observed in subgroups of STEMI patients who were referred for urgent reperfusion, as well as in patients with spontaneous reperfusion (Fig. 4). Compared to patients who underwent urgent reperfusion, in those with spontaneous reperfusion HFMI values tended to be lower during admission, post angiography, and 24h. This difference was not statistically significant, possibly due to the small sample size.

HFMI value decreased from admission ECG to 24h ECG in 71% of the patients in the analysis group, and in 79% of the patients who were revascularized by angioplasty.

A noteworthy case of a patient excluded from the analysis group is shown in Figure 5. The patient, 30-year-old male with no risk factors was admitted due to acute chest pain and elevated Troponin-T (0.8 ng/mL), following 5 days of viral common cold disease. Admission ECG showed diffuse ST-segment elevations (Fig. 5) and the patient was referred for urgent angiography, which demonstrated normal coronary arteries. HFQRS analysis revealed normal signal morphology, with apparent RAZ in only one lead (Fig. 5). The discharge diagnosis was perimyocarditis, and no adverse cardiac events were documented during a 7-month follow-up period.

DISCUSSION

The ECG is a cardinal, widely used tool for evaluating patients with chest pain and establishing

Figure 5. ECG and HFQRS signals of a 30-year-old patient with perimyocarditis and symptoms of acute MI. Resting ECG at ICCU admission (A) shows significant ST-elevation, whereas HFQRS signals (B) reveal normal signal morphology, with mild RAZ pattern in only one lead (V₃). Angiography demonstrated normal coronary arteries.

the diagnosis of myocardial ischemia or infarction. Yet, ST-segment abnormalities may be absent or nonspecific, and when present may be due to nonischemic disorders. Since the initial ECG is frequently nondiagnostic, repeated ECGs are recommended for symptomatic patients,²⁰ and a combination of prehospital and serial in-hospital ECGs has been reported to improve the sensitivity for acute coronary syndrome.²¹ Utilization of depolarization indices of ischemia may have added diagnostic value in triaging patients with chest pain. Fragmented QRS (fQRS) was reported to be a moderately sensitive but highly specific sign for STEMI and NSTEMI, as well as an independent predictor of mortality in patients with acute coronary syndrome (ACS).²² Analysis of the upward and downward slopes of the QRS complex has recently been argued to be a robust method of depolarization evaluation.^{23,24} These suggested methods are based on examining the conventional "low-frequency" QRS complex.

Analysis of ventricular late potentials using signal-averaged ECG is typically performed in a higher frequency band of 40–250 Hz.²⁵ However, this technique has been mostly used for predicting risk of sudden cardiac death, rather than for acute care diagnosis.

As most ECG devices employ low-pass filtering for noise robustness, HFQRS components above 100 Hz are typically removed, and their potentially valuable information is overlooked. High-frequency mid-QRS analysis enables quantification and diagnostic interpretation of this information.

Morphological changes of HFQRS components during myocardial ischemia were first observed in animal models,^{8–10,26–28} as well as humans undergoing PCI.^{11,12,29} The term RAZ was coined to define the morphological pattern of HFQRS splitting during induced supply ischemia.³⁰ Different methods for identifying clinically significant RAZ patterns have been proposed and were suggested as an aid to ischemia monitoring.¹⁶ However,

previous studies that characterized changes of HFQRS indices induced by myocardial ischemia focused either on demand ischemia during exercise testing,^{31,32} reversible perfusion defects during adenosine myocardial perfusion imaging,³³ or effects of old MI.^{34,35} To the best of our knowledge, the current study is the first to report quantitative assessment of HFQRS morphology in patients with AMI. The novel index, HFMI, effectively quantifies the extent of RAZ morphology in the HFQRS signals. The observation that HFMI values are lower after revascularization and after additional 24h, compared to the values at ICCU admission, implies that this index may be a manifestation of ischemia. In patients with spontaneous reperfusion (N = 8), HFMI values in admission ECG were still high, although there were no ST-segment deviations or other ECG abnormalities. Among patients with abnormal or inconclusive admission ECG (N = 21) the 24h ECG remained abnormal or inconclusive in 90% of the cases, whereas HFMI decreased in 75% of them. This indicates the HFQRS analysis may provide complementary diagnostic information to conventional ST-T and Q-wave abnormalities. The potential of HFQRS analysis to aid in ruling out acute myocardial ischemia in patients with chest pain was anecdotally demonstrated in the our patient with perimyocarditis in whom invasive coronary angiography was considered clinically necessary to exclude AMI.³⁶

The study has several limitations. The small size of the study group and the predominance of STEMI patients do not allow us to draw firm conclusions regarding the important group of NSTEMI patients, in whom conventional ECG-based diagnosis is often less reliable. In addition, the ECG acquired in the ICCU may sometime differ from the initial ECG in the emergency department or the prehospital ECG, due to evolution over time as well as the effect of initial treatment. Patients with prior MI were excluded from the current study, to exclude possible interference of the old infarct with the HFQRS signals. However, HFQRS analysis may be clinically valuable in patients with a history of MI, as well as in patients with wide QRS. Future studies are necessary to establish the required adjustments to the analysis in these subgroups. Future studies will also be needed to address the clinical usefulness of HFQRS analysis in triaging and monitoring patients with acute chest pain.

In summary, we have shown that analysis of HFQRS morphology in patients with AMI

is feasible and that HFQRS-derived index of ischemia decreases in these patients following reperfusion, thus tracking the severity of ischemia. HFQRS analysis may aid in risk stratification of patients with suspected myocardial ischemia by providing clinical information complementary to the conventional ECG.

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