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High-frequency QRS analysis compared to conventional ST-segment analysis in patients with chest pain and normal ECG referred for exercise tolerance test

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Abstract

Background: *The novel analysis of high-frequency QRS components (HFQRS-analysis) has been proposed in patients with chest pain (CP) and normal electrocardiography (ECG) referred for exercise tolerance test (ex-ECG). The aim of the study was to compare the diagnostic value of ex-ECG with ex-HFQRS-analysis.*

Methods: *Patients with CP and normal ECG, troponin, and echocardiography were considered. All patients underwent ex-ECG for conventional ST-segment-analysis and ex-HFQRS-analysis. A decrease ≥ 50% of the HFQRS signal intensity recorded in at least 2 contiguous leads was considered an index of ischemia, as ST-segment depression ≥ 2 mm or ≥ 1 mm and CP on ex-ECG. Exclusion criteria were: QRS duration ≥ 120 ms and inability to exercise. End-point: The composite of coronary stenosis ≥ 70% or acute coronary syndrome, revascularization, cardiovascular death at 3-month follow-up.*

Results: *Three-hundred thirty-seven patients were enrolled (age 60 ± 15 years). The percentage of age-adjusted maximal predicted heart rate was 89 ± 10 beat per minute and the maximal systolic blood pressure was 169 ± 23 mm Hg. Nineteen patients achieved the end-point. In multivariate analysis, both ex-ECG and ex-HFQRS were predictors of the end-point. The ex-HFQRS-analysis showed higher sensitivity (63% vs. 26%;* $p < 0.05$*), lower specificity (68% vs. 95%;* $p < 0.001$*), and comparable negative predictive value (97% vs. 96%;* $p = 0.502$*) when compared to ex-ECG-analysis. Receiver operator characteristics analysis showed the incremental diagnostic value of HFQRS (area: 0.655, 95% CI 0.60–0.71) over conventional ex-ECG (0.608, CI 0.55–0.66) and CP score (0.530, CI 0.48–0.59), however without statistical significance in pairwise comparison by C-statistic.*

Conclusions: *In patients with CP submitted to ex-ECG, the novel ex-HFQRS-analysis shows a valuable incremental diagnostic value over ST-segment-analysis.* (Cardiol J 2015; 22, 2: 141–149)

Key words: chest pain, coronary artery disease, diagnosis, exercise tolerance test, stress testing, prognosis, emergency medicine

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Introduction

Chest pain (CP) consistent with myocardial ischemia is a frequent worldwide cause of visits to the Emergency Department in adults. However, less than 30% of these patients are recognized as having ST-segment changes associated with myocardial ischemia. Today, the separation of high-risk from low-risk patients for short-term coronary events is mandatory in the emergency setting, and exercise tolerance test electrocardiography (ex-ECG) is considered a valuable first-line testing for prognostication in patients with non-diagnostic baseline screening for myocardial ischemia, inclusive of ECGs, troponins, and echocardiography [1, 2]. However, the prognostic value for stress-induced ischemia by ex-ECG is poor when compared to exercise stress echocardiography (ex-ECHO) or exercise stress myocardial perfusion imaging (ex-SPECT), or coronary computed tomography angiography (CTA). Indeed, sensitivity and specificity for coronary disease diagnosis of ex-ECG is reported to be up to 50% and 90%, respectively, compared to 85% and 88% of ex-ECHO, respectively; 92% and 97% of ex-SPECT, respectively; and 99% and 83% of CTA, respectively [3].

Recently, the analysis of high-frequency mid-QRS components has been proposed in chest pain patients referred for exercise tolerance test. This novel ECG technique allows detection of stress-induced ischemia by examining the high-frequency QRS (HFQRS) intensity and its components in 150 to 250 Hz frequency band [4–8]. Nevertheless, the value of this novel technique has not been validated yet in emergency medicine and emergency cardiology setting.

The aim of this study was to compare the diagnostic value of exercise HFQRS analysis to conventional ST-segment analysis for detection of high-risk patients for coronary artery disease (CAD) or short-term adverse cardiac events in patients with low-risk chest pain referred for exercise tolerance test in the emergency setting.

Methods

Study population

Unselected consecutive patients suitable for enrolment were those who presented with typical CP consistent for angina pectoris and myocardial ischemia between January and December 2013. The study setting was the Emergency Department of the tertiary care teaching Careggi General Hospital, Florence, Italy, with a catchment area serving a population of half-million. Each patient was categorized at baseline with physical examination, instrumental evaluation inclusive of ECG and the biomarker of myocardial injury troponin (cTnI). The Department of Cardiology was on call for serial evaluations and choosing wisely the diagnostic strategy. Patients with negative first-line evaluation were subjected to a 6–12 h observation period with serial ECGs, serial cTnI tests, and resting echocardiography [1, 9–11].

Inclusion and exclusion criteria

The inclusion criterion was the presence of visceral chest pain consistent for angina pectoris lasting less than 24 h. Chest pain was characterized with a validated CP score, as CP characteristics were encoded according to a modified CP score, which takes into account pain characteristics (crushing, pressing, heaviness = 3; sticking, pleuritic, pinprick = 1), localization (substernal or precordial = 3; epigastric, left chest, neck, lower jaw = 1), radiation (as either arm, shoulder, back, neck, lower jaw = 1; absence = 0), associated symptoms (as dyspnea, nausea, diaphoresis = 2; absence = 0), recurrence in the previous 48 h (yes = 3, no = 0) [12, 13]. We considered patients with a pre-test likelihood of CAD between 15% and 85% calculated using a model suggested by Diamond et al. [14], and patients with normal cTnI levels (i.e. < 0.10 ng/mL) [15].

The exclusion criteria were represented by the presence of hemodynamic instability (i.e.: systolic blood pressure lower than 100 mm Hg) or Killip class 2 or more, and the presence of acute coronary syndrome (ACS) or stroke defined by the European and North American Guidelines [3, 16, 17]. Due to analysis of HFQRS, we excluded patients when presenting with cardiac pacemaker or QRS duration ≥ 120 ms. Patients with inability to exercise were also excluded.

Tourists and inhabitants outside the catchment area of Careggi Hospital were not enrolled in the study because of the probability to lose them at follow-up.

Each patient gave informed consent to participate in the study and publication of personal data. The study was conducted according to good clinical practice and principles of the Declaration of Helsinki of clinical research involving human patients. The institutional review board approved the protocol. Departmental sources supported the work and no contributorship or competing interest existed.

Patient management

Twelve lead ECG was performed on presentation and was repeated if patients complained about recurrent CP. Troponin I test was performed on presentation and after 3–6 h, or up to 12 h as required by clinical evolution. Patients were considered having normal ECG in the presence of normal ST-segment, measured at 60 ms from J point, and normal T-wave. Patients were considered having non-diagnostic ECG in the presence of mild changes like ST-segment elevation or depression less than 0.05 mV (0.5 mm), or asymmetrical T-wave inversion less than 0.2 mV (2 mm); no Q wave or Q waves less than 0.03 s.

Patients showing ischemic ECG changes or troponin elevations, or new cardiac wall motion abnormalities at echocardiography before and during observation, and after the first-line evaluation were considered at high-risk of cardiac events were admitted. Patients with negative troponins, negative ECGs, nondiagnostic echocardiography were considered at low-risk of CAD were enrolled and underwent exercise tolerance test program. Each patient underwent ex-ECG for conventional ST-segment analysis and ex-HFQRS analysis [2, 18].

Stress testing

A symptom-limited graded exercise tolerance test was performed after the first 6 h of observation and no later than 24 h from presentation using the Bruce protocol. High-resolution 12-lead ECG (HyperQ Stress System, BSP Ltd., Tel Aviv, Israel) was continuously recorded throughout the exercise test and used for offline quantitative assessment of ST-segment changes and HFQRS intensity analysis. Conventional ECG monitoring during the exercise test was extracted automatically from the high-resolution ECG traces. The ST-segment level was measured 60 ms after the J point using commercial software (HyperQ Stress System). The ST-segment analysis and the ECG response was considered positive if horizontal sloping (defined as ST-segment slope ≥ 0.5 mm) or downsloping (defined as ST-segment depression ≥ 2 mm) was found in ≥ 2, in two contiguous leads or ST-segment depression ≥ 1 mm associated with CP, measured at 60 ms from J point ensued. Contiguous leads were considered among those exploring the antero-lateral V1–V6 leads, lateral aVL–D1 leads, or inferior D2–D3–aVF leads. Overall, diagnostic results were not possible in cases of unavailability of optimal technical analysis of HFQRS; patients were excluded from analysis in the presence of leads that exhibited erratic or upsloping/downsloping ST-segment changes in ≥ 60% of the exercise test as they were considered noisy. If a patient was given nitrates or calcium channel blockers or beta-blockers, they were discontinued at least ≥ 12–24 h before testing. The exercise tolerance test was performed aiming to reach at least 85% of the age-adjusted maximal predicted heart rate [%MP – HR: (220 – age in years) × 0.85]. The HFQRS intensity was calculated and a decrease ≥ 50% of the signal recorded in at least 2 contiguous leads was considered an index of ischemia. Also in HFQRS analysis, contiguous leads were considered among those exploring the antero-lateral V1–V6 leads, lateral aVL–D1 leads, or inferior D2–D3–aVF leads. Peak exercise capacity from the graded test was estimated in METs, using data from standard predicted equations [1].

Patients recognized as having positive ex-ECG or positive ex-HFQRS were considered at high-risk of cardiac events were admitted and considered for angiography. Patients with negative stress testing were regarded as at very low-risk of coronary events and were discharged home and submitted to short-term follow-up.

End-point

The primary composite end-point was the detection of coronary stenosis ≥ 70% by angiography or the occurrence of ischemic cardiac events inclusive of ACS (ST elevation and non-ST elevation acute myocardial infarction or unstable angina), revascularization, and cardiovascular death within 3-month follow-up.

Follow-up

Follow-up was performed by reviewing the Emergency Department access archives and by phone after 3 months in patients discharged with negative clinical evaluation and negative stress testing. Data were collected by means of a physician-directed telephone interview using a standardized questionnaire. Each cardiac event of suspected myocardial ischemia was analyzed and confirmed after clinical charts, ECGs and laboratory tests review.

Statistical analysis

Continuous variables are expressed as mean ± ± standard deviation. Frequencies are shown as absolute values and percentages. Statistical comparisons of demographic and clinical features were performed using the χ^2 test (Fisher exact test) when expected frequencies were < 5% and the Pearson exact test for categorical variables.

Continuous variables were compared through one-way analysis of variance (ANOVA) and t-test. Two-tail p value < 0.05 was considered statistically significant. Univariate analysis was performed in a full-factorial model (including all the clinical variables and comorbidities considered in the study) to provide regression. The incidence at follow-up of the composite endpoint was adjusted for all the established risk factors for cardiovascular disease and comorbidities. Variables identified as potential prognostic predictors for multivariate modeling were selected by backward method. Hazard ratios (HR) were used to illustrate the probabilities of adverse events. In addition, to estimate the predictive power of single tests for predicting the presence or absence of disease, sensitivity, specificity, positive (+) and negative (−) predictive values, and likelihood ratios [LR] [(+)LR = sensitivity/ /(1−specificity); (−)LR = specificity/(1−sensitivity)] were calculated considering the follow-up data. Comparison of receiver operator characteristics (ROC) curves was performed using pairwise C-statistical test. Calculations were performed with the use of version 19, SPSS statistical package (SPSS Inc., Chicago, IL) for all analyses.

Results

Study population

Out of 377 CP patients considered, 40 were excluded due to the presence of wide QRS (n = 11) or unavailability of optimal technical HFQRS analysis due to noise (n = 29). Thus, 337 patients were enrolled (mean age 60 ± 15 years, range 18–87 years, 212 male). The chart of time of patients enrolled in the study and outcomes during in-hospital evaluation and during follow-up are shown in Figure 1. Baseline clinical characteristics of the enrolled patients and patients who were recognized as reaching the composite endpoint have been analyzed and are shown in Table 1.

Factors associated with adverse outcome

Overall, 19 patients achieved the composite end-point. In univariate analysis, the previous use of statin therapy, positive ex-ECG analysis and positive ex-HFQRS analysis were predictors of the composite end-point. Both ex-ECG-analysis HR 7.82, 95% confidence intervals [CI] 2.37–25.84, p = 0.001) and ex-HFQRS-analysis (HR 3.84, CI 1.43–10.35, p = 0.008) eventually were independent predictors of the end-point in multivariate analysis (Table 2).

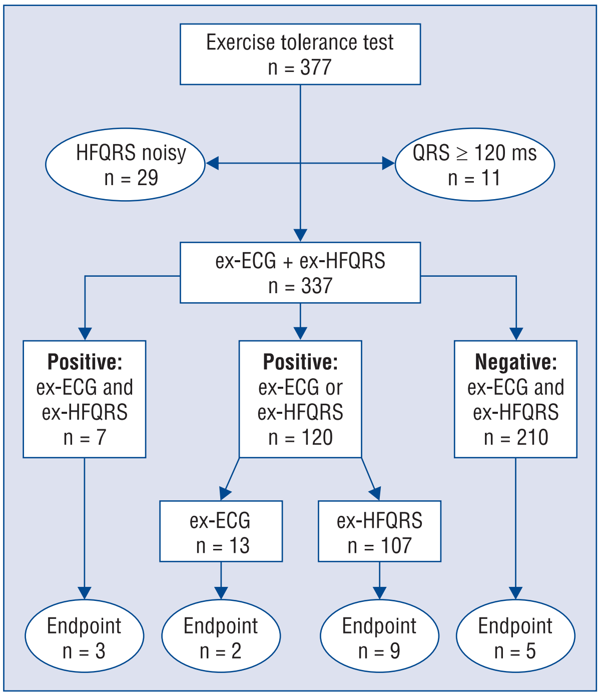

Figure 1. The chart of time to management and outcomes according to the incidence of the primary endpoint inclusive of non-fatal myocardial infarction, revascularization and cardiac death in patients presenting with chest pain enrolled in the study (n = 337); ex-ECG — exercise tolerance test electrocardiography; ex-HFQRS — exercise high-frequency QRS components.

Patients with positive stress testing

Patients were also stratified according to the results of stress testing. The final analysis covers 127 patients who were recognized as having at least one in two positive stress testing. Of these, 14 achieved the end-point; details and concordances are shown in Figure 2.

Predictive values of stress testing

The ex-HFQRS analysis was more sensitive (63% vs. 26%; p < 0.05), but less specific (68% vs. 95%; p < 0.001) than the ex-ECG analysis. The negative and positive predictive value of HFQRS analyses were comparable to the ex-ECG analysis (97% vs. 96%, respectively, p = 0.502; and 11% vs. 25%, respectively, p = 0.135) (Fig. 3).

ROC analysis

ROC analysis for diagnosis of HFQRS vs. ECG analysis demonstrated the incremental diagnostic value of HFQRS intensity analysis during stress over the CP score > 6 (consistent for high

Table 1. Baseline clinical characteristics of patients with chest pain and negative first-line screening for coronary artery disease enrolled in the study (n = 337), according to the incidence of the primary endpoint inclusive of non-fatal myocardial infarction, revascularization and cardiac death.

Parameter	Patients (n = 337)	Achieve the endpoint (n = 19)	Do not achieve the endpoint (n = 318)	P
Mean age [years]	60 ± 15	65 ± 12	60 ± 6	0.084
Male gender	212 (63%)	13 (68%)	199 (59%)	0.808
Hypertension	179 (53%)	13 (68%)	166 (49%)	0.237
Diabetes mellitus	40 (12%)	3 (16%)	37 (12%)	0.482
Hypercholesterolemia	98 (29%)	6 (32%)	92 (27%)	0.798
Active smokers	77 (23%)	4 (21%)	73 (22%)	1
Known coronary heart disease	54 (16%)	5 (26%)	49 (15%)	0.204
Familiarity for coronary artery disease	76 (23%)	4 (21%)	72 (21%)	1
Chest pain score	5.0 ± 2,9	5.8 ± 2.8	5 ± 2.9	0.212
Florence prediction rule	2.1 ± 1.8	2.5 ± 2.1	2.1± 1.8	0.359
Heart rate resting [bpm]	79 ± 15	80 ± 15	79 ± 15	0.798
Heart rate maximal [bpm]	142 ± 19	139 ± 21	142 ± 19	0.595
Heart rate percentage of maximal [bpm]	89 ± 10	90 ± 10	88 ± 10	0.518
Systolic arterial pressure baseline [mm Hg]	127 ± 15	133 ± 16	126 ± 15	0.098
Systolic arterial pressure maximal [mm Hg]	169 ± 23	173 ± 20	169 ± 23	0.406
Metabolic eqivalents	6,8 ± 3.5	6.2 ± 1.4	6.8 ± 3.6	0.140
Angiotensin converting enzyme inhibitors	140 (42%)	11 (58%)	129 (41%)	0.155
Calcium antagonist	46 (14%)	4 (21%)	42 (13%)	0.308
Statin	90 (27%)	9 (47%)	81 (24%)	0.057
Antiplatelet	92 (27%)	9 (47%)	83 (25%)	0.061
Beta-blockers	93 (28%)	9 (47%)	84 (25%)	0.063

bpm — beat per minute

probability of angina pectoris) and conventional ex-ECG parameters. However, when comparison of ROC analysis was performed using pairwise C-statistical analysis, no differences existed among the three areas. Indeed, the comparison of the area of ex-HFQRS analysis (0.655, 95% CI 0.60–0.71) vs. the area of ex-ECG (0.608, 95% CI 0.55–0.66) was statistically not significant ($p = 0.552$). Also the comparison of the area of ex-HFQRS vs. the area of CP score (0.530, 95% CI 0.48–0.59) was statistically not significant ($p = 0.364$). What is more, the comparison of ex-ECG vs. CP score was statistically not significant ($p = 0.149$) (Fig. 4).

Discussion

Main findings

This study analyses the prognostic value of the novel HFQRS analysis in exercise-induced QRS changes as a marker of myocardial ischemia. The technique has been proposed in patients with CP and non-diagnostic baseline evaluation for CAD, referred for ex-ECG, because of the poor diagnostic power of such testing [3]. Indeed, these patients usually labeled as low-risk patients, eventually will show a substantial proportion of coronary events up to 15% [3, 13, 19]. Interestingly, in this subset of low-risk patients improvements have been reported in sensitivity and specificity when ex-HFQRS analysis was compared to ex-ECG analysis, alone, in elective evaluations [18].

In the emergency setting, the results of the present study provide information to support evidence that ex-HFQRS analysis more likely allows detection of high-risk patients for CAD and short-term cardiovascular events when compared to ex-ECG, alone. Indeed, sensitivity of ex-HFQRS analysis was more than two fold higher vs. ex-ECG ($p < 0.05$), and the negative/positive predictive values were comparable between the two tests.

Table 2. Univariate and multivariate analyses in patients with chest pain and negative first-line screening for coronary artery disease enrolled in the study and subjected to 3-month follow-up (n = 337).

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P	Odds ratio	95% CI	p
Ex-ECG	7.21	2.30–22.68	0.001	7.82	2.37–25.84	0.001
Ex-HFQRS	3.63	1.39–9.50	0.009	3.84	1.43–10.35	0.008
Statin	2.63	1.03–6.71	0.042			
Antiplatelet	2.55	1.00–6.49	0.050			
Beta-blockers	2.51	0.99–6.38	0.054			
Angiotensin converting enzyme inhibitors	2.02	0.79–5.15	0.143			
Hypertension	1.98	0.74–5.35	0.176			
Coronary artery disease	1.96	0.68–5.69	0.216			
Calcium antagonist	1.75	0.56–5.53	0.339			
Diabetes mellitus	1.42	0.40–5.12	0.588			
Male gender	1.30	0.48–3.50	0.609			
Hypercholesterolemia	1.13	0.42–3.07	0.805			
Chest pain score	1.11	0.94–1.30	0.210			
Mean age	1.03	0.99–1.06	0.151			
Percentage of maximal heart rate	1.02	0.97–1.06	0.514			
Systolic arterial pressure (maximal)	1.01	0.99–1.03	0.462			
Heart rate (maximal)	0.99	0.97–1.01	0.549			
Familiarity for coronary artery disease	0.91	0.29–2.83	0.872			
Smoker	0.90	0.29–2.78	0.848			
Metabolic equivalents (maximal)	0.83	0.59–1.16	0.265			

CI — confidence interval; ex-ECG — exercise tolerance test electrocardiography; ex-HFQRS — exercise high-frequency QRS components

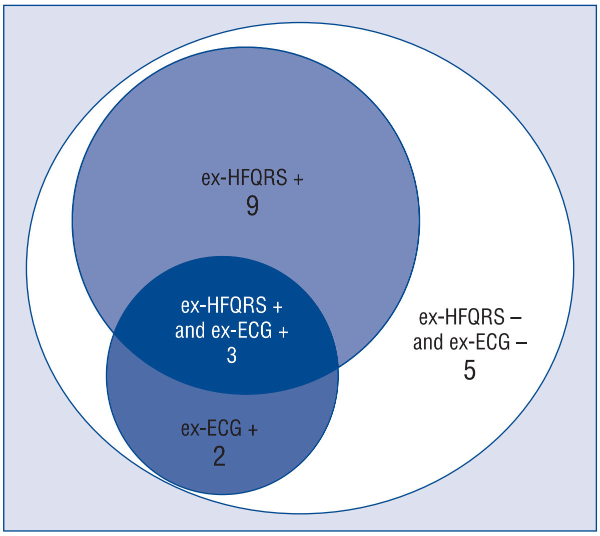

Figure 2. Concordances according to the results of stress testing between patients submitted to exercise tolerance test electrocardiography (ex-ECG) versus exercise high-frequency QRS components (ex-HFQRS) analysis in patients presenting with chest pain enrolled in the study.

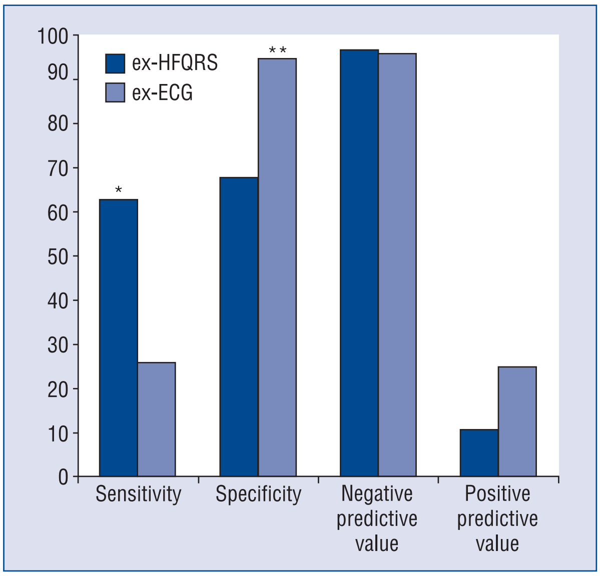

Figure 3. Predictive values of stress testing; ex-HFQRS — exercise high-frequency QRS components; ex-ECG — exercise tolerance test electrocardiography; $^{*}p < 0.05$; $^{**}p < 0.01$.

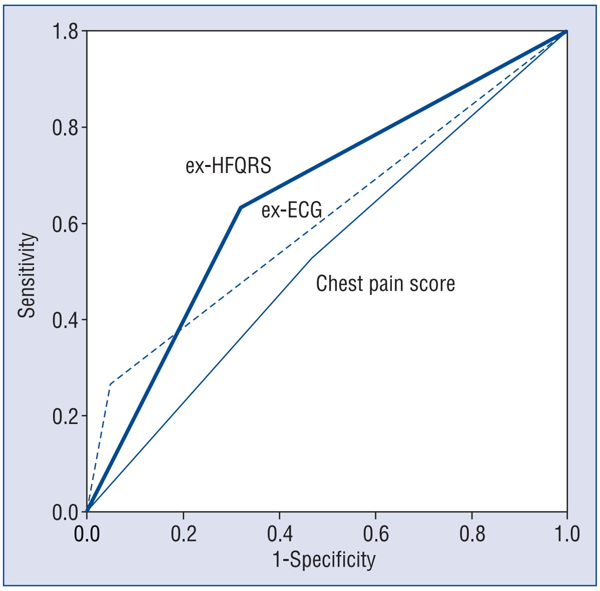

Figure 4. Receiver operator characteristics (ROC) analysis for diagnosis of coronary artery disease and adverse coronary events in patients presenting with chest pain enrolled in the study and submitted to exercise high-frequency QRS components (ex-HFQRS) analysis versus electrocardiographic (ex-ECG) analysis. C-statistical analysis for comparison of areas under the ROC analysis: $p = 0.552$.

In addition, ROC analysis showed larger area of ex-HFQRS analysis (0.655) vs. ex-ECG (0.608) and data might be related to a substantial incremental diagnostic value of HFQRS intensity over conventional ex-ECG parameters. However, comparison of ROC analysis by C-statistic did not show any difference between the two areas ($p = 0.552$).

The results of this study suggest that ex-HFQRS analysis works for a valuable diagnostic tool complementary to conventional ex-ECG testing in CP patients with normal ECG, presenting to primary or secondary care hospital with high clinical risk profile consistent with the available high specific risk scores (TIMI, Sanchis, and Florence Prediction Rule risk scores) [3, 20–23].

Introduction to computed-assisted high frequency ECG analysis

During depolarization, the myocardium is activated via myocyte-to-myocyte conduction, spreading away from the ends of the Purkinje fibers. The depolarization wavefront, which creates the QRS complex, is fragmented on the microscopic level. This fragmentation brings about low amplitude, high frequency notches on the QRS. Ischemia slows down myocyte-to-myocyte conduction due to changes in the action potential of ischemic myocytes. The slow conduction reduces the fragmentation of the depolarization wavefront and thus shifts the high-frequency components to lower frequencies. Consequently, ischemia results in high frequency QRS intensity reduction. Because the high frequency QRS signals are very low in amplitude, eventually advanced signal processing is required to extract and interpret the value physiological information embedded in them. Thus, the detection of depolarization changes during exercise using an automated analysis of high frequency QRS components allows detection of ischemia than identification of ST segment deviations. Indeed, traditional exercise ECG testing is based on ST segment analysis, yet with limited diagnostic accuracy.

Several previous studies have suggested that the decrease in HFQRS intensity precedes and is more sensitive than ST-segment changes. Indeed, these studies have demonstrated the relation between decreased HFQRS intensity and myocardial ischemia including animal models of coronary occlusion [5–7], myocardial ischemia induced by intracoronary balloon occlusion in humans, and in patients with acute ST-segment elevation myocardial infarction [24–26]. In the study of Sharir et al. [18], the HFQRS analysis was compared to conventional ST-segment analysis with a cut-off myocardial ischemia ≥ 10% derived from semi-quantitative analysis of myocardial ischemia by nuclear scan imaging that was used as the gold standard of stress-induced ischemia. The HFQRS analysis was more sensitive (69% vs. 39%, $p < < 0.005$) and more specific (86% vs. 82%, $p < 0.05$) in detecting ischemia. In the study of Sharir et al. [18], because of HFQRS intensity was sensitive in detecting moderate/severe ischemia, the technique aid conventional exercise ECG testing in risk stratification and identification of patients who might benefit from early invasive strategy.

Conversely, in the present study, we compared ex-HFQRS analysis without any thresholds for abnormality to conventional ST-segment analysis, as in emergency setting, the separation of high-risk patients who need admission from low-risk patients who can be safely discharged is mandatory. Indeed, acute CP can relate to absent or mild/moderate/severe myocardial ischemia; these subset of patients need additional risk stratification before discharge to prevent adverse events. Moreover, in order to standardize the criteria for the analysis of the two tests, the number of contiguous leads with significant changes that were considered suggestive of myocardial ischemia were two or more, and as a consequence, HFQRS decrease (plus than 50%) related with the suspected myocardial ischemia were considered in the conventional ST-segment analysis in at least two contiguous leads.

Usually, previous conventional techniques for ECG detection of exercise-induced myocardial ischemia have relied on identification of repolarization abnormalities manifested as ST-segment changes in the 0.05-Hz to 100-Hz frequency band [27, 28]. HFQRS analysis, in order to increase the diagnostic capabilities of exercise ECG, is based on detection of specific depolarization changes caused by ischemia. Fragmentation of the depolarization wavefront owing to the multisite activation nature of the myocardium on the microscopic level is manifested as high-frequency components within the QRS complex [4]. Ischemia slows activation velocity in the ischemic region [4, 7] and decreases fragmentation of the depolarization wavefront. As a result, high-frequency components of the QRS complex coming from the ischemic region are decreased.

Future clinical application

Our study provides a picture of the impact of the presence of CAD and the risk of short-term cardiac events in patients with CP and normal ECG on presentation and confirms that masked CAD exists in a substantial proportion of these patients. In the acute cardiac care, the computed-assisted stress testing HFQRS-analysis might aid cardiologists and emergency physicians stratify CP patients. Eventually, the ex-HFQRS analysis should drive the threshold approach to clinical decision making over the ex-ECG alone.

Strengths of the study

The strengths of the present study are represented by: (a) a large series of patients studied (n = 337), consecutively accessing a community hospital with recent onset chest pain and low pretest likelihood of CAD representing the population typically referred for ex-ECG; (b) detection of CAD and eventually adverse cardiac events occurring in a substantial proportion of patients comparable to data in the literature; (c) the predictive values of ST-segment analysis in this study within the range reported in previous studies; (d) the improvement of proper disposition with the evaluation of ex-HFQRS analysis.

Limitations of the study

Limitations are represented by: (a) the lack of randomization to diagnostic strategy; (b) the lack of analysis of the two diagnostic strategies costs; (c) results, per se, not applicable to the general population and requiring validation in other centers as the patients studied derive from patients presenting only to our hospital; (d) risk assessment by the first-line screening, observation, and stress testing modalities requiring evaluation in a properly designed study.

Conclusions

The ex-HFQRS analysis showed a valuable incremental diagnostic value over the conventional ST-segment-analysis. Indeed, the ex-HFQRS analysis demonstrated improved sensitivity and comparable negative/positive predictive values when compared to the validated conventional ST-segment-analysis in patients with CP and negative baseline screening for myocardial ischemia, referred for ex-ECG tolerance test.

Conflict of interest: None declared

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