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High Frequency QRS Analysis to Supplement ST Evaluation in Exercise Stress Electrocardiography: Incremental Diagnostic Accuracy and Net Reclassification

PC Balfour Jr^{#1}, JA Gonzalez^{#2}, PW Shaw³, MP Caminero⁴, EM Holland⁵, JW Melson¹, M Sobczak¹, V Izarnotegui¹, DD Watson^{1,6}, GA Beller^{1,6}, JM Bourque^{7,8}

¹Cardiovascular Division, Department of Medicine, Cardiovascular Imaging Center, University of Virginia Health System, 1215 Lee Street, Box 800662, Charlottesville, VA, 22908, USA.

²Division of Cardiovascular Disease, Scripps Clinic, La Jolla, CA, USA.

³Berkshire Medical Center, Pittsfield, MA, USA.

⁴Cardiac and Vascular Institute, Memorial Healthcare System, Hollywood, FL, USA.

⁵University of North Carolina, Chapel Hill, NC, USA.

⁶Departments of Radiology, University of Virginia Health System, Charlottesville, VA, USA.

⁷Cardiovascular Division, Department of Medicine, Cardiovascular Imaging Center, University of Virginia Health System, 1215 Lee Street, Box 800662, Charlottesville, VA, 22908, USA.
jamieson2@gmail.com.

⁸Departments of Radiology, University of Virginia Health System, Charlottesville, VA, USA.
jamieson2@gmail.com.

These authors contributed equally to this work.

Abstract

Background: Exercise stress electrocardiography (ECG) alone is underutilized in part due to poor diagnostic accuracy. High frequency QRS analysis (HF-QRS) is a novel tool to supplement ST evaluation during stress ECG. We compared the diagnostic accuracy and net reclassification of HF-QRS analysis compared with ST evaluation for substantial myocardial ischemia by exercise SPECT myocardial perfusion imaging (MPI).

Methods and Results: Exercise SPECT MPI was performed in 257 consecutive eligible patients (mean age 59 ± 12 , 67% male). An ischemic HF-QRS pattern was defined as a $>1 \mu\text{V}$ absolute reduction and a 50% relative reduction of the root mean square of the 150-250 Hz band signal in 3 leads. Left ventricular ischemia of 10% on SPECT MPI was the diagnostic standard for substantial myocardial ischemia. HF-QRS analysis demonstrated incremental diagnostic value

Address for Correspondence: Jamieson M. Bourque, M.D., M.H.S., Cardiovascular Imaging Center, Cardiovascular Division, Department of Medicine, University of Virginia Health System, Box 800662, 1215 Lee Street, Charlottesville, VA 22908, Office: (434) 243-9337 Fax: (434) 982-1998, jbourque@virginia.edu.

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to ST evaluation plus clinical risk factors (AUC 0.804 vs 0.749, $p < 0.0001$). A HF-QRS + ST analysis strategy identified 92.3% of subjects with substantial ischemia and no abnormality in 59.9% of the cohort. No cardiac events occurred in patients without substantial ischemia identified by HF-QRS analysis.

Conclusions: In this prospective analysis, exercise stress ECG with HF-QRS analysis identified any and substantial ischemia with high diagnostic accuracy and may allow more than half of referred patients to safely avoid imaging.

Introduction

Conventional exercise stress electrocardiography (ECG) remains the guideline-recommended initial test in patients with low to intermediate risk for CAD who are able to exercise and have an interpretable ECG.(1) However, despite these recommendations and the declining single-photon computed tomography myocardial perfusion imaging (SPECT MPI) positivity rate, the number of patients undergoing stress ECG without imaging remains low. (2-4) In the PROMISE Trial, exercise stress ECG was the sole functional test ordered in only 10% of cases despite high enrollment by major academic medical centers.(5) A major barrier to wider adoption of stress ECG without imaging is the poor sensitivity of ST-segment changes to identify CAD and ischemia.(6) Improvements in the diagnostic accuracy of stress ECG could encourage more frequent ischemia evaluation with stress ECG alone without imaging. Removing imaging from the evaluation could reduce costs and radiation exposure. Moreover, there is a substantial rate of normal coronary arteries or non-obstructive CAD on invasive coronary angiography even in patients referred for a positive stress test.(7) Additional tools that identify higher-risk cohorts could potentially guide invasive testing to patients more likely to have obstructive disease.

High-frequency QRS analysis (HF-QRS) is a novel ancillary electrocardiographic marker that has shown promise in identifying CAD and ischemia.(8-10) HF-QRS analysis identifies reduced electrical signal in the 150-250 Hz frequency band in patients with decreased myocardial blood flow (Figure 1). The wave front of myocardial depolarization creates fragmentation that results in high-frequency signal. Slowed myocyte-myocyte action potential conduction through ischemic myocardium disrupts the depolarization wave front and thus reduces the high-frequency signal (Figure 2). There has been limited but promising data showing a benefit of the addition of HF-QRS analysis to the standard stress ECG test. (11, 12)

Accordingly, we sought to compare the test performance characteristics, incremental diagnostic accuracy, and net reclassification of HF-QRS compared with conventional ST-segment stress ECG analysis for the identification of any and substantial myocardial ischemia ($\geq 10\%$ of the left ventricle (LV)) on SPECT MPI, early revascularization, and subsequent events.

Methods

Study Population

The derivation of the study cohort is shown in Figure 3. We examined 415 consecutive eligible patients 18 years of age referred to the University of Virginia stress nuclear laboratory for exercise stress ECG and SPECT MPI with an ECG appropriate for ST-segment analysis (no paced rhythm, left ventricular hypertrophy with repolarization abnormalities, left bundle branch block, Wolf-Parkinson-White pattern, or digoxin use). We excluded those with inadequate exercise stress from a failure to reach 7 METS of exercise capacity and at least 85% of their maximum age-predicted heart rate (MAPHR) if <10 METS and at least 80% of their MAPHR if 10 METS. In addition, we excluded those with contraindications to HF-QRS testing, including atrial fibrillation (no subjects had this finding), a QRS duration 120 msec, and noisy HF-QRS signal (lead artifact limiting HF-QRS analysis). Of the 354 patients eligible for ST-segment analysis, 97 (27.4%) were ineligible for HF-QRS analysis. The final study cohort included 257 subjects. The study protocol was approved by the UVA Institutional Review Board (IRB) and waiver of informed consent was obtained.

Stress Electrocardiography Protocol

All subjects underwent exercise treadmill stress ECG according to a Bruce or modified Bruce protocol with a 12-lead ECG recorded each minute and continuous AVF, V1 and V5 monitoring using a standard ECG recording machine (Q-Stress, Quinton, Inc., Bothell, Washington, USA). Blood pressure was obtained at rest prior to exercise, at the end of each stress stage, and during recovery. MAPHR was calculated as 220 – patient age. The rate pressure product (RPP) was obtained by multiplying the peak heart rate and peak systolic blood pressure during exercise. ^{99m}Technetium-sestamibi was injected at peak exercise, 60 seconds prior to exercise cessation to allow for tracer distribution. The test duration was symptom limited unless the patient met ACC-AHA criteria for premature study termination. (13) The stress ECG was reviewed by one of two experienced readers blinded to all other data, with equivocal studies resolved by consensus. A positive ECG response for ischemia was defined as the development of 1 mm of horizontal or downsloping ST-segment depression 60-80 msec after the J point in 2 or more contiguous leads or 1mm ST-elevation in any lead other than AVR without a diagnostic Q-wave during stress or recovery. Exercise workload was defined as the total metabolic equivalents (METS) achieved.

HF-QRS Analysis

HF-QRS analysis was performed using HyperQ software (HyperQ Stress System, BSP Ltd., Tel Aviv, Israel) by an automatic algorithm as described previously and illustrated in Figure 1.(12) Analysis was instantaneous and was performed in real-time during stress testing. In brief, a high resolution 12-lead ECG was continuously recorded throughout the study. Beat averaging was applied to each of the leads until the level of noise was 1 µV to obtain a high signal-to-noise ratio. Noisy and ectopic beats were excluded and a signal-averaged QRS was calculated. Each valid average QRS complex was filtered by a band-pass digital filter in the 150-250 Hz frequency band. The root-mean-square of the resultant HF-QRS signal was derived in real-time, was graphed over time in all 12 leads and was analyzed

throughout the study. An ischemic response in an individual lead with adequate signal quality was defined, according to the manufacturer's default configuration, as an absolute reduction of $1 \mu\text{V}$ and a relative reduction of 50% between the maximal and minimal values of the HF-QRS root-mean-square signal. The HF-QRS analysis was considered positive if 3 leads were affected, as previously validated.(11, 12)

SPECT MPI

Subjects underwent quantitative $^{99\text{m}}\text{Tc}$ -sestamibi rest/stress gated SPECT MPI under a one- or two-day protocol (for body mass index (BMI) ≥ 36) as described previously.(14, 15) One-day imaging utilized a stress dose 3 times higher than the rest dose. Images were acquired 60 minutes after resting injection and 20 minutes after stress injection. Supine images were obtained on a dual-head Infinia camera (General Electric Co., Milwaukee, WI, USA) with low-energy high-resolution collimators. Each camera head collected 60 projections over a 180° orbit using a step and shoot acquisition at 30-40 seconds per projection and a standard $^{99\text{m}}\text{Tc}$ energy window. The data from the two heads provided 360° of coverage. Projection images were filtered with a 2-dimensional Butterworth filter and reconstructed into transaxial tomograms with the use of filtered back projection with a ramp filter. No scatter or attenuation correction were applied. ECG-triggered image gating was performed at stress at 8 frames/sec with 100% acceptance.

SPECT Image Interpretation

Semi-quantitative visual interpretation of SPECT images was performed using proprietary Vquant software (Charlottesville, VA, USA) and a standard 17-segment model.(14) Images were analyzed by an experienced reader blinded to the HF-QRS result but with access to the other stress ECG data. Each segment was scored according to a 5-point scale (0: normal; 1-3: mild, moderate, or severe reduction in tracer uptake; 4: absent radiotracer uptake). The sum of segmental scores at stress and rest were calculated as the summed stress score (SSS) and summed rest score (SRS), respectively. The percentage left ventricular (LV) ischemia was calculated as the difference between the SSS and SRS divided by the maximum possible value of 68. This semi quantitative measure combines the extent and severity of LV inducible ischemia. A value of $\geq 10\%$ LV ischemia was considered substantial, as previously derived and validated.(16) Any ischemia ($\text{SSS}-\text{SRS} > 0$) was considered to represent real disease rather than artifact. LV ischemia $< 10\%$ was also assessed given the clinical importance of lower levels of ischemia. Gated LV function and body surface normalized systolic and diastolic volumes were calculated.

Follow-up

Data on all-cause and cardiac mortality, nonfatal myocardial infarction (MI), and early and late revascularization were collected through follow up telephone questionnaires. Intensive chart review was subsequently performed for patients not able to be contacted by telephone and to confirm events when possible. Follow-up of at least 6 months was available for all subjects. Early revascularization was designated as any coronary revascularization performed within 90 days after the initial MPI study unless documentation linked it to the original MPI results.

Analysis of late events excluded those with early revascularization. Events were classified by one of two reviewers blinded to the stress SPECT results to minimize bias. Cardiac death was defined as any death with a cardiac cause or without a clear noncardiac cause. A nonfatal MI was recorded for any troponin elevation ≥ 2 times the upper limit of normal, with or without typical ischemic electrocardiographic changes, in the setting of a history consistent with an acute coronary syndrome. Coronary revascularization procedures included percutaneous coronary interventions and coronary artery bypass grafting.

Statistical analysis

Continuous variables are expressed by mean $\pm$ standard deviation (SD). Comparisons between groups were performed using t-test for continuous variables and either Pearson's chi-square or Fisher's exact test for categorical variables. Sensitivity, specificity, negative predictive value and positive predictive value were calculated for HF-QRS and ST-segment analysis using any or substantial ($\geq 10\%$ LV) ischemia on SPECT MPI as a gold standard. The diagnostic techniques were compared using Wilcoxon rank-sum and chi-square analysis or Fisher's Exact Test where appropriate. Univariable logistic regression analyses of possible predictors of ischemia were performed. Variables with a p-value <0.10 were entered into a stepwise multivariable logistic regression model predicting any LV ischemia. Incremental chi-square analysis was used to assess the diagnostic utility of risk factors (age, gender, hyperlipidemia, known CAD), ST-analysis, and HF-QRS analysis. Performance of the final models was evaluated using the c-statistic, representing the discriminative power of the logistic equation, and the integrated discrimination improvement (IDI) with the methods described by Pencina et al.(17) The net reclassification index was calculated for the addition of HF-QRS analysis to ST-segment analysis for the identification of substantial ischemia. P-values of <0.05 were considered statistically significant for all analyses. All statistics analyses were performed using SAS Enterprise Guide version 6.1 and SAS version 9.4.

Univariable logistic regression of HF-QRS for early revascularization was performed. Multivariable analyses were not possible due to the low rate of early revascularization. Event rates were calculated through person-years analysis. The total events in a subgroup over the entire study period were divided by the sum of the years of follow-up for all patients in that subgroup. This value was adjusted for one person-year of follow-up and an annualized rate was determined.

Results

Baseline characteristics

The clinical baseline characteristics of the entire cohort and stratified by HF-QRS result are summarized in Table 1. Fifty seven of 257 patients (22.2%) had a positive HF-QRS response. The mean age of the study cohort was 59.2 ± 11.6 years with no difference in age, race/ethnicity, or cardiac risk factors by HF-QRS result. Subjects with a positive HF-QRS result were more often male and had a higher incidence of known CAD and thus more aspirin and beta-blocker use. The reason for referral was available in 201 of 257 patients (78.2%). Referral indications were chest pain (54%), shortness of breath (10%), both chest pain and shortness of breath (7%), evaluation of CAD therapy effectiveness (3%), pre-

operative risk evaluation (5%), and other unspecified reasons such as abnormal ECG and multiple risk factors, including diabetes (21%).

Stress ECG and Nuclear Results

The conventional stress ECG and SPECT MPI results are summarized in Table 2 stratified by FIF-QRS result. Patients with a positive HF-QRS response achieved a lower mean MAPHR, were less likely to achieve MAPHR $\geq 85\%$, and had a lower median RPP. There was no difference in the prevalence of ischemic ST-depression by HF-QRS result ($p=0.74$). However, there was a marked increase in the prevalence of any and substantial LV ischemia on SPECT MPI imaging. There was no difference in the median LV ejection fraction (LVEF) or prevalence of LVEF $<35\%$. However, those with a positive HF-QRS had higher end-systolic and end-diastolic volume indices and a higher incidence of an abnormal ESVI 25.

Test Characteristics and Disease Prevalence by HF-QRS and ST-Depression Analysis

As shown in Figure 4, HF-QRS analysis was considerably more sensitive in detecting any degree of ischemia and substantial ischemia compared with ST-analysis. Despite the significant increase in sensitivity, HF-QRS maintained an unchanged high specificity. Both positive and negative predictive values were significantly increased for HF-QRS compared with ST-analysis.

The prevalence of any ischemia was low and substantial ischemia was very low (0.6%) in those with negative ST- and HF-QRS analysis (Figure 5). Although positive ST-analysis with a negative HF-QRS result did not considerably increase the prevalence, a positive HF-QRS did result in a higher likelihood of ischemia and substantial ischemia. The highest prevalence was seen in those with positive ST-analysis and HF-QRS.

Predictors of Ischemia

The following variables were assessed by logistic regression analysis for the prediction of ischemia: gender, age, body mass index (BMI) ≥ 30 , hypertension, hyperlipidemia, diabetes mellitus, tobacco use, known CAD, HF-QRS and ST segment depression (Table 3). Univariable analysis identified age, gender (male), hyperlipidemia, known CAD, ST-depression, and a positive HF-QRS as significant predictors ($p<0.05$). In a stepwise multivariable logistic regression model, HF-QRS, known CAD, and male gender remained significant. HF-QRS was the strongest predictor by a significant margin, with a 3-fold higher X^2 compared to known CAD, the next most predictive variable.

Incremental Diagnostic Value of HF-QRS

Incremental chi-square analysis showed that HF-QRS provided additional diagnostic utility when added to risk factors and ST-analysis ($X^2=43.8$ vs 25.4 , $p<0.00001$) (Figure 6). However, ST-analysis did not add incremental diagnostic information to risk factors ($X^2=25.4$ vs 24.6 , $p=0.18$). Receiver operator characteristics (ROC) area under the curve (AUC) analysis for prediction of LV ischemia resulted in a significant increase in the AUC for models based on risk factors alone (AUC: 0.737), risk factors and ST-analysis (AUC: 0.749) and risk factors, ST-analysis and HF-QRS (AUC: 0.804, $p<0.00001$). A significant increase

in integrated discrimination improvement (IDI) ($p < 0.0001$) was observed when HF-QRS was added to the model, while ST-analysis did not improve the IDI for predicting LV ischemia ($p = 0.24$).

Net Reclassification Analysis

Standard stress ECG with ST-analysis only identified 61.5% of the subjects with substantial ischemia. However, of those without ST-changes, HF-QRS analysis correctly reclassified 80.0% as having substantial ischemia (Figure 7). In those without substantial ischemia, HF-QRS analysis correctly reclassified 86.3% of those with abnormal ST-analysis as negative, but also inappropriately reclassified 20.2% of those without abnormal ST-analysis as positive. The net reclassification was beneficial and substantial at 25.1%. Similar findings were identified when a LV ischemia threshold of 5% was used, with 65.0% identified by ST-analysis and 71.4% of the remainder identified by HF-QRS analysis.

In this study cohort, a combined strategy of ST- and HF-QRS analysis identified 92.3% of the subjects with substantial ischemia. In those without substantial ischemia, 63.1% had negative ST- and HF-QRS analysis. Although there remains utility in identifying any degree of ischemia, the value of SPECT MPI imaging in this subgroup may be diminished. The remaining 36.9% could have had their lack of substantial ischemia confirmed by MPI.

Follow up and Outcomes

Early revascularization occurred in 10 subjects, with a higher rate for HF-QRS positive patients (6/57 (10.5%) versus 4/199 (2.0%), $p = 0.004$). HF-QRS was a significant predictor of early revascularization by univariable logistic regression with odds ratio 5.7 (95% CI 1.6, 21.1) $p = 0.009$. As shown in Figure 8a, the rate of early revascularization increased from 1.3% for those with negative ST-analysis and HF-QRS to 4.4% and 4.7% with ST-analysis and HF-QRS positive, respectively and 30.8% if both ST-analysis and HF-QRS were positive ($p < 0.001$). Of those with early revascularization, 9/10 (90.0%) had ischemia on SPECT MPI. Of these, 8/9, 88.9% had either a positive ST-analysis or HF-QRS (50.0%) or both positive (50.0%). Likewise, in those with ischemia on SPECT MPI, the rate of early revascularization was 25.8% with positive ST-analysis or HF-QRS versus 7.7% if both were negative.

After excluding those with early revascularization, the median follow-up time for long-term outcomes was 5.3 years (IQR 3.4, 5.9) with no difference in follow-up length by HF-QRS positivity ($p = 0.20$). Nine subjects died of any cause, of which two were classified as cardiac. Both of these cardiac deaths occurred in subjects with a positive HF-QRS. The cardiac death rate was 0.9%/year with a positive HF-QRS versus 0% in HF-QRS negative patients, $p = 0.008$. There were 24 total events including 9 deaths, 6 nonfatal MIs, and 9 with late revascularization. As shown in Figure 8b, the annualized rate of any event increased significantly in stepwise fashion from 1.6%/year with both ST-analysis and HF-QRS negative to 3.3%/year if either the ST-analysis or HF-QRS was positive, and 7.5%/year if both were positive, $p = 0.036$. No events occurred in the subset of patients with 10% LV ischemia on SPECT MPI who had negative HF-QRS analysis.

Discussion

The use of conventional exercise stress ECG is a class I indication for evaluation of CAD in patients who can exercise.(1) Exercise stress ECG has long been considered a safe and effective diagnostic method for the detection of CAD. It also provides important prognostic information that helps the clinician to risk stratify patients and modify clinical therapy if required.(18) Despite these recommendations and clinical evidence, additional imaging is routinely used in clinical practice, and the number of studies performed using pharmacologic stress rather than exercise is now >50% and increasing.(19-21)

In the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial that included over 10,000 patients with symptoms suggestive of CAD, only 10% of subjects who were randomized to functional testing underwent conventional exercise stress ECG.(5) The vast majority of patients (90%) underwent stress testing with additional imaging (23% stress echocardiography and 67% SPECT MPI). The population in the PROMISE trial was considered low-to-intermediate risk with only 4.8% considered high risk by clinical pre-test assessment. Lack of guideline awareness was unlikely to be the reason for the low use of stress ECG without imaging, as patients were enrolled from leading academic and clinical centers. One of the possible explanations for the poor referral nationwide to stress ECG alone is the poor diagnostic accuracy of this technique when used without concurrent imaging. (6) There is wide variation in the reported sensitivities of stress ECG for CAD, with values as low as 20%.(22, 23) When only studies without workup bias are included, a mean sensitivity of 50% has been reported.(24) The reported sensitivity of this study population was lower than the mean at 35.6%. Although sensitivity is not directly influenced by the prevalence of disease, it is impacted by disease severity, and there has been a well-documented steady decline in the incidence and severity of ischemic CAD.(2, 25, 26) More accurate methods for the evaluation of CAD, such as SPECT MPI, stress echocardiography, and CT or invasive coronary angiography are expensive, invasive, or involve radiation exposure.

Current stress ECG analysis focuses primarily on the ST-segment. However, the QRS, or depolarization phase of the electrocardiogram may provide additional insight into myocardial ischemia.(27) HF-QRS analysis during exercise stress has been shown in preliminary studies to improve the diagnostic accuracy of stress ECG for the identification of CAD. When a patient's heart becomes ischemic, a slowing depolarization wave front causes the normal high frequency signals seen in non-ischemic tissues to switch to a lower frequency signal that is captured and then simulated in a computer model.(28, 29) The value of HF-QRS has been demonstrated in multiple populations. Ringborn et al.(30) showed that HF-QRS analysis correlates well with the presence of ischemia in patients with acute myocardial infarction. Lipton et al.(28) showed in a cohort of 139 patients that the decrease in HF-QRS signal was greater in patients with ischemia on SPECT MPI compared to those without ischemia. Correlation with anatomy was shown by Rosenmann et al.(31), who showed that HF-QRS analysis improves the diagnostic value of exercise ECG testing in a cohort of 113 women referred for coronary angiography, providing a sensitivity of 70% and specificity of 80% for obstructive CAD. This study provided evidence that this tool could be added to typical ST-segment analysis with little cost and no added risk.

The purpose of our study was to compare the diagnostic and prognostic accuracy and net reclassification of HF-QRS compared with standard ST-analysis for the identification of any and substantial (≥ 10% of the LV) myocardial ischemia. The diagnostic performance of the two modalities was assessed in a cohort of symptomatic patients at low-to-intermediate risk for CAD referred for non-invasive cardiac evaluation. Prior studies analyzing the efficacy and utility of HF-QRS analysis have been performed predominately in Europe and Israel. (11, 12) This is the first report in the United States assessing HF-QRS analysis in a cohort of symptomatic patients. All participants were referred for exercise MPI using contemporary protocols exclusively utilizing Tc-99m. HF-QRS analysis demonstrated a significant improvement in sensitivity, PPV and NPV for ischemia detection over conventional ST-segment evaluation with preserved high specificity. HF-QRS was able to detect 84.6% of patients with ≥ 10% LV ischemia by MPI compared to ST-segment analysis, which only detected 61.5% of these patients. The improvement in sensitivity, NPV, and diagnostic accuracy with HF-QRS analysis should increase diagnostic confidence with exercise stress ECG without imaging. In those with ≥ 10% LV ischemia and no ST segment changes, HF-QRS was able to correctly reclassify 80.0% of the patients. A combined strategy of ST- and HF-QRS analysis identified almost all patients with substantial ischemia (92.3%) while obviating the need for imaging in 63.1% of the remaining subjects. Therefore, the additional use of HF-QRS in low-to-intermediate risk patients could provide sufficient diagnostic information while reducing additional imaging, unnecessary radiation exposure, and cost.

On analysis of follow-up events, HF-QRS was not only a significant predictor of early revascularization, but the rate was substantially higher when both HF-QRS and ST-analysis were positive. Moreover, when this analysis was focused on those with ischemia on SPECT MPI, ST-analysis and HF-QRS identified almost all subjects who underwent early revascularization (8/9, 88.9%). The low event rate in the entire cohort highlights the low risk of this population able to exercise with an interpretable ECG. Moreover, the low rate of events in patients with negative HF-QRS confirms that high-risk patients were not missed.

A limitation of the HF-QRS analysis is that it cannot be performed in all patients secondary to technical reasons. In our study, 27.4% were ineligible for analysis due to ECG abnormalities such as a wide QRS or a noisy HF-QRS signal. However, this percentage was increased by inclusion of patients with baseline ST-segment abnormalities at rest. Moreover, further technological refinements should decrease this percentage. Other limitations include the small sample size compared with prior stress ECG meta-analyses and the potential for referral-bias due to the study performance at a single-center.(22, 23) Inclusion of slow-upsloping ST depression could have improved the sensitivity of ST analysis but would have led to a decrease in specificity and is not conventional. The lack of an anatomic gold standard is a limitation for the identification of diagnostic accuracy for CAD detection. However, the use of SPECT MPI as a gold standard reduces referral bias and allows for the strategy of HF-QRS and ST-analysis to be compared with the current key finding on noninvasive testing, the identification of substantial ischemia. While PET MPI has shown superior diagnostic accuracy, it is not an appropriate comparator in this instance in that it currently utilizes pharmacologic stress and HF-QRS seeks to identify exercise-induced ischemia. Access to the stress ECG data (except the HF-QRS results) during SPECT MPI evaluation was used to improve SPECT MPI diagnostic accuracy but may have biased MPI

interpretation to be concordant with the ST-analysis and thus improve ST-analysis performance.(32) We chose 10% of the left ventricle as the cutoff for substantial ischemia based on prior work showing the benefit of revascularization in patients with this degree of ischemia.(16) Future studies including multiple centers are needed to validate our results. The performance of CT coronary angiography with CT-FFR in all subjects would provide an anatomic and functional gold standard across the entire population and allow comparison with the current approach. Patients failing to achieve adequate heart rate or workload are an additional group in which HF-QRS may have an important role and should be studied. Finally, efficiency analyses and inclusion of non-academic centers could confirm that this technique can be applied easily and practically in busy clinical settings.

New Knowledge Gained

In this prospective analysis, the addition of HF-QRS to standard ST-segment evaluation during exercise stress ECG provided incremental diagnostic accuracy for the identification of any and substantial LV ischemia by SPECT MPI, predominately through a substantial increase in sensitivity and positive predictive value. HF-QRS resulted in a highly beneficial net reclassification of 25.1% when added to ST-analysis, and a negative HF-QRS identified a population with a low rate of events over a 5.3-year median follow-up. A strategy of HF-QRS and ST-analysis identified a very high percentage of those with substantial ischemia and could have limited the need for imaging in more than two-thirds of eligible patients. Use of this technique may improve compliance with guideline-recommended stress ECG alone for the identification of obstructive CAD in low to intermediate risk populations and better identify a subset at higher risk for early revascularization in those with SPECT MPI ischemia.

Conclusions

In this prospective analysis, HF-QRS analysis during exercise stress improved the diagnostic accuracy of stress ECG for any and substantial ischemia as identified by SPECT MPI and predicted early revascularization. A strategy of ST-segment evaluation and HF-QRS analysis identified a low event rate in more than half of tested subjects who may be able to safely avoid concurrent imaging. Additional research is needed to confirm these findings in larger stress populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AUC	area under the curve
CAD	coronary artery disease
ECG	electrocardiography
HF-QRS	high frequency QRS
MAPHR	maximum age-predicted heart rate
MPI	myocardial perfusion imaging
SPECT	single photon-emission computed tomography

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Figure 1.

Schematic flowchart of high frequency QRS analysis. HF-QRS: high frequency QRS; SPECT: single photon-emission computed tomography. Used with permission from HyperQ Stress System, BSP Ltd, Tel Aviv, Israel.

Figure 2.

Illustration of the depolarization wavefront and its disruption in the setting of myocardial ischemia. Ischemic tissue disrupts the depolarization wavefront and thus decreases the high-frequency signal produced.

Figure 3.

Study cohort derivation. ECG: electrocardiogram; HF-QRS: high frequency QRS; MAPHR: maximum age predicted heart rate; METS: metabolic equivalents.

HF-QRS: high frequency QRS; PPV: positive predictive value; NPV: negative predictive value.

Figure 4.

Test characteristics of conventional stress electrocardiography ST-analysis versus HF-QRS in detecting any left ventricular ischemia. HF-QRS: high frequency QRS; PPV: positive predictive value; NPV: negative predictive value.

Figure 5.
Frequency of conventional stress electrocardiography ST-analysis versus HF-QRS in detecting any and 10% LV ischemia. HF-QRS: high frequency QRS; LV: left ventricular.

Clinical variables: age, gender, HLD, CAD. HF-QRS: high frequency QRS; X^2 : chi square.

Figure 6.

Incremental diagnostic utility of ST-analysis and HF-QRS above clinical risk factors alone.

Clinical variables included age, gender, hyperlipidemia and coronary artery disease. HF-

QRS: high frequency QRS; X^2 : chi-square.

Figure 7.

Implications of a strategy of stress ECG with HF-QRS analysis for the identification of significant (10%) LV ischemia.

Figure 8.
Incidences of early revascularization and total events stratified by ST-analysis and HF-QRS result. HF-QRS: high frequency QRS.

Table 1:

Baseline Clinical Characteristics by High Frequency-QRS Status.

Characteristic	Entire Cohort (n = 257)	Positive HF-QRS (n = 57)	Negative HF-QRS (n = 200)	P-value [†]
Age [‡]	59.2 ± 11.6	59.1 ± 12.2	59.2 ± 11.4	0.94
Male	171 (66.5)	47 (82.5)	124 (62.0)	0.004 [†]
Caucasian	196 (76.3)	48 (84.2)	148 (74.0)	0.10
Hypertension	151 (58.8)	35 (61.4)	116 (58.0)	0.65
Dyslipidemia	160 (62.3)	35 (61.4)	125 (62.5)	0.88
Diabetes mellitus	47 (18.3)	7 (12.3)	40 (20.0)	0.18
Tobacco	64 (24.9)	15 (26.3)	49 (24.5)	0.78
BMI 30 [*]	104 (40.5)	26 (45.6)	78 (39.2)	0.38
Known CAD	71 (27.6)	29 (50.9)	42 (21.0)	<0.00 [†]
Prior MI [*]	20 (7.8)	5 (8.8)	15 (7.5)	0.78
Prior revascularization [*]	24 (9.3)	7 (12.3)	17 (8.5)	0.39
Medication Use				
Beta blocker	64 (25.2)	25 (43.9)	39 (19.8)	<0.00 [†]
ACE-inhibitor [*]	81 (32.0)	21 (36.8)	60 (30.6)	0.37
Statin	109 (43.3)	30 (52.6)	79 (40.5)	0.10
Aspirin	119 (47.0)	33 (58.9)	86 (43.7)	0.043 [†]
Calcium channel blocker	30 (11.8)	8 (14.0)	22 (11.2)	0.55

^{*} ACE: angiotensin converting enzyme; BMI: body mass index; CAD: coronary artery disease; HF-QRS: high frequency QRS; MI: myocardial infarction.

[†] P-values <0.05 were considered statistically significant.

[‡] Values are expressed as n (%) or mean ± standard deviation.

Table 2:

Stress ECG and SPECT MPI Results by High Frequency-QRS Status.

Characteristic	Positive HF-QRS* (n = 57)	Negative HF-QRS* (n = 200)	P-value [†]
Stress ECG *			
METS * Achieved [‡]	10.3 ± 2.2	9.7 ± 2.3	0.07
10 METS * Achieved	41 (71.9)	115 (57.8)	0.054
MAPHR *	88.1 ± 9.8	95.5 ± 8.7	< 0.0001 [†]
Achieved MAPHR * 85%	41 (71.9)	184 (92.0)	< 0.0001 [†]
RPP *(×10 ³)	26.5 ± 6.1	29.2 ± 5.3	0.004 [†]
Imm stress ST-depression	14 (23.7)	43 (21.7)	0.74
SPECT MPI *			
LV * Ischemia	27 (47.4)	18 (9.0)	< 0.0001 [†]
LV * Ischemia 1-4%	12 (21.1)	13 (6.5)	< 0.0001 [†]
LV * Ischemia 5-9%	4 (7.0)	3 (1.5)	< 0.0001 [†]
LV * Ischemia 10%	11 (19.3)	2 (1.0)	< 0.0001 [†]
Summed stress score (SSS)	4.2 ± 6.1	0.5 ± 2.0	< 0.0001 [†]
Summed rest score (SRS)	1.9 ± 4.6	0.2 ± 1.3	0.007 [†]
LVEF *	61.8 ± 24.1	66.2 ± 16.1	0.20
LVEF * <35%	2 (3.5)	2 (1.0)	0.18
EDVI *	57.9 ± 21.7	46.2 ± 16.0	< 0.001 [†]
ESVI *	25.6 ± 19.1	19.1 ± 17.6	0.020 [†]
ESVI * 25	20 (35.1)	37 (18.6)	0.008 [†]

* ECG: electrocardiography; EDVI: End-diastolic volume index; ESVI: end-systolic volume index; LVEF: left ventricular ejection fraction; MAPHR: maximum age-predicted heart rate; METS: metabolic equivalents; MPI: myocardial perfusion imaging; RPP: rate pressure product; SPECT: single photon-emission computed tomography.

[†] P-values <0.05 were considered statistically significant.

[‡] Values are expressed as n (%) and mean ± standard deviation.

Table 3:

Univariable and Multivariable Stepwise Logistic Regression Model Predicting Any Ischemia.

Variable	Univariable Logistic Analysis			Multivariable Logistic Analysis		
	χ^2	Odds Ratio (95% CI [*])	P-value [†]	χ^2	Odds Ratio (95% CI [*])	P-value [†]
Age	5.2	1.0 (1.0 – 1.1)	0.02			
Male Gender	8.9	3.9 (1.6 – 9.7)	0.003	3.9	2.7 (1.0 – 7.0)	0.0049
BMI 30 [*]	0.83	1.3 (0.7 – 2.6)	0.36			
Hypertension	1.4	1.5 (0.8 – 3.0)	0.24			
Hyperlipidemia	4.0	2.1 (1.0 – 4.4)	0.046			
Diabetes mellitus	0.3	1.3 (0.5 – 3.0)	0.60			
Tobacco use	2.1	1.7 (0.8 – 3.3)	0.15			
Known CAD	19.3	4.5 (2.3 – 8.8)	<0.0001	7.3	2.8 (1.3 – 5.9)	0.007
ST-segment depression 1 mm	4.7	2.2 (1.1 – 3.6)	0.029			
HF-QRS [*] positive	37.1	9.1 (4.5 – 18.5)	<0.0001	24.1	6.5 (3.1 – 13.6)	<0.0001

^{*} BMI: body mass index; CI: confidence interval; HF-QRS: high frequency QRS.

[†] P-values <0.05 are considered statistically significant.