

Detection of stress-induced myocardial ischemia from the depolarization phase of the cardiac cycle—a preliminary study

Eran Toledo, PhD,^{a,*} Jonathan A. Lipton, MD,^b Stafford G. Warren, MD,^c
Shimon Abboud, PhD,^d Mike Broce, BA,^c Donald R. Lilly, MD,^c Charles Maynard, PhD,^e
B. Daniel Lucas Jr, PharmD,^c Galen S. Wagner, MD^f

^aResearch and Development, BSP Ltd., Tel Aviv, Israel

^bErasmus Medical Center, Rotterdam, The Netherlands

^cDepartment of Cardiology, Charleston Area Medical Center, Charleston, WV, USA

^dDepartment of Biomedical Engineering, Tel Aviv University, Tel Aviv, Israel

^eDepartment of Health Services, University of Washington, Seattle, WA, USA

^fDuke University Medical Center, Duke University, Durham, NC, USA

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Abstract

Background: Electrocardiogram (ECG)-based detection of ischemia is typically dependent on identifying changes in repolarization. Analysis of high-frequency QRS (HFQRS) components, related to the depolarization phase of the cardiac action potential, has been reported to better identify ischemia. Our aim was to test the hypothesis that HFQRS analysis is both more sensitive and specific than standard ECG for detecting exercise-induced ischemia in patients undergoing exercise myocardial perfusion imaging (MPI).

Methods: Exercise MPI was performed in 133 consecutive patients (age, 63 ± 12 ; 100 males) and used as the gold standard for ischemia. Patients with QRS duration more than 120 milliseconds ($n = 20$), technical problems ($n = 8$), or inconclusive MPI ($n = 4$) were excluded, leaving 101 patients for analysis. Conventional ECG was combined with high-resolution ECG acquisition that was digitized and analyzed using the HyperQ System (BSP, Tel Aviv, Israel). The relative HFQRS intensity change during exercise was used as an index of ischemia.

Results: Of the 101 patients who were included in the analysis, 19 exhibited MPI ischemia. The HFQRS index of ischemia was found to be more sensitive (79% vs 41%; $P < .05$) and more specific (71% vs 57%; $P < .05$) than conventional ST analysis.

Conclusions: The HFQRS analysis was more sensitive and specific than conventional ECG interpretation in detecting exercise-induced ischemia and exhibited enhanced diagnostic performance in both women and men. Thus, it may aid in the noninvasive diagnosis of ischemic heart disease.

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Keywords:

High-frequency ECG; Exercise test; Ischemia; Ischemic heart disease

Introduction

Exercise electrocardiogram (ECG) is considered the initial diagnostic evaluation of choice for ischemic heart disease (IHD), with more than 9 million exercise tests performed annually in the United States. The advantages of this modality are the associated low cost and lack of radiation concerns. However, it has been shown in numerous studies that the diagnostic performance of exercise ECG in detecting

IHD is limited.¹ The IHD diagnosis strongly relies on the identification of specific ECG changes, namely changes in the ST segment, during exercise and recovery, reflecting repolarization abnormalities. However, ischemia may also bring about changes in the depolarization phase of the ECG, which can be detected using analysis of the high-frequency components of the QRS complex (HFQRS).^{2–9} Investigations of the physiologic origin of HFQRS components suggested that the HFQRS signal is related to the fragmentation of the electrical activation wavefront, as well as to morphological changes in the myocardial action potential. It was concluded that the HFQRS changes induced

* Corresponding author. Tel.: +972 3 6474840; fax: +972 3 6471498.

E-mail address: eran@bspmedical.com

by ischemia are explained by slowing of conduction velocity in the ischemic region. The slowed conduction apparently induces gaps in the fragmentation of the activation wavefront and thus shifts the high-frequency components to lower frequencies.^{8–11} The HFQRS components are extracted from the 150 to 250 Hz frequency band, whereas most manufacturers of ECG machines display the ECG in the 0.05 to 100-Hz band and consequently filter out the HFQRS components. Because HFQRS components are measured in microvolt, that is, 2 to 3 orders of magnitude lower than conventional ECG, extensive signal averaging is required to enable the analysis of HFQRS components. The averaging reduces noise, thus enhancing the signal-to-noise ratio. The HFQRS analysis during exercise is especially challenging due to the high noise level present at the advanced stages of exercise and has only recently become clinically available using a novel system.^{7,12}

Although extensive evidence in animal models,^{5,11,13} in selected groups of patients,^{4,14,15} during intracoronary balloon occlusion^{2,16} and during acute myocardial infarction (MI)¹⁷ (analysis performed in the 80–300 Hz) have indicated the potential of this technique in detecting myocardial ischemia, data from larger groups of consecutive, unselected patients are scarce.⁷

Accordingly, this study was performed to test the hypothesis that exercise-induced depolarization changes depicted by HFQRS are both more sensitive and more specific than repolarization changes depicted by standard ECG for detecting ischemia induced by the increased demand during exercise stress testing. Absence or presence of exercise-induced perfusion defect in the myocardial perfusion imaging (MPI) single-photon emission computed tomography was used as the gold standard for absence or presence of ischemia in the study. The use of exercise MPI was chosen over angiography despite being less accurate in detecting significant coronary stenosis because (1) referral bias is lower in patients referred for MPI compared with those referred for angiography and (2) the diagnostic accuracy of MPI is relatively high.¹⁸

Methods

Patients and protocol

The data collection has been described previously,⁷ although a different analytic approach was used. Briefly, 133 consecutive patients with known or suspected IHD undergoing dual isotope (^{99m}Tc-sestamibi/²⁰¹Tl) exercise testing at the outpatient clinic of the Charleston Cardiology Group were prospectively included in the study. The study was approved by the West Virginia University (Morgantown, WV, USA) Institutional Review Board, and written informed consent was obtained from all participants. Patients whose computerized ECG analysis indicated QRS 120 milliseconds or greater were excluded from analysis (n = 20). Demographic information was collected for each patient as follows: sex, age, body mass index (BMI), tobacco use, hypertension, diabetes mellitus, history of MI, and history of revascularization.

Stress testing was performed using the modified Bruce treadmill protocol or a bicycle protocol with 2-minute stages. A dual set of electrodes (Mason Likar lead system) was used to acquire both conventional ECG (Quinton 3000 system, Quinton Cardiology Systems, Bothell, WA, USA) and high-resolution ECG (EKG Master USB, Tapa, Ankara, Turkey). The high-resolution ECG leads were placed immediately below the standard ECG leads. High-resolution 12-lead ECG was digitized from 2 minutes before start to 6 minutes after completion of the test. The sampling was performed at a rate of 1000 samples per second and 16-bit resolution (sensitivity of 0.4 μ V), with an analog frequency response of 0.05 to 300 Hz. Clinical symptoms and grading of chest pain were registered throughout the test by one of the investigators (JAL). The stress test was considered adequate when at least 85% of maximal, age-predicted heart rate (%MPHR) was attained or when there were positive ECG changes. Choice of treadmill or bicycle was left to the discretion of the supervising physician and patient preference. Radioactive isotopes (²⁰¹Tl and ^{99m}Tc-sestamibi) were injected according to the manufacturer's protocol. Images were acquired with a rotating, double-headed γ camera (Cardio Epic; Adac Laboratories, Milpitas, CA, USA). The first set of 64 images was acquired at least 10 minutes after injection in 32 thirty-second periods, the postexercise set was done 15 to 45 minutes after injection and consisted of 64 images acquired in 32 twenty-second periods, while gated by ECG. The images were checked for motion artifact and repeated if necessary.

Clinical symptoms during exercise

In the grading of clinical symptoms during exercise for statistical analysis, typical chest pain was considered positive, atypical chest pain was considered inconclusive, and leg fatigue, musculoskeletal pain, shortness of breath, or no symptoms were considered negative results. Grading of clinical symptoms was performed by one of the investigators (JAL).

Standard ECG analysis

The 12-lead ECG tracings were reviewed by a core laboratory of 2 independent cardiologists for presence or absence of ST depression (>1 mm horizontal or downsloping or ≥ 1.5 mm upsloping, measured at 80 milliseconds after J point) in at least one lead and categorized "positive" and "negative" for ischemia, respectively. The cardiologists were blinded to other patient information. Consensus between reviewers was obtained for discordant results. Patients with ST-segment changes that did not fit the diagnostic criteria were categorized as inconclusive.

Nuclear imaging

All images were processed on a workstation (Pegasys, Adac Laboratories) with imaging software (AutoSpect Plus, version 5.0; Adac Laboratories). A core laboratory of 2 cardiologists and one radiologist independently reviewed each nuclear study, blinded to other patient information. Consensus was obtained for discordant results. A structured analysis of the resting and exercise image was done using a

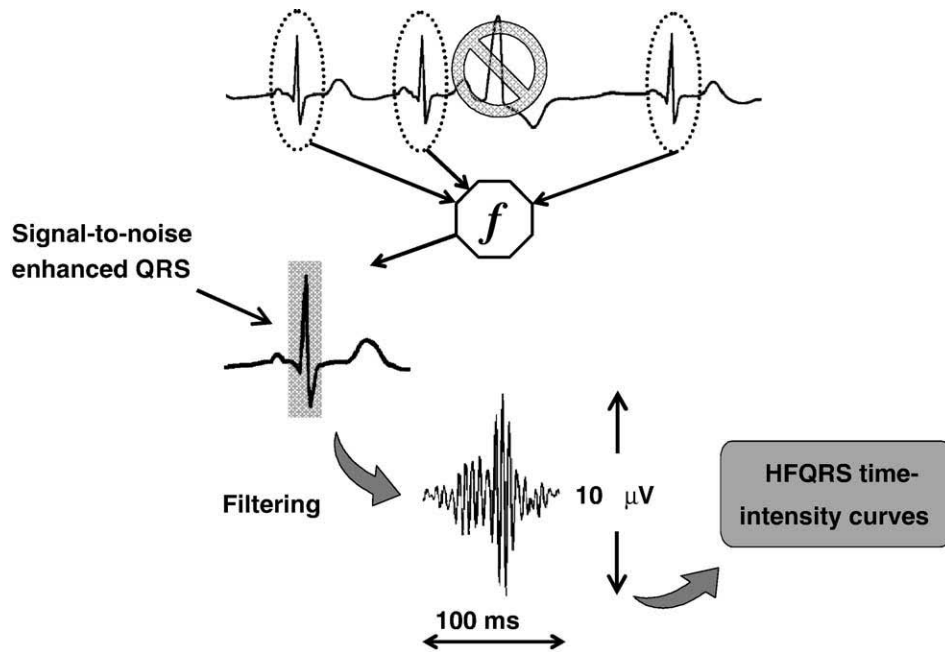


Fig. 1. A schematic flowchart of the HFQRS analysis. First, QRS complexes are detected, while rejecting arrhythmias and noisy complexes. Signal-averaging algorithms are then applied to improve the signal-to-noise ratio. Filtering in the 150 to 250-Hz band is then used to produce the HFQRS signal. The HFQRS time-intensity curve is calculated for each lead.

4-segment model of the left ventricle. Each segment was categorized as having no, small, moderate, or large perfusion defect, and wall motion was categorized as normal, reduced, or akinetic. The scan was considered ischemic (MPI ischemia) only when there was a defect with exercise that resolved at rest. Subsequently, each study was categorized as positive, negative, or inconclusive for ischemia. The presence of myocardial scarring was determined by observing fixed perfusion defects.

Analysis of HFQRS

The HFQRS data were extracted from the high-resolution 12-lead ECG using commercial software (HyperQ System, BSP, Tel Aviv, Israel). Initially, QRS complexes were detected, while excluding arrhythmias and noisy beats using cross-correlation techniques (see Fig. 1). The detected QRS complexes were accurately aligned using cross-correlation with a template and then averaged in each lead for a 150-second window in a blockwise manner to suppress noise. Averages were calculated with 10-second increments between successive averages, resulting in a 140-second overlap between successive averaged QRS complexes. To produce the HFQRS signals, averaged QRS complexes were band-pass filtered in the 150 to 250-Hz frequency band using a 61-component finite impulse response filter calculated using the Kaiser window band. The HFQRS intensity was calculated as the root-mean-square of the HFQRS signal between QRS onset and the J point.³ The HFQRS time-intensity curves were derived for each lead and were used for ischemia detection. Because high-frequency ECG components originate from the depolarization of myocytes, any high-frequency components found after the J point were therefore regarded as noise. Accordingly, the noise level for each lead was assessed at rest condition by calculating the

root-mean-square of the high-frequency ECG components measured immediately after the J point. The signal-to-noise ratio for each lead was calculated at rest condition as the ratio between HFQRS intensity (within QRS onset and offset) to noise measured after the J point. Leads with rest sound-to-noise ratio less than 3 were excluded from further analysis.

In each lead, the maximal HFQRS intensity from rest to peak exercise was identified. The minimal HFQRS intensity was identified in the time frame starting at the time of maximal intensity and ending at peak exercise. Two indices were calculated for each lead: (i) absolute reduction in HFQRS intensity as the difference between maximal and minimal HFQRS intensity and (ii) relative reduction in HFQRS intensity as the reduction relative to maximal HFQRS intensity. Based on previous studies, the reduction of HFQRS intensity in a specific lead was considered significant if the absolute reduction was more than $1 \mu\text{V}$, and the relative reduction was more than 45%.^{19,20} An HFQRS increase was not considered indicative of ischemia. The HFQRS response of a patient was considered ischemic if 3 or more leads exhibited significant HFQRS intensity reduction, regardless of the number of leads that were excluded from analysis due to noise.¹⁹ However, the HFQRS response was considered inconclusive if HFQRS data did not suggest ischemia and 3 or more leads exhibited excessive noise levels because the noisy leads might have indicated ischemia if better quality data were available (2 patients). Patients with 2 or less leads indicating HFQRS ischemia and 2 or less leads with excessive noise were considered to have negative result.

Statistical analysis

The χ^2 test was used to compare categorical variables, and the t test was used for continuous variables. Continuous variables were described by mean \pm SD where appropriate.

The sensitivity, specificity, accuracy, and positive and negative predictive values obtained with the HFQRS analysis were compared with those obtained by conventional ECG interpretation using either the Z test with Yates correction or the Fisher exact test where appropriate. A value of $P < .05$ was considered statistically significant. Forward stepwise logistic regression (SPSS version 14, SPSS Inc, Chicago, IL) was used to examine incremental diagnostic value of HFQRS data over conventional diagnosis (see Tables 1 and 2) in predicting stress-induced ischemia. In this procedure, likelihood-ratio statistic was used for forward stepwise selection of covariates. Odds ratios (ORs) and 95% confidence intervals (CIs) for the OR were calculated.

Results

Patient characteristics and exercise testing

The study included 113 patients, of whom 8 patients were excluded due to technical problems in ECG recording and 4 patients were excluded due to inconclusive MPI. Of the remaining 101 patients, age was 62 ± 13 years, BMI was 30.5 ± 6.5 kg/m², 73% were men, 44% had a history of MI, 52% had a prior coronary angioplasty, 32% had bypass surgery, 22% had diabetes mellitus, 89% had hypercholesterolemia, 72% had hypertension, and 22% had history of smoking. Nineteen patients (19%) had a positive MPI scan. Compared with patients with negative MPI, patients with positive MPI had much higher incidence of history of MI (79% vs 35%; $P < .0005$, see Table 1). Of the 44 patients with history of MI, only 21 had evidence of myocardial scarring in the MPI. In addition, 3 patients without history of MI exhibited myocardial scarring. Consequently, 24 patients had evidence of myocardial damage in their rest perfusion imaging.

In the 101 patients included in the analysis, maximal HR relative to age-predicted maximal HR (%MPHR) was $90\% \pm 7\%$, workload was 9 ± 3 metabolic equivalents, symptoms were found in 14%, and ischemic ST changes in 34%. Functional capacity and occurrence of typical chest pain or positive ST-segment response were not different between

Table 2
Exercise test results

	All	Positive MPI	Negative MPI	P
n	101	19	82	-
%MPHR	90 ± 7	89 ± 6	91 ± 8	NS
Workload (METs)	9 ± 3	9 ± 3	9 ± 3	NS
Typical chest pain, n (%)	14 (14%)	5 (26%)	9 (11%)	NS
Positive ST response, n (%)	34 (34%)	7 (37%)	27 (33%)	NS
Inconclusive ST response, n (%)	21 (21%)	2 (11%)	19 (23%)	NS

%MPHR indicates achieved maximal heart rate relative to maximal predicted heart rate; METs, metabolic equivalents.

patients with positive and negative MPI (Table 2), although there was a trend for patients with typical chest pain to have a positive MPI more often than those without typical pain (26% vs 11%; $P =$ not significant).

High-frequency QRS analysis

Patients with MPI ischemia were characterized by a reduction in HFQRS intensity during the exercise test. Fig. 2 presents an example of the HFQRS intensity calculated for all 12 leads in a patient with positive MPI. In this patient, HFQRS intensity decreased in all 12 leads during exercise and returned to baseline values in the recovery phase. The exercise-related reduction in HFQRS intensity was significant in 5 leads (II, aVF and V₄, V₅, and V₆), thus, exceeding the threshold for positive HFQRS response (ie, 3 leads with significant HFQRS reduction). Patients who did not exhibit MPI ischemia were characterized by slight or no reduction of HFQRS intensity and in many cases, an increase in HFQRS intensity. A typical example of a nonischemic patient is shown in Fig. 3. In this patient, HFQRS intensity decreased only slightly, with only 4 leads exhibiting more than 1 μ V reduction and maximal relative reduction of 36%, well below the 45% threshold. In 6 leads, an increase in HFQRS intensity occurred during exercise.

Patients with MPI ischemia had significantly higher incidence of positive HFQRS test compared with patients with negative MPI (79% vs 29%; $P < .0001$, Fig. 4). In addition, the average number of leads exhibiting significant HFQRS reduction was higher in patients with MPI ischemia compared to patients with no ischemia (4.2 ± 2.9 positive leads vs 2.3 ± 2.9 positive leads; $P < .05$).

Multivariate logistic regression of all indices that were significant in the univariate analysis (history of MI, positive HFQRS response, and the number of leads with positive HFQRS response) resulted in a model for predicting MPI ischemia that included the HFQRS response ($\chi^2 = 13.48$; $n = 101$; OR, 13.0 [3.3–51.1]) and history of MI ($\chi^2 = 8.08$; $n = 101$; OR, 6.5 [1.8–23.3]).

Compared with conventional ECG interpretation, HFQRS analysis had significantly higher sensitivity (79% [57%–92%] vs 41% [22%–64%]; $P < .05$), specificity (71% [60%–80%] vs 57% [45%–69%]; $P < .05$), negative predictive value (94% [80%–99%] vs 78% [60%–90%]; $P < .01$), and overall accuracy (72% [62%–81%] vs 54% [42%–65%]; $P < .01$). The positive predictive value (39%

Table 1
Patient demographics

	All	Positive MPI	Negative MPI	P
n	101	19	82	-
Male sex, n (%)	74 (73%)	15 (79%)	59 (72%)	NS
Age (y)	62 ± 13	61 ± 11	62 ± 13	NS
BMI (kg/m ²)	30.5 ± 6.5	29.3 ± 4.7	30.7 ± 6.8	NS
History of MI, n (%)	44 (44%)	15 (79%)	29 (35%)	<.0005
Prior angioplasty, n (%)	53 (52%)	13 (68%)	40 (49%)	NS
Bypass surgery, n (%)	32 (32%)	6 (32%)	26 (32%)	NS
Hypertension, n (%)	73 (72%)	13 (68%)	60 (73%)	NS
Diabetes mellitus, n (%)	22 (22%)	7 (37%)	15 (18%)	NS
Cholesterol, n (%)	90 (89%)	19 (100%)	71 (87%)	NS
History of smoking, n (%)	22 (22%)	5 (26%)	17 (21%)	NS

NS indicates not significant.



Fig. 2. Heart rate (top panel) and time-intensity curves of HFQRS components for all 12 leads obtained in an ischemic patient during exercise. Absolute (in microvolt) and relative (in percentage) HFQRS intensity reductions are indicated for each lead. Leads that exhibit significant HFQRS reduction are presented in red, whereas those with less pronounced reduction are presented in blue. In this patient, 5 leads were found indicative of ischemia, therefore suggesting the presence of ischemic heart disease. See text for details. (Available in color online at www.sciencedirect.com and www.jecgonline.com).

[24%–55%] vs 21% [9%–38%]; $P =$ not significant) was not significantly different between the 2 analyses.

Discussion

When attempting to diagnose IHD, clinicians have multiple invasive and noninvasive tools at hand. Of these tools, exercise ECG has several advantages over other diagnostic modalities including noninvasiveness, low cost, and wide availability. However, the use of cardiac imaging tests for IHD diagnosis has increased over recent years, whereas the use of exercise ECG is declining.²¹ Among the many factors that determine the use of a specific diagnostic tool, the limited diagnostic accuracy of conventional exercise ECG undoubtedly is a prominent factor. Multiple studies aimed at improving the diagnostic and prognostic capabilities of ECG interpretation have been conducted with variable success.^{22–24} In addition, several studies emphasized nonelectrocardiographic measures such as exercise capacity, chronotropic response, heart rate recovery, and ventricular ectopy.^{1,25–28} Although most ECG-based ischemia detection techniques are based on refining conventional ST analysis,

the current study was aimed at the clinical validation of a novel technique for electrocardiographic ischemia detection. This technique focuses on detecting ischemia-related changes in the depolarization phase, whereas most other electrocardiographic techniques for ischemia detection rely on analysis of the repolarization phase. Accordingly, it is based on detecting microvolt-level changes in the QRS complex rather than changes in the ST segment.

The results of this study confirm previous findings regarding the enhanced sensitivity of HFQRS analysis over conventional ECG interpretation in ischemia detection.^{4,7,19,20} The thresholds used in the HFQRS analysis were obtained in previous studies^{19,20} and were not optimized for the patients included in this study. Interestingly, the new technique was also found to be highly specific in this group of medium to high-risk patients, characterized by the high BMI and the prevalence of history of MI, hypercholesterolemia, and hypertension. In a realistic clinical scenario, HFQRS analysis will be embedded in the ECG machine used for recording the ECG.

Patients with positive MPI had a higher incidence of history of MI than did patients with negative MPI. In



Fig. 3. Heart rate (top panel) and time-intensity curves of HFQRS components for all 12 leads obtained in a nonischemic patient during exercise. Absolute (in microvolt) and relative (in percentage) HFQRS intensity reductions are indicated for each lead. No indication of ischemia was found in any lead; thus, the HFQRS response of this patient was considered nonischemic. See text for details.

addition, patients with positive MPI had higher rate of prior angioplasty, diabetes, and hypercholesterolemia, although none reached the required level of statistical significance. No significant differences were found between the 2 groups in functional capacity or in the prevalence of ST changes. Patients with positive MPI tended to exhibit more clinical symptoms of ischemia than patients with negative MPI, although the difference did not reach statistical significance. In contrast to the classical exercise parameters, the HFQRS response was markedly different in the 2 groups. The positive MPI group had a significantly higher proportion of positive HFQRS response than the negative MPI group, as well as higher number of leads with significant HFQRS reduction. The regression model confirmed that HFQRS data provided significant, substantial, and independent diagnostic information rather than reflecting mere differences between the groups.

The high specificity of HFQRS analysis is remarkable when taking into account the high pretest probability of IHD in this group of patients. Moreover, the sensitivity, specificity, negative predictive value, and overall accuracy were significantly higher than those obtained using conven-

tional ECG analysis. The diagnostic performance of conventional ECG was low despite careful analysis by 2 experts who were blinded to patients' clinical data and response to exercise. Therefore, the diagnostic performance of conventional ECG interpretation in this group reflects the electrophysiologic limitations of this method.

Two interesting observations of this study include the high specificity of HFQRS analysis in women and in patients

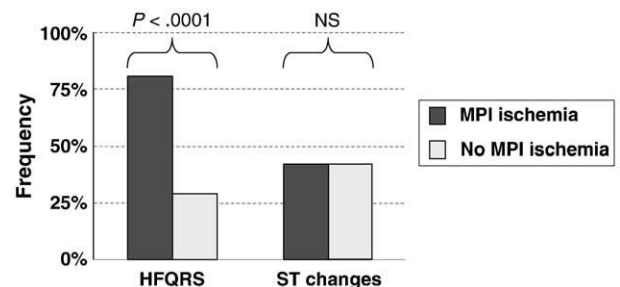


Fig. 4. Frequency of positive response of HFQRS components to exercise and significant ST changes in patients with positive MPI (dark gray) and in patients with negative MPI (light gray).

with inconclusive ST changes. In this study, the specificity of ST changes was 33% ($n = 15$), in agreement with literature.^{29,30} In contrast, the specificity of HFQRS analysis was similar to that of men, reaching a value of 70% ($n = 23$; $P < .05$). A similar value of specificity was found in patients with inconclusive ST changes (79%; $n = 19$). Because the number of subjects in each subgroup is small, testing in dedicated studies is required.

Limitations

The relatively low number of patients with positive MPI did not allow accurate subgroup analysis of the sensitivity of HFQRS nor comparison with the sensitivity of conventional ECG interpretation. Further clinical studies are in progress to evaluate the difference in sensitivity in these subgroups of patients.

In the current study, HFQRS analysis was not performed in patients with wide QRS. It has been shown that the amplitude of HFQRS is reduced in patients with right or left bundle branch block.³¹ Because the reduced signal amplitude results in compromised signal-to-noise ratio, these patients were excluded from HFQRS analysis. A dedicated study in patients with bundle branch blocks is required before extending the technique to such patients.

Referral bias, which is a known limitation in the investigation of the diagnostic performance of a new technique,^{32,33} occurs when patients participating in a study are selected if they are referred for a specific clinical examination. Because patients referred for exercise MPI have lower risk of IHD than patients referred for angiography, exercise MPI was chosen as the gold standard for comparison in this study, although it is widely recognized as being less accurate in detecting significant coronary stenosis than angiography.^{18,34}

The patients included in this study represent a local population in West Virginia with known or suspected IHD and the results may not generalize to other populations.

Conclusions

The results of this study confirm the clinical use of HFQRS analysis in detecting IHD. The HFQRS analysis outperformed conventional exercise ECG interpretation in the entire group of patients, in women and in patients with inconclusive ST changes during exercise. This technique extends conventional exercise ECG by providing an additional, quantitative, and objective tool for the diagnosis of stress-induced ischemia. Thus, HFQRS analysis may aid in the noninvasive evaluation of ischemic heart disease. Furthermore, HFQRS-based improvement in specificity may serve to reduce radiation exposure and the number of invasive procedures, thus lowering risk to the patient while cutting costs to the medical system.

References

- Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002;106:1883.
- Abboud S, Cohen RJ, Selwyn A, Ganz P, Sadeh D, Friedman PL. Detection of transient myocardial ischemia by computer analysis of standard and signal-averaged high-frequency electrocardiograms in patients undergoing percutaneous transluminal coronary angioplasty. *Circulation* 1987;76:585.
- Abboud S. High-frequency electrocardiogram analysis of the entire QRS in the diagnosis and assessment of coronary artery disease. *Prog Cardiovasc Dis* 1993;35:311.
- Beker A, Pinchas A, Erel J, Abboud S. Analysis of high frequency QRS potential during exercise testing in patients with coronary artery disease and in healthy subjects. *Pacing Clin Electrophysiol* 1996;19(12 Pt 1): 2040.
- Mor-Avi V, Shargorodsky B, Abboud S, Laniado S, Akselrod S. Effects of coronary occlusion on high-frequency content of the epicardial electrogram and body surface electrocardiogram. *Circulation* 1987;76: 237.
- Schlegel TT, Kulecz WB, DePalma JL, et al. Real-time 12-lead high-frequency QRS electrocardiography for enhanced detection of myocardial ischemia and coronary artery disease. *Mayo Clin Proc* 2004;79: 339.
- Lipton JA, Warren SG, Broce M, et al. High frequency QRS electrocardiogram analysis during exercise stress testing for detecting ischemia. *Int J Cardiol* 2008;124:198.
- Abboud S. Subtle alterations in the high-frequency QRS potentials during myocardial ischemia in dogs. *Comput Biomed Res* 1987;20:384.
- Abboud S, Cohen RJ, Sadeh D. A spectral analysis of the high frequency QRS potentials observed during acute myocardial ischemia in dogs. *Int J Cardiol* 1990;26:285.
- Abboud S, Berenfeld O, Sadeh D. Simulation of high-resolution QRS complex using a ventricular model with a fractal conduction system. Effects of ischemia on high-frequency QRS potentials. *Circ Res* 1991; 68:1751.
- Watanabe T, Yamaki M, Tachibana H, Kubota I, Tomoike H. Decrease in the high frequency QRS components depending on the local conduction delay. *Jpn Circ J* 1998;62:844.
- Toledo E, Wagner G. HyperQ—new horizons in ischemia detection. *J Electrocardiol* 2007;40:S37.
- Abboud S, Smith JM, Shargorodsky B, Laniado S, Sadeh D, Cohen RJ. High frequency electrocardiography of three orthogonal leads in dogs during a coronary artery occlusion. *Pacing Clin Electrophysiol* 1989;12 (4 Pt 1):574.
- Rahman AM, Gedevarishvili A, Bungo MW, Vijayakumar V, Chamoun A, Birnbaum Y, et al. Non-invasive detection of coronary artery disease by a newly developed high-frequency QRS electrocardiogram. *Physiol Meas* 2004;25:957.
- Tragardh E, Pahlm O, Wagner GS, Pettersson J. Reduced high-frequency QRS components in patients with ischemic heart disease compared to normal subjects. *J Electrocardiol* 2004;37:157.
- Pettersson J, Pahlm O, Carro E, et al. Changes in high-frequency QRS components are more sensitive than ST-segment deviation for detecting acute coronary artery occlusion. *J Am Coll Cardiol* 2000;36:1827.
- Goldberger AL, Bhargava V, Froelicher V, Covell J. Effect of myocardial infarction on high-frequency QRS potentials. *Circulation* 1981;64:34.
- Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging. *J Am Coll Cardiol* 2003;42:1318.
- Sharir T, Merzon K, Kruchin I, Boyko A, Silber H. Incremental diagnostic value of high-frequency QRS analysis for identifying stress-induced ischemia. *J Am Coll Cardiol* 2006;47:132A.
- Toledo E, Bregman-Amitai O, Beker A, Gadot M, Strasberg B, Zafrir N. HyperQ: a novel technique for detecting stress-induced ischemia using analysis of the electrocardiographic depolarization phase. *J Electrocardiol* 2007;40:S72.
- Lucas FL, DeLorenzo MA, Siewers AE, Wennberg DE. Temporal trends in the utilization of diagnostic testing and treatments for cardiovascular disease in the United States, 1993–2001. *Circulation* 2006;113:374.

22. Kligfield P, Lauer MS. Exercise electrocardiogram testing: beyond the ST segment. *Circulation* 2006;114:2070.
23. Okin PM, Kligfield P. Heart rate adjustment of ST segment depression and performance of the exercise electrocardiogram: a critical evaluation. *J Am Coll Cardiol* 1995;25:1726.
24. Taniai S, Koide Y, Yotsukura M, et al. A new application of the ST-HR loop to evaluate the exercise-induced reversible ischemia in healed anterior wall myocardial infarction. *Am J Cardiol* 2006;98:346.
25. Gulati M, Black HR, Shaw LJ, et al. The prognostic value of a nomogram for exercise capacity in women. *N Engl J Med* 2005;353:468.
26. Lauer M, Froelicher ES, Williams M, Kligfield P. Exercise testing in asymptomatic adults: a statement for professionals from the American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. *Circulation* 2005;112:771.
27. Raxwal V, Shetler K, Morise A, et al. Simple treadmill score to diagnose coronary disease. *Chest* 2001;119:1933.
28. Shaw LJ, Peterson ED, Shaw LK, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. *Circulation* 1998;98:1622.
29. Hlatky MA, Pryor DB, Harrell Jr FE, Califf RM, Mark DB, Rosati RA. Factors affecting sensitivity and specificity of exercise electrocardiography. Multivariable analysis. *Am J Med* 1984;77:64.
30. Morise AP, Diamond GA. Comparison of the sensitivity and specificity of exercise electrocardiography in biased and unbiased populations of men and women. *Am Heart J* 1995;130:741.
31. Tragardh E, Pettersson J, Wagner GS, Pahlm O. Reduced high-frequency QRS components in electrocardiogram leads facing an area of the heart with intraventricular conduction delay due to bundle branch block. *J Electrocardiol* 2007;40:127.
32. Froelicher VF, Lehmann KG, Thomas R, et al. The electrocardiographic exercise test in a population with reduced workup bias: diagnostic performance, computerized interpretation, and multivariable prediction. Veterans Affairs Cooperative Study in Health Services #016 (QUEXTA) Study Group. Quantitative exercise testing and angiography. *Ann Intern Med* 1998;128(12 Pt 1):965.
33. Froelicher VF, Fearon WF, Ferguson CM, et al. Lessons learned from studies of the standard exercise ECG test. *Chest* 1999;116:1442.
34. Johansen A, Hoiland-Carlsen PF, Christensen HW, et al. Diagnostic accuracy of myocardial perfusion imaging in a study population without post-test referral bias. *J Nucl Cardiol* 2005;12:530.

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Answer

A young child with palpitations

Commentary. The PR interval is short with broad QRS and delta waves appear in the initial part of the QRS complexes. Given the history of palpitations, this child has Wolff-Parkinson-White syndrome. Careful examination of the P waves shows a negative direction in lead I and axis of 120° on the frontal plane. In addition, there is a tall R wave in V₁ with lack of R-wave progression over the precordial leads. These 2 findings are indicative of dextrocardia.

Physical examination was remarkable for the presence of an apical impulse in the right fifth intercostal space at the midclavicular line. Heart sounds were normal. The liver was felt in the left hypochondrium with gastric resonance on the right side. A diagnosis of situs inversus totalis was suspected.

Localizing the accessory pathway based on the ECG in the presence of dextrocardia is challenging. In this situation, the ECG can be interpreted as a mirror image around an axis formed by aVF. So lead I can be interpreted as negative-lead I, leads II and III are switched, and leads aVR and aVL are also switched. Lead aVF is unaffected. The negative δ wave in the inferior leads suggests an inferior location of the accessory pathway. In the precordial leads, V₁ and V₂ are actually switched. We do not have the rest of the right precordial leads, but given the early transition of the delta wave from negative (in V₂) to positive (in V₁), a septal location would be expected. So, based on that, a posteroseptal location of the pathway was anticipated.

The child underwent an electrophysiologic study during which the location of the pathway was confirmed and orthodromic atrioventricular reentrant tachycardia was induced. The pathway was successfully ablated with RF application.