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High-frequency QRS electrocardiogram analysis during exercise stress testing for detecting ischemia

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Abstract

Introduction: ECG stress testing is an inexpensive and non-invasive detector of myocardial ischemia; addition of high-frequency QRS analysis (HFQRS) may improve accuracy. This study compared HFQRS during exercise in patients with and without ischemia as defined by multiple criteria.
Material and methods: High-resolution ECGs were recorded for 139 patients undergoing T99-sestamibi/T201-thallium stress testing. Twenty-three were positive by at least two and 37 were negative for ischemia by all three of the following criteria: nuclear scan, ST-segment analysis and typical angina. Sixty-four not meeting criteria for positive or negative, six with adenosine test and nine patients with ECG recording artifacts were excluded. Mean age of the study group was 62±10 years, 83% were male. Ischemic patients had a higher incidence of previous myocardial infarction and coronary intervention than non-ischemic patients (74% vs. 46%; $P=0.03$ and 70% vs. 43%; $P=0.05$, respectively), but had a lower body mass index (28.7±5 vs. 33.0±8; $P=0.015$). HFQRS analysis consisting of signal averaging (150–250 Hz) and calculation of root mean squared values for each lead at different time points was performed and was similar between the groups. The relative change in HFQRS (RCQ) was calculated for each lead: {(maxHFQRS − minHFQRS) / maxHFQRS}. For each patient an RCQ index was calculated by averaging the two leads with the greatest RCQ value. The RCQ index was greater in ischemic vs. non-ischemic patients (45% vs. 34%; $P=0.0069$).
Conclusion: Maximum decrease in HFQRS, as quantified by RCQ index, was greater in ischemic vs. non-ischemic patients. Use of the RCQ index may improve the diagnosis of ischemia during exercise stress testing.

Keywords: High frequency ECG; Exercise testing; Ischemia; Diagnostic test

1. Introduction

Coronary artery disease (CAD) is a major health problem in the western world and can present in different ways. The current gold standard for evaluation is coronary angiography, but because it is invasive, expensive and involves certain risks, the 12-lead electrocardiogram (ECG), exercise testing and a targeted patient history are commonly used for initial screening [1,2].

Exercise stress testing with ST-segment ECG monitoring is limited in its accuracy to detect CAD [3]: a meta-analysis of 147 consecutively published reports involving 24,000 patients revealed a mean sensitivity and specificity of 68±

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16% and 77±17%, respectively [4]. Addition of nuclear imaging improves the accuracy of exercise stress testing: a meta-analysis of 33 studies between 1989 and 2001 reported a mean sensitivity of 87% and specificity of 73% for detecting coronary artery stenosis of more than 50% [15]. However, the exposure of patients to radiation, nearly six-fold increase in cost [4], and extra time needed for nuclear imaging emphasize the need for a non-invasive, inexpensive and accurate test for ischemia. The current study investigates the accuracy of a non-invasive and inexpensive technique: the analysis of high-frequency components of the QRS complex (HFQRS).

The ECG changes most recognized and described (such as ST-deviation) occur in the frequency range below 100 Hz. However, smaller, high-frequency changes that are superimposed on the more prominent waveforms of the QRS complex provide additional information about the electrical conduction of the heart [5,6]. These changes can be studied by recording a high-resolution ECG, at 1000 Hz or higher [7,8]. Signal averaging and band-pass filtering techniques can be applied [9,10] to amplify and extract the HFQRS while reducing random noise. The HFQRS signal can be quantified by calculating the surface area of the high-frequency ECG as a root mean square (RMS) value of the voltages. Goldberger et al. [11–13] found that the HFQRS in the frequency range from 80 to 300 Hz was significantly higher in normal subjects than in patients with myocardial infarction, concluding that quantitative HFQRS analysis may be helpful in increasing the diagnostic accuracy of the conventional ECG. HFQRS analysis during exercise is challenging due to the high noise level, and has only recently, due to increased computing power and improved analysis software, become feasible in the clinical setting.

The current study investigates two methods quantifying the reduction in HFQRS during exercise testing for detecting myocardial ischemia in patients with and without ischemia as defined by a combination of core-laboratory nuclear imaging, core-laboratory ST-segment analysis and anginal symptoms.

2. Material and methods

This study was approved by the West Virginia University Institutional Review Board. Written informed consent was obtained from all participants.

From February through July 2004, 139 patients with known or suspected coronary artery disease underwent T99-sestamibi/T201-thallium stress testing at the outpatient clinic of the Charleston Area Medical Center Cardiology Group. Patients were in sinus rhythm with a QRS duration of ≤110 ms.

2.1. Stress testing

Stress testing was done using the modified Bruce treadmill protocol or a 2-minute per stage bicycle protocol; 12-lead ECG monitoring and recording were done (Quinton 3000 system; Quinton Cardiology Systems, USA). Stress test was considered adequate when the patient achieved at least 85% of age predicted maximum heart rate or had a positive ECG. Choice of treadmill or bicycle was left to the discretion of the supervising physician and patient preference.

2.2. Grading of symptoms

Clinical symptoms during the test were determined "positive" (for ischemia) when meeting the following criteria: chest pressure or pain during exercise that was not present before start of exercise, that resolved post exercise and could be graded on a 1–10 scale. Patients with no symptoms, leg fatigue, musculoskeletal pain or shortness of breath were determined "negative". Patients with chest burning, or chest pain/pressure not gradable on a 1–10 scale were categorized "indeterminate". A research fellow present during the exercise test graded the symptoms.

2.3. Standard ECG analysis

The 12-lead ECGs were reviewed by a core laboratory of two independent cardiologists, blinded to other patient information, for presence or absence of ST depression (1.5 mm upsloping or 1 mm horizontal measured at 0.08 seconds after J-point) and categorized "positive" and "negative" for ischemia respectively. The results from both reviewers were compared and for discordant results a consensus was obtained between the reviewers. Patients that did not fit either diagnostic category were categorized "indeterminate".

2.4. Nuclear imaging acquisition and processing

Dual Isotope (thallium 201/technetium 99m sestamibi) imaging was done for all patients. The isotopes were injected according to the manufacturer's protocol. The images were acquired with a rotating, double-headed gamma camera (Cardio Epic; Adac Laboratories, USA). The first set of 64 images was acquired at least 10 min after injection in 32 thirty-second periods, the post exercise set was done 15 to 45 min 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. All images were processed on a workstation (Pegasys; Adac Laboratories, USA) with imaging software (AutoSpect Plus, version 5.0; Adac Laboratories, USA). A core laboratory of two cardiologists independently reviewed each nuclear study, blinded to other patient information. A structured analysis of the resting and exercise image was done: four segments were categorized as no, small, moderate, or large perfusion defect; wall motion was categorized as normal, reduced or akinetic. The scan was considered ischemic only when there was a defect with exercise that resolved at rest. Subsequently, each study was categorized as "positive", "negative" or "indeterminate" for ischemia. Inter-observer disagreement was resolved by obtaining a consensus review from both reviewers.

2.5. Patient groups

Patients were stratified into an "ischemia" group when meeting two out of the three following criteria for a positive stress test: typical angina during exercise, diagnostic ST depression, or ischemia on nuclear scan. Patients with a negative stress test by all three of these criteria were included in a "no-ischemia" group. The remaining patients constituted the "indeterminate" group. These criteria were established to enable comparison between patients with and without ischemia, in the absence of a true gold standard. Baseline characteristics were obtained by directed patient history and hospital chart review.

2.6. High-resolution ECG

High-resolution 12-lead ECG was recorded from 2 min before start to 6 min after completion of the test and stored on a laptop (Thinkpad T41; IBM, USA) using a PC-based 12-lead ECG recorder (EKG Master USB; TEPA, Turkey) with ECG recording software (Biological Signal Processing, Israel). The sampling rate was 1000 Hz with an analogue frequency response of 0.05 to 300 Hz, a sensitivity of 0.4 µV and an analogue to digital conversion of 16 bits. Two sets of electrodes were used, allowing simultaneous high-resolution and standard ECG recording without influencing the clinical test. All electrodes were placed according to the Mason Likar lead system by the laboratory technicians: the high-resolution ECG leads were placed directly below the standard ECG leads.

The high-resolution ECG data were extracted and analyzed using commercial software (HyperQ™ Stress System, Biological Signal Processing, Israel). Briefly, each ECG trace was averaged in each 10 s interval using cross-correlation techniques, which were used to reject noisy QRS complexes and arrhythmias. The averaged QRS complex was band-pass filtered between 150 and 250 Hz, resulting in the HFQRS signal, containing the high-frequency components of the QRS. The RMS value of the HFQRS signal was calculated to create time–intensity curves. These curves were smoothed using a 70-s moving average process. ECG tracings with maximal HFQRS level of <2 µV were excluded from analysis. Two patients were consequently excluded from analysis as their HFQRS signal was below the 2 µV threshold in most leads.

The relative change in HFQRS signal was quantified by dividing the HFQRS value at peak heart rate (*P*) by the HFQRS value at baseline (*B*). Thus a P/B value less than 1 represents a decrease, and a value greater than 1 an increase in HFQRS signal from baseline to peak heart rate.

A second approach, which is illustrated in Fig. 1, was introduced to quantify the relative change in HFQRS during exercise testing: times of 20% and 90% of maximum HR were identified (t20% and t90% respectively). For each of the leads V1 to V6 and I, II, and III, maximal HFQRS value was identified in the segment from t20% to t90%. The time at which the max HFQRS was attained, was termed tmax. Of note: tmax was different for each ECG lead. Subsequently, the lowest HFQRS value in the segment from tmax to t90% was identified. The relative change in HFQRS (RCQ) was calculated for each lead: {(maxHFQRS − minHFQRS)/maxHFQRS}. The relative change in RCQ was defined as the average of the two maximal lead-specific relative changes over the nine leads. For each patient an RCQ index was calculated by averaging the two leads with the greatest RCQ value. The RCQ index is low when little or no change in HFQRS level was observed, and approaches 100% when the HFQRS level reduced with increasing exercise load. The augmented unipolar limb leads were excluded from the analysis.

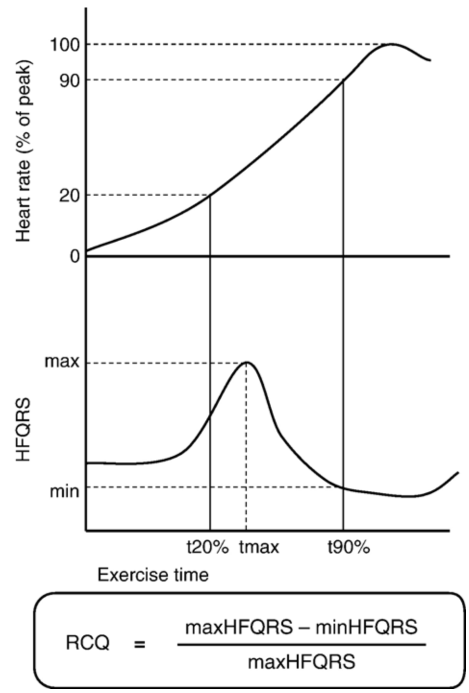

Fig. 1. Calculation of the RCQ index (see description in text). Used abbreviations: HFQRS (high-frequency QRS), min (minimum HFQRS value), max (highest HFQRS value), t20% (the time at which 20% of peak heart rate is reached), t90% (the time at which 90% of peak heart rate is reached), tmax (the time at which the maximum HFQRS value is reached), and RCQ (relative change in HFQRS during exercise test).

2.7. Statistical analysis

The chi-square test was used to compare categorical variables and the Student's *t*-test was employed for continuous variables. For each lead, the high-frequency QRS signal was compared for ischemia and no ischemia groups at baseline, 20% of peak heart rate, 80% of peak heart rate, and at peak heart rate. This resulted in 48 separate comparisons, necessitating adjustment for multiple comparisons, thus a P value of <0.001 was considered statistically significant according to the Bonferroni approach. To further understand the association among high-frequency QRS, ischemia status, and ECG lead, a 2-way analysis of variance was performed. SPSS version 10; SPSS Inc., USA was used for all analyses.

3. Results

3.1. Study population

Of the 139 patients, 64 did not meet the strict criteria (2 out of 3 positive or all 3 negative) for either "ischemia" or "no ischemia" and were categorized as "indeterminate". Additionally, six patients that underwent adenosine test and nine patients with ECG recording artifacts were excluded. Exclusion for ECG artifacts included corrupted data file ($n=1$), low signal to noise ratio due to 60 Hz interference ($n=4$) and frequent PVCs ($n=4$).

The final study group included 60 patients; 23 categorized as "ischemia" and 37 as "no ischemia". Baseline characteristics are displayed in Table 1: the mean age was 62±10 years, 83% were male, mean BMI was 31±7 kg/m^2. Demographics include history of smoking (20%), high cholesterol (92%), hypertension (77%), diabetes (30%), CABG (37%), PCI (53%) and presence of previous MI (57%). Presence of previous AMI and PCI was higher in patients with ischemia vs. no ischemia (74% vs. 46%; $P=0.03$ and 70% vs. 43%; $P=0.05$ respectively), BMI was lower in the ischemia group (28.7±5 vs. 33.0±8; $P=0.015$).

The two-way analysis of variance with factors ischemic/non-ischemic and leads for B/P ratio is displayed in Fig. 2.

Table 1
Baseline characteristics

Variables	Ischemia ($n=23$)	No-Ischemia ($n=37$)	P value
Demographics			
Male % (n)	74% (17)	89% (33)	0.12
Age in years (mean±SD)	62.1±9	61.3±11	0.76
BMI in kg/m^2 (mean±SD)	28.7±5	33.0±8	0.015
Smoking % (n)	17% (4)	24% (9)	0.53
Hyperlipidemia % (n)	91% (21)	92% (34)	0.94
Hypertension % (n)	78% (18)	76% (28)	0.82
Diabetes % (n)	39% (9)	24% (9)	0.22
AMI % (n)	74% (17)	46% (17)	0.03
CABG % (n)	39% (9)	35% (13)	0.76
PCI % (n)	70% (16)	43% (16)	0.05
Test related			
Treadmill/Bicycle (n)	20/3	30/7	0.55
Obtained HR (beats/min)	138±12	142±12	0.15

Used abbreviations: BMI (body mass index), AMI (acute myocardial infarction), CABG (coronary artery bypass grafting), PCI (percutaneous coronary intervention). Values are displayed as mean±standard deviation (n) for continuous variables.

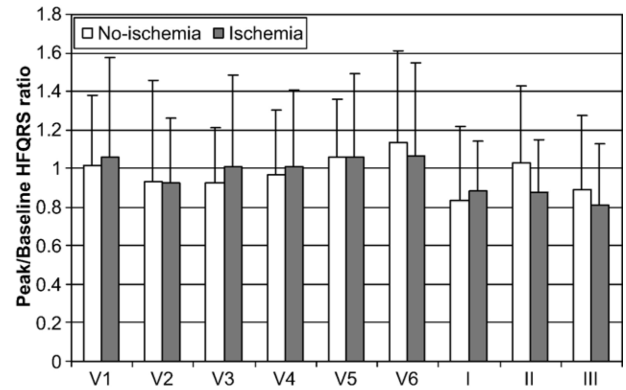

Fig. 2. Baseline to peak ratio by lead for the ischemia vs. the no-ischemia group. The bars represent the mean value, the error bars the SD. A value of greater than 1 indicates an increase in HFQRS from baseline to peak heart rate.

There was no significant ($P\leq0.05$) difference in B/P ratio between the ischemic and the non-ischemic groups, nor was there a significant difference in B/P ratio between the 12 leads. Furthermore, no decrease or increase in HFQRS signal from baseline to peak heart rate was detected ($P\leq0.05$), either in between the ischemic and non-ischemic patients, or in a certain lead.

The relative change in HFQRS signal as quantified in the RCQ index (described in the Material and methods section) is displayed between the groups in Fig. 3. The RCQ index was higher in the ischemia group than the no ischemia group (45±15% vs. 34±14%; $P=0.0069$), indicating a higher relative decrease in HFQRS signal from 20% to 90% of peak heart rate in ischemic patients. The RCQ index also shows a large inter-patient variation, but is a means of reducing the inter-lead variation by condensing the data to one parameter per patient. To determine the value of the RCQ index in separating the ischemic and non-ischemic patients, a Receiver Operator Characteristic was calculated and displayed in Fig. 4. The area under the curve was 0.694 (Standard Error 0.071; $P=0.012$), highest accuracy was

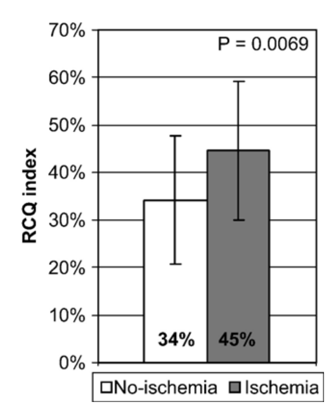

Fig. 3. RCQ index in the ischemia vs. the no-ischemia group. Bars represent the mean value, the error bars the SD. The RCQ index is a measure of decrease in HFQRS during exercise testing, as described in text and Fig. 1.

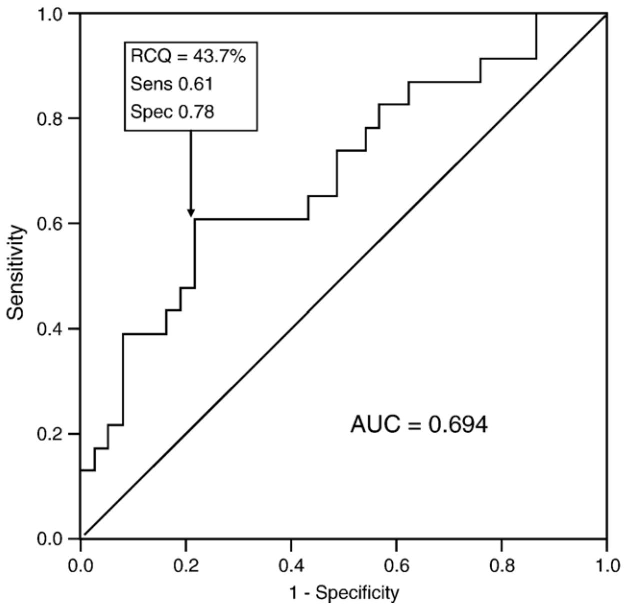

Fig. 4. Receiver operator curve for separating the ischemic vs. the non-ischemic groups using the RCQ index. AUC: area under curve. RCQ index is defined in the text, and in Fig. 1.

achieved using RCQ cutoff value of 43.7%, resulting in a sensitivity and specificity of 61% and 78% respectively for identifying the ischemic patients.

4. Discussion

The relative change in HFQRS, as measured from 20% to 90% of max heart rate during the test, and quantified in the RCQ index, was greater in the ischemic group vs. the non-ischemic group. An explanation may be found in the pathophysiology of the HFQRS, which is thought to originate from small aberrations in the conduction of the depolarization wavefront of the myocardium, which has been simulated in a computer model [7]. Enhanced electrical activity and conduction velocity in the non-ischemic areas of the myocardium associated with compensatory hyperdynamic contraction [16] and an increase in bipolar potential at border zones between ischemic and non-ischemic areas [17] could potentially lead to an increase in HFQRS signal in the presence of induced ischemia, as might occur during the initial phase of the exercise test. When ischemia progresses, as would be the case nearer to peak heart rate, a slowing of the depolarization wavefront in the ischemic tissue transposes the high-frequency signals to lower frequencies [18], resulting in a decrease in HFQRS [14] This would result in a greater relative change in HFQRS in ischemic patients.

There were large inter-individual lead variations in HFQRS signal response: this may be explained by differences in electrical conduction (due to different anatomy of heart/lungs), and differences in noise caused by muscle (different patients may employ their muscles in different manners during the exercise test). Difference in HFQRS amplitude and response seen in the different leads may be due to the difference in electrode location, the location of ischemia, distance from the heart and presence/absence of pre-existing myocardial damage. The variation if HFQRS response between leads is not yet well understood and deserves further research; combined body surface electrocardiography and MRI imaging may provide further insight into these phenomena.

The hypothesis that there would be a decrease in HFQRS signal between baseline and peak heart rate was based on a study by Abboud et al. [14] that compared 32 patients with arteriographically documented CAD with 30 healthy subjects, comparing HFQRS signals averaged from V3 through V6. Their analysis showed a significant decrease in the values from baseline to peak, post exercise and during recovery. The difference between Abboud's results and findings in the current study could be attributed to several factors. First, Abboud's study group consisted of healthy volunteers and patients with known CAD whereas all subjects in the current study were patients with known or suspected CAD. Additionally the healthy group in Abboud's study was younger than the CAD group, resulting in a difference in the maximum heart rate. The percentage of patients with a previous MI in the CAD groups was also different, being 15% in Abboud's study and 72% in the current analysis: however, there were no significant differences in the HFQRS parameters between patients with previous MI and those without. Finally different recording and signal analysis techniques used may have contributed to the different findings.

The RCQ index was developed to take into account these theories; by quantifying the decrease in HFQRS signal at any time during the test, rather than at two fixed time points as in the B/P ratio. Furthermore, the use of the RCQ index extracts the data from multiple leads and extracts only the information of the most relevant ones, being the leads with the greatest decrease in HFQRS. The RCQ index therefore provides a technique to use the HFQRS signal while taking into account the variability in the timing of HFQRS changes and the leads in which the changes take place. In this testing population the sensitivity and specificity are comparable to standard ECG stress testing [4,20], however we speculate that combining the standard ST analysis and the HFQRS analysis may achieve accuracy levels similar to that of nuclear imaging techniques. As the current study design used both ST-segment and nuclear imaging to define the groups, further studies are needed to test our cutoff value of the RCQ index, and to compare HFQRS to nuclear imaging for diagnosis of myocardial ischemia during stress testing.

5. Limitations

This study has several limitations. First, the number of patients is limited, reducing the power to detect statistically significant changes in the HFQRS parameters.

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Second, analysis of post exercise signals was not done; however correlation of peak HFQRS values and 20 s post peak was >0.95, suggesting limited value of further analyzing the early post-exercise data.

Third, HFQRS analysis was not possible for nine of the patients. Improvements in the signal recording, noise filtering and signal extraction techniques are needed.

Fourth, the study population had a mean BMI of 31 ± 7 kg/m^2. Data on the effect of obesity on the HFECG have not been reported. HFQRS could be attenuated due to an increased distance from electrode to signal origin, associated with reduced QRS voltage [19], and increased noise due to increased body mass [4]. Nuclear imaging is limited in the sensitivity and specificity for detecting ischemia (75% and 79% respectively compared to angiography) [21]. Furthermore, high BMI has been shown to reduce the accuracy of nuclear imaging [15], for these reasons, this study used two other testing modalities to improve the accuracy of ischemia detection.

6. Conclusions

Maximum decrease in HFQRS, as quantified by RCQ index, was more pronounced in ischemic vs. non-ischemic patients, defined by a combination of core-laboratory nuclear imaging, core-laboratory ST-segment analysis and anginal symptoms during exercise stress testing. However, baseline to peak HFQRS analysis did not predict ischemia. Thus use of the RCQ index to improve the diagnosis of ischemia during exercise stress testing should be tested prospectively.

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