Comparison of the Usefulness of Heart Rate Variability Versus Exercise Stress Testing for the Detection of Myocardial Ischemia in Patients Without Known Coronary Artery Disease

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Heart rate variability (HRV) has been shown to be attenuated in patients with coronary artery disease (CAD) and may, therefore, be possibly used for the early detection of myocardial ischemia. We aimed to evaluate the diagnostic yield of a novel short-term HRV algorithm for the detection of myocardial ischemia in subjects without known CAD. We prospectively enrolled 450 subjects without known CAD who were referred to tertiary medical centers for exercise stress testing (EST) with single-photon emission computed tomography myocardial perfusion imaging (MPI). All subjects underwent 1-hour Holter testing with subsequent HRV analysis before EST with MPI. The diagnostic yield of HRV analysis was compared with EST, using MPI as the gold standard for the noninvasive detection of myocardial ischemia. All subjects had intermediate pretest probability for CAD. Mean age was 62 years, 38% were women, 51% had hypertension, and 25% diabetes mellitus. HRV analysis showed superior sensitivity (77%) compared with standard EST (27%). After multivariate adjustment, HRV was independently associated with an 8.4-fold ($p < 0.001$) increased likelihood for the detection of myocardial ischemia by MPI, whereas EST did not show a statistically significant association with a positive MPI (odds ratio 2.1; $p = 0.12$). Of subjects who were referred for subsequent coronary angiography, the respective sensitivities of HRV and EST for the detection of significant CAD were 73% versus 26%. Our data suggest that HRV can be used as an important noninvasive technique for the detection of myocardial ischemia in subjects without known CAD, providing superior sensitivity to conventional EST in this population. **(Am J Cardiol 2015;115:1518−1522)**

The diagnosis of coronary artery disease (CAD) resulting in myocardial ischemia often necessitates the use of either costly procedures that may expose the patient to ionizing radiation or of procedures limited by relatively low sensitivity and specificity.[1,2] Heart rate variability (HRV) analysis is a noninvasive and relatively inexpensive test that does not expose the patient to ionizing radiation. It is based on the measurement of beat-to-beat variations and fluctuations, assessed by various statistical operations on normal R-R intervals.[3,4] Previous studies have shown that HRV is correlated with the risk of all-cause mortality and cardiovascular and sudden cardiac death.[4−8] Moreover, HRV was shown to be attenuated in patients with CAD, and it has been hypothesized that HRV analysis may be used to identify the existence of myocardial ischemia in subjects without known CAD.[8−10] Few studies have assessed the use of HRV analysis for the detection of ischemia, with somewhat conflicting results.[8−11] However, these studies were limited by heterogeneous populations and using long-term end points of cardiovascular events or death rather than the presence of myocardial ischemia at the time of HRV testing. We developed a new HRV algorithm that showed a high sensitivity for the detection of myocardial ischemia in a small pilot study.[12] Here we report the results of a prospective, multicenter, clinical trial designed to validate the diagnostic yield of the HRV algorithm in subjects without known CAD.

Methods

The HeartTrends HRV Algorithm for the Detection of Myocardial Ischemia is a prospective clinical trial designed to evaluate the yield of HeartTrends, a novel HRV algorithm

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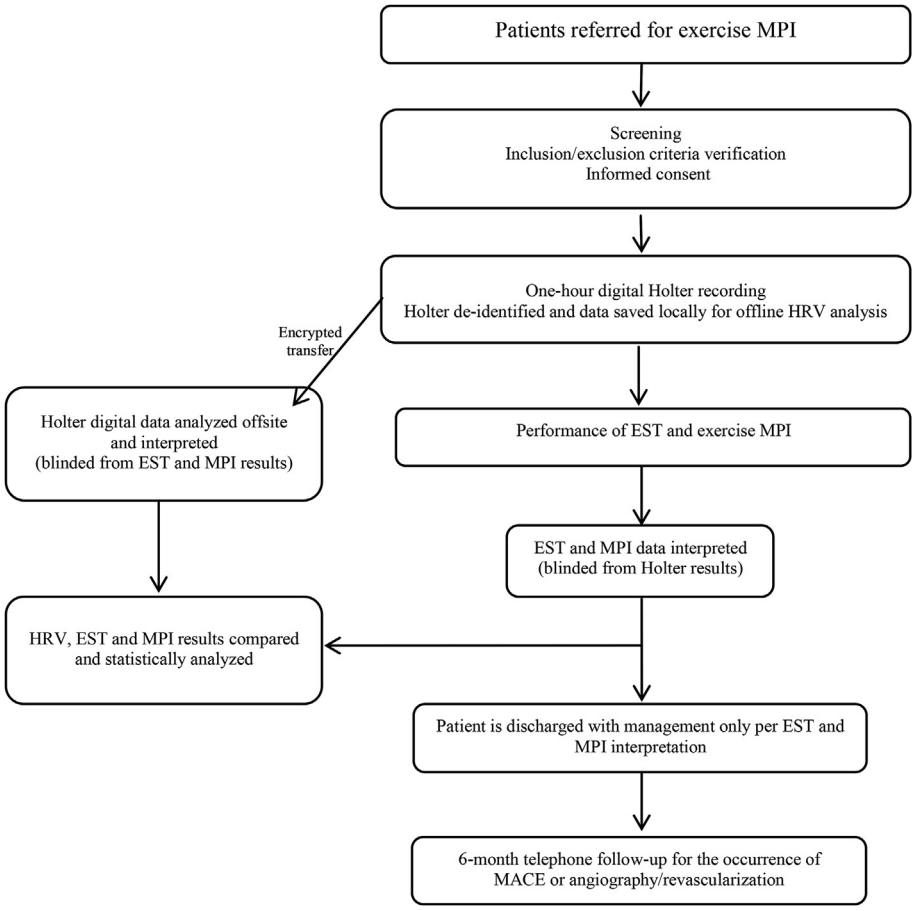

Figure 1. Flow diagram of study design. MACE = major adverse cardiac events.

of a short-term Holter electrocardiogram, for the detection of myocardial ischemia in subjects without known CAD who were referred for exercise myocardial perfusion imaging (MPI). The study was conducted in 2 tertiary referral centers in Israel. Subjects enrolled were >21 years without known CAD who were referred by their physician for noninvasive assessment through MPI. Subjects were excluded if they had any of the following exclusion criteria: established CAD, atrial fibrillation or flutter, the diagnosis of an acute coronary syndrome, the presence of a cardiac pacemaker, clinical diagnosis of heart failure, moderate or severe pulmonary disease, acute myocarditis or any presence of cardiomyopathy, known drug or alcohol dependence, the presence of left bundle branch block, significant intraventricular conduction delay, or significant (>1 mm) ST deviations at baseline.

Subjects meeting inclusion criteria who provided informed consent to participate in the study underwent 1-hour digital electrocardiographic (ECG) Holter data acquisition before the planned nuclear stress test. After data acquisition, subjects underwent a standard exercise stress test and a nuclear scan according to accepted performance criteria (mean time interval between Holter and nuclear stress testing: 30 ± 15 minutes). Analysis of recorded ECG data for HRV was performed blinded to the exercise stress testing (EST) and MPI results, off-line at an ulterior date. All subjects were further followed for clinical events and interventions at 6 months. A summary of the study design is provided in Figure 1.

The study was approved by the institutional review boards of the participating centers, and all subjects provided informed consent. Enrollment was initiated on July 1, 2012, and the study was terminated on March 1, 2014, with the final study population comprising 450 patients.

HRV acquisition is done by extracting R-R interval duration from a digital Holter electrocardiogram and further analyzing it by the Lev El Diagnostics of Heart Diseases novel patented and patent-pending algorithms. The ECG equipment used is simply an off-the-shelf Holter ECG device as HeartTrends algorithm is compatible with any device that includes the following standard characteristics. Once the Holter provides the "clean" RR time series, the HeartTrends runs its patented algorithm that results in the Dy/Dx indicator value. A detailed description of how to measure Dy/Dx has been published.[13,14] Briefly, the Multipole analysis is a new way of investigating the Poincaré Plot from complex time series. The measures obtained from this kind of analyses bear intrinsic time dependence because of the very construction of the plot, as opposed to the SD of NN intervals, which does not include any time ordering. As a result Dy/Dx, as do other Poincaré plot indexes, derives information from both the time and frequency domains and reflecting increased randomness in the RR interval time series.

EST was defined as positive when there was a ≥1 mm of horizontal or downsloping ST-segment depression ≥80 milliseconds after the J-point (compared with the level of the PQ interval) for 3 consecutive beats or ST-segment elevation ≥1 mm in a non−Q wave lead other than V1 or AVR. All other EST results were considered to be negative for myocardial ischemia. HRV analysis was defined as positive when the Dy/Dx indicator value score generated by the HeartTrends device using a proprietary algorithm was <2.0, based on calibration analyses that were carried out in a pilot study.[12] "MPI" was defined as positive when the amount of myocardial ischemia was >5% of the myocardium.

EST and MPI tests were adjudicated separately, each by 2 independent observers, blinded to the results of all other tests. Similarly, coronary angiograms performed during follow-up were reviewed and adjudicated by 2 independent observers, blinded to the results of all other tests.

We compared the diagnostic yield of the new HeartTrends HRV algorithm with the commonly used EST. MPI was used as the gold standard for the detection of a significant CAD. The sample size was calculated to show a 10% superiority of the new HRV algorithm compared with standard EST. The expected sensitivity of HeartTrends HRV testing for the gold standard exercise imaging tests is >70% compared with 60% using EST, with a corresponding 10% difference in the negative predictive value and specificity between the 2 screening techniques. Accordingly, a minimal required sample size of 450 total subjects (for a power of 0.9 and alpha of 0.05) was calculated, adjusting for an expected 5% rate of unusable Holter recordings.

Continuous variables were compared using *t* test and expressed as mean ± SD. Categorical variables were assessed using the chi-square test or Fisher's exact test, when at least one of the cells in the table had an expected number <5. For diagnostic yield assessment, we calculated the test's sensitivity, specificity, positive predictive value, and negative predictive value.

Multivariate logistic regression modeling was used to assess the likelihood for the identification of myocardial ischemia by HRV and EST. Prespecified covariates in the multivariate models included age, gender, hypertension, dyslipidemia, diabetes mellitus, body mass index, current smoking, and a family history of CAD. Analyses were performed using the SAS software (SAS Institute Inc. Cary, NC) (version 9.30).

Results

Of the 450 subjects enrolled in the study, 47 had uninterpretable Holter ECG recordings (<1 hour), 5 did not complete EST, and 4 were ultimately found to have 1 or more exclusion criteria, thus resulting in a final analysis sample of 394 subjects. The baseline clinical characteristics and medications of study subjects are presented in Table 1. Notably, the characteristics of the subjects who were included in the final analysis were similar to those who were excluded. Mean age was 62 years (±10) and 62% were men. All subjects had an intermediate pretest probability for CAD, with a relatively high frequency of cardiovascular risk factors, including hypertension and diabetes mellitus (Table 1).

Table 1
Baseline clinical characteristics of enrolled study subjects*

Characteristic	Included in the final analysis (N=394)	Excluded from the final analysis (N=56)
Age (years)	62 ± 10 years	63 ± 12 years
Men	62 %	63 %
Hypertension†	51 %	50 %
Dysplipidemia†	66 %	68 %
Diabetes Mellitus	25 %	23 %
Family history of coronary artery disease	44 %	46 %
Peripheral vascular disease	2 %	1 %
Prior cerebrovascular accident or transient ischemic attack	2 %	2 %
Smoker		
Past	18 %	16 %
Present	22 %	24 %
Body mass index (kg/m^2)	28 ± 5.4	29 ± 6
Medications		
Beta blockers‡	14 %	13 %
Calcium channel blockers	11 %	13 %
Antiarrhythmics	0.3 %	0 %

* Data are as percentages or mean ± SD; all p-values for the comparison between the two groups are >0.10.

† Hypertension and dyslipidemia were defined if subjects were receiving antihypertensive and lipid lowering therapies, respectively.

‡ Treatment with beta blockers was withheld 48 hours prior to start of study procedures.

Myocardial ischemia was detected using MPI in 7% of the study cohort. Ischemia was detected in various territories (left anterior descending, diagonal branch, and left circumflex) and ranged in magnitude from mild (5% to 10% of myocardium), moderate (10% to 20% of myocardium), or severe (>20% of myocardium).

The diagnostic parameters of the new HRV algorithm and of conventional EST for the study population are presented in Table 2. The HRV test showed a markedly higher sensitivity for the detection of myocardial ischemia compared with EST (77% vs 27%). In addition, the negative predictive value of the HRV test was very high (98% compared with 94% associated with conventional EST), whereas the specificities and positive predictive values of the 2 tests were similar (Table 2). Notably, the diagnostic yield of the HRV test was independent of the daily hour in which it was obtained.

The assessment of the likelihood for the detection of myocardial ischemia by EST and HRV was performed using multivariate logistic regression modeling (Table 3). After adjustment for age, gender, hypertension, dyslipidemia, diabetes mellitus, body mass index, smoking, and a family history of CAD, a positive HRV was independently associated with an 8.4-fold (p <0.001) increased likelihood for the detection of myocardial ischemia, whereas a positive EST did not show a statistically significant association with myocardial ischemia after multivariate adjustment (Table 3).

Table 2
Diagnostic yield of exercise stress testing and heart rate variability for the detection of myocardial ischemia*

	EST	HRV
Sensitivity	27 %	77 %
Specificity	89 %	71 %
Positive predictive value	15 %	16 %
Negative predictive value	94 %	98 %

EST = exercise stress testing; HRV = heart rate variability.
* Myocardial ischemia was defined as a positive myocardial perfusion imaging test (see Methods section for detailed definitions).

Table 3
Multivariate analysis: adjusted likelihood for the detection of myocardial ischemia by heart rate variability and exercise stress testing*

	Odds Ratio	95% confidence interval	P-Value
Positive HRV	8.4	3.1 - 23.9	<0.001
Positive EST	2.1	0.7 - 7.9	0.12

* Findings are further adjusted for age, gender, hypertension, dyslipidemia, diabetes mellitus, body mass index, current smoking, and a family history of CAD; myocardial ischemia was defined as a positive myocardial perfusion imaging test (see Methods section for detailed definitions).

Sixteen subjects with a positive MPI at the index visit were subsequently referred for coronary angiography during 6 months of follow-up. Of the 16 subjects, 15 (94%) were shown to have >70% stenosis of a major epicardial artery. Eleven of the 15 patients with angiographically detected significant CAD also had a positive HRV result (sensitivity 73%). In contrast, only 4 of the patients who showed significant CAD had a positive EST (sensitivity 26%).

Discussion

In this prospective, multicenter, clinical trial, we demonstrate that the new HRV algorithm, as used by the HeartTrends device, has greater sensitivity and NPV compared with EST. Moreover, the results of the HRV test were highly correlated with the presence of significant CAD in patients who underwent coronary angiography during follow-up. These findings suggest that HRV testing may be used as a screening tool for the detection of myocardial ischemia in at-risk subjects without known CAD.

HRV has been long known to represent sympathetic and parasympathetic activity and balance.[15] The use of HRV was evaluated in various medical settings and was found to be independently associated with the risk of all-cause mortality and cardiovascular death.[10] Hayano et al[16] have described an association between low HRV and the severity of CAD. In addition, several studies have suggested that low HRV is a predictor for the occurrence of CAD-related clinical events during long-term follow-up.[8,9] However, the statistical power of these studies was limited by a relatively small sample size.

To our knowledge, the present study is the first to evaluate the utility of HRV analysis for the detection of ischemia in subjects without known CAD. We demonstrate that the new HRV algorithm was a powerful independent predictor for the presence of myocardial ischemia (adjusted odds ratio of 8.4), whereas EST did not show a statistically significant association with the presence of myocardial ischemia after multivariate adjustment. Thus, our findings suggest that the new HRV analysis algorithm appears to have improved diagnostic yield compared with conventional EST in this population.

Of note, ß-blocker therapy was discontinued 48 hours before HRV testing and exercise MPI. In addition, only 40 study patients were treated with calcium channel blockers at the time of testing. Thus, the study is not sufficiently powered to evaluate the diagnostic yield of HRV in patients who are treated with those medications. It should also be noted that our findings are applicable only to the present study population, comprising subjects with an intermediate pretest probability for the presence of CAD without the presence of important co-morbidities (such as cardiomyopathy, atrial fibrillation, and moderate-to-severe pulmonary disease), which may be present in patients who are being evaluated for CAD.

A recent health policy statement on the use of noninvasive cardiovascular imaging has noted high growth rates for most common imaging technique, possibly because of the relatively low sensitivity of EST as an initial screening technique.[17] The results of the present study suggest that simple 1-hour Holter testing, using an HRV algorithm, can be used for the detection of myocardial ischemia in subjects without known CAD, demonstrating higher sensitivity in this population than conventional EST. These findings can be used to improve risk assessment before a decision regarding the need to proceed with more complex and costly imaging techniques for the detection of myocardial ischemia.

Disclosures

The authors have nothing to disclose.

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