A Novel Heart Rate Variability Algorithm for the Detection of Myocardial Ischemia: Pilot Data from a Prospective Clinical Trial

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ABSTRACT: **Background:** Heart rate variability (HRV) analysis has been shown to be a predictor of sudden cardiac death and all-cause mortality in patients with cardiac disease.

Objectives: To examine whether newer HRV analysis algorithms, as used by the HeartTrends device, are superior to exercise stress testing (EST) for the detection of myocardial ischemia in patients without known coronary artery disease (CAD).

Methods: We present pilot data of the first 100 subjects enrolled in a clinical trial designed to evaluate the yield of short-term (1 hour) HRV testing for the detection of myocardial ischemia. The study population comprised subjects without known CAD referred to a tertiary medical center for EST with single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI). All patients underwent a 1 hour electrocardiographic acquisition for HRV analysis with a HeartTrends device prior to EST with MPI. Sensitivity, specificity, and positive and negative predictive values (PPV and NPV, respectively) were calculated for EST and HRV analysis, using MPI as the gold standard for the non-invasive detection of myocardial ischemia.

Results: In this cohort 15% had a pathologic MPI result. HRV analysis showed superior sensitivity (85%), PPV (50%) and NPV (97%) as compared to standard EST (53%, 42%, 90%, respectively), while the specificity of the two tests was similar (86% and 85%, respectively). The close agreement between HRV and MPI was even more pronounced among patients › 65 years of age.

Conclusions: Our pilot data suggest that the diagnostic yield of the novel HeartTrends HRV algorithm is superior to conventional EST for the non-invasive detection of myocardial ischemia.

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KEY WORDS: heart rate variability (HRV), myocardial ischemia, coronary artery disease (CAD)

The diagnosis of significant coronary artery disease (CAD) resulting in myocardial ischemia is a complex task that often necessitates the use of either costly procedures which may expose the patient to ionizing radiation or procedures limited by relatively low sensitivity and specificity [1,2].

Heart rate variability (HRV) analysis is a non-invasive 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 at normal R-R intervals [3,4]. Prior studies have shown that HRV is correlated with the risk for all-cause mortality as well as cardiovascular and sudden cardiac death [4-8]. Moreover, it has been hypothesized that HRV analysis may be used to identify the existence of myocardial ischemia in patients without known CAD [8-10]. A 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 by employing long-term endpoints of cardiovascular events or death rather than the early detection of myocardial ischemia.

A new HRV algorithm was developed by Lev El Diagnostics of Heart Diseases for the early detection of myocardial ischemia and incorporated in the HeartTrends software medical device. In this report we provide pilot data of the first 100 patients enrolled in a prospective clinical trial designed to evaluate the use of a novel short-term, 1 hour HRV algorithm for the detection of myocardial ischemia in subjects without known prior CAD who were referred for exercise MPI.

PATIENTS AND METHODS

The HeartTrends HRV Algorithm for the Diagnosis of Myocardial Ischemia is a prospective multicenter randomized clinical trial designed to evaluate the yield of a novel short-term HeartTrends HRV algorithm for the detection of myocardial ischemia in subjects without known CAD who were referred for exercise MPI. The study was initiated on 1 July 2012 and the first 100 patients comprise the present study population. They were

older than 21 years old, did not have CAD and were referred by their physician for non-invasive assessment via MPI. Detailed inclusion and exclusion criteria are provided in Table 1.

The subjects who met the inclusion criteria and provided informed consent to participate in the study underwent a 1 hour digital electrocardiographic (ECG) data acquisition prior to the planned nuclear stress test. Following data acquisition, a standard exercise stress test and a nuclear scan according to accepted performance criteria were performed. Analysis of the recorded ECG data for HRV was performed offline at a later date, and blinded to the EST and MPI results.

Subjects were followed for clinical events, interventions and 6 month occurrence of major adverse cardiac events (MACE). The study was approved by the Institutional Review Boards of the participating centers.

HOLTER TESTING AND THE NOVEL HRV ALGORITHM

HRV acquisition is done by extracting R-R intervals duration from a digital Holter-ECG and further analyzing it by the Lev El Diagnostics of Heart Diseases novel patented and patent-pending algorithms. The ECG equipment we used is simply an off-the-shelf Holter ECG device since the HeartTrends algorithm is compatible with any device that has the following standard characteristics: 500 samples per second, 3 leads, 1 or 2 channels with sufficient storage memory for at least 2 hours of ECG recording, built-in R-R wave detection and ECG display, and detection and exclusion both of non-sinus rhythm beats and interference. Therefore, any Holter ECG on the market which meets these requirements is suitable for the analysis by the HeartTrends algorithm. Once the Holter provides the "clean" RR time series, the HeartTrends runs its patented algorithm that results in the Dy/Dx indicator value. Of note, validation of the RR time series is accomplished by comparing the RR input from several Holter outputs. A detailed description of how to measure Dy/Dx has been published [12,13]. Briefly, the Multipole analysis is a new way of investigating the Poincaré Plot from complex time series. The Poincaré Plot is interpreted as a two-dimensional body where each data point in the plot is assigned a unit mass in order to describe the total mass distribution within the plot. The measures obtained from this kind of analysis bear intrinsic time dependence due to the very construction of the plot, in contrast to the standard deviation of NN intervals (SDNN) which does not include any time ordering (shuffling the RR intervals lead to the same value for SDNN). As a result Dy/Dx, like other Poincaré plot indices, derives information from both the time and frequency domains, and reflects increased randomness in the RR interval time series. The Multipole Method includes the density ratio Dy/Dx which calculates the ratio between the peak-density on the y-axis (dy) and the x-axis (dx), respectively.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age ≥ 21 years	Established ischemic heart disease
Referral for exercise MPI by treating physician	Atrial fibrillation or flutter
Willing and able to provide written informed consent	Acute coronary syndrome
	Cardiac pacemaker
	Clinical diagnosis of heart failure
	Moderate or severe COPD
	Active myocarditis, constrictive pericarditis, any cardiomyopathy, cardiac or systemic amyloidosis
	Known drug or alcohol dependence or any other factors that will interfere with the study conduct or interpretation of the results, or judged by the investigator as not suitable to participate
	Any illness that might reduce life expectancy to less than 1 year from screening
	LBBB, significant IVCD or significant (>1 mm) ST deviations on baseline ECG
	Inability to perform an exercise stress test (i.e., orthopedic or neurologic limitations)
	Any significant established myocardial or valvular disease

MPI = myocardial perfusion imaging, COPD = chronic obstructive pulmonary disease, LBBB = left bundle branch block, IVCD = intraventricular conduction delay

DEFINITIONS

EST was defined as positive when there was a ≥ 1 mm of horizontal or down-sloping ST segment depression ≥ 80 msec after the J-point (as compared to the level of the PQ interval) for three consecutive beats or ST segment elevation ≥ 1 mm in a non-Q wave lead other than V1 or AVR.

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. MPI was defined as positive when the amount of myocardial ischemia was > 5% of the myocardium, which was adjudicated by two independent observers blinded to the results of EST and HRV testing.

STATISTICAL ANALYSIS

We compared the diagnostic yield of the new HRV algorithm with the commonly used EST. MPI was used as the gold standard for the detection of myocardial ischemia. 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% as compared to 60% using EST, with a corresponding 10% difference in the NPV and specificity between the two screening modalities. Accordingly, a maximal required sample size of 350 total subjects (for a 0.8-power and alpha of 0.05) was calculated, adjusting for an expected 5% rate of unusable

Holter recordings. We report here our pilot data of the first 100 subjects enrolled.

Continuous variables were compared using the *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 (PPV), negative predictive value (NPV) and test accuracy. A subgroup analysis for the diagnostic parameters was performed for subjects aged 65 years and older.

We also performed a comparative assessment of the risks of a positive test result, calculating the relative risk of having myocardial ischemia (as assessed by MPI). Risks were represented as the relative risk with a 95% confidence interval. Analyses were performed using the SPSS package (release 19.0, IBM Corp.).

RESULTS

Of the first 100 subjects enrolled in the study, 8 had uninterpretable Holter ECG recordings (< 1 hour), one subject did not complete EST, and two were ultimately found to have some exclusion criteria, thus resulting in a final study sample of 89 subjects. The baseline clinical characteristics and medications of study subjects are presented in Table 2. The mean age was 61 (± 10.2) years and 59% were males; 53% had hypertension, 64% had dyslipidemia, 21% had diabetes mellitus, and 43% had a family history of coronary heart disease. Thirteen percent of the patients were treated with beta-blockers and a similar proportion with calcium channel blockers, whereas none of the patients received anti-arrhythmic medications. All subjects had an intermediate pretest probability for CAD.

Table 2. Patients' (n=89) baseline characteristics

Age (average ± SD) Age ≥ 65	61 ± 10 years 35%
Male	59%
Condition Hypertension Dysplipidemia Diabetes mellitus Familial history of early CAD Peripheral vascular disease Prior TIA/CVA	 52% 64% 21% 44% 0% 2.4%
Smoking Past Present	 20% 25%
BMI	28.7 ± 5.6
Medications Beta-blockers Calcium channel blockers Anti-arrhythmic agents	 13% 13% 0%

CAD = coronary artery disease, TIA = transient ischemic attack, CVA = cerebrovascular accident

DETECTION OF MYOCARDIAL ISCHEMIA BY EST AND HRV

Myocardial ischemia was detected using MPI in 15% of the study cohort. Ischemia was detected in various territories (left anterior descending, diagonal branch, left circumflex) and was categorized as mild (5%–10% of myocardium), moderate (10%–20% of myocardium), or severe (> 20% of myocardium). The diagnostic parameters of the new HRV algorithm as well as for the conventional EST for the total study population are presented in Table 3A, showing a markedly higher sensitivity using the HRV test compared with EST (85% vs. 53%). NPV of the HRV test is higher as well and has an almost optimal value (97% vs. 90%). These results were even more accentuated in the subgroup of patients ≥ 65 years of age in whom the sensitivity and NPV were 100% [Table 3B].

The comparative assessment of relative risks for EST and HRV for the detection of myocardial ischemia, as defined by a positive MPI, is presented in Table 4. The likelihood of a positive EST to detect myocardial ischemia was 3.5-fold compared

Table 3. Diagnostic parameters of new HRV algorithm and standard EST

A. Total study population

	EST	HRV
Sensitivity	53%	85%
Specificity	85%	86%
PPV	42%	50%
NPV	90%	97%
Accuracy	80%	85%

B. Subjects ≥ 65 years of age

	EST	HRV
Sensitivity	50%	100%
Specificity	84%	89%
PPV	33%	57%
NPV	91%	100%
Accuracy	79%	90%

HRV = heart rate variability, EST = exercise stress testing, PPV = positive predictive value, NPV = negative predictive value

Table 4. Comparison of the relative risk for myocardial ischemia of a positive test result

Test	Relative risk for myocardial ischemia*	95% CI	*P* value
HRV (positive vs. negative)	16.8	4–71.4	< 0.001
EST (positive vs. negative)	3.48	1.34–9.00	0.018
HRV positive vs. EST positive	1.42	0.66–3.1	0.52

* As evident by myocardial perfusion imaging

HRV = heart rate variability, EST = exercise stress testing, CI = confidence interval

to nearly 17-fold by a positive HRV [Table 4]. This may reflect the relative power of HRV analysis over EST for the detection of myocardial ischemia in this population.

ANGIOGRAPHY AND FOLLOW-UP

During the 6 month follow-up, coronary angiography was performed in seven patients, of whom five were shown to have > 70% stenosis of a major epicardial artery. Four of the five patients with angiographically detected significant CAD also had a positive HRV result (sensitivity 80%). In addition, the two patients with angiographically normal coronary arteries also had a negative HRV test. During the follow-up period, no MACE were reported.

DISCUSSION

The initial diagnosis of myocardial ischemia is a challenging and complex task, often requiring both accurate clinical assessment and additional testing. Given the mediocre diagnostic parameters intrinsic to standard EST, additional costly procedures are often mandated.

In this pilot study we demonstrate that the new HRV algorithm, as utilized by the HeartTrends device, has greater sensitivity and NPV when compared with EST. Furthermore, the results of the HRV test were highly correlated with the presence (or lack) of significant CAD among patients who underwent coronary angiography during follow-up. These findings suggest that HRV testing may be used as an early screening tool for the detection of myocardial ischemia in at-risk subjects prior to proceeding to more complex and costly imaging modalities.

The Multipole Method employed in the new HRV algorithm was described previously by Olesen et al. [12]. This method is a density analysis which, in addition to the time-domain analysis, also includes the frequency-domain analysis. Of note, the analysis is susceptible to loss of density in areas where heart rate intervals would cluster in normal low risk subjects. The Dy/Dx analysis can be easily and automatically obtained from Holter monitoring; it was originally developed for risk stratification of malignant ventricular arrhythmias.

HRV has long been known to represent sympathetic and parasympathetic activity and balance [14]. The use of HRV was evaluated in various medical settings and found to have predictive value for all-cause mortality as well as cardiovascular mortality [10]. Hayano and collaborators [15] demonstrated the correlation of CAD severity with low HRV. However, their study was designed in a controlled setting and included subjects with known CAD. Liao et al. [9] and Dekker et al. [8] showed that low HRV is a predictor for the incidence of CAD-related clinical events in long-term follow-up. However, these studies had some conflicting results due to low risk ratios (mostly between 1.5 and 2) and some non-significant confidence intervals.

To our knowledge, the current study is the first to evaluate the utility of HRV analysis for the detection of ischemia in subjects without known CAD. We demonstrate higher risk ratios (relative risk 16.8) of the new HRV algorithm for the detection of myocardial ischemia [Table 4] as compared with previous studies [8,9]. Moreover, HRV analysis appears to have a better diagnostic yield when compared with EST.

STUDY LIMITATIONS

It should be noted that the comparison of relative risks of both tests did not show a significant difference as both tests had a significant positive relative risk for the detection of ischemia. We postulate that the results would become more significant in the final study which will be powered to show the differences between the tests. Furthermore, when examining the diagnostic parameters of the tests on subjects ≥ 65 years old, our results are even more pronounced.

Also noteworthy was the higher incidence of false-positive SPECT results with isolated inferior and apical defects, which in fact were not present in any of the study patients. Moreover, the present study does not aim to evaluate the diagnostic characteristics of SPECT. Our goal here was to compare the diagnostic characteristics (specificity, sensitivity, PPV, NPV, accuracy) of standard EST with the new HRV algorithm, using SPECT as the gold standard, and therefore the location of the ischemic region should not impact the analysis.

CONCLUSIONS

Our pilot data from the HeartTrends HRV Algorithm for the Diagnosis of Myocardial Ischemia suggest that a 1 hour HRV test can be used for early detection of myocardial ischemia in subjects without known CAD, demonstrating a higher sensitivity than conventional EST in this population. These promising preliminary findings need to be further validated following completion of enrollment in the trial.

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References

1. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 2010; 56: e50-103.
2. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and

the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012; 60: e44-164.

3. Xhyheri B, Manfrini O, Mazzolini M, Pizzi C, Bugiardini R. Heart rate variability today. *Prog Cardiovasc Dis* 2012; 55: 321-31.
4. Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996; 93: 1043-65.
5. Valkama JO, Huikuri HV, Koistinen J, Yli-Mäyry S, Juhani Airaksinen KE, Myerburg RJ. Relation between heart rate variability and spontaneous and induced ventricular arrhythmias in patients with coronary artery disease. *J Am Coll Cardiol* 1995; 25: 437-43.
6. Molgaard H, Sorensen KE, Bjerregaard P. Attenuated 24-h heart rate variability in apparently healthy subjects, subsequently suffering sudden cardiac death. *Clin Auton Res* 1991; 1: 233-7.
7. Bigger JT, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992; 85: 164-71.
8. Dekker JM, Crow RS, Folsom AR, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: The ARIC study. *Circulation* 2000; 102: 1239-44.
9. Liao D, Cai J, Rosamond WD, et al. Cardiac autonomic function and incident coronary heart disease: a population-based case-cohort study: The ARIC study. *Am J Epidemiol* 1997; 145: 696-706.
10. Tsuji H, Larson MG, Venditti FJ, et al. Impact of reduced heart rate variability on risk for cardiac events: the Framingham Heart Study. *Circulation* 1996; 94: 2850-5.
11. Huikuri HV, Jokinen V, Syvänne M, et al. Heart rate variability and progression of coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 1999; 19: 1979-85.
12. Olesen RM, Thomsen PE, Saermark K, et al. Statistical analysis of the DIAMOND MI study by the multipole method. *Physiol Meas* 2005; 26: 591-8.
13. Lewkowicz MLJ, Puzanov N, Shnerb N, Særmark K. Description of complex time series by multipoles. *Physica A* 2002; 311: 260-74.
14. Pomeranz B, Macaulay RJ, Caudill MA, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol Heart Circ Physiol* 1985; 248: H151-3.
15. Hayano J, Sakakibara Y, Yamada M, et al. Decreased magnitude of heart rate spectral components in coronary artery disease. Its relation to angiographic severity. *Circulation* 1990; 81: 1217-24.