Physician Factsheet

HeartTrends® - The Effortless Stress Test Alternative
Early cardiac screening for healthy individuals

Test description: HeartTrends is new a diagnostic test identifying myocardial ischemia at least as reliably as an exercise stress test in individuals without known coronary artery disease. This clinically proven test analyzes 20 minutes of heart data wearing a standard recorder without any stressful maneuvers or heart strain. It is intended for screening patients without known coronary artery disease (CAD), offering a new, *additional* "risk factor" for enhanced patient diagnosis.

HeartTrends score: HeartTrends reports a singular Multipole Parameter Weight (MPW) indicator value to evaluate your patient in conjunction with their clinical history, symptoms, risk factors, blood tests, along with the physician's clinical judgment. The indicator value may be used to supplement the diagnosis of significant coronary artery disease. HeartTrends does not offer a diagnostic opinion to the patient. That is the responsibility of the physician.

Indications: HeartTrends is indicated for the screening and evaluation of at-risk populations without known CAD. This includes symptomatic subjects exhibiting one or more cardiac risk factors such as: smoking, family history, dyslipidemia, diabetes mellitus, hypertension, obesity, age (men over 40, women over 50), or other known cardiovascular risk factors. Asymptomatic subjects may also be tested as part of their cardiovascular risk assessment as well as persons with non-cardiac Chest Pain Syndrome.

Contraindications: HeartTrends may be applied to any individual without adverse effects. See *Exclusion Criteria*.

Clinical exclusion criteria: Because the accuracy of HeartTrends relies on analysis of a normal heart rate unaffected by arrhythmias, *good clinical practice* recommends not applying the test on the following subjects: presence of a cardiac pacemaker or arrhythmias, established CAD, atrial fibrillation or flutter, diagnosis of an acute coronary syndrome or typical angina, clinical diagnosis of heart failure, moderate or severe pulmonary disease, acute myocarditis or any presence of cardiomyopathy, previous cardiac surgery, clinical depression, caffeine (e.g., Red Bull), known drug or alcohol dependence, presence of left bundle branch block, significant intra-ventricular conduction delay or significant (>1mm) ST deviations at baseline. Beta-blockers should be withheld for at least 24 hours prior to test. Athletes should use a treadmill to attain true target heart rate measurements.

Ideal testing locations: HeartTrends is ideally suited for screening or evaluation of individuals at such places as: Healthy Check-up facilities, Family Physician practices, Life Insurance companies, and more.

Minimum testing time: HeartTrends requires recording a minimum of 20 minutes of R-R intervals.

Disclosure: Similar to results of any other noninvasive test for the detection of ischemia, results should be interpreted within the clinical setting of the individual being tested. For example, low risk asymptomatic individuals with a positive HeartTrends result may be referred for more specific noninvasive evaluation and risk stratification, while high risk individuals with typical coronary symptoms should be referred for further coronary evaluation regardless of the HeartTrends results.

Medical Basis Underlying HeartTrends®

As evidenced by the Framingham Heart Study,[6] cardiologists know that heart rate variability (HRV) is a well-established marker of mortality and sudden death shown to be *attenuated* in patients with coronary artery disease (CAD) even at rest. Based on this clinical evidence, HeartTrends was developed to provide an innovative modality with a high sensitivity for detection of myocardial ischemia at rest.

The diagnostic yield of the HeartTrends test has now been established and reported in peer-reviewed journals.[9,11] Clinical studies show HeartTrends sensitivity (77%) compared with standard exercise stress testing relating both to subsequent coronary angiography. The negative predictive value for ruling out myocardial ischemia was 98%. While your actual measurements may differ – and may even be lower-- HeartTrends offers a new, *additional* "risk factor" for enhanced patient diagnosis.

The heart rate of individuals displays beat-to-beat variations that result from fluctuations in autonomic nervous system activity at the sinus node. Heart rate variability (HRV) decreases under situations of stress, either emotional or physical, whereas it increases with rest. HRV is considered a noninvasive marker of autonomic nervous system function.[1,2] Over the past decade, low HRV has been shown to have prognostic value in patients with myocardial infarction.[3] In the general population low HRV is associated with death[4,5] and, as evidenced in the Framingham Heart Study, with the risk of cardiac events.[6,7]

Several studies have shown that there is significant association between reduced HRV and incident coronary artery disease (CAD)[6,7] suggesting that the imbalance of sympathetic and parasympathetic activity is associated with increased risk of CAD. These findings provide support for the hypothesis that correlates reduced parasympathetic activity to newly diagnosed CAD in the general population.

Recent clinical trial data indicates that the unique Multipole Parameter Weight (MPW) analysis incorporated in the HeartTrends device[8] is a highly sensitive, noninvasive tool for the detection

1 **Heart rate variability: Standards of measurement, physiological interpretation, and clinical use**. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996; 93:1043-1065.

2 Hayano J, Sakakibara Y, Yamada A. **Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects**. Am J Cardiol. 1991; 67:199-204.

3 Bigger JT, et al. **The ability of several short term measures of RR variability to predict mortality after myocardial infarction**. Circulation. 1993; 88:927-934.

4 Tsuji H, Venditti FJ, et al. **Reduced heart rate variability and mortality risk in an elderly cohort: the Framingham Heart Study**. Circulation. 1994; 90:878-883.

5 Dekker JM, et al. **Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men: the Zutphen Study**. Am J Epidemiol. 1997; 145:899-908.

6 Tsuji H, et al. **Impact of reduced heart rate variability on risk for cardiac events: The Framingham Heart Study**. Circulation. 1996; 94:2850-2855.

7 Liao D, 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.

8 Rozen G, et al. **Multipole Analysis of Heart Rate Variability as a Predictor of Imminent Ventricular Arrhythmias in ICD Patients**. Pacing Clin. Electrophysiol. 2013; 36(11):1342-7.

of myocardial ischemia in subjects without known prior CAD, thereby providing an important diagnostic tool and new independent cardiac risk factor for this population.[9,10,11,12]

Why is HeartTrends MPW more accurate than other heart rate variability (HRV) analyses?

HeartTrends is unique in that it has been clinically tested and peer-reviewed showing earlier prognostic therapeutic benefit than previous HRV analyses. HeartTrends uses the *Non-linear Multipole Analysis* method for deriving information from *three* domains: time, frequency, and RR randomness as opposed to traditional one-dimensional HRV standard deviation. Notably, prior HRV algorithms were used mostly for risk stratification, while HeartTrends is the first to show that heart rate variability can be used to detect the presence of significant myocardial ischemia associated with significant coronary artery disease in individuals without known CAD.

In-depth, highly technical explanation

In clinical medicine, the dynamics of the beat-to-beat (RR) time series is commonly represented by a phase-space (or Poincaré) plot, where each RR interval is plotted against the previous one. The classification of the phase-space plot is traditionally performed by visual inspection and semi-quantitative analysis describing the features of the plot, as length or width, but that approach ignores the varying density of points leading to similar plots due to hearts with very different dynamics.

The Multipole MPW analysis is a relatively new way of investigating the Poincaré plot from complex time series. Interpret the Poincaré plot 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. As a result the *Multipole method derives information from both the time- and the frequency-domains as well as reflecting increased randomness in the RR interval time series*. Traditional HRV-measures derive only information from one of the two domains, which seems to be the reason that the Multipole Method has shown more prognostic power than previous suggested risk markers.

From the time series one may calculate the leading multipoles: quadrupoles, octoupoles, and the hexadecapoles, and from which the new HRV parameter MPW is derived. The Quadrupole (Qyy), for example, describes the overall distribution of data points in the Poincaré Plot (i.e., the shape of the plot). It was found to be a strong predictor of mortality in a population of post-myocardial infarction (MI) patients with both depressed and preserved LVEF.[13] It has sometimes been used in combination with MPW as a weighted multipole parameter shown to be a stronger predictor of mortality after MI than SDNN and the short-term scaling exponent Alpha-1.[14]

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9 Oieru D, et al. **A Novel Heart Rate Variability Algorithm for the Detection of Significant Coronary Artery Disease – Pilot Data from a Prospective Clinical Trial.** IMAJ 2015; 17:161-165.

10 Goldkorn I, et al. **Comparison of the Usefulness of Heart Rate Variability vs. Exercise Stress Testing for the Detection of Myocardial Ischemia in Patients Without Known Coronary Artery Disease**. Am. J. Cardiology 2015; 115:1518-1522.

11 **Clinical Trials.gov:** US National Institute of Health (www.clinicaltrials.gov -- search for 'HeartTrends').

12 Goldenberg I, et al. **Heart Rate Variability for Risk Assessment of Myocardial Ischemia in Patients Without Known Coronary Artery Disease: The HRV-DETECT Study.** J. Am. Heart Assoc. 2019; 8:e014540.

13 Joergensen RM, et al. **Prediction of ventricular tachycardia in ICD patients based on the multipole method.** European Heart Journal 2007; 28:414 (Abstract Supplement).

14 Olesen RM et al. **Statistical Analysis of Diamond MI Study by the Multipole Method.** Physiol. Meas. 2005; 26:591-598.

The varying density of data points implies that some other measures based on analysis of the plot incorrectly add the same significance to low populated areas of the plot as to higher populated areas. This is for example the case for SD12 which is the ratio between the length (SD2) and the width (SD1) of an imaginary ellipse fitted to the Poincaré Plot with the center in the average RR interval. In contrast to SD12, MPW is a relative density measure obtained from the plot with prevalence of the densest populated area

Joergensen et al. compared the Multipole method with the traditional HRV measures in the Nordic ICD study. Patients with AMI were screened with 2D Echocardiography and 24h Holter-recording 2-14 days post-MI. Reduced MPW predicted both all-cause, cardiovascular mortality and sudden cardiovascular death in univariate Cox proportional hazard analysis.

In multivariate analysis with correction for known risk factors, MPW continued to show independent predictive value with a hazard value of 2.1 (C.L. 1.1-4.2), whereas none of the traditional HRV measures reached statistical significance. The assumption is that, due to MPW obtaining information from time as well as frequency intervals combined with focusing on only dense populated areas of the recurrence plot, prognostic power for VT/VF arrhythmias is enhanced relative to traditional HRV-measures which do not receive information from the time domain.

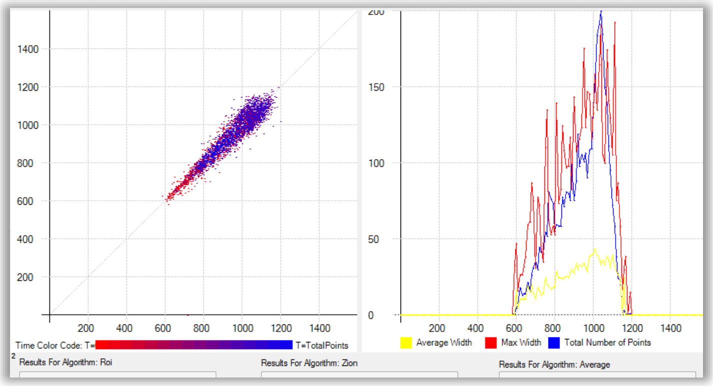


Figure 1: Typical MPW & Density Plots (for visual information purposes only)

How does Coronary Artery Calcium (CAC) Scoring compare with HeartTrends?

- HeartTrends is a tool that was developed for the noninvasive detection of myocardial ischemia. In contrast to HeartTrends, the **CAC score** is an independent **marker** of <u>future</u> risk for the development of coronary artery disease and cardiac events, but has no role in the assessment of current myocardial ischemia. In addition, CAC provides additional prognostic information to other cardiovascular risk **markers**. Accordingly, proposing a study comparing CAC scoring to HeartTrends is of little benefit since the two tools are designed for different measures

What is HeartTrends' uniqueness?

- Besides being more convenient and an order of magnitude less expensive, HeartTrends is a measurement of physiological characteristics functional indicator for the presence of ischemia, thereby facilitating immediate risk assessment beyond long-term prediction.

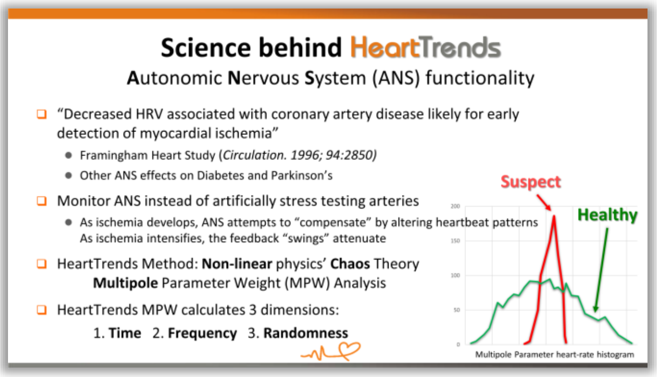
How does CT Angiography compare with HeartTrends?

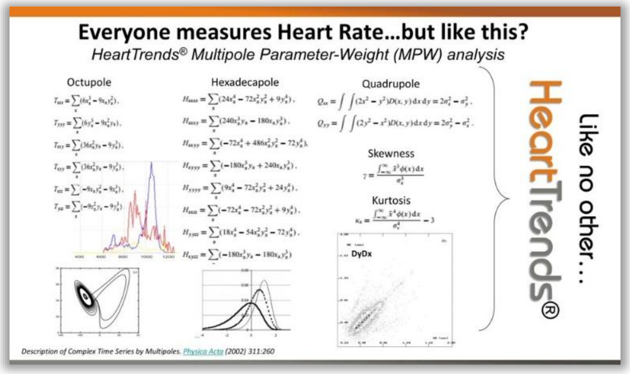
- In addition to higher cost and use of radiation, recent studies show that Coronary CT is over/under-estimating the presence of significant CAD[15].[16]. Current recommendations are to employ the test in specific populations of those intermediate symptoms and intermediate CAD risk. In contrast, HeartTrends provides noninvasive risk assessment in a wider populations with proven efficacy in several clinical trials. Thus, comparison of the two tests will be very limited to specific populations who are eligible for CT angiography, and this will limit the use of HeartTrends as a screening modality in the general population.

What noninvasive testing is recommended for *asymptomatic* individuals? Why should HeartTrends be part of that?

- Heart health testing for adults under 35 is vital at the stage in life of consolidating careers (becoming financially independent, seeking life insurance, or jobs which demand regular cardiologic evaluation to reduce the likelihood of sudden incapacitation such as pilots, divers, drivers, rescue workers). According to the recent Dallas Heart Study,[17] there are ***5 simple, noninvasive tests*** recommended for cardiovascular risk stratification in healthy, asymptomatic individuals. HeartTrends should be the 6th.
  1. **12-lead EKG** for information about hypertrophy (thickening of the heart muscle)
  2. **Coronary calcium scan**, to identify calcified plaque buildup in the coronary arteries
  3. **C-reactive protein** indicating inflammation
  4. **NT-proBNP** hormone blood test indicating stress on the heart
  5. **High-sensitivity troponin** (hS-cTnT) indicating damage to heart muscle and which detects small amounts of damage that can be detected in individuals without any symptoms or warning signs.
  6. **HeartTrends** for early ischemia detection using clinically proven heart rate analysis

Summary:





15 Stefanini et al, ***Coronary Computed Tomography Angiography Cannot Replace Invasive Angiography.*** Circulation 2015; 131:418)

16 "*Conversely, stable patients at low pretest probability (<15%) and asymptomatic patients* ***should not be evaluated by CCTA****, because the latter may lead to more frequent false-positive results compared with the pretest risk. In conclusion, CCTA does not compete but rather complements invasive CA when applied in appropriately selected patients.*" – Circulation. 2015

17 De Lemos, JA, et al, **Multimodality Strategy for Cardiovascular Risk Assessment: Performance in 2 Population-Based Cohorts.** Circulation 2017; 135:2119.