Combined assessment of heart rate recovery and T-wave alternans during routine exercise testing improves prediction of total and cardiovascular mortality: The Finnish Cardiovascular Study

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BACKGROUND Identification of individuals who are at risk for cardiovascular death remains a pressing public health challenge. Derangements in autonomic function acting upon an electrically unstable substrate are thought to be critical elements in triggering cardiovascular events.

OBJECTIVE The purpose of this study was to analyze heart rate recovery (HRR) in combination with T-wave alternans (TWA) to improve risk assessment.

METHODS The Finnish Cardiovascular Study (FINCAVAS) enrolled consecutive patients (N = 1,972 [1,254 men and 718 women], age 57 ± 13 years [mean ± SD]) with a clinically indicated exercise test using bicycle ergometer. TWA was analyzed continuously with the time-domain modified moving average method. Maximum TWA at heart rates <125 bpm was derived.

RESULTS During 48 ± 13 months of follow-up (mean ± SD), 116 patients died; 55 deaths were cardiovascular. In multivariable Cox analysis after adjustment for common coronary risk factors, high exercise-based TWA (≥60 μV) and low HRR (≤18 bpm) yielded relative risks for all-cause mortality of 5.0 (95% confidence 2.1–12.1, $P < .01$) and for cardiovascular mortality of 12.3 (95% confidence interval 4.3–35.3, $P < .01$). High recovery-based TWA (≥60 μV) and low HRR (≤18 bpm) yielded relative risks for all-cause death of 6.1 (95% confidence interval 2.8–13.2, $P < .01$) and for cardiovascular mortality of 8.0 (95% confidence interval 2.9–22.0, $P < .01$). Prediction by HRR and TWA, both singly and in combination, exceeded that of standard cardiovascular risk factors.

CONCLUSION Reduced HRR and heightened TWA powerfully predict risk for cardiovascular and all-cause death in a low-risk population. This novel approach could aid in screening of general populations during routine exercise protocols as well as improve insights into pathophysiology.

KEYWORDS Exercise test; Heart rate recovery; Mortality; Prognosis; T-wave alternans

ABBREVIATIONS **EF** = ejection fraction; **FINCAVAS** = Finnish Cardiovascular Study; **HRR** = heart rate recovery; **SCD** = sudden cardiac death; **TWA** = T-wave alternans

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Introduction

An abnormal autonomic nervous system response in terms of heart rate recovery (HRR) during or after clinical exercise testing predicts all-cause and cardiovascular mortality in a variety of relatively low-risk cohorts,[1–7] including ours.[8] The reduction in heart rate during the first 30 to 60 seconds after exercise appears to be caused principally by reactivation of the parasympathetic nervous system but subsequently by withdrawal of sympathetic tone.[9]

T-wave alternans (TWA) is an ECG phenomenon indicating an electrically unstable myocardial substrate.[10] This beat-to-beat alternation in the shape, amplitude, or timing of the ST segment and the T wave has been found to predict sudden cardiac death (SCD) and cardiovascular and total mortality independent of standard factors in relatively low-

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risk populations,[11,12] including ours[13,14] as well as in higher-risk groups.[15–19] We applied the time-domain modified moving average method,[20] which permits TWA measurement during routine symptom-limited exercise.[13,14]

HRR and TWA reflect different pathophysiologic mechanisms. The aims of this study were to determine whether the combined analysis of HRR and TWA during routine exercise testing enhances their predictive power for cardiovascular and all-cause mortality over independent assessment of either variable and to compare their predictive strength to that of other standard risk factors.

Methods

Study cohort

All consecutive patients who were referred for an exercise stress test at Tampere University Hospital between October 2001 and the end of 2004 and were willing to participate in The Finnish Cardiovascular Study (FINCAVAS)[21] were recruited. A total of 1,972 patients (1,254 men and 718 women) with technically successful exercise tests were enrolled in the study. A test was considered technically adequate if storing the hemodynamic data and continuous digital ECG signal was successful. Patients with atrial fibrillation (N = 31) were excluded because atrial fibrillation is an exclusion criterion in HRR studies.[2,3] The main indications for the exercise test were suspicion of coronary heart disease (frequency 45%); testing vulnerability to arrhythmia during exercise (22%); evaluation of work capacity (18%) and the adequacy of treatment of coronary heart disease (16%); and obtaining an exercise test profile prior to an invasive procedure (13%) or after a myocardial infarction (8%). Some patients had more than one indication. The study protocol was approved by the Ethics Committee of the Tampere University Hospital District, Finland, and all patients gave informed consent prior to the interview and measurements as stipulated in the Declaration of Helsinki.

Study flow

After written informed consent was obtained, the medical history of each patient was collected via a computer-based questionnaire form. The exercise test then was performed.

Exercise test protocol

The subject lay down in the supine position for 10 minutes, and the resting ECG was digitally recorded. The upright routine exercise test then was performed using a bicycle ergometer with electrical brakes. The lead system consisted of the Mason-Likar modification of the standard 12-lead system. The initial workload varied from 20 to 30 W, and the load was increased stepwise by 10 to 30 W every minute. Continuous ECGs were digitally recorded at 500 Hz using the CardioSoft exercise ECG system (version 4.14, GE Healthcare, Freiburg, Germany). During the test, heart rate and ST segment deviation were continuously registered on the ECG, while systolic arterial pressure and diastolic arterial pressure were measured with a brachial cuff every 2 minutes.

Measurement of HRR

HRR was determined as the difference between maximum heart rate during exercise minus heart rate during the first minute following cessation of exercise. We used the HRR cutpoint of $\leq$18 bpm, which has been suggested for exercise tests with an abrupt end.[22] Differences in recovery protocols have not negated the predictive strength of HRR.[22]

Measurement of TWA

Assessing the relationship between TWA and mortality is one of the original goals of FINCAVAS.[21] We used the time-domain, Food and Drug Administration–cleared modified moving average method because of its intrinsic flexibility and demonstrated capacity to measure TWA accurately under dynamic conditions, including changing heart rates, myocardial ischemia, exercise, activity, and behavioral stress.[11,13,14,16,19,23] In brief, the modified moving average algorithm reports TWA as the maximum difference in T-wave morphology between successive beats. It separates odd from even beats, calculates average morphologies of both the odd and even beat streams separately, and continuously updates the result by a weighting factor of 1/8 of the difference between the ongoing average and the new incoming beat. The method performs at a resolution of 1 μV and has undergone extensive validation.[20]

TWA values were calculated automatically and continuously by the released version of GE Healthcare's modified moving average algorithm during rest, exercise, and recovery using all standard precordial leads (V_1–V_6). Maximum TWA values at heart rates <125 bpm were derived. TWA values at higher heart rates were excluded because inaccuracies in TWA measurement can result at heart rates exceeding this range. Precordial leads have been shown to be optimum for TWA measurement.[24,25] The exercise-based TWA cutpoint of 60 μV, which yielded excellent Cox regression results in our previous study,[14] was used. Recovery-based TWA values were analyzed according to cutpoints 20 μV and 60 μV.[14,26] TWA cutpoint of 20 μV was chosen because it has shown the highest sensitivities compared with other cutpoints.[26]

Left ventricular ejection fraction

Measurement of left ventricular ejection fraction (EF) is not routine for patients referred for a clinical exercise test. However, EF was determined for 1,200 (55%) of the study patients using echocardiography or isotope techniques within 6 months of the exercise test. More than one fifth (N = 408 [21%]) of the patients were examined with coronary angiography.

Follow-up

Death certificates were received from the Causes of Death Register, maintained by Statistics Finland, in May 2007, a source that has been shown to be reliable.[27] The certificates included causes of death using the tenth revision of the International Classification of Diseases (ICD-10). The diagnosis numbers and certificate texts were used to classify the