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The Prognostic Power of the Clinical Exercise Test

ACADEMIC DISSERTATION
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1 LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following publications, which are referred to in the text by their Roman numerals:

I Leino J, Virtanen M, Kähönen M, Nikus K, Lehtimäki T, Kööbi T, Lehtinen R, Turjanmaa V, Viik J, Nieminen T (2010): Exercise-test-related heart rate variability and mortality. The Finnish Cardiovascular Study. International Journal of Cardiology 144(1):154-155.

II Nieminen T, Leino J, Maanoja J, Nikus K, Viik J, Lehtimäki T, Kööbi T, Lehtinen R, Niemelä K, Turjanmaa V, Kähönen M (2008): The prognostic value of hemodynamic parameters in the recovery phase of an exercise test. The Finnish Cardiovascular Study. Journal of Human Hypertension 22(8):537-543.

III Nieminen T, Verrier RL, Leino J, Nikus K, Lehtinen R, Lehtimäki T, Minkkinen M, Kööbi T, Turjanmaa V, Viik J, Kähönen M (2010): Atrioventricular conduction and cardiovascular mortality: Assessment of recovery PR interval is superior to pre-exercise measurement. Heart Rhythm 7(6):796-801.

IV Leino J, Minkkinen M, Nieminen T, Lehtimäki T, Viik J, Lehtinen R, Nikus K, Kööbi T, Turjanmaa V, Verrier RL and Kähönen M (2009): 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. Heart Rhythm 6(12):1765-1771.

V Leino J, Verrier RL, Minkkinen M, Lehtimäki T, Viik J, Lehtinen R, Nikus K, Kööbi T, Turjanmaa V, Kähönen M, Nieminen T (2011): Importance of regional specificity of T-wave alternans in assessing risk for cardiovascular mortality and sudden cardiac death during routine exercise testing. Heart Rhythm 8(3):385-90.

2 ABBREVIATIONS

ABCD Trial	the Alternans Before Cardioverter Defibrillation Trial
APD	action potential duration
AV	atrioventricular
BMI	body-mass index
cAMP	cyclic adenosine monophosphate
CHD	coronary heart disease
CI	confidence interval
DAP	diastolic arterial pressure
DI	diastolic interval
ECG	electrocardiography
EF	ejection fraction
FINCAVAS	Finnish Cardiovascular Study
HF	high frequency
HR	hazard ratio
HRV	heart rate variability
ICD	implantable cardioverter-defibrillator
ICD-10	tenth revision of the international classification of diseases
LF	low frequency
MET	metabolic equivalent of task
MI	myocardial infarction
MMA	Modified Moving Average
NN50	percentage of difference between N-N intervals that exceed 50ms
pcSD	standard deviation of Poincare plot
pNN50	proportion of NN50 by the total number of N-N intervals
RMSSD	square root of the mean squared differences in N-N intervals
RPP	rate-pressure product
RR	risk ratio
SAP	systolic arterial pressure

SCD	sudden cardiac death
SCD-HeFT	the Sudden Cardiac Death in Heart Failure Trial
SD	standard deviation
SDANN	standard deviation of the mean value of all 5-minute segments of N-N intervals
SDNN	standard deviation of N-N intervals
TWA	T-wave alternans
ULF	ultra low frequency
VLF	very low frequency

3 ABSTRACT

The more than 20,000 cardiovascular deaths per year in Finland have made the identification of individuals at risk for cardiovascular death a pressing public challenge. The clinical exercise test and exercise-based ST segment deviation are widely accepted methods for diagnosing coronary heart disease (CHD). However, beyond ST segment analysis, a clinical exercise test provides much more information when estimating a patient's risk for future cardiovascular events. As a part of the Finnish Cardiovascular Study (FINCAVAS), the present study was designed to investigate the prognostic power of single and multiple variables derived from a clinical exercise test.

The FINCAVAS population includes all patients scheduled for an exercise stress test due to clinical reasons using a bicycle ergometer at Tampere University Hospital and willing to participate in the study between October 2001 and December 2008. The follow-up lasted until September 2009. The final number of participants was 4,568 (1,765 women), but smaller study populations were created after shorter follow-up periods. In addition to repeated measurement of standard parameters such as heart rate and blood pressure, digital high-resolution ECG at 500Hz was recorded continuously during the entire exercise test, including the resting and recovery phases. T-wave alternans (TWA) was analyzed continuously with the time-domain Modified Moving Average (MMA) Method.

During the follow-up (55±26 months) 321 patients died, including 138 cardiovascular deaths and 63 sudden cardiac deaths (SCD). The prognostic power of exercise-test-based variables was determined by means of Cox multivariate regression analysis after adjustment for common coronary risk factors. Diminished heart rate variability (HRV) during the pre-exercise phase was associated with an increased risk of all-cause mortality according to several parameters (log VLF power, log LF power, log LF power n.u, log HF power%, pcSD2, log RMSSD), but during peak exercise HRV did not predict worse prognosis. At peak exercise TWA predicted worse prognosis both as a categorized variable (≥60 µV) and a continuous variable, especially in lead V5. During the recovery after exercise TWA ≥60 µV predicted worse prognosis. A prolonged PR interval and first-degree atrioventricular (AV) block during recovery were associated with increased risk of cardiovascular death. Abnormal heart rate recovery (≤18 bpm) after exercise was a significant predictor of all-cause death and cardiovascular mortality. The combination of abnormal heart rate recovery and

TWA ≥60 µV was a significant predictor of all-cause and cardiovascular mortality when TWA was measured either during peak exercise or during recovery. A decreased recovery of rate-pressure product (RPP) was significantly associated with an increased risk of SCD, cardiovascular mortality and all-cause death.

An exercise test utilising the bicycle ergometer has unused prognostic potential when evaluating patients' risk for future all-cause and cardiovascular mortality as well as for SCD. To enhance the prognostic power of the exercise test, the test should be considered as a continuum from rest via peak exercise to the recovery phase. Combinations of single parameters can increase the accuracy of the exercise test by reflecting cardiovascular health from several perspectives. However, more studies are needed before universal recommendations for exercise testing in risk stratification can be constructed.

4 TIIVISTELMÄ

Kliinistä rasituskoetta ja sen aikaisia ST-segmentin muutoksia käytetään yleisesti sepelvaltimotaudin diagnostiikassa. Diagnostiikan lisäksi kliinistä rasituskoetta voidaan käyttää myös arvioitaessa potilaan ennustetta sekä sydäntapahtumien riskiä tulevaisuudessa. Riskinarviointiin kliininen rasituskoe tarjoaa ST-segmentin muutosten lisäksi useita muita muuttujia. Osana Finnish Cardiovascular Study (FINCAVAS) -tutkimusta tämän väitöskirjatutkimuksen tarkoituksena oli tutkia sekä yksittäisten rasituskokeen aikaisten muuttujien että eri muuttujien yhdistelmien kykyä ennustaa tulevaisuuden kuolleisuutta.

FINCAVAS -tutkimusaineisto sisältää rasituskokeen aikaiset tiedot potilailta, jotka tulivat vuoden 2001 lokakuun ja vuoden 2008 joulukuun välisenä aikana kliiniseen rasituskokeeseen Tampereen Yliopistolliseen Sairaalaan ja olivat halukkaita osallistumaan tutkimukseen. Seuranta-aika oli syyskuun 2009 loppuun asti. Kokonaisuudessaan tutkimusaineisto sisältää tiedot 4568 potilaasta (1765 naista), mutta pienempiä aineistoja otettiin analysoitavaksi lyhyempien seuranta-aikojen jälkeen. Säännöllisen sykkeen ja verenpaineen mittaamisen lisäksi rekisteröitiin digitaalinen EKG 500Hz:n taajuudella koko kokeen ajan. T-aallon vuorottelu (T-wave alternans, TWA) analysoitiin Modified Moving Average (MMA) -metodilla.

Seuranta-aikana (55±26 kuukautta) kuoli 321 potilasta. Kuolemista 138 oli sydän- ja verisuoniperäisiä, joista edelleen 63 oli sydänäkkikuolemaa (sudden cardiac death, SCD). Rasituskokeen aikaisten muuttujien yhteys seuranta-ajan kuolleisuuteen määritettiin Coxin monimuuttuja-analyysilla, jossa muina muuttujina käytettiin tunnettuja sydän- ja verisuonitautien riskitekijöitä. Rasitusta edeltävän lepovaiheen aikana vaimentunut sydämen sykevaihtelu (heart rate variability, HRV) oli yhteydessä huonoon ennusteeseen usean muuttujan osalta (log VLF power, log LF power, log LF power n.u, log HF power%, pcSD2, log RMSSD). Maksimirasituksen aikainen HRV ei ennustanut kuolleisuutta. Maksimirasituksen aikainen TWA oli yhteydessä kuolleisuuteen sekä luokiteltuna (≥60 µV) että jatkuvana muuttujana, erityisesti kytkennässä V5. Rasituksen jälkeisen palautumisvaiheen aikana TWA ≥60 µV oli yhteydessä huonoon ennusteeseen. Myös pidentynyt PR-intervalli sekä ensimmäisen asteen eteiskammiokatkos (AV-katkos) ennustivat sydän- ja verisuoniperäistä kuolleisuutta rasituksen jälkeisen palautumisvaiheen aikana. Hidastunut sykkeen palautuminen (≤18 bpm) rasituksen jälkeen oli yhteydessä niin kokonaiskuolleisuuteen

kuin sydän- ja verisuoniperäiseen kuolleisuuteenkin. Poikkeuksellisen suuri TWA (≥60 µV) yhdistettynä hidastuneeseen sydämen sykkeen palautumiseen oli yhteydessä huonoon ennusteeseen, kun TWA oli määritetty joko rasituksen tai palautumisvaiheen aikana. Hidastunut syke-paine-tulon (rate-pressure product, RPP) palautuminen rasituksen jälkeen ennusti merkitsevästi kaikkia kolmea kuoleman luokkaa.

Kliininen rasituskoe tarjoaa merkittävästi tietoa riskinarviointiin. Rasituskoe tulisi nähdä kokonaisuutena, johon kuuluvat lepovaihe, rasitus sekä rasituksen jälkeinen palautumisvaihe. Yhdistämällä yksittäisiä muuttujia voidaan rasituskokeen ennustearvoa lisätä ja samalla vähentää virheellisiä riskiarvioita. Kuitenkin tarvitaan vielä uusia ja laajempia tutkimuksia suurilla potilasaineistoilla, ennen kuin voidaan tehdä yleisiä suosituksia rasituskokeen käytöstä riskinarvioinnissa.

5 INTRODUCTION

In 2008, there were over 20,000 cardiovascular deaths in Finland, with 58% of them attributed to CHD. (Laatikainen et al. 2005, http://www.stat.fi/til/ksyyt/tau.html, referred 25.9.2010). Besides CHD, several other causes can lead to cardiac death as well, including structural abnormalities of the heart, inherited arrhythmia syndromes, hypertrophic and dilated cardiomyopathy, various valvular diseases, and acute illnesses such as myocarditis. SCD is usually defined as a natural death due to cardiac causes, heralded by an abrupt loss of consciousness within an hour of the onset of acute symptoms. If the death is unwitnessed and the victim is known to have been alive and functioning normally prior to being discovered, the time limit has been settled as 24 hours. Pre-existing heart disease may or may not have been previously diagnosed, but the time and mode of SCD are unexpected. (Priori and Zipes 2006.) Despite the fact that many patients have anatomic and functional cardiac substrates that predispose them to developing ventricular arrhythmias, only a small percentage of these patients will face SCD or cardiac death. In addition to the underlying arrhythmia mechanisms, a chain of events leading to SCD usually requires a transient event that perturbs the physiological balance of the cardiovascular system. Because of this complex and diverse background of cardiac death, identifying patients at high risk for SCD or cardiac death due to other causes has been a challenge. The assessment of conventional risk factor burden is necessary but may not accurately estimate the risk of future cardiovascular events. (Brindle et al. 2006.) Therefore, there is a need for easily available non-invasive methods to detect individuals at high risk for future cardiovascular events and who would benefit the most from preventive measures. (Laukkanen 2005.)

Exercise is the most common form of physiologic stress for the body and requires a controlled adaptation of the cardiovascular system to various physiological conditions between rest and maximal exercise. Exercise can elicit such cardiovascular abnormalities that are not evident at rest. During the clinical exercise test, these changes in the cardiovascular system are measured under rigorously controlled and reproducible conditions. Previously, the main focus in exercise testing has been on electrocardiogram (ECG) recordings and chest pain during the exercise for screening CHD and evaluating its severity in a medium-risk population. The clinical usefulness of the exercise test as a diagnostic tool has been limited, however, by deficient sensitivity of visual ST

segment analysis but also by false positive outcomes. (Froelicher et al. 1998, Fowler-Brown et al. 2004, Kligfield and Lauer 2006.) Therefore, increased attention has been focused on the exercise test as a prognostic modality. The ST segment has proven to be a relatively minor predictor of risk, but beyond ST segment analysis, a modern exercise test provides several indices that are strong predictors of cardiovascular outcomes such as blood pressure, heart rate and exercise capacity. TWA is a relatively new variable, reflecting repolarisation abnormalities in the heart, and its prognostic power in risk stratification has been under thorough investigation during recent years. The method is yet to spread to wide clinical use. Because the factors leading to a cardiac death are complex, a single test is unlikely to predict the risk reliably. In improving the prediction of cardiovascular events, multiple variables have been shown to perform better than single variables. (Redwood et al. 1997.)

An exercise test is inexpensive, it is performed in most cases without the presence of a cardiologist, and it offers the highest predictive accuracy of any of the non-invasive tests for CHD. (Ashley et al. 2000.) Identifying high-risk patients should lead to aggressive prevention and treatment with optimized drug or revascularization therapy, and the patients who are at high risk of ventricular fibrillation or ventricular tachycardia should be considered as to whether they would benefit from an implantable cardioverter-defibrillator (ICD) to prevent potentially fatal tachyarrhythmias. Lower-risk patients should be guided with primary prevention methods. The present study was designed to investigate and identify those single and multiple variables derived from an exercise test that can be used in clinical risk stratification for future mortality.

6 BACKGROUND

6.1 Clinical exercise test

6.1.1 History

In 1908 William Einthoven documented ST segment changes in the ECG during exercise, but it was not until 1932 when Goldhammer and Scherf proposed ECG during exercise as a diagnostic tool for angina pectoris. (Ashley et al. 2000.) At the same time, A. M. Master presented the first applications of the exercise test for diagnosing symptomless patients who were suspected to have CHD. Master developed a two-step exercise test which was first used as a means of estimating cardiovascular function by determining the response of the blood pressure and heart rate to a standardized form of exertion by using trips up and down nine-inch steps. (Wener et al. 1953.) In the 1940s Master included ECG in the exercise test to obtain objective evidence of the presence of ischemia. (Wener et al. 1953.) In the single two-step exercise test, the workload of the heart was increased by a standard amount of work in 1.5 minutes. In the patients who were suspected of having CHD, the work imposed upon the heart was found to be insufficient to produce the ECG changes characteristic of coronary insufficiency. The double two-step test was introduced for those patients whose single two-step test was normal. In the double two-step test the patient performed twice the amount of work in twice as long a time as in the single test. (Wener et al. 1953.) The first criteria for positive exercise testing were a depression of the RS-T segment of more than 0.5 mm in any lead with or without flattening, or the inversion of a previously upright T-wave, even though these criteria led to 16–39% of the false-positive and 12–49% of the false-negative results. (Thomas 1951, Davis et al. 1953, Friedberg et al. 1962.)

Master's two-step test was in clinical use for many decades, although it provided little information about the patient's physical working capacity. During the 1960s multi-stage tests were designed to satisfy both of the requirements; provoking ECG abnormalities and other symptoms and signs of CHD, as well as providing quantitative information of the patient's physical working capacity. Treadmill and bicycle ergometer tests were performed in parallel with the Master two-step test because of their better ability to provide information about patients' physical working capacity.

At the time, a large number of different stress protocols were used, including continuous tests with stepwise load increment every one to three minutes; continuous tests with an initial rapid increase in work load and subsequent adjustment of the workload level to reach a predetermined heart rate which was then maintained for two to three minutes; as well as five to six minutes of exercise at each level in a series of progressively heavier workloads interspersed with rest periods. (Blomqvist 1971.) In 1967 Mason and Likar introduced a multiple lead system for exercise ECG to decrease the distortion of the ECG signal due to muscular activity, respiration and electrode artefacts. In the Mason-Likar modification, the ECG limb leads of the arms and legs are placed on the shoulders and on the hip. (Mason et al. 1967.)

6.1.2 Methods

Today, an exercise test is usually performed as a treadmill or bicycle test. Walking on a treadmill provides a greater diagnostic ability to detect CHD than cycling. (Hambrecht et al. 1992.) However, it is more expensive, requires more space in the testing room, and might be inappropriate for those patients who are severely obese or have problems with extended periods of walking (Lear et al. 1999). In the United States the treadmill test according to Bruce's protocol is the preferred modality for exercise (Palatini 2008). The Bruce's protocol begins with the treadmill set to a low speed and a 10% incline, with an increase in the speed and incline every three minutes. The test continues for a maximum of 27 minutes, or until the patient stops or develops signs or symptoms of ischemia or arrhythmias. (Miller 2008.) Despite the wide use of the Bruce's protocol, there are disadvantages, such as too large or rapid work-rate increments lowering the sensitivity for detecting CHD, a tendency to overestimate exercise capacity, and poor reliability in testing the effects of therapy (Ashley et al. 2000). In addition, unfit patients may not be able to complete even the first stage, corresponding to 5 metabolic equivalents of task (MET), in the Bruce's protocol. An alternative to the Bruce's protocol is ramp testing where the patient is exercising from rest to maximum exercise through a linear increase in workload over approximately 10 minutes. Focusing on total workload rather than on exercise time, and avoidance of fatigue are the benefits of this protocol.

In Finland exercise tests are mainly performed by bicycle ergometer (Table 1). Usually, the exercise test begins with the workload of 25–50 W, which is then increased every three minutes by 25–50 W. The exercise protocol varies between hospitals, depending on the indication for the exercise test and the adopted practice. A bicycle exercise test produces lower peak oxygen uptake in comparison to a treadmill test, because untrained subjects usually terminate the bicycle exercise at a

peak work rate that is 10–20% lower due to leg muscle fatigue. (Hambrecht et al. 1992.) Heart rate increase as a response to exercise is significantly higher in treadmill exercise than in bicycle exercise, and the drop in heart rate after the exercise is significantly lower in treadmill than in bicycle exercise. In addition, abnormal responses to exercise are more frequent in treadmill exercise than in bicycle exercise. (Rahimi et al. 2006.) The maximal heart rate for ruling out CHD should be at least 90% of the age-related maximum heart rate during the exercise test to avoid false-negative test results due to a too low level of exercise. The advantages of using bicycle exercise as a test mode are the fact that the population is, particularly in Europe, quite familiar with the bicycle, in addition to lower costs, better quality of ECG tracings and higher accuracy of blood pressure measurements due to reduced upper body movement. (Rahimi et al. 2006.) The comparisons between treadmill and bicycle exercise have shown that these tests are, in fact, testing different stressors leading to different haemodynamic and clinical responses (Hambrecht et al. 1992, Klein et al. 1994). Therefore, the results of treadmill and bicycle exercise tests may not be intercomparable.

The patient's symptoms are controlled for the entire duration of the exercise test. In addition to the symptoms, numerous ECG-based and haemodynamic variables could be measured. The ECG-based variables include all variables that are measured from normal resting ECG and the changes in those variables between rest and exercise, with the ST segment as an example. The haemodynamic variables include heart rate, heart rate response to and recovery after exercise as well as blood pressure. The mechanical function and local hypokinesias of the heart muscle can be estimated using echocardiography before and after the exercise test. Maximal working capacity and the duration of the test describe the patient's general fitness and, on occasion, also the co-operation between the tester and testee. An ortostatic test could be performed before exercise. During the ortostatic test, ECG and haemodynamic variables, such as heart rate and blood pressure, are measured at rest and during 3–8 minutes of standing.

Roughly 20–40% of patients with suspected CHD are unable to perform the maximal exercise test due to orthopaedic, vascular or pulmonary disease, or poor physical condition or motivation (Sovijärvi et al. 2003). If the clinical exercise test cannot be performed, the pharmacologic stress test combined with isotope perfusion imaging is a possible alternative stress method. Other suggested alternative test methods, although rarely used, are arm ergometry, inotropic stimulation, handgrip test, right atrial pacing and a cold pressure test (Niemeyer et al. 1992, Sovijärvi et al. 2003).

Table 1. Exercise test in Finland.

Rest **10 min**	**(Ortostatic test)** **3-8 min**	**Exercise** **Usually 3 min steps**	**Recovery** **5-10 min**
ECG	ECG	ECG	ECG
Heart rate	Heart rate	Heart rate	Heart rate
Blood pressure	Blood pressure	Blood pressure	Blood pressure
Breathing frequency	Breathing frequency	Breathing frequency	Breathing frequency
$Sa0_2$	$Sa0_2$	$Sa0_2$	$Sa0_2$
PEF/FEV1		Subjective feeling of exertion	PEF/FEV1

ECG= electrocardiography; FEV= forced expiratory volume; PEF= peak expiratory flow; $Sa0_2$= oxygen saturation.

6.1.3 Exercise test a s a diagnostic tool for coronary heart disease

Because only a limited proportion of patients undergo coronary angiography after exercise testing, the diagnostic accuracy of the exercise test is difficult to determine. In a large meta-analysis the sensitivities of the exercise test varied from 23% to 100%, with a mean of 68%, while the specificities varied from 17% to 100%, with a mean of 77% (Gianrossi et al. 1989, Gibbons et al. 1997). However, a marked work-up or verification bias existed in the majority of the studies (Gibbons et al. 1997). In the study where work-up bias was avoided by having patients agree to undergo both coronary angiography and an exercise test, the approximate sensitivity of 1mm ST segment depression was 33–50%, with a specificity of 84–96% (Morise and Diamond 1995). In the meta-analysis, the sensitivity of the exercise test in diagnosing CHD was found to be significantly decreased when equivocal tests were considered normal and when the exercise test was compared to other tests (publication bias; Gibbons et al. 1997).

When the exercise test is used as a purely diagnostic tool, a positive exercise test result is much more likely to be false-positive than true-positive for asymptomatic subjects, which may lead to unnecessary testing, overtreatment and labelling (Fowler-Brown et al. 2004). According to Bayes' theorem, the probability of a patient having CHD after a test is the product of the CHD probability before the test and the probability that the test provided a true result. If the pre-test possibility for CHD is low, an exercise test is not recommended for detecting underlying CHD because of the high occurrence of false-positives test results. In contrast to this, in screening higher-risk groups, such as persons with one or more risk factors for CHD, an exercise test will probably perform better. (Fowler-Brown et al. 2004.) However, typical or definite angina makes the pre-test probability of disease so high that the test result does not change the probability dramatically. If the

pre-test possibility for CHD is >75%, guidelines suggest proceeding directly with coronary angiography. (Gibbons et al. 2003.) For diagnostic purposes, an exercise stress test is most valuable in the intermediate pre-test probability category, because the test result has the largest potential effect on diagnostic outcome.

6.1.4 Exercise test as a prognostic tool for cardiovascular events

Although the diagnostic accuracy of the exercise test depends greatly on the prevalence of CHD in the population studied, exercise testing has been suggested to be valuable and less dependent on the patient's pre-test possibility for the purpose of risk stratification (Lauer 2007, Gibbons 2008). The results regarding the prognostic accuracy of ST segment deviation have demonstrated only limited predictive utility for this purpose (Gordon et al. 1986, Rautaharju et al. 1986, Okin et al. 1991, Okin et al. 1996). The limited sensitivity of ST segment deviation has been attributed to the pathophysiology behind the cardiac events. Acute cardiac events frequently occur secondarily to a rapid transformation of an atherosclerotic lesion, such as plaque rupture or thrombosis. The risk of plaque disruption may not be related to the pre-existing severity of coronary artery stenosis, which is detected in an exercise stress test. (Coplan and Fuster 1990.) Symptomatic obstructive plaques that typically result in exercise-mediated ischaemia may be less relevant with regard to infarction and SCD than less obstructive unstable plaques (Libby and Theroux 2005).

Heart-rate-adjusted indexes of ST segment deviation, such as the ST/HR index and the ST/HR slope, have been developed to improve the performance of the exercise ECG. Other variables received during the exercise test – such as exercise hypotension or hypertension, chronotropic incompetence and heart rate recovery – also carry prognostic value. (Gibbons et al. 2000, Lauer et al. 2005, Miller 2008, Laukkanen et al. 2009, Scott 2009.) One of the strongest prognostic markers identified in exercise testing is maximum exercise capacity, which is influenced by the extent of resting left ventricular dysfunction and the amount of further left ventricular dysfunction induced by exercise. Several exercise parameters are used to reflect exercise capacity, including exercise duration, maximum MET level achieved and maximum workload achieved. Maximum heart rate, blood pressure response to exercise as well as the combination of heart rate and systolic arterial pressure (SAP), namely double product or RPP, are other markers used in exercise-test-based risk stratification. (Gibbons et al. 1997.)

Several studies have attempted to determine exercise test scores that incorporate clinical and demographic risk factors not based on the exercise test itself. An example of such is the Duke

Treadmill Score, adding exercise duration and the presence and test-limiting severity of angina to ST segment depression, and the method is well-validated and clinically useful for risk assessment in younger (<75 years) patients with either established or suspected CHD for whom the desirability of additional invasive testing must be determined (Mark et al. 1991, Kwok et al. 2002). In asymptomatic women, however, the predictive value of the Duke Treadmill Score has been stated to be entirely due to the exercise capacity component of the score, because exercise time is part of the score and essentially reflects exercise capacity (Gulati et al. 2005).

6.2 Haemodynamics during exercise test and prognosis

6.2.1 Overview of the autonomic nervous system

The autonomic nervous system is a part of the peripheral nervous system that functions to regulate the processes needed for the maintenance of body homeostasis. Its effects include controlling heart rate and contraction of the heart, the constriction and dilation of blood vessels, the contraction and relaxation of smooth muscle in various organs, and glandular secretion, all independently of voluntary control. (Freeman et al. 2006.) The autonomic nervous system consists of three parts: the sympathetic and parasympathetic divisions as well as the enteric nervous system. These three parts of the autonomic nervous system function between the central nervous system and peripheral organs, controllig each other via a feedback system. The sympathetic and parasympathetic nerve fibres mainly secrete one of two synaptic transmitter substances, acetylcholine by cholinergic nerve endings or noradrenalin by adrenergic nerve endings. The sympathetic nervous system has synapses in peripheral ganglias which constitute paravertebral sympathetic chains to both sides of the vertebral column. Parasympathetic ganglias are located in the wall of the organ that is to be controlled. The enteric nervous system controls the gastrointestinal system. It consists of the myenteric and submucous plexus, both of which are embedded in the wall of the digestive tract and extend from the oesophagus to the anus. The enteric nervous system can function on its own, but stimulation of the sympathetic or parasympathetic nervous system can further activate or inhibit gastrointestinal functions, because both the myenteric and the submucosal plexuses connect with the sympathetic and parasympathetic nerve fibres.

6.2.1.1 Parasympathetic nervous system

All parasympathetic preganglionic neurons are cholinergic neurons with nicotinic acetylcholine receptors, while most of the parasympathetic postganglionic neurons are cholinergic neurons with muscarinic receptors. The cholinergic nerve endings contain high concentrations of acetylcholinesterase, and therefore the transmitter acetylcholine does not diffuse into the bloodstream, making the cholinergic effects discrete and very short-lived. (Levy 1997.) Because of the very short duration of action, the swift and accurate regulation by the parasympathetic nervous system is possible, enabling, for example, beat-to-beat regulation of heart rate (Levy 1971). The main effects of acetylcholine are vasodilatation in essentially all vascular beds, negative chronotrophy, deceleration in conduction velocity, or negative dromotrophy in the sinoatrial node, AV node and the His-Purkinje system, and negative inotrophy especially in atrial muscle. (Higgins et al. 1973, Kent and Cooper 1974, Feigl 1998, Brodde and Michel 1999.)

6.2.1.2 Sympathetic nervous system

At exercise the sympathetic nervous system prepares the body for activity, constituting a major mediator of the fight or flight response. Preganglionic neurons are cholinergic also in the sympathetic nervous system, while postganglionic neurons are adrenergic. Adrenergic activation increases the heart rate, blood pressure and cardiac output, and dilates large muscular arteries and bronchioles. (Curtis and O'Keefe 2002.) Noradrenalin is synthesized at adrenal medulla where approximately 80% of the noradrenalin is methylated to form adrenaline. There are two types of adrenergic receptors: α and β receptors. Noradrenalin mainly excites α receptors, causing the constriction of essentially all the blood vessels of the body, increased activity of heart, the inhibition of the gastrointestinal tract, and so forth. Adrenaline excites both α and β receptors approximately equally, having greater effect on cardiac stimulation and lesser effect on blood vessels in muscles than noradrenalin. Secreted noradrenalin and adrenaline are removed from the secretory site in three ways: reuptake into adrenergic nerve endings, diffusion into blood and other bodily fluids, and destruction by tissue enzymes. Noradrenalin and adrenaline secreted directly into the tissue remain active for a few seconds, while the activity can last from one to several minutes when secreted into the blood. From the blood noradrenalin and adrenaline diffuse into tissue where they are destroyed by catechol-O-methyl transferase occurring mainly in the liver. Chronic sympathetic hyperactivity is common in the conditions that require increased vascular tone and it leads to an increase in the

cardiovascular workload. It is one of the factors predisposing to endothelial dysfunction, coronary spasm, left ventricular hypertrophy and serious arrhythmias. (Metra et al. 2000.)

6.2.1.3 Regulation of cardiovascular function by the autonomic nervous system

Cardiovascular autonomic reflexes help to control blood pressure and heart rate in particular. All blood vessels except for the capillaries, pre-capillary sphincters and most of the metarterioles are innervated by sympathetic nerves. The sympathetic stimulation of the small arteries and arterioles increases the resistance of the blood flow, decreasing the rate of blood flow into the tissues. In the large veins, sympathetic stimulation decreases the volume of the vessels, translocating blood into the heart and regulating heart's function as a pump. Cardiac sympathetic effects are mainly mediated by β receptors; most of the effects of α receptors are indirect. Sympathetic stimulation of the heart both increases the heart rate and enhances the strength of pumping. The parasympathetic nervous system plays a more minor role than the sympathetic one in regulating circulation. Its main effects are a decrease in heart rate and heart muscle contraction as mediated by the vagus nerve.

The principal relation between mean blood pressure, stroke volume and total peripheral resistance is parallel to Ohm's law (Form. 1):

$$\begin{aligned} \text{Blood pressure} &= \text{cardiac output} \cdot \text{total peripheral resistance} \\ &= \text{stroke volume} \cdot \text{heart rate} \cdot \text{total peripheral resistance} \end{aligned} \quad (1)$$

Long-term regulation of blood pressure mainly involves the regulation of extracellular fluid volume by the kidneys via the renin-angiotensin system. The most important factor in long-term regulation is the balance between intake and output of fluid and electrolytes. The main regulator of short-term regulation of arterial blood pressure is the baroreceptor reflex. In the aortic arch and internal carotid arteries are stretch receptors called baroreceptors. Baroreceptors transmit a signal of heightened arterial pressure to the vasomotor centre in the brain stem when they become stretched. The vasomotor centre starts to inhibit sympathetic impulses to the heart and blood vessels and to excite the vagal parasympathetic centre. The net effects are the vasodilatation of veins and arterioles as well as a decrease in heart rate and the strength of heart contraction, leading to a decrease in blood pressure. Heart rate, discussed more in the next section, is mainly determined by the balance between parasympathetic inhibitory influences and sympathetic excitatory actions on the rate of impulses discharged from the pacemaker cells comprising the sinoatrial node. The relationship

between vagal and adrenergic action is also dependent on the existing level of basal autonomic activity. (Mason 1968.) The stroke volume of the heart is determined by the degree of filling of the heart, and hence also the venous return according to Frank-Starling's law; the greater the volume of blood entering the heart during diastole, the greater the volume of blood ejected during systolic contraction. Total peripheral resistance is directly proportional to the length of the vessel and the viscosity of the blood, and inversely proportional to the radius to the fourth power. The resistance is controlled by vasoconstriction and vasodilatation, mediated mainly by the sympathetic nervous system.

6.2.2 Overview of hemodynamic parameters received from exercise test and prognosis

Impaired autonomic modulation has been shown to be a key factor in the development of a cardiac arrest (Exner 2009). Several haemodynamic measures received during the exercise test are independent predictors of adverse cardiovascular events. Heart rate during and after exercise as well as blood pressure and RPP are often quoted as markers reflecting sympathovagal balance. Chronotropic incompetence reflects the inability of heart rate to increase as a response to exercise. Whether these measures reflect a primary abnormality of the autonomic nervous system or a pathological end organ response to normal autonomic nervous system input has not been elucidated. (Freeman et al. 2006.)

6.2.3 Heart rate during and after exercise

6.2.3.1 Physiology behind heart rate regulation

Heart rate is regulated from the sinoatrial node by both intrinsic and extrinsic mechanisms. Intrinsic regulation establishes the diastolic depolarisation in the sinoatrial node regulated by voltage-sensitive pacemaker-currents, particularly the hyperpolarisation-activated "funny" current I_f, which is Na^+-K^+-current-regulated by cyclic adenosine monophosphate (cAMP). (DiFrancesco and Borer 2007, Verrier and Tan 2009, DiFrancesco 2010.) The name of the current is due to its atypical property of being an inward current slowly activating upon hyperpolarisation and causing the membrane potential to begin to depolarise spontaneously, thereby initiating the diastolic depolarisation. When at the end of a sinoatrial action potential, the membrane potential is at a very

low level, roughly -60 mV; the I_f current is then activated and responsible for initiating the diastolic depolarisation phase. After the membrane potential has reached approximately -50 mV, Ca^{++} channels also open, supplying the inward Ca^{++} current. The opening of these channels causes depolarisation, which continues until the action potential threshold level is reached, usually at between -40 and -30 mV. The other atypical features of I_f are its dual activation by voltage and internal cAMP, which binds directly to channel proteins and acts as a second messenger, and a very small single-channel conductance. (DiFrancesco 2006.) Sympathetic stimulation raises the level of cAMP molecules which bind to f channels and shift the I_f activation range to more positive voltages, leading to an increase in the current at diastolic voltages and, therefore, to an increase in the steepness of diastolic depolarisation and heart rate acceleration. Parasympathetic stimulation reduces cAMP and decreases the heart rate by the opposite action – that is, by shifting the I_f activation curve towards more negative voltages. Selective inhibition of the I_f current can be caused pharmacologically by "heart-rate-reducing" drugs, such as ivabradine, and it has therefore been suggested to offer a better prognosis in, for example, patients with CHD. (DiFrancesco 2006.) The intrinsic heart rate of healthy individuals is approximately 100 bpm as observed during complete autonomic blockade (Katona et al. 1982).

Extrinsic regulation consists of the influence of the sympathetic and the parasympathetic nervous system as well as circulating hormones and reflex regulation associated with cardiorespiratory and baroreceptor inputs (Verrier and Tan 2009). Sympathetic stimulation via noradrenalin alters membrane permeability to Na^+ and Ca^{++} ions causing more positive resting potential in the sinus node, thus accelerating the self-excitation. Increased permeability to Na^+ ions also leads to decreased conduction time in the AV node when the impulse is proceeding from the atria to the ventricle. Acetylcholine, as a transmitter of the parasympathetic nervous system, alters the membrane permeability to K^+ ions, allowing the rapid leakage of K^+ ions out of the conductive fibres, in addition to causing hyperpolarisation and reducing the self-excitation in the sinus node.

The main mechanisms for heart rate acceleration during exercise are a steepening of the slope of spontaneous diastolic depolarisation and a decrease in the resting potential as a result of a release of noradrenalin and adrenaline (Colucci et al. 1989, Verrier and Tan 2009). Even during peak high-intensity exercise, the parasympathetic system has a small, but significant effect on heart rate, indicating that parasympathetic withdrawal is not complete under such conditions (Kannankeril et al. 2004). In normal asymptomatic subjects, there is a rapid fall in heart rate during the first 30 seconds after exercise, followed by a shallower fall. An attenuated heart rate recovery immediately after exercise is thought to be a marker of reduced parasympathetic activity, with vagal activity via acetylcholine release from the efferent vagal nerve in particular. (Huang et al. 2005.)

One minute after the cessation of exercise the β-adrenergic effect of the sympathetic nervous system starts to withdraw. Interestingly, after both β-adrenergic and parasympathetic blocking, heart rate recovery prevails, indicating a non-autonomic component at play, although in a lesser role, in heart rate recovery. (Sundaram et al. 2008.)

6.2.3.2 Heart rate and mortality

A low resting heart rate is associated with high levels of parasympathetic nervous system tone, and it is typically seen in athletes (Lauer 2009). An elevated heart rate at rest is a risk factor for future cardiovascular disease as well as all-cause and cardiovascular mortality according to many epidemiological investigations (Dyer et al. 1980, Cook et al. 2006, Fox et al. 2007, Palatini 2007, Palatini 2009). In most epidemiologic studies, patients have been defined to be tachycardic if they have belonged to the top quintile of the heart rate distribution, which has been approximately 80–90 bpm (Palatini 1999). Increased resting heart rate is considered to be a sign of increased sympathetic tone, which in turn is associated with metabolic disorders such as increased glycaemia, triglycerides, body-mass index (BMI) and total cholesterol (Perret-Guillaume et al. 2009).

Maximal heart rate during exercise generally declines with age. Other known factors affecting maximal heart rate include the mode of exercise and general level of fitness. Vagal withdrawal can result in an increase of 30 to 50 bpm in heart rate, but further increases are thought to be due to sympathetic activation. Chronotropic incompetence refers to the inability of heart rate to increase appropriately during exercise and it is present in 11% to 26% of healthy middle-aged adults, but it has been associated with greater risk of adverse cardiac events in asymptomatic men and in symptomatic referral populations. (Lauer et al. 1996, Lauer et al. 1999, Curtis and O'Keefe 2002, Eldenhy et al. 2003, Jouven et al. 2005, Savonen et al. 2006, Savonen et al. 2008.) Abnormal chronotropic response has been hypothesized to be related to abnormal autonomic balance because of decreased sympathetic sensitivity of the sinus node, resulting from cardiac disease and compensatory parasympathetic hyperactivity due to inappropriate vagal activation during exercise (Colucci et al. 1989, Townend 2006). The association between chronotropic response during exercise and non-sudden death from myocardial infarction (MI) is low, indicating that this risk factor is directly associated with a particular susceptibility to cardiac arrhythmia and does not reflect the development of atherosclerosis (Jouven et al. 2005). For healthy persons with an abnormal heart rate profile during exercise, a possible therapeutic approach might be the correction of the autonomic imbalance, because autonomic imbalance precedes the symptoms of

cardiovascular disease and aid in the early identification of patients with increased risk for SCD (Jouven et al. 2005). However, chronotropic incompetence may also reflect the inability of end organs such as the heart to respond appropriately to normal autonomic nervous input.

Abnormal heart rate recovery after exercise has been studied among different patient populations, including heart failure patients (Imai et al. 1994, Sheppard et al. 2007), left ventricle dysfunction patients (Watanabe et al. 2001), CHD patients (Diaz et al. 2001), and the healthy population including important subgroups, namely the elderly, women, patients with a normal chronotropic response during exercise, and those taking β-blockers (Cole et al. 1999). An attenuated heart rate recovery after maximal as well as sub-maximal exercise has been shown to indicate worse prognosis (Cole et al. 1999, Cole et al. 2000), but for angiographic CHD, heart rate recovery is a poor diagnostic test with a sensitivity of only 31% and a specificity of 76% (Vivekananthan et al. 2003). However, heart rate recovery has proven to be more predictive in non-cardiovascular than cardiovascular mortality (Cole et al. 1999). Cardiac rehabilitation has improved heart rate recovery by reviving the parasympathetic activation (Oldbridge et al. 1988). If there is a cool-down period after exercise, 12 bpm is usually defined as an abnormal heart rate recovery one minute after exercise (Cole et al. 1999, Nishime et al. 2000). If the exercise test is stopped abruptly, a heart rate recovery of ≤18 bpm in the first minute after exercise is considered to be abnormal (Watanabe et al. 2001, Bilsel et al. 2006). Although heart rate recovery is usually defined one minute after the cessation of exercise, heart rate recovery at two minutes after exercise surpassed other time points in predicting of death, and the limit of 22 bpm at two minutes after exercise identified the high-risk group of patients (Shetler et al. 2001).

Of all the heart rate parameters measured during the exercise and recovery, the heart rate increase from resting level to peak exercise has been found to be the most powerful predictor of cardiovascular prognosis after adjustment for potential confounders during treadmill exercise testing (Leeper et al. 2007). Heart rate and heart rate recovery are simple and non-invasive methods for evaluating sympathovagal balance, in addition to being provably independent risk factors for cardiovascular deaths, but the association with cardiovascular death may also be secondary via other cardiovascular risk factors. As a limitation, heart rate only communicates the net effect of the autonomic inputs of the sinus node, providing no direct information regarding either sympathetic or parasympathetic input individually. (Lahiri et al. 2008.)

6.2.4 Blood pressure during and after exercise

6.2.4.1 Physiology behind blood pressure during exercise

In the beginning of exercise, sympathetic activity predominates over vagal tone, increasing heart rate and cardiac output. As a result of increased cardiac output, mean arterial pressure increases by approximately 40% with a progressive increase in SAP. (Myers 1994.) Diastolic arterial pressure (DAP) exhibits little or no change (<10 mmHg) during exercise because of peripheral vasodilatation (Kharabsheh et al. 2006). Dysfunction in endothelium-dependent vasodilatation also plays an important role in abnormal SAP increase during exercise (Chang et al. 2004). Abnormally low blood pressure during exercise is associated with severe CHD, reduced ejection fraction (EF), or both (Le et al. 2008). Compared to blood pressure measurements at rest, blood pressure recordings during exercise are less influenced by nervousness and external factors such as noise or talking (Lund-Johansen 2002). SAP recording during bicycle exercise is reasonably practicable by means of the cuff method, while DAP may be grossly over- or underestimated (Lund-Johansen 2002). The rise in SAP can exceed the normal level if there is decreased aortic distensibility resulting from aging or aortic atherosclerosis, or increased left ventricular mass amplifying the effect of increased sympathetic tone (Le et al. 2008). Increased arterial stiffness increases pulse wave velocity along the aorta during systole, and the velocity of the later-arriving reflected pulse wave from the periphery also increases. The accelerated velocity of the reflected pulse wave causes a reflected wave from peripheral reflecting sites to the heart during systole when the ventricle is still ejecting blood. This phenomenon can be expressed in absolute terms (augmented pressure) or as a percentage of pulse pressure (augmentation index). Increased augmented pressure and augmented index at rest have been previously associated with higher cardiovascular mortality, in most cases because of underlying CHD, but among the Framingham study population the augmentation index was not associated with the risk of cardiovascular events in models that included standard risk factors (Mitchell et al. 2010). The augmented systolic and pulse pressures, an effect that increases arterial wall stress, potentiates the development of atherosclerosis, elevates left ventricular afterload, and increases left ventricular mass and oxygen demand while decreasing stroke volume. Movement of the reflected wave from diastole to systole diminishes coronary perfusion pressure and has been shown to produce ischaemia in 29 dogs both with and without epicardial coronary stenoses. (Buckberg et al. 1972.) Because this wave reflection does not contribute positively to the ejection of blood, the effect of the extra workload is wasted energy (Peterson et al. 2003, Weber et al. 2004). During exercise the augmented pressure is reduced with the increasing intensity of

exercise, persisting for up to 60 minutes into recovery. This reduction could be due to altered heart rate or ventricular ejection characteristics, large artery stiffness or pulse wave velocity, or a change in the tone of muscular arteries influencing pressure wave reflection. (Munir et al. 2008.)

Upon recovery after exercise, SAP usually normalises quickly due to a reduction in sympathetic output and an increase in vagal tone, leading to a decrease in heart rate and peripheral resistance (Le et al. 2008). Diminished SAP recovery after exercise reflects the over-activity of the sympathetic nervous system and attenuated vagal reactivation (Laukkanen et al. 2004, Ushijima et al. 2009). Impaired chronotropic response in the later phase of exercise leads to diminished SAP recovery, reflecting the sympathetic hyperactivity which may suppress parasympathetic reactivation (Ushijima et al. 2009). Peripheral vasoconstriction may occur during exercise as a compensatory response to ischemic-induced left ventricular systolic dysfunction, and this compensatory vasoconstriction may well persist during the first few minutes of recovery, preventing normal SAP recovery (McHam et al. 1999). Catecholamine levels continue to increase during the first three minutes after the cessation of exercise, thus having an inverse correlation with the SAP level (Dimsdale et al. 1984). It is biologically plausible that without metabolic needs, the increasing level of catecholamines leads to SAP elevations beyond the normotensive range (Laukkanen et al. 2004). The catecholamine response could be a reflex effort to maintain SAP at a level set during the peak exercise, but this has not been verified. There is a relationship between attenuated heart rate recovery and noradrenalin desensitization (Ushijima et al. 2009). Under continuous sympathetic excitation, the sympathetic down-regulation is a possible cause for the desensitization to noradrenalin, and this may cause SAP to remain above normal until several hours post-exercise (Le et al. 2008, Ushijima et al. 2009). An attenuated decrease in SAP after exercise has also been suggested to be caused by structural changes such as poor arterial compliance together with underlying vascular smooth muscle hypertrophy and subclinical arteriosclerotic changes (Morrow et al. 1993). Nitroglycerin-induced vasodilatation of muscular arteries demonstrates that reduction in pressure wave reflection is an independent mechanism underlying exercise-induced changes in pulse waveform morphology. Reduced pressure augmentation after exercise could be one mechanism contributing to the phenomenon known as warm-up angina, where an initial period of exercise in patients with CHD limits subsequent angina. (Munir et al. 2008.)

6.2.4.2 Exercise blood pressure and mortality

Exercise hypotension is most frequently defined as a drop in exercise SAP below the resting value, or an initial increase followed by a drop of 20 mmHg or greater while exercising (Le et al. 2008). In the general population the prevalence of exercise hypotension is between 5% and 8% and among persons with known CHD the prevalence rises up to 8–10% (Le et al. 2008). Exercise hypotension reflects a failure of cardiac output to increase during exercise and it is associated with severe CHD, aortic stenosis or left ventricular systolic dysfunction – therefore it is also associated to an increased risk of death, especially when associated with a prior MI or exercise-induced ischemia (Dubach et al. 1988). However, the increased risk has not been observed in patients with no prior MI or ischemia during exercise testing (Dubach et al. 1988).

There is no widely accepted normal blood pressure response to exercise, making the estimation of exaggerated blood pressure response to exercise difficult (Le et al. 2008). In most cohort-based studies, the prevalence of exaggerated SAP, with varying definitions, during exercise has been shown to be 3–4%, with one in three subjects having normal resting values (Le et al. 2008). In the Framingham study population, an abnormal rise in SAP or DAP to a level greater than or equal to the 95^{th} percentiles of sex- and age-specified blood pressures in patients with a normal resting blood pressure predicted an increased risk for future sustained hypertension (Singh et al. 1999a). The same results were also seen in a Finnish population where patients with a SAP response to exercise of ≥30 mmHg or a DAP response of ≥15 mmHg were at a nearly four-fold risk of becoming hypertensive in comparison to the patients with lower blood pressure response to exercise (SAP response <10 mmHg, DAP response, <5 mmHg) (Everson et al. 1996). When the end point was cardiovascular or all-cause mortality, neither submaximal nor maximal blood pressure during exercise yielded additive prognostic information on blood pressure at rest in a study of 143 hypertensive men (Fagard et al. 1991). Resting blood pressure has been found to have a stronger association to cardiovascular death than maximal blood pressure during exercise (Weiss et al. 2010). On the contrary, exercise hypertension has been found an important independent risk factor for all-cause long-term mortality among patients with known or suspected peripheral artery disease (De Liefde II et al. 2008), but also among healthy patients (Allison et al. 1999). Some studies have stated that the ability of exercise blood pressure to predict mortality has been attenuated when blood pressure has been measured at maximum capacity, and therefore the early and steep rise in SAP during the exercise should be considered as a warning sign (Mundal et al. 1994, Laukkanen et al. 2006).

On the other hand, a higher SAP during exercise has been associated with lower rates of SCD (Irving et al. 1977), cardiovascular mortality (Morrow et al. 1993, Gupta et al. 2007) and all-cause mortality (Bouzas-Mosquera et al. 2010). Among chronic heart failure patients and those with a previous MI, low SAP response to exercise is a significant predictor of worse prognosis, because the SAP response reflects an increase in cardiac output (Hedberg et al. 2009, Nishiyama et al. 2010). A weaker SAP rise during exercise has also been suggested to be a result of a more powerful reduction in systemic vascular resistance (Hedberg et al. 2009). In a healthy population, a higher exercise blood pressure may indicate hypertension or prehypertension, instead of normal vascular function, and it is therefore associated with worse long-term prognosis. In a population with a high burden of heart disease, the highest-risk subjects with the most extensive cardiac disease may not be capable of generating pressure or workload to allow the manifestation of exercise systolic hypertension. By comparison, therefore, those with exercise hypertension have a better prognosis. (Smith et al. 2009.) The association between exercise blood pressure and worse prognosis is supposed to have a J curve shape (Le et al. 2008).

Abnormal SAP recovery is usually defined as a ratio of SAP after a certain time of recovery versus SAP during peak exercise or earlier during the recovery (Le et al. 2008). Abnormal SAP response to recovery has been demonstrated to be a significant prognostic factor for future hypertension (Singh et al. 1999a, Lund-Johansen 2002), CHD and cerebrovascular disease, as well as acute MI (McHam et al. 1999, Laukkanen et al. 2004, Yosefy et al. 2006), but contradictory results have also been reported (Ellis et al 2004). The differences in blood pressure during recovery from exercise between healthy people and patients with severe CHD have been thought to result from rapid amelioration of left ventricular asynergy, leading to an improvement in cardiac output as well as increased levels of circulating catecholamines, which in turn causes the increased peripheral vascular resistance (McHam et al. 1999).

Even though several investigations have published imposing results about the association between abnormal SAP during exercise and during recovery, among middle-aged adults participating in the Framingham Heart Study, DAP was a significant predictor of cardiovascular disease during exercise and recovery, while SAP was not (Lewis et al. 2008). As large-artery stiffness increases in elderly subjects, especially during CHD, SAP begins to rise and DAP fall, causing increments in pulse-pressure but no effect on mean arterial pressure. The fall in DAP in the elderly signals a preponderance of large artery stiffness as the cause of further rise in SAP. Franklin and colleagues showed that when assessed individually, increments in pulse-pressure at a fixed SAP were associated with a greater risk for CHD than were increments in SAP at a fixed pulse-pressure (1997). Based on these findings, the authors hypothesized that CHD risk is related more to the

pulsatile stress caused by large-artery stiffness during systole than to the steady-state stress due to small-vessel resistance during diastole. The same elevation in SAP does not lead to the same CHD risk; those with lower DAP, and therefore wider pulse-pressure, have greater CHD risk, possibly due to greater pulsatile stress. (Franklin et al. 1997) These facts about the decrease in DAP among clinical and subclinical CHD patients may explain the results from the Framingham Heart Study. In any case, the significance of DAP during the recovery was diminished when resting blood pressure was taken into account (Lewis et al. 2008).

In summary, in populations with a high risk of CHD, a relatively low SAP at peak exercise is independently associated with severe CHD and cardiovascular events. In contrast, despite strong evidence to the effect that exaggerated SAP among an apparently healthy population is associated with a risk of cardiovascular events, partially contradictory findings exist to confuse the issue (Le et al. 2008).

6.3 Prognostic ECG markers during exercise test

6.3.1 Overview of ECG parameters received from exercise test and prognosis

The most frequently used parameter for diagnostic estimation received from the exercise stress test is ST segment depression. However, exercise ECG offers a considerable amount of information beyond the ST segment. Various non-invasive tools for evaluating conduction abnormalities and vulnerability to arrhythmias are received during exercise testing. The number of leads showing changes in the ST segment as well as the duration of ST deviation into recovery after exercise have been demonstrated to associate with poor prognosis (Gibbons et al. 1997). Heart-rate-adjusted ST segment depression (ST/HR) analysis improves the prognostic capacity of standard exercise ECG (Elamin et al. 1980, Kligfield et al. 1987, Bigi et al. 2005). Analysis could be represented by the ST/HR index utilising only the information from the exercise phase or by ST/HR hysteresis which represents a heart-rate-corrected average difference in the ST segment depression between the recovery and the exercise phase of the exercise test (Lehtinen et al. 1997, Svart et al. 2010).

Ventricular premature beats occur in both healthy and unhealthy hearts. Premature ventricular complexes have been observed among heart failure–free patients during or after exercise in more than half of the individuals (Jouven et al. 2000, Dewey et al. 2008). During recovery the occurrence of frequent ventricular ectopy (ventricular premature beats ≥7/min) – including ventricular bigeminy, ventricular trigeminy, ventricular couplets, ventricular triplets, sustained or

nonsustained ventricular tachycardia, ventricular flutter, torsade de pointes, or ventricular fibrillation – has been stated to be strongly predictive of an increased risk of death from all causes, whereas the occurrence of frequent ventricular ectopy only during exercise is not connected with an increased risk of death (Frolkis et al. 2003). In suitable settings ventricular premature beats can reflect a damaged myocardium, constituting a marker of the presence of an arrhythmogenic substrate and thus acting as a trigger of ventricular tachycardia (Tapanainen 2003). During recovery after exercise, premature beats can reflect the attenuated vagal reactivation (Frolkis et al. 2003).

During the repolarisation, the myocardial cell transmembrane potential returns to its baseline level following a passing depolarising electrical impulse. Repolarisation takes place in wide areas simultaneously. (Tapanainen 2003.) The heterogeneity of repolarisation is present in various pathological cardiac disorders, creating a substrate for ventricular arrhythmias (Tapanainen 2003). The arrhythmogenic mechanism is probably due to the facilitation of re-entry (Spargias et al. 1999). The first variable representing the heterogeneity of cardiac repolarisation was QT dispersion, but later it was considered to be nothing more than an approximate and simplistic expression of repolarisation abnormality, and the reliability of both automatic and manual measurement of QT dispersion was low and significantly lower than that of the QT interval (Malik and Batchvarov 2000). Dynamic repolarisation measures, such as QT variability and TWA provide more information on risk than static measures, such as QT dispersion, because of the unpredictable nature of most cardiac arrests (Exner 2009). TWA, reflecting the ventricular repolarisation, is discussed more thoroughly later.

Other ECG markers that have been linked to poorer prognosis include HRV and PR interval. HRV is the parameter representing beat-to-beat alternation in heart rate, which reflects cardiovascular responses to autonomic activity. HRV is one of the investigated parameters in the present study and it is discussed more thoroughly in the next section. PR interval, representing atrium-ventricle conduction, is also discussed in more detail later.

6.3.2 Heart rate variability

6.3.2.1 Physiology behind heart rate variability

HRV, or differences in beat-to-beat interval (R-R interval) between successive heart rate cycles, is a tool for assessing cardiovascular responses to autonomic activity. The clinical relevance of HRV

was first appreciated in 1965 when Hon and Lee noted that foetal distress was preceded by alterations in interbeat intervals before any perceivable change occurred in heart rate itself. (Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology 1996). In 1981 the power spectral analysis of heart rate fluctuations was introduced for the quantitative evaluation of beat-to-beat cardiovascular control (Akselrod et al.). The clinical importance of HRV became appreciated in the late 1980s, when the relationship between HRV and cardiovascular mortality was discovered (Kleiger et al. 1987, Malik et al. 1989, Bigger et al. 1992).

HRV is predominantly dependent on extrinsic regulation of the heart rate, including respiration, baroreflexes and thermal regulation (Malpas 2002, Perini and Veicsteinas 2003). The degree of HRV provides information about the functioning of the nervous control on the heart rate and the ability of heart to respond, namely the balance between the sympathetic and parasympathetic nervous system (Acharya et al. 2006). The parasympathetic nervous system has the main response of high frequency (HF) HRV, while the sympathetic nervous system affects low frequency (LF) HRV, due to the physiological features of the autonomic nervous system described earlier (Malpas 2002, Acharya et al. 2006). Considering this, it is surprising that it has been found in many studies that HF-HRV increases gradually during exercise, whereas LF-HRV decreases during exercise (Dixon et al. 1992, Perini et al. 1993, Pichon et al. 2004). The results of a study on 1,297 male veterans who were exercise-tested at the Palo Alto Veterans' Affairs Hospital indicated that LF-HRV, namely normalized LF power, was greater in the two-minute period immediately after exercise than in the last two minutes during the exercise. At the same time, normalised HF power was found to be lower during the recovery than in the last two minutes of exercise. This supports the supposition that, in addition to sympathetic and parasympathetic function, there are additional mechanisms, such as baroreceptor function, accounting for HRV during exercise and HRV is probably best explained by the complex interplay of multiple inputs to the heart, rather than simply autonomic imbalance. (Freeman et al. 2006.)

6.3.2.2 Measurement of heart rate variability

Time domain analysis calculates a number of variables that describe beat-to-beat changes in heart rate. These changes include the standard deviation (SD) of all normal R-R intervals (N-N intervals) in the entire 24-hour ECG-recording (SDNN), the SD of the mean value of all five-minute segments of normal R-R intervals (SDANN) and the percentage of difference between adjacent normal R-R

intervals that exceed 50 ms (NN50) as well as the proportion derived by dividing NN50 by the total number of N-N intervals (pNN50) and the square root of the mean squared differences of successive N-N intervals (RMSSD). (Barron and Lesh 1996.) Other time domain measurements that can be used are variations in instantaneous heart rate secondary to respiration, tilt, the Valsalva manoeuvre, or phenylephrine infusion. All HRV variables are dependent on the length of the recording period, and therefore the recordings of different durations are not directly comparable.

Spectral analysis of HRV allows the assessment of frequency-specific fluctuations in heart rate behaviour and provides prognostic information beyond the time-domain measures (Bigger et al. 1993). In the spectral analysis, power spectral density of the R-R intervals is calculated and then analyzed by calculating powers and peak frequencies for different frequency bands. The HF (0.15-0.4 Hz) band is thought to represent the parasympathetic component of the autonomic nervous system. The LF (0.04-0.15 Hz) component is mediated by both the parasympathetic and the sympathetic nervous system and is influenced by the baroreceptor system. The very low frequency (VLF, 0.0033-0.04 Hz) and ultra low frequency (ULF <0.0033 Hz) bands are influenced by many factors, including thermoregulation and the renin-angiotensin system. (Barron and Lesh 1996.) The VLF peak is generally quoted in absolute units and as a percentage of total power (the total area under the HRV spectrum curve), whereas the LF and HF peaks are usually quoted in absolute units, as a percentage of total power, and in units that are normalized to total power (after subtracting the contribution of the VLF component). The Poincaré plot is a geometric method for dynamic analysis of HRV where each R-R interval is plotted as a function of the previous R-R interval. The SDs of the Poincare plots are referred to as pcSD1 and pcSD2, respectively. PcSD1 is related to the fast beat-to-beat variability in heart rate, while pcSD2 describes the longer-term variability. Measures derived from different frequency bands of heart period variability are especially attractive candidates for predictors of mortality after MI, because certain frequency bands of the heart period power spectrum have been associated with autonomic nervous system control of sinus node period. (Pomeranz et al. 1985, Pagani et al. 1986.) A recent study has shown that HRV measurements, particularly those in the frequency domain, may vary largely and unpredictably from day to day in the same subject, making the assessment difficult (Maestri et al. 2009).

6.3.2.3 Heart rate variability and mortality

Reduced HRV has been suggested to be a reflection of elevated sympathetic activity which is known to attenuate baroreceptor reflexes, presumably decreasing the threshold for ventricular

fibrillation and predisposing an individual to life-threatening arrhythmias. Lower HRV may also reflect an intrinsic impairment in the physiological regulatory and adaptive mechanisms that regulate heart rate, causing the individual to be less able to tolerate a perturbation such as an ischemic event or more routine rhythm disturbances. Heritable factors may explain a substantial proportion of the variance in heart rate and HRV. (Singh et al. 1999b.) It has been shown in several studies that HRV alters before ventricular tachyarrhytmias (Vybiral et al. 1993, Valkama et al. 1995, Huikuri et al. 1996, Shusterman et al. 1998) and during balloon angioplasty created acute coronary occlusion (Airaksinen et al. 1993, Airaksinen et al. 1999).

Depressed HRV has been shown to be associated with increased mortality among the Framingham cohort (Tsuji et al. 1994), among survivors of acute MI (Kleiger et al. 1990, Zuanetti et al. 1996, Bulleccetti et al. 2009), among women (Janszky et al. 2004) and among diabetics (Kataoka et al. 2004). Depressed HRV has also been associated with an increased risk of new cardiac events (Tsuji et al. 1996) and cardiovascular mortality in subjects without CHD (Dekker et al. 2000). Impaired HRV has been associated with heart failure and the progression of atherosclerosis (Huikuri et al. 1999), a greater risk for developing hypertension (Singh et al. 1998) as well as high plasma glucose levels (Singh et al. 2000).

In the CARISMA study, ECG was recorded six weeks after an acute MI. SDNN, VLF and HF were significant predictors of fatal or near-fatal arrhythmias during the two-year follow-up (Huikuri et al. 2009). In the REFINE study, measured either two to four weeks or 10 to 14 weeks after an acute MI, depressed SDNN had no prognostic power as regards future cardiovascular events, though the later recordings were nearly significant (Exner et al. 2007). Reduced HRV after MI is more powerful in predicting SCD and symptomatic ventricular tachycardia than EF <35%, indicating that reduced HRV probably reflects the lack of an autonomic defence against ventricular fibrillation, which indentifies those patients who are at high risk of SCD or arrhythmic complications (Malik and Camm 1994, Copie et al. 1996). Reduced EF is more likely to reflect a liability to cardiac failure and thus identify patients who are at risk of non-sudden death. Survivors of MI probably constitute the population of patients who may benefit most from HRV assessment. According to both the CARISMA and the REFINE study, measurement of cardiovascular autonomic function late (over six weeks) after an MI provides more powerful information on the risk of fatal or near-fatal arrhythmic events than do measurements performed early after MI. (Exner et al. 2007, Huikuri et al. 2009.)

The prognostic power of HRV during exercise has not been adequately studied. On the contrary to the results concerning HRV at rest, greater short-term HRV during peak exercise and recovery have been associated with all-cause and cardiovascular mortality (Dewey et al. 2007). It

has been postulated that non-neuronal mechanisms such as the mechanical effect of increased respiratory activity dominate the HRV spectrum at increasing workloads (Bernardi et al. 1990, Pichon et al. 2006), and the prognostic findings during peak exercise may be caused by this non-neuronal stimulus and its differences between patients.

6.3.3 T-wave alternans

TWA is a specific form of ECG alternans that is related to repolarisation abnormalities. Macroscopic TWA was first time reported as early as 1908 by H.E. Hering and it has always been associated with poor prognosis (Garcia 2008). In 1948 H.H. Kalter published a review of 48 patients with macroscopic TWA. Among this relatively small patient group, the 24-hour mortality was 60% (Osman and Gold 2002). The microscopic TWA was first reported in the 1980s by Richard Cohen and his colleagues (Adam et al. 1984). They found that reducing the ventricular fibrillation threshold level in 20 dogs resulted in the development of TWA. TWA was calculated from the power spectrum of the T-wave fluctuations. Ventricular fibrillation has been indicated as a manifestation of repolarisation heterogenetics in cardiac muscle (Nearing and Verrier 2003, Weiss et al. 2000). During the 21st century, TWA has been investigated in numerous patient groups, including dilated cardiomyopathy patients (Hohnloser et al. 2003a, Verrier et al. 2003a, Klingenheben et al. 2005, De Ferrari and Sanzo 2009), hypertrophy cardiomyopathy patients (Momiyama et al 1997, Kuroda et al. 2002, Puntmann et al. 2010), ischemic cardiomyopathy patients (Chow et al. 2006, Chan et al. 2008), patients with Brugada syndrome (Chinushi et al. 2001, Ikeda et al. 2001, Morita et al. 2002, Ohkubo et al. 2003), patients with congenital heart disease (Alexander et al. 2006, Schmitt et al. 2009), patients with reduced left ventricular EF (Hennesdorf et al. 2000, Kondo et al. 2001, Hohnloser et al. 2003b, Huikuri et al. 2003, Bloomfield et al. 2004, Cantillon et al. 2007), diabetics (Molon et al. 2007, Martin et al. 2009), CHD patients (Ikeda et al. 2000, Krittayaphong and Chotinaiwatarakul 2002) and healthy subjects (Garcia et al. 2009). Microscopic TWA has been associated with an increased risk of life-threatening arrhythmias and some of the TWA researchers have regarded TWA as a bifurcation point preceding ventricular fibrillation (Narayan 2006). On the other hand, in some study populations TWA has not been a prognostic factor for ventricular tachyarrhytmias (Chow et al. 2008), SCD or ICD discharge, though it has been associated with all-cause mortality (Gold et al. 2008).

6.3.3.1 Physiology behind T-wave alternans

In primary TWA, repolarisation alternans is present without concurrent fluctuations in other ECG components. In secondary TWA, the QRS complex also alternates in bigeminal rhythm and in response to conduction changes, such as fusion beats, MI or heart failure. Most of the clinical studies are based on primary TWA, although the distinction between these two phenomena is not always clear. The physiology behind TWA is based on beat-to-beat alternation of action potential duration (APD) at the level of the cardiac myocytes. There are two major conceptual frameworks which have been proposed to explain the cellular mechanisms of TWA; APD restitution and calcium cycling dynamics (Armoundas et al. 2002).

According to the first proposal, APD alternans by the mechanism of steep restitution is the primary event in a series of events linked to TWA and arrhythmogenesis. Action potential restitution means the relationship between APD and the diastolic interval (DI). (Narayan 2006, Narayan 2008; Fig 1.) In the case of a steep restitution curve (>1), the shortening of DI produces a short APD in the next cycle and, given that cycle length is constant, a long DI. This in turn gives rise to a long APD with an associated short DI, leading to concordant alternation. (Myles et al. 2008; Fig 2.)

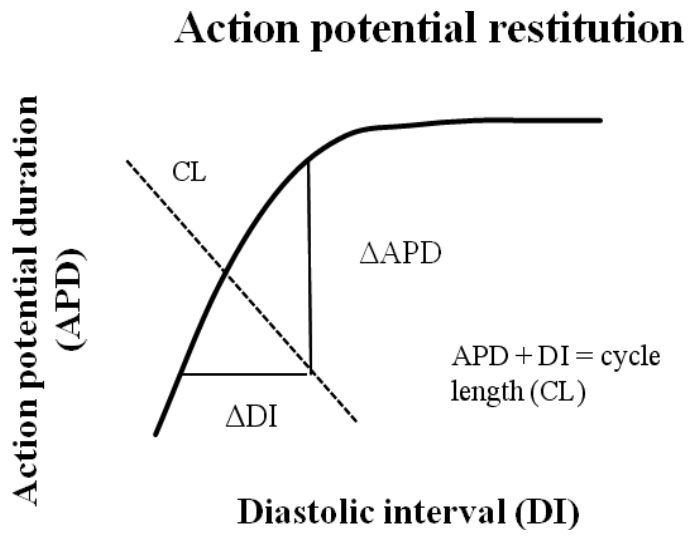


Fig. 1. Action potential restitution is the interval separating the current action potential from the prior one. If the restitution is steep (slope >1), diastolic interval (DI) shortening abruptly shortens action potential duration (APD), which lengthens the next DI and APD leading to APD alternans.
CL= cycle length

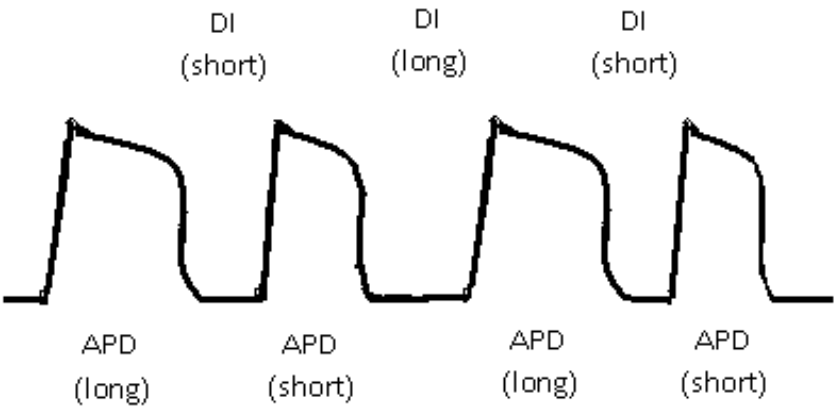


Fig. 2. Temporal dispersion of repolarization. Action potential duration (APD) alternates between cycles, either from alternans of cytosolic calcium or steep APD restitution. DI=diastolic interval

At an ionic level, action potential alternans may be caused by alternans of cytosolic Ca^{2+} (Hirayama et al. 1993). Intracellular Ca^{2+} modulates the magnitude of ionic currents during the repolarisation phase of the action potential. Under normal conditions the amount of Ca^{2+} released from the sarcoplasmic reticulum in the ventricular myocyte equals the sarcoplasmic reticulum reuptake by Ca^{2+} -adenosine triphosphatase (SERCA2a). Repolarisation alternans can occur whenever the myocyte's capabilities to maintain the balance between the release and reuptake are compromised, such as when heart rate is elevated. (Verrier et al. 2009.)

Cardiac alternans may be spatially concordant or disconcordant. In the spatially concordant alternans, all the tissue regions alternate in the same phase. In the spatially discordant case, some regions of tissue alternate in a long-short-long pattern, whereas other regions alternate in a short-long-short pattern. These regions are separated by a nodal line, in which no alternans is present. At a nodal line, the spatial gradients in APD or Ca^{2+} transient amplitude are the steepest, predisposing to localized conduction block. (Weiss et al. 2006.)

Highly arrhythmogenic conditions occur when TWA progresses from concordant to discordant, namely when the alternation in one area is out of phase with an adjoining area. This situation is conductive to re-entry and wave break. (Karma 1993, Pastore et al. 1999, Weiss et al. 1999, Weiss et al. 2006.) Among the most significant anatomical barriers leading to gradients in APD is myocardial scar resulting from MI, or abnormal myocardial fibre orientation or fibrosis in patients with hypertrophy.

6.3.3.2 Measurement of T-wave alternans

Microvolt TWA is generally too small to be detected by visual inspection of the ECG, but it can be measured using several distinct computer analysis methodologies. The two most common and most investigated methods are the Spectral Method and MMA Method. In 1988 Smith and colleagues developed the Spectral Method which allowed the measurement of alternans at the level of 1 µV (1988). A slightly modified version was presented in 1994 (Rosembaum et al.). In the Spectral Method, sequential ECG cycles are aligned to their QRS complex and the amplitude of the ST segments and T-waves at a predefined point are measured. Thereafter, this beat-to-beat series of amplitude fluctuations is divided into 128 segments and processed with Fast Fourier transform to generate a separate spectrum for each point. These spectra are averaged to produce a composite spectrum. The peaks in the composite spectrum correspond to respiratory variation, pedalling if bicycle exercise is performed, and noise. The peak at 0.5 beats is due to TWA, if present. The alternans voltage in microvolts represents the square root of alternans power and it is defined as the voltage difference between the overall mean beat and the even or odd numbered mean beats. The alternans ratio represents the ratio of the alternans amplitude to the SD of the background noise. (Osman and Gold 2002.) An alternans level of >1.9 µV with an alternans ratio of >3 sustained over two minutes is defined as a positive test result. Test results below this level are negative. The Spectral Method has been the most prolific one and has been reported in all clinical populations involved in TWA screening. (Garcia 2008.) It is also included in commercial equipments, such as CH2000 and Heartwave (Cambridge Heart Inc, Bedford; MA). One of the strengths of the Spectral Method is its ability to differentiate between true alternans and non-specific noise in the ECG signal (Armoundas and Cohen 1997). The major limitation is that it requires stationary data, which is achieved by elevating and stabilising heart rate at a predetermined level by atrial pacing or exercise. This process, together with unsustained TWA, ventricular ectopy and noise during the exercise, increases the number of indeterminate tests, which occur in 20–40% of cases. (Kaufman et al. 2006.) Therefore, the Spectral Method is not compatible for ambulatory ECG monitoring during patients' daily activities. Because of the large number of indeterminate test results, a test classification of "abnormal due to patient factors" has been introduced. This classification includes excessive ectopies, the lack of capacity to reach target heart rate, and non-sustained TWA. Abnormal test results due to patient factors carry the same risk level than positive test results. (Kaufman et al. 2006.) Technically indeterminate test results have no prognostic power (Kaufman et al. 2006). Atrial fibrillation typically leads to irregulations in R-R intervals and prevent controlled

heart rate elevations. Therefore, atrial fibrillation patients are typically excluded from TWA analysis with the Spectral Method.

Nearing and Verrier developed the MMA Method to allow TWA measurement in freely moving individuals (2002, Verrier et al. 2003b, Verrier et al. 2005). The MMA Method allows microvolt TWA measurements during routine exercise testing and ambulatory ECG monitoring by circumventing the heart rate stationarity requirements. In this time-domain method the MMA algorithm reports TWA as the maximum difference in T-wave morphology between successive beats. It separates odd beats from even beats, creates median complexes of both the odd and even beat streams separately, and the maximum difference between odd and even median complexes at any JT segment is reported as a TWA value. Results are updated every 10–15 seconds by an update factor, usually 1/8, which is the fraction of morphology change that an incoming beat can contribute to the median complex. (Nearing and Verrier 2002.) The MMA Method is included in commercial equipment such as the CASE-8000 by GE Medical Systems. Because the MMA Method generates high-resolution templates of superimposed QRS-aligned complexes showing the alternation pattern, the method permits visual examination to verify the presence and magnitude of TWA (Minkkinen et al. 2009, Slawnych et al. 2009). If the cut-off point for positive TWA results is used, TWA values above the cut-off point should be reread for verification. If numerical values are reported, they should be reread down to 20 μV. For exercise testing, the MMA Method employs the TWA cut-off point of ≥60 μV to indicate significantly enhanced risk of SCD when used as a single screening test (Minkkinen et al. 2009), and for ambulatory monitoring, TWA values ≥46 μV indicate increased risk (Verrier et al. 2003b, Sakaki et al. 2009, Slawnych et al. 2009). The precise cut-off points for different patient populations remain to be determined.

The comparisons between time-domain and frequency-domain TWA methods have shown that TWA magnitude measured by the Spectral Method is smaller than that derived with the MMA Method (Hostetler et al. 2005, Selvaraj and Chauhan 2009). The Spectral Method reports one half of the average TWA magnitude across the entire JT interval for 128 beats, whereas the MMA Method reports the peak TWA level at any point within the JT interval for a 15-second interval. Furthermore, the update factor can account for a several-fold difference in the detected TWA level. The MMA Method can detect short-term TWA better than the Spectral Method (Hostetler et al. 2005), but the MMA Method also falsely detects or overestimates TWA in the presence of noise (Selvaraj and Chauhan 2009). The Spectral Method can better distinguish physiologic signals, for example T-wave amplitude modulation by respiration, from real TWA, because frequency-domain analysis is more robust at discriminating 0.5 cycles per beat TWA signal from periodic noise at lower frequencies (Selvaraj and Chauhan 2009). After Selvaraj and Chauhan published their results

concerning TWA and noise, prefiltering has became an essential part of TWA measurements by means of the MMA Method. Even though prefiltering probably improves the MMA Method, noise has been considered to be one of the fundamental problems with the method.

6.3.3.3 The autonomic nervous system and T-wave alternans

TWA is a heart-rate-dependent property of the heart and it typically occurs at elevated heart rates. In comparison to heart rate, sympathetic stimulation does not have similar effect on the amplitude of TWA. (Kaufman et al. 2000.) Above a specific heart rate threshold, TWA increases monotonically independently of the autonomic state and TWA is therefore usually measured at heart rates above rest but below rates likely to cause false positives (Kaufman et al. 2000). The optimal heart rate for the measurement of TWA is between 100 and 120 bpm (Kavesh et al. 1998). When the Spectral Method is used, sustained TWA has been settled to occur at heart rates <120 bpm to be considered abnormal. When the MMA Method is used, it is suggested that TWA values above the cut-off points be reread for verification, or if numerical values are reported, they should be reread down to 20 μV to verify the presence and magnitude of TWA. However, the investigations about the heart rate limit and the MMA Method are still ongoing. For patients at risk for SCD, TWA develops at lower heart rates as compared to the healthy population. (Kaufman et al. 2000.) Too excessive and too rapid increase in heart rate would cause an overshoot of heart rate into ranges that could induce TWA also in low-risk individuals (Cutler and Rosembaum 2009a). Both exercise and pacing have been used for accelerating heart rate, but bicycle exercise has been shown to be superior to pacing in clinical risk stratification (Rashba et al. 2002a, Tanno et al. 2004). On the other hand, simultaneous atrial and ventricular pacing significantly more rarely leads to indeterminate test results than bicycle exercise and atrial pacing (Raatikainen et al. 2005). Atropine has been used for accelerating heart rate, but the effect of atropine on the T-wave has not been studied enough yet (Rashba et al. 2002b).

The results concerning the influence of the sympathetic nervous system on TWA are contradictory. There is strong evidence that an increase in sympathetic activity plays a critical role in triggering ventricular tachyarrhythmias (Schwartz and Malliani 1975, Kavesh et al. 1999, Harada et al. 2003, Murata et al. 2003). β-blocking also reduces arrhythmic events and TWA magnitude and, in some cases, this may cause false negative TWA values (Klingenheben et al. 2001, Rashba et al. 2002b, Chan et al. 2010). Furthermore, β-blocking might prevent patients from reaching an adequate heart rate during the study. Based on these assumptions, it has been suggested that β-

adrenergic therapy should not be continued during TWA testing. On the contrary, Zacks et al. have provided evidence that oral β-blocker therapy has no effect on the predictive value of TWA in patients with CHD, diminished left ventricular function or a history of non-sustained ventricular tachycardia (Zacks et al. 2007). However, acute and intravenous β-blocker therapy cannot be compared with the chronic oral therapy (Zacks et al. 2007).

6.3.3.4 T-wave alternans and mortality

The prognostic power of TWA has been evaluated in many large clinical studies during the last decade (Table 2). At the same time, when TWA has been associated with an increased risk of life-threatening arrhythmias, the most hopeful researchers have expected TWA to be a new guide when selecting patients for ICD therapy. Though several TWA studies have used cut-off points when dividing the study population into high-risk and low-risk groups, MMA-based TWA studies support the concept that TWA represents a continuum of risk – the higher the level of TWA, the greater the risk. (Nearing et al. 1994, Minkkinen et al. 2009, Slawnych et al. 2009.) In 2003 the ATRAMI researchers published results concerning the association between TWA measurement from ambulatory 24-hour ECG and cardiac events in 1,284 post-MI patients. Using the MMA Method for detecting TWA, they found the odds ratios of cardiovascular events during 21±8 months' follow-up to fall between 4.2 and 7.9 ($p<0.01$) for patients who have TWA above the 75th percentile at 2 to 25 days following an MI, as compared to patients with lower levels of TWA. (Verrier et al. 2003b.) In 2004 the results from the MADIT II study were published revealing out that in 1,232 post-MI patients with impaired EF, the increased TWA during an exercise test, as measured by the Spectral Method, yielded the hazard ratio (HR) of 4.8 ($p=0.020$) for two-year mortality, when compared to the patients with normal TWA (Bloomfield et al.).

In the REFINE study, 322 post-MI patients underwent a submaximal exercise test including TWA measurements with the Spectral Method. At two to four weeks after the MI, the exercise-based TWA was not predictive of long-term outcomes, but when the test was performed 10 to 12 weeks after the MI, the HR for non-negative TWA was 2.75 (95% confidence interval [CI] 1.08–7.02, $p=0.034$) as compared to those with negative TWA. (Exner et al. 2007.) The first results concerning TWA in FINCAVAS indicated an association between TWA ≥65 μV and all-cause and cardiovascular mortality as well as SCD during 45 months' follow-up in 1,037 low-risk patients referred to a clinical exercise test. The main indications for exercise testing in FINCAVAS were suspicion of CHD (46%), adequacy of CHD treatment (24%), vulnerability to arrhythmia during

exercise (18%), evaluation of working capacity (19%), obtaining an exercise test profile prior to an invasive procedure (13%) and obtaining an exercise test profile after an MI (10%) (Table 2) (Nieminen et al. 2007). In the EPHESUS study, abnormal TWA (≥47 μV), measured from the ambulatory ECG at 2 to 10 days after an MI using the MMA Method, was a powerful predictor of SCD for 493 patients with left ventricular dysfunction (Table 2) (Stein et al. 2008).

Contradictory evidence on TWA as a prognostic marker was received from the MASTER Trial and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). In the MASTER Trial, the association between TWA and ICD discharge was tested with 575 post-MI patients who met the MADIT-II criteria. Non-negative (including 81% positive and 19% indeterminate) TWA by the Spectral Method during a treadmill exercise test was not associated with ventricular tachyarrhytmic events, although it was associated with total mortality (HR 2.04 [95% CI 1.10-3.78], p=0.02) (Chow et al. 2008). In the SCD-HeFT study, 490 patients with symptomatic heart failure were TWA-tested with the Spectral Method (Gold et al. 2008). During the approximately 30 months of follow-up, there were no differences between TWA-positive and TWA-negative patients in SCD, ventricular arrhythmias, or ICD discharge. Although TWA was a significant predictor of arrhythmias in a study of 286 patients with left ventricular dysfunction, the event rate in the TWA-negative group did not differ from the TWA-non-negative group, suggesting that TWA alone may not be capable of identifying a sufficiently low-risk subset in that particular population to obviate the need for ICD implantation (Cantillon et al. 2007). The Alternans Before Cardioverter Defibrillation (ABCD) trial is the only study so far where TWA has been used as one of the criteria for ICD implantation. In the study of 566 patients with ischemic cardiomyopathy and low left ventricular EF, the primary end point (appropriate ICD discharge or SCD) rates were significantly higher among patients with either a positive TWA (HR 2.1, p=0.03) or a positive electrophysiologic study (HR 2.4, p=0.007) than in those whose TWA and electrophysiologic tests were non-positive at one year. Patients with negative results for both of these tests had significantly lower event rates than those with two positive tests (2% vs. 12%; p=0.017). In the ABCD study TWA predicted endpoint events at one year but not at two years of follow-up, suggesting a time-dependent nature of TWA predictivity. (Constantini et al. 2009, Amit et al. 2010.)

The discussion on TWA testing and its prognostic power has been intensive in recent years, and the clinical utility of TWA remains controversial. As a marker of areas predisposed to arrhythmias, TWA has been suggested to aid in decision-making as regards the patients' need for and benefits from ICD (Cutler and Rosembaum 2009b). Many studies have found that the rate of ventricular tachyarrhythmic events among patients who test TWA negative is exceedingly low, suggesting that ICD therapy may not benefit such patients (Klingenheben et al. 2000, Ikeda et al.

2002, Kitamura et al. 2002, Hohnloser et al. 2003b, Armoundas et al. 2005, Bloomfield 2006, Chow et al. 2007, Ikeda et al. 2006, Salerno-Uriarte et al. 2007). Therefore, TWA has been proposed as a means of guiding ICD therapy in patients with risk factors for SCD but no prior history of sustained ventricular tachyarrhythmic events, namely primary prevention patients. The negative results from the MASTER and SCD-HeFT studies were controversial in regard to this hypothesis. The controversy in the results has been suggested to arise from diverse patient populations, testing protocols and endpoint definitions in the various studies. (Bansal and Berger 2010.) In the SCD-HeFT trial, the amount of indeterminate TWA tests were 2- to 4-fold greater than in other studies. The survival rates of TWA-positive versus TWA-negative patients in the study population examined in the SCD-HeFT sub-study began to diverge from each other after 14 to 28 months of follow-up, which was precisely the period of time when the SCD phenotype emerged in the main SCD-HeFT study population. Therefore, this study population was proposed to characterise the late-appearing SCD phenotype which has a strong correspondence with the TWA signal. (Rosenbaum 2008.) The predictive accuracy of ICD discharge has been strong in the TWA studies enrolling relatively few patients with ICDs, as compared to the studies with high ICD use (Hohnloser et al. 2009). Recently, it has been theorised that TWA may be dependent on T-wave amplitude, but there are no studies to date to prove or reject this statement. The TWA index, by the amplitude of corresponding T-waves-adjusted TWA, could provide some advantage over maximum TWA value (Madias 2009a-e).

In summary, TWA is a promising marker of ventricular arrhythmias and SCD, and therefore it may also be valuable when deciding on patients' ICD therapy (Gehi et al. 2005). The applications of signal procession techniques to quantify TWA clinically have generated a sizeable literature of prognostic clinical studies enrolling a total of more than 12,000 patients. The strength of TWA is its up to 97% negative predictivity value for cardiovascular mortality and SCD (Gehi et al. 2005). However, many questions remain to be addressed, including the connection between heart rate and TWA as well as TWA's reflection on the surface ECG. (Cutler and Rosembaum 2009) Moreover, uniform guidelines about the measurement and interpretation of TWA are yet to be determined.

Table 2. Clinical studies of T-wave alternans with the Modified Moving Average Method

Study	Patient population	LVEF	Follow-up period	Recovery time after MI	HR for end-point
Verrier et al. 2003b	1284 post-MI patients in ambulatory ECG	moderately depressed (42±3%)	21 months	15±10 days	Maximal TWA: 7.9 (1.9-33.1) for cardiac arrest due to VF or arrhythmic death in lead V5
Exner et al. 2007	322 post-MI patients in ambulatory ECG	moderately depressed (38-48%)	47 months	2-4 weeks	NS
				10-14 weeks	TWA ≥5 μV: 2.94 (1.10–7.87) for CVD or resuscitated cardiac arrest
Nieminen et al. 2007	1037 patients in routine exercise testing	preserved (65±15%, 529 patients)	45 months		TWA ≥65 μV: 3.3 (1.8-6.3) for all-cause death
					TWA ≥65 μV: 6.0 (2.8-12.8) for CVD
					TWA ≥65 μV: 7.4 (2.8-19.4) for SCD
Stein et al. 2008	493 post-MI patients in ambulatory ECG	depressed (34±5%)	16 months	2-10 days	TWA ≥65 μV: 5.5 (2.2-13.8) for SCD in lead V3
Sakaki et al. 2008	295 cardiomyopathy patients in ambulatory ECG	depressed (34±6%)	1 year		TWA ≥65 μV: 17.1 (6.3-46.6) for CVD
					TWA ≥65 μV: 22.6 (2.6-193.7) for witnessed SCD
Minkkinen et al. 2009	2119 patients in routine exercise testing	preserved (60-66%)	47 months		TWA ≥90 μV: 6.4 (2.0-21.2) for CVD
					TWA ≥60 μV: 4.6 (1.7-12.3) for SCD
Slawnych et al. 2009	322 post-MI patients, 681 CAD patients	moderately depressed, preserved (38-63%)	48 months		TWA ≥60 μV: 2.5 (1.1-6.0) for CVD
					TWA ≥20 μV: 2.5 (1.2-6.1) for CVD
Maeda et al. 2009	21 controls, 21 post-MI with VT and 21 post-MI without VT in ambulatory ECG	depressed (36-43%) for post-MI group	6 years		TWA ≥65μV: 6.1 (1.1-34.0) for sustained VT or VF
Stein et al. 2010	general population patients (49 cases, 98 controls) in ambulatory ECG	assumed preserved	14 years		TWA ≥37μV: 4.8 (1.5-15.8) for SCD

CVD=cardiovascular death; LVEF=left ventricular ejection fraction; MI=myocardial infarction; SCD=sudden cardiac death; VF=ventricular fibrillation; VT=ventricular tachycardia;

6.3.4 PR interval

The PR interval is determined by the conduction time from the sinus node to the ventricles. Therefore, it integrates information about a number of sites in the conduction system of the heart. The situation where the PR interval exceeds 200 ms is known as first-degree AV block. This block may result from conduction delay in the atrium, the AV node or the His-Purkinje system. More than one site of conduction delay is often present. (Cheng et al. 2009.) First-degree AV block has been considered a benign and functional phenomenon since recently (Mymin et al. 1986, Cheng et al. 2009). Among healthy adults of 20–40 years of age, 1–2% have a prolonged PR interval, and the prevalence of first-degree AV block increases to 3–4% by the age of 60 years (Packard et al. 1954, Perlman et al. 1971, Rose et al. 1978).

6.3.4.1 Physiology behind the PR interval

The PR interval represents the time required for an electrical impulse from the sinoatrial node to conduct through the atria, the AV node, the bundle of His, bundle branches, and Purkinje fibres. Prolongation of the PR interval may be due to a conduction delay within any of these sites or a combination of several sites. AV nodal dysfunction accounts for the majority of cases. (Zipes 1997.) A conduction delay in the His-Purkinje system is often associated with bundle-branch block. As early as in 1982, the possible mechanisms of conduction delay were detailed as follows: a decrease in adrenergic and increase in vagal tone; local liberation of metabolites (such as adenosine) in response to ischemia; structural changes in the AV node or the vicinity thereof, giving rise to complete or partial bypass of the impulses which normally pass through the AV node; and changes in AV conduction brought on by altered autonomic nervous activity as elicited by myocardial ischemia (Erikssen et al.). Structural changes appear in the cardiac skeleton after 40 years age, and responses to catecholaminergic or inotropic stimuli are blunted in older age. Therefore, one of the early ECG manifestations of these abnormalities representing advanced physiological age may be the prolongation of the PR interval, which may be related to progressive alterations in the conduction system or cardiac structure, or both.

6.3.4.2 PR interval and mortality

Isolated first-degree AV block has generally not been associated with an increased risk of SCD, syncope or progression to higher degrees of AV block. In a 30-year longitudinal study of 3,983 Royal Canadian Air Force Pilots, moderate first-degree AV block was concluded as a benign phenomenon, suggesting that first-degree AV block does not convey prognostic information among young, healthy men (Mymin et al. 1986). In the Tecumseh Community Health Study there was no excess incidence of cardiovascular disease or mortality among the persons with long PR intervals (>210 ms) during a 4-year observation of 4,678 adult men and women (Perlman et al. 1971). After a 7-year follow-up, a moderate but significant association was observed between prolonged PR interval and lower incidence of CHD in a study on 1,832 healthy males aged 40 to 59 years (Erikssen and Otterstad 1984). Similar results were found when 18,403 middle-aged male civil servants collected from the National Health Service Register were investigated. Among 366 men with prolonged PR intervals (>220 ms), the CHD mortality rate was slightly lower than among the study group as a whole, though the difference was within chance limits. (Rose et al. 1978)

First-degree AV block has been associated with CHD over a 5-year follow-up (Blackburn et al. 1970). Last year, Cheng and colleagues showed an association between abnormal AV conduction at rest and the outcomes including atrial fibrillation (approximately 2-fold risk) and all-cause mortality (approximately 1.4-fold risk) among 7,575 individuals from the Framingham Heart Study population with a follow-up period of 20 years (Cheng et al. 2009).

According to these results, prolonged PR interval is rarely an indicator of more severe conduction disturbances during a follow-up of less than five years. Exceptions to these results include patients with non-isolated first-degree AV block, where intra-atrial conduction delays prone to atrial fibrillation, acute MI, or bundle branch disease offer a possibility of developing a higher degree of AV block.

7 AIMS OF THE STUDY

The aim of the present dissertation, including five sub-studies, was to investigate the prognostic power of the exercise test in predicting mortality. The more detailed aims of each study are listed below.

STUDY I: To investigate the prognostic power of HRV measured during the exercise test and the recovery phase after the exercise for mortality.

STUDY II: To evaluate the hypothesis that the change from the peak to recovery values in SAP and RPP can be used to predict all-cause and cardiovascular mortality as well as SCD in patients referred to a clinical exercise test.

STUDY III: To evaluate the association between future cardiovascular mortality and the PR interval measured at rest and during the recovery phase after exercise.

STUDY IV: To determine whether the combined analysis of heart rate recovery and TWA enhances the predictive power for cardiovascular and all-cause mortality over the independent assessment of either variable, and to compare their predictive strength to other standard risk factors.

STUDY V: To take a more thorough look to the appearance, magnitude and prognostic power of TWA in precordial leads. Is TWA in some specific precordial lead or leads associated with poorer prognosis than in others? Is it more dangerous to have high values of TWA in one lead or low TWA in several leads?

8 MATERIALS AND METHODS

8.1 The Finnish Cardiovascular Study (FINCAVAS)

The purpose of the FINCAVAS project is to construct a risk profile using ECG as well as haemodynamic and genetic markers of individuals at a high risk of cardiovascular diseases, events and deaths (Nieminen et al. 2006). The second objective is to elucidate the effects and interactions of exercise, commonly used cardiovascular medications and a variety of candidate genes in people with no cardiac diseases as well as patients with CHD.

8.1.1 Study population

A detailed description of the FINCAVAS population is presented in Table 3. The total study population consists of patients who were referred to a clinical exercise test at Tampere University Hospital between October 2001 and December 2008 and were willing to participate in the study. Patients with technically successful storage of exercise test data were included. The exercise test was considered technically adequate if the hemodynamic data and continuous digital ECG signal were stored successfully. The duration of total follow-up was until September 2009 (Data 3), but smaller data (Data 1, 2) were gathered after shorter follow-up periods. At the end of follow-up, the survival status of each patient was checked and the causes of death were gathered from the Causes of Death Register maintained by Statistics Finland; this source has been determined to be reliable (Pajunen et al. 2005.) 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 deaths as all-cause, cardiovascular or SCD (defined as a cardiac death within 24 hours after the onset of symptoms). The classification of deaths was assessed by blinded adjudication to the results of exercise test findings. Data 2 was used in the first four sub-studies (Studies I, II, III and IV). In the fifth study (Study V), all data for 4,568 patients (Data 3) were available. Of these, 1,352 (30%) patients had a diagnosis of CHD before the exercise testing (Data 3). After the exercise testing, coronary angiography was performed on 755 (17%) patients, and over 50% stenosis was found in 291 (6.4%) of these patients (Data 3).

8.1.2 Exercise protocol

Before the exercise test, each patient signed an informed consent, after which the medical history of each patient was collected with a computer-based questionnaire form. Prior to the exercise test, the patient lay down in the supine position for 10 minutes, and the resting ECG was recorded digitally. The upright routine exercise test was performed using a bicycle ergometer with electrical brakes. The lead system was the Mason-Likar modification of the standard 12-lead system. The initial workload varied from 20 W to 30 W, and the load was increased stepwise by 10–30 W every minute. Continuous ECGs were digitally recorded at 500 Hz with the CardioSoft exercise ECG system (Versions 4.14, 4.2 and 6.51, GE Healthcare, Freiburg, Germany). During the test, heart rate was continuously registered on the ECG, while SAP and DAP were measured manually with a brachial cuff every two minutes. Most of the tests were sign- and symptom-limited maximal tests, but some tests on special occasions (for example, after an MI) had an upper limit of 120–130 bpm for heart rate. 75% of the patients reached the maximal heart rate of over 130 bpm (Data 3). The main reasons for discontinuing the exercise testing were fatigue (42%), difficulty in breathing (6.9%) and chest pain (3.7%) (Data 3). The recovery phase after the exercise was at least five minutes. In the post-exercise phase, heart rate and blood pressure were defined in the sitting position at one to four minutes after the cessation of exercise.

For HRV analysis (Study I), R-R interval data during the pre-exercise phase, first and last minute of exercise as well as during the first two minutes of recovery were analysed using HRV Analysis Software (version 1.1, Biosignal Analysis and Medical Imaging Group, University of Kuopio, Kuopio, Finland). The following time domain HRV variables were analysed: mean R-R, SDNN and RMSSD. In addition, the Poincare plot analysis (pcSD1, pcSD2) was run. For the frequency domain HRV variables, the R-R interval data was resolved into HF (>0.15 Hz), LF (0.04-0.15 Hz) and VLF (<0.04 Hz) components including absolute power of each bandwidth (pow), power in normalised units (pow n.u.) and percentage power (powprc) using nonparametric Fast Fourier transform. The baseline trend in heart rate was removed using the smoothness priors method (Tarvainen et al. 2002.) After detrending, all the R-R intervals of the frequency domain HRV variables were re-sampled with cubic interpolation at a rate of 4 Hz.

TWA was measured using the time-domain FDA-cleared MMA Method by GE Healthcare. In Study IV, peak TWA values were analysed at the heart rates of <125 bpm, whilst in Study V, TWA values were analysed with no regard to the exercise heart rate. In Study V, TWA values of ≥46 μV were reread by a physician investigator and corrected if necessary, or discarded based on noise or baseline wander. The cut-off point 46 μV were chosen based on previous study where this

cut-off point, coinciding with the 75th percentile, was used to predict cardiac arrest and arrhythmic death. (Verrier et al. 2003b) The investigators who analysed the TWA test results were blinded to the events.

PR intervals were assessed to the nearest millisecond one minute before the start of exercise and two minutes after the cessation of exercise using the CASE Workstation (version 1.82, GE Healthcare). The software composed a spatial ECG vector from the 12 standard ECG leads. An average complex was calculated based on the normal cardiac cycles. In the averaged cycle, P-onset and QRS-onset were defined. The first deflections from the 0 lines of the P-wave and the QRS complex were used for measurement of the PR interval. All extreme PR interval values (>250 ms or <90 ms) were reread by a physician investigator and corrected if necessary. Manually and automatically measured PR intervals at the pre- and post-exercise phases were compared in a subset of 100 randomly chosen ECGs. The PR intervals in lead II were reread by a physician, and three random measurements were averaged. Bias between manually and automatically derived values was defined as the mean difference between the paired PR intervals, and limits of agreement were calculated as bias ±2 SD of the measurement pairs. The bias for the pre-exercise phase was 4 ms (limits of agreement −10 ms to 18 ms) and for the post-exercise phase 5 ms (−17 ms to 26 ms).

Table 3. The FINCAVAS population

	Period of data collected	End of follow-up	Study population	Female	Age (Mean± SD)	Follow-up (Months)	Mortality	Indication for exercise test
Data 1	October 2001─ January 2003	January 2006	1037	364 (35.1%)	58±13	44±7	All-cause death 59 (5.7%) CV death 34 (3.3%) SCD 20 (1.9%)	suspicion of CHD 46% evaluation of work capacity 19% vulnerability to arrhythmia during exercise 18% adequacy of CHD treatment 24% obtaining an exercise test profile prior to an invasive procedure 13% obtaining an exercise test profile after an MI 10%
Data 2	October 2001─ December 2004	May 2007	2431	867 (35.7%)	57±13	47±13	All-cause death 142 (5.8%) CV death 69 (2.8%) SCD 36 (1.5%)	suspicion of CHD 44% evaluation of work capacity 18% vulnerability to arrhythmia during exercise 21% adequacy of CHD treatment 16% obtaining an exercise test profile prior to an invasive procedure 13% obtaining an exercise test profile after an MI 8%
Data 3	October 2001─ December 2008	September 2009	4568	1765 (38.6%)	56±13	55±13	All-cause death 321 (5.4%) CV death 138 (3.0%) SCD 63 (1.4%)	suspicion of CHD 45% evaluation of work capacity 18% vulnerability to arrhythmia during exercise 21% adequacy of CHD treatment 16% obtaining an exercise test profile prior to an invasive procedure 13% obtaining an exercise test profile after an MI 8%

CHD= coronary heart disease; CV=cardiovascular; MI=myocardial infarction; SCD=sudden cardiac death; SD=standard deviation;

8.1.3 Ethical aspects

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.

8.2 Statistical analysis

Statistical analyses were made using SPSS release 14.0 (Studies I, II, IV) or release 16.0 (Studies III, V) for Windows (SPSS, Inc., Chicago, IL, USA). All statistical tests were two-tailed and used an α-level of <0.05. The t-test for independent samples and Mann-Whitney U-test were used to compare continuous parameters, and the χ^2-test was applied for dichotomous variables. Before statistical analysis, patients with atrial fibrillation and atrial flutter were excluded. HRs were analysed for all-cause and cardiovascular mortality as well as for SCD by Cox regression analysis. In the multivariate Cox analysis, we used standard coronary risk factors as covariates, namely sex, age, BMI, smoking, hypercholesterolemia, diabetes, use of β-blockers, prior MI, prior diagnosis of CHD, heart rate and QRS complex width. The exact combination of covariates varied, to a degree, between studies because of the progression of the FINCAVAS data and for the purposes of developing our analysis. The physiology of the investigated parameter had an effect on selected covariates as well. The proportionality assumption for all covariates was checked by using the correlations of the survival rankings with the Schoenfeld residuals. The significance of mortality rates by quintiles was determined with Poisson regression (Studies III and V). In Study IV Harrell's C indices were calculated by STATA 10.1 for Windows (StataCorp LP, College Station, TX, USA). Harrell's C index is a generalisation of the area under the receiver operator curve for survival data with censored cases.

9 RESULTS

9.1 Heart rate during and after exercise

The mean of the achieved percentages of age-adjusted expected heart rate during the exercise was 84±14% (mean±SD). The maximum heart rate reached during the exercise and heart rate recovery one minute after exercise were significantly higher among survivors than non-survivors in Study IV (Fig. 3). To evaluate the heart rate recovery one minute after the cessation of exercise as a categorised variable, we used the cut-off point of 18 bpm, because of the abrupt end of the exercise (Studies II, IV). After adjustment for common coronary risk factors (sex, age, BMI, smoking, use of β-blockers, reached maximum heart rate, prior MI, CHD, diabetes and hypercholesterolemia), heart rate recovery was a significant predictor of all-cause mortality (HR 2.5, 95% CI 1.6-3.7, p<0.01 [Study IV], HR 2.4, 95% CI 1.6-3.6, p<0.01[Study II]) and cardiovascular mortality (HR 2.3, 95% CI 1.3-4.2, p=0.01 [Study IV], HR 2.4, 95% CI 1.3-4.3, p<0.01 [Study II]) when applying the cut-off point of 18 bpm. For SCD heart rate recovery with the cut-off point of 18 bpm was not a significant predictor of mortality (Study II). (Table 5.) As a continuous variable, heart rate recovery produced statistically significant HR for all-cause mortality (0.97, 95% CI 0.95-0.99, p<0.01), but not for cardiovascular mortality or SCD (Study II).

The differences in maximal heart rate during the exercise might have an influence on the prognostic power of heart rate recovery. Therefore, we also tested the prognostic power of heart rate recovery separately to the patients with maximal heart rate ≤130 bpm (N=1141) and the patients with maximal heart rate >130 bpm (N=3427) (Data 3). Among patients with maximal heart rate ≤130 bpm, heart rate recovery with the cut-off point of 18 bpm was a significant predictor of all-cause mortality (HR 2.3, 95% CI 1.6-3.4, p<0.01) and cardiovascular mortality (HR 2.8, 95% CI 1.6-5.1, p<0.01), but not for SCD (Data 3). Among patients with maximal heart rate >130 bpm, heart rate recovery with the cut-off point of 18 bpm was a significant predictor of all-cause mortality (HR 2.2, 95% CI 1.6-3.1, p<0.01), but not for cardiovascular mortality or SCD (Data 3).

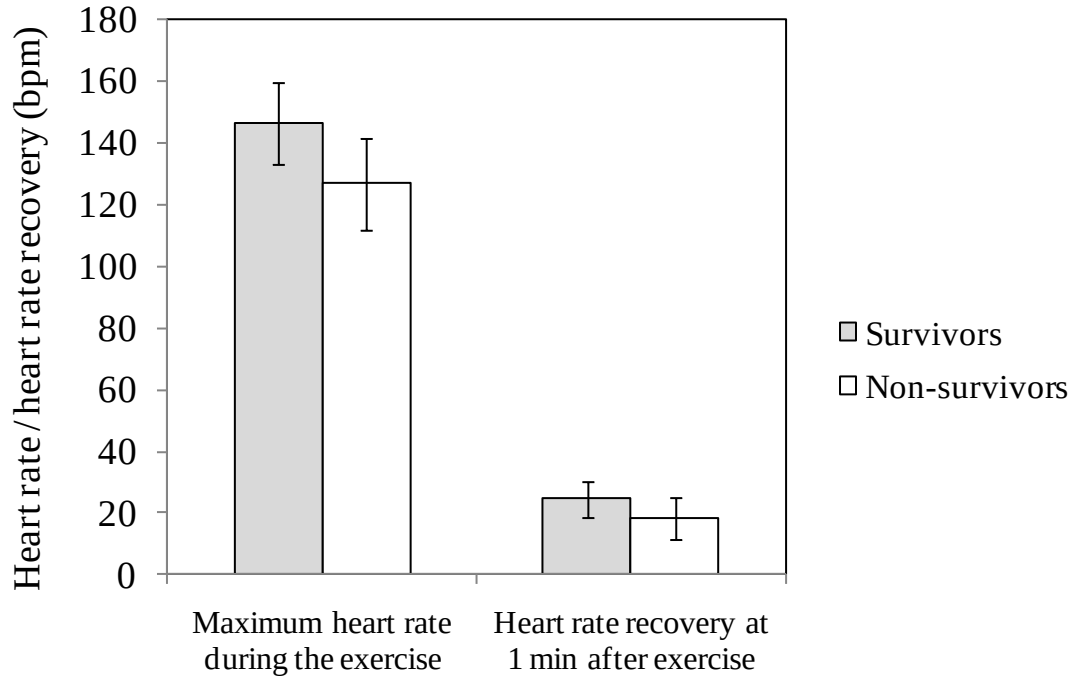


Fig. 3. Maximum heart rate±standard deviation (SD) during the exercise and heart rate recovery±SD after exercise among survivors and non-survivors. The differences between the groups were statistically significant ($p<0.01$). (Study IV.)

9.2 Blood pressure during and after exercise

SAP did not differ significantly between survivors and non-survivors during the pre-exercise phase, while DAP was significantly ($p<0.05$) higher among survivors (80 mmHg [Study I, IV, V]) than non-survivors (75 mmHg [Study I], 76 mmHg [Study IV], 78 mmHg [Study V]). During the exercise SAP as well as DAP were significantly higher among survivors than non-survivors (Fig 4.) (Study IV). As a predictor of mortality, SAP during peak exercise was not associated with any classes of mortality, although for all-cause mortality it reached near significance (HR 0.99, 95% CI 0.98-1.00, $p=0.01$) after adjustment for common coronary risk factors. $SAP_{recovery}$ ($SAP_{peak\text{-}exercise}$ − $SAP_{post\text{-}exercise}$) was not a significant predictor of any class of mortality (Study II). (Table 5.)

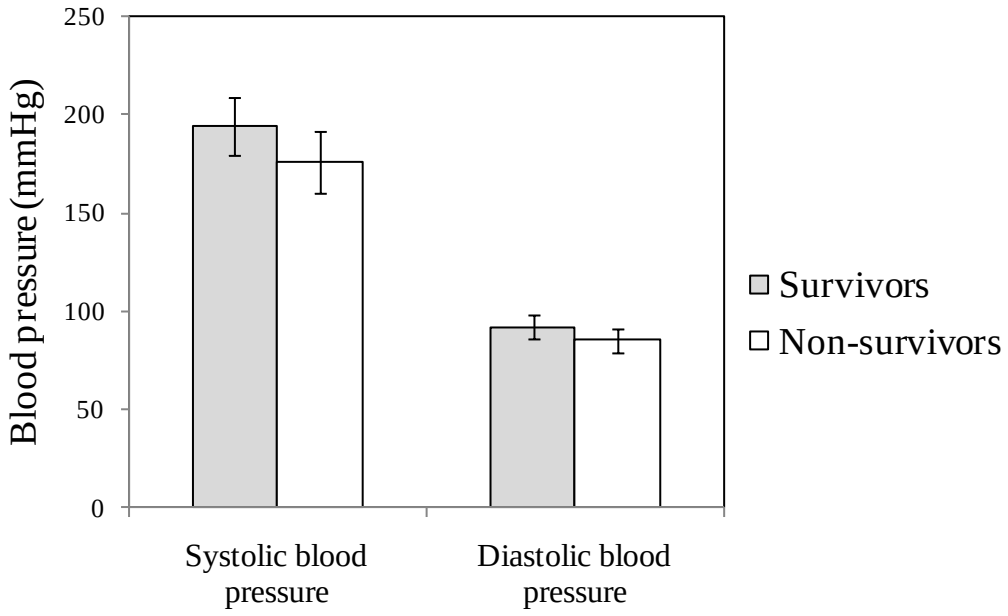


Fig. 4. Systolic and diastolic blood pressures±standard deviations (SD) during peak exercise among survivors and non-survivors. The differences between the groups were statistically significant ($p<0.01$). (Study IV.)

9.3 Heart rate variability during and after exercise

We investigated the behaviour and prognostic power of HRV during and after the exercise test (Study I). As the exercise intensified, mean R-R interval and RMSSD decreased with a significant ($p<0.01$) trend, while the influence of the HF component increased and the influence of the LF band decreased ($p<0.01$) (Fig. 5).

During the pre-exercise phase, log VLF power (HR 0.56, 95% CI 0.43–0.72), log LF power (HR 0.58, 95% CI 0.45–0.74), log LF power (n.u.) (HR 0.75, 95% CI 0.64–0.87), log HF power% (HR 1.44, 95% CI 1.09–1.88), pcSD2 (HR 0.61, 95% CI 0.43–0.86), and log RMSSD (HR 0.72, 95% CI 0.56– 0.92) were significant ($p<0.01$) predictors of better prognosis after adjustment for coronary risk factors (age, BMI, MET, sex, smoking, use of β-blockers, diabetes, CHD, prior MI). (Table 5.) During the first minute of exercise, smaller log LF power (HR 0.70, 95% CI 0.55–0.94, $p<0.01$) was associated with increased risk of mortality. None of the HRV parameters were connected with mortality at peak exercise or during the recovery phase. (Table 5.)

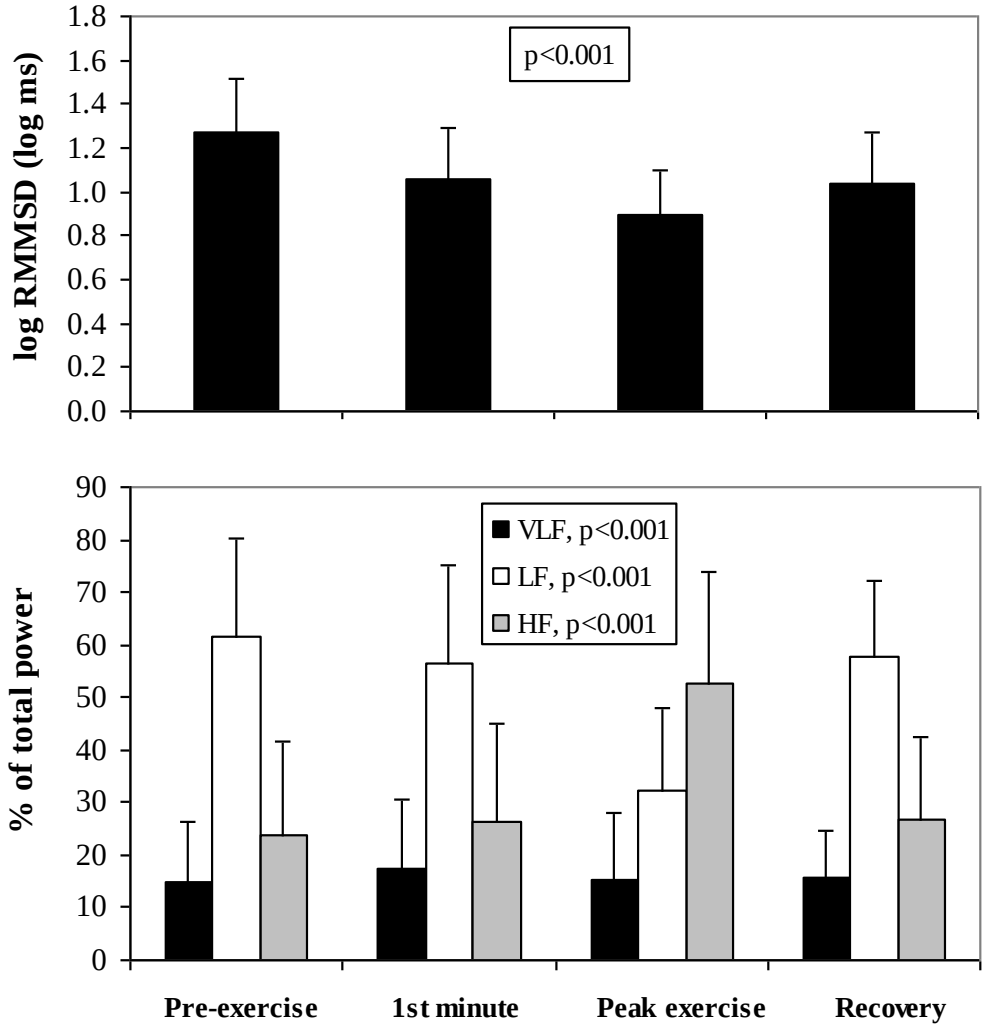


Fig. 5. Log RMSSD and VLF, LF and HF frequency bands during the exercise test. (Study I.) HF=high frequency; LF=low frequency; RMSSD=square root of the mean squared differences in N-N intervals; VLF=very low frequency;

9.4 T-wave alternans during and after exercise

During maximum exercise, heightened TWA was found in 5.2% of 1,972 patients when we used the cut-off point of 60 µV (Study IV). Maximum TWA during exercise as a continuous variable in every precordial lead differed significantly (p=0.04) between survivors 35.8 (±21.8) µV and non-survivors 39.9 (±23.3) µV (Study IV). After adjustment for coronary risk factors (sex, age, BMI, smoking, use of β-blockers, reached maximum heart rate, prior MI, CHD, diabetes and hypercholesterolemia), the HR of heightened TWA (≥60 µV) for all-cause mortality was 2.5 (95%

CI 1.4-4.5, p<0.01) and for cardiovascular mortality 5.8 (95% CI 3.1-11.1, p<0.01) (Study IV). After extending the study population to over 3,000 patients (Data 3), the TWA values of ≥46 µV were reread by a physician investigator and corrected if necessary or discarded based on noise or baseline wander. The analysis of every precordial lead separately yielded significant differences in leads V1 and V3-V6 between survivors (N=3367) and non-survivors (N=231) (Fig. 6) (Study V).

In Data 3, maximum TWA during exercise in all precordial leads was a significant predictor for cardiovascular mortality and all-cause mortality (Table 4), but not for SCD (Study V). Analysing each precordial lead separately and in lead combinations, TWA in lead V5 exceeded all other single leads as well as combinations of leads for all-cause mortality. For cardiovascular death, combination of anterior and lateral precordial leads (V3-V6) yielded the greatest HR. Leads V3 and V5, as well as combinations of the leads V3, V4 and V5, were significant predictors of SCD.

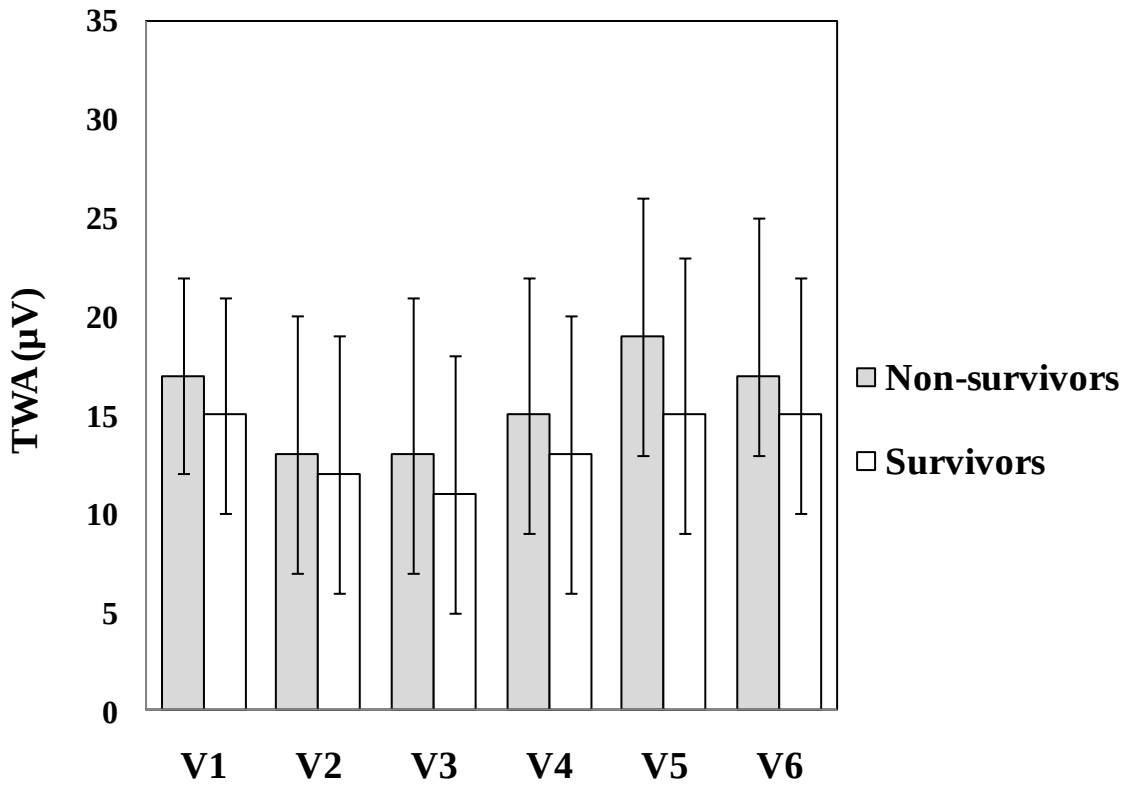


Fig. 6. Maximum TWA (median and interquantile range) during exercise in precordial leads between survivors and non-survivors. The differences between these two groups were significant (p<0.05) in leads V1 and V3–V6. (Modified from Leino et al. 2011.)

During the recovery after the exercise, heightened TWA was found in 3.9% of patients when we used the cut-off point of 60 µV (Study IV). Lowering the cut-off point to 20 µV led 51.3% patients to be classified as abnormal. During the recovery phase, TWA was different between the survivors and the non-survivors (26.7±23.4 µV versus 31.3±19.5 µV, p=0.03). After adjustment for the previously mentioned covariates, TWA ≥60 µV during recovery was associated with all-cause mortality (HR 2.4, 95% CI 1.3-4.4, p<0.01) and cardiovascular mortality (HR 3.5, 95% CI 1.6-7.9, p<0.01) (Study IV). Using a TWA cut-off point of 20 µV, the association between TWA and mortality was not significant with regard to either all-cause or cardiovascular mortality (Study IV).

Table 4. Statistically significant hazard ratios (HR) and 95% confidence intervals (CI) for T-wave alternans (TWA) in precordial leads using Cox multivariable regression analysis. Covariates in the multivariable analysis were sex, age, body-mass index (BMI), smoking, use of β-blockers, reached maximum heart rate, prior myocardial infarction (MI), coronary heart disease (CHD) and diabetes. (Study V.)

	All cause death			
	HR	95 CI (lower)	95 CI (upper)	p
TWA in all precordial leads	1.011	1.001	1.021	0.026
TWA in V5	1.015	1.004	1.020	0.006
TWA in V2, V3, V4, V5 or V6	1.012	1.003	1.022	0.012
TWA in V3, V4, V5 or V6	1.013	1.003	1.023	0.007
TWA in V4, V5 or V6	1.012	1.002	1.022	0.019
TWA in V5 or V6	1.014	1.003	1.025	0.010
TWA in V4 or V5	1.012	1.002	1.021	0.021
TWA in V3, V4 or V5	1.012	1.003	1.022	0.012

	Cardiovascular death			
	HR	95 CI (lower)	95 CI (upper)	p
TWA in all precordial leads	1.020	1.006	1.034	0.005
TWA in V5	1.022	1.007	1.038	0.004
TWA in V2, V3, V4, V5 or V6	1.023	1.010	1.036	0.001
TWA in V3, V4, V5 or V6	1.024	1.011	1.038	0.000
TWA in V4, V5 or V6	1.022	1.009	1.036	0.001
TWA in V5 or V6	1.023	1.008	1.038	0.003
TWA in V4 or V5	1.021	1.007	1.035	0.003
TWA in V3, V4 or V5	1.022	1.009	1.036	0.001

	SCD			
	HR	95 CI (lower)	95 CI (upper)	p
TWA in V3	1.023	1.003	1.044	0.025
TWA in V5	1.023	1.002	1.045	0.033
TWA in V4 or V5	1.022	1.002	1.041	0.031
TWA in V3, V4 or V5	1.021	1.002	1.041	0.029

9.5 PR interval before and after exercise

The 135 (6.8%) patients who had first-degree AV block, 6.7% of whom faced cardiovascular death during follow-up, were significantly older (64 vs. 56 years, $p<0.01$) and more obese (BMI 29 vs. 27, $p<0.01$). They were more often men (73 vs. 62%, $p<0.01$), non-smokers (84 vs. 72%, $p<0.01$) and users of β-blockers (81 vs. 40%, $p<0.01$). Furthermore, their heart rate during pre-exercise (65 vs. 74 bpm, $p<0.01$), exercise (127 vs. 147 bpm, $p<0.01$) as well as two minutes after exercise (82 vs. 99 bpm, $p<0.01$) was significantly lower than of those with no AV block. PR interval quintiles did not differed significantly between cardiovascular death patients and survivors when measured during the pre-exercise phase. During the recovery after the exercise the trend of cardiovascular mortality rates was significantly ($p<0.01$) higher toward the highest quintiles of PR interval (Fig. 7). According to Cox regression analysis after adjustment for typical risk factors (sex, age, BMI, use of β-blockers, heart rate, QRS-complex width, CHD and diabetes), first-degree AV block at the recovery phase was a significant predictor of cardiovascular mortality (HR 2.73, 95% CI 1.25-5.95, $p=0.01$). The adjusted PR interval as a continuous variable also predicted mortality significantly (HR 1.36, 95% CI 1.15-1.62, $p<0.01$). During the pre-exercise phase the PR interval did not predict mortality either as a continuous or a dichotomized variable. (Table 5.) (Study III.)

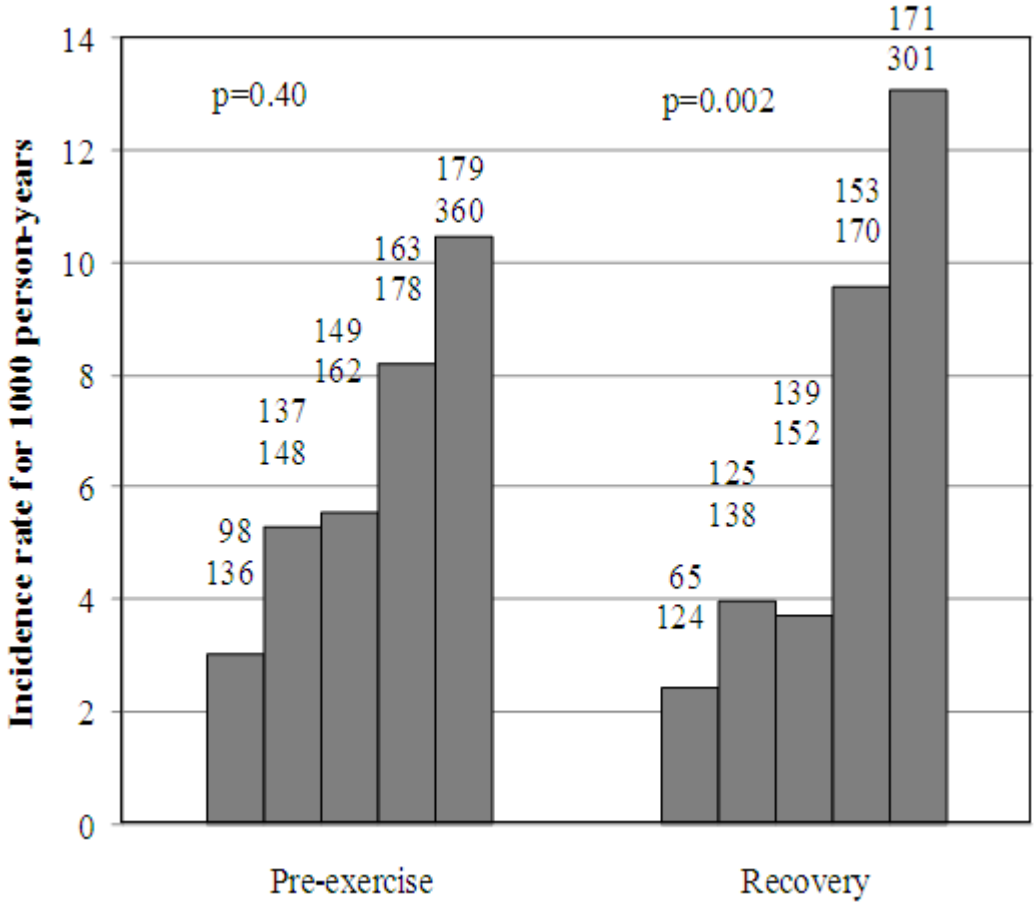


Fig. 7. Unadjusted incidence rate of cardiovascular mortality per 1,000 person-years among patients divided into quintiles based on PR intervals in the pre- and post-exercise phases. The range of PR intervals (ms) is given for each bin. The p-values for trends are calculated with Poisson regression. (Nieminen et al. 2010.)

9.6 Combinations of exercise test variables

9.6.1 Rate-pressure product

The product of SAP and heart rate during the exercise (RPP_{peak}) was not significantly associated with an increased risk for either all-cause or cardiac mortality or SCD (Study II) (Table 5). The recovery of RPP after exercise ($RPP_{recovery}$) yielded the HRs of 0.85 for SCD (95% CI 0.73-0.98, p=0.02), 0.87 for cardiovascular death (95% CI 0.78-0.97, p=0.01) and 0.87 for all-cause mortality (95% CI 0.81-0.94, p<0.01). The prevalence of death was clearly higher in the quintile with the lowest $RPP_{recovery}$ than the one with the highest. (Fig. 8.)

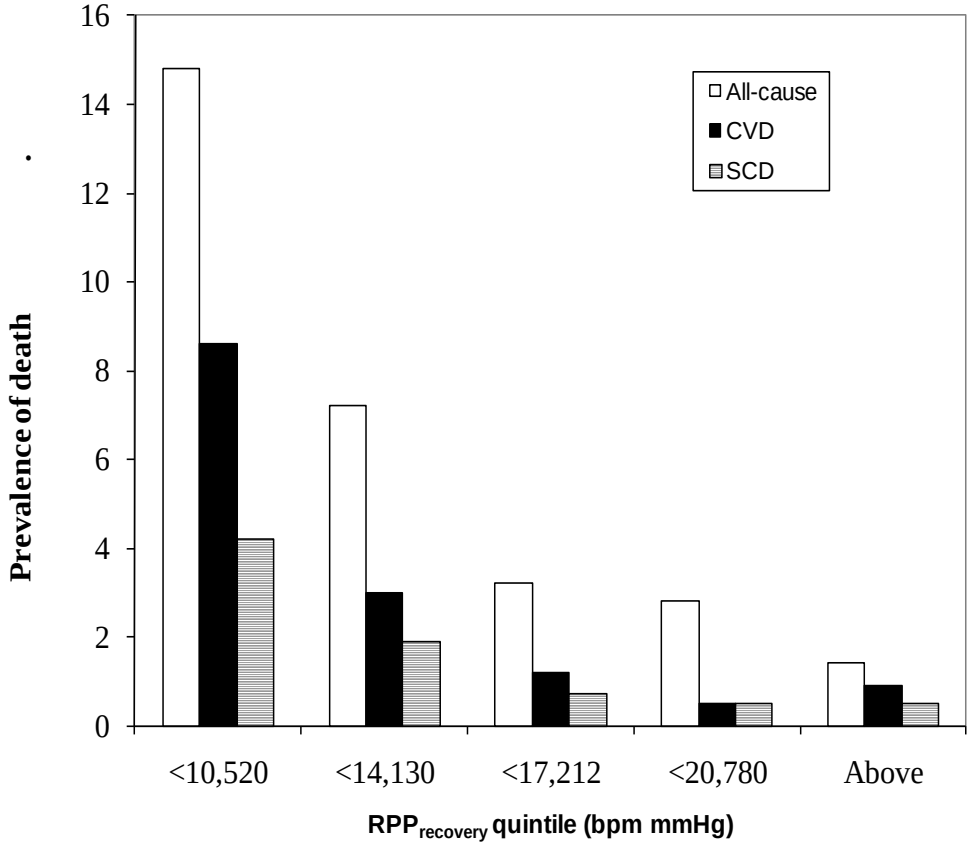


Fig. 8. Prevalence (%) of unadjusted all-cause and cardiovascular (CVD) mortality as well as sudden cardiac death (SCD) for the recovery of rate-pressure product ($RPP_{recovery)}$ quintiles. (Nieminen et al. 2008.)

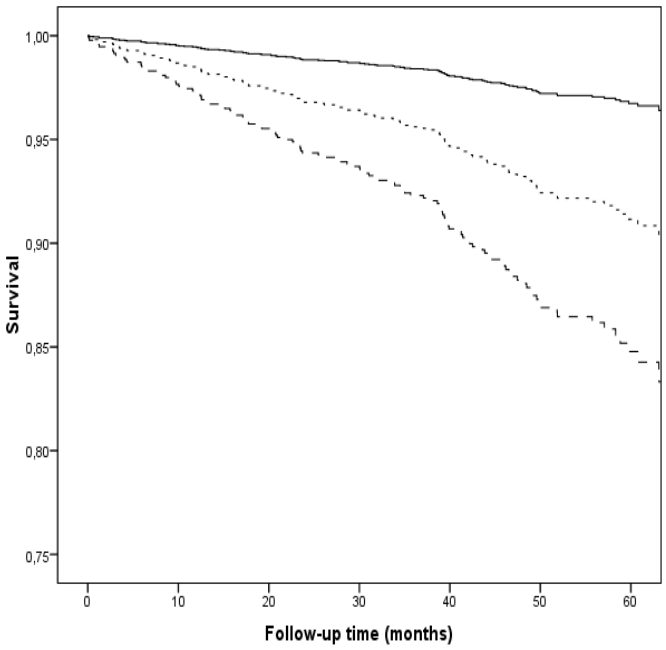
9.6.2 Combination of heart rate recovery and T-wave alternans

Heart rate recovery lower than 18 bpm one minute after the cessation of exercise, combined with TWA greater than 20 µV measured during the recovery, yielded the HRs of 3.0 for all-cause mortality (95% CI 1.6-5.5, p<0.01) and 5.2 for cardiovascular mortality (95% CI 1.8-14.4, p<0.01) (Table 5.). When only one of these variables was classified as abnormal, the HRs were 2.0 for all-cause mortality (95% CI 1.2-3.5, p=0.01) and 3.5 for cardiovascular mortality (95% CI 1.3-9.1, p=0.01) (Table 5.). The cut-off point of 60 µV for TWA measured during the recovery as combined with abnormal heart rate recovery yielded an HR of 6.1 for all-cause mortality (95% CI 2.8-13.2, p<0.01) and 8.0 for cardiovascular mortality (95% CI 2.9-22.0, p<0.01) (Table 5.). When TWA was measured during the exercise, the cut-off point of 60 µV combined with abnormal heart rate recovery predicted all-cause mortality with an HR of 5.0 (95% CI 2.1-12.1, p<0.01) and

cardiovascular mortality with an HR of 12.3 (95% CI 4.3-35.3, p<0.01) (Table 5.). All these combinations exceeded the predictive power of ST segment deviation (0.1 mV) during the exercise. Survival curves for the exercise-based TWA ≥60 μV in combination with abnormal heart rate recovery are shown in Fig. 9.

We also calculated the Harrell's C indices for all parameters in combination with HRR and TWA. The Harrell's C index is a generalisation of the area under the receiver-operating characteristic curve that allows for censored data. Of all the combinations tested, the highest C indices were yielded by exercise-based TWA ≥60 μV in combination with abnormal heart rate recovery, namely 0.677 for all-cause mortality (95% CI 0.631-0.723) and 0.713 for (95% CI 0.648-0.777) cardiovascular mortality. (Study IV.)

A) All-cause mortality

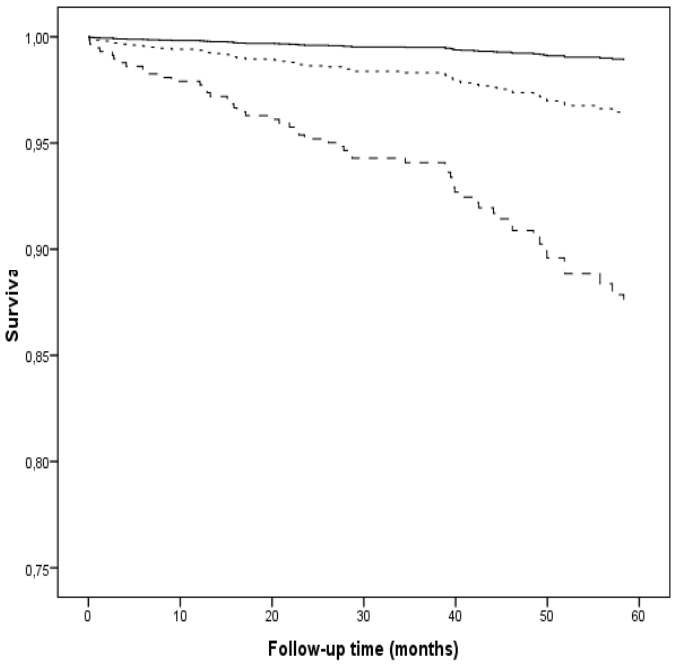


TWA(exercise) <60 µV and HRR >18 bpm

TWA(exercise) ≥60 µV or HRR ≤18 bpm

TWA(exercise) ≥60 µV and HRR ≤18 bpm

B) Cardiovascular mortality



TWA(exercise) <60 µV and HRR >18 bpm

TWA(exercise) ≥60 µV or HRR ≤18 bpm

TWA(exercise) ≥60 µV and HRR ≤18 bpm

Fig. 9. Adjusted survival curves by Cox regression for the exercise-based TWA ≥60 µV in combination with abnormal heart rate recovery. In the Cox regression analysis, the difference in survival between groups was statistically significant ($p<0.01$). Please note that the scale for the y-axis is from 0.75 to 1.00. (Leino et al. 2009.)

Table 5. Hazard ratios and 95% confidence intervals for the exercise test parameters during pre-exercise, peak exercise and recovery. All results are statistically significant ($p<0.05$).

		Pre-exercise		
		All-cause death	**CVD**	**SCD**
HRV (log) (VLF power)	Study I	0.56 (0.43-0.72)		
HRV (log) (LF power)	Study I	0.58 (0.45-0.74)		
HRV (log) (LF power n.u.)	Study I	0.75 (0.64-0.87)		
HRV (log) (HF power %)	Study I	1.44 (1.09-1.88)		
HRV (log) (RMSSD)	Study I	0.72 (0.56-0.92)		
HRV (pcSD2)	Study I	0.61 (0.43-0.86)		
PR interval (ms)	Study III		NS	
First-degree AV block	Study III		NS	

		Peak exercise		
		All-cause death	**CVD**	**SCD**
HRV (log) (VLF power)	Study I	NS		
HRV (log) (LF power)	Study I	NS		
HRV (log) (LF power n.u.)	Study I	NS		
HRV (log) (HF power %)	Study I	NS		
HRV (log) (RMSSD)	Study I	NS		
HRV (pcSD2)	Study I	NS		
SAP (mmHg)	Study II	0.99 (0.98-1.00)	NS	NS
TWA (μV)	Study V	1.011 (1.001-1.021)	1.020 (1.006-1.034)	NS
TWA ≥60 μV	Study IV	2.5 (1.4-4.5)	5.8 (3.1-11.1)	
TWA in lead V5 (μV)	Study V	1.015 (1.004-1.020)	1.022 (1.007-1.038)	1.023 (1.002-1.045)
TWA ≥60 μV+ HRR ≤18 bpm	Study IV	5.0 (2.1-12.1)	12.3 (4.3-35.8)	
RPP (1000 bpm mmHg)	Study II	NS	NS	NS

		Recovery		
		All-cause death	**CVD**	**SCD**
Heart rate recovery ≤18 bpm	Study IV	2.5 (1.6-3.7)	2.3 (1.3-4.2)	
Heart rate recovery ≤18 bpm	Study II	2.4 (1.6-3.6)	2.4 (1.3-4.3)	NS
HRV (log) (VLF power)	Study I	NS		
HRV (log) (LF power)	Study I	NS		
HRV (log) (LF power n.u.)	Study I	NS		
HRV (log) (HF power %)	Study I	NS		
HRV (log) (RMSSD)	Study I	NS		
HRV (pcSD2)	Study I	NS		
SAP (mmHg)	Study II	NS	NS	NS
TWA ≥60 µV	Study IV	2.4 (1.3-4.4)	3.5 (1.6-7.9)	
TWA ≥20 µV	Study IV	NS	NS	
PR-interval (ms)	Study III		1.36 (1.15-1.62)	
First-degree AV block	Study III		2.73 (1.25-5.95)	
TWA ≥60 µV+ HRR ≤18 bpm	Study IV	6.1 (2.8-13.2)	8.0 (2.9-22.0)	
RPP (1000 bpm mmHg)	Study II	0.87 (0.81-0.94)	0.87 (0.78-0.97)	0.85 (0.73-0.98)

CVD=cardiovascular death; HF=high frequency; HRR=heart rate recovery; HRV=heart rate variability; LF=low frequency; NS=non significant; pcSD =standard deviation of Poincare plot; RMSSD=square root of the mean squared differences in N-N intervals; RPP=rate-pressure product; SAP=systolic arterial pressure; SCD=sudden cardiac death; TWA=T-wave alternans; VLF=very low frequency;

10 DISCUSSION

10.1 Requirements for estimating cardiovascular prognosis

The background of cardiovascular health and prognosis is multifactorial. Therefore, screening high-risk patients among large populations is challenging. Screening CHD patients who are at risk for an acute MI leading to SCD is only a single aspect in the risk stratification. Other cardiovascular endpoints besides SCD should also be taken into account. In addition to CHD, such factors as vulnerability to arrhythmias, anatomical abnormalities, electrolyte imbalances, genetic disturbances, valvular disturbances and many others could raise patient into the high-risk group.

The risk for cardiovascular events is much more likely to be a continuum from low-risk to high-risk than a single cut-off point dividing patients into either group. Choosing the cut-off points has been considered a major problem in prognostic studies, because creating non-clinically based cut-off points has been suggested to generate false outcomes. A negative value of a parameter cannot relieve the patient from facing the investigated end-point in future. However, cut-off points can aid clinicians in decision-making and provide assistance when generating guidelines for further examinations and therapy. Choosing the cut-off points should be based on the study population's pre-test possibility for cardiovascular events, and different cut-off points should be determined for different populations. Conventional dichotomy limits derived from or used in univariate analyses do not provide the best prediction of events when several predictors are combined. (Redwood et al. 1997.) Therefore, optimal prediction of future cardiovascular events is obtained by changing these dichotomy limits when variables are combined. Optimal dichotomy limits are also influenced by the combination of variables used and by the clinical event selected. (Redwood et al. 1997.)

With low-risk patients, the clinical focus in terms of cardiovascular diseases should be on primary prevention. High-risk patients should undergo further investigations, such as coronary angiography, if necessary. In some cases treatment could be commenced immediately. (Gibbons et al. 1997, Gibbons 2008, Miller 2008.) In the ideal test, the test protocol would be uniform between hospitals. Because cardiovascular death could be derived from several reasons, the ideal test would take account of all the possibilities for abnormal cardiovascular function, including the autonomic

function of the cardiovascular system, the mechanical function of the heart as well as anatomical abnormalities and possible origins for arrhythmias.

10.2 Sudden cardiac death

When the definition of one hour from the onset of symptoms is applied, the proportion SCDs in all natural deaths is 13% (Zipes et al. 2006). In contrast, a community-wide study reported that more than 18% of all deaths were SCDs, using a 24-hour definition (De Vreede-Swagemakers et al. 1997). The proportion of SCDs among all cardiovascular deaths has been shown to be over 60% (Zheng et al. 2001). The limit of 24 hours is likely to overestimate the true SCD incidence, while the limit of 1 hour after symptom onset might result in an underestimation (Adabag et al. 2010a). Approximately 25% of patients will be misclassified if time is the only criterion used (Greene et al. 1989). The longer the follow-up, the smaller the proportion of SCDs among all deaths, indicating that a major amount of SCDs occur in the near future after the chain of events which have led to starting the follow-up. Because SCD occurs shortly after the onset of symptoms, there is little or no time for effective medical interventions. Therefore, effective and clinically useful markers of risk as prevention appear to be only the viable approach to decrease the incidence of SCD.

In FINCAVAS we have used the 24-hour definition, and 1.4–1.9% of the study patients have faced SCD during the follow-up. This figure accounts for approximately 45–59% of all cardiovascular deaths and 20–34% of all deaths during the follow-up. This is parallel to the previous literature (Myerberg et al. 1993, Myerberg et al. 1997). The classification of deaths between SCD and other cardiovascular deaths is never clear-cut, and this classification is also not faultless in FINCAVAS. However, the mortality data was received from the Causes of Death Register which has been ascertained as a reliable source (Pajunen et al. 2005). The death certificates were assessed and classified into death classes by independent experts. Many of the causes of death were also confirmed by autopsy. The autopsy rate was approximately 40% for all deaths and 60% for SCD in Data 2 (Minkkinen et al. 2009).

In the past, biological death was an immediate consequence of cardiac arrest, usually occurring within minutes. Because life-supporting systems have developed, patients may today remain biologically alive for a long period after the onset of a pathophysiological process that has caused irreversible damage. (Priori and Zipes 2006.) In these cases the death would be defined as a cardiovascular death due to the time limits, although the basic nature of death would be SCD. Patients with long-term and severe cardiovascular disease may also confuse the distribution

between SCDs and other cardiovascular deaths. These individuals have had a great risk for SCD, but another type of cardiovascular death – for example, heart failure – had caused the death first. Therefore, the death has been classified as a cardiovascular death, even though it might have been an SCD as well. However, the absolute diagnosis of SCD would require continuous ECG monitoring. Including only those patients who have had their ECG monitored during the last days before death in the study population would lead a marked work-up bias.

The underlying factors behind SCD include a complex interplay between the anatomic and functional substrates, modulated by the transient events that perturb the balance, and the impact of the underlying potential arrhythmia mechanisms of all hearts that precipitate SCD (Akhtar et al. 1991, Myerburg et al. 1993, Zipes and Wellens 1998, Huikuri et al. 2001, Chugh et al. 2008, Buxton 2009) (Fig. 10). Any of these factors can interact with the others in almost endless permutations and combinations. Usually, the interaction of two factors is insufficient to produce SCD, unless the single abnormality is extremely severe. (Zipes and Wellens 1998.) Combining a third factor to this process is much more likely to lead to SCD. Because of this multifactorial basis of SCD, and because many of the victims do not have symptoms or signs identifying them as being at high risk before the event, the prevention of SCD is complicated. (Adabag et al. 2010b.) Furthermore, testing the effectiveness of primary preventive measures – such as abstinence from smoking, exercise, weight reduction as well as the controlling of blood pressure and lipid abnormalities – in patients with no history of cardiovascular disease is impossible with satisfactory accuracy. Testing the effectiveness should include the randomisation of preventive versus non-preventive measures as well as accurate categorizing of causes of death. (Zipes and Wellens 1998.) However, because most cases of SCD occur in the population suffering from CHD, it is logical that in recent years the most attention has been given to secondary preventive therapy in patients with proven CHD and especially to survivors of an MI (Zipes and Wellens 1998, Zheng et al. 2001).

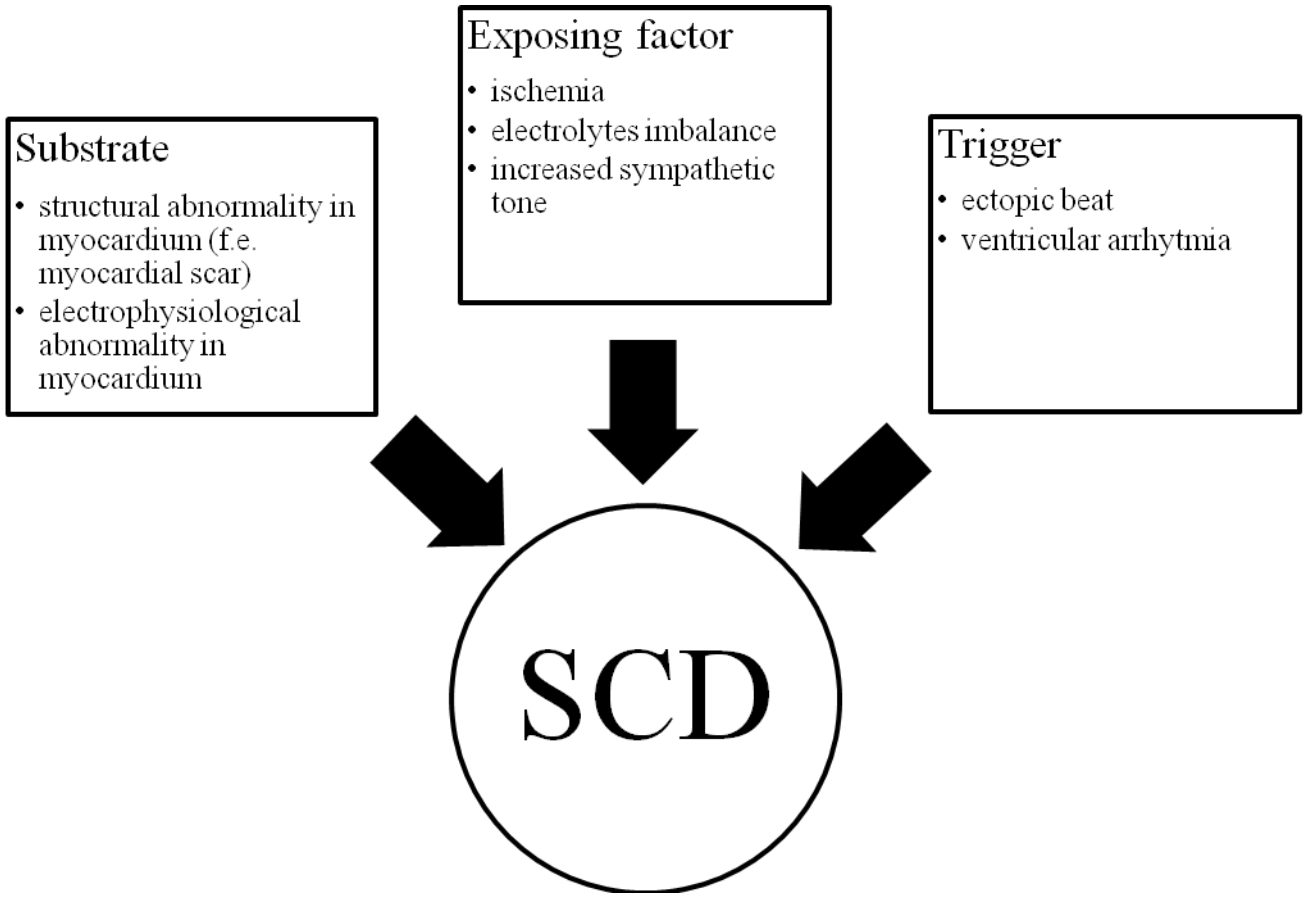


Fig. 10. Multifactorial basis of sudden cardiac death (SCD). (Myerburg et al. 1993, Zipes and Wellens 1998, Huikuri et al. 2001.)

10.3 Major findings in the present study

10.3.1 Haemodynamic parameters

10.3.1.1 Heart rate recovery

For abnormal heart rate recovery we used the cut-off point of 18 bpm one minute after the cessation of exercise. Abnormal heart rate recovery as a categorised variable was significantly associated with increased risk of cardiovascular and all-cause mortality, with HRs of 2.3–2.5 in our study with almost 2,000 patients (Studies II, IV), but for SCD it was not a significant predictor (Study II). Of the 122 deaths that occurred during the follow-up, only 33 were classified as SCDs, which may

have decreased the statistical significance of the results. In previous studies, abnormal heart rate recovery has been a significant predictor for all-cause and cardiovascular death as well as SCD, although the cut-off points and recovery protocols have varied substantially (Cole et al. 1999, Cole et al. 2000, Nishime et al. 2000, Jouven et al. 2005). Furthermore, many of the previous studies have used treadmill exercise which has been investigated to lead to abnormal heart rate recovery more frequently than bicycle exercise. Therefore, a direct comparison between the results is difficult.

Heart rate recovery reflects the withdrawal of the sympathetic nervous system and the activation of the parasympathetic nervous system, offering an important component of risk stratification within the clinical exercise test. Abnormal interplay between these two has been proposed to be arrhytmogenic. Abnormal heart rate recovery can also reflect the patient's poor physical fitness and aerobic capacity, which is associated with poorer prognosis. For instance, in our study heart rate recovery is usually determined as an absolute difference between heart rate at peak exercise and heart rate after the exercise. Because maximal heart rate during the exercise as well as at rest can vary greatly, absolute values might lead to similar results in very different physiological situations. Especially a too low level of exercise may lead to too low heart rate at peak exercise and therefore to too low heart rate recovery, although the recovery to the basic level would be normal. In our analysis heart rate recovery with the cut-off point of 18 bpm was associated with worse outcome among patients with high (>130 bpm) maximal heart rate as well among patients with low (≤130 bpm) maximal heart rate. Nevertheless, the prognostic power of heart rate recovery was greater among patients with low maximal heart rate, potentially indicating the greater relative influence of the same heart rate recovery values compared to the maximal heart rate. Therefore, heart rate response to exercise should be seen as a continuum from the resting level to peak exercise and, finally, to the recovery phase after the exercise.

10.3.1.2 Blood pressure

We were able to demonstrate that the higher the SAP during peak exercise, the lower the risk of all-cause mortality (Study II). This reflects the fact the patients with an underlying heart disease are not able to generate elevated blood pressures. Underlying heart disease may also lead to a short total working time that does not allow enough time for the blood pressure to increase normally. In previous studies, exercise hypotension has been a sign of worse prognosis in patients with a previous MI and chronic heart failure (Hedberg et al. 2009, Nishiyama et al. 2010). Therefore,

abnormal SAP behaviour in any direction during the exercise should not be ignored, but it should be consireded in proportion to the patient's cardiovascular background.

The recovery of SAP after exercise did not predict any type of mortality (Study II). We defined blood pressure recovery as a difference between maximal SAP during the exercise and SAP 4 minutes after the cessation of exercise. During the first few minutes of recovery, the changes in the autonomic nervous system are fast, enabling the autonomic nervous system to return to the normal level. Patients with only minor abnormality in shifting from the sympathetic to the parasympathetic tone may not be detactable after more than 4 minutes of recovery. However, the limit of 4 minutes is probably more specific than shorter time limits.

The differences in maximal heart rate during the exercise might have an influence on the maximal blood pressure during the exercise. Therefore, we tested the difference in maximal SAP during the exercise between the patients with maximum heart rate ≤130 bpm (N=1,141) and the patients with maximal heart rate >130 bpm (N=3,427). Patients with maximum heart rate ≤130 bpm had significantly lower SAP levels (182±29 mmHg vs. 197±28 mmHg, $p<0.01$) during exercise than other patients and also the difference between maximum SAP during the exercise and the lowest SAP during the recovery was significantly lower (37±24 mmHg vs. 54±24 mmHg, $p<0.01$) than other patients (Data 3). However, our final data do not include SAP values obtained after 4 minutes of recovery. We therefore did not compare the prognostic power of SAP during the recovery between these two groups.

10.3.2 ECG parameters

10.3.2.1 Heart rate variability

Before the exercise, greater HRV in all frequency bands (HF, LF, VLF) and in the time-domain variable (RMSSD) was significantly associated with better prognosis, supporting the previous results (Study I). During the exercise, the influence of the HF band strengthens over the LF band. This is a compelling fact, noticed also in the previous literature (Perini and Veicsteinas 2003), because the HF band represents the vagal activity which is supposed to decrease as exercise intensity increases. One explanation might be the incapability of the sympathetic nervous system to control heart rate as swiftly and accurately as the parasympathetic nervous system, leading to HF band overdrive during the exercise. In support of a relationship between the HF and LF bands during the exercise, previous results have also shown that the influence of the HF band was lower in

the recovery period than in the last two minutes of exercise. (Freeman et al. 2006.) Because of these findings, HRV is considered to reflect the autonomic nervous system, but other, still unknown mechanisms also create a complex interplay with the autonomic nervous system. Atrial stretch, direct mechanical oscillations related to increased respirations, and metaboreflexes have proposed to interact with the autonomic nervous system in producing HRV. (Bernardi et al. 1990, Iellamo et al. 2006.) During maximum exercise, we did not find greater HRV to be a significant predictor of mortality. The shortening of R-R intervals during the exercise decreases the possibility for variation in heart rate. In the study by Dewey and colleagues (2007), greater HRV during exercise and recovery was associated with increased risk of death, which was discordant with the literature on HRV at rest. Our hypothesis was that these compelling results might due to different basic heart rate levels between patients. A broad range in R-R intervals makes the comparison between patients impossible, which leads to a misinterpretation of HRV changes. Therefore, we suggested heart rate correction before HRV analysis to make the HRV parameters comparable between patients. For heart rate correction, we multiply every R-R interval with the square of the heart rate of the corresponding ECG segment. After this heart rate correction, HRV during peak exercise remained a non-significant predictor of death. During the recovery after the exercise, HRV was not associated with mortality in our study.

Our study confirms the previous result concerning attenuated resting HRV as a prognostic marker of increased risk of mortality. Though the prognostic power of HRV at rest has undoubtedly been stated, it seems that during the exercise it does not offer valuable information about a patient's prognosis. Nevertheless, the pathophysiology of HRV is still unclear, particularly during physical exercise. More physiological studies are needed to fill this gap.

10.3.2.2 PR interval

A prolonged PR interval at pre-exercise, determined as PR interval >200 ms, was not associated with cardiovascular mortality in our study (Study III). This supports the earlier findings that first-degree AV block at rest has not predicted cardiovascular outcomes during 10 years' follow-up, even though the follow-up in FINCAVAS was shorter (Perlman et al. 1971, Mymin et al. 1986). To the best of our knowledge, a prolonged PR interval or first-degree AV block during the recovery after exercise has not been investigated earlier. We found first-degree AV block during the recovery phase to be significantly associated with cardiovascular mortality, with an HR of 2.73 (95% CI 1.25-5.95, p=0.012) (Study III). The explanation and pathophysiology behind this finding are

unclear, but the most plausible explanation relates to intrinsic factors affecting the intracardiac conduction and, therefore, the PR interval. In our study PR interval was measured two minutes after the cessation of exercise. At that time point heart rate was markedly elevated in many patients, even though it was lower than during maximal exercise. Dysfunctional intrinsic AV node regulation may be manifested only at elevated heart rates, leading to prolonged PR interval. This dysfunctionality may be a precursor of a prolonged PR interval at rest, which will develop over the years. In a recent study, an association was demonstrated between prolonged PR interval and increased risk of cardiovascular events over a 20-year follow-up (Cheng et al. 2009), and based on these results it would be interesting to see how the PR interval will behave later on in the follow-up among the FINCAVAS study population.

The PR interval is a valuable tool in risk stratification with a clinical exercise test, because it reflects both autonomic and electrophysiological properties of the cardiovascular system. Although first-degree AV block at rest hardly associates with an increased risk of cardiovascular events, the measurement of PR interval during the recovery from exercise may be more useful in clinical practice. Determining PR interval during recovery may identify patients who will develop an AV block at rest during the following years, and enhanced primary prevention could be directed at those patients.

10.3.2.3 T-wave alternans

TWA has proved to be associated with future cardiovascular events in many patient groups, including the FINCAVAS population. In our study with almost 2,000 patients, abnormal TWA (≥60 μV) measured during peak exercise has prognostic power for future cardiovascular and all-cause mortality with an HR of 5.8 and 2.5, respectively. During the recovery, the prognostic power for cardiovascular mortality was slightly weaker (HR 3.5), while the risk of all-cause mortality remains almost the same (HR 2.4) (Study IV). After expanding the study population to almost 4,000 patients, the maximum TWA became a statistically significant predictor for all-cause mortality (HR 1.01) and cardiovascular mortality (HR 1.02) but not for SCD (Study V). Despite the statistical significance, the clinical significance of HRs between 1.01 and 1.02 is questionable. The differences between the two sub-studies, with partly the same study population, are probably due to the following reasons. In Study IV we took account of TWA values at heart rates of <125 bpm, because at high heart rates TWA values may be influenced by noise. At the time of expanding the study population the TWA data was reread, meaning that TWA values of ≥46 μV were checked by

a physician investigator and corrected if necessary or discarded based on noise or baseline wander. After controlling noise by rereading, we abandoned the heart rate restriction.

The prognostic power of TWA monitored in single and combined precordial leads had not been studied systematically prior to our study (Study V). In ambulatory ECG, TWA in leads V1, V3 or V5 has been reported to be associated with increased risk of cardiovascular outcomes (Maeda et al. 2009, Sakaki et al. 2009). We found that during the exercise the greatest TWA values were measured from leads V1, V5 and V6. Lead V5 achieved the most powerful prediction for SCD as well as cardiovascular and all-cause mortality, indicating that restricting the assessment of TWA to lead V5 alone may perform better in risk stratification than using all precordial leads. Monitoring generalised elevations in TWA across the precordium did not offer an advantage in the prediction of mortality. TWA is thought to be a regionally specific phenomenon, the magnitude of which reflects the degree of heterogeneity of repolarisation.

Our findings concerning the prognostic power of TWA for the study population of almost 4,000 patients are modest. Compared to, for example, heart rate recovery or PR interval, TWA is a relatively new variable in prognosis estimation, and studies in different subpopulations are sporadic. According the current study, general elevations in TWA may not become a common risk marker for worse prognosis among the low-risk population, but the variable may provide helpful additional information about prognosis for selected patient populations. According to Bayes' theorem, the positive accuracy of a test might be lost when dealing with low mortality rates, and the accuracy of a test may improve when changing from the general population to more specific groups. The advantage of TWA is its high specificity when compared to other risk markers, but more studies are still needed to investigate who are the patients who will benefit from TWA analysis. According to our findings, TWA is worth further investigations, and combinated to other prognostic variables, namely heart rate recovery in this study, it exceeds the prognostic power of single variables.

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10.3.3 Combinations of parameters; rate-pressure product and combination of heart rate recovery and T-wave alternans

10.3.3.1 Rate-pressure product

RPP has been reported to be a significant marker of mortality at rest and during peak exercise, but its significance during the recovery phase after exercise had not been studied earlier (Ciaroni et al. 1993, Sadrzadeh Rafie et al. 2008). During peak exercise, RPP was not significantly associated with an increased risk of SCD or cardiovascular or total mortality, but $RPP_{recovery}$ had an inverse relation with all three types of death with an HR of 0.85–0.87 (Study II). Both decreased heart rate recovery and $SAP_{recovery}$ mainly reflect abnormal recovery of the autonomic nervous system, namely increased sympathetic activity which increases cardiac stress. Maximal heart rate during the exercise has an effect on both; heart rate recovery and $SAP_{recovery.}$ Therefore, $RPP_{recovery}$ is probably dependent on maximal heart rate during the exercise. In this study we did not tested the influence of maximal heart rate on $RPP_{recovery.}$ In previous reports, a close correlation has been observed between RPP, myocardial oxygen consumption and coronary blood flow during exercise (Kitamura et al. 1972). As a part of a clinical exercise test, $RPP_{recovery}$ may be useful in identifying patients with underlying CHD. As $RPP_{recovery}$ is simple to measure and interpret, it is worthy of more detailed investigations. More studies are needed also for determining abnormal values of $RPP_{recovery}$ for different patient groups.

10.3.3.2 Combination of heart rate recovery and T-wave alternans

For enhancing the the sensitivity and specificity of the clinical exercise test, we hypothesised that heart rate recovery, reflecting the autonomic recovery of the cardiovascular system, and TWA reflecting an electrically unstable myocardium, could provide a picture of cardiovascular function by scoping it from two different perspectives. Abnormal heart rate recovery could indicate impaired vagus nerve activation and lessened capacity to withdraw sympathetic nerve tone, both of which are known to be arrhythmogenic. Therefore, the presence of both abnormal heart rate recovery and TWA would be suggested to be associated with a high risk of cardiovascular events. The prognostic power for all-cause and cardiovascular mortality of this combination exceeded the prognostic power of either variable alone as well as that of the traditionally used ST segment deviation. Patients with abnormal values for both of these variables suffered from cardiovascular mortality significantly more often than patients with normal values. (Study IV.)

However, conventional dichotomy limits used in univariate analyses have been proposed to not provide the best prediction of events when several predictors are combined (Redwood et al. 1997). The optimum cut-off points should be selected individually for each combination of variables and by the clinical event selected. Therefore, the prognostic power of the combination of heart rate recovery and TWA may be even higher than the results of the present study would suggest.

10.3.4 Cardiovascular risk stratification and exercise test in future

Cardiovascular risk stratification is based on the evaluation of patients' current risk state and the probability that a given patient will progress to a higher-risk state in future. Factors representing the current risk state include the mechanical function of the left ventricle, the existence and severity of CHD, the electrical stability of the heart, evidence of a recent coronary plaque rupture indicating an increased short-term risk, and general health including non-coronary co-morbidity. (Gibbons et al. 1997.) The probability for a given patient to progress to a higher risk state depends primarily on factors predisposing to the progression of an underlying atherosclerotic disease, such as smoking, hypercholesterolemia, diabetes and hypertension (Gibbons et al. 1997). The same factors are widely known in primary prevention for patients free from cardiac diseases. Exercise capacity has been suggested to be the most important marker of risk during exercise testing, but alone it describes only one aspect of cardiovascular prognosis (Gibbons et al. 1997, Fowler-Brown et al. 2004, Lauer et al. 2005).

According to Bayes' theorem, any test used in a low-risk population will provide poor positive accuracy. Because SCD can be the first signal of an underlying cardiovascular problem, screening the low-risk population is important. To increase the accuracy of the tests used, the future of cardiovascular risk stratification in the low-risk population will probably focus on multiple variables or risk scores, which will take into account the current risk and the progression of risk alike. Multiple variables have been shown to perform better than single variables for predicting future mortality and arrhythmic events (Redwood et al. 1997). Furthermore, in the current study, the prognostic power of combined variables exceeded single parameters. Combined parameters have not been adopted into wide clinical use yet, but the possibility to estimate the cardiovascular state from several different perspectives would offer a great addition to risk stratification. Although the multiple variables as well as cardiovascular risk scores have been under investigation during the last few decades, the optimal combinations of variables are yet to be determined.

More attention should be paid to the recovery phase after exercise. In addition to maximal exercise, recovery after exercise is also a challenge to the heart as it requires a change in the function of the autonomic nervous system and the mechanical function of the heart. Therefore, the exercise test provides two sequential challenges to the heart to change its function. Abnormal working order in either the autonomic nervous system or the heart may lead to abnormal recovery and the emergence of abnormalities that would not be visible during exercise.

10.4 Bicycle exercise test versus treadmill exercise test

All exercise tests in the FINCAVAS population were performed by bicycle. Due to less upper body motion, the blood pressure and ECG measurements are easier to assess with this testing modality. Moreover, some elderly or obese patients prefer the bicycle, where less coordination is required and the risk of falling is lower. (Wolber et al. 2005.) The heart rate response to exercise has been reported to be significantly lower in a bicycle exercise test than a treadmill test due to the lower workload achieved. At the same time, similar RPP values have been reported due to higher SAP values during the bicycle test. (Wicks et al. 1978.) Another study reported differences in RPP values due to a significant difference in heart rate, whereas the values for SAP did not differ (Hambrecht et al. 1992). The treadmill exercise test has proven more sensitive in diagnosing CHD in asymptomatic men, because of better sensitivity in inducing ischemia and ST segment changes (Hambrecht et al. 1992). However, the sensitivity of the bicycle exercise test has been demonstrated to exceed treadmill testing in patients with critical CHD, because a sizeable group of patients with critical CHD could not adequately perform an exercise treadmill test (Timmis et al. 1979). Bicycle exercise will probably perform at least equally to the treadmill test as a prognostic means due to the higher accuracy of blood pressure measurements and ECG tracings, although the treadmill test might be slightly superior in diagnosing CHD (Wicks et al. 1978, Rahimi et al. 2006). However, because of the different body positions in bicycle and treadmill exercise protocols, direct comparison between the test results is difficult. Also, the results between different studies may not be compared because of various different exercise testing protocols and different patient populations.

The reached exercise level is strongly dependent on the patient's previous experience of the exercise mode. Subjects who are not experienced with the exercise mode usually stop exercise before reaching their maximum oxygen uptake. In Finland, bicycling is a very common mode of

exercise and the mode of the exercise has not been a problem in FINCAVAS. However, it is not possible to say what the results would have been had treadmill exercise been used.

10.5 Application and limitations of FINCAVAS

Worldwide, FINCAVAS is one of the largest clinical exercise test studies with continuous digital ECG. All patients in FINCAVAS were referred to a clinical exercise test at a university hospital. Exercise tests in Finland are performed in various healthcare provision facilities, including university hospitals. In addition to normal cardiovascular patients, the diagnosis and treatment of the most critical and challenging patients are centralised to university hospitals, which has raised a question concerning selection bias. Nevertheless, because of the low mortality rate among the FINCAVAS population, this population has been classified as a low-risk population and it probably reflects, in the best possible way, the variety of the population who are referred to exercise testing for clinical reasons. The heterogeneity of the patients referred to exercise testing has been ascertained as one of the strengths of FINCAVAS, but on the other hand, it makes the study settings challenging. Our study population consists of patients with a wide spectrum of ages, life styles, medications and histories of cardiac disease. The prognostic power of the parameters we have tested probably varies from one patient group to another. An investigated parameter may be a clear risk factor for one group of patients but not for others. The study does not separate different patient groups; in spite of the high total number of patients, dividing the population into subgroups led to an inadequately small number of outcomes for risk stratification. Because of various clinical indications for exercise testing, the exercise protocols varied from submaximal to maximal exercise. However, according to our original idea, including all patients with any clinical indication for exercise testing in our study is the optimal way to describe the large and varied population which performs exercise tests.

The total number of patients is almost 5,000, 321 of whom died from any cause. Of these deaths, 138 were defined as cardiovascular and 63 as SCDs. The small number of end point events, especially with regard to Data 1 and 2, may have affected the statistical power of our results. Defining milder cardiovascular events, such as an MI or the necessity of a pacemaker, as end points might have increased the prognostic power of the variables we studied. On the other hand, death is more unequivocal to define.

Cox regression analysis is a widely used method in risk stratification. In the multivariable Cox regression analysis, we used common cardiovascular risk factors as covariates, but the exact

combination of covariates differed between studies. Therefore, the direct comparison between the studies is difficult. Our purpose was to choose the most relevant covariates for every analysis. The Cox proportional regression model assumes that the effects of the predictor variables are constant over time, but as one of the limitations in FINCAVAS, we do not have information about the changes in the patients' lifestyle or medications during the follow-up.

11 SUMMARY AND CONCLUSIONS

This study provides evidence that the bicycle exercise test has prognostic potential when evaluating patients' risk for future all-cause and cardiovascular mortality as well as for SCD. To enhance the prognostic power of the exercise test, the test should be taken as a continuum from rest to the recovery phase. Combinations of single parameters can increase the accuracy of the exercise test by reflecting cardiovascular health from several perspectives. However, more studies are needed before exercise testing recommendations for risk stratification can be constructed. The principal findings and conclusions are:

I During the physical exertion or recovery phase after exertion, HRV does not have prognostic potential for future mortality. However, this study supports the previous notions that attenuated HRV at rest is a predictor of death.

II $RPP_{recovery}$ is a prognostic marker for all-cause and cardiovascular mortality as well as for SCD, exceeding the prognostic power of heart rate recovery or $SAP_{recovery}$ alone. $SAP_{recovery}$ measured alone is not a significant predictor of SCD or cardiovascular or all-cause mortality.

III Prolonged PR interval as well as first-degree AV block measured during the recovery phase after physical exertion is a risk stratifier for cardiovascular mortality. However, neither of these two variables have prognostic power during the pre-exercise phase.

IV Reduced heart rate recovery after exercise as combined with the heightened TWA during peak exercise powerfully predicts future all-cause and cardiovascular mortality. The prognostic power of this combination exceeds the prognostic power of either parameter alone or the commonly used ST segment deviation.

V Maximum TWA monitored from the anterolateral precordial lead V5 is a predictor of all-cause and cardiovascular mortality as well as of SCD during routine exercise testing. Peak TWA values rather than lower TWA elevations among several precordial leads should be employed for risk assessment.

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14 ORIGINAL PUBLICATIONS

Exercise-test-related heart rate variability and mortality The Finnish cardiovascular study

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Heart rate variability (HRV) or differences in beat-to-beat interval (*R–R* interval) is believed to reflect the status and the balance between the sympathetic and parasympathetic nervous systems [1]. Previously, it has been shown that lower resting HRV is associated with worse prognosis in many different patient populations, including survivors of acute myocardial infarction and patients without coronary heart disease (CHD) [2]. In contrast to the results at rest, a recent study found that greater HRV during an exercise treadmill test was linked to increased risk of death [2]. Specifically, a greater root mean square difference in *R–R* intervals (RMSSD) and several frequency domain variables were associated with increased risk of all-cause and cardiovascular death during peak exercise and the recovery phase [2]. We analyzed whether HRV parameters predict mortality in the patients of the Finnish Cardiovascular Study (FINCAVAS).

All consecutive patients coming in for a clinically indicated exercise test using a bicycle ergometer at Tampere University Hospital and willing to participate in the study were recruited between October 2001 and December 2004. The main indications for the exercise test were diagnosis of CHD (frequency 45%), testing vulnerability to arrhythmia during exercise (20%), and evaluation of work capacity (18%) and adequacy of the CHD treatment (16%). After excluding patients with insufficient recordings, marked arrhythmias or ectopic heartbeats, the total data included 1876 patients, 1190 men and 686 women. *R–R* interval data during the pre-exercise phase, the first and last minute of exercise, as well as during the first 2 min of recovery were analyzed using HRV Analysis Software [3]. The following time domain HRV variables were analyzed: mean *R–R*, standard deviation in *R–R* (SDNN), the square root of the mean squared differences in successive *R–R* intervals

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(RMSSD) and the Poincare plot analysis (pcSD1, pcSD2). For the frequency domain HRV variables, the *R–R* interval data was resolved into high frequency (HF, >0.15 Hz), low frequency (LF, 0.04–0.15 Hz), and very low frequency (VLF <0.04 Hz) components including absolute power of each bandwidth (power), power in normalized units (power n.u.), and percentage power (power%) using nonparametric fast Fourier transform. Non-normally distributed HRV variables were log-transformed prior to statistical analysis. A 2-sided *P* value <0.05 was considered statistically significant in the comparison of patient characteristics. Due to the large number of HRV parameter comparisons, $p<0.01$ was considered an appropriate threshold for significance in these analyses. The detailed study protocol of FINCAVAS has been described earlier [4].

Baseline characteristics of the study population and exercise test variables were compared using 2-tailed *t*-tests (for normally distributed continuous variables), Mann–Whitney *U*-tests (for non-normally distributed continuous variables), or χ^2 tests (for categorical variables). Changes in exercise test variables during different exercise periods were analyzed using one-way analysis of variance (ANOVA). Prognostic power of HRV variables were determined using Cox regression analysis. Univariable Cox analysis was first run for each HRV variable separately. Thereafter, the HRV variables with predictor effect in univariable analyses were evaluated in separate multivariable models with nine covariates: age, body mass index (BMI), metabolic equivalent of task (MET), sex, smoking (no/yes), use of β-blockers (no/yes), diabetes (no/yes), coronary heart disease (no/yes), and previous myocardial infarction (no/yes).

There were 101 (5.4%) deaths during the follow-up of 47.5±12.8 months (mean±SD). Patients who survived were significantly younger (56.0 years vs. 64.9 years, $p<0.01$), and they were more often female (37.5% vs. 19.8%, $p<0.01$). Smokers died significantly more often than non-smokers (36.7% vs. 26.8%, $p=0.03$). Survivors were less frequently on ACE inhibitors (22.7% vs. 31.7%, $p=0.02$) and β-blockers (59.6% vs. 82.2%, $p<0.01$) than non-survivors. Also, survivors were less likely to suffer from diabetes (11.5% vs. 18.8%, $p=0.03$), CHD (38.6% vs. 48.5%, $p=0.05$) and valvular heart disease (2.9% vs. 6.9%, $p=0.02$). Patients who died had exhibited significantly lower pre-exercise diastolic arterial pressure (80 mmHg vs. 75 mmHg, $p<0.01$), shorter duration of the test (7.7 min vs. 6.4 min, $p=0.01$), smaller exercise capacity (7.4 MET vs. 5.5 MET, $p<0.01$), and lower heart rate during exercise (148 bpm vs. 127 bpm, $p<0.01$). In ANOVA, mean *R–R* interval ($p<0.001$) and RMSSD ($p<0.001$) decreased as the exercise intensified. Of the spectral components, the influence of HF component increased and the influence of LF band decreased with the intensity of exercise ($p<0.001$). In Cox multivariable analysis, log VLF power (hazard ratio [HR] 0.56, 95% CI 0.43–0.72), log LF power (HR 0.58, 95% CI 0.45–0.74), log LF power (n.u.) (HR 0.75, 95% CI 0.64–0.87), log HF power% (HR 1.44, 95% CI 1.09–1.88), pcSD2 (HR 0.61, 95% CI 0.43–0.86), and log RMSSD(HR 0.72, 95% CI 0.56–0.92) were significant predictors of better prognosis ($p<0.01$) during the pre-exercise phase. During the first minute of exercise, smaller log LF power (HR 0.70, 95% CI 0.55–0.94, $p<0.01$) was associated with increased risk of mortality. None of the HRV parameters were connected with mortality at peak exercise or during the recovery phase.

Our results with an inverse association between mortality and the resting HRV parameters are in unison with the existing literature. The hazard ratios were comparable to published results. Short-term HRV is most probably caused by fluctuation in the parasympathetic activity [1], which has a known ability for the beat-to-beat regulation of HR [5]. In the beginning of exercise, heart rate increases as vagal activity fades and the sympathetic system takes the role of major controller. The changed physiological state may be the background for no existing link between HRV and mortality at peak exercise in the present large study population. In contrast, a recent study [2] showed prognostic value for HRV during exercise treadmill test. The data analyzed in our study is from bicycle ergometer tests, and the results may not directly be extrapolated to treadmill tests. Also, the study populations between these two studies have some differences, for example, proportion of women was greater in our study. These differences may have influence on results.

In conclusion, HRV does not seem to have prognostic implications during physical exertion. However, our results support the notion that decreased HRV at rest is a predictor of death.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [6].

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ORIGINAL ARTICLE

The prognostic value of haemodynamic parameters in the recovery phase of an exercise test. The Finnish Cardiovascular Study

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We tested the hypothesis that the change from the peak to recovery values of systolic arterial pressure ($SAP_{recovery}$) and rate–pressure product ($RPP_{recovery}$) can be used to predict all-cause and cardiovascular mortality, as well as sudden cardiac death (SCD) in patients referred to a clinical exercise stress test. As a part of the Finnish Cardiovascular Study (FINCAVAS), consecutive patients ($n = 2029$; mean age ± SD = 57 ± 13 years; 1290 men and 739 women) with a clinically indicated exercise test using a bicycle ergometer were included in the present study. Capacities of attenuated $SAP_{recovery}$, $RPP_{recovery}$ and heart rate recovery (HRR) to stratify the risk of death were estimated. During a follow-up (mean ± s.d.) of 47 ± 13 months, 122 patients died; 58 of the deaths were cardiovascular and 33 were SCD. In Cox regression analysis after adjustment for the peak level of the variable under assessment, age, sex, use of β-blockers, previous myocardial infarction and other common coronary risk factors, the hazard ratio of the continuous variable $RPP_{recovery}$ (in units 1000 mm Hg × b.p.m.) was 0.85 (95% CI: 0.73–0.98) for SCD, 0.87 (0.78–0.97) for cardiovascular mortality, and 0.87 (0.81 to 0.94) for all-cause mortality. $SAP_{recovery}$ was not a predictor of mortality. The relative risks of having HRR below 18 b.p.m., a widely used cutoff point, were as follows: for SCD 1.28 (0.59–2.81, ns), for cardiovascular mortality 2.39 (1.34–4.26) and for all-cause mortality 2.40 (1.61–3.58). In conclusion, as a readily available parameter, $RPP_{recovery}$ is a promising candidate for a prognostic marker.

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Keywords: prognostics; exercise test; rate–pressure product; recovery

Introduction

An abnormal response of the autonomic nervous system during and after an exercise stress test is believed to be a marker of increased risk of death. Autonomic imbalance is reflected in, for example, the heart rate (HR) profile during and after exercise, which has been shown to associate with all-cause or cardiac mortality during follow-up.[1–4] Furthermore, short-term regulation of blood pressure (~HR × stroke volume × peripheral resistance) is dominated by the autonomic nervous system, and the levels of and changes in systolic arterial pressure (SAP) during the exercise have been found to represent determinants of cardiovascular mortality in several studies.[5,6] Moreover, the recovery of SAP ($SAP_{recovery}$) from the peak to the post-exercise level might mirror changes in the autonomic balance. In that case, $SAP_{recovery}$ could also prove valuable in predicting mortality during follow-up, but earlier studies on this hypothesis have been scarce.[7–9]

Several computed parameters have been derived with the idea that they would integrate several (patho) physiological markers or phenomena into a

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single variable. Such markers have not yet, however, broken through into wide-scale clinical use. Rate pressure product (RPP = HR × SAP) is a simple calculatory parameter based on two variables regulated by the autonomic nervous system. RPP is used as an indicator of myocardial oxygen uptake and coronary blood flow in the exercise test.[10] Moreover, resting and peak RPP during exercise have been linked to cardiovascular mortality,[6,11–18] but the prognostic value of the recovery of RPP ($RPP_{recovery}$) from the peak to the post-exercise level is unknown.

As a part of the Finnish Cardiovascular Study (FINCAVAS), we evaluated the hypothesis that the recovery of two readily available variables, SAP and RPP, can be used to predict all-cause and cardiovascular mortality, as well as sudden cardiac death (SCD) in patients referred to a clinical exercise stress test.

Materials and methods

Study cohort

As described in the detailed study protocol of FINCAVAS,[19] all consecutive patients coming in for a clinically indicated exercise stress test at Tampere University Hospital and willing to participate in the study were recruited between October 2001 and December 2004. A total of 2029 patients (1290 men and 739 women) with technically successful storage of exercise test data were included in the study (Tables 1 and 2). The main indications for the exercise test were a diagnosis of coronary heart disease (CHD, frequency 46%), testing vulnerability to arrhythmia during exercise (21%), evaluations of working capacity (18%) and the adequacy of CHD treatment (16%), in addition to obtaining an exercise test profile prior to an invasive operation (13%) or after a myocardial infarction (8%); some patients had more than one indication. The study protocol was approved by the Ethical Committee of the Tampere University Hospital District (Finland), and all patients gave an informed consent prior to the interview and measurements as stipulated in the Declaration of Helsinki Principles.

Study flow

After an informed consent was signed, the medical history of each patient was collected with a computer-based questionnaire. Thereafter, the subject lay down in the supine position for 10 min. The exercise test was performed using a bicycle ergometer with electrical brakes.

During the test, HR was continuously recorded with electrocardiography, whereas arterial pressure was measured with a brachial cuff every 2 min. The highest HR and SAP values during the exercise were used in the calculation of RPP_{peak}. In the post-exercise phase, HR and SAP in the sitting position

Table 2 Unadjusted percentage of women, frequency of β-blocker use, as well as the prevalence of cardiovascular disease, symptoms, risk factors and death for all participants according to the HRR cutoff point of 18 b.p.m. during the first minute of recovery

	HRR ⩾ 18 b.p.m. (%)	*HRR < 18 b.p.m. (%)*	*P-value*
Women	37	34	0.13
β-Blockers	53	72	0.00
Smoking	27	27	0.85
CHD	35	47	0.00
Prior MI	19	26	0.00
Hypercholesterolaemia	48	55	0.01
Diabetes	10	18	0.00
SCD	1	3	0.03
Cardiovascular death	2	6	0.00
All-cause death	4	13	0.00

Abbreviations: CHD, coronary heart disease; HRR, heart rate recovery; MI, myocardial infarction; SCD, sudden cardiac death.
The *P*-values have been calculated with the χ^2 test.

Table 1 Patient characteristics and exercise test variables for all participants according to the HRR cutoff point of 18 b.p.m. during the first minute of recovery

	HRR ⩾ 18 b.p.m., n = *1498*		*HRR < 18 b.p.m.*, n = *531*		P-*value*
	Mean	*s.d.*	*Mean*	*s.d.*	
Age (years)	55	13	63	12	0.00
BMI (kg/m^2)	27	4	29	5	0.00
Weight (kg)	80	15	83	16	0.00
Height (cm)	171	9	171	9	0.05
HR at rest (b.p.m.)	63	11	66	13	0.00
HR at peak exercise (b.p.m.)	152	23	131	31	0.00
Reached HR of expected maximum (%)	81	13	73	16	0.00
HR at 4 min of the recovery (b.p.m.)	85	17	82	20	0.00
SAP at rest (mm Hg)	135	18	137	20	0.06
SAP at peak exercise (mm Hg)	197	28	180	29	0.00
SAP at 4 min of recovery (mm Hg)	141	21	144	21	0.02

Abbreviations: BMI, body mass index; HR, heart rate; HRR, heart rate recovery; SAP, systolic arterial pressure.
The *P*-values have been derived with the *t*-test for independent samples.

at 4 min post-exercise were used in the calculation of $RPP_{post\text{-}exercise}$. $RPP_{recovery}$ was defined as $RPP_{peak}-RPP_{post\text{-}exercise}$. Similarly, $SAP_{recovery}=SAP_{peak}-SAP_{post\text{-}exercise}$. HRR was calculated as an HR difference at the peak level and 1 min after the exercise.

Follow-up
Death certificates were received from the Causes of Death Register maintained by Statistics Finland in May 2007; this source has been proven reliable.[20] The certificates included causes of death using the 10th revision of the International Classification of Diseases (ICD-10). The diagnosis numbers and certificate texts were used to classify the deaths as all cause, cardiovascular and SCDs (defined as a cardiac death within 24 h after the onset of symptoms).

Statistical analysis
An HRR cutoff point of 18 b.p.m. within the first minute has been suggested by several authors for exercise tests with an abrupt end.[4,] We used the same cutoff point in addition to handling HRR as a continuous variable. Because no previous cutoff points for the decline in SAP and RPP have been published, we used $SAP_{recovery}$ and $RPP_{recovery}$ only as continuous variables.

The *t*-test for independent samples was used to compare continuous patient characteristics and exercise test variables between those with normal and abnormal recovery values (Table 1), and the χ^2 test was applied for dichotomous variables (Table 2).

The hazard ratios and relative risks implied by recovery values with regard to all-cause and cardiovascular deaths, as well as SCD were estimated with a Cox proportional hazards model using the following covariates: the peak level of the variable under assessment, sex, age, body mass index (BMI), daily smoking (no/yes), use of β-blockers (no/yes), prior diagnoses of CHD (no/yes), myocardial infarction (no/yes), diabetes (no/yes) and hypercholesterolaemia (no/yes). The statistical analyses were performed with the SPSS release 14.0 for Windows (SPSS Inc, Chicago, IL, USA). All statistical tests were two-tailed and used an α-level of <0.05.

Results

During the follow-up period of 47 ± 13 months (mean ± s.d.), there were 122 deaths (6.0% of the population), 58 (2.9%) of which were classified as cardiovascular deaths and 33 (1.6%) further as SCD (Figure 1). Patient characteristics, exercise test variables and the number of deaths for those with HRR $\geqslant$18 b.p.m. ($n=1498$) and HRR $<$18 b.p.m. ($n=531$) are given in Tables 1 and 2.

Mortality and recoveries in HR, SAP and RPP
In Cox regression with adjustments for the peak level of the variable to be assessed, sex, age, BMI, smoking, use of β-blockers, and prior diagnoses of CHD, myocardial infarction, diabetes and hypercholesterolaemia, the hazard ratios of the continuous variable $RPP_{recovery}$ (in units 1000 mm Hg × b.p.m.) were statistically significant for all the three categories of death (Table 3). The continuous variable $SAP_{recovery}$ did not predict any type of mortality (Table 4).

The relative risks of HRR when applying the cutoff point of 18 b.p.m. were 1.28 for SCD (95% confidence interval 0.59–2.81, $P=0.53$), 2.39 for

Table 3 Adjusted hazard ratios and relative risks for sudden cardiac, cardiovascular and all-cause death in the Cox regression models with $RPP_{recovery}$

	SCD				*Cardiovascular mortality*				*All-cause mortality*			
	RR	*95% CI*		P-*value*	*RR*	*95% CI*		P-*value*	*RR*	*95% CI*		P
		Lower	*Upper*			*Lower*	*Upper*			*Lower*	*Upper*	
$RPP_{recovery}$ (1000 b.p.m. per mm Hg)	0.85	0.73	0.98	0.02	0.87	0.78	0.97	0.01	0.87	0.81	0.94	<0.001
RPP_{peak} (1000 b.p.m. per mm Hg)	1.03	0.91	1.16	0.64	1.01	0.92	1.10	0.86	1.02	0.96	1.08	0.51
Age (years)	0.99	0.96	1.03	0.60	1.02	0.99	1.05	0.13	1.04	1.02	1.06	0.00
Sex (M/F)	0.14	0.03	0.60	0.01	0.35	0.17	0.73	0.01	0.55	0.36	0.84	0.01
BMI (kg/m^2)	0.95	0.87	1.03	0.21	0.94	0.88	1.00	0.05	0.94	0.89	0.98	0.00
Smoking (no/yes)	1.08	0.49	2.38	0.84	0.85	0.47	1.53	0.59	0.64	0.43	0.96	0.03
Diabetes (no/yes)	0.68	0.28	1.63	0.39	0.69	0.37	1.30	0.26	0.80	0.51	1.28	0.36
β-Blocker (no/yes)	0.49	0.15	1.58	0.23	0.51	0.23	1.17	0.11	0.83	0.52	1.33	0.43
CHD (no/yes)	1.02	0.36	2.88	0.97	1.09	0.51	2.34	0.82	1.66	0.98	2.81	0.06
Prior MI (no/yes)	0.57	0.22	1.46	0.24	0.56	0.28	1.12	0.10	0.60	0.35	1.02	0.06
Hypercholesterolaemia (no/yes)	0.88	0.42	1.85	0.73	1.43	0.84	2.42	0.18	1.22	0.84	1.75	0.29

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; F, female; RR, hazard ratio/relative risk; M, male; MI, myocardial infarction; RPP_{peak}, peak rate–pressure product during exercise; $RPP_{recovery}$, recovery of rate–pressure product; SCD, sudden cardiac death.

Table 4 Adjusted hazard ratios and relative risks for sudden cardiac, cardiovascular and all-cause death in the Cox regression models with $SAP_{recovery}$

	SCD				*Cardiovascular mortality*				*All-cause mortality*			
	RR	*95% CI*		P-*value*	*RR*	*95% CI*		P-*value*	*RR*	*95% CI*		P-*value*
		Lower	*Upper*			*Lower*	*Upper*			*Lower*	*Upper*	
$SAP_{recovery}$ (mm Hg)	0.99	0.97	1.01	0.28	0.99	0.97	1.00	0.15	0.99	0.98	1.00	0.21
SAP_{peak} (mm Hg)	0.99	0.97	1.01	0.21	0.99	0.97	1.00	0.08	0.99	0.98	1.00	0.01
Age (years)	1.00	0.97	1.04	0.86	1.03	1.01	1.06	0.01	1.05	1.03	1.07	0.00
Sex (M/F)	0.18	0.05	0.61	0.01	0.33	0.17	0.67	0.00	0.50	0.33	0.77	0.00
BMI (kg/m^2)	0.98	0.90	1.06	0.58	0.96	0.90	1.02	0.20	0.95	0.91	0.99	0.03
Smoking (no/yes)	0.96	0.45	2.04	0.91	0.82	0.46	1.44	0.48	0.64	0.44	0.95	0.02
Diabetes (no/yes)	0.66	0.28	1.59	0.36	0.69	0.37	1.30	0.26	0.76	0.47	1.20	0.24
β-Blocker (no/yes)	0.44	0.14	1.38	0.16	0.46	0.20	1.02	0.05	0.78	0.49	1.23	0.28
CHD (no/yes)	0.99	0.36	2.72	0.98	1.08	0.51	2.29	0.83	1.59	0.94	2.69	0.08
Prior MI (no/yes)	0.61	0.24	1.58	0.31	0.58	0.29	1.18	0.14	0.62	0.37	1.06	0.08
Hypercholesterolaemia (no/yes)	0.87	0.41	1.81	0.70	1.47	0.88	2.46	0.15	1.25	0.87	1.80	0.22

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; F, female; RR, hazard ratio/relative risk; M, male; MI, myocardial infarction; SAP_{peak}, peak systolic arterial pressure during exercise; $SAP_{recovery}$, recovery of systolic arterial pressure; SCD, sudden cardiac death.

cardiovascular mortality (1.34–4.26, $P=0.003$) and 2.40 for all-cause mortality (1.61–3.58, $P<0.001$). HRR as a continuous variable produced a significant hazard ratio for all-cause mortality 0.971 (0.954–0.988, $P<0.001$), but not for cardiovascular (0.987 0.961–1.013, $P=0.32$) or sudden cardiac (0.981, 0.949–1.015, $P=0.27$) mortality.

Discussion

The exercise stress test is a routine tool in the diagnostics and follow-up of CHD, as well as in determining cardiovascular status prior to a major procedure. In addition, the merits of the exercise test as a prognostic means have been increasingly recognized during the last two decades.[21] It remains a continuous challenge to develop new approaches and enhance the existing techniques to screen large general cardiovascular patient populations—not only those at a particularly high risk—for increased risk of cardiac death. Because the exercise stress test is a widespread and relatively inexpensive tool, it will be of special interest if the applicability of the test can be expanded from evaluating the prevailing cardiovascular status to cardiovascular prognosis.

Several markers of vagal tone and autonomic imbalance at rest have been connected to cardiovascular events and mortality: elevated resting HR, impaired HR variability, decreased baroreflex sensitivity,[22,23] and so on. During exercise, HR and SAP increase steadily because of the gradual activation of the sympathetic and concomitant deactivation of parasympathetic nervous system. HRR after exercise is considered to be a function of the reactivation of the parasympathetic nervous system, which is important primarily during the first minute after exercise. HRR has been used as a predictor of overall and cardiovascular mortality in studies with various types of patients: healthy subjects and those with or without CHD.[1,3,8,24] Our unselected hospital population that comprises consecutive patients coming in for a clinically indicated clinical exercise test repeated this finding when using the cutoff point of 18 b.p.m. at 1 min after an abrupt discontinuation of the exercise.

Poor decrease of SAP after the exercise has been linked to CHD or the severity of myocardial ischaemia,[25,26] stroke[27] and myocardial infarction,[28] but the previous studies on mortality have yielded conflicting results. In one of these previous studies, abnormal post-exercise SAP response stratified the all-cause mortality in patients ($n=217$) after an acute myocardial infarction.[9] However, two other studies, with either 12 379 low-risk[7] or 2428 consecutive adult patients,[8] did not support this finding, which is consistent with our results: we did not find an association between $SAP_{recovery}$ and overall, cardiovascular or sudden cardiac mortality. Given the impact of the large studies, $SAP_{recovery}$ does not seem to be applicable in risk stratification. The peak-level SAP reached significance for all-cause mortality: the higher the peak SAP, the lower the risk of death. This has also been found in earlier reports,[29] suggesting that better trained subjects exhibit a higher SAP response to exercise.[29]

To the best of our knowledge, this is the first report of the value of $RPP_{recovery}$ in prognostics. Because no previous cutoff points were available, we used only $RPP_{recovery}$ as a continuous variable. This parameter had an inverse relation with all three types of end points used: the greater the drop in RPP, the lower the risk of death. This is clearly supported by Figure 1, where the prevalence of death is clearly higher in the quintile with lowest than highest $RPP_{recovery}$. It deserves to be mentioned

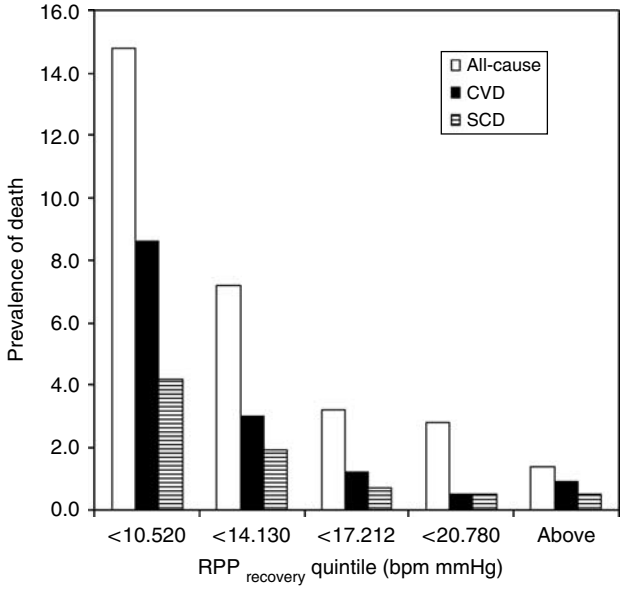

Figure 1 Prevalence (%) of unadjusted all-cause and cardiovascular (CVD) mortality, as well as sudden cardiac death (SCD) for the $RPP_{recovery}$ quintiles.

that $RPP_{recovery}$ emerged as the sole haemodynamic parameter with a statistically significant hazard ratio for SCD. There are many possible mechanisms to explain why delayed decrease in RPP after the exercise would be an indicator of increased mortality. Both HR and blood pressure are adjusted by several mechanisms, but the autonomic nervous system is the dominant regulator in acute changes. Autonomic dysfunction or abnormalities in vasoreactivity may thus cause low $RPP_{recovery}$. Moreover, $RPP_{recovery}$ may reflect aerobic capacity and physical fitness, which have been linked to prognosis.

Because we used no cutoff points for RPP or SAP, the demographic data presented are divided by HRR at 18 b.p.m. The groups with HRR of at least 18 b.p.m. and <18 b.p.m. differ from each other regarding several known cardiovascular risk factors (Tables 1 and 2). Therefore, we used many covariates to clarify the importance of each of these risk factors as determinants of poorer prognosis (Table 3). In the models with $RPP_{recovery}$, sex and $RPP_{recovery}$ were the only statistically significant independent risk factor for SCD and cardiovascular death, whereas BMI, age and smoking status appeared as significant covariates in addition to $RPP_{recovery}$ and sex for all-cause mortality. Surprisingly, age was a prognostic marker only for all-cause mortality. This is probably due to the duration of follow-up. Smoking and BMI had a paradoxical negative association with all-cause mortality; however, smoking and BMI had a positive link to mortality if they were the only covariates in the model.

One disparity between our study groups was the use of β-blockers (Table 2). Medication with the β-blockers causes reduced increase in HR and SAP, and thus reduced maximal RPP. The medication status upon the exercise test depends on the indication the test is performed for. Our patients with a clinically indicated exercise test were tested, for example, to evaluate working capacity (18% of the tests) and the adequacy of CHD treatment (16%). These tests are performed with the prevailing medications, whereas those tested for CHD diagnostics (46%) enter the test after discontinuing their β-blockers for at least 5 days. We used the β-blocker status as a covariate in the Cox regression analyses, but it did not prove to be a significant risk factor in any of the models.

The standard exercise stress test with a bicycle has certain advantages compared with treadmill tests.[10,30] One of these is the easier measurement of blood pressure during exertion. On the other hand, the present study is subject to some limitations. We included all patients scheduled for a clinical exercise stress test at a university setting, and the population comprises patients with a wide spectrum of ages, life styles, histories and statuses of cardiac disease. The impact of the heterogeneity is diminished if not eliminated by using several covariates in the analysis.

In conclusion, the readily available parameter $RPP_{recovery}$ is a promising candidate for a prognostic marker. The validity of this variable needs to be tested further in other exercise stress test populations, before a more widespread clinical use of the markers can be recommended. $SAP_{recovery}$ does not seem to serve as a prognostic tool.

What is known about the topic
- Levels of and changes in systolic arterial pressure and heart rate during an exercise test are associated with mortality.
- Suppressed heart rate recovery, an index of parasympathetic re-activation after the exercise phase, is a predictor of mortality.
- Peak rate–pressure product (heart rate × systolic arterial pressure) during exercise is a prognostic marker.

What this study adds
- Recovery of rate–pressure product after the exercise phase is linked to cardiovascular and all-cause mortality, as well as sudden cardiac death independently of traditional risk factors.
- Recovery in systolic arterial pressure is not associated with any of the three types of mortality.

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Conflict of interest

The authors do not have any conflict of interest.

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Atrioventricular conduction and cardiovascular mortality: Assessment of recovery PR interval is superior to pre-exercise measurement

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BACKGROUND A prolonged electrocardiographic PR interval at rest has been considered a benign phenomenon until recently.

OBJECTIVE We hypothesized that measurement of the PR interval during recovery from physical exertion could improve cardiovascular mortality risk stratification because it would track the dynamic influences of homeostatic mechanisms controlling atrioventricular (AV) conduction.

METHODS A total of 1,979 consecutive patients (1,244 men and 735 women) with clinically indicated bicycle ergometer tests enrolled in FINCAVAS (the Finnish Cardiovascular Study) were included in the study. The PR interval was measured at 1 min before and at 2 min after exercise.

RESULTS During the mean follow-up period of 47 months (interquartile range: 37 to 59 months), 50 cardiovascular deaths (end point) were registered. The unadjusted hazard ratios (HR) in Cox regression analyses were significant for both continuous PR interval and first-degree atrioventricular (AV) block for pre- and post-exercise phases. After adjustment for standard markers, the PR interval for 20-ms increments (HR: 1.17, $P = .117$) and first-degree AV block (HR: 1.85, $P = .138$) during the pre-exercise phase were not prognostic. However, during recovery from exercise, prolonged AV conduction achieved significance both in continuous (HR: 1.29, $P = .006$) and dichotomized analyses (HR: 2.41, $P = .045$).

CONCLUSION The PR interval before exercise is not a robust risk stratifier for cardiovascular death during 4-year follow-up. Post-exercise assessment of AV conduction may offer improved prediction because of functional abnormalities that become manifest only during this physiologic challenge to the heart.

KEYWORDS Atrioventricular conduction; Exercise test; Cardiovascular mortality; PR interval; Prognostics

ABBREVIATIONS AV = atrioventricular; **CI** = confidence interval; **ECG** = electrocardiographic; **HR** = hazard ratio; **NYHA** = New York Heart Association

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Conduction time of the electrical signal from the sinus node to the ventricles is clinically measured as electrocardiographic (ECG) PR interval. Deceleration of atrioventricular (AV) conduction above the typical upper limit of 200 ms, or first-degree AV block, is primarily due to excessive delay in the AV node and, less frequently, in the His-Purkinje system, whereas conduction within the right atrium is typically not affected.[1] Among healthy adults of 20 to 40 years of age, 1% to 2%[2–5] have a prolonged PR interval, and the prevalence of first-degree AV block increases to 3% to 4%[3,5] by the age of 60 years.

Decelerated AV conduction has been considered a benign, functional phenomenon for 5 decades. None of the studies during that period suggested a link between first-degree AV block and mortality among healthy young[2,6] or middle-age[3] men, or in a community-based epidemiological study.[5] Three studies provided contradictory evidence of an association between first-degree AV block and coronary heart disease among middle-age men.[3,7,8]

Recently, Cheng et al[9] published results from the Framingham Heart Study showing an association between ab-

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normal AV conduction at rest and the outcome measures of incident atrial fibrillation, pacemaker implantation, and all-cause mortality. The importance of the recovery PR interval has not been studied. We hypothesized that measurement during recovery from physical exertion could improve risk stratification, as it would track the dynamic influences of homeostatic mechanisms controlling AV conduction. Therefore, we investigated the PR interval both at rest and also during the recovery phase of a clinical bicycle ergometer test in FINCAVAS (the Finnish Cardiovascular Study). Our follow-up data include cardiovascular death as an end point, which is more specific than all-cause mortality for conduction abnormalities.

Methods

Study cohort

All consecutive patients referred for an exercise stress test at Tampere University Hospital between October 2001 and the end of 2004 and willing to participate in the FINCAVAS trial[10] were enrolled. This substudy included a total of 1,979 consecutive patients (1,244 men and 735 women) with sinus rhythm, technically successful exercise tests, and a valid PR interval measurement during the pre-exercise phase. Due to technical reasons, 29 post-exercise PR interval values were missing. A test was technically adequate if storing the hemodynamic data and continuous digital ECG signal was successful. The main indications for the exercise test were suspicion of coronary heart disease (frequency 46%), testing vulnerability to arrhythmia during exercise (21%), and evaluation of work capacity (18%) and adequacy of the coronary heart disease treatment (15%), as well as obtaining an exercise test profile prior to an invasive procedure (13%) or after a myocardial infarction (MI) (8%); some patients had more than 1 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.

Exercise test protocol

After an informed consent was signed, the medical history of each patient was collected on a computer-based questionnaire form. Thereafter, the subject maintained a supine position for 10 min. The pre-exercise ECG was recorded while the patient sat upright on the bicycle ergometer. The upright routine exercise test was then performed using a bicycle ergometer with electrical brakes. The lead system was 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. The recovery phase after the physical stress lasted for 4 to 6 min. Continuous ECGs were digitally recorded at 500 Hz with the CardioSoft exercise ECG system (version 4.14, GE Healthcare).

Measurement of ECG and clinical variables

The PR interval for the pre-exercise phase was measured at 1 min before the start of exercise. The post-exercise PR interval was assessed at 2 min after cessation of exercise. The PR intervals were measured to the nearest millisecond automatically using the CASE Workstation (version 1.82, GE Healthcare). The software composes a spatial ECG vector from the 12 standard ECG leads. An average complex is calculated based on the normal cardiac cycles. In the averaged cycle, P-onset and QRS-onset are defined. The first deflections from the 0 lines of the P wave and the QRS complex are used for measurement of the PR interval. All extreme PR interval values ($>$250 ms or $<$90 ms) were overread by a physician investigator and corrected if necessary. Manually and automatically measured PR intervals at the pre-exercise and post-exercise phases were compared in a subset of 100 randomly chosen ECGs. The PR intervals in standard lead II were overread by a physician, and 3 random measurements were averaged. Bias between manually and automatically derived values was defined as the mean difference between the paired PR intervals, and limits of agreement were calculated as bias $\pm$2 SD of the measurement pairs.[11] The bias for the pre-exercise phase was 4 ms (limits of agreement $-$10 to 18 ms), and for the post-exercise phase was 5 ms ($-$17 to 26 ms).

Follow-up

Death certificates were received from the Causes of Death Register, maintained by Statistics Finland, in May 2007; this source has been shown to be reliable.[12] 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 deaths as all-cause or cardiovascular (end point applied in the study).

Statistical analysis

The t test for independent samples and the χ^2 test were used as applicable to compare parameters of patient characteristics (Table 1) for those with and without first-degree AV block during the pre-exercise phase. Unadjusted cardiovascular mortality rate for the pre- and post-exercise PR interval quintiles are presented in Figure 1, with significance determined by Poisson regression. In Cox regression analysis, we considered the PR interval both as a continuous variable and as dichotomized at the most commonly used cut point of 200 ms for first-degree AV block. Cox regression analysis was performed both unadjusted and adjusted with several typical risk factors (Table 2) as covariates. The New York Heart Association (NYHA) score, a surrogate for heart failure, was transformed into a dichotomous variable by differentiating the classes with good (II or better) or poor (III) function. Results for continuous PR intervals are given for increments of 20 ms.[9] All covariates fulfilled the proportionality assumption based on correlations with survival rankings with Schoenfeld residuals. Statistics were analyzed with the SPSS release 16.0 for Windows (SPSS, Inc., Chi-

Table 1 Patient characteristics according to the pre-exercise PR interval

	PR interval ≤200 ms (n = 1,844)	PR interval >200 ms (n = 135)	
	Mean (SD)	Mean (SD)	*P*
Age (yrs)	56 (13)	64 (12)	<.001
Body mass index (kg/m^2)	27 (4)	29 (5)	.001
Pre-exercise assessment			
Heart rate (beats/min)	74 (15)	65 (13)	<.001
Width of the QRS complex (ms)	98 (15)	111 (26)	<.001
PR interval (ms)	154 (21)	224 (27)	<.001
Exercise assessment			
Maximum heart rate (beats/min)	147 (26)	127 (31)	<.001
Length of the exercise (min)	7 (2)	7 (2)	.13
Post-exercise assessment			
Heart rate at 2 min (beats/min)	99 (21)	82 (20)	<.001
Width of the QRS complex (ms)	99 (15)	112 (24)	<.001
PR interval (ms)	144 (25)	202 (34)	<.001
Female	38%	27%	.01
Smoking	28%	16%	.003
Beta-blocker use	60%	81%	<.001
Diabetes	13%	12%	.89
Coronary heart disease	33%	33%	.85
Myocardial infarction	21%	22%	.91
New York Heart Association class III	8.1%	9.8%	.51
Cardiovascular death	2.2%	6.7%	.006

cago, Illinois). All statistical tests were 2-tailed and used an alpha level <0.05.

Results

Patient characteristics and prevalence of first-degree AV block

Patient characteristics according to the presence of first-degree AV block at baseline are presented in Table 1. Most of the continuous variables differed significantly between the groups; only duration of the exercise test was similar. Sex, smoking, and use of β-blockers were also different between the groups. Regarding the entire population, the PR interval in the pre-exercise phase was 158 ± 28 ms (mean ± SD) and in the post-exercise phase 148 ± 30 ms. Prevalence of first-degree AV block in the age groups below 40 years, 40 to 59 years, and at least 60 years was 2.8%, 3.9%, and 11.0%, respectively, in the pre-exercise phase and 1.9%, 3.1%, and 8.1% in the post-exercise phase.

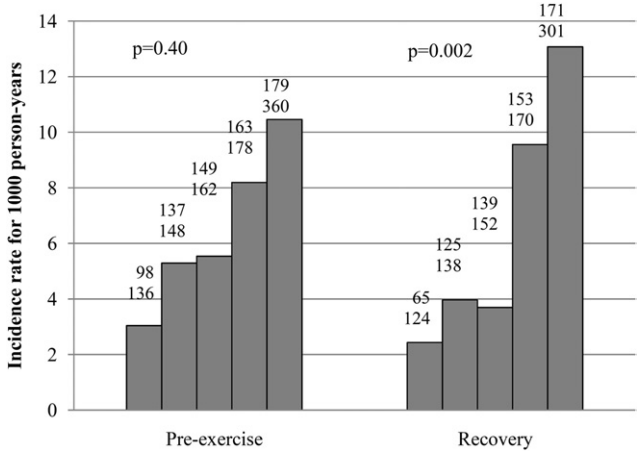

Figure 1 Unadjusted incidence rate of cardiovascular mortality per 1,000 person-years among patients divided into quintiles based on PR intervals in the pre- and post-exercise phases. The range of PR intervals (ms) is given for each bin. The p values for trends are calculated with Poisson regression.

Mortality and the PR interval

The mean follow-up period was 47 months (interquartile range 37 to 59 months). A total of 107 deaths were registered, and 50 (2.5% of the population) of those were from cardiovascular causes, the latter of which was the end point used. Therefore, cardiovascular mortality was 0.64%/year.

Cardiovascular mortality rates differed between patients in the PR interval quintiles in the recovery phase but not in the phase before physical stress (Figure 1). The unadjusted hazard ratio (HR) in Cox regression analyses was 1.31 ($P <$ .001, 95% confidence interval [CI]: 1.14 to 1.51) for each 20-ms increment in the pre-exercise PR interval, and similarly, 1.47 ($P <$.001, 95% CI: 1.27 to 1.69) for the recovery PR interval. The unadjusted HR for first-degree AV block before exercise was 3.04 ($P =$ .003, 95% CI: 1.47 to 6.25), and for after exercise was 4.00 ($P <$.001, 95% CI: 1.94 to 8.22).

After adjustment for typical risk markers, the PR interval (HR: 1.17, $P =$ .092, 95% CI: 0.97 to 1.18) and first-degree AV block (HR: 1.74, $P =$ .170, 95% CI: 0.79 to 3.82) (Table 2) during the pre-exercise phase were not prognostic. However, during recovery from exercise, prolonged AV conduction achieved significance both in continuous (HR: 1.36, $P <$.001, 95% CI: 1.15 to 1.62) and dichotomized analyses (HR: 2.73, $P =$ .012, 95% CI: 1.25 to 5.95) (Table 2). Survival curves for the adjusted first-degree AV block

Table 2 Results of adjusted Cox regression models with first-degree AV block for the pre- and post-exercise phases

	Hazard ratio	95% confidence interval		*P*
		Lower	Upper	
Pre-exercise first-degree AV block				
First-degree AV block (no/yes)	1.74	0.79	3.82	.170
Age (yrs)	1.05	1.02	1.08	.002
Sex (female/male)	2.62	1.20	5.73	.016
Body mass index (kg/m^2)	0.93	0.86	1.00	.052
Coronary heart disease (no/yes)	1.16	0.63	2.12	.635
Diabetes (no/yes)	1.37	0.65	2.87	.406
Beta-blocker use (no/yes)	3.32	1.24	8.91	.017
Pre-exercise QRS complex width (ms)	1.07	0.94	1.22	.298
Pre-exercise heart rate (beats/min)	0.99	0.79	1.24	.935
Post-exercise first-degree AV block				
First-degree AV block (no/yes)	2.73	1.25	5.95	.012
Age (yrs)	1.05	1.02	1.08	.003
Sex (female/male)	2.94	1.29	6.71	.010
Body mass index (kg/m^2)	0.93	0.86	1.00	.060
Coronary heart disease (no/yes)	1.28	0.69	2.37	.426
Diabetes (no/yes)	1.41	0.67	2.95	.369
Beta-blocker use (no/yes)	2.94	1.08	8.05	.036
Post-exercise QRS complex width (ms)	1.07	0.93	1.24	.317
Post-exercise heart rate (beats/min)	0.99	0.83	1.18	.912

Hazard ratios for QRS width and heart rate are given for increments of 10. The covariates with no or yes as potential values have no as a reference level. The same applies for sex: the first parameter value (female) is the reference level. Therefore, for example, being male is a considerable risk factor.

AV = atrioventricular.

are given in Figure 2. The change in PR interval from the pre- to post-exercise measurement was not prognostic.

Discussion

Our main finding is that the PR interval prolongation assessed during recovery from exercise contains prognostic information, whereas its measurement at rest, prior to an exercise test, is not prognostic in adjusted analyses (Figure 2). Because our results differ from those of a recent study[9] but are in agreement with several earlier studies, it is of particular importance to consider possible differences among the methodologies and study populations.

Previous studies

The first estimation of the prognostic implications of the prolonged PR interval was based on an investigation in 1,000 United States Navy pilots and flight students between 20 and 30 years of age.[2] Only 1 of these young men died of cardiac causes during the follow-up of 10 years, rendering it impossible to detect potential differences in cardiovascular mortality between those with a normal and an abnormal AV conduction time. The Manitoba study recruited 3,983 Royal Canadian Air Force pilots in the late 1940s[6] for a follow-up of 30 years, but first-degree AV block did not predict ischemic heart disease or mortality even over this lengthy time span. These results suggested that first-degree AV block does not convey prognostic information among young healthy men. It is well known that first-degree AV block is the most common ECG abnormality among amateur athletes,[13] arguably a reasonable comparison group for Air Force pilots, and it has even been considered a normal finding among highly trained athletes.[14] This decelerated AV conduction in athletes stems from elevated vagal tone versus sympathetic excitation, which is typically considered a beneficial balance.

Regarding older age groups, neither cross-sectional association between first-degree AV block and symptomatic coronary heart disease nor the 5-year coronary heart disease

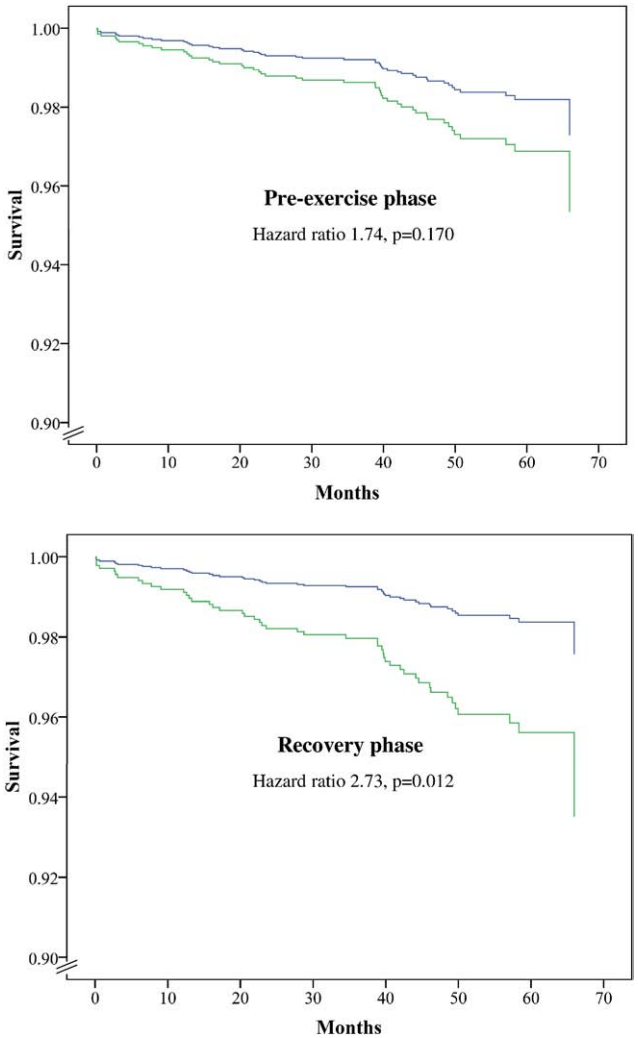

Figure 2 Results of adjusted Cox regression analysis for cardiovascular mortality among patients with *(lower line)* or without *(upper line)* first-degree atrioventricular block (PR interval >200 ms) during pre-exercise and recovery phases. Note that the y-axis scale is not to 0. The covariates (means for the pre-exercise and recovery analyses, respectively) were age (56.5, 56.4 years), sex (0.63, 0.62), body mass index (27.5, 27.5 kg/m^2), diagnosis of coronary heart disease (0.33, 0.33) or diabetes (0.13, 0.13); use of beta-blocker (0.61, 0.61), QRS complex width (98.7, 98.5 ms), and heart rate (73.6, 73.6 beats/min).

mortality differed significantly between those with a prolonged (>220 ms) or a normal PR interval among 18,000 male civil servants ages 40 to 64 years.[3] Erikssen and Otterstad[7] recruited 1,832 men ages 40 to 59 years and free from coronary heart disease, among whom the incidence of all cardiovascular events during 7-year follow-up was moderately but significantly even lower in men with a prolonged PR interval than among men with a PR interval ≤210 ms. Only 1 study with 12,770 middle-age men observed an unadjusted positive association between first-degree AV block and coronary heart disease over a 5-year follow-up.[8]

Two community-based epidemiologic studies pursued the significance of the prolonged PR interval. Almost 4 decades ago, a study with 4,678 adult men and women from Tecumseh, Michigan, found no excess incidence of cardiovascular disease or mortality among subjects with a prolonged PR interval (>210 ms) during the mean follow-up period of 4 years.[5] These results were recently challenged by an investigation in 7,575 individuals enrolled in the Framingham Heart Study demonstrating a 1.44-fold risk of all-cause mortality, a 2.1-fold risk of atrial fibrillation, and a 2.9-fold risk of pacemaker implantation associated with first-degree AV block (>200 ms).[9] The follow-up period in the Framingham Heart Study was censored at 20 years, roughly 5 times that of the Tecumseh study. Collectively, these findings indicate that a prolonged PR interval monitored at rest is rarely an indicator of more severe conduction disturbances during a follow-up period of ≤5 years.

Current investigation

The results of our study, which had a 4-year follow-up, did not repeat the findings of Cheng et al[9] for prolonged PR intervals monitored before the exercise test as a prognostic marker (Table 2), which may be due to shorter follow-up. However, a prolonged PR interval during the post-exercise period was a robust risk marker (Table 2, Figure 2). The traditional risk factors of age and sex were prognostic covariates, whereas coronary heart disease and diabetes were clearly nonsignificant in our relatively heterogeneous population. QRS duration, a marker with an unclear role in risk stratification,[15] showed HRs suggestive of heightened risk for increasing QRS duration, but the CIs clearly overlapped with the value 1.

In patients with clearly prolonged AV conduction, atrial systole begins too early in diastole, resulting in superimposition of atrial contraction on the early left ventricular filling phase[16] and an inefficient contribution of atrial systole to ventricular filling. The resulting decrease in cardiac output is poorly tolerated in patients with congestive heart failure or mitral regurgitation,[16] among whom prolonged AV conduction is common. This mechanism does not explain the excess mortality among subjects with first-degree AV block in our investigation, as the prevalence of remarkably prolonged PR intervals (>300 ms) was small, affecting 3 and 1 patients during the pre- and post-exercise phases, respectively.

Short-term regulation of AV conduction is based on both extrinsic and intrinsic mechanisms.[17,18] The extrinsic regulation is mainly due to the autonomic nervous system. Prompt resumption of autonomic balance after exercise with decreased sympathetic tone and increased vagal activation, which slows AV conduction, is generally considered beneficial. Accordingly, these autonomic influences are unlikely to account for the paradoxically deleterious effects of prolonged PR interval during recovery from exercise. An alternative explanation relates to intrinsic factors affecting the dynamic behavior of the AV node regarding recovery, facilitation, and fatigue.[19] These factors are independent of autonomic tone and can counteract PR shortening during periods of elevated heart rates.[18,19,20] In the present study, heart rates were substantially elevated at 2 min after cessation of exercise, the recovery measurement point of PR interval (Table 1). This was the case despite the fact that the recovery heart rate for patients with first degree AV block was lower than for patients without prolongation because of an even larger difference in peak heart rate between the 2 groups. Thus, a plausible explanation is that dysfunctional intrinsic AV node regulation, manifest only at elevated heart rates, is a precursor of prolonged resting PR interval, which over the course of years or decades may increase risk of death or necessitate pacemaker implantation.[9]

Study limitations

Our study is subject to certain limitations. First, we did not have records of nonmortality end points to confirm the previous results regarding incident atrial fibrillation and pacemaker implantation. Neither do we have information on changes in parameters affecting mortality risk (e.g., smoking, lifestyles, and medication) during follow-up.

Conclusion

The PR interval prior to exercise is not a robust risk stratifier for cardiovascular death during a follow-up of 4 years. Post-exercise assessment of first-degree AV block may offer improved prediction because of functional abnormalities that become manifest only during this physiologic challenge to the heart. These findings are consistent with growing evidence that the recovery phase of clinical exercise testing has considerable promise in the diagnosis of coronary heart disease[21,22] and risk stratification.[23–26] Thus, a lengthened PR interval during the post-exercise phase should be added to the set of potential noninvasive markers that may be useful in predicting cardiovascular mortality.

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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

(Heart Rhythm 2009;6:1765–1771)

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-

Dr. Verrier is co-inventor of the modified moving average method for T-wave alternans analysis, with patent assigned to Beth Israel Deaconess Medical Center and licensed by GE Healthcare. Financial support was received from the Medical Research Fund of Tampere University Hospital, Tampere Tuberculosis Foundation, and Finnish Cultural Foundation. **Address reprint requests and correspondence:** Dr. Mika Kähönen, Department of Clinical Physiology, Tampere University Hospital, FI-33520, Tampere, Finland. E-mail address: mika.kahonen@uta.fi. (Received March 15, 2009; accepted August 12, 2009.)

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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 ≤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

Table 1 Patient characteristics of the study population

	Survivors (N = 1,856)		Deaths (N = 116)		
Parameter	Mean	SD	Mean	SD	*P* value
Age (years)	56.5	13.1	65.1	11.3	<.01
Weight (kg)	80.5	15.2	79.0	15.8	.27
Height (cm)	171.0	9.3	171.6	9.3	.49
Body mass index	27.5	4.5	26.7	4.1	.07
	N	%	N	%	*P* value
Sex: female	776	37.8	30	23.6	<.01
Smoking: yes	534	26.0	41	32.3	.12
Nitrates	695	33.9	66	52.0	<.01
Beta-blockers	1,174	57.3	99	78.0	<.01
Hypercholesterolemia	1,024	49.9	64	50.4	.91
Diabetes	238	11.6	23	18.1	.03
Coronary heart disease	784	38.2	64	50.4	.01
Left ventricular hypertrophy	91	4.4	7	5.5	.57
History of myocardial infarction	425	20.7	44	34.6	<.01

deaths as all cause or cardiovascular. The investigators who analyzed TWA test results were blinded to events.

Statistical analysis

The t-test for independent samples was used to compare continuous parameters of patient characteristics (Table 1) and exercise test variables (Table 2) for survivors and nonsurvivors. The Chi-square test was applied for dichotomous variables. *P* values were derived with the t-test and the Chi-square test for independent samples. Relative risks for total and cardiovascular mortality were analyzed for HRR, TWA, and their combinations as well as for ST-segment deviation by Cox regression analysis after adjustment by standard covariates (Table 3). The proportionality assumption for all covariates was checked by using correlations of the survival rankings with the Schoenfeld residuals. All of the covariates fulfilled the proportionality assumption. Harrell's C indices also were calculated (Table 4). The calculations for combination variables were based on three categories: no parameter positive, either parameter positive, and both parameters positive. Harrell's C index is a generalization of the area under the receiver operator characteristic (ROC) curve for survival data with censored cases. Values above 0.5 show better than random prediction, and a value of one represents perfect concordance between predicted and observed numbers.

Statistics were analyzed using SPSS release 14.0 for Windows (SPSS, Inc., Chicago, IL, USA) and Stata 10.1 for Windows (StataCorp LP, College Station, TX, USA). All statistical tests were two-tailed and used an alpha level <.05.

Results

Baseline characteristics

During the follow-up period of 48 ± 13 months (mean ± SD) in our study population of 1,972 consecutive patients referred for clinical exercise testing, there were 116 deaths (5.9% of the population), including 55 (2.8% of the popu-

Table 2 Exercise test variables of the study population

	Survivors (N = 1,856)		Deaths (N = 116)		
Parameter	Mean	SD	Mean	SD	*P* value
Duration of test (minutes)	7.5	2.1	6.2	2.0	<.01
Age-adjusted expected maximum HR (bpm)	176.8	6.7	172.5	5.6	<.01
Reached maximum HR (bpm)	146.6	26.4	127.0	29.6	<.01
Maximum SAP during the exercise (mmHg)	193.6	28.5	175.6	32.0	<.01
Maximum DAP during the exercise (mmHg)	92.3	11.9	85.1	13.4	<.01
HR at rest (bpm)	63.1	11.6	64.5	14.5	.19
SAP at rest (mmHg)	136.1	18.6	135.2	25.8	.62
DAP at rest (mmHg)	79.7	9.6	75.7	11.4	<.01
Maximum TWA at rest before exercise (μV)	19.4	11.5	25.5	17.2	<.01
Maximum TWA during exercise (μV)	35.8	21.8	39.9	23.3	.04
Maximum TWA during recovery (μV)	26.7	23.4	31.3	19.5	.03
Maximum left ventricular ejection fraction	65.9	13.8	60.2	15.6	<.01
HRR at 1 minute postexercise (bpm)	24.7	11.5	18.2	13.8	<.01
ST-segment deviation during exercise (mV)	0.08	0.10	0.11	0.14	.01

DAP = diastolic arterial pressure; HR = heart rate; HRR = heart rate recovery; SAP = systolic arterial pressure; TWA = T-wave alternans.

Table 3 Results of Cox multivariable regression analysis (N = 1,972) of relative risks for all-cause mortality and cardiovascular mortality

	All-cause mortality				Cardiovascular mortality			
		95% CI				95% CI		
	RR	Lower	Upper	*P* value	RR	Lower	Upper	*P* value
HRR ≤18 bpm	2.5	1.6	3.7	<.01	2.3	1.3	4.2	.01
Exercise-based TWA ≥60 μV	2.5	1.4	4.5	<.01	5.8	3.1	11.1	<.01
Recovery-based TWA ≥20 μV	1.1	0.7	1.6	.73	1.5	0.8	2.5	.18
Recovery-based TWA ≥60 μV	2.4	1.3	4.4	<.01	3.5	1.6	7.9	<.01
HRR ≤18 bpm and exercise-based TWA ≥60 μV	5.0	2.1	12.1	<.01	12.3	4.3	35.3	<.01
HRR ≤18 bpm or exercise-based TWA ≥60 μV	2.8	1.8	4.3	<.01	3.4	1.8	6.6	<.01
HRR and recovery-based TWA ≥20 μV	3.0	1.6	5.5	<.01	5.2	1.8	14.4	<.01
HRR or recovery-based TWA ≥20 μV	2.0	1.2	3.5	.01	3.5	1.3	9.1	.01
HRR and recovery-based TWA ≥60 μV	6.1	2.8	13.2	<.01	8.0	2.9	22.0	<.01
HRR or recovery-based TWA ≥60 μV	2.3	1.5	3.5	<.01	2.2	1.2	4.2	.01
ST-segment deviation (0.1 mV) during exercise	1.3	0.9	1.9	.18	1.8	1.0	3.0	.04

Results after adjustment for sex, age, body mass index, smoking (yes/no), use of beta-blockers (yes/no), reached maximum heart rate, and prior diagnoses of coronary heart disease (yes/no), history of myocardial infarction (yes/no), diabetes (yes/no), and hypercholesterolemia (yes/no).

CI = confidence interval; HRR = heart rate recovery; RR = relative risk; TWA = T-wave alternans.

lation; 47.4% of all deaths) that were classified as cardiovascular deaths. Thus, the cardiovascular mortality of the present patients was 0.7% per year. Patient characteristics and exercise test variables for survivors (N = 1,856) and nonsurvivors (N = 116) are given in Tables 1 and 2, respectively.

Mortality, HRR, and TWA

HRR was abnormal in 29.5% (N = 590) of the population. Exercise-based TWA ≥60 μV was found in 5.2% (N = 107). During recovery, 51.3% (N = 1,063 patients) had TWA ≥20 μV, including 3.9% (N = 81 patients) with TWA ≥60 μV. Thus, the present approach classified the majority of the patients as low risk. Combined Cox proportional hazard analysis of depressed HRR and heightened exercise- or recovery-based TWA more than doubled the prognostic capacity for total and cardiovascular mortality after adjustment for standard risk factors and exceeded exercise-induced ST-segment deviation (Table 3). In addition to standard covariates, maximum left ventricular EF, blood pressures at rest, maximum blood pressures during exercise, and resting heart rate were added to the multivariate analysis with the combination of HRR and TWA. None of these factors exceeded the predictive power of the combination of HRR and TWA. Incidence rates of all-cause and cardiovascular deaths in subgroups are shown in Figure 1.

Harrell's C indices were calculated for all single and combination parameters as well as for ST-segment deviation (Table 4). For the single parameters, HRR provided the highest C index for both total and cardiovascular mortality. Adding exercise-based TWA ≥60 μV to reduced HRR yielded highest C index for all-cause and cardiovascular mortality, although confidence intervals overlapped with HRR alone.

Survival curves depict events across 4 years of follow-up for the combined analysis of reduced HRR and elevated TWA during exercise (Figure 2) and recovery (Figure 3).

Discussion

Our study is the first to demonstrate that the presence of high levels of TWA during exercise or recovery adds significantly to the prognostic power of poor HRR for all-cause and cardiovascular mortality. Because both markers are automated and widely used parameters that can be moni-

Table 4 Harrell's C indices for cardiovascular and all-cause mortality

	All-cause death	95% CI		Cardiovascular death	95% CI	
		Lower	Upper		Lower	Upper
HRR ≤18 bpm	0.655	0.609	0.702	0.650	0.583	0.718
Exercise-based TWA ≥60 μV	0.539	0.507	0.570	0.594	0.535	0.653
Recovery-based TWA ≥20 μV	0.555	0.508	0.601	0.606	0.544	0.668
Recovery-based TWA ≥60 μV	0.526	0.499	0.553	0.550	0.535	0.653
HRR ≤18 bpm and/or exercise-based TWA ≥60 μV	0.677	0.631	0.723	0.713	0.648	0.777
HRR ≤18 bpm and/or recovery-based TWA ≥20 μV	0.655	0.608	0.702	0.691	0.633	0.749
HRR ≤18 bpm and/or recovery-based TWA ≥60 μV	0.661	0.614	0.709	0.671	0.602	0.740
ST-segment deviation (0.1 mV) in exercise test	0.558	0.510	0.606	0.580	0.511	0.649

Calculations for combination variables were based on three categories (0, 1, or 2 parameters positive).

CI = confidence interval; HRR = heart rate recovery; TWA = T-wave alternans.

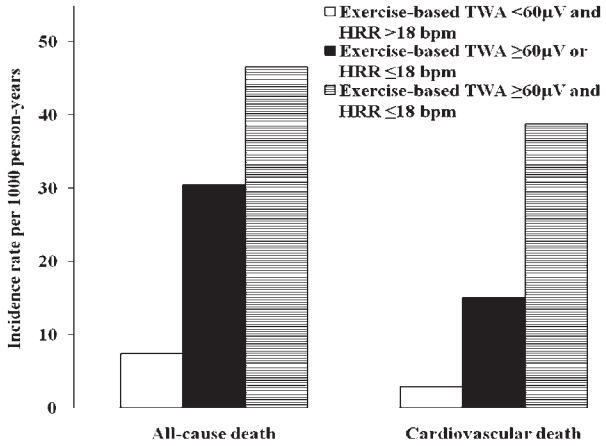

Figure 1 Incidence rate of all-cause and cardiovascular mortality per 1000 person-years among patients according to exercise-based T-wave alternans (TWA) and heart rate recovery (HRR).

tored in conjunction with routine exercise testing, their combination may serve as a new risk stratification tool for screening low-risk patient populations.

Previous studies

The significant influence of autonomic nervous system activity on cardiovascular and total mortality has been amply

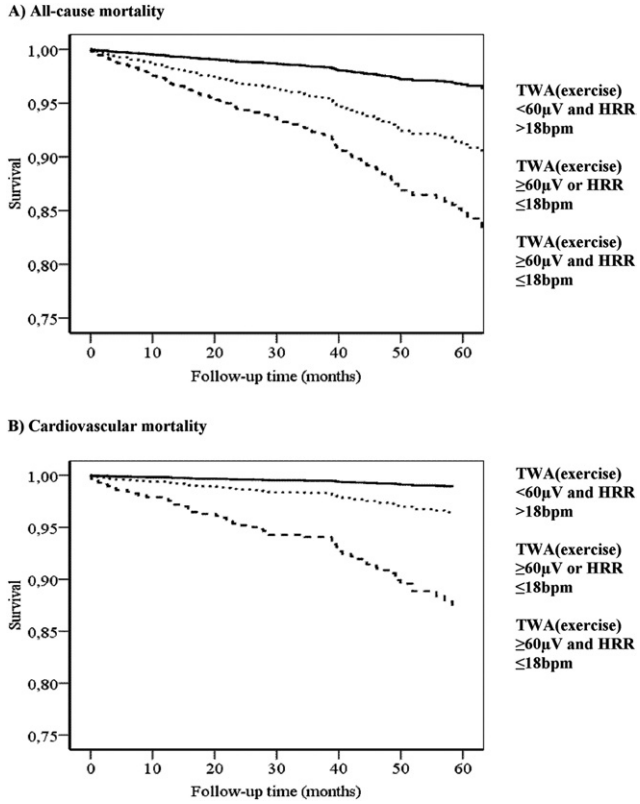

Figure 2 Adjusted survival curves by Cox regression for subjects with exercise-based T-wave alternans (TWA) <60 μV and heart rate recovery (HRR) >18 bpm (*top curve* in both panels), TWA ≥60 μV or HRR ≤18 bpm (*middle curve* in both panels), and TWA ≥60 μV and HRR ≤18 bpm (*bottom curve* in both panels) for all-cause mortality (**A**) and cardiovascular mortality (**B**). Note that the scale for the y-axis is from 0.75 to 1.00.

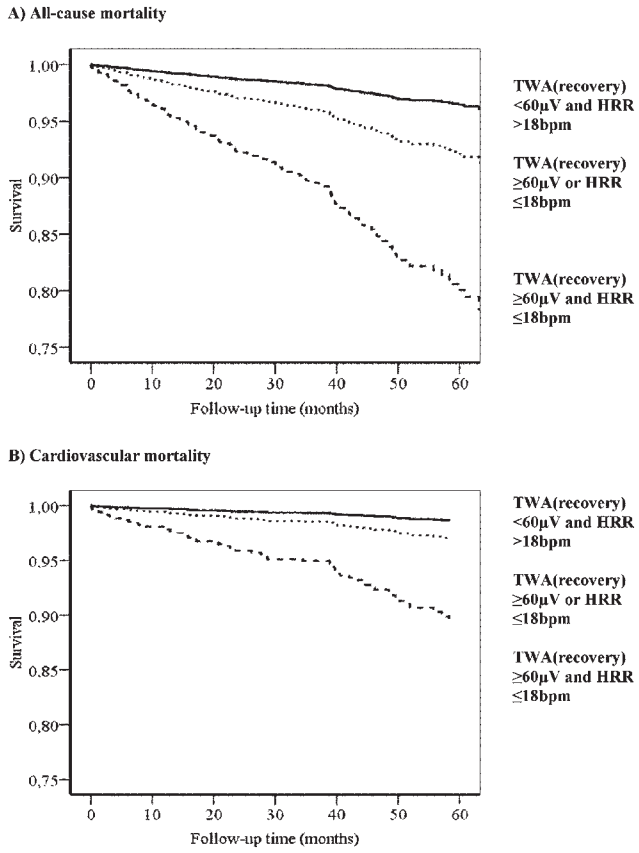

Figure 3 Adjusted survival curves by Cox regression for subjects with recovery-based T-wave alternans (TWA) <60 μV and heart rate recovery (HRR) >18 bpm (*top curve* in both panels), TWA ≥60 μV or HRR ≤18 bpm during recovery (*middle curve* in both panels), and TWA ≥60 μV and HRR ≤18 bpm during recovery (*bottom curve* in both panels) for all-cause mortality (**A**) and cardiovascular mortality (**B**). Note that the scale for the y-axis is from 0.75 to 1.00.

demonstrated, most recently by baroreceptor sensitivity (BRS)[28] and noninvasive assessment with heart rate variability,[28,29] heart rate turbulence,[30] and HRR.[1–8] The latter is a strong predictor of cardiovascular mortality in asymptomatic patients[5,7,8] and in broad populations[4] as well as of SCD.[1] Importantly, impaired HRR is not attributable to ischemic burden[3] or lipid abnormalities.[6] Treadmill exercise scores strongly predict mortality among intermediate- to high-risk patients if HRR is abnormal.[6]

The accuracy and utility of exercise-based TWA in predicting arrhythmic events and death have been investigated.[12–15] Most TWA studies have been performed in high-risk populations, such as patients with heart failure,[15,17–19] cardiomyopathies,[15,18] or history of myocardial infarction.[11,12,15–19] We previously reported in approximately 2,000 FINCAVAS patients that TWA analyzed with the modified moving average method is a strong predictor of all-cause and cardiovascular mortality as well as of SCD in this low-risk population.[14] Especially high specificity when compared with other cardiovascular parameters has characterized the prognostic value of elevated TWA,[13] suggesting suitability to confirm suspected risk.

The potential to improve prediction of cardiovascular and total mortality by combining TWA with the ambulatory ECG-based autonomic marker of heart rate turbulence was recently confirmed in a high-risk population of postmyocardial infarction patients with left ventricular dysfunction.[16] The present study, which enrolled a 6.9-fold larger, lower-risk population of almost 2,000 patients, demonstrated further improvements in odds ratio.

Current investigation

The present study confirms and extends the findings of our previous investigations of TWA[13,14] and HRR[8] in the low-risk FINCAVAS patient population. When analyzed together, TWA and HRR provide high relative risk ratios for all-cause death and for cardiovascular mortality after adjustment for standard risk factors (Table 3), indicating a marked independent prognostic capacity and exceeding the predictive value of either parameter alone or ST-segment deviation. The combinations of reduced HRR with heightened TWA were superior to exercise-induced ST-segment deviation in our low-risk population using Cox proportional hazards models (Table 3) and Harrell's C indices (Table 4). The incidence rate of all-cause as well as cardiovascular deaths was clearly higher among patients with reduced HRR and heightened TWA compared to patients with normal values (Figure 1).

The mechanistic basis for the improvement in prediction resulting from combined analysis of HRR and TWA is unclear. A plausible explanation is that a more complete picture of underlying pathophysiologic factors is rendered by information regarding both autonomic function and cardiac electrical instability. As HRR is thought to reflect the dynamic interplay between sympathetic and parasympathetic nerve activity as influenced by changes in baroreceptor gain,[1] a reduced HRR may indicate autonomic imbalance as a basis for cardiovascular events. Moreover, HRR may reflect aerobic capacity and physical fitness, which have been linked to prognosis.[31] The independent association between increased risk for all-cause and cardiovascular mortality and TWA[13,14] is consistent with the finding that TWA indicates increased heterogeneity of repolarization.[10,32] Although the incidence of SCD was not evaluated in the current investigation, because both TWA[13,14] and reduced HRR[1] have been independently associated with SCD in low-risk populations, it is possible that a number of the cardiovascular deaths were arrhythmic in origin. Atherosclerotic heart disease, typical of 29 (48%) of patients who died of cardiovascular causes, predisposes to ventricular fibrillation and SCD.[33] Accordingly, reduced HRR could indicate impaired vagus nerve activation and lessened capacity to withdraw sympathetic nerve tone, both influences known to be arrhythmogenic.[27,34] Thus, the presence of both abnormal HRR and elevated TWA, reflecting derangements in autonomic function as well as in cardiac electrical instability, would be expected to be associated with the highest risk for cardiovascular events, as demonstrated in the present study.

Study limitations

We do not have information on changes in parameters affecting mortality risk (e.g., smoking, lifestyles, medication) during follow-up. In addition, data on EF were not available for 45% of patients. It is likely that patients in whom no need was found for EF determinations had even better cardiovascular health than did those with EF measurement. EF is an arrhythmia risk stratifier only when EF levels are below normal.[35]

Conclusion

A broad implication of the study finding is that routine exercise testing discloses increased risk for cardiovascular as well as all-cause death among patients with both depressed HRR and abnormal TWA who are not identified by standard risk factors. In addition to improving predictivity, the combined assessment of HRR and TWA may be helpful in gaining insight into the pathophysiologic mechanisms on an individual patient basis that could help to guide therapy. In particular, patients with markedly depressed HRR could be directed toward an exercise training regimen that improves vagus nerve tone, BRS, and long-term prognosis.[31] TWA results reflective of an unstable cardiac substrate could signal the need for antiarrhythmic therapy. Finally, particularly as the measurements can be performed noninvasively during routine exercise testing in the typical flow of clinical care, these parameters can readily be incorporated, either singly or in combination, into routine risk assessment paradigms.

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Importance of regional specificity of T-wave alternans in assessing risk for cardiovascular mortality and sudden cardiac death during routine exercise testing

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BACKGROUND T-wave alternans (TWA) indicates increased risk for life-threatening arrhythmias. However, the regional distribution and predictivity of TWA among precordial leads remain unknown.

OBJECTIVE We analyzed the magnitude and prognostic power of TWA in precordial leads separately and in combination during routine exercise stress testing in the largest TWA study conducted to date.

METHODS The Finnish Cardiovascular Study (FINCAVAS) enrolled consecutive patients (n = 3,598, 56 ± 13 [mean ± standard deviation] years old, 2,164 men, 1,434 women) with a clinically indicated exercise test with bicycle ergometer. TWA was analyzed with the time-domain modified moving average method.

RESULTS During a follow-up of 55 months (interquartile range of 35–78 months), 231 patients died; 97 deaths were cardiovascular, and 46 were classified as sudden cardiac deaths (SCDs). In Cox analysis after adjustment for common coronary risk factors, each 20-μV increase in TWA in leads V1–V6 multiplied the hazard ratio for cardiovascular mortality by 1.486-fold (95% confidence interval [CI] 1.127–1.952; $P = .005$). Each 20-μV increase in TWA in lead V5 amplified the hazard ratio for cardiovascular mortality by 1.545 (95% CI 1.150–2.108; $P = .004$) and for SCD by 1.576 (95% CI 1.041–2.412; $P = .033$).

CONCLUSIONS Maximum TWA monitored from anterolateral precordial lead V5 is the strongest predictor of cardiovascular mortality and SCD during routine exercise testing in our analysis. Higher TWA values indicate greater cardiovascular mortality and SCD risk, supporting the concept that quantification of TWA should receive more attention.

KEYWORDS T-wave alternans; Precordial leads; Exercise test; Mortality; Prognosis

ABBREVIATIONS **BMI** = body-mass index; **CHD** = coronary heart disease; **CI** = confidence interval; **DAP** = diastolic arterial pressure; **ECG** = electrocardiogram, electrocardiographic; **FINCAVAS** = Finnish Cardiovascular Study; **HR** = hazard ratio; **LVH** = left ventricular hypertrophy; **MI** = myocardial infarction; **MMA** = modified moving average; **NYHA** = New York Heart Association; **SAP** = systolic arterial pressure; **SCD** = sudden cardiac death; **SD** = standard deviation; **TWA** = T-wave alternans

(Heart Rhythm 2011;8:385–390)

Introduction

T-wave alternans (TWA) is an electrocardiographic (ECG) phenomenon indicating an electrically unstable myocardial substrate.[1,2] This beat-to-beat alternation in the shape, amplitude, or timing of the ST segment and the T wave has demonstrated utility in predicting ventricular arrhythmias, sudden cardiac death (SCD), and cardiovascular and total mortality independent of standard factors in relatively low-risk populations,[3,4] including ours,[5,6] as well as in higher risk groups.[7–17] Especially high specificity and negative

RL Verrier is co-inventor of the modified moving average method for T-wave alternans analysis, with patent assigned to Beth Israel Deaconess Medical Center and licensed by GE Healthcare. The other authors declare no conflicts of interest. Financial support was received from the Finnish Cultural Foundation, Finnish Medical Foundation, Orion-Farmos Foundation, Tampere University Foundation, Medical Research Fund of Tampere University Hospital, Paavo Nurmi Foundation, Paulo Foundation, Emil Aaltonen Foundation, and Tampere Tuberculosis Foundation. **Address reprint requests and correspondence:** Tuomo Nieminen, M.D., Ph.D., Department of Pharmacological Sciences, Medical School, FI-33014 University of Tampere, Tampere, Finland. E-mail address: tuomo.nieminen@iki.fi. (Received October 28, 2010; accepted November 1, 2010.)

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predictive value characterize the prognostic strength of elevated TWA compared with other cardiovascular parameters.[5]

TWA is a regionally specific phenomenon that occurs in the ischemic zones of the heart and is linearly projected to the precordium.[18] Usefulness of TWA in limb leads is also limited by higher noise levels than in the precordial leads.[6] Therefore, TWA studies have generally used precordial leads, and limb leads are often excluded.[6,18–21] However, the regional distribution of TWA in the precordial leads is still poorly understood. Does a single precordial lead or combination of several precordial leads offer greater prognostic power than others? Also, it remains unknown whether peaks in TWA in selected leads indicate greater risk than wider but lower elevations in TWA values among several leads. This, the largest TWA study thus far, investigates the distribution and the prognostic value of TWA in single precordial leads as well as in the combinations of several precordial leads during routine clinical exercise testing.

Materials and methods

Study cohort

All consecutive patients who were referred for an exercise test at Tampere University Hospital between October 2001 and December 2008 and who were willing to participate in the Finnish Cardiovascular Study (FINCAVAS)[22] were recruited. A total of 3,598 patients (2,164 men, 1,434 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 = 209) were excluded. The main indications for the exercise test were suspicion of coronary heart disease (CHD; frequency 47%), evaluation of work capacity (26%), testing vulnerability to arrhythmia during exercise (25%), and adequacy of CHD treatment (13%), as well as obtaining an exercise test profile before an invasive procedure (9%) or after a myocardial infarction (MI; 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 before the interview and measurements as stipulated in the Declaration of Helsinki.

Study flow

After an informed consent was signed, the medical history of each patient was collected with a computer-based questionnaire form. Thereafter, the subject lay down in the supine position for 10 minutes, and the resting ECG was digitally recorded. The upright routine exercise test was performed using a bicycle ergometer with electrical brakes. The Mason-Likar modification of the standard 12-lead system was used. The initial workload was 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 with the CardioSoft exercise ECG system (Version 4.14, GE Healthcare, Freiburg, Germany). During the test, heart rate was continuously registered on the ECG, while systolic (SAP) and diastolic (DAP) arterial pressures were measured with a brachial cuff every 2 minutes.

Measurement of TWA

Assessing the relationship between TWA and mortality is one of the original goals of FINCAVAS.[21] We employed the time-domain modified moving average (MMA) 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.[3,5,6,13,14,16,22–24] In brief, the MMA 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, measures the difference between the average morphologies, and continuously updates the result by a weighting factor of 1/8 of the difference between the ongoing average and the new incoming beat.[25] TWA values were calculated automatically and continuously by the released version of GE Healthcare's MMA algorithm during routine exercise testing using all standard precordial leads (V1–V6), which have been shown to provide improved prediction over limb leads or other configurations.[6,18–20,26] Peak TWA values were analyzed without regard to exercise heart rate. TWA values $\geq 46\ \mu V$ were overread by a physician investigator and corrected if necessary or discarded based on noise or baseline wander.

Follow-up

Death certificates were received from the Causes of Death Register maintained by Statistics Finland; this source has been shown to be reliable.[27] The certificates included causes of death using the tenth revision of the International Classification of Diseases. The diagnosis numbers and certificate texts were used to classify the deaths as all-cause, cardiovascular, or SCD, which was defined as a cardiac death within 24 hours after the onset of symptoms. The investigators who analyzed TWA test results were blinded to events.

Statistical analysis

The Student's *t*-test for independent samples was used to compare continuous parameters of patient characteristics and exercise test variables for survivors and nonsurvivors, and the χ^2-test was applied for dichotomous variables. The *P*-values were derived with the *t*-test and the χ^2-test for independent samples. The Mann-Whitney *U*-test was used to compare maximum TWA values in every precordial lead between survivors and nonsurvivors. Rates of mortality by quintiles of TWA in lead V5 are presented with the significance determined by Poisson regression. Relative risks for maximum TWA were analyzed for all precordial leads, for each precordial lead separately, and for combinations of precordial leads using Cox regression analysis after adjust-

Table 1 Baseline characteristics and exercise test variables separated for survivors (n = 3,367) and nonsurvivors (n = 231)

	Survivors (n = 3,367)		Nonsurvivors (n= 231)		
	Mean	SD	Mean	SD	*P*
Age	55.1	12.8	63.7	11.4	<.001
BMI, kg/m^2	27.5	4.6	27.9	4.6	.159
Duration of test, minutes	8.2	2.0	6.7	2.0	<.001
Reached maximum heart rate of age-related expected value, %	85.3	13.3	75.0	16.1	<.001
Heart rate at rest, bpm	63.4	11.3	65.3	12.7	.025
SAP at rest, mmHg	136.7	18.8	136.6	22.6	.915
DAP at rest, mmHg	80.2	9.6	77.9	11.2	.003
Heart rate recovery at 1 minute postexercise, bpm	25.1	11.1	16.9	11.1	<.001
Performance in metabolic equivalents (MET)	7.9	2.9	5.5	2.4	<.001
	n	%	n	%	*P*
Sex: female	1,367	40.6	67	29.0	<.001
Smoking: yes	760	22.6	72	31.2	.003
Use of nitrates: yes	919	27.4	107	46.3	<.001
Use of beta-blockers (or pause <48 hours before the test): yes	1,656	49.3	172	74.5	<.001
Hypercholesterolemia: yes	864	49.4	111	59.7	.008
Diabetes: yes	356	10.9	39	17.0	.005
CHD: yes	947	28.1	94	40.7	<.001
LVH: yes	167	5.0	14	6.1	.461
History of MI: yes	603	17.9	69	29.9	<.001

ment by standard risk factors for cardiovascular events, specifically, sex, age, body mass index (BMI), smoking, CHD, diabetes, use of β-blockers, and prior MI. The combination lead data were derived by choosing the highest TWA value among the leads. Also, we tested the prognostic power of widespread TWA (TWA_{sum}), calculated by adding maximum TWA values in every precordial lead at each point in time and using Cox regression analysis after adjustment for standard risk factors. The endpoints in all analyses were all-cause, cardiovascular, and SCD. All of the covariates fulfilled the proportionality assumption by using correlations of the survival rankings with the Schoenfeld residuals. Statistics were analyzed with the SPSS release 16.0 for Windows (SPSS Inc., Chicago). All statistical tests were two tailed and used an alpha level <.05.

Results

Baseline characteristics

Patient characteristics and exercise test variables separated according to all-cause mortality are shown in Table 1. The age of the 3,598 patients was 55.6 ± 12.9 years (mean ± standard deviation [SD]). Most of the patients (71.5%) were categorized as New York Heart Association (NYHA) class I, while other classes included 21.6% (NYHA II) and 6.9% (NYHA III) of the patients. During the follow-up period of 55 months (interquartile range from 35 to 78 months), there were 231 deaths (6.4% of the population), including 97 (2.7% of the population; 42.0% of all deaths) that were classified as cardiovascular deaths and 46 (1.3% of the population; 19.9% of all deaths) that were classified as SCD.

TWA magnitude in precordial leads

The maximum TWA achieved during exercise testing in each precordial lead is shown in Figure 1. Leads V1 and V3–V6 exhibited significant differences in maximum TWA values between survivors and nonsurvivors. The trend in incidence of cardiovascular and all-cause mortality as well SCD showed an increase from the lower to the higher quintiles of TWA in lead V5 (Figure 2).

Prognostic power of TWA in precordial leads

We tested the prognostic power of maximum TWA in each precordial lead separately for all-cause and cardiovascular mortality as well as for SCD using multivariable Cox regression analysis (Table 2). Maximum TWA in all precordial leads was a significant predictor of cardiovascular and

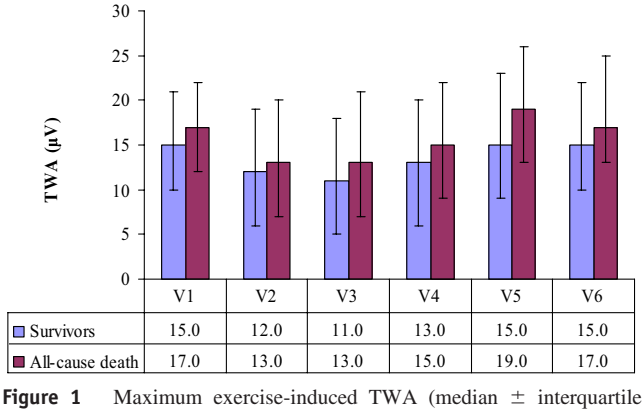

Figure 1 Maximum exercise-induced TWA (median ± interquartile range) in precordial leads of survivors and nonsurvivors. The distribution of TWA values differed significantly in leads V1 and V3–V6.

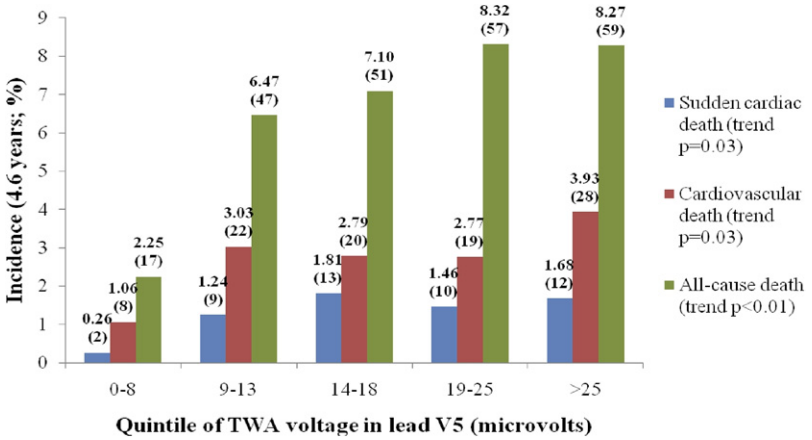

Figure 2 Rates of total and cardiovascular mortality as well as SCD at 4.6 years by quintile of TWA in lead V5. Number of deaths in each category is given in parentheses.

all-cause mortality but not for SCD. Maximum TWA in lead V5 significantly predicted SCD and cardiovascular and all-cause mortality, while maximum TWA in lead V3 was significant only for SCD. TWA in leads V1, V2, V4, or V6 was not significant for any classes of mortality. Hazard ratios (HRs) increased by 55% and 58% for each 20-μV rise in TWA for cardiovascular mortality and SCD, respectively, in lead V5. For prediction of all-cause death, TWA in lead V5 exceeded all other single leads as well as all combinations of leads.

We also tested the prognostic power of TWA in combinations of precordial leads. Maximum TWA in the higher lead of certain combinations, namely, in V2–V6, V3–V6, V4–V6, V5–V6, V4–V5, or V3–V5, yielded significant prediction for cardiovascular and all-cause mortality in Cox multivariable regression analysis (Table 2). Excluding lead V1 markedly improved the prediction of cardiovascular and all-cause mortality.

Prognostic power of widespread TWA

A further aim of this study was to investigate whether or not high peak values of TWA indicate greater risk than general elevations in TWA values across the precordium. For this purpose we calculated a new variable, $TWA_{sum} = TWA_{V1} + TWA_{V2} + TWA_{V3} + TWA_{V4} + TWA_{V5} + TWA_{V6}$. In Cox regression analysis after adjustment with standard cardiovascular risk factors, TWA_{sum} did not show significant prognostic power for SCD or cardiovascular mortality but was significant for all-cause mortality.

Discussion

The aim of this study, the largest TWA study to date with almost 3,600 patients enrolled, was to investigate the regional distribution of TWA in assessing risk for total and cardiovascular mortality as well as SCD. TWA is a widely investigated phenomenon with promising risk stratification potential.[3–17,23,24,28] However, the prognostic value of

Table 2 HRs and 95% CIs for each 20-μV increase in TWA in precordial leads using Cox multivariable regression analysis

	SCD				Cardiovascular deaths				All-cause deaths			
	HR	95% CI (lower)	95% CI (upper)	*P*	HR	95% CI (lower)	95% CI (upper)	*P*	HR	95% CI (lower)	95% CI (upper)	*P*
Max TWA in all precordial leads	1.269	0.818	1.952	0.293	**1.486**	**1.127**	**1.952**	**0.005**	**1.245**	**1.020**	**1.515**	**0.026**
Max TWA in V1	1.173	0.678	2.149	0.625	0.980	0.641	1.545	0.949	1.173	0.905	1.545	0.237
Max TWA in V2	1.173	0.710	1.952	0.526	1.150	0.802	1.671	0.434	1.150	0.905	1.457	0.255
Max TWA in V3	**1.576**	**1.062**	**2.366**	**0.025**	1.269	0.923	1.737	0.157	1.220	0.980	1.515	0.071
Max TWA in V4	1.457	0.961	2.191	0.076	1.295	0.942	1.737	0.104	1.173	0.942	1.429	0.147
Max TWA in V5	**1.576**	**1.041**	**2.412**	**0.033**	**1.545**	**1.150**	**2.108**	**0.004**	**1.347**	**1.083**	**1.486**	**0.006**
Max TWA in V6	0.980	0.544	1.771	0.943	1.321	0.905	1.878	0.146	1.269	1.000	1.607	0.058
Max TWA in V2, V3, V4, V5, or V6	1.321	0.869	1.990	0.194	**1.576**	**1.220**	**2.029**	**0.001**	**1.269**	**1.062**	**1.545**	**0.012**
Max TWA in V3, V4, V5, or V6	1.220	0.942	2.108	0.088	**1.607**	**1.245**	**2.108**	**0.000**	**1.295**	**1.062**	**1.576**	**0.007**
Max TWA in V4, V5, or V6	1.401	0.923	2.108	0.120	**1.545**	**1.196**	**2.029**	**0.001**	**1.269**	**1.041**	**1.545**	**0.019**
Max TWA in V5 or V6	1.374	0.887	2.191	0.158	**1.576**	**1.173**	**2.108**	**0.003**	**1.321**	**1.062**	**1.639**	**0.010**
Max TWA in V4 or V5	**1.545**	**1.041**	**2.234**	**0.031**	**1.515**	**1.150**	**1.990**	**0.003**	**1.269**	**1.041**	**1.515**	**0.021**
Max TWA in V3, V4 or V5	**1.515**	**1.041**	**2.234**	**0.029**	**1.545**	**1.196**	**2.029**	**0.001**	**1.269**	**1.062**	**1.545**	**0.012**
TWA_{sum}	1.083	0.818	1.196	0.102	1.062	1.000	1.150	0.067	**1.062**	**1.000**	**1.105**	**0.024**

Note: Statistically significant results are presented in boldface type.

TWA monitored from single and multiple precordial leads has not been studied before this investigation.

Previous studies

Prediction by TWA in precordial leads has been stated for ambulatory ECGs, but no systematic analysis for individual leads has been reported for exercise-induced TWA. Sakaki et al[16] found that TWA ≥65 μV in either lead V1 or V5 during Holter recording predicted cardiac mortality (HR 17.1; 95% CI 6.3–46.6; $P<.001$) and SCD (HR 22.6; 95% CI 2.6–193.7; $P<.005$) with 1-year follow-up in a Japanese population with ischemic and nonischemic cardiomyopathy. Maeda et al[11] reported that TWA ≥65 μV in either lead V1 or V5 was a statistically significant predictor of life-threatening ventricular arrhythmias (HR 6.1; 95% CI 1.1–34.0; $P = .041$) but not of all-cause mortality among patients with an old MI. In the EPHESUS study,[14] the prognostic power of TWA in lead V1 was nearly the same (HR for SCD 5.2; 95% CI 1.8–14.6; $P = .002$) as in lead V3 (HR 5.5; 95% CI 2.2–13.8; $P<.001$) among high-risk acute post-MI patients; prognosis was improved based on the higher TWA value in either lead. ATRAMI researchers[3] demonstrated that the prediction by TWA in modified lead V5 (odds ratio 7.9; 95% CI 1.9–33.1; $P = .005$) is superior to that in lead V1 (odds ratio 4.2; 95% CI 1.1–16.3; $P = .04$) in ambulatory ECGs. Nearing et al[18] determined that lead V5 showed greater resolution than lead II in detecting TWA in the study of 61 chloralose-anesthetized dogs. Furthermore, maximum TWA during angioplasty of the left anterior descending coronary artery in seven patients was detected in leads V2–V4, which overlay the ischemic zone.[18] Martinez and coworkers[26] elegantly demonstrated the regional specificity of TWA during angioplasty of the right and left coronary arteries.

Current investigation

We tested the prognostic power of TWA in single precordial leads and lead combinations using Cox multivariable regression analysis. Restricting the analysis to specific single leads or lead groups improved prognosis over using all precordial leads.

Our data concur with previous findings with the MMA method,[3,6,11,13,14,16] complex demodulation method,[18] and Laplacian likelihood ratio method,[26] that TWA magnitude is elevated in anterolateral precordial leads in subjects who either died or had coronary artery occlusion compared with controls (Table 2, Figure 1). Similar to previous studies,[6,13,14,28] we noted that increases in TWA magnitude detected mainly in lead V5 were associated with increased incidence of SCD and cardiovascular and total mortality during the 4-year follow-up (Figure 2). This finding underscores the value of quantifying TWA rather than analyzing single cut points to assess risk.

Although TWA achieved relatively high values in lead V1, the prognostic power of TWA in this lead during exercise was null. This finding contrasts with several TWA studies using ambulatory ECGs.[3,11,14,16] A potential explanation is that poor signal-to-noise ratio in the exercise environment lessens the predictive capacity of lead V1, particularly if T-wave amplitude is relatively low in this lead.

We found that monitoring generalized elevations in TWA across precordium offered no advantage in prediction of SCD or cardiovascular mortality. A potential explanation lies in the facts that TWA is regionally specific and that its magnitude reflects the degree of heterogeneity of repolarization, which underlies cardiac electrical instability and risk for ischemia- and reperfusion-induced ventricular fibrillation.[29]

Limitations

The current analysis is not without limitations. We do not have information on changes in parameters affecting mortality risk (e.g., smoking, lifestyles, and medication) during follow-up. Also, our analysis contained a relatively high number of statistical comparisons, which may produce false-positive results. Data with borderline significance should be interpreted with caution. It is unclear why TWA monitored in all the precordial leads did not predict SCD, although it predicted cardiovascular and all-cause mortality. Potentially, patients with long-term and severe cardiovascular disease, who were at a great risk for SCD, died from other precipitating factors, for example, heart failure. Therefore, their deaths were classified as cardiovascular. Most of the SCDs in FINCAVAS were out-of-hospital, unwitnessed cardiac deaths that occurred within 24 hours after the onset of symptoms. The widely accepted definition of SCD is unexpected, witnessed death that occurs within 1 hour after the start of symptoms or, when death is unwitnessed, within 24 hours of being seen alive and well.[30] The limit of 24 hours is likely to overestimate the true SCD incidence, while the limit of 1 hour after symptom onset might underestimate the SCD incidence.[30] Approximately 25% of patients will be misclassified if time is the only criterion used.[31]

Conclusions

Maximum TWA monitored from the lateral precordial lead V5 is the main predictor of SCD and cardiovascular and total mortality during routine exercise testing. These findings support the concept that quantification of TWA is important in addition to using the marker in a dichotomous formulation. Higher TWA values indicate greater cardiovascular mortality and SCD risk, with 55% and 58% increases in HRs per each 20-μV change, respectively, in lead V5. Peak TWA values rather than lower TWA elevations among several precordial leads should be used for risk assessment.

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