Tampereen teknillinen korkeakoulu
Julkaisuja 299

Tampere University of Technology
Publications 299

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Thesis for the degree of Doctor of Technology to be presented with due permission for public examination and criticism in Festia Small Auditorium 1, at the Tampere University of Technology, on the 6th of October 2000, at 12.00 o'clock noon.

Tampere 2000

ISBN 952-15-0464-1 (printed)
ISBN 952-15-1414-0 (PDF)
ISSN 0356-4940

TTKK- PAINO, Tampere 2000

To my dearest Marjo, Mikael and Samuel

ACKNOWLEDGEMENTS

This study was carried out at the Ragnar Granit Institute, Tampere University of Technology. The clinical measurements were made in Tampere University Hospital and in the UKK Institute. Scientific research is today a matter of teamwork, and any credit for this work is equally due to my co-workers and colleagues who have been involved in the research projects. Especially I wish to thank several people and organizations who have had an important influence on this undertaking and my research.

I would like to take the opportunity of expressing my gratitude to the director of the Institute and the supervisor of the thesis, Professor Jaakko Malmivuo, who provided me with the facilities to conduct research at the Ragnar Granit Institute. His guidance during the project has been invaluable. I am equally indebted to Assistant Professor Jari Hyttinen, PhD, for his guidance and support in the field of ECG research. Profoundest thanks go likewise to Rami Lehtinen, PhD, for his valuable contribution during this work. Co-operation with him at the time of the preparation of individual articles was interesting and very fruitful. The important contribution of Henri Vänttinen, Lic.Tech, to this project is here also acknowledged.

My sincere thanks must also go to Professor Väinö Turjanmaa, MD, Head of the Department of Clinical Physiology, and Docent Kari Niemelä, MD, of the Division of Cardiology in the Department of Internal Medicine at Tampere University Hospital for the opportunity to use their clinical materials and for their valuable suggestions in articles where they operated as co-authors. I would also express my gratitude to Docent Harri Sievänen and Professor Ilkka Vuori from the UKK Institute for their valuable contribution to this project. Rainer Harjunpää, MSc, Ari Virtanen, MSc, Jukka Niemi, MSc, Mika Isotalo, MSc, Mika Järvinen, Tiina Metsäranta, MA, Anne Puustelli and Raimo Lamminen are sincerely thanked for their technical support in the processing data material, and at the same time I also thank all those who were involved in the collection of clinical materials.

It was an honor to have as examiner of this thesis Docent Jaakko Hartiala (University of Turku), Docent Markku Mäkijärvi (Helsinki University Hospital) and Docent Ilkka Korhonen (VTT Information Technology, Tampere). I acknowledge with deep gratitude their comments and the effort and time they spent on my thesis.

I would like to thank Robert MacGilleon, MA, for his careful revision of the English of this thesis. Also the many comments made during the preparation of individual articles by Professor Martin Arthur, PhD, Simon Walker, PhD, and Jim Rowland are acknowledged.

I thank the staff of the Ragnar Granit Institute for the exceptional spirit and inspiring working atmosphere I was privileged to enjoy. Especially I express my thanks to Professor Hannu Eskola and Assistant Professor Juha Nousiainen; I greatly appreciate their useful suggestions and encouragement in the preparation of this work. I also wish to express my gratitude to our secretary Soile Lönnqvist, who has handled many practical issues and situations so kindly and readily.

I gratefully acknowledge the financial support received from the Academy of Finland, Tampere University of Technology, the Finnish Cultural Foundation (Pirkanmaa Fund), the Emil Aaltonen Foundation, the Ella and Georg Ehrnrooth Foundation, the Wihuri Foundation the Ida Montin Foundation, the Tampere City Science Foundation, the Finnish Cardiac Society, and the Ragnar Granit Foundation; the assistance has been essential during this project.

I wish to record my indebtedness to all my friends for much needed diversions and for having time to listen to never-ending detailed accounts of my researches. I express my appreciation to my parents Matti Viik and Riitta Venekoski for all their support and care and special thanks belong to my sister Kristiina and to my brother Ari-Pekka for being so helpful in many practical matters. In addition, I would like to thank my mother- and father-in-law, Helvi and Antti Saarinen, for unselfish support in everyday issues.

My deepest gratitude and warmest thanks belong to my beloved wife Marjo and my wonderful sons Mikael and Samuel. Marjo has had the strength to encourage and understand me and my sons have cheered me up in countless ways during this long procedure despite the fact that I have had all too little time for them.

Tampere, Finland
August, 2000

Jari Viik

ABSTRACT

In Finland, coronary artery disease (CAD) is the main cause of death among the middle-aged population. The exercise electrocardiographic (ECG) test is the most widely used non-invasive method of assessing CAD. However, diagnostic performance in conventional analysis of the exercise ECG is limited to approximately 75%; many patients in need of treatment may thus be excluded from subsequent examinations and too many are needlessly referred for further investigation, causing unnecessary anxiety. The objectives of this series of studies were to compare and assess the diagnostic properties of the ECG leads and to evaluate the effect of number and selection of leads on these properties in the detection of CAD, using different ST and ST/HR variables.

Studies of the diagnostic properties of the standard 12 ECG leads and comparisons of the ST and ST/HR variables have been made in different clinical populations comprising 409 patients and subjects undergoing the computerized exercise ECG test: 128 patients with significant CAD proved by coronary angiography, 220 patients with a low likelihood of CAD, and 61 asymptomatic volunteer subjects. The principal statistical method adopted in comparing the discriminative capacities of the exercise ECG variables was receiver operating characteristic (ROC) analysis. Comparisons of sensitivity at fixed specificity were made using McNemar's modification of the χ^2-test for paired proportions.

Marked differences were observed in the diagnostic properties of individual leads. In each variable the highest areas under the ROC curves were in chest leads V_5 and V_6, and in limb leads I and –aVR. However, the cut-off criterion applied to leads I and aVR should be 50% smaller. The most deficient areas under the ROC curves were distinctly chest lead V_1 and limb lead aVL in all variables ($p < 0.0001$ vs. V_5 and I in each variable). The areas under the ROC curves for end-exercise ST-segment depression defined as maximum value over the lead set with 5, 9 and 12 leads were 0.894, 0.859 and 0.791, respectively. A statistically significant difference was observed between each lead set. Comparison between the ECG variables showed the superiority of ST/HR hysteresis.

In conclusion, the exercise ECG leads have dissimilar diagnostic properties in the detection of CAD and the fixed partition criterion for each lead is inappropriate. The diagnostic properties of ST/HR hysteresis were significantly better than those of the other exercise ECG variables used.

Keywords: exercise ECG, ECG leads, coronary artery disease

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following articles, referred to in the text by Roman numerals.

I Jari Viik, Rami Lehtinen, Väinö Turjanmaa, Kari Niemelä and Jaakko Malmivuo.
Correct Utilization of Exercise Electrocardiographic Leads in Differentiation of Men with Coronary Artery Disease from Patients with a Low Likelihood of Coronary Artery Disease Using Peak Exercise ST-Segment Depression.
*The American Journal of Cardiology 1998:81(8):964-969.**

II Jari Viik, Henri Vänttinen and Jaakko Malmivuo.
ECG Variable Cine: Computer Program for Presentation of Temporal Changes in ECG Variables Over Different Number of ECG Leads.
Computer Methods and Programs in Biomedicine 2000:63(2):147-155.

III Rami Lehtinen, Harri Sievänen, Jari Viik, Väinö Turjanmaa, Kari Niemelä and Jaakko Malmivuo.
Accurate Detection of Coronary Artery Disease by Integrated Analysis of the ST-Segment Depression/Heart Rate Patterns During the Exercise and Recovery Phases of the Exercise Electrocardiography Test.
*The American Journal of Cardiology 1996:78(9):1002-1006.***

IV Rami Lehtinen, Harri Sievänen, Jari Viik, Ilkka Vuori and Jaakko Malmivuo.
Reproducibility of the ST-Segment Depression/Heart Rate Analysis of the Exercise Electrocardiographic Test in Asymptomatic Middle-Aged Population.
The American Journal of Cardiology 1997:79(10):1414-1416.

V Jari Viik, Rami Lehtinen, Väinö Turjanmaa, Kari Niemelä and Jaakko Malmivuo.
The Effect of Lead Selection on Traditional and Heart Rate-Adjusted ST-Segment Analysis in the Detection of Coronary Artery Disease During Exercise Testing.
*American Heart Journal 1997:134(3):488-494.**

VI Jari Viik, Rami Lehtinen, and Jaakko Malmivuo.
Detection of Coronary Artery Disease Using Maximum Value of ST/HR Hysteresis Over Different Number of Leads.
Journal of Electrocardiology 1999:32(Suppl):70-75.

VII Jari Hyttinen, Jari Viik, Rami Lehtinen, Robert Plonsey and Jaakko Malmivuo.
Computer Model Analysis of the Relation of ST-Segment and ST/HR Slope Response to the Constituents of the Ischemic Injury Source.
Journal of Electrocardiology 1997:30(3):161-174.

The author's contribution to the original publications was as follows. In publications I, II, V and VI he was the first author, being the main study designer and writer of these four publications. In publications I, V and VI the author was responsible for data processing and analysis and in publication II he was the main designer of a computer program for its implementation.

The author's contribution to publication VII was to participate in design and writing in respect of the simulation of myocardial ischemia, especially in the definition of the myocardial areas and discussion of the influence of the ischemic injury on individual leads.

In publications III and IV the author participated in study design, data processing and writing.

**) publications abstracted in the textbook Exercise and the Heart (4th edition), by Froelicher and Myers, published by W.B. Saunders Company.*
***) publication abstracted in the 1997 Year Book of Sport Medicine published by Mosby-Year Book, Inc.*

LIST OF ABBREVIATIONS

3-D	Three-dimensional
A12, A9, A5	Lead sets exploited 12, 9 (aVL, III and V_1 excluded) and 5 (I, -aVR, V_4, V_5 and V_6) standard leads, respectively
Ave12	Average value of ST-segment alteration defined from all 12 leads
Bpm	Beats per minute
CAD	Coronary artery disease
CRI	Chronotropic index indicating heart rate response to exercise
ECG	Electrocardiography, electrocardiogram
HR	Heart rate
LAD	Left anterior descending coronary artery
LCX	Left circumflex coronary artery
Max12	Maximum value of ST-segment depression over 12 leads
MI	Myocardial infarction
MIBI	Technetium-99m sestamibi
PC	Personal computer
RCA	Right coronary artery
ROC	Receiver operating characteristic
SD	Standard deviation
SPECT	Single-photon emission computed tomography
ST0, ST40, ST60, ST80	Measurement points for the ST-segment; 0, 40, 60 and 80 ms after QRS-offset, J point
ST_{end}	End-exercise ST-segment depression
ST_{rec}	ST-segment depression at 3-minute recovery

1 INTRODUCTION

Despite the aggressive and effective treatment of acute episodes of coronary syndromes and intensified efforts in primary and secondary prevention, cardiovascular disease remains the major cause of death in most Western industrial societies. The major component in cardiovascular disease mortality is atherosclerotic coronary artery disease (CAD). In Finland, CAD is the direct cause of death in one out of three cases in the middle-aged population. According to Statistics Finland[244] the age-standardized annual mortality rate for ischemic heart disease has declined markedly during the last 30 years, from 820 (in 1969) to 490 (in 1997) cases per 100,000 individuals. However, stabilizing rates of incident myocardial infarction combined with an aging population tend to increase the total number of CAD patients. Thus, the total burden of ischemic heart disease to the community has decreased less than one would expect on the basis of age-standardized mortality rates[231]. The statistics[244] also indicates that the annual mortality rate (13,000) among Finns with CAD has been more or less constant for some 30 years. The annual mortality rate among men with CAD has slightly decreased, whereas that among women has increased 40% during these three decades. Furthermore, the statistics of the Finnish Heart Association[81] reflect that more than 600,000 Finns suffer from cardiovascular disease, half of them from CAD. No considerable decrease in the total annual CAD mortality rate is thus to be expected in the near future.

Generally, the first laboratory examination undertaken in a case of suspected CAD is the exercise test with electrocardiogram (ECG). This mode of testing constitutes a noninvasive tool for evaluation of the cardiovascular system's response to exercise under carefully controlled conditions. In spite of the development of other more sophisticated diagnostic techniques, the exercise ECG test remains an important and the most widely adopted diagnostic approach in the evaluation of individuals with suspected or known CAD. If the test result is positive or unreliable the patient is referred for more detailed examinations: exercise isotope myocardial imaging or exercise echocardiogram or, if the need for surgery is obvious, directly to coronary angiography. In view of the major role of the exercise ECG in this procedure, its diagnostic accuracy should be high. The conventional analysis of the exercise ECG for the detection of CAD is based on ST-segment changes, mainly the magnitude of the ST depression. However, according to reports where the diagnostic accuracy of the ST depression has been evaluated by meta-analyses or multicenter databases[60, 61, 91], the mean sensitivity and specificity were limited (68% and 77%, respectively). This means that many patients in need of treatment may be excluded from the following examinations while too many are needlessly referred for further investigation and will inevitably suffer unnecessary anxiety.

In view of the limited diagnostic accuracy of the conventional ST-segment criteria, new ECG variables, computerized exercise scores, multivariate and compartmental analysis, and other novel methods have been proposed to improve the diagnostic accuracy of the exercise ECG. During the last two decades, research has emphasized the adjustment of ECG variables to heart rate (HR). A number of researchers claim that the heart rate-adjusted variables improve diagnostic accuracy over the conventional criteria in CAD detection[7, 25, 72, 73, 80, 102, 107, 114, 123, 125, 129, 133-135, 151-153, 184, 186, 193, 195-200, 204, 206-210, 232, 234, 236-238]. However, inconsistent results have also been obtained[27, 86, 106, 145, 185, 219, 250]. Another important research field in the area of exercise ECG has been detailed observation of the recovery phase and merging of exercise and recovery phases[25, 29, 30, 47, 49, 108, 123, 127, 144, 146-148, 151, 152, 187, 194, 195, 200, 226, 230, 233].

Interest in improving the exercise ECG variables has focused on a search for new variables and their verification in different study populations. The basis in evaluation has been the use of the maximum value of the variable as a diagnostic parameter. The effects arising from the exercise ECG leads used and their number and selection on the diagnostic properties of the variables have been less intensively investigated and discussed.

The present study was designed to compare the diagnostic properties of the standard exercise ECG leads, to examine the effect of number and selection of leads on the diagnostic properties of ST and ST/HR variables and to assess the diagnostic properties of ST/HR hysteresis in the detection of CAD.

2 REVIEW OF THE LITERATURE

2.1 Purpose of exercise test

The main purpose of the exercise test is to determine the condition and capacity of the cardiovascular and respiratory organ systems[86, 158]. During exercise both systems are stressed and the ability to respond adequately to this stress is a measure of their physiological condition. The oxygen lack in the myocardium arising from increased stress is closely related to ECG changes and angina pectoris. Thus, the ECG is always recorded during the exercise test and plays an essential part in the detection of CAD. In addition to the resting ECG, the exercise ECG test is the most widely used means of diagnosis in patients with suspected ischemic heart disease and in functional evaluation of patients with known heart disease[86, 158].

The test may consist of static (isometric) or dynamic (isotonic) exercise or a combination of both[82]. In static exercise the patient maintains constant muscular contraction without movement (e.g. handgrip). The purpose of dynamic exercise is to generate rhythmic muscular activity resulting from movement. By merit of the progressive workloads, increasing heart rate and increasing oxygen uptake, dynamic exercise is better for the diagnosis of ischemia and is more widely used in clinical testing[82]. The exercise test modalities can also be divided into arm or leg and supine or upright exercise testing[82, 86, 92, 214]. Despite the development of a wide variety of modalities for dynamic exercise testing (e.g. steps, escalators, ladder mills and walking test), the most common means are the bicycle ergometer and the treadmill[82, 86]. In Europe the majority of exercise tests are performed with a bicycle ergometer in upright position, whereas in the United States treadmill exercise tests predominate.

Protocols for the exercise test vary in different countries and even in different hospitals. The objective common to all is nonetheless to obtain the subjective maximal stage in about 12 minutes with an incremental workload[82, 92, 214]. In principle, the protocols developed can be divided into slow progressive (tetraangular) or fast progressive (triangular) (Figure 2.1). In the former the uniform workload increment occurs every 3-4 minutes and is generally 40-50 W for men and 25-40 W for women (bicycle ergometer), whereas in the triangular test the increment is generally 10-20 W and the duration of each load shorter, normally 1 minute. The exercise protocols are generally individualized for each patient such that the duration of exercise time would be appropriate[82, 86].

The exercise test can be maximal or submaximal. The true maximum is achieved when the measured oxygen uptake is not increased despite an increase in workload. The exercise test is considered to be maximal when the patient appears to make maximum effort, reaches the predicted maximum heart rate calculated by age, or when other clinical endpoints are reached[82, 92, 120, 214]. In the case of a submaximal exercise test, the test is terminated when the patient reaches 85% or 90% of age-predicted maximal heart rate. The use of the heart rate as a measure of maximality of exercise is questionable[82, 86, 92, 184, 214]. The formulas for the age-predicted maximum rate are mean values defined from different studies; the age-predicted target rate is thus maximal for some subjects and submaximal for others. In addition, the heart rate response to exercise can be altered by medication. In consequence of these problems the subjective intensity of the exercise must also be evaluated during exercise testing. Subjective intensity can be measured using the Borg scale[33, 34], linear or nonlinear, where the patient expresses a subjective grade of exercise using numerical values.

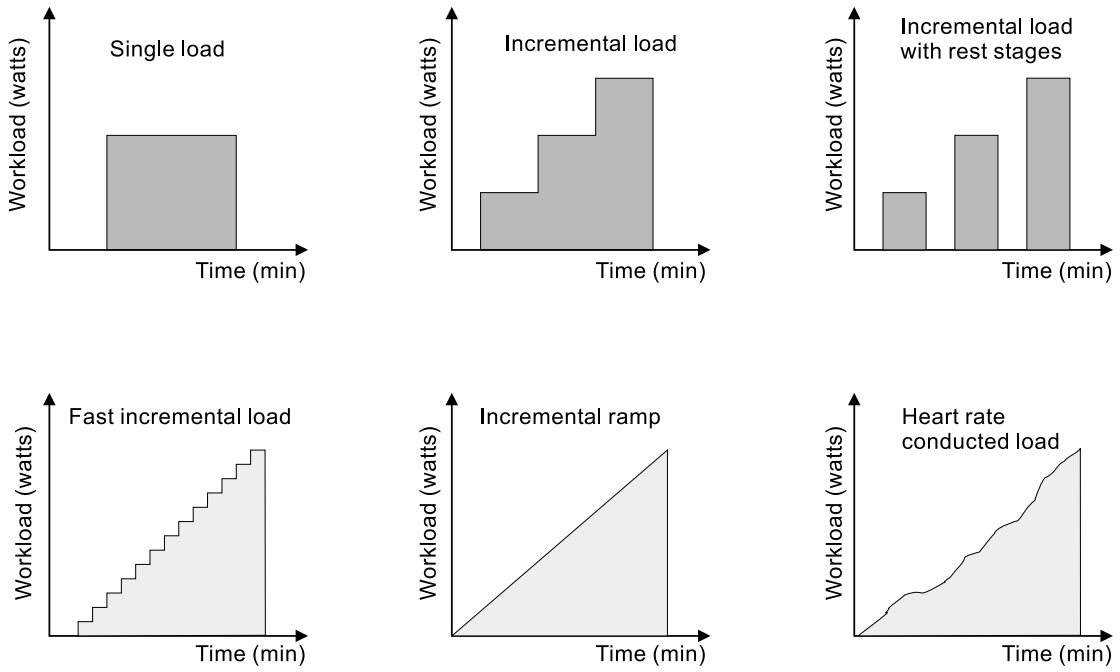

Figure 2.1. The different exercise protocols. The upper three are tetraangular and the lower three triangular. In each case the subjective maximum exertion should be obtained in 12 minutes. The most popular protocols are incremental loading and fast incremental loading.

2.2 Ischemia-induced electrophysiological disorders

In ischemic conditions the blood flow in the heart muscle is insufficient, usually due to a stenosis in the coronary artery. Myocardial ischemia leads to a deviant electrical condition and a partial loss of mechanical contraction of the heart. The electrophysiological changes it causes can be to detected by ECG on the body surface (illustration of ECG complex with named waveforms is presented in figure 2.2). In the first state of the ischemia recharge (repolarization) of the myocardial cells is delayed, and this can be seen in changes of T-wave[105, 157]. A continued ischemic state generates constant injury currents, which produces ST-segment changes. Prolonged lack of oxygen hampers myocardial activation (depolarization) or even causes a total local loss of depolarization (infarct). In the infarct condition all electrical activity in that region of the myocardium ceases[86, 105, 157].

2.3 Exercise-induced changes in ECG

Besides the increase in heart rate, exercise-induced electrical changes can be seen in ECG waveforms. During exercise P-wave magnitude increases and the P-axis becomes more vertical. The T-wave magnitude decreases during early exercise and after exercise, but at maximum exercise increases. Changes in Q-wave are usually very small, but it may become slightly larger at maximal exercise. The R-wave amplitude is observed to decrease near maximal effort and the S-wave increases. The obvious response to the increase in heart rate is shortening of the PR, QRS and QT intervals. These changes occur in normal subjects and are usually related to a normal heart rate response[86, 120, 158, 240, 270].

The most prominent abnormal response in ECG during the exercise test is an ST-segment deviation, mostly depression caused by subendocardial ischemia[269]. ST-segment elevation is less common [190] and has been associated with reciprocal changes for the ST depression, transmural or epicardial injury, and also coronary spasm[89, 156, 272]. In addition to ST-segment deviation a deep T-wave inversion[46, 88], an increase in R-wave[17, 31, 32, 54, 55, 100], Q-waves[19, 20, 53, 78, 98, 189, 191], QRS changes[4, 5, 15, 36, 37, 93, 111, 119, 168-171, 174, 178, 254] and QT interval[8, 136, 137, 149, 227, 229, 243, 245, 246] are considered to be sensitive in the detection of CAD. However, there are also many

studies yielding discrepant results, which would suggest that ST-segment deviation is still the most accurate exercise ECG variable for CAD detection[56, 58, 64, 83, 114, 241, 252, 271].

2.4 Traditional ST-segment analysis

The conventional interpretation of the exercise ECG in the context of CAD detection is based on analysis of ST-segment changes during the exercise test. It has indeed been stated that an exercise-induced ST depression is a better marker for CAD than is exercise-induced angina[180]. However, there are controversies as to the interpretation of exercise-induced ST-segment changes. Depending on the site of the ischemia in the myocardium and the location of the ECG lead, depression or elevation of the ST-segment is detected. The most common type of ischemia, the subendocardial, produces ST-segment depression in electrodes above the ischemic region. Generally, an ST depression of 0.10 mV (1.0 mm) or more with respect to baseline (PR-segment) is considered to constitute an ischemic response. Not only the absolute amount of ST depression, but also the shape is meaningful (Figure 2.2). If the ST depression is horizontal or downsloping it is held to be of greater clinical significance and to indicate more severe CAD. One textbook in this field[86] gives the precept that ST depression should be considered abnormal only if horizontal or downsloping. However, there is also controversy as to whether an ascending ST depression should be considered an ischemic ECG response[43, 62, 124, 141, 222, 235, 247] and whether the horizontal or downsloping signify more severe CAD[30]. Furthermore, the ST depression can be determined by the absolute value of the depression at peak exercise or by its relative value between rest and peak exercise (ΔST depression). The latter, moreover, can be defined using absolute values of ST-segment deviation or ignoring all ST elevation values (i.e. changing these to zero values) at rest and peak exercise.

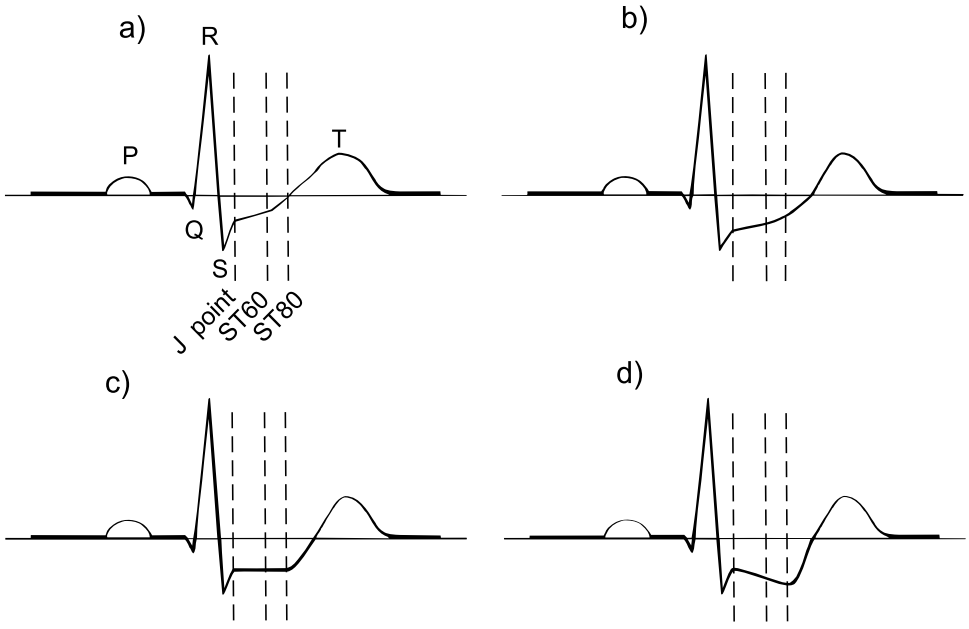

Figure 2.2 The categories of ST-segment depression. a) rapidly upsloping, b) slowly upsloping, c) horizontal, and d) downsloping.

Computerized ECG: Computerized ECG measurement facilitates interpretation of the ECG during exercise by reducing the noise level using averaging or median methods[71, 158, 228]. In addition, it improves interpretation by quantitative ECG analysis. Comparison between computer ECG analysis and visual interpretation for characterization of ST-segment depression has shown that the computer algorithm using median averaged beats is a reasonable surrogate for visual interpretation of the exercise ECG (with at least similar diagnostic accuracy), which

makes it a valuable source of confirmation for physician readings in large research trials and in clinical settings[10, 11, 57, 63, 68, 79, 85, 112, 176, 187, 218, 239, 242].

In computerized exercise ECG, the ST-segment depression is usually measured at fixed time intervals from the QRS-offset, the J point. However, no standard prevails for the length of this interval. In the literature the most widely used intervals are 60 (ST60) and 80 (ST80) ms after the J point (Figure 2.2). Selection of the optimal point is not self-evident. ST80 is widely used, but it is not applicable at high heart rates because the earlier depolarization of the ventricles causes this measurement point to slip over the T-wave. The use of ST40 has been suggested to avoid this problem, but it is disturbed by the repolarization of the atria. ST60 is thus recommended as a compromise especially in automated computer systems[239, 242]. Supporting this, several authors have found ST60 to be the most accurate in identification of exertional ischemia[57, 66, 152, 196, 201, 205, 228, 236, 241]. However, the use of the J point (ST0) has also proved viable[218, 225] and a textbook by Froelicher and Myers[86] as well as exercise standards[82] recommend that ST-segment measurements be made at the J point.

Recovery phase: At the beginning of the era of exercise testing, ECG measurements were made only before and after stress. With technical development of ECG apparatus and signal analysis facilitating ECG measurements during stress, the main interest is currently focused on ECG changes during the exercise phase. However, several investigators suggested that the diagnostic accuracy of the exercise test can be improved by considering also ST-segment changes during recovery[1, 25, 29, 77, 85, 108, 123, 127, 144, 151, 194, 226, 230, 233].

It is generally assumed that early onset of ST-segment depression and its prolonged recovery after exercise signify more severe CAD. Ellestad and co-workers[77] studied the time course of ST-segment depression during and after exercise testing in 462 subjects, who also had coronary angiograms taken. It emerged that patients with early onset and late offset ST depression and patients with resting ST depression which was accentuated with exercise had a high prevalence of significant CAD and three-vessel disease. Observation of the time course of ST depression during and after exercise was found to add significantly to the information gained during exercise testing. Other researchers have also stressed the importance of relating ST-T changes to the time of their occurrence during and after exercise[14, 95, 257].

Bogaty and associates[29] explored the pattern of appearance and disappearance of ST-segment depression in 12-lead exercise testing of subjects with CAD and its relation to the severity of disease in 34 consecutive patients. They noted that the first lead to show positivity during exercise also developed maximum ST depression in three out of four patients and was the last lead to lose positivity in recovery in 94% of cases. They also noted that the greater ST depression was associated with a greater number of positive leads. However, the correlation of ST depression and recovery time with the severity of CAD was poor.

Resting ECG abnormalities: The presence of ST-T-wave abnormalities in the resting ECG has been reported as a predictor of CAD especially in men[51, 52, 75, 117, 179, 182]. Meyers and associates[166] in a study of 95 patients who underwent isotope exercise test concluded that ST-segment analysis with exercise testing is not reliable in patients with resting ECG abnormalities. On the other hand, Kalaria and Dwyer[122] studied the ability of the exercise ECG test to detect ischemia in stable CAD patients with ST depression on the resting ECG and found that the presence of ST depression on the resting ECG does not impair detection of ischemia by exercise ECG. Recently, Fearon and colleagues[79] obtained similar results in a large cohort of patients with resting ST-segment depression and no prior myocardial infarction.

ST-segment and CAD severity: Several researchers have studied the relation between the ST-segment changes and CAD severity. Many note the importance of a downsloping ST depression together with early onset and prolonged duration in detecting 3-vessel or left main CAD[18, 40, 95, 162, 257]. Ribisl and associates[219], in their study of 607 male patients using discriminant function analysis, demonstrated that the maximum amount of horizontal or downsloping ST depression in exercise and/or recovery was the most powerful predictor of

severe CAD. Also other researchers[12, 57, 216, 232] using the conventional criterion of the degree of ST depression have found similar results evidencing a relation between ST depression and severity of CAD. Recently, Tavel and Shaar[249] in a study of 331 patients with ischemic myocardial nuclear defects have shown that the magnitude of ST depression and lead distribution correlate directly with the extent of ischemia. It is apparent that extensive CAD is more likely to be present in a patient who evidences substantial ST-segment changes, which can be seen in multiple leads.

ST-segment and R-wave: In addition, ST-segment changes combined with R-wave amplitude changes on exercise testing have been held to improve the diagnostic accuracy of the exercise ECG in the detection of CAD[23, 32, 113]. Ellestad and associates[76] report that correction of ST depression for R-wave amplitude is especially useful in patients with a low precordial R-wave. Cheng and co-workers[45] demonstrated that a ΔST-segment depression of 0.5 mm and a decrease in R-wave amplitude in the same lead during exercise testing improved the sensitivity, specificity and positive predictive value of the exercise ECG. However, the mechanism of such interaction between ST depression and a decrease in R-wave amplitude remains unclear.

ST-segment in women: It is evident that the diagnostic accuracy of exercise-induced ST-segment changes depends on the prevalence of CAD in a given study population, but several studies have shown that the accuracy of ST changes is lower in women than in men[16, 39, 65, 97, 116, 204, 215, 220, 223]. A meta-analysis of the accuracy of exercise ECG[91] with 147 studies including 24,074 patients (most of whom were men) indicated a weighted mean sensitivity of 68% and a specificity of 77%. Using similar selection criteria a meta-analysis[142] comprising 19 studies including 3,721 women showed a weighted mean sensitivity of 61% and a specificity of 70%. The increased fraction of false-positives in women results in part from the lower incidence of CAD in females.

2.5 Standard ECG leads in detection of CAD

The exercise ECG lead systems commonly applied are bipolar, the Mason-Likar 12-lead and the three-dimensional vectorcardiographic. The most widely used is the Mason-Likar modification of the standard 12-lead system[164], where the conventional wrist and ankle electrodes are placed at the base of the limbs. The 12-lead system comprises six limb and six chest leads. The chest leads are unipolar, the reference for them being the so-called Wilson central terminal (average of the potentials at the right and left arms and left leg). Three of the limb leads are bipolar, measuring the potential difference between two points, and another three are augmented unipolar leads, when the reference for the measurement electrode is the average of two other limb leads. Figure 2.3 illustrates the electrode placement in the Mason-Likar 12-lead system and the corresponding lead directions.

Number of ECG leads: The number of ECG leads has been a difficult topic over a number of decades in the matter of detecting CAD by exercise ECG. As far back as the 1970s, several researchers[18, 42, 224, 251] demonstrated that the sensitivity of the exercise test could be improved by using multiple leads. Subsequently other researchers[38, 84, 85, 177, 187, 241] suggested that the use of 12 leads does not significantly improve the sensitivity or diagnostic accuracy of the exercise ECG in the detection of CAD over lead V_5. Several studies[181, 188] have shown that ST-segment changes isolated to inferior sites are frequently false-positive responses. Recently, Tavel and Shaar[249] established that virtually all ECG abnormalities detected included the lateral precordial leads (V_4 to V_6). Involvement of anterior or inferior leads was almost always seen in conjunction with changes in ≥1 of the lateral leads, and reflected extensive ischemia with greater magnitude of ST depression. However, the diagnostic criterion of ST depression is generally applied to the ECG lead with the deepest ST depression occurring at peak exercise. Using this kind of approach, the sensitivity of the ECG test can be enhanced. Although sensitivity can be improved by increasing the number of leads, the number of false-positive responses increases concomitantly and the specificity of the test is thus reduced. In view of this

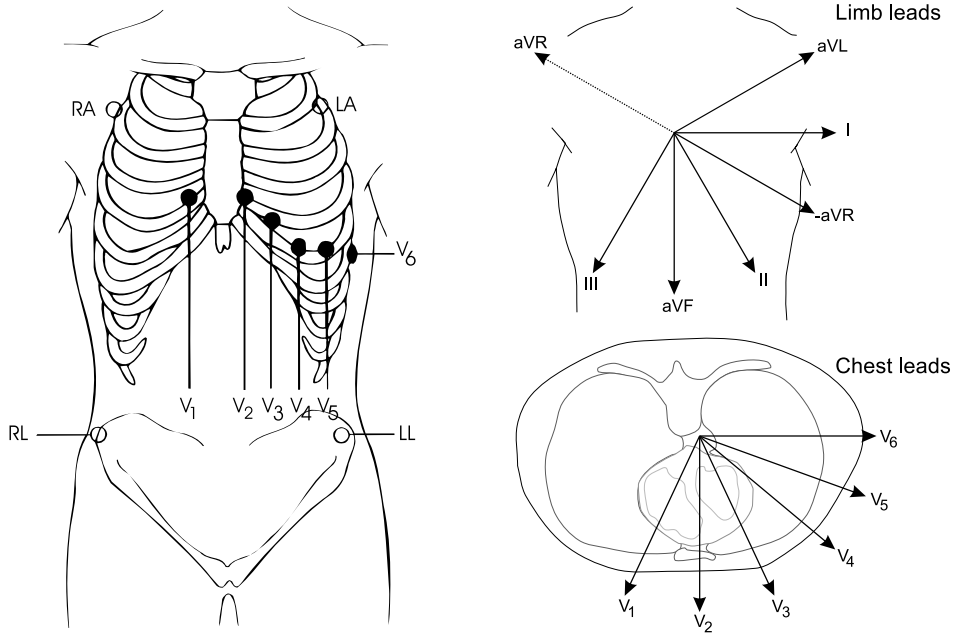

Figure 2.3. The Mason-Likar modification of the standard 12-lead electrode placement for exercise test and corresponding idealized lead directions of limb and chest leads.

problem, the exercise standards[82] and guidelines[92] recommend use of V_5 with some bipolar or inferior lead patterns. A textbook by Froelicher and Myers[86] likewise states that lead V_5, or a similar bipolar lead along the long axis of the heart is adequate for patients with normal resting ECG and that at least two additional leads orthogonal to lead V_5 are required for patients with abnormal resting ECG. Recently, Michaelides and associates[172] have demonstrated that the use of right precordial leads along with the standard six left precordial leads during exercise ECG greatly improves the sensitivity of exercise testing for the diagnosis of CAD. The most surprising result in their study was that the improvement in sensitivity was achieved without any loss of specificity. However, the result has as yet not been confirmed by other researchers.

Bertolet and associates[24], on the basis of a study of the influence of varying precordial ECG electrode placement on the detection of exercise-induced ST-segment shifts, concluded that serial ECGs recorded from similar but not exactly the same precordial ECG electrode positions should yield similar results for the detection of ischemia, but time-to-onset or -offset of ischemia may differ.

Localization of ischemia: The correlation between ST-segment deviation and ischemia site has occupied many researchers. Several have reported a positive correlation between ST-segment depression[101, 165, 167, 173, 224, 248] on exercise and the site of coronary arterial obstruction, but others[2, 38, 69, 74, 84, 88, 104, 140, 163, 249, 259-261] have found no correlation between the site of ST-segment depression and that of myocardial ischemia. Instead many studies[44, 69, 70, 88, 89, 101, 156, 163, 167, 173, 249, 256] have shown uncommon ST-segment elevation to be useful in predicting the site of coronary artery narrowing. Froelicher and Myers[86] note in their textbook that the subendocardial and nontransmural locations of most exercise-induced ischemia make it unreasonable to expect surface ECG recordings to reflect the extent, magnitude and location of the ischemic tissues.

2.6 ST/HR analysis

ST/HR slope: The inclusion of heart rate in ST-segment analysis was proposed over 30 years ago. In 1969 Bruce and McDonough[35] demonstrated the competence of ST-segment changes as a function of heart rate in CAD detection. In 1980 Elamin and colleagues[73] reported results with a new exercise test parameter, the ST/HR slope, assumed to detect the presence and severity of CAD. The ST/HR slope was measured as the maximal rate of progression of ST-segment depression relative to increases in heart rate. The unit for the ST/HR slope is μV/beats per minute (bpm) (Figure 2.4). The steepest ST/HR slope in each lead was obtained by comparing the statistically significant slope (p for correlation coefficient <0.05) of the final three points with that obtained by progressively including further points at earlier levels of exercise. The diagnostic variable was defined as the steepest statistically significant ST/HR slope. Since this initial study several other researchers have proved the ability of the ST/HR slope in the detection of CAD and even in discrimination of the severity of the condition[6, 7, 13, 21, 80, 94, 99, 126, 130, 132, 135, 192, 196, 200, 202, 204, 206, 207, 209, 217, 232, 234, 236].

ST/HR index: Apparently in consequence of the complexity of calculating the ST/HR slope, a simple modification of the slope, designated the ST/HR index, was introduced by Detrano and associates[64]. This index proportions the ST segment alteration during exercise to the change in heart rate from rest to peak effort (Figure 2.4). The unit for the ST/HR index is μV/bpm. Identically to the ST/HR slope, the ST/HR index was calculated for each ECG lead and the diagnostic variable was the maximum value of these ST/HR indices. Two kinds of ST/HR index definitions have been used in the literature, the differences between them lying in the processing of the ST elevations. The original definition introduced by Detrano's group[64] stated that the ST/HR index is calculated as the overall change in ST-segment depression divided by the overall change in heart rate during exercise. Accordingly, both the ST depression and the ST elevation are included at the beginning and end of the exercise phase.

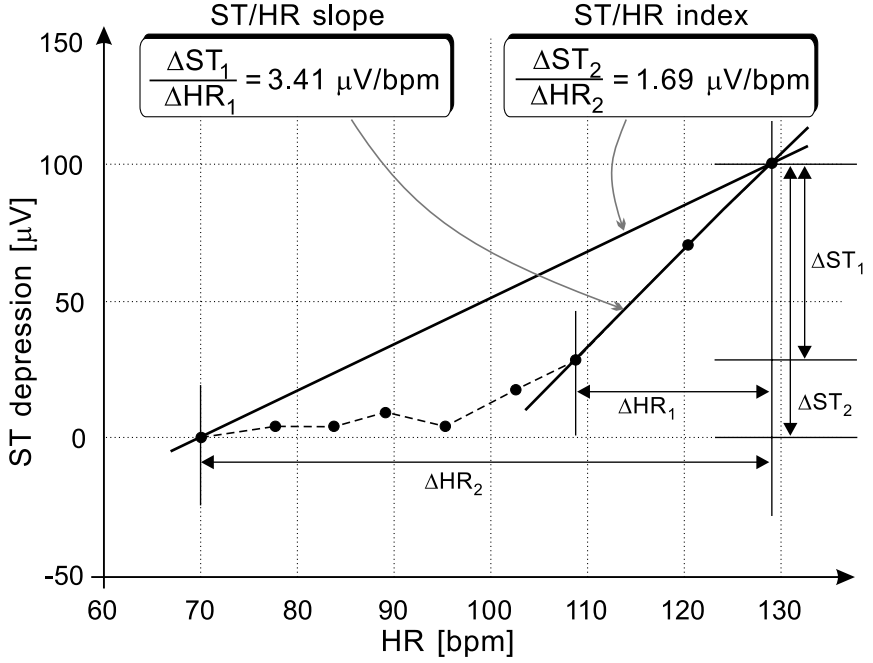

Figure 2.4. Calculation of the ST/HR slope and ST/HR index. ST-segment depression (positive magnitude on vertical axis) is plotted against exercise heart rate. The ST/HR slope is defined by linear regression as the final three (or more) data points. When more than one linear correlation is statistically significant, the greatest value is taken as the test result for the patient. The ST/HR index is obtained by dividing the total change in ST-segment depression by the total change in HR.

HR = heart rate; bpm = beats per minute.

However, other researchers have modified (or applied) the definition in such a way that all ST elevations have been ignored, corresponding to the zero value of ST depression. The precise mathematical ST/HR index equation using the ST-segment alterations with sign produces a negative ST/HR index value if the ST-segment descends during exercise; the positive responses, however, are agreed to have positive values in the ST/HR index. Since the introduction of the ST/HR index several researchers have demonstrated its superior diagnostic capability over the conventional ST depression[57, 102, 107, 114, 130-132, 135, 150, 152, 186, 195, 196, 199, 200, 202, 208-210, 236].

Some researchers have nevertheless expressed suspicion regarding the superior capability of the ST/HR index; several studies have failed to find any advantage over the conventional ST depression[27, 28, 85, 106, 145, 185, 219]. On the other hand, the one major observation made by Morise and coworkers[184, 186] was that the accuracy of the ST/HR index was only marginally better than standard ST-segment criteria in patients who underwent angiography, but when clinically normal subjects were used, the index was definitely more accurate than standard criteria. On this basis they concluded that the demonstration of improved accuracy with the ST/HR index depends on the population being tested.

HR recovery loop: Although the diagram of the ST-segment depression against the heart rate during the postexercise recovery phase was alleged by Bruce and McDonough[35] to be different for normal patients and for patients with ischemic heart disease as far as back 1969, this observation was only quantitatively proved in 1989 by Okin and associates[194]. This Cornell group introduced a dichotomous diagnostic variable, the HR recovery loop[194, 195, 200, 205], which provided significantly better diagnostic accuracy in the detection of CAD than did the standard ST depression criterion. The HR recovery loop records whether the ST depression at 1 minute of recovery is less or greater than that at matched heart rate during exercise. The direction of the HR recovery loop is considered to be clockwise (i.e. the non-ischemic direction) or counterclockwise (ischemic direction) when the ST depression at 1 minute of recovery is smaller or greater, respectively. A further development to the HR recovery loop was introduced by Kamata and associates[123], using two additional categories for the ST/HR loop pattern, one for clockwise rotation with quick ST recovery and one for ST depressions recovering at a constant rate. However, the HR recovery loop considers only the first minute of the recovery period, although the subsequent period may convey relevant information. In addition, the magnitude of the ST depression difference between the exercise and recovery phases relative to heart rate may have independent diagnostic potential. For this reason, the continuous ST/HR variables which utilize the diagnostic information provided by the ECG during the postexercise recovery phase, have recently been a target for development and study[25, 108, 151].

3 OBJECTIVES OF THE STUDY

The objectives of this serial study were:

1) to compare the diagnostic properties of the individual exercise ECG leads in the detection of CAD using different ST and ST/HR variables [I, V],
2) to evaluate the effect of the number and selection of leads on the diagnostic properties of the variables [I, VI],
3) to evaluate the importance of the cut-off criterion for different leads and variables [I, V, VI],
4) to assess and compare the overall diagnostic performance of the variables [III, IV, V],
5) to evaluate the reproducibility of the variables in an asymptomatic middle-aged population [IV],
6) to develop a computer program for the visualization of the temporal changes in ECG variable [II] and
7) to investigate the effect of the extent and location of the myocardial ischemic injury on the ST-segment and ST/HR slope using computer model simulations [VII].

Structure of the serial publication article by article:

Publication I. The diagnostic properties of the individual exercise ECG leads of the standard 12-lead system were compared in discrimination of male patients with CAD from patients with a low likelihood of the disease. Furthermore, the importance of the number of leads was evaluated when using the maximum ST-segment depression value derived from three different lead sets and the effect of a lead-specific cut-off criterion applied to leads I and -aVR was studied.

Publication II. The computer program, ECG Variable Cine, was constructed for visualization of continuous ECG variable (e.g. ST-segment) analysis simultaneously over all measured leads during the exercise test. The program also includes the 3D-presentation mode for stationary images of ECG variable alteration during the whole exercise test simultaneously in all leads.

Publication III. The novel diagnostic variable, ST/HR hysteresis, which integrates ST/HR analysis of both the exercise and postexercise recovery phases in the exercise ECG test, was evaluated with 347 clinical patients. The diagnostic properties of ST/HR hysteresis were compared to the end-exercise ST depression, ST depression during recovery, or the ST/HR index, all of which variables cover either the exercise or recovery phase alone, using the maximum value defined from nine leads.

Publication IV. The reproducibility of ST/HR hysteresis, ST/HR index and end-exercise ST depression was determined in an asymptomatic middle-aged population, the age-cohort most often referred to exercise ECG tests. Maximal exercise ECG tests were performed twice within a period of 6 to 8 months.

Publication V. The diagnostic performances of the individual ECG leads and the effect of lead selection on the ST/HR and ST depression variables were compared in the discrimination of patients with angiographically proven CAD from those with a low likelihood of the disease.

Publication VI. The effect of the number and the selection of ECG leads on the diagnostic properties of ST/HR hysteresis was assessed when using the maximum value over different numbers of ECG leads in the detection of CAD. In addition, the effects arising from an increase in the number of leads were examined in relation to the cut-off criterion applied.

Publication VII. The relation between ST-segment deviation and features of ischemic injury was studied by computer model. The presumed linear relationship between the ST/HR slope and the extent and location of ischemia was studied in detail, and simulations were carried out for the case of single and multivessel CAD. This article describes an application of an accurate source-volume conductor model in the theoretical evaluation and analysis of the ST-segment deviation and ST/HR slope arising from the exercise ECG.

4 MATERIAL AND METHODS

4.1 Patient material

The patient material comprised 409 patients and subjects who had undergone the computerized exercise ECG test. Clinical measurements for 348 patients (214 men and 134 women) were made in Tampere University Hospital (Tampere, Finland) and 61 asymptomatic subjects (28 men and 33 women) were exercised in the UKK Institute (Tampere, Finland). The patient group consisted of 128 patients with significant CAD proved by coronary angiography and 13 patients with no significant CAD according to coronary angiography, 18 patients, who had no myocardial ischemia or infarction according to technetium-99m sestamibi (MIBI) single-photon emission computed tomography (SPECT), and 189 patients with a low likelihood of CAD. Coronary angiographies and MIBI SPECT myocardial perfusion imaging were carried out in Tampere University Hospital.

Tampere University Hospital patient material: The computerized exercise data on 1507 consecutive patients were digitally stored for later analysis in Tampere University Hospital. All patients had been referred for routine clinical exercise ECG testing and there were no voluntary subjects. Patients with either left or right bundle branch block pattern in resting ECG were excluded, likewise those with recent myocardial infarction (MI) and those without ECG recording of at least 3 minutes during the recovery phase. The patients' usual medication was not discontinued.

The maximum time between the exercise test and coronary angiography was set at 180 days. The inclusion criteria for patients with CAD were ≥50% coronary artery stenosis according to coronary angiography in at least one major coronary artery and no angioplasty or surgical operations between the exercise test and coronary angiography. After these restrictions there were 128 patients (101 men and 27 women) who comprised the CAD group. Of these, 49 had significant stenosis in all three major coronary arteries or in the left main coronary artery, 33 had two-vessel and 46 one-vessel disease.

The reference group consisted of 13 patients (4 men and 9 women) with no significant stenosis according to coronary angiography within 180 days of the exercise test, no angioplasty or surgical operations between the exercise test and angiography and no previous MI. Also the 18 patients (9 men and 9 women) free of any perfusion defects in MIBI SPECT were included in the reference group. In addition, 189 patients (100 men and 89 women) who had no history of any cardiac disease, had normal resting ECG, had no anginal-type chest pain and cardiac medication were included in this group. In probabilistic assessment, the reference group can be assumed to have a low likelihood ($p < 0.05$) of CAD[67].

UKK Institute patient material: The 61 middle-aged (51 to 54 years) asymptomatic volunteers completed a maximal exercise ECG test twice at the UKK Institute within a period of 6 to 8 months. The subjects gave informed consent prior to the study. Each subject was sedentary (vigorous exercise no more than twice a week), non-smoking, non-dieting, and not excessively obese (body mass index <33). The subjects accustomed themselves to the exercise procedure by performing a submaximal test one month before the first maximal test. Careful medical screening was undertaken prior to both maximal tests, and none was found to yield an abnormal resting ECG or a history or symptoms of cardiovascular, musculoskeletal, respiratory or other chronic disease which might limit maximal exercise testing. Between the repeated tests the subjects were asked to maintain their living habits unchanged, and during the study period none showed any clinical signs of evolving heart or other disease.

4.2 Exercise ECG test

All exercise tests were performed on a bicycle ergometer using a computerized recording system. The ECG recordings were made with a SYSTEM II EXES recorder (Siemens-Elema, Solna, Sweden) and with a Marquette Case 12 recorder (Marquette Inc., Milwaukee, WI, U.S.A) in Tampere University Hospital and in the UKK Institute, respectively. The lead system used was the Mason-Likar modification of the standard 12-lead system[164] in both centers. In Tampere University Hospital the graded protocol followed a standard clinical routine with an initial workload of 40W for women and 50W for men and an increment of 40W and 50W every 4 minutes for women and men, respectively. In the UKK Institute the initial workload was 10 W for women and 20 W for men and the incremental load was 10 W and 20 W every minute for women and men, respectively. The exercise tests were sign- and symptom-limited maximal tests using the recommended criteria for termination[9, 82, 92, 105, 158]; fatigue or chest pain were the reasons for termination in most cases.

ST-segment amplitude, heart rate and workload data were automatically determined by commercial analyzers from the representative ECG complex at intervals of 60 seconds by SYSTEM II EXES and at intervals of 12 seconds by Marquette CASE 12 throughout the exercise test. The ST-segment amplitudes were measured with an accuracy of 10 μV in both systems. Computer-determined ST-segment amplitudes were defined at 60 ms after the J-junction[152, 196], considering the end of PR-segment as the isoelectric line, for each of the 12 leads from the beginning of the exercise test up to the first three consecutive minutes of post-exercise recovery. ST-segment amplitude, heart rate and workload data were stored digitally for further processing and analysis.

4.3 Exercise ECG variables

ST-segment depression: Representing the conventional ST-segment analysis, the end-exercise ST depression (ST_{end}) and ST depression at 3 minutes of recovery (ST_{rec}) were determined from the 12-lead system.

HR recovery loop: The HR recovery loop was determined as described by Okin and colleagues[194]. The ST-segment depression at one minute of recovery was compared with that at the matched heart rate. If the depression at one minute of recovery was less than that at matched heart rate during recovery, the direction of the HR recovery loop was considered to be clockwise (i.e. nonischemic), and if the ST depression at one minute of recovery was greater than or equal to that at matched heart rate during recovery, the direction of the loop was considered to be counterclockwise (i.e. ischemic). The HR recovery loop was determined in the lead with deepest end-exercise ST-segment depression.

ST/HR index: Calculation of the ST/HR index was made as suggested by Detrano and associates[64]: The overall ST-segment deviation at end of exercise was divided by the exercise-induced change in heart rate. Thus, both the ST depression and the ST elevation are included in the beginning and in the end of the exercise phase. The ST-segment depressions are expressed as positive values and ST-segment elevation as negative. Calculation of the ST/HR index is illustrated in Figure 4.1.

ST/HR hysteresis: ST-segment changes during the exercise phase and up to three minutes of recovery were plotted as a function of heart rate, termed here the ST/HR diagram. ST-segment depression was plotted in upward direction on the vertical axis, and negative values represent ST-segment elevation. ST/HR hysteresis was calculated by integrating the difference in ST depression between the exercise and recovery phases over the heart rate from the minimum heart rate during recovery to the maximum heart rate in the exercise test. The integral was divided by the heart rate difference over the integration interval in order to normalize the ST/HR hysteresis with respect to the recovery heart rate decrement. This variable represents the average difference in ST depressions between the exercise and recovery phases at an identical heart rate up to three minutes of recovery. The determination of ST/HR

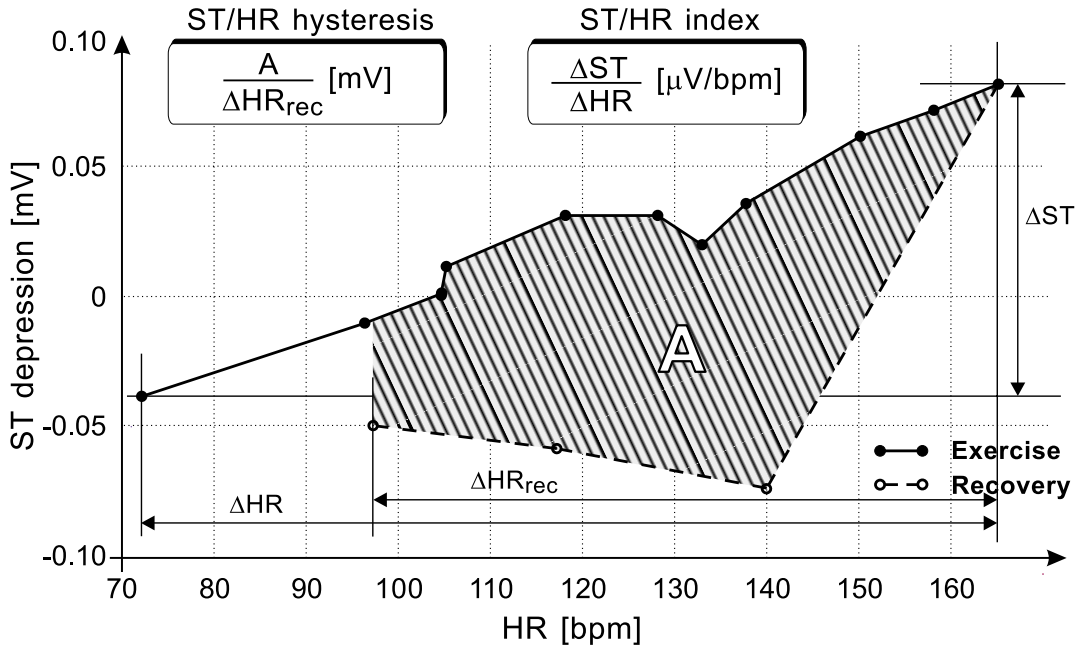

Figure 4.1. Determination of ST/HR hysteresis and ST/HR index from the ST/HR diagram of a single ECG lead. ST and HR data pairs are plotted immediately prior to start of exercise, at the end of each minute of exercise, at peak exercise, and at the end of the first three minutes of recovery. The ST-segment depression is plotted in upward direction on the vertical axis (negative values represent ST elevation). This figure illustrates the contradictory results between the ST/HR hysteresis and the ST/HR index arising from the inclusion of the recovery phase; the sign and value of the ST/HR hysteresis would be negative, indicating non-ischemic response, whereas the sign and value of the ST/HR index would be positive, indicating ischemic response.

A = area between the recovery and exercise ST depression values; HR = heart rate; bpm = beats per minute.

hysteresis using a single lead ST/HR diagram is graphically illustrated in Figure 4.1.

The pairs of ST depression and heart rate were measured before commencement of exercise, at the end of each minute of exercise, at the end of exercise and at the end of the first three consecutive minutes of the recovery phase. Data on the subjects in the UKK Institute were recorded by the Marquette Case 12, which provided the higher 12-second sampling interval. Thus the data pairs for every 12 seconds during the first three minutes of the recovery phase were included in the ST/HR diagram in the UKK Institute subjects.

4.4 Coronary angiography

Selective coronary angiography was performed using the Judkins technique[50, 96]. In all cases each coronary artery was imaged in multiple views. The degree of stenosis was defined as the greatest percentage reduction in luminal diameter in any view compared with the nearest normal segment. Coronary artery disease was considered significant when ≥50% luminal narrowing was present in at least one major coronary artery (left main, left anterior descending, left circumflex, or right coronary artery). Coronary angiograms were interpreted without knowledge of the exercise ECG data.

4.5 Myocardial perfusion imaging

The isotope studies were carried out using technetium-99m sestamibi (MIBI) myocardial perfusion imaging. The MIBI imaging procedure followed the standard clinical routine[22, 90, 159]. Distribution images were determined by computer analysis of the results obtained from single-photon emission computed tomography (SPECT). Regional perfusion defects were determined

visually in the anterior, lateral, posterior, inferior, apical, and septal regions of the left ventricle. Abnormalities in myocardial perfusion were identified as abnormal distribution images. Perfusion defects were classified into four categories: (1) reversible, (2) persistent but partially reversible, (3) normal, and (4) fixed, those types corresponding to (1) myocardial ischemia, (2) a combination of myocardial ischemia and infarction, (3) no perfusion defects, and (4) myocardial infarction (MI) or scar tissue. Patients with categories 1 and 2 in at least one region of the left ventricle were classified as having myocardial ischemia.

4.6 Computer thorax model

An accurate computer model of the thorax as a volume conductor was constructed by the finite difference method[118, 253]. The torso geometry was constructed from a digitized computed tomography scan with 10 mm spacing obtained from a 40-year-old man. The model comprised 91,282 elements defined by a nonuniform rectangular grid. In the heart region extra layers were interpolated between those obtained from computed tomography to provide 5 mm resolution. The lungs, spine, sternum, heart, aorta and intracavitary blood masses, all of which have different resistivities, were included in the model.

The analysis was based on experimental evidence and on the solid angle approach following the framework suggested by Okin and Kligfield[203, 205]. However, in the solid angle theory the foundation derives from the assumption that the human thorax can be described as a homogeneous unbounded volume conductor[161]. We extended this conception by including the effects of the constituents of the volume conductor and the basic factors arising in multivessel CAD. By reason of the solid angle approach, the source-volume conductor model assumed a linear relationship between heart rate and extent of ischemia.

A homogeneous, subendocardial, stationary, radially-oriented double-layer source was used to simulate ischemic injury sources[110, 160, 183, 221]. Double-layer sources were defined within the myocardial region of the thorax model in the anterior, lateral, inferior, posterior, septal and apical sections of the endocardium of the left ventricle. Larger ischemic sources were formed by combining the effects of the smaller regional sources. Anteroseptalapical and posteroinferior sources were formed representing the regions supplied by the left anterior descending coronary artery (LAD) and right coronary artery (RCA), respectively. The lateral source represented the region supplied by the left circumflex coronary artery (LCX). A double-layer source strength of 65 mV was used as a source which emerges at the end of an exercise ECG test[121, 128].

4.7 Data analysis and statistical methods

The age of the patients, maximum workload, maximum heart rate achieved and continuous diagnostic variables are given as means and standard deviations (SD). Sensitivity and specificity were used as parameters of the accuracy of a diagnostic test/variable. Sensitivity describes the number of abnormal (positive) patients revealed by the test divided by all diseased patients. Specificity is defined as the number of normal (negative) patients identified in the test divided by all patients without disease. Diagnostic accuracy was derived by dividing the correct classifications by all patients tested. Sensitivity, specificity and diagnostic accuracy are given as percentages.

The quantitative and non-quantitative study population variables were analyzed by Student's *t* test and non-parametric χ^2-test with Yates' correction, respectively. The principal statistical method for comparison of the discriminative capacities of exercise ECG variables was receiver operating characteristic (ROC) analysis. In addition, when comparisons of sensitivity at fixed specificity were made, McNemar's modification of the χ^2-test for paired proportions was used.

ROC analysis was used because it allows comparison of continuous diagnostic variables without any partition value (i.e. cut-off criterion or operating point). In ROC analysis the sensitivity and specificity values are plotted in the ROC space over the range of test

measurement partition values (Figure 4.2). The area under the ROC curve represents the overall diagnostic performance, i.e. the probability that a random pair of patients with and without CAD will be correctly diagnosed[103]. Due to the nature of the ROC method, the area under the ROC curve can always be assumed to be at least 50%. Statistical differences between the areas under two ROC curves were compared using nonparametric analysis of correlated ROC curves[59] with a routine written by Vida (version 2.5)[258].

In study IV, which examined the inherent non-diagnostic variability of ST/HR hysteresis, ST/HR index and end-exercise ST depression, the reproducibilities of the exercise ECG variables between repeated measurements were determined as recommended by Bland and Altman[26]. The definition of reproducibility was ±1.96 times SD of the differences between the pairs of measurements (SD_{BA}) using the same method. This range corresponds to 95% limits of agreement, within which intra-individual changes should be considered non-significant due to the inherent variability of the method. As a further measure of reproducibility, the agreement of interpretation between repeated measurements was defined as the percentage of subjects in whom the interpretation of both measurements was the same.

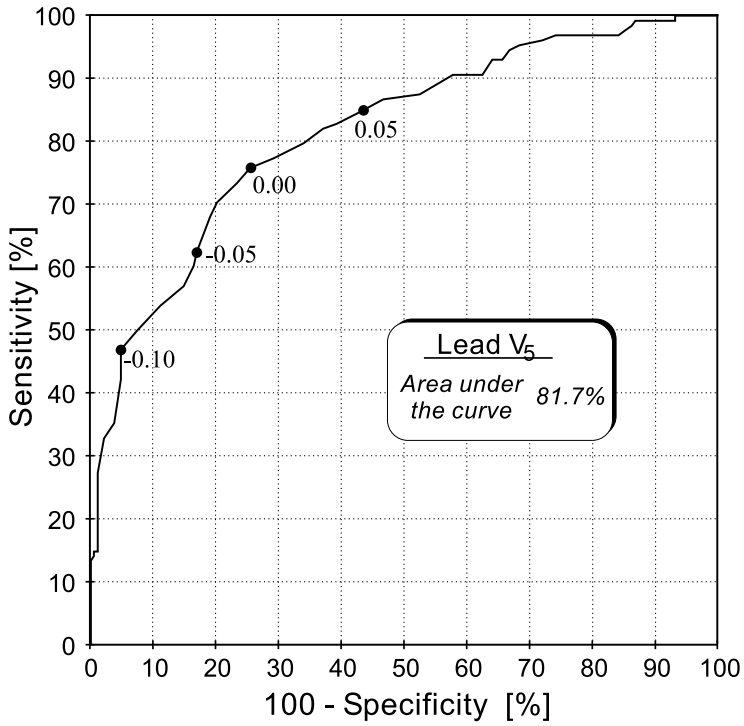

Figure 4.2. The receiver operating characteristic curve for chest lead V_5 in ST-segment value at end of exercise. Cut-off criteria presented in the curve are in millivolts (-0.10 mV indicates a 1.0 mm ST depression). The highest diagnostic performance (diagonally the closest point to the left upper corner) is achieved using a cut-off criterion of 0.00 mV, giving a sensitivity of 75.8% and a specificity of 74.6%.

5 RESULTS

5.1 Individual leads in detection of CAD

Comparison of the mean values of ST/HR hysteresis, ST/HR index, ST_{rec} and ST_{end} between the patient and reference groups showed statistically highly significant differences in almost every lead [V]. Only lead aVL did not evince significant differences at a level of $p < 0.0001$ in any of the variables used and lead V_1 attained a significant difference only in the case of ST/HR hysteresis. Despite the good discriminative capacity of the individual leads, the results in publication V also reveal differences between the leads. The areas under the ROC curves for ST/HR hysteresis, ST/HR index ST_{rec} and ST_{end} in each individual standard lead as a lead direction presentation are presented in Figure 5.1 [V]. In each variable the highest areas under the ROC curves were in chest leads V_5 and V_6, and in limb leads I and –aVR. The most deficient areas under the ROC curves were distinctly those in chest lead V_1 and in limb lead aVL in all variables ($p < 0.0001$ vs. V_5 and I in each variable).

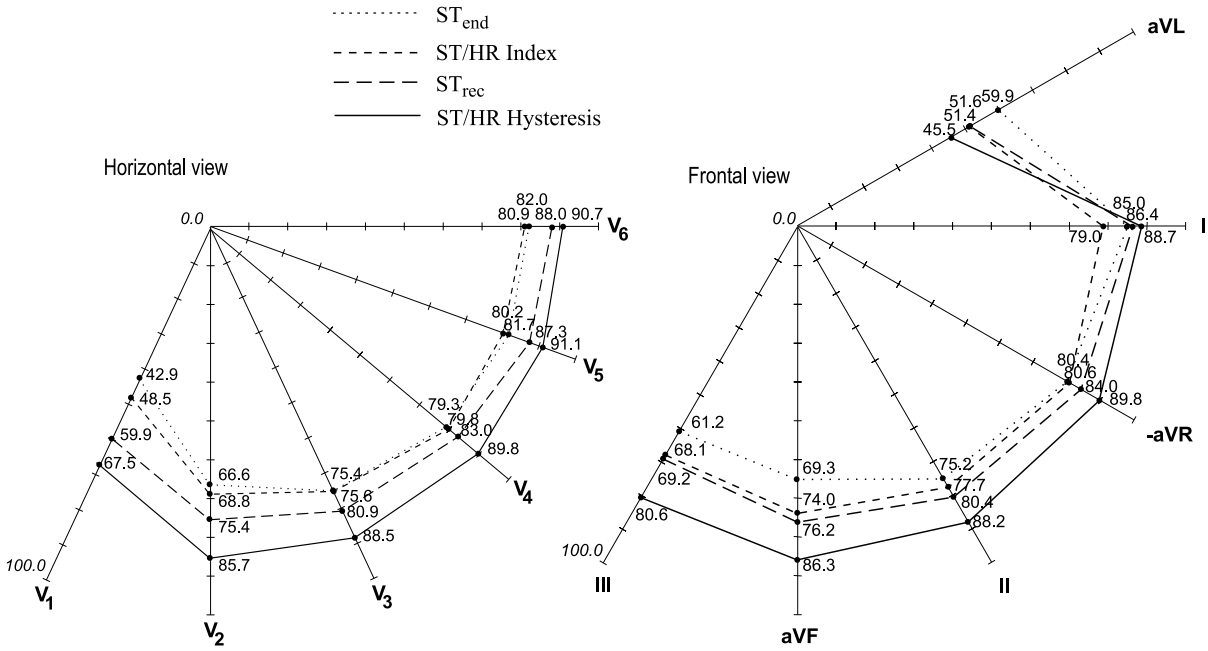

Figure 5.1. The areas under the receiver operating characteristic (ROC) curves in standard leads for ST/HR hysteresis, ST/HR index, ST_{rec} and ST_{end} shown on scales (0% to 100%) in direction of lead. The horizontal view presents the results for chest leads and the frontal view results for limb leads. Values are percentages of total ROC space. [V, Figure 1]

HR = heart rate; ST_{end} = end-exercise ST-segment depression; ST_{rec} = ST-segment depression at 3 minute recovery.

A more detailed presentation (mean, standard error and standard deviation) of the values of ST_{end} in each individual lead among male patients is given in Figure 5.2 [I]. The ST_{end} values in the CAD and reference groups are illustrated side-by-side, starting with the CAD group. Also in this study statistical comparison of the leads showed that the areas under the ROC curves in leads aVL, and V_1, as well as in leads aVF, III, V_2, were highly significantly smaller than in lead V_5 ($p \leq 0.0001$ in all cases), and no significant differences were detected when comparing leads I, -aVR, V_4, and V_6 with lead V_5. In addition, the sensitivity values obtained at 95% specificity showed statistically highly significant differences when comparing leads III, aVL, aVF, V_1 and V_2 with lead V_5 (in all cases $p < 0.0001$), but not in the case of leads I, -aVR, V_4 and V_6.

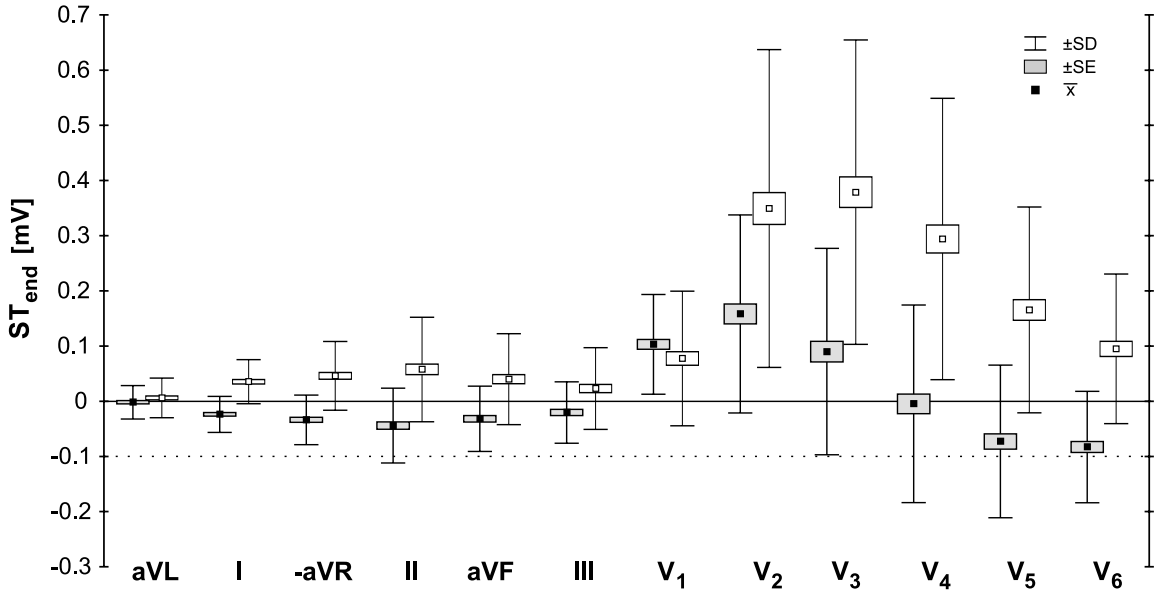

Figure 5.2. Standard deviations (SD), standard errors (SE) and means ($\bar{x}$) of the ST-segment values at end of exercise lead by lead. Shaded symbols indicate the coronary artery disease group and open symbols patients with a low likelihood of the disease. [I, Figure 1]

ST_{end} = end of exercise ST-segment value.

5.2 Number and selection of ECG leads when using maximum value

The importance of the number of leads for ST_{end} using the maximum search procedure (i.e. maximum value of ST_{end} defined from the selected leads) was evaluated among male patients with three different lead sets [I]. The lead sets exploited i) all 12 leads, ii) 9 leads (aVL, III and V_1 were excluded) and iii) 5 leads (I, -aVR, V_4, V_5 and V_6) of the standard 12-lead ECG, and were denoted by A12, A9 and A5, respectively. The most interesting sections of the ROC curves for lead sets A12, A9 and A5 are presented in Figure 5.3 [I]. In comparing the areas under the ROC curves, significant differences were found between A5 and A9 ($p = 0.0152$), A5 and A12 ($p < 0.0001$) and A9 and A12 ($p = 0.0001$). Comparison of the different lead sets with lead V_5 (area under the ROC curve was 0.873) brought out a significant difference only in the case of V_5 and A12 ($p = 0.0023$). No significant differences were observed between A5 and V_5 ($p = 0.0906$) or V_5 and A9 ($p = 0.4181$).

By comparing the sensitivities between lead sets at fixed 95% specificity, significant differences were detected between A5 and A12 ($p < 0.0001$), A5 and A9 ($p = 0.0060$) and A9 and A12 ($p = 0.0008$). A significant difference was also found when comparisons were made between lead set A5 and lead V_5 ($p = 0.0133$) and between V_5 and A12 ($p = 0.0003$), but no significant difference was observed between V_5 and A9 ($p = 0.4227$) [I].

The effect of number and selection of leads on the overall diagnostic performance of ST/HR hysteresis when using the maximum value over the selected leads was assessed in study VI. The lead sets were composed by increasing the number of leads one by one in the maximum search procedure so that the area under the ROC curve was as high as possible at every step. The best individual lead was used as the initial lead. The results obtained with the increase in the number of leads using the maximum search procedure are presented in Figure 5.4 [VI]. The figure also shows the order of inclusion of leads.

The maximum value for the area under the ROC curve was achieved when the fourth lead was included in the maximum search procedure; however, the increase was not significant (90.7%, $p = 0.2960$ vs. V_5). Inclusion of the eighth lead cut down the area under the curve

significantly compared to the set giving maximum area, p = 0.0257 vs. the lead set with 4 leads.

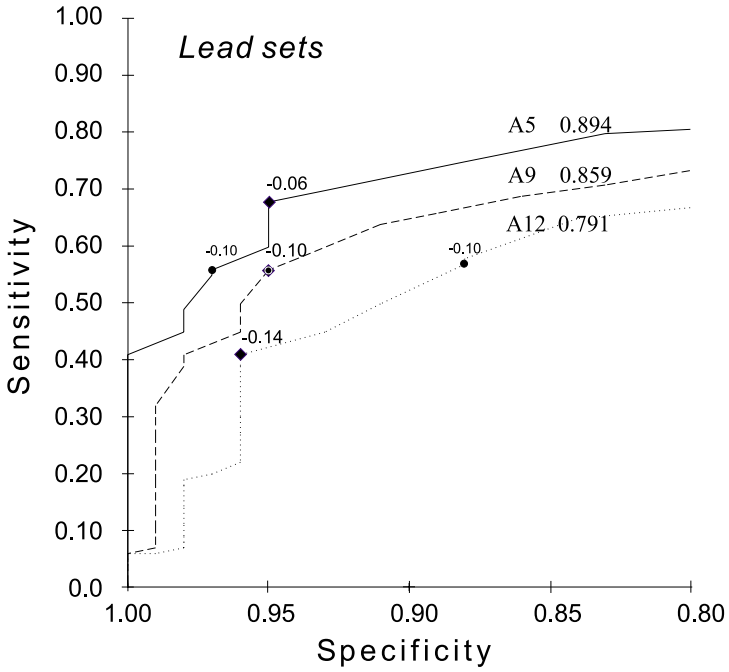

Figure 5.3. The receiver operating characteristic (ROC) curves for three different lead sets using the maximal ST-segment values at end of exercise derived from each lead set. Values adjacent to the name of the lead set indicate the areas under the ROC curves. Circles indicate a value of 0.10 mV ST-segment depression and squares indicate the nearest cut-off criterion at 95% specificity. [I, Figure 3]

A12 = all leads of the 12-lead system; A9 = aVL, III and V_1 excluded; A5 = leads I, -aVR, V_4, V_5 and V_6.

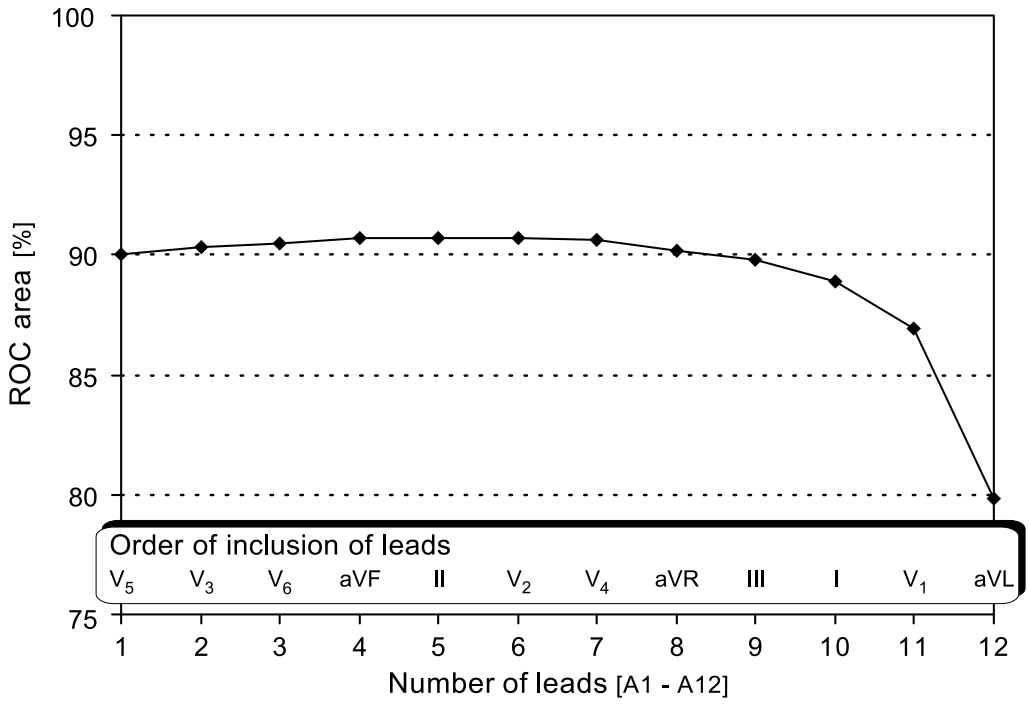

Figure 5.4. The areas under the receiver operating characteristic (ROC) curves for lead sets having 1 to 12 leads using ST/HR hysteresis. The diagnostic classifier was the maximum value of ST/HR hysteresis determined from the leads in each lead set. The number of leads was increased one by one to the maximum search procedure in such a way that the area under the ROC curve was as high as possible at every step. The order of inclusion of leads is presented in the keybox. [VI, Figure 3]

When using all 12 leads in the procedure the decrease in the area under the ROC curve was highly significant ($p < 0.0001$ vs. the lead set with 4 leads). Inclusion of leads aVL and V_1 in the maximum search procedure considerably reduced the area under the curve.

5.3 Use of cut-off criteria for ECG leads

The cut-off criteria as well as sensitivities at fixed specificity varied between the individual leads. This behavior was discernible in all variables. Figure 5.5 [V] presents the ROC curves of leads V_5, I, V_1 and aVL with the cut-off criteria yielding nearest to 90% specificity.

The influences of the different cut-off criteria when using several leads were observed in greater detail for the ST_{end} [I] and ST/HR hysteresis [VI]. The specificities and sensitivities for the maximum values defined from lead sets A12, A9 and A5 using different cut-off criteria are

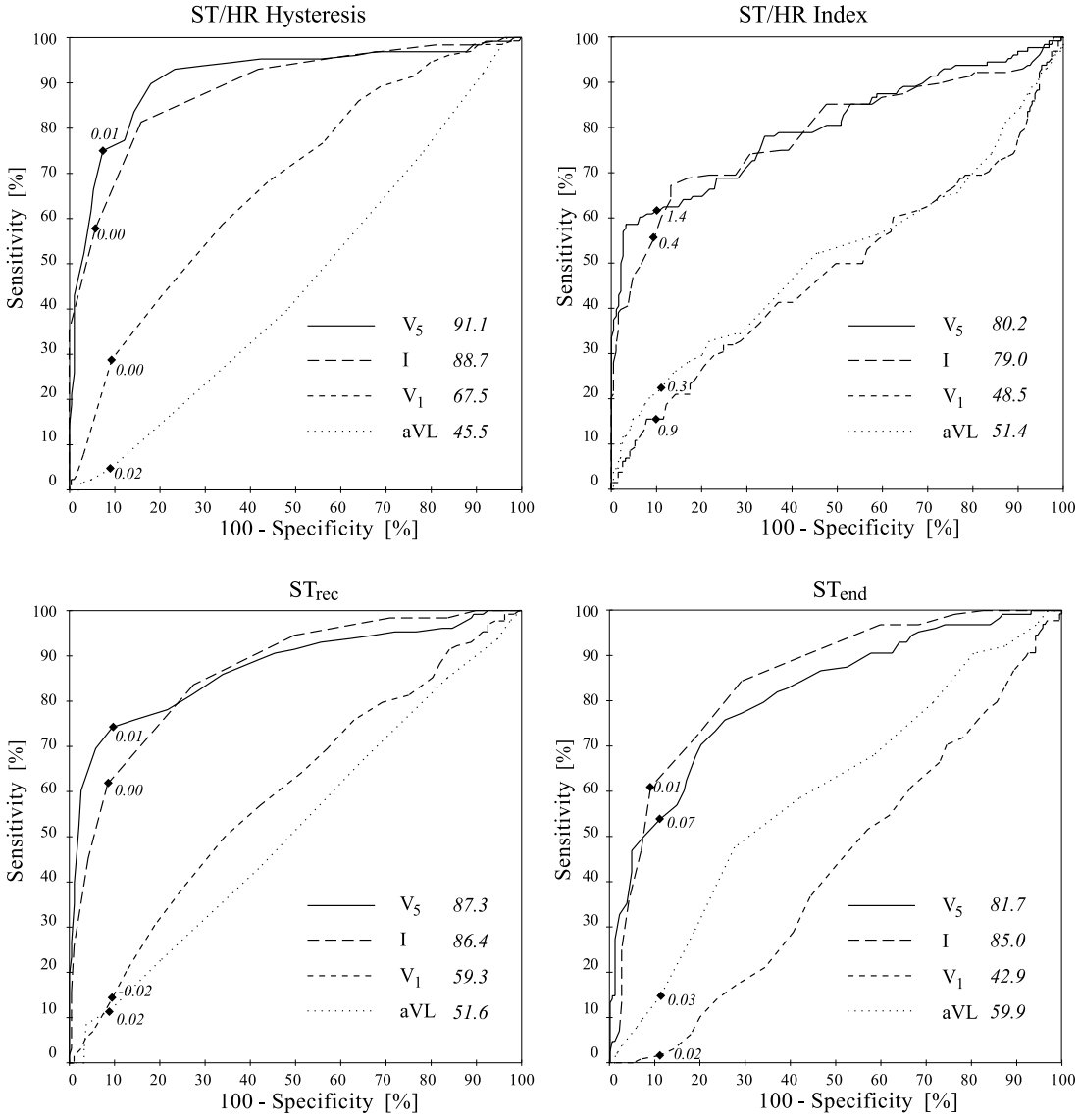

Figure 5.5. The receiver operating characteristic (ROC) curves for chest leads V_5 and V_1 and limb leads I and aVL in each study variable. Cut-off criteria presented in curves indicate variable values yielding a specificity of 90% (in millivolts for ST/HR hysteresis, ST-segment depressions and in microvolts per beat per minute for ST/HR index). Numbers after marking of lead express area under the ROC curves as percentages. Differences between the areas under the curves in leads V_5 or I and V_1 or aVL were highly significant in each method. No statistically significant differences were observed between leads V_5 and I with any of these variables. [V, Figure 2]

HR = heart rate; ST_{end} = end-exercise ST-segment depression; ST_{rec} = ST-segment depression at 3 minute recovery.

presented in Figure 5.6 (denoted by A to D). For cases A and C the specificity and sensitivity values were determined using different cut-off criteria for leads I and -aVR and for the other leads; for example for cases labeled C in the figure, a cut-off criterion of -0.05 mV for test positivity was applied to leads I and -aVR and a cut-off criterion of -0.10 mV was applied to the other leads. Using the -0.05 mV criterion for leads I and -aVR, the sensitivity improved by 5 percentage points. Further improvement in sensitivity was achieved when the cut-off criterion for test positivity was reduced, but at the same time the specificity of the test decreased. This loss of specificity was smaller in lead set A5 than in lead sets A9 or A12. The specificity of the lead sets at different cut-off criteria indicated that lead set A5 was superior to lead sets A9 and A12. Comparing the traditional criterion D (ST_{end} from all leads ≤ -0.10 mV) and criterion C ($ST_{I, -aVR}$ ≤ -0.05 mV or ST_{Other} ≤ -0.10 mV) a significant difference was observed in the case of lead set A5 ($p = 0.0412$). The effects arising from the use of different global cut-off criteria on the sensitivity and specificity using the maximum value over different number of leads are demonstrated in Figure 5.3 [I].

Figure 5.7 presents the sensitivity and specificity values obtained using a fixed cut-off criterion, 0.01 mV, for the maximum values of ST/HR hysteresis defined from lead sets having 1 to 12 leads [VI]. Up to 3 leads, the rate of increase in sensitivity was much higher than the rate of decrease in specificity. After the inclusion of the fourth lead, the decrease in specificity was dominant. A marked decrease in specificity was observed when leads V_1 and aVL were included in the set.

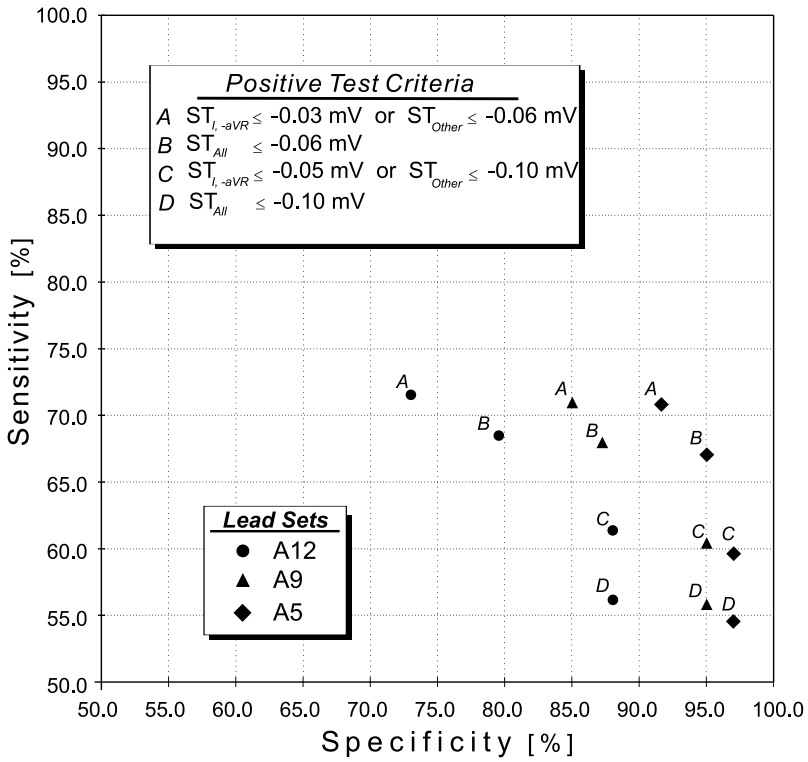

Figure 5.6. The sensitivity and specificity values of three different lead sets using the ST-segment values at end of exercise for each lead set. Points A to D illustrate the specificity and sensitivity values for different positive test criteria. The first criterion in A and C is for leads I and -aVR and the second for the remaining leads (for example in case C, a cut-off criterion of -0.05 mV for test positivity was applied to leads I and -aVR and a criterion of -0.10 mV was applied to the other leads). [I, Figure 4]

A12 = all leads of the 12-lead system; A9 = aVL, III and V_1 excluded; A5 = leads I, -aVR, V_4, V_5 and V_6.

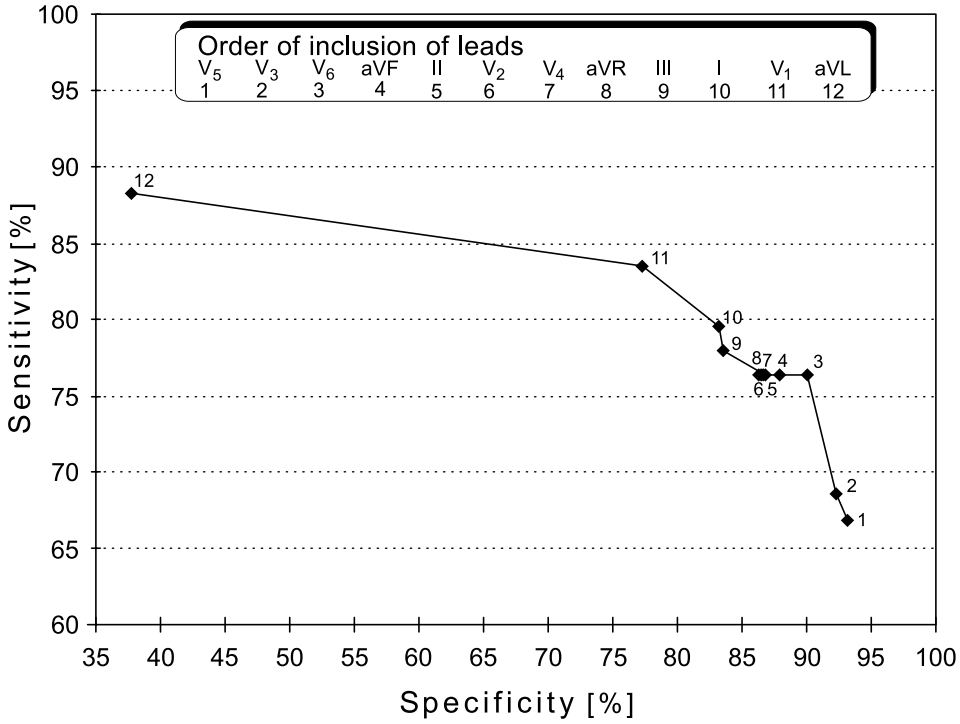

Figure 5.7. The sensitivity and specificity values using the fixed 0.01 mV cut-off criterion for the maximum values of ST/HR hysteresis defined from each lead set. The number near the diamond indicates the number of leads used. The order of inclusion of leads is presented in the keybox. [VI, Figure 4]

5.4 Comparison between variables used

In the population of 347 patients, the diagnostic capabilities of ST/HR hysteresis were compared with the ST_{end}, ST_{rec}, ST/HR index and HR recovery loop [III]. The area under the ROC curve for ST/HR hysteresis (89%) was significantly larger than that for other diagnostic variables. Also the sensitivity of ST/HR hysteresis at a high specificity level (>80%) was superior to that of the others. The area under the ST_{end} (76%, $p < 0.0001$ vs. ST/HR hysteresis) was the smallest, whereas the areas of the ST_{Rec} (84%, $p = 0.0063$) and ST/HR index (83%, $p = 0.0023$) indicated fairly compatible overall diagnostic performance. Due to the dichotomous nature of the HR recovery loop a ROC curve could not be constructed, instead it resulted in 85% specificity and 72% sensitivity.

Comparison of the areas under the ROC curve between the different variables (values in Figure 5.1) showed that ST/HR hysteresis also had higher areas under the curves in each individual lead except for lead aVL [V]. Next was ST_{rec}, whereas the order of the ST/HR index and ST_{end} varied between the individual leads. The area under ROC in lead V_5 for ST/HR hysteresis was significantly higher than for ST_{rec} ($p = 0.0029$), ST/HR index ($p < 0.0001$), and ST_{end} ($p < 0.0001$). Significant differences were also detected between ST_{rec} and ST_{end} ($p = 0.0011$) as well as ST_{rec} and ST/HR index ($p = 0.0025$), whereas there was no significant difference between ST_{end} and ST/HR index ($p = 0.3967$).

In addition, the agreement between the repeated measurements of the ST/HR hysteresis (97%) was significantly better than that of the ST/HR index (79%) or ST_{end} (74%), and no significant difference was observed between these two variables [IV].

5.5 Reproducibility of the maximum value of ST and ST/HR variables

The reproducibility of ST/HR hysteresis, ST/HR index and ST_{end} was evaluated in 61 asymptomatic middle-aged healthy volunteers who completed the exercise test twice during 6

to 8 months [IV]. Both testing sessions were maximal for all subjects (maximum heart rate achieved 172 ± 11 bpm vs. 172 ± 11 bpm and respiratory quotient 1.15 ± 0.06 vs. 1.14 ± 0.07). The maximum values determined from the lead set with nine leads (leads aVL, aVR and V_1 were excluded) were used as a representative parameter for each variable. The reproducibilities were ±0.040 mV, ±1.24 µV/bpm, and ±0.11 mV for ST/HR hysteresis, ST/HR index and ST_{end}, respectively. The Bland-Altman plots of these variables are presented in Figure 5.8. The agreement of interpretation between the repeated measurements was 97% (59 of 61), 79% (48 of 61), and 74% (45 of 61) for ST/HR hysteresis, ST/HR index and ST_{end}, respectively. The agreement between the repeated measurements of ST/HR hysteresis was significantly better than that for the ST/HR index ($p = 0.0045$) or ST_{end} ($p = 0.0010$). No significant difference was observed between these last mentioned ($p = 0.32$).

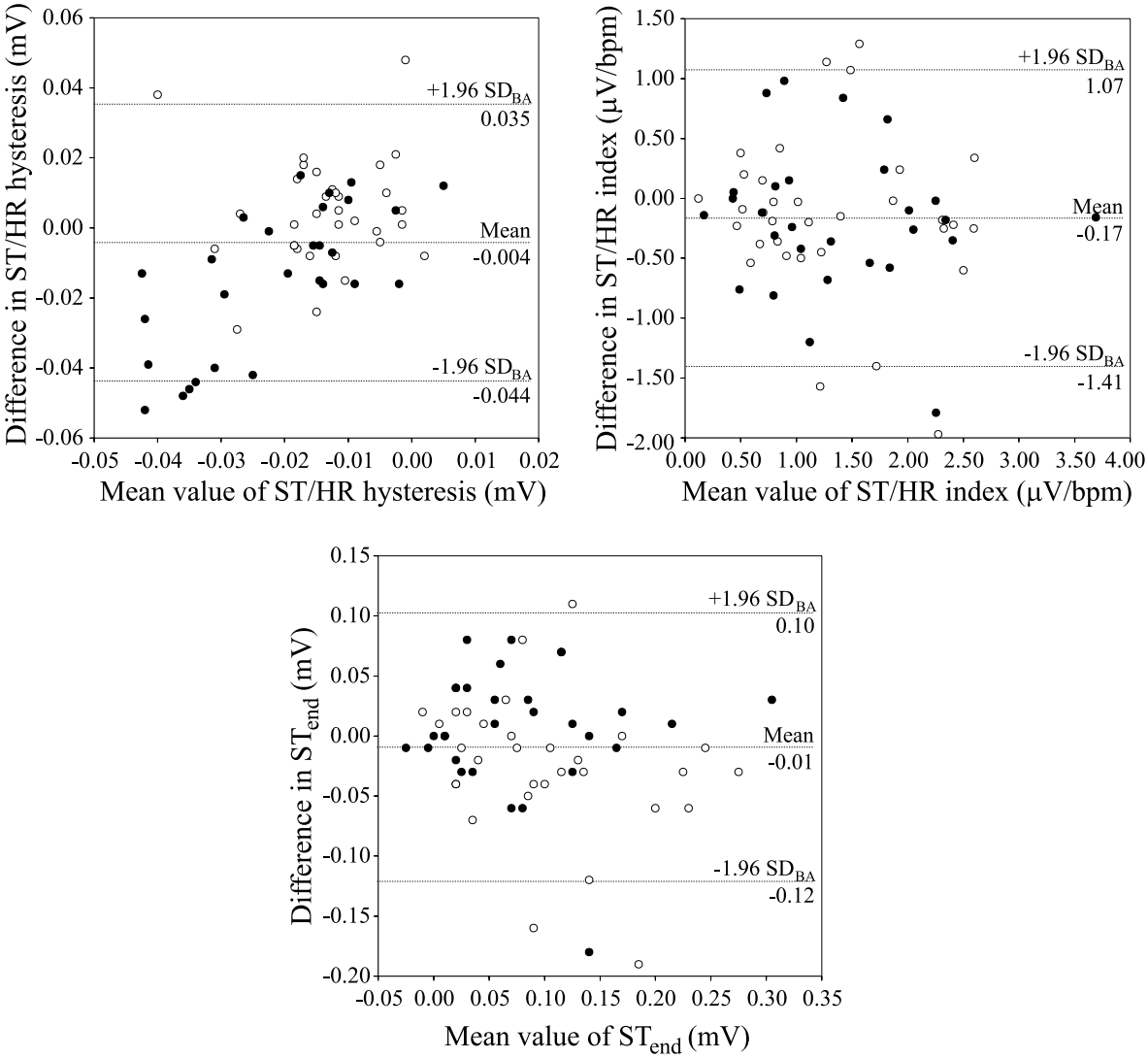

Figure 5.8. Bland-Altman reproducibility plots of ST/HR hysteresis, ST/HR index and ST_{end} between repeated exercise ECG tests. Closed and open circles represent the data points for men and women, respectively. The differences in exercise ECG variables between repeated measurements (vertical axes) were calculated by subtracting the value of the second test from that of the first. [IV, Figure 1]

SD_{BA} = standard deviation of the difference between the repeated measurements; ST_{end} = end-exercise ST depression; HR = heart rate; bpm = beats per minute.

5.6 Computer program for visualization of temporal changes in ECG variables

A computer program, ECG Variable Cine, was developed for analysis of the ECG variables gathered during an exercise test. The program makes it possible to image discrete ECG variables as a continuous cine presentation over the measurement interval. In addition to Cine presentation the program also includes fast and easy observation of the ECG variable in a stationary three-dimensional (3-D) image. Figure 5.9 presents the user interface in both program modes [II]. The Cine and 3-D presentations facilitate observation at a glance of the ECG variable throughout the entire exercise test and over the selected lead system, making for faster and more detailed analysis of the exercise ECG. The user can define the number and order of the leads displayed, and can thus focus more effectively on the leads desired and compare values between the leads as well as temporal changes in each lead.

Furthermore, the program determines two parameters; the average value of the variable over the selected leads at every sample moment, and the chronotropic index (CRI), a parameter which describes the percentage of the heart rate reserve used (assessed by calculating the ratio of maximum heart rate reserve achieved to the age-predicted maximum heart rate reserve). The importance of the average value and the CRI was evaluated in the detection of CAD using a study population comprising 201 male patients, 101 with CAD and 100 clinically normal. The areas under the ROC curves for the CRI, the average of ST-segment alteration from all 12 leads (Ave12) and the maximum values of ST-segment depression (Max12) at end of exercise were 88.7%, 85.8% and 79.1%, respectively. The CRI and Ave12 had a significantly higher area under the ROC curve than the Max12 ($p = 0.0176$ and $p = 0.0290$, respectively), but the difference between CRI and Ave12 was not significant ($p = 0.3560$). The sensitivity values at 90% specificity were 67.5%, 59.4% and 49.4% for the CRI, Ave12 and Max12, respectively. Statistical comparison showed a significant difference between the CRI and Max12 ($p = 0.0271$).

The program allows saving of the values of average and CRI in separate files, which makes it a very useful tool for scientific researches. The computer program is compatible with a program previously developed for comprehensive ST/HR analysis[154].

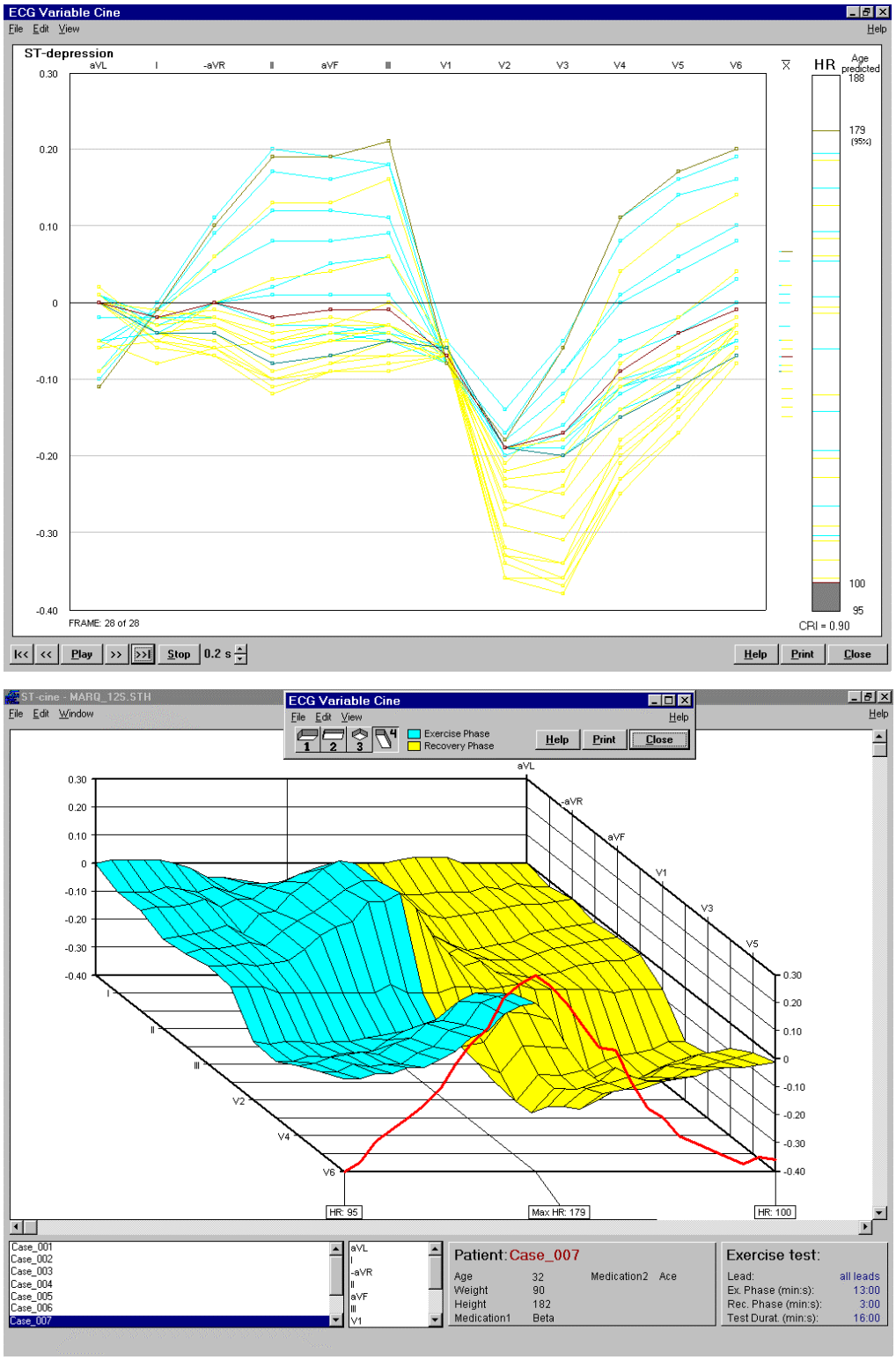

Figure 5.9. The upper figure shows a ECG Variable Cine presentation and the lower figure 3-D Graphics as a mesh presentation. Control of the Cine presentation is with buttons located in the lower left-hand margin. Exercise and recovery phases are distinguished by different colors and the previous values are presented as a shadow on the screen. In the 3-D Graphics heart rate values are presented with a continuous curve from the beginning to the end of the data. The lower left-hand window is a menu for patient selection adjacent to which is the menu for leads. [II, Figures 1 and 3]

HR = heart rate; CRI = chronotropic index.

5.7 Relation between the ST-segment parameters and ischemic injury sources by computer modeling

The simulations demonstrated that in some cases the ST-segment response may be related to the extent of ischemia. However, linear regression analysis indicated that the number of vessels occluded and the ST-segment value (which incorporate the ST/HR slope) had a low likelihood of linear relationship (the range of responses in each lead was wide). The average and range of the ST-segment deviations (or relative values of ST/HR slope) in leads I, II, V_1, V_5 and maximal ST-segment depression over all 12 leads in four different injury source categories are presented in Figure 5.10 [VII].

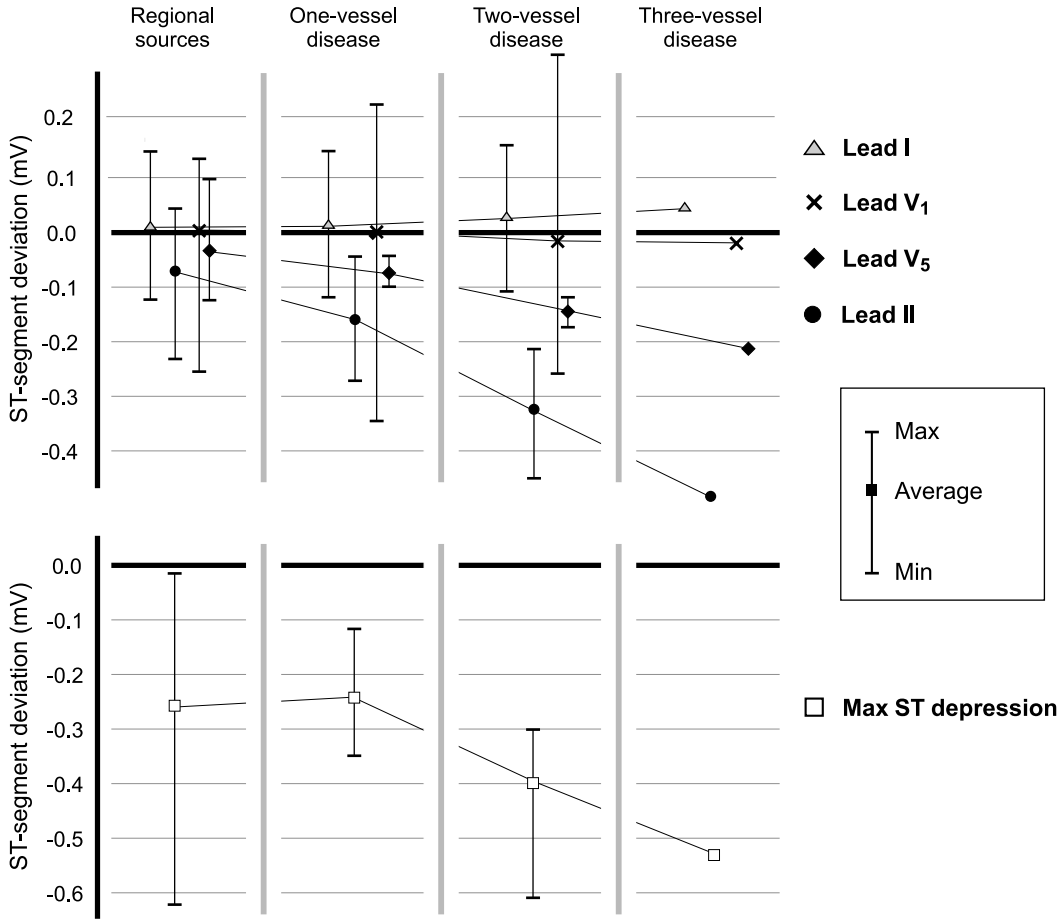

Figure 5.10. Relationship between ST-segment deviation (proportional ST/HR slope) and number of vessels occluded, showing the average and range of the ST-segment deviation in lead I, II, V_1, V_5, and the maximal ST-segment depression of the 12-lead ECG generated by different sources configurations. Six regional localized sources, three cases of one-vessel disease, three cases of two-vessel disease, and one case of three-vessel disease are included. [VII, Figure 4 (modified)]

Figure 5.11 illustrates the ST/HR response in leads I, V_2 and V_5 to increased extent of ischemia and the response to varying characteristics of the sources produced by different occlusions in the coronary arteries [VII]. The figure represents one hypothetical example comprising a variety of sources where the relationship between the heart rate and ST-segment changes is considered identical. Other levels of heart rate where different areas become ischemic are possible, as well as different coefficients describing the relationship between heart rate and ST-segment changes.

The simulations revealed that larger ischemic sources produce various responses depending on the source geometry and the ECG lead employed. Linearity of the ST/HR relation in multivessel disease depends on source geometry and the capabilities of the detecting lead. For

example, in LAD+RCA disease, lead V_2 indicated a nonlinear ST/HR relation, detecting ischemia caused by RCA as an ST-segment elevation and that of by LAD as an ST-segment depression (Figure 5.11g). On the other hand, lead I gave a linear ST/HR slope in LCX+RCA disease (Figure 5.11i) because it did not indicate the RCA disease (Figure 5.11c). Noteworthy is that lead V_5 indicated all source areas as an ST-segment depression, producing ST/HR relations which appeared quite linear in all cases.

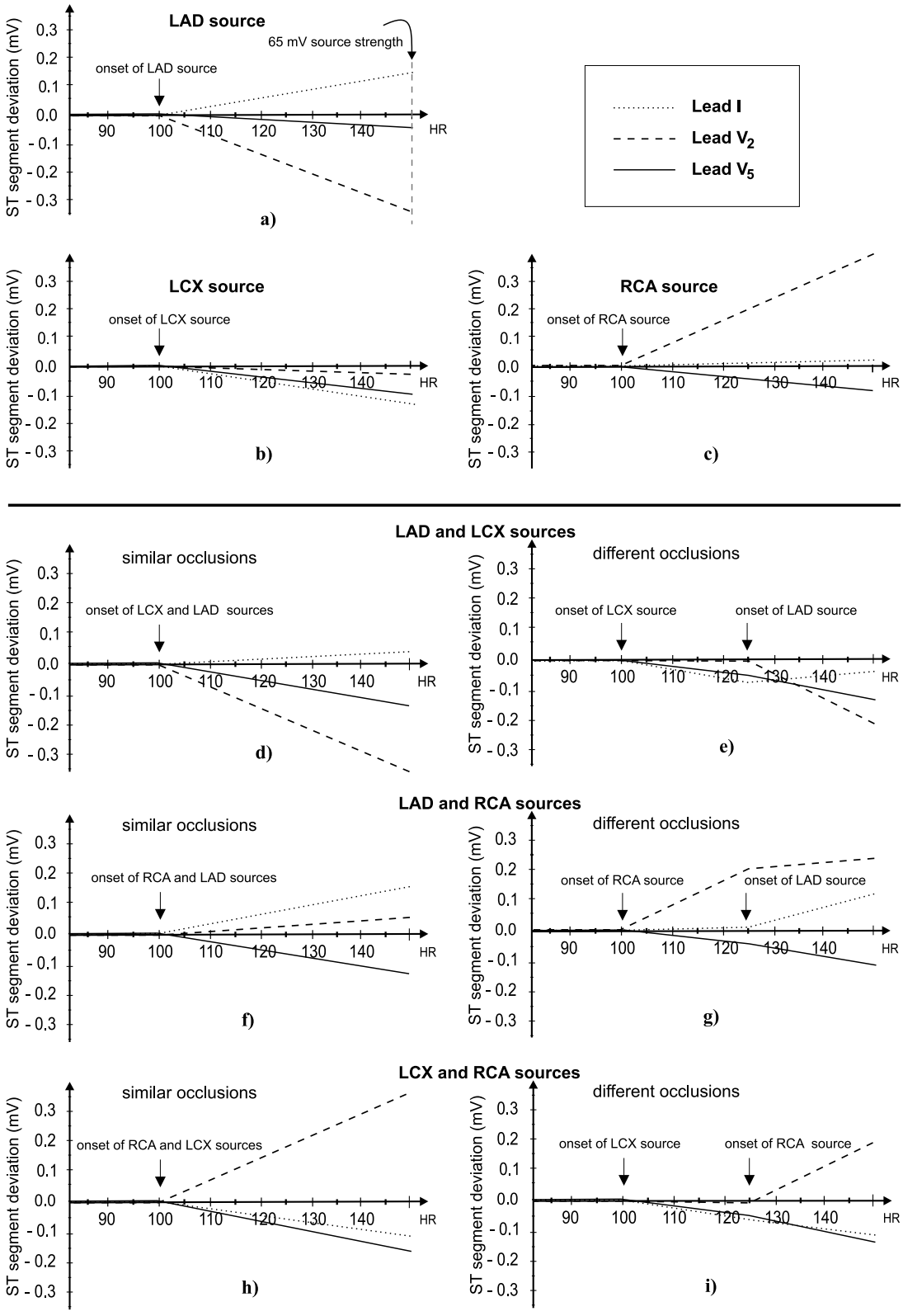

Figure 5.11. Illustration of ST/HR relations in single- and multivessel disease. ST/HR relations of lead I, V_2 and V_5 generated by double-layer subendocardial ischemic injury sources: a) LAD source, b) LCX source, c) RCA source in single-vessel disease; d), f) and h) sources representing two-vessel disease of LAD+LCX, LAD+RCA and LCX+RCA, respectively, with similar occlusions in the vessels; e), g) and i) sources representing two-vessel disease of LAD+LCX, LAD+RCA and LCX+RCA, respectively, with different occlusions in the vessels producing injury sources at different HR. [VII, Figure 5]

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery; HR = heart rate.

6 DISCUSSION

6.1 Individual leads

For each variable the highest overall diagnostic performances according to ROC analysis were achieved in chest leads V_4, V_5, V_6 and limb leads I, -aVR[I, V]. The excellent overall diagnostic performances of chest leads V_5 and V_6 are apparently maintained irrespective of the analysis method employed. The results support those obtained in previous studies, where the lateral precordial leads have been found to detect most ST depressions[82, 87, 177, 181, 241, 249]. Contrary to the current conception, leads I and –aVR achieved an overall diagnostic performance comparable to that with lateral precordial leads in each variable. By reason of the low overall measurement sensitivity, these leads are commonly underestimated in conventional CAD diagnosis. The relatively low signal value hampers manual analysis and the maximum values very seldom appear in these leads. One further indubitable reason for the underestimation of lead aVR is that it is not usually used inverted[211, 212]. The results here revealed that more efficient utilization of these leads requires the use of lead-specific cut-off criteria especially for computerized analysis of the exercise ECG.

Leads aVL and V_1 were the most unreliable in the discrimination of patients with CAD and patients with a low likelihood of the disease. The areas under the ROC curves were the smallest and highly significantly smaller than those obtained with lead V_5 in each variable. Also inclusion of these leads in the maximum search procedure reduced the overall diagnostic performance of variables used. Consistent with this observation, leads V_1 and aVL have been excluded in many studies employing the standard 12 leads during exercise tests[129, 130, 135, 186, 194, 196-200, 202, 207, 237]. This poor overall diagnostic performance is understandable considering the measurement orientation (lead direction) of those leads. The directions in leads aVL and V_1 are perpendicular to that of the main injury current arising from subendocardial ischemia in the left ventricle[86]. Thus, the majority of ischemic responses shown in these leads are modest and might be observed as either ST depression or ST elevation, which tends to complicate analysis of the ECG. Moreover, the low diagnostic performance of leads aVL and V_1 might derive from the sensitivity of the leads to interindividual differences in position and rotation of the heart[3, 60, 109, 115, 118]. On the other hand, the use of these deficient leads is justified for particular patients. For example ST elevation in V_1 and/or aVL in the absence of anterior Q-waves has been claimed to predict anterior myocardial ischemia with severe LAD obstruction[69, 70, 156]. However, diagnostically significant ST elevation during exercise ECG in patients without resting Q-waves is uncommon[41, 69, 156] and when present usually indicates a region of severe myocardial ischemia[69, 156].

6.2 Number and selection of leads in CAD detection

The effect of number and selection of ECG leads on the diagnostic properties of the ECG variables was studied in studies I, V, VI. Several authors have demonstrated an improvement in the detection of CAD using multiple leads during the exercise test[18, 42, 224, 251]; contradictory results have also been reported[38, 84, 85, 177, 187, 249] and the current recommendation claims that lead V_5 (or a combination of V_5 and lead II) is adequate for detection of the main ischemic responses when using the conventional ST depression criterion[92]. However, in most studies the usual approach to the analysis of ST and ST/HR variables is to apply the maximum value defined over several leads (i.e. maximum search procedure) as an ischemic response, the rationale for such an approach presumably being to ensure adequate sensitivity. However, it is obvious that increasing the number of leads used in a analysis of ischemic response detection increases sensitivity, but a problem often arises in the form of an increase in false-positive

responses (specificity decreases) and the diagnostic accuracy of the lead set does not necessarily increase.

The results reported in publication I showed that increasing the number of leads to maximum search procedure has a significant effect on the diagnostic properties of $ST_{end.}$ The use of a lead set comprising the five best leads improved the diagnostic capacity significantly compared to sets with nine or twelve leads. Furthermore, the area under the ROC curve for a set of five leads, as well as its sensitivity at a fixed 95% specificity, were more viable than the corresponding values for any individual lead. The results also indicated that if a certain specificity level is desired, the number and selection of the leads will also have the crucial effect on the cut-off criterion used.

According to the results of study VI, the overall diagnostic performance in ST/HR hysteresis could be enhanced when the number of leads for maximum search procedure was increased. Especially when using a fixed cut-off criterion, the rate of increase in sensitivity was markedly higher than rate of decrease in specificity at the beginning of the increase in the number of leads (Figure 5.7). However, the increase in the overall diagnostic performance accruing from the inclusion of number of leads was insignificant. In contrast, the decrease after the ninth lead was marked and reduced below the level achieved with the single lead V_5 alone.

As stated in section 6.1, the overall diagnostic performances of the individual leads were different; clearly then the selection of leads has an influence on the diagnostic performance of the variable used. According to the results the selection of the leads for the maximum search procedure was of great importance, even more so than the total number of leads. Leads aVL and V_1 reduced the overall diagnostic performance of the variables. This was somewhat surprising, in the respect that inclusion of perpendicular leads in the analysis might be assumed to provide independent information for analysis and thus enhance the overall diagnostic performance of the variable. This phenomenon might be explained by the fact that the majority of ischemic responses in these leads are modest and might be observed as either ST depression or ST elevation, which tends to complicate analysis of the ECG.

The relevance of the number and selection of leads was especially emphasized when comparison was made between the ST/HR index and ST_{end}. With the single lead V_5, or any individual lead, there was no significant difference between the overall diagnostic performances of the ST/HR index and ST_{end}. In contrast, when the maximum value of the variable defined from nine leads was used the ST/HR index attained a significantly higher overall diagnostic performance than ST_{end}.

6.3 Use of cut-off criteria for the ST and ST/HR variables

Guidelines and standards for the detection of ischemia by conventional ST-segment depression analysis recommend use of the same fixed cut-off criterion (0.10 mV or 1.0 mm) for every lead[82, 92, 105, 120]. Furthermore, many studies[84, 155, 177, 251] have shown lead V_5 to be capable of detecting the majority of ischemic responses when a positive test criterion of ≥0.10 mV ST-segment depression is used. The results in publication I indicate that larger cut-off criteria are most suitable for the lateral precordial leads (V_4-V_6) and detailed study with ST_{end} showed that the highest sensitivities at a cut-off criterion of -0.10 mV were to be found in leads V_5 and V_6, which is in accord with the foregoing. Using the same -0.10 mV criterion for leads I and -aVR the number of true-positive responses was extremely low (poor sensitivity). However, the areas under the ROC curves for these leads indicated overall diagnostic performances as good as those of the lateral precordial leads and the sensitivities at fixed 95% specificity did not significantly differ from that with lead V_5. Since the different sensitivity distributions of the individual ECG leads mean that a fixed global cut-off criterion does not treat individual leads equally, it would be quite natural to use dissimilar cut-off criteria for different ECG leads, especially for computerized analysis. For example, according to the results here the cut-off criterion for leads I and -aVR when using ST_{end} should be 50% smaller than for the lateral

precordial leads. These arguments can be verified in the light of Figures 5.1, 5.2, 5.5 and 5.6, and the results of our computer modeling study [VII] are likewise in accord with these findings. The results support those in previous studies[87, 181, 262] in which it has been suggested that more detailed, lead-specific criteria should be defined and applied for the ST depression.

Another important issue is the effect of the number of leads on the cut-off criterion. It is quite obvious that an increase in the number of leads will have an effect on the diagnostic properties of the variable used. The present results revealed that using the same fixed partition criterion an increase in the number of leads produces some improvement in sensitivity but at the same time a loss of the specificity (Figures 5.3. and 5.7). Thus overall diagnostic performance, as well as diagnostic accuracy, depend in large measure on the population under investigation (i.e. prevalence of CAD) and it does not necessarily increase but may even be reduced. Thus, if an equal specificity level is desired, operation with maximum search procedure over several numbers of leads usually requires a larger cut-off criterion than when using a single lead. It is apparent that in addition to the number of leads, the selection of the leads plays an essential role in connection with the maximum search procedure. This would be more marked if the criterion for optimization of the lead set were based on a fixed cut-off criterion instead of ROC analysis. On the other hand, the results here also revealed that the diagnostic accuracy of a variable could be improved using individualized cut-off criteria for different leads, i.e. applying compartmental analysis.

6.4 Exercise ECG variables

According to the results obtained here, the superiority of ST/HR hysteresis over other variables was evident [III, IV, V]. ST/HR hysteresis achieved the highest overall diagnostic performance in each individual lead, except for aVL, and when using the maximum value of variables defined from the nine leads. Furthermore, the sensitivity of ST/HR hysteresis at a high specificity (>80%), which is the most important portion of the ROC curve for a diagnostic test such as the exercise ECG, was higher than that of the others. ST/HR hysteresis had the most uniform areas under the ROC curves over all 12 leads and the areas under the curves were over 85% in the majority of individual leads. This makes it possible to use ST/HR hysteresis with greater efficiency and greater versatility than the other variables. The improved overall diagnostic performance and greater reliability of ST/HR hysteresis may be explained in that the method integrates the diagnostic information of both the exercise and the recovery phases of the test. The results of our additional studies go to confirm the superior capability of ST/HR hysteresis[48, 152, 263-266]. Likewise, other groups[25, 108] using a similar methodology combining ST-segment analysis during the exercise and recovery phases of the test have achieved improved diagnostic accuracy over the traditional ECG variables.

One interesting observation was the capacity of the ST depression method during the recovery phase. ST_{rec} gave greater overall diagnostic performances than ST_{end} in each lead and the areas under the ROC curves for ST_{rec} were even greater than the corresponding areas of the ST/HR index, indicating high information content in the recovery phase. This result supports those in previous studies where the recovery phase has been shown to be of relevance in detecting CAD[1, 25, 29, 77, 108, 123, 127, 144, 151, 194, 226, 230, 233]

The difference between ST_{rec} and ST/HR index diminished when the maximum value of the variable over several leads was used compared to the values of individual leads. On the other hand, use of the maximum value over nine leads increased the difference between the ST/HR index and ST_{end}. It would thus appear that the effective utilization of the ST/HR index in the detection of CAD requires the maximum search procedure over several leads. Here might lie one essential reason for the contradictory results in studies where the ST/HR index has been evaluated. In general, ST_{end} yielded the poorest overall diagnostic performances; the results were nonetheless of the level described in the literature[61, 86, 91].

6.5 Reproducibility of ST and ST/HR variables

The wide intra-individual variability of resting ECG recordings was already reported 30 years ago[175, 268]. Thus, the reproducibility of exercise ECG variables is also bound to be relatively poor, a circumstance which the results of this reproducibility study with asymptomatic middle-aged individuals confirmed. The magnitude change in the variable, which has to be observed if the clinician is to be assured that a real diagnostic change has occurred, was surprisingly large. Similar results were achieved with middle-aged women using ST_{end}[267]. However, the present results indicated that the agreement of the interpretation with ST/HR hysteresis appeared to be significantly better than those with the ST/HR index or ST_{end}.

6.6 Computer program for visualization of temporal changes in ECG variables

Temporal analysis of the ECG variables and comparison between different phases of the exercise test are difficult and time-consuming, especially simultaneous examination of the variables over several leads. The computer program constructed, ECG Variable Cine, was designed to assist in this problem. It facilitates visualization of temporal changes in values of exercise ECG variables over a selected ECG lead system. In addition to a cine feature, the program includes stationary 3-D presentation for alteration in variables simultaneously in all selected leads over the measurement data. The user can define the number and order of the leads displayed, and thus focus more effectively on the leads desired and compare values between the leads as well as temporal changes in each lead. The Cine and 3-D presentations facilitate observation at a glance of an ECG variable throughout the entire exercise test and over the selected lead system enabling a faster and more detailed analysis of the exercise ECG.

In addition to visualization the program determines two diagnostic parameters, the average value of an ECG variable over the selected leads at every sample moment, and the CRI, which indicates heart rate response to exercise. A summing method over all 12 leads, similar to our, has previously been used in the analysis of ST-segment alteration when evaluating patients with myocardial infarction during and after percutaneous transluminal coronary angioplasty[138, 139, 213]. However, the crucial difference in our method is that whereas in the summing method the absolute values (values without sign) of ST-segment deviation are summed over 12 leads, our method uses signed values. The CRI has been shown to improve the diagnostic accuracy of the traditional and heart rate-adjusted ST-segment depression criteria for identification of CAD[209] and to be predictive of an increased coronary heart disease incidence[148]. According to the results here the average value of ST-segment deviation at the end of the exercise over the leads and CRI were clinically more competent in the detection of CAD than the maximum value of end-exercise ST-segment depression.

By merit of Windows-based implementation the ECG Variable Cine program is easy to use and easy to implement on personal computer (PC)-based ECG apparatus and analyzers. Until now the program has been used exclusively in research projects.

6.7 Relation between the ST-segment parameters and ischemic injury sources by computer modeling

The ST-segment, and especially the ST/HR slope, has been held to provide information regarding ischemic injury sources, for example the extent and location of the injury and the number of vessels occluded[110, 203, 205]. The simulations with a computer model of thorax and heart demonstrated that neither the ST-segment deviation nor the ST/HR slope was directly proportional to either the area of the ischemic site or the number of vessels occluded. A linear ST/HR slope representing the entire ischemic section of the exercise test may be expected only in single-vessel CAD. In multivessel CAD, when the severity and location of the occlusions in each coronary artery are different, the temporal and spatial diversity of the multiple injury sources generated will distort the presumed linearity between ST-segment deviation and heart rate. Thus, in multivessel CAD the ST-segment depression may be lower than in single-vessel

disease. Furthermore, the linearity of the ST/HR relation depends on the source geometry and the capabilities of the detecting lead. In addition, the variance of clinical ST/HR slopes is further increased by interindividual anatomic differences.

On the other hand, according to the present results lead V_5 indicated all source areas as an ST-segment depression, producing ST/HR relations which appeared somewhat linear in all cases. Furthermore, simulations demonstrated that using a criterion of 0.10 mV for a positive test result most ischemic responses can be detected with lateral precordial leads.

Since the final linear segment of the ST/HR slope (generally used as a clinical parameter) did not include all available information on the disease, the view of the ST/HR relation should be expanded and all the leads in the 12-lead ECG should be considered. Furthermore, more detailed analysis than that based on a linear regression model of the behavior of the ST/HR relation of the 12-lead ECG during the exercise test may provide information regarding extent of injury, number of diseased vessels and extent of occlusions.

6.8 Limitations of the study

The major limitations of the present study pertain to the selection of the study population. The CAD patients had angiographically proven coronary artery disease, but most of the reference patients were defined only by clinical history. In an ideal study the entire study population would have been examined by angiography. This kind of referral bias is of course unavoidable, since it is unreasonable to investigate all patients by coronary angiography. Furthermore, retrospective studies always involve the possibility that the interpretation of the exercise ECG probably affected the decision to proceed with coronary angiography. Taking into account the more frequent use of exercise ECG testing as a screening test in large populations, the use of a bipartite study population, which in any case represents real clinical material, would seem nonetheless to be a relevant approach to this study. In addition, when using ROC analysis as a statistical method the effect of referral bias on the results is minimized and the results are more reliable and can more easily be extended to different populations. In any case, the verification of results must be undertaken with a different patient material.

The implications of the study may be limited in the case of women due to the marked predominance of men in the material. However, the superiority of ST/HR hysteresis over the traditional ECG variables among women has been shown in our additional study[264]. Cardiac medication (the majority of CAD patients were using beta-blockers) clearly influenced the results. However, the influence can be assumed to be identical for each lead and thus comparison of the leads could be made regardless of medication. The number of patients with one-, two- and three-vessel disease in the CAD group might affect the comparison of the leads. On the other hand, the patients were distributed quite evenly over all these categories. Conversely, comparison of the ST and ST/HR analyses might be more susceptible to these factors. The reproducibility of the exercise ECG variables was studied in asymptomatic middle-aged subjects. Thus the results for reproducibility are not applied to symptomatic individuals or to patients with CAD. A reproducibility study with symptomatic or CAD patients requires markedly shorter interval between repeated exercise ECG tests.

Additional limitations arise from the exercise test protocol used and from computerized storing. All exercise tests in Tampere University Hospital were performed with a bicycle ergometer using 4-minute incremental workload. The purpose of this slow progressive protocol is to produce a steady-state condition at every exercise phase, where by a linear relationship between the ST-segment and heart rate changes is not to be expected. For this reason the acceptable number of ST/HR slope values was very small and the ST/HR slope was therefore not included in the studies. The type of exercise test should not exert any major influence on the studies, but reproduction of the studies should also be performed with the treadmill. Digital saving of average complexes and heart rate values during the recovery phase was carried out every minute. This somewhat scanty sample rate might affect the diagnostic properties of

ST/HR hysteresis. Usually the heart rate and ST-segment changes during the first minute of the recovery phase are important and thus a more frequent sampling rate is required for the accurate determination of ST/HR hysteresis. Especially when the exercise test is not maximal, the importance of frequent sampling is emphasized. However, sampling rate effects on the diagnostic properties of ST/HR hysteresis were not studied.

There were several limitations in the computer model study. Although the accuracy of the numerical methods was validated[118, 143], the computer thorax model represents the anatomy of one individual, and results thus indicate only one case and divergences are to be assumed when they are applied to other cases or population studies[109, 115, 255]. In addition, the model did not consider all inhomogeneities, the most important being anisotropy of the heart muscle. This may further smooth the body surface potential distributions, thus reducing the ability of the ECG to identify the injury sources. Also a more detailed model of the source, including the exact form of the ischemic regions as well as membranic ionic currents, would increase the accuracy.

7 CONCLUSIONS

The purpose of this series of studies was to compare and assess the diagnostic properties of the standard exercise ECG leads and to evaluate the effect of number and selection of leads on these properties in the detection of CAD when using different ST and ST/HR variables.

The following conclusions can be drawn on the basis of the results of this series:

1) The exercise ECG leads have dissimilar diagnostic properties in the detection of CAD. The properties of leads I, -aVR, V_5 and V_6 are most influential, whereas those of leads aVL and V_1 are insufficient in each ST and ST/HR variable.
2) The number and selection of leads has an influence on the diagnostic performance of the variable used and more attention should thus be paid to the lead chosen for ECG analysis. The leads aVL and V_1 should be excluded when using the maximum value over leads. The relevance of the number and selection of leads was emphasized when comparison was made between the ST/HR index and ST_{end}. On the other hand, the overall diagnostic performance of ST/HR hysteresis was uniform and competent in each standard lead. Thus, ST/HR hysteresis is less sensitive to lead selection than other variables.
3) A use of a fixed cut-off criterion for each individual lead is inappropriate. The effective use of the ST_{end} with leads I and -aVR requires the cut-off criterion applied to these leads to be 50% smaller than that used for lateral precordial leads. An increase in the number of leads and the selection of leads for the maximum search procedure has an effect on the diagnostic properties of the variable. If an equal specificity level is desired, operation with maximum search procedure over several numbers of leads usually requires a larger cut-off criterion than when using a single lead.
4) In clinical evaluation, the diagnostic properties of ST/HR hysteresis proved highly competent and significantly better than other variables. The overall diagnostic performance of the exercise ECG test in the detection of CAD can thus be significantly improved by computerized analysis of the heart rate-adjusted ST depression pattern during the exercise and recovery phases of the test.
5) The reproducibility of the ECG variables was poor, indicating that the observed change in an exercise ECG variable between repeated measurements must be substantial for the clinician to be confident that a diagnostically significant change has occurred. However, the results indicated that the agreement of the interpretation with ST/HR hysteresis appeared to be significantly better than those with the ST/HR index or ST_{end}.
6) The constructed computer program, the ECG Variable Cine with a 3-D presentation mode, facilitates observation at a glance of an ECG variable throughout the entire exercise test and over a selected lead system, allowing a faster and more detailed analysis of the exercise ECG. Furthermore, the program determines two parameters; the average value of the variable over selected leads at every sample moment, and the CRI parameter, which indicates the heart rate response to exercise. The program is easy to use and easy to implement on PC-based ECG apparatus and analyzers.
7) Computer model analysis suggested that ST-segment deviation and the ST/HR slope were not able to indicate the extent of ischemic injury or the number of vessels occluded.

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***) publication abstracted in the 1997 Year Book of Sport Medicine published by Mosby-Year Book, Inc*

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