Karolinska Institutet

Thesis for doctoral degree (Ph.D.) 2009

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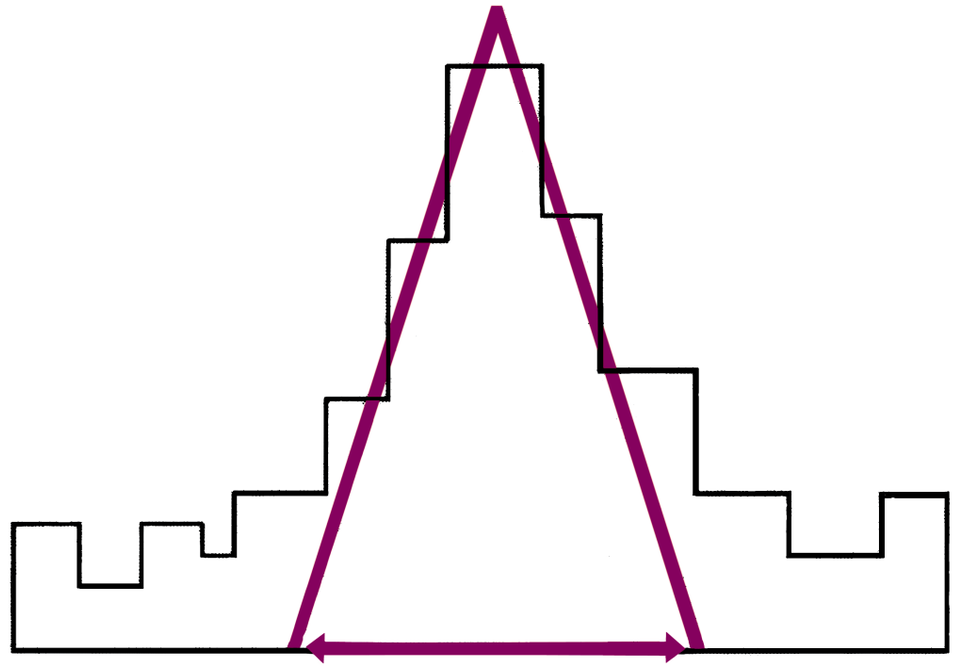
DIFFERENTIAL INDEX



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Everything is possible, but the impossible takes a little bit more time….

ABSTRACT

The rate and modulation of the heart beat (i.e. heart rate variability; HRV) are controlled by the autonomic nervous system. Cardiac sympathetic activation decreases, and parasympathetic increases HRV. Measurements of HRV can be performed in the frequency domain or the time domain; also simple geometric methods are used for time domain measurements. HRV has provided important prognostic information in patients following an acute myocardial infarction and in heart failure patients. The aims of these studies in patients with stable angina pectoris were (1) to develop and validate a graphical method for the assessment of HRV, (2) to examine the long term stability of HRV measurements, and changes after an acute myocardial infarction, (3) to study the prognostic information of HRV, and (4) to evaluate the effects of beta-adrenoceptor blockade (metoprolol) and calcium antagonist treatment (verapamil) on HRV.

We evaluated 24 h ambulatory ECG recordings in the Angina Prognosis Study in Stockholm (APSIS). HRV was evaluated before and during double-blind treatment with metoprolol or verapamil in 678 patients with stable angina pectoris with a median follow-up of 40 months. The results showed that the differential index (DI) a novel and simple graphical method fore HRV measurements, mainly reflects cardiac parasympathetic control and agrees well with conventional indices of HRV. The DI and conventional indices in the frequency domain and time domain appeared stable over 3 years. An acute myocardial infarction was associated with indices of increased cardiac sympathetic activity, while changes in parasympathetic activity appeared to be small. A low HRV in both the frequency and time domains predicted cardiovascular mortality, independently of conventional risk factors, whereas no such relation was seen for non-fatal myocardial infarction. Thus, a cardiac autonomic imbalance seems to be of importance for fatal arrhythmic events, but not for the atherosclerotic process and plaque vulnerability. The DI appeared to predict cardiovascular death somewhat better than traditional time domain indices of HRV. The best sensitivity and specificity was obtained with a DI of approximately 320 ms. The results indicate that reduced cardiac parasympathetic activity is a major factor associated with a poor prognosis in stable angina pectoris. In addition, diabetic patients had a lower HRV and a worsened prognosis. Metoprolol increased HRV somewhat, whereas verapamil had no effects. However, these short term influences on HRV did not seem to relate to prognosis.

In conclusion, HRV is a valuable method for the evaluation of cardiac autonomic control. The DI is a simple and robust method that shows good agreement with established, more complicated measurements. The DI and other indices of HRV which reflect parasympathetic cardiac control may be useful predictors of the future risk of suffering a fatal cardiovascular event in patients with stable angina pectoris.

Key words: Ambulatory electrocardiographic registrations, autonomic nervous system, coronary artery disease, differential index, heart rate variability, prognosis

SAMMANFATTNING PÅ SVENSKA

Hjärtfrekvensvariabilitet hos patienter med stabil kärlkramp (angina pectoris)

Hjärtfrekvensen regleras av det autonoma nervsystemets två komponenter, där en sympatisk nervaktivering höjer och en parasympatisk aktivering sänker hjärtfrekvensen. En ökad sympatisk och minskad parasympatisk aktivitet ökar därför hjärtfrekvensen men påverkar variabiliteten olika. Det har tidigare visats att en sänkt hjärtfrekvens-variabilitet är förenligt med dålig prognos hos patienter som haft hjärtinfarkt, hos diabetespatienter och patienter med svår hjärtsvikt. Det finns två etablerade tekniker att värdera variabiliteten, frekvensdomän och tidsdomän. Till tidsdomän räknas också de grafiska metoderna. Vi har utvecklat en egen grafisk metod, differential index, där vi från ett 24 timmars bandspelar-EKG sammanställer variationerna i tidsskillnader mellan hjärtslagen i ett histogram.

Registreringarna i de aktuella studierna kommer från 678 patienter som ingått i Angina prognos studien i Stockholm (APSIS). Där studerades naturalförloppet hos patienter med stabil kärlkramp som behandlades med antingen metoprolol eller verapamil, och följdes under i medeltal 40 månader. Vi visar att de flesta variabilitetsmått är stabila över lång tid (3 år). Differential index visar mycket god överensstämmelse med tidigare etablerade mätmetoder men har fördelar av att vara enkel och mindre känslig för störningar och extraslag. Låg hjärtfrekvensvariabilitet är förenat med ökad risk för död i hjärt-kärlsjukdom. Vår metod är snarast något bättre i att urskilja patienter med ökad risk för hjärt-kärldöd. Differential index speglar starkt den parasympatiska grenen av det autonoma nervsystemet och tycks inte påverkas mycket av en akut hjärtinfarkt, i motsats till andra mått som också speglar sympatisk aktivitet. Vid samtidig diabetes mellitus, där det är känt att en autonom störning föreligger, finner vi lägre variabilitet, och sämre prognos. Behandling med metoprolol eller verapamil påverkade hjärtfrekvensvariabiliteten olika men detta avspeglade sig inte i prognos.

Sammanfattningsvis är hjärtfrekvensvariabilitet en värdefull metod för att värdera autonoma nervsystemets påverkan på hjärtat. Differential index är ett enkelt och robust mått för att värdera risken för död i hjärt-kärlsjukdom hos patienter med stabil kärlkramp. Metoden skulle kunna hjälpa oss att tidigt urskilja patienter med hög risk där det är särskilt angeläget att ge effektiv behandling.

LIST OF PUBLICATIONS

This thesis is based on the following original papers, which will be referred to by their Roman numerals:

I. Forslund L, **Björkander I**, Ericson M, Held C, Kahan T, Rehnqvist N, Hjemdahl P. Prognostic implications of autonomic function assessed by analyses of catecholamines and heart rate variability in stable angina pectoris. *Heart. 2002; 87:415-22.*

II. **Björkander I**, Kahan T, Ericson M, Held C, Forslund L, Rehnqvist N, Hjemdahl P. Differential index, a novel graphical method for time-domain measurements of heart rate variability. *Int J Cardiol. 2005; 98:493-499.*

III. **Björkander I**, Forslund L, Kahan T, Ericson M, Held C, Rehnqvist N, Hjemdahl P. Differential index - a simple time domain heart rate variability analysis with prognostic implication in stable angina pectoris. *Cardiology. 2008;111:126-133.*

IV. **Björkander I**, Forslund L, Ericson M, Rehnqvist N, Hjemdahl P, Kahan T. Long term stability of heart rate variability in chronic stable angina pectoris, and the impact of an acute myocardial infarction. *Submitted*.

LIST OF ABBREVIATIONS

APSIS	Angina prognosis study in Stockholm
AMI	acute myocardial infarction
CAD	coronary artery disease
DI	differential index
ECG	Electrocardiogram
HF	high frequency
HRV	heart rate variability
LF	low frequency
MI	myocardial infarction
ms	milliseconds
mmol/l	millimoles per litre
RMSSD	the square root of the mean of the sum of squares of differences between adjacent normal RR intervals
pNN50	the percent of differences between adjacent normal RR intervals greater than 50 ms
SD	standard deviation
SDNN	standard deviation of all normal RR interval
SDNNIDX	mean of the standard deviations of all normal RR intervals for all 5-min segments
TP	total power
VLF	very low frequency

CONTENTS

INTRODUCTION

Autonomic nervous control of heart rate and heart rate variability

The neural control of the heart is complex due to the dual innervation with sympathetic and parasympathetic nerves of the autonomic nervous system.[1, 2, 3] Cardiac sympathetic activation stimulates the sinus node and increases heart rate, whereas vagal activation reduces heart rate. Furthermore, as described already long ago, the two divisions of the autonomic system interact both at centers in the central nervous system and within the heart itself.[4, 5] These interactions between the sympathetic and parasympathetic limbs determine their respective effects on heart rate. The effect of one limb may be enhanced by increased activity of its counterpart.[6]

V*ariability* of the heart rate (i.e. heart rate variability; HRV) reflects the *modulation* of heart rate caused by the sympathetic and parasympathetic limbs of the autonomic nervous system (Figure 1). An isolated increase in cardiac sympathetic tone reduces the RR interval (i.e. increases heart rate), whereas isolated activation of the parasympathetic cardiac nerves increases the RR interval (i.e. decreases heart rate). HRV is considered to be a marker of the integrated influence of the autonomic nervous system on the sinus node, as it reflects the balance between sympathetic and parasympathetic influences rather than the two distinct parts of the system. Indeed, a decrease in sympathetic tone and an increase in parasympathetic tone will both slow the heart, but this does not result in the same changes in HRV.

The first clinical documentation of alterations in variability of the RR interval was described by Hon and Lee 1965.[7] They found that foetal distress was preceded by a decrease in HRV that occurred before any changes in the actual heart rate. However, several background factors influence HRV and need to be considered in addition to pathophysiological conditions (as discussed in more detail below). For example, there are gender differences in HRV. Short term indices of HRV (i.e. those reflecting parasympathetic activity) are generally greater in women, whereas long term indices (i.e. those corresponding to the parasympathetic/sympathetic balance) appear to be greater in men. Furthermore, HRV is inversely related to heart rate and to age.[8, 9, 10] Interestingly, HRV is more strongly related to heart rate in healthy subjects than in

patients with cardiac disease, illustrating that heart rate and its variability are in part modulated by different mechanisms.[11]

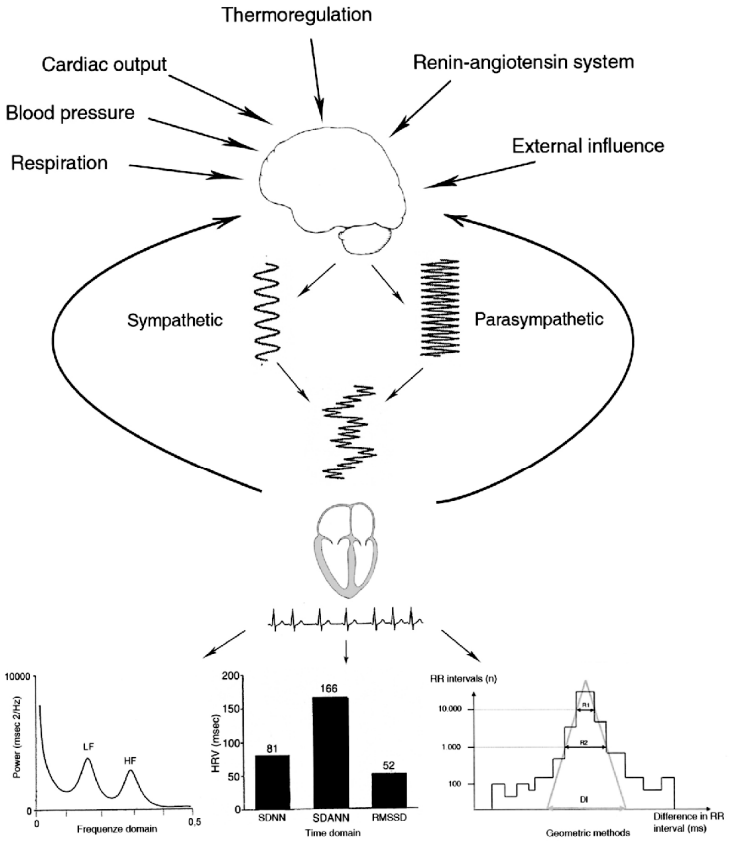

Figure 1
A schematic illustration of cardiac autonomic nervous control, and how HRV can be assessed by different methods.

Assessment of heart rate variability

Measurements of HRV are based on the beat-to-beat variations of the RR interval and thus require sinus rhythm. There are several different methods by which one may assess HRV[12, 13] (Figure 1). They can be performed with short term (i.e. minutes) or long term (i.e. 24–72 h) ambulatory electrocardiographic (ECG) registrations. Calculation of time domain indices of HRV is a relatively simple technique. Variations in the absolute RR intervals or the differences in RR intervals are described in statistical terms. Commonly used measures include the standard deviation of normal RR intervals (SDNN), the square root of the mean of the sum of squares of differences between adjacent normal RR intervals (RMSSD), and the percentage of normal RR intervals that differ by >50 ms (pNN50). The proposed relationships between various time domain measurements of HRV and the sympathetic and parasympathetic components of the autonomic nervous system are shown in Table 1.

Time domain measurements of HRV can also be assessed by simple geometric methods, such as the differential index (DI), which has been developed in the present project, and the described triangular index and triangular interpolation of normal-to-normal RR interval histograms.[14, 15, 16, 17] All geometric methods for the assessment of HRV are robust and may be particularly valuable when the quality of data is imperfect, i.e. when there are artefacts or extra beats in the ECG recordings. However, they have the disadvantage that a substantial number of RR intervals are needed to construct a sample density histogram. Furthermore, geometric methods may lack the statistical exactness provided by conventional time domain and frequency domain methods although the information provided could be of greater clinical value.[18]

Frequency domain measurements of HRV are more complicated. The sinus wave corresponding to the heart rhythm is analysed by power spectral density analysis and fast Fourier transformation. The power spectrum can subsequently be divided into different frequency intervals, which are associated with various components of the autonomic nervous system. One may compare this to a beam of light going into a prism in which the composed light is divided and quantified as light with different colours (wave lengths), in analogy with the composed sinus rhythm of the heart.

Table 1 Selected measures of indices of heart rate variability

Frequency domain	Time domain	Cardiac autonomic control
Total power (TP)	SDNN Triangular index TINN (Differential index)	Circadian Sympathetic/parasympathetic
High frequency (HF)	pNN50 RMSSD Differential index	Parasympathetic
Low frequency (LF)	SDNNINDX	Sympathetic/parasympathetic
Very low frequency (VLF)	SDANN	Circadian

High frequency power (HF 0.15–0.40 Hz); low frequency power (LF 0.04–0.15 Hz); very low frequency (VLF 0.0033–0.04 Hz); total power (TP <0.40 Hz); pNN50, the percent of differences between adjacent normal RR intervals greater than 50 ms; RMSSD, the square root of the mean of the sum of squares of differences between adjacent normal RR intervals; SDNN, the standard deviation of all normal-to-normal RR intervals; SDANN, standard deviation of the average of normal-normal intervals in all 5 min segments; SDNNIDX, the mean value of the standard deviation of all normal-to-normal RR intervals for all 5-min segments of the entire registration; TINN, triangular interpolation of normal-normal intervals.

The overall measure is total power, and the frequency range components are very low frequency (VLF 0.0033–0.04 Hz), low frequency (LF 0.04–0.15 Hz) and high frequency (HF 0.15–0.4 Hz) HRV (Table 1). The proposed relationships between various frequency domain measurements of HRV and the sympathetic and parasympathetic components of the autonomic nervous system is shown in Table 1. In addition, frequency domain measurements of HRV can identify very low frequency variation, which correspond to physiological variations such as day/night, thermoregulation, influences of the renin-angiotensin-aldosterone system, and other circadian rhythms.[19]

There is currently no gold standard for the assessment of HRV, and the various techniques may be considered to be complementary. In general, frequency domain measurement are better suited than time domain measurements for assessments of HRV in short term registrations, whereas both frequency domain, time domain, and geometric methods are well suited for HRV measurements based on long term registrations. In contrast to the geometric methods, the traditional time domain and frequency domain methods for assessment of HRV are sensitive to the quality of the registration with regard to artefacts and other disturbances, and the presence of premature beats. Registrations must be carefully filtered (automatically and manually) to provide valid assessments of HRV. Not surprisingly, there are strong relationships between several time domain and frequency domain indices of HRV (Table 1). For example, the global measure SDNN is strongly related to total power, whereas RMSSD, pNN50 and DI, which reflect short term variability, are related to the HF component.

There are also other methods to assess cardiac autonomic nervous control, such as the non-linear dynamics of heart rate variability,[20, 21] measurements of baroreflex sensitivity[22] and heart rate recovery,[23] and studies of the effects of sympathetic and parasympathtic blockade by denervation or drug treatment. These techniques are, however, beyond the scope of this presentation.

Heart rate variability in health and disease

It appears that HRV is an important marker for adverse prognosis both in healthy populations, and in patients with cardiac disease.[24, 25, 26] Women have higher HRV than men,[8, 10] and HRV decreases more rapidly with age in women; by the age of 60–70 years women and men have similar HRV values.[27] Whether differences between women and men are influenced by the lower incidence of coronary artery disease in women is not yet known.

Diabetes mellitus may cause severe autonomic dysfunction.[28, 29] Indeed, studies in diabetic patients have shown that indices of HRV are disturbed, suggesting abnormal cardiac autonomic activity, already before clinical signs of neuropathy occurred.[19, 30] Cardiac autonomic neuropathy is believed to contribute to the increased mortality in patients with diabetes mellitus.[31]

Disorders of the central and peripheral nervous systems may influence HRV. Thus, neurological diseases may independently affect variability mediated by the sympathetic and parasympathetic cardiac fibres. For example, decreased HRV has been described in patients with Parkinson's disease, multiple sclerosis, severe brain damage, and depression.[32, 33, 34]

In patients with established cardiovascular risk factors for a poor prognosis, such as a low left ventricular ejection fraction, heart failure, or a high resting heart rate, HRV indices are reduced.[35, 36] This may be a result of worsening heart failure with a subsequent increase in cardiac sympathetic activity. Accordingly, HRV improved in heart failure patients treated with cardiac resynchronisation therapy, presumably as a result of reduced sympathetic overdrive.[37] Indeed, the autonomic imbalance described by measurements of HRV seems to be a better predictor of prognosis than hemodynamic measurements of disease progression.[38] Similar to patients who have suffered a myocardial infarction (MI), HRV in heart failure subjects predicts all cause mortality (but not non-fatal coronary artery disease events).[39]

In the setting of an acute MI, HRV is markedly depressed. This is most likely due to increased cardiac sympathetic activation.[40, 41] The depression of HRV is most marked during the first one or two weeks following the acute event.[42, 43] The optimal timing of HRV analysis after an MI has not been clearly defined, but recommendations suggest that registrations should be performed within two weeks after the acute event.[13]

Low HRV after an acute MI predicts cardiac events such as arrhythmias and sudden death. This was first demonstrated by Wolf and collaborators,[44] and has subsequently been confirmed by others.[14, 45, 46] Indeed, the ATRAMI study showed that HRV, baroreflex sensitivity, and non-sustained ventricular tachycardia were the strongest predictors for cardiac mortality during a two-year follow up after an acute MI.[47] That study also found that the combination of HRV and non-sustained ventricular tachycardia, both derived from the ECG, provided a stronger predictive value for cardiac mortality than either phenomenon *per se*.[47] However, in the prospective, unblinded DINAMIT study, which was performed to test the effectiveness of implantable cardioverter defibrillator therapy in patients with an acute MI who had

reduced HRV (measured as SDNN) in combination with a low left ventricular ejection fraction, HRV failed to identify patients benefited from an implantable cardioverter defibrillator.[48] Fatal arrhythmic events were reduced, but non-arrhythmic cardiac mortality was higher in the implantable cardioverter defibrillator arm in the DINAMIT study. Similarly, low HRV did not predict all cause mortality in the ALIVE study of treatment with a class III antiarrhythmic drug in patients following an acute MI.[49]

Thus, a low HRV indicates an imbalance between sympathetic and parasympathetic activity of the cardiac autonomic nervous system.[50] Depressed cardiac parasympathetic activity in patients with a low HRV is associated with a reduced threshold for ventricular fibrillation, and may explain the association between low HRV and cardiac mortality.[51] However, fatal arrhythmogenic events may not fully explain the unfavourable prognosis in patients with low HRV. Thus, the mechanisms by which HRV relate to prognosis are not yet fully understood.

Angina pectoris and heart rate variability

Angina pectoris is a well defined clinical condition, which was first described by Heberden[52] in 1768. The principal symptoms are discomfort or pain in the chest, usually provoked by physical exercise. It is considered to be caused by myocardial ischemia, as a result of an imbalance between metabolic needs and the available blood flow supplying the myocardium. This is usually due to flow limiting coronary stenosis, but it also occurs in patients with angiographically normal coronary arteries, and in vasospastic angina pectoris.

The incidence and prevalence of angina pectoris is difficult to evaluate as it depends on the criteria used, the varying nature of the disease, and that the diagnosis is based mainly on clinical history. In a Swedish study from the 1980´s, the prevalence of chest pain, judged by a cardiologist to be of cardiac origin, was estimated to be 5% in males aged 50–57 years.[53] The prevalence increases with age, and is some 10 to 15% in subjects aged 70 years.[54] However, the variations in prevalence are considerable.[55] The annual incidence of angina pectoris, according to a study in the United Kingdom, is 1.1 per 1000 male and 0.5 per 1000 female inhabitants aged 31–70 years.[56] In Finland, the

incidence, defined as a positive stress test in subjects aged 45–89 years, was found to be 6.0 per 1000 men and 3.3 per 1000 women.[57]

Because angina pectoris is strongly related to coronary atherosclerosis, it is linked to an increased risk of cardiovascular events, such as an acute MI or sudden death. In an unselected population of patients with stable angina pectoris, it is important to identify patients at high risk of future cardiovascular complications, in order to commence proper treatment. Simple clinical characteristics, such as high age, male gender, smoking, cholesterol levels, hypertension, diabetes mellitus, and a previous MI are generally considered to indicate a worsened prognosis. However, there is need for better tools to select patients with low or high risk. Given the strong prognostic information of HRV in patients with a previous MI, assessments of HRV in patients with stable angina pectoris may be of value. However, only few studies in patients with stable angina pectoris have evaluated the prognostic information of HRV regarding cardiovascular events.[58, 59, 60]

The primary aim of the Angina prognosis study in Stockholm (APSIS) was to compare the long term effects of treatment with the beta-adrenoceptor blocker metoprolol and the calcium antagonist verapamil on cardiovascular outcome in patients with stable angina pectoris.[61] The study was planned so that we would be able to describe the natural history of patients with stable angina pectoris, and to analyze the prognostic implications of various risk markers and risk factors thought to be involved in the progression of coronary artery disease. Thus, the prognostic impact of metabolic factors such as glucose and lipids,[62, 63, 64] haemostatic mechanisms,[65, 66] arrhythmias and ST segment depression, as evaluated by exercise testing and by ambulatory 24-hour ECG registrations[67, 68, 69] have been reported elsewhere. This thesis focuses the potential clinical importance of HRV in patients with stable angina pectoris.

AIMS OF THIS THESIS

The present thesis is based on HRV analyses performed in ambulatory 24-hour ECG registrations in patients with stable angina pectoris for the following purposes:

1. To develop and validate a simple graphical method for the assessment of HRV.
2. To study the stability over time of HRV in patients with stable angina, and changes in HRV indices by an acute MI.
3. To study the prognostic information of HRV in patients with stable angina pectoris.
4. To evaluate the effects of the beta-adrenoceptor blockade by metoprolol and calcium antagonist treatment with verapamil on HRV, and the possible prognostic importance of such influences.

MATERIAL AND METHODS

Patients and control subjects

From 1987 until 1993 altogether 1276 patients with a presumed diagnosis of stable angina pectoris were examined at the Cardiovascular Research Laboratory at Danderyd University Hospital, Stockholm, Sweden. We eventually included 809 patients (561 men) aged less than 70 years with symptoms, as originally described by Heberden.[52] The symptoms should be localized in the central part of the chest, with or without radiation, elicited by either physical or psychological stimuli, and should diminish gradually by rest, or quickly by sublingual nitroglycerine. Inclusion was based on clinical history only. If symptoms were atypical, complementary tests, such as exercise tests, myocardial perfusion scintigraphy, radiological or gastroenterological examinations were performed. Exclusion criteria included a previous MI within the last three years, unstable or severe angina pectoris with an anticipated need for revascularization within a month, coronary interventions within the last year, or severe congestive heart failure (New York Heart Association class III–IV), a systolic blood pressure below 100 mm Hg, obstructive pulmonary disease, significant valvular disease, alcohol or drug abuse, or other obvious risks for poor patient compliance. Patient demographics and background information are presented in Table 2.

A total of 50 healthy subjects matched for birth dates and gender were recruited from the population registry and were invited for an examination, which included a thorough medical history and physical examination. Reasons for exclusion were ongoing drug treatment (including non-steroid anti-inflammatory agents, or hormone replacement therapy), bifascicular block or a pathological Q wave on the standard 12-lead ECG, a diastolic blood pressure above 95 mm Hg suggesting hypertension, significant cardiac murmurs, or non-cardiac disease.

Study design

The APSIS trial was a large single-center study in which patients were randomized to receive treatment with metoprolol (Seloken ZOC, AstraZeneca AB, Mölndal, Sweden) or verapamil (Isoptin Retard, Knoll AG, Ludwigshafen, Germany).

Table 2 Baseline characteristics in the Angina prognosis study in Stockholm

	Metoprolol	Verapamil
n	406	403
Age	59±7	59±7
Women (%)	27	34*
Previous history (%)		
Acute myocardial infarction	16	16
Congestive heart failure	6	7
Hypertension	28	26
Cerebrovascular event	5	4
Coronary intervention	5	7
Intermittent claudication	4	2
Diabetes mellitus	8	9
Therapy at baseline (%)		
Acetyl salicylic acid	39	38
Long acting nitrates	49	53
Beta-adrenoceptor blockers	56	54
Calcium antagonists	14	16
Smoking habits (%)		
Smoker	22	22
Ex-smoker	50	36*
Non-smoker	28	42*
Duration of angina pectoris (years)	2 [0,5; 5,0]	2 [0,5; 6,0]

Mean values ± SD; however, the duration of angina pectoris is presented as median values and interquartiles. Differences between the groups are indicated as *p <0.05.

Double-blinding was achieved by the use of matching placebos for both drugs, and the double dummy technique. Target doses (metoprolol 200 mg od or verapamil 240 mg bid) were reached after 2 weeks, if tolerated. All patients were followed with clinical evaluations at 1 month and thereafter at 6-month intervals. More extensive examinations, including ambulatory 24-hour ECG registrations and other experimental procedures, were performed at baseline, after 1 month and after 3 years or at the end of the study. The median follow-up was 40 (range 6 to 76) months, corresponding to a total follow-up amounting to 2766 patient years. The endpoints of the APSIS trial are shown in Table 3.

However, in the present analyses (I−IV) only cardiovascular death and non-fatal MI only were used as endpoints. Cardiovascular death was defined as a fatal acute MI, sudden death (within 2 hours of onset of symptoms) or death from other vascular causes. An acute MI was defined as a typical clinical presentation and a significant rise in cardiac biomarkers and/or development of a new Q wave on the electrocardiogram (with or without hospitalisation).

Concomitant hypertension was defined as a history of treated hypertension or a blood pressure of 160/100 mm Hg or above. Congestive heart failure was defined as a history of heart failure treatment or clinical signs of heart failure. Diabetes mellitus was defined as a fasting blood glucose above 6.4 mmol/l on two or more occasions, or drug treatment for diabetes mellitus.

The study populations of the present studies are illustrated in Figure 2. Demographic and background information are presented in detail in papers I–IV, and was generally comparable to the entire APSIS trial population (see Table 2). In brief, in the study on prognostic information from measurements of frequency domain indices of HRV (I) we were able to include 641 patients (449 men) with ambulatory 24-hour ECG registrations allowing analyses of HRV. Urinary catecholamines were measured in 455 patients (386 men) and plasma catecholamines in 583 patients (389 men). The study in which DI and other time domain indices of HRV were evaluated regarding prognostic implications (III) comprised 678 patients (474 men) with ambulatory 24-hour ECG registrations of sufficient quality to assess HRV. In the study describing the new graphical DI method for measuring HRV (II) we enrolled 130 patients with sufficient ambulatory 24-hour ECG registrations at inclusion to ensure at least 100 evaluable patients. However, only 10 registrations were excluded. In addition, 50 matched control subjects were included; one of these registrations was later excluded. In the study in which the long term stability of HRV was evaluated (IV), we assessed HRV at 1 and 36 months by the DI method in 261 patients; 63 of these patients had evaluable ambulatory registrations for analyses in both time and frequency domain. In addition, 27 patients who suffered an acute myocardial infarction after the study was terminated were re-examined after this event.

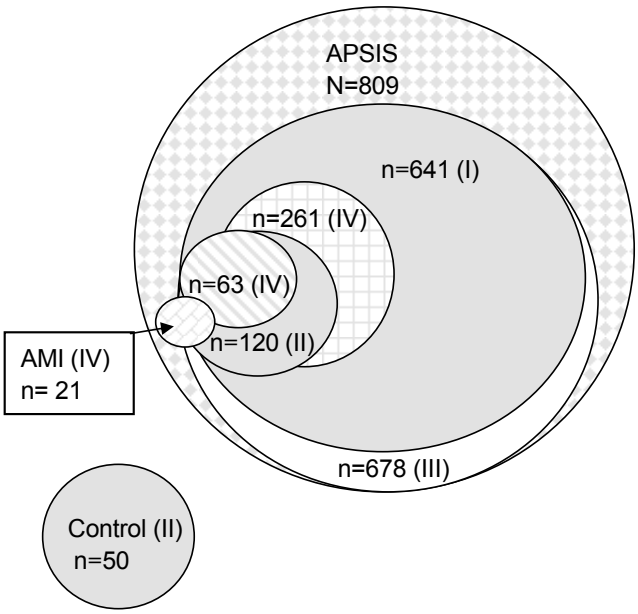

Figure 2
Diagram showing the different study populations within the APSIS trial. AMI, patients with a subsequent acute myocardial infarction, as examined in (IV).

Ambulatory 24-hour electrocardiographic registrations and calculations

Recordings were obtained by Oxford Medilog type 4000 or 4500 two cannel tape recorders with a sampling frequency of 128 Hz and the tapes were analyzed with manual overview on an Oxford Medilog Exel system (Oxford Medical Equipment Ltd., Abington, United Kingdom). A cardiologist visually inspected all recordings. All calculations were made without knowledge of the outcome of the patient. We only analyzed tapes with 17 hours or more of technically acceptable quality. Registrations in which atrial flutter or atrial fibrillation was present for more than half of the recorded time were excluded regarding HRV analysis. The DI was calculated by a geometric method. In brief, the 24-hour recording was computerised without any filtering process, and a sample density histogram of the differences in RR intervals for successive beats was constructed. Based on the widths of the histogram at 10000 intervals and at 1000 intervals a triangle was constructed. The intercepts with the base of the histogram determine the DI (II) (Figure 1).

The conventional time domain measures calculated were the standard deviation of normal RR intervals (SDNN), the mean value of the standard deviation of normal RR intervals for all 5-min segments of the entire registration (SDNNIDX) the root of the mean square differences of successive normal RR intervals (RMSSD), and the percentage of normal RR intervals that differ by >50 ms (pNN50). All of these measures except SDNNIDX were computed using the entire 24-hour recording as a single segment, and with well-established techniques.[13]

The frequency domain of the time series of RR intervals was analyzed with an autoregressive method described by Kay and Marple.[70] The model order and number of coefficients in the polynomial describing the time series was constantly set to 18. The mean RR interval of each time series was subtracted and then detrended by applying linear regression. Frequency domain measures of RR variability were computed by integrating their frequency intervals in three frequency bands as described by Bigger,[71] and later generally recommended.[13] The following frequency domain measures of RR variability were calculated: very low frequency (VLF 0.0033–0.04 Hz), low frequency (LF 0.04–0.15 Hz) and high frequency power (HF 0.15–0.40 Hz), total power (<0.40 Hz), and the low-to-high frequency power ratio (LF/HF).

Because frequency domain measurements are more sensitive to disturbances and premature beats than time domain measurements, there are generally fewer registrations that fulfil accepted quality criteria for analyses of frequency domain indices of HRV than for time domain indices.

Biochemical analyses

Venous blood samples for the analyses of catecholamines were drawn from an indwelling antecubital catheter. Plasma catecholamine concentrations were determined by high performance cation exchange liquid chromatography, as previously described and validated.[72] During the ambulatory 24-hour ECG registration, urine was collected for catecholamine analyses, with separate canisters for day and night urine. In order to avoid confounding by sampling errors, the excretion of catecholamines was adjusted for creatinine excretion. Urinary catecholamine concentrations were analyzed with a similar methodology as for plasma.[73] Blood glucose and serum lipids were analyzed by standard techniques.

Statistics

Data are presented as median values and interquartile ranges, or as mean values ± SD, as appropriate. Statistical comparisons were performed by non-parametric tests (Mann-Whitney U test, Wilcoxon signed rank test, and x^2 tests), or by Student's *t*-test and multivariate analyses of variance, following logarithmical transformation of all skewed data, as appropriate. The initial model included age and gender. The Tukey Compromise procedure was used for *post-hoc* comparisons. Regression lines were constructed by the least squares' method. Receiver operating characteristic (ROC) curves were constructed by standard techniques and the relationship between false-positive and true-positive rates was evaluated as the area under the curve. To investigate associations between HRV variables and events, univariate proportional hazard (Cox) analyses, and Kaplan-Meier plots with log rank statistics were performed as a first step. The follow-up time until the index event was used. Since revascularisation might influence the proportional risk of an event, patients were censored at the actual dates of such procedures. In a second step, variables that showed some relationship to events were further evaluated with a multivariate Cox proportional hazard model including adjustments for risk factors such as age, sex, left ventricular ejection fraction, history of a previous MI, hypertension, and diabetes. The influence of treatment was analysed in the same multivariate model using treatment allocation (i.e. study drug) and treatment effects (i.e. study drug effects on HRV) as covariates. All analyses were performed using Statistica 5.1 (Stat Soft, Tulsa, OK, USA) or JMP v 5 (SAS Institute Inc., Cary, NC, USA). A probability (p) <0.05 was considered significant.

RESULTS AND COMMENTS

Main results from the entire Angina prognosis study in Stockholm (APSIS)

The main findings of the APSIS trial have been presented elsewhere.[61, 63] In brief, 47 patients died, 22 (5.4%) in the metoprolol group and 25 (6.2%) in the verapamil group (p=0.63) during the follow-up (median 3.4 years). The mode of death did not differ between the two treatment groups as 19 cardiovascular deaths (4.7%) occurred in both groups (Table 2). Non-fatal cardiovascular events occurred in 106 patients in the metoprolol group, and in 98 patients in the verapamil group (p=0.56). Non-fatal cardiovascular events were also similar in the two treatment groups (Table 3). At the end of the study the odds ratios and 95% confidence intervals for suffering events during metoprolol compared to verapamil treatment were 0.87 (0.48; 1.56) for mortality and 1.03 (0.84; 1.30) for the combined events. Using a Cox regression model which takes the time course into account, the corresponding figures were 0.94 (0.53; 1.67) and 1.22 (0.95; 1.52), respectively. Patients with concomitant diabetes mellitus had a worse prognosis than non-diabetic patients.[63, 74] Interestingly, patients who did not have known diabetes mellitus but a fasting blood glucose above 6.1 mol/l (9%) had an equally worsened prognosis as patients with manifest and treated diabetes.[63]

The APSIS trial appears to be the largest study showing that a beta-adrenoceptor blocker, metoprolol, and a heart rate lowering calcium antagonist, verapamil, have similar effects on the prognosis of patients with stable angina pectoris. These results confirm results from two previous studies.[75, 76] The all-cause mortality was less than 2% per year. This was confirmed in an extended open follow-up of the APSIS study population over a period of nine years, where the annual all-cause mortality rate was 2% and cardiovascular mortality was 1%.[74] Female patients had a mortality rate similar to females in the healthy control population. Men, however, showed a higher mortality rate than the controls during the first three years, after which the survival curves became parallel. Other studies in stable angina pectoris have also shown a somewhat higher mortality in male patients with stable angina pectoris than in female patients.[55] Our findings that diabetic patients have a higher risk are in agreement with those of other reports.[57, 77] Taken together, this indicates that patients with stable angina pectoris have a fair long term prognosis with conservative treatment, even without present-day

additional treatment (the study was performed in the pre-statin era). Recent results suggest that outcomes with conservative treatment or a strategy based on coronary artery intervention are similar.[78, 79] Thus, a conservative strategy may be preferred for most patients with stable angina pectoris

Table 3 Endpoints in the Angina prognosis study in Stockholm

	Metoprolol	Verapamil
n	406	403
All cause mortality	22 (5.4%)	25 (6.2%)
Cardiovascular mortality		
Sudden death (within 2 h)	5	6
Acute myocardial infarction	12	11
Vascular events	2	2
Malignancy	3	6
Non-fatal cardiovascular events		
Acute myocardial infarction	17	14
Coronary artery bypass surgery	46	39
Percutanous coronary interventions	12	5
Coronary angiography without intervention	7	20
Other progressive angina pectoris	0	5
Cerebrovascular disease	11	13
Peripheral vascular disease	3	2

Fatal vascular deaths were one patient with pulmonary embolism and three cerebrovascular events.

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Prognostic implications of frequency domain indices of heart rate variability, and of autonomic function assessed by catecholamines (I)

There was a clear relationship between all studied indices of HRV in the frequency domain (VLF, LF, HF and total power) except the ratio LF/HF and prognosis concerning cardiovascular death (Figure 3). Patients suffering a subsequent cardiovascular death had lower HRV values than those with no such event. There was, however, no prognostic impact of HRV regarding non-fatal MI.

Multivariate Cox proportional hazard analyses confirmed that these results were independent of known confounding cardiovascular risk factors.

Neither catecholamine levels in plasma nor catecholamine excretion in urine provided any prognostic information.

Treatment with metoprolol and verapamil had different effects on HRV. Following one month of treatment the metoprolol group had higher HRV values than the verapamil group. The effects on catecholamine excretion in urine were also different, as noradrenaline excretion decreased among verapamil treated patients and did not change among those treated with metoprolol. Importantly, however, the treatment effects on frequency domain indices of HRV and on catecholamines did not seem to impact on prognosis.

Myocardial ischemia is closely related to the activity of the autonomic nervous system. As HRV reflects the cardiac autonomic balance, measurements of HRV may provide valuable information regarding cardiac autonomic activity. We found a reduced HRV, considered to reflect mainly a decrease in vagal activity, in the frequency domain among patients with a subsequent cardiovascular fatal event. This confirms previous observations in patients following an acute MI or patients with congestive heart failure.[26, 35, 36, 45] Our results extend findings from previous studies in angina pectoris.[58, 59] The previous studies did, however, not provide unequivocal results regarding relationships between HRV and cardiovascular morbidity or mortality. Thus, a low HRV appears to be a consistent finding in patients with coronary artery disease, including stable angina pectoris as well as a previous MI.

Catecholamines, whether assessed in plasma or urine, did not show any prognostic impact. Sympathetic nerve activity can be assessed in various ways, but invasive techniques are needed to study nerve activity in individual organs. Measurements of noradrenaline in venous plasma or urine will reflect overall sympathetic nerve activity, which may not correlate well with cardiac sympathetic nerve activity.[80, 81]

Prognostic implications of conventional time domain indices of heart rate variability (III)

Patients having a fatal cardiovascular event displayed lower HRV in the time domain (SDNN and pNN50, with a trend also for RMSSD), compared to those who did not have an event. Patients suffering a non-fatal MI, however, had similar HRV indices as patients who remained free from a non-fatal coronary event. Kaplan-Meier plots show that SDNN and pNN50 below the median value predicted cardiovascular death, again with a trend for RMSSD (Figure 3). No such relationships were obtained for non-fatal MI. Multivariate Cox proportional hazard analyses including age, sex, previous MI, hypertension, and diabetes mellitus as co-variates confirmed the independent prognostic information of a low HRV in the time domain. Left ventricular ejection fraction and the amount of signs and symptoms suggesting myocardial ischemia during an exercise test did not provide additional prognostic information.

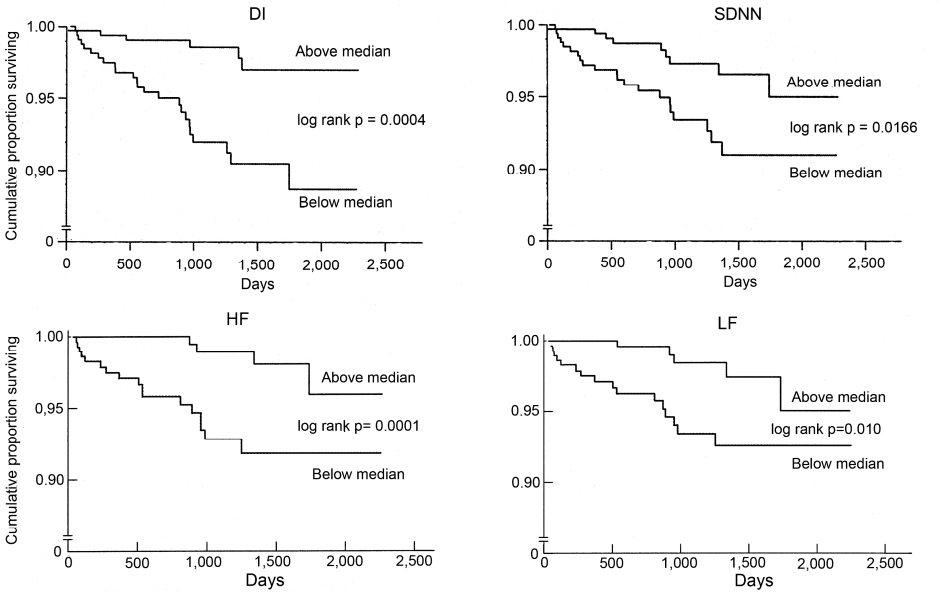

Figure 3
Kaplan-Meier plots illustrating the prognostic implications of HRV in the time domain and frequency domain regarding the risk of suffering cardiovascular death. Each HRV variable was dichotomized at the median value. The upper left hand panel shows the differential Index (DI), upper right SDNN, lower left HF, and the lower right panel LF. DI values above vs. below median provided the best visual separation of the survival curves. From (I, II).

Treatment with metoprolol increased pNN50 and RMSSD, whereas verapamil treatment had no influence. SDNN did not change in either treatment group. However, neither the drug given nor the short-term effect of treatment carried any independent prognostic information.

We thus found that low HRV in the time domain carries independent prognostic information regarding future cardiovascular death in patients with stable angina pectoris. This is in agreement with previous reports.[25, 45, 82] Furthermore, our findings with time domain indices of HRV are in good agreement with our results obtained in the frequency domain (I), and suggest that a low HRV, mainly reflecting a decrease in cardiac vagal activity, can predict an increased risk for a cardiovascular fatal event in patients with stable angina pectoris.

Evaluation of heart rate variability by differential index (II, IV)

Women had higher DI values than men. Also other indices of HRV in the frequency and time domain showed higher values for women than for men. There was a small reduction in DI with increasing age ($\log[DI] = 2.71 - 0.0030 \times age$, $r = -0.13$, $p < 0.001$, $n = 727$). This corresponds to an approximate 2 ms reduction of the DI per year. Also other frequency domain and time domain indices of HRV showed no or small inverse relationships with time. There was a significant inverse relation between DI and heart rate ($\log[DI] = 3.01 - 0.0066 \times age$, $r = -0.39$, $p < 0.001$, $n = 727$), which corresponds to an approximate 5 ms reduction of the DI per 1 beat increase in heart rate per minute. The DI was most closely related to short-term components of HRV (i.e. HF, pNN50), as shown in Table 4. There were also close relationships between DI and overall components of HRV (i.e. total power, SDNNIDX; see Table 4). The DI was quite similar in healthy control subjects and patients with angina pectoris. However, HRV was reduced in patients with angina pectoris and concomitant diabetes mellitus (Figure 5).

There was an excellent agreement between DI values calculated before, and recalculated after editing the same recordings for ectopic beats and artefacts ($r = 0.99$). The DI was also not sensitive to moderate reductions of the number of RR intervals, as a 25% reduction in the number of RR intervals had little effect on the DI. Thus, the DI technique was quite robust.

The long term stability of DI measurements was evaluated by comparing values at months 1 and 36. The DI was essentially unchanged, with a ratio for month 36/month 1 of 1.00±0.06 (the results were similar in patients treated with verapamil and with metoprolol). Most other time domain indices of HRV also remained largely unchanged from month 1 to 36. Our findings of a higher level of HRV in women, and an inverse relation between HRV and age are in agreement with previous findings.[8, 10] We present DI as a novel simple graphical time domain measure of short-term HRV.

Table 4 Correlation coefficients for various indices of heart rate variability

	DI	pNN50	SDNNIDX	RMSSD	SDNN	Total power	VLF	LF	HF
pNN50	0.81***	—							
SDNNIDX	0.72***	0.72***	—						
RMSSD	0.35***	0.66***	0.35***	—					
SDNN	0.46***	0.54***	0.62***	0.62***	—				
Total power	0.72***	0.73***	0.98***	0.34***	0.59***	—			
VLF	0.59***	0.55***	0.94***	0.21*	0.59***	0.94***	—		
LF	0.64***	0.60***	0.92***	<0.1	0.53***	0.97***	0.90***	—	
HF	0.84***	0.83***	0.84***	0.52***	0.52***	0.86***	0.69***	0.79***	—
LF/HF	0.36***	0.46***	<0.1	0.38***	<0.1	<0.1	0.25**	0.24*	0.33***

Data from (II). See text for abbreviations. *p<0.05, **p<0.01, ***p<0.001.

Our validation shows good agreement between the DI and established short-term time domain (pNN50) and frequency domain (HF) indices of HRV, which are considered to reflect vagal activity. Results obtained by the DI method also relate to time domain (SDNNIDX) and frequency domain (VLF and LF) measures, which are considered to reflect the cardiac autonomic parasympathetic/sympathetic balance. Thus, the DI appears to reflect mainly cardiac parasympathetic control.[13]

The triangular index and triangular interpolation of normal-to-normal RR interval histograms are geometric methods that are well suited when the histogram of RR

intervals displays a single dominant peak.[14, 16, 17] Recordings over 24 hours in subjects with a high level of activity at daytime and rest during the night may register histograms with two or more distinct peaks. In this case geometric methods will underestimate the HRV.[18] However, the DI method would be less sensitive to skewed or bimodal distributions of RR interval histograms.[18]

Prognostic implications of differential index (III)

The DI was inversely related to the risk of a having a fatal cardiovascular event (Figures 3 and 4). The independent important prognostic information of a low DI value was confirmed by multivariate Cox proportional hazard analyses including age, sex, previous MI, hypertension and diabetes mellitus. Of note, DI appeared to separate patients with low and high risks of suffering cardiovascular death more clearly than other indices of HRV. When the study population was arbitrarily divided into tertiles according to DI values of <250, 250–399 and ≥ 400 ms, there was a graded increase in the risk of suffering a fatal cardiovascular event with lower DI, with a 5−6-fold increase in risk between the lowest and highest tertile (Figure 4). Reciver operator characteristics (ROC) curves suggest that a cut-off for DI values at approximately 320 ms gives the best sensitivity and specificity. Similar to the findings with frequency domain indices and traditional time domain indices of HRV (I, III), the DI did not differentiate between patients who later suffered a non-fatal acute MI and those who did not. Diabetes mellitus was associated with lower HRV, as assessed by the DI (Figure 5). There were eight fatal cardiovascular events among the diabetic patients, and six of them had DI values ≤ 250 ms.

Treatment with metoprolol increased DI values, whereas verapamil treatment did not influence the DI. Neither the drug given nor the short-term effect of treatment carried any independent prognostic information.

The simple DI method provided equally good or better prognostic information compared to conventional and more laborious methods to assess HRV in the frequency domain or time domain. The simplicity of the DI method, and its ability to separate patients with low and high risk, suggest that it could be a useful tool for risk stratification of patients with stable coronary artery disease.

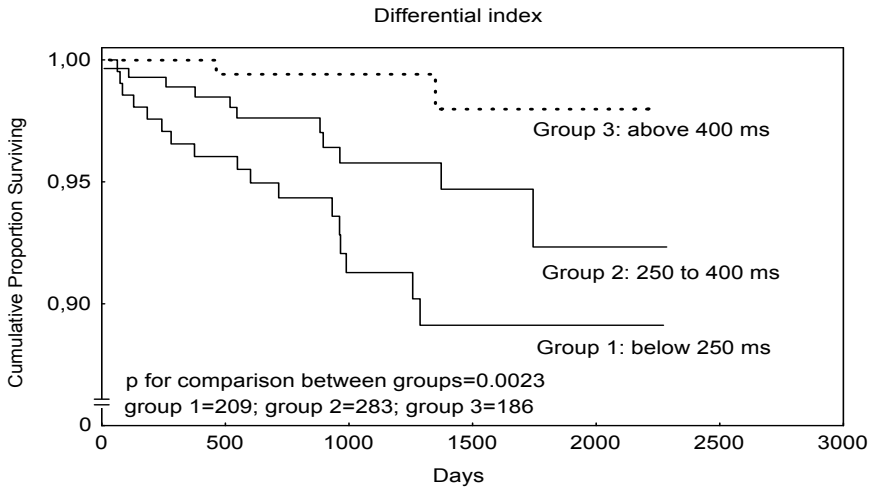

Figure 4
A Kaplan-Meier plot illustrating the risk of suffering cardiovascular death with DI values of <250 (n = 209), 250–399 (n = 283) or ≥400 ms (n = 186). Prognosis was worse with decreasing DI values. From (III).

The impact of an acute myocardial infarction on heart rate variability (IV)

We examined 21 patients in sinus rhythm who had completed the APSIS trial without having an event but who experienced an acute MI after the completion of the study. The HRV analysis indicates that SDNN, SDNNIDX, total power, VLF, LF, and LF/HF were all reduced following the acute MI, whereas DI, pNN50, and HF remained largely unchanged after the event.

As high frequency indices of HRV (e.g. HF, DI, and pNN50) are considered to reflect parasympathetic cardiac autonomic control,[83, 84, 85] our results suggest that cardiac parasympathetic control is essentially unchanged after an acute MI. In contrast, indices of low frequency HRV (e.g. VLF, LF, LF/HF, SDNN, SDNNIDX, and total power), which are supposed to reflect the balance of parasympathetic/sympathetic cardiac autonomic control,[2, 85, 86] were all reduced in following the acute MI. An acute MI elicits cardiac sympathetic activation.

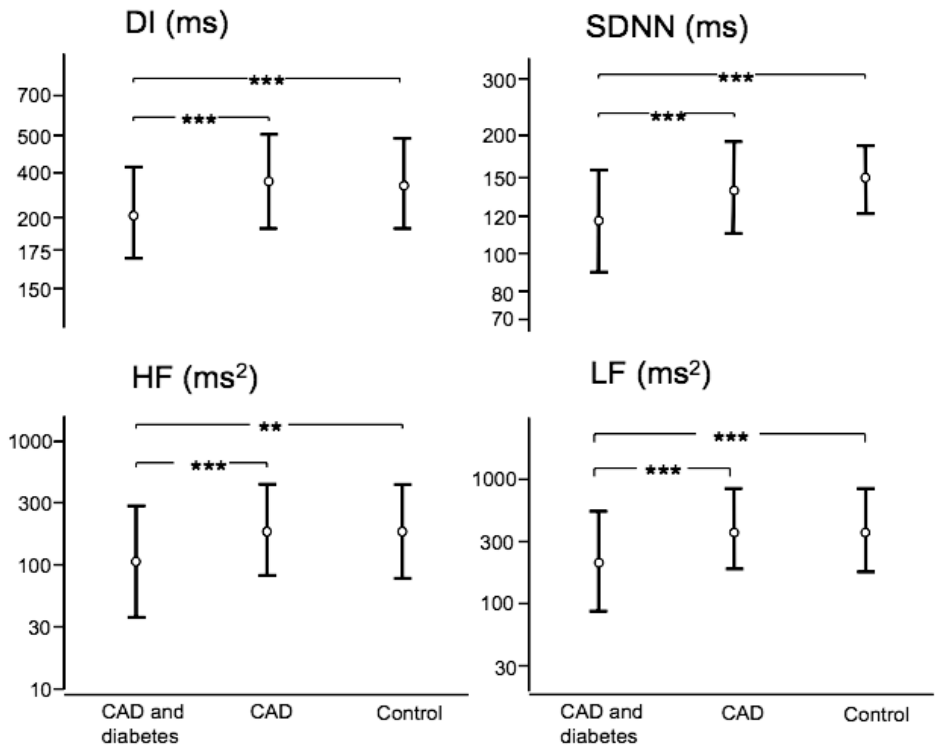

Figure 5
HRV indices in patients with coronary artery disease (CAD) and concomitant diabetes (n= 61), CAD without diabetes (n=662), and a healthy control group (n=49). Mean values ± SD.**p<0.01, ***p<0.001.

In agreement with other reports,[14, 43] our results suggest an increased cardiac sympathetic influence following an acute MI. Thus, DI and other indices of high frequency HRV may be well suited to predict future risk for a fatal cardiovascular event in patients with chronic stable angina pectoris, even in the presence of a recent acute coronary event.

GENERAL DISCUSSION

Heart rate variability provides independent prognostic information

It is well established that HRV provided prognostic information in patients who had suffered an acute MI.[16, 44, 45] Later, studies have also shown prognostic value of HRV measurements among healthy subjects, and in patients with congestive heart failure.[24, 25, 26] The current results show that similar clinically important information is also provided for patients with stable angina pectoris, thus expanding these findings to a much larger group of patients with coronary artery disease. Most importantly, this prognostic information is independent of other traditional risk factors such as age, gender, myocardial ischemia, left ventricular function, hypertension or diabetes mellitus.

Diabetes mellitus is associated with an increased risk for cardiovascular complications, and is a common finding among patients with coronary artery disease.[87, 88] Of interest, patients in the present study with previously unknown diabetes mellitus had a similarly worsened prognosis as those with an established diagnosis of diabetes.[63] Similar findings have been made in hypertensive patients,[89, 90] and suggest that diabetes mellitus confers an increased risk already at an early stage of the disease. We found that patients with diabetes mellitus had a reduced HRV (Figure 5), indicating a disturbed cardiac autonomic control of heart rate.[31, 91, 92] Sudden cardiac death may be linked to the presence of autonomic neuropathy in diabetic patients.[93] Accordingly, a majority of diabetic patients who suffered a fatal cardiovascular event in the current study displayed a very low HRV. Taken together, assessments of HRV may provide an especially useful tool for the identification of high risk subjects within subpopulation of angina patients with diabetes mellitus.

Although the prognostic information of HRV regarding cardiovascular mortality is striking, we found no association between HRV and non-fatal MI. This is in agreement with other studies in patients with cardiac disorders.[45, 71] Similarly, a reduced HRV does not appear to predict atherosclerotic progression, pump failure in congestive heart failure, or worsening of the metabolic control in diabetic patients (I).[19, 25, 26, 35] Reduced cardiac parasympathetic activity is strongly associated with a reduced threshold for

ventricular fibrillation, especially when sympathetic hyperactivity coexists. This may cause fatal ventricular arrhythmias and subsequent sudden death.[17, 94] Thus, the cardiac autonomic imbalance may be of importance for fatal arrhythmic cardiovascular events in stable coronary artery disease, but is not closely related to the slow development of atherosclerotic disease and plaque vulnerability resulting in an acute MI.

Different methods to assess heart rate variability

Evaluation of variations in the heart rate may be performed by several methods. Generally, it is easier to study HRV in the time domain than to perform frequency domain analyses. Due to physiological and mathematical relationships there are strong correlations between measurements performed in the frequency and in time domains (Table 4). Their approximate correspondence when applied to a 24 h ambulatory ECG recording is summarized in Table 1. There is, however, still considerable controversy as to how the different components of HRV should be interpreted in terms of cardiac parasympathetic and sympathetic nerve activity. Vagal activity is the major contributor to HF variability, whereas LF variability has been claimed to contain components of both sympathetic and vagal nerve activity.[95, 96] Although all measurements of HRV in the frequency domain are influenced by vagal activity, relationships between the two components have not yet been fully clarified.[95, 97] The vagal components in the time domain appear to be best reflected by pNN50, RMSSD, and DI, whereas the balance between sympathetic and parasympathetic cardiac autonomic control in the time domain is best assessed by SDNN.

We found that measurements of VLF, LF, and HF all independently predicted cardiovascular fatal events. However, cardiovascular mortality appeared to be best predicted by HF, which is most strongly associated with vagal activity. In the time domain we found that SDNN, pNN50, and DI carried significant prognostic information concerning cardiovascular mortality. This indicates that reduced cardiac parasympathetic activity is a major factor associated with a poor prognosis in stable angina pectoris.

Frequency domain measurements require data of high technical quality, and a low prevalence of abnormal beats. It is thus best suited for recordings of short duration, when the environment can be controlled, and in experimental situations.

Conventional time domain measurements are best suited for longer registrations (12–24h). They are less sensitive to external disturbances but still require high technical quality recordings. These conventional analyses of HRV are laborious and time consuming due to the overview and need for filtering of artefacts before the actual analysis. Also, it may be difficult to obtain acceptable recordings in many cardiovascular conditions due to frequent findings of arrhythmias. Thus, simplified procedures for HRV analyses would be most helpful.

Geometric methods are insensitive to recording artefacts and other short-lasting disturbances of sinus rhythm.[18] This insensitivity is obtained as the processing of the histogram focuses on the major peak of the sample density curve, resulting in small (or no) influences of abnormal RR intervals. This is illustrated in Figure 6. No filtering process of the signal is thus required and the handling of data is straightforward. The triangular index, and triangular interpolation of normal-to-normal RR interval histograms are two geometric methods that are particularly well suited when the histogram of RR intervals displays a single dominant peak.[14, 16, 17] One advantage of the DI method is that this method is less sensitive to skewed or bimodal distributions of RR interval histograms.[18] All geometric methods have the disadvantage that a substantial number of RR intervals are needed to construct a sample density histogram. Thus, we required registrations of at least 17 h (i.e. approximately 60000 RR intervals). Of note, however, a further reduction of the number of RR intervals by 25% had little effect on the differential index. Geometric methods for the assessment of HRV may lack the statistical exactness provided by conventional time domain and frequency domain methods.[18] However, they appear to give a good estimate of HRV with simple data management, and can be performed in any laboratory performing 24 h ambulatory ECG recordings.

The differential index is a simple geometric method with prognostic value

The DI is closely related to several indices of HRV, which have been shown to predict future cardiovascular mortality. Accordingly, we confirmed that the DI carries prognostic information concerning cardiovascular death in stable angina pectoris independently of traditional cardiovascular risk factors. Compared to traditional time domain indices of HRV (i.e. SDNN, pNN50, and RMSSD), the DI appears to predict

cardiovascular death somewhat better. There was a graded increase in the risk of suffering a cardiovascular death with lower DI values (Figure 4). The best sensitivity and specificity was obtained with a cut-off at approximately 320 ms.

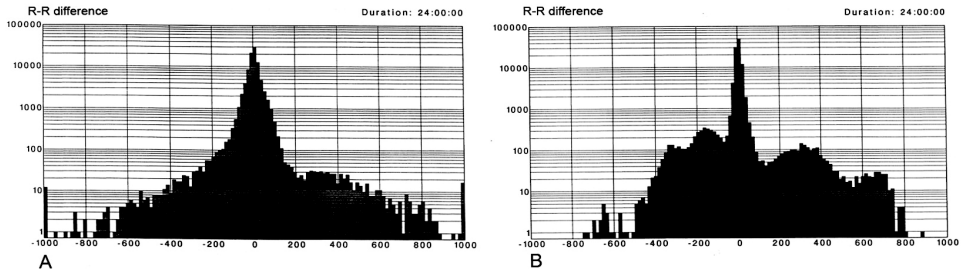

Figure 6
Authentic 24 hour ambulatory ECG registrations. The left hand panel shows a patient with a high HRV and a moderate level of premature beats, and the right hand panel shows a patient with a low HRV and more than 2500 premature beats.

It is likely that DI values reflect mainly cardiac parasympathetic control. Thus, the present results support our conclusions based on frequency domain and conventional time domain indices of HRV that reduced vagal activity is associated with an increased risk for a fatal cardiovascular event in patients with stable angina pectoris. The simplicity of the DI method and its power to separate patients at low and high risk suggest that it could be a useful tool for the risk stratification of patients with stable coronary artery disease in institutions with access to long-term ECG recording equipment.

The impact of an acute myocardial infarction on heart rate variability

We recorded HRV a few days after an acute MI in several previous participants in the APSIS study and found that indices of low frequency HRV (VLF, LF, LF/HF, SDNN, SDNNIDX, and total power), which reflect the balance of parasympathetic/sympathetic cardiac autonomic control, were reduced. Only minimal changes in the measures that are related most closely to the parasympathic limb of cardiac autonomic control

(HF, pNN50, and DI) were observed. This suggests that an acute MI is associated with increased sympathetic cardiac nerve activity, while changes in parasympathetic cardiac control are small. Results concerning HRV both before and after an acute MI in the same individuals have not been published previously. However, our results are in agreement with findings performed in patients *after* an acute cardiac event only. The results of such studies have suggested that there is an increase in cardiac sympathetic activation during an acute MI, and that this will gradually disappear, at least in part.[42, 43] From these results, we propose that DI and other high frequency indices of HRV may be the best measurements to predict the future risk for a fatal cardiovascular event in patients with chronic stable angina pectoris, even in the presence of a recent MI.

The effects of beta-adrenoceptor blockade and calcium antagonist treatment

We assessed the effects of treatment on HRV after one month, and found increases in the metoprolol group. Verapamil treatment had no effects. Long term (3 years) effects on HRV were, however, small in both treatment groups. Increases in HRV, especially the HF component, have been shown with several beta-adrenoceptor blockers, and this has been attributed mainly to influences on vagal activity.[98, 99] Calcium antagonists are a heterogeneous class of drugs, and calcium antagonist treatment has given variable results with regard to HRV, depending on the drug used. Thus, one study found an increase in HF with nifedipine, while another study with the heart rate reducing calcium antagonist verapamil could not confirm this.[58, 100]

More important, however, is that short term influences of metoprolol and verapamil treatment on measures of HRV did not relate to prognosis. Thus, the prognostic information obtained by HRV measurements at one month of study drug treatment was similar to that obtained from recordings made at baseline, before study drug treatment had started. The statistical power to show prognostic benefit of treatment effects on HRV was, however, limited with relatively few index events.

Future clinical implications

While HRV measurements in the frequency domain can provide results from short registration periods, all geometric methods have the disadvantage that a substantial number of RR intervals are needed to construct a sample density histogram. We required registrations of at least 17 h in the present studies (corresponding to

approximately 60000 RR intervals) but noted that a further 25% reduction of the number of RR intervals had little effects on the DI. Thus, it is likely that shorter periods of registration can be used after appropriate adjustment of the levels of number of RR intervals used in the histogram for the calculation of the DI. This warrants further study.

Our results show that HRV is a valuable method for the evaluation of autonomic cardiac control, and the DI is a simple time domain method that shows good agreement with established measurements. The use of HRV measures may have several potentially important clinical applications. It would be of interest to examine if HRV could identify individuals at high risk for future complications already at a very early stage of disease progression. This would require properly designed long term prospective studies in e.g. subjects with impaired glucose tolerance or diabetic patients, subjects with congestive heart failure, or high risk hypertensive patients.

Furthermore, it would be interesting to study if intensified treatment according to risk stratification by use of HRV could improve prognosis in patients at high cardiovascular risk. Generally, patients with stable angina pectoris have a fair long term prognosis, and conservative treatment and a strategy based on coronary artery intervention yield similar results[78, 79]. In patients with an acute MI, early reperfusion with thrombolytic therapy [101] and percutanous coronary intervention[102] have shown an improved parasympathetic/sympathetic balance with a subsequent increase in HRV. Whether it is possible to use HRV to identify which patients with stable angina pectoris that would best improve long term prognosis by conservative treatment or coronary intervention therapy deserves further study.

GENERAL CONCLUSIONS

1. The differential index is a simple and robust geometric method for the evaluation of heart rate variability (HRV). It mainly reflects cardiac parasympathetic control, and agrees well with conventional indices of HRV in the frequency and time domains. The differential index and most conventional indices in the frequency and time domains appeared to be stable over 3 years.

2. HRV was inversely related to heart rate, and there was a small significant decrease in HRV with increasing age and time. Women displayed a greater HRV in the measurements reflecting cardiac parasympathetic activity.

3. An acute myocardial infarction was associated with signs of increased cardiac sympathetic nerve activity, while changes in parasympathetic activity appeared to be small.

4. A low HRV in both the frequency and time domains predicted cardiovascular mortality, independently of conventional risk factors, whereas no such relationship was present for non-fatal myocardial infarction. Thus, the cardiac autonomic imbalance may be of importance for fatal arrhythmic cardiovascular events, but is not closely related to the slow development of atherosclerotic disease and plaque vulnerability.

5. Diabetes mellitus is associated with a lower HRV, as assessed in both the frequency, and time domains, and by the differential index, and confers a worsened prognosis in patients with stable angina pectoris.

6. Compared to traditional time domain indices of HRV, the differential index appeared to predict cardiovascular death somewhat better. A differential index of approximately 320 ms showed the best sensitivity and specificity regarding the risk of suffering a cardiovascular death. The results indicate that reduced cardiac parasympathetic activity is an important factor which is associated with a poor prognosis in stable angina pectoris.

7. Treatment with the beta-adrenoceptor blocker metoprolol or the calcium antagonist verapamil affected HRV differently, but did not appear to carry any prognostic information concerning cardiac events.

8. In conclusion, HRV can be used to evaluate cardiac autonomic control. The differential index is a simple and robust time domain method that shows good agreement with established measurements of HRV. The differential index and other indices of HRV that reflect parasympathetic cardiac control may predict the risk for a fatal cardiovascular event in patients with stable angina pectoris Due to its insensitivity to artefacts and abnormal beats in the ECG recordings, the differential index may be particularly suited for routine use when large numbers of registrations need to be evaluated.

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