Mirja Peltola

ANALYSIS OF HEART RATE VARIABILITY FROM 24-HOUR AMBULATORY ELECTROCARDIOGRAPHIC RECORDINGS

SIGNIFICANCE OF PREPROCESSING OF R-R INTERVAL TIME SERIES
MIRJA PELTOLA

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Significance of preprocessing of R-R interval time series

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Abstract

Heart rate variability (HRV) is used in the assessment of cardiovascular health. However, often contradictory results have impeded the efficient use of HRV in clinical practice. HRV signals can contain artifacts leading to errors in the interpretation of HRV results. Various methods have been used for artifact editing, but there is relatively little information on how the actual editing can influence the HRV measures. The main aim of this thesis was to improve the reliability of HRV analysis by concentrating on the HRV signal preprocessing methods.

The effects of three editing methods on the HRV of short (512 R-R) and long-term (24-hour) R-R interval data were studied with non-edited and edited data from healthy subjects (n=10) and patients with acute myocardial infarction (AMI) (n=10). The effects of ectopic beats on short (α1) and long-term (α2) fractal scaling exponents were studied by inserting artificial ectopic beats into the HRV signals of 20 healthy subjects and 20 AMI patients. The prognostic significance of edited and non-edited α1 and α2 was studied in random elderly (n=84) and post-AMI (n=84) populations. A new method to quantify respiratory sinus arrhythmia (RSA) was developed based on the HRV signals of 13 healthy subjects. A new measure, the RSA index, was defined to evaluate the risk to sudden cardiac death (SCD) in 1631 AMI patients. Lastly, a new algorithm was developed in order to edit heart rate (HR) turbulence occurring immediately after a ventricular premature beat (VPB). The effects of HR turbulence editing on the HRV analysis were studied in 267 AMI patients.

Editing had distinct effects on the HRV analysis depending on the editing method and data type. Deletion editing was found to be unsuitable for the HRV spectrum analysis. There was no universal editing method for the time and frequency domain HRV analyses. Unedited ectopic beats increased the randomness of short-term R-R interval dynamics, especially in AMI patients. However, unedited α1 differed significantly between survivors and those who died during the follow-up. Ectopic beats do not necessarily need to be edited if fractal analysis is used in the risk evaluation. A depressed RSA index was found to be a strong predictor of SCD but a weak predictor of non-SCD in AMI patients. Editing of HR turbulence affected differently the various HRV measures. ULF and VLF components were most clearly influenced by HR turbulence removal. The amount of VBP/hour had an important impact on the results. When the VBP/hour were >50, ULF and VLF were >30% lower after turbulence removal.

The results of this thesis highlight the importance of editing the erroneous or irrelevant R-R interval oscillation in an HRV analysis. The careful choice of preprocessing method is essential if one wishes to obtain reliable HRV analyses for clinical purposes.

Keywords: ectopic, editing, heart rate turbulence, heart rate variability, respiratory sinus arrhythmia
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Abbreviations

$\alpha_1$  short-term scaling exponent of fractal-like correlation properties
$\alpha_2$  intermediate-term scaling exponent of fractal-like correlation properties
$\beta$  negative scaling exponent, slope of the power-law relationship
AMI  acute myocardial infarction
ANS  autonomic nervous system
ApEn  approximate entropy
AR  autoregressive modeling
AF  atrial fibrillation
AUC  area under the curve
AV  atrioventricular
BP  blood pressure
CABG  coronary artery bypass surgery
CHF  chronic heart failure
DFA  detrended fluctuation analysis
DFT  discrete Fourier transform
EF  ejection fraction
ECG  electrocardiogra/m, -phic, -phy
FA  atrial fibrillation
FFT  Fast Fourier transform
HF  high frequency
HR  heart rate
HRV  heart rate variability
HRVI  heart rate variability triangular index
LF  low frequency
MI  myocardial infarction
pNN50  percentage of the differences between adjacent normal R-R interval greater than 50 ms
PB  premature beat
PSD  power spectrum density
PVC  premature ventricular contraction
ROC  receiver operating characteristic curve
R-R  R-peak-to-R-peak interval
RSA  respiratory sinus arrhythmia
RSA index  quantity of respiratory sinus arrhythmia
<table>
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<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>RMSSD</td>
<td>square root of the mean of the squared differences between successive R-R intervals</td>
</tr>
<tr>
<td>SCD</td>
<td>sudden cardiac death</td>
</tr>
<tr>
<td>SDANN</td>
<td>standard deviation of the average R-R intervals of analyzed segments</td>
</tr>
<tr>
<td>SDNN</td>
<td>standard deviation of all normal-to-normal R-R intervals</td>
</tr>
<tr>
<td>SLOPE</td>
<td>slope of the regression line of the logarithmic power spectrum</td>
</tr>
<tr>
<td>TINN</td>
<td>triangular interpolation of normal-to-normal interval histogram</td>
</tr>
<tr>
<td>TO</td>
<td>turbulence onset</td>
</tr>
<tr>
<td>TS</td>
<td>turbulence slope</td>
</tr>
<tr>
<td>ULF</td>
<td>ultra low frequency</td>
</tr>
<tr>
<td>VF</td>
<td>ventricular fibrillation</td>
</tr>
<tr>
<td>VLF</td>
<td>very low frequency</td>
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<tr>
<td>VPB, VPC</td>
<td>ventricular premature beat/contraction</td>
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List of original publications

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


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Original publications
1 Introduction

Over the last 30 years there has been a growing interest in studying the oscillations of the heart rate (HR) calculated from the electrocardiogram (ECG). These oscillations are termed as heart rate variability (HRV). HRV is a physiological phenomenon driven mainly by the balance of the two branches of the autonomic nervous system, sympathetic and parasympathetic. Measurement of the HRV from short and long-term ECG recordings is a non-invasive method, which can be used in the assessment of cardiovascular autonomic regulation since it may provide information about cardiovascular health (Malik & Camm 1995). One important clinical application is to measure HRV from patients suffering acute myocardial infarction (AMI); in this condition a diminished HRV is linked with an increased risk of death (Kleiger et al. 1987). However, the widespread acceptance of the HRV assessment in clinical practice has not been achieved due to the often contradictory results of the HRV analyses in different study settings.

The HRV signal is usually obtained from an ECG recording by recognizing the QRS-complexes and R–peaks. Consecutive R–peaks constitute an R-R interval time series i.e. the HRV signal, which is often called the R-R interval tachogram. HRV can be analysed with conventional methods in time and frequency domains but also with nonlinear methods, which aim to evaluate the intrinsic complexity of the R-R interval time series. However, the majority of the ECG recordings are imperfect including both technical and biological artefacts and their inclusion can bias the HRV analysis. For instance, technical artefacts may result from poorly fastened electrodes or be due to motion artefacts. Premature beats and atrial fibrillation are examples of biological artefacts. In conjunction with the increased usage of HRV analyses, various editing and signal processing methods have been introduced for the artefact correction. Nonetheless, when analysing the HRV, it is important to pay attention to the way one is handling and editing the artifacts appearing in the R-R interval tachogram. The editing method itself should not have any detrimental effect on the HRV analysis. Further information is needed on the effects of the artefacts and editing methods on the different HRV analysis.

This study is a methodological approach to deal with the artefacts such as ectopic beats in the HRV signals. The main aim of this thesis was to improve the quality of the HRV analyses by concentrating on the editing methods of the R-R interval time series. In addition, the secondary aim was to develop new preprocessing methods for the HRV signals in order to gain new insights which
could be applied in the risk evaluation of AMI patients. This aim concerns two approaches how to emphasize relevant R-R intervals in particular HRV analyses: 1) how to quantify the respiratory sinus arrhythmia and 2) how to diminish the effects of the HR turbulence on the other time and frequency domain HRV analyses and fractal scaling analysis.
2 Review of the literature

2.1 History of heart rate variability

Periodic cardiovascular signals, such as the HR and blood pressure (BP), and the fluctuations occurring in these signals have interested physicians for generations. The earliest documented finding of cardiovascular signal variation was observed in 1733 by Stephen Hales in arterial BP, long before the invention of the electrocardiographic or other modern measuring instruments for analyzing HRV signals. Hales observed rhythmic changes in the blood level in a test tube that was connected to the carotid artery of a horse (Hales 1733). A few decades later, in 1778, Albrecht von Haller recognized that the beat of a healthy heart was not absolutely regular (von Haller 1778) and that these HR fluctuations were in synchrony with respiration. The oscillations at the pulse rate along with inspiration and exhalation in the dog were observed by Carl Ludwig in 1847 (Ludwig 1847). This alteration of the HR during the respiratory cycle is known as respiratory sinus arrhythmia (RSA). The phenomenon where rhythmical variations in BP could be related to variations in the vasomotor tone, was discovered by Ludvig Traube in 1865 and confirmed by Karl Hering in 1869 (Traube 1865, Hering 1869).

However, HRV research was somewhat neglected over the next decades since it was based mostly on simple HR measurements. In practical cardiology, for long the changes in HR were generally concerned as irregular, even pathological events. It was not until the latter century, that HRV was subjected to more intensive study. In 1965, the clinical relevance of the HRV was noted by Hon and Lee who reported that the diminution in beat-to-beat variability in fetus was correlated with fetal viability (Hon & Lee 1965). In the 1970s, Ewing and colleagues performed various simple bedside tests investigating the short-term R-R interval differences in order to detect autonomic neuropathy in diabetic patients (Ewing et al. 1984).

The development in technology and computers has invigorated the research in the field cardiovascular signals. The possibility to record electrocardiographic signals has formed the foundation the HRV research. Various different ways to analyze the variation of the HR have been developed during past few decades. During the 1980s, a power spectral analysis of the HRV was introduced (Akselrod et al. 1981, Kay & Marple 1981). In the late 1980s, the clinical relevance of HRV
became obvious i.e. it was confirmed that a decline in HRV increased the risk for arrhythmic events and mortality in patients with myocardial infarction (MI) (Kleiger et al. 1987, Farrell et al. 1991, Bigger et al. 1992). Subsequently, algorithms based on the chaos theory and nonlinear dynamics of the HR have been developed in order to evaluate in greater detail the intrinsic complexity of the HRV compared with the conventional time and frequency domain methods.

2.2 Physiological background of the HRV

Normal heart rhythm is defined by the rate of the sinus node depolarization. Sinus rhythm oscillates around the mean HR, which is subjected to continuous regulation by the autonomic nervous system (ANS). The main components of the ANS include vagal (parasympathetic) and sympathetic centers. For the heart, the vagus nerve innervates the sinoatrial node (SA node, sinus node), the atrioventricular (AV) pathways and the atrial muscle. Sympathetic nerve fibers innervate the entire heart, including the SA node, AV conducting pathways and the arterial and ventricular myocardium (Kamath & Fallen 1993). Therefore, HR represents the balance of various influences from the sympathetic and parasympathetic (vagus) nerves. The sinus node is frequently innervated by both autonomic divisions, and it is the interaction between the sympathetic center and vagal center which determines the final pace of the HR. Increased parasympathetic activity has a decelerating effect on the HR, this being mediated via synaptic release of acetylcholine, which has a short latency period and a high turnover rate. This rapid response enables parasympathetic activation to be regulated on a beat-to-beat basis. Correspondingly, sympathetic activity results in an increase in the HR, which is attributable to the release of norepinephrine. Sympathetic activation affects the cardiovascular function, but this has a slower time course due to relatively slow re-uptake and metabolism of norepinephrine. The dynamic balance between parasympathetic and sympathetic activity causes a continuous oscillation of the HR which is called HRV (Levy & Martin 1979). Under resting conditions, the parasympathetic tone is dominant and the fluctuations of the HR are mainly controlled by the parasympathetic modulation (Levy 1971, Chess et al. 1975). HRV can be used as a perspective into the cardiorespiratory control system and as a tool for examining the sympathetic and parasympathetic function of the ANS. In addition, HRV can be considered as a reflection of various physiological factors modulating the normal rhythm of the
heart. A short view of some factors affecting the HR and HRV will be provided in the next sections.

2.2.1 Respiratory influences on HRV

Respiration is one of the main sources that influence the HR oscillations. Cyclical changes in the HR appear in association with respiration in normal subjects (Pagani et al. 1986). As mentioned earlier, this HR oscillation in synchrony with the respiration is called respiratory sinus arrhythmia (RSA). Typically, HR accelerates during an inspiration and slows down during expiration, but the current respiration rate contributes to the phase relationship between the respiratory and HR fluctuation (Eckberg 1983). The respiratory related R-R interval oscillation is considered to typically occur in the frequency band from about 0.15 Hz to 0.4 Hz.

The influence of the respiration on the HR is complex involving central and reflex interactions (Anrep et al. 1936). In general, it is assumed that RSA is predominantly mediated through the changes in the cardiac vagal nerve traffic. On this account, the magnitude of the respiratory related HR fluctuation has been suggested as providing an index which in some way describes the vagal activity (Eckberg 1983, Fouad et al. 1984). RSA can be abolished by atropine or vagotomy and thus one can exclude the influence of the parasympathetic regulation (Akselrod et al. 1985). HR decreases if the vagus nerve is active and decreases the firing of the SA node. The vagal activity is increased during the expiration by the stimulation of the arterial chemoreceptors and baroreceptors (Katona et al. 1970, Davidson et al. 1976). During inspiration, the vagal regulation is almost abolished and the HR fluctuations coincide with the breathing frequency (Davidson et al. 1976, Eckberg 1983).

Furthermore, peripheral hemodynamic reflexes and thoracic stretch receptors have an influence on the RSA (Hirch & Bishop 1981, Akselrod et al. 1985). HR fluctuation increases when the respiration rate attains the frequency of the intrinsic HR fluctuations connected to the baroreflex. Therefore, maximal RSA in adults occurs at a breathing frequency of 0.1 Hz, which corresponds to a breathing rate of 6 per minute (Hirch & Bishop 1981, Mehlsen et al. 1987).

Although the RSA has been used as an index of cardiac vagal tone, the central, neural, humoral and mechanical feedback mechanisms affecting the RSA are a complex interplay of integrated respiratory and cardiovascular responses (Jordan & Spyer 1987, Spyer 1990, Grossman & Kollai 1993). RSA is also a physiologic
phenomenon that reflects the respiratory-circulatory interaction, thus it may not be a perfect index of the vagal tone *per se* (Grossman *et al*. 2004).

### 2.2.2 Reflexes affecting the HRV

The baroreflex is one of the mechanisms participating the maintenance of the BP. The baroreflex involves BP monitoring with stretch-sensitive mechanoreceptors called baroreceptors. Baroreceptors are situated in the heart, aortic arch, carotid sinus and in other large vessels (Karemaker 1987). The baroreflex operates as a negative feedback loop, *i.e.* an increase in the BP produces a reflexive BP decrease. Similarly, decreased BP evokes a rise in the BP by depressing the baroreflex. The baroreflex has been proposed as being a vagally mediated control system between the HR and BP. Stimulation of the baroreceptors increases the efferent vagal activity, causing a deceleration in the HR. Similarly a decline in the arterial BP decreases the vagal activity resulting in an acceleration of the HR. This relation of the HR deceleration and rise in the BP is called baroreflex sensitivity (Rea & Eckberg 1987). The response function of this relation displays the classical sigmoid shape. The baroreflex loop causes mainly a low frequency oscillation in the R-R intervals. The influence of the baroreflex has also been postulated as being the origin for the Mayer waves that correspond to the oscillation of the arterial pressure in conscious subjects at a frequency lower than respiration (~0.1Hz in humans) (Cooke *et al*. 1999, Furlan *et al*. 2000).

The atrial reflex, called the Bainbridge reflex, causes acceleration in the HR. The HR accelerates due to an increase in the atrial volume, which is detected by the stretch receptors situated in both atria, at the venoatrial junctions. The Bainbridge reflex is involved in the RSA, thus during inhalation, the intrathoracic pressure become decreased, triggering the venous return and causing an activation of the sympathetic nervous system (Ledsome & Linden 1964, Carswell *et al*. 1970).

Chemoreceptors detect the carbon dioxide levels in the blood by monitoring the concentration of hydrogen ions. Chemoreceptors are situated in the medulla oblongata, carotid arteries and aortic arch. Chemoreceptor activity increases during arterial hypoxia, hypercapnia or acidemia (Sampson *et al*. 1972). HR becomes accelerated in response to a high concentration of carbon dioxide due to an increment of nervous impulses passing through the sympathetic ganglia. The coronary chemoreflex, known as Bezold-Jarisch reflex, is a decompressor reflex involving a variety of cardiovascular and neurological processes and causing
bradycardia, hypopnea and vasodilatation (Hainsworth 1991, Bell et al. 1993). Bradycardia and systemic vasodilatation are responses that occur after the activation of the unmyelinated vagal afferents (Dawes 1947, Bell et al. 1993).

In addition to cardiovascular reflexes and chemoreceptors, the renin-angiotensin system, the control of blood volume and thermoregulation system (Sayers 1973) may have an input into cardiovascular regulation.

2.2.3 Other factors affecting HRV

HRV has been reported being dependent also on age and gender (Agelink et al. 2001). Aging itself reduces the HRV and age-related changes seem to be modified by gender (Huikuri et al. 1996, Stein et al. 1997, Fukusaki et al. 2000). Several studies have reported a negative correlation of age with HRV, i.e. HRV declines with increasing age (Shannon et al. 1987, Korkushko et al. 1991, Liao et al. 1995, Acharya et al. 2004, Antelmi et al. 2004). However, the change in the HRV along with age is dependent on the age range being studied as well as the analysis methods and conditions used in the quantification of HRV. During childhood, there is an increased variation of the HR (Korkushko et al. 1991), while the reduction of an overall HRV measured in the time and frequency domain is diminished with increasing age during adult life (Hayano et al. 1991, Korkushko et al. 1991, Bigger et al. 1995). Higher levels of HRV often appear in women compared to men although this difference tends to even out during and after the fifth decade of life (Shannon et al. 1987, Antelmi et al. 2004).

HRV can be significantly affected by many different types of drugs. It may even be possible to observe the effects of the specific drugs in the HRV analyses and hence, the influence of medication needs to be taken into account in any analyses. One of the first drugs to have been examined in relation to HRV was atropine. This was observed to abolish RSA after high dose (Akselrod et al. 1985). The effects of beta-blockers and calcium channel blockers have been examined in postinfarction and hypertensive patients (Guzzetti et al. 1988, Bekheit et al. 1990, Cysarz et al. 2000). By utilizing the HRV spectral analysis, it is possible to observe the sympathetic and parasympathetic activities of these drugs and their effects on cardiac diseases. Studies on the effects of drugs on the HRV have been performed also with antiarrhythmic agents, anesthetics, narcotics, sedatives and chemotherapeutic agents (Task Force of ESC & NASPE 1996).

Smoking has been shown to increase the sympathetic tone and reduce the parasympathetic activity and also to reduce the HRV. Smoking has effects on
ANS control and it impairs the cardiovascular function (Hayano et al. 1990, Niedermaier et al. 1993, Luchini et al. 1996). Alcohol is another chemical substance that has an effect to reduce the HRV. Compared with the situation in normal volunteers, lower indices of the cardiac vagal nerve activity have been reported for the acute alcoholic subjects (Malpas et al. 1991).

Exercise training is also considered to be a factor that can modify the autonomic balance and correlates with the HRV (De Meersman 1993, Tulppo et al. 1998, Hautala et al. 2009). Endurance-trained subjects have been demonstrated to display an increased sympathetic activity and a higher HRV compared with the sedentary subjects (Goldsmith et al. 1992, De Meersman 1993). Regular physical training has been observed reducing the resting HR and to increase the HRV in elderly subjects (Stein et al. 1999). Among trained subjects, an increased HRV has been linked with the improved maximal oxygen consumption (Loimaala et al. 2000). During exercise, a decrease in the HRV has been reported: this being proposed to be due to the withdrawal of vagal input to the heart (Yamamoto et al. 1991, Tulppo et al. 1996).

2.3 Changes of HRV in pathological conditions

Several cardiac and non-cardiac diseases have been documented as having a reductive effect on the HRV (Kleiger et al. 1987, Malliani et al. 1991, Kamath & Fallen et al. 1993). HRV analysis has been used to assess autonomic function in various types of cardiac and non-cardiac diseases. These diseases include myocardial infarction (MI), congestive heart failure (CHF), coronary artery disease (CAD), essential hypertension, diabetes mellitus, end-stage renal disease and multiple sclerosis (Ewing et al. 1980, Kleiger et al. 1987, Välimäki et al. 1988, Casolo et al. 1989, Malik et al. 1989, Niklasson et al. 1989, Bigger et al. 1992). Cardiac diseases such as CAD and CHF are associated with a reduced vagal tone and on the other hand with elevated sympathetic activity, thus having an effect on the HRV (Airaksinen et al. 1987, Saul et al. 1988, Malliani et al. 1991).

2.3.1 HRV after acute myocardial infarction

The connection between decreased HRV and mortality in patients suffering acute MI was first reported in 1978 by Wolf et al. Since then, numerous studies have been performed and they have confirmed the reduction of the HRV with time or
frequency domain analysis in MI patients, measured in a short time span after MI.
In particular, the frequency domain HRV analysis has been widely
investigated in post-MI patients. In frequency domain measures, a reduction in
total power, the power of the ultra low frequency (ULF) and high frequency (HF)
components have been reported in many studies. However, an increase in the low
frequency (LF) power has been observed in post-MI patients and this is believed
to be a reflection of a sympathovagal imbalance (Lombardi et al. 1987). In MI
patients, a diminished HRV may be related to the decreased vagal neural activity,
which is attributable to the prevalence of sympathetic neural regulation and to
cardiac electrical instability (Task Force of ESC & NASPE 1996). Sympathetic
activity decreases the threshold to fibrillation and increases the risk of ventricular
fibrillation. On the contrary, cardiac vagal activity increases the threshold for
fibrillation and seems to be protective against malignant ventricular
tachyarrhythmias (Schwartz et al. 1992).
The reduction of the HRV after MI has been assumed to be a reversible
feature. Observations have been made of a restoration in HRV after MI (Bigger
et al. 1991). However, after MI, the overall HRV has been shown to remain at a
lower level compared with healthy controls (Bigger et al. 1991). An incomplete
restoration of the HRV after a MI may be associated with a dismal prognosis.

2.3.2 HRV in other diseases
In addition to MI, observations have been made about various other cardiac and
non-cardiac diseases, which can influence the HRV. For instance, HRV is reduced
in patients with a stable CAD. A clinical depression has been found to be a risk
factor for cardiac morbidity and mortality in patients suffering CAD (Barth et al.
2004). In terms of the decreased HRV, lower values of the HRV analysis have
been associated with severe depression in patients with stable coronary heart
disease in various studies (Stein et al. 2000). A low HRV in CAD patients is also
associated with a rapid progression of the CAD (Huikuri et al. 1999). In patients
with uncomplicated CAD, also the circadian rhythm of the cardiac neural
regulation has been documented as being altered (Huikuri et al. 1994).
Patients with CHF have been characterized with an autonomic dysfunction
consisting of sympathetic over-activity and parasympathetic withdrawal (Floras
Sympathetic over-activity includes certain features such as increased resting HR and high levels of plasma norepinephrine. The diminished values of the HRV have been observed in various studies conducted in CHF patients (Nolan et al. 1998, Fauchier et al. 1999, Galinier et al. 2000, Bilchick et al. 2002). Diabetic autonomic neuropathy can produce severe autonomic dysfunction and is one cause of morbidity and mortality among diabetic patients. Neuropathy associated with diabetes mellitus is characterized by widespread neurological degeneration affecting the small nerve fibers of the parasympathetic and sympathetic branches of the ANS. Decreased beat-to-beat variability in diabetic patients during sleep was first documented in 1973 (Wheeler & Watkins, 1973) and later, the decreased HRV has been confirmed in many other studies (Kitney et al. 1982, Pfeifer et al. 1982, Ewing et al. 1984, Pagani et al. 1988, Freeman et al. 1991, Schroeder et al. 2005). Cohorts which have examined the large patient populations have demonstrated the presence of associations between a low HRV and the prevalence of diabetes (Gerritsen et al. 2000, Singh et al. 2000).

Over the last decades, different changes in the HRV have been found in different patient populations. In addition to above mentioned cardiac and non-cardiac conditions, reduced HRV analyzed by low frequency power (LF) and reduced circadian HRV patterns have been demonstrated in patients with hypertension (Guzzetti et al. 1991). In addition, in patients with a denervated transplanted heart, there has been evidence of a reduction in HRV (Sands et al. 1989).

2.3.3 Examples of diagnostic use of HRV

As mentioned, the analysis of the HRV can provide insights into autonomic nervous function. HRV has been considered as a tool for quantifying the risk of different arrhythmic events or even death occurring in various cardiac and non-cardiac disorders. HRV measurements are noninvasive and easy to perform and they have relatively good reproducibility. HRV provides information about the sympathetic-parasympathetic autonomic balance and in that way it may reveal information about the risk for sudden cardiac death (SCD) especially in post MI patients.

Analysis of the HRV has had its most valuable cardiologic use in risk stratification and in the evaluation of risk for arrhythmic events in post-MI patients. The prognostic significance of the HRV in post-MI patients and the
relationship between the increased risk of mortality and decreased HRV was first published by Wolf et al. (1978). Since then, various studies have been described how an abnormal HRV can be associated with the increased risk of mortality after an AMI (Kleiger et al. 1987, Bigger et al. 1992, Huikuri et al. 2000, Camm et al. 2004, Mäkikallio et al. 2005, Stein et al. 2005). Although, HRV analysis has been verified as a predictor of mortality, the predictive values of most of the HRV parameters are still not powerful enough to be used as a stand-alone routine screening test (Task Force of ESC & NASPE 1996). However, by combining the HRV parameters with other traditional clinical risk factors, such as the left ventricular ejection fraction (LVEF) and the occurrence of ventricular premature contractions (VPC), one can improve the clinical utility of the decreased HRV in the risk evaluation in patients with AMI (Voss et al. 1998). The greatest benefit of the HRV analysis in the AMI patients has been postulated as being in the identification of those patients with a high risk of SCD and those who might benefit from an implantable cardioverter defibrillator (ICD) (Kleiger et al. 2005).

Clinical application of the HRV analysis has been utilized also in the detection of the autonomic neuropathy in the association of diabetes mellitus. A decreased HRV has been found to identify those diabetic patients with autonomic neuropathy and who require effective treatment (Malpas & Maling 1990). Low HRV has been considered as a risk factor for SCD in type 2 diabetic patients (Kataoka et al. 2004).

The first report on the HRV in heart failure patients was published in 1988 by Saul et al. (1988), and subsequently several studies have been performed to examine the possible correlation between the HRV and cardiac function of heart failure patients (Yoshikawa et al. 1999, Aronson & Burger 2000, Malik et al. 2000). Numerous studies have shown the prognostic power of HRV measures to predict mortality in MI patients, which encouraged the proposal that HRV parameters could be used as a predictor of mortality in the wider population with heart failure (Nolan et al. 1998, La Rovere et al. 2003, Aronson et al. 2004).

2.4 Measurement of the HRV

Analysis of the HRV from the start to its final interpretation requires different measurement devices and software in addition to computational know-how. Devices such as ECG recorder including electrodes are needed for recording the ECG signal. Specific software is needed for obtaining the HRV signal from the ECG recording and preprocessing and analysis of the HRV signal. For example,
preprocessing of the HRV signal can include editing of artifacts of the HRV signal. Analysis of the HRV signal can involve computation of different HRV parameters in time and frequency domains and with nonlinear techniques. A short description of the different phases and methods in the HRV measurement is provided in the following paragraphs.

2.4.1 Assessing of the HRV signal

If one wishes to obtain a HRV signal, then first the ECG data must be collected and analyzed over the required period of time. ECG recording is traditionally done with a portable Holter monitor. The Holter monitor is an ambulatory electrocardiography device that is capable of monitoring electrical activity and recording the heart rhythm continuously in out-patients over periods of 24-hours or more. ECG data can be collected also from patients being monitored in laboratory conditions in hospitals. The Holter monitor is connected to a patient via a series of wired non-invasive electrodes on the chest. Electrical signals originating from the heart are recorded via electrodes, whose number varies usually from three to eight depending on the model of the Holter monitor. The monitor is worn by the patient during his/her normal daily activities for the recording period. In the older models of the Holter devices, the ECG was recorded onto a reel-to-reel tape or a standard audio 60 or 90-minute cassette tapes. In modern Holter devices, a digital flash memory is used to store the ECG data. The sampling frequency of the ECG recording systems varies in the range of 100Hz to 1000 Hz or more. It is recommended that the ECG sampling frequency in general should not be lower than 250 Hz in order to ensure the accuracy of the R-R interval determination (Task force of ECS & NASPE 1996). After recording the ECG data, it is uploaded to the computer for further processing and analysis.

The HR time series (tachogram, HRV signal) is defined as the reciprocal of the duration between successive heart beats. The healthy human has an average value of the inter-beat interval of about 1000 ms, and the standard deviation of 60 ms (Task force of ECS & NASPE 1996). However, taking account of the individual alteration in these values may reveal values with a wide range. The HR time series is commonly obtained by estimating the event series of the ECG. ECG recording is recommended as being performed with appropriate data acquisition equipment with a satisfactory signal/noise ratio, bandwidth and common mode rejection (Task force of ECS & NASPE 1996). QRS complexes are identified from the ECG recording and usually the peak of the R-wave is used as a fiducial
point, because it normally has a distinguishable amplitude. R-peak detection requires a robust algorithm, i.e. the more accurate the R-peak detection, the less there will be error in the HRV signal and analysis.

Next, the differences in time of each of two consecutive R waves are computed. The occurrence of times of two consecutive R waves are defined as \( r(t) \) and \( r(t + 1) \), where \( t = 1, \ldots, N \). Durations of the consecutive R-R intervals are defined as \( R(t) = r(t + 1) - r(t) \), where the consecutive R-R interval durations form the \( R(t) \), called the discrete R-R interval time series. The R-R interval time series is also known as the HRV signal, or the R-R interval tachogram. R-R interval time series is not sampled at uniform intervals due to differences between the duration of adjacent heart beats. For example, uniform sampling can be performed by using different interpolation methods in order to achieve equally spaced R-R intervals. Finally, the R-R interval time series is displayed versus the beat index and it contains the information of the duration of each consecutive heart beat expressed in milliseconds. Figure 1 illustrates the generation of the R-R interval time series from the ECG signal.

In order to obtain a reasonable quality of the HRV identification, the recommended sampling rate should be at least in the range of 250–500 Hz, which corresponds to resolution of \( \leq 4 \) ms (Task force of ESC & NASPE 1996). Lower sampling frequency may cause dispersion in the R peak estimation.
Fig. 1. (a) ECG with an event series of R peaks. (b) Interpolated interval function. (c) Uniformly sampled R-R interval time series.

2.4.2 Artifacts in the HRV signal

In the ideal situation, the HRV analysis is performed with the R-R interval time series including only pure sinus beats. However, R-R interval time series obtained from ambulatory ECG recordings are in most cases imperfect, since they contain a different number of abnormal R-R intervals. Abnormal R-R intervals differ from sinus rhythm in length. These artifacts represent disturbances of both technical and physiological origins and are present almost in all Holter ECG recordings. Physiological artifacts occur especially in patients suffering from different cardiovascular diseases. If steady state conditions are maintained in a laboratory study during the recording of prescribed duration, then it may be possible to achieve an ECG recording without artifacts at least in healthy subjects not suffering cardiovascular diseases. However, in infants or uncooperative patients
or during ECG recordings lasting for several hours, it is virtually impossible to obtain steady state conditions throughout the entire recording duration. Therefore, since ectopic beats and other artifacts may occur in both normal subjects and heart disease patients, artifacts represent a significant problem in the measurement of the HRV. HRV is extremely difficult to analyze reliably in subjects who are not in sinus rhythm (Task Force of ESC & NASPE 1996).

Physiological artifacts appear in the R-R interval time series when an abnormal electrical activity in the heart produces abnormal heart rhythms, arrhythmia. The normal rhythm of the heart beat originates from the sinoatrial (SA) node located in the right atrium of the heart. The SA node consists of specific tissue capable of generating impulses; it is called the primary pacemaker. The SA node is the source of repetitive electrical impulses which produce the waveforms of the ECG. From the SA node, electrical impulses spread to the additional latent pacemakers, atrioventricular node (AV node) and His-Purkinje tissue. These latent pacemakers may interpose additional electrical impulses, which appear in the ECG as ectopic or premature beats. Disturbances due to abnormal impulse formation or abnormal impulse conduction generate non-sinus beats that disrupt the normal sinus-originated R-R interval oscillation. Abnormal impulse formation produces disturbances in the normal rhythm such as ectopic beats of ventricular or AV junction origin, atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular tachycardia and ventricular fibrillation. These kinds of disturbances are observed in the ECG signal as divergent waves and QRS complexes. Disturbances in the impulse conduction can produce disturbances in ECG such as pauses due to AV block or SA block or due to various other kinds of blocks.

Almost everyone experiences ectopic beats at sometime during their life. Ectopic beats can even be common events in the ECG recording, especially patients with cardiovascular disease, but they appear also in healthy subjects. Nonetheless the prevalence of ectopic beats will produce a major source of error in the HRV measurement. Ectopic beats, especially of ventricular origin, are usually followed by a compensatory pause, before a return to the pre-ectopic baseline heart rhythm. In the R-R interval time series, the appearance of an ectopic beat with a compensatory pause is seen as an R-R interval of a short duration followed by a beat, which has a longer duration as compared with a normal sinus R-R interval. Figure 2 shows an example of an ectopic beat in the segment of the R-R interval time series of a MI patient.
A premature beat of ventricle origin is known as a ventricular premature beat (VPB), or premature ventricular contraction (PVC). Correspondingly, an ectopic beat of atrial origin is known as a premature atrial contraction (PAC). This kind of heart arrhythmia is called bigeminy, in which premature beats appear every other adjacent beat. Typical bigeminy contains VPBs with compensatory pauses. If every third beat is premature, the disrupted heart rhythm is called trigeminial and if every fourth is premature, it is called quadrigeminial. If every fifth or more beat is non-normal, it is referred to as an occasional aberrant beat.

Cardiac fibrillation refers to an irregular contraction of the heart muscle fibers at a rapid frequency and it can appear as either atrial or ventricular fibrillation. Atrial fibrillation (AF or FA) is an abnormal heart rhythm involving the fibrillation of the two upper chambers of the heart (atria) instead of their beating effectively. The risk of an AF event increases with age and it is considered as the most common heart arrhythmia. AF usually causes irregularity into the baseline of ECG, which results in irregular and random behavior of the HRV signal where the baseline of the signal cannot be verified. Ventricular fibrillation (VF) involves an irregular and rapid contraction of the ventricles and this is a medical emergency. VF is a life-threatening event and death may occur in a matter of minutes if VF continues for more than a few seconds. The waveform of the VF is irregular and
the ECG is bizarre with no clearly identifiable QRS complexes. Similar to AF, also the VF event causes random behavior in the HRV signal.

Tachycardias refer to a rapid beating of the heart at a frequency of over 100 beats per minute. However, tachycardia is not always considered as an arrhythmic event. Physical or emotional stress increases the HR mediated by the sympathetic nervous system and this is called sinus tachycardia. Tachycardia that does not involve the heart beats of the sinus origin results from the occurrence of abnormal heart beats.

In addition to physiological artifacts, there may also be errors attributable to the technical aspects of the ECG recording. Problems may appear in the software used to detect the R-R intervals in ECG. For example, the R-R interval detection algorithm may fail if the threshold for R-R interval identification is set too low or too high, resulting in faulty R-R intervals. Technical artifacts may result also from poorly fastened electrodes or they can result from motion or sweating of the patient during the ECG recording. Technical artifacts occur usually in larger epochs containing several consecutive abnormal R-R intervals in the HRV signal. Technical artifact epochs in R-R interval series often resemble random noise. Due to the appearance of the different type of artifacts in ECG recordings, it is highly recommended to inspect both the ECG and HRV data visually. Most of the Holter analysis software includes a performance of automatic ECG recognition with the detection of QRS complexes and classification of beats. Beat detection may also include the possibility of labeling or annotating individual beats (Malik & Camm 1995: 77). However, the visual scanning of different morphologies of the QRS complexes and labeling individual beats can be time consuming especially in the case of long-term ECG recordings. For this reason, the presence of an experienced Holter analysis specialist is very important in the process of obtaining reliable HR data for HRV analysis.

If the number of abnormal R-R intervals in the HRV signal is relatively small and the artifact occurrence is occasional, it is possible to reject or replace these abnormal R-R intervals and artifacts by using various different correcting and editing methods before the final analysis of HRV. However, if R-R interval time series contain abundance or recurrent artifacts, it is recommended that one should eliminate the segments with artifacts from further HRV analysis or even reject the entire recording if there is a large amount of erroneous data. (Malik & Camm 1995: 78).
2.5 Editing of the HRV signal

It has been recommended that one should use the R-R interval time series that are free of ectopic beats and other disturbances (Task force of ESC & NASPE 1996). However, in many cases the HRV signal of pure sinus beats includes only short periods of the ECG recording. These short periods of HRV signal may not be appropriate for such various HRV analyses that require long-term ambulatory recorded HRV signal. Arrhythmic events, ectopic beats and other artifacts are known to have serious impact on the results of the HRV analysis in the time and frequency domain. Ectopic beats and other artifacts introduce erroneous beat-to-beat variability into the R-R interval time series. The growing interest in HRV measurement in the assessment of autonomic regulation of the HR has generated the need for the efficient handling of the artifacts in the HRV signal. Different approaches to this problem have been devised. For instance, the exclusion of the R-R interval segments with duration of less than 80% of the duration of normal beats has been recommended (Rottman et al. 1990). In addition, the removal of the R-R interval segments with more than five events of non-normal beats has been proposed (Lombardi et al. 1996a).

Automatic, commercial, artifact correction systems have been introduced with different levels of accuracy, leading to differences in frequency and time domain HRV analyses (Jung et al. 1996). For example, there are automatic filtering systems of the R-R interval time series intended to exclude the non-normal R-R intervals that differ by more than 20% from the previous normal intervals. These kinds of automatic filtering systems should not replace the manual editing due unsatisfactory quality (Task force of ECS & NASPE 1996). Manual editing with visual verification by a specialist is still the most reliable method of editing, especially when the inspection of the ECG signal is available in the cases of uncertain R-R intervals.

Various algorithms for editing or correcting the abnormal R-R intervals have been developed and tested to see if they can achieve more reliable results of the HRV measurement (Cheung 1981, Malik et al. 1989, Berntson et al. 1990, Cripps et al. 1991, Sapoznikov et al. 1992, Lippmann et al. 1994). A short presentation of some of the common methods of artifact editing and correction for the HRV analysis will be given in the next section.
2.5.1 Deletion of the R-R intervals

Probably the simplest way of editing the HRV signal is to delete the distorted R-R intervals. In the deletion process, the abnormal R-R intervals in the HRV signal are removed from the time series and the preceding normal R-R intervals originated from the sinus node are then shifted to replace the removed R-R intervals. Deletion editing decreases the length of the HRV signal with the number of the deleted R-R intervals. Thus, if the number of the R-R intervals were initially \( N \) and the \( K \) represents the number of the artifact beats, then the final number of the R-R intervals after the deletion would be \( N-K \). Decreasing the number of the R-R intervals is an important feature of the deletion editing, especially when assessing the power spectrum of the HRV signal or analyzing short-term R-R interval segments. If all the segments containing ectopic beats are deleted to rule out any possible interference with the HRV analysis, this can lead to an unacceptable and systematic loss of information.

However, deletion is a fast and simple editing method and perhaps on this account it is commonly used for the artifact editing in the HRV signals. Although, the deletion method may not be the optimal choice of editing especially with the respect to the power spectrum HRV analysis, it is the most common method for artifact removal in the case of the disturbances lasting for longer periods (Kamath & Fallen 1995). These include artifacts such as frequent ectopic beats and AF, the duration of which can last from several minutes to several hours (AF).

2.5.2 Interpolation of the R-R intervals

Interpolation editing methods replace the non-normal R-R intervals with new interpolated R-R intervals. Unlike the deletion method, interpolation methods preserve the initial number of R-R intervals. If the R-R interval time series contains occasional ectopic beats and artifacts, it is recommended to use interpolation methods, especially in the power spectrum HRV analysis (Kamath & Fallen 1995). There are various algorithms which can be used to perform interpolation including linear, spline and nonlinear predictive interpolation, to mention only a few. A short representation of four commonly used interpolation methods in the artifact correction will follow.

Presumably the easiest interpolation method is obtained by substituting the non-normal R-R intervals with an average value that is computed from the neighboring normal R-R intervals of sinus origin. This interpolation method is
also known as the interpolation of degree zero. If an erroneous beat occurs in the HRV signal at the instant \( x \), the interpolation of the degree zero is computed by:

\[
y(x) = \frac{1}{n} \cdot \sum_{k=1}^{n} x_k,
\]

(1)

where \( y(x) \) is the result from the interpolation and \( n \) is the window, the number of neighboring normal sinus R-R intervals. The window \( n \) is often set between 3 and 10. Large segments cannot reasonably be edited with the interpolation of degree zero, \( i.e. \) it has a tendency to produce flat shapes in the R-R time series. Flat shapes are produced since the interpolation of degree zero will be using the same average value over the whole segment of successive non-normal R-R intervals. However, occasional artifacts are easy and quick to edit with the technique of interpolation of degree zero.

Interpolation of degree one replaces the non-normal R-R intervals with the points obtained from a fitted straight line over the non-normal R-R intervals. If the non-normal R-R interval in the HRV signal occurs at instant \( x \), then the interpolation of degree one is computed by (Kreyszig 1988)

\[
y(x) = y_0 + (x - x_0) \frac{y_1 - y_0}{x_1 - x_0},
\]

(2)

where \( y(x) \) is the new value for the interpolated non-normal R-R interval.

Interpolation of degree one produces a straight line that passes through the points \((x_0, y_0)\) and \((x_1, y_1)\), and replaces the successive non-normal R-R intervals situated between the surrounding normal beats. Interpolation of degree one is also known as linear interpolation (Lippmann et al. 1994).

Interpolation of R-R intervals can also be performed with spline interpolation. Spline interpolation involves an interpolant called the spline, which is a special function defined piecewise by polynomials. The simplest form of the spline interpolation is the first degree spline, which is equivalent to the linear interpolation and is called linear spline interpolation. In the second degree of spline interpolation, a parabola is fitted over the data points being interpolated. In the cubic spline interpolation, a third degree polynomial is fitted to the data points. The basic idea of the cubic spline interpolation is to estimate smooth curves through a number of data points. Cubic spline interpolation uses the coefficients of the cubic polynomials, which are used for “bending” the line in order to generate a continuous curve passing through each of the data points without erratic behavior or breaks. In the process of the cubic interpolation, the aim is to fit a piecewise function of the following form (Press et al. 1992):
where $S(x)$ is a cubic polynomial that is defined by

$$S_i(x) = a_i(x - x_i)^3 + b_i(x - x_i)^2 + c_i(x - x_i) + d_i$$

If $S(x)$ represents the spline function the requirements of the continuous piecewise function are as follows (Press et al. 1992):

$$S_i(x_i) = y_i, \quad (4)$$
$$S_i(x_{i+1}) = y_{i+1}. \quad (5)$$

Since the aim of the cubic spline interpolation is to obtain as smooth a curve as possible, it is essential that the first and second derivatives are continuous on the data points $x_i$ (Press et al. 1992):

$$S'_i(x_i) = S'_i(x_{i+1}), \quad (6)$$
$$S''_i(x_i) = S''_i(x_{i+1}). \quad (7)$$

2.5.3 Other artifact correction methods

In addition to deletion and different interpolation methods, various other artifact correction methods have been developed. A few additional artifact correction methods for the HRV analysis will be shortly described below.

Cheung (1981) described an algorithm for correcting beats with false triggering. The detection of errors in this algorithm is based on the assumption that the beat-to-beat variation in R-R intervals does not exceed a certain critical percentage of the preceding interval. In other words, each R-R interval is compared with the preceding one. The error correction of the algorithm consists of iteratively merging the interval in question with the preceding or the
succeeding interval or subdividing it in such a manner that the resultant beat-to-beat variability is minimized. (Cheung 1981)

Albrecht & Cohen (1988) proposed a method of estimating the power spectrum of the HRV signal containing ectopic or missing beats. This method estimates the HRV spectrum using the fast Fourier transform (FFT) of the HR autocorrelation. Autocorrelation is computed without making explicit assumptions about the specific value of the HR in the bad intervals. The autocorrelation, $R[k]$, of the HRV signal, $HR[n]$, is defined in the absence of bad intervals where $n$ is the sample number $0...N$ as follows:

$$
\hat{R}[k] = \frac{1}{N-k} \sum_{n=0}^{N-|k|-1} HR[n]HR[n+k], \quad (8)
$$

In the case of bad intervals, the $R[k]$ is estimated from the normally conducted beats as follows:

$$
\hat{R}[k] = \frac{1}{N_k} \sum_n HR[n]HR[n+k], \quad (9)
$$

where $N_k$ is defined as the number of terms for which $HR[n]HR[n+k]$ is computed without ectopic beats. (Albrecht & Cohen 1988)

Lippman et al. (1993) introduced an algorithm of the nonlinear predictive interpolation for artifact correction. This algorithm is based on the fact that beat-to-beat variations in HR appear in a deterministic way. This algorithm utilizes the methods of the chaos theory for locating ectopy-free portions of the R-R interval sequence. The purpose of the ectopy-free R-R interval sequence is to describe trajectories in phase space that are locally similar to those of the segments containing ectopic beats. A trajectory is chosen such that it approximates most accurately to the particular segment with ectopic beats and it is used to determine the replacement R-R intervals for the ectopic beats (Lippman et al. 1993).

### 2.6 Heart rate variability analysis

HRV is usually measured in two different settings of the HRV signal or ECG recording. First, HRV signal recordings can be obtained under controlled laboratory conditions with different events such as the tilt, metronomic ventilation, drugs, or other physiological maneuvers that have an effect on the autonomic nervous system. These kinds of laboratory settings usually concern short-term ECG measurements. Secondly, the HRV signal can be obtained from long term...
ECG recordings lasting up to 24-hour or even longer. Diurnal ECG recordings are
normally taken while the individual is doing his/her daily activities.

Variation in the HR can be evaluated by different methods, which can be
categorized as time domain methods, frequency domain methods, geometric
methods and methods based on the nonlinear dynamics of the HR. In addition,
HR turbulence and baroreflex sensitivity are commonly analyzed HRV measures.

2.6.1 Time domain analysis

Time domain indices are often considered as the simplest HRV analysis. Time
domain analysis usually contains various statistical variables, but also geometrical
methods can be used to measure HRV in the time domain. The simplest time
domain variables include the following HRV parameters: the mean value of the
normal-to-normal (N-N) intervals, called usually as the mean HR, the difference
between the longest and the shortest N-N interval and the difference in the HR
between night and day. More complex time domain methods involve the higher
degree of statistical analysis or geometrical methods.

Statistical time domain analyses are divided into two classes, 1) methods
derived from the measurements of the N-N intervals directly, and 2) methods
derived from the differences between N-N intervals. Both of these methods can be
derived from both short-term and long-term ECG recordings. One of the easiest
statistical time domain variables to calculate is the standard deviation of the N-N
intervals (SDNN). Due to the fast and straightforward computation of the SDNN
it is a popular HRV measurement. SDNN equals the square root of the variance
and is computed by:

\[
SDNN = \sqrt{\frac{1}{n-1} \sum_{i=1}^{n} (NN_i - \bar{NN})^2},
\]

where \(NN_i\) is the normal R-R intervals for \(i\) is 1…\(N\) and \(\bar{NN}\) is the arithmetic
mean value of the normal R-R intervals (Malik 1997). SDNN is computed over a
24-hour period in most of the studies. The variation of the SDNN is the standard
deviation of the average N-N interval (SDANN), which is computed over short
periods, usually around five minutes, of R-R interval data. Another variation of
the SDNN is the mean value of the five minute standard deviation of the N-N
intervals called the SDNN index. The SDNN index is computed over 24 hours in
segments of five minutes.
Another commonly used time domain HRV parameter that is derived from the R-R interval differences is the square root of the mean squared differences of the successive N-N interval, abbreviated as RMSSD. The mathematical representation of the RMSSD is (Malik 1997):

$$RMSSD = \sqrt{\frac{1}{n-1} \sum_{i=1}^{n-1} (NN_{i+1} - NN_i)^2},$$

(11)

In addition to the above-mentioned HRV parameters various other time domain variables are defined. For instance, the number of the R-R interval differences of the successive NN intervals that are greater than 50 ms denoted as NN50 is commonly used. In addition, the proportion of the successive difference of the R-R intervals which differ by more than 50ms expressed as a percentage of the total number of the R-R intervals and denoted as pNN50 is often computed. The mathematical representation for the pNN50 is:

$$pNN50 = \frac{NN50}{n-1} \times 100\%,$$

(12)

where NN50 is the number of R-R intervals that are greater than 50 ms and n is the total number of the R-R intervals.

All the above mentioned short-term time domain HRV measurements tend to estimate the high frequency fluctuations in the HR and are highly correlated. (Task Force of ESC & NASPE 1996)

2.6.2 Frequency domain analysis

The current view is that the HR power spectral analysis can assess the cardiac autonomic balance (Malliani et al. 1991, Montano et al. 1994). It is considered that high frequency HRV reflects mainly the cardiac parasympathetic nerve activity and the low frequency HRV represents the cardiac sympathetic and parasympathetic nerve activity. The power spectral methods for the HRV signal have been applied to provide information on the distribution of the power as a function of frequency (Kay & Marple 1981).

Information on spectral estimates can be obtained by decomposing the spectrum of the R-R interval time series into quantified frequency components or by integrating the signals over a defined frequency band. Decomposition of the HRV power spectrum reflects the HRV in the function of frequency and describes the magnitude of the frequency components. Various studies have shown that HRV signal contains specific rhythms with physiological information (Penaz et al.
The power spectrum of the HRV signal contains three main frequency bands that are well distinguished from each other and are i.e.: very low frequency (VLF), low frequency (LF) and high frequency (HF) components. The definitions for these frequency components are summarized below. A HRV spectrum from a healthy subject is shown in Figure 3 illustrating the main frequency components of the R-R interval time series.

Fig. 3. HRV power spectrum from a healthy subject.

Long period HR rhythms are included in the VLF component, which is situated in the frequency range of to 0.0033 to 0.04 Hz (Task force of ECS & NASPE 1996). The origin of these long period fluctuations of the R-R intervals is not understood in detail, but they are suggested as being affected by the thermoregulation systems, the renin-angiotensin system and perhaps other humoral factors (Kitney & Rompelman 1977). Furthermore, also some non-stationarities or low frequency trends may affect the HRV power spectrum as an increased VLF power.

The LF component between the frequencies 0.04 Hz and 0.15 Hz is created in a heart rhythm that is usually observed around 0.1 Hz. This slow oscillation of the heart rhythm has been suggested as being caused by the mechanisms regulating the BP (Kitney et al. 1985, Kamath & Fallen 1993). However, the physiological interpretation of the LF rhythms is controversial. Contributions from both parasympathetic and sympathetic systems are involved in the LF rhythms. An increase in the LF power has been proposed as being a marker for sympathetic activation (Kamath & Fallen 1993, Malliani et al. 1991). On the other hand, also the parasympathetic regulation has been reported having an influence on the LF power (Akselrod et al. 1985, Pomeranz et al. 1985).
The HF component of the HRV spectrum is usually identified in the frequency range between 0.15 Hz to 0.4 Hz, which is related to the respiratory frequency. Respiration related HF rhythm is affected by the changes in the intrathoracic pressure and mechanical changes caused by the breathing. This activity which is mediated by the vagus nerve, is considered to be a marker of the parasympathetic activation (Katona & Jih 1975, Hirsch & Bishop 1981, Pagani et al. 1986). The balance between sympathetic and parasympathetic outflow is often measured by the ratio of the LF and HF components (LF/HF ratio). This ratio has been suggested being a marker of the sympathovagal balance (Malliani et al. 1991, Pagani et al. 1986).

In addition to the above three main frequency components, the ultra low frequency (ULF) component can be determined. The ULF component is situated in the frequency range \( f < 0.0033 \) Hz (Kamath & Fallen 1993). The physiological background of the ULF component has still not been specified in detail, but the major underlying factors of the ULF are speculated as being involved in the day and night variation, with large infrequent events such as awakening and falling asleep (Roach et al. 1998).

Studies of the HRV in the frequency domain employ the computation of the power spectrum density (PSD). The methods used to obtain the PSD of the HRV signal can be classified as either non-parametric or parametric methods. Non-parametric methods are usually based on the Fourier Transformation and the parametric methods are usually based on the autoregressive (AR) modeling.

**FFT spectrum estimation**

Power spectrum estimation based upon the Fourier transform can be evaluated using the fast Fourier transform (FFT) algorithm (Kay & Marple 1981). The FFT method utilizes the discrete Fourier transform (DFT) algorithm and reduces the number of computations needed for \( N \) points from \( 2N^2 \) to \( 2N \cdot \lg(N) \), where \( \lg \) is the base-2 logarithm. A commonly used FFT algorithm was introduced by Cooley and Tukey (1965). FFT based methods are widespread due to their computational efficiency, easy applicability and the comprehensibility of the results. However, the spectrum estimation with the FFT method is preferred to be performed with long-term data segments to obtain a reasonably high frequency resolution (Task Force of ESC & NASPE 1996). In theory, the FFT method is determined on time series of infinite length. Due to this reason, this method may suffer from a leakage in the PSD due to the windowing of the data. FFT spectral estimation is
conventionally based on a Fourier series model of the data involving a set of harmonically related sinusoids. If the HRV signal is the discrete R-R interval time series \( f(k) \), where \( k \) is 0,1,2…\( N \), then the discrete Fourier transform \( F(n) \) is computed by:

\[
F(n) = \frac{1}{N} \sum_{k=0}^{N-1} f(k)e^{-j2\pi kn/N},
\]

where \( n \) is frequency in the range of 0,1,2,…,\( -1 \) and \( N \) is the number of samples (R-R intervals). If \( F(n)^* \) is the complex conjugate of the \( F(n) \), the PSD can now be computed by:

\[
|F(n)|^2 = F(n) \cdot F(n)^*,
\]

where the PSD of the R-R interval time series is notated by \( |F(n)|^2 \).

**AR spectrum estimation**

Parametric spectrum estimation refers to the signal modeling with a parametric model. Especially in the HRV analysis, the parametric power spectrum estimation is usually based on AR modeling that will be shortly presented here. The AR spectrum estimation provides smooth spectral components and an accurate PSD estimate even with a short-term data segment with a small number of R-R intervals. However, it is assumed that the short-term R-R interval recording can maintain its stationarity. If the stationary time series is \( x(t) \) and \( \epsilon(t) \) is the residual time series or the driving error process, then the AR model can be defined as:

\[
x(t) = \sum_{k=1}^{p} a_k x(t - k) + \epsilon(t),
\]

where the \( a^i \) are the AR coefficients or the model parameters being estimated, and \( p \) is the model order. The estimation of the relevant power spectrum \( P(f) \) is carried out by determining a computation of the Z transform for the above equation. The AR power spectrum of the process \( x(t) \) with a model order \( p \) can be written as (Marple 1987):

\[
P(f) = \frac{\sigma^2}{|1 + \sum_{k=1}^{p} \hat{a}_k^*|},
\]

where \( z \) is denoted as \( e^{j2\pi f} \), \( \hat{a}_k \) are estimated AR model parameters and \( \sigma^2 \) is an estimated variance of \( \epsilon(t) \).

The AR modeling is advantageous in the short-term data segments compared with the FFT method, because the length of the R-R interval time series is not
essential for the frequency resolution in the AR method. However, the AR method may introduce some error in the estimation of very and ultra low frequency components. This is due to the lack of an additive sine component in the frequency range of the ULF and VLF, where the spectrum usually has a shape of the 1/f spectrum. A signal with a 1/f spectrum is not preferred as being represented with the AR method. The AR method is especially suitable for a signal that produces sharp frequency peaks. In the AR modeling process, it is an important task to choose an appropriate model order. Basically, the higher the order, the better frequency resolution that can be achieved. However, a too large model order may introduce spurious peaks into the power spectrum (Kay & Marple, 1981). Correspondingly, a too low model order will result in an over-smoothed spectrum. The model order is recommended as being twice as large as the presumed number of frequency peaks. With the R-R interval time series, the model order, \( p \), is often 15 to 20. With large AR coefficients, the AR modeled spectrum approaches the FFT-spectrum. For instance, more mathematically detailed presentations of the AR and FFT spectrum estimation can be found in Kay & Marple (1981).

Other frequency domain HRV analysis

HRV signal can be analyzed by estimating a higher order spectrum. The power spectrum is based on the second order statistics of the time series. The bispectrum is obtained with the Fourier transform of the third order statistics of the time series. The white Gaussian random process has a zero bispectrum which can be used to examine the deviation from the gaussianity and identify the process by utilizing the information about the phase character of the signal (Hinich 1982). In addition, a bispectrum estimation makes it possible to reveal relevant information on the nonlinear interactions by detecting the quadratic phase coupled harmonics (Sigl & Chamoun 1994, Nikias & Raghuveer 1987).

The time-frequency (TF) spectral analysis enables the tracking of the spectral parameters as time elapses. TF analysis is an advanced method enabling the generation of multiple spectra with time compared with the single spectrum for the whole data segment obtained with the FFT method (Boashash 1991). In contrast to the ordinary spectrum analysis, where it is presupposed that the signal is stationary, the TF analysis is performed on non-stationary signals. Various methods in order to obtain TF analysis are currently available, including short
time Fourier transform (STFT), continuous wavelet transform (CWT), Wigner-Ville transform to mention only a few.

The STFT method applies a moving window to the signal and Fourier transform is computed within the window as it slides along the time axis (Keselbrener & Akselrod 1996). The STFT tends to suffer from increased high frequency information due to restricted time window size which cuts the signal sharply. The CWT method accomplishes this problem by using a reference wavelet known as the *mother wavelet*. The *Mother wavelet* is the source for the *daughter wavelets*, which are scaled and translated versions of the mother wavelet. In the CWT method, a waveform can be decomposed into a series of shifted and stretched versions of the prototype function (*mother wavelet*). By definition, the CWT is a computation with the FFT, the convolution of the input data sequence with a set of *daughter wavelets* (Daubechies 1990). Wigner-Ville distribution (WVD) does not encounter problems due the windowing. WVD can be considered as a Fourier transform of the auto-correlation function of a signal. For instance, more detailed and mathematic presentations of the TF methods in HRV analysis can be found in Naidu & Mahalakshmi (2004).

### 2.6.3 Geometrical HRV analysis

The geometrical analysis of the HRV represent R-R intervals in geometric patterns such as the sample density histogram of R-R intervals, the sample density distribution of differences between successive R-R intervals, and Lorenz plots or Return maps.

Popular geometrical HRV methods utilize the sample density histogram of the R-R intervals with the assumption that the false or incorrect R-R intervals are either notably shorter or longer in comparison with normal R-R intervals. Incorrect R-R intervals are assumed as falling outside the main peak of the R-R interval histogram and thus they can be identified.

The HRV triangular index (HRVI) is a measure where the total number of the NN intervals is divided by the largest number of equally long NN intervals. The HRVI is based on the idea that when the major peak of the histogram is a triangle, its baseline width is equal to its area divided by its height (Malik *et al.* 1989). In the HRVI representation, the durations of the NN intervals are placed in the $x$-axis and the number of each interval length serves as the $y$-axis. From the sample density distribution, the most frequent NN interval length is established by approximating the main peak of the density distribution.
The triangular interpolation of the NN or R-R interval histogram (TINN or TIRR) is the baseline width of the distribution measured as the base of a triangle, which approximates to the NN interval distribution, the minimum of the HRV (Farrell et al. 1991). The triangular index is considered as being insensitive to artifacts, especially to substantial ectopic beats, because they are left outside the histogram triangle as outlier samples (Malik et al. 1989). However, the major advantage of the geometrical methods is conferred by the lack of the sensitivity to the analytical quality of the NN interval series.

In addition to using the R-R interval histogram in the HRV analysis, it is possible to examine the histogram derived from the differences between successive R-R intervals. This method produces a much narrower histogram and it concentrates on viewing the sharpness of the differential histogram peak. (Malik & Camm 1995)

2.6.4 Nonlinear HRV analysis

Interest in the HRV analysis based on the chaos theory and nonlinear dynamics has increased during the last couple of decades. Chaos represents irregular or apparently random time-dependent behavior in deterministic systems. Nonlinear chaos refers to a constrained kind of randomness which is possibly involved in fractal geometry. The chaotic system differs from the stochastic system for its internal nonlinearity and it is sensitive to the initial state. A small difference in initial conditions can produce a large difference after some steps of time. Conventional methods in the time and frequency domain methods tend to measure the overall R-R interval fluctuation or the magnitude of the R-R interval variability in a certain frequency range. Nonlinear methods are based on the assumption that the mechanisms involved in the HR regulation interact with each other in a nonlinear way. The basic concept of the nonlinear HRV methods is to try to capture the non-periodic behavior of the HRV and the complexity that exists inside the R-R interval dynamics. Various different nonlinear methods including return maps, fractal scaling analysis and different complexity measures have been tested in various sets of R-R interval data (Bigger et al. 1996, Lombardi et al. 1996b, Mäkikallio et al. 1997, 1998, 1999a, 1999b, Huikuri et al. 1998, 2000).
Fractal correlation properties

Mandelbrot (1983) introduced the term “fractal”. A fractal describes a set of points that resembles the whole set even when examined at very small scales. The quantification of fractal properties assesses the self-similarity of the HR oscillation over multiple time scales. The presence or absence of the fractal correlation properties in an R-R interval time series can be examined with the detrended fluctuation analysis (DFA) technique (Peng et al. 1995). The DFA method is a modified root mean square analysis of a random walk. With the DFA, it is possible to detect long-range correlations that are embedded in a seemingly non-stationary time series. The DFA tends to avoid the spurious detection of apparent long-range correlations that are artifacts of non-stationarity. A short description of the DFA method will be presented here. A more detailed description of the DFA computation can be found in Peng et al. (1995).

Interbeat interval time series RR(i), for i is 1…k is first integrated by:

\[ y(k) = \sum_{i=1}^{k} (RR(i) - \bar{RR}), \tag{17} \]

where \( \bar{RR} \) is the mean value of the R-R interval time series. The integrated time series \( y(k) \) is next divided into windows of the same length \( n \). Detrending is accomplished on every window by fitting a trend line with a least-squares method. The fluctuation function \( F(n) \), is obtained by computing a root mean square for the sum of the difference between the integrated time series \( y(k) \) and the local trend \( y_n(k) \) as

\[ F(n) = \frac{1}{\sqrt{N}} \sum_{k=1}^{N} [y(k) - y_n(k)]^2, \tag{18} \]

Finally, the amount of the randomness in R-R interval time series is reflected with a scaling exponent \( \alpha \), which is obtained as the slope of the logarithmic \( F(n) \) versus logarithmic \( n \). The scaling exponent \( \alpha \) differs between uncorrelated and correlated data. For the uncorrelated data, \( \alpha \) obtains values near 0.5, which is associated with a completely random time series. The highest values of \( \alpha \) are about 1.5 and are associated with a totally correlated time series. If there is a correlation where a large R-R interval value is probably followed by another large interval, the \( \alpha \) obtains values between 0.5…1.0. When 0 < \( \alpha \) < 0.5, there is a correlation between large and small values of interval time series. When \( \alpha \) equals 1, this corresponds to the 1/f -noise. For \( \alpha > 1 \), there exists some correlations, but they do not behave in the power-law form. The scaling exponent \( \alpha \) represents the “roughness” of the
time series. Large values of $\alpha$ indicate a smooth time series. Values of the scaling exponent for the normal healthy subject are typically near 1, which indicates fractal-like HR behavior, while patients with cardiovascular diseases or with advancing age have been reported as displaying altered fractal-like behavior of HR (Goldberger et al. 2002). The fractal scaling analysis in a variety of life-threatening cardiac pathologies has revealed significant alterations in short and long-term HR correlation properties (Mäkikallio et al. 1999a, 1999b, Huikuri et al. 2000).

Return maps

Return Map -methods provides a beat-to-beat graphical representation of time series data in a two-dimensional space. In a return map, the time series $x(t)$ is plotted versus $x(t + \tau)$, where $\tau$ is a lag of time. Signals with random or unperiodic behavior fill the plot space with no organized pattern. Periodic signals exhibit a pattern where trajectories have cycles that resemble each other. The Poincare plot is a return map method where the previous R-R interval $RR_n$ is represented in the function of the preceding R-R interval $RR_{n+1}$. This is called a first order Poincaré plot. Correspondingly, the second order Poincaré plot is obtained by plotting the $RR_{n+2} - RR_{n+1}$ versus $RR_{n+1} - RR_n$. The Poincaré plot is useful and an easy method for visualizing the regularities or randomness that may lie in the beat-to-beat variability (Kamen et al. 1996, Brennan et al. 2001). An R-R interval time series with a high R-R interval variability produces a plot with a widespread pattern around a straight line at 45 degrees from the horizontal axis. For an HRV signal with low variability, the Poincaré pattern will accumulate in a small-sized area. Examples of Poincaré plot for a healthy subject and an AMI patient are shown in Figure 4.

The standard descriptors of the Poincaré plot are $SD1$ and $SD2$ (Brennan et al. 2001, 2002). The line of identity is the 45 degree imaginary diagonal line on the Poincaré plot (see Figure 4). $SD1$ measures the dispersion of data points perpendicular to the line of identity and it represents the instantaneous beat-to-beat variability. $SD2$ measures the dispersion of data points along the line of identity and it represents the continuous long-term beat-to-beat variability. The ratio of these parameters, $SD1/SD2$, represents a measure of heart activity (Tulppo et al. 1996).

The descriptors of the Poincaré plot are possible to define with different techniques. A popular method is to fit an ellipse on a Poincaré plot (Brennan et al.
2001). However, in many papers, despite of the appearing term “fitting”, an actual ellipse fitting is not performed. Commonly, the ellipse with axes (SD1, SD2) centered on the mean of the two vectors $RR_1 = (RR_{n+1}, RR_{n+2}, \ldots, RR_{N-1})$ and $RR_2 = (RR_{n+2}, RR_{n+3}, \ldots, RR_{n})$ is used only to visualize the short (SD1) and long term (SD2) variations of the RR interval time series (Piskorski & Guzik 2005). Basically, SD1 can be quantified by the standard deviation of the distances of the points from the line of identity (Brennan et al. 2002). Respectively, SD2 can be quantified by the standard deviation of the data points along the line of identity (Brennan et al. 2002). For instance, detailed mathematical representations of SD1 and SD2 can be found in Brennan et al. (2001).

![Fig. 4. Poincaré plots of a healthy subject (left) and AMI patient (right).](image)

**Power-law correlation**

In addition to conventional power spectrum estimation, the spectrum analysis of the HRV signal can be performed using the regression analysis of the logarithmic power on the logarithmic frequency and calculating the power-law relationship of the HRV in the frequency range of usually $10^{-4}$ to $10^{-2}$ Hz. In this method, after editing of the possible artifacts in the R-R interval time series, the power spectrum is computed over the entire recording interval (Saul et al. 1988). The point power spectrum is logarithmically smoothed in the frequency domain by computing the common logarithm of the frequency and then the power is integrated into bins spaced 0.0167 log(Hz) apart. If $f$ is the frequency, the power spectral density $P$ can be computed as:

$$P = Cf^\beta,$$

(19)
where $C$ is the proportionality constant (Saul et al. 1987) and $\beta$ is the negative exponent corresponding to the slope of the logarithmic $P$ versus logarithmic $f$ relation:

$$\log(P) = \log(C) + \beta \cdot \log(f), \quad (20)$$

The regression analysis of the log(power) on the log(frequency) is performed on the linear portion of the smoothed power spectrum between $10^{-4}$ to $10^{-2}$ Hz and the slope of the computed regression line and the intercept at $10^{-4}$ Hz is derived (Bigger et al. 1996).

The analysis of the power-law correlation requires large data sets with adequate stationarity and periodicity. The power-law analysis is usually performed on the long term HRV data containing R-R interval time series obtained from 24-hour ECG recordings. The slope of the regression line corresponds to the negative scaling exponent $\beta$ and provides an index for long-term scaling characteristics (Saul et al. 1987) and it has been found to be steeper for values from a myocardial infarction patient and transplant patient compared with the slope computed from a healthy subject (Bigger et al. 1996).

**Other nonlinear HRV analysis methods**

The periodicity or complexity in the output of the dynamic process can be reflected with the approximate entropy ($\text{ApEn}$). $\text{ApEn}$ quantifies the likelihood that runs in patterns that are close, will remain close in the next incremental comparison (Pincus et al. 1992, 1994). A time series with high unpredictability provides larger values of the $\text{ApEn}$, whereas if there is regularity in the time series, this will result in small $\text{ApEn}$ values. For order to determine statistical estimate for the $\text{ApEn}$, two input parameters $m$ and $r$ must be fixed. The parameter $m$ determines the length of compared runs of R-R interval time series and the parameter $r$ is the tolerance for the comparison of these runs. Higher values of the $\text{ApEn}$ in post-infarction patients compared with healthy subjects have been documented (Mäkikallio et al. 1996, Ho et al. 1997).

The Lyapunov exponent is a measure that can be used to quantify the sensitive dependence on initial conditions (Eckmann & Ruelle 1985, Wolf et al. 1985). The Lyaponov exponent defines an average divergence rate for two neighboring trajectories and it is used to distinguish between chaotic dynamics and periodic signals. However, the usefulness of the Lyapunov exponent in HRV analysis is limited due to its requirement for large stationary data sets.
Fractal dimension is a parameter for describing geometrical structure. Correlation dimension ($D_2$) is a common measure of the fractal dimension that describes the complexity of a deterministic system. An efficient algorithm for calculating the correlation dimension was proposed by Grassberger and Procaccia (Grassberger & Procaccia 1983). A valid evaluation of the correlation dimension requires non-stationary data and this can only be obtained from long-term ECG recordings. Therefore, a pointwise correlation dimension ($PD_2$) is often alternatively used (Skinner et al. 1991, 1993) due to its ability to allow operations irrespective of whether the data is stationary in time.

Kolmogorov entropy ($K$) is another measure which has been proposed to characterize a deterministic complex dynamical process. The Kolmogorov entropy also suffers from the requirement for long-term data and therefore ApEn has become a more common method in order to classify the complexity of relatively short-term HR data (Pincus & Goldberger 1994).

### 2.6.5 HR turbulence

HR turbulence (HRT) is a measure involving the quantification of the perturbed sinus R-R interval fluctuation immediately after an isolated ventricular premature beat (VPB). As can be seen in Figure 5, the normal physiological pattern of the HR turbulence consists of a short acceleration of the sinus rhythm immediately after a single VPB followed by a gradual rhythm deceleration lasting up to ten or fifteen R-R intervals before there is reversion back to the baseline level which was present before the VPB. (Bauer & Schmidt 2003)
Quantification of the HR turbulence is undertaken in two phases by computing two parameters: turbulence onset (TO) referring to an early acceleration of the sinus rhythm immediately after the VPB and turbulence slope (TS) referring to the slower gradual later deceleration. Turbulence onset is described as the percentage value of the difference between the sinus R-R intervals before and after the VPB. Turbulence onset is computed as:

$$TO = \frac{(RR_{-1} + RR_2) - (RR_{-2} + RR_1)}{(RR_{-2} + RR_{-1})} \times 100\%$$

(21)

where $RR_{-2}$ and $RR_{-1}$ are the two consecutive sinus R-R intervals before the VPB, and $RR_1$ and $RR_2$ are the two R-R intervals directly after the compensatory pause of the VPB (Bauer & Schmidt 2003). Turbulence onset is presented as a percentage value in which a positive value (TO > 0%) corresponds to the deceleration of the sinus rhythm after a VPB. A negative value of the TO (TO < 0%) corresponds to the acceleration of the sinus rhythm. The optimal dichotomy for the TO is defined as 0%. The initial sinus rhythm alteration after the VPB in normal subjects is connected with negative turbulence onset. (Bauer & Schmidt 2003)

The steepest regression line between the R-R interval count and duration quantifies the subsequent deceleration termed as Turbulence Slope (TS). The TS defines the maximum positive slope of the regression line calculated over any sequence of five subsequent sinus R-R intervals within the first 15 sinus R-R intervals after the compensatory pause of the VPB and is expressed in milliseconds per R-R. The optimal dichotomy for the TS is determined as 2.5 ms per R-R interval and in normal subjects the subsequent deceleration is
characterized by a positive TS (TS > 2.5ms). (Bauer & Schmidt 2003, Bauer et al. 2008)

Both measures, the TO and the TS are computed for single VPBs and then averaged to attain the turbulence value for each patient. The quantification of the HR turbulence is dependent on the accurate identification of VPBs. Furthermore, the verification of the sinus R-R intervals immediately preceding and following the VPB being free of artifacts or arrhythmia is required in order to obtain usable turbulence analysis (Bauer & Schmidt 2003). If one wishes to characterize turbulence pattern accurately, then the HR turbulence is usually computed from long term Holter recordings (~24 h) with a reasonable number of VPBs (> 5). Surroundings of the VPBs should include two sinus R-R intervals before and at least 15 sinus R-R intervals after the VPB. Short periods of Holter recordings are not recommended for the HRT analysis due the possibility of obtaining usefulness results (Berkowitsch et al. 2004).

The HR turbulence phenomenon is influenced by a number of different factors, but essentially HR turbulence reflects the function of the baroreflex (Malik et al. 1999, Watanabe 2003). The early acceleration of the sinus rhythm after the VPB is proposed as being a consequence of the chain reaction. First, this chain involves an inefficient ventricular contraction due to VPB, which causes a lack of the baroreflex afferent input. This leads to a vagal inhibition and acceleration of the HR (Malik et al. 1999). Correspondingly, the late deceleration of the sinus rhythm after the VPB is believed as being a result from the overshoot of the arterial pressure due to sympathetic activation, causing a vagal launch and a deceleration of the HR (Malik et al. 1999).

HR turbulence is used in order to evaluate the risk of subsequent mortality in post-MI patients, where the absence of HR turbulence after VPBs is a relevant post-infarction risk stratifier. (Schmidt et al. 1999).
3 Aims of the study

The main goal of this dissertation was to improve the quality and reliability of the HRV analyses by concentrating on certain preprocessing methods such as the artifact editing of the HRV signal. Another aim of this study was to develop and study novel preprocessing methods of the HRV signal, especially in the evaluation of the risk of SCD in post-AMI patients. The specific aims of the individual Studies I–IV were as follows:

Study I: To clarify the effects of editing on the HRV analysis and specify the optimal ways to analyze the HRV more reliably. The aim was to study how the different editing methods can influence the different time and frequency domain HRV analysis and to define the number of qualified beats needed for a reliable HRV analyses. In addition, one aim was to identify the possible differences between the editing effects on the HRV analysis of healthy subjects with high overall HRV and AMI patients with low HRV.

Study II: To examine the effects of ectopic beats on the analysis of the fractal correlation properties of the HRV signal. An additional aim was to examine the following question: is it possible that the short-term and long-term fractal scaling exponents, $\alpha_1$ and $\alpha_2$, measured either from original R-R interval time series including the premature beats or from the R-R interval data after editing the premature beats can differentiate between patients who will remain alive from those who will suffer cardiac death during the follow-up.

Study III: To develop a method in order to quantify the respiratory related HRV, the RSA. The target was to quantify RSA more reliably from an ambulatory 24-hour common ECG recording without any information about individual breathing rate. The aim was also to test the hypothesis that the quantity of the RSA can be used as a risk marker for SCD in the population of AMI patients. The goal was to compare the RSA quantity between patients who survived and those who died during the follow-up.

Study IV: To examine the effects of the HR turbulence editing on time and frequency domain HRV analysis and fractal scaling analysis. The aim was to extract the effects of fifteen consecutive R-R intervals that occur immediately after a VPB, since these are considered as being under the influence of the HR turbulence phenomenon.
4 Study data

The study population of this thesis contained a total of 122 healthy subjects and 2007 AMI patients. Different AMI groups were examined in Studies I–IV and healthy groups in Studies I–III. The main figures of AMI groups are summarized in Table 1 and healthy groups in Table 2. Cells with the NA notation in the Tables 1 and 2 indicate that the specific information of the population was not available.

Table 1. Study populations of post-AMI patients in Studies I–IV.

<table>
<thead>
<tr>
<th>Variable</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 10</td>
<td>n = 15</td>
<td>n = 84</td>
<td>n = 267</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ± 6</td>
<td>54 ± 5</td>
<td>69 ± 8</td>
<td>59 ± 10</td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>15</td>
<td>52</td>
<td>1279</td>
</tr>
<tr>
<td>Female</td>
<td>–</td>
<td>–</td>
<td>32</td>
<td>352</td>
</tr>
<tr>
<td>Diabetes</td>
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<td>NA</td>
<td>NA</td>
<td>288</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>NA</td>
<td>NA</td>
<td>936</td>
</tr>
<tr>
<td>NYHA I–II</td>
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<td>NA</td>
</tr>
<tr>
<td>NYHA III</td>
<td>NA</td>
<td>NA</td>
<td>30</td>
<td>NA</td>
</tr>
<tr>
<td>EF</td>
<td>NA</td>
<td>NA</td>
<td>41 ± 10</td>
<td>NA</td>
</tr>
<tr>
<td>SDNN [ms]</td>
<td>76 ± 41</td>
<td>85 ± 35</td>
<td>81 ± 29</td>
<td>99 ± 42</td>
</tr>
<tr>
<td>Recording duration</td>
<td>512 R-R, 24h</td>
<td>8000 R-R</td>
<td>24h</td>
<td>24h</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation unless otherwise indicated. EF = ejection fraction; NYHA = New York Heart Association Classification; SDNN = standard deviation of normal-to-normal R-R intervals.

Table 2. Study populations of healthy subjects in Studies I–III.

<table>
<thead>
<tr>
<th>Variable</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 10</td>
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<td>n = 84</td>
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<tr>
<td>Age (years)</td>
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<td>72 ± 4</td>
</tr>
<tr>
<td>Male</td>
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</tr>
<tr>
<td>Female</td>
<td>–</td>
<td>–</td>
<td>38</td>
</tr>
<tr>
<td>NYHA I–II</td>
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<td>NYHA III</td>
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<td>SDNN [ms]</td>
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<td>139 ± 35</td>
</tr>
<tr>
<td>Recording duration</td>
<td>512 R-R, 24h</td>
<td>8000 R-R</td>
<td>24h</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation unless otherwise indicated. NYHA = New York Heart Association Classification; SDNN = standard deviation of normal-to-normal R-R intervals.
4.1 Research data in Study I

The data in Study I consisted of R-R interval time series that were recorded from a group of ten healthy subjects and ten patients with AMI. The healthy subjects had no history of heart disease. The mean age of the healthy subjects was 41 ± 11 years and that of the AMI patients 58 ± 6 years. The R-R interval time series of the healthy subjects was selected on the grounds that they contained relatively high R-R interval fluctuations, and thus the mean SDNN was high (SDNN = 175 ± 50 ms). Correspondingly, the R-R interval time series of the AMI patients contained low R-R interval variability (SDNN = 76 ± 41 ms).

R-R interval time series were obtained with an R-R recorder, i.e. a real-time microprocessor QRS detector system (Polar Electro Oy, Kempele, Finland). The R-R recorder was connected to the patient via two ECG electrodes and had a timing accuracy of 1 ms. The measured R-R intervals were saved onto a computer disk for further processing. Both short-term and 24-hour R-R interval recordings were used. The short-term R-R interval data included 15 tachograms from healthy subjects and 15 tachograms from AMI patients. The length of the short-term data was 512 R-R intervals. The effects of the editing were studied also with long-term R-R interval time series containing the R-R interval data of 24-hours from ten healthy subjects and ten AMI patients. Short-term R-R interval data segments contained only pure sinus beats and long-term data contained 99% of pure sinus beats.

4.2 Research data in Study II

Study II contained two different populations of AMI patients and two populations of healthy subjects. First, the effects of artificially generated premature beats on the nonlinear HRV measures were studied with R-R interval segments. These R-R interval segments contained 8000 R-R intervals of pure sinus beats. The measurements of 8000 R-R interval data segments were conducted with a RR recorder, i.e. a real time microprocessor QRS detector system (Ruha et al. 1997) (Polar Electro Oy, Kempele, Finland). Twenty R-R interval time series were recorded from 15 healthy subjects that were selected from a larger (n = 114) healthy population (Pikkujämsä et al. 1999). Correspondingly twenty R-R interval time series were obtained from 15 post-AMI patients that were selected from a larger (n = 379) AMI population (Tapanainen et al. 2001). The mean age of the healthy subjects was 45 ± 11 and they had no history of heart disease,
hypertension or diabetes. The mean age of the post-AMI patients was 54 ± 5 years. General R-R interval variation was measured with SDNN and it was significantly lower (P < 0.001) among the post-AMI patients (SDNN = 85 ± 35 ms) compared with healthy subjects (SDNN = 175 ± 50 ms).

The effects of the real premature beats on the nonlinear HRV measures were studied with 24-hour R-R interval data recorded from post-AMI patients and a random elderly population. The 24-hour electrocardiographic recordings were performed with a portable two-channel tape recorder (Oxford Medilog, Oxford, UK) with a sampling frequency of 256 Hz. Measured R-R intervals were saved on a computer for additional processing.

Forty-two post-AMI patients, who died during the follow-up of 14 ± 8 months, and 42 post-AMI patients matched with age, sex, functional class, and ejection fraction, who were alive after the follow-up, were selected from a larger (n = 379) post-AMI population (Tapanainen et al. 2001). Beta-blocker drugs had been given to 80 patients (95.2%), digoxin treatment provided to 8 patients (9.5%), and a calcium antagonist to 10 patients (11.9%). Correspondingly, forty-two healthy elderly subjects, who died during the follow-up of 120 months and 42 controls, who were alive, matched with age, sex, and functional class were selected from the large (n = 480) survey of the health status of the elderly living in the city of Turku, Finland (Sourander et al. 1986, Räihä et al. 1994, Mäkikallio et al. 2001). None of the 42 healthy elderly subjects that were included in this study were taking any medications. The mean age of the selected elderly healthy subjects was 72 ± 4 years and that of post-AMI patients 69 ± 8 years. All deaths in both study populations were classified as cardiac deaths. The general R-R interval variation was measured by SDNN and it was significantly lower (P < 0.001) also in this post-AMI group (SDNN = 81 ± 29 ms) compared with the elderly subjects (SDNN = 139 ± 35 ms). The mean occurrence of the ectopic beats in post-AMI population was 29 ± 56 ectopic beats per hour and 19 ± 23 in the population of elderly healthy subjects.

### 4.3 Research data in Study III

The study population in Study III consisted of two different populations: 1) a group of healthy subjects used for the development of the RSA quantification algorithm and 2) a group of MI patients for the testing of the developed algorithm. First, during the algorithm development, ECG and breathing signals were recorded from 13 subjects who were healthy male volunteers. The ECG signals
were recorded with Cardiolife recorder (TEC-7721K, Nihon Kohden, Tokyo, Japan) and simultaneous breathing signals were obtained with a temperature sensor (Hewlett Packard, Germany). Signals were obtained with a sampling frequency of 512 Hz and recorded under laboratory conditions.

In the test part of the RSA quantification, a large population of MI patients (Mäkikallio et al. 2005) was used. From a total of 2130 MI patients, 1631 patients were selected, but 499 patients were excluded due to a large number of technical and biological disturbances, such as periods of atrial fibrillation, a large amount of ectopic beats and lack of periodic R-R interval fluctuation in order to fulfill the later described criteria defined in the RSA algorithm. The ambulatory 24-hour ECG signals of the MI patients were recorded in Oulu University hospital and in the University of Munich using an Oxford Holter system (Oxford Instruments, Abingdon, UK) or a Pathfinder 700 system (Reynolds Medical, Hertford, UK). The mean age of the post-AMI patients was 59 ± 10 years. The AMI population contained 1279 males and 352 females. The characteristics of the patient population are shown in Table 3. Patients were followed up for 40 ± 17 months after the MI. In cases of death, the causes of death were verified from the hospital and autopsy records and from either the primary physicians or those who had witnessed the death. Modes of death were defined as cardiac and non-cardiac deaths by the end point committees of the participating institutes. The cardiac deaths were further classified as sudden or non-sudden (Huikuri et al. 2003, Mäkikallio et al. 2005). Cardiac death was defined as sudden if it was as one of the following: 1) a witnessed death occurring within 60 minutes from the onset of new symptoms unless a cause other than a cardiac event was obvious, 2) an unwitnessed death (within < 24 hours) in the absence of pre-existing progressive circulatory failure or other causes of death, or 3) death during attempted resuscitation.
Table 3. Clinical characteristics of the MI population (n = 1631) in Study III.

<table>
<thead>
<tr>
<th>Type of variable</th>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Age (years)</td>
<td>59 ± 10</td>
</tr>
<tr>
<td></td>
<td>Gender (male/female)</td>
<td>1279/352</td>
</tr>
<tr>
<td></td>
<td>Smoking (ex or current)</td>
<td>984 (61%)</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>288 (18%)</td>
</tr>
<tr>
<td></td>
<td>Prior MI</td>
<td>199 (12%)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>936 (57%)</td>
</tr>
<tr>
<td>Treatment</td>
<td>PCI/CABG</td>
<td>1142 (70%)</td>
</tr>
<tr>
<td></td>
<td>Q-MI no revasc</td>
<td>82 (5%)</td>
</tr>
<tr>
<td>Medical</td>
<td>ASA/warfarin</td>
<td>1567 (96%)</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers</td>
<td>1541 (95%)</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
<td>1152 (71%)</td>
</tr>
<tr>
<td></td>
<td>ACE/AT II</td>
<td>1206 (74%)</td>
</tr>
<tr>
<td></td>
<td>Diuretic</td>
<td>529 (32%)</td>
</tr>
</tbody>
</table>

Data are presented as n (%). Abbreviations are: ACE = angiotensin -converting enzyme; AT II = angiotensin II receptor; CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention; Q-MI no revasc = Q wave myocardial infarction without revascularization; ASA = acetylsalicylic acid.

4.4 Research data in Study IV

In Study IV, the study population was collected from a Multicenter study including ten European centers. A total of 5869 AMI patients were screened in the acute phase of AMI during 2–7 days after the event. Of these, an impaired left ventricular function (LVEF ≤ 0.40) was defined in 1393 patients. After exclusions, the total number of patients who were included in this study was 267. All the patients that were included had an impaired LVEF (≤ 0.40) and in their ECG recording they showed an occurrence of ectopic beats, VPBs. All patients underwent an 24-hour ambulatory two- or three-channel ECG recording (Oxford Medilog 4500, Oxford Medical Ltd., England) immediately after the index MI (between days 5 and 21) and again at 6 weeks post-MI. The clinical characteristics of the population in Study IV are described in Table 4.

Reasons for exclusion of the patients from Study IV or the analysis were mainly the refusal of the patient or inability of the patient to participate in the study due to other serious illness, coronary bypass graft surgery or death before the implantation of the loop-recorder (Huikuri et al. 2009). Other reasons for exclusion were pregnancy, life expectancy < 1 year for non-cardiac reasons. In addition, the exclusion of the patient from the analysis could be due the lack of
VPBs or ECG recording failure. Patients were followed-up for 24 months and arrhythmic events were documented with an ECG loop-recorder that was implanted between 5 to 21 days after the AMI (Huikuri et al. 2009). Clinical follow-up was done in every three months during the two-year time period.

Fatal or near-fatal cardiac arrhythmia was the primary endpoint of Study IV. Arrhythmic events containing resuscitated cardiac arrest due to primary arrhythmia, symptomatic sustained ventricular tachycardia (VT), or arrhythmic death were obliged to have been documented with the implanted loop-recorder, implanted cardioverter-defibrillator (ICD), pacemaker, Holter recording or with a telemetry slip.

Table 4. Characteristics of the MI patients (n = 267) in Study IV.

<table>
<thead>
<tr>
<th>Type of variable</th>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Age (years)</td>
<td>64 ± 11</td>
</tr>
<tr>
<td></td>
<td>Male gender</td>
<td>208 (78%)</td>
</tr>
<tr>
<td></td>
<td>Prior MI</td>
<td>100 (37%)</td>
</tr>
<tr>
<td></td>
<td>Prior CHF</td>
<td>20 (7%)</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>52 (19%)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>118 (44%)</td>
</tr>
<tr>
<td></td>
<td>Ejection fraction (%)</td>
<td>33 ± 6</td>
</tr>
<tr>
<td>Medical</td>
<td>Beta-blockers</td>
<td>246 (92%)</td>
</tr>
<tr>
<td></td>
<td>ACE-inhibitor/AT blocker</td>
<td>227 (85%)</td>
</tr>
<tr>
<td></td>
<td>Statin</td>
<td>214 (80%)</td>
</tr>
<tr>
<td></td>
<td>Antiplatelet agent</td>
<td>246 (92%)</td>
</tr>
</tbody>
</table>

Values are reported as n patients (% of population) or as means ± SD. Abbreviations: ACE = angiotensin converting enzyme; AMI = acute myocardial infarction; AT = angiotensin; CHF = congestive heart failure;
5 Methods

Methods of this dissertation included mainly the preprocessing of the HRV signals including editing of the HRV signals and the development of new algorithms for the HRV analysis. The presentation of the methods in individual Studies I–IV is as follows.

5.1 Editing effects in time and frequency domain HRV analysis (I)

The effects of editing in HRV analyses were examined with the R-R interval time series of healthy subjects and AMI patients containing both short-term and 24-hour R-R interval recordings. Short-term R-R interval data segments contained only pure sinus beats. Long-term data contained 99% of pure sinus beats and 1% artifacts that were first pre-edited.

The R-R intervals to be edited were selected randomly and defined as artifacts. Three random selections of the R-R intervals were made in order to analyze the average effects of the editing methods. The portion of the edited R-R intervals was gradually increased from 5% to 50% of all R-R intervals in 5% steps. The editing methods were deletion, interpolation of degree zero, and interpolation of degree one. The local neighborhood for the interpolation of degree zero was three R-R intervals.

After the editing process, the HRV analysis was carried out in the time and frequency domains. The time domain HRV analyses for the short-term data of 512 R-R intervals were: SDANN, RMSSD and pNN50. These time domain parameters were computed over a data segment of 512 R-R intervals. In the frequency domain, the power spectrum of the short-term data of 512 R-R intervals was computed using FFT and AR spectrum estimation methods. From power spectra, the frequency components of LF and HF were quantified. Detrending was used in the spectrum estimation to de-emphasize the unwanted trends in the data and it was performed over a block of 512 R-R intervals. In the AR spectrum estimation, the model order was 20.

In the time domain analysis of the long-term 24-hour R-R interval data, the SDNN was computed. In the frequency domain, the power spectrum analysis of the long-term 24-hour data was performed with the FFT spectrum estimation. The power of the VLF and ULF spectrum components were computed. In addition, the slope of the regression line of the log (power) versus log (frequency) of the HRV between frequencies $10^{-4}$ Hz and $10^{-2}$ Hz was computed (SLOPE).
HRV analyses were performed for the non-edited data that included only real sinus intervals in order to obtain reference values for the HRV parameters. The values of the HRV parameters for the edited R-R interval data were compared with the HRV values of the reference data, in order to assess the quality of the different editing methods. Percentage differences were computed between the reference values of the HRV parameters and the values of the randomly edited data. The mean error of the HRV parameter for the study groups was obtained by computing the average percentage difference. In addition, standard deviations and 95% confidence intervals were computed for each value of the percentage difference to show the quality of the measurements and the deviations of the HRV parameters. The acceptable error of the editing methods was chosen to be less than 5% of the reference value (the error of the mean and its upper limits of 95% confidence intervals ≤ 5%).

The following Figures 6 and 7 show examples of the R-R interval tachograms of a healthy subject (Fig. 6) and an AM1 patient (Fig. 7) edited with different methods. The edited R-R intervals are marked with triangles in Figure 6 and 7.

![Fig. 6. An example of R-R interval tachogram from a healthy subject. The small arrows above the real R-R interval tachogram (No editing) represent the abolished beats before editing. The other tachograms have been generated after the application of different editing methods.](image-url)
each editing method. The two superimposed tachograms in bottom are generated after interpolation of degree zero (white columns) and degree one (black columns). Interpolation of degree zero generates step-like shapes into the tachogram, while interpolation of degree one tends to smooth the tachogram.

Fig. 7. An example of R-R interval tachogram from an AMI patient. The small arrows above the real R-R interval tachogram (No editing) represent the abolished beats before editing. The other tachograms have been generated after the application of each editing method. The two superimposed tachograms in bottom are generated after interpolation of degree zero (white columns) and degree one (black columns).

5.2 Ectopic beats in the fractal scaling HRV analysis (II)

First, the effects of the artificial premature beats on nonlinear HRV measures were studied. Artificial ectopic beats were generated into the tachograms of 8000 R-R intervals that included only pure sinus beats. Single premature beats followed by a compensatory pause were uniformly distributed over the whole R-R interval tachograms in random places. Ectopic beats with compensatory pauses replaced the original sinus beats so that the total number of the R-R intervals remained the same (8000 R-R intervals) and the tachograms were not shifted. There always existed at least three pure sinus beats between two generated ectopic beats, Several levels of ectopy were used, thus the amount of the ectopy varied from
0.125% to an ectopy level where 35% of all the R-R intervals were qualified as ectopic beats with compensatory pauses. Three different types of prematurity classes were used so that the premature beats and the compensatory pauses differed by 30%, 20%, or 10% compared with the previous normal R-R interval. Only one type of prematurity was used at a time. Insertion of the artificial premature beats in random places was conducted three times in order to obtain an average effect of the ectopy insertion on the nonlinear HRV parameters. The analysis of the fractal scaling exponents was performed for the original data with pure sinus beats and for the data with different number of artificial premature beats.

Next, the performance of four different editing methods in the HRV fractal scaling analysis was examined by editing the previously generated artificial premature beats with four different methods. Methods of the editing were: deletion, interpolation of degree zero and one, and cubic spline interpolation. The local non-ectopic neighborhood in this study for the interpolation of degree 0 was three R-R intervals. The analyses of the fractal scaling exponent $\alpha_1$ and $\alpha_2$ were performed for original data with no premature beats or editing and for data with different number of edited premature beats.

The effects of the authentic premature beats on detrended fluctuation analysis were studied with 24-hour R-R interval data. For all 24-hour data, the pre-editing of artifacts was done with the interpolation of degree 0. First, premature beats were left unedited and secondly, premature beats were edited with the interpolation of degree 0. The analyses of the fractal scaling exponent $\alpha_1$ and $\alpha_2$ were performed for pre-edited data including premature beats and for data with edited premature beats.

Detrended fluctuation analysis (Peng et al. 1995) was performed and the fractal scaling exponents $\alpha_1$ and $\alpha_2$ were computed to quantify the fractal scaling properties of short-term ($\leq 11\text{R-R intervals}$, $\alpha_1$) and intermediate-term R-R interval time series ($> 11\text{R-R intervals}$, $\alpha_2$). For the data of 8000 R-R intervals, the analyses of the fractal scaling exponents were computed over the whole segment and for the 24-hour data the analyses were done in the segments of 8000 R-R intervals in order to achieve an average value for the entire recording period.

In the statistical evaluation of the results for the effects of real premature beats, an independent samples t test was used to analyze the differences of the fractal scaling exponent values between the patients who died and those who remained alive during the follow-up. Differences were examined in post-AMI and
general population alike. A value of $p < 0.05$ was considered to be statistically significant.

### 5.3 Quantification of the RSA (III)

Study III contained an algorithm development of the RSA quantification. This algorithm development started with processing of simultaneously recorded ECG and breathing signals. The breathing signal was recorded with the temperature sensor, such that the maximum of the respiration signal occurred at the end of expiration and correspondingly the minimum occurred at the end of the inspiration. The mean duration of the signal recordings was $38 \pm 4$ minutes. Recordings were obtained containing both metronome-guided (15 breaths per minute) and spontaneous breathing. To obtain possible irregularities in the R-R interval fluctuation, the test individuals were subjected to various physiological stimulations, such as cold face, handgrip and cold hand tests which were performed during the recordings of the metronome-guided breathing.

In the development of the algorithm for the RSA quantification, the R-R interval oscillation was examined during the metronome-guided expiration and inspiration. Expiration and inspiration were separated from the breathing signals and the maximums and minimums of the respiration signal were recognized to observe the behavior of the HR during one breath. Peak detection for the R-R interval time series was performed to identify the local R-R interval maximums and minimums. Local minimums of the R-R interval time series occurred at the end of the inspiration (the minimum of the breathing signal) and correspondingly the maximum of the R-R series occurred at the end of the expiration (the maximum of the breathing signal). The distances between adjacent local R-R interval maximums and R-R interval minimums were examined in order obtain an average number of the R-R intervals during a breathing cycle.

The forward and reverse zero-phase low-pass digital filtering was performed to attain an adaptive threshold for the R-R interval time series. Filtering utilizes the information of the R-R intervals before and after the current R-R interval in order to avoid the phase distortion. In other words, the filtering is first performed from the beginning of the R-R interval time series and then the filtered R-R interval sequence is reversed and filtered again, now starting from the end of the R-R interval time series. If $x[n]$ is the R-R interval time series and $b_i$ indicates the filter coefficients, then the filter can be described by the difference equation:
The filtering of the R-R interval time series, \( y[n] \) results in an adaptive threshold that follows the oscillation pattern of the R-R interval time series. The adaptive threshold corresponds to a moving average of the R-R interval time series and it was computed in windows of fixed length (\( N = 100 \)). Next, the threshold criteria for the R-R intervals were defined. Threshold criteria included the following requirements for the successive R-R intervals: 1) The R-R interval fluctuation pattern around the adaptive threshold was observed so that the local R-R interval maximums and minimums that are corresponding to the maximums and minimums of the breathing signal appear alternately around the adaptive threshold. 2) Maximums of the R-R interval time series preceded a fixed number of decelerating R-R intervals (1 to 8 R-R intervals). 3) Correspondingly, accelerating R-R intervals (1 to 9 R-R intervals) preceded the minimums of the R-R interval time series. The number of the R-R intervals between the maximums and the minimums varied between different patients due to individual difference in the mean rate and variation of the R-R intervals. Figure 8 illustrates the basic idea of the filtering process for R-R interval time series in the RSA quantification algorithm.

\[
y[n] = b_0 x[n] + b_1 x[n-1] + \cdots + b_N x[n-N],
\]

(22)

Successive R-R intervals matching the threshold criteria were saved for the later processing. In order to achieve an adequate number of R-R intervals for the short-term spectrum analysis of the HF power, the minimum size of the respiratory R-R
interval segments was defined as 256 R-R intervals, corresponding to 3–5 minutes of ECG recordings. The minimum number of respiratory R-R interval segments that one ECG recording had to include was defined as 10. The developed algorithm was run on the R-R intervals during the spontaneous breathing and during the physiological stimulations in order to study its functionality with the possible irregular variation of the R-R intervals. The R-R interval segments that matched the above-defined criteria were separated for the analysis of the HF power and the new RSA index. Figure 9 illustrates an example of how the non-respiratory R-R interval changes were discarded from the RSA analysis. The average value for the HF power of the respiratory associated R-R interval segments was computed with the fast Fourier method in order to obtain the power of the respiratory-linked HF fluctuation, called the RSA index.

**Fig. 9.** Example of the non-respiratory sudden changes in the R-R interval time series that are discarded from the RSA analysis (light gray segment). On the top an R-R interval tachogram, in the middle the ECG printout, and below the corresponding breathing signal.

Lastly, the developed RSA algorithm was tested in a large MI population (n = 1631). In addition to the RSA index computation, traditional HRV parameters, such as SDNN, standard HF, LF and VLF spectral powers were estimated from the 24-hour R-R interval time series of the AMI patients. Ectopic beats and other disturbances that occurred in the R-R interval time series were edited with the interpolation of degree zero before the HRV analysis.
The results of the RSA quantification and standard HRV analysis were statistically evaluated using SPSS software (SPSS 11.0, SPSS Inc., Chicago, Illinois, USA). The primary end point of this study was SCD. The selection of a sample size of more than 1500 patients with an average follow-up of over 36 months was based on the assumption that the annual incidence of the primary end point would vary from 0.5% to 4% in the current treatment era. A reliable SCD analysis was evaluated to require a minimum of 30 end points. Survival curves were estimated by the Kaplan-Meier method with the comparisons of cumulative end points based on logarithmic transformations. Multivariate analyses were performed using the Cox proportional hazards model and adjusted with the significant clinical risk factors (diabetes, advanced age, and depressed left ventricular function). The effects of the factors investigated are given as hazard ratios with 95% confidence intervals. All statistical tests, including log-rank tests in the Cox model, were two-sided and assessed at a 5% significance level. Cox regression analysis was performed using the optimum cutoff points based on the receiver operating characteristic curves.

5.4 Effects of post-ectopic HR turbulence on HRV analyses (IV)

First, in Study IV, ECG recordings were obtained from the AMI patients. Recordings of 24-hour ambulatory 2 or 3-channel ECG were performed twice for the study patients. The first (baseline) ECG recording was performed soon after the AMI, i.e. within 5 to 21 days after the event. The second ECG recording was obtained at six weeks after the AMI. For the processing of the ECG recordings, an Oxford Excel Holter system was used. 24-hour ECG recordings were examined by an experienced technician and an individual classification of the QRS complexes was performed. QRS complexes were classified into different beat classes such as normal sinus beats, VPBs and supraventricular ectopic beats. Single VPBs were carefully verified and marked with labels.

Next, the 24-hour R-R interval time series containing labeled VPBs were formed from the ECG recordings. 24-hour R-R interval time series that could be HRV analyzed were successfully obtained on 267 patients i.e. 237 patients during the baseline phase and 222 patients at 6 weeks after the AMI. The need to discard or the failure of the R-R interval time series obtaining for the HRV analysis was mainly due to appearance of a large amount of disturbances (> 20% of R-R intervals). For instance, disturbances were long episodes of atrial fibrillation (FA) or bigeminy or a large number of frequent ectopic beats. VPBs and R-R interval
oscillation after every single VPB, determined as HR turbulence (Schmidt et al. 1999), was excluded from the HRV analysis. Each verified and labeled single VPB and fifteen R-R intervals immediately after VPB were edited with the deletion method. Other possible episodes of disturbances were also removed; thereby, analyzed data included only normal R-R intervals. Deletion method was used instead of different interpolation methods to avoid the production of the false trends into R-R interval time series due to long segment of R-R intervals in the HR turbulence phenomenon (VPB + turbulence = 17 R-R intervals).

After the removal of the HR turbulence, HRV analysis was performed including analysis in the time and frequency domains and in addition a short-term DFA analysis. These kinds of HRV measures were chosen, as they have shown to posses the most powerful prognostic power in post-AMI populations. The time domain HRV analysis contained the computation of the SDNN. In the frequency domain, the HF and LF components of the HRV power spectrum were estimated with the FFT method over blocks of 512 R-R intervals. In addition, in the spectrum analysis also VLF and ULF components were computed with the FFT method on the entire R-R interval time series. DFA concerned the computation of the fractal scaling exponent, $\alpha_1$, for the short-term HRV (Peng et al. 1995).

The statistical analysis of the data was performed with the PASW Statistics software (PASW 18.0.1, SPSS Inc., Chicago, Illinois, USA). First, the effects of the HR turbulence editing were examined by computing the percentage differences between the HRV results of the traditionally edited (VBPs and other disturbances were edited) and HR turbulence edited (VBPs+15 R-R intervals and other disturbances were edited) R-R interval time series. In addition, paired two-sample t-test was performed to analyze the differences of the HRV results of the traditionally edited and HR turbulence edited data. Values of p < 0.05 were considered to be statistically significant. Next, the result data was split into deciles according to the number of VPBs. The percentage differences of the HRV parameters between original and HR turbulence edited data were computed in every decile to examine the effects of the VPB amount in the HR turbulence removal process.

Lastly, the effects of the HR turbulence removal in the risk evaluation of the arrhythmic events were analyzed. The receiver operating characteristic curve (ROC) was graphed and the area under the curve (AUC) was computed for the HRV analysis results with the primary endpoint for traditionally edited and HR turbulence edited R-R interval time series.
6 Results

6.1 Editing effects in time and frequency domain HRV analysis (I)

6.1.1 Short-Term recordings

In the time domain analysis of the short-term RR-interval data, the SDANN was least affected by the editing. The best outcome of the editing process for the SDANN analysis was achieved with the deletion method in both AMI and healthy groups. On the contrary, both RMSSD and pNN50 were highly sensitive to editing. The performance of the interpolation of degree zero was somewhat better in the editing process compared with the other editing methods in the RMSSD analysis. With respect to the pNN50, the interpolation of degree one was the best editing method in both study groups. Table 5 shows the effects of the three editing methods on the short-term time domain measures of HRV in healthy subjects and in AMI patients. The percentage differences ± 95% confidential intervals with different amounts of edited segments are shown in Figure 10. The italicized values of the HRV parameters in Table 5 highlight the editing limits for each parameter at which the mean error with its 95% confidence interval exceeds the value of 5%.
Table 5. Effects of editing methods on the short-term time domain parameters in healthy subjects (upper) and AMI patients (lower).

<table>
<thead>
<tr>
<th>Population</th>
<th>Edit %</th>
<th>Interpolation of degree 0</th>
<th>Interpolation of degree 1</th>
<th>Deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDANN [ms]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>84.73 ± 56.98</td>
<td>84.73 ± 56.98</td>
<td>84.73 ± 56.98</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>84.22 ± 55.09</td>
<td>84.16 ± 55.03</td>
<td>84.53 ± 55.70</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>82.20 ± 52.38</td>
<td>82.31 ± 52.54</td>
<td>84.18 ± 55.30</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>81.27 ± 51.52</td>
<td>81.20 ± 51.81</td>
<td>84.38 ± 56.05</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>78.80 ± 48.12</td>
<td>79.16 ± 50.30</td>
<td>84.38 ± 55.74</td>
<td></td>
</tr>
<tr>
<td>RMSSD [ms²]</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8002.9 ± 21158.9</td>
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</tr>
<tr>
<td>pNN50 [%]</td>
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<td></td>
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<tr>
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</tr>
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</tr>
<tr>
<td>AMI</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SDANN [ms]</td>
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<td></td>
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<td>19.00 ± 12.82</td>
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<td>18.73 ± 12.87</td>
<td>18.96 ± 12.93</td>
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<td>18.49 ± 12.76</td>
<td>18.91 ± 12.89</td>
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<td>RMSSD [ms²]</td>
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<td></td>
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</tr>
<tr>
<td>5</td>
<td>95.0 ± 91.3</td>
<td>90.6 ± 88.3</td>
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</tr>
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<td>20</td>
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<td>73.6 ± 70.2</td>
<td>106.4 ± 100.5</td>
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<tr>
<td>30</td>
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<td>61.6 ± 58.1</td>
<td>111.0 ± 102.8</td>
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<tr>
<td>50</td>
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<td>130.3 ± 115.6</td>
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<tr>
<td>pNN50 [%]</td>
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</tr>
<tr>
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<td>0.080 ± 0.260</td>
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<tr>
<td>5</td>
<td>0.100 ± 0.305</td>
<td>0.087 ± 0.278</td>
<td>0.104 ± 0.334</td>
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<tr>
<td>20</td>
<td>0.151 ± 0.360</td>
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<td>0.164 ± 0.450</td>
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<td>0.149 ± 0.375</td>
<td>0.082 ± 0.271</td>
<td>0.182 ± 0.490</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>0.178 ± 0.423</td>
<td>0.062 ± 0.208</td>
<td>0.382 ± 0.723</td>
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</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation. The italicized values indicate the editing limits for each parameter at which the mean error with its 95% confidence interval exceeds the value of 5%.

Abbreviations: Edit % = amount of the edited R-R intervals in percentages; SDANN = standard deviation
Fig. 10. Effects of the three different editing methods on the values of the time domain parameters for the R-R interval data of the healthy subjects (left) and the AMI patients (right). The percentage difference with 95% confidence intervals as a function of the editing percentage.

In the frequency domain analysis of the short-term R-R interval data, the estimations of both the HF and LF spectral components were dependent mostly on the editing method. The estimation of the HF spectral component turned out to be highly sensitive to editing with any of these editing methods. However, both interpolation methods performed better than the deletion method in the editing process with the HF component. The deletion method was least suitable for estimating the HF spectral component in both study groups. Editing by the deletion method produced a distinctive increase in the mean error of the HF component, especially in healthy subjects. There were no remarkable differences between the results obtained with the spectrum estimation of AR modeling and FFT. In the estimation of the LF spectral component, the interpolation of degree one was the most suitable editing method for the healthy group, however the results obtained with the interpolation of degree zero were almost equally good. In the AMI patients, on the other hand, the results obtained with the interpolation
of degree zero were slightly better than those with the interpolation of degree one. It is particular noteworthy, that in the LF component analysis, the deletion method was clearly the least suitable editing method for the AMI patients.

There were some differences in the sensitivity to editing when the different spectrum estimation methods were used. In the healthy subjects, the performance was slightly better in the FFT spectrum computation with the interpolation of degree one, but worse with the deletion method compared with the results of the AR spectrum computation. The AMI patients revealed no significant differences between the results obtained with two different spectrum estimation methods. Table 6 shows the effects of three editing methods on the short-term frequency domain measures of HRV with AR spectrum estimation and Table 7 with the FFT method. The italicized values of the percentage differences in Table 6 and Table 7 point out the editing limits for the parameter in question at which the mean error with its 95% confidence interval exceeds the value of 5%. The percentage differences are shown as a function of the number of the edited segments in Figure 11A (AR) and Figure 11B (FFT).
Table 6. Effects of the editing on the spectral parameters with AR spectrum estimation method in healthy (upper) and AMI (lower) groups.

<table>
<thead>
<tr>
<th>Population</th>
<th>Edit %</th>
<th>Interpolation of degree 0</th>
<th>Interpolation of degree 1</th>
<th>Deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF [ms²]</td>
<td>0</td>
<td>2690.9 ± 7016.0</td>
<td>2690.9 ± 7016.0</td>
<td>2690.9 ± 7016.0</td>
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<tr>
<td></td>
<td>5</td>
<td>2855.0 ± 7579.7</td>
<td>2837.0 ± 7558.2</td>
<td>2742.1 ± 6975.7</td>
</tr>
<tr>
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<td>10</td>
<td>2856.7 ± 7786.6</td>
<td>2821.0 ± 7776.2</td>
<td>2855.5 ± 7397.3</td>
</tr>
<tr>
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<td>15</td>
<td>2640.2 ± 7163.6</td>
<td>2520.5 ± 6930.7</td>
<td>2962.5 ± 7616.5</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>2214.3 ± 5947.9</td>
<td>1832.9 ± 4931.4</td>
<td>3057.0 ± 7437.4</td>
</tr>
<tr>
<td>LF [ms²]</td>
<td>0</td>
<td>2116.6 ± 3120.3</td>
<td>2116.6 ± 3120.3</td>
<td>2116.6 ± 3120.3</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2122.9 ± 3141.0</td>
<td>2157.9 ± 3192.8</td>
<td>2117.5 ± 3011.4</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2098.4 ± 3199.8</td>
<td>2168.8 ± 3237.3</td>
<td>2202.7 ± 3286.9</td>
</tr>
<tr>
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<td>2077.4 ± 3256.8</td>
<td>2249.5 ± 3524.4</td>
<td>2203.1 ± 3293.5</td>
</tr>
<tr>
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<td>50</td>
<td>1916.5 ± 3012.2</td>
<td>2364.4 ± 4098.9</td>
<td>2149.1 ± 3173.7</td>
</tr>
<tr>
<td>AMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF [ms²]</td>
<td>0</td>
<td>22.3 ± 23.9</td>
<td>22.3 ± 23.9</td>
<td>22.3 ± 23.9</td>
</tr>
<tr>
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<td>21.2 ± 22.2</td>
<td>21.5 ± 22.2</td>
<td>22.0 ± 22.4</td>
</tr>
<tr>
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<td>10</td>
<td>19.7 ± 20.8</td>
<td>20.7 ± 20.9</td>
<td>22.6 ± 22.8</td>
</tr>
<tr>
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<td>15</td>
<td>18.3 ± 18.5</td>
<td>19.5 ± 19.1</td>
<td>22.2 ± 22.2</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>14.8 ± 14.3</td>
<td>16.0 ± 14.7</td>
<td>26.2 ± 24.5</td>
</tr>
<tr>
<td>LF [ms²]</td>
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<td>61.5 ± 76.4</td>
<td>61.5 ± 76.4</td>
</tr>
<tr>
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<td>60.7 ± 73.3</td>
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<tr>
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<td>10</td>
<td>59.8 ± 72.0</td>
<td>61.9 ± 74.2</td>
<td>67.8 ± 78.1</td>
</tr>
<tr>
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<td>15</td>
<td>58.4 ± 69.8</td>
<td>61.3 ± 72.0</td>
<td>72.1 ± 80.9</td>
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<tr>
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<td>50</td>
<td>56.8 ± 66.8</td>
<td>61.1 ± 68.7</td>
<td>87.7 ± 102.5</td>
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</tbody>
</table>

Mean values of the spectral components ± standard deviation in function of the editing percentage. The italicized values of the HRV parameters indicate the editing limits for each parameter at which the mean error with its 95% confidence interval exceeds the value of 5%. Abbreviations: Edit % = amount of the edited R-R intervals in percentages; LF = low frequency power; HF = high frequency power; AR = autoregressive spectrum estimation method.
Table 7. Effects of the editing on the spectral parameters with FFT spectrum estimation method in healthy (upper) and AMI (lower) groups.

<table>
<thead>
<tr>
<th>Population</th>
<th>Edit %</th>
<th>Interpolation of degree 0</th>
<th>Interpolation of degree 1</th>
<th>Deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF [ms²]</td>
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<td>2819,5 ± 7446,0</td>
<td>2819,5 ± 7446,0</td>
<td>2819,5 ± 7446,0</td>
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<tr>
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<td>2958,9 ± 7911,3</td>
<td>2952,2 ± 7929,1</td>
<td>2596,3 ± 6857,6</td>
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</tr>
<tr>
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<td>2846,0 ± 7709,4</td>
<td>2805,2 ± 7680,3</td>
<td>2691,9 ± 7214,1</td>
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</tr>
<tr>
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<td>2587,8 ± 6928,7</td>
<td>2460,9 ± 6657,9</td>
<td>2791,3 ± 7424,7</td>
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<tr>
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<td>1795,7 ± 4755,2</td>
<td>2881,3 ± 7251,6</td>
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<tr>
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<td>2220,1 ± 3439,3</td>
<td>2220,1 ± 3439,3</td>
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<td></td>
</tr>
<tr>
<td>HF [ms²]</td>
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</table>

Mean values of the spectral components ± standard deviation in function of the editing percentage. The italicized values of the HRV parameters indicate the editing limits for each parameter at which the mean error with its 95% confidence interval exceeds the value of 5%. Abbreviations: Edit % = amount of the edited R-R intervals in percentages; LF = low frequency power; HF = high frequency power; FFT = fast Fourier spectrum estimation method.
Fig. 11. Effects of different editing methods in the frequency domain with AR (A) and FFT method (B) for the R-R interval data of the healthy subjects and the AMI patients.
6.1.2 Long-Term Recordings

Effects of three editing methods on the long-term time and frequency domain measures of the HRV are shown in Table 8 for healthy subjects and for AMI patients in Table 9. Percentage differences including 95% confidential intervals with different amounts of edited segments are shown in Figure 12 for healthy subjects and for AMI patients in Figure 13. The italicized values of the HRV parameters in Table 8 and Table 9 indicate the editing limits for each parameter at which the mean error with its 95% confidence interval exceeds the value of 5%. The analysis of the SDNN was not affected in any major way by editing with any of the editing methods in both of the study groups. In the frequency domain analysis of the long-term recordings, an evident difference was observed between the results with interpolation methods and with the deletion method. The performance of the interpolation methods in the editing process in the estimation of the ULF spectral component was superior to the performance of the deletion method. In the estimation of the VLF component, the situation was somewhat similar to the estimation of the ULF component. Again, both interpolation methods performed better than the deletion method in the editing process in both study groups. Editing with both interpolation methods did not have any significant effect on the analysis of the power law slope. Once more, the deletion method was not suitable for the power-law slope analysis (SLOPE) with either study group.
Table 8. Effects of editing method on the long-term time and frequency domain parameters in healthy subjects.

<table>
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<th>Variable</th>
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<th>Interpolation of degree 1</th>
<th>Deletion</th>
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<td>15972,5 ± 10758,3</td>
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<tr>
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<td>15951,2 ± 10365,6</td>
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<td>15835,3 ± 10099,4</td>
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<td>15953,4 ± 10353,6</td>
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<td>VLF [ms²]</td>
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<td>-1,222 ± 0,160</td>
<td>-1,216 ± 0,168</td>
<td>-1,389 ± 0,189</td>
</tr>
</tbody>
</table>

Mean values of the parameters ± standard deviation in function of the editing percentage. The italicized values indicate the editing limits for each parameter at which the mean error with its 95% confidence interval exceeds the value of 5%. Abbreviations: Edit % = amount of the edited R-R intervals in percentages; SDNN = standard deviation of the normal-to-normal R-R intervals; ULF = ultra, low frequency power; VLF = very low frequency power; SLOPE = slope of the regression line of the log(power)-log(frequency) of the HRV at a frequency of $10^{-4}$ Hz.
Table 9. Effects of editing method on the long-term time and frequency domain parameters in AMI patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Edit %</th>
<th>Interpolation of degree 0</th>
<th>Interpolation of degree 1</th>
<th>Deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN [ms]</td>
<td>0</td>
<td>75.80 ± 40.94</td>
<td>75.80 ± 40.94</td>
<td>75.80 ± 40.94</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>75.80 ± 39.51</td>
<td>75.80 ± 39.51</td>
<td>75.73 ± 39.59</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>75.80 ± 39.51</td>
<td>75.80 ± 39.51</td>
<td>75.80 ± 39.62</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>75.80 ± 39.51</td>
<td>75.80 ± 39.51</td>
<td>75.80 ± 39.68</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>75.60 ± 39.63</td>
<td>75.53 ± 39.52</td>
<td>75.83 ± 39.65</td>
</tr>
<tr>
<td>ULF [ms²]</td>
<td>0</td>
<td>3546.65 ± 2931.03</td>
<td>3546.65 ± 2931.03</td>
<td>3546.65 ± 2931.03</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>3545.71 ± 2828.16</td>
<td>3546.48 ± 2827.92</td>
<td>3697.18 ± 3037.10</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>3545.46 ± 2826.10</td>
<td>3546.26 ± 2826.94</td>
<td>3813.21 ± 3232.36</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>3545.58 ± 2826.61</td>
<td>3545.30 ± 2826.62</td>
<td>3561.99 ± 3320.42</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>3545.45 ± 2827.12</td>
<td>3542.97 ± 2823.50</td>
<td>2232.62 ± 2202.66</td>
</tr>
<tr>
<td>VLF [ms²]</td>
<td>0</td>
<td>474.94 ± 359.93</td>
<td>474.94 ± 359.93</td>
<td>474.94 ± 359.93</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>474.89 ± 347.35</td>
<td>475.22 ± 347.41</td>
<td>488.15 ± 372.28</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>474.06 ± 346.83</td>
<td>475.20 ± 347.06</td>
<td>495.15 ± 388.98</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>475.43 ± 348.97</td>
<td>476.48 ± 348.09</td>
<td>435.16 ± 374.16</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>472.31 ± 345.31</td>
<td>476.31 ± 346.17</td>
<td>252.37 ± 218.16</td>
</tr>
<tr>
<td>SLOPE</td>
<td>0</td>
<td>-1.212 ± 0.127</td>
<td>-1.212 ± 0.127</td>
<td>-1.212 ± 0.127</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>-1.213 ± 0.123</td>
<td>-1.212 ± 0.123</td>
<td>-1.261 ± 0.129</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>-1.215 ± 0.119</td>
<td>-1.213 ± 0.125</td>
<td>-1.258 ± 0.158</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>-1.217 ± 0.122</td>
<td>-1.210 ± 0.129</td>
<td>-1.311 ± 0.169</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>-1.215 ± 0.123</td>
<td>-1.211 ± 0.123</td>
<td>-1.408 ± 0.191</td>
</tr>
</tbody>
</table>

Mean values of the parameters ± standard deviation in function of the editing percentage. The italicized values indicate the editing limits for each parameter at which the mean error with its 95% confidence interval exceeds the value of 5%. Abbreviations: Edit % = amount of the edited R-R intervals in percentages; SDNN = standard deviation of the normal-to-normal R-R intervals; ULF = ultra, low frequency power; VLF = very low frequency power; Slope = slope of the regression line of the log(power)-log(frequency) of the HRV at a frequency of 10⁻⁴ Hz.
Fig. 12. Effects of the three different editing methods on the values of the time and frequency domain parameters of the long-term R-R intervals data of the healthy subjects. The percentage difference with 95% confidence intervals as a function of the editing percentage.
Fig. 13. Effects of the three different editing methods on the values of the time and frequency domain parameters of the long-term R-R intervals data of the AMI patients. The percentage difference with 95% confidence intervals as a function of the editing percentage.
6.2 Ectopic beats in detrended fluctuation analysis (II)

6.2.1 Effects of the Generated Artificial Premature Beats

Figure 14 shows the effects of the artificial premature beats on the analysis of the fractal scaling exponents $\alpha_1$ and $\alpha_2$.

Fig. 14. Effects of the artificial premature beats on fractal scaling analysis in post-AMI patients and healthy subjects. The symbols indicate following prematurity of ectopic beats: — original, —o— prematurity of 30%, —□— prematurity of 20%, and —∆— prematurity of 10%.

Analysis of the $\alpha_1$ was more sensitive to the insertion of the synthetic premature beats in the AMI patients compared with healthy subjects. Even a small number of ectopic beats produced a large decrease in the $\alpha_1$ values with all three types of the artificial premature beats. A mere 0.25% of artificial premature beats of 20% prematurity produced an over 25% decrease in the $\alpha_1$ values in the AMI data. In the healthy subjects, more than 4% of artificial premature beats of 20% prematurity were needed to produce an over 25% decrease in the $\alpha_1$ values. In the AMI patients, only 1% of artificial premature beats of 20% prematurity decreased the $\alpha_1$ values by under 0.75, while in the healthy subjects an amount of 10% of premature beats was needed to reduce the $\alpha_1$ values by under 0.75. Also, in the
analysis of $\alpha_2$, the effects of the ectopy addition were more remarkable in the AMI patients compared with the healthy subjects. Figure 15 shows an example of the effects of the artificial premature beats (30% prematurity) on the HRV power spectrum of both a post-AMI patient and a healthy subject. With even a small inclusion of premature beats, the power spectrum of an AMI patient included a larger degree of false frequency components, especially in the higher frequency areas compared to the power spectrum from a healthy subject.

![Image]

**Fig. 15.** Example of a HRV power spectrum of a post-AMI patient (A) and a healthy subject (B) as a function of the percentage of the artificial premature beats. Note the different scaling in (A) and (B) due a different intensity of the spectral components.

### 6.2.2 Performance of Editing Methods

Figure 16 shows the performance of different editing methods in the analysis of the fractal scaling exponents $\alpha_1$ and $\alpha_2$. In the $\alpha_1$ analysis, the interpolation of degree 0 performed best in the editing of the artificial ectopic beats in both AMI
patients and in healthy subjects. In the analysis of $\alpha_2$, the cubic spline interpolation produced the smallest error for the healthy subjects. However for the AMI patients, the best performance of editing in the $\alpha_2$ analysis was achieved with the interpolation of degree one.

Fig. 16. Effects of four different editing methods on the values of the DFA analyses for the RR data of post-AMI patients and healthy subjects. Mean values of the $\alpha_1$ and $\alpha_2$ analyses are as a function of the amount of the edited R-R intervals. $\alpha_1$ and $\alpha_2$ indicate the scaling exponents of the DFA analysis from short and intermediate time windows respectively. The symbols indicate following editing methods: — original, —o— deletion, ---□--- interpolation of degree zero, ---∆--- interpolation of degree one and ---◊--- cubic spline interpolation

6.2.3 Effects of the Real Premature Beats on Fractal Scaling Analysis of 24-Hour Data

Comparisons of the $\alpha_1$ and $\alpha_2$ analysis in the post-AMI patients and in the elderly population between those who died and those who survived during the follow-up are shown in Table 10. In the post-AMI group, both edited and unedited $\alpha_1$ values differed between survivors and non-survivors ($P < 0.01$ for edited, and $P < 0.05$ for unedited). In the general healthy population, there were no significant
differences between those who died and the survivors in the edited $\alpha_1$ value. However, $\alpha_1$ analyzed from the unedited data differed significantly between the elderly healthy subjects who survived or experienced cardiac death ($P < 0.05$). In the analysis of $\alpha_2$, there was no significant difference between the survivors and those who died either in post-AMI or the general population.

Table 10. Measures of HR dynamics among the post-infarct patients (left) and healthy subjects (right) who died due to cardiac causes during the follow-up and among the matched survivors.

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Post AMI</th>
<th></th>
<th></th>
<th>Healthy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dead (n = 42)</td>
<td>Alive (n = 42)</td>
<td>P Value</td>
<td>Dead (n = 42)</td>
<td>Alive (n = 42)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age</td>
<td>69 ± 8</td>
<td>68 ± 8</td>
<td>NS</td>
<td>73 ± 4</td>
<td>72 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Men/Women</td>
<td>26/16</td>
<td>26/16</td>
<td>NS</td>
<td>23/19</td>
<td>23/19</td>
<td>NS</td>
</tr>
<tr>
<td>EF(%)</td>
<td>39 ± 12</td>
<td>42 ± 10</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>NYHA class II–III</td>
<td>67%</td>
<td>67%</td>
<td>NS</td>
<td>90%</td>
<td>90%</td>
<td>NS</td>
</tr>
<tr>
<td>Number of premature beats/hour</td>
<td>26 ± 42</td>
<td>32 ± 68</td>
<td>NS</td>
<td>23 ± 28</td>
<td>14 ± 17</td>
<td>NS</td>
</tr>
</tbody>
</table>

Measures of HR dynamics

<table>
<thead>
<tr>
<th></th>
<th>Post AMI</th>
<th></th>
<th></th>
<th>Healthy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>76 ± 25</td>
<td>87 ± 32</td>
<td>NS</td>
<td>133 ± 38</td>
<td>144 ± 32</td>
<td>NS</td>
</tr>
<tr>
<td>$\alpha_1$-unedited</td>
<td>0.71 ± 0.33</td>
<td>0.89 ± 0.36</td>
<td>0.05</td>
<td>0.83 ± 0.27</td>
<td>0.96 ± 0.19</td>
<td>0.05</td>
</tr>
<tr>
<td>$\alpha_1$-edited</td>
<td>1.01 ± 0.31</td>
<td>1.19 ± 0.27</td>
<td>0.01</td>
<td>1.10 ± 0.18</td>
<td>1.16 ± 0.15</td>
<td>NS</td>
</tr>
<tr>
<td>$\alpha_2$-unedited</td>
<td>1.08 ± 0.20</td>
<td>1.09 ± 0.16</td>
<td>NS</td>
<td>1.10 ± 0.12</td>
<td>1.11 ± 0.09</td>
<td>NS</td>
</tr>
<tr>
<td>$\alpha_2$-edited</td>
<td>1.21 ± 0.11</td>
<td>1.17 ± 0.12</td>
<td>NS</td>
<td>1.17 ± 0.08</td>
<td>1.14 ± 0.09</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation unless otherwise indicated. EF = ejection fraction; NYHA = New York Heart Association Classification; SDNN = standard deviation of normal-to-normal R-R intervals; $\alpha_1$ = short-term scaling exponent; $\alpha_2$ = long-term scaling exponent; unedited = analysis of fractal measures of R-R interval variability including the premature beats; edited = analysis of fractal measures of R-R interval variability after editing of the premature beats.

6.3 Respiratory sinus arrhythmia as a predictor of sudden cardiac death after myocardial infarction (III)

The performance of the RSA quantification algorithm was manually examined in 13 healthy subjects. Visual analysis revealed that the algorithm could extract the respiratory-related R-R intervals with high accuracy.

With respect to the AMI patients, during a mean follow-up of 40 months, the total number of deaths was 147. Of these deaths, 89 were cardiac and 58 were non-cardiac. When only the cardiac deaths were considered, 47 were non-SCDs
and 42 were SCDs. The annual incidence of SCD was 0.8%. The hazard ratios of the various HRV risk variables for SCD and non-SCD are listed in Table 11. In the univariate analysis, various Holter-based risk indexes, including the standard deviation of R-R intervals and spectral measures of HRV, were associated with an increased risk of SCD and non-SCD, as seen in Table 11. Depressed respiratory-associated HF fluctuation, expressed by a reduced RSA index (< 200 ms²), was the measure with specific predictive value for SCD, indicating a 7-fold risk of a sudden death during the follow-up (Relative risk 7.4; 95% CI 3.6 ± 15.1; P > 0.0001). In a multivariate analysis after adjustment for age, left ventricular systolic function, and history of diabetes, the abnormal RSA index maintained its predictive value, particularly SCD (Relative risk 4.7; 95% CI 2.3 ± 9.9; P < 0.0001) but no longer predicted non-SCD (Table 11). The other indexes of HRV were strong predictors of both non-SCD and SCD but they had no ability to predict SCD in particular (Table 11).

The Kaplan-Meier survival curve in Figure 17 shows that especially for the patients with a preserved RSA index (> 200 ms²), the SCD rate was very low, approximately 1% up to 3 years, and < 2% even after 4 years.

### Table 11. Relative risk variables as predictors SCD and non-SCD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SCD</th>
<th>Non-SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative risk</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Univariate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF &lt; 45 (%)</td>
<td>5.76 (2.89 ± 11.47)</td>
<td>0.000</td>
</tr>
<tr>
<td>SDNN &lt; 90 (ms)</td>
<td>2.14 (0.51 ± 8.91)</td>
<td>0.296</td>
</tr>
<tr>
<td>HF &lt; 70(ms²)</td>
<td>3.79 (1.89 ± 7.57)</td>
<td>0.000</td>
</tr>
<tr>
<td>LF &lt; 170(ms²)</td>
<td>4.23 (1.85 ± 9.67)</td>
<td>0.001</td>
</tr>
<tr>
<td>VLF &lt; 700(ms²)</td>
<td>3.85 (1.92 ± 7.69)</td>
<td>0.000</td>
</tr>
<tr>
<td>RSA index &lt; 200(ms²)</td>
<td>7.40 (3.64 ± 15.06)</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Multivariate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN &lt; 90 (ms)</td>
<td>1.25 (0.29 ± 5.29)</td>
<td>0.004</td>
</tr>
<tr>
<td>HF &lt; 70(ms²)</td>
<td>2.35 (1.13 ± 4.89)</td>
<td>0.022</td>
</tr>
<tr>
<td>LF &lt; 170(ms²)</td>
<td>1.74 (0.72 ± 4.19)</td>
<td>0.216</td>
</tr>
<tr>
<td>VLF &lt; 700(ms²)</td>
<td>1.99 (0.90 ± 4.00)</td>
<td>0.093</td>
</tr>
<tr>
<td>RSA index &lt; 200(ms²)</td>
<td>4.74 (2.28 ± 9.85)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

EF = ejection fraction; HF = standard 24-hour high frequency power; LF = low frequency power; RSA index = respiratory sinus arrhythmia index; SCD = sudden cardiac death; SDNN = standard deviation of normal-to-normal R-R intervals; VLF = very low frequency power.
6.4 Effects of post-ectopic HR turbulence on HRV analyses (IV)

First, in the Study IV, the mean effects of the HR turbulence removal on the HRV analysis were examined in the whole data. The absolute values of the HRV measures with standard deviations and the percentage differences with interquartile ranges between the HRV values of the original data and HR turbulence edited data are shown in Table 12. The largest changes were found in the values of the ULF and VLF components when analyzed both at the baseline phase and at 6 weeks after the AMI. The ULF component was reduced by 4.3% (p = 0.006) at the baseline analysis and by 6.8% (p < 0.001) at the 6 week analysis between the original and HR turbulence edited data. Respectively, the reduction of the VLF values was 3.9% (p = 0.031) in the baseline phase and 5.6% (p = 0.001) at the 6 week analysis. LF and HF components diminished between 2.2% to 4.1% after the HR turbulence removal. SDNN was least affected by the HR turbulence editing so that the differences in the SDNN values between the original and HR turbulence edited data were only around 1.0%. A slight significant increase in the $\alpha_1$ values was observed after the turbulence removal (p < 0.001) as seen in Table 12.

Fig. 17. Kaplan-Meier survival curves for sudden cardiac death (SCD) among patients with depressed respiratory sinus arrhythmia (RSA) index and RSA index over 200 ms$^2$. 
Table 12. Absolute values and percentage differences of HR variability measures between original and HR turbulence edited data.

<table>
<thead>
<tr>
<th>Data type</th>
<th>Original</th>
<th>HR turbulence edited</th>
<th>Percentage difference (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>6 weeks</td>
<td>baseline</td>
<td>6 weeks</td>
</tr>
<tr>
<td>ULF (ms²)</td>
<td>7304 ± 6000</td>
<td>8737 ± 5698</td>
<td>4.3 ± 1.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>VLF (ms²)</td>
<td>856 ± 767</td>
<td>1172 ± 920</td>
<td>3.9 ± 1.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>94 ± 32</td>
<td>111 ± 35</td>
<td>0.9 ± 0.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>α1 (ms)</td>
<td>1.12 ± 0.24</td>
<td>1.16 ± 0.23</td>
<td>1.6 ± 1.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>313 ± 328</td>
<td>508 ± 624</td>
<td>2.2 ± 2.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>205 ± 292</td>
<td>328 ± 526</td>
<td>2.7 ± 1.9</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Absolute HR variability values are reported as mean ± standard deviation and percentage differences (%) are reported as mean ± interquartile range.

Next, the effects of the HR turbulence editing were examined in more detail. HRV analysis data was split into deciles, i.e. 10 quantiles, according to the VPB amount. The effects of the VPB amount in the HR turbulence editing process are presented in Table 13, where the percentage differences of the HRV parameters between original and HR turbulence edited data are shown in deciles of different VPB amount. In the lower half quantiles (Q1–Q5) at the baseline phase, VPBs were infrequent (Q5: 15–41 VPBs per 24h, 0.02–0.04%) and thus the effects of the HR turbulence editing for HRV parameters were minor (percentage difference < 1%). Correspondingly, in the HRV analysis at 6 weeks after the AMI with about equally small amount of VPBs (Q3: 10–40 VPBs per 24h, 0.013–0.03%) the percentage differences remained small between the original and HR turbulence edited data (< 1%) with the exception of the LF values of which the difference was about 2%.

SDNN analysis was least affected by the HR turbulence removal. The differences in the SDNN values remained small up to the 9th quantile in both phases, the baseline and at 6 weeks after the AMI. Also the analysis of the α1 was not affected to any major extent by the HR turbulence removal until the 10th quantile (Table 13). The ULF and VLF components were affected most notably by the HR turbulence removal. When the number of VPBs was over 0.44% (Q9: 339–1431 VPBs per 24h, 0.44–1.38%) in the baseline phase, the percentage difference was 6.41% ± 4.23% for ULF and 3.79% ± 3.18% for the VLF. In the
data collected 6 weeks after the AMI, the ULF and VLF component had changed considerably due to the HR turbulence removal already in the 6\textsuperscript{th} quantile (Q6: 39–204 VPBs per 24h, 0.11–0.19\%) of which the percentage differences were 8.76\% ± 23.4\% for the ULF and 8.64\% ± 24.2\% for the VLF. In the last 10\textsuperscript{th} quantile, the percentage differences were significantly increased for every HRV parameter tested. The most notable changes were obtained in the ULF and VLF parameters in the 10\textsuperscript{th} quantile, i.e. the differences were at baseline 35\% for ULF and 30\% for VLF and at 6 weeks after the AMI 39\% for ULF and 32\% for VLF. In addition, in the 10\textsuperscript{th} quantile the percentage differences in the LF and HF components were rather large (> 10\%) at both baseline phase and at 6 weeks after the AMI (Table 13). Figure 18 displays the power spectra of a patient with frequent VBPs before and after the turbulence removal.
Table 13. Percentage differences of the HRV measures between original and HR turbulence edited data at baseline phase and at 6 weeks after the AMI split into 10 quantiles according to the percentage amount of the VPBs.

<table>
<thead>
<tr>
<th>Data</th>
<th>VPBs (%)</th>
<th>VPBs/24h</th>
<th>ULF</th>
<th>VLF</th>
<th>SDNN</th>
<th>σ1</th>
<th>LF</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>min-max</td>
<td>min-max</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>0.001–0.004</td>
<td>1–4</td>
<td>0.05±0.05</td>
<td>0.28±0.33</td>
<td>0.00±0.00</td>
<td>0.23±0.56</td>
<td>0.26±0.57</td>
<td>0.33±0.98</td>
</tr>
<tr>
<td>Q2</td>
<td>0.004–0.007</td>
<td>3–7</td>
<td>0.13±0.15</td>
<td>0.65±1.04</td>
<td>0.00±0.00</td>
<td>1.16±2.24</td>
<td>0.40±0.42</td>
<td>0.16±0.41</td>
</tr>
<tr>
<td>Q3</td>
<td>0.007–0.01</td>
<td>5–11</td>
<td>0.10±0.07</td>
<td>0.43±0.30</td>
<td>0.00±0.00</td>
<td>0.43±0.46</td>
<td>0.45±0.53</td>
<td>0.23±0.54</td>
</tr>
<tr>
<td>Q4</td>
<td>0.01–0.02</td>
<td>7–27</td>
<td>0.16±0.14</td>
<td>0.47±0.42</td>
<td>0.04±0.18</td>
<td>0.80±0.97</td>
<td>0.44±0.72</td>
<td>0.62±0.82</td>
</tr>
<tr>
<td>Q5</td>
<td>0.02–0.04</td>
<td>15–41</td>
<td>0.27±0.24</td>
<td>0.50±0.36</td>
<td>0.16±0.46</td>
<td>0.77±0.66</td>
<td>0.66±0.70</td>
<td>0.60±0.87</td>
</tr>
<tr>
<td>Q6</td>
<td>0.04–0.08</td>
<td>29–80</td>
<td>0.68±0.60</td>
<td>1.01±1.02</td>
<td>0.27±0.52</td>
<td>0.59±0.66</td>
<td>1.06±1.20</td>
<td>0.63±1.14</td>
</tr>
<tr>
<td>Q7</td>
<td>0.08–0.16</td>
<td>55–144</td>
<td>1.35±0.93</td>
<td>1.30±1.29</td>
<td>0.18±0.47</td>
<td>1.00±1.26</td>
<td>1.79±1.65</td>
<td>1.49±1.59</td>
</tr>
<tr>
<td>Q8</td>
<td>0.16–0.42</td>
<td>142–377</td>
<td>2.22±1.93</td>
<td>2.84±2.36</td>
<td>0.26±0.53</td>
<td>1.63±2.42</td>
<td>2.08±1.88</td>
<td>2.31±2.86</td>
</tr>
<tr>
<td>Q9</td>
<td>0.44–1.38</td>
<td>339–1431</td>
<td>6.41±4.23</td>
<td>3.79±3.18</td>
<td>0.83±1.21</td>
<td>2.07±1.60</td>
<td>4.39±3.65</td>
<td>2.80±3.01</td>
</tr>
<tr>
<td>Q10</td>
<td>1.39–10.12</td>
<td>1124–10322</td>
<td>34.7±34.8</td>
<td>29.8±39.9</td>
<td>7.37±10.7</td>
<td>7.65±9.95</td>
<td>11.5±12.8</td>
<td>19.2±21.6</td>
</tr>
<tr>
<td>6 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>0.001–0.006</td>
<td>1–6</td>
<td>0.08±0.07</td>
<td>0.26±0.22</td>
<td>0.00±0.00</td>
<td>0.86±2.28</td>
<td>0.20±0.31</td>
<td>0.25±0.47</td>
</tr>
<tr>
<td>Q2</td>
<td>0.006–0.013</td>
<td>5–15</td>
<td>0.17±0.14</td>
<td>0.50±0.17</td>
<td>0.03±0.16</td>
<td>0.53±0.71</td>
<td>0.45±0.45</td>
<td>0.42±0.58</td>
</tr>
<tr>
<td>Q3</td>
<td>0.013–0.03</td>
<td>10–40</td>
<td>0.25±0.22</td>
<td>0.61±0.48</td>
<td>0.00±0.00</td>
<td>0.58±0.71</td>
<td>2.03±7.02</td>
<td>0.39±0.51</td>
</tr>
<tr>
<td>Q4</td>
<td>0.04–0.07</td>
<td>27–65</td>
<td>0.44±0.39</td>
<td>0.62±0.42</td>
<td>0.03±0.13</td>
<td>1.14±1.86</td>
<td>1.61±2.24</td>
<td>0.98±1.88</td>
</tr>
<tr>
<td>Q5</td>
<td>0.07–0.10</td>
<td>53–130</td>
<td>0.94±0.75</td>
<td>0.98±0.99</td>
<td>0.16±0.37</td>
<td>1.10±2.20</td>
<td>1.35±1.57</td>
<td>1.87±4.05</td>
</tr>
<tr>
<td>Q6</td>
<td>0.11–0.19</td>
<td>39–204</td>
<td>8.76±23.4</td>
<td>8.64±24.2</td>
<td>3.33±11.2</td>
<td>1.86±3.38</td>
<td>6.08±19.4</td>
<td>6.23±19.9</td>
</tr>
<tr>
<td>Q7</td>
<td>0.19–0.36</td>
<td>115–330</td>
<td>2.27±2.25</td>
<td>2.11±1.70</td>
<td>0.32±0.61</td>
<td>1.12±1.32</td>
<td>4.27±8.12</td>
<td>4.30±8.13</td>
</tr>
<tr>
<td>Q8</td>
<td>0.36–0.66</td>
<td>248–686</td>
<td>7.46±4.86</td>
<td>4.72±8.86</td>
<td>1.03±1.39</td>
<td>2.18±5.18</td>
<td>3.62±3.34</td>
<td>3.81±3.56</td>
</tr>
<tr>
<td>Q9</td>
<td>0.71–2.20</td>
<td>487–1983</td>
<td>10.1±73.33</td>
<td>6.80±5.09</td>
<td>1.21±1.62</td>
<td>1.71±2.58</td>
<td>5.46±5.90</td>
<td>3.98±3.07</td>
</tr>
<tr>
<td>Q10</td>
<td>2.21–9.96</td>
<td>1812–9265</td>
<td>38.7±21.0</td>
<td>32.2±22.0</td>
<td>4.81±4.34</td>
<td>5.77±6.66</td>
<td>16.7±18.2</td>
<td>16.6±14.8</td>
</tr>
</tbody>
</table>

Percentage differences (%) of the HRV parameters are reported as mean ± standard deviation and amount of the VPBs during 24 hours are reported as range from minimum to maximum as a percentage value (column 2) and absolute number (column 3). Quantiles are numbered as Q1…Q10.
Fig. 18. Power spectra of the R-R interval time series of a patient with frequent VPBs (> 50/h). The upper curve represents the spectrum where only VPBs and the compensatory pauses are edited. The lower curve represents the spectrum after removal of VPBs and 15 consecutive R-R intervals after VPBs.

Finally, the effects of the HR turbulence removal on the risk evaluation were studied. During the follow-up of 22 months, 20 patients experienced the primary endpoint (7.4%) out of the 267 enrolled patients. Ten of these were due to symptomatic sustained monomorphic ventricular tachycardia and ten were SCDs or resuscitated cardiac arrests due to ventricular fibrillation. The prediction of primary endpoint was evaluated by the values of area under the curve (AUC) for SDNN, spectrum parameters (HF, LF, VLF, ULF) and the fractal scaling exponent for the short-term HRV ($\alpha_1$) analyzed from 24-hour Holter recordings. The values of the AUC for the original data and HR turbulence edited data are listed in Table 14. The HR turbulence removal slightly improved the predictive value of ULF spectral component, analyzed 6 weeks post-AMI (AUC: 0.69->0.74). Likewise, the predictive power of VLF component slightly improved (AUC: 0.69->0.71). No noticeable differences were observed in any other HRV indexes in their ability to predict the primary endpoint after turbulence removal.
Table 14. HRV measures as predictor of primary endpoint.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR turbulence edited data</th>
<th>Original data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC ± SD, p-value</td>
<td>AUC ± SD, p-value</td>
</tr>
<tr>
<td>ULF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>0.71 ± 0.06, p = 0.002</td>
<td>0.72 ± 0.06, p = 0.002</td>
</tr>
<tr>
<td>6 weeks</td>
<td>0.74 ± 0.07, p = 0.003</td>
<td>0.69 ± 0.08, p = 0.02</td>
</tr>
<tr>
<td>VLF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>0.63 ± 0.07, p = 0.068</td>
<td>0.64 ± 0.05, p = 0.11</td>
</tr>
<tr>
<td>6 weeks</td>
<td>0.71 ± 0.07, p = 0.008</td>
<td>0.69 ± 0.07, p = 0.02</td>
</tr>
<tr>
<td>SDNN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>0.65 ± 0.07, p = 0.03</td>
<td>0.65 ± 0.07, p = 0.03</td>
</tr>
<tr>
<td>6 weeks</td>
<td>0.65 ± 0.09, p = 0.07</td>
<td>0.66 ± 0.08, p = 0.05</td>
</tr>
<tr>
<td>α1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>0.63 ± 0.09, p = 0.06</td>
<td>0.60 ± 0.08, p = 0.13</td>
</tr>
<tr>
<td>6 weeks</td>
<td>0.57 ± 0.10, p = 0.37</td>
<td>0.59 ± 0.09, p = 0.25</td>
</tr>
<tr>
<td>LF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>0.51 ± 0.08, p = 0.94</td>
<td>0.51 ± 0.08, p = 0.92</td>
</tr>
<tr>
<td>6 weeks</td>
<td>0.59 ± 0.09, p = 0.25</td>
<td>0.61 ± 0.09, p = 0.18</td>
</tr>
<tr>
<td>HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>0.42 ± 0.07, p = 0.22</td>
<td>0.43 ± 0.07, p = 0.29</td>
</tr>
<tr>
<td>6 weeks</td>
<td>0.57 ± 0.10, p = 0.40</td>
<td>0.58 ± 0.10, p = 0.29</td>
</tr>
</tbody>
</table>

Values of the area under receiver operating characteristics curve (AUC) are reported as means ± standard deviation. Baseline is tested 5–14 days after AMI.
7 Discussion

HRV is a patient-friendly method to obtain information about the autonomic nervous function. HRV has had its most valuable diagnostic use in the AMI patients in the risk evaluation of death or arrhythmic events (Kleiger et al. 1987, Bigger et al. 1992, Huikuri et al. 2000, Camm et al. 2004, Mäkikallio et al. 2005, Stein et al. 2005). However, R-R interval data usually contain both biological and technical artifacts. Editing of the artifacts has been recommended and it has become an important preprocessing task of the R-R interval time series to obtain more reliable analysis of the HRV (Task Force of ESC & NASPE 1996). However, there are problems with the reliability of the HRV analysis due to different handling of ectopic beats and other artifacts in the R-R interval time series (Jung et al. 1996). More information is still needed of handling the artifacts and relevant R-R intervals to gain possible consensus of the matter.

7.1 Effects of editing on time and frequency domain HRV analysis (I)

Study I of this dissertation examines the effects of different editing methods with the different type of R-R interval data. The main findings of this section were that (1) some parameters of the HRV analysis are more sensitive to the editing of R-R intervals than the others. This infers that the error in the values of one HRV parameter may not increase significantly as a function of the editing proportion, while the error in some other parameter may increase strongly with even a moderate amount of editing. (2) The editing of the R-R interval tachograms should ideally be performed by using different editing methods for the different HRV analyses. The same editing method that gave a minimum error for a simple time domain analysis, such as the SDANN, was not suitable for a more complex HRV analysis, such as the estimation of the spectral components of the HRV. (3) Deletion of the artifacts or ectopic beats was not a suitable editing method for the analysis of the long-term power spectral components of HRV. (4) Finally, there were substantial differences between healthy subjects and AMI patients in the results of HRV analysis obtained with different editing methods.

Deletion editing simply removes the edited R-R intervals. The number of samples is reduced by the number of the edited R-R intervals. The deletion method has an influence especially on the high-frequency fluctuation in the tachogram. The deletion method produces step-like shapes into the tachogram,
resulting in sudden changes in the R-R interval time series. This effect is significant, especially if abrupt changes are produced in a portion of smooth natural changes. Unlike the deletion method, the interpolation methods retain the number of the samples unchanged. Both interpolation methods can be considered as serving as low-pass filters with different filter capacities. Interpolation of degree zero produces flat-like shapes in the tachogram, while interpolation of degree one produces slope-like shapes, especially in the tachograms of high-frequency fluctuation.

In the time domain analysis of short-term R-R interval sequences, the SDANN technique was least affected by the editing. The deletion method performed best in the editing process for the analysis of SDANN. The situation with RMSSD and pNN50 was different. These parameters were significantly more sensitive to editing than SDANN. With only a small amount of editing, the error in the RMSSD analysis increased strongly with all three editing methods. In the time domain analysis of the long-term R-R interval data, SDNN was not affected significantly by editing with any of the three editing methods. The mean error of the SDNN remained small even with a large number of edited R-R intervals. Due to the large number of the samples collected during a 24-hour ECG recording (approximately 90,000 R-R intervals), even extensive editing does not clearly affect the SDNN analysis and the overall variability of the data can be retained close to the original situation. These findings have some practical implications, i.e., that SDNN can be reliably analyzed even for noisy data and recordings with frequent ectopy after careful editing.

In the frequency domain analysis of short-term data, the estimation of the HF and LF spectral components was dependent on the study group and the editing method. In addition, the method of the spectral computation, either AR or the FFT, also had a slight effect on the performance of the editing process. The deletion method was not suitable for the estimation of either the HF or the LF component. By increasing the HF fluctuation in the tachogram and shortening the waveform of the signal, it was found that the deletion method produced false frequency components in the HF parts in the power spectrum and broadened the LF, especially the HF component. By this broadband flattening of the spectra, the deletion method increased especially the power of the HF but also the power of the LF component. This is especially obvious in the data with high R-R interval variation as seen in Figure 19, which shows an example of the power spectrum for a healthy subject.
In the spectral analysis of the long-term data, the deletion method produced the largest errors. In the estimation of the ULF, none of the interpolation methods affected the ULF analysis to any major extent while the deletion method produced large errors in healthy subjects and AMI patients. Similar results also were obtained with the VLF power estimation. The mean error also in the analysis of the slope of the power-law regression line at a frequency between $10^{-4}$ Hz and $10^{-2}$ Hz remained small with both interpolation methods while the deletion method produced the largest errors for both study groups. The long-term spectrum components (ULF and VLF) are situated in the frequencies near to the zero. The results of the long-term analysis are mostly affected by a change in the number of the R-R intervals, which affects the waveform of the HRV signal. Since the deletion method reduces the number of samples, it is the least suitable method for the long-term spectrum analysis.

The use of the different editing methods in Study I emphasizes the need for not only one but several different editing methods for different HRV analyses and different types of R-R interval data. Different researchers have recommended different ways to deal with and edit the noise and artifacts in HRV data. Recommendations concerning deleting and interpolating the artifacts, have been presented depending on the study. Vybiral et al. (1991) recommended the use of splining with the interpolation for data files with complex arrhythmias. Lippmann et al. (1994) considered the deletion method to be equally good or even better than the more complicated editing methods in both time and frequency domain analyses with relatively short (5 min) R-R interval sequences. In Study I, in the time domain analysis, the deletion method was found to be the most suitable method only for the analysis of SDANN and SDNN. Birkett et al. (1991) reported an increase in the low-frequency (0–0.05 Hz) and mid-frequency (0.05–0.15 Hz) ranges of the HRV power spectrum with the editing methods of the cubic spline and linear interpolation in the case of CHF patients with a high degree of ectopy (> 5%). In this study, linear interpolation (interpolation of degree one) produced an increase in the LF component (0.04–0.15 cycles/beat) in short-term data of healthy subjects and a very slight increase in the VLF component (0.005–0.04 cycles/beat) in long-term data of healthy subjects. Various proportions of edited intervals, ranging from 1% to 30%, have been accepted for an analysis of HRV in scientific articles. Study I shows that none of the editing methods is superior to the others, and that investigators should perform their own validation for editing, depending on the study population and the particular HRV measure. The findings of Study I can be partly used as a reference for the optimal editing method for
different HRV parameters and the acceptable number of edited beats for different HRV analysis methods.

![Image of an HRV power spectrum](image)

**Fig. 19.** An example of an HRV power spectrum for a healthy subject with deletion editing. The peak of the HF component diminishes markedly as a function of editing percentage, but at the same time the HF component broadens out because of the appearance of false frequency components. This results in an increase in the power of the HF spectral component.

### 7.2 Effects of ectopic beats and editing on detrended fluctuation analysis (II)

The time and frequency domain analysis of HRV is typically based on the assumption that various indices of HRV can describe the input of the ANS to the sinus node (Task Force of ESC & NASPE 1996). Therefore, the ectopic beats are traditionally deleted and replaced or edited by artificial R-R intervals. A similar assumption may not be applicable in the analysis of dynamic behavior of R-R intervals by methods based on nonlinear dynamics. Unlike the traditional
measures of HRV from Holter recordings containing ectopic beats, nonlinear analysis methods may describe true R-R interval dynamics without the deletion and replacement of real R-R intervals caused by ectopic beats (Tapanainen et al. 2002). Study II of this dissertation was designed to assess the effects of premature beats on fractal scaling exponents analyzed by the DFA methods. This particular analysis method was chosen because the short-term fractal scaling exponent has provided important prognostic information in various patient populations. The following principle observations were made: 1) premature beats cause quantitatively different effects on the short-term scaling exponent among the healthy subjects and post-AMI patients, 2) various editing methods may have divergent effects on fractal scaling exponents. Interpolation of degree zero appeared to be the most suitable for the editing of premature beats when short-term scaling exponent is analyzed by the DFA method. Finally, the non-edited short-term scaling exponent provided prognostic information both in the post-AMI population and in the random general population.

7.2.1 Effects of premature beats on fractal scaling exponents

Analysis of fractal-like HR behavior by the DFA methods has shown that healthy subjects may exhibit only little inter-individual variation in the short term scaling exponent, its values being typically near 1 (Peng et al. 1995, Goldberger et al. 2002). Study II indicated that a relatively large amount of premature beats is needed before this normal fractal-like HR behavior is broken down toward higher random dynamics in the subjects without any evidence of structural heart disease. On the contrary, in post-AMI patients, even a small amount of premature beats resulted in random R-R interval dynamics. There is an obvious explanation why a smaller amount of premature beats is needed in post-AMI patients to break down the normal fractal-like R-R interval dynamics. The post-AMI patients revealed a smaller overall HRV, measured by SDNN, as well as smaller beat-to-beat R-R interval oscillations, estimated by the HF component. The scaling exponent $\alpha_1$ is obtained from the slope of the logarithmic fluctuation function versus logarithmic R-R intervals. Therefore, $\alpha_1$ describes the “roughness” of the R-R interval time series in the pre-defined time window. A larger value of the $\alpha_1$ represents a smoother signal. This may explain, why in a post-AMI patient even a small amount of premature beats causes a major increase in the high frequencies of the power spectrum, while in a healthy subject, a larger amount of premature beats is required to evoke a similar effect in the power spectrum.
7.2.2 Methods of editing in the fractal scaling analysis

In the Study II $\alpha_1$ analysis of the short-term data, the best performance of editing was achieved with the interpolation of degree 0 in both the post-AMI and the healthy population. If a large number of R-R intervals are edited with the interpolation of degree one or spline interpolation, the $\alpha_1$ value increases because of a smoothening effect of the spline interpolation on the HRV signal. The deletion method conversely decreases the $\alpha_1$ value by increasing the “roughness” of the HRV signal. This may happen with the R-R time series where there is a high beat-to-beat variability (healthy subjects). However for the time series with low R-R variability (AMI patients), the effects of the deletion method can even be opposite: the deletion method may produce an increase in the $\alpha_1$ value by removing only a few high frequency fluctuations (smoothening effect) that may have appeared.

7.2.3 Edited and unedited fractal scaling exponent and mortality

In the Study II the subjects of the general population who subsequently died due to cardiac problems had a lower short-term scaling exponent than those who survived when the analysis was conducted from the real R-R interval data including the premature beats. The edited short-term scaling exponent or the number of ectopic beats itself could not differentiate the survivors from those who died. Thus, reduced overall HRV together with frequent ectopy in the subjects without a known structural heart disease seems to result in altered R-R interval dynamics toward more random behavior. This change in the dynamic pattern of fractal-like HR behavior seems to be associated with an increased risk of cardiac death, independent of the study population.

7.3 Quantification of the RSA and mortality (III)

The main finding of the Study III of this dissertation was that depressed RSA, as measured by the RSA index, was found to be a specific risk marker for SCD in patients with prior MI. Although other risk markers, such as conventional HRV measures and left ventricular function, have been shown to be associated with an increased risk of cardiac mortality in the AMI population (Mäkikallio et al. 2005), these indexes have only limited value for elucidating the risk for either SCD or non-SCD. The RSA index was the only measure that appeared to be a specific
indicator of increased risk for the SCD even after adjustments with significant clinical risk factors, such as advanced age, diabetes, and depressed left ventricular systolic function.

Previous observational follow-up studies have shown that the 24-hour HF spectral component has the low predictive accuracy for mortality compared with other spectral indexes in patients with MI (Kleiger et al. 1987, Bigger JT Jr et al. 1992, Lanza et al. 1998, Huikuri et al. 2000, 2003, Mäkikallio et al. 2005). Consistently with these findings, the HF spectral component has not been able to differentiate between patients with and without life threatening events in case-control studies, nor has it been able to predict the onset of imminent life threatening arrhythmic events (Huikuri et al. 2003). Methodological differences may well account for these differences in the results between previous studies and the present one. For example, despite the HF spectral component being mostly associated with respiration, the HF spectral area analyzed from the standard 24-hour Holter recordings includes R-R interval oscillations that are not attributable to respiration. Non-autonomic, erratic oscillations that affect the HF spectral area produce a bias in the quantification of the RSA with the standard 24-hour HF spectral analysis methods. These kinds of non-respiratory fast changes in the R-R interval time series increase the power of the HF spectral component. This type of non-respiratory fast R-R interval oscillations has been most commonly observed in patients with CHF, resulting in fan-shaped Poincaré plots (Woo et al. 1992, Huikuri et al. 1996) and increased indexes describing short-term HRV by standard analysis methods (Tulppo et al. 1998). Furthermore, most of the 24-hour Holter recordings include both biological and technical disturbances. In Study I, it was shown that spectral analysis of the HRV was sensitive to editing, and careful attention needed to be paid to the selection of the method of editing the disturbances in the R-R interval time series. The commonly used deletion method of R-R interval editing had a clear effect on the HF fluctuation spectral values. The deletion method increases the HF spectral component in high-risk patients with frequent ectopic beats. Indeed, the HF spectral component, analyzed by the standard method, performed somewhat better in Study III of this dissertation than in previous studies (Kleiger et al. 1987, Bigger JT Jr et al. 1992, Lanza et al. 1998, Huikuri et al. 2000, 2003, Mäkikallio et al. 2005), perhaps owing to an improved editing method. Furthermore, physical activity also influences the level of 24-hour HF-power, i.e. patients who are more active paradoxically have a reduction in the 24-hour HF band because the HF oscillations become reduced during physical activity (Grossmann et al. 2004).
In Study III, all traditional HRV indexes predicted cardiac mortality. However, these indexes lack the ability to predict specifically SCD. The long-term HRV indexes, which have been most commonly used in previous studies (Lanza et al. 1998, Huikuri et al. 2000, 2003 Mäkikallio et al. 2005) predicted non-SCD far better than they predicted SCD. These indexes partly describe the sactivity level of the patients and thereby seem to reflect frailty and poor overall health of the patients. Short-term HRV measures, such as RSA, seem to be better indexes of specific autonomic disturbances that any increase in vulnerability towards SCD.

The findings of Study III confirm the results of the experimental studies that vagal activity plays an important role in preventing fatal arrhythmias (Schwartz et al. 1988). Patients with well-preserved RSA had an extremely low risk for SCD despite depressed left ventricular function after MI. A preserved RSA index had a high negative predictive accuracy for SCD, and its predictive power for SCD was better than that of the ejection fraction. This suggests that the RSA index could be a useful tool in selecting the patients suitable for implantable cardioverter-defibrillator and, especially for excluding patients with depressed left ventricular function from costly and sometimes cumbersome therapy.

Several indexes of HRV have been used and tested in various clinical settings since the original observation of Ewing et al. (1984) that short-term HRV predominantly quantifies the cardiac vagal outflow, and the finding of Kleiger et al. (1987) that SDNN predicts mortality after MI. RSA does not always reflect cardiac vagal activity (Hayano et al. 1996, Hayano & Yasuma 2003, Yasuma & Hayano 2004), and none of the HRV indexes have become a routinely used clinical tool. This is mostly due to the fact that none of the HRV indexes have been able to predict specific modes of death. Therefore, the HRV variability indexes have not been found to be very useful for tailoring specific therapy, such as the implantation of cardioverter-defibrillator. Study III suggests that modern signal processing of R-R interval time series may offer some advantages over previously described methods in specific prediction of SCD. In future trials, the role of the RSA index, measured from standard Holter recordings, needs to be tested in comparison to other risk markers.

7.4 Effects of the post-ectopic HR turbulence on HRV analysis (IV)

As mentioned earlier, ECG signals are in most cases imperfect, containing disturbances and abnormal R-R intervals. Usually, the long term (~24 hours) HRV signals include a different amount of ectopic beats, which are known to be one
source of error in the HRV analysis, especially in the frequency domain (Peng et al. 1995). VPBs appear almost in every human being at least during some life, but especially in patients with cardiac diseases, VPBs are a common occurrence. In most cases, it is recommended that HRV analysis should be done using R-R interval data that is free of artifacts and ectopic beats. However, R-R interval data free of ectopy is achieved usually only in short term ECG recordings under laboratory conditions lasting only a few minutes. For this reason, careful editing is recognized as being necessary, particularly for the spectrum analysis of the HRV signals with ectopic beats and other disturbances (Task Force of ESC & NASPE 1996). It has been recommended that if there are R-R interval time series with over 20 VPBs per hour then these should be excluded from the HRV analysis (Kamath & Fallen 1995).

Even though it is known that the R-R interval rhythm after the VPB oscillates according to the HR turbulence pattern, this phenomenon has not been studied in detail, i.e. does the turbulence behavior of the R-R intervals have any effects on the other HRV measures. One needs to take into consideration the fact, that in the editing process of the individual ectopic beats, most of the commercial HRV editing methods delete or replace with interpolating only the premature R-R interval and the following compensatory pause.

In Study IV it was found that different HRV parameters were differently sensitive to HR turbulence removal. The studied parameters reacted differently also to the increase of the VPB amount in the HR turbulence removal process. SDNN and $\alpha_1$ were the least affected by the HR turbulence removal so that the percentage differences remained small even with the large amount of VPBs. HRV power frequency components, especially ULF and VLF were the most sensitive to the HR turbulence removal. The changes in the ULF and VLF parameters were prominent due to HR turbulence removal since the 9th quantile (339–1431 VPBs, 0.44–1.38%) at the baseline phase and since the 6th quantile (39–204 VPBs, 0.11–0.19%) at six weeks after the AMI. In addition, the LF and HF components were notably affected by the HR turbulence removal especially in the data collected 6 weeks after the AMI since the 6th quantile (39–204 VPBs, 0.11–0.19%). The recommendation that VPB amount should be less than 20 VPBs per hour (Kamath & Fallen 1995) corresponds to the maximum of 480 VPBs per 24 hours. The results of Study IV support this recommendation of the maximum VPB amount in the R-R interval data. However, the VPB amount of less than 480 VPBs evoked significant changes especially in the HRV spectrum analysis. Thus, the limit of the maximum number as 20 VPBs per hour (Kamath & Fallen 1995)
could be even stricter according to the results of Study IV especially in the period at 6 weeks after the AMI. A stricter limit with a maximum of 10 premature beats per hour (Kleiger et al. 1995) has also been recommended; this would correspond better to the results of the Study IV, especially in the analysis conducted at 6 weeks after the AMI. The results of this study support the view that at least in cases where there are frequent ectopic beats, HR turbulence of 15 beats should ideally be deleted from the analysis.

The normal pattern of the HR turbulence involving a short acceleration followed by a gradual deceleration can be suggested as corresponding to a slow frequency R-R interval fluctuation. Therefore, in an R-R interval time series containing a large number of VPBs, the HR turbulence phenomenon presumably introduces a low frequency trend into the R-R interval time series, leading to an increase in the power in the lower frequencies of the HR variability power spectrum.

In the earlier parts (I–III) of this dissertation, a careful editing in the HRV analysis, especially in the frequency domain analysis was recommended and HRV analysis as a risk predictor for SCD in AMI patients was found to being improved with the correctly chosen editing method and with accurate editing. In Study IV, it was observed that editing the HR turbulence with the deletion method slightly improved the prediction of primary endpoint especially if the spectrum analysis involved the analysis of ULF and VLF spectral components. These findings in the risk analysis of Study IV are in agreement with the previous findings in the Studies I–III about the importance of careful editing of R-R interval data when spectral measures of HRV are being used in risk stratification.

The results of Study IV imply that even a moderate number of VPBs in the 24-hour R-R interval time series may cause distorted decreases in the spectrum parameters due to HR turbulence and may lead to the biased interpretation of the spectrum results. According to these results, it can be recommended that when analyzing HRV parameters other than HR turbulence and especially the spectrum HRV parameters, one needs to consider carefully whether it is necessary to edit or remove also the 10 to 15 following R-R intervals after a VBP in the 24 hour R-R interval data in which there are a substantial number of VPBs (> 0.11%). In the future, it would be important to conduct more investigations about the HR turbulence effects on the other HRV parameters in different patient populations and standardize the accurate maximum level of VPBs in the R-R interval time series.
7.5 Practical implications

The most reliable HRV analysis is performed with R-R interval data of pure sinus beats. Because, it is practically impossible to achieve data of 24-hours free of artifacts, one should pay attention to preprocessing and editing methods and try to reduce the number of technical artifacts. The development in recording devices has reduced the number of technical artifacts in the ECG recordings. Carefulness in the attachment and the improvement in the technology and materials of the electrodes have decreased the technical artifacts. Also a choice of the recording device may affect the accuracy of the R-R interval time series (Tapanainen et al. 1999). Nevertheless, it is not possible to prevent the occurrence of all the artifacts.

Typical R-R interval data of the AMI patients and other patients suffering different heart diseases may contain abundantly artifacts, especially ectopic beats. For instance, the R-R interval data of the AMI patients (n = 1631) in the Study III contained 4 ± 5% even after discarding such R-R interval time series with frequent ectopic beats or other artifacts. 4% of artifacts refer to over 3000 artifact beats in 24-hour R-R interval time series. Different preprocessing and editing methods of the R-R intervals have been introduced and proposed (Cheung 1981, Malik et al. 1989, Berntson et al. 1990, Cripps et al.1991, Sapoznikov et al. 1992, Lippmann et al. 1994). Many automatic systems for artifact correction can be based, for instance, in some prematurity threshold extracting such R-R interval that exceeds the threshold. This kind of automatic R-R interval editing may perform adequately in the cases of R-R intervals time series with low beat-to-beat variability and distinct ectopic beats. As mentioned before, manual editing with a visual verification of the R-R intervals is a reliable method of editing and not to be fully replaced by current automatic correction systems.

However, there is no consensus of how to deal with ectopic beats and other artifacts. For instance, there are no standardized limits for how many edited R-R intervals one 24-hour R-R interval time series is allowed to contain without biasing the HRV analysis or what is the most suitable editing method for different HRV analyses. The first part of this dissertation provides information about the effects of the R-R interval editing methods on time and frequency domain HRV analysis and on fractal scaling analysis. The results of the Study I and II provide important recommendations for handling artefacts and ectopic beats in order to obtain more reliable HRV analyses.

Also different preprocessing methods of the R-R interval time series are needed to gain information about the HRV related to specific physiological
phenomena. With a particular preprocessing method it is possible to extract the relevant R-R interval and gain more reliably HRV analysis related to the phenomenon in question. In the latter part of this dissertation (Study III and IV), the aim was to develop an algorithm for use in HRV signal preprocessing. In Study III, a new method was developed for RSA quantification from a HRV signal. The new RSA index proved to be able to be used as a predictor for the risk of the SCD in the post-AMI population. Finally, a new editing method of HR turbulence was developed that provided new information about the effects of the HR turbulence on the other HRV analyses.

Many Holter device manufacturers have HRV analysis in their commercial software. The reliability of these systems can be questionable because there is usually lack of information how the software deals with ectopic beats, e.g. which method are used for editing. Furthermore most of the commercial HRV analysis systems use pre-defined cutoff values for defining the ectopic beats. Therefore, currently available commercial Holter systems should be used with caution, especially in research work of HRV. The present studies provide some insight how the HRV should be ideally analyzed from real-time RR-interval data including also frequent ectopy.
8 Conclusions

There is no uniform way to handle artifacts and other irrelevant beat-to-beat variability, which partly restrains the efficient usage of the HRV in clinical practice. Due to the prevalent occurrence of ectopic beats and artifacts in the HRV signals obtained from 24-hour ambulatory ECG recordings, it is important to pay attention to the editing methods of the R-R interval time series in order to obtain more reliable HRV results. The reliability of the traditional HRV analysis can be improved by concentrating on the preprocessing methods of the HRV signal. In the future, accurate editing with a careful choice of the best editing method for particular HRV indices and new preprocessing methods for specific HRV measures may mean that HRV analyses can be used more efficiently for clinical purposes. From these Studies (I–IV) the following conclusions can be drawn:

1. The amount and method of editing R-R interval data have remarkably different effects on different HRV indices. There is no universal method for editing ectopic beats that can be used in both the time domain and the frequency domain analysis of HRV.

2. Unedited premature beats result in an increase in the randomness of short-term R-R interval dynamics, particularly in post-AMI patients. Premature beats do not necessarily need to be edited when fractal analysis is used for risk stratification.

3. The HRV signal can be preprocessed to include only respiratory related R-R intervals. Reduced respiratory-related HR dynamics, as detected by the RSA index, can be used as a specific marker for an increased risk of SCD among post-MI patients.

4. HR turbulence has an effect on the HRV measures, especially the ULF and VLF spectral components. The editing of the HR turbulence should be considered when HRV is measured from Holter recordings.
References


Hales S (1733) Statistical essays: containing haemastaticks; or, An account of some hydraulic and hydrostatical experiments made on the blood and blood-vessels of animals. London: Innys W, Manby R & Woodward T.


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Original publications


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1075. Kinnunen, Urpo (2010) Blood culture findings during neutropenia in adult patients with acute myeloid leukaemia : the influence of the phase of the disease, chemotherapy and the blood culture systems


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1081. Alahuhta, Maija (2010) Tyypin 2 diabeteksen riskiryhmään kuuluvien työikäisten henkilöiden painonhallinnan ja elintapamuutoksen tunnuspiirteitä

1082. Hurskainen, Merja (2010) The roles of collagens XV and XVIII in vessel formation, the function of recombinant human full-length type XV collagen and the roles of collagen XV and laminin α4 in peripheral nerve development and function

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ANALYSIS OF HEART RATE VARIABILITY FROM 24-HOUR AMBULATORY ELECTROCARDIOGRAPHIC RECORDINGS

SIGNIFICANCE OF PREPROCESSING OF R-R INTERVAL TIME SERIES