Analysis of Heart Rate Variability from RR-Interval Recordings of Implantable Cardioverter-Defibrillators

T. FETSCH
Institute for Clinical Cardiovascular Research, Munich, Germany

T. PODSTUFKA, G. RIEGER
Biotronik GmbH, Berlin, Germany

Summary

Heart rate variability is an indirect electrical measure of autonomic heart rate modulations. Heart rate variability parameters have been used as components of risk stratification procedures and have been found to be independent risk markers in specific patient groups. More recently, attention has been focused on a period of several hours preceding episodes of ventricular tachycardia or ventricular fibrillation. It is of special clinical interest to reliably predict the occurrence of such potentially life-threatening arrhythmias so that preventive therapy can be administered. It is now possible to assess prospectively the heart rate variability preceding spontaneous arrhythmic episodes by using the extended RR-interval Holter of the implantable cardioverter-defibrillator models Phylax XM, mycroPhylax, mycroPhylax plus, and Tachos DR. The HAWAI Registry has been launched with the primary objective of assessing HRV characteristics prior to the onset of spontaneous ventricular tachycardias. The trial will make considerable contributions toward answering the question of whether there are reproducible and statistically significant changes in heart rate variability parameters prior to the onset of ventricular tachycardias as well as the use of ICDs for the early diagnosis of ventricular tachycardia and fibrillation.

Key Words
Heart rate variability, arrhythmia prevention, risk stratification, implantable cardioverter-defibrillator

Introduction

The heart rate at any specific point in time represents the summary of the accelerating (sympathetic) and decelerating (vagal) dynamic influences of the autonomic nervous system on the sinus node, the conduction system of the heart, and the myocardial cells. The resulting beat-to-beat changes in the heart rate are designated as the heart rate variability (HRV), which has long been recognized as an indirect electrical measure for these autonomic modulations of the heart rate. There are many approaches to analyzing HRV, including the traditional time domain parameters, geometrical and spectral methods, as well as non-linear, parametric or symbolic parameters. A number of clinical studies have shown that certain heart rate variability measures are useful clinical markers for the prediction of death, especially from arrhythmic causes [1,11]. Specific heart rate variability parameters have consequently been used as a component of the risk stratification procedure in specific patient groups, for example in patients after myocardial infarction and patients with idiopathic dilated cardiomyopathy [1,3,12,14]. Other investigators have analyzed complex changes in the heart rate using nonlinear multi-parametric analysis [18]. In summary, HRV has been found to be an independent risk factor, providing information in addition to other risk factors such as impaired left-ventricular function or the analysis of signal-averaged electrograms.
History of HRV Analysis for Arrhythmia Prediction

More recently, HRV measures have been investigated with respect to their use as possible predictive markers for the occurrence of ventricular arrhythmias [4,8,9,10,17]. Attention is being focused on a time period of several hours preceding episodes of ventricular tachycardia (VT) or fibrillation (VF). It is of special clinical interest to reliably predict the occurrence of such potentially life-threatening arrhythmias so that prophylactic therapeutic strategies such as preventive pacing or antiarrhythmic drug treatment can be administered.

A recent study [16] of Holter electrogram data from patients with a recorded VT found that HRV changes within the 15 minutes immediately prior to the VT were dependent on the changes in HRV in the 2-hour period before the VT. In patients with an initial high power in the low frequency band (LFP) and a higher ratio of low frequency power/high frequency power (LFP/HFP), the HRV was reduced 15 minutes prior to the VT. In patients who initially had a low LFP and a lower LFP/HFP ratio, these parameters actually increased before the event. Another study [13] suggested that a sustained higher-power increase occurs in normal and instantaneous heart rates 12 min before a ventricular arrhythmia, followed by a sudden elevation in spectral power 100 s prior to the event.

The publications from studies so far have provided controversial data on the clinical evidence and have not been able to show conclusive data concerning the predictive capability of the studied HRV measures. A systematic investigation has been hindered in the past by retrospective study designs, small patient numbers, and by the fact that analysis was mainly limited to episodes coincidently recorded during Holter electrocardiography [5].

HRV Analysis with ICDs

It is now possible to routinely, systematically, and prospectively assess HRV preceding episodes of spontaneous VT or VF, using the current implantable cardioverter-defibrillator (ICD) models Phylax XM, mycroPhylax, mycroPhylax plus, and Tachos DR (all Biotronik, Germany).

These ICDs incorporate an extended RR-interval Holter featuring a maximum storage capacity of up to 18,000 (Tachos DR: 36,000) RR-intervals recorded from the near field bipolar intracardiac electrogram. The detection rate for QRS complexes is 8 kHz; the analog-digital conversion is carried out at 128 Hz, and the time resolution for the RR-interval storage after resampling is 3.9 ms. These technical Holter characteristics offer accurate HRV analysis results comparable to those derived from standard digitally processed, high time-resolution surface electrograms. A previous trial [7] has shown a high correlation between time and frequency domain parameters independent of the patients’ position, and during deep breathing when comparing HRV parameters calculated from RR intervals stored in the ICD Holter with those calculated from simultaneous recordings of the surface ECG. In addition, a significant equivalence could be proven for the most important parameters by performing the population bioequivalence test.

HAWAI Registry

Organization

The HAWAI Registry (Heart Rate Analysis with Automated ICDs) was officially launched in late 1998.

<table>
<thead>
<tr>
<th>HRV parameter</th>
<th>Description</th>
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<tbody>
<tr>
<td>SDNN</td>
<td>standard deviation of all RR intervals</td>
</tr>
<tr>
<td>SDANN</td>
<td>standard deviation of 5 min RR-means</td>
</tr>
<tr>
<td>SD</td>
<td>mean of the 5 min RR standard deviation</td>
</tr>
<tr>
<td>CV</td>
<td>mean of all 5 min epochs</td>
</tr>
<tr>
<td>TI</td>
<td>triangle interpolation width of the RR histogram</td>
</tr>
<tr>
<td>pNN50</td>
<td>percentage of successive RR differences &gt; 50 ms</td>
</tr>
<tr>
<td>TP (total power)</td>
<td>total power spectrum 0.04 - 0.85 Hz</td>
</tr>
<tr>
<td>ULF (ultra low frequency band)</td>
<td>integral power spectrum 0.005 Hz</td>
</tr>
<tr>
<td>VLF (very low frequency band)</td>
<td>integral power spectrum 0.005 - 0.04 Hz</td>
</tr>
<tr>
<td>LF (low frequency band)</td>
<td>integral power spectrum 0.04 - 0.15 Hz</td>
</tr>
<tr>
<td>HF (high frequency band)</td>
<td>integral power spectrum 0.15 - 0.85 Hz</td>
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*Table 1. Time and frequency domain parameters.*
The protocol of this trial was approved by the institutional review board/international ethics committee (Freiburg, Germany). The rationale for the HAWAI Registry is a prospective multicenter investigation of HRV patterns prior to the onset of spontaneous tachyarrhythmias recorded by implantable cardioverter-defibrillators. To improve the scientific value of the trial and the quality of data, the IKKF (Institute for Clinical Cardiovascular Research, Munich, Germany) organized a meeting of experts in the field of cardiology. According to the experts’ opinion, the objectives and the design of the HAWAI Registry are suitable for the ICD-based HRV analysis prior to the onset of spontaneous tachyarrhythmias. The suggestions of the expert group for optimizing the study protocol were the major part of the first study amendment.

**Members of the Steering Committee**
- Prof. Dr. Breithardt, Muenster (Germany)
- Dr. Boecker, Muenster (Germany)
- Dr. Fetsch, Munich (Germany)
- Dr. Hatala, Bratislava (Slovakia)
- Dr. Hoh, Wittenberg (Germany)
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- Dr. Hintringer, Innsbruck (Austria)
- Prof. Dr. Strasberg, Tel Aviv (Israel)

The ECG Evaluation Committee and the Episode Committee are responsible for the validation of all arrhythmic events.

**Objectives**

The primary objective of the study is the assessment of HRV characteristics at least 1 hour (approximately 9,000 RR intervals) prior to the onset of spontaneous ventricular tachyarrhythmias. The result of this pattern analysis may lead to the identification of reliable criteria for the prediction of subsequent ventricular tachyarrhythmias. This offers the opportunity to develop preventive pacing strategies.

**Design**

The projected sample size of the trial will be 560 patients. This calculation is based on publications and data of the Clinic of Cardiology and Angiology, University of Muenster, Germany [2]. Patients will be enrolled over 3 years with a mandatory follow-up time of 1 year.
All HAWAI patients will be included in one study group. There is no specific control group. The HRV of the 9,000 RR intervals prior to the onset of spontaneous VT/VF will be compared with the individual HRV over a 24-hour period and to a similar event-free period. Normal RR intervals are recorded at the patient's inclusion, at every follow-up visit and at the time of changes in antiarrhythmic drug medication. In order to determine the baseline status of the HRV under standardized conditions, a master data set of simultaneous RR intervals recorded by ICD and 24-h ECG is generated at the examination upon hospital discharge. The event-independent recording of RR intervals at each follow up enables both the comparison with pre-event RR recordings, and the analysis of the time course of individual changes in the HRV pattern. More information regarding the study procedure is given in Figure 1.

Since little is known about the influence of the basic cardiac disease on HRV, the HAWAI Survey will investigate a defined sub-population of ICD patients. Accordingly, patients implanted with Biotronik ICDs with extended memory function may be included into the study.

The current basic inclusion criteria are:
- diagnosed coronary artery disease, and
- documented sustained tachycardias or VF or resuscitation.

The current exclusion criteria are:
- pacemaker dependency,
- chronic atrial fibrillation,
- acute myocardial infarction,
- life expectancy less than 6 months due to another disease or medical conditions,
- heart transplantation scheduled,
- acute disease with incessant tachycardias, and
- arrhythmias that are not suitable for HRV analysis.

Until the end of April 2000, about 170 patients have been enrolled into the HAWAI Registry. Up to now, 30 implantation centers from all over Europe and Israel are participating in the trial. RR intervals from more than 100 VT/VF episodes have been recorded.

**Prospects**

The HAWAI Registry will considerably contribute toward answering the question if there are reproducible and statistically significant changes of HRV parameters prior to the onset of ventricular tachyarrhythmias. Additionally, the trial will provide us with more information about the suitability of ICDs for the early diagnosis of VT and VF. Figure 2 illustrates the utilization of an HRV analysis system, which combines conventional time and frequency domain parameters with current methods, such as non-linear dynamic calculation and heart-rate turbulence, in the course of VT/VF prevention strategies [15]. The HRV pattern identification is the prerequisite for the design and validation of preventive pacing or drug therapies. Potential benefits of preventive therapies extend from the reduction of the VT/VF incidence and the improvement of quality of life to the prolongation of ICD life span by avoiding high-energy therapies.

Prospective randomized trials will be necessary to investigate the efficacy and safety of these future prophylactic therapies.

**References**


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**Figure 2. Prevention of VT/VF episodes.**

![Figure 2. Prevention of VT/VF episodes.](image-url)


