Multipole Analysis of Heart Rate Variability as a Predictor of Imminent Ventricular Arrhythmias in ICD Patients

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Background: *Contemporary implantable cardiac defibrillators (ICD) enable storage of multiple, preepisode R-R recordings in patients who suffered from ventricular tachyarrhythmia (VTA). Timely prediction of VTA, using heart rate variability (HRV) analysis techniques, may facilitate the implementation of preventive and therapeutic strategies.*

Aim: *To evaluate the novel multipole method of the HRV analysis in prediction of imminent VTAs in ICD patients.*

Methods: *We screened patients from the Biotronik HAWAI Registry (Heart Rate Analysis with Automated ICDs). A total of 28 patients from the HAWAI registries (phase I and II), having medical records, who had experienced documented, verified VTA during the 2-year follow-up, were included in our analysis. HRV during preepisode recordings of 4,500 R-R intervals were analyzed using the Dyx parameter and compared to HRV of similar length recordings from the same patients that were not followed by arrhythmia.*

Results: *Our study population consisted mainly of men 25 of 28 (89%), average age of 64.8 ± 9.4 years, 92% with coronary artery disease. HRV during 64 preevent recordings (2.3 events per patient on average) was analyzed and compared with 60 control recordings. The multipole method of HRV analysis showed 50% sensitivity and 91.6% specificity for prediction of ventricular tachycardia/ventricular fibrillation in the study population, with 84.5% positive predictive value. No statistically significant correlation was found between various clinical parameters and the sensitivity of imminent VTA predetection in our patients.*

Conclusion: *The multipole method of HRV analysis emerges as a highly specific, possible predictor of imminent VTA, providing an early warning allowing to prepare for an arrhythmic episode. (PACE 2013; 00:1–6)*

heart rate variability, ventricular arrhythmia, ICD

Introduction

Scientific evidence of the association between autonomic nervous system (ANS) deregulation and cardiovascular mortality, including sudden cardiac death, encouraged the development of quantitative markers for autonomic activity.[1–3] Heart rate variability (HRV) is one of such markers, representing an indirect electrical measure of autonomic heart rate modulations, influenced mainly by the permanent interplay between the two branches of ANS. Numerous methods were developed to assess HRV including the traditional time-domain parameters; geometrical and spectral methods; as well as nonlinear, parametric, or symbolic parameters.[4–11]

Various studies showed that decreased HRV correlates with the occurrence of ventricular tachyarrhythmias (VTAs).[12–15] Certain measures of HRV were shown to be independent predictors of sudden death in specific patient groups as in postmyocardial infarction (post-myocardial infarction) patients[10,11,16–20] and in patients with idiopathic dilated cardiomyopathy.[21,22]

One of the HRV evaluation methods, exhibiting more prognostic power than others in comparative studies, is the multipole analysis

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developed by our group during the last decade.[23,24] This is a relatively new HRV assessment method to describe time series with a highly complex time evolution, computing various parameters (the multipoles) descriptive of the time series.[23,25] The measures obtained from this kind of analysis bear intrinsic time dependence due to the very construction of the method, as opposed to other analyses which do not include any time ordering (shuffling the R-R intervals results in the same HRV measurements), thus thought to be more applicable for "on-line monitoring" of HRV.

Interest in developing methods to predict imminent arrhythmias in implantable cardiac defibrillator (ICD) patients that may be implemented in future ICDs as an alarm mechanism has existed for a long time.[6,26,27] Attention has been focused on the several hours preceding episodes of VTA.[1,6,28–31] The availability of ICDs with extended memory capabilities, storing R-R intervals for over an hour preceding ventricular arrhythmias, provides an opportunity to study variations in HRV in that exact time of interest.[14,32–34] Accurate, timely prediction of VTA occurrence can allow implementation of behavioral changes as well as preventive and therapeutic strategies. For this purpose the test must be reasonably sensitive and highly specific to avoid needless disturbances of daily activity. Previous studies that looked at traditional HRV methods as predictors of imminent arrhythmia failed to achieve sufficient sensitivity and specificity to be useful in clinical practice.[24]

The aim of our study was to evaluate a novel multipole method for HRV analysis accuracy in prediction of imminent VTAs in ICD patients.

Methods

The Study Population

Our study population consisted of patients from the HAWAI Registry (Heart Rate Analysis with Automated ICDs). The HAWAI registry was officially launched in late 1998 and the trial protocol has been described in detail elsewhere.[35] The primary objective of the study was the assessment of HRV characteristics prior to the onset of spontaneous VTAs. We used the recordings from these patients to test the multipole method. The protocol was approved by the Institutional Review Board/International Ethics Committee.

Patients, the vast majority with ischemic cardiomyopathy, implanted with Biotronik ICDs (LEXOS family, PHYLAX XM and microPHYLAX, Biotronik GmbH, Berlin, Germany) with extended memory function, were screened for our study. Of the 38 patients with documented, verified VTA from the original HAWAI I trial, clinical data were available on 22 patients. Twenty-six additional patients were added to the HAWAI registry since 2008, all having clinical records, twelve of who experienced tachyarrhythmias, detected by the ICD during the study period. The events were reviewed by an electrophysiologist, who confirmed VTAs in seven of the patients. A technical problem prevented adequate R-R interval recording in one of those patients. Finally, 28 patients from the HAWAI registry (phase I and II), who had a medical record and had experienced documented, verified VTA during a 2-year follow-up period, were included in our analysis. The baseline clinical parameters of the study population included age; height; weight; and echocardiographic parameters including left ventricular ejection fraction (LVEF), past history of coronary artery disease (CAD), and MI and New York Heart Association (NYHA) functional class.

Study Design

Recordings were obtained of 4,500–9,000 R-R intervals prior to the onset of what was detected by the ICDs and confirmed by an electrophysiologist as spontaneous ventricular tachycardia/ventricular fibrillation (VT/VF). Sixty-four preevent recordings from 28 different patients were analyzed and compared with 60 recordings of similar length from the event-free period. Control recordings of similar duration that were not followed by an arrhythmia were obtained from the same patients at the patient's inclusion and/or follow-up visits. Eventually, HRV analysis, using the multipole method, was performed as following and compared to the traditional methods as standard deviation of N-N intervals and detrended fluctuation analysis. In order to achieve standardization of the HRV calculations between the different patients, the analysis was eventually performed on the 4,500 R-R interval recordings in all of the patients.

The Multipole Method

The Multipole method has been described in detail elsewhere.[23,24] Briefly, the multipole HRV analysis is a relatively new way of investigating the Poincaré Plot derived from complex time series. We interpret the Poincaré Plot as a two-dimensional body, where each data point in the plot is assigned a unit mass, in order to describe the total mass distribution within the plot. Bearing intrinsic time dependence due to the very construction of the plot, the multipole method, as do other Poincaré plot indices, derives information from both the time and frequency domains as well as reflecting increased randomness in the R-R interval time series.

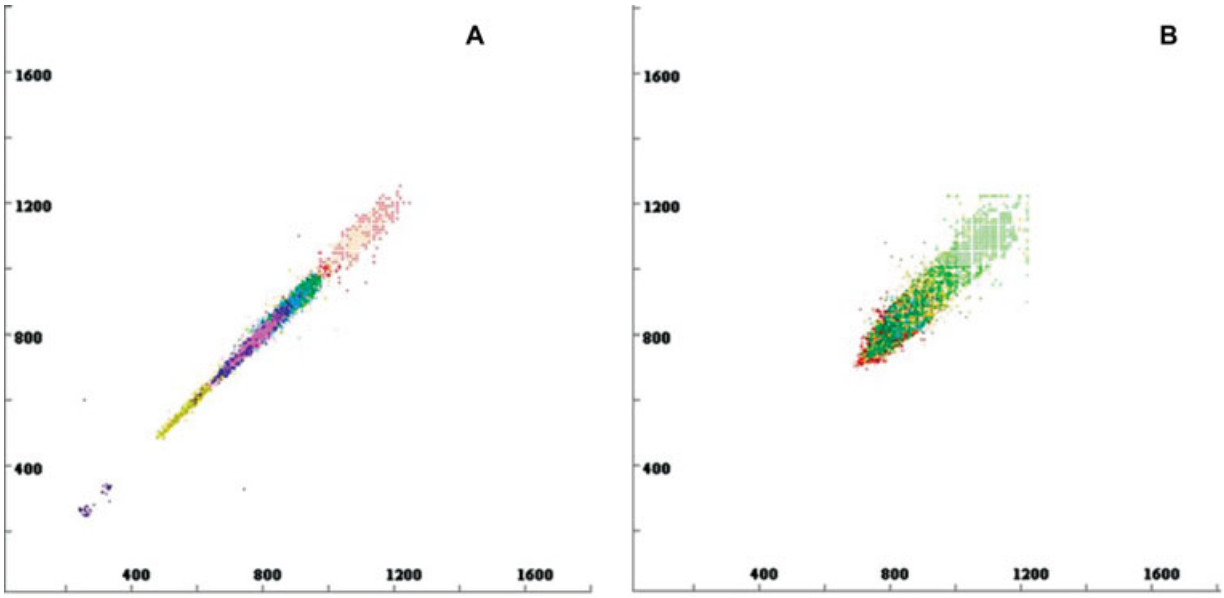

Figure 1. *Recurrence plots from the same patient from day with ventricular tachycardia (A) and day without ventricular tachycardia (B).*

Different multipoles can be calculated from the detrended RR time series; quadrupoles, hexadecapoles, mathematically describing the shape of the plot. From the latter, we derived the new HRV parameter Dyx, which is obtained from the densest populated area in the plot (Fig. 1).

We used a so-called running average to get a "real time" picture of the Dyx parameter. The first Dyx value is obtained from the first 400 R-R intervals. The next is obtained from the R-R intervals from number 1 until number 401, the next from R-R interval number 2 until R-R interval number 402, etc. In this way, a time-dependent Dyx parameter is obtained, which generally changes with a frequency of a little more than one per second.

Due to the relatively short 4,500 R-R interval recordings we could not use the Qyy (quadrupoles) parameter in this study, relying mainly on the Dyx. A Dyx value of less than 3 or greater than 6 was defined as pathological pattern, used for predetection of VTA in our patients. These values are based on preliminary analysis of R-R recordings before VT/VF episodes partly obtained from ICD patients (not those included in this study and partly from Holter-recordings of 12–24 hours). We found that the occurrence of "false positive" could be reduced substantially by adding a real-time parameter representing instant accelerations of the pulse. Those accelerations emerged typically between 30 minutes and 120 minutes prior to onset of VT/VF. By combining the two parameters and applying the Dyx criteria only if the acceleration criterion was fulfilled, namely that there has been eight consecutive R-R intervals all smaller than 600 ms, we hoped to increase the overall predictive accuracy of the analysis.

Results

Sixty-four preevent recordings from 28 patients with validated VT/VF during the follow-up period were analyzed and compared with 60 recordings of similar length from the same patients, during "event-free" period. Our study population consisted mainly of men (89%), with an average age of 64.8 ± 9.4. Average body mass index was 27.1. The majority of patients suffered from ischemic cardiomyopathy, 92% with proven CAD, and 64% after one or more myocardial infarctions. The average LVEF was 34.7% with an average NYHA functional capacity of 1.9. During the 2-year follow-up period, patients suffered 2.3 confirmed VT/VF events in average, with one to six events per patient.

Applying the multipole method of HRV analysis showed a pathological pattern in 32 of 64 preevent recordings (50%). In five of the 60 control recordings of similar length, a pathological pattern was detected, yet not followed by arrhythmia. Three of the five "false positive" recordings belonged to the same patient. Another "false positive" result was detected in patient whose additional control recording were "negative."

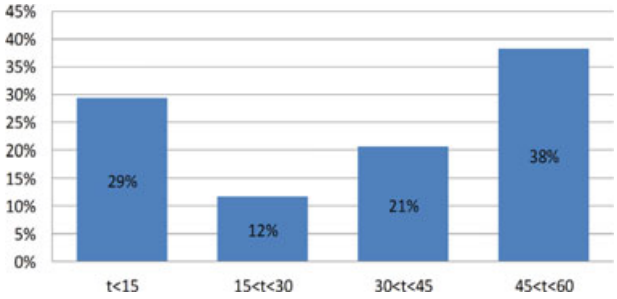

Figure 2. *Timing (t) of the pathological HRV changes, predicting VTV (minutes).*

About 29% of the recordings revealed pathological pattern of the HRV, analyzed by the multipole method, during the 15 minutes immediately presiding the arrhythmia. In 71% of the recordings, the pattern was detected between 15 minutes and 60 minutes before the VTA (Fig. 2).

The sensitivity and specificity measurements were patient-weighted using the number of detections received from a given patient. The multipole method showed 50% sensitivity and 91.6% specificity for early detection of VT/VF in the study population with a positive predictive value of 84.5%. No statistically significant correlation was found between clinical parameters and the sensitivity of an imminent VTA predetection in our patients. Interestingly less than 10% of the VTA events in women participants were predetected by the multipole HRV analysis.

Discussion

This is a preliminary investigation of the multipole method of HRV analysis as a predictor of imminent VTA in patients implanted with ICD. Our study showed 50% sensitivity and 91.6% specificity with 84.5% positive predictive value for VTA occurrence in patients with pathological pattern on a multipole analysis of relatively short (4,500 R-R intervals) preepisode heart rate recordings.

The study population included mainly men, with a mean age of 64 years, the majority suffering from ischemic cardiomyopathy—consistent with the general ICD patients' population.[36–38]

The multipole method extracts information both in the frequency domain as well as in the time domain, and therefore performs better than the traditional HRV methods, which are imbedded in one of the two domains.[23,24] Olesen et al. showed this method's superiority in the HRV analysis of 24-hour Holter recordings (5–10 days post-MI) in patients from the DIAMOND MI study,[24] predicting death during the follow-up period.

This type of information is valuable in the risk stratification of patients post-MI, yet the phase just prior to the VT/VF event is of even greater interest, bearing the opportunity to assist with proper identification of the tachyarrhythmia or to interfere and prevent the VTA.

Intracardiac rate measurement from ICDs were used in the past to assess HRV changes just before VTA.[6,14,33,34] Although certain properties in the HRV were found, no VTA predictor was explicitly suggested. Recently Thong and Raitt have described a simple predictor based on a beat-by-beat heart rate analysis.[26] A particular pattern or heart rate acceleration was found to occur frequently before an episode of VTA but the specificity of this finding was low (57%), while attempts to improve the prediction by using "double acceleration," or using lower limit of the accelerated rhythm >86 beats/min, led to sharp decrease in the sensitivity down to 21%.

Previous pilot analysis by our group, using the multipole method to analyze preevent recordings, showed that multipole parameters became typically pathological between 800 and 5,000 R-R intervals (i.e., approximately 10–60 minutes) before the onset of VTA. The timing of pathological HRV pattern predetection using our model during our current study is shown in Figure 2.

Our study is the first to apply the multipole method in that exact time frame of interest. We used the Dyx parameter dynamics to predict imminent VTA in our patients. Comparing our method with the literature data regarding various HRV measures shows significantly higher specificity (91.6%), which is extremely important for implementation of therapeutic strategies.[24]

The main limitation of our study is the small size of the study population and the small number of events, as well as the marked male majority. An additional large, gender-balanced, multicenter trial is needed to validate our results. On account of the different lengths of R-R recording from patients recruited in the different time periods we had to "cut" the analyzed R-R interval length to 4,500 in order to achieve standardization. Analyzing longer recordings (up to 9,000 preevent R-R intervals) could have increased the sensitivity by additional 10–15%. Having larger memory modules, the contemporary ICDs allow us to collect longer preevent recordings, which should be used in future studies. Another limitation due to the retrospective nature of our work is the fact that, having only the R-R interval recordings for the patients from the earlier period and not the actual arrhythmia (which was previously confirmed as VTA), we could not analyze the data per VT or VF to comprehend difference in prerecognition pattern.

We conclude that the multipole method of heart rate analysis emerges as a possible predictor of imminent VTA, providing an early warning that can be used for better identification of ventricular arrhythmias as well as for possible implementation of therapeutic strategies. For instance, modifying activity (cessation of physical activity, driving, etc.) in anticipation of arrhythmia can be extremely important for the ICD patients. The patient can turn to a nearby clinic for medical assistance, where better monitoring such as continuous 12-lead electrocardiogram can be performed. Further studies with larger, gender balanced populations, using longer R-R recordings are needed to confirm our observations.

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