HEART RATE VARIABILITY AND P WAVE CHARACTERISTICS AFTER ATRIAL FIBRILLATION

SUMMARY: Despite the development of pharmacological therapy and/or device therapy, atrial fibrillation remains a leading cause for morbidity and mortality. Heart rate variability (HRV) is studied only in the presence of sinus rhythm. Currently, three different categories of methods in HRV analysis are being used: the time domain, frequency domain, and non-linear dynamic analysis. Both time domain and frequency domain analyses of HRV have been investigated extensively regarding their use as a prognostic marker for cardiovascular mortality. The non-linear dynamic analysis is the latest tool that has shown to have an even higher predictive value than any of the traditional parameters. The relationship heart rate variability and atrial fibrillation is less studied and poorly understood. It is well known that depressed heart rate variability (HRV) in heart failure is associated with increased mortality. The aim of our study was to highlight the complex heart rate modulation after atrial fibrillation and to analyze the behavior of RR intervals dynamics after restoration of the sinus rhythm. Some challenges during our study have been: which is the role of the autonomic tone modulation in the onset of atrial fibrillation and is the autonomic tone involved in the restoration of the sinus rhythm? In this study we recorded ECG at bedside using an ECG Cardiax device and we analyzed the relationship between the heart rate variability parameters and the characteristics of the P wave, like P wave axis, P wave duration and the PQ duration (ms). Also we implement the coefficient of variance (CV) as the ratio of SD of RR intervals and the mean RR. Heart rate variability parameters are measured in both time domain - RR intervals (ms), standard deviation of all RR intervals SD (ms) and spectral domain - as very low frequency (VLF, 0.01-0.04 Hz), low frequency (LF, 0.05 - 0.15 Hz) and high frequency (HF, 0.15-0.50 Hz), LF/HF ratio, respectively nonlinear dynamics parameters like sample entropy, detrended fluctuation analysis, and Poincare plots. Dynamic analysis techniques may quantify abnormalities in heart rate variability (HRV) based on nonlinear and fractal analysis (chaos theory). Approximate entropy (ApEn) was applied to quantify the regularity and complexity of time series, as well as unpredictability of fluctuations in time series. This study suggests that nonlinear analysis technique may complement conventional atrial fibrillation analysis. We consider that it is necessary to consider also P wave axis and P wave duration together with the linear and nonlinear parameters of heart rate variability as complex P wave remodeling elements with complex contribution in restoring the sinus rhythm after atrial fibrillation.

Keywords: Heart rate variability, P wave, atrial fibrillation

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Cuvinte cheie: variabilitate, unde P, fibrilație atrială.

VARIABILITATEA FRECVENȚEI CARDIACE ȘI A UNDEI P POST-FIBRILAȚIE ATRIALĂ

Rezumat: Fibrilația atrială continuă să rămână o cauza importantă de morbiditate și mortalitate în ciuda dezvoltării terapiei farmacologice și nonfarmacologice. Variabilitatea de frecvență cardiacă este studiată doar în prezența ritmului sinusal. La ora actuală se utilizează 3 moduri diferite de studiu a variabilității de frecvență cardiacă (VFC): analiza în domeniu timp, analiza spectrală de putere, analiza non-lineară. Atât analiza în domeniul timp cât și analiza spectrală de putere au fost studiate exhaustiv în raport cu riscul de moare subită. Analiza non-lineară este un instrument recent utilizat în prelucrarea electrocardiogramei (ECG) în scopul de a demonstra capacitatea predictivă mai înaltă comparativ cu oricare altă metodă traditională. Relația dintre variabilitatea de frecvență cardiacă și fibrilația atrială este mai puțin studiată iar mecanismele implicate sunt mai complexe. Scopul studiului este de a demonstra complexitatea modulării frecvenței cardiacă a rolului tonusului autonom post fibrilație atrială și să analizze dinamica intervalor RR după relua rea ritmului sinusal. Electrocardiogramele (ECG) au fost înregistrate la un lot de 18 pacienți (12 femei, 6 bărbați; varsta medie: 66.8 ani) cu fibrilație atrială convertită la ritm sinusal. Înregistrările s-au efectuat în condiții de repaus folosind un sistem de monitorizare CARDIAX v. 3.50.4 IMED Co. LTD. Am analizat relația dintre parametrii VFC și principalele caracteristici ale undei P (durata, axa, și intervalul PQ). Parametrii analizei non-linearare a frecvenței cardiacă permit stabilirea gradului de omogenitate, respectiv complexitatea intervalor RR și se corelează cu caracteristicile undei P. Dimensiunile undei P determinate ecocardiografic au fost corelate cu parametrii undei P. Acest studiu sugerează că parametrii undei P pot fi utilizați în evaluarea gradului de stabilitate electrică a atrului după reluarea ritmului sinusal la pacienții cu fibrilație atrială.

BACKGROUND

Atrial fibrillation is one of the most important cardiovascular diseases involving an important number of patients, implying comorbidities, complications like stroke and systemic embolic events and hospitalization. All studies highlight that atrial fibrillation incidence is increasing with age (Piccini et. all), and also represents and important cause of death among the general population. The data about incidence and prevalence are limited, more of this the data for 2005 from the Centers for Disease Control and Prevention (Atlanta, USA) estimated for 2010 an incidence of 2.66 million people and for 2050 the incidence of atrial fibrillation will rise to 12 million people (CDC/NCCDPHP/DHDP). Various statistics shows that the incidence is higher in older men and women population. The median age for patients with atrial fibrillation is 66.8 years for men and 74.6 years for women.

Electrical remodeling is one of the features of atrial fibrillation and it is related to decreased conduction velocity of electricity signals. Heart rate variability is closely related to homeostasis of the autonomous nervous system. The dynamics of interbeat intervals come to change after the onset of atrial fibrillation. Patients without any atrial fibrillation showed some patterns in the Poincaré plots and these patterns were regular. The plots of atrial fibrillation patients, however, were very irregular and changed too much in the course of time (Jinho Park et. all).

Despite the development of pharmacological therapy and/or device therapy, atrial fibrillation remains a leading cause for morbidity and mortality. Heart rate variability (HRV) is studied only in the presence of sinus rhythm. Currently, three different categories of methods in HRV analysis are being used; the time domain, frequency domain, and non-linear dynamic analysis. Both time domain and frequency domain analyses of HRV have been investigated extensively regarding their use as a prognostic marker for cardiovascular mortality. The non-linear dynamic analysis is the latest tool that has shown to have an even higher predictive value than any of the traditional parameters. The relationship heart rate variability and atrial fibrillation is less studied and poorly understood. It is well known that depressed heart rate variability (HRV) in heart failure is associated with increased mortality. In the past, a few clinical studies were made in order to verify the existence of a link between atrial fibrillation episodes and autonomous nervous system. In most instances, particularly in subjects with paroxysmal atrial fibrillation (PAF), a pro-arrhythmic role of sympathetic or vagal activation was recognised. The inference, however, was mainly based on the analysis of the environmental context in which atrial fibrillation initiated. Accordingly, exercise-induced atrial fibrillation was considered to depend upon sympathetic activation, whereas arrhythmic episodes occurring during rest or night time were classified as of vagal origin.

More recently, by applying heart rate variability analysis, signs of abnormal autonomic modulation of sinus node have been described in patients with episodes of atrial fibrillation during Holter recordings or after DC cardioversion (Federico Lombardi et. all).

The aim of our study was to highlight the complex heart rate modulation after atrial fibrillation and to analyze the behavior of RR intervals dynamics after restoration of the sinus rhythm. Some challenges during our study have
been: which is the role of the autonomic tone modulation in the onset of atrial fibrillation and is the autonomic tone involved in the restoration of the sinus rhythm?

METHOD

Our study was performed at the Cardiology Clinic of the Emergency County Hospital Timis, University of Medicine and Pharmacy “V. Babes” Timisoara. We have analyzed ECG signals from 18 patients (men: 6,33%, women: 12,66 %) with mean age: 66.8 years, by continuous bedside monitoring for a mean period of 30 minutes after restoration of the sinus rhythm using an ECG Holter system- Cardiav x.v.3.50.4 IMED Co. Ltd. All the recordings were done in sinus rhythm, after recovering from atrial fibrillation. With the patients in supine position we recorded 12 leads standard ECG signal, at 25mm/s, and a sampling frequency of 100 Hz. Automatically have been measured the following parameters: heart rate (b/min), mean RR interval (ms), P wave axis, P wave duration (ms), PQ duration (ms). standard deviation of all RR intervals (ms), QRS complex duration (ms), QT (ms), respectively QTc(ms). Heart rate variability (HRV) parameters have been measured in time domain: mean RR interval (ms) and standard deviation of all RR intervals (ms), respectively in frequency domain: very low frequency (VLF, 0.01-0.04 Hz), low frequency (LF, 0.05-0.15 Hz) and high frequency (HF, 0.15-0.50 Hz), LF/HF ratio. Kubios v. 2.1, Finland (http://kubios.uku.fi) was used for the measurement of the nonlinear parameters of the RR series. Approximate Sample entropy, detrended fluctuation analysis, and Poincare plots, have been used in our study.

Left atrium dimension (mm) and left ventricular ejection fraction (LVEF, % ) has been measured echocardiographic by an independent member of the team.

A control group of 11 ECG signals was obtained from subjects without cardiac diseases published on the Physiobank database (http://physionet.org/physiobank/database/MIT) and has been used to compare the recorded data.

Statistical analysis

For the statistical analysis we have used Graph Pad Prism. All numeric variables were expressed as mean and the statistical analysis was performed using Student’s t-test and correlation analysis by Pearson method. A p value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSIONS.

The main data of the patient group are represented in table 1.

The incidence of atrial fibrillation was higher in women compared to men (12 pts. vs 6 pts). Also the mean age of the patients was over 60 years (mean age: 66.8 years). In all the atrial fibrillation subjects, we noticed that the sinus rhythm was restored in less than 12 hours from the admission in the Cardiology Clinic. The mean heart rate in the study group was 68.8 b/min vs. 80 b/min (p: 0.003), suggesting a better control of heart rate, or a vagal modulation of the heart rate. The LVEF (%) was 52.4 %, probably that the sinus rhythm is restored quickly or they are patients with relatively preserved left ventricular ejection fraction.

The P wave duration was longer in the patients group compared to the control group (110 ms vs. 93 ms, p: 0.03).

Left atrium dimension correlates negatively with P wave axis and P wave duration (r: -0.42, respectively r: -0.30).

The heart rate (HR) variability parameters and the nonlinear dynamic parameters are summarized in table 2 and are compared with those obtained in the control group.

Atrial fibrillation patients, seems to have after restoring the sinus rhythm a higher LF/HF ratio, as a marker of the autonomic imbalance, reflecting a high sympathetic activity (2.78 vs. 1.67, p: 0.05). Also P wave duration and PQ interval have a higher value as the values obtained in the control group (p <0.005).

Approximate entropy (ApEn) correlates well with the values of the P wave axis (r: 0.49), as results in figure 1.

Table 1. Clinical parameters of the study group (n: 18)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Age (yrs)</th>
<th>Mean Heart Rate (b/min)</th>
<th>Left atrium (mm)</th>
<th>LVEF %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients group (N: 18)</strong></td>
<td>6</td>
<td>12</td>
<td>66.8</td>
<td>68.8</td>
<td>46.9</td>
<td>52.4</td>
</tr>
</tbody>
</table>

LVEF - Left ventricle ejection fraction
In the patients group the correlation between the P wave axis and the ApEn parameter reflects the contribution of the entropy in restoring the sinus rhythm after atrial fibrillation. Left atrium dimension (mean value: 47 mm) measured by 2D echocardiography correlates directly with approximate entropy (ApEn: 1.08), r: 0.54. The left atrium dimension correlates with P wave axis (51.1), r: 0.49, and respectively negatively with P wave duration (104.2 ms), r: -0.42, figure 2.

**CONCLUSIONS**

All this findings seems to consider that after restoring sinus rhythm from atrial fibrillation we can notice the presence of a remodeling of the left atrium, this remodeling occurs in both electric, like presence of P waves but also by the participation of the entropy, and mechanic (left atrium dimension, duration and axis) component. This observation could have consequences in the therapy and approach of the patients how are developing atrial fibrillation.

The study is limited by the low number of patients, but opens new perspectives in the approach of the patients with coronary artery disease, hypertension, or heart failure and who develops atrial fibrillation, respectively regarding the outcome of these patients. Restoring the sinus rhythm after atrial fibrillation improves the outcome of the patients, reduce the hospitalization and prevents embolic incidents.

**Table 2.** Linear and nonlinear parameters in the study group compared to the control group.

<table>
<thead>
<tr>
<th>Study Group (n: 18)</th>
<th>Mean HR (b/min)</th>
<th>Mean NN (ms)</th>
<th>SDNN (ms)</th>
<th>VLF (ms2)</th>
<th>LF (ms2)</th>
<th>HF (ms2)</th>
<th>LF/HF</th>
<th>Pax</th>
<th>Pdur (ms)</th>
<th>PQ (ms)</th>
<th>ApEn</th>
<th>DFA ( \alpha_1 )</th>
<th>DFA ( \alpha_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>66.8</td>
<td>945</td>
<td>99</td>
<td>1950</td>
<td>989</td>
<td>818</td>
<td>2.54</td>
<td>1.07</td>
<td>0.73</td>
<td>0.81</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n: 11)</td>
<td>80</td>
<td>769</td>
<td>130</td>
<td>8105</td>
<td>1208</td>
<td>707</td>
<td>1.67</td>
<td>93</td>
<td>105</td>
<td>0.98</td>
<td>1.22</td>
<td>1.03</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Approximate entropy (y axis) vs. P wave axis (x axis)

**Figure 2.** Left atrium dimension (mm) and P wave axis relationship (r: 0.49)

In the patients group the correlation between the P wave axis and the ApEn parameter reflects the contribution of the entropy in restoring the sinus rhythm after atrial fibrillation. Left atrium dimension (mean value: 47 mm) measured by 2D echocardiography correlates directly with approximate entropy (ApEn: 1.08), r: 0.54. The left atrium dimension correlates with P wave axis (51.1), r: 0.49, and respectively negatively with P wave duration (104.2 ms), r: -0.42, figure 2.

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