Abstract

Atrial fibrillation (AF) is known to worsen over time. Beat-to-beat P-wave variability is used to evaluate the risk of developing AF, but it has not been used to monitor arrhythmia progression in a comprehensive model. The aim of this study is to create a method to measure beat-to-beat P-wave variability to evaluate AF types.

ECG recordings of 5 minutes were measured on 159 AF patients. The first three principal components (PCs) of the ECG signal were added to the analysis. The temporal beat-to-beat P-wave variability was assessed through the normalized Euclidean Distance and the Similarity Index. The spatial P-wave similarity was measured as the percentage of variance explained by the first 2 PCs. A binomial logistic regression model was built for each lead and parameter, with AF type as dependent variable. To assess variability due exclusively to the P-waves, we considered, as confounding factors, other sources of ECG-variability, such as the noise level, the variability of the RR series and of the heart axis.

Both temporal (e.g. 0.94±0.12 for paroxysmal AF and 0.85±0.28 for persistent AF in lead I, p=0.001) and spatial P-wave similarities (95.35±3.29% for paroxysmal AF vs 94.44±4.14% for persistent AF, p=0.001) were significantly higher in paroxysmal than in persistent AF, suggesting them as promising tools to evaluate AF types.

1. Introduction

Atrial Fibrillation (AF) is the most common arrhythmia with an important contribution to population morbidity and mortality [1]. Since the onset of the pathology, AF causes electrophysiological and/or structural remodeling in the atria, promoting its perpetuation [1], [2] and a more difficult restoration of sinus rhythm (SR). According to the temporal pattern of the arrhythmia, three types of AF were identified [3]: paroxysmal, when episodes terminate spontaneously, usually within seven days and mostly in less than 24 hours; persistent, when the arrhythmia continues for more than a week, requiring pharmacological or electrical treatment for termination; permanent, when AF last for more than 1 year and cardioversion is not indicated, has failed or has not been attempted. Early knowledge of the AF type can help clinicians in the choice of best treatment and in the application of risk management procedure to avoid adverse events. Beat-to-beat P wave variability has been associated with higher risk of developing AF [4]–[6] and its increase has been related to the presence of heterogeneous conduction [7].

The aim of this study is to find whether spatio-temporal P-wave variability of AF patients is able to give information about the condition of the atria and discriminate between AF types.

2. Methods

2.1. Population

The studied population comprised of 159 AF patients enrolled in the Atrial Fibrillation Ablation (AFAB) study, scheduled for AF ablation at the Maastricht University Medical Center (MUMC+). The study protocol was approved by the institutional review board and informed written consent was obtained from each participant. Each subject had a 5-minute ECG recorded with CAM-USB (GE Healthcare, sample frequency = 500 Hz) or YRS-100 ECG device (YourRhythms B.V., sample frequency = 2000 Hz). Only subjects presenting with sinus rhythm (SR) were considered in the analysis.

Three additional unipolar leads were added to the standard 12 leads for their sensitivity to high P-wave complexity [8], [9]: A1 (cranial end of sternum, beneath jugulum), A2 (8 cm above V6, mid-axillary line) and A3 (same height as A2, above V9, 4 cm medial of posterior axillary line). The population characteristics are depicted in Table 1.
2.3. ECG preprocessing

The recordings were filtered (high-pass filter, Butterworth, 4th-order, fc = 0.5 Hz; low-pass filter, FIR, Hamming window, fc = 80 Hz and non-linear notch filter fc= 50 Hz) in order to reduce the noise influence on the variability estimate [10]. Then, the first three principal components (PCs) of the ECG leads were added to the analysis.

The Principal Component Analysis (PCA) is a statistical procedure to obtain a set of uncorrelated and orthogonal variables from a dataset. The first component is built to explain the majority of the variance in the data. All the other components are built in an iterative procedure to explain the major part of the remaining variance with the constraint to be orthogonal to all the precedent ones [11]. In this way, the first three components of the ECG signal represent the three more representative directions of heart depolarization.

In order to avoid missing detection of low-amplitude peaks, R-peak detection was performed on the 2 leads with highest QRS amplitude. A window going from 80 ms before and 200 ms after each R peak was selected. The abnormal beats were identified through the cross-correlation with an average template and discarded from further analysis [12].

2.4. Statistical Analysis

Comparison of clinical characteristics and ECG parameters was performed through Wilcoxon rank sum test. Categorical variables were tested with the two-proportion z-test and reported in number and percentage. A binomial logistic regression model was built for each lead and parameter, with AF type as dependent variable. In order to consider the effect of the variability due only...
to the P-wave, all the models were adjusted for all other sources of ECG-related variability. A p-value < 0.05 was considered statistically significant. All analyses were performed using Matlab R2017a (The MathWorks, Natick, MA).

3. Results

It was found that the ED was consistently higher in persistent AF patients than in paroxysmal AF and, accordingly, SI was lower in persistent AF. In Table 2 the leads that showed a significant difference between paroxysmal and persistent AF are reported for both ED and SI. The spatial similarity was higher in the population with paroxysmal AF (95.35±3.29% for paroxysmal AF vs 94.44±4.14% for persistent AF, p=0.001).

4. Discussion

To our knowledge, few studies are present in literature about differences between paroxysmal and persistent AF in ECG parameters during SR [10], [13], [14], and none of these focus on beat-to-beat P-wave variability, taking into account also other possible sources of variability in ECG.

During the ECG analysis, an accurate procedure to detect only physiological P-waves was performed, avoiding influence of noisy or false P-waves that could deeply compromise the beat-to-beat comparison. Furthermore, the quantification of other sources of ECG-related variability allows the adjustment for their effect on the assessment of the association between P-wave variability and AF types.

The beat-to-beat P-wave variability is a direct measure of the changes in the atrial depolarization pathways occurring beat-to-beat. A higher P-wave variability has been associated to higher risk of developing AF in several studies [4]–[6]. Pezzuto et al. showed in an in-silico study

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>paroxysmal</th>
<th>persistent</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Median/IQR / % (N)</td>
<td>Median/IQR / % (N)</td>
<td>Median/IQR / % (N)</td>
<td></td>
</tr>
<tr>
<td>Euclidean Distance:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>(3.56±2.58)x10^{-1}</td>
<td>(3.31±2.27)x10^{-1}</td>
<td>(4.55±3.31)x10^{-1}</td>
<td>0.015</td>
</tr>
<tr>
<td>A2</td>
<td>(3.94±2.49)x10^{-1}</td>
<td>(3.61±2.32)x10^{-1}</td>
<td>(4.76±4.01)x10^{-1}</td>
<td>0.001</td>
</tr>
<tr>
<td>I</td>
<td>(3.98±3.74)x10^{-1}</td>
<td>(3.78±3.03)x10^{-1}</td>
<td>(5.47±5.10)x10^{-1}</td>
<td>0.001</td>
</tr>
<tr>
<td>II</td>
<td>(2.66±1.41)x10^{-1}</td>
<td>(2.61±1.14)x10^{-1}</td>
<td>(3.03±2.02)x10^{-1}</td>
<td>0.009</td>
</tr>
<tr>
<td>V6</td>
<td>(3.82±1.91)x10^{-1}</td>
<td>(3.54±1.66)x10^{-1}</td>
<td>(4.19±2.76)x10^{-1}</td>
<td>0.002</td>
</tr>
<tr>
<td>aVR</td>
<td>(2.79±1.80)x10^{-1}</td>
<td>(2.66±1.58)x10^{-1}</td>
<td>(3.37±2.68)x10^{-1}</td>
<td>0.001</td>
</tr>
<tr>
<td>PC1</td>
<td>(1.99±1.29)x10^{-1}</td>
<td>(1.92±1.09)x10^{-1}</td>
<td>(2.23±2.11)x10^{-1}</td>
<td>0.009</td>
</tr>
<tr>
<td>Similarity Index:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>(9.45±0.91)x10^{-1}</td>
<td>(9.52±0.79)x10^{-1}</td>
<td>(9.13±1.37)x10^{-1}</td>
<td>0.011</td>
</tr>
<tr>
<td>A2</td>
<td>(9.30±1.02)x10^{-1}</td>
<td>(9.40±0.87)x10^{-1}</td>
<td>(8.92±2.01)x10^{-1}</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I</td>
<td>(9.29±1.58)x10^{-1}</td>
<td>(9.37±1.15)x10^{-1}</td>
<td>(8.54±2.75)x10^{-1}</td>
<td>0.001</td>
</tr>
<tr>
<td>II</td>
<td>(9.69±0.31)x10^{-1}</td>
<td>(9.70±0.27)x10^{-1}</td>
<td>(9.59±0.61)x10^{-1}</td>
<td>0.008</td>
</tr>
<tr>
<td>V6</td>
<td>(9.38±0.56)x10^{-1}</td>
<td>(9.45±0.53)x10^{-1}</td>
<td>(9.20±1.11)x10^{-1}</td>
<td>0.001</td>
</tr>
<tr>
<td>aVR</td>
<td>(9.65±0.49)x10^{-1}</td>
<td>(9.70±0.43)x10^{-1}</td>
<td>(9.51±0.91)x10^{-1}</td>
<td>0.002</td>
</tr>
<tr>
<td>PC1</td>
<td>(9.83±0.25)x10^{-1}</td>
<td>(9.84±0.21)x10^{-1}</td>
<td>(9.77±0.52)x10^{-1}</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 2. P-wave parameters presenting significant differences between patients with paroxysmal and persistent AF. P-value calculated using a binomial logistic regression model adjusted for other ECG-related variability’s sources.
that the beat-to-beat P-wave variability is related to the degree of heterogeneous atrial conduction and the variability of the sinoatrial node’s exit points. According to these findings, a higher P-wave variability in the persistent population was expected, related to the more compromised substrate due to the worsening of the pathology. The results of the study sustain this hypothesis. In a study by Laureanti et al., the beat-to-beat P-wave variability in lead II and in the first principal component was computed to evaluate possible sex-related differences in the Swiss-AF cohort, but also differences between paroxysmal and persistent AF, finding no significant difference related to the AF type [10]. However, a comparison between the AFAB-Registry from Maastricht and the Swiss-AF population shows major demographic and treatment differences. The Swiss-AF patients were older (on average 6 years), were smaller and lighter, and were more frequently on antiarrhythmic drugs. Furthermore, the clustering procedure implemented in this study to better identify the P-waves to be analyzed was absent in [10] and no source of other ECG-related variability was considered as a confounding variable.

In conclusion, the use of an extended ECG and an accurate procedure in each lead to avoid noisy or false P-waves that could affect the variability, along with an assessment of other sources of ECG variability that could influence both ED and SI, are useful tools to quantify the degree of atrial remodeling and give preliminary information about the possible stage of the AF.

References


Address for correspondence:
Rita Laureanti
Via Camillo Golgi, 39, 20133 Milano, Italy
rita.laureanti@polimi.it