Investigating Amiodarone Arrhythmia Treatment

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Abstract. The study examines the subjects with supraventricular (SVA) and ventricular (VA) disorder of the cardiac rhythm. Subjects were monitored before and after three weeks of amiodarone monotherapy. Beat to beat analysis of pulse interval (PI) and systolic blood pressure (SBP) was done using delay vector variance (DVV) and approximate entropy (ApEn) approach trying to assess the changes in the presence of nonlinearities and predictability before and after treatment. The presence of nonlinearities in PI time series was significantly decreased after amiodarone treatment, as measured by DVV analysis. The same analysis revealed the significant increase in predictability in SBP of VA subjects 30 min after taking 200mg amiodarone dose. ApEn, however, remained unchanged after three weeks of therapy in both PI and SBP. It was generally noticed that subjects with ventricular arrhythmias responded better to the amiodarone treatment.

Keywords: amiodarone, approximate entropy, arrhythmias, delayed vector variance, heart rate variability

1. Introduction

Heart rate variability (HRV) is an indicator of autonomic influences on modulation of cardiac rhythm. Efficient interactions between sympathetic and parasympathetic nervous system lead to the homeostasis of cardiovascular system. Autonomic functions imbalance results in domination of one of the autonomic influences, which may lead to the life-threatening types of arrhythmias. Amiodarone (potassium-channel blocker) is an antiarrhythmic agent used in the treatment of supraventricular (SVA) and ventricular (VA) tachyarrhythmia. A number of studies investigate effectiveness of amiodarone in patients with ischemic heart disease and atrial fibrillation [Sassi et al., 2006; Shabalin et al., 2002; de Silva et al., 2002; Malik et al., 1998; Pedretti et al., 1998, Zuanetti et al., 1991]. Our study examines the patients of Clinical Hospital Centre Bezanijska Kosa with supraventricular and ventricular disorder of rhythm. All patients were tested first before (BASELINE), 30 minutes after first oral 200 mg amiodarone dose (AMIODARONE) and three weeks after monotherapy with amiodarone (THERAPY).

The presence of nonlinearities and/or determinism in HRV time series can be one of the indicators of health status. A change in the nature of HRV signal may convey important information of change in the health condition. This study tries to determine the nature of HRV signal in patients with SVA and VA, before and after amiodarone monotherapy based on delayed vector variance (DVV) method [Gautama et al., April 2004; Gautama et al., May 2004], observing the change in predictability and degree of nonlinearity during the course of experiment.

Complexity analysis was done as well using approximate entropy (ApEn) approach. The proper application of ApEn statistics requires the selection of the three parameters: $m$, $r$, and $\tau$, referred to as pattern length (embedding dimension), normalized threshold (tolerance, filter) and time delay, respectively. Several studies have recently questioned the choice of $m$, $r$ and $\tau$, influence of data length and sample frequency [Lu et al., 2008; Chen et al., 2005; Kaffashi et al., 2008]. This study takes into account the guidelines given in [Lu et al., 2008; Chen et al., 2005] for the selection of $m$ and $r$, and $\tau$ is chosen as the first minimum of autocorrelation function as proposed in [Kaffashi et al. 2008].
2. Material and Methods

2.1. Study protocol

The study included 35 subject divided into two groups. The group with SVA consisted of 8 males (average age 84.4 years) and 10 females (average age 55.6 years). The other group, VA had 8 males (average age 47.1 years) and 9 females (average age 52.9 years). A control group consisted of 10 male and 12 female healthy subjects. The Task Force Monitor (CNSystems, Graz, Austria) was used for beat-to-beat analysis of heart rate (HR) and blood pressure (BP) variability, baroreflex sensitivity and hemodynamic parameters.

After a week of placebo pretreatment, BASELINE measurement was performed, including: autonomic function and hemodynamic status assessment, 24h ambulatory electrocardiography (ECG) monitoring with HRV analysis and 24 hour ambulatory blood pressure (ABP) monitoring. After baseline evaluation we investigated the effects of first 200 mg dose of AMIODARONE on autonomic function and hemodynamic status in all patients using Task Force monitor.

In the third stage of experiment all patients were assigned 200-600 mg of amiodarone, first week 3x1, second week 2x1 and once daily during the third week of the treatment. After amiodarone THERAPY the evaluation of autonomic function and hemodynamic status was repeated using both Task Force Monitor and 24 h ambulatory ECG and BP monitoring.

Study was approved by the Scientific Ethical Committee of Clinical Hospital Center Bezanijska Kosa. All participants gave written informed consent in accordance with the declaration of Helsinki.

2.2. Signal preprocessing

Due to large number of analysis and recordings, the focus of this study is oriented towards short term Task Force Monitor recordings of beat-to-beat pulse interval (PI) and systolic blood pressure (SBP). For the purpose of analysis and proper comparison of the results, the length of PI and SBP series was limited to 5000 samples. After careful manual visual examination and artifacts removal, PI and SBP were detrended using approach proposed in [Tarvainen et al., 2002] to ensure stationarity necessary for the applied analysis.

2.3. Delayed vector variance approach

Delayed vector variance (DVV) is the method for detecting the presence of determinism and nonlinearity in a time series proposed in [Gautama et al., April 2004]. The method examines local predictability of a signal. Standardization within the DVV method enables both the statistic test for the presence of nonlinearities, and the visual inspection of DVV scatter diagram.

To apply the method it is necessary to represent a time series as a set of delay vectors (DVs) of a given embedding dimension \( m \), denoted by \( X(k)=[x_{k},x_{k-τ},...,x_{k-τd}] \), where the subscript indexes time and \( τ \) is a time lag which is set to minimum of auto mutual information function, here \( τ=3 \), which is an average value for all of the time series under study. Every DV is associated with a corresponding target, i.e. the next sample \( x_{k} \).

In the first stage of analysis the predictability of time series is examined. The analysis for a given embedding dimension \( m \) includes the following steps:

- The mean, \( \mu_{d} \), and standard deviation, \( \sigma_{d} \), are computed over all pairwise distances between DVs.
- The spans, \( r_{d} \), are taken from the interval \([\mu_{d}-n_{d}\sigma_{d}, \mu_{d}+n_{d}\sigma_{d}]\), e.g., uniformly spaced, where \( n_{d} \) is a parameter controlling the span over which to compute the DVV-plot. The set \( \Omega_{d}(m,r_{d}) \) consists of all DVs that lie within a distance to \( X(k) \) equal to the span \( r_{d} \).
- For every set \( \Omega_{d}(m,r_{d}) \), the variance of the corresponding targets is computed. The average over all sets, divided by the variance of the time series, yields the inverse measure of predictability, namely the ‘target variance’, \( \sigma^{*2} \). The variance is computed only if set contains at least \( N_{0}=30 \) DVs.

DVV plot actually plots target variance \( \sigma^{*2} \) vs. span \( r_{d} \) for a given dimension \( m \). The presence of the deterministic component leads to the small values of \( \sigma^{*2} \) for small spans, indicating that similar DVs have similar targets. The minimal target variance for a given \( m \) is denoted as \( \sigma^{*2}_{\text{min}} \). The optimal embedding dimension is chosen by running the analysis for different values of \( m=1,..10 \) and choosing the value for which the minimal target variance (over all spans \( r_{d} \), \( \sigma^{*2}_{\text{min}} \) is minimal. Therefore, \( m \) is calculated for every time series based on this criterion, while the other parameter of DVV analysis remained the same.

The DVV plot should converge to unity at right: for maximal spans all DVs belong to the same set and targets variance is equal to variance of the time series. If it is not the case, the value of parameter \( n_{d} \) should be increased (\( n_{d} \) in this analysis equals to 3). As showed in [Gautama et al., May 2004], \( \sigma^{*2}_{\text{min}} \)
should only be used as a comparative measure between time series of the same length using the fixed value for \( N \).

In the second stage, nonlinear nature of the signal is investigated using surrogate data generated by iterative amplitude adjusted Fourier transform (iAAFT) approach [Gautama et al., April 2004]. DVV-plots are generated for both the surrogate data and the original time series for the same \( m \) determined for original time series. If the DVV-plots are significantly different, the null hypothesis (linearity) is rejected, and the original time series is considered nonlinear in nature. To visualize and qualify the results, DVV scatter plots are used: target variances averaged over 99 surrogates are plotted against the ones of the original time series for corresponding standardized distances. If the DVV scatter diagram coincides with the bisector line, the time series is linear. Conversely, if the original time series is nonlinear, the curve deviates from the bisector line which is an indication of a deviation from the null hypothesis of linearity. It can be quantified by the root-mean-square error (RMSE) which are ‘similar’ (that is within a set of \( \sigma^{*\text{w}} \) of the original time series and the \( \sigma^{*\text{w}} \) averaged over the DVV-plots of the surrogates (note that while computing this average and RMSE, only the valid measurements are taken into account). In this way, a single test statistic is obtained, used for testing the validity of the null hypothesis using non-parametric rank-based test. For each original time series, 99 surrogates were generated and the test statistics for both the original and surrogate time series was computed. These values are sorted in increasing order, and a right-tailed test is rejected at the level of \( \alpha=0.01 \) if rank of the original time series exceeds 90.

For the application of the method the Matlab code provided by one of the authors of [Gautama et al., May 2004], D.P.Mandic, was used and slightly modified to calculate \( m \) for which \( \sigma_{\text{w}}^{*\text{ave}} \) was minimal and to set the adequate parameter values.

2.4. Approximate Entropy Approach

Given a time series \( \{x_i\}, i=1,...,N \), where \( N \) is the length of the time series, form the vectors of the length \( m \)

\[
X_m(i) = [x_i, x_{i+1}, ..., x_{i+(m-1)\tau}] \quad \text{for} \quad i = 1, ... , N-(m-1)\tau
\]

where \( \tau \) was calculated as the first minimum of the sample autocorrelation function (\( \tau=3 \) for majority of signals). For each of the vectors \( X_m(i), i=1,...,N-(m-1)\tau \), the number \( B_\tau(i) \) has to be determined as the number of vectors \( X_m(j) \) for which the distance \( d\text{'}(X_m(i),X_m(j))<\tau \), where \( \tau \) is some predefined threshold value. The function:

\[
C^\tau(r) = \frac{B_\tau(i)}{N-(m-1)\tau}
\]

estimates the probability that any vector \( X_m(j) \) is within the distance \( r \) from the vector \( X_m(i) \). Another function:

\[
\Phi_\tau(r) = \frac{1}{N-(m-1)\tau} \sum_{i=1}^{N-(m-1)\tau} \ln[C^\tau(r)]
\]

is average of the natural logarithms of the previous functions. The procedure is then repeated for vectors of the length \( m+1 \), and the approximate entropy is defined as:

\[
\text{ApEn}(m, r, N) = \Phi_\tau(r) - \Phi_{\tau+1}(r)
\]

The values of ApEn are calculated for \( m=2 \) [Lu et al., 2008; Chen et al. 2005] and, as an illustrative example, for \( m=3 \). The values of \( r \) range from 0 to 0.5 times standard deviation of the time series in order to identify the \( r_{\text{Max}} \) value for which ApEn reaches its maximum. The analysis was done for \( r=1 \) as well, but the results were less consistent, with lower entropy values.

ApEn\( (m, r, N, \tau) \) analysis fixes the \( m \) value trying to determine whether the patterns of length \( m \) are ‘similar’ (that is within a set \( \Omega_m(m,r,\tau) \) in the vocabulary of DVV), will be ‘similar’ in the next sample as well. Due to the heavy dependence of ApEn on signal length \( N \) and threshold \( r \) values, the meaningful comparison is possible only for the time series of the same length, and for the same threshold value. The embedding dimension \( m \), stays fixed throughout analysis, determined using False Nearest Neighbor method. On the other hand, DVV analyses starts from the DVs of the length \( m \) within the distance \( r_{\text{sh}} \) trying to assess the variances of the target sample that follows. The bigger the variance, the signal is considered less predictable. Minimal target variance is achieved for some value of \( m \), which is determined for each of the time series and therefore differs through DVV analysis.

2.5. Statistics

Results are given as mean±SE. The statistical significance was assessed using ANOVA test. Significance levels \( p<0.05 \), \( p<0.01 \), \( p<0.001 \) indicated by the shades of gray increasing in darkness compared to corresponding BASELINE condition, or by the * compared to the HEALTHY group.
Rank based test, described in 2.3 was used for rejection of hypothesis of linearity for each time series, based on its RMSE value as compared with mean RMSE values of its generated surrogate data.

3. Results

Mean and SEM of the PI and SBP for both of the groups are given in Table 1. While there is no change in SVA group, in the VA group RR interval is increased after therapy, with no significant changes in SBP. Fig. 1 shows the RR time series before and after amiodarone treatment for one VA subject.

![Figure 1](image_url)

**Table 1.** RMSE AND ApEn (2,r,N,3).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Therapy</th>
<th>Amiodarone</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR[ms] SVA</td>
<td>821.1±35.18</td>
<td>861.3±55.71</td>
<td>899.1±54.43</td>
<td>838.8±29.68</td>
</tr>
<tr>
<td>VA</td>
<td>851.3±40.91</td>
<td>928.3±31.86</td>
<td>978.7±42.18**</td>
<td></td>
</tr>
<tr>
<td>SBP [mmHg] SVA</td>
<td>141.1±8.19</td>
<td>138.1±6.450</td>
<td>142.4±5.184</td>
<td>125.5±3.366</td>
</tr>
<tr>
<td>VA</td>
<td>120.6±5.495</td>
<td>116.7±4.590</td>
<td>122.5±5.018*</td>
<td></td>
</tr>
<tr>
<td>RMSE PI</td>
<td>0.213±0.021</td>
<td>0.105±0.015*</td>
<td>0.154±0.015</td>
<td>0.202±0.021</td>
</tr>
<tr>
<td>SBP</td>
<td>0.170±0.02*</td>
<td>0.164±0.019*</td>
<td>0.162±0.015*</td>
<td>0.076±0.0152</td>
</tr>
<tr>
<td>σ*_{m=PI} SVA</td>
<td>0.297±0.05</td>
<td>0.444±0.04</td>
<td>0.362±0.0456</td>
<td>0.288±0.0313</td>
</tr>
<tr>
<td>VA</td>
<td>0.252±0.021</td>
<td>0.331±0.064</td>
<td>0.283±0.034</td>
<td></td>
</tr>
<tr>
<td>σ*_{m=SBP} SVA</td>
<td>0.332±0.0406</td>
<td>0.379±0.0631</td>
<td>0.152±0.065*</td>
<td>0.395±0.0214</td>
</tr>
<tr>
<td>VA</td>
<td>0.186±0.044*</td>
<td>0.331±0.0384</td>
<td>0.092±0.037***</td>
<td></td>
</tr>
<tr>
<td>ApEn –PI (2,τ_{MAX},N,3) SVA</td>
<td>1.588±0.0271</td>
<td>1.605±0.0291</td>
<td>1.805±0.030**</td>
<td>1.539±0.0186</td>
</tr>
<tr>
<td>VA</td>
<td>1.534±0.0385</td>
<td>1.571±0.020</td>
<td>1.754±0.0203***</td>
<td></td>
</tr>
<tr>
<td>ApEn –PI (3,τ_{MAX},N,3) SVA</td>
<td>1.09±0.042</td>
<td>1.13±0.023</td>
<td>1.24±0.033**</td>
<td>1.06±0.016</td>
</tr>
<tr>
<td>VA</td>
<td>1.10±0.042</td>
<td>1.09±0.017</td>
<td>1.21±0.017*</td>
<td></td>
</tr>
<tr>
<td>ApEn –SBP (2,τ_{MAX},N,3) SVA</td>
<td>1.568±0.0406</td>
<td>1.534±0.0318</td>
<td>1.732±0.038*</td>
<td>1.539±0.0184</td>
</tr>
<tr>
<td>VA</td>
<td>1.526±0.0321</td>
<td>1.525±0.0223</td>
<td>1.619±0.0368</td>
<td></td>
</tr>
<tr>
<td>ApEn –SBP (3,τ_{MAX},N,3) SVA</td>
<td>1.07±0.033</td>
<td>1.06±0.025</td>
<td>1.17±0.042*</td>
<td>1.07±0.017</td>
</tr>
<tr>
<td>VA</td>
<td>1.03±0.047</td>
<td>1.05±0.021</td>
<td>1.04±0.038</td>
<td></td>
</tr>
<tr>
<td>τMAX – PI m=2 SVA</td>
<td>0.199±0.010</td>
<td>0.196±0.007</td>
<td>0.160±0.006**</td>
<td>0.215±0.006</td>
</tr>
<tr>
<td>VA</td>
<td>0.180±0.011*</td>
<td>0.213±0.008</td>
<td>0.173±0.003*</td>
<td></td>
</tr>
<tr>
<td>τMAX – PI m=3 SVA</td>
<td>0.377±0.012</td>
<td>0.399±0.011</td>
<td>0.334±0.007*</td>
<td>0.395±0.01</td>
</tr>
<tr>
<td>VA</td>
<td>0.346±0.017</td>
<td>0.401±0.011</td>
<td>0.347±0.009</td>
<td></td>
</tr>
<tr>
<td>τMAX – SBP m=2 SVA</td>
<td>0.185±0.006</td>
<td>0.176±0.009</td>
<td>0.157±0.006</td>
<td>0.208±0.0057</td>
</tr>
<tr>
<td>VA</td>
<td>0.142±0.007</td>
<td>0.187±0.011</td>
<td>0.142±0.007</td>
<td></td>
</tr>
<tr>
<td>τMAX – SBP m=3 SVA</td>
<td>0.355±0.0129</td>
<td>0.325±0.018</td>
<td>0.317±0.013***</td>
<td>0.380±0.009</td>
</tr>
<tr>
<td>VA</td>
<td>0.308±0.020***</td>
<td>0.344±0.026</td>
<td>0.280±0.017***</td>
<td></td>
</tr>
</tbody>
</table>

Results are given as mean±SE. The statistical significance was assessed using ANOVA test. Significance levels p<0.05, p<0.01, p<0.001 indicated by the shades of gray increasing in darkness compared to corresponding BASELINE condition, or by the * compared to the HEALTHY group.)
The DVV method was applied and the nonlinearity was detected in all of the time series under study, both PI and SBP, with statistical significance \( \alpha = 0.01 \) using the nonparametric rank based test. The degree of nonlinearity measured by \( RMSE \) showed great inter-subject variability, but, generally, \( RMSE \) values of PI time series significantly decreased after three weeks of amiodarone monotherapy in both SVA group and VA group, while there was insignificant decrease of PI RMSE 30 min after acute AMIODARONE. On the other hand, there was no significant change in \( RMSE \) value for SBP time series through the course of experiment, except that it was noticed that HEALTHY subjects have significantly lower \( RMSE \) values for SBP series. PI DVV scatter plots are shown in Fig. 2 for one VA subject. The \( \sigma^{*2} \) values are in proximity of 0.3 - 0.4, indicating the presence of stochastic nature as well, probably due to the presence of noise. Values of \( RMSE \) and \( \sigma^{*2} \) are given in Table 1. Minimal \( \sigma^{*2} \) values varied quite a lot among the subjects.

As for the PI time series, in both SVA and VA group there was no significant increase in \( \sigma^{*2}_{min} \) towards the values characteristic for the healthy group of subjects. As for the SBP series, it was noticed that \( \sigma^{*2}_{min} \) values are significantly lower in VA group, compared to the healthy subjects, while in SVA group the relationship is the same, but not significant. In the THERAPY stage, \( \sigma^{*2}_{min} \) increases without significant change compared to BASELINE values, but after acute AMIODARONE dose there is a significant decrease in \( \sigma^{*2}_{min} \) especially in VA group. The minimal value \( \sigma^{*2} \) for SBP series is typically obtained for \( m \approx 4 \).

ApEn reflects the likelihood that “similar” patterns of time series will not be followed by additional “similar” observations. The ApEn analysis, applied to SVA and VA group, revealed that there is no significant change in ApEn of PI time series due to the amiodarone treatment. Consistent plots were obtained for all subjects belonging to the same group, unexpectedly, with non-significant difference when compared to the healthy subjects group! The obtained values are given in Table 1. On the other hand, there was a significant change in the \( r_{max} \), i.e. the values of \( r \) for which ApEn reaches its maxima. \( r_{max} \) is significantly lower 30 min after AMIODARONE dose than in BASELINE and THERAPY stage (where it remains practically the same). Therefore, evaluation ApEn for a single \( r \) value could lead to the wrong conclusions. It is noticeable that there is a significant decrease in maximal ApEn values when \( m=3 \) is used.
When the subjects’ analysis is based on the response to the amiodarone therapy, according to the clinicians’ opinion, the improvement after amiodarone treatment could generally be noticed in VA group. The VA group responded either positively or with small but positive changes on amiodarone treatment. SVA group had some subjects that responded the treatment in a negative fashion, imposing that care should be taken of possible adverse amiodarone influence.

4. Conclusion

These are some of the results of the study done on amiodarone treated patients with superventricular and ventricular arrhythmias. The aim of the study was amiodarone therapy influence on the nature of the HRV signal, as well as the eventual change in complexity due to the treatment. DVV analysis implies that introducing amiodarone reduces to some extent the presence of nonlinearities in the PI time series. On the other hand ApEn analysis does not report significant change of maxima of ApEn. There is, however, the repositioning of r_{MAX} towards the lower values, which is significant after acute amiodarone dose. The results obtained so far are characterized with large variability among the subject, which may be caused by degrees of illness severance, or even some present pathology of other type. The small study sample is due to small number of patients with recordings in sinus rhythm. It is generally noticed that subjects with ventricular arrhythmias respond better to the amiodarone treatment. The valuable result would certainly be some kind of parameter whose value would be pre-indication that subject would benefit from the amiodarone therapy. The undergoing study includes the analysis that may convey better insight in perturbed sympathovagal balance that is a usual background of life-threatening arrhythmias.

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References


