Lau, Stephan; Haueisen, Jens; Schukat-Talamazzini, Ernst G.; Voss, Andreas; Görmig, Matthias; Leder, Uwe; Figulla, Hans-R.: Low HRV entropy is strongly associated with myocardial infarction
Low HRV entropy is strongly associated with myocardial infarction

Stephan Lau1,2, Jens Haueisen2,4,*, Ernst G. Schukat-Talamazzini1, Andreas Voss2, Matthias Goernig2, Uwe Leder5 and Hans-R. Figulla5

1 Institute of Computer Science, Friedrich Schiller University Jena, Jena, Germany
2 Biomagnetic Center Jena, Friedrich Schiller University Jena, Jena, Germany
3 Department of Medical Engineering, University of Applied Sciences Jena, Jena, Germany
4 Institute of Biomedical Engineering and Informatics, Technical University of Ilmenau, Ilmenau, Germany
5 Clinic of Internal Medicine I, Friedrich Schiller University Jena, Jena, Germany

Abstract

Heart rate variability (HRV) is a marker of autonomous activity in the heart. An important application of HRV measures is the stratification of mortality risk after myocardial infarction. Our hypothesis is that the information entropy of HRV, a non-linear approach, is a suitable measure for this assessment. As a first step, to evaluate the effect of myocardial infarction on the entropy, we compared the entropy to standard HRV parameters. The entropy was estimated by compressing the tachogram with Bzip2. For univariate comparison, statistical tests were used. Multivariate analysis was carried out using automatically generated decision trees. The classification rate and the simplicity of the decision trees were the two evaluation criteria. The findings support our hypothesis. The meanNN-normalized entropy is reduced in patients with myocardial infarction with very high significance. One entropy parameter alone exceeds the discrimination strength of multivariate standards-based trees.

Keywords: Burrows-Wheeler compression; Bzip2; decision tree; entropy estimation; heart rate variability.

Introduction

The autonomous nervous system mediates a number of control mechanisms such as oxygen and carbon dioxide concentrations and blood pressure. Heart rate variability (HRV) is a marker of the activity of the autonomous nervous system. In particular, following myocardial infarction, HRV is reduced, an observation that is used to stratify patient risk [1].

The basic signal used in HRV analysis is the tachogram, which demonstrates the consecutive sequence of beat-to-beat intervals, also called normal-to-normal (NN) intervals. Figure 1 shows the difference between the tachogram of a healthy individual and a patient with recent myocardial infarction.

Standard measures

The most widely used HRV measures [2] are from the time and frequency domains, such as those in Table 1. However, non-linear HRV methods represent a promising area for research because the abstract concept of variability can be modeled more effectively than just with signal-centered measures and counts.

Information entropy

Information entropy is such a non-linear method. In information theory, the entropy of a message is a measure of the amount of information or complexity contained in it. A random signal would have large entropy, while a constant signal has small entropy. The more order or repetition or redundancy is in a signal, the lower is its entropy.

Hypothesis and objective

The concept of HRV is very similar to that of entropy. A healthy tachogram (Figure 1) with considerable variability is unordered and non-repetitive; its entropy is high. A pathological tachogram with low variability has lower entropy. The hypothesis adopted here is that the entropy of the tachogram is an effective measure of HRV.

The primary objective was to test this hypothesis in patients with myocardial infarction. The univariate and multivariate discrimination strength between patients and controls was compared to one of the traditional HRV measures. A secondary objective was to identify the signal preprocessing steps necessary for entropy estimation.

Figure 1 Tachogram of a healthy individual and a post-infarct patient (no diabetes, coronary heart disease degree 3); both were ≈50 years of age and female.
Table 1  Time- and frequency-domain measures.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>meanNN</td>
<td>Mean of NN intervals</td>
<td>ms</td>
</tr>
<tr>
<td>sdNN</td>
<td>Standard deviation of all NN intervals</td>
<td>ms</td>
</tr>
<tr>
<td>cvNN</td>
<td>Ratio sdNN/meanNN</td>
<td>–</td>
</tr>
<tr>
<td>sdENN1</td>
<td>sdNN averaged over periods of 1 min</td>
<td>ms</td>
</tr>
<tr>
<td>rmssd</td>
<td>Root of the mean-squared differences of successive NN intervals</td>
<td>ms</td>
</tr>
<tr>
<td>pNN50</td>
<td>Proportion of successive interval differences ≥50 ms within all NN intervals</td>
<td>%</td>
</tr>
<tr>
<td>pNN10 (pNN20)</td>
<td>Proportion of successive interval differences ≤10 (20) ms within all intervals</td>
<td>%</td>
</tr>
<tr>
<td>VLF</td>
<td>Power in the very low range (≤0.04 Hz)</td>
<td>ms²</td>
</tr>
<tr>
<td>LF</td>
<td>Power in the low range (0.04–0.15 Hz)</td>
<td>ms²</td>
</tr>
<tr>
<td>HF</td>
<td>Power in the high range (0.15–0.4 Hz)</td>
<td>ms²</td>
</tr>
<tr>
<td>P</td>
<td>Power over the whole range (0–0.4 Hz)</td>
<td>ms²</td>
</tr>
<tr>
<td>LF/HF</td>
<td>Ratio LF/HF</td>
<td>–</td>
</tr>
<tr>
<td>LF/P</td>
<td>Ratio LF/P</td>
<td>–</td>
</tr>
<tr>
<td>HF/P</td>
<td>Ratio HF/P</td>
<td>–</td>
</tr>
</tbody>
</table>

Materials and methods

Data set

In 114 subjects (Table 2), combined MCG and ECG recordings were obtained in a supine position. Each recording was of 10 min duration with a sampling frequency of 1000 Hz and demonstrated a sinus rhythm with less than 10% extrasystoles. Of the 114 recordings, 59 were from patients with myocardial infarction; the remaining 55 were from healthy controls without a history of heart disease. The time between myocardial infarction of patients and the recording was 11.9 ± 6.9 days.

Preprocessing

The NN intervals were extracted using template matching with a QRS complex as template (Figure 2). Artifacts, mainly extrasystoles, were then replaced by a random value matching the adaptive mean and standard deviation [3]. Every recording was reduced in length to that of the shortest. Both the resulting tachogram and its successive differences were used as separate inputs for HRV analysis.

Quantization of the tachogram was an entropy-specific step. Compression-based entropy requires alphabetical symbols as input. The raw intervals falling between 400 and 1400 ms were resampled at a rate of 128 Hz. This is similar to sorting the intervals into histogram bins of size 1000 ms/128 = 7.8125 ms. Thus, there were exactly 128 bins (or symbols) in the alphabet.

Entropy definition and estimation

Shannon’s Theorem formally defines entropy: Imagine a message source that has \( n \) possible messages with probabilities \( p_1, \ldots, p_n \). Then the entropy of message \( i \) is:

\[
E_i = -\sum_{i=1}^{n} p_i \log p_i \quad \text{[bit]}.
\]  

This is intuitive because a message with high probability will have low entropy and vice versa. The average entropy \( E \) of all messages, also called the entropy of the message source, is then:

\[
E = -\sum_{i=1}^{n} p_i \log p_i \quad \text{[bit]}.
\]  

In this study, each NN interval is considered a message and the sinus node is the source. A tachogram is a sample of the messages that a source emits [4].

There are two principal methods for estimating the entropy. The first is to estimate the probabilities in some

Table 2  Population characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Post-infarct</th>
<th>Controls</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>54.0±9.4</td>
<td>49.3±11.2</td>
<td>51.7±10.5</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>42/17</td>
<td>27/28</td>
<td>69/45</td>
</tr>
</tbody>
</table>

Figure 2  Data processing steps and study design.
statistical manner, then to compute the entropy directly
from this estimate. The second indirect way is to com-
press the message, thereby eliminating the redundancy
contained in it. The compression ratio is then an upper
bound of the entropy. The better the compression, the
closer is the estimation [4].

In this study, the entropy was estimated by compress-
ing the quantized tachogram with Burrows-Wheeler com-
pression [5], which is one of the most efficient
algorithms. Each interval was encoded as 1 byte = 8 bit
in a file. The file was then compressed using Bzip2 [6],
an implementation of the Burrows-Wheeler compression.
The entropy per bit of the input signal was estimated by:

\[ E = \frac{\text{compressed file size}}{\text{# of values} \times \text{# of bit per value}} \text{[bit]}. \] (3)

The compressed file size divided by the number of val-
ues, the intervals, yields the entropy per interval.
Because each interval was encoded by \( 7 = \log_2(128) \) bit
during quantization, we normalized by dividing by 7. The
resulting value could then be interpreted as proportion of
information in the quantized tachogram.

For the first sample (Figure 1), the entropy was \( 323 \times 8 \)
bit/4800 = 0.77 bit/5. However, the post-infarct
patient only had entropy of \( 161 \times 8 \times 7 = 0.39 \) bit
\( /5 \). The entropy parameters used here were:
[BZIP2,Cut], [BZIP2,Diff], [BZIP2,Cut]/m and [BZIP2,
Diff]/m. [BZIP2,Cut] means Bzip2 is applied to the tacho-
gram, whereas in [BZIP2,Diff] it is applied to the suc-
cessive differences. The extension ‘/m’ means divided by
meanNN.

Classification

Decision trees were chosen as the classification model
because they explicitly state the choice of parameters
and how they are combined. The decision trees were
generated using the CART algorithm [7].

First, a tree was generated and then pruned based on
the misclassification costs in a ten-fold cross-validation.
To establish the classification rate, leave-one-out vali-
dation was performed. These steps were performed for
the parameter set in Table 1, in which all parameters
except LF/P and HF/P were taken directly from the stan-
dard [2], and the augmented set including the entropy.
The criteria for assessing the decision trees were: (1) the
classification rate, and (2) the simplicity and stability. The

best classification rule is the one that represents an
effective compromise between both.

Results

Statistical tests

Wilcoxon tests (Table 3) showed that [BZIP2,Cut]/m had
the highest significance (\( p = 0.00004 \)) for all recordings
and for just men. In women, [BZIP2,Cut]/m was only out-
performed by cvNN. [BZIP2,Diff]/m was only slightly less
significant than [BZIP2,Cut]/m for all and female sub-
jects; for males its \( p \)-value was 0.0513. [BZIP2,Cut]/m
was the only parameter with significant mean differences
in all three groups.

Standards tree

The tree in Figure 3 shows the most frequent tree during
validation and is thus selected as classifier 1. The clas-
sification rate is 65%. During leave-one-out validation,
one recording is left out at a time. This produces a
different tree each time. The number of leaves varies from
3 to 26, with an average of 5.4. The parameters in Figure
3 are the most frequent ones. Classifier 1 is therefore an
unstable classification rule. Additional tests with com-
posite classifiers produced a maximum classification rate
of 68%, bearing in mind that these trees are even more
complex and unstable.

Figure 3 Classifier 1: decision tree based on standard parameters and its visualization.

<table>
<thead>
<tr>
<th>Table 3 Wilcoxon test results.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>meanNN</td>
</tr>
<tr>
<td>sdNN</td>
</tr>
<tr>
<td>cvNN</td>
</tr>
<tr>
<td>sdaNN1</td>
</tr>
<tr>
<td>pNN50</td>
</tr>
<tr>
<td>LF</td>
</tr>
<tr>
<td>HF</td>
</tr>
<tr>
<td>P</td>
</tr>
<tr>
<td>LF/P</td>
</tr>
<tr>
<td>[BZIP2,Cut]</td>
</tr>
<tr>
<td>[BZIP2,Diff]</td>
</tr>
<tr>
<td>[BZIP2,Cut]/m</td>
</tr>
<tr>
<td>[BZIP2,Diff]/m</td>
</tr>
</tbody>
</table>
that it achieved a high classification rate with a simple analysis entropy expressed the variability as a whole. The information rule is much more stable than that of classifier 1. This decision tree has a higher classification rate of 70%. In addition, the very same tree was found in every leave-one-out validation step. This means that this classification rule is much more stable than that of classifier 1. Additional tests with composite classifiers produced a maximum classification rate of 74%.

Standards and entropy tree

Augmentation with entropy parameters produces the decision tree in Figure 4. The entropy parameter [BZIP2,Diff]/m supersedes all standard parameters. In fact, this simple [BZIP2,Diff]/m threshold outperforms any multivariate classification rule that uses standard parameters and combinations with entropy parameters. This decision tree has a higher classification rate of 70%. In addition, the very same tree was found in every leave-one-out validation step. This means that this classification rule is much more stable than that of classifier 1. Additional tests with composite classifiers produced a maximum classification rate of 74%.

Figure 4 Classifier 2: decision tree based on standard and entropy parameters and its visualization.

Discussion

Standard parameters

The standard parameters showed discrimination strength in females. In males, only LF/P was significant. The multivariate trees often had LF as the first decision node (Figure 3). A low LF value characterizes infarcts. This complies with the clinical observation that HRV is reduced after infarction [1]. Additional tests with composite trees showed that the combination of meanNN with a parameter such as LF, LF/P or sdNN covers most of the achievable classification rate.

Entropy parameters

[BZIP2,Cut]/m was the only parameter with discrimination strength in all groups and showed stronger significance than standard parameters. Especially in males, the main patient group, [BZIP2,Cut]/m outperformed the standard parameters. Multivariate analysis identified [BZIP2,Diff]/m as the best classification parameter. In the [BZIP2,Diff]/m threshold, the entropy [BZIP2,Diff] is combined with meanNN. This is similar to the parameter cvNN=sdNN/meanNN [2]. However, [BZIP2,Diff] captured the variability, not only the variance. The information entropy expressed the variability as a whole.

Entropy fulfilled both of the quality criteria very well, in that it achieved a high classification rate with a simple and stable discrimination rule. This extends the previous findings of Baumert et al. [8] on arrhythmias. An advantage over other entropy-related approaches [9, 10] is that the entropy definition is not altered or decomposed. Thus, the original information theory concept of entropy is retained.

In conclusion, we evaluated the usefulness of entropy as an HRV parameter with the long-term goal of risk stratification. In contrast to previous entropy-based approaches, we applied the original information-theoretic definition of entropy. The entropy was estimated by a straightforward compression-based method. To obtain optimal multivariate classification rules, an automated decision tree generator was used. The key findings are:

• [BZIP2,Cut]/m is reduced in post-infarction patients with very high significance (p < 0.00004).
• The discrimination strength of [BZIP2,Diff]/m alone exceeds that of multivariate standards-based decision trees by 5–10%, while being simpler and more stable.
• The tachogram length required is only 500–600 beats or ≈10–12 min. A suitable quantization step width is 1/128 s = 7.8125 ms.

This confirms the hypothesis that entropy is an effective measure of HRV and highly associated with myocardial infarction. We suggest that the application of BZIP2 entropy is suitable for post-infarct risk stratification.

References