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Low HRV entropy is strongly associated with myocardial infarction

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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].

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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.

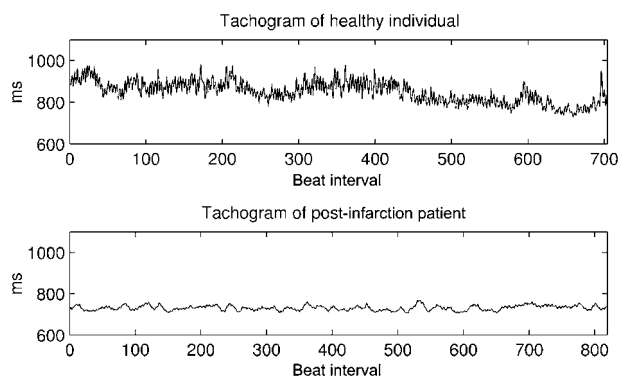


Figure 1 Tachogram of a healthy individual and a post-infarction patient (no diabetes, coronary heart disease degree 3); both were ≈ 50 years of age and female.

Table 1 Time- and frequency-domain measures.

Parameter	Description	Units
meanNN	Mean of NN intervals	ms
sdNN	Standard deviation of all NN intervals	ms
cvNN	Ratio sdNN/meanNN	–
sdaNN1	sdNN averaged over periods of 1 min	ms
rmssd	Root of the mean-squared differences of successive NN intervals	ms
pNN50	Proportion of successive interval differences ≥ 50 ms within all NN intervals	%
pNNi10 (pNNi20)	Proportion of successive interval differences ≤ 10 (20) ms within all intervals	%
VLF	Power in the very low range (≤ 0.04 Hz)	ms ²
LF	Power in the low range (0.04–0.15 Hz)	ms ²
HF	Power in the high range (0.15–0.4 Hz)	ms ²
P	Power over the whole range (0–0.4 Hz)	ms ²
LF/HF	Ratio LF/HF	–
LF/P	Ratio LF/P	–
HF/P	Ratio HF/P	–

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 $1000 \text{ ms}/128 = 7.8125 \text{ ms}$. 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, \dots, p_n . Then the entropy of message i is:

$$E_i = -\log_2 p_i \quad [\text{bit}]. \quad (1)$$

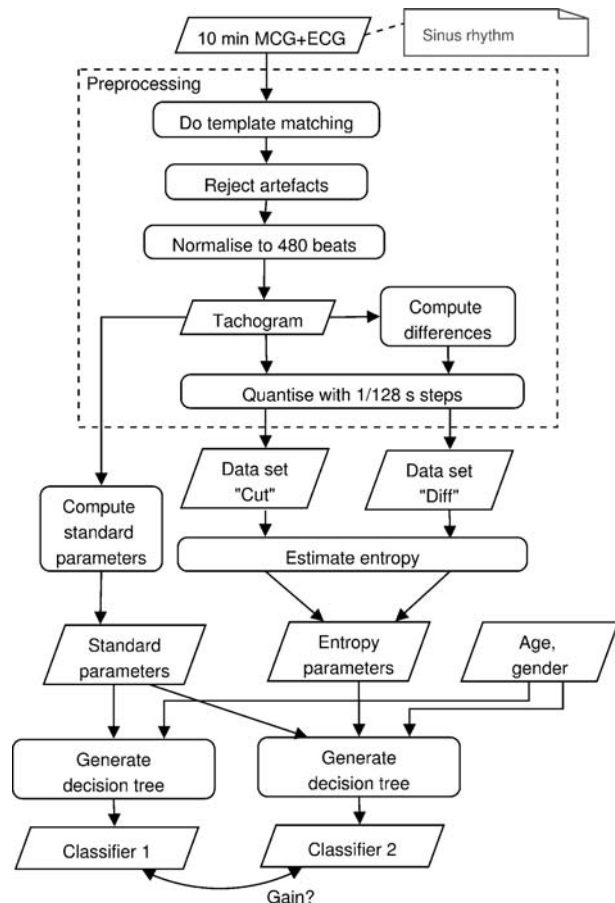
This is intuitive because a message with high proba-

bility will have low entropy and vice versa. The average entropy E of all messages, also called the entropy of the message source, is then:

$$E = -\sum_{i=1}^n p_i \log_2 p_i \quad [\text{bit}]. \quad (2)$$

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

**Figure 2** Data processing steps and study design.**Table 2** Population characteristics.

	Post-infarct	Controls	All
Age (mean \pm SD) (years)	54.0 \pm 9.4	49.3 \pm 11.2	51.7 \pm 10.5
Gender (M/F)	42/17	27/28	69/45

statistical manner, then to compute the entropy directly from this estimate. The second indirect way is to compress 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 compressing the quantized tachogram with Burrows-Wheeler compression [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:

$$E \approx \frac{\text{compressed file size}}{\# \text{ of values} * \# \text{ of bit per value}} \quad [\text{bit}]. \quad (3)$$

The compressed file size divided by the number of values, 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 $323 \times 8 \text{ bit} / 480 \times 7 = 0.77 \text{ bit} \approx 4/5$. However, the post-infarct patient only had entropy of $161 \times 8 \text{ bit} / 480 \times 7 = 0.39 \text{ bit} \approx 2/5$. 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 tachogram, whereas in [BZIP2,Diff] it is applied to the successive 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 validation 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 standard [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

Table 3 Wilcoxon test results.

Parameter	Male	Female	All
meanNN	n.s.	n.s.	0.03742
sdNN	n.s.	0.00151	n.s.
cvNN	n.s.	0.00012	0.00331
sdaNN1	n.s.	0.00192	n.s.
pNN50	n.s.	0.04094	n.s.
VLF	n.s.	0.01185	n.s.
LF	n.s.	0.00151	0.01522
HF	n.s.	0.02861	n.s.
P	n.s.	0.00208	n.s.
LF/P	0.02330	n.s.	0.04121
[BZIP2,Cut]	n.s.	0.01304	n.s.
[BZIP2,Diff]	n.s.	0.01862	n.s.
[BZIP2,Cut]/m	0.01569	0.00092	0.00004
[BZIP2,Diff]/m	n.s.	0.00151	0.00027

Parameters with no significance at all were omitted; n.s., not significant.

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 outperformed by cvNN. [BZIP2,Diff]/m was only slightly less significant than [BZIP2,Cut]/m for all and female subjects; 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 classification 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 composite classifiers produced a maximum classification rate of 68%, bearing in mind that these trees are even more complex and unstable.

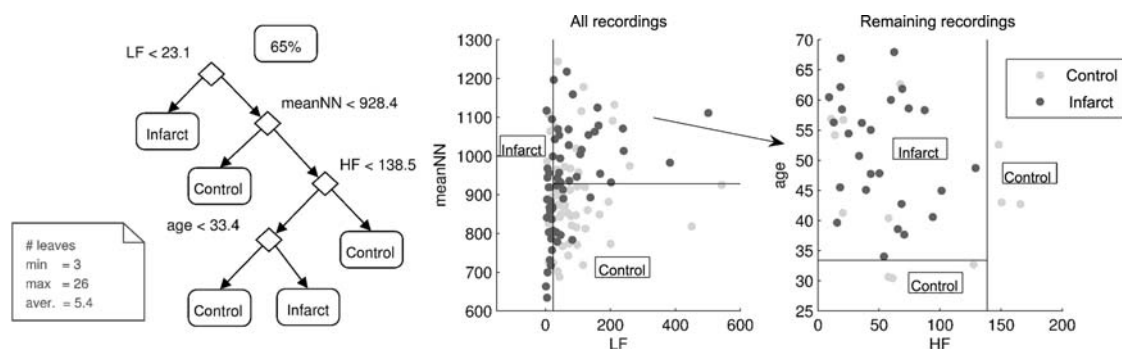


Figure 3 Classifier 1: decision tree based on standard parameters and its visualization.

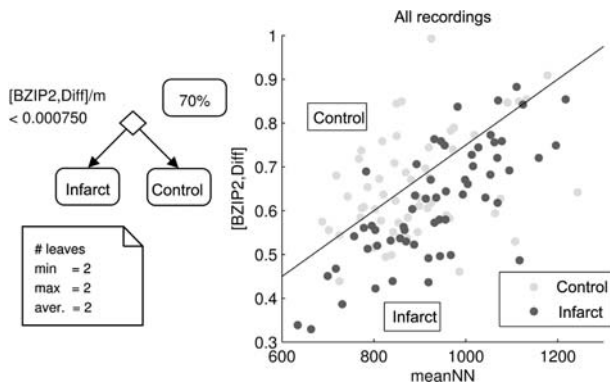


Figure 4 Classifier 2: decision tree based on standard and entropy parameters and its visualization.

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%.

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.

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