In-vivo and Isolated HRV Analysis by Hidden Markov Model

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Abstract

Analysis of details of heart rate variability (HRV) series may improve diagnosis of nervous system activity. The aim of this study was to quantify oscillation character in HRV series details with usage of Hidden Markov model (HMM).

Five New Zealand white rabbits and five isolated New Zealand rabbit hearts at Langendorff setup were studied. All oscillation-related coefficients of HMM transient matrix were significantly lower in isolated heart HRV series than in in-vivo ones. Significant tendency to compensate immediately the changes in RR interval duration is characteristic for isolated heart. Compensation process is very prompt, based on only one previous RR interval.

1. Introduction

HRV reflects sympathetic and parasympathetic activity of nervous system and may be used for non-invasive studies of autonomous nervous system, diagnosis and prediction of heart failure.

Numerous methods for HRV analysis have been published with aim to provide a reliable tool for heart diagnosis [1, 2]. Most of them are based on overall HRV series interpretation. Global overview of HRV series may cause lack of temporal-based changes in HRV series. We suggest that analysis of temporal aspect of HRV series may supplement diagnosis information obtained from overall-based methods.

In this study, we focused on details of HRV series. The immediate changes of consecutive RR intervals were studied instead of long-term behavior of HRV series. These details reveal temporal behavior of HRV series.

Typical *in-vivo* heart HRV series has a complex character as a result of non-linear processes involved in heart control. A representative segment of *in-vivo* HRV series is shown in upper part of Figure 1. HRV series of isolated heart is different from those of *in-vivo* heart in details. Isolated heart HRV series exhibits many segments, with oscillation character. Although oscillation segments are not present in the whole HRV series, they dominate over typical complex character segments. A representative segment of isolated heart HRV series is shown in bottom part of Figure 1.

The aim of this study was to quantify oscillation tendency in HRV series. Oscillation tendency was quantified with usage of Hidden Markov model (HMM). HMM can quantify the temporal aspect of the HRV series. Oscillation-related coefficients of HMM transient matrixes were compared between *in-vivo* and isolated HRV series.

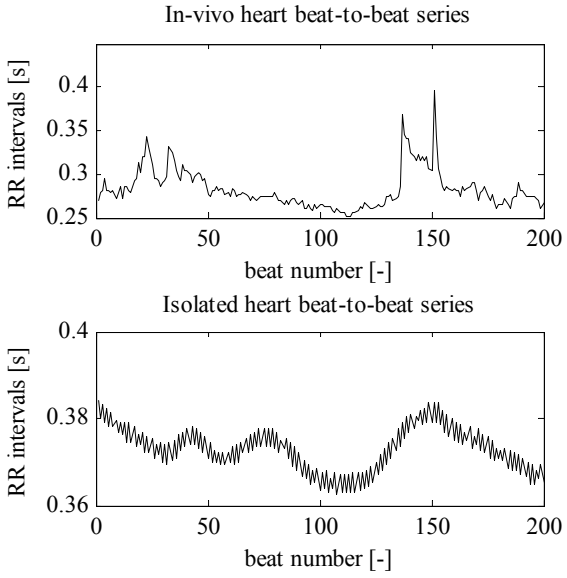

Figure 1. Representative segments of HRV series. Upper: *in-vivo* heart. Bottom: isolated heart.

2. Methods

Five *in-vivo* hearts of New Zealand white rabbits and five isolated New Zealand rabbit hearts at Langendorff setup were studied. All experiments followed the guidelines for animal treatment approved by local authorities and conformed to the EU law.

2.1. In-vivo hearts

ECG signals from five New Zealand rabbits were recorded using a SEIVA recording system. Body surface wire electrodes were attached to the skin with miniature clips. Location of electrodes did not restrict free posturing of the animals in sitting position. In order to get stable signals in awaked animals, rabbits were placed in a plastic box. The box was sufficiently high for preventing of rabbit's looking out, which makes the animal restless.

2.2. Isolated hearts

Five New Zealand rabbits were included in the study. Their isolated hearts were perfused according to Langendorff in the mode of constant perfusion pressure (85 mmHg). In deep anaesthesia with xylasin and ketamin, the hearts were excised and fixed on perfusion apparatus filled with Krebs-Henseleit solution (1.25 $mMCa^{2+}$, 37 °C) and placed in a thermostatically-controlled bath. The hearts were stabilized for 30 minutes.

ECG signal was recorded by touch-less method [3,4]. Briefly, three orthogonal Ag-AgCl disc electrodes were placed in the walls of the bath which is a part of the perfusion system. ECG signals were recorded by data acquisition multifunction card PCI-6111E (National Instruments, USA) with sampling frequency of 2000 Hz. ECG signals were acquired by software designed in LabView 7.1 (Texas Instrument, 2008). The 12-bit analogue to digital conversion was used. The digital signal was stored on a hard disk for off-line processing.

2.3. Data processing

ECG signals degraded by noise were excluded from further processing. R-peaks were detected automatically by own R-wave detector designed in Matlab R2013a (MathWorks, 2013). The results of automatic analysis were reviewed and errors in detection were corrected manually.

Tachograms have been created from five minutes long segments of corresponding ECG records. Tachograms has not been resampled.

2.4. Symbolic dynamics

Before HMM training each tachogram was pre-processed by computing of differences between consecutive samples of tachogram, indicating local increment or decrement of RR interval duration.

Resulting differences of RR intervals were transformed into symbol sequences as a result of symbolic dynamics application. Symbolic dynamics is nonlinear technique, which reduces the complexity of the signal preserving its robust information [5]. The principle of symbolic dynamics is to transform signal samples into series of few symbols, simplifying the study of the dynamical behaviour of original signal.

Tachograms were pre-processed by mapping of difference of tachograms's consecutive samples into three symbols: (↑) step-up, (↔) steady state, (↓) step-down. A transformation rule was based as follows:

$$S_n = \begin{cases} \uparrow & : RR_{n+1} - RR_n > 0 \\ \leftrightarrow & : RR_{n+1} - RR_n = 0 \\ \downarrow & : RR_{n+1} - RR_n < 0 \end{cases} \quad \text{for } n = 1{:}N-1$$

where S_n is *n*-th symbol in symbol series, RR is length of RR interval, and *N* is total number of RR intervals in tachogram.

Representative details of symbol series are shown in Figure 2 together with tachograms. Oscillation tendency is clearly observable in isolated heart symbol series.

Series of symbols were used for training of two HMM models corresponding to *in-vivo* and isolated heart.

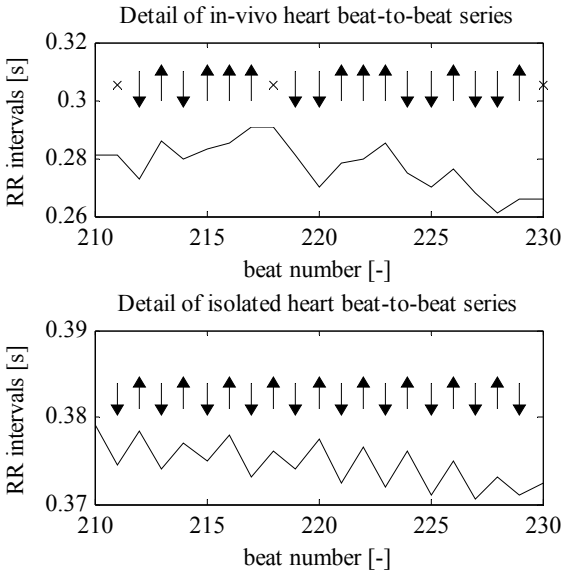

Figure 2. Symbol series for *in-vivo* (upper) and isolated (bottom), shown together with corresponding tachograms. Symbols ↑ and ↓ represents local increment or decrement of RR interval between consecutive RR intervals, symbol x represents no change between RR intervals.

2.5. Hidden Markov model

The HMM is a statistical tool used for characterization of observed sequence by a probability density function which varies according to the states of non-observable underlying Markov chain.

Since HMM estimates probability of changes between consecutive symbols in symbol series, its parameters may be used for distinguishing of those series.

HMM characterizes the sequence of observation O:

$$O = \{O_1, O_2, \dots, O_T\},$$

by probability density function Q:

$$Q = \{q_t | t = 1, \dots, T\},$$

which varies according to state of Markov model and where T represents total number of symbols in observed sequence representing RR interval differences. Variable q_t defines the state in the time t.

Since in this study the behaviour of consecutive RR interval differences is simplified to three situations only (step-up, steady state, step-down), the HMM has three states S:

$$S = \{S_1, S_2, S_3\},$$

where S_1 is step-up, S_2 is steady state and S_3 is step-down. Diagram of three-states HMM model used in this study is shown in Figure 3.

The state transition matrix of HMM is defined as $A = \{a_{ij}\}$ with coefficients a_{ij}:

$$a_{ij} = P[q_{t+1} = S_j | q_t = S_i] \quad 1 \le i, j \le 3.$$

The observation probability matrix $B = \{b_j(k)\}$ defines the distribution of the observed symbols in the state j. Observation probability matrix coefficients are defined as $b_j(k)$:

$$b_j(k) = P[v_k \text{ in } t | q_t = S_j] \quad 1 \le j \le 3, 1 \le k \le 3,$$

where v_k is symbol from character set $V = \{\uparrow, \leftrightarrow, \downarrow\}$.

Initial distribution probabilities of the states is defined as $\pi = \{\pi_i\}$, where π_i:

$$\pi_i = P[q_1 = S_i] \quad 1 \le i \le 3,$$

All coefficients π_i have been set equally to $\pi_i = 1/3$ for $1 \le i \le 3$ with aim to train HMM with no presumption of oscillation in symbol series. Viterbi algorithm was used for HMM training.

In this study, the coefficients of HMM transient matrix A have been used for *in-vivo* and isolated heart HRV series differentiation.

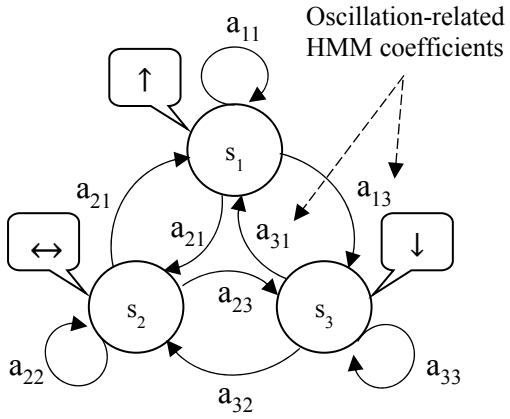

Figure 3. Three-states HMM model. HMM transient matrix coefficients a_{13} and a_{31} quantifies oscillation tendency in symbol series.

3. Results

An oscillation tendency of symbol series manifests itself in those two coefficients of HMM transient matrix, which represents transit from ↑ to ↓ and from ↓ to ↑. Coefficients a_{13} and a_{31} were therefore chosen for distinguishing between *in-vivo* and isolated heart symbol series.

A typical representative of HMM transient matrixes for *in-vivo* and isolated heart symbol series is shown in Fig. 4.

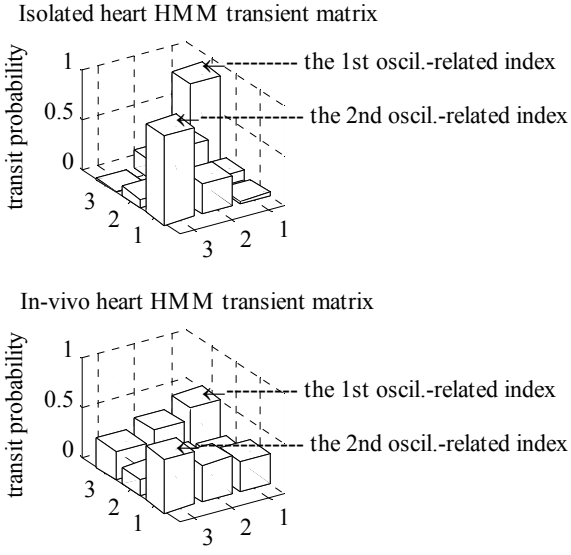

Figure 4. HMM transient matrixes of symbol series for isolated heart series (upper) and *in-vivo* heart series (bottom).

It can be seen in Figure 4 that values of coefficients a_{13} and a_{31} dominate in isolated heart symbol series. On the contrary to previous finding, in *in vivo* heart symbol series, the a_{13} and a_{31} values are close to other coefficients of transient matrix.

A statistical analysis was applied to both *in-vivo* and isolated heart groups of symbol series. Wilcoxon rank sum test with $\alpha = 0.05$ has been used. All oscillation-related coefficients of HMM transient matrix were significantly lower in isolated heart symbol series than in *in-vivo* ones. Results are summarized in Table 1 and depicted in Figure 5. Probability of occurrence of RR-interval oscillation is 1.6-times higher in isolated hearts comparing with *in-vivo* ones.

Table 1. Comparison of oscillation-related HMM transient matrix coefficients in *in-vivo* and isolated heart symbol series.

oscillation-related coefficients	isolated p [-]	in-vivo p [-]	stat. signif. (α=0.05)
a_{31}	0.85±0.19	0.52±0.05	yes
a_{13}	0.86±0.19	0.54±0.03	yes

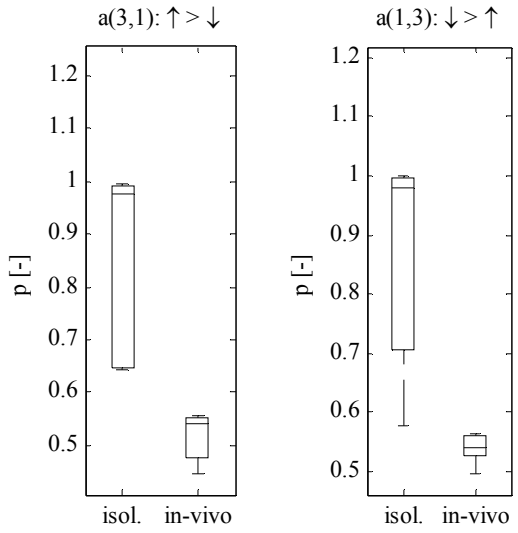

Figure 5. Boxplots of oscillation-related coefficients a_{31} (left) and a_{13} (right) for five isolated hearts and five *in-vivo* hearts.

4. Conclusions

The significant tendency to immediately compensate the changes in RR interval duration is characteristic for isolated hearts. Compensation process is very prompt, based on only one previous RR interval.

This phenomenon was not observed in *in-vivo* heart HRV series, where the process of gradual prolongation of RR interval takes a few subsequent samples of tachogram. The same holds for RR interval shortening.

Oscillations in tachogram reflect the fact that after each prolongation of RR interval immediately follows shortening of subsequent RR interval and vice versa. It seems that some intrinsic mechanisms of heart stabilize beating frequency in isolated heart.

Occurrence of oscillation in consecutive RR intervals may be used for intrinsic regulatory system behaviour assessment, however further studies are needed to understand the origin of oscillations.

Acknowledgements

The work was supported by European Regional Development Fund - Project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123), grant projects of the Grant Agency GACR 102/12/2034, and MUNI/A/0957/2013.

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