Chaos, Solitons and Fractals 000 (2016) 1–10

Contents lists available at ScienceDirect

Chaos, Solitons and Fractals

Nonlinear Science, and Nonequilibrium and Complex Phenomena

journal homepage: www.elsevier.com/locate/chaos

Network tools for tracing the dynamics of heart rate after cardiac transplantation

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ARTICLE INFO

Article history:
Received 17 March 2016
Revised 17 March 2016
Accepted 17 March 2016
Available online xxx

Keywords:
Time series
Transition networks
Heart period dynamics
Heart transplantation
Erratic heart rhythm

ABSTRACT

A network representation of time intervals between subsequent heart contractions is proposed as a way to qualify and quantify short-term dynamical patterns, obtained from ECG recordings. It allows the observation of the development of arrhythmia in a non-invasive and patient-oriented way. As an example, a network is constructed from the nocturnal Holter recordings of a male heart transplant patient, who had been in good overall health for 17 years after the surgery. The biatrial surgical technique applied to him led to interference between the recipient and donor pacemakers, which resulted in misleading information provided by standard heart rate variability measures. The noticeable differences in the network structure observed in the patient follow-up study serve to reveal and quantify changes in the leading mechanisms underlying the dynamics of heart contractions.

1. Introduction

Innervation of the healthy heart — the efferent and afferent nerves of the parasympathetic and sympathetic parts of the autonomic nervous system (ANS) — plays an important role in regulating cardiac function [1]. Activity of these parts is commonly considered to be the primary source of the phenomenon called heart rate variability (HRV) [2], which refers to changes in the length of time intervals between subsequent heart contractions (RR-intervals). Transitions in the functioning of the complex interplay between these two parts of the ANS can have the effect of noticeable alterations in the cardiac interbeat RR-interval dynamics. Such alterations have been found to be related to various cardiovascular diseases (see, e.g., [3] for a review), and also to the aging process (see, e.g. [4–7]).

A normal cardiac contraction is initiated by the sinus node—the heart's natural pacemaker. The automatic firing of the sinus node rate exceeds that of the heart's other pacemakers. However, incidents (100–200 per twenty four hours) of abnormal beats are commonly present in a healthy heart rhythm. Such incidents may especially occur during the night, when the parasympathetic tone is high, which slows down the rhythm of the sinus node. This is because some atrial cells have the ability to initiate impulses for heart contractions by themselves. As a consequence, it can happen that atrial fibres trigger abnormal impulses, and so-called premature atrial contractions (PACs) take place [8]. In general, PACs are rarely dangerous to a healthy human and are usually asymptomatic. They do not require any treatment. However, in some cases they can be a sign of an early stage of more severe atrial arrhythmias [8]. When PACs become permanent, which means that the arrhythmia is clinically well developed, the survival rate of the patient strongly decreases.

A systematic study of abnormal cardiac events has to be exhaustive. It demands strongly insightful analysis of every part of an electrocardiogram (ECG). Each P wave, each QRS-complex, each T wave —all parts of an ECG representation of a single heart contraction — has to be carefully reviewed to see whether it represents a normal (originating from the sinus node) or abnormal heart contraction. Moreover, PACs are usually not visible in the ECG recording because the difference in initiation, extra P waves, is hidden by the depolarization wave of the ventricles. Additionally, in the early stage of arrhythmia, abnormal contractions are rare, which means that extremely large recordings have to be considered to obtain a representative set of these extraordinary events for further clinical analysis.

The heart rhythm of heart transplant (HTX) patients is distinct from that of a healthy person. The donor heart is

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http://dx.doi.org/10.1016/j.chaos.2016.03.024
0960-0779/

completely denervated during transplantation. In particular, the lack of parasympathetic activity results in most HTX patients having a higher than average resting heart rate and significantly reduced HRV. The improved longevity of HTX patients allows for progressive alterations in the donor heart and in the neurohumoral milieu. Both sympathetic and parasympathetic reinnervation can occur. Methods based on HRV have been used to measure the degree of reinnervation [9–11]. Detailed cardiac tissue investigations, using scans to visualize the sympathetic nerve re-uptake of norepinephrine, have established that this reinnervation is incomplete, non-uniform, variable between patients and heterogeneous within the same patient [9,12]. As a consequence, a wide spectrum of arrhythmias with clinical implications is observed among HTX patients [13]. Moreover, the rhythms of the heart contractions of individual HTX patients differ strongly. Therefore only methods aimed at resolving these rhythms individually — for each patient separately — can be successful in stratification of the risk factors for the HTX patient [14].

Here, we investigate the dynamics of RR-intervals of an exceptional HTX recipient—a male who survived for 17 years after the transplantation in a good functional state, and therefore one could be tempted to compare his heart status to a healthy peer. This patient underwent the heart transplantation by means of the biatrial technique. This technique involves linking the donor and recipient hearts at the midatrial level. The suture line separates both the part of patient's atria with the sinus node and the patient's autonomic nerves from the donor sinus node. However, with the passing of time after the surgery, this line can start to transmit electrochemical signals from the patient's part of the atria to the donor atria. Therefore, in the case of this HTX patient, we have three factors fostering the development of atrial arrhythmias: (1) changes in the donor atrial tissue caused by immunosuppressive drugs and also resulting from biological aging; (2) inhomogeneous reinnervation; (3) transmission of electrical and chemical impulses from the patient's own atria through the suture line.

Detection and then classification of arrhythmic incidents is challenging for data science. Standard methods of estimates of HRV based on statistical measures of the set of RR-intervals [2] provide unsatisfactory and often misleading results. Various approaches to studying arrhythmia have been taken [14], but their clinical usage is still limited. Nevertheless all investigations into this problem push forward our understanding of both phenomena: HRV and arrhythmia [3].

Since the problem of arrhythmia involves dynamical aspects of the subject's heart rate, we concentrate on characterizations of differences in RR-intervals, called RR-increments. The HTX patient was undergoing the standard follow-up control procedures at our outpatients' clinic. Consequently, his earlier recordings could also be utilized in characterizing the progression to each of the follow-up stages and in tracing the consecutive differences in the dynamics of heart contractions. In Section 2, we describe the signals studied and discuss their properties detected with standard HRV tools.

In the following, we hypothesize that unusual patterns consisting of two subsequent RR-increments could indicate some abnormality in the basic heart rhythm, and hence possibly indicate arrhythmia. The method becomes especially efficient when the set of follow-up signals is accessible. Therefore, our first aim is to describe the basic features of the normal dynamics of the patient within these patterns. Next, we use this description as a filter for extracting arrhythmic episodes.

To achieve the goals described above, in Section 3, we develop a network representation [15] suitable for the analysis of signals of RR-increments. This network serves as a framework to study dynamical patterns in the heart rate; see Sections 4.1and 4.2. This framework was used in our earlier investigations of the complexity of RR-intervals in healthy people and patients after HTX [16–18]. The modular structure in networks, also called the community structure, has been shown to be relevant to the problem of understanding the structure and dynamics of the system [19]. This problem has been found to be difficult and has not yet been satisfactorily solved [20,21]. However, it occurs that modularity in the case of networks constructed from the follow-up signals can be effectively investigated by the subtraction of one network from another.

Sleep provides a window to observe ANS unperturbed by diurnal activity, during which the whole organism is subject to strong parasympathetic stimuli [22,23]. For this reason, we concentrate on nocturnal recordings only. Based on the transition network relations, it will be shown that suitable binning applied to the signals with RR-increments works successfully as the filter separating basic dynamics from extraordinary events; see Section 4.3.

2. Deficiency of the standard HRV analysis

2.1. Signal pre-processing

Twenty-four-hour Holter ECG recordings during a normal sleep–wake cycle of the HTX patient are analyzed. The signals were recorded progressively over time, in the 129th, 156th, 164th, 170th and 206th months after surgery. These signals will be denoted as HTX_xxx, where 'xxx' encodes the number of months after surgery. The signals were first analyzed using Del Mar Reynolds Impresario software. Time domain and frequency domain analysis of HRV was carried out, preceded by visual inspection of the automatic ECG recording. All supraventricular and ventricular extra systoles were excluded.

Only nocturnal parts the sinus rhythm were selected and examined because of the smaller number of artefacts and presumed absence of sympathetic nervous activity, as well as the low level of adrenergic stimulation. The hours of sleep were selected for each signal individually, according to the day–night switch in the length of RR-intervals. Then a six-hour period, covering the longest RR-intervals, was extracted. Perturbations in a signal (artefacts or not normal-to-normal RR-intervals), consisting of less than five consecutive RR-intervals, were replaced by the median calculated from the last seven proper RR-intervals. Other perturbations were deleted. As the control group, called the *60's*, fifteen Holter signals of healthy sexagenarians (males) were pre-processed, applying the same quality standards. All the signals studied were constructed from more than 20,000 RR-intervals. In Fig. 1, we show the signals analysed.

2.2. Symbolization

The Holter equipment used provides data with a 128 Hz sampling frequency, which results in a signal resolution approximating 8 ms. Accordingly, all the values for the RR-intervals and RR-increments obtained are multiples of 8 ms, which means that the signals are naturally adapted to analysis by symbolic dynamics methods.

Let $\mathbf{RR} = \{RR_0, \ldots, RR_i, \ldots, RR_N\}$ be a time sequence of RR-intervals, where i is a time index. Let the resulting signal of RR-increments be denoted as $\mathbf{\Delta RR} = \{\delta RR_1, \ldots, \delta RR_i, \ldots, \delta RR_N\}$ with $\delta RR_i = RR_i - RR_{i-1}$. An event described by $\delta RR_i > 0$ is called a deceleration, an event characterized by $\delta RR_i < 0$ is called an acceleration, and when $\delta RR_i = 0$, a no-change event occurs. Because of the signal resolution, the state space of RR-increments consists of a finite number of multiplies of 8: 0, ±8, ±16, …, which are enumerated as

$$\Delta_J \in \{-\Delta_K, \ldots, 0, \ldots, \Delta_K\}, \quad \Delta_K = \max_i\{|\delta RR_i|\}. \tag{1}$$

Please cite this article as: D. Makowiec et al., Network tools for tracing the dynamics of heart rate after cardiac transplantation, Chaos, Solitons and Fractals (2016), http://dx.doi.org/10.1016/j.chaos.2016.03.024