Medical Engineering & Physics 35 (2013) 559–568

Contents lists available at SciVerse ScienceDirect

Medical Engineering & Physics

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

Comparison of different methods of heart rate entropy analysis during acute anoxia superimposed on a chronic rat model of pulmonary hypertension

Hernâni Gonçalves[a,*], Tiago Henriques-Coelho[b], Ana Paula Rocha[c,d], André P. Lourenço[b], Adelino Leite-Moreira[b], João Bernardes[a,e,f]

[a] Center for Research in Health Technologies and Information Systems (CINTESIS), Faculty of Medicine, University of Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
[b] Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine, University of Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
[c] Departamento de Matemática, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre, s/n, 4169-007 Porto, Portugal
[d] Centro de Matemática da Universidade do Porto, Rua do Campo Alegre, s/n, 4169-007 Porto, Portugal
[e] Department of Obstetrics and Gynecology, Faculty of Medicine, University of Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
[f] INEB – Instituto de Engenharia Biomédica, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal

ARTICLE INFO

Article history:
Received 9 December 2011
Received in revised form 19 June 2012
Accepted 27 June 2012

Keywords:
Heart rate variability (HRV)
Time and frequency domain analysis
Entropy
Anoxia

ABSTRACT

Acute life-threatening situations are particularly critical when superimposed on chronic diseases. The objective of this study was the assessment of heart rate (HR) dynamics during episodes of acute anoxia superimposed on a rat model of chronic pulmonary hypertension. In 10 adult Wistar rats, five weeks after pulmonary hypertension induction with Monocrotaline, we analysed eight 1-min HR segments, during episodes of baseline, mechanical ventilation and acute anoxia, using linear indices, approximate entropy (ApEn), sample entropy (SampEn) and multiscale entropy (MSE). The transition from baseline or mechanical ventilation to early anoxia was identified through almost all indices, but SampEn(2,0.6) was the index that better identified all the transitions. MSE presented limited performance, possibly due to the non-stationary nature and short duration of the acute anoxia episodes. A systematic evaluation of all computed HR indices may help to identify which indices or combination of indices more adequately discriminates and monitors critical acute events superimposed on chronic clinical conditions.

1. Introduction

Clinicians are often confronted with acute life-threatening situations superimposed on chronic diseases, both during pre and postnatal life, such as acute anoxia during labour superimposed on a severely growth retarded fetus or acute myocardial infarction superimposed on a chronic heart failure condition. Accordingly, intensive monitoring of patients with severe chronic conditions is mandatory when they suffer, or are at high risk of suffering, an acute insult, namely during labour, surgery or intensive care treatment. In this setting, heart rate (HR) analysis remains as one of the most used and useful monitoring tools.

Linear methods for HR variability (HRV) analysis, in both time and frequency domains, have been applied in human studies and standard guidelines were established [41]. Spectral analysis, in particular, allows the identification of two distinct peaks, linked to the activities of the two branches of the autonomic nervous system [41]. However, the application of these methods to animal studies, needs to be adapted to every situation [2], considering results heralded from previous research, that may be used as guidelines, although it should be noted that different experimental settings may lead to significant differences in HRV parameters.

Nonlinear methods have also been applied to HRV analysis [1,2]. The two main categories of these methods are: (i) indices that describe the scaling behaviour of a system; (ii) indices that describe the complexity of a system. The scaling behaviour of a system may be evaluated through fractal dimension (FD), $1/f$ slope or detrended fluctuation analysis (DFA). The analysis of a system in the phase space enables the assessment of its complexity. The correlation dimension indicates the dimension of the phase space, Lyapunov exponents provide the sensitivity of the system to initial conditions and approximate entropy (ApEn) is a measure of the system complexity [2].

ApEn [34,36] has been widely applied in both human [17,18,23,40] and animal studies [19,20,32]. Nevertheless, the selection of ApEn parameters may significantly influence the analysis between normal and heart failure human groups [29]. Indeed, although reference values for the embedding dimension m and the threshold r have been proposed [36], recent work underline the critical role of parameter choice, particularly the threshold r [7,30]. Therefore, research on this topic is required, namely pertaining to

* Corresponding author. Tel.: +351 225513622; fax: +351 225513601.
E-mail addresses: hernanigoncalves@med.up.pt, hernani.goncalves@fc.up.pt (H. Gonçalves).

1350-4533/$ – see front matter © 2012 IPEM. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.medengphy.2012.06.020

the application of ApEn to animal studies. Moreover, traditional entropy-based measures yield higher values for systems exhibiting long-range correlations than for random systems, such as in the case of white noise and for 1/*f* noise. These contradictory results led Costa et al. to propose the multiscale entropy (MSE) analysis, a new entropy-based method which incorporates both entropy and scale [6,8,11]. This method may be more appropriate for a correct estimation of system complexity and also enables the distinction between synthetic and physiological time series [9], since synthetic time series are simpler than physiologic time series, which under healthy conditions, present a complex temporal structure with multiscale correlations. However, little is known about the applicability of MSE analysis to animal studies [5,43].

The objective of this study was the assessment of HR dynamics with linear and nonlinear methods during episodes of acute anoxia superimposed in a rat model of chronic pulmonary hypertension, with particular emphasis on common and novel entropy-based methods.

2. Methods

2.1. Animal model

Pulmonary hypertension was induced, with a single subcutaneous 60 mg/kg Monocrotaline injection (Sigma, Barcelona, Spain), in 10 adult female Wistar rats (Charles River Laboratories; Barcelona, Spain), weighing 215–260 g, with ages ranging between 6 and 8 weeks, previously used in another study [20], were housed in groups of 5 rats/cage, in a controlled environment, under a 12:12-h light–dark cycle, at a room temperature of 22 °C, with a free supply of food and water. All rats initially had ECG monitoring during 20 min (week 0) under ketamine anaesthesia (50 mg/kg, intraperitonealy) and were subsequently monitored in a similar way weekly for 5 weeks (weeks 1–5). By the end of the third week, one rat died and the other rats presented signs of overt heart failure, namely lethargy, laboured breathing, cachexia, vein and liver engorgement, pleural effusion and ascites, as well as significant changes in linear and nonlinear HR indices [20]. In the last week (week 5), after 20 min of acquisition, they were also mechanically ventilated with 100% O_2 at a respiratory rate of 1.25 Hz and a tidal volume of 2 mL, during 1 min and then with 5% CO_2 and 95% N_2 during 5 min of induced anoxia. All animal experiments were performed according to the Portuguese law on animal welfare and the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Pub. No. 85-23, Revised 1996).

2.2. Heart-rate acquisition and pre-processing

HR acquisition and pre-processing was performed as described elsewhere [19,20]. Shortly, one electrode was placed subcutaneously in each leg, to acquire the ECG signal at a sampling rate of 500 Hz, according to a standardized procedure [19]. The tachogram obtained after automatic R wave detection and expert validation was subsequently resampled at a frequency of 8 Hz – in order to provide a correct coverage of the considered spectral bands in HR analysis – and then converted to the HR signal, in beats per minute (bpm), using cubic spline interpolation. Due to experimental difficulties already mentioned in Section 2.1 and to some periods of signal loss, only some segments were available for analysis: 8 in the baseline period, 6 during mechanical ventilation and 7, 6 and 7 segments in the first, second and third minutes of induced anoxia, respectively. In order to provide some insight on the occurrence rate of ectopic beats, HR values which are 10% above or below from their previous HR value were considered as potentially being associated with an ectopic beat. Accordingly, the average of this occurrence rate was found to be 0.0% in the baseline, 0.4% during mechanical ventilation and around 2.2% in the anoxia period.

2.3. Heart rate analysis

Eight 1-min segments (each segment corresponding to 480 points) without signal loss (signal loss was manually identified) were analysed: the first 4 min during baseline recording (excluding the first 2 min in order to ensure a stable tracing) assigned

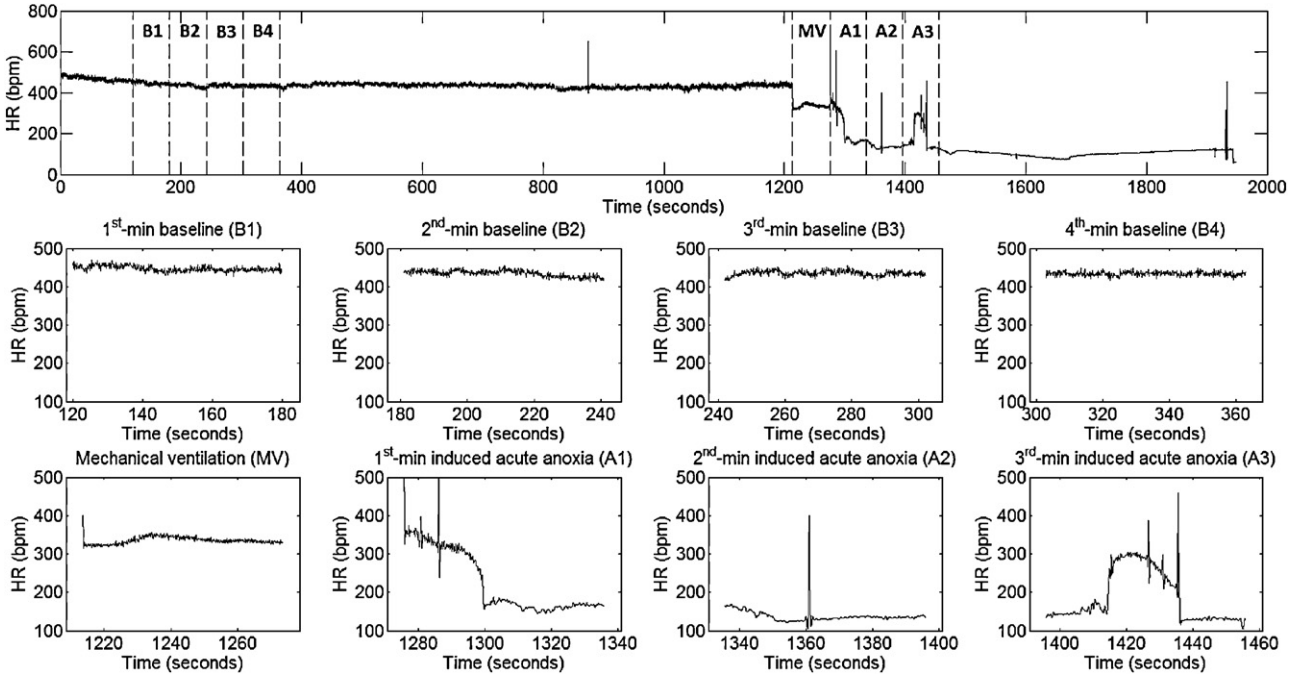

Fig. 1. Typical HR record of a rat model of chronic pulmonary hypertension, during 20 baseline minutes, followed by 1 min of mechanical ventilation at 1.25 Hz and 5 min of induced anoxia. In the top the complete record is shown, and below eight selected segments. The dashed vertical lines in the upper plot represent the limits of the eight selected segments represented in the lower plots.