Changes in Instantaneous Complex Dynamics during Exercise in Chronic Mountain Sickness

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Abstract

The combination of persistent polycythemia with decreased physical and cognitive performances while living in high-altitude is defined as 'Chronic Mountain Sickness' (CMS). To date, the role of the autonomic nervous system in CMS is still unknown. In this study, we analyze instantaneous tracking of cardiovascular complexity in order to increase the knowledge on CMS physio-pathology. To this extent, we processed heartbeat dynamics gathered from 13 CMS males and 7 high-altitude male dwellers, taken as healthy controls (HC), during semi-supine bicycle tasks performed at 25W, 50W, and 100W, along with a recovery session. Instantaneous Dominant Lyapunov exponents (IDLE), as estimated through point-process nonlinear models with Laguerre and Volterra expansions, were evaluated from such series. Results showed that instantaneous heartbeat complex dynamics was significantly altered in CMS. In particular, IDLE increases were associated to CMS, with respect to HC, during the 25W and 50W exercise sessions ($p < 0.01$). Conversely, no statistical differences were found when analyzing the 100W session, and first recovery after exercise.

1. Introduction

Chronic Mountain Sickness (CMS), also known as Monge's disease, is defined as a persistent combination of polycythemia (an abnormally increased concentration of hemoglobin in the blood) in associations with hypoxemia impairment in cerebral function, and, in some cases, moderate or severe pulmonary hypertension that may evolve to cor pulmonale, leading to congestive heart failure [1–4]. Usually, this disease begins during adult life in high altitude regions, and its marked systemic vascular dysfunction may predispose CMS patients to premature cardiovascular disease [1, 2, 4].

To date, physiological mechanisms underlying CMS are still unknown. Although CMS was previously associated to a reduced vagal activity and baroreflex sensitivity in resting state conditions [5], its patho-physiology during physical activity, especially related to the Autonomic Nervous System (ANS) dynamics, still needs further investigation. To this aim, we here propose the study of Heart rate Variability (HRV) in CMS during semi-supine bicycle exercise. This choice is also justified by the fact that exercise intolerance is often found in CMS patients [1]. As ANS dynamics can significantly change as a function of the intensity of physical activity, proper investigation should be performed along several intensity levels and, consequently, data should be processed using a time-varying method of HRV analysis.

Accordingly, we here propose the use of a point process-based approach on heartbeat series [6], allowing for instantaneous cardiovascular and autonomic assessment without any interpolation requirement. This stochastic approach defines the probability function predicting the time of the future heartbeat given knowledge on past events, and physiological constraints [7]. Accordingly, each RR interval is characterized by an Inverse-Gaussian (IG) distribution whose first-order moment (the mean RR) is defined at each moment in time, with a fully parametric and autoregressive formulation.

Since cardiovascular oscillations have been widely demonstrated to represent the complex output of a nonlinear system interacting with several others (e.g., neural, respiratory, endocrine) [8], a comprehensive systems characterization of ANS activity through HRV time-varying analysis should include complex estimates. We recently proposed the estimation of Lyapunov Exponents, an important class of quantifiers of system complexity, within a point-process framework, defining the so-called instantaneous dominant Lyapunov exponent (IDLE) [6]. Of note, besides all the advantages given by the point-process modeling, IDLE estimates are not affected by physiological noise underlying cardiovascular dynamics, and are defined through a parsimonious number of parameters, according to the Laguerre expansion of the linear, quadratic, and cubic terms of a Wiener-Volterra series [6]. A brief descrip-

tion of the signal processing methodology, and experimental results on IDLE estimates during physical activity in patients with CMS follow below.

2. Methods

In this section, we report essential methodological details on the models involved in this study, and provide a brief description of the experimental protocol and subjects recruitment. Further details on the methodology of signal processing and experimental setup can be found in [6, 7], and in [2–4], respectively.

2.1. Point-Process Nonlinear Models of Complex Heartbeat Dynamics

Considering an ECG observation in the time domain, within the interval $t \in (0, T]$, it is possible to define $RR_{\widetilde{N}(t)}$ as the j^{th} R–R interval, with $j = \widetilde{N}(t)$ the index of the previous R-wave event before time t related to the cardiac left-continuous counting process $\widetilde{N}(t)$. Assuming history dependence, a physiologically-plausible IG distribution can be adopted to characterize the probability distribution of the waiting time from t to the next R-wave event [7]. H_t stands for the mathematical representation of the past R-events, and $\xi(t)$ represents the vector of the model parameters. Here, Laguerre functions [6] are used to expand the Wiener-Volterra terms defining IG first-order moment, $\mu_{RR}(t, H_t, \xi(t))$, and reduce the number of unknown parameters that need be estimated. The generic i^{th}-order discrete time Laguerre function, $\phi_j(n)$ [6] is defined as:

$$\phi_i(n) = \alpha^{\frac{n-i}{2}}(1-\alpha)^{\frac{1}{2}} \sum_{j=0}^{i}(-1)^j \binom{k}{j}\binom{i}{j}\alpha^{i-j}(1-\alpha)^j$$

where $(n \geq 0)$, and $\alpha \in (0, 1)$ is the discrete-time Laguerre parameter which determines the rate of exponential asymptotic decline of these functions. The instantaneous $\mu_{RR}(t, H_t, \xi(t))$ for the 3^{rd} nonlinear Wiener-Volterra model becomes [6]:

$$\begin{aligned}\mu_{RR}(t, H_t, \xi(t)) = g_0(t) + \sum_{i=0}^{p} g_1(i,t)\, l_i(t) + \\ \sum_{i=0}^{p}\sum_{j=0}^{q} g_2(i,j,t)\, l_i(t)\, l_j(t) + \\ \sum_{i=0}^{k}\sum_{j=0}^{k}\sum_{k=0}^{k} g_3(i,j,k,t)\, l_i(t)\, l_j(t) l_k(t) \quad (1)\end{aligned}$$

where $g_k(...)$ are the regression coefficients of the model and:

$$l_i(t) = \sum_{n=1}^{\widetilde{N}(t)} \phi_i(n)(RR_{\widetilde{N}(t)-n} - RR_{\widetilde{N}(t)-n-1}) \quad (2)$$

According to eq. 2, the nonlinear regression is performed on the derivative RR series in order to improve the achievement of stationarity within the sliding time window $W = 90$ sec [6].

A Newton-Raphson procedure is used to maximize the local log-likelihood defined in [7] in order to estimate the unknown time-varying parameter set $\boldsymbol{\xi}(t)$. The optimal model order $\{p, q, k\}$ is estimated by means of the point-process model goodness-of-fit applied to the heartbeat data [7]. Such a goodness-of-fit is based on the Kolmogorov-Smirnov (KS) test. Autocorrelation plots are also considered to test the independence of the model-transformed intervals [7].

Once the parameter in eq. 1 are estimated, it is possible to calculate Instantaneous complex statistics based on the Dominant Lyapunov Exponent (IDLE) as follows [6]:

$$IDLE(t, H_t, \xi(t)) = \frac{1}{\Delta H}\sum_{j=0}^{Y-1} \ln R_{(j)11}(t)$$

where Y is the available number of matrices within the local likelihood window of duration W, Δ is the sampling time step, and $R_{(jj)ii}$ is a positive diagonal elements the upper triangular matrix $R(t)$ derived by a QR decomposition of the Jacobian of nonlinear autoregressive parameter estimated over the time series [6]. This provides a time-varying vector $IDLE(t)$, able to track the dominant Lyapunov exponent in an instantaneous fashion. Of note, these estimates are unique in the literature and, to our knowledge, can be achieved only using nonlinear point process models [6].

2.2. Subjects Recruitment and Experimental Setup

Thirteen male Bolivian patients with CMS (age 52±11) and seven male Healthy Control (HC) subjects (age 49±10) born and permanently living in La Paz or its surroundings (at 3600-4000 m) were enrolled in the study. All patients were initially referred to the Instituto Boliviano de Biologia de Altura for CMS symptoms, and the diagnosis was based on the consensus statement on chronic high altitude disease [9]. Inclusion criteria for patients with CMS were excessive erythrocytosis (hemoglobin concentration >20 g/dL) in the presence of a normal pulmonary function and no history of smoking or working in the mining industry.

Graded semi-supine exercise was performed on a bicycle ergometer (Ergoline 900EL; Ergoline Company) with

a 30 degrees rotation to the left. Experimental protocol started with an initial resting state session of minimum 30 seconds. Then, a workload of 25W was set for 3 minutes, followed by a 50W session of 3 minutes, and a 100W session of 2 minutes. A recovery session of 3 minutes followed the exercise. Further details can be found in [3].

2.3. Feature Vectors and Statistical Analysis

The first 90 seconds of data were used to fit the model parameters. All heartbeat series were pre-processed through a previously developed real-time R-R interval error detection and correction algorithm based on the point-process statistics (local likelihood) [10]. IDLE and $\mu_{RR}(t, H_t, \xi(t))$, as estimated through point-process nonlinear models described in the previous section, were calculated instantaneously, from each series, with a $\Delta = 5$ ms temporal resolution. For each of the exercise (25W, 50W, and 100W) and recovery sessions, we condensed the information about the time-varying dynamics of features through its median across time. The within-group variability of a feature X, chosen among the mean RR interval μ_{RR} and IDLE, is here expressed as $\mathrm{Median(X)} \pm \mathrm{MAD(X)}$ where $\mathrm{MAD(X)} = \mathrm{Median(|X - Median(X)|)}$. P-values were gathered from non-parametric Mann-Whitney tests under the null hypothesis that the between-subject medians of the two groups are equal.

3. Results

Goodness-of-fit analysis showed very satisfactory results. Optimal NARL orders of $p = 4$, $q = 1$, and $k = 0$. In all of the recordings, both KS plots and more than 98% of the autocorrelation samples fell within 95% confidence intervals. KS distances were as low as 0.0316±0.0051, with minimum at 0.0217. Instantaneous series from a representative patient with CMS and HC are shown in Figs. 1 and 2.

Tables 1-4 show group statistics for CMS vs. HC during exercise sessions at 25W, 50W, 100W, and consequent recovery session, respectively. Bold indicates significant differences between groups.

We found that instantaneous heartbeat complex dynamics was significantly altered in CMS. Significant differences were found between CMS and HC during the 25W and 50W exercise sessions ($p < 0.01$). Specifically, CMS were associated to a significantly increased heartbeat complexity than HC. Conversely, differences were not significant when analyzing the 100W, and recovery session after exercise ($p > 0.05$). No group-wise significant differences were found in the classical μ_{RR} index.

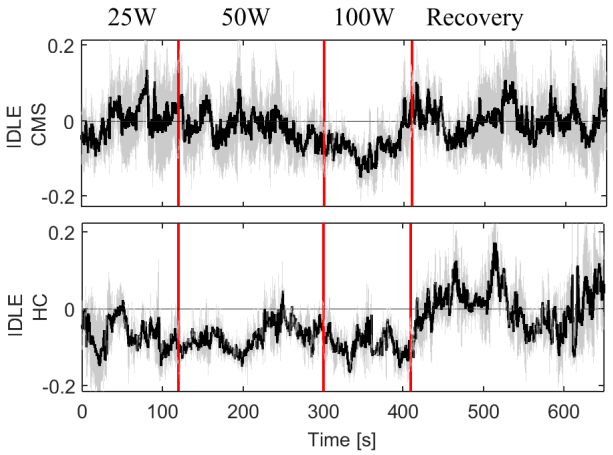

Figure 1. Instantaneous Dominant Lyapunov exponent (IDLE) statistics in CMS patients (top panel) and HC (bottom panel). Red vertical lines separate the 25W, 50W, 100W, and recovery sessions. Black lines refer to median across subjects, whereas gray area refers to MAD range.

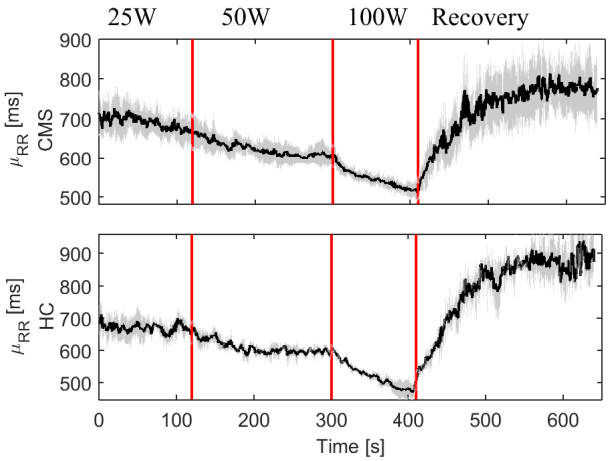

Figure 2. Instantaneous mean RR (μ_{RR}) statistics in CMS patients (top panel) and HC (bottom panel). Red vertical lines separate the 25W, 50W, 100W, and recovery sessions. Black lines refer to median across subjects, whereas gray area refers to MAD range.

Table 1. Group statistics during exercise at 25W.

25W	HC	CMS	p-val
μ_{RR}	682.45± 20.91	689.17±37.10	0.482
IDLE	**-0.0768± 0.0378**	**-0.0037±0.0591**	**0.005**

Table 2. Group statistics during exercise at 50W.

50W	HC	CMS	p-val
μ_{RR}	604.82±6.43	614.29±25.06	0.553
IDLE	**-0.1283±0.0081**	**0.0075±0.0794**	**0.009**

Table 3. Group statistics during exercise at 100W.

100W	HC	CMS	p-val
μ_{RR}	517.79±17.00	542.96±12.94	0.120
IDLE	-0.1081±0.0187	-0.0809±0.0438	0.340

Table 4. Group statistics during recovery after the exercise sessions.

Recovery	HC	CMS	p-val
μ_{RR}	628.57±34.78	628.02±61.71	0.751
IDLE	-0.0183±0.0271	-0.0066±0.0318	0.773

4. Discussion and Conclusion

In conclusion, we demonstrated that heartbeat complex dynamics is significantly altered in CMS patients, with respect to HC. Specifically, differences were found during physical activity at 25W and 50W, with higher complexity level associated to CMS. Such differences are plausibly due to an altered ANS activity in CMS, which was previously confirmed through baroreflex sensitivity and vagal activity measures in resting state [5]. Conversely, similar complexity changes between groups were found during high-intensity (100W) physical activity, and recovery after exercise. It is important to note that most of the subjects involved in this study were not familiar with bicycle exercise. Therefore, we do not exclude that having no differences in cardiovascular dynamics during the 100W session could be due to a consequent high inter-subject variability. Concerning classical heart rate measures, estimated through the instantaneous mean RR interval μ_{RR}, no differences were found between groups at any sessions.

From a methodological point of view, it is important to note that instantaneous complexity estimates performed on unevenly heartbeat samples, within a narrow 3 minutes session, were possible because of the use of the point-process paradigm. Furthermore, goodness-of-fit measures, long-term memory of the autoregressive orders, and reduced number of parameters to be estimated are features of our modeling which are worthwhile mentioning.

Importantly, although Lyapunov exponents are mathematical quantifiers able to identify chaotic behavior of a nonlinear system, we do not conclude on such behavior in CMS because of the presence of intrinsic stochastic terms in the cardiovascular control dynamics.

We here speculate on the possible use of IDLE estimates as simple diagnostic tool for CMS, which would require ECG monitoring exclusively, although we are aware that these promising results should be further validated through a study involving a larger number of subjects, and a more comprehensive collection of instantaneous linear and nonlinear HRV measures (see, e.g., [11, 12]).

Acknowledgements

The research leading to these results has received partial funding from the Department of Anesthesia, Critical Care & Pain Medicine, Massachusetts General Hospital, and Harvard Medical School, Boston, MA, USA, and European Union Seventh Framework Programme FP7/2007-2013 under Grant No. 601165 of the project WEARHAP.

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