Physica A 389 (2010) 1861–1868

Contents lists available at ScienceDirect

Physica A

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

Concurrent sympathetic activation and vagal withdrawal in hyperthyroidism: Evidence from detrended fluctuation analysis of heart rate variability

Jin-Long Chen [a,b], Yuo-Hsien Shiau [c], Yin-Jiun Tseng [d], Hung-Wen Chiu [e], Tzu-Chien Hsiao [f], Niels Wessel [b,g], Jürgen Kurths [g,h], Woei-Chyn Chu [d,*]

[a] *Department of Medical Informatics, Tzu Chi University, Hualien, Taiwan*
[b] *Institute of Physics and Astronomy, University of Potsdam, Potsdam, Germany*
[c] *Graduate Institute of Applied Physics, National Chengchi University, Taipei, Taiwan*
[d] *Institute of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan*
[e] *Graduate Institute of Medical Informatics, Taipei Medical University, Taipei, Taiwan*
[f] *Department of Computer Science, National Chiao Tung University, Hsinchu, Taiwan*
[g] *Institute of Physics, Humboldt University, Berlin, Germany*
[h] *Potsdam Institute for Climate Impact Research, Potsdam, Germany*

ARTICLE INFO

Article history:
Received 29 August 2009
Available online 13 January 2010

Keywords:
Hyperthyroidism
Autonomic nervous system
Heart rate variability
Detrended fluctuation analysis
Nonlinear dynamics

ABSTRACT

Despite many previous studies on the association between hyperthyroidism and the hyperadrenergic state, controversies still exist. Detrended fluctuation analysis (DFA) is a well recognized method in the nonlinear analysis of heart rate variability (HRV), and it has physiological significance related to the autonomic nervous system. In particular, an increased short-term scaling exponent $\alpha 1$ calculated from DFA is associated with both increased sympathetic activity and decreased vagal activity. No study has investigated the DFA of HRV in hyperthyroidism. This study was designed to assess the sympathovagal balance in hyperthyroidism. We performed the DFA along with the linear analysis of HRV in 36 hyperthyroid Graves' disease patients (32 females and 4 males; age 30 ± 1 years, means $\pm$ SE) and 36 normal controls matched by sex, age and body mass index. Compared with the normal controls, the hyperthyroid patients revealed a significant increase ($P < 0.001$) in $\alpha 1$ (hyperthyroid 1.28 ± 0.04 versus control 0.91 ± 0.02), long-term scaling exponent $\alpha 2$ (1.05 ± 0.02 versus 0.90 ± 0.01), overall scaling exponent α (1.11 ± 0.02 versus 0.89 ± 0.01), low frequency power in normalized units (LF%) and the ratio of low frequency power to high frequency power (LF/HF); and a significant decrease ($P < 0.001$) in the standard deviation of the *R–R* intervals (SDNN) and high frequency power (HF). In conclusion, hyperthyroidism is characterized by concurrent sympathetic activation and vagal withdrawal. This sympathovagal imbalance state in hyperthyroidism helps to explain the higher prevalence of atrial fibrillation and exercise intolerance among hyperthyroid patients.

1. Introduction

Hyperthyroidism is characterized by clinical manifestations that resemble those of a hyperadrenergic state. Moreover, the fact that beta-adrenergic receptor blockers ameliorate these symptoms and signs has further suggested enhanced

* Corresponding address: Institute of Biomedical Engineering, National Yang-Ming University, 155 Li-Nong St. Sec. 2, Beitou, Taipei 112, Taiwan. Tel.: +886 2 28267025; fax: +886 2 28210847.
E-mail address: wchu@ym.edu.tw (W.-C. Chu).

0378-4371/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.physa.2009.12.062

sympathetic activity in hyperthyroidism [1]. This concept is supported by a recent study that disclosed the presence of increased 24 h urinary catecholamine excretion in hyperthyroid patients [2]. However, previous studies of the catecholamine metabolism indicated that the plasma levels and secretion rate of catecholamines are normal or even reduced in hyperthyroidism [3–6]. Proposed possible mechanisms to explain the apparent hyperadrenergic state in hyperthyroidism include enhanced sensitivity of the heart to catecholamines mediated by an increase in the number or affinity of the beta-adrenergic receptors [7,8]; alterations in the quantity of guanine nucleotide-binding proteins [9]; an increase in catecholamine turnover at neural synapses [5,6]; and structural similarities between thyroid hormones and catecholamines [10]. Notwithstanding these possibilities, the notion that hyperthyroidism is associated with an increased sympathetic tone could not be fully verified from these studies. On the other hand, a smaller increase in heart rate induced by atropine during the hyperthyroid state compared with the euthyroid state implied reduced vagal inhibition of heart rate in hyperthyroidism [11,12].

Analysis of the heart rate variability (HRV) provides a non-invasive and sensitive tool for the evaluation of autonomic regulation of the heart [13,14]. In clinical applications, reduced HRV is associated with increased cardiac mortality after acute myocardial infarction [15] and is an early warning sign of diabetic neuropathy among diabetic patients [16,17]. HRV analysis can be categorized into linear and nonlinear methods [14]. Conventionally, the beat-to-beat variation exhibited by the sinoatrial node is analyzed using linear methods. Previous studies have applied the linear analysis of HRV to investigate the autonomic nervous system of hyperthyroid patients; some have disclosed reduced [18–20] or normal [21] vagal activity, whereas others have shown both increased sympathetic and decreased vagal modulation of the heart rate in patients with hyperthyroidism [2,22].

However, multiple nonlinear mechanisms such as sympathetic nerves, vagal nerves, hormones and hemodynamics are involved in the regulation of the heart rate and these affecting factors interact mutually. Consequently, the heart rate regulating system appears to be a possible example where chaos theory can be applied [23,24]. These nonlinear phenomena could affect the genesis of heart rate fluctuation [25] and therefore a nonlinear analysis of HRV would be a more appropriate approach to interpreting the complex phenomena of heart rate dynamics. A recent study using a nonlinear analysis of HRV with the correlation dimension for hyperthyroidism has shown reduced complexity and impaired tolerance to cardiovascular stresses in hyperthyroid patients [26].

Nonlinear analysis of HRV can be quantified using parameters derived from chaos and fractal theory [27]. Detrended fluctuation analysis (DFA) is a nonlinear analysis of HRV [28]. Recent studies have indicated that DFA could be used not only to differentiate various patient groups from normal controls [29,30] but also to stratify high risk patient groups among post-myocardial infarction patients [31,32]. In addition, the short-term scaling exponent $\alpha 1$, which is calculated from the DFA, could be related to the state of the autonomic nervous system. An increased $\alpha 1$ is associated with concurrent increased sympathetic activity and decreased vagal activity. Conversely, a decreased $\alpha 1$ is related to co-activation of both the sympathetic and the vagal components of the autonomic nervous system [33].

At present, no study has investigated the DFA of HRV in hyperthyroidism. This study was designed to assess the autonomic nervous system in hyperthyroidism by the nonlinear analysis of HRV with DFA. We hypothesized that the autonomic dysfunction in hyperthyroid patients is caused by the joint effect of increased sympathetic activity and decreased vagal activity.

2. Subjects and methods

2.1. Subjects

A group of 36, newly diagnosed, untreated hyperthyroid Graves' disease patients from the outpatient clinic of a university hospital and a group of 36 healthy normal control subjects were recruited for this study. The hyperthyroid and control groups were matched for sex (32 females and 4 males versus 32 females and 4 males, hyperthyroid versus control), age (30 ± 1 versus 29 ± 1 years, means $\pm$ SE) and body mass index (20.7 ± 0.4 versus 21.8 ± 0.5 kg/m^2). The diagnosis of Graves' disease was established on the basis of clinical, biochemical, immunological, thyroid scintigraphic scanning and uptake data. Individuals with diabetes, cardiac arrhythmia, cardiovascular disease, pregnancy or those using medication were excluded. The study protocol was approved by the local ethics committee and all participants gave their informed consent. The study was conducted according to the principles of the Helsinki declaration.

2.2. Study protocol

The hyperthyroid patients were studied at the time of diagnosis before any medication was administered. For all participants, no alcoholic or caffeine-containing drinks were taken for at least 24 h before the study. The examination was performed in a quiet room during the daytime. Subjects received one-channel electrocardiogram (ECG) measurement for 30 min in the supine position after five minutes rest. During the ECG measurement, the subjects were instructed to fully relax, stay awake, breathe regularly, and not to speak.

2.3. Measurement of the ECG

The acquired analog ECG signals were transformed into digital signals by a 16-bit analog-to-digital converter with a sampling rate of 500 Hz. The digitized ECG signals were processed off-line. First, the *R* waves were detected and then