Journal of Diabetes and Its Complications 24 (2010) 48 – 54

Journal of Diabetes and its Complications

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Modified orthostatic load for spectral analysis of short-term heart rate variability improves the sensitivity of autonomic dysfunction assessment

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Received 5 April 2008; received in revised form 12 September 2008; accepted 17 October 2008

Abstract

Aim: To evaluate the impact of orthostatic load for sensitivity of short-term spectral analysis of heart rate variability (HRV) assessment of potential early autonomic dysfunction in diabetes mellitus. **Methods:** Comparison of results of short-term time- and frequency-domain analysis of HRV during single positions and during modified orthostatic load (supine 1–standing–supine 2, each position 300 s) in diabetic subjects with good glycemic control (n=80, age 38±14, diabetes duration 16±10 years) and without autonomic neuropathy as assessed by a standard bedside reflex test battery, and in nondiabetic controls (n=150, age 40±13 years). **Results:** None of the short-term frequency-domain parameters [absolute and logarithmic (LN) values of spectral powers in total- (TF), low- (LF), and high-frequency (HF) bands and its centroid frequencies] as obtained in single positions "supine" or "standing" revealed a significant difference between well-controlled patients and healthy controls (P>.3). However, during modified orthostatic load, significant differences in ΔLN $TF_{(supine\ 1-supine\ 2)}$ and in ΔLN $LF_{(supine\ 1-supine\ 2)}$ as well as in ΔLN $LF_{(standing-supine\ 2)}$ values between diabetic and healthy subjects were recorded [−0.2±0.5 vs. −0.1±0.4 LN (ms^2), P=.05; −0.3±0.8 vs. 0.1±0.7 LN (ms^2), P=.001 and 0.2±1.0 vs. 0.4±0.9 LN (ms^2), P=.05, respectively] with insignificant intergroup differences in related centroid frequencies. This finding suggests a delayed recovery of LF spectral power in diabetic subjects after orthostatic challenge. **Conclusions:** When compared with single position measurements, the modified orthostatic load protocol improves the sensitivity of short-term HRV examination. In well-controlled diabetic subjects without cardiovascular autonomic neuropathy (as excluded by standard cardiovascular reflex testing), the delayed recovery of LF band spectral power after orthostatic load with standing up indicates diminished parasympathetic activation.
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Keywords: Autonomic neuropathy; Spectral analysis; Heart rate variability; Diabetes mellitus; Orthostatic test

1. Introduction

Cardiovascular autonomic neuropathy (CAN) in diabetes mellitus is a typical late complication that is associated with up to fivefold increase in mortality when compared with diabetic patients without CAN (O'Brien, McFadden, & Corrall, 1991). Analysis of heart rate variability (HRV) allows indirect assessment of cardiac autonomic control. Evaluation of HRV permits the diagnosis of autonomic dysfunction in diabetes (American Diabetes Association: Diabetic Neuropathy, 1996; Maser & Lenhard, 2005; Vinik & Mehrabyan, 2004; Ziegler et al., 1992) and risk stratification in congestive heart failure and/or coronary heart disease (Adamopoulos et al., 1992; American College of Cardiology Cardiovascular Technology Assessment Committee, 1993; Nolan et al., 1998; Task Force of the European Society of Cardiology & North American Society of Pacing and Electrophysiology, 1996). Clinical evidence

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1056-8727/08/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.jdiacomp.2008.10.003

was found for the association between incidence of lethal arrhythmias and signs of an increased sympathetic and reduced vagal activity (Kleiger, Miller, Bigger, & Moss, Multicentre Post Infarction Research Group, 1987; Malliani, Lombardi, Pagani, & Cerutti, 1994; Priori et al., 2001). A reduced HRV is an indicator of compromised health (Dekker et al., 1997, 2000) and/or increased mortality in population studies (Tsuji et al., 1996).

Analysis of HRV can be performed during a standardized short-term examination procedure such as the battery of bedside reflex tests (Ewing, Martyn, Young, & Clarke, 1985; Opavsky, 1988), or using nonstandardized long-term data, typically Holter 24-h ECG monitoring. The immediate variability of short-term spectral measures of HRV was found to be low (Freed, Stein, Gordon, Urban, & Kligfield, 1994). Moreover, short, 2- to 15-min samples were reported to be excellent predictors of mortality and were correlated with prognostically important data from sustained recording periods (Bigger, Fleiss, Rolnitzky, & Steinman, 1993; Fei, Copie, Malik, & Camm, 1996). These studies suggest that easy applicable short-term HRV analysis may have an important clinical role. Early techniques for assessment of HRV were based on simple evaluation of heart rate change during standardized bedside reflex tests as proposed by Ewing et al. (1985) two decades ago. These tests are quite robust but sometimes not sensitive enough for identification of early stages of autonomic dysfunction where the interventions towards restoration of autonomic control are still possible and effective (Howorka, Pumprla, Haber, Koller-Strametz, & Mondrzyk, 1997; Howorka, Pumprla, & Schabmann, 1997). Moreover, strong stimulus used to evoke the single reflex may be responsible for temporarily changing the cardiovascular function that might significantly influence the test result (Batin & Nolan, 1996). A newer method, based on frequency/spectral analysis approach, identifies harmonic, cyclical changes in heart rate course (Task Force of the European Society of Cardiology & North American Society of Pacing and Electrophysiology, 1996). This allows to differentiate and to quantify the energy content of both main branches of autonomic control, the sympathetic and parasympathetic one. Due to high sensitivity, hence vulnerability, of spectral methods to various influences occurring during the recording, it is necessary to carefully standardize the examination protocol (Howorka, Pumprla, & Schabmann, 1998). Usually, HRV obtained from 2- to 10-minute recordings in a supine position is analyzed. However, in contrast to the aforementioned conventional bedside reflex test battery, there is no widely accepted gold-standard examination procedure yet, despite recommendations made by the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology (1996).

The aim of our study was (a) to evaluate the cardiovascular autonomic response as obtained during short-term modified orthostatic load (Opavsky, 1988) in diabetic patients without clinically obvious CAN, as well as (b) to compare these results with nondiabetic controls. Specifically, the effect of implementation of short-term orthostatic load (standing up) is to be investigated.

2. Patients and methods

In our outpatient databases, we identified a group of 80 diabetic subjects (for details see Table 1) with good glycemic control, using functional insulin treatment—discriminating between prandial, basal, and correctional insulin use—to prevent neuropathic dysfunction (Howorka, Pumrla, Haber, et al., 1997; Howorka et al., 1997, 1998). These patients had no clinical signs of any late diabetic complications. Inclusion criteria were (1) age between 15 and 80 years; (2) no cardioactive medication such as beta-blockers; (3) no evidence of heart disease, as assessed by history and physical examination; (4) no evidence of concomitant disease or late complication of diabetes that might interfere with quality of autonomic control; (5) good metabolic control of diabetes, with HbA_{1c} up to 175% of reference mean (=100%); (6) no hypoglycemia during and up to 12 h before the examination; (7) blood pressure under 150/90 mmHg; and (8) body mass index (BMI) <30 kg/m^2. Nondiabetic controls were selected in accordance with the above inclusion criteria.

The presence of CAN in diabetic subjects was assessed by a conventional battery of cardiovascular reflex tests to standardized stimuli (Ewing et al., 1985) including deep breathing, Valsalva maneuver, and orthostatic load. Each single test of Ewing's battery was scored with 0 when normal, 0.5 when borderline, and 1 when out of age-related normal values range (Ewing et al., 1985), summing up the total Ewing score. Diabetic patients with total score of 0–0.5 were free of detectable CAN and therefore eligible for the study.

Short-term spectral analysis of HRV was obtained from recordings consisting of 256 s of artifact-free records each, using a VariaCardio system (Advanced Medical Diagnostics Group, UK) (Salinger et al., 1999). High-resolution one-channel ECG was recorded and identification of R-R intervals with sampling rate of 1000 Hz was performed to be telemetrically transferred into a receiver connected to a PC-compatible computer and displayed on-line together with an

Table 1
Clinical characteristics of study subjects

Diabetic patients
• n=80
• Age 38±14 years (range 18–80 years)
• Type 1 diabetes: n=72
• Diabetes duration: 16±10 years
• Functional insulin treatment: n=76
• HbA_{1c} 146±21% of mean reference range
• Gender (f/m): 46/34
Nondiabetic controls
• n=150
• Age 40±13 years (range 18–72 years)
• Gender (f/m): 81/69

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