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Original research article

Heart rate variability evaluation in the assessment of cardiac autonomic neuropathy in patients with type 2 diabetes

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ARTICLE INFO

Article history:
Received 25 January 2017
Accepted 1 May 2017
Available online xxx

Keywords:
Cardiac autonomic neuropathy
Spectral analysis of heart rate variability
Supine–Standing–Supine test
Functional age of ANS
Diabetes mellitus

ABSTRACT

Introduction: Heart rate variability (HRV) is a respected measure used in the assessment of cardiac autonomic neuropathy (CAN) and it can serve as an independent prognostic indicator of sudden arrhythmic death risk. Despite the importance of early detection, the diagnosis of CAN is often made too late, especially in diabetics. Besides the long subclinical phase of CAN, reasons for this include great diversification of employed diagnostic methods and absence of universally accepted normal values; the latter applies mostly in HRV evaluated using short-term spectral analysis (SAHRV).

Aim: The aim of this cross-sectional study involving patients with type 2 diabetes was to summarize the real potential of using a testing method for CAN diagnosis by short-term SAHRV, including an autonomic load imposed during an orthoclinostatic test (Supine1–Standing–Supine2, short 5-min recordings). Three different normative approaches to the postprocessing analysis of acquired data described by different authors were employed.

Secondary aim of the study was to assess the benefit of rate-controlled breathing. The next aim was to compare the HRV data measured with the selected clinical and laboratory indices in patient examined.

Materials and methods: The study included 43 patients with type 2 diabetes (12 women, 31 men, mean age 51.1 ± 10.7 y) and no history of manifest CAN or serious cardiovascular illness, except uncomplicated hypertension. Using a diagnostic system DiANS PF8 with telemetric transfer of ECG and respiratory rate, series of reflex tests according to Ewing and SAHRV (Fourier tachogram analysis, window 256) during autonomic load imposed by Supine1–Standing–Supine2 test (SSS test) and during 5 min of rate-controlled, non-deepened breathing (PB, 12 cycles/min) were performed. Acquired spectral indices were analyzed and compared with normatives of 3 authors using the same recording algorithm, SSS test, but different data postprocessing analysis. These were (1) so called ''functional age'' of autonomic nervous system (ANS), (2) assessment of CAN severity according to age-stratified medians and percentiles, (3) assessment of CAN severity according to cumulative spectral power during the entire test (cumLFHF).

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http://dx.doi.org/10.1016/j.crvasa.2017.05.001

Results: According to the total Ewing score (ETS), 11.6% patients were categorized as CAN-free (ETS = 0), 32.6% were diagnosed with possible CAN (ETS = 1), and 55.8% labeled with manifest CAN (ETS = 2–3). Moderate correlation between ETS and individual SAHRV parameters following orthoclinostasis (test SSS) in Supine2 position was described [ms^2]: TP (total power, $f = 0.02–0.5$ Hz): $r = -0.4$, $p < 0.006$; LF component (low frequency, 0.05–0.15 Hz): $r = -0.31$, $p < 0.04$; HF component (high frequency, 0.15–0.5 Hz): $r = -0.45$, $p < 0.003$) and the same applied to rate-controlled breathing PB (TP, [ms^2]: $r = -0.56$, $p < 0.0001$; LF: $r = -0.38$, $p < 0.018$; HF: $r = -0.52$, $p < 0.001$). Moderate correlation was also found between ETS and HRV assessment using a complex indicator – ''functional age of ANS'' ($r = 0.37$, $p < 0.015$), ETS and cumLFHF [ms^2, ln ms^2]: $r = -0.46$, $p < 0.002$). In most patients, significant difference between functional age of ANS and calendar age was confirmed (mean 21.8 ± 12.9 y, median 23.5 years, $p < 0.0001$). An attempt to assess the severity CAN using age-stratified medians and percentiles of TP, LF, HF, and LF/HF was not successful.

As for SAHRV and clinical indices (anthropometric, echocardiographic, QTc, laboratory), moderate correlation between the glycated hemoglobin on one side and basic SAHRV indices (TP, LF, HF, LF/HF), functional age of ANS and cumLFHF on the other side was prominent ($r = 0.36–0.53$, $p < 0.0004$ to $p < 0.02$).

Conclusion: Assessment of CAN using evaluation of HRV can optimally be performed (and simply realized in clinical practice) using SAHRV based on short ECG recordings during autonomic load imposed by orthoclinostatic test (Supine1–Standing–Supine2) and on post-processing data analysis using complex indicator called ''functional age of ANS''. In the detailed evaluation of sympathovagal balance, it complements the screening assessment with cardiovascular reflex tests (Ewing's battery). Besides the orthoclinostatic load, pronounced vagal provocation using rate-controlled, non-deepened breathing (12 cycles/min) represents a recommended facultative load option increasing the yield of the SAHRV method.

The detection and assessment of CAN severity while applying the cumulative indicator of HRV (cumLFHF) showed a good discrimination power in the frontline screening for CAN, albeit without the possibility to distinguish between the sympathetic and vagal branch of ANS.

Presented cross-sectional study in type 2 diabetes mellitus demonstrated a significant autonomic dysfunction in majority patients examined, independently of diabetes duration. It supports the recommendation to assess the ANS integrity in type 2 diabetes already at diagnosis, within the initial staging of the illness. The severity of CAN correlates well with metabolic control of diabetes as evaluated by glycated hemoglobin.

Introduction

According to available data, the prevalence of diabetic autonomic neuropathy (DAN) is between 1.6% and 90% while the prevalence of cardiac autonomic neuropathy (CAN) varies from 1% to 90% in patients with type 1 diabetes and from 20% to 73% in patients with type 2 diabetes [1–3]. The reasons for this immense variability of DAN prevalence include its diverse symptomatology, long subclinical phase leading to late diagnosis of organ-specific neuropathy, absence of uniformity during selection of a population sample of diabetics, diversity of diagnostic methods, and absence of uniform normative data. It is aimed to define norms (age-stratified normative data) in this context to enable CAN diagnosis during its subclinical phase, prevent irreversible changes, and widen the therapeutic window for early intervention.

Reflex tests of autonomic cardiovascular functions according to Ewing are considered the basis of these aims and the ''gold standard'' [4,5]. In these reflex tests, autonomic cardiovascular functions are evaluated by simple indices describing changes in heart rate during deep breathing, orthostatic test, Valsalva maneuver or a handgrip. Methods analyzing sympathovagal balance in more details using heart rate variability (HRV) – defined as physiological oscillations of R-R interval on the electrocardiogram (ECG) – most often using short-term spectral analysis (SAHRV), developed historically from the Ewing's tests. The basic consensual methodological material for HRV assessment is a TASK Force from 1996 [5].

To name the largest studies dealing with normal values of outcome short-term SAHRV data, Agelink et al. (2001) [6] tested 309 healthy volunteers and Nunan et al. (2010) published a meta-analysis on this topic [7] summarizing the results of other 44 studies published from 1996 to 2008 (21 438 probands). The main feature of these trials is the usage of short ECG recordings and analysis of R-R tachograms in the supine position. Despite an immense effort, uniform norms enabling valid assessment and monitoring of cardiovascular autonomic functions were not defined.

In the Czech Republic, trials dealing with normative short-term SAHRV data in the entire age spectrum include works of Stejskal et al. [8] from 2002 (216 probands aged 12–70 years) and Vlčková et al. [9] from 2010 (167 healthy probands aged 20–80 years). Methodological work of Howorka et al. (1998) [10],

Please cite this article in press as: R. Metelka et al., Heart rate variability evaluation in the assessment of cardiac autonomic neuropathy in patients with type 2 diabetes, Cor et Vasa (2017), http://dx.doi.org/10.1016/j.crvasa.2017.05.001