Clinical Neurophysiology 127 (2016) 1639–1644

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Hemodynamic profile and heart rate variability in hyperadrenergic versus non-hyperadrenergic postural orthostatic tachycardia syndrome

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ARTICLE INFO

Article history:
Accepted 31 August 2015
Available online 4 September 2015

Keywords:
Postural orthostatic tachycardia syndrome
Hyperadrenergic
Non-hyperadrenergic
Heart rate variability
Head-up tilt test

HIGHLIGHTS

- We found significant differences in hemodynamic profile of hyperadrenergic versus non-hyperadrenergic postural orthostatic tachycardia syndrome (POTS).
- Based on these differences we developed criteria which, when implemented in our cohort, detected non-hyperadrenergic POTS with 76% sensitivity and 80% specificity.
- Results of HRV analysis indicate that hyperadrenergic POTS patients' have diminished vagal tone even at rest.

ABSTRACT

Objectives: To investigate differences in hemodynamic profile between hyperadrenergic and non-hyperadrenergic postural orthostatic tachycardia syndrome (POTS) in response to head-up tilt test (HUTT).
Methods: Ten patients with hyperadrenergic and 33 patients with non-hyperadrenergic POTS underwent HUTT consisting of a 10-min supine phase and 30-min 70° tilted phase. Heart rate (HR), systolic and diastolic blood pressure (dBP), and heart rate variability (HRV) parameters of the two groups were compared.
Results: Hyperadrenergic patients had higher supine HR (82.6 ± 16.3 bpm vs. 73.8 ± 10.4 bpm, $p = 0.048$). Supine HRV analysis showed significantly lower cardiac vagal activity and possible predominance of cardiac sympathetic activity in the hyperadrenergic group. Non-hyperadrenergic patients had lower dBP during the first four minutes of tilt. Furthermore, 60% of non-hyperadrenergic patients had lower average dBP in the 1st minute of tilted phase when compared to supine values, whereas only 2 of 10 hyperadrenergic patients exhibited the same response. Syncope or intolerable symptoms, causing early ending of HUTT, developed earlier in the non-hyperadrenergic group (8.9 ± 6.8 min vs. 21.2 ± 3.5 min, $p = 0.001$).
Conclusion: Hyperadrenergic and non-hyperadrenergic type of POTS seem to have distinctly different response to HUTT.
Significance: This study has shown significant differences in hemodynamic response to HUTT between hyperadrenergic and non-hyperadrenergic type of POTS indicating possible differences in their pathophysiology.

1. Introduction

Postural orthostatic tachycardia syndrome (POTS) is becoming recognised as one of the more frequent forms of orthostatic intolerance (Robertson, 1999). Though true prevalence of POTS is unknown, one study estimates it to be around 170 cases per 100,000 people of the general population (Schondorf et al., 1999).

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http://dx.doi.org/10.1016/j.clinph.2015.08.015
1388-2457/

Still, it is often under-recognised or misdiagnosed due to unspecific and overlapping symptoms (Khurana, 2006; Pandian et al., 2007; Sullivan et al., 2005; Hoad et al., 2008), therefore prevalence may be even higher. POTS usually affects the younger population, and women are affected up to five times more often than men (Grubb, 2008). There is a number of pathophysiological mechanisms thought to be underlying POTS including peripheral autonomic denervation (Thieben et al., 2007), blood volume and renin–angiotensin–aldosterone system perturbation (Stewart et al., 2006), abnormal norepinephrine (NE) clearance (Jacob et al., 1999) and reduced norepinephrine transporter protein expression (Lambert et al., 2008). A study by Parsaik et al. (2012) which included 84 POTS patients has shown that 95% of them had some degree of deconditioning, implying deconditioning has a significant role in the pathophysiology of POTS. Some studies suggest autoimmune mechanisms are possibly linked with preceding viral illnesses in some percentage of POTS patients (Li et al., 2014; Thieben et al., 2007). Also, some psychological factors such as anxiety and depression have been linked with sympathetic predominance and elevated heart rate (Benarroch, 2012). The most frequent type of POTS is the neuropathic or "partial dysautonomic" form caused by peripheral autonomic denervation (Grubb, 2008; Carew et al., 2009). On the other hand, it has been found that 29–61% of POTS patients have standing NE values of 3.5 nmol/L or more (Thieben et al., 2007; Garland et al., 2007). This is often referred to as the hyperadrenergic type of POTS and is the second most commonly addressed type of POTS in current literature. Although POTS is a heterogenic disorder, classifying POTS into hyperadrenergic or neuropathic type seems to be clinically useful, especially with regards to treatment response (Grubb, 2008). Both forms of POTS can be primary or secondary to other diseases such as chronic diabetes mellitus (Grubb, 2008).

In the present study we investigated the differences in hemodynamic response to orthostatic provocation between hyperadrenergic and non-hyperadrenergic POTS patients during the head-up tilt table test (HUTT) with a 30 min standing phase.

2. Methods

2.1. Patients

Altogether 1723 patients presenting with symptoms of orthostatic intolerance who underwent HUTT between January 2013 and October 2014 were considered for this prospective study. Criteria for diagnosing POTS were based on history of three or more months of orthostatic intolerance symptoms associated with increment of heart rate (HR) $\geqslant$30 bpm for adults, and $\geqslant$40 bpm for patients younger than 19 years in the absence of orthostatic hypotension (Freeman et al., 2011). Also, in order to narrow down possible causes of POTS we used the following inclusion criteria: (a) absence of prolonged bed rest, (b) absence of conditions associated with hypovolemia, (c) absence of dehydration was evaluated clinically (skin turgor, dryness of mucus membranes, thirst, and urine output and colour), (d) absence of other systemic illnesses, (e) disuse of medications that can affect blood pressure and/or heart rate. After implementing the abovementioned inclusion criteria, and signing the informed consent approved by the Ethical committee of the University Hospital Centre Zagreb, 43 patients were finally included in the study. Each of 43 POTS patients was invited for additional HUTT and plasma catecholamine level analysis within a week (protocol described below). Depending on standing plasma NE levels during the tilted phase of HUTT, the patient was categorised into one of two groups. Group 1 consisted of patients with hyperadrenergic POTS defined by standing NE $\geqslant$3.5 nmol/L, and patients with non-hyperadrenergic POTS (standing NE <3.5 nmol/L) formed group 2. If there were any clinical indications for other possible causes of elevated heart rate, patients underwent additional evaluation; however none were found.

2.2. Head-up tilt table test

All tests were performed in a quiet and dimly lit room. Patients were instructed not to drink coffee or smoke before the testing. After the patient was supine on the testing table, pressure cuff and ECG electrodes were adjusted at appropriate sites. A peripheral vein catheter was installed in the antecubital or radial vein of the right arm, and 15 min of settling period was given before recording. The HUTT consisted of 10-min supine phase followed by a 30-min 70° tilted phase. The table was tilted continuously from 0° to 70° over a period of 15 s. Blood pressure and heart rate beat-to-beat values were continuously recorded using Task Force Monitor (TFM) (CNSystems Medizintechnik AG, Austria). Blood samples for plasma catecholamine level analysis were collected from peripheral vein catheter in the 10th minute of the supine phase and in 10th minute of the tilted phase. Some patients could not finish entire test due to vasovagal syncope or other intolerable symptoms (these will be referred to as early-enders hereafter). In cases where tilted phase had to be ended before the 10th minute, blood samples were collected just before or during returning to supine position.

2.3. Plasma catecholamine levels

The aforementioned blood samples were collected directly in chilled tubes containing EGTA and reduced glutathione for determination of plasma catecholamine levels during the supine and tilted phase of HUTT (Kabevette® N, Kabe Labortechnik GmbH). Plasma catecholamine levels were measured on high pressure liquid chromatography (HPLC Prominence; Shimadzu GmbH) with an electrochemical detector CLC 100 (Chromsystems GmbH, Germany) using a commercially available HPLC kit and a reverse phase analytical column for HPLC analysis of catecholamines in plasma (Chromsystems GmbH, Germany).

2.4. Data and statistics

The following data were collected for every patient and used in the analysis: gender; age; possible early end of tilted phase; tilted phase endurance (TPE) (i.e. the amount of time that patient managed to endure in tilted position expressed in minutes); cause of early HUTT interruption (vasovagal syncope or patient reported intolerable symptoms); supine and head-up tilt plasma epinephrine (E) and NE levels; average HR, systolic (sBP) and diastolic (dBP) blood pressure values during 10-min supine phase; average values of HR, sBP and dBP for thirty 1-min intervals during tilted phase of HUTT (averaging of the beat-to-beat values was performed by TFM). When testing had to be ended before full completion, hemodynamic data immediately preceding vasovagal syncope or other intolerable symptoms were not used in the analysis. To avoid work-up bias all the analysis was performed by persons blinded for the group affiliation.

Power spectral analysis of heart rate variability (HRV) was performed by Kubios HRV 2.2 software (Department of Applied Physics, University of Eastern Finland, Kuopio, Finland) using time and frequency domain methods. Autoregressive (AR) spectral estimation method was used in the spectral analysis of the frequency domain variables. The data used for the HRV analysis were recorded by the TFM and subsequently inspected and edited for missing data. Medium artefact correction option and Smoothness priors based detrending approach were used to ensure data quality. HRV was analysed in 5-min intervals of beat-to-beat data recorded during the testing (Task Force, 1996). HRV analysis on