Comparison of active standing test, head-up tilt test and 24-h ambulatory heart rate and blood pressure monitoring in diagnosing postural tachycardia

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Summary

Protocols for the assessment of postural tachycardia differ in both type of orthostatic challenge and test duration. We therefore compared heart rate (HR) and blood pressure responses during an active standing test (AST) and a head-up tilt test (HUT) in 34 patients with orthostatic intolerance and 31 asymptomatic subjects. A subset also performed 24-h ambulatory blood pressure monitoring (ABPM). HR responses were similar between AST and HUT both in asymptomatic and in orthostatic intolerant subjects. Specificity of HR increase ≥30 bpm for orthostatic intolerance was high (above 0.85) with both AST and HUT and was similar at 3 minutes and at 9 minutes. HR changes recorded during self-performed AST (in the context of 24-h ABPM) and circadian HR difference corresponded well to changes recorded during AST in the autonomic laboratory. We conclude that AST and HUT are comparable methods for the assessment of postural tachycardia, that 3-min and 9-min tests are appropriate, and that ABPM is a useful ancillary test in the assessment of orthostatic responses.

KEY WORDS: ambulatory blood pressure monitoring, head-up tilt test, orthostatic intolerance, postural tachycardia syndrome

Introduction

Postural tachycardia syndrome (POTS) has been defined, by consensus, as a sustained heart rate (HR) increment of ≥30 beats/min (bpm) within 10 minutes of standing or head-up tilt in the absence of orthostatic hypotension (Freeman et al., 2011; Mathias et al., 2011). This definition thus allows for two types of orthostatic challenge, either the active standing test (AST) or the head-up tilt test (HUT), both of which are used in research and in clinical practice, with different test durations (Carew et al., 2009; Sandroni et al., 1999; Low et al., 1995; Diehl, 2005). Although, physiologically, active standing and passive tilting are not equivalent maneuvers, after one minute of upright posture, no difference in HR or blood pressure (BP) responses between the two tests has been found in healthy individuals (Tanaka et al., 1996; Wieling and van Lieshout 2008). However, in patients with POTS, Braune et al. (1999) found AST to be more sensitive for provoking postural tachycardia than HUT, at least in the first two minutes of upright posture, while Matsuhima et al. (2004) described a higher HR increase with AST than with HUT in children with orthostatic intolerance and syncope. A continuous increase in HR throughout 10 minutes of upright posture, specific for POTS patients (Diehl, 2005; Petersen et al., 2000), suggests that longer tests may not be more suitable than shorter tests for the detection of postural tachycardia. In view of these observations, it would be useful to clarify whether different types of orthostatic stress and different test durations affect HR changes to an extent capable of affecting the sensitivities and specificities of test protocols. For this purpose we directly compared HR and BP responses to AST and HUT in a mixed population of patients with postural tachycardia, patients with orthostatic intolerance, and asymptomatic subjects. In addition, HR changes detected on continuous monitoring were compared with HR changes detected on single measurements, which can be obtained during bedside testing. The second aim of the study was to evaluate 24-h ambulatory HR and BP monitoring (ABPM) as a diagnostic tool for postural tachycardia.

Materials and methods

Participants

To obtain a heterogeneous sample in terms of orthostatic symptoms and HR responses, subjects were recruited from: i) consecutive patients, referred to our center for disorders of the autonomic nervous system due to orthostatic intolerance or syncope, who had postural tachycardia on previous HUT (HR increase ≥30 bpm in the first 10 minutes of HUT), ii) age- and sex- matched patients without excessive tachycardia on past HUT, and iii) healthy volunteers (Fig. 1, over). Only subjects aged between 18 and 40 years were recruited as this is the typical age range of patients with POTS. Exclusion criteria were pregnancy, breastfeeding, any known arrhythmias, cardiovascular, cerebrovascular or thyroid disorders, and use of medications that could interfere with orthostatic responses. In the absence of a gold standard test, orthostatic intolerance was assessed through a structured interview performed by an investigator with a longstanding interest in this field. To avoid inter-rater variability, all interviews were conducted by the same investigator. For the purpose of this study, the criteria for orthostatic intolerance were: disturbing typi-

cal symptoms of orthostatic intolerance (dizziness, blurring of vision, nausea, sweating, etc.) occurring at least weekly and only or predominantly during upright posture, both upon getting up and during prolonged standing. Subjects with a history of neurocardiogenic syncope were not excluded from the study and neurocardiogenic syncope, per se, was not considered a criterion of orthostatic intolerance. On the basis of the interview, subjects were allocated to the orthostatic intolerant or asymptomatic group (Fig. 1). The study was approved by the Commission for Medical Ethics of the Republic of Slovenia. All participants signed a written informed consent form prior to participating in the study.

Orthostatic test protocols

All studies were performed at our autonomic laboratory between 8 a.m. and 1 p.m. in a quiet room with stable temperature and humidity levels. Subjects were asked to refrain from consumption of alcohol, caffeine and tobacco from the night before testing and not to eat for at least five hours before testing. In the event of illness or injury in the week prior to testing, the test was postponed. The testing procedure began when instrument setup had been completed, which was about 30 minutes after the patient had entered the laboratory and about 10 minutes after he/she had lain down. Orthostatic testing consisted of 10 minutes of quiet rest in the supine position, 10 minutes of quiet active standing at the side of the bed, followed by 15 minutes of supine rest and 20 minutes of 60° HUT. For the latter, patients were passively tilted up on a tilt table with footplate support. The left forearm, used for continuous BP recording, was kept comfortably supported at heart level throughout AST and HUT. A right forearm vein was cannulized at least 10 minutes before commencing the protocol and blood samples for blood count and serum sodium testing were drawn in the last minute of supine rest and in the last minute of standing. HR and BP were monitored continuously with a 3-channel ECG and radial artery tonometry (Colin CBM-7000, Colin Medical Instrumentation, Komaki), which was calibrated with sphygmomanometric measurements taken at the brachial artery. The sampling frequency was 500 Hz. Recordings were analyzed using the NevroEKG software package (Jozef Stefan Institute, Ljubljana). The ECG lead with the highest quality was selected for recognition of R waves (usually lead II), and correct recognition was reviewed by inspection of each single R wave in the recording. Single HR and BP measurements were taken at the brachial artery using an automated sphygmomanometer, twice in the last five minutes of supine rest prior to each test and during the 3rd, 6th and 9th minute of upright posture.

On a different day, but within three weeks of testing in the autonomic laboratory, a subset of participants agreed to perform 24-h ABPM. Studies were performed with a BR-102 plus device (Schiller AG, Switzerland) using a protocol adapted from the London Autonomic Units protocol (Mathias and Bannister, 2002). Automatic measurements were taken every 20 minutes during the day and every two hours during the night; intervals were set individually on the basis of the participant's habits. Participants were equipped with a diary in which they noted activity and symptoms at each measurement. They were asked to self-perform an AST three times in the course of 24 hours; each AST consisted of five minutes of lying supine followed immediately by five minutes of quiet standing, and the subjects manually started a measurement at the end of each interval.

Statistical analysis

In analysis of single HR and BP measurements, the average of the last two supine measurements before standing/tilting was taken as the baseline value and

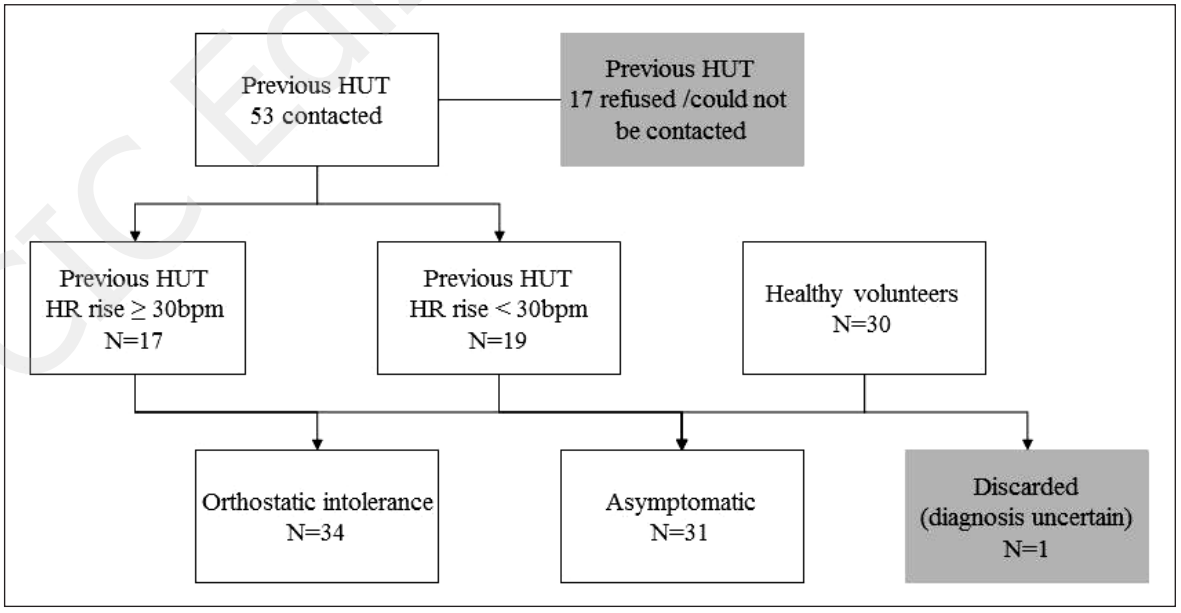

Figure 1 - Flowchart of participant selection. HUT=head-up tilt test, HR=heart rate.

compared to single measurements taken during the 3rd and 9th minutes of upright posture. For continuous monitoring, average HR 240 seconds to 60 seconds before standing up was taken as baseline and compared to 60-second averages for the 3rd and 9th minutes of upright posture. The last minute of supine rest and the last minute of active standing were avoided because drawing of blood could affect HR values. Correlations between single and continuous measurements were tested by calculation of correlation coefficients between pairs of variables. Agreement of methods was assessed using the Bland-Altman approach. Mean HR and BP changes were compared between AST and HUT, and between the 3rd and the 9th minute of upright posture in the whole sample and in the orthostatic intolerant and asymptomatic subgroups. For each parameter, we calculated the specificity of HR increases ≥30 bpm for orthostatic intolerance (as assessed using the interview). Paired t-test was used for comparisons of numerical variables and Pearson's chi-square test or Fisher's exact test for comparisons of proportions. A p value below 0.05 was taken to indicate statistical significance. SPSS Statistics 17.0 software (2008) was used for statistical analyses.

Results

The study participants were 36 patients, invited to take part on the basis of previous HUT results, and 30 healthy volunteers (Fig. 1). One subject was subsequently excluded due to an unclear history of orthostatic intolerance. Table I shows the baseline characteristics of the remaining 65 participants; some patients from the previous HUT group were classified as asymptomatic in terms of orthostatic intolerance while some of the healthy volunteers were found to suffer from orthostatic symptoms. No subject was taking medications for orthostatic intolerance at the time of recruitment or testing. No subject classified as asymptomatic had a history of reflex syncope. Eight participants had HR increases ≥30 bpm, four from the orthostatic intolerant and four from the asymptomatic group. No subject had orthostatic hypotension. Blood counts and serum sodium levels were normal in all subjects.

Comparison of continuous monitoring and single measurements

Comparisons of continuous monitoring and single measurements of HR are presented in table II. The

Table I - Basic characteristics of the participants with orthostatic intolerance and the asymptomatic subjects.

	Orthostatic intolerance (n=34)	Asymptomatic (n=31)	p
Age, years	25.7 (6.51)	27.7 (6.74)	0.235
Women, n (%)	39 (85)	22 (71)	0.229
HR supine (bpm)	68.3 (11.73)	68.4 (8.766)	0.836
SBP supine (mmHg)	113.6 (11.31)	115.6 (11.09)	0.493
DBP supine (mmHg)	65.4 (9.54)	64.5 (8.08)	0.730
ΔHR 9min HUT (bpm)	20.7 (7.10)	17.6 (10.64)	0.620
ΔSBP 9min HUT (mmHg)	-0.85 (10.31)	-3.1 (11.95)	0.466
ΔDBP 9min HUT (mmHg)	6.2 (9.09)	6.3 (10.13)	0.985

Data are presented as mean (standard deviation) except where stated otherwise.
Abbreviations: HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Table II - Comparison of single measurements and continuous monitoring of HR using paired t-test and the Bland-Altman approach.

		HR – single measurements (bpm) mean (SD)	HR – continuous monitoring (bpm) mean (SD)	Difference between methods (bpm) mean (SD)	95% CI	p (paired t-test)	Lower limit of agreement (bpm)	Upper limit of agreement (bpm)
AST	Lying	68.7 (10.4)	68.7 (10.4)	-0.11	[-0.72 – 0.51]	0.733	-4.9	4.7
	3 min	86.4 (13.0)	84.3 (12.7)	0.80	[-0.52 – 2.1]	0.230	-9.1	10.7
	6 min	87.8 (14.6)	87.9 (13.8)	0.06	[-1.2 – 1.3]	0.925	-9.2	9.3
	9 min	87.4 (13.5)	90.0 (14.9)	-0.57	[-2.0 – 0.85]	0.424	-10.6	9.5
HUT	Lying	65.2 (10.5)	65.0 (10.0)	-0.27	[-0.71 – 0.18]	0.235	-3.7	3.2
	3 min	82.8 (12.6)	82.3 (12.0)	0.50	[-1.1 – 1.1]	0.050	-8.2	8.2
	6 min	84.1 (13.0)	83.2 (12.5)	0.31	[-0.81 – 1.4]	0.586	-8.1	8.7
	9 min	84.3 (14.0)	83.5 (13.0)	0.29	[-0.85 – 1.4]	0.607	-8.1	8.7

Abbreviations: HR=heart rate; SD=standard deviation; CI=confidence interval; AST=active standing test; HUT=head-up tilt test.

mean values of HR changes did not differ between the two methods. Only HR increase calculated from single measurements in the 3rd minute of HUT was relatively higher than obtained by continuous monitoring (p=0.05), but the absolute difference (0.5 bpm) was small. Correlation coefficients were above 0.92 for all pairs of variables. However, analysis of agreement between the two methods revealed considerable differences between continuous monitoring and single measurements in individual participants (Table II). As regards BP, differences between single measurements and continuous monitoring were found in comparisons of mean values; 95% confidence intervals for difference between methods reached 10.9 mmHg. Differences in BP were not systematic – one method did not consistently under- or overestimate BP change relative to the other.

Active standing test and head-up tilt test

Continuous HR measurements were used to make comparisons between AST and HUT because they were considered more accurate. Mean HR changes during AST and HUT, compared at the same time point, were similar both in the whole sample and in the subgroups with and without orthostatic intolerance. HR change in the 9th minute of upright posture was higher than in the 3rd minute with both tests, the only exception being the change found in asymptomatic subjects during HUT (Table III). No statistically significant relationship was found between orthostatic intolerance and measurement method (p=0.786). In comparisons of BP changes between AST and HUT, we found a slight fall in systolic BP at 9 minutes of HUT in the orthostatic intolerant group [change from baseline -1.4/6.7 (10.30/9.77) mmHg] which was not present during AST [change from baseline 5.9/8.1 (14.64/10.21) mmHg, p<0.05]. BP changes in the 3rd minute of upright posture did not differ significantly between the two tests (p>0.05). Syncope or presyncope was induced in 23 (35%) subjects during the first 10 minutes of AST and in 23 (35%) during HUT; in 20 subjects syncope or presyncope was induced during both tests.

Table IV shows specificity and sensitivity of HR increase ≥30 bpm for orthostatic intolerance as assessed through the structured interview. In general, the specificity of postural tachycardia for orthostatic intolerance was high regardless of the test protocol, while the sensitivity was low. We compared specificities between AST and HUT, between the 3rd and the 9th minute, and between values obtained by single and continuous measurements of HR. Chi-square tests revealed no significant differences (p>0.05) in any of the compared pairs and the 95% confidence intervals always overlapped.

24-h blood pressure and heart rate monitoring

Forty-three subjects completed 24-h ABPM. Of these, two were excluded because more than 33% of measurements were unsuccessful and three because they failed to return the diary. The remaining 38 patients completed the diary adequately and performed at least two ASTs. BP and HR values were, on average, normal in those with and those without orthostatic intolerance. Nocturnal BP dip was below 10% in six subjects: three with ortho-

Table III - Comparison of changes in heart rate during active standing test and head-up tilt test at different time intervals.

	AST 3 min	AST 9 min	p	HUT 3 min	HUT 9 min	p
Orthostatic intolerance	19.8 (7.53)	24.4 (8.57)	<0.001	18.6 (6.42)	22.1 (8.65)	0.006
Asymptomatic	13.0 (9.76)	18.1 (12.57)	0.001	16.2 (8.60)	17.6 (10.60)	0.217
Whole sample	16.6 (9.23)	21.4 (11.0)	<0.001	17.5 (7.53)	20.0 (9.77)	0.003

Abbreviations: AST=active standing test; HUT=head-up tilt test.
Values are presented as mean (standard deviation); p value is given for comparisons of values in the 3rd and 9th minute.

Table IV - Specificity and sensitivity of heart rate increase above 30 bpm for orthostatic intolerance using different test protocols.

	AST 3 min	HUT 3 min	AST 9 min	HUT 9 min
Specificity				
Continuous monitoring	0.88 [0.70 – 0.98]	0.97 [0.83 – 0.99]	0.88 [0.69 – 0.97]	0.84 [0.64 – 0.95]
Single measurements	0.93 [0.76 – 0.99]	0.97 [0.83 – 0.99]	0.88 [0.69 – 0.97]	0.81 [0.62 – 0.94]
Sensitivity				
Continuous monitoring	0.13 [0.04 – 0.30]	0.06 [0.01 – 0.20]	0.10 [0.02 – 0.27]	0.14 [0.02 – 0.27]
Single measurements	0.10 [0.02 – 0.25]	0.06 [0.01 – 0.20]	0.11 [0.02 – 0.27]	0.15 [0.05 – 0.32]

Abbreviations: AST=active standing test; HUT=head-up tilt test. Values are presented with 95% confidence intervals in square brackets.

static intolerance and three asymptomatic. All subjects showed a normal decline in HR during the night.

We analyzed three potential predictors of postural tachycardia: mean HR change during self-performed AST, difference between the mean of all daytime measurements taken while upright minus the mean of all daytime measurements taken while supine, and difference between 24-h mean diurnal and nocturnal heart rate values (Table V). All three variables were similar to HR changes recorded during AST in the autonomic laboratory and also correlated with each other ($p>0.05$). The specificity of HR increase ≥30 bpm was 0.89 for the mean HR change during self-performed AST, 0.88 for the difference between all upright and all supine measurements, and 0.87 for the nocturnal dip in HR. BP changes during self-performed AST corresponded less well to those detected in the autonomic laboratory.

Discussion

There is no specific biomarker for POTS, whose diagnosis is based solely on clinical history and on the arbitrary limit of postural increase in HR, agreed on the basis of data from samples of healthy volunteers (Braune et al., 1999; Schondorf and Low, 1993; Streeten et al., 1988). It is therefore important to clearly establish which orthostatic test protocols are reliable for the assessment of postural tachycardia in accordance with the current definition (Freeman et al., 2011). However, there exist few comparisons of the different tests, particularly those available outside highly equipped autonomic laboratories. Non-invasive continuous HR monitoring is, for example, usually available only in specialized units.

In our study we found that continuous HR monitoring and single HR measurements using a sphygmomanometer, a common way of measuring HR in clinical bedside testing, can give considerably different values within single individuals, although the mean results in the sample are similar. The two methods also showed similar specificity of postural tachycardia for orthostatic intolerance. These findings suggest that the single measurement approach will not systematically overrate or underrate the number of subjects with postural tachycardia and will not give a higher number of "false positives" (asymptomatic subjects with HR increase above 30 bpm). We therefore conclude that single measurements are reliable for basic assessment of postural tachycardia, but for a more detailed insight into hemodynamic responses and for research purposes continuous monitoring is needed. The latter point is particularly true of BP assessment, for which, as with HR assessment, the literature contains no direct comparisons of continuous non-invasive monitoring and single measurements in orthostatic testing.

We found no differences between HR changes during AST and during HUT, either in the whole sample or in the subgroups with and without orthostatic intolerance. As regards the test duration, two time points for evaluation of postural tachycardia were compared: three and nine minutes. The three-minute duration was chosen because it was considered suitable for bedside testing and because it was used in the studies of normal HR increase ranges on which the POTS diagnostic limit was initially based (Braune et al., 1999; Schondorf and Low, 1993; Streeten et al., 1988). The nine-minute duration was chosen because the definition of POTS refers to a sustained HR rise within 10 minutes of upright posture (the 10th minute was avoided because the drawing of blood at that time point could have affected the HR). A continuous HR increase was recorded between the 3rd and 9th minutes of AST in the subjects with orthostatic intolerance as well as in the asymptomatic subjects and this was not associated with a drop in BP. During HUT, a significant HR increase was observed only in the subjects with orthostatic intolerance, which is in agreement with the report by Diehl (2005). He observed a significant difference in HR increase between POTS patients and controls after just one minute, but a continuous rise in HR, over a period of 10 minutes, only in POTS patients. The author suggested that this continuous increase in HR could be a consequence of increased blood pooling and capillary filtration, but given the absence of this difference during AST, a more detailed explanation has to be sought. In our study, the sensitivity of HR increase ≥30 bpm for orthostatic intolerance was low, while the specificity was high, and also similar between AST and HUT and between the 3rd and 9th minute of upright posture. So even though a continuous HR increase is found in POTS patients, the finding that appears to be specifically associated with postural tachycardia is that of a prominent HR increase as early as the first few minutes of upright posture. Overall, our results suggest that both active standing and passive tilting are appropriate for assessment of HR changes and that for basic orientation about the presence of postural tachycardia, a 3-minute bedside AST is adequate (Braune et al., 1999; Schondorf and Low, 1993).

Although 24-h ABPM has been used for evaluation of POTS (Mathias and Bannister, 2002; Hagen et al.,

Table V - Variables from 24-h ambulatory heart rate and blood pressure monitoring.

	Self-performed AST (n=43)	Mean HR standing – mean HR supine (n=43)	Nocturnal HR dip (n=43)	*AST in laboratory (for comparison)*
HR (bpm)	18.6 (12.69)	22.0 (10.13)	18.8 (7.09)	*19.8 (7.53)*
SBP (mmHg)	1.2 (6.70)	6.7 (7.38)	13.0 (11.35)*	*3.8 (15.23)*
DBP (mmHg)	11.6 (5.05)	10.6 (6.74)	12.4 (9.28)	*8.7 (11.79)*

Abbreviations: AST=difference between active standing and supine values during the active standing test; HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure.

* $p<0.05$ for comparison with 3-minute active standing test in the autonomic laboratory (continuous measurements).

2012), it has not been formally compared to other methods of assessment of orthostatic responses. The advantage of 24-h ABPM is that it offers several measurements taken at different times and in the patient's everyday environment. The disadvantages are that it requires a motivated and cooperative patient (14% of investigations in our study were discarded due to technical issues) and that the measurements are not supervised. Despite these shortcomings, our findings support the view that 24-h ABPM is useful for assessment of postural HR changes. Namely, HR changes during self-performed AST were similar to HR changes after 3 minutes of AST in the autonomic laboratory and HR increase ≥30 bpm during self-performed AST showed high specificity for orthostatic intolerance. The difference between all measurements taken supine and all measurements taken upright was on average similar to HR changes during AST, which thus suggests that this parameter can be used for assessment of postural HR changes. However, it is time-consuming for the patient and the physician and in an attempt to overcome this, we analyzed nocturnal dip in HR as a parameter that does not require the patient's active cooperation. The rationale behind this is that the majority of measurements during the day are taken either while standing or while seated and the day-night difference in HR therefore reflects not only circadian, but also postural HR variability. Indeed, nocturnal dip in HR was on average similar to HR changes during AST. It would be sensible to include self-performed AST in the 24-h ABPM protocol at least when orthostatic intolerance is suspected, but if ASTs are not performed, a very prominent nocturnal dip in HR should alert the interpreting physician to the possibility of postural tachycardia, which should then be confirmed by orthostatic tests. According to our results, self-performed AST is less reliable for assessment of orthostatic BP changes, so whether it may be used for detection of orthostatic hypotension remains to be clarified in further studies. Similarly, as in a recent report (Hagen et al., 2012), we did not repeat the findings of a study performed in children, which showed that circadian BP variability is attenuated in subjects with orthostatic intolerance (Chen et al., 2009).

One of the limitations of our study is the small number of patients fulfilling the criteria for POTS at the time of testing, in spite of the design of the study which aimed to ensure an adequate number of subjects with postural tachycardia. This is probably a consequence of imperfect reproducibility of postural HR increase and of the favorable prognosis of POTS – the majority of those with postural tachycardia on previous HUT failed to meet the ≥30 bpm criterion when tested in our study (Sandroni et al., 1999; Sousa et al., 2012). No patient was taking drugs for orthostatic intolerance, which on the one hand reflects conservative treatment decisions among patients and treating physicians in the local setting, but could also mean that only relatively mild cases of POTS were included in the study, which could have affected the results. Due to the small sample size, we could not compare hemodynamic responses in our POTS patients with the aforementioned findings of Braune et al. (1999) or Diehl (2005). However, this was not the primary aim of our study; our aim, instead, was to compare different tests with regard to their usefulness in everyday clinical practice. Although the heterogeneity of the study sample – we included orthostatic intolerant subjects, patients with syncope and subjects without orthostatic intolerance – may be viewed as a drawback when studying specific physiological responses, it also means that our sample better reflects the population on which the tested protocols will presumably be used. An important limitation of our study is that we did not attempt to reverse the order of testing. As shown in table II, baseline supine HR was higher prior to AST compared to HUT. The absolute difference was, however, small (3.5 bpm) and resting periods before both tests were similar and comparable to those used in other studies (Tanaka et al., 1996).

In conclusion, our results indicate that AST and HUT are comparable methods for evaluation of postural HR changes and that both 3 minutes and 9 minutes are appropriate orthostatic test durations. For basic assessment of postural tachycardia, single measurements are as specific as continuous monitoring, but for detailed insight into hemodynamic responses continuous HR and BP monitoring is needed. 24-h ABPM with self-performed AST is a useful test for the assessment of postural HR responses.

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