Postural tachycardia during head-up tilt test predicts persistent orthostatic intolerance in young adults

Posturalna tahikardija med testom z nagibno mizo je napovedni dejavnik ortostatske intolerance pri mlajših odraslih

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Ključne besede:
test z nagibno mizo, sindrom posturalne tahikardije, ortostatska intoleranca, sinkopa, nevrokardiogena sinkopa

Izvleček

Izhodišča: Testiranje z nagibno mizo (TNM) je pogosta preiskava pri retrogradnem ugotavljanju vzroka sinkope. Ker sta posturalna tahikardija in ortostatska intoleranca povezani, smo predpostavili, da bi spremembo srčne frekvence (SF) med testiranjem z nagibno mizo lahko uporabljali kot parameter, s pomočjo katerega bi pri posameznem bolniku lahko ocenili tveganje za ortostatsko intoleranco v prihodnosti.

Metode: V presečno raziskavo z osnovno kohorto (n = 73) in s potrditveno kohorto (n = 67) smo vključili zaporedne preiskovance, stare 18–40 let, ki so bili v našo ustanovo napoteni na TNM. Z njimi smo 9–12 mesecev po preiskavi opravili telefonski intervju o ortostatskih simptomih in morebitnih ponovnih sinkopah ter izsledke intervjuja primerjali z izidi TNM.

Rezultati: Ortostatsko intoleranco je v času intervjuja navedlo 52 (71 %) preiskovancev v osnovni kohorti in 41 preiskovancev (61 %) v potrditveni kohorti. Pozitivna napovedna vrednost (PNV) porasta SF ≥ 30 utripov/min je bila v potrditveni kohorti 0,88. V osnovni kohorti je imel tako stopnjo tahikardije le en bolnik. Kot meja porasta SF z visoko specifičnostjo za ortostatsko intoleranco se je v naši raziskavi izkazal porast ≥ 23 utripov/min s PNV 0,89 v osnovni in 0,87 v potrditveni kohorti. Izid TNM pa je imel PNV za ortostatsko intoleranco 0,84 oziroma 0,62. Porast SF in izid TNM sta imela nizko napovedno vrednost za ponovitev sinkope.

Zaključki: Posturalna tahikardija v prvih desetih minutah TNM je v populaciji mladih odraslih, napotenih na TNM, napovedni dejavnik za ortostatsko intoleranco neodvisno od izida testiranja.

Abstract

Background: Head-up tilt (HUT) test is an important tool in establishing the cause of past syncope. As postural tachycardia is associated with orthostatic intolerance, we hypothesise that heart rate (HR) increase during the early phase of HUT can be used as a surrogate test outcome to predict future orthostatic intolerance in an individual patient.

Methods: Patients aged 18 to 40 years who had undergone HUT test at our centre were included in the cross-sectional study. Telephone interviews about orthostatic symptoms and recurrent syncope were performed 9 to 12 months after HUT with 73 consecutive patients in the exploratory and 67 consecutive patients in the confirmatory cohort. Data from interviews were related to past HUT test results.

Results: Orthostatic intolerance was reported by 52 (71 %) patients in the exploratory and 41 (61 %) in the confirmatory cohort. Positive predictive value (PPV) of HR increase ≥ 30 bpm for orthostatic intolerance in confirmatory cohort was 0.88 (only one patient had this level of tachycardia in the exploratory cohort). HR increase ≥ 23 bpm was established as cut-off value with high specificity for orthostatic intolerance, its PPV was 0.89 in exploratory and 0.87 in confirmatory cohort. PPVs of HUT test outcome for orthostatic intolerance were 0.84 and 0.62, respectively. Both prominent HR increase and HUT test outcome had low PPV for recurrent syncope.

Conclusions: In young adults referred for HUT test postural tachycardia in the early phase of HUT predicts orthostatic intolerance a year after testing independently of test outcome.

Key words:
tilt table test, postural orthostatic tachycardia syndrome, orthostatic intolerance, syncope, neurally mediated syncope

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Introduction

Head-up tilt (HUT) as a stimulus of neurocardiogenic syncope is well established in diagnosing transient loss of consciousness.[1-3] Its sensitivity for past neurocardiogenic syncope is assessed to be in the range between 67 % and 83 %, specificity between 75 % and 100 % and reproducibility around 80 %.[1,4] These wide ranges partly depend on HUT test protocol–passive HUT, HUT using provocation with venepuncture, glyceryl trinitrate, isoproterenol or lower body negative pressure. Regardless of the protocol, prognostic value of HUT test outcome for syncope recurrence appears to be low and there are, to the best of our knowledge, no published data on prognostic value of the test for persistent orthostatic intolerance.[5,6] The latter is of interest in this context because it frequently overlaps with syncope and is therefore expected to be prevalent among patients referred for HUT test.[7,8]

Despite several attempts to replace HUT test with more comfortable and less time consuming procedures, it remains the most reliable and most commonly used tool in investigation of neurocardiogenic syncope.[9-13] The main test outcome is provocation of syncope/presyncope and comparison of provoked symptoms to those occurring during spontaneous events. In addition to syncope and hypotension, HUT test can provoke tachycardia. And because postural tachycardia is known to be associated with orthostatic intolerance, one can assume it could help to identify those patients who are likely to suffer from persistent orthostatic symptoms in the future.[8,14] If this assumption is confirmed, then heart rate (HR) changes during the early phase of HUT could be used as a surrogate test outcome, which would allow to predict further orthostatic events and would help guide patient care. In our present study, we tested the hypothesis that in patients referred for HUT test prominent HR increase during the early phase of HUT is a predictor of persistent orthostatic intolerance a year after testing.

Methods

In the cross-sectional study we analysed data from two cohorts of patients aged between 18 and 40 years who were referred for HUT test to the Centre for Autonomic Neurology at the Department of Neurology, University Medical Centre Ljubljana. The first, exploratory cohort, consisted of 147 consecutive patients evaluated between September 2008 and January 2009 and the second, confirmatory cohort, of 84 consecutive patients evaluated between July 2011 and September 2011. Data on past HUT were collected from test protocols, and information on orthostatic intolerance and syncope was obtained by a structured telephone interview conducted between 9 and 12 months after HUT test by an investigator with long-standing experience in the field of orthostatic intolerance and syncope. Consent was obtained from each participant prior to the interview. Patients with blood pressure (BP) fall greater than 20/10 mmHg within 10 min of HUT were excluded from statistical analysis to avoid compensatory tachycardia due to orthostatic hypotension as a confounding factor.[3] The study is part of a wider study on the predictive value of hemodynamic responses to upright posture, which was approved by the National Medical Ethics Committee of the Republic of Slovenia.

Head-up tilt test

Tests were performed between 8:00 and 14:00 in a quiet room. HUT test with pharmacological provocation with glyceryl trinitrate was used in all patients. The test consists of 5 min supine rest, followed by 25 min of passive 60° HUT, sublingual administration of 0.5 mg glyceryl trinitrate while tilted up and further 20 min of 60° HUT. Supine rest period commences when instrumentation has been completed and the patient is comfortably settled on the tilt table, usually between five and ten minutes after the patient has been lain down. An electronically driven tilt table with footplate support is used. During the test, beat-to-beat BP is measured using TaskForce monitor (CN Systems, Austria) and HR is recorded with a three channel ECG. In addition, single bra-

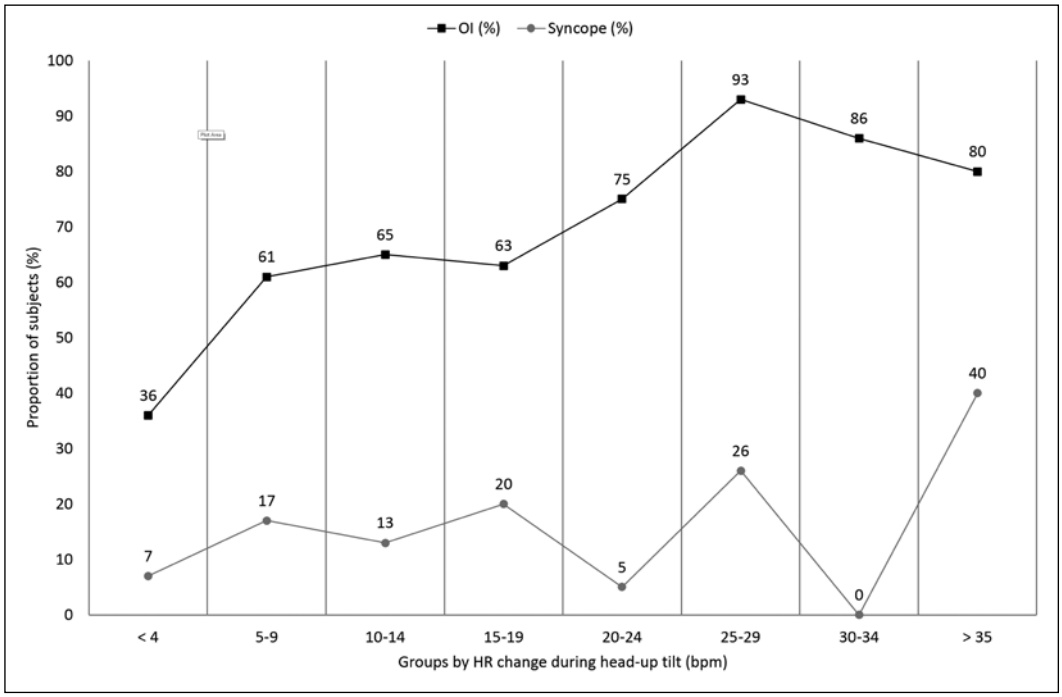

Figure 1: Proportion of participants with orthostatic intolerance and syncope regarding heart rate increase at 10 min of head-up tilt test. *HR = heart rate, OI = orthostatic intolerance*

chial sphygmomanometric measurements of BP and HR are taken every two minutes and recorded in the test protocol. A positive HUT test is defined as a fall in BP and/or HR below baseline values and accompanied by symptoms matching those of spontaneous syncopal or presyncopal episodes.

Interview

To avoid inter-rater variability, all interviews were performed by the same investigator who was blind for HUT test result at the time of interview. Interviews included open questions on any events with loss of consciousness and orthostatic intolerance and closed-type questions on specific symptoms (dizziness, blurring of vision, palpitations, vertigo, nausea, yawning during upright posture, headaches, fatigue and exercise intolerance). Subjects were requested to report only on symptoms during the last month before the interview, except for loss of consciousness for which they were asked to report on all events since the HUT test. For the purpose of this study, recurrent syncope was defined as transient loss of consciousness occurring during upright posture with preceding symptoms typical for cerebral hypoperfusion and without indications of cardiac syncope, epileptic seizures or preceding trauma. Ongoing orthostatic intolerance was defined as common, at least weekly, disturbing symptoms of cerebral hypoperfusion occurring only or predominantly during upright posture, both upon getting up and during prolonged standing. For example, occasional blurring of vision after standing up did not qualify for orthostatic intolerance nor did back ache and tiredness after half an hour of quiet standing.

Data processing and statistical analysis

In the study single measurements at 2-min intervals were used for BP and HR analyses. Average of the last two measurements during supine rest (corresponding to the last 5 min of supine rest) were taken as baseline values and were compared to single measurements in upright posture. Sensitivity and specificity of the postural HR increase $\geq$ 30 bpm (accepted diagnostic limit of the postural tachycardia syndrome–POTS[3]) in relation to persistent orthostatic intolerance were calculated. A receiver operating characteristic (ROC) diagram using R language for statistical computing [15] was constructed with HR increase as the test variable and persistent orthostatic intolerance as the state variable (Figure 1). Using the curve, cut-off HR increase with specificity above 90 % was determined. Then posi-

tive predictive values (PPV) and negative predictive values (NPV) of HUT test outcome and of postural HR increase for orthostatic intolerance nine to twelve months after testing were calculated and are presented as estimates with appropriate 95 % confidence intervals (CI). Predictive values were calculated for the 30 bpm postural HR increase and for the cut-off value with 90 % specificity for orthostatic intolerance in our sample (as described above). Each cohort was analysed separately except when stated otherwise. Independent t-test was used for comparisons of numeric variables and Pearson's chi-square test or Fisher's exact test for comparisons of proportions. P value below 0.05 was set as statistically significant. SPSS Statistics 17.0 software (2008) was used for statistical analyses.

Results

Exploratory and confirmatory cohort characteristics

In the exploratory cohort, 147 consecutive patients were called by telephone, of them 69 could not be contacted, three refused to participate, two were excluded due to orthostatic hypotension and 73 (50 %) participated in the study. In the confirmatory cohort, 84 patients were called, of them 17 could not be contacted and all remaining 67 (80 %) participated in the study. Characteristics of both cohorts together with frequencies of recurrent syncope and persistent orthostatic intolerance are shown in Table 1. Groups differed in baseline and upright systolic BP values, but not in demographic characteristics, average HR values, rates of positive HUT results, recurrent syncope or orthostatic intolerance.

Orthostatic responses

In pooled sample, orthostatic intolerance was reported at the time of interview by 82

Table 1: Characteristics of the exploratory and the confirmatory cohorts.

	Exploratory cohort (n = 73)	Confirmatory cohort (n = 67)	p
Age (years)	29.6 (6.5)	29.8 (6.1)	0.829
Female gender, n (%)	54 (74)	46 (69)	0.487
Referring diagnosis, n (%)			0.733
Syncope	53 (73)	52 (78)	
Presyncope, dizziness	12 (16)	8 (12)	
Other	8 (11)	7 (10)	
Baseline supine HR (bpm)	71.5 (9.7)	69.1 (12.8)	0.217
Baseline supine BP (mmHg)	123.4 / 70.5 (10.8 / 7.3)	112.9 / 71.5 (9.8 / 7.6)	0.001/0.410
HR in 10th min of HUT (bpm)	87.2 (11.9)	85.8 (15.4)	0.540
BP in 10th min of HUT (mmHg)	120.7 / 76.7 (10.7/ 7.6)	114.8 / 76.2 (12.2 / 9.6)	0.003/0.730
Positive HUT test, n (%)	37 (51)	44 (66)	0.073
Recurrent syncope, n (%)	13 (18)	9 (13)	0.477
Ongoing OI, n (%)	52 (71)	41 (61)	0.209

Data are expressed as mean (standard deviation), unless otherwise specified.
BP = blood pressure, HR = heart rate, HUT = head up tilt test, OI = orthostatic intolerance.

(60 %) subjects who completed 10 min of HUT, of them 29 and 10 patients had postural HR increase ≥ 23 bpm and ≥ 30 bpm, respectively. Among asymptomatic subjects, four had postural HR increase ≥ 23 bpm and two ≥ 30 bpm. Calculated from these data, postural HR increase ≥ 30 bpm had 96 % specificity and 11 % sensitivity for orthostatic intolerance. Area under the curve of the constructed ROC diagram was 0.67 (95 % CI 0.58, 0.77; p = 0.001). Although the area under the curve was relatively low, it still was considered relevant. The cut-off for postural HR increase with specificity for orthostatic intolerance above 0.90 was determined at 23 bpm, the sensitivity of this cut-off was 32 %.

HUT test was positive in 81 (58 %) subjects; in 61 (66 %) who reported ongoing orthostatic intolerance and in 20 (43 %) asymptomatic.

Predictive values of postural HR increase for orthostatic intolerance and recurrent syncope 9 to 12 months after the HUT test are presented in Table 2a, separately for each cohort. They reveal high PPV and low NPV of prominent postural HR increase for orthostatic intolerance. In the confirmatory cohort, PPV for orthostatic intolerance was similar for both levels of postural HR increase (p = 0.735); only one patient with postural HR increase ≥ 30 bpm precluded such comparison in the exploratory cohort. HUT test outcome had high PPV for orthostatic intolerance in the exploratory cohort; in the confirmatory cohort the PPV was lower, but the difference between values was not statistically significant (p = 0.105, Table 2b). In both cohorts, HUT test outcome and postural HR increase had high NPV and low PPV for recurrent syncope (Table 2b).

We also compared predictive values between genders. Altogether, average (standard deviation) postural HR increase was 15.1 (8.7) bpm in women and 18.8 (11.4) bpm in men (p = 0.046), orthostatic intolerance was reported by 69 (69 %) women and 24 (60 %) men (p = 0.308). Data on patients with prominent postural HR increase by gender are presented in Table 3. PPV of postural tachycardia for orthostatic intolerance

Table 2: Positive and negative predictive values of (a) heart rate increase in the first 10 min of head-up tilt test and (b) head-up tilt test results for recurrent syncope and persistent orthostatic intolerance.

(a)

Parameter / Cohort		ΔHR ≥ 30 bpm		ΔHR ≥ 23 bpm	
		Exploratory	Confirmatory	Exploratory	Confirmatory
Recurrent syncope	PPV [95 % CI]	*	0.18 [0.02, 0.52]	0.17 [0.04, 0.41]	0.20 [0.04, 0.48]
	NPV [95 % CI]	*	0.88 [0.77, 0.96]	0.82 [0.69, 0.91]	0.90 [0.78, 0.97]
Orthostatic intolerance	PPV [95 % CI]	*	0.82 [0.48, 0.98]	0.89 [0.65. 0.98]	0.87 [0.60, 0.98]
	NPV [95 % CI]	*	0.41 [0.28, 0.55]	0.35 [0.23, 0.49]	0.44 [0.30, 0.59]

(b)

Parameter / Cohort		Head-up tilt test outcome	
		Exploratory	Confirmatory
Recurrent syncope	PPV [95 % CI]	0.30 [0.16, 0.47]	0.14 [0.05, 0.27]
	NPV [95 % CI]	0.94 [0.81, 0.99]	0.87 [0.66, 0.97]
Orthostatic intolerance	PPV [95 % CI]	0.84 [0.68, 0.94]	0.68 [0.52, 0.81]
	NPV [95 % CI]	0.42 [0.25, 0.59]	0.52 [0.31, 0.73]

CI = confidence interval, HR = heart rate, NPV = negative predictive value, PPV = positive predictive value, ΔHR = heart rate increase.
** No values are given for heart rate rise ≥ 30 bpm in the exploratory cohort because only one patient had heart rate increase above this value.*

appeared higher in women, but the frequencies in individual subgroups were low and the difference in PPV between men and women did not reach statistical significance.

In pooled results of both cohorts the proportion of subjects with orthostatic intolerance appeared to rise with larger postural HR increase during HUT (Figure 1). The same pattern was not clear for syncope recurrence (Figure 2). When HUT test outcome and postural HR increase ≥ 23 bpm were combined, 18 (90 %) subjects in whom both parameters were positive experienced persistent orthostatic symptoms and 4 (20 %) reported recurrent syncope (pooled data). In those in whom both parameters were negative, 21 (46 %) reported orthostatic symptoms and 3 (7 %) reported recurrent syncope.

Symptom profile

All analyses of symptom frequency were done with pooled data from both cohorts. Among patients with orthostatic intolerance (n = 93), upright-posture associated dizziness was reported by 85 (91 %), blurring of vision or positive visual phenomena by 77 (83 %), palpitations by 29 (31 %), vertigo by 35 (38 %), nausea by 54 (58 %) and yawning by 49 (53 %). All three evaluated non-orthostatic symptoms were more common among orthostatic intolerant subjects. The absolute difference in symptom frequency was biggest and the p value lowest for fatigue, which was reported by 55 (59 %) of those with orthostatic intolerance and by 8 (17 %) asymptomatic subjects ($p < 0.001$). Differences in proportions of those with frequent headaches (59 % and 36 %) and with exercise intolerance (33 % and 15 %) were statistically significant ($p < 0.05$), but less prominent. We also compared the frequencies of individual symptoms in those with HR rise above and below 30 bpm and HR rise above and below 23 bpm, but no significant differences were found ($p > 0.05$ for all tested symptoms).

Discussion

To the best of our knowledge, this is the first study examining the hypothesis that in young adults referred for HUT test prominent postural HR increase during the early phase of HUT can be a predictor of persistent orthostatic intolerance a year after testing. We found that both postural HR increase ≥ 30 bpm, a standard diagnostic criterion for POTS, and postural HR increase ≥ 23 bpm, a cut-off value with 90 % specificity for orthostatic intolerance in our study, had high PPV for persistent orthostatic intolerance; this was consistent in two separate patient cohorts (Table 2). The association of postural HR increase with orthostatic intolerance was further supported by the steady increase in specificity with rising HR change in the ROC curve and by higher prevalence of orthostatic intolerance among individuals with higher postural HR increase (Figure 1). However, both examined limits of postural HR increase had low sensitivity and this was consciously accepted because the focus of

Table 3: Positive predictive values of heart rate increase for orthostatic intolerance by gender.

	Exploratory cohort			Confirmatory cohort		
	n	OI	PPV for OI [95 % CI]	n	OI	PPV for OI [95 % CI]
Men	18	13		19	11	
ΔHR ≥ 30 bpm	0	0	*n.a.*	8	6	0.75 [0.35, 0.97]
ΔHR ≥ 23 bpm	5	4	0.80 [0.28, 0.99]	9	7	0.78 [0.40, 0.97]
Women	54	38		46	31	
ΔHR ≥ 30 bpm	1	1	1.00 [0.03, 1.00]	3	3	1.00 [0.29, 1.00]
ΔHR ≥ 23 bpm	13	12	0.92 [0.64, 1.00]	6	6	1.00 [0.54, 1.00]

CI = confidence interval, ΔHR = heart rate increase, n.a. = not applicable, OI = number of subjects with orthostatic intolerance, PPV = positive predictive value.

the study was to search for the limit of postural HR increase that would be specifically associated with orthostatic intolerance, to avoid too many false positives.

The outcome of HUT had a similar PPV for orthostatic intolerance as prominent postural HR increase, but was less consistent between cohorts (Table 2). The outcome of HUT in terms of syncope provocation is, according to our results, a less reliable predictor of orthostatic intolerance than HR increase. This is consistent with the view that orthostatic tachycardia can reflect profound activation of compensatory mechanisms countering central hypovolemia and so indicates diminished hemodynamic reserve for upright posture which can lead to orthostatic intolerance.[16-18] Neurocardiogenic syncope, on the other hand, is a one-off reflex event which does occur in patients with POTS and other forms of orthostatic intolerance, but is by no means limited to them.[8,14,19]

Taken together, our observations suggest that HR change during early HUT can be used as additional information that alerts the interpreting physician to the high probability of persistent orthostatic symptoms independently of HUT test outcome. Notably, the probability of orthostatic intolerance is high already at postural HR increase ≥ 23 bpm (i.e. below the standard 30 bpm criterion for POTS). Such patients can, of course, not be diagnosed with POTS and their postural HR increase is within limits considered normal in healthy population.[20-22] But within a population with high prevalence of orthostatic intolerance, such as those referred for HUT test, it should be recognised that also patients not reaching the diagnostic limit of POTS are prone to orthostatic complaints.

Regarding syncope recurrence, low PPV of HUT test outcome is in accordance with previous reports.[5,6] The negative predictive value of HUT outcome for syncope recurrence was high, but the recurrence rate was low also in subjects with a positive test (Table 2). Therefore, while a negative HUT test makes a new episode of neurocardiogenic syncope within one year very unlikely – especially in combination with absence of prominent postural HR increase – not much can be deduced about risk for syncope in the event of a positive test.

We observed a trend that HR rise had relatively higher PPV for orthostatic intolerance in women, despite similar relative frequency of orthostatic intolerance between genders. In our study, the proportion of subjects with HR rise ≥ 23 bpm (and ≥ 30 bpm) was higher in men, which is in accordance with another observation.[20] This could imply that postural tachycardia is not causally related to orthostatic intolerance or that women have lower threshold for orthostatic symptoms caused by postural tachycardia; this is a topic that warrants further studies.

Orthostatic and non-orthostatic symptoms

The profile of orthostatic symptoms in our study was in line with reports of others.[23,24] All three analysed non-orthostatic symptoms were significantly more common in orthostatic intolerant subjects. The association with orthostatic intolerance seems to be especially strong for fatigue which is in accordance with a previous report.[25] We did not find a significant difference in any symptom frequency between those with HR increase above or below 30 bpm nor above or below 23 bpm, suggesting these symptoms are not directly related to tachycardia.

Limitations of the study

We included only crude parameters, such as positive/negative HUT outcome and HR increase at 10 min of HUT calculated from single measurements, because we sought for a measure that could be used across a wide range of autonomic laboratories. Information on anthropometric parameters, medications, physical fitness, hydration state, activity prior to HUT test etc. was not included in the analysis because the study aimed to reproduce everyday clinical practice where these parameters are usually not tightly monitored. Besides, such data cannot be reliably collected in retrospective. An important variable, which was not controlled for, was treatment of orthostatic intolerance after the HUT test. However, falsely posi-

tive results, which are the major concern when aiming for high specificity, would be produced if those with lower postural HR increase or a negative HUT test outcome received treatment more often than those with higher postural HR increase or a positive test and this is in our opinion extremely unlikely.

Age limit between 18 and 40 years was selected as the typical age range in POTS and orthostatic intolerance and because young adults have few cardiovascular and other chronic diseases which could confound the results.[7,8] Lower age limit was set because of ethical considerations in under aged subjects. Telephone interviews were considered an appropriate method in the selected age group, while we would be more cautious to use it in elderly populations more prone to cognitive and hearing impairment and less easily available through cell phones. The practically universal usage of cell phone numbers given as contact information, which was slightly less present in 2008, is in our opinion also the cause for fewer non-contactable patients in the confirmatory cohort. There was a difference in baseline systolic BP between cohorts, but as BP values were not significantly associated with HUT test outcome, recurrence of syncope or orthostatic intolerance, we consider this difference not to be of vital importance. Only a limited set of symptoms was evaluated, but symptom description was not the primary focus of this study and served predominantly to distinguish orthostatic intolerance and syncope from other conditions.

Conclusions

Postural HR increase during the early phase of HUT is a predictor of orthostatic intolerance independently of test outcome in the population of adults below 40 years of age referred for HUT test. Moreover, even prominent postural HR increase below the threshold of POTS is associated with persistent orthostatic intolerance a year after HUT test and this group should receive appropriate counselling. Both HUT test outcome and postural HR increase during HUT are poor prognostic factors for recurrent syncope.

The authors declare that they have no conflict of interest.

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List of abbreviations

BP	blood pressure
bpm	beats per minute
CI	confidence intervals
HR	heart rate
OI	orthostatic intolerance
NPV	negative predictive value
POTS	postural tachycardia syndrome
PPV	positive predictive value
ROC	receiver operating characteristic

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