openheart

Syndromes of orthostatic intolerance and syncope in young adults

Viktor Hamrefors,[1,2,3] Jasmina Medic Spahic,[1,3] David Nilsson,[1] Martin Senneby,[1,2] Richard Sutton,[4] Olle Melander,[1,3] Artur Fedorowski[1,5]

To cite: Hamrefors V, Spahic JM, Nilsson D, *et al*. Syndromes of orthostatic intolerance and syncope in young adults. *Open Heart* 2017;**4**:e000585. doi:10.1136/openhrt-2016-000585

Received 14 December 2016
Revised 15 February 2017
Accepted 29 March 2017

[1]Department of Clinical Sciences, Lund University, Malmö, Sweden
[2]Department of Medical Imaging and Physiology, Skåne University Hospital, Malmö, Sweden
[3]Department of Internal Medicine, Skåne University Hospital, Malmö, Sweden
[4]National Heart and Lung Institute, Imperial College, Hammersmith Hospital Campus, London, UK
[5]Department of Cardiology, Skåne University Hospital, Malmö, Sweden

Correspondence to
Dr Viktor Hamrefors; viktor.hamrefors@med.lu.se

ABSTRACT

Objective To explore the clinical and neuroendocrine characteristics of syndromes of orthostatic intolerance and syncope in young adults.

Methods Two hundred and thirty-six patients aged 18–40 years with orthostatic intolerance and/or syncope were examined by head-up tilt test (HUT). Plasma levels of epinephrine, norepinephrine, renin, C-terminal-pro-arginine-vasopressin (CT-proAVP), C-terminal-endothelin-1 and mid-regional-fragment of pro-atrial-natriuretic-peptide (MR-proANP) were analysed. Patients' history, haemodynamic parameters and plasma biomarkers were related to main diagnoses such as vasovagal syncope (VVS), postural tachycardia syndrome (POTS), orthostatic hypotension (OH) and negative HUT.

Results No self-reported symptom of orthostatic intolerance was highly specific for any diagnosis. Patients with VVS (n=103) were more likely to be men (p=0.011) and had lower resting heart rate (HR; 66±11) compared with POTS (73±11; n=72; p=0.001) and negative HUT (74±11; n=39; p=0.001). Patients with POTS demonstrated greater rise in norepinephrine (p=0.008) and CT-proAVP (p=0.033) on standing compared with negative HUT, and lower resting MR-proANP compared with VVS (p=0.04) and OH (p=0.03). Patients with OH had lower resting renin (p=0.03). Subjects with a resting HR <70 and MR-proANP >45 pm/L had an OR of 3.99 (95 % CI 1.68 to 9.52; p=0.002) for VVS compared with subjects without any of these criteria; if male sex was added the OR was 21.8 (95% CI 3.99 to 119; p<0.001).

Conclusions Syndromes of orthostatic intolerance and syncope share many characteristics in younger persons. However, patients with VVS are more likely to be men, have lower HR and higher MR-proANP at rest compared with POTS, which might be taken into account at an early stage of evaluation.

INTRODUCTION

Syncope, a common clinical problem affecting between 30% and 40% of all humans during their lifetime,[1] is clearly dominated by reflex aetiology in the first four decades of life.[2] The vasovagal reflex, by far the most common mechanism of loss of consciousness, is frequently related to orthostatic intolerance.[3 4] Within syndromes of orthostatic intolerance, three distinct syncope-related conditions are traditionally defined on the grounds of haemodynamic response to orthostatic challenge: orthostatic hypotension (OH),[5] postural tachycardia syndrome (POTS)[6] and orthostatic (vasovagal) reflex syncope, the latter showing no haemodynamic signs of the two former conditions during the presyncopal phase.[3] While POTS is a condition typically observed in younger patients, especially women,[6] the prevalence of OH in the younger population is <5% and increases with advancing age.[5]

The treatment of reflex syncope and orthostatic intolerance poses a challenge for clinicians, especially when symptoms are frequent and pronounced.[3 4] Recent reports have suggested that syndromes of orthostatic intolerance may have antiadrenergic autoimmune background[7 8] and that they demonstrate different neuroendocrine patterns,[9 10] especially in children.[11] In particular, abnormalities in resting and orthostatic levels of catecholamines, vasopressin, renin-angiotensin system, endothelin and natriuretic peptides were detected, however, with partially contradicting results in regard to vasopressin in VVS versus OH.[11 12] Consequently, there is a need for more data to define typical clinical and neuroendocrine features of the main syncope-related syndromes of orthostatic intolerance in younger populations, both as a possible diagnostic tool and therapeutic guide.

In the present study, we determined patients' history, haemodynamic parameters and neuroendocrine biomarkers in a consecutive series of young adults (aged 18–40 years) who were investigated for suspected syncope and/or orthostatic intolerance with a standardised head-up tilt test (HUT).

METHODS

Study population

The Syncope Study of Unselected Population in Malmö cohort has been previously described.[9] In brief, 836 consecutive patients with unexplained syncope and/or symptoms of orthostatic intolerance were

KEY QUESTIONS

What is already known about this subject?

Syncope and orthostatic intolerance are common clinical problems. The vasovagal reflex, the most common mechanism of loss of consciousness in young adults, is frequently related to orthostatic intolerance. Within syndromes of orthostatic intolerance, three distinct syncope-related conditions are traditionally defined: orthostatic hypotension, postural tachycardia syndrome and orthostatic (vasovagal) reflex syncope, the latter showing no haemodynamic signs of the two former conditions during the presyncopal phase. The treatment of reflex syncope and orthostatic intolerance in young adults poses a clinical challenge, especially when symptoms are severe. Since the treatment strategies for common diagnoses of orthostatic intolerance may differ, an accurate diagnosis is essential in order to alleviate symptoms and prevent syncope recurrence.

What does this study add?

In this study, young patients with unexplained syncope and/or orthostatic intolerance were investigated with head-up tilt testing non-invasive beat-to-beat monitoring in specialised syncope unit. Surprisingly, none of the clinical features reported by the patients, such as palpitations or prodromal symptoms of syncope, was highly specific for any diagnosis. Furthermore, this study demonstrates that patients diagnosed with vasovagal syncope and postural tachycardia syndrome are different regarding sex (higher proportion of men among the patients with vasovagal syncope) and seem to show opposite patterns of both haemodynamic factors (resting heart rate lower among patients with vasovagal syncope) and neuroendocrine markers (resting mid-regional-fragment of pro-atrial-natriuretic-peptide (MR-proANP) lower in postural tachycardia syndrome.

How might this impact on clinical practice?

When diagnosing syncope and orthostatic intolerance, the uncertainty of the final diagnosis if based on patient's history must be accepted with caution. While it has been shown that a level of accuracy when an expert takes history is very high, this study emphasises the utility of head-up tilt testing with non-invasive beat-to-beat monitoring as a method of diagnosis in unexplained syncope, especially in the absence of a syncope expert. The study also suggests that sex, resting heart rate and MR-proANP, the latter easily assessed through commercially available test kits, may be valuable as additional tools in the initial evaluation of young patients with unexplained syncope.

referred to and investigated at the Syncope Unit of Skåne University Hospital between August 2008 and October 2013. Of these, we identified 671 patients who underwent HUT according to the Italian protocol[13] and accepted serial blood sampling during the test. For the current study, we selected participants aged 18–40 years, yielding a series of 236 eligible patients (figure 1). These patients were managed post-test according to the current European Society of Cardiology syncope guidelines.[3]

Examination protocol

The patients were asked to take their regular medication and fast for 2 hours before HUT, although they were allowed to drink water ad libitum. Prior to examination, the patients were asked to fill a questionnaire, which explored past medical history, as well as duration, frequency and features of syncope-related symptoms. Time from the first-ever syncope to examination <6 months was assigned symptom duration equal to 0 years in the database and the values were rounded up to 1 year.

The HUT protocol included peripheral vein cannulation, supine rest for 10 min, blood sampling both at supine rest and in the upright position 3 min after elevation of the table at an angle of 60–70° and optional nitroglycerin provocation according to the Italian protocol.[13] Nitroglycerin (400 µg spray sublingually) was administrated first after 20 min of passive HUT if syncope had not occurred and the haemodynamic parameters were stable , that is, no significant hypotension (systolic blood pressure (SBP) <90 mm Hg) or orthostatic intolerance due to sinus tachycardia >120 beats per minute (bpm) were observed. Thus, this nitroglycerin phase played no part in any of the neuroendocrine measurements, but contributed to the ultimate diagnosis of VVS. Beat-to-beat blood pressure (BP) and ECG were recorded using a non-invasive validated method (Nexfin monitor, BMEYE, Amsterdam, The Netherlands),[14] and subsequently analysed offline using dedicated software provided by the manufacturer. Mean BP and heart rate (HR) in supine position, after 3 min of HUT, and at the lowest BP/highest HR during passive orthostasis were calculated as an average of a 30 s period. The predefined point for the second haemodynamic assessment and blood sampling assigned to 3 min of HUT was selected to comply with the time point when postural haemodynamic stability is usually achieved in normal individuals.[15]

The third assessment of the haemodynamic parameters between 3 and 20 min of HUT, corresponding to lowest SBP/highest HR prior to either activation of vasovagal reflex and/or syncope or end of the passive HUT, was intended to identify those with delayed haemodynamic instability, that is, if significant haemodynamic changes were observed beyond the first 3 min of HUT. The onset of vasovagal reflex was identified by typical prodrome and/or an abrupt change in haemodynamic parameters such as bradycardia and/or pronounced hypotension.

VVS was defined as a reproduction of syncope associated with a characteristic pattern of pronounced hypotension, bradycardia or asystole. For the current study, patients were classified as VVS only if they had no signs of POTS or OH during the test. OH was defined as a sustained decrease in SBP ≥20 mm Hg and/or decrease in diastolic BP (DBP) ≥10 mm Hg, while POTS as reproduction of symptoms of orthostatic intolerance (lightheadedness, dizziness or discomfort) with HR increase >30/min or tachycardia >120/min during HUT.[3]

The Regional Ethical Review Board in Lund, Sweden accepted the study protocol (ref no 82/2008), and all study participants gave their written informed consent.

Neuroendocrine biomarkers

As neuropeptides, in particular atrial natriuretic peptide, endothelin-1 and vasopressin, are characterised by

Table 1 Patient characteristics

	All (n=236)	No Dx (n=39)	VVS (n=103)	p Value*	POTS (n=72)	p Value*	OH (n=22)	p Value*	p Value†
Age, years	28.1 (6.7)	30.2 (6.3)	28.2 (6.8)	0.335	26.6 (6.4)	**0.030**	28.2 (6.7)	0.632	0.053
Sex, % male	32.6	38.5	41.7	–	20.8	–	18.2	–	**0.011**
BMI, kg/m^2	23.7 (3.9)	24.7 (4.9)	24.0 (3.5)	0.785	22.8 (3.4)	0.074	23.9 (4.8)	0.852	0.076
Symptoms reported by the patients									
Duration of symptoms, years, (median, (IQR))	3 (9)	4 (8)	5 (10)	0.698	3 (9)	0.998	2.5 (5)	0.813	0.247
Total no of syncope (median, (IQR))	5 (18)	5 (22)	5 (7)	0.734	5 (28)	1.000	9 (18)	0.979	0.266
Prodrome (nausea, perspiration, etc), %	72.4	65.5	77.6	–	65.0	–	88.9	–	0.128
Palpitations, %	39.1	51.7	32.8	–	31.7	–	66.7	–	**0.017**
Traumatic fall, %	55.1	53.8	52.0	–	60.6	–	54.5	–	0.731
Dizziness on standing, %	73.2	82.1	61.2	–	81.7	–	86.4	–	**0.003**

Values displayed as mean (SD) if not otherwise stated.
*p Value for Tukey's or Games-Howell post hoc test in relation to no Dx (reference group) for continuous variables.
†ANOVA or Welch test p value for continuous variables and Pearson's χ^2 p value for dichotomous variables.
ANOVA, analysis of variance; no Dx, no diagnosis; OH, orthostatic hypotension; POTS, postural tachycardia syndrome; VVS, vasovagal syncope. The use of medications in the study population was generally very low. Blood pressure-increasing medication was used in seven patients (one negative HUT, two VVS, three POTS, one OH). β-Blockers were used by two patients (both POTS); calcium antagonists was used in one patient (VVS) as were angiotensin receptor blockers (VVS), levothyroxine was used by two patients (POTS; OH) and anti-EP medications were used by four patients (two negative HUT, one POTS, one OH). Antidepressants in the form of selective serotonin-reuptake inhibitors were used by 14 patients (3 negative HUT, 5 VVS, 2 POTS, 4 OH) and other antidepressants were used by two patients (both POTS). Symptomatic drugs including sedatives, analgetics and sleep agents were used in no more than five patients for each class of drugs. No patient used antidiabetic medication, platelet inhibitors, oral anticoagulants, diuretics, ACE-inhibitors, α-blockers, long-acting nitroglycerine, lipid-lowering drugs, digoxin, opiates, anti-Parkinson medication or cytostatics.

a short half-life of a few minutes, we applied newly developed laboratory assays to detect their stable fragments, thus allowing better estimation of neurohormone biosynthesis. Blood samples collected in the supine position before HUT and at 3 min of HUT were used for determination of epinephrine, norepinephrine, renin, C-terminal-pro-arginine-vasopressin (CT-proAVP), C-terminal-endothelin-1 (CT-proET-1) and

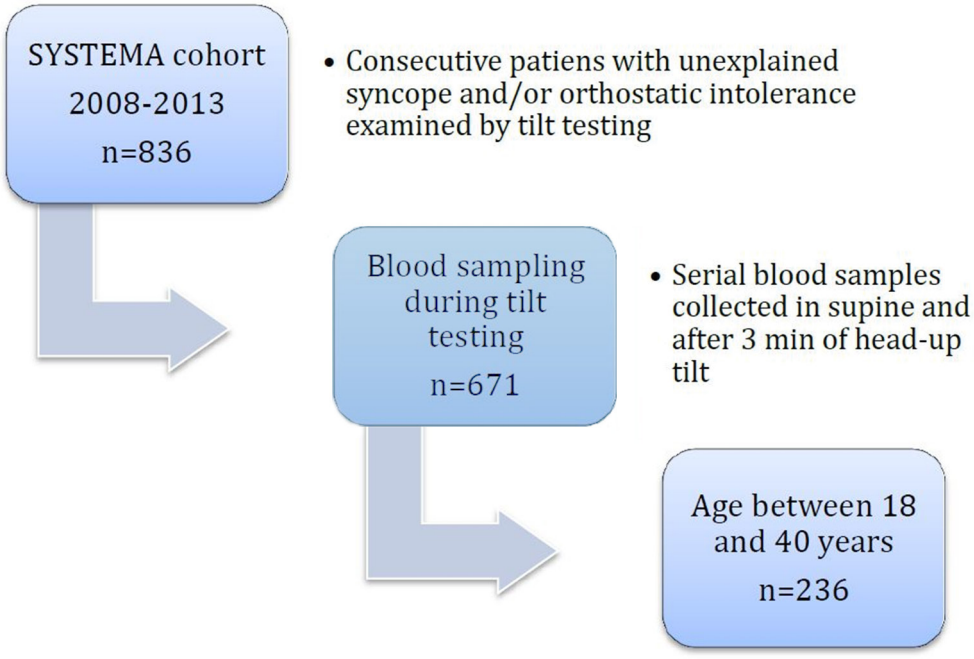

Figure 1 Flow chart of patient selection. The selection of patients for the current study. SYSTEMA, Syncope Study of Unselected Population in Malmö.

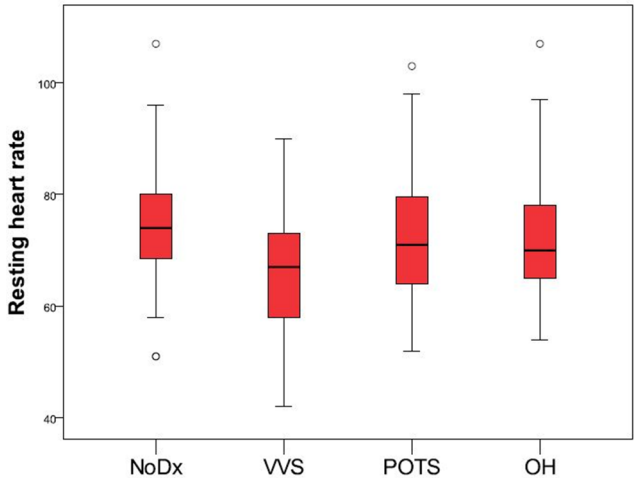

Figure 2 Resting heart rate according to diagnosis. Resting heart rate stratified according to final diagnosis at head-up tilt test. NoDx, no diagnosis; VVS, vasovagal syncope; POTS, postural tachycardia syndrome; OH, orthostatic hypotension.

mid-regional-fragment of pro-atrial-natriuretic-peptide (MR-proANP). The total amount of blood drawn for the analyses was 60 mL (30+30 mL), and no fluid substitution was given. Plasma biomarkers were measured from blood samples (16×250 µL aliquots of EDTA plasma in plastic thermotubes) that had been frozen at −80°C after collection.

CT-proAVP, CT-proET-1 and MR-proANP were measured using the assays provided by the manufacturer: Thermo Fisher Scientific BRAHMS CT-proAVP KRYPTOR, Thermo Fisher Scientific BRAHMS CT-proET-1 KRYPTOR and Thermo Fisher Scientific BRAHMS MR-proANP KRYPTOR (BRAHMS GmbH, part of Thermo Fisher Scientific, 16761 Hennigsdorf, Germany). Concentrations of epinephrine and norepinephrine were determined by high-performance liquid chromatography with fluorescence detection.[16] Plasma renin concentrations were analysed using an immunoradiometric assay (Renin III Generation; Cisbio Bioassays International, 30200 Codolet, France).

Statistics

One-way analysis of variance (ANOVA) with Tukey's post hoc test was used to determine the difference in baseline characteristics, haemodynamic parameters and neuroendocrine biomarkers between the patients with negative HUT and those diagnosed with VVS, POTS or OH, respectively, or between the diagnostic groups, if appropriate. If the assumption of homogeneity of variances was violated (indicated by Levene's test $p<0.05$), a Welch test with Games Howell post hoc was run instead. For dichotomous variables, Pearson's χ^2 test was used. Any continuous variables with skew deviation were log-transformed in the statistical analyses. When appropriate, significant findings from the χ^2, ANOVA and Welch models were further explored by testing the relation between those variables and diagnosis in logistic regression models yielding OR with 95% CI. All analyses were performed using IBM SPSS Statistics V.23 (SPSS, Chicago, Illinois, USA). All tests were two-sided, whereby $p<0.05$ was considered to be statistically significant.

RESULTS

Study population characteristics

The proportions of final diagnoses and patients' characteristics are displayed in table 1. There was a predominance of females. The median duration of syncope-related symptoms was 3 years with no difference between the diagnostic groups. Patients diagnosed with POTS were more often female and younger compared with patients with negative HUT. In contrast, the proportion of male subjects was highest among patients diagnosed with VVS. Moreover and somewhat surprisingly, patients with POTS tended to report palpitations

Table 2 Haemodynamic parameters at rest and during HUT

	All (n=236)	No Dx ref (n=39)	VVS (n=103)	p Value*	POTS (n=72)	p Value*	OH (n=22)	p Value*	p Value†
SBP rest	121.6 (13.0)	122.9 (13.3)	120.0 (12.2)	0.660	123.0 (12.4)	1.00	121.7 (17.6)	0.987	0.437
DBP rest	70.7 (7.6)	73.2 (7.8)	69.3 (6.8)	**0.034**	71.5 (7.6)	0.671	70.0 (9.9)	0.378	**0.035**
HR rest	69.9 (11.8)	74.2 (10.9)	66.0 (11.3)	**0.001**	72.5 (11.0)	0.880	71.6 (13.1)	0.818	**<0.001**
SBP 3'	122.1 (16.0)	128.7 (14.9)	121.5 (13.8)	0.068	122.6 (15.4)	0.192	111.0 (22.7)	**<0.001**	**<0.001**
DBP 3'	77.3 (10.8)	81.1 (11.5)	76.6 (9.2)	0.096	78.7 (10.0)	0.648	68.6 (14.1)	**<0.001**	**<0.001**
HR 3'	86.7 (15.5)	82.6 (11.6)	79.6 (11.9)	0.600	99.9 (13.6)	**<0.001**	83.1 (15.2)	0.999	**<0.001**
SBP min	108.7 (15.3)	116.1 (11.5)	110.1 (12.3)	0.111	107.7 (16.8)	**0.015**	91.8 (16.4)	**<0.001**	**<0.001**
DBP min	70.8 (10.8)	75.1 (9.6)	71.0 (9.2)	0.125	72.0 (10.8)	0.418	58.0 (10.8)	**<0.001**	**<0.001**
HR max	93.3 (18.2)	85.8 (14.9)	84.1 (12.8)	0.920	111.0 (14.6)	**<0.001**	91.5 (13.6)	0.404	**<0.001**

Displayed as mean (SD).
*p Value for Tukey's or Games-Howell post hoc test in relation to no Dx (reference group) for continuous variables.
†ANOVA or Welch test p value for continuous variables and Pearson's χ^2 p value for dichotomous variables.
ANOVA, analysis of variance; DBP, diastolic blood pressure; HR, heart rate; HUT, head-up tilt test; no Dx, no diagnosis; OH, orthostatic hypotension; POTS, postural tachycardia syndrome; SBP, systolic blood pressure; VVS, vasovagal syncope.

to a less extent than patients with negative HUT, whereas the proportion of patients reporting palpitations were similar among the VVS and POTS groups. Orthostatic dizziness was less common among patients with VVS, even though it was not very specific for any diagnosis (table 1). In the group who tolerated tilt testing without significant haemodynamic changes (negative HUT), five patients demonstrated psychogenic pseudosyncope, and four other patients were subsequently monitored with implantable loop recorder without diagnostic findings, that is, no syncope during monitoring or fainting episodes recorded with normal heart rhythm only. Patients with psychogenic pseudosyncope did not significantly differ in haemodynamic parameters and biomarkers from the rest of HUT-negative patients.

Haemodynamic parameters

At rest, patients with VVS showed significantly lower HR compared with negative HUT (table 2, figure 2), and with POTS (p=0.001). In agreement with the predefined diagnostic criteria, the small number of patients with OH showed significantly lower SBP and DBP during HUT, whereas those with POTS showed higher HR during HUT (table 2), both at 3 min of HUT and at the point of lowest BP.

Neuroendocrine biomarkers

Patients with POTS showed a significantly higher rise in norepinephrine at 3 min of HUT (table 3) and had lower resting MR-proANP in relation to VVS (p=0.039) and OH (p=0.030), but not to negative HUT (p=0.96). Patients with POTS also had a greater increase in CT-proAVP compared with negative HUT (table 3) but not VVS (p=0.768) or OH (p=0.693). Patients with OH also had lower resting renin level compared with negative HUT (p=0.030). There were no other significant differences between patients with negative HUT and those with VVS, POTS or OH, respectively (table 3). Furthermore, resting MR-proANP was inversely related to resting HR in a linear model (p=0.009).

Multivariable models for diagnosis

Based on our findings of variables associated with VVS in the study population, we constructed a 'VVS score' including sex (male), resting HR (<study population median of 70 bpm) and resting MR-proANP levels (>study population median of 45 pm/L). The score was then related to a diagnosis of VVS (compared with any other diagnosis, including negative HUT) in a logistic regression model, with age as a covariate. Subjects that had all of the three characteristics male sex, resting

Table 3 Neuroendocrine biomarkers at rest (0') and at 3 min head-up tilt (3')

	All (n=163–187)	No Dx ref (n=24–30)	VVS (n=79–87)	p Value*	POTS (n=44–55)	p Value*	OH (n=16–17)	p Value†	
P-renin 0'	15.0 (13)	17.0 (12)	15.5 (12)	0.573	14.0 (14)	0.550	10.5 (38)	**0.030**	0.054
P-renin 3'	15.5 (13)	16.5 (15)	16.0 (14)	0.816	15.0 (13)	0.658	10.0 (9)	0.074	0.106
ΔRenin	0.0 (2.0)	0.0 (2.5)	0.0 (3.0)	0.369	0.0 (2.0)	0.993	0.0 (1.5)	0.995	0.101
P-epinephrine 0'	0.10 (0.1)	0.09 (0.1)	0.10 (0.1)	0.999	0.085 (0.1)	0.998	0.10 (0.2)	0.976	0.937
P-epinephrine 3'	0.19 (0.2)	0.17 (0.2)	0.21 (0.2)	0.846	0.18 (0.2)	0.825	0.14 (0.2)	0.932	0.457
ΔEpinephrine	0.07 (0.13)	0.06 (0.09)	0.09 (0.2)	0.690	0.07 (0.1)	0.628	0.04 (0.11)	1.00	0.452
P-NE 0'	1.40 (0.9)	1.70 (1.0)	1.30 (0.8)	0.071	1.48 (0.9)	0.137	1.30 (0.6)	0.524	0.097
P-NE 3'	2.40 (1.4)	2.45 (1.4)	2.30 (0.9)	0.513	2.90 (1.5)	0.744	2.00 (1.1)	0.744	**0.018**
ΔNE	1.00 (0.7)	0.85 (0.5)	0.90 (0.5)	0.733	1.40 (1.2)	**0.008**	0.90 (0.9)	0.987	**0.013**
MR-proANP 0'	45.0 (23.9)	37.9 (30.2)	48.0 (25.4)	0.349	40.1 (23.0)	0.955	52.7 (25.8)	0.145	**0.009**
MR-proANP 3'	45.7 (24.7)	40.4 (33.1)	50.6 (24.5)	0.122	41.0 (18.5)	0.999	53.7 (38.0)	0.168	**0.015**
ΔMR-proANP	2.25 (4.2)	1.18 (4.4)	2.22 (2.8)	0.992	2.55 (5.0)	1.00	3.63 (7.3)	0.999	0.958
CT-proET1 0'	43.3 (13.5)	47.4 (23.2)	41.9 (11.8)	0.998	43.8 (14.0)	1.00	43.3 (8.7)	0.991	0.891
CT-proET1 3'	42.5 (14.2)	39.4 (22.1)	42.3 (11.2)	0.996	41.7 (15.5)	1.00	43.3 (12.8)	0.791	0.769
ΔCT-proET1	0.40 (4.6)	0.80 (6.2)	0.50 (4.3)	0.796	0.40 (4.7)	0.932	−0.18 (3.6)	0.712	0.723
CT-proAVP 0'	6.14 (5.9)	6.68 (4.8)	5.65 (5.0)	0.834	6.75 (6.9)	0.933	5.04 (5.6)	0.859	0.824
CT-proAVP 3'	6.77 (6.7)	6.16 (5.5)	6.13 (6.8)	0.576	7.24 (8.2)	0.641	6.79 (7.1)	0.62	0.615
ΔCT-proAVP	0.16 (2.3)	−0.29 (1.5)	0.34 (2.5)	0.098	0.18 (3.9)	**0.033**	0.07 (1.3)	0.533	0.052

Displayed as median (IQR) in pm/L.
Number of patients displayed as range of available samples in the diagnosis groups.
*p Value for Tukey's or Games-Howell post hoc test in relation to no Dx (reference group) for continuous variables.
†ANOVA or Welch test p value for continuous variables and Pearson's χ^2 p value for dichotomous variables.
ANOVA, analysis of variance; no Dx, no diagnosis; OH, orthostatic hypotension; POTS, postural tachycardia syndrome; VVS, vasovagal syncope.

HR <70 and resting MR-proANP levels >45 pm/L had an OR of 21.8 (95 % CI 3.99 to 119; p<0.001) for being diagnosed with VVS compared with subjects that lacked all of these characteristics (table 4). When excluding male sex as a criteria, patients with fulfilling the criteria of resting HR <70 bpm plus MR-proANP >45 pm/L had an OR of 3.99 (95 % CI 1.68 to 9.52; p=0.002) of being diagnosed with VVS compared with any other diagnosis in relation to subjects without these two criteria in a sex-adjusted and age-adjusted logistic regression model. On the contrary, the patients with HR ≥70 bpm plus MR-proANP <45 pm/L had an increased probability of being diagnosed with POTS (OR 3.66; 95 % CI 1.40 to 9.58; p=0.008).

DISCUSSION

In this study, we report that resting HR in patients with vasovagal reflex syncope during tilt testing was lower compared with those who had postural orthostatic tachycardia syndrome and with those whose tests were negative. Furthermore, MR-proANP was significantly higher among those with VVS compared with POTS, and MR-proANP was inversely related to supine HR. When these variables were combined, patients with both a resting HR <70 bpm plus MR-proANP levels >45 pm/L had an OR of approximately four times for reflex syncope compared with subjects without any of these criteria; the OR increased to 22 if male sex was also included as a criteria in the model. We also showed that patients with OH had lower resting renin, while patients with POTS demonstrated pronounced increase in norepinephrine. Patients with POTS also demonstrated greater increase in CT-proAVP during HUT than patients with negative HUT, however, not compared with any other group. Finally, we have observed that patient's history and symptoms during syncope may not be specific for any diagnosis.

Our previous reports suggested that lower values of MR-proANP were predictive of both VVS[12] and orthostatic tachycardia[9] in the general syncope population. In this study, the head-to-head comparison between age-matched younger patients with VVS and patients with POTS demonstrated that lower MR-proANP is more suggestive of POTS.

Table 4 Markers of vasovagal syncope in relation to diagnosis

Number of markers	OR for VVS	95 % CI	p Value
0	1.00		
1	1.89	0.77 to 4.63	0.164
2	2.47	0.99 to 6.15	0.052
3	21.8	3.99 to 119	<0.001
Model trend	1.98	1.37 to 2.87	<0.001

OR and 95% CI for vasovagal syncope in relation to occurrence of the following markers in individual subjects: male sex, resting heart rate <70 bpm; resting plasma MR-proANP levels >45 pm/L.

The finding of lower resting HR among patients with VVS implies higher vagal tone and/or a lower sympathetic tone affecting the heart at rest compared with patients with a negative test. Interestingly, this difference in HR seems to be attenuated during orthostatic challenge, which may be explained by either a marked vagal withdrawal or a more pronounced increase in adrenergic drive. For obvious reasons, patients with POTS demonstrated greatest increase in HR during HUT, outperforming that of VVS positive and negative HUT but the difference between patients with VVS and negative HUT was also significant. However, although orthostatic increase in HR in POTS is pathognomonic for this syndrome, less is known about chronotropic response in patients with VVS compared with normal subjects. Our reference group with negative HUT do not represent normal subjects, but they are autonomically more integrated and do not demonstrate the hypotensive tendency usually detected by tilt testing.[17] Consequently, the attenuation of difference in HR between patients with VVS positive and negative HUT during orthostatic challenge may be due to counteracting the hypotensive tendency in standing in the former by increasing HR and cardiac output. Interestingly, epinephrine elevation during early HUT phase did not differ between the groups, an observation that suggests a baroreceptor-mediated vagal withdrawal as the main mechanism of HR increase in patients with positive VVS.

Compared with patients with POTS, MR-proANP was significantly higher among those with VVS, which corroborates our previous findings of decreased ANP in postural tachycardia.[9] Also, we found that higher MR-proANP was inversely related to resting HR. Thus, patients with VVS show lower HR, which is in turn associated with higher ANP. The most important stimulus for ANP secretion is stretching of atrial walls, which takes place with a high blood volume and raised atrial pressure.[18 19] One could hypothesise that the lower resting HR of pateints with VVS would lead to greater filling of these cardiac chambers during the cardiac cycle, which in turn would trigger increased release of ANP in these patients. On the contrary, patients with POTS may have underfilling of the atria, leading to reduced ANP. Whether higher resting MR-proANP levels may in itself also predispose to a vasovagal reaction during orthostatic stress remains to be determined.

Current clinical guidelines[3] emphasise the need for careful history taking when evaluating patients with unexplained syncope. VVS is by far the most common cause of syncope in young patients[2 3] and it is suggested by some authors that VVS may be diagnosed solely by careful history taking.[20] In this study, none of the clinical features such as the total number of attacks, how many years ago the first syncope occurred, dizziness on standing and palpitations or typical prodrome preceding syncope was highly specific for any diagnosis. Of interest, the proportion of patients with POTS that reported palpitations was low (3 of 10), and this

proportion was the same among patients with VVS. Furthermore, even though the proportion of patients reporting dizziness on standing was slightly lower among VVS compared with other diagnoses, 6 of 10 patients with VVS still reported this symptom. The history is without doubt a powerful tool in diagnosing syncope, in particular when taken by a trained expert.[21] In this study, patients were asked to fill a standard questionnaire prior to tilt testing. Self-reported history obtained by filling a questionnaire is similar to history taking by a non-expert yielding around 60% accuracy.[22] While it has been shown that a level of accuracy when an expert takes history is very high, as much as 90%.[23] We believe that these results indicate that tilt testing with non-invasive beat-to-beat monitoring should be considered in unexplained syncope associated with symptoms of orthostatic intolerance, especially in the absence of a syncope expert. When an expert is available, tilt testing may be seen as a diagnostic tool for confirmation of diagnosis and an additional test in unresolved cases.

VVS and POTS are diagnoses that are very common in young subjects, yet the treatment strategies for these diagnoses may differ[6] and an accurate diagnosis is essential when attempting to prevent syncope recurrence. Since patients with VVS and POTS seem to show opposite patterns of both haemodynamic factors (resting HR lower among patients with VVS) and neuroendocrine markers (resting MR-proANP lower in POTS), we suggest the possibility that resting HR and MR-proANP, easily assessed through commercially available test kits, may be considered as additional tools in the evaluation of young patients with unexplained syncope. Moreover, the lower HR in patients with VVS would tend to make them unsuitable for treatment with β-blockers, a strategy, which has failed in randomised trials on prevention of syncope recurrences.[3] The lower resting HR in patients with VVS may be closer to 'normal' as corroborated by other data from the Malmö population. In the Malmö Preventive Project, 8370 healthy individuals aged 27–40 years had resting HR of 67±10 bpm,[24] similar to VVS in our study. Consequently, patients with VVS can be considered normal except when they are having reflex syncope. In contrast, POTS and OH are patients with persistent manifestations of their condition, expressed by abnormal adrenergic activation or vagal withdrawal at rest and higher HR. Patients with negative HUT are, on the other hand, a non-homogenous group, possibly with over-representation of anxiety disorders, which would explain the higher pretest HR. The fact that the proportion of men is higher among patients with VVS than among patients with POTS is consistent with the well-known fact that POTS is more often diagnosed in women.[6]

Among other observations, lower renin in OH is supported by earlier studies in diabetic patients with OH,[25] but has not been recently confirmed[11] in very young subjects and thus warrants further study, possibly including other components of renin-angiotensin system. In contrast, a significant increase in norepinephrine during HUT in patients with POTS can be considered confirmatory, as it has been previously demonstrated in several studies.[9 11 26] The finding of a greater increase in AVP during orthostasis in patients with POTS may have physiological basis in that a low blood volume is a well-known strong stimulus for AVP release. Of possible clinical relevance relating to these findings, copeptin levels have been suggested to predict the outcome of treatment with midodrine hydrochloride[27] and β-blockers in children with POTS.[28]

Our study has some limitations that should be mentioned. First, no control subjects without a history of syncope and/or orthostatic intolerance were included. However, the fact that only patients with unexplained syncope and/or orthostatic intolerance referred for further evaluation were included also makes the results clinically relevant. Second, the neuroendocrine data were measured at rest and at 3 min during HUT only. Further changes in these parameters might have occurred later during HUT, as well as after syncope. Third, there is an overlap between POTS and VVS in that many patients with POTS also experience syncope by VVS. In our study, 47 out of the 72 patients with POTS (65%) also had VVS during HUT. However, as treatment in these patients should probably be directed to the precipitating factors in form of their main diagnosis including the postural tachycardia and orthostatic intolerance rather than the VVS per se, we still find the distinction between 'pure VVS' and POTS (±VVS) important for successful treatment outcome. Fourth, the strict cut-off for HR in the diagnosis of POTS means that some patients with haemodynamic findings that are suggestive of, but not diagnostic for, POTS may be classified as either VVS or negative HUT. Finally, even though the use of medications influencing HUT results was very low in the study population should not affect results on the group level, such medications may of course have affected test results for a small number of individual patients.

In conclusion, we have shown that among young patients with unexplained syncope, patients with VVS are more likely to be men, have lower HR and higher MR-proANP at rest than patients with POTS. We propose that these parameters might be taken into account during the initial evaluation of unexplained syncope in young patients.

Acknowledgements The authors would like to thank the staff at the head-up tilt lab at the Department of Clinical Physiology and Nuclear Medicine at Skåne University Hospital: Shakilla Modaber, Elisabet Andersson, Amna Ali, Lejla Halilovic, Hajer Kachroudi. Furthermore, we would like to thank Philippe Burri at the Department of Internal Medicine at Skåne University Hospital, for the work with blood samples and the patient database.

Contributors All authors (VH, JMS, DN, MS, RS, OM, AF) participated in 1) conception and design or analysis and interpretation of data; 2) drafting of the manuscript or revising it critically and 3) final approval of the manuscript submitted.

Competing interests AF and OM are listed as co-inventors on a patent application 'Biomarkers for the diagnosis, prognosis, assessment and therapy stratification of

syncope' (PCT/EP2013/001081) for the use of BRAHMS CT-proAVP, CT-proET-1, MR-proADM and MR-proANP for diagnosis of syncope. RS is a consultant to Medtronic.

Patient consent All patients signed an informed consent, however not a specific BMJ form. All data were unidentified and results are presented on group level only.

Ethics approval The Regional Ethical Review Board in Lund, Sweden accepted the study protocol (ref no 82/2008).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Any requests for data sharing should be made to the corresponding author.

REFERENCES

1. Ganzeboom KS, Mairuhu G, Reitsma JB, *et al*. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35-60 years. *J Cardiovasc Electrophysiol* 2006;17:1172–6.
2. Romme JJ, van Dijk N, Boer KR, *et al*. Influence of age and gender on the occurrence and presentation of reflex syncope. *Clin Auton Res* 2008;18:127–33.
3. Moya A, Sutton R, Ammirati F, *et al*. Guidelines for the diagnosis and management of syncope (version 2009): the task force for the diagnosis and management of syncope of the European Society of Cardiology (ESC). *Eur Heart J* 2009;30:2631–71.
4. Fedorowski A, Melander O. Syndromes of orthostatic intolerance: a hidden danger. *J Intern Med* 2013;273:322–35.
5. Ricci F, De Caterina R, Fedorowski A, *et al*. Prognosis, and treatment. *J Am Coll Cardiol* 2015;66:848–60.
6. Sheldon RS, Grubb BP, Olshansky B, *et al*. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm* 2015;12:e41–e63.
7. Li H, Kem DC, Reim S, *et al*. Agonistic autoantibodies as vasodilators in orthostatic hypotension: a new mechanism. *Hypertension* 2012;59:402–8.
8. Fedorowski A, Li H, Yu X, *et al*. Antiadrenergic autoimmunity in postural tachycardia syndrome. *Europace* 2016.
9. Nilsson D, Sutton R, Tas W, *et al*. Orthostatic changes in Hemodynamics and Cardiovascular biomarkers in dysautonomic patients. *PLoS One* 2015;10:e0128962.
10. Krishnan B, Patarroyo-Aponte M, Duprez D, *et al*. Orthostatic hypotension of unknown cause: unanticipated association with elevated circulating N-terminal brain natriuretic peptide (NT-proBNP). *Heart Rhythm* 2015;12:1287–94.
11. Wagoner AL, Shaltout HA, Fortunato JE, *et al*. Distinct neurohumoral biomarker profiles in children with hemodynamically defined orthostatic intolerance may predict treatment options. *Am J Physiol Heart Circ Physiol* 2016;310:H416–H425.
12. Fedorowski A, Burri P, Struck J, *et al*. Novel cardiovascular biomarkers in unexplained syncopal attacks: the SYSTEMA cohort. *J Intern Med* 2013;273:359–67.
13. Bartoletti A, Alboni P, Ammirati F, *et al*. 'The Italian Protocol': a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. *Europace* 2000;2:339–42.
14. Eeftinck Schattenkerk DW, van Lieshout JJ, van den Meiracker AH, *et al*. Nexfin noninvasive continuous blood pressure validated against Riva-Rocci/Korotkoff. *Am J Hypertens* 2009;22:378–83.
15. Finucane C, O'Connell MD, Fan CW, *et al*. Age-related normative changes in phasic orthostatic blood pressure in a large population study: findings from The Irish Longitudinal Study on Ageing (TILDA). *Circulation* 2014;130:1780–9.
16. van der Hoorn FA, Boomsma F, Man in 't Veld AJ, *et al*. Determination of catecholamines in human plasma by high-performance liquid chromatography: comparison between a new method with fluorescence detection and an established method with electrochemical detection. *J Chromatogr* 1989;487:17–28.
17. Sutton R, Brignole M. Twenty-eight years of research permit reinterpretation of tilt-testing: hypotensive susceptibility rather than diagnosis. *Eur Heart J* 2014;35:2211–2.
18. Dietz JR. Mechanisms of atrial natriuretic peptide secretion from the atrium. *Cardiovasc Res* 2005;68:8–17.
19. Walsh KP, Williams TD, Spiteri C, *et al*. Role of atrial pressure and rate in release of atrial natriuretic peptide. *Am J Physiol* 1988;254:R607–10.
20. Sheldon R, Rose S, Connolly S, *et al*. Diagnostic criteria for vasovagal syncope based on a quantitative history. *Eur Heart J* 2006;27:344–50.
21. Wieling W, van Dijk N, de Lange FJ, *et al*. History taking as a diagnostic test in patients with syncope: developing expertise in syncope. *Eur Heart J* 2015;36:277–80.
22. van Dijk N, Boer KR, Colman N, *et al*. High diagnostic yield and accuracy of history, physical examination, and ECG in patients with transient loss of consciousness in FAST: the Fainting Assessment study. *J Cardiovasc Electrophysiol* 2008;19:48–55.
23. Sutton R, van Dijk N, Wieling W. Clinical history in management of suspected syncope: A powerful diagnostic tool. *Cardiol J* 2014;21:651–7.
24. Fedorowski A, Stavenow L, Hedblad B, *et al*. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). *Eur Heart J* 2010;31:85–91.
25. Christlieb AR, Munichoodappa C, Braaten JT. Decreased response of plasma renin activity to orthostasis in diabetic patients with orthostatic hypotension. *Diabetes* 1974;23:835–40.
26. Garland EM, Raj SR, Black BK, *et al*. The hemodynamic and neurohumoral phenotype of postural tachycardia syndrome. *Neurology* 2007;69:790–8.
27. Zhao J, Tang C, Jin H, *et al*. Plasma copeptin and therapeutic effectiveness of midodrine hydrochloride on postural tachycardia syndrome in children. *J Pediatr* 2014;165:290–4.
28. Zhao J, Du S, Yang J, *et al*. Usefulness of plasma copeptin as a biomarker to predict the therapeutic effectiveness of metoprolol for postural tachycardia syndrome in children. *Am J Cardiol* 2014;114:601–5.

Syndromes of orthostatic intolerance and syncope in young adults

Viktor Hamrefors, Jasmina Medic Spahic, David Nilsson, Martin Senneby, Richard Sutton, Olle Melander and Artur Fedorowski

Open Heart 2017 4:
doi: 10.1136/openhrt-2016-000585

Notes