

Outcomes of Fast-track Outpatient Clinic for Rhythm and Conduction Disorders: Focus on Postural Tachycardia Syndrome and Literature Review

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Authors' contributions

This work was carried out in collaboration between both authors. Author SAMS designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Author RB managed the analyses of the study and managed the literature searches. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJCR/2018/45477

Editor(s):

(1) Dr. Scicchitano Pietro, Medical Doctor in Cardiology, Department of Cardiology, "F. Perinei" Hospital, Altamura (BA), Italy.

Reviewers:

(1) Paulo Roberto Barbosa Evora, University of São Paulo, Brazil.

(2) Zeynep Cerit, Near East University, Cyprus.

(3) Franco Mantovan, University of Verona, Italy.

Complete Peer review History: <http://www.sciedomain.org/review-history/27670>

Review Article

Received 19th September 2018

Accepted 26th November 2018

Published 8th December 2018

ABSTRACT

Aims: To highlight the outcomes of nurse-led fast-track outpatient clinic for rhythm and conduction disturbances yielding patients with postural tachycardia syndrome.

Patients and Methods: In the setting of fast-track nurse-led outpatient clinic for rhythm and conduction disturbances of 483 Caucasian subjects who were evaluated for palpitation, presyncope and syncope, fatigue and dyspnea between May 2014 and August 2016. Analysis for exclusion of any cardiac cause included medical history, physical examination, resting ECG, laboratory testing, Holter recording, exercise tolerance testing (ETT), echocardiography (TTE), and when postural tachycardia syndrome (PoTS) was suspected a head-up tilt test (HUT) was performed. During HUT, electrocardiogram, encephalogram, blood pressure was recorded.

Results: Focused on patients with PoTS, among 47 (46 F and 1 M) subjects who underwent HUT, ten patients (mean age 42.1, range 22-62 years) had PoTS. Patients had a cluster of symptoms and presented with a history of presyncope and syncope (n = 7), fatigue (n = 5), mood change (n =

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5), palpitation (n = 5), nausea (n = 4) and exercise intolerance (n = 3). Resting recumbent ECG depicted regular sinus rhythm in all. Echocardiography findings were normal. ETT was normal in 9 and inconclusive in one. Holter recording revealed normal rhythm variation and sinus tachycardia (n= 8). PoTS was confirmed during HUT test in all 10 subjects. Different non-pharmacological measures and trials of pharmacological regimens were initiated.

Conclusions: Fast-track outpatient clinics for rhythm and conduction disturbances may lead to earlier recognition of PoTS. When PoTS is timely diagnosed, tailored management may be established.

Keywords: Fast-track outpatient clinics; rhythm and conduction disorders; postural tachycardia syndrome; palpitation; Presyncope; syncope; head-up tilt test.

1. INTRODUCTION

Fast-track nurse-led outpatient clinics covering large area of health care patient's management are increasingly reported covering cardiovascular [1], pulmonology [2], rheumatological management [3-6] and oncology care [7-9]. Fast-track outpatient clinics for rhythm and conduction disorders, is promising and may timely unravel such disorder as postural tachycardia syndrome facilitating its earlier recognition and possible appropriate management. Postural tachycardia syndrome is probably under-diagnosed and may mimic or be mistaken for many other cardiovascular disorders.

PoTS is defined as an autonomic disorder which is characterised by symptoms that worsen by standing and improve with recumbence, symptoms lasting ≥ 6 months, and the absence of other causes of orthostatic symptoms or tachycardia and a sustained heart rate increment of ≥ 30 bpm within 10 minutes of standing or head-up tilt test (HUT) in the absence of orthostatic hypotension [10,11]. The standing heart rate for most subjects is often >120 bpm [12,13]. PoTS was brought into focus in 1993 by Low's team at the Mayo Clinic [14]. The true incidence is unknown. PoTS may be primary or secondary to a myriad of disorders, and is common in the age group 12-50 years with a female predominance and a female to male ratio of 5:1 [15]. Although PoTS has been reported in younger patients, reversible PoTS has also been recognised in an older subject [16]. Some drugs are contra-indicated and others are to be avoided; furthermore, several conditions may aggravate the syndrome.

The present study is focusing on 10 Caucasian female patients with PoTS proven by head-up tilt test, in whom assessment was made in the setting of fast-track nurse-led outpatient clinics

for rhythm and conduction disorders. The international literature is briefly discussed.

2. PATIENTS AND METHODS

From the fast-track outpatient clinic for rhythm and conduction disorders of Hospital Group Twente, Hengelo, the Netherlands between May 19, 2014 and August 16, 2016, 483 novel referrals participants (Fig. 1) were assessed and in 47 subjects (46 females) HUT test was performed for suspected PoTS. Of those head-up tilt test confirmed the diagnosis of PoTS in ten subjects. Indication for HUT test was persistent symptoms after excluding cardiac causes and indicative intake list (Fig. 2) with rating for the presence of symptoms from none, mild, moderate to severe (scale from -, +, ++ to +++) with (-) reflecting an absence of symptoms and (+++) indicating presence of drastic complaints.

The intake list was filled in by each of the patients (n= 47) suspected of PoTS to guide evaluation, assessment and diagnostic requirements.

Patients were evaluated and analysed by a nurse practitioner and a cardiologist for dizziness, palpitation, pre-syncope and syncope. Of all fast-track patients, participants satisfaction (response rate 48.2%) was earlier reported [17]. All patients underwent non-invasive cardiac evaluation, including medical history, physical examination, resting 12-lead electrocardiography (General Electric Medical Systems Healthcare, MAC 5500 HD system, Freiburg, Germany), thoracic X-ray, laboratory testing, ambulatory ECG recording (General Electric Medical Systems Healthcare, MARS, Freiburg, Germany), exercise tolerance testing (General Electric Medical Systems Healthcare, Case 0459, Freiburg, Germany) and echocardiogram (General Electric Medical Systems Healthcare, Vivid E9, Freiburg, Germany) to exclude any

cause of tachycardia. Myocardial perfusion imaging (MPI) and coronary arteriography (CAG) were performed in three and two subjects, respectively.

Physical examination besides age, gender, and height and weight allowing calculation of body-mass index (BMI) was assessed by nurse practitioner.

Resting supine 12-lead electrocardiography recording rhythm, frequency, intervals and duration allowing calculating corrected QT interval (QTc) according to Bazett formula.

Thoracic X-ray (postero-anterior and lateral view): Was judged by an experienced staff radiologist.

Laboratory testing for assessment of haemoglobin, C-reactive protein, leucocyte and thrombocyte counts, gamma glutamyl transferase (γ GT), alanine aminotransferase (ALAT), urea, creatinine, natrium, potassium, glucose and thyroid stimulating hormone.

Ambulatory ECG recording: recorded tapes of 24 or 48 hours duration were analysed by an experienced technician and finally approved by a cardiologist on a separate work station.

Exercise tolerance testing was performed under the supervision of cardiologist on a bicycle ergometer under comfortable conditions. Starting exercise with 25-50 Watt with 60-80 revolution per minute and increment of 20 Watt every 1-2 minutes combined with simultaneous recording of ECG and registration of blood pressure. Blood pressure was measured by a non-invasive hemodynamic monitor.

Trans-thoracic 2-D echocardiogram (TTE) with colour Doppler imaging was performed by a certified technician. The following standard parameters were recorded: dimensions of cardiac chambers, kinetics of the ventricles and valvular velocity across the semilunar and atrioventricular valves. Right ventricular systolic pressure (RVSP) was estimated by measuring the tricuspid regurgitation (TR) jet maximum velocity by continuous wave (CW) spectral Doppler.

The current report was a single-center observational study of newly referred subjects focusing on PoTS patients conducted in a nurse-

led outpatient clinic for rhythm and conduction disorders.

Indications for HUT testing were persistent symptoms after excluding cardiac causes and an indicative intake list. An example of positive questionnaire is shown in Fig. 3.

2.1 Definition and Diagnostic Criteria for PoTS

Adopted from previous publications [18,19]. An increase in heart rate of ≥ 30 bpm within 10 minutes of head-up tilt is considered diagnostic of PoTS during the head-up tilt test [18]. Furthermore, increase of heart rate by ≥ 30 bpm from supine to standing posture, symptoms that worsen by standing and improve with recumbence, symptoms lasting ≥ 6 months, and the absence of other causes of orthostatic symptoms or tachycardia [19].

2.2 Head-up Tilt Test Protocol

The test was performed in a neighbouring teaching institute. The protocol consisted of 70° head-up tilt for 30 minutes after supine rest for 10 minutes. During the test, concomitant continuous registration of heart rate, blood pressure and electroencephalogram (EEG) was performed. The test took place between 09.00 a.m. and 04.00 p.m. in the non-fasting state at standard room temperature.

The head-up tilt table test involves a test where the blood pressure and heart rate are measured in supine position for 10 minutes; subsequently the table is tilted with 70 degrees while monitoring the blood pressure (BP) and heart rate. A peripheral intravenous cannula is placed before testing to administer intravenous fluid. The test is positive when the heart rate increases with ≥ 30 beats/min (≥ 40 beats/min in individuals < 19 years of age) with an absolute heart rate of ≥ 120 beats/min in the absence of orthostatic hypotension [20]. The tilting table is electrically driven and equipped with footplate support.

One patient (case 9) of the current series was the subject of earlier publication [21].

2.3 Ethical Considerations

The study was approved by the Medical Ethical Committee of Hospital Group Twente, Almelo-Hengelo, the Netherlands and waived the

requirement to obtain informed consent due to the retrospective nature of the study.

3. RESULTS

Between May 19, 2014 and August 16, 2016, HUT test was performed in 47 subjects (46 F and 1 M) collected from the fast-track nurse-led outpatient clinic for rhythm and conduction disorders, ten adult Caucasian patients with a mean age of 42.1 years (range 22 - 62) were diagnosed with PoTS proven by head-up tilt test. PoTS was suspected based on history, data of the filled personal intake list and confirmed by HUT test (Fig. 1).

These ten female patients were analysed in the fast-track nurse-led out-patient clinic because of presyncope and syncope, fatigue, palpitations, and exercise intolerance. Analysis included medical history, physical examination, resting 12-lead ECG, thoracic X-ray, laboratory testing, ambulatory ECG monitoring, exercise tolerance testing and transthoracic echocardiogram.

Patients had a cluster of symptoms and presented with a long-lasting history of multiple complaints. The presenting symptoms were palpitation and rapid heart rate in 7 patients, presyncope and syncope in 7 patients, 4 had nausea, 3 experienced intolerance of exercise, 6 complained of fatigue and 5 presented with mood change. Chest pain and dyspnea on exertion were in 2 patients each.

Patients characteristics are summarised in (Table 1). Ten patients met the criteria of PoTS and had heart rate rise of more than 30 bpm within 10 minutes during HUT test.

3.1 Duration of Symptoms before Establishing the Diagnosis (Table 1)

The initial PoTS-related symptom duration varied from half a year (n = 3) up 8 years (n = 7) prior to diagnosis.

3.2 Previous History and Concomitant Disorders

Antecedent medical history included ablation of atrio-ventricular nodal re-entry tachycardia (n=1, patient 1), hormonal substitution for hypothyroidism (n=1, patient 3) and family history of sudden death (n=1, patient 4). Exacerbation of

symptoms occurred in the pre-menstrual period in one patient (patient 1). No patient had risk factors or a family history of coronary artery disease. Furthermore, no patient had hypermobility of the joints.

3.3 Physical Examination

No cardiovascular or pulmonary abnormalities were found on physical examination. No patient was anemic. Acrocyanosis of the lower extremities was demonstrated in 5 patients (patients 1, 2, 6, 8 and 10).

3.4 Laboratory Findings

Hematological and biochemical values of hemoglobin and thyroid function were all within normal limits (Table 1).

3.5 Functional Tests

Data of the current series is summarised in (Table 2).

3.6 Supine 12-lead ECG

Resting recumbent ECG depicted regular sinus rhythm in all. Resting ECG revealed sinus rhythm (SR) in 7 and sinus tachycardia in three (patients 1, 9 and 10) of the patients. The QTc-interval demonstrated normal variation from 375 to 457 with a mean of 407 millisecond. All patients had normal repolarisation and conduction intervals on their surface ECG. In patient 1, the recumbent ECG showed normal sinus rhythm of 76 bpm and sinus tachycardia of 112 bpm when standing (Fig. 4A and B).

3.7 Trans-thoracic Echocardiographic

Was performed in all to exclude structural heart ailments or cardiac involvement. Normal dimensions and kinetic were found. Trivial valvular regurgitation was recognised. TTE findings were normal in 3 patients (patient 2, 9 and 10) and demonstrated mild tricuspid (n=5), mild mitral (n=4) and mild aortic (n=1) regurgitation. The estimated right ventricular systolic pressure was normal in all patients. None of the patients had tachycardia-induced cardiomyopathy or pulmonary hypertension. The left ventricular ejection fraction varied from 51% to 74% with a mean of 65%.

Table 1. Characteristics of 10 patients with postural tachycardia syndrome

Case/age (years)	Clinical presentation	Duration of symptoms (years)	RR (mmHg)	Hb (N= 7.5-10.0 mmol/l)	TSH (N= 0.3-4.2 mU/l)
1-48	Palpitation, reduced exercise tolerance, presyncope	4	110/80	8.8	1.9
2-52	Palpitation, reduced exercise tolerance, presyncope	2	140/86	7.9	2.0
3-35	Palpitation, presyncope	0.5	136/74	8.2	4.0
4-62	Palpitation, chest pain	2	120/70	7.8	1.7
5-24	Palpitation, syncope	2	131/73	8.2	2.2
6-32	Syncope	0.5	115/74	8.3	1.7
7-39	Syncope, migraine, headache	since childhood	120/78	8.8	1.3
8-22	Rapid heart rate, fatigue	0.5	108/71	8.2	1.5
9-47[21]	Rapid heart rate, presyncope tremulousness	8	143/90	8.1	1.4
10-60	Palpitation, reduced exercise tolerance, tremulousness acrocyanosis	1	138/82	8.8	1.1

Hb= hemoglobin; N= normal; RR= blood pressure; TSH= thyroid stimulating hormone

Table 2. Data of functional tests of 10 patients with postural tachycardia syndrome

Case	Resting recumbent ECG	QTc-interval (ms)	24-h ECG recording	TTE	LVEF (%)	ETT (%) predicted value
1	N, SR, on standing ST	457	SR, ST	Mild AR TR MR	55	68
2	N	413	SR, PAC's, PVC's	N	51	125
3	N	375	SR, ST	Mild TR	60	142
4	N	383	SR, ST	Mild TR MR	74	89
5	N	410	SR, ST	Mild MR	71	159
6	N	426	SR, ST	Mild TR	79	134
7	N	403	SR	Mild TR MR	70	130
8	N	390	SR, ST	Mild TR MR	56	112
9 [21]	ST	432	SR, ST	Mild TR MR	59	69
10	ST	444	SR, ST	N	54	90

AR= aortic regurgitation; ETT= exercise tolerance testing; LVEF= left ventricular ejection fraction; MR= mitral regurgitation; N= normal; PAC's= premature atrial contractions; PVC's= premature ventricular contractions; SR= sinus rhythm; ST= sinus tachycardia; TTE= trans-thoracic echocardiography; TR= tricuspid regurgitation

Table 3. Data of head-up tilt test, concomitant disorders and management of 10 patients with postural tachycardia syndrome

Case	Heart rate increase during HUT testing (bpm)	EEG	Time (minutes)	Concomitant disorder	Management
1	48	N	7	Previous ablation of AVNRT	ERP/fluid and salt intake propranolol, bisoprolol, fludrocortisone, ivabradine
2	50	Low voltage	1	Daughter has PoTS	ERP/fluid and salt intake fludrocortisone, midodrine, ivabradine
3	50	Epileptic activity	1	Substitution for hypothyroidism	euthyrax/ERP/ fluid and salt intake, ivabradine
4	34	N	5	Family history of sudden death	fluid and salt intake /ERP ivabradine
5	52	N	10	None	fluid and salt intake/Atrovent / ventolin/flixotide when needed /ERP
6	30	N	9	Sibling has PoTS	fluid and salt intake /ERP
7	39	N	10	Sibling has PoTS	fluid and salt intake /ERP
8	33	N	10	Mother has PoTS	fluid and salt intake /ERP
9[21]	59	N	10	On 2 earlier occasions 2007 and 2013 diagnosis of PoTS was missed	fluid and salt intake /ERP
10	31	1x SSW bilateral temporal and 1x unilateral right frontal. Suspected epileptic activity	10	DM Polymyalgia rheumatica	fluid and salt intake /ERP

AVNRT= atrio-ventricular nodal reentry tachycardia; EEG= electroencephalogram; ERP= exercise rehabilitation program; N= normal; PoTS= postural tachycardia syndrome

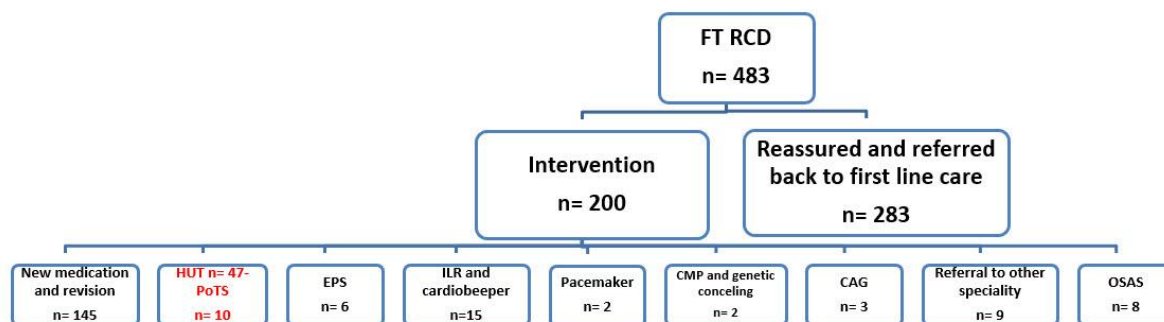


Fig. 1. Flow chart of patients of fast-track nurse-led outpatient clinic for rhythm and conduction disorders

CAG= coronary angiography; CMP= cardiomyopathy; EPS= electrophysiologic study; FT-RCD= fast-track rhythm and conduction disorders; HUT= head-up tilt test; ILR= implantable loop recorder; OSAS= sleep apnea syndrome; PoTS= postural tachycardia syndrome

Symptom	Score			
	-	+	++	+++
Sweating				
Weakness/extreme fatigue				
Sleep disorders				
Palpitations/tachycardia				
Exercise intolerance				
Light-headedness				
Headache				
Mental clouding				
Blurred or tunneled vision				
Shortness of breath				
Hyperventilation				
Tremulousness (shaking)				
Chest discomfort				
Vomiting				
Presyncope				
Syncope/fainting				
Anxiety				
Memory difficulty and concentration disturbances				
Facial flushing				
Acrocyanosis				
Mood changes				
Attention disturbances				

Fig. 2. Intake list used for assessment of presenting symptoms in suspected postural tachycardia syndrome, adopted from previous publications [10,39,41]

Abbreviations: - = none; + = discrete; ++ = moderate; +++ = severe

Mogelijke symptomen bij Posturale Orthostatische tachycardie (POTS)

+ Licht
 ++ Matig
 +++ Ernstig

Zweten	+ +
Zwakheid	++
Slaapstoornis	+++
Snelle hartslag/hartkloppingen	++
Verminderde inspanning	+++
Licht in het hoofd	++
Extreme vermoeidheid/uitgeput	+++
Hoofdpijn	+
Watten in het hoofd	+
Wazig zien	+
Kortademig	+
Hyperventilatie	++
Beven	+
Ongemakkelijk gevoel op de borst	++
Misselijkheid	+
Neiging tot flauwvallen	++
Flauwvallen	++
Onrust	+++
Concentratiestoornissen	++
Moeite met aandacht houden	++
Blauwe verkleuring benen	+
Opvliegers	+
Stemmingswisselingen	++++

Fig. 3. Intake list filled (in Dutch) by one of the subjects suspected of postural tachycardia syndrome

Abbreviations: - = none; + = discrete; ++ = moderate; +++ = severe

3.8 Exercise Tolerance Testing (ETT)

ETT was normal (varying from 89% to 159% of predicted value) at maximal exercise tolerance in all except two patients (patients 1 and 9) who had an inconclusive test of a submaximal result reaching 68% and 69% of the predicted value, respectively.

3.9 Ambulatory ECG Recording

This revealed regular sinus rhythm, normal rhythm variations, premature atrial and ventricular complexes and episodes of sinus tachycardia in eight (n= 8) patients (Fig. 4 C and D).

3.10 Myocardial Perfusion Imaging (MPI)

MPI was performed in 3 subjects (patients 1, 3 and 4). MPI demonstrated normal

myocardial perfusion without segmental wall abnormalities.

3.11 Head-up Tilt Test

(Table 3) (Fig. 5): PoTS was confirmed during HUT test in all 10 subjects. The mean heart rate increase during HUT test was 43 (range 30-50 bpm). All 10 patients had an increase in heart rate of ≥ 30 beats per minute occurring within 10 minutes of standing and HUT test was not associated with orthostatic hypotension. The average time to onset of recognised symptoms was 7.3 minutes (range 1-10).

3.12 Coronary Angiography (CAG)

Two patients (Patients 2 and 4) underwent CAG for analysis of suspected anginal complaints upon effort and no coronary arterial atherosclerotic changes were found.

3.13 Non-pharmacological Management and Drug Trial

Symptoms were alleviated in 9 patients with a combination of different non-pharmacological and pharmacological management. Advice for high fluid intake (8-10 cups of water daily equals 2-3 liters per day) and common salt (3-5 gram/day) intake (patient 2) was given. Out-patient exercise rehabilitation program (ERP) was offered to all patients.

3.14 Pharmacological Trial Regimen

Pharmacological trial regimen included beta blocker (patients 1, 3), ivabradine (patients 1, 2 and 4) (Fig. 6), midodrine (patient 2), and fludrocortisone (patients 1, 2).

3.15 Follow-up

All patients except one (patient 2) were feeling well after the implementation of pharmacological and non-pharmacological measures. One patient (patient 2) did not fully benefited either from different pharmacological regimens in combination with ERP, but symptoms gradually resolved on 5 mg ivabradine twice a day. In one patient (Patient 1), symptoms relapsed after laparoscopic cholecystectomy, which was managed with the temporary addition of fludrocortisone.

3.16 Statistics

Categorical data were expressed as numbers with percentages, and continuous variables were expressed as means with a range.

4. DISCUSSION

From the fast-track nurse-led outpatient clinic for rhythm and conduction disturbances, 10 patients were found to have PoTS proven by HUT test. This report is focusing on patients with PoTS aiming to increase the awareness of this infrequently recognised syndrome among clinical practitioners.

To the best of our knowledge this is the first report of fast-track nurse-led outpatient clinic for rhythm and conduction disorders addressing postural tachycardia syndrome.

Brinth et al. [22] showed in Denmark that the growing number of publications in the world literature concerning PoTS goes hand-in-hand

with increasing recognition and awareness of the condition among clinicians.

Nurse-led outpatient clinics are rapidly evolving in many fields of cardiovascular diseases [7,23-25], and several studies are upcoming to measure the effects of such care not only on health-related quality of life in patients with atrial fibrillation [26] but also to investigate the potential benefit of lifestyle modification and role of remote nurse-led outpatient clinics in primary prevention [27].

It is widely accepted that PoTS predominantly affects young female subjects and has heterogeneous clinical presentations which contributes to the diagnostic and management difficulties and challenges confronting patients and healthcare providers [28]. Symptoms include those due to cerebral hypoperfusion, autonomic dysfunction and chronic insidious symptoms [10,11,28,29]. The true prevalence remains undetermined, but current estimates suggest that approximately half a million subjects are affected in the United States [29].

Generally, PoTS is under diagnosed and underestimated because many clinical features are highly nonspecific; some of its clinical presentation may mimic numerous cardiovascular disorders or overlap with several conditions such as vasovagal syncope (VVS), inappropriate sinus tachycardia syndrome (IST), fibromyalgia [30] and chronic fatigue syndrome (CFS) [31]. Interestingly, in patients with CFS, it has recently been demonstrated that cardiac magnetic resonance imaging showed mild reduction of left ventricular function in 12 female patients compared with healthy controls [32]. An association with Tako-tsubo "stress cardiomyopathy has also been reported [33]. In none of our patients Tako-tsubo was suspected.

It has been recognised that PoTS may be primary or secondary. The primary subtype is often idiopathic and is categorised as neuropathic or hyperadrenergic.

PoTS can cause significant physical and cognitive impairment [34].

Neuropathic PoTS: associated with partial autonomic denervation. Is the most common form and is usually precipitated by inflammation, surgery or trauma [11,29]. In some cases, it may possibly have an autoimmune aetiology [28,35].

Hyperadrenergic PoTS: related to central sympathetic activation. Is less common and has an underlying pathophysiologic aspect involving excessive cerebral sympathetic discharge with elevated standing norepinephrine [11,28,29]. Is usually idiopathic but it may be genetically present in more than one family member [11]. We believe that PoTS in our patients belongs to the primary subtype.

PoTS may be associated with flushing due to release of vasodilators from activated mast cells [36].

The secondary subtype of PoTS occurs in association with several medical disorders including diabetes mellitus, amyloidosis, sarcoidosis, lupus erythematosus, Sjögren syndrome, paraneoplastic syndrome, alcoholism, chemotherapy, or heavy metal poisoning [28,29], joint hypermobility syndrome (Ehlers-Danlos syndrome (EDS)), multiple-system atrophy, and optic-spinal multiple sclerosis and medications that impair autonomic functions or norepinephrine levels [11,18,29,30,37].

4.1 Clinical Features

The main presentation in the current case series were presyncope and syncope, fatigue, palpitation and mood change. PoTS distinctively affects middle-aged patients, with a higher prevalence in females, usually from the 3rd decade of life to the 5th decade [15,30]. In agreement with this observation, in our series, the majority (n= 8) were \leq 52 years of age. It has been reported that, the onset of PoTS may be sudden or insidious, and for some patients, there will be no indicative cause [38]. In the series of Kavi et al. [39] the patients presented with a triad of symptoms (fatigue, palpitation and lightheadedness). In 2015, Deb et al. [10] reported that the most common features (Table 4) are palpitation (92%), light-headedness (87%), headache (87%) and fatigue (90%) in 39 subjects presented with PoTS. Furthermore, sleep disorders are reported in 32% of PoTS patients[40]. The most presenting symptoms in USA are fatigue, palpitation and lightheadedness found in agreement with the findings in Europe. However headache, blurred or tunneled vision, shortness of breath, memory difficulty and concentration disturbances are more frequently reported in the USA than in Europe [10,39,41]. The differences might be attributed to patient's selection, absence of uniform question list,

severity of symptoms, ethnic or racial disparities, cultural dissimilarities and individual perception of complaints. Furthermore, differences may depend on kind of studies whether they are a review or survey conducted in a retrospective or prospective manner.

4.2 Conditions that May Precipitate PoTS

Several conditions may precipitate PoTS, such as surgery and traumas [11,18,42,43] and post-surgical procedure for an aortic coarctation coexisting with obstructive sleep apnea syndrome [44]. Other conditions that may precipitate PoTS are: period of growth spurt, traumatic or immunologic triggers such as vaccination [45] or Epstein-Barr viral infection [30]. Furthermore, in postpartum period associated with the joint hypermobility syndrome (Ehlers-Danlos syndrome) [46], heat exposure, strenuous exercise, post-prandial and premenstrual states [28] and optic-spinal multiple sclerosis [37].

It has been demonstrated that the prevalence of Ehlers-Danlos syndrome in patients with PoTS (15-18%) is significantly higher than the expected prevalence of EDS in the general population (0.02%) [10,47]. None of the patients of the current series had Ehlers-Danlos the joint hypermobility syndrome.

4.3 Medications and Conditions that May Trigger or Exacerbate Symptoms of PoTS are

Diuretics, α -antagonists, β -receptor blockers, calcium channel blockers and mineralocorticoid receptor antagonist [18,30]. It has been emphasised that some stressors may contribute to exacerbation of the symptoms including premenstrual states, surgery, trauma, sepsis, fever, strenuous exercise, medications such as diuretics and vasodilators and heavy food intake [28,41,48-50]. Moreover, there are some conditions that are recommended to be avoided, such as dehydration, heat exposure and excessive alcohol consumption.

4.4 Differential Diagnosis

Unfortunately, PoTS is often misdiagnosed during visits to several health care professionals such as general practitioners and ear, nose and throat physicians while screening patients for

lightheadedness and dizziness. Due to the importance of detecting PoTS in the screening process of this young population, a reliable screening tool is important for this age group. Among differential diagnosis of PoTS are tachyarrhythmias, active bleeding, inappropriate sinus tachycardia syndrome, chronic fatigue syndrome, vasovagal syncope, dehydration, anemia, hyperthyroidism, hypoglycemia, infection, pulmonary embolism, medications and drug stimulant abuse, fibromyalgia, Addison disease and pheochromocytoma [30,51-53].

Misdiagnosis of PoTS was more common in female patients than males. Frequently, symptoms were attributed to psychological or psychiatric disorders. In a survey in 2016, Kavi et al. [39] reported that cardiologists were most likely to be the first to suggest the diagnosis of PoTS, as was the case in the present report.

4.5 Diagnosis and Diagnostic Modalities

Head-up tilt test is considered the gold standard for diagnosis of PoTS [30]. It has been suggested by Lee et al. [51] that extension of the duration of HUT test up to 20 minutes would increase its diagnostic yield. Initial work-up includes excluding common causes of tachycardia (anemia, dehydration, hyperthyroidism and medications). It is challenging to diagnose PoTS in a timely manner; it may take months to years before the diagnosis is fully established [10].

There are several validated questionnaires that may help to explore the presence of different features of PoTS and track the severity of symptoms [30]. In our series, an intake list was filled in by each of our patients who were suspected of PoTS to guide evaluation, assessment and diagnostic requirements (Fig. 2). Heart rate and blood pressure should be measured in recumbent and upright positions. PoTS can be diagnosed with simple bedside measurements of heart rate and blood pressure taken in the supine and standing up position at 2, 5 and 10-minute intervals. With this latter simple maneuver, PoTS was highly suspected in some of our patients either during routine ECG (Fig. 4 A and B) or on ambulatory ECG recording (Fig. 4C and D). PoTS has been reported to be not associated with increased morbidity or mortality in pregnancy [54], due to increased circulating volume.

Other suggested diagnostic methods which may help differentiating between the subtypes of

PoTS include recumbent and standing serum nor-epinephrine levels [11,28,29]; measuring plasma or red cell volume [55,56]; immunologic assessment [57]; sympathetic skin prick testing [36,48]; Doppler ultrasound to measure cerebral blood flow velocity [58,59]; and investigations, depending on presenting features, involving sweat test and urinary bladder, gut and pelvic examination [48].

4.6 Duration between Onset of Symptoms and Establishing the Diagnosis

In our series, the initial symptom duration varied from half a year ($n = 3$) up eight years ($n = 7$). Furthermore, Welford et al. [34] found that the average time between first symptom and diagnosis was 6.99 years. Reported diagnostic delay may be up to 20 years [39]. In one study, mean time between presentation and establishing diagnosis was 3.7 years [39], and in other studies this interval varied from 0.5 to 5 years [60], furthermore, in the study of Deb et al. [10] the period was less than one year to more than ten years. In our series, the average duration until establishing a diagnosis was 2.3 years; the longest was 8 years and the shortest was 0.5 years, indicating the difficulty in achieving such a diagnosis.

Generally, management (Table 5) of PoTS is multidisciplinary consisting of educational, physical, psychological and pharmacological measures.

4.7 Non-pharmacological Measures

Avoidance of precipitating factors, triggers and stressors are advised. Patients need to be fully evaluated to establish the diagnosis of PoTS and consequently to tailor and guide treatment comprising of non-pharmacological and lifestyle management (high fluid intake (2-3 liters per day), common salt intake 3-5 grams/day). Exercise rehabilitation program and training programs of physical activity including aerobic exercise three times a week for 20 minutes have been recommended and behavioral-cognitive therapy [18,40,61]. Eating frequent small meals (reduces postprandial hypotension) together with a reduction of alcohol consumption is recommended. Successful out-patient Exercise rehabilitation program was offered to all patients of the presented series. Six patients (patients 5, 6, 7, 8, 9 and 10) benefited from this non-pharmacological approach.

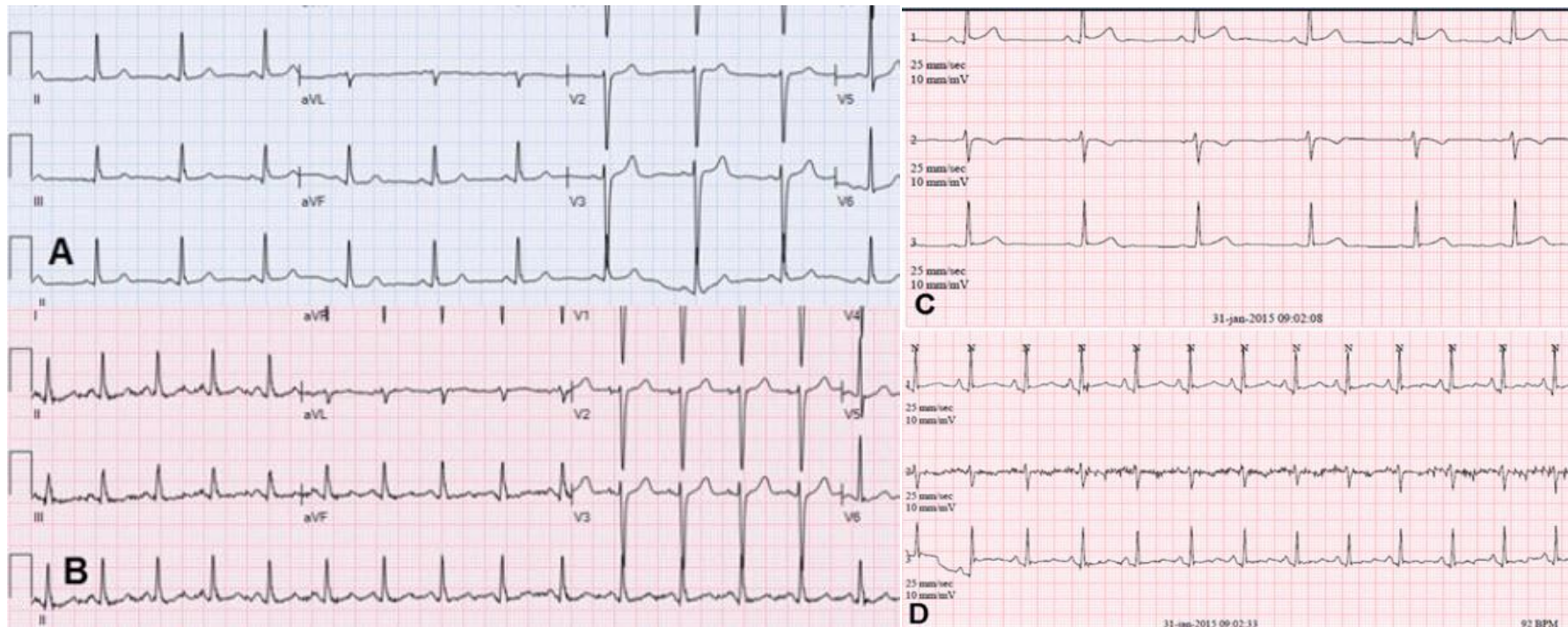


Fig. 4. Routine resting 12-lead ECG during A) Sinus rhythm of 76 bpm in supine and B) Sinus rhythm of 112 bpm after 8 minutes in standing position. Rhythm strips during 24-h ECG recording, demonstrating heart rate increase C) from 52 bpm in recumbent position to D) 100 bpm in upright position

Table 4. Comparison of reported most common symptoms in USA versus Europe in the period 2015-2016 [10,39]

Symptoms	Country author/ year/ references	
Number of patients/mean age (years)	USA /Deb/ 2015 [10]	Europe Kavi 2016 [39]
% Female/male	n= 39/ (35±12)	n= 779 (18-49)
Kind of study	89%/11%	92%/8%
Sweating	Survey	Survey
Fatigue	-	> 40%
Sleep disorders	90%	91%
Palpitation/tachycardia	51%	> 40%
Exercise intolerance/weakness	92%	86%
Lightheadedness	-	> 40%
Headache	87%	90%
Blurred or tunneled vision	87%	> 40%
Shortness of breath	69%	> 40%
Tremulousness	64%	> 40%
Chest discomfort	49%	> 40%>
Nausea and vomiting	-	> 40%
Syncope/fainting/blackouts	-	> 40%
Anxiety	54%	58%
Memory difficulty and concentration	-	> 40%
Facial flushing	77%	> 40%
Acrocyanosis	77%	-
	-	> 40%

- = not reported

Table 5. Overview of studies in relation to pharmacological and non-pharmacological management of postural tachycardia syndrome

Author/year	Number (F/M)	Age (years)	Method	Treatment	Exclusion	Measurement	Outcomes
Arnold 2013 [70]	20 mg: 11 (11/0) 80 mg: 5 (5/0)	20 mg: 32±2 80 mg: 29±5	Randomized double-blind crossover study	Propranolol (20 mg, 80 mg) vs placebo	Prolonged bed rest dehydration or on medication predisposing to tachycardia Deconditioning	VO ₂ max, peak oxygen consumption and peak heart rate responses	↑ maximal exercise capacity and ↓ peak HR responses and ↑ SV

Author/year	Number (F/M)	Age (years)	Method	Treatment	Exclusion	Measurement	Outcomes
Fu 2011 [71]	19 (18/1)	27±9	Double-blind	Propranolol 80 mg vs placebo and 3 months exercise training	-	HR, SV and cardiac output. Plasma volume. QoL	↑ plasma/blood volume. Modest ↑ of aldosteron-renin ratio after exercise training. QoL improved after exercise training. Standing HR was ↓.
Raj 2009 [62]	20 mg: 54 (49/5) 80 mg: 18 (16/2)	20 mg: 34±10 80 mg: 33±8	Randomized single blind crossover study	Propranolol (20 mg and 80 mg) vs placebo	Deconditioning On medication predisposing to tachycardia	HR symptom burden reported by patients	Low-dose 20 mg was better than high-dose 80 mg regimen. ↓ upright HR and ↓ symptom burden with 20 mg.
Lai 2009 [72]	47 Midodrine n 13 (8/5) Beta blocker n 14 (11/3)	Midodrine 14.3 Beta blocker 15.1	Retrospective single center chart review analysis	Beta blocker vs midodrine vs no medication	-	QoL	

Abbreviations: F = female; HR = heart rate; M = male; PoTS = postural tachycardia syndrome; QoL = quality of life; RCT = randomized controlled trial; SV = stroke volume; VO₂ max = peak oxygen consumption; ↑ = increase; ↓ = decrease

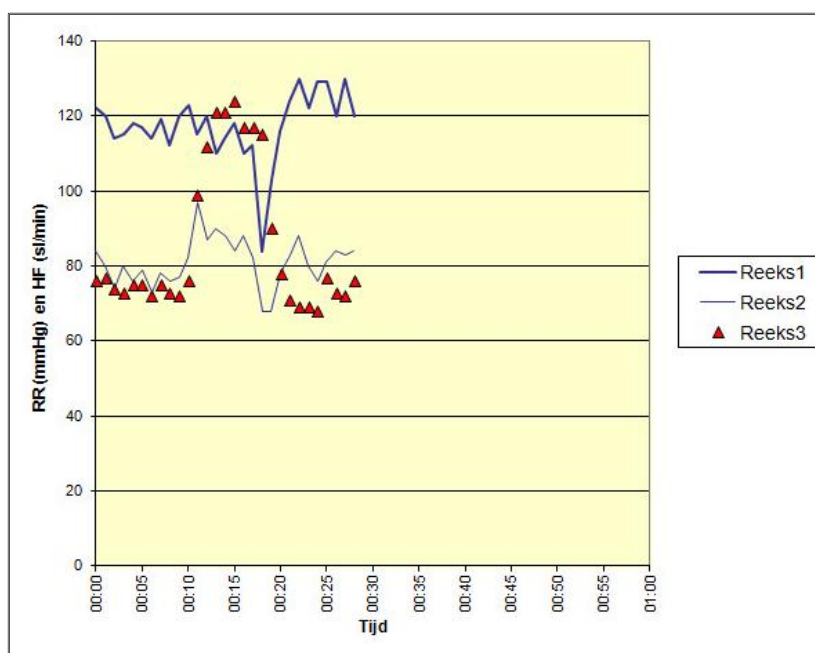


Fig. 5. Heart rate increase from 74 to 124 bpm after 1 minute of tilting without drop in blood pressure during head-up tilt test

Positive tilt table test of one of the patients. The first 10 minutes is in supine position. At 10 minutes the table was tilted, with an increase in heart rate up to 124 beats/min. after 10 minutes in upright position. RR = blood pressure, dark blue line = systolic blood pressure; light blue line = diastolic blood pressure; red triangles = HF = heart frequency

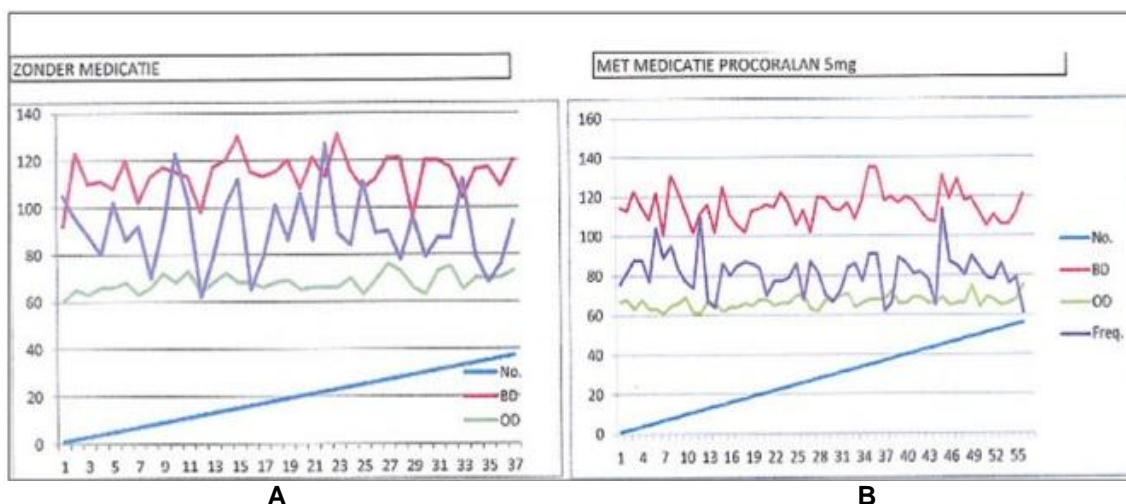


Fig. 6. Heart rate (purple line) before (left panel) and after ivabradine use (right panel) with the alleviation of symptoms and reduction of heart rate

Red line = systolic blood pressure, green line = diastolic blood pressure, purple line = heart frequency

Welford et al. [34] presented a study of 201 adults with a female majority (96.6%) diagnosed with PoTS with a mean age of 33 years and concluded that PoTS has a significant negative impact upon occupation and is associated with high morbidity. Moreover, they recommended the support of occupational therapists for supportive management of patients with PoTS.

4.8 Pharmacological Management

This depends on the pathophysiological subtypes of PoTS in the individual patient (primary, secondary PoTS or associated with flushing). Combination therapy may be the rule. Low dose combination therapy is better than high dose monotherapy to avoid side effects. Drugs

that cause vasoconstriction or increase circulating volume are suggested alone or in combination (fludrocortisone, midodrine, pyridostigmine, venlafaxine, methylphenidate, mestinon, erythropoietin and somatostatin analog octreotide) [29,40]. Another line of therapy may include beta blockers (metoprolol extended-release, carvedilol and labetalol with α - and β -blocking activity) as they may be effective in PoTS patients with beta-receptor supersensitivity, high noradrenaline levels and/or hyperadrenergic states [29,62,63].

Recently, ivabradine has been shown to improve both heart rate and symptoms in patients with inappropriate sinus tachycardia syndrome [64] and along this line it may also prove beneficial in patients with PoTS [19,30,65-67]. In a retrospective study (n= 20), McDonald et al. [67] reported symptomatic improvement in 60% of PoTS patients [67]. Few case reports and small series have been published presenting the beneficial effects of ivabradine in patients with PoTS [65,66,68]. The use of ivabradine (5 mg twice a day) in reported cases [65,66] and case series [67] was associated with improvement of symptoms with a considerable clinical benefit [39,69].

It remains challenging to find the optimal pharmacological management. In the current series, management was individually tailored; besides the non-pharmacological measures, a pharmacological regimen, after several drug trials, finally included ivabradine which was successfully conducted in four patients. Under regular follow-up of heart rate, control may be performed. After failure of several drugs to alleviate symptoms in (patients 1, 2, 3 and 4), ivabradine was prescribed with a favorable outcome. Duration and severity of symptoms may play a role, it is believed that the longer the duration of symptoms the more difficulties men may face of successful management. Although the symptoms are nonspecific, these patients should be taken seriously otherwise management would be troublesome.

5. CONCLUSION

In conclusion, since postural tachycardia syndrome may be infrequently recognised, nurse-led fast-track outpatient's clinic may help in early detection of the condition. Postural tachycardia syndrome has multi-factorial pathophysiological mechanisms, demonstrated with multi-diagnostic modalities due to overlap

with many other conditions (chronic fatigue syndrome, fibromyalgia, vasovagal collapse, inappropriate sinus tachycardia), confirmed with the head-up tilt testing and requires multidisciplinary management. Ivabradine may be promising in the treatment of selected PoTS patients.

Fast-track outpatient clinics for rhythm and conduction disorders may timely unravel such disorder as PoTS facilitating its earlier recognition and possible appropriate management. In the present study, PoTS was confirmed by head-up tilt test. Ivabradine may be promising in the treatment of selected patients with PoTS.

6. LIMITATIONS OF THE STUDY

One of the major limitation of our study is its retrospective nature and limited number of subject. From the nurse-led fast-track rhythm and conduction disorders a limited number of female subjects were found to have postural tachycardia syndrome. Head-up tilt test was only performed when the intake list raises high suspicion of postural tachycardia syndrome. Whether postural tachycardia syndrome may have been present in subjects with negative intake list remains unanswered. In only 47 subjects with suspected PoTS an intake list was used. The yield of PoTS would have been higher if all 483 subjects had received an intake list. An intake list or standard questionnaire may be implemented as a part of assessment of fast-track nurse-led outpatient clinic for rhythm and conduction disorders.

To the best of our knowledge this is the first report of fast-track nurse-led outpatient clinic for rhythm and conduction disorders addressing postural tachycardia syndrome.

Fast-track nurse-led outpatient clinics may prove useful in early detection and recognition of postural tachycardia syndrome.

Ivabradine may be beneficial in certain subtype of postural tachycardia syndrome.

To recommend the initiation of fast-track nurse-led outpatient clinic for screening and assessment of patients complaining of lightheadedness and dizziness for early detection of postural tachycardia syndrome.

The use of an intake list or questionnaire is highly recommended to unravel the cluster of

symptoms in patients with postural tachycardia syndrome.

To encourage a low threshold for performing head-up tilt test when postural tachycardia syndrome is suspected.

A large prospective study is warranted to address the value of fast-track nurse-led outpatient clinic for rhythm and conduction disorders in early detection of postural tachycardia syndrome. Postural tachycardia syndrome should be highly suspected in young female subjects evaluated for lightheadedness and dizziness.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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