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Managing the patient with episodic sinus tachycardia and orthostatic intolerance

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Abstract

Patients with episodic sinus tachycardia and associated orthostatic intolerance present a diagnostic and management dilemma to the clinician. We define this group of disorders to include sinus node reentrant tachycardia (SNRT), inappropriate sinus tachycardia (IAST), and postural orthostatic tachycardia syndrome (POTS). After a brief review of the current understanding of the pathophysiology and epidemiology of this group of disorders, we focus on the diagnosis and management of IAST and POTS. Our approach attempts to recognize the considerable overlap in pathophysiology and clinical presentation between these two heterogeneous conditions. Thus, we focus on a mechanism-based workup and therapeutic approach. Sinus tachycardia related to identifiable causes should first be ruled out in these patients. Next, a basic cardiovascular and autonomic workup is suggested to exclude structural heart disease, identify a putative diagnosis, and guide therapy. We review both nonpharmacologic and pharmacologic therapy, with a focus on recent advances. Larger randomized control trials and further mechanistic studies will help refine management in the future. (Cardiol J 2014; 21, 6: 665–673)

Key words: inappropriate sinus tachycardia, postural orthostatic tachycardia syndrome, sinus node reentrant tachycardia, sinus tachycardia, orthostatic intolerance, ivabradine, autonomic

Introduction

Patients with episodic sinus tachycardia (ST) and associated orthostatic intolerance (OI) present a diagnostic and management dilemma to the clinician. These patients often experience severe symptoms exacerbated in the upright position. Although ST in the absence of any significant heart disease is usually associated with a benign prognosis, increased heart rate (HR) over time may be an independent risk factor for all-cause mortality in selected populations [1]. The dictum for approaching patients with ST is to treat the underlying cause, because so often ST represents a normal heart's response to physiologic stress. Despite multiple investigations, for many patients this "underlying cause" cannot be determined. Patients frequently have a combination of paroxysmal or nonparoxysmal ST, palpitations, atypical chest discomfort, exercise intolerance, OI, presyncope, and syncope. The differential diagnosis in patients with symptomatic ST includes sinus node reentrant tachycardia (SNRT), inappropriate ST (IAST), and postural orthostatic tachycardia syndrome (POTS). While our understanding of the underlying pathophysiologic mechanisms remains limited, recent research has provided new insights into the proper evaluation and treatment of this group of patients.

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Definitions and clinical presentation

Sinus tachycardia is defined as an atrial rate more than 100 bpm with P waves originating from the sinoatrial node at the superior aspect of the crista terminalis, resulting in a positive wave in leads I, aVL, II, III, and aVF. Four heterogenous conditions have this finding: normal ST, SNRT, IAST, and POTS. Normal ST is the most common ST and is the appropriate increase in sinus node rate in response to physiologic stimuli. We will not review this well-described entity [2, 3].

Sinus node reentrant tachycardia is a primary arrhythmia that involves a reentry circuit in the region of the sinoatrial node, likely mediated by the anisotropic conduction [4]. It is characterized by paroxysmal episodes of tachycardia, generally 100–150 bpm [5, 6]. In contrast, IAST is not paroxysmal, with an average daily HR of 95 bpm or higher. It is thought to represent increased automaticity of the sinus node that is inappropriate for the degree of physiologic demand [3, 7]. The intrinsic HR changes with age; thus the specific threshold used to define IAST may be better conceived of as an age-dependent variable. However, consensus on an age-adjusted definition has not been reached. Although IAST is not paroxysmal, the symptoms may be intermittent and often include atypical chest discomfort, exercise intolerance, and OI. POTS is characterized by marked tachycardia in the upright posture accompanied by labile blood pressure and severe OI. Symptoms are thought to be related to relative cerebral hypoperfusion [3, 8]. POTS has been defined as an increase in HR of 30 bpm or more within 10 min of adopting upright posture in the absence of orthostatic hypotension [9, 10]. The clinical definitions of IAST and POTS are compared in Table 1.

Orthostatic intolerance is the occurrence of palpitations, fatigue, nausea, malaise, presyncope, or syncope upon assuming an upright posture [11–13], secondary to relative cerebral hypoperfusion, which distinguishes it from hyperventilation [14, 15] and psychogenic pseudosyncope [16]. While ST is not always associated with OI, the two findings intersect to varying degrees among patients with POTS, IAST, and SNRT. The differential diagnosis of these conditions and their approximate association with OI are depicted in Figure 1.

Epidemiology and pathophysiology

In general, SNRT, IAST, and POTS are uncommon and the epidemiological data is incomplete. SNRT is distinguished from the other two conditions in that it is a primary arrhythmia. It is reported to occur more commonly in patients with structural heart disease, and like other reentry tachycardias, it can be induced during an electrophysiologic study by programmed stimulation and localized to the area of the sinus node in the region of superior crista terminalis. Pacing maneuvers such as entrainment can confirm a reentry mechanism [17].

IAST occurs more frequently in young women in their fourth decade of life. Although the precise causes are ill-defined, the following plausible mechanisms have been proposed: increased resting sympathetic tone, decreased parasympathetic response, impaired baroreflex sensitivity, elevated intrinsic sinus node rate, enhanced automaticity of the sinus node, or positive chronotropic effects of anti–beta adrenergic receptor antibodies [18–20]. Given the early age of onset, there may be a developmental component to IAST, although no direct evidence exists at this time.

POTS also occurs more frequently in young women (female:male ratio — 4.5:1), and most cases occur between the ages of 15 and 25 years. Up to 50% of cases have an antecedent viral illness, and 25% have a family history of similar complaints [9, 10]. The primary mechanism is venous pooling and central hypovolemia during upright posture, resulting in secondary sympathetic excitation that perpetuates the tachycardic response [21, 22].

Table 1. Clinical features of inappropriate sinus tachycardia (IAST) and postural orthostatic tachycardia syndrome (POTS).

	IAST	POTS
Heart rate	"Inappropriate" for physiologic need > 90–100 bpm at rest or with minimal exertion	Persistent increase > 30 bpm or absolute rate > 120 bpm within 10 min when moving from supine to upright position
	Mean > 95 bpm on Holter	Absence of orthostatic hypotension
Symptoms	Frequently multi-system	Frequently multi-system, though greater associated with orthostatic intolerance

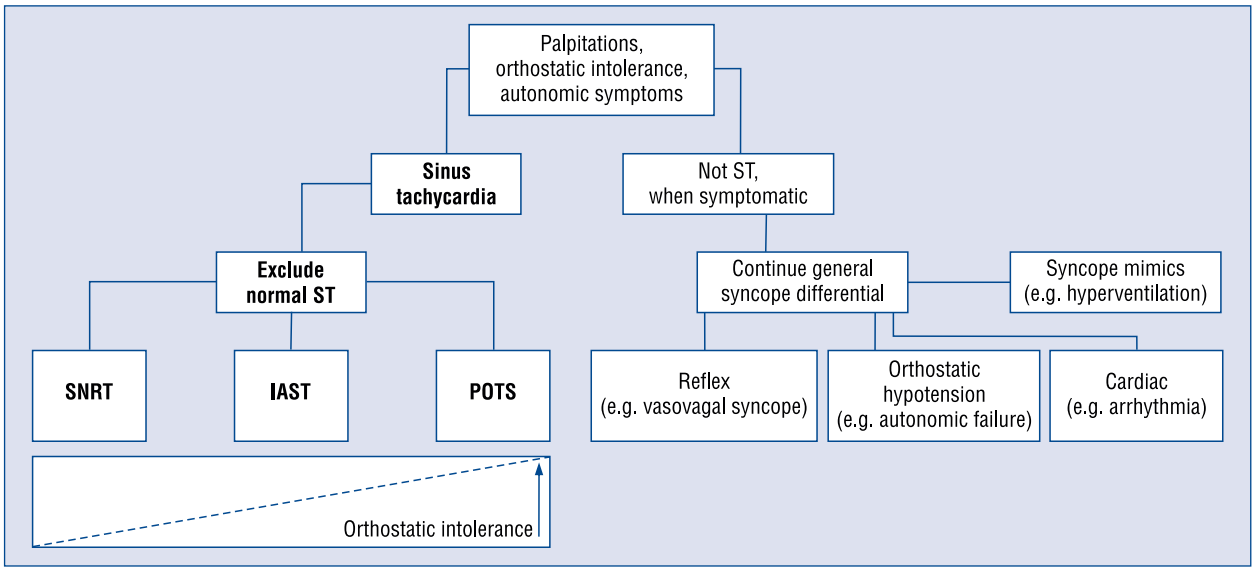

Figure 1. Differential diagnosis of sinus tachycardia (ST) with orthostatic intolerance (OI); general approach and differential diagnosis of patients with ST who present with palpitations, autonomic symptoms, and varying levels of OI. The variable association of sinus node reentrant tachycardia (SNRT), inappropriate sinus tachycardia (IAST), and postural orthostatic tachycardia syndrome (POTS) to OI is depicted.

Autoimmunity may exert an effect; elevated alpha-1 receptor partial antagonist and beta-1 receptor, beta-2 receptor agonist autoantibodies were identified in the serum of POTS patients [23]. Anxiety and depression are not uncommon in POTS and IAST patients, but the psychiatric contribution to symptoms is unclear. One recent study suggests that palpitations are an effect of sympathetic stimulation and independent of the actual HR. Studies also demonstrated that POTS patients did not differ in somatosensory amplification compared to controls, suggesting that symptoms are not psychogenic [24]. The apparent decrease in symptoms upon administration of placebo may be because of physiological changes over time, rather than a psychologically conditioned response [25]. The question remains whether POTS and IAST are two distinct syndromes with significant overlapping clinical features or whether there are "shared" mechanisms. A recent study comparing POTS with IAST demonstrated that the intrinsic HR did not differ between the two conditions and healthy controls after autonomic blockade with propranolol and atropine. However, patients with IAST showed a larger HR reduction after sympathetic blockade with propranolol when compared with POTS patients. This study elegantly demonstrated that the tachycardia of IAST is mainly mediated by enhanced sympathetic tone; however, a limited autonomic dysregulation in POTS during orthostatic stress cannot be excluded [22].

Evaluation and diagnosis

Patients with SNRT, IAST, or POTS often present with similar symptoms, including palpitations, lightheadedness, presyncope, and sometimes syncope with various degrees of OI. The overall approach to these patients has three facets: (1) to exclude underlying structural heart disease and primary metabolic causes; (2) to determine a diagnosis; and (3) to define a mechanism for the patient's symptoms in order to guide effective therapy [26].

A thorough history is taken to characterize the patient's symptoms. Special consideration should be given to the symptom onset, chronicity, and correlation with posture. Cardiovascular risk factors should be assessed. Symptoms that would indicate a secondary cause of normal ST should be elicited by a thorough review of systems. Both patients with POTS and those with IAST often have multi-system complaints with autonomic features (temperature sensitivity, genitourinary or gastrointestinal symptoms, and tremor) [9], and autonomic features do not reliably distinguish between diagnoses [26].

Initial studies should routinely include twelve-lead electrocardiography (ECG) and 24-h Holter monitoring to exclude other causes of supraventricular tachycardia and assess the diurnal variation in HR. The P wave morphology should be carefully examined and compared to P waves on prior ECGs. An echocardiogram is recommended to rule out

structural heart disease [8, 26]. Tachycardia-induced cardiomyopathy is rare in patients with IAST or POTS; thus, left ventricular dysfunction should elicit consideration of alternative diagnoses. For paroxysmal episodes that have not been documented electrocardiographically, a cardiac event recorder or implantable loop recorder can be helpful to document a spontaneous clinical event. While there are no absolute ECG diagnostic criteria for these conditions, SNRT is likely when short episodes of paroxysmal ST are captured on a cardiac monitor. IAST is diagnosed in a symptomatic patient when persistent ST is demonstrated repeatedly on ECG and extended cardiac monitoring. If incidentally found asymptomatic HR changes are observed that meet IAST criteria, 1 year follow-up is reasonable to reassess for normal ST and exclude the very rare development of tachycardia-induced cardiomyopathy. POTS is diagnosed by documenting a HR increment of 30 bpm or more within 10 min of standing or head-up tilt in the absence of orthostatic hypotension; orthostatic symptoms must be present.

Laboratory studies are performed to exclude anemia, infection, and renal and endocrine abnormalities. Plasma norepinephrine, urinary metanephrines, and 24-h urine assays for sodium and cortisol are useful in selected patients to rule out Cushing's disease, pheochromocytoma, and neuroendocrine tumors. Medication and recreational drug use should be reviewed for anticholinergics, catecholamines, exogenous thyroid hormone, alcohol, caffeine, cocaine, and tobacco.

SNRT is suspected if the patient has brief paroxysms of ST that are variably related to activity. Confirmation of the mechanism requires an electrophysiologic study. Induction of SNRT during programmed stimulation, demonstration of entrainment, and localization of the tachycardia origin in the region of the sinus node confirms the diagnosis. Further autonomic testing is not required for this condition.

If POTS or IAST with overlap features such as OI or other autonomic features are suspected, autonomic testing can be helpful. Not only does such testing assist in diagnosis, but it can also help identify putative mechanisms that underlie the patient's symptoms, thereby directing therapy [27, 28]. The most useful form of evaluation in these patients is head-up tilt table testing. The normal response to head-up tilt table testing is vagal withdrawal and sympathetic activation, leading to a physiologic increase in blood pressure and HR to preserve cerebral perfusion. Patients with POTS features may demonstrate a hyperadrenergic response during tilt with a sustained increase in HR and a narrowed pulse pressure, as seen in Figure 2 [27]. Other methods of autonomic testing may be helpful in determining whether there is postganglionic sudomotor failure or cardiovagal dysfunction. Sudomotor function is assessed with the quantitative sudomotor axon reflex test (QSART), which quantifies sweating upon acetylcholine challenge. Patients with POTS features may have variable sudomotor dysfunction. Cardiovagal function is assessed with HR variability. An abnormality in HR variability with deep breathing suggests parasympathetic dysfunction. Finally, the Valsalva maneuver also can be used to assess abnormalities in both adrenergic and cardiovagal function. Although the availability of autonomic testing is often limited to highly specialized centers, patients with severe and refractory symptoms should be referred for this testing. The role of autonomic testing in patients with IAST has not been clearly defined.

Therapy

SNRT can be terminated acutely by vagal maneuvers because the sinus node is sensitive to vagal inputs. Intravenous adenosine, beta-blockers, verapamil, or diltiazem can also be effective acutely. Recurrent or symptomatic SNRT can be successfully treated with radiofrequency ablation, which permanently interrupts the reentry circuit. Once the diagnosis is confirmed during an electrophysiology study, low power (10–30 Watt) is used during ablation to minimize damage to the sinus node itself. Multiple studies have demonstrated the safety and efficacy of ablation [17, 29, 30].

Management of IAST and POTS is considered together since as there is often significant overlap in the clinical presentation, putative mechanism, and treatment [26]. Management of IAST and POTS can be difficult, often requiring a multi-modal approach due to the heterogeneity of these syndromes. Traditionally, treatment of POTS and IAST has focused on intravascular volume expansion [9] and suppression of the HR [7], respectively. However, a mechanistic strategy may be helpful in these patients, especially for those who have features of both disorders. Our approach is to define the physiologic basis of a patient's symptoms with the cardiovascular and autonomic testing discussed, in order to form a basis for targeted therapy (Fig. 3). Autonomic testing combined with head-up tilt table testing most frequently identifies one of four particular responses: (1) hypovolemia and

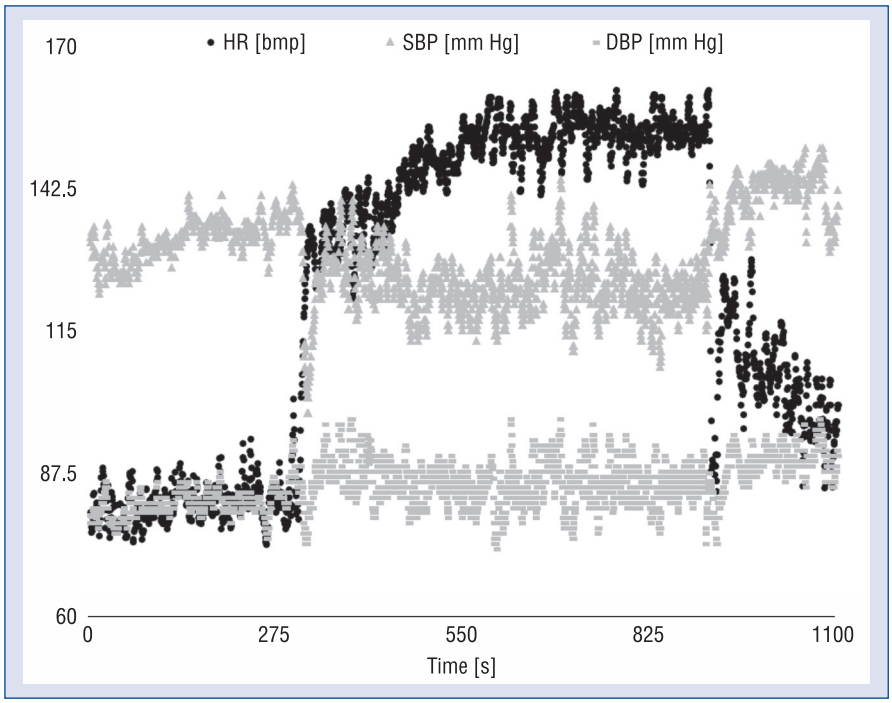

Figure 2. Tilt response in postural orthostatic tachycardia syndrome (POTS). Heart rate and blood pressure response to tilt in a typical POTS patient. Tilt occurs at approximately 275 s. Please see text for discussion; HR — heart rate; SBP — systolic blood pressure; DBP — diastolic blood pressure.

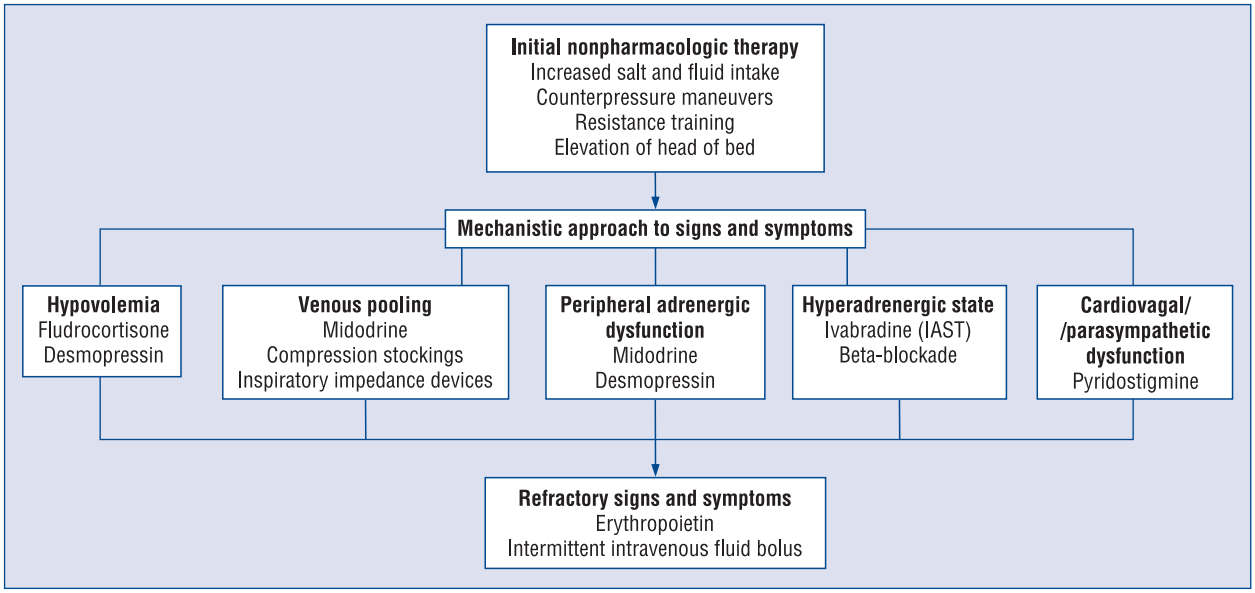

Figure 3. Overview of the approach to therapy in inappropriate sinus tachycardia (IAST) and postural orthostatic tachycardia syndrome (POTS).

venous pooling with variable transient orthostatic hypotension, (2) adrenergic failure, (3) cardiovagal dysfunction, or (4) a hyperadrenergic state.

Most patients with POTS or IAST will benefit from intravascular fluid expansion and elevation of the head of the bed to at least 15 degrees. Initially,

plasma expansion can be achieved with generous salt supplementation (> 10 g daily) and fluid intake (> 2 L daily). If evidence of hypovolemia persists, fludrocortisone can be initiated at 0.1 mg/day and titrated up to 1 mg/day in young patients. There is also evidence from a recent randomized crossover study that desmopressin (0.2 mg, once) decreases tachycardia and ameliorates symptoms in POTS [31].

Patients with venous pooling benefit from compression stockings, which are recommended if discomfort does not preclude their use. Isometric exercises in the form of physical counterpressure maneuvers have been found to successfully abort syncope in patients with vasovagal syncope by acutely increasing venous return and peripheral resistance [32]. Although physical counterpressure maneuvers have not been systematically evaluated in patients with POTS, these interventions are associated with minimal risk and are potentially useful in patients who are prone to syncope. Chronically enhancing venous return through resistance training has shown some benefit as well. Inspiratory resistance devices, which are thought to increase negative intrathoracic pressure, have also demonstrated positive results in patients with orthostatic hypotension [33], but effectiveness in patients with POTS or IAST and OI has yet to be demonstrated. If conservative measures are ineffective, then midodrine may reduce OI by increasing venous return via alpha agonist activity. However, midodrine can cause supine hypertension because of its vasopressor effect. Midodrine is also useful for patients experiencing peripheral adrenergic failure or dysfunction, revealed by a loss or attenuated late phase II response during the Valsalva maneuver [28].

In patients with cardiovagal dysfunction, as evidenced by both an abnormal HR response to deep breathing and an abnormal Valsalva ratio, acetylcholinesterase inhibition with pyridostigmine may have symptomatic benefit both acutely and over time [34, 35]. Pyridostigmine has been studied in patients diagnosed with POTS but may be helpful in IAST if there is mechanistic evidence of cardiovagal dysfunction. The most common side effect is gastrointestinal disturbance.

Autonomic testing may reveal an exaggerated phase IV of Valsalva, indicating a hyperadrenergic state. Although this mechanism is most often associated with IAST, hyperadrenergic POTS has been described. Recent studies have demonstrated increased exercise capacity in POTS with use of low-dose propranolol [36, 37]. POTS and IAST patients may be highly sensitive to beta-blockers and develop many side effects; thus these agents should be initiated at a low dose and titrated slowly. Ivabradine is a specific I_f current blocker that directly slows the HR by inhibiting sinus node automaticity. It has been approved in Europe for the treatment of patients with coronary disease and ischemic symptoms. Ivabradine has been studied in patients with IAST with POTS features, and it relieved symptoms in approximately 60% of subjects in a retrospective study of 20 patients. In a crossover study of 21 patients with IAST and randomization to ivabradine or placebo, the ivabradine cohort experienced significantly decreased HR and concomitantly improved symptoms, with 47% reporting complete symptom elimination [38]. Similarly, in a more recent study of 20 patients with IAST, 70% achieved symptomatic relief when randomized to ivabradine, while only 45% achieved symptomatic relief from metoprolol succinate [39]. Thus ivabradine has shown particular benefit in IAST; however, larger trials with longer follow-up are needed.

Catheter ablation in patients with POTS or IAST has produced disappointing results. Although the ablation can be effective in slowing the sinus rate, symptoms often persist and may even intensify. Additional risks include a new requirement for a pacemaker, phrenic nerve paralysis, and superior vena cava stenosis. We do not recommend catheter ablation for sinus node modification in POTS [40]. Trials of catheter ablation in IAST have demonstrated a high rate of symptom recurrence, even with resolution of tachycardia. Lee et al. [41] reported 12 patients undergoing initially successful sinus node modification, with 2 developing recurrent IAST and 4 others developing recurrent symptoms. Man et al. [42] reported a series of 29 patients who underwent endocardial radiofrequency ablation after mapping sites of earliest activation during isoproterenol infusion; 34% of patients had recurrent symptoms. Marrouche et al. [43] reported a 44% recurrence of symptoms after 39 patients with IAST underwent sinus node modification guided by nonfluoroscopic electroanatomic mapping, even though implanted loop recorder monitoring failed to identify recurrent IAST in symptomatic patients. Evidence from these observational cohort studies does not support routine consideration of sinus node modification in patients with IAST.

Future

While management of SNRT is straightforward, management of IAST and POTS continues to be largely inadequate. The primary issue with treating

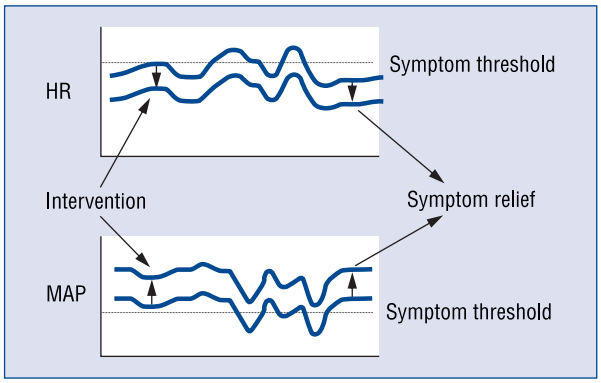

Figure 4. A model of chronic maintenance therapy to treat paroxysmal symptoms; HR — heart rate; MAP — mean arterial pressure.

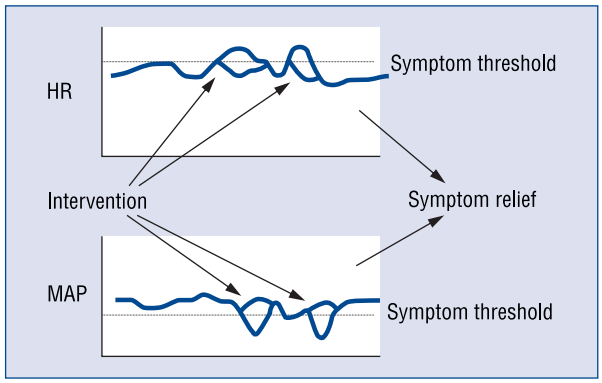

Figure 5. A model of acute intermittent therapy to treat paroxysmal symptoms; HR — heart rate; MAP — mean arterial pressure.

patients with orthostatic intolerance and ST is finding a single target to treat. The traditional targets have been total body fluid (salt, hydration, fludrocortisone), sinus node modulation (beta-blockers, ivabradine), and blood pressure (midodrine, desmopressin). The problem is that each of these treatments is a continuous maintenance therapy for paroxysmal symptoms. For pharmacologic interventions, this results in a situation where patients have a higher burden of side effects than relief of symptoms.

Conceptually, there are three models of disease treatment for these conditions. The first (Fig. 4) is a model of the current state of therapy, where chronic maintenance medications or a procedure with permanent consequences is used to try to shift the patient's current physiological parameters so that the patient crosses the symptom threshold fewer times. If the blood pressure is targeted (such as treatment with midodrine), supine hypertension may occur. If the HR is targeted (such as with treatment with a beta-blocker), the blood pressure may worsen. Time has proved that this paradigm is inadequate for many patients.

In vasovagal syncope, symptom-initiated interventions have been shown to be effective in selected patients. These include isometric exercises such as physical counterpressure measures and acutely ingesting a glass of cold water. This therapeutic strategy is shown in Figure 5.

A pharmacologic strategy utilizing this approach might involve a "pill-in-the-pocket" approach, a fast-acting medication that would exert a therapeutic effect quickly and could be delivered rapidly. At this time, no such therapy exists. However, Raviele et al. [44] demonstrated in their small randomized study of 10 patients that patients could recognize initial symptoms of vasovagal syncope during head-up tilt testing and deliver a dose of phenylephrine in this premonitory phase. Compared to placebo, patient-triggered injection of phenylephrine was significantly more effective in decreasing symptoms and hypotension during the test. A non-pharmacologic strategy utilizing a similar approach is currently being pursued. Selective electronic stimulation of the autonomic nervous system is, in concept, an excellent way to provide targeted therapy for patients with autonomic dysfunction. Sympathetic stimulation via the renal veins is currently being studied in animal models [45]. It is foreseeable that an implantable renal vein stimulator coupled with an invasive hemodynamic monitor could be developed that would provide therapy only as the blood pressure approached a programmed threshold that had been associated with symptoms of cerebral hypoperfusion in the particular patient. Similarly, patients with cardiovagal dysfunction and intermittent tachycardia may benefit from intermittent vagus nerve stimulation.

Finally, the most appealing model of disease treatment would be to identify the factors responsible for the autonomic dysregulation and treat these upstream of the effects (Fig. 6). Further research is needed to articulate these underlying upstream mechanisms. For instance, autoantibody-mediated autonomic dysfunction could be treated by immunomodulatory medications. It is not unreasonable to speculate that pharmacologic therapy in the form of a neurotransmitter modulator, a neuroprotective agent, or a neuroregenerative agent could potentially restore normal physiology. Nonpharmacologic treatments in the form of central nervous system stimulation or stem cell therapies could potentially act in this upstream fashion. This approach depends on further research

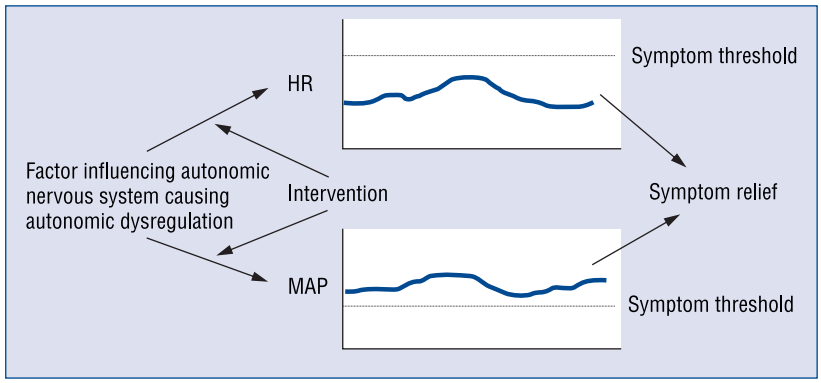

Figure 6. Upstream treatment of causative factors to prevent the development of paroxysmal symptoms; HR — heart rate; MAP — mean arterial pressure.

into the underlying mechanisms behind IAST and POTS. Given the heterogeneity and overlap in each disorder, there are likely multiple and distinct upstream mechanisms at work.

Conclusions

Patients with episodic ST and associated OI present a diagnostic and management dilemma to the clinician. Secondary ST should first be ruled out. The subsequent differential diagnosis includes SNRT, IAST, and POTS. Management of SNRT is straight forward with catheter ablation if the patients cannot tolerate their symptoms. Patients with POTS or IAST often have disabling symptoms despite extensive medical investigations and multiple empiric therapies. Both patients and clinicians are frustrated by the lack of clear diagnostic algorithms, treatment targets, and efficacious therapies.

We favor a multidisciplinary approach involving at minimum primary care, cardiology, and neurology, with input from mental health and physical therapy providers when needed. Our approach to treatment focuses on defining abnormal cardiac and autonomic parameters during the diagnostic workup and then attempting to target treatment to the putative mechanism. Side effects of the current available pharmacologic and nonpharmacologic therapies are frequent. Conservative therapy by making lifestyle adjustments and a trial of medications is recommended as the initial approach. Midodrine and fludrocortisone are available to treat hypovolemia, venous pooling, and adrenergic dysfunction; but monitoring is recommended to avoid supine hypertension. Beta-adrenergic antagonists reduce the HR and may provide symptomatic benefit. Ivabradine has demonstrated efficacy in multiple small trials in IAST.

The knowledge gap regarding the mechanisms underlying these conditions is a major barrier in developing effective therapies. A better understanding of the plausible autonomic dysregulation mediating POTS or IAST and a paradigm shift in considering "pulse therapy" or "upstream therapy" in autonomic intervention warrants further investigation.

Conflict of interest: None declared

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