Clinical Overview of Postural Orthostatic Tachycardia Syndrome (POTS)

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Introduction

Postural Orthostatic Tachycardia Syndrome, POTS, affects 1-3 million Americans and is most common in young women younger than 35. POTS has a female to male ratio of 5:1. The syndrome is not inherited, but the factors contributing to POTS development can be inherited (GARD 2017). POTS is an autonomic dysfunction syndrome, where the autonomic nervous system does not work correctly. The nervous system usually regulates blood vessel dilation and heart rate to compensate for blood flow changes when going from sitting to standing. With POTS, the heart cannot compensate for the blood flow dysregulation, and blood flow to the heart and brain are compromised, resulting in characteristic symptoms of dizziness and fainting (NHS 2019). There is incomplete knowledge as to the pathophysiology of POTS. POTS has different subtypes for the causative agent of postural tachycardia, and each subtype has multiple possible factors that all ultimately cause the same symptoms (Wells et al. 2018). The multifactorial possibilities include autonomic dysfunction, increased sympathetic tone, severe deconditioning, autoimmunity, mast cell activation, and post-viral infection (Wells et al. 2018).

POTS' pathophysiology considers the multiple possible subtypes: Neuropathic, hyperadrenergic, volume dysregulation, deconditioning, hypovolemic, norepinephrine transporter deficiency, and mast cell activation. There are unique barriers to diagnosing POTS that include inconclusive testing and assumed mental illness in patients who complain of heart symptoms that mimic anxiety. Lastly, the treatment of POTS incorporates pharmacological and nonpharmacological treatments to reduce orthostatic tolerance and increase plasma blood volume.

Pathophysiology

Symptomology

Postural orthostatic tachycardia syndrome presents in individuals with a few distinct symptoms and many non-specific symptoms to POTS. The main complaints seen in clinical settings include cardiac symptoms and noncardiac symptoms. The cardiac symptoms seen most often include rapid palpitation, lightheadedness, dyspnea (difficulty breathing), and chest discomfort. The noncardiac symptoms most often seen include headaches, nausea, tremulousness, sleep difficulties, mental clouding (brain fog), exercise intolerance, and chronic fatigue (Halstead 2018). Noncardiac symptoms specific to the GI include chronic nausea, vomiting, bloating, diarrhea, or severe constipation (Mehr et al. 2018). Symptoms cause difficulties in completing daily activities like bathing oneself, performing housework, attending school or one's vocation, and performing said activities results in fatigue and an exacerbation of symptoms (Halstead 2018).

POTS' most characteristic symptoms are pre syncope, orthostatic intolerance, tachycardia, difficulty concentrating, and lightheadedness. Many other symptoms present in POTS patients, but it is often unclear and not correctly investigated whether the symptoms are from comorbid factors or are distinctly from POTS. Unclear comorbidities create a diagnostic dilemma because symptoms like sleep issues, headaches, diarrhea, and bloating are only assumed to be caused by the POTS when these signs are seen in the general population separate from POTS. It's hypothesized that the ill-defined symptoms have caused an increase in POTS diagnosis resulting in a lack of diagnostic focus. The major problem is that there is no set

POTS symptoms that are universally accepted, and POTS itself is not a disease but a syndrome and often overlaps with other conditions (Olshansky et al. 2020). The symptoms shown in Table 1 (Fedorowski 2019, p. 354) give a broad overview of patients' most popular complaints in a clinical setting and is sorted by the body system they affect. Cardiovascular symptoms are characterized as main symptoms, while the noncardiovascular symptoms are accompanying symptoms.

Patients' cognitive impairment is often hard to explain in clinical and has come to be known as brain fog. A New York medical college study used a 38-item questionnaire and the Wood mental fatigue inventory to explore brain fog symptoms. The results of the study showed that 96% of the POTS patients experience brain fog and most commonly described brain fog as "forgetful," "difficulty thinking," "difficulty focusing," "cloudy," and "mental fatigue." The least common descriptors were "thought moving too quickly" and "detached." These descriptors are indicative of cognitive impairment. Brain fog persists while standing and also reported to continue when lying down. Recorded brain fog treatments include therapeutic interventions that fall outside POTS' standard diagnostic treatment category (Ross et al. 2013).

A major complaint among patients with POTS is gastrointestinal symptoms. GI symptoms can make it difficult to diagnose a patient and often leads to misdiagnosis. The substantial problems seen with GI symptoms are significant weight loss, malnutrition, and the need for invasive treatment to support caloric intake. Decreased oral intake of fluids and electrolytes especially concerns physicians, because electrolyte and fluid intake are essential to POTS treatment. The explained GI symptoms are seen in patients with comorbid diseases of the connective tissue like Ehlers Danlos - hypermobile type and autonomic neuropathy. Delayed gastric emptying is a significant abnormality seen in these patients. The symptoms likely have

Table 1. Clinical Presentation of Symptoms in POTS

Cardiovascular symptoms *(pathognomonic*)	
Cardiovascular system	Main: *Orthostatic intolerance, orthostatic tachycardia, palpitations, dizziness, lightheadedness, pre-syncope, exercise intolerance*
	Other frequent symptoms: dyspnoea, chest pain/discomfort, acrocyanosis, Raynaud's phenomenon, venous pooling, limb oedema
Noncardiovascular symptoms (accompanying)	
General symptoms	General deconditioning, chronic fatigue, exhaustion, heat intolerance, fever, debility, bedriddenness
Nervous system	Headache/migraine, mental clouding ('brain fog'), cognitive impairment, concentration problems, anxiety, tremulousness, light and sound sensitivity, blurred/tunnel vision, neuropathic pain (regional), sleeping disorders, involuntary movements
Musculoskeletal system	Muscle fatigue, weakness, muscle pain
Gastrointestinal system	Nausea, dysmotility, gastroparesis, constipation, diarrhoea, abdominal pain, weight loss
Respiratory system	Hyperventilation, bronchial asthma, shortness of breath
Urogenital system	Bladder dysfunction, nycturia, polyuria
Skin	Petechiae, rashes, erythema, telangiectasias, abnormal sudomotor regulation, diaphoresis, pallor, flushing

Table 1. Summarizes the most common symptoms in clinical presentations of POTS. Symptoms organized as cardiac or noncardiac and according to the body system.
Note: Reprinted from "Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management", by Fedorowski A., 2019, J Intern Med. 285(4):352–366.

multifactorial causes and thus depend on other comorbid conditions the patient has. Current thoughts on the causes of these symptoms include GI connective tissue structural abnormalities and GI tract motility abnormalities, and hormonal secretions by the gut that could directly impair autonomic transmissions (Mehr et al. 2018). The severe GI symptoms such as impaired gastric emptying and abdominal pain are more often comorbid with POTS than a sign of POTS and must be treated separately from POTS. Some patients require more than one diagnosis to treat all their symptoms properly (Chelimsky 2018).

The onset of POTS can occur from multiple factors. Most commonly, onset occurs after an immunological stressor on the body like pregnancy, vaccination, viral infection, surgery, and psychosocial stress. The cause of POTS is not known but current theories include autoimmune disorder, increased sympathetic activity, catecholamine excess, and sympathetic denervation (loss of nerve supply) that causes central hypovolemia (decreased blood flow) and reflex tachycardia (increased heart rate in response to decreased blood pressure) to name a few. Long-term prognosis is not well known, but around 50% of the patient population will spontaneously recover within 1-3 years (Fedorowski 2019).

POTS Demographic

POTS is estimated to affect 500,000 Americans, with 25% of those being disabled and unable to work (Grubb 2008), and is considered one of the most common presentations of orthostatic intolerance globally. Global prevalence studies estimate a range of 0.2 to 1% prevalence of POTS in developed countries (Zhao 2020). POTS affects younger pre-menopausal women between the ages of 15-45 years, with around an 80% female predominance (Fedorowski 2019), and other estimates found a female to male ratio of 5:1 (Arnold 2018).

Subtypes of POTS

The subtypes of POTS are descriptive classification schemes representing heterogeneous etiologies. Possible explanations for the underlying mechanisms of POTS are outlined in Figure 1 (Arnold 2018, p.6). The multiple pathways involved all conclude in orthostatic tolerance, POTS' main symptom (Goodman 2018). Subtypes of POTS include hypovolemic, neuropathic, hyperadrenergic, volume dysregulation, deconditioning, norepinephrine transporter deficiency, and mast cell activation.

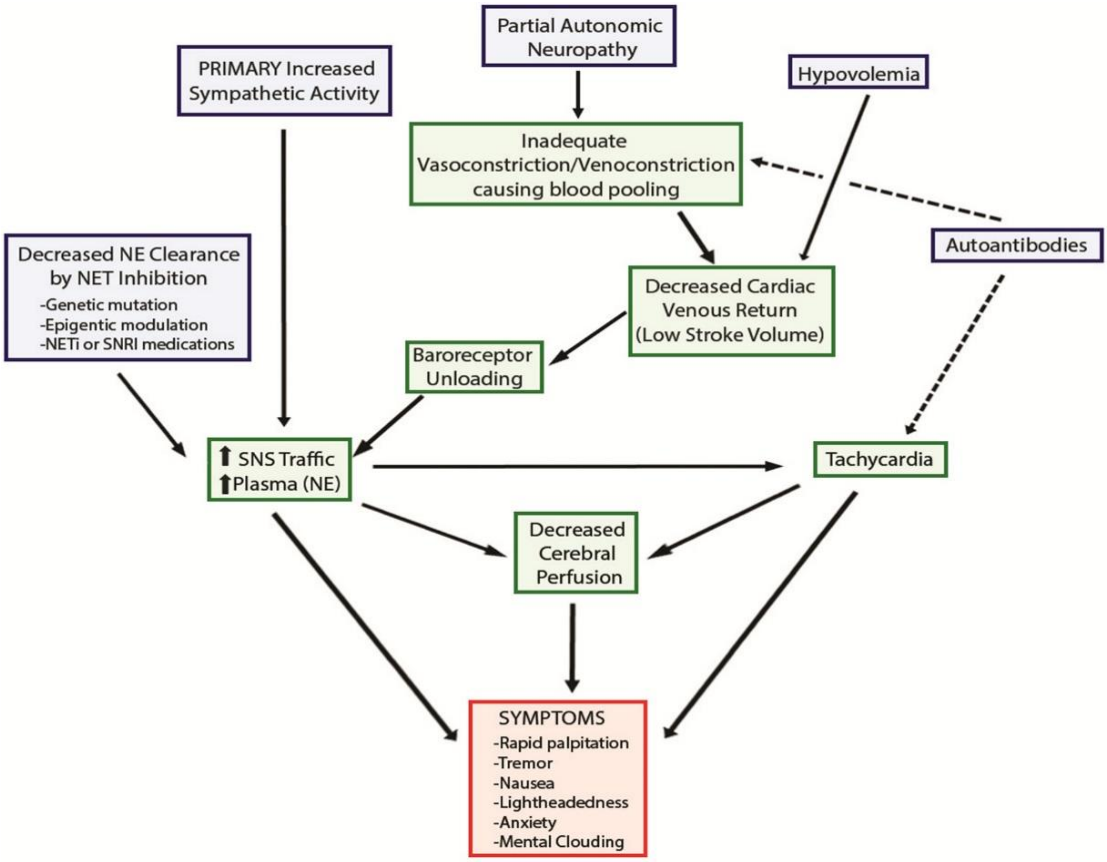

Figure 1. Multi-pathophysiology of POTS
NE, norepinephrine; NET, norepinephrine transporter; NETi norepinephrine transporter inhibitor; SNRI, selective norepinephrine reuptake inhibitor; SNS, sympathetic nervous system.
Note: Reprinted from "Postural tachycardia syndrome – Diagnosis, physiology, and prognosis", by Arnold AC, 2018, Autonomic Neuroscience Basic Clin. 215:3–11. Copyright 2018 by Elsevier.

Hypovolemia occurs in 70% of POTS patients and is the decrease of plasma volume (Zhao 2020)(Lei 2019). Secondary hypovolemic states include GI conditions that cause excessive fluid loss from nausea, vomiting, and diarrhea (Zhao 2020). Figure 2 gives a physical representation of hypovolemia in the body of a POTS patient. Hypovolemia is triggered from tachycardia paired with vasodilation in the lower limbs resulting in the cardiac baroreceptors further increasing tachycardia and resulting in hypovolemia. The hypovolemia then activates reflex tachycardia in response to the decreased blood pressure and activates vasodilation of splanchnic arteries that control blood flow to the abdominal and GI organs (Fedorowski 2019, p.355). The heart is overworking to compensate for the low blood pressure, but the body responds by vasodilating important blood vessels leading to increased tachycardia.

Studies have shown that the average plasma volume deficit in POTS patients is 13% and can cause heart rate changes and changes in norepinephrine levels (Lei 2019). Norepinephrine, along with adrenaline, increases heart rate and blood pumping in the heart, increasing blood pressure. High norepinephrine levels are indicative of reduced standing renin and aldosterone levels. Patients have an impaired vasopressor response to angiotensin II. POTS patients have high angiotensin II levels without increasing angiotensin, giving further support to an abnormal renin-angiotensin-aldosterone axis. The renin-angiotensin-aldosterone axis involves hormones that regulate blood pressure and fluid balance (Goodman 2018). Prolonged hypovolemia results in cardiac atrophy resulting in reduced stroke volumes that further induces tachycardia to maintain blood pressure and restore blood volume (Arnold 2018). If POTS patients' renin-aldosterone axis worked correctly, then renal sodium and water reabsorption would sufficiently restore blood volume (Arnold 2018). The degree of hypovolemia varies in patients and involves treatment that targets the renin-angiotensin system (Zhao 2020).

Neuropathic POTS is reported in 50% of patients and characterized by sympathetic denervation in the lower limbs (sympathetic 'fight or flight' response of vasoconstriction is blocked in the lower limbs) with inadequate vasoconstriction upon standing, resulting in venous pooling (instead of blood vessels in the legs constricting upon standing they relax) (Lei 2019)(Arnold 2018). Patients have decreased norepinephrine spillover in the lower extremities than normal systemic norepinephrine spillover, leading to the theory that there is norepinephrine reuptake dysfunction (Zhao 2020). There are currently no criteria to diagnose neuropathic POTS. Still, a presentation of patchy anhidrosis (inability to sweat normally) in the lower extremities during a thermoregulatory sweat test is common and can indicate neuropathic POTS (Arnold 2018).

Hyperadrenergic POTS Also presents in 50% of patients (Lei 2019)(Arnold 2018), and for other surveys, 30 – 60% prevalence was found (Zhao 2020). A characteristic of hyperadrenergic is norepinephrine levels ≥600pg/mL with a systolic blood pressure of at least 10mmHg within 10 minutes of standing (Lei 2019)(Zhao 2020)(Goodman 2018). Symptoms of sympathetic activation occur and include palpitation, anxiety, and tremulousness (Lei 2019).

A genetic mutation to the NET gene causes norepinephrine transporter deficiency; the loss of function gene mutation results in deficient norepinephrine transport (Zhao 2020). An increase in the supine heart rate can result, putting the body into a hyperadrenergic state with elevated sympathetic nerve activation (Lei 2019). Certain medications can have negative consequences in someone with a norepinephrine transporter deficiency. Antidepressant, attention deficit disorder, and norepinephrine reuptake inhibitor medications must be prescribed sparingly to patients with POTS because they lead to elevated catecholamine levels leading to tachycardia (Zhao 2020)(Arnold 2018).

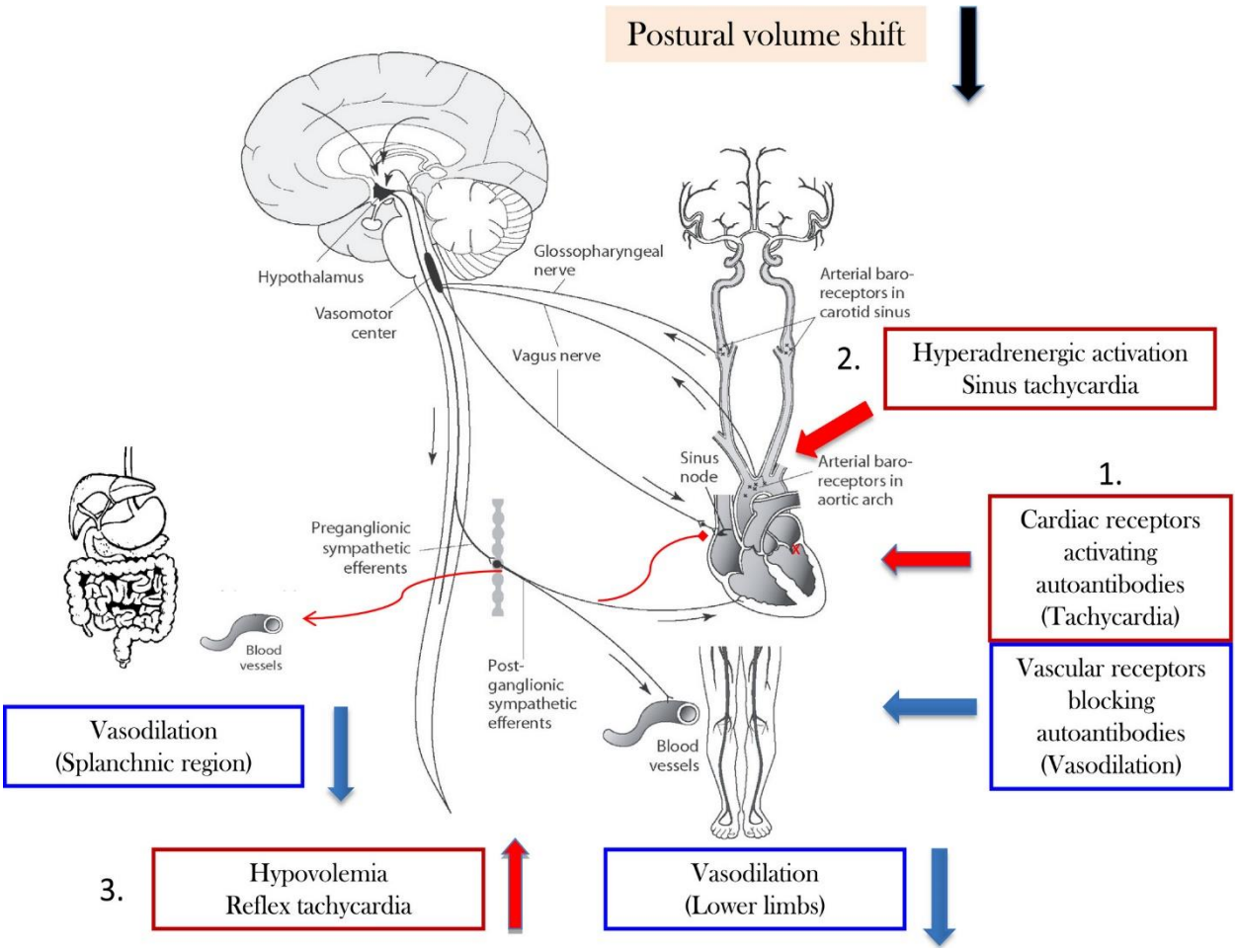

Figure 2. Mechanisms of Orthostatic Intolerance and Tachycardia in POTS. Increased sympathetic activity and circulatory catecholamine excess (2). Autoantibodies acting on adrenergic and cardiovascular receptors (1). Venous pooling, central low blood pressure, and peripheral sympathetic denervation (3).
Note: Reprinted from "Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management", by Fedorowski A., 2019, J Intern Med. 285(4):352–366. Copyright 2018 by The Association for the Publication of the Journal of Internal Medicine.

The relationship between mast cell activation and POTS is still being explored. The association is poorly understood and presents as sinus tachycardia with severe episodic flushing (Lei 2019). Mast cells are a type of white blood cell residing close to blood vessels and peripheral nerves that play roles in the inflammatory response. Mast cells are rich in histamine and other neuropeptides that, when activated, elicit sympathetic activation in POTS patients (Arnold 2018) (Fedorowski 2019). Patients have a hyperadrenergic response to a postural change

resulting in elevated urine methyl and histamines during a flushing episode. The patient will also commonly have allergic reactions and food sensitivities (Lei 2019). Flushing episodes can be triggered by multiple stimuli that include standing, exercise, meals, sexual intercourse, and menstruating with the associated symptoms of lightheadedness, dizziness, shortness of breath, nausea, and headache (Arnold 2018).

An autoimmune-mediated or inflammatory cause of POTS is also under research. Autoantibodies have been reported and include M1 to M3 receptors in 87% of POTS patients (Lei 2019). Positive antinuclear antibodies are present in up to 25% of patients, and a study has shown an increased proinflammatory level in POTS patients (Zhao 2020). Increased sympathetic drive and autoimmune markers such as non-specific autoantibodies, G protein-coupled receptors, and ganglionic ACHR have presented in POTS populations. They are further being studied as diagnostic indications of POTS (Zhao 2020).

Deconditioning is a result of impaired health-related quality of life and functional disability. The physical stress seen in those with POTS is comparative to prolonged bed rest and spaceflight (Arnold 2018). Physical deconditioning and cardiovascular deconditioning are evident with POTS, and the cause is not clear (Zhao 2020). It is undecided if deconditioning is a primary cause of POTS or secondary to a chronic illness (Arnold 2018). Gravity dependent roles may underlie POTS because it has been shown that POTS-like symptoms were induced in healthy individuals when they were in microgravity environments (Zhao 2020). Short term exercise programs reduce orthostatic tachycardia and improve systemic hemodynamic blood volume and left ventricular mass, and improve exercise tolerance in POTS patients (Arnold 2018). Exercise should be considered a promising treatment since a decreased cardiac size and

ventricular mass decrease of 16% and reduced plasma volume by 20% are commonly seen in deconditioned patients and could be reversed with exercise (Zhao 2020).

Diagnosis

Steps to diagnose POTS

POTS is a heterogeneous disorder that involves a thoughtful diagnostic approach considering the individual patients' circumstances (Goodman 2018). The standard diagnostic requirements of POTS are a heart rate increase of 30bpm that is sustained or a heart rate that exceeds 120 bpm that is maintained and occurs within the first 10 minutes of standing and is not associated with orthostatic hypotension (Grubb 2008)(Lei 2019)(Chung 2020)(Arnold 2018). Contrary to what's expected, patients can have a small decline or a modest increase in their blood pressure when being monitored (Grubb 2008). No other debilitating condition can cause the above-described criteria for POTS; the criteria needs to be specifically the result of POTS. Literature states a patient must be symptomatic for 3 (Grubb 2008) to 6 (Chung 2020)(Arnold 2018) months to receive a POTS diagnosis, but others have concern over the long wait period. A case study by Ha-Yeun Chung describes the case of two females who had a sudden onset and severe manifestation of POTS with apparent diagnostic symptoms. With a sudden onset of symptoms, these patients could not wait 3-6 months to receive a diagnosis and proper treatment, leading Chung to argue that the ≥6-month criteria can lead to misdiagnosis and continued suffering (2020). A summary of the specific diagnostic criteria for POTS is provided in Table 2.

Table 2. Diagnostic Criteria for POTS

1. Heart rate increase ≥30 bpm within 10 min of upright posture in adults. Heart rate increase of ≥40 bpm within 10 min is required in adolescents age 12–19 years.
2. Absence of orthostatic hypotension defined as a sustained drop in blood pressure ≥ 20/10 mm Hg within 3 min of upright posture.
3. Symptoms of orthostatic intolerance for ≥6 months.
4. Absence of overt causes for sinus tachycardia such as acute physiological stimuli, dietary influences, other medical conditions and medications.

Table 2. Defines the diagnostic criteria for a diagnosis of Postural Orthostatic Tachycardia Syndrome (POTS).
Note: Reprinted from "Postural tachycardia syndrome – Diagnosis, physiology, and prognosis", by Arnold AC, 2018, Autonomic Neuroscience Basic & Clinical. 215:3–11. Copyright 2018 by Elsevier.

Upon first meeting with a patient, there is a set method to properly diagnosis said patient. A detailed history, physical examination, and proper medical testing lead to the diagnosis of POTS. The first step is to obtain a detailed medical history. The medical history should document medications, other medical conditions, and a family history (Arnold 2018). Specifics should be obtained regarding the history of their illness. When did symptoms begin, was the onset gradual or sudden, were there specific events associated with onset, and what conditions improve or worsen symptoms are examples of questions to be investigated with a patient (Grubb 2008). A patient's history determines the symptom burden of tachycardia and what its severity and triggers are. Specifically, the presence of syncope and impact on daily function and quality of life should be assessed (Lei 2019). Identifying other comorbid conditions or medications that could account for the presenting symptoms is essential.

A POTS diagnosis is one of elimination when other factors cannot account for the symptoms seen. Acute physiological stimuli like panic attacks, pain, exercise, dietary influences like caffeine and alcohol, medications like anticholinergics and rebound effects of beta-blocker

withdrawal and other medical conditions like anemia, dehydration, hyperthyroidism, and inappropriate sinus tachycardia need to be ruled out as other causes of the tachycardia experienced by the patient (Arnold 2018). When obtaining a medical history from patients, some may have already had extensive testing completed and have seen multiple doctors. From a survey of 700 participants, 27% of patients reported being seen by more than ten physicians before receiving a proper diagnosis, with a median time of diagnosis being just under six years (Goodman 2018). Specific comorbid illnesses to be aware of include cardiac disease, joint hypermobility, chronic fatigue syndrome, bowel irregularities, and autoimmunity or neurological disorders (Arnold 2018). The majority of patients report onset during early teens to late ’50s and is standard for symptoms to be reported as modest to start out and then gradually become more severe. Symptoms can develop acutely, less than a month, subacutely, 1-3 months, and insidiously, more than three months (Goodman 2018). The most commonly reported precipitating factors include viral infection, post-concussion, and pregnancy, but most patients will not have a specific precipitating event (Goodman 2018).

A comprehensive physical examination assesses the biological parameters of the patient. Laboratory testing is used to rule out other causes of symptoms and includes a complete blood cell count with hematocrit, thyroid-stimulating hormone levels, electrolyte panel (Lei 2019), cortisol level, vitamin B12 level, celiac testing, antinuclear antibody testing, and Sjögren syndrome antibody panel as well as plasma catecholamines when supine and standing. The extent of laboratory testing should be on a patient by patient basis (Goodman 2018). In all patients, cardiac testing should be considered and consists of electrocardiography to investigate cardiac abnormalities (Lei 2019). EEG for intra-arterial blood pressure monitoring and expanded electrocardiography and transthoracic echocardiograph tests are all necessary to rule

out other conditions. These tests can have normal results in a patient with POTS but will rule out pathologies like orthostatic syncope, heart rhythm disorders, arrhythmia, and drug side effects (Chung 2020). A thorough examination of heart rate and blood pressure should be performed on the patient while supine, sitting, and immediately upon standing (Grubb 2008).

Tilt table testing is a gold standard for diagnosing POTS. Typical results of a POTS patient compared to a healthy patient during a head-up tilt test is shown in figure 3 (Arnold 2018, p.5). Figure 3 demonstrates how an excessively high heart rate in POTS patients doesn't increase blood pressure like expected but will maintain blood pressure, showing the blood volume system's dysregulation. The two types include standing tilt table test and head-up tilt test. Upright (head up) tilt table testing identifies vasovagal syncope but can result in false positives. Healthy patients will experience induced syncope, and thus POTS patients' results cannot be considered conclusive (Stewart 2019). The difference in Physiology between active and passive standing is not accounted for in the current POTS diagnostic criteria according to a study performed by Walker Plash and associates that specifically tests whether a passive head-up tilt table test would produce a more significant increase in heart rate then an active stand test would. The researchers agree that physicians need to differentiate between testing patients with a tilt test and a stand test; 15% of healthy subjects experienced vasovagal episodes with the passive tilt test representing 15% false positives. They concluded that an active stand test is more specific than a passive tilt test (Plash2013).

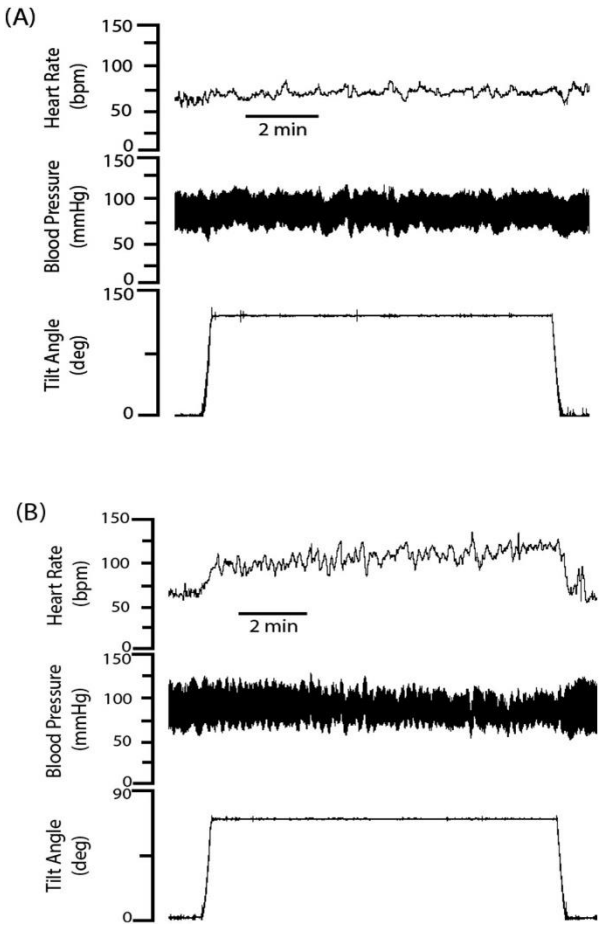

Figure 3. Head-Up Tilt Table Testing: Hemodynamic Pattern in healthy control and POTS patients.
(A) Modest heart rate increase with no change in blood pressure seen in a healthy individual.
(B) Excessive rise in heart rate with a stable blood pressure seen in patient with POTS.
Note: Reprinted from "Postural tachycardia syndrome – Diagnosis, physiology, and prognosis", by Arnold AC, 2018, Autonomic Neuroscience Basic Clin. 215:3–11. Copyright 2018 by Elsevier.

Formal autonomic testing analyzes neurovascular responsiveness to assess hypovolemia (Lei 2019). Exercise testing can be used in patients that complain of exercise intolerance to quantify exercise capacity (Lei 2019). During a physical examination, extremities can appear blueish with discoloration that suggests peripheral vascular pooling (Grubb 2008). Other tests specific to the autonomic nervous system include thermoregulatory sweat testing and

sympathetic skin potential serum samples (Grubb 2008). MRI of the head and cervical spine can view cerebral spinal fluid and see if any obvious abnormalities are present. The duplex ultrasound of arteries that supply the brain is a useful diagnostic test to find syncopal collapse evidence (Chung 2020). A neurological and psychiatric evaluation can be completed to rule out psychosomatic etiology (Chung 2020). These evaluations are especially important since Brent Goodman's study found 83% of respondents being given a psychiatric diagnosis before being diagnosed with POTS (2018). A group of researchers from the European Society of Cardiology studied the relationship between cerebral tissue oxygenation saturation and heart rate. It was found that POTS patients have lower cerebral tissue oxygen saturation during head up tilt compared to patients with normal responses to the head up tilt and that the heart rate increase was associated with a decrease of cerebral tissue oxygenation and this association was not seen in the controls. Previous studies measured cerebral blood flow and found that it was inconsistent, showing that both higher and lower levels of cerebral blood flow in POTS patients was seen. These results led the researchers to conclude that there is an unknown variable still left as to the mechanism of POTS (Kharraziha 2019).

There is not a single test to exclusively diagnosis POTS. Much of diagnosing POTS focuses on excluding conditions that mimic or exasperate POTS and identify comorbid conditions that impact management (Goodman 2018). Recommendations from the Heart Rhythm Society are summarized in table 3 and include steps that should be taken when seeing a patient who is possibly presenting with POTS (Arnold 2018, p. 5). Evaluation of possible POTS involves a careful history, thorough clinical examination, and thoughtful diagnostic evaluation. POTS is a convergence of multiple pathophysiological processes, and therefore the precise etiology remains unknown. Several subtypes of POTS are described that have overlapping

clinical features without clearly accepted definitions and thus are not currently helpful as individual patient labels. Patients must be treated on a patient by patient basis, based on their symptoms and the context they present within.

Table 3. Heart rhythm society recommendations for evaluation of POTS

Investigation	Utility	Comment
Initial Evaluation		
Medical history	Essential	Document medications, other medical conditions, diet and exercise history, family history, and details on nature of tachycardia including chronicity, triggers, modifying factors, presyncopal or syncopal episodes, symptoms and impact on daily activities.
Physical examination	Essential	Detailed cardiovascular, neurologic, autonomic, and other systems assessment.
Orthostatic vitals	Essential	Blood pressure and heart rate should be measured while lying down (>5 min) and ideally again after 1, 3, 5, and 10 min of standing.
Electrocardiogram	Essential	Rule out pre-existing cardiovascular disease and cardiovascular conduction abnormalities.
Additional Evaluation		
Blood work	Some patients	In patients with evidence for specific underlying causes such as dehydration, anemia, and hyperthyroidism. Supine and standing norepinephrine levels in patients with evidence for hyperadrenergic POTS.
Cardiovascular testing	Some patients	In patients with suspected cardiac conduction or structural abnormalities (e.g. Holter monitor, echocardiogram, exercise stress testing).
Head-up tilt table testing	Some patients	In patients with normal orthostatic vital signs with high clinical suspicion, or in patients with convulsions or seizure disorder.
Autonomic function tests	Some patients	In patients with symptoms of autonomic neuropathy, or in patients whose symptoms do not resolve or markedly improve with treatment.

Table 3. The Heart Rhythm Society recommendations for evaluating POTS in patients, explaining when certain diagnostic tests are helpful for a correct diagnosis.
Note: Reprinted from "Postural tachycardia syndrome – Diagnosis, physiology, and prognosis", by Arnold AC, 2018, Autonomic Neuroscience Basic & Clinical. 215:3–11.

Misdiagnoses

A survey of 4835 participants explored the diagnostic journey of patients living with POTS. The study used an online community-based cross-sectional survey with POTS patients diagnosed by a physician. The survey included predominantly white (93%) and female (94%) POTS patients of childbearing age, with half of the participants having developed symptoms around the age of 14. Clinicians assessed around 9% of respondents at expert sites in autonomic disorders. Table 4 (Shaw 2019, p.442) summarizes the essential information provided by participants about their diagnostic journey. Frequently reported were patients being misdiagnosed with other ailments, seeing many physicians prior to diagnosis with POTS, and suggesting POTS as a potential diagnosis to their physician. Respondents reported on average that they saw 7±11 physicians before a diagnosis, and 21% reported having to see more than ten doctors before a diagnosis was made. On average, patients waited a median time of 24 months after the presentation of initial symptoms before a POTS diagnosis was made (Shaw 2019).

In the same study, patients who waited more than ten years after initially visiting a physician for symptoms made up 15% of the respondents. Interestingly female participants reported longer diagnostic delays of 5 ±7.2 years than their male counterparts, waiting 3 ±4.4 years even though the illness is more prevalent in females. There was no difference in diagnostic delays seen between races. Improvement has been seen in diagnostic delays with 11.6-month shorter wait times for patients diagnosed after 2009 compared to those diagnosed from 2000 – 2009. Despite the improvement in diagnostic delay, since 2009, there is still 4.7±6.9 years of delay time. Of the correspondents, 75% of patients reported that a physician misdiagnosed their POTS symptoms before being diagnosed with POTS, as is seen in Table 4, and prior to diagnosis, 67% of patients saw a physician who acknowledged a physical illness but was unsure

how to proceed. Of participants, 77% encountered a physician who suggested their symptoms were due to a psychiatric or psychological problem before receiving a POTS diagnosis. Furthermore, 28% of patients report that they were suffering from psychological issues before they were diagnosed with POTS. Of the patients diagnosed with POTS, 37% of participants reported being told that they were suffering from a psychiatric problem. Misdiagnosis is likely to occur in POTS because of the many possible and common comorbid diseases seen with POTS that include asthma, autoimmune diseases, iron deficiency anemia, and gastroparesis, with prevalence rates higher in the POTS population than the general public (Shaw 2019).

Table 4. Diagnostic Journey in POTS

	Number (%) or mean (SD)
Misdiagnosed prior to POTS diagnosis	3421 (75%)
POTS diagnosis suggested by patient	1557 (34%)
Number of physicians seen prior to diagnosis	7 (11)
Number of ED visits prior to diagnosis	9 (16)
Specialty of physician who made diagnosis	
Cardiologist	1973 (41%)
Cardiac electrophysiologist	696 (15%)
Neurologist	889 (19%)
Family physician	392 (8%)
Emergency room physician	79 (2%)
Rheumatologist	74 (2%)
Other	711 (15%)

Emergency department, ED. The total number of respondents to this question was 4760. Additional physicians who made the diagnosis under the category 'other' included nephrologists, gynaecologists, otolaryngologists and unsure/not specified.

Table 4. Diagnostic Journey in POTS
Note: Reprinted from "The face of postural tachycardia syndrome – insights from a large cross-sectional online community-based survey", by Shaw BH, 2019, Journal of Internal Medicine. 286(4):438–448. Copyright 2019 by the authors.

Julian Stewart and associates conducted a study to evaluate false positives with tilt table testing. Upright tilt table tests were found to result in false positives because of tilt induced fainting. It was found that POTS like fainting is induced in healthy volunteers because splanchnic blood volume was markedly decreased, causing splanchnic pulling in the legs. The head-up tilt table was inducing fainting in normal patients and cannot be used to diagnose POTS patients reliably (Stewart 2019).

Andrew Owens and associates investigated the hypothesis that POTS patients experience atypical anxiety phenotypes with affective symptoms related to apprehension and vigilance of physiological feedback rather than neurotic or trauma-related factors. They found that patients with POTS were more sensitive to anxiety than the controls regarding the anxiety sensitivity index; specifically, all patient groups scored higher on the item "it scares me when I feel faint" than controls. POTS patients scored higher than controls on the global body vigilance scale. There was no difference between controls and POTS patients regarding the childhood traumatic events scale. There were no significant differences in the self-consciousness scale revised. This study provides important insight when diagnosing a patient with POTS and gives variables to compare what is normal in a POTS patient and what is not, allowing proper diagnosis of psychosomatic disorders (Owens 2017).

Quality of Life After Diagnosis

A study conducted by Elizabeth Keating and associates focused on physical functioning and disability in children and adolescents with chronic pain. The study included 141 pediatric patients from the ages of 7 to 20 years, with all patients experiencing chronic pain and clinical symptoms that suggest POTS. Respondents completed the FDI's functional disability inventory,

a 15-item questionnaire that measures physical functioning and disability in children and adolescents with chronic pain. No difference was found between pain patients with and without POTS in regard to depression or functional disability. There was a significant difference between the groups for anxiety, with POTS patients reporting more anxiety. The symptoms reported by the POTS patients include suffering from fatigue 94%, with dizziness 69%, nausea and vomiting 69%, memory and concentration problems 61%, and with fainting 23%. The most common chronic pain locations were abdominals pain 49%, headaches 49%, joint/extremity pain 43%, back/neck pain 38%, and chest pain 19%. From the study, adolescents with chronic pain and adolescents with chronic pain and POTS experience the same moderate functional disability and score similarly (Keating 2017).

A postal survey conducted on POTS patients from a hospital in Southwest England assessed patient demographics, diagnosis times, diagnosis methods, treatments, and treatment response. They found that having POTS causes life quality to decline by around 4 pts from 7.5 to 3.75 on a 10-point scale. Around ½ of the respondents reported improved day-to-day functioning from 3.21 to 6.14 after receiving treatment. A delay in receiving a diagnosis was reportedly as common as seeing multiple healthcare professionals before receiving adequate treatment. Acute physicians and cardiologists diagnosed the majority of patients. Every patient diagnosed with POTS was also continuously experiencing dizziness and fatigue. A majority of patients were experiencing brain fog, palpitations, nausea, temperature disturbance, tremor, chest pain, bladder disturbance, visual changes, and sleep disturbances. Around 45% of patients had injured themselves directly because of POTS. After diagnosis and effective treatment, symptomatic relief is had in POTS patients, and quality of life improvements are possible (Flack 2018).

A study examined self-reported autonomic symptoms in POTS patients and used the COMPASS-31 to compare POTS patients' scores, compare autonomic function/neuropathy (AF/N), and compare healthy controls. Patients with POTS diagnosis reported more significant symptom burden across all functional domains of autonomic function with findings consistent with clinical experience and prior reports by POTS patients. The study used regression analysis to exclude the possible influence of age, gender, and effective scores on the gathered data. The article concluded that POTS patients have significantly higher autonomic symptom burden than healthy controls with scores spanning multiple autonomic function domains. It was also confirmed that the severity of POTS' overall symptom burden is similar to AF/N autonomic failure/neuropathy (Rea 2017). POTS quality of life can be compared to other patients of AF/N.

Lastly, a study on the quality of life after diagnosis with 1702 patient reports found that patient symptoms had generally improved a little, 42% of patients. While 29% said their symptoms had improved a lot, and 10% of patients reported no change in symptoms, with 44% of patients claiming their symptoms had worsened, and 63% of respondents believed they have always had a tendency to have POTS-like symptoms for most of their lives. And of the participants who said that their symptoms improved, 29% reported medications as the predominant reason for this improvement. The survey saw that 83% of respondents also suffered from at least one additional medical condition (Shaw 2019).

Treatment

Pharmaceutical Medication

Drug therapy should be used when nonpharmacological interventions do not adequately relieve symptoms. Treatment needs to be tailored to the patient because of the heterogeneity of POTS. No medications are currently approved by the US Food and Drug Administration or Health Canada, specifically for treating POTS. Several drugs can expand blood volume and lead to a reduced orthostatic tachycardia response. Erythropoietin addresses the deficit in red blood cell volume in POTS patients. The medication causes vasoconstrictor effects and improves red blood cell volume in patients without exceeding plasma volume, ultimately reducing orthostatic tachycardia. Drawbacks include a high cost, subcutaneous administration, and risk of life-threatening complications such as myocardial infarction and stroke.

Desmopressin is a synthetic version of a natural antidiuretic hormone that increases kidney mediated free water reabsorption without sodium retention. The water reabsorption reduces the upright heart rate in patients with POTS and improves symptom burden. Adverse effects include edema, headache, and hyponatremia and are a concern with daily use. Patients are advised to use desmopressin no more than once a week for acute improvement in symptoms, and intermittent monitoring of serum sodium levels is recommended for safety. Fludrocortisone is a synthetic aldosterone analog that enhances sodium and water retention. There is currently no high-level evidence that this medication is effective for POTS and possible adverse effects include hyperkalemia, hypertension, fatigue, nausea, headache, and edema (Lei 2019).

A systematic review and meta-analysis that included eight studies assessing beta-blockers efficacy and treating POTS in children and adolescents found that beta-blockers had significantly higher efficacy than their comparable controlled treatments. Beta-blockers might also be more effective than controlled treatments. During a standing test, the beta-blocker group lowered the heart rate increment and significantly decreased in symptom scores than the controlled treatments. Overall, it was concluded that beta-blockers are effective in treating POTS in adolescents and alleviate orthostatic intolerance, improving hemodynamic abnormalities. Metoprolol, a beta-blocker, had efficacy in 79.5% of POTS patients in this study, and the control group had 57.3% efficacy. Beta-blocker efficacy comes from blocking cardiac β-1 receptors and provides a negative inotropic effect, slowing the heart and decreasing tachycardia. Another hypothesis is that beta blockers inhibit renin secretion by inhibiting β-1 receptors of the juxtaglomerular cells. Inconsistencies in the efficacy of beta-blockers are found throughout multiple studies, and reasons for these contradictions seem to be multifaceted. POTS is a heterogeneous disorder, and one drug is unlikely to treat all manifestations (Deng 2019).

Lifestyle Changes

POTS' nonpharmacological treatment involves physical reconditioning through exercise training and volume expansion from increased salt and fluid intake. Cardiovascular deconditioning is a common feature in POTS patients regardless of the etiology. Heart size and mass can be smaller in patients with POTS, even when compared to age and sex-matched healthy individuals. Plasma and blood volume reduction are seen in those with POTS. A barrier to treatment is that most individuals have significant limitations for low-intensity physical activity. A small heart coupled with low blood volume causes a fall in stroke volume during standing with the heart rate increasing to compensate, known as the baroreflex. Studies done on astronauts in

zero gravity environments that induce bed rest deconditioning to study how to counteract deconditioning can be used to brainstorm POTS treatments. Patients will often experience periods of bed rest during their illness. Studies show that exercise training combined with replenishing plasma and blood volume increases cardiac size and mass, preventing cardiovascular deconditioning. To increase blood volume exercise training and increased salt and fluid intake is a necessary part of POTS treatment. Fu put together an effective treatment plan that involves 4 categories of nonpharmacological treatments geared towards reversing body deconditioning and improving blood volume. These treatments are considered cost-effective, simple, and provide low side effects (Fu 2018).

Regular exercise is a pillar of POTS treatment and is especially needed when an illness presents in a chronic and debilitating fashion. A workout regimen should contain aerobic endurance reconditioning with partial strength resistance training focused on the lower body. Supervised training is mo preferred. Current exercise training programs for POTS are based on spaceflight / head-down bedrest exercise countermeasures. How to train muscles in zero gravity are focused on exercising that promote proper blood flow. Exercise training increases peak oxygen uptake by 8% and cardiac size and mass by 12% and 8%, and blood volume by 6%.

Contrary to pharmacological therapies (β-blockers), exercise training improved patient well-being and quality of life. Research has shown 53% of patients in studies, and 71% in the POTS registry improved with exercise therapy and ‘no longer meet the objective criteria for POTS’ and are in remission. Factors that would limit an exercise program for a POTS patient include medical problems, personal reasons, and training being ‘too difficult’ (Fu 2108).

Endurance training for POTS patients should begin with a horizontal mode of training. A specific recommendation is to row; rowers have the largest hearts of all competitive athletes.

Spread all workouts throughout the week to abstain from taking multiple days of no exercising. As a patient continually exercises, they will gradually increase heart mass and continuously become more fit. Each increase in ability should be met with an increase in training difficulty; this builds endurance overtime (Fu 2018).

Resistance training focuses on the lower body and core to strengthen the muscles that act as a pump in an effort to increases venous return. Weightlifting is recommended and can start from once a week to twice a week and so on and so forth. It is recommended that workouts are performed on seated equipment until the patient is appropriately strong and fit. Other options are to use a floor mat, resistance bands, or physio-ball similar to Pilates. Weight training causes muscle soreness for days after exercise and can be done after cardio workouts but not too often, ensuring there are days between resistance workouts (Fu 2018).

Volume expansion of plasma and blood is necessary for POTS patients who have reduced plasma and blood volumes. Low volume causes small stroke volume and activates reflex tachycardia while standing. Patients need chronic volume expansion through salt and fluid intake and/or sleeping in a head-up position. Both therapies increase plasma volume and support exercise training. Salt loading of up to 10g/day increases plasma volume and orthostatic tolerance. Salt can be consumed progressively and slowly increased every day by adding salt to foods. Salt tablets are not recommended and cause osmotic loading in the stomach, resulting in nausea, vomiting, dehydration, and further blood/plasma volume reduction. Water uptake should increase with salt uptake. 3L per day is a starting recommendation. High salt and water regimen should be started when exercise training is started. Another method for volume expansion is sleeping in the head-up position. Sleeping is done with the head, or the body elevated during sleep either by extra pillows or hard objects under the front bedposts. Sleeping in this position

allows the body to retrain itself gradually. Mild orthostatic stress promotes blood volume to move to the lower extremities causing a decreased central blood volume and activating the angiotensin-aldosterone system resulting in saltwater retention and volume expansion. Head-up tilt at night causes chronic volume expansion in patients with autonomic failure. The magnitude of volume expansion using head-up tilt is unknown and needs to be further investigated (Fu 2018).

Physical countermeasures require little or no equipment and involve using your body to combat orthostatic tolerance. Table 5 (Fu 2018, p.24) summarizes physical maneuvers to counter orthostatic tolerance. Squeezing a rubber ball increases mean arterial pressure. The muscle contraction promotes sympathetic activation or vagal withdrawal, commonly known as the exercise pressor reflex. To increase arterial pressure, patients can contract their abdominal and leg muscles while squeezing a rubber ball. These measures are best used to counter or delay neutrally mediated syncope. It will not provide long-term relief but acts as a quick fix when needed (Fu 2018).

Similar to ball squeezing is leg crossing and muscle tensing. The Dutch leg-crossing maneuver done by crossing one foot in front of the other and squeezing the thigh and gluteal muscle together will restore venous return and prevent further blood pooling in the lower body and increases cardiac output as well as mean arterial pressure while upright. With the increase in intramuscular pressure, the vein's transmural pressure decreases such that venous distension is reduced, and cardiac output increases shifting blood centrally. Muscle pumping of the legs translocates blood against a substantial gradient. Squatting is effective because it involves bending, muscle tensing, and sitting. For a brief increase in circulation, forceful coughing can be effective. The forceful cough raises intrathoracic pressure forcing blood into the aorta and its

branches, and during inspiration, blood is drawn into the right heart, completing an established circulation. Cough cardiopulmonary resuscitation can prevent loss of consciousness when time is needed before conventional cardiopulmonary measures can be taken (Fu 2018).

Table 5. Physical maneuvers to counter orthostatic tolerance

Maneuvers	Brief description	Action mechanisms
Squeezing a rubber ball	Static or rhythmic muscle contraction to increase mean arterial pressure and prevent orthostatic intolerance or syncope	Sympathetic activation, vagal withdraw, or both via the exercise pressor reflex
Leg crossing and muscle tensing	Crossing one foot in front of the other and squeezing the thighs and gluteal muscles together	Restoration of venous return and prevention of further blood pooling in the lower body
Muscle pumping	Swaying, shifting, tiptoeing, or walking	Activation of the muscle pump in the legs to increase venous return
Squatting, sitting, lying down	Squatting is a combination of sitting, bending and muscle tensing; sitting and lying down to reduce/eliminate gravitational stress	Facilitating venous return from the legs to the heart and increasing central blood volume
Cough cardiopulmonary resuscitation	Forceful coughing	Increasing intrathoracic pressure to force blood out of the chest into the aorta and its braches
Negative-pressure breathing maneuver	Breathe through an inspiratory impedance threshold device	Using endogenous respiratory pump to increase venous return and central blood volume
Skin surface cooling	Spray cold water, use fan and cooling towel to cool the skin in a hot environment	Decreasing blood supply to the skin and reducing clinical symptoms

Table 5. Physical maneuvers to counter orthostatic tolerance
Easy, low-equipment maneuvers that act as physical countermeasures to combat orthostatic tolerance symptoms and increased cardiac output.
Note: Reprinted from "Exercise and non-pharmacological treatment of POTS", by Fu Q, 2018, Autonomic Neuroscience Basic and Clinical. 215:20–27. Copyright 2018 by Elsevier.

A multitherapeutic/multidisciplinary approach has been used to aid patients. It can include physical therapy, biofeedback, occupational therapy, recreational therapy, relaxation training, stress management, wellness instruction, and pain/physical symptom management training (Fu 2018).

Apparel

Compression stockings are effective at reducing peripheral venous pooling and enhance venous return to the heart. Waist-high stockings with compression of 30-40 mm HG deliver the best results (Lei 2019). By regulating fluid distribution in the lower extremities, orthostatic symptoms can be prevented. Compression stockings are effective at treating lower extremity edema by distributing blood and extravascular fluid with the help of external forces. Stockings aren't often adhered to as a treatment because stockings are reported to be uncomfortable. Particularly difficult is putting on and taking off the waist-high stockings. A new type of compression stocking is being designed by the University of Minnesota College and Design Wearable Technology Lab that can switch compression on and off, allowing removal with minimal friction. With their design, the degree of compression can be altered based on comfort level. It was found that Change in heart rate was significantly lower when garments of compression were worn during the tilt table test. They concluded that the compression garments cause a decrease in venous pulling, which allowed an increase in venous return to the heart, causing a higher stroke volume and ultimately reducing heart rate. Also found was that the fit of a compression garment is important in correctly producing the intended cardiovascular changes. The garments can ultimately serve to improve venous return to the heart and is designed as an active compression garment. These active garments have similar results to compression

stockings and are a new novel treatment alternative. The athletic garments allow patients to adhere to their compression regimen and improve patient quality-of-life (Kelly 2019).

Gradient compression stockings decrease venous pooling, increase systolic blood pressure, reduce stroke volume and cardiac output, and prevent tachycardia upon standing. Leg and abdominal compression are more effective than solo leg compression. Abdomen-high compression stockings are the recommendations. NASA garments consist of three pieces of two-legs talking and a biker-style short, less intimidating than the commercially offered one-piece stocking. Also included in the astronaut attire are zippers at the ankles and on the shorts to lessen compression during necessary times. This feature would be helpful in commercial compression garments (Fu 2018). A summary of nonpharmacological treatments for POTS is summarized in figure 4 (Fu 2018 p.23). Each therapy is useful for a different pathway within POTS. When combined, it creates an effective treatment plan to return a patient to functioning levels with a higher quality of life.

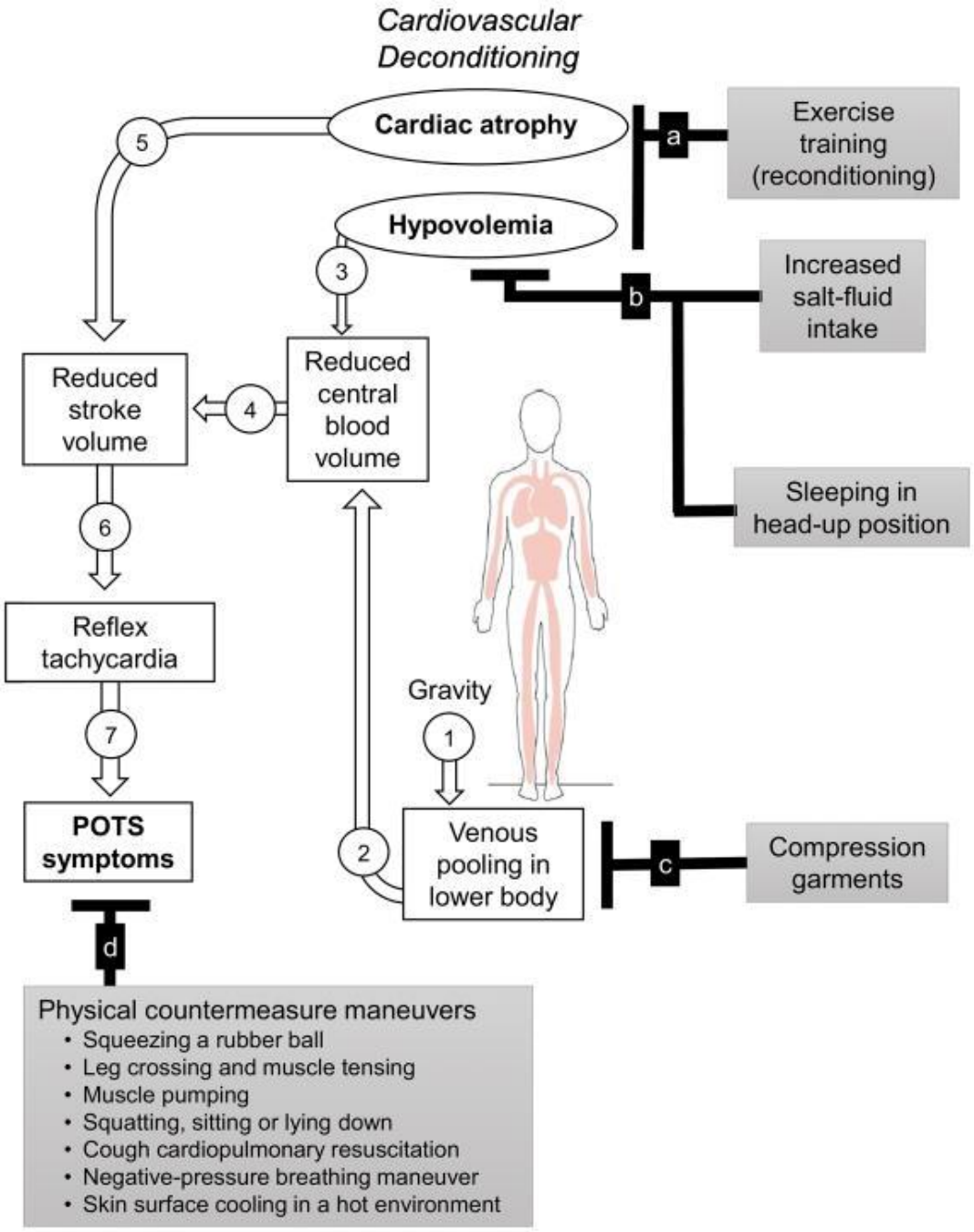

Figure 4. Nonpharmacological treatments of POTS
Each treatment is aimed towards a different physiological process found within POTS. (a) Exercise trainingdecreases cardiac atrophy. (b) Salt-fluid intake and upright sleeping deaacrease hypovolemia. (c) Compression garments mechanically reduce venous pooling in legs. (d) Physical countermeasures relieve the symptoms of POTS from reflex tachycardia. *Note*: Reprinted from "Exercise and non-pharmacological treatment of POTS", by Fu Q, 2018, Auton Neurosci Basic Clin. 215:20–27. Copyright 2018 by Elsevier

Summary

Postural Orthostatic Tachycardia syndrome affects a large majority of the younger female population. POTS presents as a heart rate increase of 30bpm that is sustained or a heart rate that exceeds 120 bpm that is maintained and occurs within the first 10 minutes of standing and is not associated with orthostatic hypotension. The symptoms that occur from the body's dysregulation ranges from pre-syncope, palpitations, and heat intolerance to abdominal pain, polyuria, and nausea. POTS affects females more than males and is more prevalent in Caucasian females. The multiple subtypes of POTS make diagnosis sometimes trickier but ultimately leads to a well-rounded treatment plan for the individual. Diagnosing POTS takes a healthcare provider that addresses the multiple steps in diagnosing a patient with POTS. Collecting a detailed history and running the correct diagnostic tests. Misdiagnosis is more common in POTS because comorbidities are in a large percentage of the POTS population. Quality of life generally increases after receiving a diagnosis and subsequent treatments. Nonpharmacological treatments are preferred because they are proven to be as effective as pharmaceutical medications. Treatment focuses on reducing orthostatic tolerance and increasing plasma blood volume. Changing sleeping habits and learning easy equipment-free techniques fulfills a comprehensive treatment program. Regular exercise helps condition the body into correct responses to tachycardia, and increasing salt and water allows the body to build up its blood volume. Lastly, compression stockings are effective co-treatment to support the body throughout the day by supporting blood flow and prevent venous pooling. POTS is debilitating but can be successfully treated with a proper diagnosis and treatment plan.

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