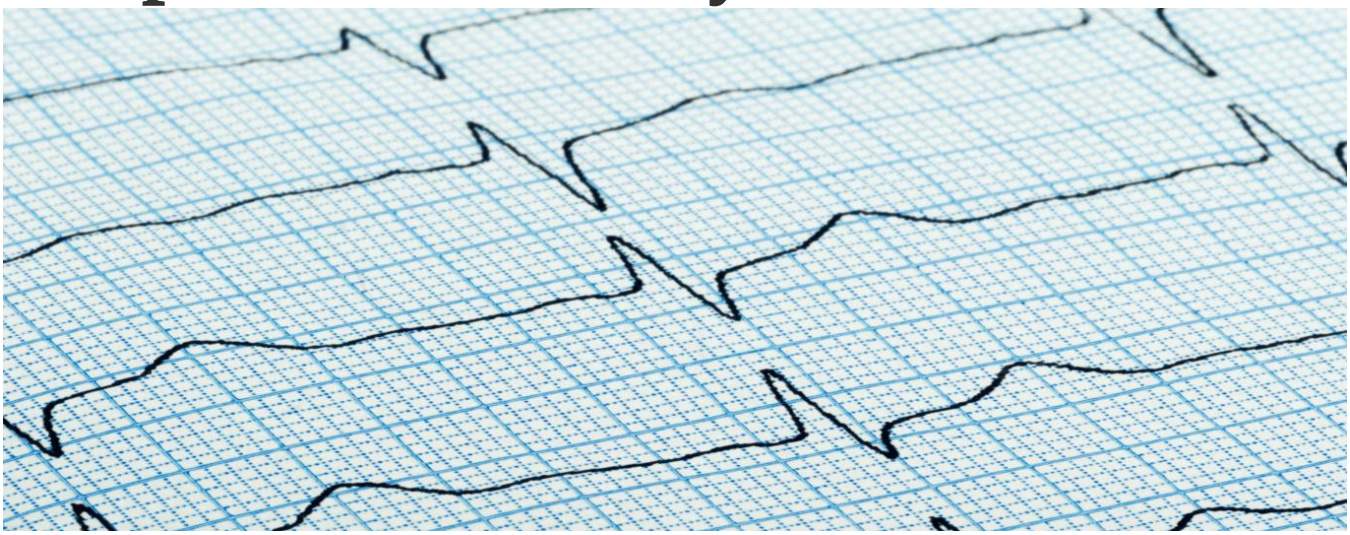
How Tachycardia Affects Healthy People with Anxiety and Stress



Many physical symptoms of anxiety can cause further anxiety as mimic serious health problems. One of the most common is tachycardia, also known as "rapid heartbeat." A healthy heartbeat is (depending upon their age and physical condition) generally is between 60 and 90 beats a minute. Tachycardia is a heartbeat described as over 90 - 100 beats per minute in a healthy adult and it is often followed by other symptoms due to the way tachycardia affects your body.

Tachycardia often causes a considerable amount of fear because when it feels like it is occurring randomly it can make you think that something is wrong with your heart. But often it's anxiety that causes the symptoms.

How Anxiety Causes Tachycardia

There is more than one type of tachycardia, and more than one cause of tachycardia related to stress and anxiety. There are two primary causes/types of tachycardia with anxiety. These include:

Sinus Tachycardia (SVT)

The vast majority of experts in the anxiety field focus on one type of tachycardia: sinus tachycardia, which is caused by activation of the fight or flight system. This is the response that is most active during anxiety, triggering the nervous system to react. Normally your body rushes with adrenaline during times of intense fear to trigger a series of responses that prepare your body to fight or run..

Those with anxiety are thought to have an overactive fight or flight system (Sympathetic Dominance) that is active throughout the day even when there are no immediate dangers. This floods adrenaline into your bloodstream which causes your heart to speed up as a response. Those with severe anxiety and anxiety attacks may experience this sensation even when they're not aware of having anxious thoughts.

When people talk about their heartbeat increasing because of anxiety, and when experts refer to anxiety tachycardia, this is almost always what they're talking about. Patients with sympathetic dominance can often experience periods of Sinus Tachycardia many times during the day. So here is the problem: because SVT happens sporadically, it can be difficult to diagnose. An electrocardiogram (ECG) done in the doctor's office records the heart's electrical activity for only about 5 - 15 minutes. However, an HRV test will reveal patients in sympathetic dominance and the patients increased probability of having SVT.

"The Effect of Anxiety on the Heart *

When someone is anxious, their body reacts in ways that can put an extra strain on their heart. The physical symptoms of anxiety can be especially damaging among individuals with existing cardiac disease.

Anxiety may have an association with the following heart disorders and cardiac risk factors:

- **Rapid heart rate (tachycardia)** – In serious cases, can interfere with normal heart function and increase the risk of sudden cardiac arrest.
- **Increased blood pressure** – If chronic, can lead to coronary disease, weakening of the heart muscle, and heart failure.
- **Decreased heart rate variability** – May result in higher incidence of death after an acute heart attack."

*Johns Hopkins Medicine: "Anxiety and Heart Disease" https://www.hopkinsmedicine.org/health/conditions-and-diseases/anxiety-and-heart-disease

Supraventricular Tachycardia

However, it is not the only type of tachycardia that is related to anxiety. An often forgotten type of tachycardia is supraventricular tachycardia, a heart arrhythmia that can trigger tachycardia during periods of anxiety, especially when that anxiety causes hyperventilation.

Rapid breathing is very common for those with anxiety, and hyperventilation itself plays a prominent role in panic attacks. Some people develop hyperventilation syndrome, which is a tendency to hyperventilate even without anxiety.

When you hyperventilate, you expel too much carbon dioxide and take in too much oxygen. This throws off your body's balance and causes your blood vessels to constrict. When your ventricles constrict, this makes your heart need to work harder to get blood around your body, and that's what triggers the tachycardia.

Deep breathing is a good way to calm the body when you are struggling with anxiety. By slowing down your breathing, you are able to control your hyperventilation and your anxiety at the same time.

Cognitive behavioral therapy and medication can also be useful, as can many self-help techniques. Anxiety is treatable and manageable, so taking these steps is a good way to regain some control over the way your heart feels.

I'm a Physician Battling Long COVID. I Can Assure You It's Real

Monica Verduzco Gutierrez, MD
October 27, 2022

Dr. Monica Verduzco Gutierrez, MD

One in 5. It almost seems unimaginable that this is the real number of people who are struggling with long COVID, especially considering how many people in the US have had COVID-19 at this point (more than 96 million). Yet I continue to hear of people who are struggling, and we continue to see a flood of people in the long COVID clinic. It isn't over, and long COVID is the new pandemic.

Even more unimaginable at this time is that it's happening to me. I've experienced not only the disabling effects of long COVID, but I've also seen, firsthand, the frustration of navigating diagnosis and treatment. It's given me a taste of what millions of other patients are going through.

I caught COVID-19 (probably Omicron BA.5) that presented as sniffles, making me think it was probably just allergies. However, my resting heart rate was up on my Garmin watch, so of course I got tested and was positive.
With my symptoms virtually nonexistent, it seemed, at the time, merely an inconvenience because I was forced to isolate away from family and friends, who all stayed negative.

But 2 weeks later, I began to have urticaria — hives — after physical exertion. Did that mean my mast cells were angry? There's some evidence these immune cells become overactivated in some patients with COVID. Next, I began to experience lightheadedness and the rapid heartbeat of tachycardia. The tachycardia was especially bad any time I physically exerted myself, including on a walk. Imagine me — a lover of all bargain shopping — cutting short a trip to the outlet mall on a particularly bad day when my heart rate was 140 after taking just a few steps. This was orthostatic intolerance (POTS caused by Sympathetic Dominance).

Then came the severe worsening of my migraines — which are often vestibular, making me nauseated and dizzy on top of the throbbing.

I was of course familiar with these symptoms, as professor and chair of the Department of Rehabilitation Medicine at the Joe R. and Teresa Lozano Long School of Medicine at University of Texas Health Science Center San Antonio. I developed a post-COVID recovery clinic to help patients.

So I knew about postexertional malaise (PEM) and postexertional symptom exacerbation (PESE), but I was now experiencing these distressing symptoms firsthand.

Clinicians really need to look for this cardinal signs of long COVID as well as evidence of myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS). ME/CFS is marked by exacerbation of fatigue or symptoms after an activity that could previously be done without these after effects. In my case, as an All-American Masters miler with several marathons under my belt, running 5 miles is a walk in the park. But now, I pay for those 5 miles for the rest of the day on the couch or with palpitations, dizziness, and fatigue the following day. Busy clinic day full of procedures? I would have to be sitting by the end of it. Bed by 9 PM was not always early enough.

Becoming a Statistic

Here I am, one of the leading experts in the country on caring for people with long COVID, featured in the national news and having testified in front of Congress, and now I am part of that lived experience. Me — a healthy athlete, with no comorbidities, a normal BMI, vaccinated and boosted, and after an almost asymptomatic bout of COVID-19, a victim to long COVID.

You just never know how your body is going to react. Neuroinflammation occurred in studies with mice with mild respiratory COVID and could be happening to me. I did not want a chronic immune-mediated vasculopathy.

So, I did what any other hyperaware physician-researcher would do. I enrolled in the RECOVER trial — a study my own institution is taking part in and one that I recommend to my own patients.

I also decided that I need to access care and not just ignore my symptoms or try to treat them myself.

That's when things got difficult. There was a wait of at least a month to see my primary care provider — but I was able to use my privileged position as a physician to get in sooner.

My provider said that she had limited knowledge of long COVID, and she hesitated to order some of the tests and treatments that I recommended because they were not yet considered standard of care. I can understand the

hesitation. It is engrained in medical education to follow evidence based on the highest-quality research studies. We are slowly learning more about long COVID but acknowledging the learning curve offers little to patients who need help now.

This has made me realize that we cannot wait on an evidence-based approach — which can take decades to develop — while people are suffering. And it's important that everyone on the front line learn about some of the manifestations and disease management of long COVID.

I left this first physician visit feeling more defeated than anything and decided to try to push through. That, I quickly realized, was not the right thing to do.

So again, after a couple of significant crashes and days of severe migraines, I phoned a friend: Ratna Bhavaraju-Sanka, MD, the amazing neurologist who treats patients with long COVID alongside me. She squeezed me in on a non-clinic day. Again, I had the privilege to see a specialist most people wait half a year to see. I was diagnosed with both autonomic dysfunction (Sympathetic Dominance) and intractable migraine.

- Acknowledge and recognize that long COVID is a disease that is affecting 1 in 5 Americans who catch COVID. Many look completely "normal on the outside." Please listen to your patients.
- Autonomic dysfunction (Sympathetic Dominance) is a common manifestation of long COVID. A 10-minute stand test goes a long way in diagnosing this condition, according to this consensus statement from the American Academy of Physical Medicine and Rehabilitation. It is not just anxiety.
- "That's only in research" is dismissive and harmful. Think outside the box. Follow guidelines. Consider encouraging patients to sign up for trials.
- Screen for PEM/PESE, and teach your patients to pace themselves because pushing through it or doing graded exercises will be harmful.
- We need to train more physicians to treat post acute symptoms of SARS-CoV-2 infection (PASC) and other postinfectious conditions, such as ME/CFS.

If long COVID is hard for physicians to understand and deal with, imagine how difficult it is for patients with no expertise in this area.
It is exponentially harder for those with fewer resources, time, and health literacy. My lived experience with long COVID has shown me that being a patient is never easy. You put your body and fate into the hands of trusted professionals and expect validation and assistance, not gaslighting or gatekeeping. Along with millions of others, I am tired of waiting.

Little-known illness turning up in COVID long-haulers

Health Jun 1, 2021 4:45 PM EST

The day Dr. Elizabeth Dawson was diagnosed with COVID-19 in October, she awoke feeling as if she had a bad hangover. Four months later she tested negative for the virus, but her symptoms have only worsened.

Dawson is among what one doctor called “waves and waves” of “long-haul” COVID patients who remain sick long after retesting negative for the virus. A significant percentage are suffering from syndromes that few doctors understand or treat. In fact, a yearlong wait to see a specialist for these syndromes was common even before the ranks of patients were swelled by post-COVID newcomers. For some, the consequences are life altering.

Before fall, Dawson, 44, a dermatologist from Portland, Oregon, routinely saw 25 to 30 patients a day, cared for her 3-year-old daughter and ran long distances.

Today, her heart races when she tries to stand. She has severe headaches, constant nausea and brain fog so extreme that, she said, it “feels like I have dementia.” Her fatigue is severe: “It’s as if all the energy has been sucked from my soul and my bones.” She can’t stand for more than 10 minutes without feeling dizzy.

Through her own research, Dawson recognized she had typical symptoms of postural orthostatic tachycardia syndrome, or POTS. It is a disorder of the autonomic nervous system, which controls involuntary functions such as heart rate, blood pressure and vein contractions that

assist blood flow. It is a serious condition — not merely feeling lightheaded on rising suddenly, which affects many patients who have been confined to bed a long time with illnesses like COVID as their nervous system readjusts to greater activity. POTS sometimes overlaps with autoimmune problems, which involve the immune system attacking healthy cells. Before COVID, an estimated 3 million Americans had POTS.

Many POTS patients report it took them years to even find a diagnosis. With her own suspected diagnosis in hand, Dawson soon discovered there were no specialists in autonomic disorders in Portland — in fact, there are only 75 board-certified autonomic disorder doctors in the U.S.

Other doctors, however, have studied and treat POTS and similar syndromes. The nonprofit organization Dysautonomia International **provides a list** of a handful of clinics and about 150 U.S. doctors who have been recommended by patients and agreed to be on **the list.**

In January, Dawson called a neurologist at a Portland medical center where her father had worked and was given an appointment for September. She then called Stanford University Medical Center's autonomic clinic in California, and again was offered an appointment nine months later.

Using contacts in the medical community, Dawson wrangled an appointment with the Portland neurologist within a week and was diagnosed with POTS and chronic fatigue syndrome (CFS). The two syndromes have overlapping symptoms, often including severe fatigue.

Dr. Peter Rowe of Johns Hopkins in Baltimore, a prominent researcher who has treated POTS and CFS patients for 25 years, said every doctor with expertise in POTS is seeing long-haul COVID patients with POTS, and every long-COVID patient he has seen with CFS also had POTS. He expects the lack of medical treatment to worsen.

"Decades of neglect of POTS and CFS have set us up to fail miserably," said Rowe, one of the authors of **a recent paper** on CFS triggered by COVID.

The prevalence of POTS was documented in an international survey of 3,762 long-COVID patients, leading researchers to conclude that all COVID patients who have rapid heartbeat, dizziness, brain fog or fatigue "should be screened for POTS."

A "significant infusion of health care resources and a significant additional research investment" will be needed to address the growing caseload, the American Autonomic Society said in a recent **statement**. Lauren Stiles, who founded **Dysautonomia International** in 2012 after being diagnosed with POTS, said patients who have suffered for decades worry about "the growth of people who need testing and treating but the lack of growth in doctors skilled in autonomic nervous system disorders."
On the other hand, she hopes increasing awareness among physicians will at least get patients with dysautonomia diagnosed quickly, rather than years later.

Congress has allocated $1.5 billion to the National Institutes of Health over the next four years to study post-COVID conditions. Requests for proposals have already been issued.

"There is hope that this miserable experience with COVID will be valuable," said Dr. David Goldstein, head of NIH's Autonomic Medicine Section.

A unique opportunity for advances in treatment, he said, exists because researchers can study a large sample of people who got the same virus at roughly the same time, yet some recovered and some did not.

Long-term symptoms are common. A **University of Washington study** published in February in the Journal of the American Medical Association's Network Open found that 27% of COVID survivors ages 18-39 had persistent symptoms three to nine months after testing negative for COVID. The percentage was slightly higher for middle-aged patients, and 43% for patients 65 and over.
The most common complaint: persistent fatigue. A **Mayo Clinic study** published last month found that 80% of long-haulers complained of fatigue and nearly half of "brain fog." Less common symptoms are

inflamed heart muscles, lung function abnormalities and acute kidney problems.
Larger studies remain to be conducted. However, “even if only a tiny percentage of the millions who contracted COVID suffer long-term consequences,” said Rowe, “we’re talking a huge influx of patients, and we don’t have the clinical capacity to take care of them.”

Symptoms of autonomic dysfunction are showing up in patients who had mild, moderate or severe COVID symptoms.

Yet even today, some physicians discount conditions like POTS and CFS, both much more common in women than men. With no biomarkers, these syndromes are sometimes considered psychological.

The experience of POTS patient Jaclyn Cinnamon, 31, is typical. She became ill in college 13 years ago. The Illinois resident, now on the patient advisory board of Dysautonomia International, saw dozens of doctors seeking an explanation for her racing heart, severe fatigue, frequent vomiting, fever and other symptoms. For years, without results, she saw specialists in infectious disease, cardiology, allergies, rheumatoid arthritis, endocrinology and alternative medicine — and a psychiatrist, “because some doctors clearly thought I was simply a hysterical woman.”

It took three years for her to be diagnosed with POTS. Testing for heart rate variability will detect POTS: Patients lie down for fifteen minutes and have their heart rate variability, blood pressure and heart rate taken. The heart rate of those with POTS will increase by at least 30 beats per minute, and often as much as 120 beats per minute within 10 minutes. POTS and CFS symptoms range from mild to debilitating.

The doctor who diagnosed Cinnamon told her he didn’t have the expertise to treat POTS. Nine years after the onset of the illness, she finally received treatment that alleviated her symptoms. Although there are no federally approved drugs for POTS or CFS, experienced physicians use a variety of medicines including **fludrocortisone**, commonly prescribed for Addison’s disease, that can improve symptoms. Some patients are also helped by specialized physical

therapy that first involves a therapist assisting with exercises while the patient is lying down, then later the use of machines that don't require standing, such as rowing machines and recumbent exercise bicycles. Some recover over time; some do not.

Dawson said she can't imagine the "darkness" experienced by patients who lack her access to a network of health care professionals. A retired endocrinologist urged her to have her adrenal function checked. Dawson discovered that her glands were barely producing cortisol, a hormone critical to vital body functions.

Medical progress, she added, is everyone's best hope.

Stiles, whose organization funds research and provides physician and patient resources, is optimistic.

"Never in history has every major medical center in the world been studying the same disease at the same time with such urgency and collaboration," she said. "I'm hoping we'll understand COVID and post-COVID syndrome in record time.

The New York Times

By Shannon Gulliver Caspersen, M.D.
Oct. 21, 2020

VOICES

When the Doctor Is a Covid ‘Long Hauler’

Coronavirus may leave patients with a condition called POTS that makes the heart rate soar after even the mildest activities.

Credit...Sam Caspersen

By Shannon Gulliver Caspersen, M.D.
Oct. 21, 2020

I am a physician who contracted what was initially a fairly mild case of Covid-19 in early March. Seven months later, I remain substantially debilitated, with profound exhaustion and a heart rate that goes into the stratosphere with even the tiniest bits of exertion, such as pouring a bowl of cereal or making a bed. I may never get better, despite receiving the best care available. And there are likely to be many more like me.

My early symptoms were fairly typical, with a sore throat, headache, body aches and fatigue. When I developed shortness of breath and chest pain, an emergency department physician I was seeing via telemedicine recommended I go to the E.R. My chest X-ray and oxygen saturation were normal, so I was sent home with an inhaler and was on the mend within two weeks.

But then the sequelae — the medical word for longer-term consequences — set in. My ongoing symptoms are familiar to many of the so-called Covid "long-haulers": in addition to the exhaustion and careening heartbeat, I have headaches, shortness of breath, tremulousness, and numb and tingling extremities. Sounds are too loud, light is too bright, nine hours is too little sleep at night. I am fortunate to have been spared some of the other symptoms that plague long-haulers, such as "brain fog," memory problems and PTSD-like anxiety. (So far)

Like many long-haulers, I was young — 37 — and healthy when I got Covid-19. I was working full-time in private practice and teaching at an academic medical center. I was doing pro bono work, raising my daughter, exercising most days, going out to museums and shows, serving on multiple nonprofit boards, and getting ready to host 20 kindergartners for an at-home birthday party the week I got sick (we canceled it).

Post-Covid, I can still do some of these things, which is more than many long-haulers can say, but only because they are virtual and therefore sedentary: pandemic life allows for visiting museums and viewing the performing arts virtually and attending work and board meetings online. So I can do it all from a seated position. I read endlessly on the couch to my daughter, and we play pretend games with me in a supine pose, while my husband does the vertical parenting that I can no longer do. He cooks for the family, he does the bike rides with our daughter. He would replace me as the chaperone to swimming lessons and ballet class, but for the pandemic.

Thanks to my medical background, good referrals from friends and an online forum called Body Politic, which includes a discussion group for Covid long-haulers, I have been diagnosed with dysautonomia, a disorder of the autonomic nervous system that is commonly triggered by viral infections. The autonomic nervous system controls involuntary functions in our bodies such as heart rate variability, blood pressure and digestion. When it is damaged by an infection or other cause, these functions go out of whack.

My specific form of dysautonomia, called postural orthostatic tachycardia syndrome, or POTS, was coined in 1993 by Dr. Phillip Low and his team at the Mayo Clinic, though it went by other names throughout history. POTS precludes standing for more than a few minutes at a time, because autonomic damage prevents blood vessels in the lower extremities from properly returning blood to the heart and brain against gravity. Heart rate can double or triple on standing, and lack of oxygen to the brain and upper body lead to many of the symptoms seen in POTS patients: dizziness, headaches, shortness of breath, chest pain, "brain fog."

If a POTS patient does stay vertical for a prolonged period, he or she can be left with massive fatigue, light and sound sensitivity, tingling extremities, temperature intolerance and gastrointestinal problems (again, all the bodily functions of the autonomic nervous system gone awry).

POTS is usually not life-threatening, unless a patient faints and suffers a serious head injury, but the degree of disability that it causes is equated to that of congestive heart failure or chronic obstructive pulmonary disease. Data from the Mayo Clinic shows that about half of POTS patients have some improvement in symptoms over an average of five years. It's too soon to know how the course of Covid-induced POTS might unfold.

Increasingly, doctors are recognizing that POTS appears to account for many of the Covid long-haul symptoms being reported around the world. It's a condition with no known cure, but the symptoms can be managed with medications, a physical rehabilitation program and dietary interventions. To even have a diagnosis and a management plan makes me one of the lucky ones.

Here's why else I am lucky: My medical specialty is psychiatry. I can work from home using a telemedicine platform to see my patients and Zoom to do my teaching. My job is sedentary, so I can continue to work full time in my physically debilitated state. If I were a surgeon, or a gynecologist, or an ophthalmologist, let alone a construction worker or hair stylist or other professional in a physically demanding field, I would be unable to continue to work and would be a candidate for formal disability benefits.

What of other Covid long-haulers who have more physically demanding jobs than I do? What about those who are single parents? How and when will they return to work and normal parenting? What if they never can?

On good days, when my heart rate is controlled and I'm not shaky or short of breath, I go outdoors. I wear a mask (or two), keep my distance from others and avoid even outdoor restaurants. As reports about genetically confirmed repeat Covid-19 infections surface, I worry about getting infected again. If I had a repeat Covid infection, would it be more severe, or more mild, than my first? Any kind of infection tends to exacerbate POTS symptoms and could undo all the hard work I am putting into illness management.

Unlike the more than a million people lost to Covid worldwide, I am alive. That said, in addition to a disease's mortality rate, it's also important to consider its morbidity rate — the long-term consequences for those who do not die. How much disability will we accumulate by the end of this pandemic? How much hopelessness? Knowledge about POTS and how to manage it gives me hope. Many long-haulers, mired in morbidity, aren't so lucky.

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Heart rate and heart rate variability comparison between postural orthostatic tachycardia syndrome versus healthy participants; a systematic review and meta-analysis

Joel Swai[1,2*], Zixuan Hu[3], Xiexiong Zhao[4], Tibera Rugambwa[5] and Gui Ming[2]

Abstract

Background: A number of published literature has reported that, physiologically, heart rate variability (HRV) in patients with postural orthostatic tachycardia syndrome (POTS) to be greatly confounded by age, sex, race, physical fitness, and circadian rhythm. The purpose of this study was to compare between POTS patients versus healthy participants, in terms of heart rate (HR) and HRV after Head-Up tilt test (HUTT), by systematic review and meta-analysis of available published literature.

Methods: MEDLINE (using PubMed interphase), EMBASE and SCOPUS were systematically searched for observational studies comparing POTS patients versus healthy patients, in terms of HR and HRV. HRV was grouped into Time and frequency domain outcome measurements. The time domain was measured as mean RR- interval and mean the square root of the mean of squares of successive R-R waves (rMSSD) in milliseconds. The frequency domain was measured as mean values of Low frequency power (LF), High frequency power (HF), LF/HF-ratio, LF-normalized units (LF(n.u)) and HF-normalized units (HF(n.u)). Demographic data, comorbidities, and mean values of HR, RR- interval, rMSSD, LF, HF, LF/HF-ratio, LF-(n.u) and H.F-n.u were extracted from each group and compared, by their mean differences as an overall outcome measure. Computer software, RevMan 5.3 was utilized, at a 95% significance level.

Results: Twenty (20) eligible studies were found to report 717 POTS and 641 healthy participants. POTS group had a higher mean HR ($p < 0.05$), lower mean RR-Interval ($p < 0.05$), lower rMSSD ($p < 0.05$) than healthy participants. Furthermore, POTS group had lower mean HF($p > 0.05$), lower mean LF($p > 0.05$), and lower mean HF(n.u) ($p > 0.05$), higher LF/HF-Ratio ($p > 0.05$) and higher LF(n.u) ($p > 0.05$) as compared to healthy participants.

Conclusion: POTS patients have a higher HR than healthy patients after HUTT and lower HRV in terms of time domain measure but not in terms of frequency domain measure. HR and time domain analyses of HRV are more reliable than frequency domain analysis in differentiating POTS patients from the healthy participants. We call upon sensitivity and specificity studies.

Keywords: Postural orthostatic tachycardia syndrome, Heart rate, Heart rate variability, Head-up tilt test, Meta-analysis, Systematic review

* Correspondence: joel.swai@hotmail.com
[1]Department of Internal medicine, Benjamin Mkapa Hospital, Dodoma city, Tanzania
[2]Department of Nephrology and Rheumatology, Xiangya Third Hospital, Central South University, Changsha city, Hunan, People's Republic of China
Full list of author information is available at the end of the article

Background

Blood circulation, blood pressure, and adequate tissue perfusion are closely coordinated with the autonomic nervous system in that, body postural changes will result in smaller and bearable changes in hemodynamics [1]. Inadequate blood volume, dysfunctional autonomic nervous system and sometimes, old-age and postprandial status, can result in altered hemodynamics when raising to the upright position (Orthostasis) [1, 2]. The altered hemodynamics results in a variety of symptoms collectively known as orthostatic intolerance (OI). Orthostatic intolerance could be classified as either Orthostatic Hypotension (OH), postprandial hypotension or Postural orthostatic tachycardia syndrome (POTS), also known as Chronic orthostatic intolerance [3].

Orthostatic intolerance presents with immediate clinical manifestations that follow cerebral hypoperfusion [4]. These could range from, generalized weakness, dizziness or lightheadedness, visual blurring or darkening of the visual fields, hypotension, tachycardia, pallor and in severe cases, syncope [4, 5]. Orthostatic hypotension is characterized by hypotension when raising to an upright position without a compensatory increase in heart rate (HR) while postprandial hypotension results into hypotension characterized by hypotension when raising to an upright position after eating. On the other hand, POTS is characterized by tachycardia and normal blood pressure [6].

POTS is the most prevalent form of orthostatic intolerance. It is diagnosed relying on a sustained HR increase of greater than 40 beats per minute or an increase to 120 beats per minute or greater within the first 10 min of tilt, without arterial hypotension. It is estimated that 3,000,000 Americans, suffer from this disorder at female: male ratio of 4:5.1 [7]. It occurs particularly in children and younger adults between 14 and 45 years, as compared to other OI which commonly occurs in the elderly [3]. Adverse manifestations such as hypotension and syncope almost never occur in POTS patients because they have preserved autonomic nervous functions [8].

Among others, the autonomic nervous function is one of the key players in maintaining hemodynamics and preventing POTS. Sympathetic denervation in lower extremities, preserved cardiac innervation and increased sympathetic activities (hyper-adrenergic state) have been shown to be sole etiologies of POTS [2, 3, 6, 8]. Other postulated theories include Cardiovascular deconditioning, abnormal venous function with reduced venous return, baroreflex abnormalities, hypovolemia and genetic abnormalities [4, 7]. To assess cardiac autonomic innervation and function, a number of tests have been developed with HRV widely used [9].

HRV analysis attempts to assess cardiac autonomic regulation through quantification of sinus rhythm variability. The sinus rhythm interval-time series is obtained from the QRS to QRS interval sequence of the electrocardiogram (ECG), by extracting only normal sinus to normal sinus in between two consecutive beats [9, 10]. High frequency alterations in sinus rhythm signify parasympathetic modulation, while slower variations reflect a combination of both parasympathetic and sympathetic modulation and non-autonomic factors. HRV measures are measured in two ways; time domain measures (TDM) and frequency domain measures (FDM) [9–11].

A few published literature have reported HRV to be greatly confounded by factors including age, sex, race and circadian rhythm. This study compared between POTS patients versus healthy patients, in terms of their HR and HRV after head-up tilt test (HUTT), by systematic review and meta-analysis of available published literature.

Methods

Eligibility criteria

This study included two kinds of participants; patients with POTS syndrome as cases, healthy participants as controls. The main outcomes were; HR and HRV as TDM and FDM. Only observational studies comparing suitable outcomes between the two groups were eligible for inclusion. To increase the external validity of this study, accessible literature from across the world was eligible for inclusion as long as they fulfill the aforementioned inclusion criteria. Only English published literature was eligible for inclusion.

Information sources

Three online databases, namely PubMed, EMBASE and the SCOPUS were systematically searched to come up with eligible included studies. The searches were not be customized for searching within any restricted date ranges. Secondary referencing of eligible studies was done to extend the search scope and the last date of the search was 29th September 2019.

The search

To generate a set of citations that are relevant to our study's search question, an advanced search tool was used, utilizing MeSH terms and keywords in all of the three databases aforementioned. Using PubMed, MeSH terms were generated, a search was built and the advanced search was done as; ("Postural Orthostatic Tachycardia Syndrome"[Mesh]) AND "Heart Rate"[-Mesh]. Again the search was repeated with; (("postural orthostatic tachycardia syndrome"[MeSH Terms] OR ("postural"[All Fields] AND "orthostatic"[All Fields] AND "tachycardia"[All Fields] AND "syndrome"[All

Fields]) OR "postural orthostatic tachycardia syndrome"[All Fields]) OR ("postural orthostatic tachycardia syndrome"[MeSH Terms] OR ("postural"[All Fields] AND "orthostatic"[All Fields] AND "tachycardia"[All Fields] AND "syndrome"[All Fields]) OR "postural orthostatic tachycardia syndrome"[All Fields] OR "pots"[All Fields])) AND (("heart rate"[MeSH Terms] OR ("heart"[All Fields] AND "rate"[All Fields]) OR "heart rate"[All Fields]) AND variability [All Fields]). Using EMASE, on the other hand, advanced search tool was utilized firstly using MeSH terms ((postural AND orthostatic AND tachycardia AND syndrome OR pots) AND heart AND rate) and then a repeated by using a combination of key words (postural AND orthostatic AND tachycardia AND syndrome OR pots) AND heart AND rate AND variability. The searches were independently performed by two authors; JS and XZ. Results were exported to computer software, *EndNote X9 (Builld 12, 062)* which was used to manage and keep track of references throughout this study.

Study selection process

All studies resulting from online database search independently conducted by two authors were initially screened by their titles and abstracts to initially assess their relevance to our study question. This was level-one screening and was done independently by two authors, JS and XZ. Compiled results of level-one screening were exported to EndNote software and then searched for their full-text articles. Level-two screening involved assessing the retrieved full text articles for eligibility for inclusion or exclusion. Any differences of thoughts in the search process were settled by the third author, TR. The entire study search, screening, and selection are summarized in Fig. 1.

Data extraction

Before the data extraction process from full-text articles meting eligibility criteria for inclusion, assessment for methodological biases was done. PRISMA (preferred reporting items for systematic reviews and meta-analyses) tool [12] was used for this study write-up to minimize reporting bias.

The process of data extraction was independently performed by two authors, namely; JS and XZ. Any difference in thoughts was settled by the third author, TR. Data collected included participants' demographics, study characteristics and reported outcomes in line with our study question.

Demographic data included participants' mean/median ages, setting and sample sizes in each group. HUTT procedure details; angle of tilt, time of tilt, duration of orthostasis and device used to measure HR and HRV; whether ECG or Holter. Diagnoses and comorbidities among participants were also recorded.

In line with this study question, two outcomes were recorded from the eligible studies; HR and HRV measured by either TDM and FDM. These outcomes were recorded in both comparison groups.

Analysis

Data were analyzed separately according to the two main outcomes of interest. TDM was sub-grouped into RR interval and rMSSD while the FDM outcome was sub-grouped into LF, HF, LF/HF-ratio, LF (n.u) and HF (n.u). In that case, comparison of TDM between POTS versus healthy participants groups was in terms of the mean differences of RR-Interval and rMSSD. On the other hand, comparison of FDM between POTS versus healthy participants groups was in terms of the mean differences of LF, HF, LF/HF-ratio, LF (n.u) and HF (n.u).

The overall effect of POTS was diagrammatically be depicted by forest-plots. Data synthesis, analysis, and generation of forest-plots were done utilizing computer software, ***Review Manager (RevMan Version 5.3)***. The software was customized to a random or fixed effect model depending on the heterogeneity (I^2) of the studies when analyzing the outcomes. The fixed effect model was used when I^2 was less than 50% and the random effect model was used when I^2 was more than 50%.

Assumptions and simplifications

For this study purpose, all participants were considered to have been correctly diagnosed and correctly classified as to be having POTS, or otherwise healthy. All participants, despite the study country, were considered to have received standard care.

Results

Study selection

The literature search identified a total of twenty-eight [13] studies that seemed relevant and were sought for full-text. Eight of these were excluded due to various reasons; *Nakao* et al. (2012) [14] used comorbid than healthy control; *Goldstein* et al. (2005) [15] did not assess our outcome of interest; *Yoshiuchi* et al. (2004) [16] used POTS participants comorbid with chronic fatigue syndrome; Singer et al. (2003) [17] intervened the control group with isoproterenol infusion similarly *Freitas* et al. (2000) [18] who intervened with cardio-selective beta-blocker and/or fludrocortisone and *Stewart* et al. (2007) [19] who employed hand-grip maneuver than HUTT. Furthermore, *Bongiovanni* et al. (2013) [20], and *Aoki* et al. (2008) [21] were excluded for not accessible full-text and use of Japanese language in the full-text retrieved, respectively. A total of twenty [21] studies

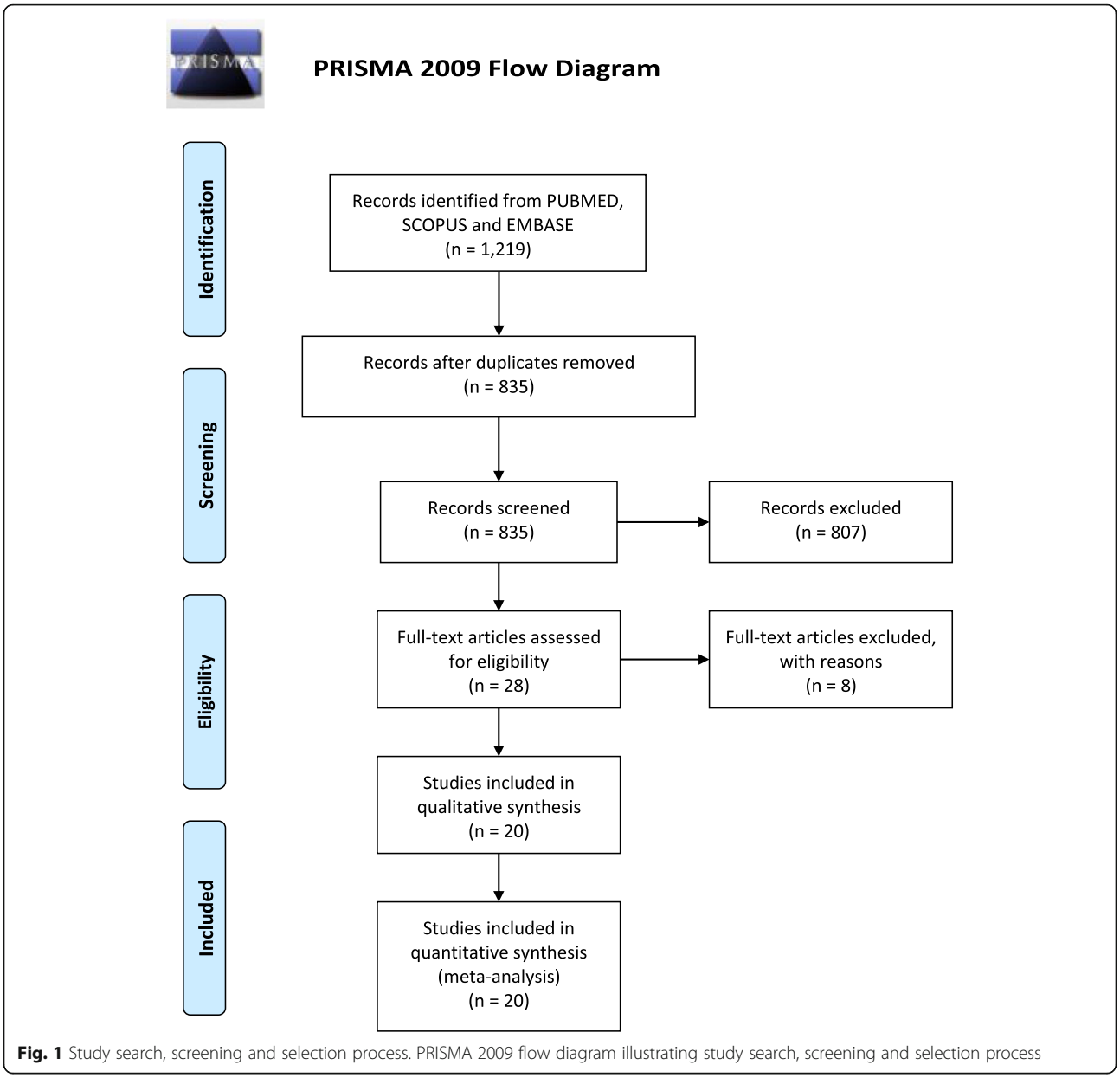


Fig. 1 Study search, screening and selection process. PRISMA 2009 flow diagram illustrating study search, screening and selection process

fulfilled the eligible criteria for inclusion. Figure 1, summarizes search results, screening, and selection process.

Study characteristics

Table 1 summarizes the study characteristics of our twenty [21] studies that were eligible for inclusion in our study. A total number of participants reported was 1358, of these, 717 POTS and 641 were healthy participants. Regarding participants demographics, while other studies recruited both gender equally [38], other only recruited one gender participants [29], and other studies randomly involved both gender [23]. While other studies matched the groups by age [15, 29], other studies did not [25]. Furthermore, the majority of studies reported participants' ages central tendencies by mean, two studies utilized median instead [28, 40]. While other studies used a larger sample size [39], other used smaller sample sizes [13].

All twenty studies were case-control observational studies and none was interventional. These were conducted in different settings from a diverse number of countries all around the world. Eleven studies were done in the USA, two in Australia and other were conducted in Israel [22], UK [23], Portugal [26], Japan [27], Germany [29], Korea republic [25] and The Netherlands [38], each contributing one study. This was thought to increase the external validity of this study.

Despite the fact that the search was not confined to any specified range of dates, none of the included studies

Table 1 Study characteristics

Study, Year	Study size (POTS, Healthy)	Mean Aged (POTS, Healthy)	Matched case-control or not?	Duration of HR/HRV parameter measurement (Angle of tilt)	Orthostasis induction method	Country of study	Outcome Recorded
Jacob 2019 [22]	12,10	30 ± 1.8, 32 ± 3	Unmatched	30 Minutes (75^0)	HUTT	Israel	**HF, HR**
Owens 2018 [23]	20,20	36 ± 10.84, 35 ± 7.56	Unmatched	10 Minutes (60^0)	HUTT	UK	**HF, LF**
Goff 2017 [24]	9,20	NA, NA	Unmatched	24 Hours	Daily life activity	Australia	**rMSSD**
Moon 2016 [25]	46,67	28.9 ± 1.9, 49.4 ± 2.1	Unmatched	20 Minutes	Active standing	Korea Republic	**HR**
Freitas 2015 [26]	10,12	29.4 ± 8.5, 33.8 ± 5.9	Matched	40 min (70^0)	HUTT	Portugal	**HR, HF**
Yoshida 2014 [27]	70,38	13.7 ± 0.1, 13.5 ± 0.1	Unmatched	7 min (90^0)	Active standing	Japan	**HR, LF/HF-Ratio**
Medow 2014 [28]	12,19	Median: 20.8, 21.4	Unmatched	10 Minutes (70^0)	HUTT	USA	**HR, LF(n.u), LF(n.u)**
Mallien 2014 [29]	38,31	25.3 ± 7, 26.2 ± 6.3	Matched	Overnight	HUTT	Germany	**HR, LF, HF, LF/HF-Ratio**
Plash 2013 [30]	15,15	36 ± 3, 33 ± 2	Unmatched	30 Minutes	Active standing	USA	**HR**
Ocon 2012 [31]	16,20	21 ± 1, 23 ± 1		10 Minutes (75^0)	HUTT	USA	**HR**
Brewster 2012 [32]	54,26	35 ± 2, 27 ± 1	Unmatched	5 Minutes	Active standing	USA	**HR**
Galbreath 2011 [33]	17,17	27 ± 9, 31 ± 10	Unmatched	5 Minutes (60^0)	HUTT	USA	**HR, HF, LF, rMSSD, RR-Interval, HF (n.u), LF (n.u)**
Baumert 2011 [34]	13,12	(32 ± 13, 23 ± 2),	Unmatched	10 Minutes (40^0)	HUTT	Australia	**HR**
Fu 2010 [35]	27,16	26 (21–33), 28 (23,35)	Unmatched	45 Minutes (60%) *grip	HUTT	USA	**HR**
Ocon 2009 [13]	9,7	NA, NA	Unmatched	10 Minutes (70^0)	HUTT	USA	**RR-Interval, LF, HF, LF/HF-Ratio, LF(n.u), HF(n.u), HR**
Garland 2007 [36]	150,63	34.5 ± 10.7, 30.2 ± 9.3	Unmatched	5 Minutes	Active standing	USA	**HR**
Stewart 2006 [37]	20,10	17 ± 2, 17 ± 1	Matched	10 Minutes (70^0)	HUTT	USA	**HR, LF/HR-Ratio, HF, LF**
Meier 2006 [38]	21,39	15.5 ± 2.2, 11.7 ± 2.7	Unmatched	12 Minutes (60^0)	HUTT	The Netherlands	**HR**
Garland 2005 [39]	136,191	29.1 ± 8.0, 32.2 ± 9.9	Unmatched	30 Minutes (60^0)	HUTT	USA	**HR**
Stewart 2000 [40]	22,10	Median: 15.2, 15.8	Unmatched	30 Minutes (70^0)	HUTT	USA	**HR, HF(n.u), LF(n.u), LF/HF-Ratio, HF, LF, rMSSD, RR-Interval**

POTS Postural orthostatic tachycardia, *rMSSD* square root of mean of squares of successive R-R interval, *LF* Low frequency power, *HF* High frequency power, *LF(n.u)* Low frequency power -normalized units, *HF(n.u)* High frequency power -normalized units, *HR* Heart Rate, *NA* Data not accessed

was found to have been published before the year 2000. Fifteen studies (75%) were published in the last decade.

Different studies reported different outcomes, but all aligned with our study questions. Eighteen studies compared HR, three studies compared RR-Interval, three studies compared to rMSSD, six studies compared LF, eight studies compared HF, six compared LF/HF-Ratio and four studies compared LF(n.u) and HF(n.u) each. Studies comparing similar outcomes were analyzed together in the same forest-plot.

Sources of bias

All 20 eligible articles included in this study were assessed for risk of bias in two levels; at study level and at the review level. Regarding study level bias assessment; different studies involved a different numbers of

sample sizes. Other studies included a large number of participants [39] while other used low [13]. It follows that large sample sizes are more representative of the general population as compared to small sample sized studies. Furthermore, none of these 20 studies reported having had calculated the required sample size prior to their conduction.

Despite the fact that all studies were similar in that, they compared POTS versus healthy participants, some studies matched the comparison groups to reduce confounding factors while other studies did not [24]. This might have introduced confounding factors to our study as factors such as female gender, BMI, physical fitness and race, each has been reported to independently alter HRV [41].

Different studies utilized different methods to induce orthostasis, with others using the HUTT and others applying active standing [27]. Whether HUTT or active standing was used to induce orthostasis, different durations, ranging from 5 to 45 min, were applied depending on the participant's tolerance to orthostasis. Furthermore, different angles of tilt were set, ranging from 40^0 [34] to 75^0 in other studies. While the majority involved awake patients, other studies [29] utilized sleeping participants. While other studies used ECG to measure HRV in a short session [35], others used the Holter device to record mean HRV per 24 h while participants are carrying on with their daily activities [24]. These different conditions were thought to increase heterogeneity hence influence our results.

At the review level, on the other hand, a number of loopholes for biases were also identified. Although, other studies had our data of interest, readily available to extract from tables in text, from one [23] study data had to be extracted by estimations and extrapolation from a graphical figure. This led to conducting sensitivity analysis excluding this study. Furthermore, the overall mean ages of POTS and/or healthy group could not be calculated because data could not be accessed in other studies [13, 24], because the median was utilized than the mean [28, 40].

Heart rate (HR)

Figure 2 illustrates eighteen of twenty eligible studies that compared HR outcomes between POTS versus Healthy participants. The overall mean difference between the two groups was 19.88 (15.24, 24.52) signifying a higher HR in the POTS group. This difference reached statistical significance (P-value< 0.05). A random-effect model was used since heterogeneity, I^2, was 99% (i.e. $I^2 > 50\%$).

RR- interval

Figure 3a illustrates three of twenty eligible studies that compared TDM outcomes between POTS versus Healthy participants in terms of mean RR intervals. The overall mean difference between the two groups was − 162.89 (− 172.65, − 153.12) signifying lower HRV in terms of RR-interval in the POTS group. This difference reached statistical significance (P-value< 0.05). Fixed-effect model was used since heterogeneity, I^2, was 0% (i.e. $I^2 < 50\%$).

The root of the mean of squares of successive R-R interval differences (rMSSD)

Figure 3b illustrates three of twenty eligible studies that compared TDM outcomes between POTS versus Healthy participants in terms of rMSSD. The overall mean difference between the two groups was − 15.16 (− 18.28, − 12.03) signifying lower HRV in terms of rMSSD in the POTS group. The difference reached statistical significance (P-value< 0.05). A fixed-effect model was used since heterogeneity, I^2, was 2% (i.e. $I^2 < 50\%$).

Low frequency power (LF)

Figure 4a illustrates five of twenty eligible studies that compared the FDM outcomes between POTS versus Healthy participants in terms of LF. The overall mean difference between the two groups was − 80.89 (− 211.37, 49.58) milliseconds^2 signifying lower HRV in terms of LF in the POTS group. The difference, however, did not reach statistical significance (P-value> 0.05). A random-effect model was used since heterogeneity, I^2, was 96% (i.e. $I^2 > 50\%$).

High frequency power (HF)

Figure 4b illustrates seven of twenty eligible studies that compared the FDM outcome between POTS versus Healthy participants in terms of HF. The overall mean difference between the two groups was − 113.20 (− 275.52, 49.13) milliseconds^2 signifying lower HRV in terms of HF in the POTS group. The difference did not reach statistical significance (P-value> 0.05). A random-effect model was used since heterogeneity, I^2, was 84% (i.e. $I^2 > 50\%$).

Low frequency power /high frequency power ratio (LF/HF- ratio)

Figure 4c illustrates five of twenty eligible studies that compared the FDM outcome between POTS versus Healthy participants in terms of the LF/HF- ratio. The overall mean difference between the two groups was 0.29 (− 0.25, 0.83) signifying higher HRV in terms of the LF/HF- ratio in the POTS group. The difference did not reach statistical significance (P-value> 0.05). A random-effect model was used since heterogeneity, I^2, was 95% (i.e. $I^2 > 50\%$).

Low frequency power-normalized unit

Figure 4d illustrates four of twenty eligible studies that compared the FDM outcome between POTS versus

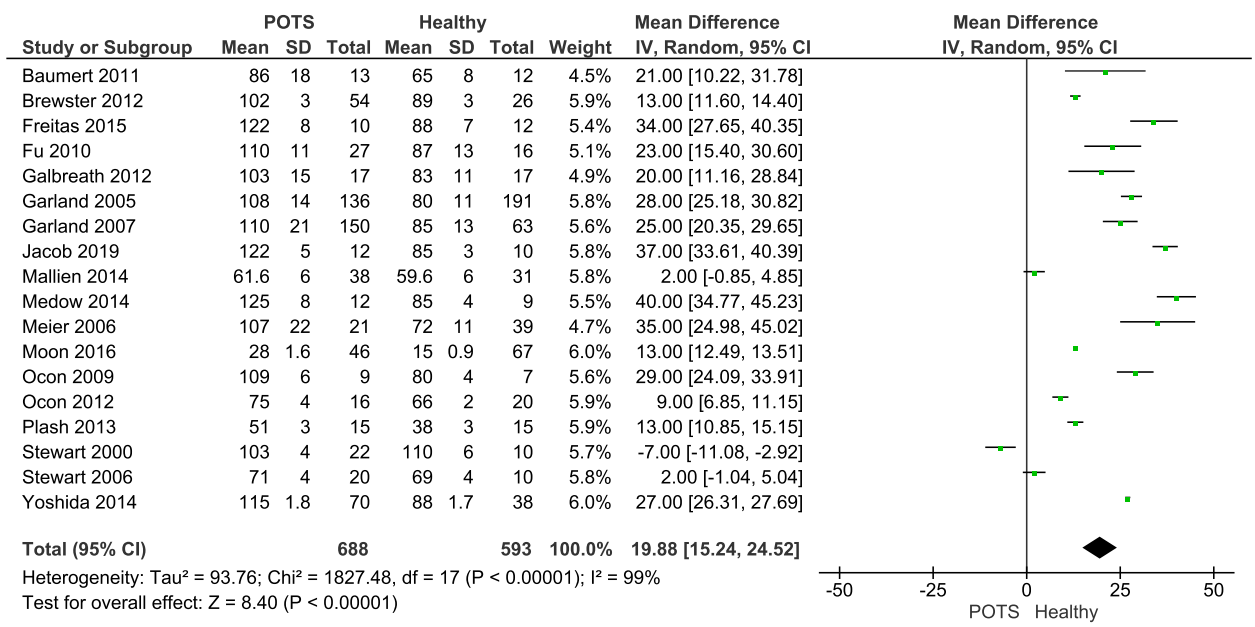


Fig. 2 Heart rate comparison between postural orthostatic tachycardia syndrome versus healthy participants**.** A forest plot illustrating eighteen of twenty eligible studies that compared the mean heart rate outcome between postural orthostatic tachycardia syndrome versus healthy participants

Healthy participants in terms of LF (n.u). The overall mean difference between the two groups was 0.05 (– 0.04, 0.13) signifying higher HRV in terms of LF (n.u.) in the POTS group. The difference, however, did not reach statistical significance (*P*-value> 0.05). A random-effect model was used since heterogeneity, I^2, was 96% (i.e. $I^2 > 50\%$).

High frequency power-normalized unit

Figure 4e illustrates four of twenty eligible studies that compared the FDM outcome between POTS versus Healthy participants in terms of HF (n.u). The overall mean difference between the two groups was – 0.03 (– 0.11, 0.04) signifying lower Heart variability in terms of HF (n.u.) in the POTS group. The difference, however,

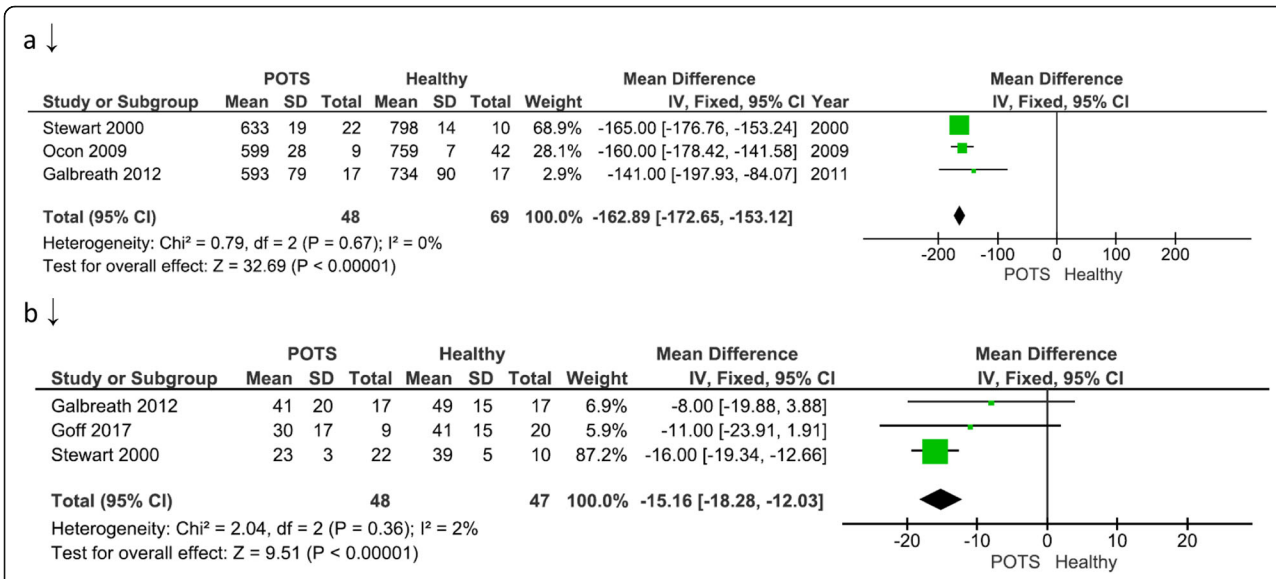
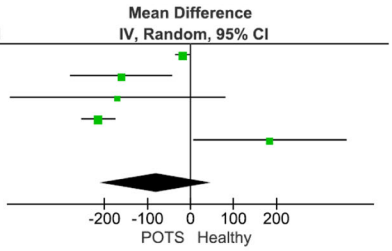


Fig. 3 Time domain measure comparison between postural orthostatic tachycardia syndrome versus healthy participants. **a** illustrates three of twenty eligible studies that compared time domain measure outcome in terms of mean RR-intervals; **b** illustrates three of twenty eligible studies that compared time domain measure outcome in terms of mean rMSSD

a

Study or Subgroup	POTS Mean	POTS SD	POTS Total	Healthy Mean	Healthy SD	Healthy Total	Weight	Mean Difference IV, Random, 95% CI
Galbreath 2012	90	12	17	108	33	17	24.8%	-18.00 [-34.69, -1.31]
Mallien 2014	336.68	246.03	38	498.09	251.62	31	20.7%	-161.41 [-279.58, -43.24]
Ocon 2009	418	151	9	588	310	7	13.0%	-170.00 [-419.94, 79.94]
Stewart 2000	387	60	22	602	49	10	24.4%	-215.00 [-254.38, -175.62]
Stewart 2006	1,111	366	20	926	123	10	17.1%	185.00 [7.40, 362.60]
Total (95% CI)			**106**			**75**	**100.0%**	**-80.89 [-211.37, 49.58]**

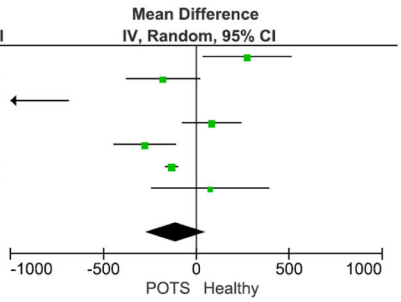
Heterogeneity: Tau² = 17770.23; Chi² = 92.54, df = 4 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.22 (P = 0.22)



b

Study or Subgroup	POTS Mean	POTS SD	POTS Total	Healthy Mean	Healthy SD	Healthy Total	Weight	Mean Difference IV, Random, 95% CI
Freitas 2015	628	340	10	354	200	12	14.0%	274.00 [34.81, 513.19]
Galbreath 2012	144	176	17	324	379	17	15.4%	-180.00 [-378.64, 18.64]
Jacob 2019	430	130	12	1,680	900	10	5.9%	-1250.00 [-1812.64, -687.36]
Mallien 2014	333.1	206	38	250.91	407	31	16.9%	82.19 [-75.34, 239.72]
Ocon 2009	138	42	9	416	223	7	16.5%	-278.00 [-445.46, -110.54]
Stewart 2000	178	46	22	312	43	10	19.9%	-134.00 [-166.86, -101.14]
Stewart 2006	1,742	504	20	1,667	363	10	11.4%	75.00 [-240.29, 390.29]
Total (95% CI)			**128**			**97**	**100.0%**	**-113.20 [-275.52, 49.13]**

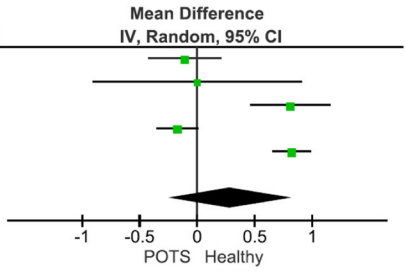
Heterogeneity: Tau² = 34191.31; Chi² = 38.02, df = 6 (P < 0.00001); I² = 84%
Test for overall effect: Z = 1.37 (P = 0.17)



c

Study or Subgroup	POTS Mean	POTS SD	POTS Total	Healthy Mean	Healthy SD	Healthy Total	Weight	Mean Difference IV, Random, 95% CI
Mallien 2014	0.82	0.61	38	0.93	0.71	31	21.1%	-0.11 [-0.43, 0.21]
Ocon 2009	4	0.8	9	4	1	7	13.8%	0.00 [-0.91, 0.91]
Stewart 2000	3.14	0.45	22	2.33	0.47	10	20.8%	0.81 [0.46, 1.16]
Stewart 2006	0.73	0.11	20	0.9	0.28	10	22.1%	-0.17 [-0.35, 0.01]
Yoshida 2014	4.63	0.41	70	3.81	0.42	38	22.2%	0.82 [0.66, 0.98]
Total (95% CI)			**159**			**96**	**100.0%**	**0.29 [-0.25, 0.83]**

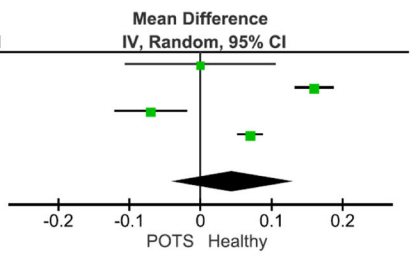
Heterogeneity: Tau² = 0.33; Chi² = 78.84, df = 4 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.06 (P = 0.29)



d

Study or Subgroup	POTS Mean	POTS SD	POTS Total	Healthy Mean	Healthy SD	Healthy Total	Weight	Mean Difference IV, Random, 95% CI
Galbreath 2012	0.36	0.18	17	0.36	0.13	17	19.6%	0.00 [-0.11, 0.11]
Medow 2014	0.96	0.01	12	0.8	0.04	9	27.3%	0.16 [0.13, 0.19]
Ocon 2009	0.78	0.07	9	0.85	0.03	7	25.5%	-0.07 [-0.12, -0.02]
Stewart 2000	0.47	0.03	22	0.4	0.02	10	27.7%	0.07 [0.05, 0.09]
Total (95% CI)			**60**			**43**	**100.0%**	**0.05 [-0.04, 0.13]**

Heterogeneity: Tau² = 0.01; Chi² = 71.10, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.04 (P = 0.30)



e

Study or Subgroup	POTS Mean	POTS SD	POTS Total	Healthy Mean	Healthy SD	Healthy Total	Weight	Mean Difference IV, Random, 95% CI
Galbreath 2012	0.08	0.05	17	0.11	0.09	17	25.5%	-0.03 [-0.08, 0.02]
Medow 2014	0.77	0.08	12	0.63	0.11	9	20.5%	0.14 [0.06, 0.22]
Ocon 2009	0.64	0.06	9	0.77	0.04	7	25.4%	-0.13 [-0.18, -0.08]
Stewart 2000	0.21	0.02	22	0.29	0.02	10	28.6%	-0.08 [-0.09, -0.07]
Total (95% CI)			**60**			**43**	**100.0%**	**-0.03 [-0.11, 0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 33.10, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 0.95 (P = 0.34)

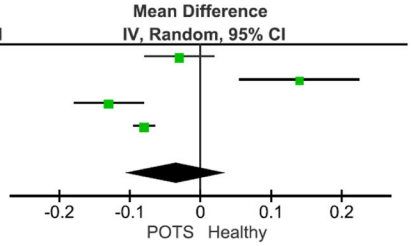


Fig. 4 (See legend on next page.)

(See figure on previous page.)
Fig. 4 Frequency domain measure between postural orthostatic tachycardia syndrome versus healthy participants. **a** illustrates five of twenty eligible studies that compared the frequency domain measure outcome in terms of mean LF. **b** illustrates seven of twenty eligible studies that compared the frequency domain measure outcome in terms of mean HF. **c** illustrates five of twenty eligible studies that compared frequency domain measure in terms of mean LF/HF- ratio; **d** illustrates four of twenty eligible studies that compared the frequency domain measure outcome in terms of mean LF (n.u); **e** illustrates four of twenty eligible studies that compared the frequency domain measure outcome in terms of mean HF (n.u)

did not reach statistical significance (*P*-value> 0.05). A random-effect model was used since heterogeneity, I^2, was 91% (i.e. $I^2 > 50\%$).

Sensitivity analysis

Eliminating three studies; one study for utilizing 24 h parameters recording [24]; another study for including a period of parameters measurements during sleeping [29]; and one study [23], in which data were collected by estimates and extrapolations from a graphical figure, none of the outcome results changed statistical significance. The newly, obtained results were as follows; mean difference rMSSD = – 15.41(– 18.63,-12.2), *p*-Value< 0.00001, I^2 = 38%; mean difference HF = -156(– 344.05,31.17), *p*-Value = 0.1, $I^{2=}$84%; mean difference LF/HF =0.39(– 0.24, 1.03), *p*-Value = 0.23, I^2 = 96%; and lastly, mean HR = 20.98(16.27,25.69), *p*-Value< 0.00001, I^2 = 99%.

Publication bias

Figure 5 illustrates a funnel-plot for publication biases among studies included in comparing HR between POTS versus healthy groups. Medium sample sized studies at the middle of the funnel-plot were more symmetrically distributed as compared to large sample sized studies at the top. This suggests heterogeneity of the study estimates as well as likely publication bias favoring studies with medium sample sizes than large sample sizes.

Discussion

Age, sex, race, BMI, physical fitness and circadian rhythm are among a number of factors that have been reported to physiologically influence HRV. HRV in patients with POTS is no exception. This study was aimed to compare POTS patients versus healthy patients, in terms of their HR and HRV after HUTT, by systematic review and meta-analysis of available published literature.

From the results of our study, mean difference for TDM outcome measures between POTS versus healthy participants were found to be; RR interval = – 162.89 (– 197.93, – 84.07), *P*-value< 0.05; rMSSD = – 15.16 (– 18.28,12.03), *P*-value< 0.05. In this case, both outcomes showed statistically significant results that illustrate lower HRV in terms of TDM measure in the POTS group than in the comparison groups. Despite authors regarded R-R interval and rMSSD separately, it worth to note that rMSSD is calculated from R-R interval and they are directly proportional to one another. These findings concur with available base of literatures by; *De Wandele* et al.(2014) [42], *Galland* et al. (2008) [43], *Gergont* et al. (2019) [44], *Lewis* et al. (2013) [45] and *Pengo* et al.(2015) [46], ,all of whom reported reduced HRV in POTS than in non-POTS patients

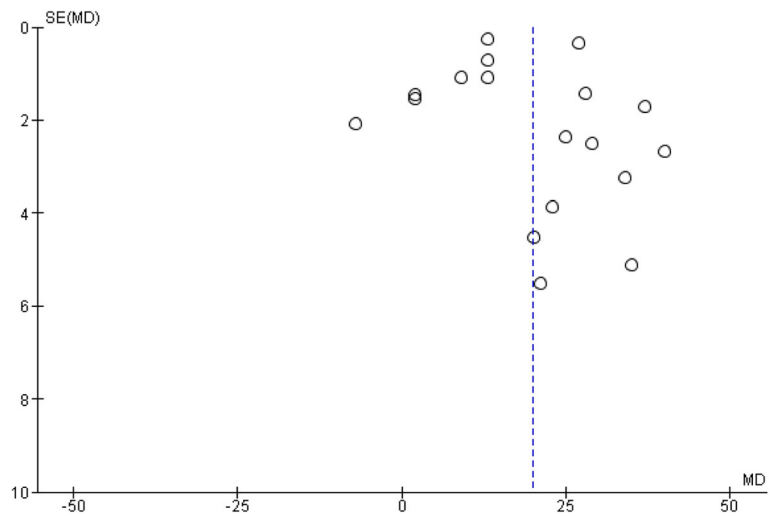


Fig. 5 Publication biases**.** A funnel-plot illustrating publication biases for included studies comparing heart rate between postural orthostatic tachycardia syndrome versus healthy participants

or otherwise heathy individuals. On the other hand, mean differences for FDM outcome between POTS versus healthy participants were: LF, = − 80.89 (− 211.37, 49.58), *P*-value> 0.05; HF, = − 113.20 (− 275.52, 49.13), *P*-value> 0.05 and HF (n.u) = − 0.03 (− 0.11, 0.04), all of which did not show statistically significant results that POTS patients have lower HRV than healthy participants in terms of FDM. Our study's LF results align with those reported by *Mallien* et al. (2012) but contradict with those reported by *Stewart* et al. (2006). Our results for HF align with those reported by *Ocon* et al. (2009) but contradicts with those of *Freitas* et al. (2005).

Moreover, from our study, LF/HF- ratio was found to be 0.29 (− 0.25, 0.83), *P*-value> 0.05; LF (n.u), = 0.05 (− 0.04, 0.13), *P*-value> 0.05; all of which showed higher HRV in POTS patients in comparison to healthy participants in terms of FDM without reaching statistical significance. Our results for LF/HF-Ratio align with those reported by *Yoshida* et al. (2014) and contradict with those reported by *Mallien* et al. (2014). Our LF(n.u) results align with those previously reported by *Medow* et al. (2014) but contradict those reported by *Ocon* et al. (2009).

Regarding HR, our study strongly shows a statistically significant higher HR in POTS than healthy patients following HUTT with a mean difference of 19.88(15.24, 24.52), *P*-value< 0.05. These results align with the majority of previously published literature but contradict with those reported by *Meier* et al. (2006) who reported otherwise.

Authors of this study believe that the reasons for variations and contradictions among all aforementioned studies and their outcomes to greatly be due to methodological reasons, especially inadequate and/or improper matching of participants. Authors, therefore, recommend more robust researches to be conducted in the topic, matching participants with age, gender, ethnicity, BMI, physical fitness and circadian rhythm.

Amid a number of theories explaining low HRV in POTS patients, one is a hyperadrenergic state [15, 36, 47]. Physiologically, POTS patients have been reported to have increased sympathetic activity following a suggested hyperadrenergic state. Another theory for low HRV in POTS patient is, distal denervation predominantly in lower extremity, with preserved cardiac innervation leading to lower extremity anhidrosis, impaired norepinephrine spillover in the lower extremities and decreased muscle sympathetic activity recruitment in the lower extremity in response to a nitroprusside-induced hypotensive stimulus [38, 48, 49]. Other studies have reported hypovolemia, decreased venous posture in an upright position, baroreflex abnormality and cardiac deconditioning to contribute [50].

Despite promising results, the results of this study need to be addressed with care. This follows a number of bias sources that were encountered and assumptions that were made during the conduction of this study. Different studies involved different number sample sizes and none of these twenty studies reported to have calculated the required sample size prior to their conduction. Furthermore, improper matching as explained earlier, different methods of inducing orthostasis including variable angles of tilt from 40^0 to upright; different methods of measuring outcomes including the use of ECG and/or Holter device and different durations for measurement of HRV parameters and HR (i.e. short term or 24 h term). Moreover, at the review level, a sensitivity analysis was conducted due to high heterogeneity observed across different parameter outcomes especially in the FDM and HR. Three peculiar studies were eliminated but none of the initially calculated results changed their statistical significance. Again, rMSSD has been shown to have an association with HR which could have confounded our results [51]. From fewer otherwise eligible studies reporting the two parameters, meta-regression could not be conducted. To help mitigate biases, authors firstly appraised all eligible studies and used team work in conducting database search and data extraction. To mitigate reporting biases, PRISMA tools were used in the study writeup.

Conclusion

Despite a number of unavoidable sources of biases, it worth to note that despite the massively supported fact that POTS patients have a higher HR than healthy patients after HUTT, POTS patients have lower HRV in terms of TDM but not in terms of FDM. It follows that HR and TDM analyses of HRV are more reliable than FDM analysis in differentiating POTS patients from a health participant. We, though, call upon more extensive observational (preferably sensitivity and specificity studies) and interventional studies to further mitigate biases encountered in this study.

Abbreviations

BMI: Basal metabolic index; ECG: Electrocardiogram; FDM: Frequency domain measure; GM: Gui Ming (author); HF: High frequency power; HF(n.u): High frequency normalized unit; HR: Heart rate; HRV: Heart rate variability; HUTT: Head-up tilt test; JS: Joel Swai (author); LF: Low frequency power; LF(n.u): Low frequency normalized unit; MeSH: Medical subject headings; OH: Orthostatic hypotension; OI: Orthostatic intolerance; POTS: Postural orthostatic tachycardia syndrome; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; rMSSD: Square root of the mean of squares of successive R-R waves; RR-Interval: Interval between R and R waves of the electrocardiogram; TDM: Time domain measure; TR: Tibera Rugambwa (author); XZ: Xiexiong Zhao (author); ZH: Zixuan Hu (author)

Acknowledgements

Authors acknowledge supervisory input from Dr. Alphonce Chandika, Executive Director, Benjamin Mkapa Hospital, Dodoma city, Tanzania, East Africa.

Authors' contributions

Study designing: JS and ZH; data search JS, XZ and TR; data extraction: JS, XZ, and TR; data analysis and interpretation: JS and GM; Manuscript drafting: JS and ZH; manuscript critical intellectual content revision: GM and TR. All authors read and approved the final version of the manuscript.

Funding
No funds were given.

Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Internal medicine, Benjamin Mkapa Hospital, Dodoma city, Tanzania. [2]Department of Nephrology and Rheumatology, Xiangya Third Hospital, Central South University, Changsha city, Hunan, People's Republic of China. [3]Department of Gastroenterology, Xiangya Third Hospital, Central South University, Changsha city, Hunan, People's Republic of China. [4]Department of Cardiology, Xiangya Third Hospital, Central South University, Changsha city, Hunan, People's Republic of China. [5]Department of Obstetrics and Gynecology, Mbeya Zonal Referral Hospital, Mbeya city, Tanzania.

Received: 16 October 2019 Accepted: 5 December 2019
Published online: 30 December 2019

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Publisher's Note

Postural Orthostatic Tachycardia Syndrome (POTS)

Before the Covid-19 pandemic, Postural Orthostatic Tachycardia Syndrome (POTS) was a relatively rare condition affecting a few million Americans. However, since the Covid-19 breakout, it is estimated that now **1 in 5 people who contracted Covid-19 have developed a form of POTS that is much more serious**. It is a condition that seriously affects blood flow. POTS causes the development of symptoms -- usually lightheadedness, fainting and/or an uncomfortable, rapid increase in heartbeat -- that come on when standing up from a reclining position and relieved by sitting or lying back down.

- Postural: related to the position of your body
- Orthostatic: related to standing upright
- Tachycardia: increased heart rate
- Syndrome: a group of symptoms

OVERVIEW

What is postural orthostatic tachycardia syndrome (POTS)?

Postural orthostatic tachycardia syndrome (POTS) is a condition that affects circulation (blood flow). **It involves the autonomic nervous system (which automatically controls and regulates vital bodily functions) and sympathetic nervous system (which activates the fight or flight response).**

POTS is a form of orthostatic intolerance, the development of symptoms that come on when standing up from a reclining position, and that may be relieved by sitting or lying back down. The primary symptom of an orthostatic intolerance is lightheadedness, fainting and an uncomfortable, rapid increase in heartbeat.

Heart rate and blood pressure work together to keep the blood flowing at a healthy pace, no matter what position the body is in. People with POTS can't coordinate the balancing act of blood vessel squeeze and heart rate response. This means the blood pressure can't be kept steady and stable.

Each case of POTS is different. POTS patients may see symptoms come and go over a period of years. In most cases, with adjustments in diet, medications and physical activity, a person with POTS will see an improvement in quality of life. And POTS symptoms may subside if an underlying cause is found and treated. **However, we are now finding that the form of POTS that is developed with the Covid-19 virus has become much more serious and debilitating. (See the Attached Articles)**

There are various forms of POTS. The most common are:

- **Neuropathic POTS**: Peripheral denervation (loss of nerve supply) leads to poor blood vessel muscles, especially in the legs and core body.
- **Hyperadrenergic POTS**: Overactivity of the sympathetic nervous system.
- **Low blood volume POTS**: Reduced blood volume can lead to POTS. Low blood volume can cause similar symptoms that may overlap in neuropathic and hyperadrenergic POTS.

Who is at Most Risk for Developing POTS?

The majority of POTS patients are women ages 13-60 years old. **However, approximately 1 in 5 people who developed Covid-19 now suffer from POTS in the United States.**

- **Patients are at a elevated risk of developing POTS after getting Covid-19**, a viral illness, serious infections, medical illness, pregnancy and trauma such as head injury. The condition may develop as aftermath of a significant illness (especially associated with hospitalization and prolonged immobilization).
- POTS may develop in those who have had a recent history of mononucleosis.
- People with certain autoimmune conditions such as Sjogren's syndrome and celiac disease can be at higher risk. Sjogren's can be evaluated by blood testing, dry eye test, lip biopsy and rheumatology consult. Celiac disease can be tested through blood work, gastroenterology consult and if needed biopsies of the small intestines.

SYMPTOMS AND CAUSES

What are the symptoms of postural orthostatic tachycardia syndrome (POTS)?

POTS symptoms can be an uncomfortable and frightening experience. Patients with POTS usually suffer from two or more of the many symptoms listed below. Not all patients with POTS have all of these symptoms.

- High blood pressure/low blood pressure.
- High/low heart rate; racing heart rate.
- Chest pain.
- Dizziness/lightheadedness especially in standing up, prolonged standing in one position, or long walks.
- Fainting or near-fainting.
- Exhaustion/fatigue.
- Abdominal pain and bloating, nausea.
- Temperature deregulation (hot or cold).
- Nervous, jittery feeling.
- Forgetfulness and trouble focusing (brain fog).
- Blurred vision.
- Headaches and body pain/aches (may feel flu-like); neck pain.

- Insomnia and frequent awakenings from sleep, chest pain and racing heart rate during sleep, excessive sweating.
- Shakiness/tremors especially with adrenaline surges.
- Discoloration of feet and hands.
- Exercise intolerance.
- Excessive or lack of sweating.
- Diarrhea and/or constipation.

DIAGNOSIS AND TESTS

How is postural orthostatic tachycardia syndrome (POTS) diagnosed?

POTS can be difficult to diagnose due to so many symptoms occurring in the body over time. Before diagnosis of POTS, various symptoms may lead patients to try many doctors. Patients with POTS may have symptoms for months to years before finally being diagnosed with the condition.

The Most Accurate Testing For Detecting POTS:

- Heart Rate Variability (HRV) Test.
- Blood and urine test for causes of POTS and conditions that mimic POTS.
- Autonomic (Valsalva) breathing test (to measure how your blood rate and pressure respond during exercise).
- TST (tuberculin skin test).
- Skin nerve biopsy.
- Echocardiogram.(ECG)
- Blood volume with hemodynamic studies
- QSART (a test that measures the autonomic nerves that control sweating).

MANAGEMENT AND TREATMENT

How is postural orthostatic tachycardia syndrome (POTS) treated?

- **Medications** like salt tablets, fludrocortisone, pyridostigmine, midodrine, and/or a beta blocker may be prescribed to help control POTS.
- You may prescribe thigh-high **medical compression stockings**. These stockings help push the blood up from the legs to reduce POTS symptoms.
- Patients should obtain a blood pressure monitor to **check blood pressure and pulse**. Blood pressure monitors may be purchased at most drug stores, online or at a medical supply store. Also have them check their blood pressure their visits to your office to make sure their at home BP readings correlate with your blood pressure readings.
- Although their heart may still be healthy, they may need to enter a **cardiac rehab program**. This exercise template uses the cardiac rehab model to recondition and help improve health and control POTS. Some of the best data for treating POTS comes from cardiac rehab.

What are everyday ways to help manage POTS?

Diet and nutrition

- Increase sodium in your diet to 3,000 mg to 10,000 mg per day.
- Drink 2-2.5 liters per day of fluids. Water is a good choice. Sports drinks are OK, but watch calories and if you have food sensitivities to these drinks' ingredients.
- Small and frequent meals are better tolerated and reduce POTS symptoms.
- Diet with high fiber and complex carbohydrates may help reduce blood glucose (sugar) spikes and lessen POTS symptoms.
- Keep your nutrition balanced with protein, vegetables, dairy and fruits.
- Plan meals as POTS patients may occasionally not have stamina for grocery shopping and preparing meals. Plan meals when your energy is at its peak. If possible, make it a family plan to prepare food and share grocery shopping responsibilities.
- Don't over-rely on processed foods. Processed foods are easy to prepare and are appealing when you have reduced energy, but usually have less nutritional value.
- Beneficial salty snacks may include chicken or beef broth, vegetable broth, pickles, olives, salted fish like sardines/anchovies and nuts. Don't over-rely on snack chips and crackers for salt.
- Plan grocery store shopping using a list to make sure you pick up healthy food choices and POTS care (hydration and salty supplements). If your stamina is reduced have someone help you shop, carry and put away your groceries.
- Health conditions can be costly. Do your best not to compromise nutrition and food choices to save money.
- You may need a dietary and nutrition consult ordered by your doctor to help you with your diet. This consult can be especially helpful for those with celiac and other dietary sensitivities.
- Often in early phase of POTS patients don't like how their bodies feel and look. Be careful of fad diets or diet supplements for weight loss.

Monitoring POTS

HRV testing on a quarterly basis will show how severe the condition is and how treatments are working over time.

Taking and writing down the vital information (blood pressure and pulse) can give insight and better control over POTS, and helps doctors fine tune the treatment.

Check blood pressure and pulse at the same time daily (in the morning and after dinner). It's very helpful to do this for the first few months of your diagnosis. Also check blood pressure and pulse when you aren't feeling well.

Heart rate/pulse

Measuring heart rate can give you insight as you deal with POTS. Other facts about heart rate and POTS:

- A normal heart rate is between 60 to 95 beats per minute.
- A fast heart rate over 95 beats per minute can be a condition called tachycardia.
- A slow heart rate under 60 beats per minute is called bradycardia.
- High or low rates can cause symptoms of POTS.

Blood pressure

Blood pressure is the pressure of the blood in the blood vessels in the circulatory system. Blood pressure is related to the heart beating and the diameter and elasticity of the artery walls.

- Blood pressure has two components, systolic and diastolic. Blood pressure is recorded as systolic/diastolic. For example, a blood pressure reading of 120/80 represents the systolic number as 120 and the diastolic number as 80.
- The systolic refers to the amount of pressure in the arteries during the contraction of your heart muscles (heart beats). The diastolic refers to the blood pressure between heart beats.
- Normal blood pressure is between is 90-120 for systolic and 60-80 for diastolic.
- Many patients will have stable blood pressure readings since the adrenergic response to keep heart rate increased will reduce blood pressure drops.
- POTS patients can have moments of hypertension with the systolic over 140 or diastolic over 85. If hypertension occurs in many readings, inform your POTS specialist of these consistent readings of hypertension.
- Low blood pressure is below 90/60. Blood pressure logging that reveal low blood pressure readings can be helpful for POTS treatment.

Exercise and physical activity

Exercise and physical activity are key to managing POTS. Here are important things to know as you undergo an exercise program such as cardiac rehab, as well as other physical activities. Talk with your healthcare provider for specific instructions on these exercises.

- **Isometric exercises** involve contracting your muscles without actually moving your body. Isometrics squeeze the muscle and push the blood back toward the heart. They are simple to do and can be done lying in bed or seated in a comfortable chair. It's a good idea to do these in bed before getting up to prepare your body for sitting and standing.
- **Transition slowly with your body**. Go from lying to sitting on the edge of the bed. Stay there for several minutes, allowing the body to naturally adjust to the change in position. Once you are standing, pause and wait before walking to allow blood pressure to adjust again. If you feel lightheaded at any point, wait for a few minutes in that position to see if it resolves. If not, then return to the prior position as your body isn't adjusting properly. SLOWLY is the key.

- **Begin a modest walking program**. Count how many steps you can do without inducing symptoms. These steps are your initial baseline. Start with walking once a day and go a little further in time, distance or by adding steps. If you feel good, add a second walk in the day. A simple strategy for counting steps is to do 100- 300 steps per awakening hour during the day. Fitness trackers can monitor steps and distance easily. Every week or every few weeks add more steps to your daily total.
- **Simple yoga** with focusing on breathing may help reduce POTS symptoms.

As you do better with your POTS, more fitness and exercise regimens may be started.

Sleep

- Try to maintain a typical sleep schedule. Go to bed consistently at a certain time and set a consistent time to wake up. The best sleep hygiene and good rest comes from staying consistent with your sleep schedule every day. Even if you had a poor night of sleep, try to get up at your regular time. A consistent sleep schedule, even with a bad night's sleep, helps you feel better in the long term.
- Excessive daytime napping may make nighttime sleep less restful.
- Most people need 7 to 10 hours sleep at night.
- Be aware of POTS symptoms of chest pain, sweating, restlessness and racing heart rate during bedtime. These symptoms interfere with sleep quality and may have to be addressed by your POTS specialist.
- Avoid excessive television viewing or use of tablet/smartphone/computer in bed. These technologies can interfere with sleep quality.
- Raise the head of your bed 6-10 inches to help alleviate POTS symptoms. The entire bed must be at an angle. Raising the head of the bed will reduce urine formation overnight and increase fluid volume in your circulation in the morning. This may help you wake up more easily.
- Make sure the temperature is ideal in your bedroom to help you get proper rest.

LIVING WITH

How do I coordinate and organize my care with postural orthostatic tachycardia syndrome (POTS)?

- Start a binder or folder containing your basic notes and testing results. Periodically review this binder to remove out-of-date data. As a rule, about 20-30 pages of pertinent medical data will help guide your POTS medical team most effectively.
- You'll need a healthcare provider or primary care physician to go to for routine care and health wellness management. Your POTS specialist may ask you to see your healthcare provider periodically. Get copies of your medical visit notes from your healthcare provider — especially any additional testing results — to have in your record binder (see above).
- If you're feeling very ill or something doesn't feel right, you may need to go to the ER or Urgent Care immediately. If you call your POTS specialist you may be told to go to the ER or Urgent Care
- Be sure to follow up with your POTS specialist.

How do I cope emotionally with POTS?

- Be open and honest with loved ones and support groups about your diagnosis of POTS. Talk about your fears, hopes, struggles and challenges with the condition. Encourage the people who support you to learn more about POTS.
- Get enough sleep and eat well to help manage stress.
- Shared medical appointments and POTS support groups (either online or in person) will help reduce the feeling of being alone and different.
- Be careful with social media. Be mindful of the accuracy of any particular website's data. Some POTS patients find comfort in social media. For others, social media can cause unnecessary and excessive stress and worry.
- Be very cautious of quick solutions from non-medical sources and people. Quick solutions usually don't help POTS and can even cause more emotional distress.
- We recommend counseling to help you learn to cope with a chronic health condition. Counseling may help to control other co-existing mental health issues that may negatively influence POTS.
- Meditate or take even just a few minutes of a time-out to help reduce some of your POTS symptoms.
- Emotions can have a significant influence on your daily life and health. Identifying them can be useful if you are talking with a counselor or POTS support group.