DO I HAVE POTS?

Postural orthostatic tachycardia syndrome, also known as POTS, is a disorder where the heart rate increases significantly in patients when they assume the upright position within a ten minute period of time and can cause a constellation of symptoms. The symptoms are part of a spectrum of orthostatic intolerance (OI).

Before understanding exactly what POTS is, one needs to understand the symptoms of orthostatic intolerance. Orthostatic intolerance is the development of symptoms which occurs when an individual stands upright from a lying or sitting position. These symptoms are relieved when the patient reclines. When orthostatic intolerance can occur in an acute setting when patients are dehydrated or have taken medications that can lower blood pressures when they stand up, these are termed secondary orthostatic intolerance. Primary orthostatic intolerance occurs in the absence of dehydration or medications causing the abrupt symptoms that occur when an individual assumes the upright position.

When an individual stands, this is actually a fundamental stressor. This requires the abrupt working of circulation and neurological compensatory mechanisms to maintain blood flow especially to the head, that is cerebral blood flow. When an individual stands up, approximately 1/2 of a liter to approximately 3/4 of a liter (500-700 ml) of blood, which is located within the chest or thorax, is quickly directed to the lower extremities. Normally, when one assumes the upright position, this downward shift of blood, which occurs mainly in the legs and somewhat in the abdomen, will decrease venous return to the heart. This in turn will decrease cardiac output and will lower the blood pressure. This lowering of the blood pressure and an effective volume within the thorax immediately triggers a reflex sympathetic activation from the autonomic nervous system. The sympathetic nervous system is the fight or flight, or accelerator of the body. It causes an increase in heart rate and vasoconstriction, which is a squeezing of the blood vessels to force blood upward to the heart so that it can pump it to the brain. This increase in heart rate and the vasoconstriction, which squeezes the arteries and veins, counteracts the initial decrease in blood pressure which occurs on standing up. Usually when one assumes the upright position the heart rate will increase 10 to 20 beats per minute. The systolic blood pressure will not change as the compensation has corrected for any potential drop, and there is actually a 5 mm or so increase in diastolic blood pressure.

In individuals with orthostatic intolerance, these compensatory mechanisms are deficient. Oftentimes, we see a lack of the sympathetic nervous system activation, and therefore the vessels in the lower extremities would not become constricted, and the blood pools in the lower extremities. This can cause a significant amount of symptoms, such as altered vision. The patient will often get blurred vision or claim that they get a graying-out, whiting-out or blacking-out of their vision. Occasionally they describe it as double-vision. This will also cause tremulous anxiety. Short and long-term effects can include fatigue, and, in fact, almost all cases of chronic fatigue are associated with some degree of orthostatic intolerance in our experience. Exercise intolerance can be quite marked and patients become short of breath on minimal

activity, as they cannot maintain a good cardiac output because the blood is being pooled in the lower extremities. Headaches can occur and heart palpitations can occur because the heart attempts to race to compensate for the falling blood pressure with blood still remaining in the legs and not returning to the heart. Difficulty breathing and swallowing can occur, and patients may have a hyperventilation syndrome. Sweating also can occur along with tremulousness. Weakness over the entire body is often noted and even after lying down patients can become weak for an extended period of time, even hours or up to a day. Lightheadedness and brain fog are one of the most common symptoms due to lack of cerebral blood flow. Venous pooling may cause a violet/red discoloration in the feet.

Orthostatic intolerance can be acute or chronic. It can occur throughout the entire day. These patients oftentimes will have nausea, difficulty concentrating, difficulties finding words, or word-finding difficulties and memory deficits. They will have a chronic pallor appearance. They are often sensitive to heat and sometimes cold weather. They invariably will have sleeping problems and thermoregulatory problems with their temperature regulation. Relief with lying down is common, and many patients often have to lie down and even elevate their legs above their head. Hot weather appears to be one of the worst environments for this orthostatic intolerance. Also, in early morning when one arises is often the worst time of day.

We can measure some of the mechanisms involved with orthostatic intolerance with various tests including tilt testing and cardiorespiratory testing with stand responses. We measure heart rate intervals oftentimes coupled with respiration, and we can get an idea if the sympathetic nervous system is failing when one stands up and not acting appropriately.

It is estimated that over half a million Americans are affected with orthostatic intolerance, but this number may even be quite higher. They are usually undiagnosed. They are usually younger individuals under the age of 35, and women are affected more than men. Often these symptoms are misdiagnosed as psychiatric or anxiety related.

There are complicated neural and humoral mechanisms involved in the stand response, which included change in hormones such as vasopressin, renin, angiotensin and aldosterone levels. These also can be defective in people with orthostatic intolerance.

Most patients with orthostatic intolerance symptoms can manage these with salt and fluid. Indeed, they have mild cases and can function; however some have very disabling courses and need more aggressive treatment including pharmacology and compression garments.

Postural orthostatic tachycardia, or POTS, is a more extreme form of orthostatic intolerance. This occurs when one goes from a lying to standing position and has an abnormally large increase in heart rate. The symptoms that occur are the same as those that occur with orthostatic intolerance but are usually more dramatic, including the lightheadedness, difficulty thinking, the blurred vision, and the weakness. Also, there are other associated symptoms and complexes associated with postural orthostatic tachycardia including Ehlers-Danlos syndrome, chronic fatigue syndromes, fibromyalgia, chronic headaches, and insomnia. Rarely patients with

postural orthostatic tachycardia faint or have overt syncope, but they have presyncope and feel like they are going to faint and have to lie down for relief of symptoms. Usually, they will feel their heart pound quite rapidly on standing up.

To define POTS or to diagnose POTS, usually there is an absence of a drop in blood pressure known as orthostatic tachycardia, although occasionally we see a drop in blood pressure occur with people who do have simultaneous POTS syndrome diagnosed. To diagnose POTS, one needs to have symptoms of orthostatic intolerance for at least six months and a heart rate increase of at least 30 beats per minute or greater within ten minutes of assuming an upright position in the absence of orthostatic tachycardia, although rarely we do see drops in blood pressure in these patients. However, if the blood pressure drops by more than 20 mm systolic or 10 mm diastolic, we cannot make a clear diagnosis of POTS, and rather we make a diagnosis of generalized autonomic dysfunction. Also, postural orthostatic tachycardia needs to be diagnosed in the absence of secondary causes, such as deconditioning or prolonged bed rest, the overuse of diuretics or blood pressure medications that can cause such changes, and in the absence of certain antidepressants, which also can cause heart rate accelerations on standing. Also, hypothyroidism, dehydration and anemia need to be excluded.

We can test for POTS with a tilt test or with various heart rate variability tests, which are simple techniques performed in the office setting. Many physicians do what is known as a "poor man's POTS test." This test involves having the patient lie down and take their heart rate, then wait two minutes and stand the patient up and take heart rates over a ten minute period of time to see if the criteria are met, that is a heart rate increase over 30 beats per minute. In younger patients, we often like to see the heart rate increase by more than 40 beats per minute. We also like to see the heart rate exceed 120 beats per minute.

Some symptoms of POTS can be non-positional, such as fatigue and headaches.

When assuming the upright position, patients with POTS often get short of breath because of decreased cardiac output. They often complain of chest pain and chest discomfort. They have a mental clouding of brain fog and nausea. Some will actually faint, but usually they can recognize the symptoms and will lie down.

The severe tachycardia that occurs with patients with POTS on standing makes the patients very symptomatic. These symptoms are more marked in the morning. Dependent acrocyanosis, which is a purplish discoloration in the feet occurs on the upright position in patients with POTS. This is a dark, red purple discoloration and the feet become very cold to touch as do the hands. This is due to venous pooling.

When an individual's heart rate rises above 120 beats per minute but does not exceed 30 beats from the baseline, the patient may still have postural orthostatic tachycardia. Also, we have found that patients do not meet the strict criteria for POTS, that is their heart rate does not quite rise 30 beats per minute or does not go above 120 beats per minute, but they have a tendency towards reaching these numbers. We often look at a cardiorespiratory test, which is a

simple test performed in the office, and calculate the slope of the heart rate increase on standing, and see an increasing slope as the heart rate slowly rises. This is a type of pre-postural orthostatic tachycardia response. Also, we can test for what we call sympathetic withdraw, that is a lack of sympathetics kicking in or working when one stands up, and this usually causes orthostatic intolerance, but may not necessarily cause an increase in heart rate. This does not classify as POTS, but is seen in the early stages prior to POTS.

As mentioned, patients with POTS have various other autonomic dysfunction symptoms, such as irritable bowel, abnormalities with sweating, temperature regulation and bowel and bladder function abnormalities. A good majority of patients with Ehlers-Danlos syndrome will exhibit POTS. If one has severe orthostatic intolerance without significant heart rate increases and does not qualify for POTS, their mechanism and symptoms may be almost identical to those patients who have POTS and treatment is usually also the same, however. Therefore, it is not an all or none phenomenon in autonomic dysfunction to diagnose or not diagnose POTS based on heart rate responses.

Recent research has shown there are several types or variants of postural orthostatic tachycardia. These include a central, or brain-mediated high adrenalin or hyperadrenergic stimulation, a norepinephrine transmitter dysfunction, which is quite rare, and autoimmune antibodies against cholinesterase receptors. There are also episodes of POTS associated with deconditioning and hypovolemia. There is some data that suggests POTS may be associated with autonomic cardiac neuropathy using very sophisticated and state of the art testing involving 1231-meta-iodo-benzylguanidine testing in postural orthostatic tachycardia syndrome. However, this is not routinely available in most clinical settings. POTS may be associated with trauma, infections, mononucleosis, Lyme disease, electrocution, multiple sclerosis, and mitochondrial disorders. It has also been seen after ablations by electrophysiologists for supraventricular tachycardias. There is also a form of chronic hypovolemia where many patients with POTS have a low blood volume.

There are many complex pathophysiological mechanisms involving postural orthostatic tachycardia. In general, the mechanisms of orthostatic intolerance in POTS patients include impaired sympathetic vasoconstriction, as noted, leading to venous pooling. This can lead to low blood volume, deconditioning and a secondary hyperadrenergic state where the sympathetic nervous system is extremely over-activated, and the heart rate goes very high. This excessive reflex sympathetic excitement is oftentimes triggered by orthostatic stress by reduced baroreceptors in areas of the brain, in particular the solitary tract (NTS) and also activation of the vestibulosympathetic reflexes (VSR) relayed by the medial vestibular nucleus (MVN). This results in an increased activity of the sympathetic excitation neurons in a part of the brain known as the rostral ventrolateral medulla. This causes an increase in sympathetic excitation. Many of the other symptoms of POTS, which are visceral pain, motility disorders of the GI tract and bladder, chronic pain, headaches, dizziness and fibromyalgia-type symptoms actually reflect abnormal central processing of inflammation relayed by the nucleus and solitary tract (NTS) and the parabrachial nucleus (PBN). This goes through the ventromedial portion of the thalamus, which is a relay station, to higher levels in the brain including the anterior

cingulate cortex, insula, amygdala, hypothalamus, and periaqueductal gray regions. The amygdala is a portion of brain that has been involved in significant research and has been shown to be affected by acute and chronic stress. It is by this mechanism where the amygdala is affected by acute and chronic stress conditions that dysautonomia gets perpetuated (an excellent diagram can be seen in a figure in the Mayo Clinic Proceedings, 2012, December, pages 1214 to 1225). It describes these pathways and clearly demonstrates the brain-body connections in autonomic dysfunction. It nicely explains the increasing sympathetic hyperactivity that can be seen in orthostatic intolerance symptoms, such as POTS, and also explains how orthostatic stress can decrease cardiac output and cause orthostatic intolerance symptoms due to decreased baroreceptor input. Postural changes are a key mechanism here, that is assuming the upright position from a lying or sitting position.

To diagnose the various mechanisms of POTS is not necessarily important. For example, measuring blood volumes, aldosterone-renin levels, serum norepinephrine and plasma norepinephrine levels, and working up mast cell activation with 24-hour urine tests, or blood tryptase levels are not mandatory, although patients who have frequent flushing may have abnormal increases in methylhistamine, and may require additional treatment directed against histamine production. Sophisticated labs will measure norepinephrine levels, lying and standing. If the levels with standing are above 600 pg/mL, the hyperadrenergic type of POTS is diagnosed. These people also have very hypertensive responses on standing along with increased heart rate.

The normal individual when they stand has a 750 cc fluid shift in the lower extremities, which decrease venous return, decreases to stroke volume and blood pressure. The normal baroreflexor activation will increase the sympathetic nervous system, increase the resistance to the blood vessels and increase blood pressure, and will also decrease parasympathetic intake, which increases heart rate and increases cardiac output. In patients with POTS, the venous return on standing is diminished; however, the baroreflexor activation is abnormal. For some reason, they have a hyperactive sympathetic response with too much sympathetic discharge occurring in a delayed fashion, which can increase the heart rate excessively, sometimes to levels above 120 to 130 beats per minute. The cardiac output does not increase sufficiently as the stroke volume becomes much more diminished in what appears to be a small heart cavity size. Females are more predisposed to this.

The treatment for POTS is similar to most orthostatic intolerance symptoms, which do not demonstrate high heart rate rises, and includes increased fluids, increased salt and compression garments. There is also exercise training. Some patients with POTS periodically require intravenous saline for relief at 1-2 liters, and many times they will go to the emergency room for such treatment. Some extreme cases even have it given at home several times from an indwelling port. Waist-high compression garments at 30-40 mm are oftentimes better than just leg garments for counterpressure maneuvers to combat venous pooling.

Classes of drugs include volume expanders, such as fludrocortisone and desmopressin. We prefer not to use these as first-line, but rather use vasoconstrictor therapy with Midodrine

starting at 2.5 mg three times a day. The duration of Midodrine is usually four hours, and one should not lie down during that period of time as the blood pressure may shoot up too high. To combat the increase in heart rate, which is most uncomfortable, low doses of propranolol or other beta-blockers can be used. We prefer propranolol 10 to 20 mg by mouth three times a day. Clonidine and methyldopa have also been used at night. We find clonidine very effective at night, which prevents the excessive rise in heart rate when people arise in the morning. We also like the head of the bed slightly elevated when the patient sleeps. Also, we like the patient to drink a bottle of water and take a salt tablet prior to even standing while they dangle their legs over the bed in the early morning.

Exercise is important. One cannot run on a treadmill and do high impact aerobics right away. Gradually, the intensity is increased over a period of time. Resistance training is focused on the lower extremity. We recommend a rowing machine or recumbent bicycle, or swimming. We attempt to get the target heart rate equivalent to 75% of the maximum target heart rate. Also, 150 minutes a week of exercise is recommended. Many times patients have to build up to that.

In terms of fluids, we recommend 6 to 8 glasses of water or equivalent a day and have patients put in electrolyte solutions of powder at times to get more solute. Six to eight grams of sodium a day is sometimes required. Physical maneuvers to enhance venous return and prevent pre-fainting or fainting episodes, such as sitting with the feet folded up or squatting are often used. These are used especially in acute episodes where a patient gets an onset of rapid heart rate, brain fog, dizziness, and a fainting sensation on standing up. Standing in lines for long periods of time can also be a problem.

Occasionally, we will use pyridostigmine 30 to 60 mg up to three times a day, as this attenuates a tachycardia and can be combined with a beta-blocker such as propranolol. This is oftentimes a very effective medication, especially in patients who are constipation-predominate. We do not use fludrocortisone as first-line but usually use with propranolol and Midodrine. However, we can start fludrocortisone if individuals are sensitive to Midodrine or if they have not had a complete response. We usually start at a very low dose of 0.05 mg Monday, Wednesday and Friday. This causes a blood volume expansion and may cause some swelling of the lower extremities, high blood pressure, fluid retention and low potassium, and electrolytes have to be checked. This is a very effective technique when used with salt and water intake increases. Desmopressin is rarely used as an acute blood volume expander, as it can cause low sodium, and we attempt to avoid this and only use it as a third-line medication if other agents have failed. Its mechanism is to increase blood volume via a different mechanism than fludrocortisone.

In regard to Midodrine, we start at 2.5 mg a day and after two weeks increase to twice a day and at three weeks three times a day. We usually give it before meals and not at bedtime, as one should not lie down after taking it. The reason we give it with meals is many times blood flow is diverted to the GI tract after eating and makes orthostatic intolerance symptoms worse, as less cerebral blood flow can occur. Midodrine is a vasoconstrictor via an alpha 1 adrenergic receptor agonist mechanism. It can cause itching of the scalp or pruritus of the scalp, urinary

retention and mild high blood pressure when standing, but more pronounced when lying down. The piloerection may give chills. We have found Midodrine effective in decreasing the reflex heart rate, or sinus tachycardia, and improves venous return to the heart and is very effective with used with compression stockings. Lower doses can be used when low doses of Florinef are used, and we describe this as a Midodrine-sparing effect. Midodrine can be taken up to 10 mg four times a day, but rarely more.

Medicines which are extremely effective, especially in decreasing the heart rate, and used off-label are Corlanor and Northera. The former lowers heart rate directly and does not lower blood pressure. It is more effective than a beta-blocker but is extremely expensive and oftentimes difficult to get precertification from insurance companies. The latter medicine is used more for orthostatic tachycardia where blood pressure drops, but is a norepinephrine analog and is oftentimes effective in patients with POTS who have not responded to Midodrine or Florinef. Some insurance companies will approve it off-label despite the lack of orthostatic tachycardia as long as dysautonomia is present and the patient has failed a trial of Midodrine and Florinef in combination.

One must realize that POTS is a multisystem disease. Lightheadedness, pre-fainting, brain fog concentrating difficulties and fatigue are very common along with headaches. Medicines that stimulate the brain, such as Adderall, Provigil and other amphetamine salt-type derivatives are harmful, as they can potentially increase the heart rate and have cardiac side-effects, and we are definitely against these agents for primary treatment. Some patients with POTS become severely disabled and cannot work, leave the house or drive.

A multisystem approach requiring exercise training, volume resuscitation, salt intake, compression garments and other physical maneuvers as well as aggressive pharmacology are often necessary to get the patients to begin to improve and to be able to have more good days than bad days. Once they attain this confidence and learn how to live with their disability, they can function much better in society. Some young people who do have evidence of POTS, which comes on quickly, can go into remission within a two-year period of time. One study had suggested that maybe 85% of people in this category can go into remission within a two-year period of time. We often find that when patients become pregnant their symptoms dramatically get better or go away, and this is because of increased blood volume. However, after delivery they "crash" and need to be followed by an autonomic specialist and administered pharmacology and volume measures immediately post delivery. Also, most of these medicines need to be stopped immediately when a person believes they are pregnant, especially Midodrine, but also the other medicines we have discussed. One should consult with their physician as soon as they believe they might be pregnant and stop all of their medications until tested.

Counseling and reassurance increased dietary salt and water, orthostatic training and counterproductive measures along with pharmacology are the keystone of treatment. Oftentimes, a patient is relieved when they know that they have a real medical problem that can be treated, and this is not purely a psychiatric problem.

One should seek out a physician, some of whom are cardiologists or neurologists who have experience in treating patients with POTS syndrome.