

Why Only Manage POTS?!? POTS MAY BE CURED!! A Review

by

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NO ABSTRACT

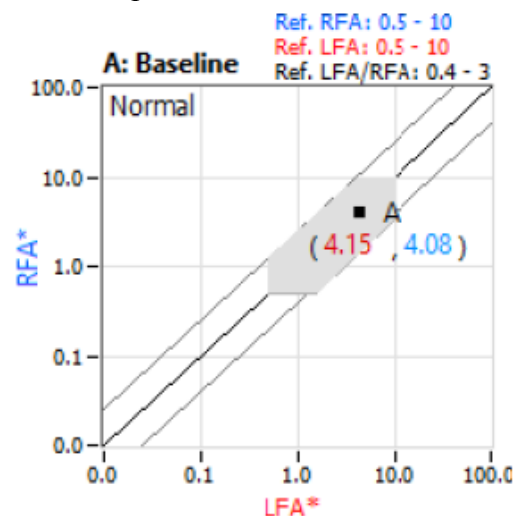
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DIAGNOSING POTS

Postural Orthostatic Tachycardia Syndrome (POTS), many “experts” will state it is not real. That may be because they cannot measure it effectively to diagnose it consistently. POTS is often co-morbid with Vasovagal Syncope (VVS). Many of the same experts claim that POTS and VVS cannot be co-morbid. This is because, for the most part, they have never been able to measure both together; therefore, “it must not exist.” Yet the two dysautonomias are mediated by two different branches of the autonomic nervous system; three, in fact: 1) alpha-Sympathetic Withdrawal (α SW, an alpha-adrenergic reflex) underlies Orthostatic dysfunction [1] (the “O” in POTS), 2) Parasympathetic Excess (PE; aka., Vagal, referring to Vagus Nerve, is another name for Parasympathetic; a cholinergic response) [2]; and 3) beta-Sympathetic Excess (β SE, a beta-adrenergic response) underlies Syncope [3]. β SE may be a result of the “adrenaline storms” released by the brain to increase cerebral perfusion, compensating for either or both Orthostatic dysfunction (*i.e.*, POTS) or VVS [4]. The good news is that any or ALL three of these autonomic dysfunction mechanisms leading to dysautonomias are treatable, simultaneously [5]. Furthermore, for many

patients they may be relieved (including reversible or cured) and the patient returned to a normal lifestyle, quality of life and productivity, assuming no co-morbid chronic condition that imbalances the Parasympathetic and Sympathetic (P&S) nervous systems.

Another reason why so many providers miss POTS is because the patient seems normal. Of course they do! When does the typical doctor assess a patient? When the patient is resting (sitting or supine). The vast majority of POTS patients are indeed normal at rest.

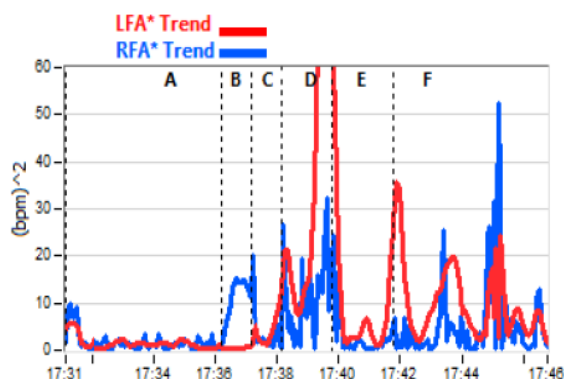


As shown in the resting baseline response graph above, this typical POTS patient's resting response is point 'A' which is right in the middle of the normal area as indicated by the gray shaded region. These POTS

better be normal at rest. As our typical patient reports, they have had dozens of doctors over decades of time working very hard to make them normal ... at rest!

The patient's problem is not while the patient is resting. In fact, the P&S nervous systems are rarely at rest, and when the patient is resting the P&S systems are typically most active! The problems that POTS causes are when the patient is active, as in the cases of POTS, while upright, standing, and the heart must fight gravity.

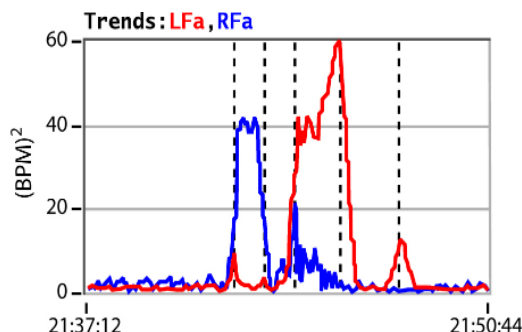
Abnormal Trends Plot of a POTS Patient



Continuing with this same patient from whom the Resting Baseline response plot was captured, a female in her early twenties, we have her P&S Trends Plot (blue & red curves, respectively in the “Abnormal Trends Plot of a POTS Patient” plotted above). These are her P&S responses to the standard P&S clinical study. On average (data not shown) they are all within normal limits. Furthermore, for the instantaneous levels (data shown in the above abnormal Trends plot), the Resting Baseline (‘A’), the Parasympathetic challenge of deep breathing (‘B’), a return to baseline (‘C’) before the Sympathetic challenge of short Valsalva maneuvers (‘D’), and a return to baseline (‘E’) before the Stand or postural change challenge (‘F’) are all normal. The Stand phase (‘F’) even starts normally with a

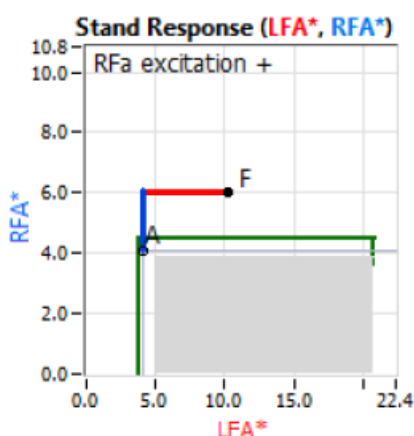
proper Sympathetic response to the Gravitational challenge during the first 15 seconds of Stand or so. Again, all of the first five phases of the test (‘A’ through ‘E’) are within normal limits (compare with a Normal Trends Plot from a normal patient, in the next plot).

Normal Trends Plot

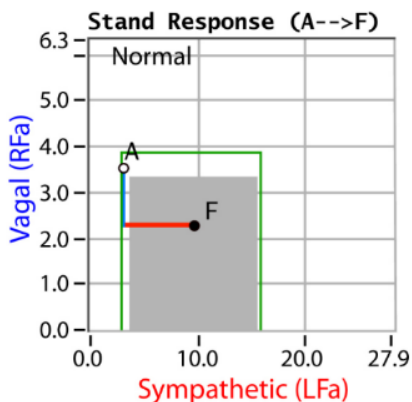


However, the rest of the Stand response is filled with all sorts of abnormal P&S activity indicating the struggle of the P&S to maintain an upright posture (proper cerebral perfusion). This is not seen during the quiet portion of the normal stand response. Yet, in this patient, it takes a relatively similar amount of P&S energy (cumulative) to remain standing as it does to support the stress simulated by the Valsalva challenge. Physiologically, that makes no sense (compare normal Stand with Valsalva responses in Normal Trends plot, above, with the abnormal Trends plot, previous).

The excessive beta-Sympathetic (red) activity during the quiet portion of the Stand phase (after the first 15 seconds, as seen in the abnormal Trends plot above) indicates a (β)SE. The (red) Sympathetic surges are known as “Syncope Spikes,” literally, evidence of the brain “calling for more blood.” The excess Parasympathetic (blue) activity in the abnormal Trends plot is confirmed by the abnormal Stand Response plot below; RFA is the engineering term for Parasympathetic activity).



Normally, during Stand first the Parasympathetics (the blue portion of the Stand response curve) should decrease from point 'A' (the resting Baseline response) and then the (alpha-)Sympathetics should increase to the point 'F' (the Stand response), in the middle of the gray (normal) area as in the next plot, below.



This is much like the brakes and accelerator on a car. To go, first you take your foot off the brake pedal, then you apply your foot to the accelerator. In cases of PE, it is like the "car" is driven with the foot still on the brakes (PE), forcing excess acceleration (β SE) and undue wear and stress on the car and the brakes, just like the human body. Combined, the PE indicated in the Stand Response plot and the β SE indicated in section 'F' of the Abnormal Trends plot, VVS is documented (PE & β SE indicates pre-clinical or clinical VVS).

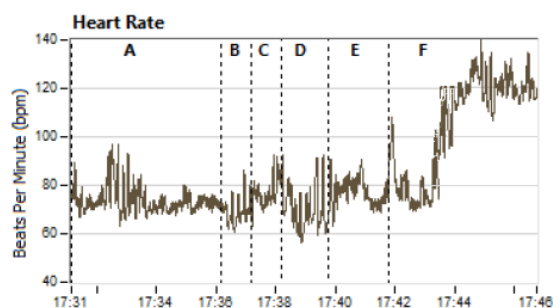
Because of the PE and β SE, the α SW is often masked, as in this case. However, the resulting symptoms of α SW, and in this case POTS, are documented elsewhere in the clinical study report, in the BP responses to Stand (the 'O', the Orthostatic dysfunction, is the clue) and the instantaneous HR responses to Stand (section 'F' of the cardiogram or HR plot). A portion of the summary data table is in the next insert, documenting the (average) responses for each of the phases of the test.

Summary:

	Event	Duration	meanHR	BP
A:	Baseline	05:00	74	120 / 87
B:	Deep Breathing	01:00	69	111 / 81
C:	Baseline	01:00	77	121 / 82
D:	Valsalva	01:35	71	154 / 96
E:	Baseline	02:00	77	125 / 84
F:	Stand	05:00	121	111 / 86

From the Table above, the average or mean HR increases upon standing from 74 bpm at rest to 121 bpm with Stand, documenting the Tachycardia associated with POTS (the 'T' in POTS). The BP responses drops from Resting Baseline at 120/87 mmHg to 111/86 mmHg with Stand, documenting Orthostatic dysfunction (the 'O' in POTS). Note, there may not be as much of a drop as indicated here, but there is typically an abnormal BP response to Stand, even if it is only a weak rise in BP (< a 10% increase over the resting BP).

The instantaneous HR plot depicting the cardiogram in response to the test is the next graph, below. shows a typical POTS response during the Stand ('F') portion of the test, in this case a sharp rise in HR after an initial (normal) return to baseline before the onset of the tachycardia. With these three indications and experience, we have the confidence to diagnose masked SW and add therapy for Orthostatic dysfunction to the plan.



Marked symptoms in POTS patients are more often seen early in the morning and these symptoms may normalize later in the day especially when they acclimate with compensatory mechanisms and properly hydrate throughout the day. Therefore, POTS symptoms may be intermittent and not consistently documented by conventional means, however the P&S dysfunction(s) remain regardless of symptoms. As a result, later in the day, POTS patients may not demonstrate significant HR and BP changes. Also, in warm ambient temperatures, POTS signs and symptoms may be significant, whereas in a more temperate climate the symptoms may be masked or controlled.

RESTORE AND IMPROVE QUALITY OF LIFE

We do not accept, as too many others seem to do, that the poor quality of life for these POTS patients is their new normal; even if the patient cannot remain standing while s/he brushes their teeth in the morning or washes their hair in the shower while standing. For most, POTS came on suddenly, apparently from nowhere. But you have to go back three to six months before the onset to determine a potential cause (such as COVID-19 causing Long-COVID, or some other mental or physical trauma or chronic disease causing P&S dysfunction of which POTS is a type, or it may be puberty and the child will grow out

of it) [6,7,8,9,10,11]. Often the P&S nervous systems will struggle to maintain normal function even when they are abnormal before they may fail to maintain normal function. There are many possible causes: concussion, psycho-social stress, all sorts of abuses (physical as well as mental), serious viral infections (including COVID-19) and other types of infections (molds, mildews and bacterial), in other words, trauma of some sort, as well as puberty. However, those for whom it is caused by puberty often do grow out of it and find significant relief with proper daily hydration, including electrolytes.

POTS typically affects young women because they typically have physically smaller hearts (smaller stroke volume) than men and older women. Sorry, that is just the way it is. (Notice we say physically, this has nothing to do with the fact that most women are “bigger hearted” than men; emotionally and nurturing. ☺). Due to the smaller cardiac stroke volume, when the brain calls for more blood, the smaller heart does not have the mass to leverage more pressure, so it must leverage more rate to increase blood flow to the brain.

To help healthcare providers, more information is needed. P&S monitoring is more information. As shown in the graphs and tables above, P&S monitoring may document if VVS is involve with POTS requiring additional therapy to relieve PE so the β SE may normalize organically. Relieving PE will relieve β SE, which in turn will relieve Tachycardia and other beta-Sympathetically mediated symptoms. In other words, by taking the foot off the brakes, the need to accelerate harder is relieved, which in turn, relieves stresses on the engine and the brakes. P&S monitoring is able to document both at the same time in one single test. POTS may involve (pre-

clinical) Orthostatic Intolerance or Orthostatic Hypotension and as well as the underlying α SW (possibly masked, if VVS). Therapy may unmask α SW and it may be documented upon follow-up testing to help properly titrate therapy to the individual patient.

DIAGNOSTIC SUMMARY

The separate parts of the ANS may be involved and all at the same time (especially in more serious and complex cases):

- ‘O’ = SW, an α -adrenergic dysfunction,
- ‘V’ = PE, a Vagal dysfunction,
- ‘S’ = SE, an β -adrenergic dysfunction.

α SW & PE are associated with the following: lightheadedness, cognitive dysfunction or “brain fog”, and frequent headache or migraine, sleep difficulties, fatigue, exercise intolerance, difficult to control BP, blood glucose, hormone level, or weight, difficult to describe pain syndromes (including CRPS), unexplained arrhythmia (palpitations) or seizure, GI disturbance, temperature dysregulation (both response to heat or cold and sweat responses), and symptoms of depression or anxiety, ADD/ADHD, and sex dysfunction.

The “brakes and accelerator” model is the better way to consider the P&S (or autonomic) nervous systems. The brakes represent the Parasympathetics and the accelerator represent the beta-Sympathetics. The “see-saw” model taught in Medical School is still included and addresses resting conditions. Typically, at rest or under normal conditions, your foot is either on the brakes and off the accelerator or vice versa; there is the “see-saw.” For some normal as well as abnormal responses to challenge, the “see-saw” model often fails. For example, as mentioned above, upon standing, first the Parasympathetics should decrease and then

the alpha-Sympathetics should increase. This is much like the brakes and accelerator on a car. To go, first you take your foot off the brake pedal, then you apply your foot to the accelerator. Upon releasing the brakes, the car already begins to roll (accelerate, the other end of the “see-saw” has not increased yet). At this point without touching the accelerator, known as coasting, just releasing the brakes minimizes and potentiates the amount of acceleration, stress, and wear, required to normally reach speed. If the brakes are not released, and the accelerator is depressed, the car will still go, but it takes more acceleration (now both ends of the see-saw are up, the car model provides a better analogy). In effect, the acceleration is amplified (even though these speeds are reduced compared with normal, because the brakes are engaged), and so are the results of acceleration. This is the effect of PE. PE also often causes secondary β SE that is the “adrenaline storm” or β -Sympathetic stimulus of the heart meant to increase blood flow to the brain and everywhere above the heart. It often presents in P&S Monitoring reports as “Syncope Spikes” in the Stand portion of the clinical study

To extend the brake and accelerator analogy, α SW (an abnormal α -Sympathetic response) is like hitting the accelerator and abnormally low amounts of gas gets to the engine, so either the engine barely goes (fatigue, brain-fog, sleep difficulties, memory or cognitive dysfunction, vision effects, ringing in the ears, lightheadedness, taste or smell disorders, etc.) or the engine stalls (fainting or you feel like fainting and you have to sit or lay down). In the case of α SW, blood pools in the feet, ankles and lower legs, causing poor coronary (heart) and cerebral (brain) perfusion. These symptoms are also caused by PE.

In the body, the results of PE induced amplified acceleration (amplified β -Sympathetic activity) may be Anxiety, Inflammation, allergic or histaminergic over-reactions, amplified pain, hypertension or difficult to control BP or blood sugar, tachy-arrhythmia, amplified stress responses, ADD/ADHD, OCD and even high-functioning Autism, and more. All of these are Sympathetic symptoms, and some may be critical in nature. As indicated above, there are two Sympathetic branches in the body: the alpha-branch, the α -Sympathetic branch, which primarily controls and coordinates the vasculature outside the thorax (the rib cage); and the beta-branch, the β -Sympathetic branch, which primarily controls and coordinates the heart and lungs (inside the rib cage). The β -Sympathetic symptoms may be secondary to either or to both α SW (an α -Sympathetic response) or PE. Regardless of the mechanism (α SW or PE or both), not enough blood gets to the brain (poor cerebral perfusion), resulting in the β -Sympathetic symptoms due to the β -Sympathetic response compensating by attempting to stimulate the heart to pump more. If the physician does not think to consider the β -Sympathetic responses as secondary, attempting to treat only the β -Sympathetics or treating them as the primary, may exacerbate the conditions and cause the potentially critical nature of β SE (heart attack or stroke) to become a self-fulfilling prophecy.

THERAPY OPTIONS

In either case (SW or PE or both), proper daily hydration is required, often with electrolytes. This includes a minimum of 64 oz of water taken throughout the day with an additional 5.5 g of electrolytes dosed every two hours throughout the day. The electrolytes may be Sodium from salt (1

tablespoon, including flavored salts) if the patient's BP is normal to low, less than approximately 160/90 mmHg, history dependent. If BP is high, then the electrolytes may be Potassium from (bananas or prunes, for example). For days with more activity (loosing water and electrolytes through sweat for example) or in women days of their period, more water is required, up to 96 oz with up to 8.25 g of electrolytes.

For SW, low-dose, oral vasoactive therapy (e.g., Midodrine, 2.5 mg tid, history dependent; an α -1 Sympathetic agonist or stimulant) typically relieves the β -Sympathetic symptoms organically, after relieving any Orthostatic dysfunction caused by the SW. In other words, vasoactive therapy helps to relieve blood pooling in the lower extremities, moving the blood to the abdomen, helping the heart pump blood to the brain, thereby restoring proper brain perfusion. This in turn prevents the need for adrenaline storms, thereby relieving the β -Sympathetic symptoms, like tachycardia, stress, and inflammation. Checking to "see if gas is getting to the engine" (α SW) and treating to ensure it does (e.g., unclogging the fuel filter or fuel line), relieves β SE organically (reducing the amount of acceleration needed), ultimately relieves the β -Sympathetic symptoms.

Of course, this process takes time. It is not a quick fix. In fact, it may take up to 24 months, depending on the patient's history, including daily stress levels. The oral vasopressor helps to speed the recovery as much as possible, but not everyone responds to it. The first line alternate therapy is 600 mg, tid, r-Alpha-Lipoic Acid. Compression garments are also recommended in the interim. Still the oral vasopressor does not help to speed recovery all that much. To use another analogy: the P&S Nervous systems

are like a pendulum, if to correct it you hit it hard or fast, you knock the pendulum off its hinge and create more problems. Therapy must be slow, gentle, easy nudges over time, or for another analogy, it is like stopping a bad habit and establishing and maintaining a good habit.

Similarly, checking to see if the brakes are “on” (PE) and treating to release the brakes may resolve all of the beta-Sympathetic abnormalities. Relieving PE (releasing the brakes), relieves β SE (reducing the amount of acceleration needed), and ultimately relieves the β -Sympathetic symptoms. Low-and-slow exercise is the primary alternative remedy for PE. PE may also be relieved with low-dose anti-cholinergic therapy (very, low-dose antidepressant therapy; *e.g.*, no more than 10.0 mg Nortriptyline, qd, 12 hrs before waking, as it also helps to pattern sleep). Of course this process takes time as well. Again, it is not a quick fix. In fact, it may also take up to 24 months. Remember, the P&S Nervous systems are like a pendulum, if to correct it you hit it hard or fast, you knock it off its hinge and create more problems. Therapy must be slow, gentle, easy nudges over time. It is like stopping a bad habit and establishing and maintaining a good habit.

Unfortunately, most autonomic tests only test total autonomic activity and are not able to independently and simultaneously measure the two autonomic branches without assumption and approximation. Even tilt table is often unrevealing because of complications and its inability to independently and simultaneously differentiate P from S without assumptions, approximations, chemicals or ignoring symptoms until they are so bad that the assumptions are valid. However, even then, as soon as therapy is implemented the assumptions are no longer valid and

therefore Tilt-testing is no longer revealing. As an aside, for VVS, the stress and anxiety (Sympathetic stimuli) caused by the tilt table itself temporarily “cures” VVS (balances the Parasympathetics), leaving the physician with no diagnosis to treat and believing that the patient is normal. Further, in many suspected POTS cases, often the real issue is that there is no POTS to begin with. It is VVS and the stress of the tilt-table “cures” the VVS by balancing P&S.

SUMMARY

The good news with P&S monitoring is that all three dysautonomias may be documented and are treatable, all simultaneously. Again, however, it is not “quick fix” it may take up to 24 months. Therapy must be low-and-slow. Again, like correcting a pendulum, or essentially breaking one or more “bad habits” and establishing good habits, never fast. Therapy may be both pharmaceutical, and for those that have been put on high doses and are desensitized, non-pharmaceutical therapies have been developed (see summary diagram at the end: “Autonomic Dysfunction Therapy Algorithm” [adapted from 5], this figure includes more therapy than just for POTS, as POTS is usually but one type of Autonomic Dysfunction. The remaining therapies are discussed in [5]). The main issue is that the heart is made to act as if it is deconditioned by the P&S nervous systems and must be reconditioned. At the same time the lower vasculature must be re-integrated with the heart. Once all of this is done, symptoms are relieved and Quality of Life is restored or improved, until some other clinical event. The only reason for maintenance dosing of any kind, let alone life-long therapy, is if there is some remaining end-organ dysfunction or chronic condition that will continue to pull the P&S systems out of

balance. A summary therapy plan for POTS is included below.

often the first to present and most difficult dysautonomia to fully correct [12,13].

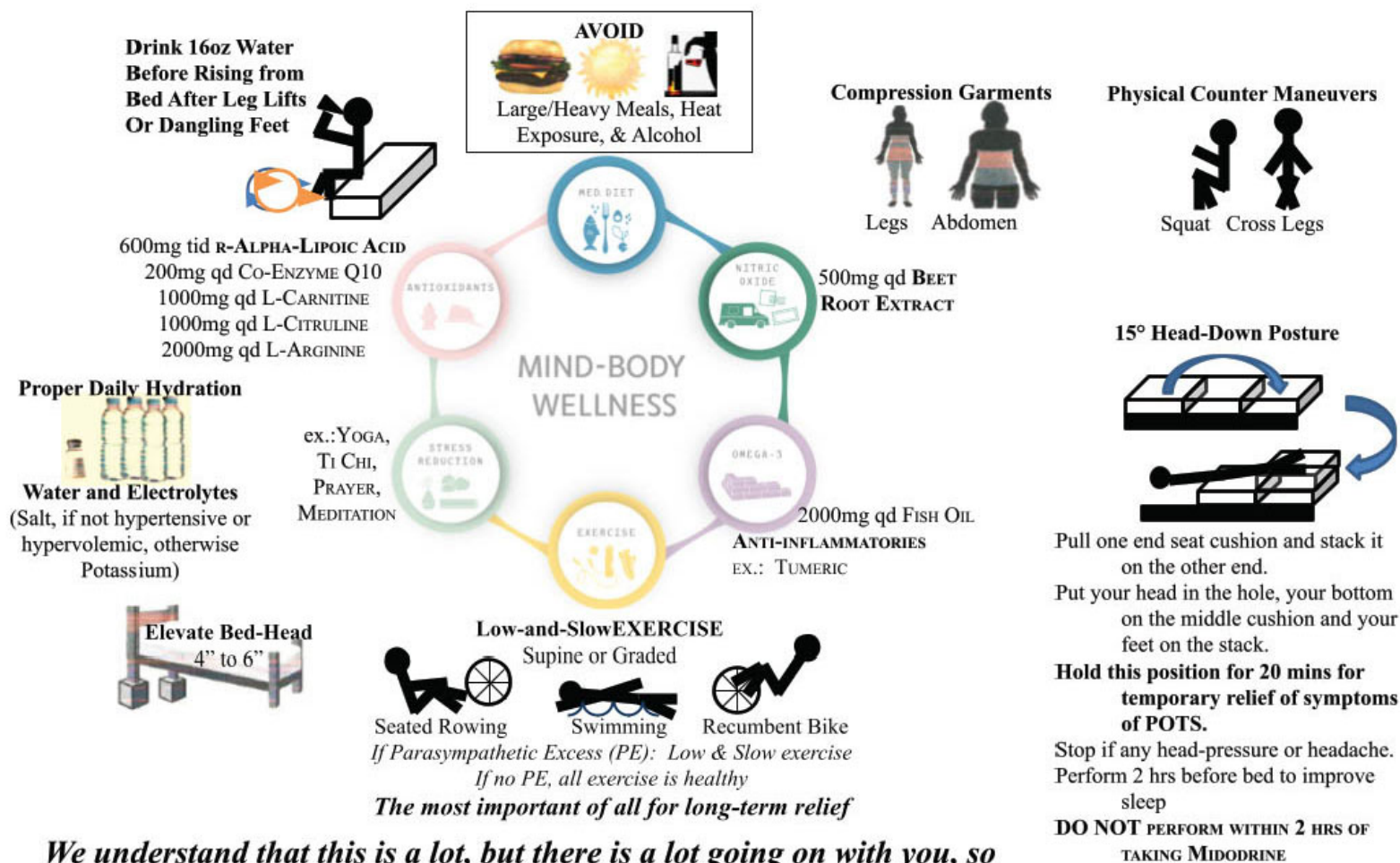
- First, suppress any β -Sympathetic stimulation with low-dose β -blockers, such as Propranolol or Nadolol. This is typically short-term, to reduce and prevent palpitations and rapid HR, until the nervous system is re-trained to respond normally upon standing. Typically, the patient will self-wean.
- Second, stimulate α -1 Sympathetics with oral vasoactives, fluids, electrolytes, compression garments, and Alpha-Lipoic Acid. The oral vasoactives are also often short-term. All of this is to relieve the brain-fog, cognitive and memory difficulties, lightheadedness, fatigue, etc., associated with POTS.
- Typically, these first two steps are administered simultaneously.
- Third, if blood volume remains an issue (*e.g.*, water and electrolytes are not sufficient), then low-dose volume expanders are recommended (*i.e.*, Florinef or Desmopressin).
- Last is low and slow exercise to relieve PE, if the POTS is not relieved by the second step or VVS is documented, possibly they may need to relieve PE with low-dose anti-cholinergic treatment.

Treating Sympathetic issues as primary typically exacerbates the patient's condition, including making them more difficult to manage, or they do not tolerate the therapy. Granted mortality risk(s) need to be addressed, such as high resting BP or high Standing HR, but recognize that these may be secondary and typically are ultimately relieved with the relief of SW underlying POTS or PE underlying VVS. SW or PE therapy must be "low and slow" with SW

Ultimately, POTS is (and all other neurogenic forms of Orthostatic dysfunction are) blood flow issues that are caused by “bad nerves,” P or S dysfunction(s).

Without testing for both P&S activity, independently and simultaneously, at rest and in response to challenge, the best that may be offered the patient is a guess and a bad guess at that [4]. This is the reason why the general sentiment towards POTS has moved to a life-long management: 1) to keep it a research project and 2) to sell more drugs. Without a clear, objective, quantitative measure of the Parasympathetic nervous system, and therefore a clear, objective, quantitative measure of the Sympathetic nervous system patients are being done a dis-service, as evidenced by the millions of patients taking matters into their own hands and still diligently seeking more information.

AUTONOMIC DYSFUNCTION THERAPY ALGORITHM



We understand that this is a lot, but there is a lot going on with you, so let's get started!

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AUTONOMIC DYSFUNCTION THERAPY ALGORITHM

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