THE NORTHERN HOSPITAL

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS)

Untitled, Harvard Panels 1, 2 and 3, Mural Triptych, 1962, Mark Rothko;
Virtual restoration under multiple digital light sources, 2015. (Harvard Art Museum).

"If you are only moved by color relationships, you are missing the point".

Mark Rothko

By the early 1960s Mark Rothko was the most famous Artist in America. Abstract Art was at its apogee, and Artists vied with each other to be more "abstract" than their rivals. Though Art critics and public alike struggled mightily to understand the works of Rothko, Jackson, De Kooning, Klein, Newnan and many other "Abstract Expressionists", there was no question their works were very much de rigueur at the time. Art historians today "classify", Rothko, though he himself would have rejected any classification of his

work, as a "Colour Field" painter, a sub-genre of Abstract Expressionism, an art form that included nothing intentionally representational from the real world. Instead the purpose was to evoke pure emotion, and as there were no clear objective cues of the real world of any type in his works, indeed most of Rothko's works do not even have titles, the interpretation of them was purely within the eye of the beholder. For many they simply evoked no emotion or feeling at all, but for others, who would sit and stare at them in solitude for hours, as for some powerful hallucinogen, deep emotions could be evoked, joy, sadness, ecstasy, nostalgia, deja vu, jamais vu, uncontrollable sobbing, religious epiphany. Rothko himself would sit for hours at a time, cigarettes and whiskey in hand, contemplating sections of a work before continuing. Creating the work itself for Rothko was akin to a religious experience.

The striking visage of a Rothko, is pure color, great swathes of it, one colour morphing into another, the colors seem to hover and shimmer over the canvas, a portal to other dimensions of the mind. All of this was no mere gimmick for Rothko, he famously turned down a staggering for the time commission, of 2 million dollars to paint murals for the swish Four Seasons Hotel in New York, after eating at the high-end restaurant, claiming that no rich person he saw there could possibly understand his work! This of course merely made Rothko all the more famous. He would only send his "children out into the world if he thought they were going to a good and nurturing home; "A picture lives by companionship, expanding and quickening in the eyes of the sensitive observer", he once explained, "it dies by the same token. It is therefore a risky and unfeeling act to send it out into the world...".

And so it was considered quite a coup when the directors of Harvard University secured a commission for Rothko in 1962. He would paint them a series of six murals for the top floor of the Holyoke Center. Perhaps in Rothko's mind high academia would appreciate his Art. If he held any hopes for immortality, then in the Harvard murals that hope would very quickly fade…literally. The only "thing" in his works to a casual observer was color, and though Rothko took obsessional care with his colors and the way he arranged them, he once quipped, "If you are only moved by color relationships, you are missing the point". To Rothko it was all about the experience; but he hastened to qualify, "A painting is not ***about*** *an experience, it* ***is*** *an experience".*

Though his works are dominated by huge swathes of shimmering colour, it was not the color ***itself****, he was interested in, only its effect on the viewer. It was simply that he had no option but to use colour, given that he wasn't interested in doing anything representational of the concrete world. "Since there is no line", he asked, "what is there left to paint with, if not colour?". Rothko really worked for the now, he used many of the relatively new synthetic pigments that were developed from coal tar in the late Nineteenth century. His red in particular was one of these know as Lithol Red, developed in 1899. It gave a brilliant vibrant primary red, and was low cost which Rothko, always extremely fugal, appreciated. But lithol red's great drawback was that it was not lightfast. Exposed to the ultraviolet rays of the Sun it quickly faded away to a washed out insipid light blue. Lithol red was used in the mass consumer markets of "this weeks" newspaper, comics, or magazines. Cheap and momentarily visually attractive it was never meant to last beyond the "now". Whether or not Rothko was aware of the failure of lithol red as a lasting pigment is unknown. As colour was supposedly not his main point, then perhaps he*

simply never gave it very much thought. Academics of the highest order as the custodians of Harvard University of the time no doubt were, they had not the slightest clue when it came to great works of Art. More chuffed at owning a "Rothko" when their rivals did not, they simply hung the six murals in their boardroom in the full face of the bright sunlight streaming in though its large windows. In just a few years, the brilliant reds had faded to a barely perceptible turquoise! Though Rothko claimed that colour itself was not his point, nevertheless it was colour that helped convey the "experience", and in the Harvard Murals, that experience most certainly faded along with the lithol red. So light damaged had the murals become by the opening of the 21st century that it was possible to trace out the daily circuit of the Sun around the room by the relative amounts of blueness in the panels! Perhaps the only of interest by that stage in the murals lay with the faculty of Astronomy.

The great tragedy of the whole story was summed up by Pater Boris of the Pace Gallery, New York in the 1990s. "Rothko's works are not just paintings. For me they are more like passages or corridors, or if you could imagine, the space between zero and one. When you sit in front of them the colour guides you to a place in your own perception, which you can't see, you just sense".

The great battle that Art preservationists daily struggle with is the old one of "preservation" versus "restoration". Too much of the former may lead to the inevitable ravages of time, whilst too much of the latter may lead to a loss of integrity of the original work. The Rothko Harvard murals, most certainly have not been preserved well…or at all really. Restoration seemed out of the question for this type of work, and yet the brilliance of Harvard science in 2015 came up with a partial solution, a method of restoration that did not touch the original work or alter it in any way. In a radical experiment a team of highly skilled curators using high end digital computed lighting was able to display the murals close to the way in which they originally appeared! By using multiple synchronized and specially filtered wavelengths of light, they were able to change the way the viewer perceived the murals. The old lithol red was resurrected in the minds of the viewer! Though as in 1962, just what that lithol red induces in any individual mind, still very much resides in the eye of the beholder!

The condition known as postural orthostatic tachycardia syndrome or "POTS" may seem an enigmatic as a Rothko. The only objective "colour" it imparts to the casual medical observer is a sinus tachycardia on assuming the upright position from the supine. But its color is not entirely the point when it comes to the patient themselves - the whole experience can lie very much within the eye of the sufferer!

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS)

Introduction

Postural Orthostatic Tachycardia Syndrome (or "POTS") is a disorder in which the **autonomic nervous system** fails to compensate for **upright body posture**, but there is *disagreement* surrounding the precise definition.

A particular point of contention relates to the presence, or otherwise of hypotension, thus calling into question whether "POTS" is even a meaningful diagnosis, or simply a symptoms labelled disease that may have diverse underlying pathologies.

Postural Orthostatic Tachycardia Syndrome has been most generally defined as a form of **orthostatic intolerance** characterized by:

- An excessive increase in heart rate that occurs on standing

Without

- Arterial hypotension

Numerous autonomic type symptoms may also be associated with the tachycardia.

Symptom severity may range from mild to severe.

This syndrome probably describes a range of conditions with differing pathophysiology, thus making specific treatment problematic in any given individual. Accordingly treatment will need to be tailored to each individual patient who suffers the syndrome.

Further research is clearly required to effectively classify the range of underlying pathophysiology that can produce this syndrome and to guide optimal management.

POTS is an uncommon and under recognized syndrome.

There is a paucity of long-term data for this condition but some researchers suggest that where the condition arises during adolescence, **most** patients will eventually recover from it.

Other patients have a variable / relapsing course with some overall improvement.

Some patients, suffer ongoing long term debilitating symptoms.

The optimal therapy of POTS has not been established.

History

POTS was first well described by Schondorf and Low at the Mayo clinic in 1993 although the condition was recognised as early as 1940.

Epidemiology

POTS is thought to be uncommon, although it is probably under-diagnosed

Patients are usually in the age group 15 - 50 years old.

The majority of patients are female, (around 80% of cases).

Physiology

When upright, the human body pools a certain amount of blood in the veins of the legs resulting in a transient reduction in venous return and a mild reduction in blood pressure.

Moving from the supine to upright posture requires rapid and effective neurologic and circulatory compensatory reflexes to ensure an adequate blood pressure and cerebral perfusion. Intrinsic cerebral autoregulation of blood flow is also important.

Normal compensation is swift and asymptomatic, acting primarily through sympathetic neuronal stimulation. The heart rate is increased, but rarely exceeds 100 beats per minute. Peripheral venoconstriction also occurs to help maintain the circulating volume and blood pressure.

Pathophysiology

Postural Orthostatic Tachycardia Syndrome likely reflects a range of underlying pathologies that may interfere with the normal autonomic neuronal reflexes that occur upon standing.

There is a range of theories including:

1. Abnormal autonomic reflex response to standing:

    - Several clinical and empiric observations suggest the presence of distal, predominantly lower extremity, autonomic denervation with preserved cardiac innervation in patients with POTS

      Blood pooling in the veins of the lower body appears to be a significant factor in most POTS patients, thus supporting the theory of an abnormal autonomic response.

      A significant tachycardia is required to overcome the abnormal degree of venous pooling, presumably due to an inadequate peripheral venoconstriction response.

2. Abnormal receptor receptivity:

- Venous pooling has also been attributed to both beta-2 (i.e. vasodilator) adrenergic receptor super-sensitivity and α-1 receptor hyposensitivity.

3. Post -viral induced autoimmune neuropathy:

   - The clinical observation that some cases originate after systemic infection suggests the possibility, of a post-viral immune-mediated neuropathy

     The finding of ganglionic acetylcholine receptor antibodies in some patients gives some support to this hypothesis.

4. Renin-angiotensin-aldosterone system dysfunction:

   - Some POTS patients have low renin and aldosterone levels leading to salt and water loss, with consequent hypovolaemia

5. Hyperadrenergic state:

   - Some investigators suggest that increased sympathetic activation (hyperadrenergic state) may be a **primary** aetiologic factor in some POTS patients, as suggested by elevated arterial norepinephrine levels at rest.

Some symptoms suggest **cerebral hypoperfusion** despite a normal systemic blood pressure, however, **no** *definitive* evidence of abnormal cerebral blood flow or deficient cerebral autoregulation in patients with POTS has been found.

There are a *host* of other theories.

Clinical features

POTS features generally described include the following:

1. An excessive increase in heart rate that occurs on standing:

Adults (> 19 years):

   - Defined as an increase in heart rate by **30 b**eats per minute

   Or

   - A rate of > **120** beats per minute.

   Within standing 5 - 30 minutes of standing. [2]

   There should also be no arrhythmias, sympathomimetic drugs being taken or other conditions that cause tachycardia. [4]

Children: [2]

Different criteria could be more appropriate in children and adolescents. In one series of children 8 to 19 years old, many normal control children were found to have the changes described above in adults.

In this series, criteria that discriminated between patients and controls were:

For children < 14 years:

- A sustained heart rate increase of > 40 beats per minute

Or

- An increase to 130 beats per minute or greater within the first five minutes of tilt.

For children 14 -19 years:

- A sustained heart rate increase of > 40 beats per minute

Or

- An increase to 120 beats per minute or greater within the first five minutes of tilt.

2. Without arterial hypotension:

   Opinions however diverge on the inclusion, or exclusion, of blood pressure changes (i.e orthostatic hypo- or hyper- tension) as a delineating feature of POTS.

Lying and standing pulse and blood pressures should be recorded - blood pressure is usually static but can be reduced or elevated

An **automated ECG recording** can be taken to document the change in pulse rate from the supine to standing positions.

A host of autonomic type and vague subjective symptoms may also be associated with the tachycardia, and may include:

1. Light-headedness
2. Anxiety
3. Diaphoresis/ flushing
4. Tremor

5. Palpitations

6. Exercise intolerance/ fatigue / lethargy

7. Recurrent near syncope or actual syncope on assuming an upright posture

8. Postprandial hypotension.

The **onset** of symptoms may be abrupt, (often after a viral illness); but others may experience a more insidious onset.

The **severity** of symptoms is widely variable. Some patients experience only mild symptoms and often only in the setting of additional orthostatic stress (e.g., menstrual cycle, relative dehydration), while others may be profoundly incapacitated.

Complications:

Lack of a clear diagnosis and uncertainty over treatment may lead to significant secondary psychological/ psychiatric complications (which make treatment even more problematic), including:

1. Anxiety

2. Depression

3. Somatization disorders

Natural history:

There is a paucity of long-term data for this condition but some researchers suggest that where the condition arises during adolescence, **most** patients will eventually recover from it.

Other patients have a variable / relapsing course with some overall improvement.

Some patients, suffer ongoing long term debilitating symptoms.

Differential diagnosis:

In most cases, careful historical information and neurologic examination specifically looking for other evidence of autonomic failure, neuropathy, and extrapyramidal signs, will distinguish alternate diagnoses.

The possible differential diagnoses of POTS include:

1. True orthostatic hypotension:

   In particular:

- Volume loss
- Drug effects (diuretics)

2. Anxiety
3. Drugs effects (sympathomimetic)
4. Other autonomic neuropathies
5. Central dysautonomias
6. Bedrest deconditioning
7. Inappropriate sinus tachycardia syndrome:
    - The syndrome of inappropriate sinus tachycardia is characterized by an elevated heart rate that is **not** influenced by postural changes.

Investigations

An important part of investigation is the ruling out of other serious conditions including

Blood tests:

1. FBE:
    - Hb (exclude anaemia)
2. U&Es / glucose
    - Exclude potassium anomalies, diabetic neuropathy.
3. Plasma noradrenaline levels:
    - A high plasma level of noradrenaline level is also considered useful to identify a subgroup of a "hyper-adrenergic" form of POTS.

      Some centres measure norepinephrine levels in the supine and upright position after 15 minutes each.

      A rise in norepinephrine (> 600 ng/mL) in the upright position compared to the supine levels identifies a hyperadrenergic subgroup of patients.

      These patients tend to have orthostatic **hyper**tension with systolic blood pressures that can be greater than 200 mm Hg in the standing position in addition to the tachycardia that is the hallmark of the condition.

4. Renin and aldosterone levels:

    - The levels of renin and aldosterone in some POTS sufferers are low. These hormones increase plasma volume by promoting sodium retention and so **low** levels may cause/ aggravate the condition.

5. 24 hour urinary sodium levels:

    - Some patients with POTS have low 24 hour sodium excretion (<100 mEq).

      These patients may benefit from salt supplementation.

Troponin and D-dimer levels are normal

Head-up tilt table (HUT) testing:

This is a standard method to assess a patient's reaction to postural change.

It involves placing the patient on the tilt table, and measuring blood pressure and heart rate.

The table is then tilted upright 60 - 80 degrees to the vertical for approximately 45 min and blood pressure and heart rate are again measured, either continuously, or at least every 2-3 min.

Management

Preventive:

Preventive measures include:

1. Avoidance of prolonged standing

2. Avoidance of dehydration

3. Avoidance of medications that may aggravate hypotension:

    - ACE inhibitors
    - Sartans
    - Diuretics
    - α-blockers.

Treatment:

The optimal therapy of postural tachycardia syndrome (POTS) has not been established.

The following treatment modalities have been advocated, though none are curative:

1. Dietary:

    - Smaller meals:

        - ♥ Eating smaller meals has been said to reduce the severity of **postprandial** hypotension, because the amount of blood required for digestion is reduced

    - Increasing fluids:

        - ♥ Increasing fluid intake (up to **3 litres** per day) may decrease tachycardia in POTS patients with idiopathic forms of the disease, as a result of increased blood pressure through increasing blood volume.

          This is thought to be helpful in POTS patients with pooling blood and/or hypovolemia.

          It is **not** recommended in the hyperadrenergic subgroup of patients.

    - Increasing salt intake:

        - ♥ Increasing salt intake (**3 - 10 grams per day**) is an option for POTS patients found to have impaired urinary sodium retention, which may precipitate episodes of hypovolaemia.

          The levels of renin and aldosterone in some POTS sufferers are found to be low. These hormones increase plasma volume by promoting sodium retention.

          Thus, increasing sodium intake by taking salt tablets or an electrolyte solution helps expand blood volume, which will alleviate the hypotension some POTS patients suffer.

2. Compression stockings:

    - These may help reduce venous pooling in the legs

      Thigh length compression hosiery and abdominal bands have been advocated although there is little evidence as to their benefit.

3. Exercise:

- Some clinicians advocate that exercise should have a central role in treatment of POTS

  Exercise has been reported to be beneficial both in alleviating POTS symptoms.

  Patients may be trained to gradually move from lying to sitting to a standing position during different activities, such as swimming, rowing, and cycling.

4. Pharmacotherapy:

Many agents have been advocated as potentially useful, including:

Fludrocortisone:

- Because many patients with POTS have a **low plasma volume**, correction with oral volume expansion, a high salt diet, and fludrocortisone, a mineralocorticoid receptor agonist may improve symptoms. This regimen is similar to that used in orthostatic hypotension in general

  Fludrocortisone increases plasma volume in patients with POTS due to salt and water retention and also sensitizes the blood vessels to vasoconstriction.

  Fludrocortisone (e.g., 0.05 - 0.2 mg per day) is most effective when combined with increased salt and water intake.

Beta blockers:

- Beta blockers have been reported to be a useful treatment for POTS patients with beta-receptor super-sensitivity, high noradrenaline levels and/or hyper-adrenergic states.

  They may **attenuate tachycardia** and **improve debilitating adrenergic** symptoms.

  Beta blockers however may exacerbate hypotension and reduce renin levels.

  Thus, Beta blockers must be used with caution since some POTS patients have low blood pressure and/or plasma renin. Consequently, beta blocker usage in hypovolemic patients may be counterproductive.

  In the hyperadrenergic subgroup where patients can also have high blood pressure recordings during standing, β-blockers can cause unopposed α-1

adrenoceptor activity with worsening of their symptoms and so labetalol may be a preferable option as it has both β and α-1 receptor blockade.

Ivabradine:

- Ivabradine, is reported to improve their symptoms in some patients with significant sinus tachycardias.

  Ivabradine may be preferable to beta-blockers as it reduces the heart rate without the many potential adverse effects the beta blockers, In particular negative inotropic effects and vasodilation.

Midodrine:

- Midodrine is an α-1 agonist prodrug that is converted by the liver to desglymidodrine, the active metabolite.

  It acts by causing vasoconstriction and increasing peripheral resistance, thereby reducing pooling and the ensuing reflex tachycardia.

  Midodrine 2.5 - 10 mg three times daily has been advocated, however, benefit from chronic therapy is not established.

Pyridostigmine:

- There is some evidence suggests that the acetylcholinesterase inhibitor pyridostigmine (30 mg daily) may attenuate the tachycardia and improve symptoms in some patients.

5. Fluid resuscitation:

   This appears to be beneficial for POTS patients who suffer relative hypovolaemia caused by sympathetic neuropathy, leading to venous pooling during upright posture, or other idiopathic causes.

   2 - 3 litres of normal saline can be infused for acute symptoms corresponding to objective improvement in tilt testing response. However, it is not clear that this confers any benefit in the longer term.

Disposition:

POTS is an uncommon, complex and poorly understood condition and so referral should be made to Cardiologists or Neurologists who have a particular interest/ expertise in the condition.

Panel 5 Harvard Murals, 1962, Mark Rothko. Photograph taken in 1968, (Harvard University Archives)

Painted in highly light sensitive synthetic pigments, and poorly hung with insufficient protection from sunlight, Mark Rothko's Harvard Murals were badly and irreparably light damaged within just a few years of being displayed in the top floor of Harvard's Holyoke Center.

Mark Rothko in his studio, 1964, Hans Namuth.

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