

## **Vascular Compression Syndromes in Postural Orthostatic Tachycardia Syndrome (POTS)- a Preliminary Report**

Postural orthostatic tachycardia syndrome (POTS) is characterized by orthostatic symptoms and dramatic increase in heart rate on standing in the absence of long-term chronic diseases and medications that can affect the autonomic or vascular tone. <sup>(1)</sup> In a study of 33 consecutive patients with established POTS, all were shown to have one or more venous compression syndromes. 28 were shown to have popliteal vein compression syndrome (17 with complete obstruction and 11 with partial obstruction,) while 25 (of 27 tested) had thoracic outlet vein (axillary or subclavian) compression. Twenty had both popliteal (either partial or complete) and thoracic outlet vein compression. This study examined the incidence of these 2 vascular compression syndromes in POTS, and examines possible associations of these with the pathogenesis of POTS. Current re-evaluation of these and 32 subsequent new patients is in progress for Pelvic Vein Compression with particular emphasis on “Nutcracker Syndrome.” Within these new patients, and revision of older patients, 12 have confirmed “Nutcracker Syndrome” at the time of publication.

### **Background**

#### **Postural Orthostatic Tachycardia Syndrome**

POTS is defined as orthostatic intolerance associated with tachycardia exceeding 120 beats per minute or an increase in the heart rate of 30 beats per minute from baseline within 10 minutes of changing the posture from a lying to standing position, in the absence of long-term chronic diseases and medications that affect the autonomic or vascular tone. There is no drop in blood pressure; it may even rise in the upright posture. Patients experience symptoms such as headache, nausea, tremors, sweating, palpitations and near-syncope. Symptoms always occur in the upright posture and disappear on lying down. <sup>(1)</sup>

POTS was first described in 1940, and it is considered one of the common conditions in young females, occurring most commonly between the ages of 12 and 50 years with a male to female ratio of one: five. <sup>(1)</sup>

In many patients symptoms start abruptly following viral infections, trauma, surgery and after pregnancy. In some cases, there is a hyperadrenergic state leading to increased noradrenalin due to impaired clearance or decreased uptake of noradrenalin by the synaptic cleft. These patients suffer from profuse sweating, anxiety, tremulousness, tachycardia and high blood pressure. Lack of understanding of POTS has meant that many patients with this condition are frequently labelled as having anxiety/neurosis or panic attacks. <sup>(1)</sup>

#### **Popliteal Vein Compression Syndrome**

In Popliteal Vein Compression Syndrome the popliteal vein is compressed when the knees are extended or straightened fully when seated, lying or standing, causing blood flow to slow or congest distal to the compression <sup>(2)</sup> potentially causing microemboli, emboli, vascular autonomic changes<sup>(14)</sup> and cascades of inflammatory chemicals<sup>(13)</sup>.

Dr David Grosser writes that “positional compression of the popliteal vein compression syndrome, or popliteal vein entrapment, often goes unrecognized. It is thought to affect at least 20% of the general population. It has been described in the medical literature for some 30 years. Only in the last few years has it been looked at seriously as a cause for deep vein thrombosis, pulmonary embolism and chronic lower limb venous disease.”<sup>(2)</sup>

“In some people when the knees/legs are extended or straightened fully the popliteal vein is squashed between the layers of muscle behind the knee. This can occur both when standing and sitting or lying with the knee extended. If that position is held for a period of time (for example; in a hospital bed, operating theatre or reading a good book with your legs out on a stool) this can cause blood flow to slow or congest in the calf with little way out. When blood flow slows/stops clotting can occur. This is now beginning to be recognised a major source of deep vein thrombosis for patients undergoing surgery or prolonged bed rest.”<sup>(2)</sup>

“Popliteal vein compression syndrome can often be silent. Chronic problems that can occur are most often related to pressure build up in the calves. This can be seen as a dark tan like stain around the lower calf accompanied by thickened dense skin. Development of large varicose veins and venous ulcers can also occur in the later stages. Although it has not been conclusively proven, it is also thought that popliteal vein compression syndrome could also trigger certain types of lung disease through prolonged exposure to multiple small clots arriving in the lungs. We have a collection of patients with pulmonary hypertension with this condition and no other cause to explain the problem.”<sup>(2)</sup>

### **Thoracic outlet syndrome**

The thoracic outlet is bordered by the scalene muscles, first rib, and clavicle. Thoracic outlet syndrome (TOS) is not the name of a single entity, but rather a collective title that encompasses a variety of conditions produced by compression of nerves, arteries and or veins (or all) because of an inadequate passageway through the thoracic outlet between the base of the neck and the axilla.

Recognized thoracic outlet syndrome symptoms include neck, shoulder pain, arm pain, numbness and paraesthesiae of the fingers and impaired circulation of the extremities (so there may be for example, discolouration of the hands.) Symptoms can be constant or intermittent depending on what activities are being performed. Any condition that results in enlargement or movement of these tissues of or near the thoracic outlet can cause the thoracic outlet syndrome. Risk factors include trauma, occupations or sports that involve heavy usage of the upper extremities against resistance, including jackhammer operators and dental hygienists, weight lifting, pregnancy, poor posture and obesity. Pregnancy is thought to affect the thoracic outlet by the loosening of joints during pregnancy. Rarely lung tumours can affect the outlet.<sup>(6)</sup>

Illig and Doyle<sup>(25)</sup> write: “the subclavian vein is highly vulnerable to injury as it passes by the junction of the first rib and clavicle in the anterior-most part of the thoracic outlet. In addition to extrinsic compression, repetitive forces in this area frequently lead to fixed intrinsic damage and extrinsic scar tissue formation. Venous thoracic outlet syndrome progressing to the point of axillosubclavian vein thrombosis, variously referred to as Paget-Schroetter syndrome or effort thrombosis, is a classic example of an entity which if treated correctly has minimal long-term sequelae but if ignored is associated with significant long-term morbidity.”<sup>(25)</sup>

### **Pelvic Congestion Syndrome**

Pelvic congestion syndrome is associated with chronic pelvic pain secondary to pelvic vein insufficiency and associated pelvic venous distension. Severe orthostatic intolerance may be accompanied by left renal vein occlusion, and chronic fatigue has been associated with high left renal vein- IVC pressure gradients. <sup>(15)</sup>

Other symptoms include noncyclical, positional lower back, pelvic, and upper thigh pain., worse before or during menses and may be associated with dyspareunia, and prolonged post-coital discomfort. Symptoms are usually

worse at the end of a day, exacerbated by standing or heavy activity, and reduced by supine positioning. Other symptoms include lumbosacral neuropathy, urinary frequency and generalized lethargy. Vulvoperineal varicosities may be seen over the buttock, posteromedial thigh, and most commonly manifest during pregnancy and regress postpartum. <sup>(16)</sup>

### Nutcracker Syndrome

“Nutcracker phenomenon, also known as left renal vein entrapment, is characterized by impeded outflow from the left renal vein into the inferior vena cava due to extrinsic left renal vein compression...Typically this implies compression of the left renal vein between the aorta and superior mesenteric artery, (anterior nutcracker), although less often the third part of the duodenum courses in front of the left renal vein between the aorta and superior mesenteric artery (SMA) . Anterior nutcracker is analogous to and may co-occur with compression of the duodenum by the SMA, known as “superior mesenteric artery syndrome.” The retroaortic or circumaortic renal vein may be compressed between the aorta and the vertebral body, called posterior nutcracker. Right sided renal vein compression due to compression of large veins by the gravid uterus has been described. <sup>(15)</sup>

Symptoms of nutcracker syndrome vary from asymptomatic micro-haematuria to severe pelvic congestion, and in particular relevance in POTS, to orthostatic intolerance. Many, especially children are asymptomatic. Haematuria is the commonest symptom. Pain, is the next most common symptom, sometimes describes as gonadal vein congestion syndrome characterized by abdominal or flank pain occasionally radiating to the posteromedial thigh and buttock, exacerbated by sitting, standing, walking or riding in a vehicle that shakes. Left sided varicoceles are common.

### **Methodology**

33 consecutive patients with an established diagnosis of POTS were assessed for the presence of popliteal vein compression syndrome using dynamic ultrasound scanning of the popliteal veins first seated with bent knees, then knee extended while watching for compression of the vein. This was then repeated while standing with knees bent then fully extended, again watching for compression of the popliteal vein. Venous thoracic outlet compression was assessed with duplex scanning in inert then in Wright's and Roos' positions.

Patient selection was from patients referred by other GPs or self-referred by patients with the dysautonomic symptoms that mark this condition. A number had had confirmatory tilt table testing, but this was not performed in those who had not been previously tested. All were assessed closely for co-morbidities and other possible diagnoses.

Heart rate variability studies were performed in patients with venous thoracic outlet compression, with patients supine, then with arms elevated in Wrights then Roos positions.

Patient histories were examined to assess the primary “drivers” of symptoms, as these commonly differed from the event/events that appeared to “activate” the POTS symptoms.

### **Study results**

In the 33 patients examined, 17 were found to have complete obstruction of the popliteal veins and 11 had partial compression using duplex scanning. 25 had axillary vein compression, 2 were negative, and 6 not tested. 20 of the

patients with thoracic compression had popliteal compression as well. Many patients with either compression were asymptomatic, especially for axillary vein compression, even when totally compressed.

In the ensuing time since completion of the preliminary study, a further 32 patients have been assessed and these too had confirmed vascular compression. Current re-evaluation of these patients is in progress for Pelvic Vein Compression with particular emphasis on "Nutcracker Syndrome." Within these new patients, 5 have confirmed "Nutcracker Syndrome."

Heart rate variability studies were performed in patients with venous thoracic outlet compression which confirmed small but consistent alteration in vascular autonomic tone when axillary /subclavian veins were compressed, whether complete or partial compression, when testing was performed in inert position, then in Roos and Wright's positions. No controls were used in the heart rate variability testing, which will be part of follow-up studies.

The response in most patients in heart rate variability demonstrated a relaxation of tone suggesting a nor-adrenergic response. In a smaller subgroup, the pattern was of increased autonomic tone suggesting an adrenergic response. This adrenergic response was seen mostly when venous compression was present in an inert position, which was found in a number of the patients, particularly in ones with previous shoulder injuries.

Some study participant reflections revealed increased fatigue and anxiety in the 24 hours after testing.

### **Demographics**

- 28 females, ages
  - under 20: 1
  - 21 to 30: 1
  - 31 to 40: 7
  - 41 to 50: 11
  - 51 to 60: 3
  - 60 to 70: 3
  - over 70: 2
- 5 males, ages 13, 20, 23 32 and 52

### **Apparent symptom driver (not activating cause)**

- Spine (usually upper cervical region, sacro-coccygeal region or T7 region): 15
- Diet (food intolerance): 6
- Thoracic outlet vein compression: 8
- Popliteal vein compression: 3
- Stress: 1

### **Co-morbidities**

- Fibromyalgia: 17 (51%)
- Migraine: 21 (10 with aura, 1 hemiplegic, and 1 vertebrobasilar) (63%)
- Cerebral hyperintensities on MRI: 9 from 20 tested (45%)
- Hashimotos Disease: 9 (27%)

- Significant spinal symptoms: 19 (57%)
- IBS: 18 (54%)
- Other autoimmune disease: 2 (<1%)

## **Discussion**

### **Thoracic outlet venous compression**

Many of the POTS patients studied reported paraesthesiae in their hands/ arms driving or lifting forward, and there was often unexpected fatigue and sometimes shortness of breath with elevated arms, or arms down carrying weights (e.g. shopping or wheelbarrow use)- and this has been clearly shown in this study, including panic attacks driving with outstretched arms.

Venous thoracic outlet compression has been associated with intractable migraine.<sup>(9)</sup> From ongoing research underway at present in the association between popliteal vein compression syndrome and migraine, this is most likely from cascades of inflammatory chemicals (and /or microemboli that form when the blood is stagnant when the popliteal, axillary or subclavian veins are compressed.) There is also some research that has associated TOS with autoimmune disease, and depression.<sup>(19,20,21,22)</sup>

Silva and Selmonosky<sup>(17)</sup> studied 85 Multiple Sclerosis patients demonstrating all had undiagnosed thoracic outlet syndrome, unilateral or bilateral, and usually predominantly of a venous type. These patients also had a complicated TOS, having unilateral or bilateral jugular retrograde blood flow inversion. They also showed that no jugular vein retrograde blood flow inversion in TOS patients without multiple sclerosis.

Thrombosis of the subclavian/axillary veins has been associated with pulmonary emboli, just as popliteal vein compression is a cause of DVT and pulmonary emboli. Paget-Schroetter Syndrome (or effort thrombosis) is a rare diagnosis in the general population, a subset of the venous subgroup of thoracic outlet syndrome- first described in 1875 by Paget. It is more common in younger, physically active individuals, with a predisposition to baseball, softball, wrestling, swimming, hockey, martial arts, backpacking and billiards.<sup>(25)</sup> Overhead workers and manual labourers are considered "industrial athletes," subjecting their upper extremity to similar forces, which increases the likelihood of this condition.<sup>(23)</sup>

### **Popliteal vein compression**

Similar findings were found from popliteal compression, where simply standing in a line for long periods, or sitting watching TV with knees straight and legs extended, provoking headaches, anxiety, neuropathic symptoms, hypersensitivity to sound and light, sleep disruption etc.

Symptoms found in the POTS group that may reflect popliteal compression include restless legs, cramps, spider veins, peripheral neuropathy (particularly when the popliteal nerves are also compressed), unexplained syncope, oedema, calf pain and tenderness with positive Honan's sign and negative duplex scans for DVTs and CTPA, despite elevated D-Dimer.

### **Sympathetic activation**

Vaddadi et al <sup>(14)</sup> at the Baker Heart Research Institute routinely determined whole-body spillover of noradrenaline to plasma, as a neurochemical measure of sympathetic nervous system activity, finding an excessive rise in heart rate and increased sympathetic nerve firing. <sup>(14)</sup>

### **Catecholamine release a possible culprit**

In an extreme form of POTS in one of the patients seen, the finding of recurring cardiac failure when lifting repetitively followed a severe shoulder injury and damage to her thoracic outlet. This would support a hypothesis that this in her, symptoms were catecholamine-driven similar to Takotsubo Cardiomyopathy. But POTS is not simply a catecholaminic response, although likely to be part of the pathogenesis.

### **Inflammatory and Mast Cell Activation**

Lattimer et al <sup>(13)</sup> showed that blood drawn from the site of varicose veins appears to have significantly increased concentrations of IL-6, IL-8, and MCP-1 when compared to the same patient's arm blood. This supports the hypothesis that inflammation is activated from the tissues drained by the varicose veins. <sup>(13)</sup>

The Nutcracker Syndrome provides the link with its association with orthostatic intolerance. <sup>(15)</sup> Inflammatory release, especially of IL-6 would also seem to be part of the equation, as is the mast cell activation response and its individual symptomatology, thought to be dependent on an individual's DNA profile.

As there is no apparent research in this area of inflammatory impact of vascular compression, this research from Baker Institute and Lattimer et al provide some valuable clues to possible mechanisms operating in POTS. The work by Silva and Selmonosky <sup>(17)</sup> in Multiple Sclerosis takes on importance in POTS by suggesting a common inflammatory cause associated with venous compression. Yet this inflammatory response is inadequate to fully explain the pathogenesis of POTS. The altered autonomic response demonstrated using heart rate variability as in keeping with Vaddadi et al's findings. As no controls were used in the heart rate variability studies it cannot be assumed this represents a pathological change.

Further evidence for Mast Cell Activation as well as autonomic changes in POTS is provided by Shibao, C. et al <sup>(10)</sup> who found exaggerated sympathetic activation with high plasma noradrenaline levels as well as elevated levels of urinary methylhistamine after triggered responses, with fatigue and orthostatic intolerance, eventually leading to a disabling condition. <sup>(10)</sup>

### **Association with other diseases/ co-morbidities**

It seems evident that the vascular compression syndromes -Popliteal Vein Compression Syndrome, Thoracic Outlet Syndrome (and Pelvic Congestion Syndrome / Nutcracker Syndrome) are integral in the anatomy in POTS patients, but they do not appear to be the activating cause, although do at times appear to be primary drivers of symptoms. The findings of Silva and Selmonosky <sup>(17)</sup> in multiple sclerosis patients demonstrating all had undiagnosed thoracic outlet syndrome, unilateral or bilateral, and usually predominantly of a venous type, draws analogies between diseases such as multiple sclerosis and POTS, and implies an inflammatory mechanism at the heart of these conditions.

The high association of POTS in Ehlers-Danloss Syndrome provides another important clue, and this is supported by this study. People with hypermobility, with increased stretch of blood vessels (or compression) have increased baroreceptor signalling. A lot of mast cells are around major key branch points (including the root of the aorta) and

released histamine is a co-factor in sensory nerve activation thresholds, and this would seem to be a probable explanation for the increased Mast Cell Activation typically found in POTS.

These compression syndromes appear also to be significant in other conditions especially Multiple Sclerosis <sup>(17)</sup>, Fibromyalgia, Migraine and Hashimotos Disease, either by production of microemboli released as the venous blood is released back into the circulation or the vein itself is compressed through sympathetic and inflammatory response. As over 30% of POTS patients in the study had co-existing autoimmune disease (primarily Hashimotos), it provides a possible clue to the pathogenesis of these diseases, likely from production of inflammatory responses to vein compression. This may also explain the association between thoracic outlet vein compression and Multiple Sclerosis.

### **Syncope and Pulmonary Emboli**

Recent research from USA looking at people who are seen at emergency departments after syncope or sudden collapse, 20% have been found to have had pulmonary emboli. <sup>(4)</sup> Dyspnoea in patients with known chronic obstructive pulmonary disease (COPD) can be a clinical challenge due to the nonspecific nature of atypical presentations. Typical features of fever, productive cough, and wheezing on presentation support COPD exacerbation, while absence of such findings may warrant further evaluation for underlying aetiologies, including pulmonary embolism (PE). It is suspected that one in four patients with atypical COPD exacerbation may have PE as an underlying or concomitant cause of acute dyspnoea. <sup>(6)</sup>

### **Drivers in POTS and co-morbidities**

Patients in the study group with fibromyalgia, dysautonomia and POTS have been able to differentiate the different “drivers” to these patterns. Clinically there was a blurring of the boundaries between them all, appearing to reflect the individual driver (s) in each patient. In many, there were multiple drivers reflecting sources of inflammatory response. For example, someone with popliteal compression may now recognize the paraesthesiae in their feet with posture, and those with mid-thoracic spine injuries especially around T7 can recognize the tachycardia and wave of anxiety with rotation of the spine. Simply driving with arms outstretched can produce typical symptoms of a panic attack, and weight lifting can produce fatigue, headache and other symptoms.

While there is a blurring of boundaries, generally as each driver is worked out, these can be nullified or modified by simple changes- most commonly with diet, posture, lifestyle, targeted pilates programs, and above all, knowledge of the underlying causes. In a clinical setting, the most effective management commenced with acupuncture to reduce the inflammatory response before physical therapies were attempted.

### **Opening Pandora’s Box**

Ultimately the key to the pathogenesis of POTS lies in the measurement of the inflammatory responses when the popliteals, subclavian or pelvic veins are compressed. There are no population studies looking at the incidence of thoracic compression in the community, but it does appear to be prevalent in patients with POTS and fibromyalgia. Previous studies suggested around 20% incidence of popliteal vein compression but this too needs to be re-assessed. There are no population studies I have found for asymptomatic pelvic vein compression and nutcracker syndrome. While it cannot be assumed that these are the cause of POTS, but I do believe they are a significant manageable factor in pathogenesis and ultimately symptom control.

The possible presence of a patent foramen ovale is a factor that should be considered particularly when migraine with prolonged aura, or hemiplegic migraine is present as it significantly increases risk potential. The study confirms the significant association with POTS and migraine. Dr Ross Sharpe <sup>(18)</sup> describes how when vascular venous compression is present, if a patent foramen ovale is present, microemboli may shunt through this into the brain and may be responsible for cerebral damage. This brings with it an increased risk for dementia (and possibly diseases such as Multiple Sclerosis.)

The presence (or absence) of cerebral hyperintensities is valuable in the individual patient assessment, most importantly when hemiplegic migraine or migraine with prolonged auras are present. If hyperintensities are present, the presence of a PFO should be actively sought, as this is an easily correctable problem in most patients. In those where closure is not possible, it may warrant looking at the possible use of venous anti-coagulation. Trans-thoracic echocardiography is not an effective way to assess for a PFO. Trans-Cranial Doppler with follow-up Trans-Oesophageal Echocardiography when positive remains the optimal testing for a PFO at present for this.<sup>(18)</sup>

The presence of brain MRI changes of FLAIR hyperintensities does not necessarily mean that these are caused by microemboli. There are many other potential causes including ischaemic, inflammatory, demyelinating, metabolic, toxic and malignant causes. In older people these hyperintensities are usually diagnosed as microvascular ischaemia, thought to arise from chronic hypoperfusion of the white matter and disruption of the blood-brain barrier, with chronic leakage of plasma into the white matter.<sup>(11)</sup> These hyperintensities may at any age be reflective of inflammatory response following activation following vascular compression, and neither embolic nor atherosclerotic.

Unexplained lung damage including emphysema, pulmonary hypertension and fibrosis are probably associated with this microembolic phenomenon. It is possible also that the various inflammatory responses are part of the pathogenesis of autoimmune and other inflammatory diseases, with the final disease processes dependent on a person's DNA.

### **A change in management of POTS?**

In my opinion, the treatment of POTS should be aimed at removing the driving factors rather than looking simply for a medication to control symptoms. These compression syndromes are usually easily managed by awareness and positional change in the popliteal compression, and the thoracic outlet may be manageable with postural awareness and correction of postural faults, with appropriate physiotherapy thus providing a useful start for clinicians dealing with POTS. Control of autonomic instability appears to be possible through acupuncture, allowing physical therapies to be employed.

With careful questioning and investigation, the other driving causes can usually be identified, and with this, improved control of the POTS symptoms. As these compression syndromes are frequently asymptomatic, looking actively for these should be considered in all POTS patients. It is possible this may extend to fibromyalgia, Hashimotos disease and other inflammatory and autoimmune diseases.

### **Acknowledgments:**

The author wishes to thank the invaluable assistance of Dr Geoff Adsett for provision of heart rate variability monitoring facilities, Dr Peter Jackson, of QScan Radiology, Dr David Grosser, vascular surgeon, Dr Ross Sharpe, cardiologist, Prof Pete Smith, immunologist, Dr Lauren Exelby, anaesthetist, Dr Robert Fassett, physician, Dr Jon

Jenkins, retired physician, Stuart Stephenson, physiotherapist, Melanie Roberts, physiotherapist, Drew Singleton, physiotherapist, Liz Ciranni, physiotherapist, Craig Phillips, physiotherapist, Kelley Bright, dietician/exercise physiologist.

#### References:

1. Kamal Soliman; Steve Sturman; Prabodh K Sarkar; Atef Michael, "Postural wOrthostatic Tachycardia Syndrome (POTS): A Diagnostic Dilemma," Br J Cardiol. 2010;17(1):36-39.
2. Grosser, David: "Popliteal vein compression syndrome the main cause of DVT, unrecognised", <https://www.arteries-veins.com/single-post/2017/01/07/Popliteal-vein-compression-syndrome-the-MAIN-cause-of-DVT-unrecognised>
3. Milleret,Rene, "Popliteal vein entrapment: an unrecognised cause of failure in surgery for superficial venous insufficiency.", Phlebology. Vol 14 No 1 2007
4. Prandoni P et al. Prevalence of pulmonary embolism among patients hospitalized for syncope. N Engl J Med 2016 Oct 20; 375:1524. (<http://dx.doi.org/10.1056/NEJMoa1602172>)
5. A K Agarwal, R Garg, A Ritch, and P Sarkar, "Postural orthostatic tachycardia syndrome," Postgrad Med J. 2007 Jul; 83(981): 478–480.
6. Teng Moua<sup>1</sup> and Kenneth Wood<sup>2</sup> COPD and PE: A clinical dilemma, Int J Chron Obstruct Pulmon Dis. 2008 Jun; 3(2): 277–284.
7. Rosenbaum, D.A., Thornburg, M.,Silvis,M.L., Thoracic Outlet Syndrome <http://emedicine.medscape.com/article/96412-overview>.
8. Sheil, W.C. Thoracic Outlet Syndrome (TOS) [http://www.medicinenet.com/thoracic\\_outlet\\_syndrome/article.htm](http://www.medicinenet.com/thoracic_outlet_syndrome/article.htm)
9. Chahwala V, Tashiro J, Li X, Baqai A, Rey J, Robinson HR. Venous Thoracic Outlet Syndrome as a Cause of Intractable Migraines. <https://www.ncbi.nlm.nih.gov/pubmed/27531080>
10. Shibao,C.et al, Hyperadrenergic Postural Tachycardia Syndrome in Mast Cell Activation Disorders, Hypertension, 2005;45:385-390
11. Forbes,K., MRI Brain White White Matter Change:Spectrum of Change- How can we grade? J R Coll Physicians Edinburgh 2017; 47: 271-5
12. Wojcik, B. M., et al. (2011). "Interleukin-6: a potential target for post-thrombotic syndrome." Annals of Vascular Surgery 25(2): 229-239.
13. Lattimer, C. R., et al. (2016). "Are Inflammatory Biomarkers Increased in Varicose Vein Blood?" Clinical & Applied Thrombosis/Hemostasis 22(7): 656-664.
14. Vaddadi, G., Lambert, E., Corcoran, S., Esler, M.:Postural Syncope: mechanisms and management. Medical Journal of Australia, 2007, Vol 187
15. Kurlinsky,A., Rooke,T.: Nutcracker Phenomenon and Nutcracker Syndrome. Mayo Clin Proc, 2010.
16. Durham, J., Machan, L.: Pelvic Congestion Syndrome. 2013. Semin Intervent Radiol
17. Silva, R., Selmonosky, C.: The Thoracic Outlet Syndrome (TOS) and its apparent relation to Multiple Sclerosis: A Preliminary Report.
18. Sharpe,R. Cryptogenic Stroke and PFO Evidence Update. <http://www.sharpecardiology.com.au/services-consultations%20-%20migraine.htm>

19. Christo,P. New Perspectives on Neurogenic Thoracic Outlet Syndrome. Practical Pain management, 2015. Vol 14, Issue 8. <https://www.practicalpainmanagement.com/pain/neuropathic/new-perspectives-neurogenic-thoracic-outlet-syndrome>
20. Selmonosky,C. Whiplash is Thoracic Outlet Syndrome. BMJ, 2003. <https://www.bmj.com/rapid-response/2011/10/29/whiplash-thoracic-outlet-syndrome>
21. Venous Thoracic Outlet Syndrome, Washington University School of Medicine in St Louis. <http://tos.wustl.edu/What-is-TOS/Types-of-TOS/Venous-TOS>
22. Dyke,P., et al, Mayo Clinic, Department of Neurology Research, <https://www.mayo.edu/research/departments-divisions/department-neurology/programs/peripheral-nerve-disorders>
23. Mall,N., Van Thiel,G., Heard,W.,Paletta,G., Bush-Joseph,C., Bach,B. Paget-Schroetter Syndrome- A Review of Effort Thrombosis of the Upper Extremity From a Sports Medicine Perspective Sports Health. 2013 Jul; 5(4): 353–356.
24. Gregorakos,L., Sakayianni,K., Hroni,D., Geogiodou,F.: Thoracic outlet syndrome (TOS) and pulmonary embolism (PE): Report of two cases. 1999. [https://www.researchgate.net/journal/0956-3075\\_Clinical\\_Intensive\\_Care](https://www.researchgate.net/journal/0956-3075_Clinical_Intensive_Care)
25. Illig,k., Doyle, A.: A Comprehensive Review of Paget-Schroetter Syndrome, Journal of Vascular Surgery, Volume 51, Issue 6, June 2010, <https://www.sciencedirect.com/science/article/pii/S074152140902518X>