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Imaging findings of pelvic venous insufficiency in patients with postural orthostatic tachycardia syndrome

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Abstract

Objectives: Some patients with postural orthostatic tachycardia syndrome (POTS) demonstrate improved dysautonomic symptoms following treatment for pelvic venous insufficiency (PVI). This study assessed the prevalence of significant left common iliac vein (LCIV) compression in POTS patients.

Methods: Radiologists retrospectively reviewed CT images of pelvic veins for 216 women (191 with POTS and 25 age-comparable controls).Quantitative vascular analysis identified percent-diameter compression of the LCIV by the right common iliac artery. Significant LCIV compression was defined as >50%.

Results: Significant LCIV compression was found in 69% (131/191) of females with POTS versus 40% (10/25) in controls. The hypothesis that venous compression and presence of POTS are independent was rejected ($p = .005$).

Conclusions: Significant LCIV compression was noted in a majority of female POTS patients, suggesting that incidence of iliac venous obstruction may be higher than the general population. Patients with POTS and symptoms of PVI may benefit from assessment for venous outflow obstruction.

Keywords

POTS, pelvic pain, iliac vein compression, May Thurner

Introduction

Postural tachycardia syndrome (POTS) is a physiologically complex and often debilitating disorder. POTS represents one of the most common categories of orthostatic intolerance; current diagnostic criteria define the syndrome as an increase in heart rate of at least 30 beats/minute (40 in children) within 10 minutes of standing or head-up tilt testing, in the absence of orthostatic hypotension. Prevalence is estimated at 0.1-1% of the population.[1,2] Those affected are often young, between 15-40 years old, and female, with reported female:male ratios up to 5:1.[3–5] Patients with a diagnosis of POTS have been shown to experience significant reductions in quality of life owing to a constellation of physical symptoms associated with the syndrome.[6] The pathophysiology of POTS remains incompletely understood, with a spectrum of factors affecting subgroups of patients in different ways. Commonly described causative factors include autonomic dysfunction, increased sympathetic tone, as well as reduced venous return and/or increased extremity blood pooling.[2–4,7]

Neural mechanisms such as regional autonomic denervation in the lower limbs have been suggested as a contributory cause, as well as not-yet understood

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elevated plasma norepinephrine levels in patients following tilt testing. Connective tissue abnormalities are also being considered in investigations, as an association with Ehlers Danlos Syndrome has been suggested.[2] In recently presented small case studies, an association between POTS and vascular compression syndromes such as median arcuate ligament syndrome and pelvic compression syndrome has been suggested.[7–11] Occasional improvement in dysautonomic symptoms in these POTS patients treated for median arcuate ligament syndrome was reported. In our institutions' experience, some POTS patients undergoing treatment for pelvic venous insufficiency (PVI)/iliac vein compression have also demonstrated an improvement in a few of associated dysautonomic symptoms.

PVI is associated with chronic pelvic pain,[12–14] which represents a common and morbid condition affecting up to 24% of women worldwide.[15–17] Reflux into the ovarian or internal iliac veins and/or obstruction of iliac vein outflow is thought to be the underlying cause of insufficiency; PVI has additionally been shown to be strongly associated with iliac vein stenosis or outflow obstruction. In one case series, Santoshi et al. saw significant iliac vein stenosis, defined as >50% compression of the left common iliac vein (LCIV) by the right common iliac artery,[18–20] in 80% (181/227) of female patients being treated for PVI.[21]

LCIV compression in both symptomatic (May Thurner Syndrome) and asymptomatic patients, as well as its estimated 2:1 female:male prevalence, has been well described in the literature.[22] Since LCIV compression was first categorically detailed in a cadaveric study performed by May and Thurner in 1957,[23] a large body of research has sought to identify ideal corresponding diagnostic modalities, including intravascular ultrasound (IVUS) and CT venography/angiography,[18–20,24] and therapeutic interventions, most notably venous stenting.[25,26] CT, MR, and US have become commonly utilized modalities in the assessment of venous anomalies.[27]

To our knowledge no study in the literature has previously identified a relationship between LCIV compression and POTS. The purpose of this multi-institutional retrospective study is to assess the prevalence of hemodynamically significant LCIV compression in a POTS population.

Materials & methods

Study design and subjects

A retrospective chart review was performed at two tertiary care institutions, with institutional review board approval at both sites. A database of patients carrying a formal diagnosis of POTS was assessed. POTS patients were included in the study if a chart review revealed relevant cross-sectional CT imaging of the abdomen and pelvis that was amenable to vascular assessment. Study types utilized included CT (with or without intravenous contrast), and CT angiography (CTA) of the abdomen and pelvis. Non-contrast CT studies were excluded if vessel walls could not be reliably identified. Imaging study dates ranged from 2009-2019. Patients with prior iliac venous intervention were excluded.

Figure 1. Left common iliac vein (arrow) compression by the right common iliac artery (asterisk), just peripheral to the inferior vena cava confluence (arrowhead) seen on contrast enhanced CT.

Quantitative vascular analysis was performed by 2-3 radiologists at each site. CT exams were analyzed on axial, thick slice non-contrast, post-contrast, and CTA series. Examples of significant stenosis can be seen in Figure 1. In all modalities, the common iliac vein confluence and aortic bifurcation were identified. Diameter stenosis ("minimal luminal diameter") of the LCIV caused by the overlying right common iliac artery was assessed at the site of arterial-venous crossover (lesion lumen diameter - "LD-L"), and the diameter of the ipsilateral CIV peripheral to this site was used as a reference area ("reference lumen diameter - "LD-R"). Percent stenosis was calculated as (1 - LD-L/LD-R) x 100. Diameters were measured to a tenth of a millimeter (mm), from outer vessel wall to outer vessel wall, as depicted in Figure 2. The site of LD-R was selected either on the same image slice or more peripherally within several axial slices. Data were internally audited by a second radiologist.

Similar analysis was performed in a control cohort of age-matched, healthy female controls aged 20-40, who had undergone CTA as part of a renal donor workup.

At medical site 1, two radiologists judged 154 cases (194 POTS, 25 controls) independently with 94% agreement (144/154). Classification of 10 cases was

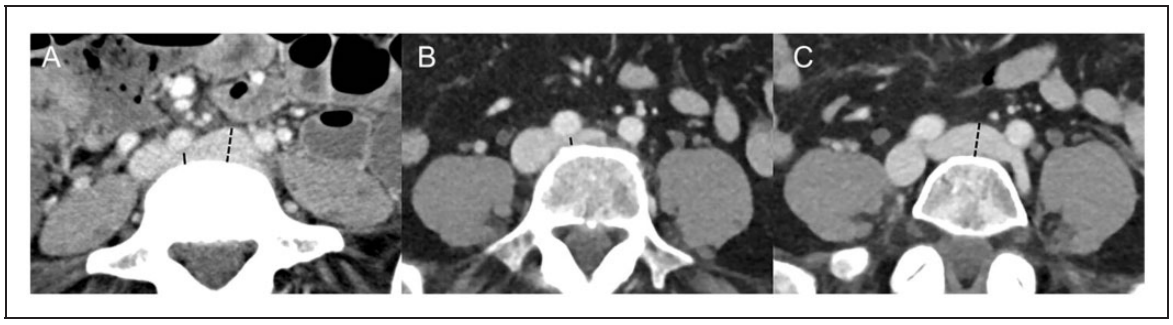

Figure 2. Stenosis measurements, including lesion lumen diameter (solid line), and reference lumen diameter (dashed line) on CT studies utilizing: single slice method (a), multiple slice method at site of compression and in normal vessel lumen peripherally (b, c).

resolved by consensus review. At site 2, 62 cases were judged independently by two radiologists, giving cases over to a third reviewer to resolve disagreements, which were reportedly rare.

Outcome measures

The primary endpoint of the study was to assess the frequency of hemodynamically significant stenosis of the LCIV, defined as >50% compression in luminal diameter.[18–20] A similar vascular assessment was performed in a small cohort of males.

Statistical analysis

Analysis was performed for each patient. The "gold standard" was defined as the percent of stenosis by LCIV IVUS >50%. After case review, subjects were categorized as low compression of the LCIV (≤50% stenosis) or highly compressed (>50% stenosis of the LCIV). The Chi-squared statistic was used to test for independence of degree of LCIV compression (low, high) versus patient population (POTS, controls).

Results

Between two study sites, cross-sectional imaging was reviewed in 191 female patients with POTS and 25 female controls. Mean female age was 34.4 (+/– 9.0) in the POTS cohort, and 32.6 (+/– 5.4) in the female control group.

As shown in Table 1, 131 (69.0%) patients in the POTS cohort demonstrated high (>50%) LCIV compression, compared to 10 (40.0%) in the control group; representing a non-random distribution of venous compression that is statistically significant [$p = .005$].

A small subgroup of male patients diagnosed with POTS (N = 16) was also assessed, with no corresponding control group. Nine of the sixteen (56.3%) patients demonstrated >50% LCIV compression.

Table 1. Numbers of POTS patients and controls with findings of low vs. high compression of the left common iliac vein.

Compression of LCIV	POTS	Control	Total
High (>50%)	131	10	141
Low (<50%)	60	15	75
Total, n	191	25	216

Note: Chi-squared comparison rejects the hypothesis that the two variables are independent with $x^2=7.97$, n = 216 and 1 df at $p=.005$.

Discussion

The present retrospective study demonstrates that female patients diagnosed with POTS demonstrate an increased prevalence of significant LCIV compression compared to normal female controls. While POTS and LCIV compression have been extensively studied independently of each other, this study represents the first to suggest a potential association between the two conditions.

As found in the control group, there is a background prevalence of LCIV compression in asymptomatic patients. In a 2004 retrospective analysis Kibbe et al reported prevalence data of LCIV compression in an asymptomatic population measured on axial CT.[28] In their cohort, 24% (12/50) of asymptomatic patients demonstrated >50% LCIV compression Comparatively, our present control cohort demonstrated a 40% prevalence rate of >50% LCIV stenosis, values which are not statistically significantly different from each other ($p = .15$) by chi-squared test. These findings are slightly increased compared to Kibbe's data, which notably included 40% male patients. Both of these asymptomatic groups remain in stark contrast to our present POTS cohort, which demonstrates 69.0% >50% LCIV compression, further strengthening a suggested association.

POTS is a complex and multifactorial entity that remains incompletely understood. Patients often reside on different points of a spectrum of multiple

proposed factors contributing to the syndrome. Causative factors have classically included autonomic dysfunction, hypovolemia, deconditioning, increased sympathetic tone, restricted adrenergic neuropathies in the extremities, as well as reduced venous return and/or increased extremity blood pooling.[2–4,7] Although the present study demonstrates only an association and not causation between LCIV compression and POTS, vascular compression could represent a compatible contributing or causative factor in known vascular findings of the syndrome – particularly with regards to sympathetic response.

Hemodynamically significant iliac vein stenosis with outflow obstruction could in theory represent a contributing etiology for increased blood pooling in the lower extremity seen in POTS. In addition, low blood volume or hypovolemia is a common finding in these patients, with many reported to have deficits in red cell and plasma volume.[1,29] Taken in tandem, and exacerbated by the normal hemodynamic changes of sudden upright positioning, the classic sympathetic cascade ensues. These factors would result in decreased cardiac venous return, resulting in baroreceptor inactivation, increased sympathetic response, and terminal clinical symptoms such as tachycardia and palpitations (Figure 3).

While LCIV compression of >50% has been proposed as hemodynamically significant,[18–21] LCIV stenosis and POTS patients, likely exist on a spectrum of physiologic changes. LCIV compression cannot solely explain all pathophysiologic abnormalities seen in POTS patients, as evidenced by POTS patients who demonstrate only minimal compression. However, based on our institutions' limited experience, a number of POTS patients who have undergone treatment of PIV/iliac vein compression with endovascular stenting have demonstrated noted improvement in dysautonomic symptoms. In keeping with the aforementioned proposed mechanism, increasing the patency of the LCIV may reduce lower extremity blood pooling, resulting in improved downstream effects.

Interestingly, similar occasional improvements in dysautonomic symptoms have been reported in small presented case studies of POTS patients diagnosed with MALS undergoing surgical MAL release.[8,10,11] While no definitive evidence or as-yet published data supports this finding, a proposed mechanism for the therapeutic benefit of MAL release involves resolving compression celiac trunk and/or celiac ganglion sympathetic nerve fibers. In both LCIV compression treatment and MAL release, a common pathway of improved vascular compression and reduced sympathetic drive could be present. With regards to iliac vein outflow obstruction in the setting of POTS, further objective studies dedicated to assessing symptomatic relief following endovascular stenting are of the utmost importance.

Limitations

Several limitations are present in our study. Our chart review was performed retrospectively on a collected database of POTS patients; by the study's nature, only an association is implied by our findings, and as such we cannot ultimately comment on a causative relationship between LCIV compression and POTS symptomatology.

Quantitative vascular analysis was performed on a variety of imaging modalities, including CT and CTA. IVUS has been generally accepted as an ideal imaging modality for measuring vessel luminal diameter or area, and was employed in a number of studies exploring diagnostic and treatment options in iliac vein obstruction.[18,19,30,31] Additional methods included multiplanar reformats on CT venography of angiography with measurements of luminal area. Unfortunately PACS systems with multiplanar reformatting capability were not available at all of the present study centers. However, in 2018 Shammas et al. retrospectively demonstrated that percent stenosis on CT venogram and CTA correlate with that on IVUS, with some underestimation of stenosis on venogram. Additionally, our study assessed luminal diameter in assessing percent

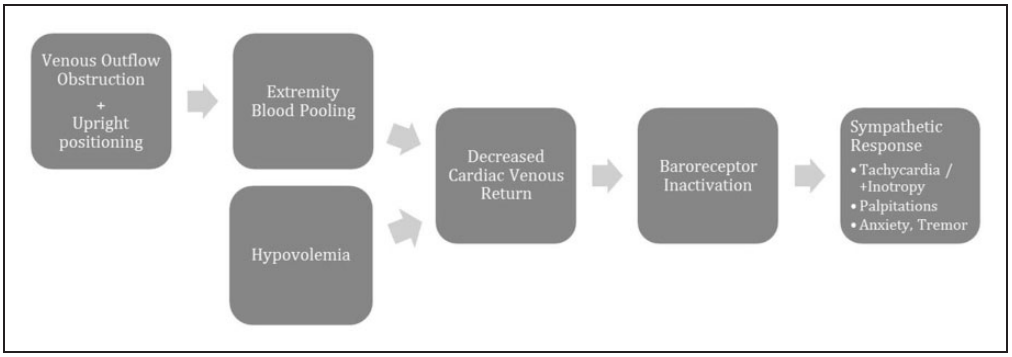

Figure 3. Theoretical pathophysiologic response to hemodynamically significant LCIV compression in POTS.

stenosis. While this is an accepted method,[32] further data or insight might be obtained by analyzing percent cross-sectional area reduction utilizing 3 D reformatting, or utilizing IVUS, and future research in this area should incorporate this in study designs.

Our study did not completely assess this relationship in male patients with POTS. A small subgroup of male POTS patients (N = 16) was assessed, with 9/16 (56.3%) demonstrating hemodynamically significant stenosis, but a corresponding control group was not analyzed. LCIV stenosis, and POTS demonstrate a female predominance as previously described; the etiology of this remains to be understood.

Conclusion

Hemodynamically and statistically significant LCIV compression was noted in a majority of female patients diagnosed with POTS (70.0%); this suggests that the prevalence of iliac venous obstruction in this subgroup of patients may be higher than in a normal patient population. Patients with POTS and symptoms of chronic pelvic pain and/or pelvic venous insufficiency may benefit from assessment for venous outflow obstruction. Further studies are needed to explore the possible pathophysiologic relationship between treated iliac venous obstruction and improved autonomic symptoms in POTS patients.

Declaration of Conflicting Interests

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Ethical approval

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Guarantor

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Contributorship

MGK, NK, AF, LAH, AL, FA, MS, BHS, SJS all developed the study concept and design, provided study supervision, and provided critical revisions of the manuscript. NK, IP, KSZ, AF, LAH, AL, FA, MS, and SJS all contributed to data collection. BHS provided statistical analysis. KSZ wrote the first draft of the manuscript. All authors edited and approved the final version of the manuscript.

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