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Authors
Ulloa, Jesus G
Gelabert, Hugh A
O'Connell, Jessica B
et al.

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Intravascular ultrasonography provides more sensitive detection of subclavian vein stenosis than venography in patients presenting with Paget-Schroetter syndrome

Jesus G. Ulloa, MD, Hugh A. Gelabert, MD, Jessica B. O'Connell, MD, Rhusheet Patel, MD, *and* David A. Rigberg, MD, *Los Angeles, Calif*

ABSTRACT

Objective: Spontaneous subclavian vein (SCV) thrombosis (Paget-Schroetter syndrome [PSS]) has been attributed to venous compression at the thoracic outlet and traditionally diagnosed using venography. Intravascular ultrasonography (IVUS) allows for a multidimensional view of vascular structures and might be more accurate in revealing venous compression. The goal of the present study was to compare venography and IVUS in patients presenting with PSS to assess the relative accuracy of each modality.

Methods: Patients presenting for evaluation of PSS from 2013 to 2019 were evaluated for SCV compression using venography and IVUS. Venography and IVUS measurements of stenosis were performed of the index and contralateral limbs in both neutral and stress (arm overhead) positions. The IVUS data included the SCV diameters in the anteroposterior (AP) plane, craniocaudal (CC) plane, and cross-sectional area (CSA). Stenosis was reported as the percentage of reduction from a reference point (lateral margin of the first rib) for the venography and IVUS data.

Results: For the 35 subjects, the average age was 35 years, 57% were women, 20% had presented with a documented pulmonary embolus, and 70% had initially been treated with thrombolysis. Venography demonstrated SCV occlusion in 3 patients (16%) with the index limb in the neutral position and in 18 patients (54%) with the limb in the stress position. The average stenosis in the index limbs was 41.5% (venography), and the average IVUS stenosis was 41.9% (CC), 61.8% (AP), and 74.5% (CSA; $P < .05$). A subset analysis revealed that in 10 of 35 patients (28%) in whom venography had identified no significant stenosis (average, 10%), IVUS had identified significant stenosis (33.5% CC, 54.3% AP, 68.7% CSA; $P < .05$).

Conclusions: IVUS proved more sensitive than venography in detecting significant stenosis leading to SCV thrombosis. A reduction in the CSA was the most sensitive measure of stenosis. IVUS identified significant stenosis in patients in whom venography failed to do so. The greatest utility of IVUS is in the evaluation of patients with PSS in whom venography shows no evident compression. (J Vasc Surg Venous Lymphat Disord 2021;9:1145-50.)

Keywords: IVUS; Paget-Schroetter; Thoracic outlet; Venogram; Venous

Spontaneous subclavian vein (SCV) thrombosis (Paget-Schroetter syndrome [PSS]) is the most common presentation of venous thoracic outlet syndrome (VTOS). Extrinsic compression of the vein by the clavicle and first rib results in chronic venous stenosis and, ultimately, spontaneous thrombosis.[1] This mechanism is thought to account for ∼60% of PSS cases.[2] Other causes of spontaneous SCV thrombosis include coagulation abnormalities and malignancy. Management of PSS relies on anticoagulation, thrombolysis, and surgical decompression. Accurate detection of extrinsic venous compression is essential to correctly treating patients with PSS.

The definitive diagnosis of PSS related to VTOS relies on catheter venography.[3] Venography provides information on extrinsic compression resulting in stenosis, the development of collateral venous channels, and the presence of postphlebitic changes. Intravascular ultrasonography (IVUS) is an imaging technique in which ultrasound evaluation of the vascular structures is accomplished by passing an ultrasound probe through the vessel lumen.[4] This allows for the recording of the vessel diameter in multiple axes and the cross-sectional area (CSA), in

From the Division of Vascular and Endovascular Surgery, David Geffen School of Medicine, University of California, Los Angeles.

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Correspondence: Jesus G. Ulloa, MD, Division of Vascular and Endovascular Surgery, David Geffen School of Medicine, University of California, Los Angeles, 200 Medical Plaza Driveway, Ste 526, Los Angeles, CA 90024 (e-mail: julloa@mednet.ucla.edu).

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addition to the vessel wall changes that can accompany venous thrombosis.

Although widely used in the management of other venous conditions such as May-Thurner syndrome, IVUS has not been routinely used to assess the SCVs in patients with PSS before surgical decompression. Our goal was to compare venography and IVUS for the evaluation of SCVs in patients presenting with PSS before intervention. We hypothesized that IVUS would prove to be more sensitive in the detection of venous compression and would be a beneficial adjunct in the preoperative management of PSS.

ARTICLE HIGHLIGHTS

- **Type of Research:** A single-center retrospective cohort study
- **Key Findings:** Intravascular ultrasonography (IVUS) is more sensitive in detecting subclavian vein stenosis than venography. In 10 of 35 patients (28%) in whom venography identified no significant stenosis, IVUS identified significant stenosis (33.5% craniocaudal, 54.3% anteroposterior, and 68.7% cross-sectional area; $P < .05$).
- **Take Home Message:** IVUS identified significant stenosis in patients in whom venography failed to do so. The greatest utility of IVUS is in the evaluation of patients with Paget-Schroetter syndrome in whom venography showed no evident compression.

METHODS

The included subjects were identified from a prospectively maintained database of PSS patients who had presented for consultation and possible VTOS decompression. For patients without adequate imaging studies available, venography and IVUS were performed to confirm the presence of SCV compression at the thoracic outlet before a decision for surgical decompression. IVUS was not performed for patients in whom the SCV was occluded or if the equipment was unavailable. The data were retrospectively abstracted from the medical records. The data from venography and IVUS were contemporaneously recorded.

The demographic and clinical data collected included gender, age, laterality, symptom duration, initial management (thrombolysis vs anticoagulation alone), evaluation of coagulation abnormalities, and documentation of pulmonary embolization.

Venography and IVUS. Our venography protocol included imaging of the index and contralateral arms in the neutral (at <90° to the body axis) and stress (limb held overhead, ~140°-150° to the body axis) positions in the anteroposterior (AP) dimension only. Imaging of the contralateral limb was not performed if we encountered difficulty accessing it from the index side. Imaging of the contralateral limb was accomplished using standard endovascular techniques by crossing at the confluence of the brachiocephalic veins from the index limb to the contralateral limb using a wire and support catheter under fluoroscopic guidance and confirmed with contrast-enhanced angiography. The diameters of the SCV were measured at the lateral margin of the first rib (reference point designated P1) and the point of maximal compression (designated P2). The resulting proportion of P2 to P1 was multiplied by 100 to calculate the percent stenosis (Supplementary Fig 1, online only). Patients who had had undergone thrombolysis were compared with those who had only received anticoagulation therapy to explore the effect of thrombolysis on the measurements of stenosis. Additionally, a subset analysis of the data was performed, stratified by the degree of stenosis noted on venography into three categories (0%-30%, 30%-70%, and 70%-100% stenosis) and compared with the IVUS measurements obtained in the SCV.

IVUS measurements were obtained in the index SCV and contralateral SCV with the limbs in the neutral and stress positions. The IVUS measurements included three values: the craniocaudal (CC) dimension, AP dimension, and a measurement of the cross-sectional area (CSA). These measurements were taken at the lateral border of the first rib (reference point designated P1) and the point of maximal compression (designated P2). The resulting proportion of P2 to P1 was then multiplied by 100 to calculate the percent stenosis for the CC plane, AP plane, and CSA.

Statistical analysis. The data are presented as the mean ± standard deviation. Statistical analysis of continuous variables was performed using the Student *t* test. Pearson correlation coefficient statistics were used to assess the correlation of values. Significance was attributed at the $P < .05$ threshold. Statistical analysis was performed using InStat, version 3.0, software (GraphPad, La Jolla, Calif).

Institutional review board approval. All work described in the present report was completed under the review and approval of our institutional review board (protocol no. 13-000624). Patient informed consent was not required.

RESULTS

All patients undergoing preoperative diagnostic venography and IVUS during the study period were eligible for inclusion. Of the 47 patients, 12 with preoperative venography were excluded because IVUS had not been concurrently obtained. Of these 12 patients, 9 had venous occlusion and for 3 patients, the IVUS equipment had not been available. A total of 35 patients were

Table I. Comparison of venography and intravascular ultrasonography

Limb	Percent stenosis						
	Venography	CC	*P* value[a]	AP	*P* value[a]	CSA	*P* value[a]
Index							
Neutral	41.6 ± 36.0	41.9 ± 25.7	NS	61.8 ± 19.5	<.05	74.5 ± 2.7	<.05
Stress	68.9 ± 39.9	70.0 ± 33.9	NS	79.7 ± 24.4	<.05	87.7 ± 16.5	<.05
Contralateral							
Neutral	17.8 ± 23.5	16.5 ± 19.8	NS	37.7 ± 20.8	<.05	45.5 ± 26.4	<.05
Stress	41.5 ± 40.9	33.8 ± 36.3	NS	53.4 ± 36.3	<.05	95.4 ± 3.4	<.05

AP, Anteroposterior; *CC*, craniocaudal; *CSA*, cross-sectional area; *NS*, not significant.
Data presented as average ± standard deviation.
[a]Comparison between venography and each intravascular ultrasonography measure.

evaluated using both venography and IVUS before the decision regarding surgical decompression. Of the 35 patients, 28 subsequently underwent surgical decompression via first rib resection, and 7 patients chose to not undergo surgical decompression. All patients had initially presented with acute deep vein thrombosis (DVT) in the index limb only (no bilateral presentations). The average age at presentation was 35 years (range, 14-59 years), and 3 of the 35 patients (10%) were adolescents. Of the 35 patients, 20 were women (57%). Significant physical activity (athletics, physical training, physical labor) was noted for 16 patients (46%). The average body mass index was 24.3 kg/m^2, and the average height was 1.71 m.

Most patients (94%) had had an initial diagnosis of DVT determined by ultrasonography. Only two patients (6%) had a DVT diagnosed using venography. Most patients (74%) had initially undergone thrombolysis, with nine (26%) initially treated with anticoagulation alone. Pulmonary embolus was documented by computed tomography pulmonary arteriography in seven patients (20%) at their initial presentation. Hematologic evaluations were obtained for 17 patients, of whom only 1 was positive for a hypercoagulable disorder (MTHFR [methylenetetrahydrofolate reductase] mutation). No patient had a history of trauma or malignancy. The left upper extremity was the index limb in 28% of the patients, and the average period from symptom onset to an established diagnosis was ∼7 days. The average period from diagnosis to evaluation in our clinic was 73 days (range, 0-129 days).

Venography of the index limb in the neutral position demonstrated three occlusions (8.6%). Two of these were pseudo-occlusions with discontinuity of the column of contrast with the arm in a neutral position, although the catheter could cross into the central venous system. When the index limb was in the stress position, 18 (51.4%) demonstrated positional occlusion. Contralateral limb venography was available for 29 patients. Of these 29 patients, venography of the contralateral limb showed 1 pseudo-occlusion (3.4%) with the limb in the neutral position and six pseudo-occlusions (21.6%) with the limb in the stress position.

When comparing the venography and IVUS data, we observed a baseline stenosis of ∼20% using venography in the asymptomatic contralateral limbs in the neutral position. Moreover, we found less variation in the measurement for the average stenosis in the CSA

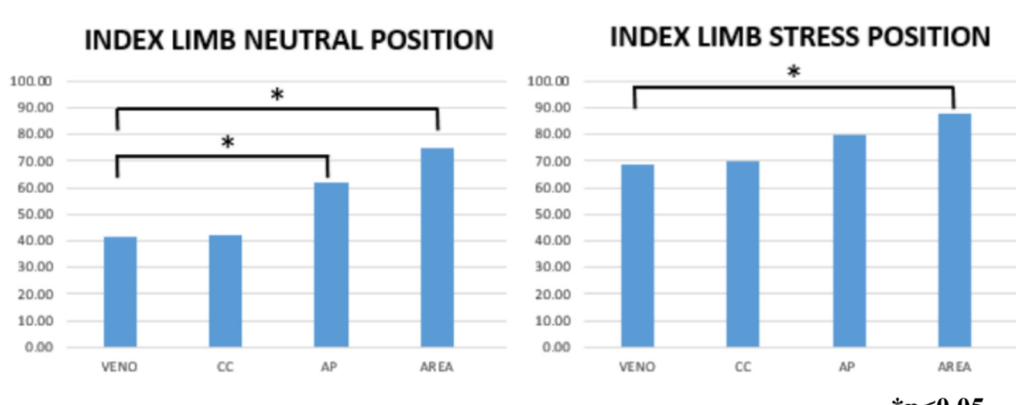

Fig 1. Comparison of percent stenosis measured using venography (*VENO*) and craniocaudal (*CC*) percent stenosis, anteroposterior (*AP*) percent stenosis, and cross-sectional area (*AREA*) percent stenosis measured using intravascular ultrasonography. *Statistically significant difference.

Table II. Lysis versus no lysis

	Percent stenosis			
Limb	Venography	CC	AP	CSA
Index, neutral				
Lysis	53.2 ± 32.6	41.9 ± 26.4	63.4 ± 18.9	75.7 ± 15.3
No lysis	57.5 ± 36.9	50.2 ± 29.7	66.0 ± 24.8	71.8 ± 18.5
Index, stress				
Lysis	70.8 ± 39.6	72.6 ± 32.8	83.1 ± 20.7	76.9 ± 36.2
No lysis	65.7 ± 42.4	61.3 ± 38.4	68.5 ± 33.0	37.5 ± 51.8
Contralateral, neutral				
Lysis[a]	19.0 ± 26.2	19.4 ± 20.9	40.6 ± 19.9	48.7 ± 27.6
No lysis	7.1 ± 7.6	7.2 ± 13.0	28.3 ± 22.5	33.1 ± 20.6
Contralateral, stress				
Lysis[a]	39.2 ± 37.6	34.0 ± 36.6	55.9 ± 30.4	86.9 ± 21.9
No lysis	46.0 ± 50.8	32.8 ± 39.0	42.6 ± 58.5	48.4 ± 57.5

AP, Anteroposterior; *CC*, craniocaudal; *CSA*, cross-sectional area.
Data presented as average ± standard deviation.
[a]Patients with thrombolysis of the index arm; no patient had thrombolysis of the contralateral arm.

measurement using IVUS (Table I). In the overall cohort, the IVUS measurement of the percent stenosis in the CC axis correlated significantly with the percent stenosis noted on venography when the limbs were in the neutral position ($R = 0.829$; $P = .016$). With the index limb in the stress position, we found no significant correlation between the CC percent stenosis and venography percent stenosis ($R = 0.0089$; $P = .966$). Significant differences were found between the AP and CSA percent stenosis recorded by IVUS compared with the percent stenosis noted using venography when the limbs were in the neutral position ($P < .05$). When the limbs were in the stress position, a significant difference remained between the percent stenosis measured using venography compared with the CSA percent stenosis (Fig 1).

When we evaluated the contralateral limbs, we identified results comparable to those found with the index limb. Again, the IVUS measurement of the percent stenosis in the CC axis correlated with the percent stenosis noted using venography with the limbs in the neutral position. Significant differences were noted between the AP and CSA percent stenosis recorded using IVUS compared with the percent stenosis recorded using venography in the neutral position. When the limbs were positioned in stress, the CSA percent stenosis remained significantly different compared with the venography percent stenosis.

IVUS revealed postphlebitic changes in all index veins. Synechiae and vein wall irregularities were seen in 24 of 35 index limbs on IVUS. The IVUS measured CSA of the index SCV was reduced on average by 28% (88.4 mm^2 vs 123 mm^2) compared with that of the unaffected contralateral vein.

The data were also analyzed to compare those patients who had undergone thrombolysis and those who had not. This analysis indicated no significant differences in the percent stenosis using venography or IVUS (Table II).

A subset analysis of data was performed, stratified by the degree of stenosis noted on venography into three categories (0%-30%, 30%-70%, and 70%-100% stenosis). The 0% to 30% stenosis category included 10 patients, the 30% to 70% category included 8 patients, and the 70% to 100% category included 17 patients. When the limb was in the neutral position, a significant difference was seen between the venography percent stenosis and the CC percent stenosis using IVUS in the upper category (70%-100%). In the middle category (30%-70%), significant differences were seen between the venography percent stenosis and the CC and CSA percent stenosis using IVUS. In the lower category (0%-30%), a significant difference was noted between the venography percent stenosis and all IVUS measurements. Although the average venography stenosis was 10% for the low stenosis category (0%-30%), the average IVUS stenosis was 33.5% for CC, 54.3% for AP, and 68.7% for CSA ($P < .05$). Venography with the limbs in the neutral position underestimated the degree of stenosis in 10 of 35 patients (28%). When the limb was in the stress position, the results were similar in the 0% to 30% category (Fig 2).

DISCUSSION

The accurate detection of extrinsic venous compression is essential to correctly treating patients with PSS. Our data have indicated that IVUS is more readily able to identify stenosis compared with venography of the SCV in PSS patients. The reduction in the CSA seen using IVUS was the most sensitive measure of stenosis.

IVUS has achieved widespread acceptance as an accurate imaging modality in venous compressive syndromes

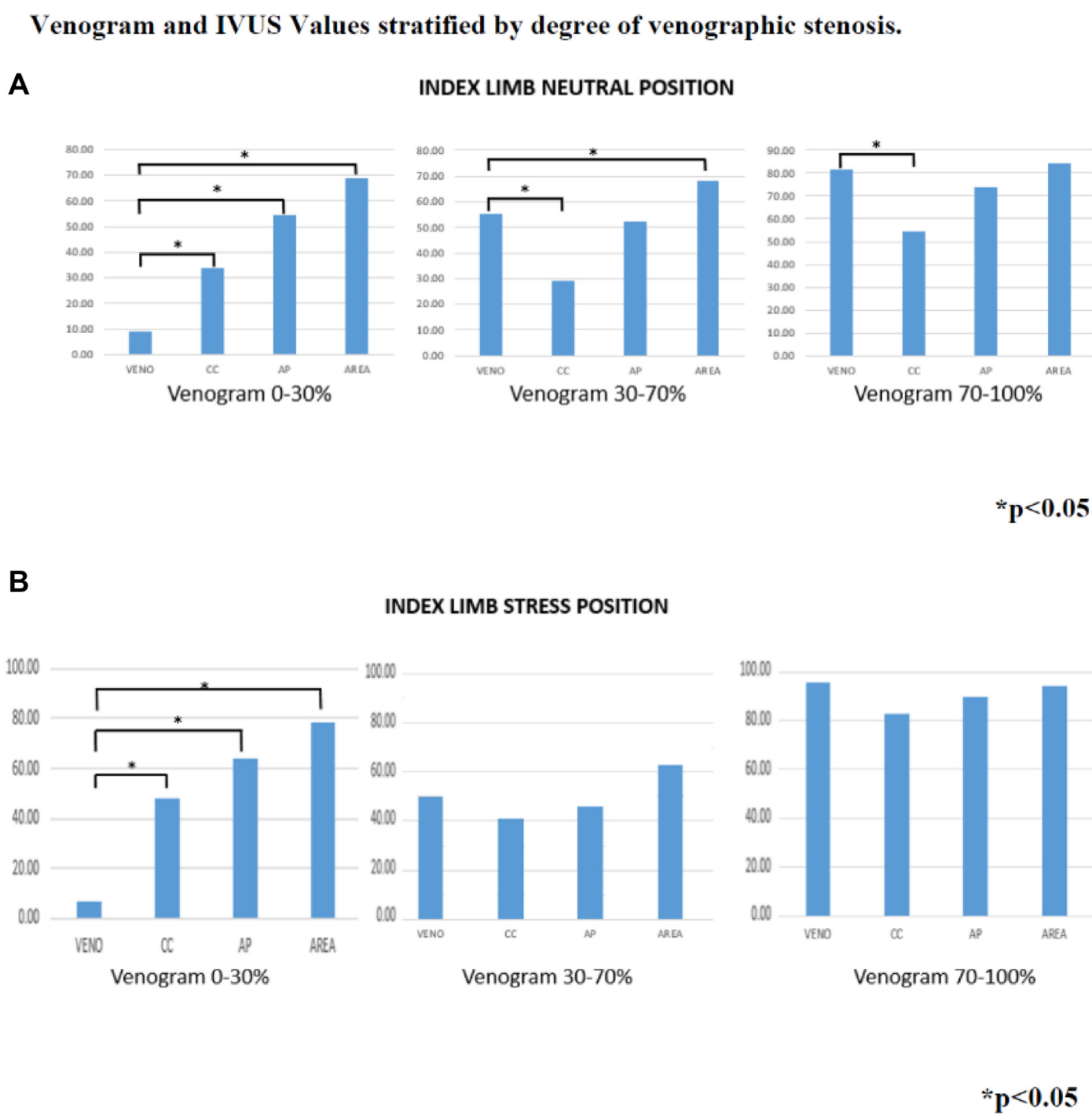

Fig 2. Comparison of limb position with category of percent stenosis measured by venography (*VENO*) and intravascular ultrasonography of craniocaudal (*CC*) percent stenosis, anteroposterior (*AP*) percent stenosis, and cross-sectional area (*AREA*) percent stenosis. *Statistically significant difference.

of the abdomen, including May-Turner syndrome[5-7] and nutcracker syndrome.[8] The advantage compared with venography for such cases is the improved sensitivity to compression in the AP axis. Venous compression at the thoracic outlet might be more complex than that seen in the abdomen. The compressive elements include the first rib and clavicle and the subclavius and anterior scalene muscles.[1] Depending on the growth and development of these structures, the predominant axis of compression might not always be in the CC plane and, thus, could escape detection using standard venography. Our findings in the present study are similar to those with the use of IVUS in the evaluation of May-Thurner syndrome in that extrinsic venous compression was not always optimally identified using AP venography.

The initial use of IVUS for the evaluation of VTOS was reported in 1994 by Chengelis et al.[9] In their study, eight patients were evaluated before VTOS decompression, of whom six had abnormal findings and four had subsequently undergone decompression. They found a good correlation between IVUS and venography.[9] They credited IVUS with improved surgical identification of the compression points, resulting in more limited surgical dissection. More recently, Kim et al[10] used IVUS

to guide angioplasty in post-VTOS decompression venography. They reported that in 27.8% of cases, IVUS identified stenosis >50% that was not apparent on venography and led to intervention.[10] Our project focused on the evaluation of the SCV in patients with PSS as a part of our initial appraisal of potential VTOS. Thus, our data reflect the condition of the SCV after thrombosis and, in some cases, catheter-directed thrombolysis, before decompression.

IVUS demonstrated a greater degree of sensitivity to stenosis, especially in the measured reduction of the CSA. Of particular importance was the finding that IVUS can detect potentially significant stenosis of the SCV in patients in whom venography failed to do so. This occurred in 28% of our patients. These were patients in whom venography had identified minimal stenosis but IVUS had revealed a 68% reduction in the CSA. These findings would argue that obtaining IVUS would be of value for patients in whom no evident compression was seen using venography (Supplementary Fig 2, online only). We also identified a baseline stenosis of the asymptomatic contralateral limb of ~20% that was most likely physiologic, reflecting positional changes that lead to vein compression at the thoracic outlet. We did not perform surgical decompression of the asymptomatic contralateral side. We hypothesized that a potential indication for thoracic outlet decompression in the contralateral asymptomatic limb could be high-grade stenosis with significant collateralization in a patient who anticipates travel to a remote, medically impoverished, location (ie, peace corps or military service). Such a person might request prophylactic rib resection given previous experience with PSS.

Study limitations. The principal limitation of the present project was the size of the study cohort. Although this reflects the relative rarity of PSS, it also limited the generalizability of the data. Corroborative studies would be required before concluding that IVUS is superior or should be the standard of care. Moreover, the routine use of an IVUS catheter could add to the average cost and case completion time. IVUS provides a view of the current state of the index vessel but does not provide a broader description of chronicity or physiologic compensation, as depicted by collateral branches, which can be seen on venography. As a retrospective report, our results are subject to inadvertent biases, such as the provider referral patterns to our institution, patient presentation, and temporal treatment trends. Finally, the use of IVUS in this context is novel and, therefore, few data are available with which to compare our results.

CONCLUSIONS

The use of IVUS provided objective characterization of the SCV in patients with PSS. Our results could help better define those patients at risk of recurrent thrombosis and who would benefit from surgical decompression. IVUS is more sensitive than venography in identifying significant stenosis of the SCV and will be most useful for patients with PSS in whom venography has shown either no or minimal stenosis. In such cases, IVUS might identify significant compression, confirm the diagnosis of VTOS, and provide an indication for surgery.

AUTHOR CONTRIBUTIONS

Conception and design: JU, HG, RP, DR
Analysis and interpretation: JU, HG, JO, RP, DR
Data collection: JU, HG, RP
Writing the article: JU, HG, JO
Critical revision of the article: JU, HG, JO, RP, DR
Final approval of the article: JU, HG, JO, RP, DR
Statistical analysis: JU, HG, JO
Obtained funding: Not applicable
Overall responsibility: JU
JU and HG contributed equally to this article and share co-first authorship.

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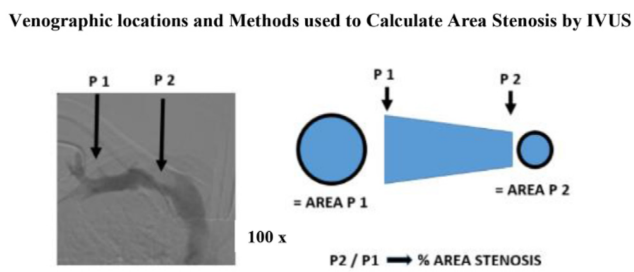
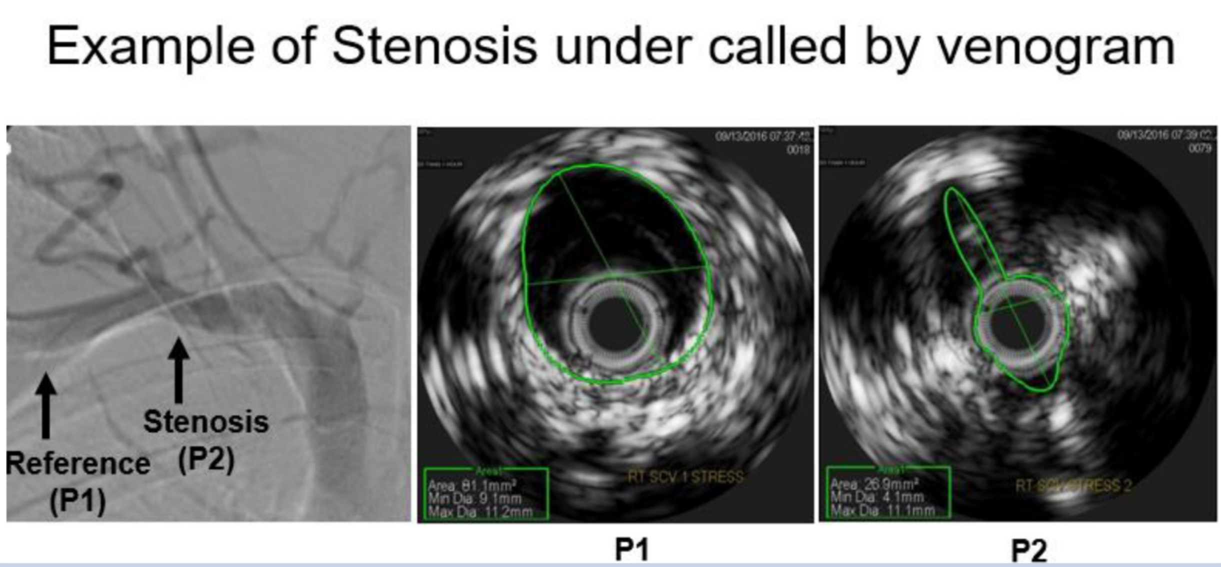


Supplementary Fig 1 (online only). Illustration of method for calculation of percent stenosis using intravascular ultrasound (*IVUS*) measurements. This example is a calculation of the cross-sectional area (CSA) percent stenosis. The CSA measured by IVUS at point 1 (P1) is used as the denominator to the CSA measured by IVUS at point 2 (P2). The ratio of these CSAs is used to calculate the CSA percent stenosis by multiplying the P2/P1 ratio by 100. A similar method was used to calculate the craniocaudal and anteroposterior percent stenosis using the CC and AP diameters measured on IVUS.



Supplementary Fig 2 (online only). Comparison of venography and intravascular ultrasonography images in a patient in whom significant stenosis was identified by intravascular ultrasonography but not by venography. P1 refers to the reference point at the lateral margin of the first rib. P2 refers to the point of maximal narrowing.