Automated Quantitative Imaging Measurements of Disease Severity in Patients with Nonthrombotic Iliac Vein Compression

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ABSTRACT

Purpose: An automated segmentation technique (AST) for computed tomography (CT) venography was developed to quantify measures of disease severity before and after stent placement in patients with left-sided nonthrombotic iliac vein compression.

Materials and Methods: Twenty-one patients with left-sided nonthrombotic iliac vein compression who underwent venous stent placement were retrospectively identified. Pre- and poststent CT venography studies were quantitatively analyzed using an AST to determine leg volume, skin thickness, and water content of fat. These measures were compared between diseased and nondiseased limbs and between pre- and poststent images, using patients as their own controls. Additionally, patients with and without postthrombotic lesions were compared.

Results: The AST detected significantly increased leg volume (12,437 cm^3 vs 10,748 cm^3, $P < .0001$), skin thickness (0.531 cm vs 0.508 cm, $P < .0001$), and water content of fat (8.2% vs 5.0%, $P < .0001$) in diseased left limbs compared with the contralateral nondiseased limbs, on prestent imaging. After stent placement in the left leg, there was a significant decrease in the water content of fat in the right (4.9% vs 2.7%, $P < .0001$) and left (8.2% vs 3.2%, $P < .0001$) legs. There were no significant changes in leg volume or skin thickness in either leg after stent placement. There were no significant differences between patients with or without postthrombotic lesions in their poststent improvement across the 3 measures of disease severity.

Conclusions: ASTs can be used to quantify measures of disease severity and postintervention changes on CT venography for patients with lower extremity venous disease. Further investigation may clarify the clinical benefit of such technologies.

ABBREVIATIONS

AST = automated segmentation technique, HU = Hounsfield unit

INTRODUCTION

Nonthrombotic iliac vein compression is frequently secondary to chronic mechanical compression of the left common iliac vein by the crossing right common iliac artery anteriorly and the lumbar vertebral body posteriorly—a condition also known as May-Thurner syndrome (1). Repeated extrinsic compression of the left common iliac vein can lead to persistent left leg swelling, aching pain, overlying skin changes and ulceration, and claudication, all of which significantly reduce quality of life. The aforementioned risk factors additionally predispose patients to iliofemoral deep vein thrombosis, which in turn can lead to postthrombotic iliac vein obstruction (2). Up to one-half of left-sided iliofemoral deep vein thromboses are estimated to be associated with external compression of the iliac vein (3).

The advent of endovascular stents has revolutionized the management of iliac vein lesions, and most patients experience excellent patency rates and outcomes (4–6). Early diagnosis is critical in selecting appropriate therapy to ensure better prognosis (7). There is no consensus imaging

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method for the diagnosis of iliac vein lesions. Patients typically receive venous ultrasound as an initial diagnostic imaging examination, which is noninvasive, quick, and nonionizing. In the absence of deep vein thrombosis, however, lower extremity duplex imaging may fail to examine all of the iliac vein segments; the diagnosis of iliac vein compression on ultrasound is technically difficult and operator dependent (8). Conventional venography with intravenous ultrasound offers many benefits, including nonionizing radiation, accurate luminal area and diameter measurements in real-time without intravenous contrast, determination of the chronicity of thrombus if present, and the ability to diagnose and treat veno-occlusive disease in 1 sitting, but intravenous ultrasound is invasive and resource intensive (9). Magnetic resonance venography is another useful nonionizing diagnostic test for iliac disease that can identify venous collateral flow and presence of iliac spurs; however, it is expensive, it can be exclusionary in patients with contraindications to magnetic imaging, and images do not account for nonlaminar flow (3). At the study institution, computed tomography (CT) venography is preferred for diagnostic workup and for follow-up of iliac stent placement because of its availability, speed, noninvasiveness, ability to identify compression of the iliac vein, and usefulness in ruling out alternative causes of iliac vein compression, such as malignant lymphadenopathy or compressive retroperitoneal hematomas (10).

Despite the wealth of diagnostic tools available, there is a lack of established quantitative imaging guidelines by which to measure and quantify disease severity and response to treatment for patients with iliac vein lesions. This study investigates the technical feasibility of an automated segmentation technique (AST) to quantify measures of disease severity on CT venography imaging for patients with nonthrombotic iliac vein compression with or without postthrombotic iliac vein obstruction. Automated image analytics may provide clinicians with an adjunctive means of quantitatively assessing disease severity and response to treatment in patients with lower extremity venous disease.

MATERIALS AND METHODS

Cohort Selection and Characterization

This retrospective study was performed with institutional review board approval. Using a comprehensive, single-institution venous disease database spanning 2007–2016, 21 patients were included in the cohort after satisfying the following inclusion criteria: (*a*) patients who underwent iliofemoral venous stenting during the study period; (*b*) patients with mention of left-sided nonthrombotic iliac vein compression in the pre- or poststent radiology report, without mention of right-sided disease; and (*c*) patients with diagnostic quality pre- and poststent lower extremity CT venography studies, including imaging from the pelvis to the mid-calves.

At the study institution, stents were placed if iliofemoral vein segments exhibited at least 70% stenosis or axial diameters of less than 4 mm, confirmed with catheter-based venography (11). Additional procedural details and periprocedural protocols were described previously (12).

The electronic medical records for each patient were systematically reviewed to record baseline patient demographic information and venous clinical history (**Table 1**). Information regarding stent placement, including count, anatomic location, and stent diameter was extracted from procedure reports, and characterized using summary statistics. Poststent patient-reported symptomatic improvement was qualitatively categorized as complete improvement, partial improvement, or no improvement through review of follow-up clinical records. Primary, primary assisted, and secondary stent patency rates were calculated in accordance with Society of Interventional Radiology definitions (13).

Image Acquisition

All axial pre- and poststent CT venography image files for the cohort were obtained via retrospective review of the institutional picture archiving and communications system. Each CT venography was verified to have followed the following institutional standard protocols: (*a*) use of Isoview 370 at a rate of 1.8–2.0 mL/kg body weight injected over 40 seconds; (*b*) use of separate time delays, including a scan from the diaphragm to the pubic symphysis at 110 seconds, followed by a scan from the pubic symphysis through the legs at 180 seconds; and (*c*) maintenance of a consistent field of view and center of reconstruction between the 2 scans, and a scan range set so that the first reconstructed image of the infrainguinal venogram was exactly 1 reconstructive interval below the last reconstructed image of the abdominopelvic venogram. Additional standardized imaging parameters included a kVp of 80, an auto mA range from 100 to 675, a pitch of 1, and the following reconstructions: 0.625, 1.25, and 2 mm. The threshold CT dose index for a 32-cm phantom was 30 mGy; for the average 80 kg patient at the study institution, the average CT dose index is 9–17.

Image Processing and Automated Segmentation

A study investigator independently verified, deidentified, and renamed each complete set of pre- and poststent CT venography image files within the picture archiving and communications system. The images were then sent to a trained radiologist for further data packaging using OsiriX (OsiriX, Bernex, Switzerland); images were curtailed to the range between just below the inguinal ligament to just above the ankle for all patients. All CT venography images contained 1-mm slices and an average of 650 images per patient, per study, after processing in OsiriX.

Table 1. Patient Demographics and Clinical History

Characteristic	Full Cohort (Nonthrombotic Iliac Vein Compression) (n = 21)	With Postthrombotic Iliac Vein Occlusion (n = 16)	Without Postthrombotic Iliac Vein Occlusion (n = 5)
Age, y, median (IQR)	43 (38–55)	47 (39–63)	43 (38–48)
Sex			
Male	6 (28.6)	5 (31.3)	1 (20.0)
Female	15 (71.4)	11 (68.8)	4 (80.0)
Prestent LLE symptoms			
Edema/swelling	21 (100.0)	16 (100.0)	5 (100.0)
Pain	14 (66.7)	11 (52.4)	3 (60.0)
Claudication	5 (23.8)	4 (19.0)	1 (20.0)
Exercise intolerance	3 (14.3)	3 (14.3)	0 (0.0)
Erythema	3 (14.3)	2 (12.5)	1 (20.0)
Ulceration	0 (0.0)	0 (0.0)	0 (0.0)
Duration of swelling, y, median (IQR)	1.5 (0.7–12.0)	1.3 (0.5–3.8)	12.0 (3.6–12.0)
Anatomic extent of disease			
Common iliac involvement	21 (100.0)	16 (100.0)	5 (100.0)
External iliac involvement	14 (66.7)	14 (87.5)	0 (0.0)
Common femoral involvement	7 (33.3)	7 (43.8)	0 (0.0)
Prestent leg circumference, cm, mean ± SD			
Left thigh	Data not available	56.3 ± 8.4	Data not available
Left calf		42.7 ± 5.0	
Left ankle		23.8 ± 2.8	
Right thigh		52.8 ± 6.7	
Right calf		39.0 ± 3.1	
Right ankle		22.5 ± 2.4	
Compression stocking use	16 (76.2)	11 (68.8)	5 (100.0)
Prior superficial vein treatment	1 (4.8)	1 (6.3)	0 (0.0)

Note–All values are no. (%) unless otherwise noted. Indented parenthetical values are subtotal percentages.
IQR = interquartile range; LLE = left lower extremity; SD = standard deviation.

An AST algorithm was developed in MATLAB (Natick, Massachusetts), which analyzed the processed CT venography images and automatically assessed radiodensity in Hounsfield units (HU) using the built-in "dicomread" function (14). The algorithm subsequently segmented various tissue layers according to radiodensity into separate images for bone, fat, muscle, and skin, using a multithreshold intensity approach. The HU thresholds were set for different tissue types as follows: bone 400–1000; fat –60 to –100; muscle 10–40; and skin –100 to 200.

The algorithm was additionally programmed to automatically calculate 3 measures of disease severity: water content of fat, leg volume, and skin thickness. The water content of fat was measured by counting "water" pixels with HU of –10 to 10 within the fat segment, and dividing this sum by the total number of pixels in the fat layer. Leg volume was estimated by calculating the area of each leg on each slice and then multiplying the average cross-sectional area by the number of slices and slice thickness (15). Skin thickness was estimated by the following process: first, for each slice, the distance from the center of the leg to the furthest radial point on the leg (denoting the most external pixel of the epidermis) was measured, using a line. Then, the algorithm measured connective pixels along this line toward the center of the leg, as long as the pixels were within the HU range for skin. The average length of this connective pixel measurement across the entire limb from the pubic symphysis to the calf was the outputted skin thickness. The AST algorithm was then applied to all CT venography images for the cohort. A graphical representation of the AST algorithm output is presented in **Figure 1**.

Statistical Analysis

The 3 measures of disease severity were compared in the following contexts: (*a*) prestent comparisons between the right and left legs; (*b*) poststent comparisons between the right and left legs; (*c*) pre- versus poststent comparisons of the stented left leg; (*d*) pre- versus poststent comparisons of the unstented right leg. Additionally, the percent change from prestent baseline across the 3 measures of disease severity was compared between patients with and without postthrombotic iliac occlusions. Statistical comparisons were performed using the Wilcoxon signed-rank test in R (16).

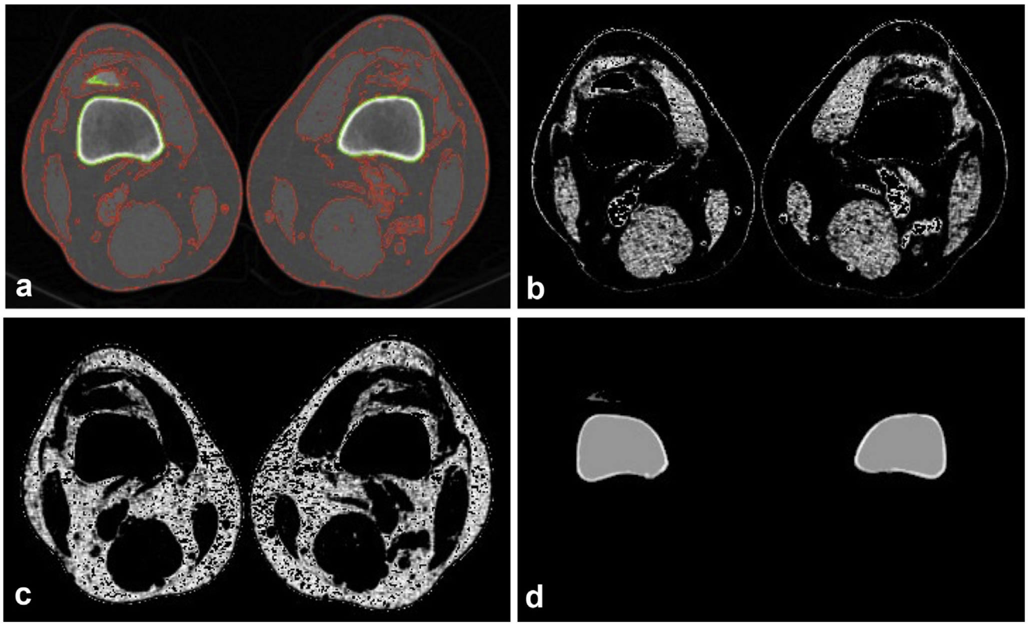

Figure 1. Composite image generated by **(a)** the automated segmentation technique algorithm that depicts all of the segmented tissue layers including skin, muscle, and subcutaneous fat (red outline) and bone (green outline). **(b–d)** The individual segmented tissue layers for muscle, fat, and bone, respectively.

RESULTS

The study cohort received a total of 47 stents, for an average of 2.2 stents per patient in the affected left lower extremity (standard deviation 1.06; range 1–5). Patient and stent characteristics are summarized in Table 2. Patency rates, patient-reported outcomes, and radiation doses are reported in Table 3. Both a pre- and poststent CT venography study was assessed for each individual in the cohort with an average follow-up of 9.3 ± 11.2 months (range 1.2–30.2) following stent administration.

On prestent imaging, significant differences were found across all 3 measures of disease severity between the left and right legs, including the water content of fat (8.2% vs 5.0%, $P < .0001$), leg volume (12,437 vs 10,748 cm^3, $P < .0001$), and skin thickness (0.531 vs 0.508 cm, $P < .0001$). On poststent imaging, significant differences were observed between the left and right leg volumes (10,802 vs 9,975 cm^3, $P = .006$) and skin thickness (0.506 vs 0.510 cm, $P = .03$); no significant difference was observed between the left and right leg water content of fat (3.2% vs 2.7%, $P = .06$).

In pre- versus poststent comparisons of the left leg, the water content of fat was significantly lower in the poststent group (8.2% vs 3.2%, $P < .0001$); however, there was no significant difference in skin thickness (0.53 vs 0.51 cm, $P = .46$) or leg volume (12,437 vs 10,802 cm^3, $P = .32$) in the left leg after stent administration. In pre- versus poststent comparisons of the right leg, the water content of fat was significantly lower in the poststent group (4.9% vs 2.7%, $P < .0001$). There were no significant differences in skin thickness (0.51 cm vs 0.51 cm, $P = .95$) or leg volume (10,747 cm^3 vs 9,975 cm^3, $P = .60$) in the right leg after stent administration.

Table 2. Patient and Stent Characteristics

Vein Segment	Patients with Stented Vein (n = 21) (%)	Total stents Placed (n = 47) (%)	Mean Stent Diameter (mm), Mean ± SD
Left common iliac	21 (100.0)	32 (68.1)	14.2 ± 0.6
Left external iliac	15 (71.4)	18 (38.3)	13.9 ± 1.1
Left common femoral	8 (38.1)	9 (19.1)	12.8 ± 1.7

Note–Total stent frequency on a vein-level basis is greater than the total number of stents because of individual stents spanning multiple vein segments. Stent overlap accounts for multiple stents within the same vein segment.
SD = standard deviation.

There were no significant differences between patients with or without postthrombotic occlusions in terms of their poststent percent decrease from baseline across the 3 measures of disease severity: water content of fat (–66.0% vs –39.2%, $P = .07$), leg volume (–17.1% vs 2.9%, $P = .79$), and skin thickness (–5.7% vs –1.0%, $P = .98$).

DISCUSSION

This proof-of-concept study suggests that automated quantitative assessment of disease severity in patients with iliac vein lesions is technologically feasible. The AST in this study detected significant differences in the water content of fat, skin thickness, and leg volume between right and left legs on prestent CT venography studies for patients with left-sided iliac vein lesions. The ability to differentiate between healthy and diseased anatomy using quantitative

Table 3. Procedural Outcomes

Outcome	Full Cohort (Nonthrombotic Iliac Vein Compression) (n = 21)	With Postthrombotic Iliac Vein Occlusion (n = 16)	Without Postthrombotic Iliac Vein Occlusion (n = 5)
Patency			
Primary	85.7	81.3	100
Primary assisted	100	100	100
Secondary	100	100	100
Poststent symptom improvement			
Complete symptom resolution	7 (33.3)	7 (43.8)	0 (0.0)
Partial symptom improvement	10 (47.6)	7 (43.8)	3 (60.0)
No symptom improvement	4 (19.0)	2 (12.5)	2 (40.0)
Radiation dose per scan (mGy), mean ± SD			
Abdomen and pelvis	14.5 ± 5.6		
Lower extremities	10.3 ± 2.4		

Note–all data presented as no. (%) unless otherwise indicated.
SD = standard deviation.

measures derived from imaging is an encouraging first step toward developing automated technologies which may eventually aid clinicians.

In comparing right and left limbs after intervention, significant differences in leg volume and skin thickness remained, but the water content of fat was no longer significantly different. In comparing the pre- and poststent CT venography studies of the affected left leg, a significant decrease was detected in the percent water content of fat after stent administration. These preliminary findings suggest that stent placement decreases the water content of fat in the lower extremity, as assessed by an AST. Chronic iliac vein compression leads to an inflammatory cascade of vein wall fibrosis, valvular dysfunction, reflux, and chronic venous insufficiency (17), which in turn trigger proliferation of adipocytes, deposition of collagen fibers, and expansion of the interstitial fluid volume (18). Stent administration may lead to improvement in the interstitial fluid volume, as evidenced by the reduction seen in the water content of fat. The water content of fat as measured by assessment of HU is a potential imaging measure of disease severity and post-intervention improvement. Further investigation of a larger cohort, with longer follow-up, correlating these imaging findings to clinical improvement would help elucidate if such technology would be useful in clinical practice.

The water content of the unaffected right leg also decreased after stent placement in the diseased left leg, albeit to a lesser degree than in the left leg. The authors hypothesize that water content could have decreased bilaterally after unilateral stenting because of an increase in ambulation following intervention and consequent symptomatic improvement. Stimulation of the calf muscle pump via increased ambulation can aid in peripheral edema reduction (19).

The volume of the left leg did not decrease significantly after stent placement. Patients with nonthrombotic iliac vein compression suffer from chronic venous insufficiency, which can overwhelm lymphatic drainage capabilities and can in turn lead to secondary lymphedema (20); in contradistinction, primary lymphedema is a result of defective lymphatics or direct damage to the lymphatic system. That the left leg volume did not decrease significantly in this cohort may reflect irreversible skin and adipose hypertrophy, stemming from longstanding secondary lymphedema (21); the preintervention duration of swelling in the cohort ranged up to 12 years. Another possibility could be the short (3-month) follow-up duration because significant changes in leg volume may only manifest after a longer follow-up period. Changes in skin thickness were also not appreciable after stent placement, which may similarly be due to irreversible changes or the relatively short follow-up period.

There were no significant differences in the poststent reduction in water content of fat, leg volume, or skin thickness, between the patients with and without postthrombotic iliac vein occlusion. The lack of statistical significance may be attributable to the small sample size because there were only 5 patients who had nonthrombotic iliac vein compression without postthrombotic disease. It is also possible that, in some of the patients without postthrombotic disease, the nonthrombotic iliac vein compression was not physiologically significant. Even though all of the stents for the patients without postthrombotic disease remained patent at follow-up, 3 of the patients experienced only partial improvement in swelling, whereas 2 had no improvement whatsoever. It is institutional practice to only place stents if there is a high clinical likelihood (as assessed by the provider) that the intervention will achieve any benefit, and only if a vein has >70% stenosis or <4-mm axial diameter (12).

All 3 measures of disease severity decreased after intervention for both patients with and without postthrombotic iliac vein occlusion, with the exception of leg volume in the subgroup of patients without postthrombotic disease, which increased by approximately 3%. The small sample size and relatively modest increase in leg volume suggest an incidental finding within the range of normal variance, rather than a clinically important outcome.

This study has several limitations. The cohort size (n = 21) was relatively small, and there was an approximately 3:1 ratio of postthrombotic to nonthrombotic lesions, limiting deeper assessment of the nonthrombotic cohort. This study was constructed to provide proof of concept, rather than to develop detailed criteria for the quantitative analysis of lower extremity images, or to suggest AST technology for use in clinical practice. Because of the retrospective nature of this study, patient follow-up duration was not standardized; standardized follow-up for a protracted period would potentially allow for the detection of more quantifiable changes in disease severity, particularly in cases with persistent limb hypertrophy and skin thickening from longstanding venous obstruction. It was also not possible to obtain validated measures of preintervention venous disease severity (eg, Villalta; clinical grade, etiology, anatomy, pathophysiology; Venous Clinical Severity Score) for the cohort because these values were not systematically collected during clinic visits until 2015. Instead, symptoms were characterized and quantified wherever possible (eg, duration of swelling).

Approximately 70% of patients with postthrombotic iliac vein occlusion and 100% of the patients without thrombotic disease used compression stockings. All such patients reported consistent compression stocking use, both before and after stent placement, and unilaterally on the left side. Given the small cohort size, the consistency of stocking use, the relatively low percentage of patients who did not use stockings, and the preliminary nature of this study, compression garment use was not controlled for in assessing the AST results. Similarly, only 1 patient with postthrombotic iliac vein occlusion received a superficial vein treatment (vein stripping procedure) before the study period. A larger cohort would allow for the statistical assessment of such potential cofounders. All stents maintained either primary or primary assisted patency at the time of follow-up scan, and so it is unlikely that stent reocclusion affected any of the results.

This study demonstrates how an AST can be used to quantify and compare pre- and poststent measures of disease severity on CT venography for patients with iliac vein lesions. The algorithm is able to clearly detect pathologic limbs and can detect some changes in parameters between pre- and poststent images using the 3 proposed measures of disease severity. At present, these measures serve only as surrogate measurements for clinical improvement rather than true markers of clinical improvement; current use of this technology is investigational. Further application of the algorithm to a larger image dataset over a protracted follow-up period will allow for better correlation of imaging findings to clinical outcomes.

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