Diagnosis of chronic iliac venous obstruction

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ABSTRACT

Stenting has become the first line of treatment for symptomatic chronic iliofemoral venous obstruction in patients with quality-of-life-impairing clinical manifestations who have failed conservative therapy. Patient selection for such intervention is, however, dependent on clear identification of relevant clinical manifestations and subsequent testing to confirm the diagnosis. In this regard, the physician engaged in management of such patients needs to be well-aware of symptoms and signs of chronic iliofemoral venous obstruction, and instruments used to grade chronic venous insufficiency and determine quality of life, in addition to diagnostic tests available and their individual roles. This review serves to provide an overview of the diagnosis of chronic iliofemoral venous obstruction and patient selection for stenting. (J Vasc Surg Venous Lymphat Disord 2024;12:101744.)

Keywords: May Thurner syndrome; Post thrombotic syndrome; Non thrombotic iliac vein lesion; Iliofemoral venous obstruction; Iliac vein stenting

Venous stenting for chronic iliofemoral venous obstruction (CIVO), has supplanted open surgery as the first line of treatment for patients with symptomatic disease who have failed conservative therapy. Such therapy includes the regular use of compression stockings, leg elevation when feasible, regular walking for exercise as tolerated, and antithrombotic therapy when appropriate. Additionally, for patients with phlebolymphedema due to CIVO without evidence of tissue damage, recent data has shown that complex decongestive therapy can help provide symptomatic relief. Over the last 20 years, multiple publications have demonstrated not only the safety and efficacy of such stenting, but more importantly, excellent long-term outcomes in terms of clinical and quality of life improvement in addition to stent patencies.[1-4] Over this period, the role of intravascular ultrasound (IVUS) in confirming the diagnosis of CIVO has also been affirmed.[5-8] However, IVUS interrogation is an invasive option and must be preferably preceded by other diagnostic studies when CIVO is suspected on history and physical examination. Such noninvasive options that have been explored over time include hemodynamic evaluation, duplex ultrasonography, and cross-sectional imaging (computed tomography and magnetic resonance imaging), besides the more invasive on-table venography. This review goes over the clinical presentation and diagnostic modalities available for the assessment for CIVO and the evidence behind them and proposes an algorithm for the diagnosis of CIVO.

DIAGNOSTIC EVALUATION

Clinical assessment

A thorough history and physical examination is important in not just diagnosing CIVO, but also in quantifying the impact of the clinical presentation on the patient's quality of life (QoL). In this regard, pertinent information should be obtained with respect to symptoms, their severity and their duration, presence of a personal or family history of venous thromboembolic event/thrombophilia, use of anticoagulation, prior venous interventions, other medical comorbidities, and the ambulatory status of the individual. Relevant symptoms can include pain, swelling, heaviness, tiredness, and leg cramps. Signs include varicose veins (potential collateral flow indicator), hyperpigmentation of the skin, lipodermatosclerosis, and venous leg ulcers. Two other manifestations that must be paid attention to include venous claudication (bursting calf pain/tightness with ambulation/running) and venous hypertension syndrome (leg pain/heaviness/tightness that occurs with dependency—sitting/standing and relieved by recumbency). Another clinical situation that may be related to CIVO is the presence of manifestations of pelvic venous disorders. These include symptoms like chronic pelvic pain and dyspareunia and should be investigated further. This aspect is covered as a separate entity in another publication that is part of the supplement. There are multiple validated classification systems/scoring instruments available to objectively or

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X

https://doi.org/10.1016/j.jvsv.2023.101744

semi-objectively assess chronic venous insufficiency, including the Clinical, Etiology, Anatomy and Pathophysiology (CEAP) classification system, Venous Clinical Severity Score (VCSS), and Villalta-Prandoni score (for post-thrombotic syndrome [PTS]). For venous disease-specific QoL assessment, there exists the Chronic Venous Insufficiency Questionnaire (CIVIQ)-20/CIVIQ-14 instrument and the VEINES (Venous Insufficiency Epidemiological and Economic Study on Quality of Life/Symptoms) instrument.

The CEAP classification was originally developed in 1993, updated in 1996, revised in 2004, and updated again in 2020.[9] The classification describes the clinical presentation of each limb at the time of examination, etiology of the pathological condition (congenital/primary/secondary/no identifiable cause), anatomy of venous involvement (superficial/perforator/deep/no identifiable location), and pathophysiology (obstruction/reflux/combined/no identifiable pathophysiology). The latest version has changes that include incorporation of corona phlebectatica as the C4c clinical subclass, expansion of secondary etiology into intravenous and extravenous causes, besides replacement of numeric descriptions of the venous anatomic segments by their common abbreviations.[9] Advantages of the CEAP classification include that the basic version is simple and easy to use, with an intraobserver reproducibility of 85% and good correlation with generic/disease-specific QoL and venous reflux.[10] Limitations include that it does not contain a specific description of some symptoms (eg, leg pain [low content validity]), static nature of the description (longitudinal follow up not possible), and a low interobserver reproducibility of 47%.[10,11]

The VCSS combines patient-reported and physician-identified items using a 30-point score based on 10 items that includes 0 to 3 point range.[12] These items include venous pain/discomfort, varicose veins, venous edema, skin pigmentation, inflammation, induration, active ulcer number, active ulcer duration (longest), active ulcer size (largest), and use of compression therapy. The revised version (rVCSS) seeks to improve its applicability.[13] Advantages of the VCSS include that it complements the CEAP classification, has good correlation with QoL measures, and can measure outcomes/clinical response over time.[14,15] Limitations include that certain symptom including claudication and paresthesias that can be seen in chronic venous insufficiency (CVI) are not included in the assessment. It is also weighted towards later stages of CEAP classification and lacks precision in assessing skin changes (dermatitis or hypodermic inflammation).[16]

The Villalta-Prandoni scale was originally published as an abstract in 1994 and includes five symptoms and six signs, with each item rated on a 4-point scale (0 to 3).[17] The symptoms are pain, cramps, heaviness, paresthesias, and pruritus, whereas the signs are pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, and pain on calf compression. If the total score was greater than 5 or an ulcer was present, a diagnosis of post thrombotic syndrome was made in that limb.[17] Advantages include that it combines symptoms/signs with grades, enabling assessment of severity/long-term follow-up. It also has excellent interobserver reliability and good correlation with QoL measures (Short Form-36 [SF-36], EuroQol-5D [EQ-5D]).[16] Limitations include that the symptoms/signs are all not specific for venous disease, it is unable to assess venous claudication, and that it has not been validated for non-PTS conditions. Additionally, even for PTS, the Villalta-Prandoni instrument has been reported to be overly sensitive to mild/moderate disease and less sensitive to severe disease.[18]

Venous disease-specific QoL measures relevant to CVI include the Venous Insufficiency Epidemiological and Economic Study on Quality of life/Symptoms (VEINES—QOL/Sym) and the CIVIQ.[19] The VEINES—QOL/Sym uses a 26-item VEINES-QOL/Sym, of which 21 items relate to symptoms,[10] limitations in daily activities,[9] time of day of greatest intensity,[1] and change over the past year,[1] whereas five items cover psychological impact. Rating is on a 2-point to 6-point response scales with the time frame covered being over the past 4 weeks.[19] Two scores are computed: the first is the VEINES-QOL score (25 items), which provides an estimate of the overall impact of venous disease on the patient's QoL, and the second is the VEINES-Sym score (10 items) which measures symptom severity. Advantages include its ease of use, applicability across multiple languages, coverage of a wide spectrum of venous disease, and that the reliability and validity of the instrument has been thoroughly evaluated.[16,20] Limitations include that it excludes anatomical and physiological parameters (guide treatment choice), is unable to assess responsiveness to different treatments, and is unable to measure clinical differences between populations.[16]

The CIVIQ is of two types: the CIVIQ-20: a 20-item questionnaire across four dimensions (pain, physical, psychological, and social) and the CIVIQ-14: a 14-item questionnaire across three dimensions (pain, physical, and psychological).[21-23] Scores are computed for each dimension in addition to a Global Index Score. Advantages include that it has good validity and responsiveness, is a reliable scale for both discriminative and evaluative results, and has undergone linguistic validation.[16,24] Shortcomings include that it has been validated for use in C0 to C4 patients, although studies have used them in more advanced disease. Additionally, there is factorial instability of the CIVIQ-20 social dimension in different populations, which makes the CIVIQ-14 a better instrument in this regard.[23]

Hemodynamic evaluation

The two criteria that hemodynamic testing, like other diagnostic tools for CIVO, need to satisfy are: first, to determine if iliofemoral obstruction exists, and second,

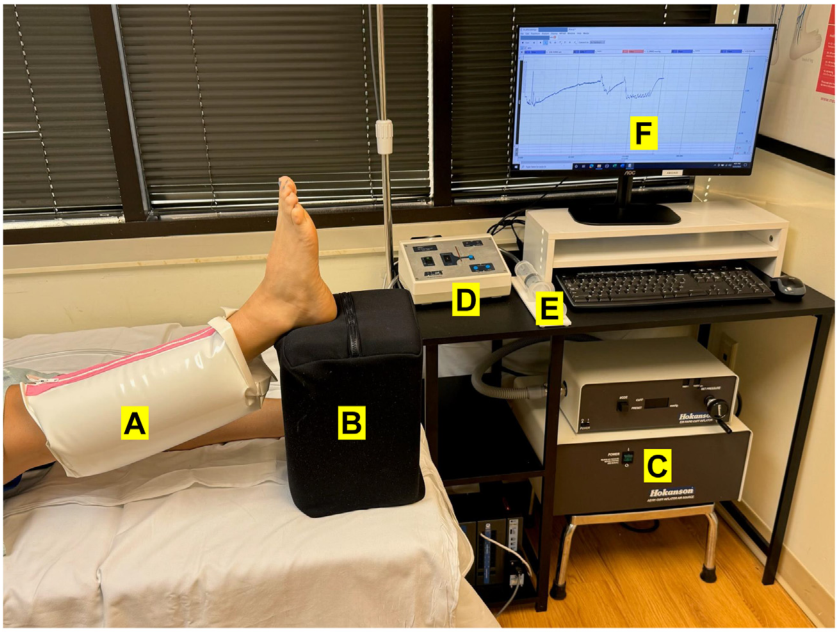

Fig 1. Venous occlusion air plethysmography (APG) device including the air chamber **(A)**, heel support **(B)**, rapid cuff inflation system **(C)**, control panel **(D)**, calibration syringe **(E)**, and output plot generation **(F)**. Control panel (ACI Corp); Rapid cuff inflation system (D. E. Hokanson, Inc). (Image Courtesy - Tracy Patridge, RVT and Alisha Cichirillo, RVT; The RANE Center, Jackson, MS)

to see if the obstruction is adequately compensated or not. There are a variety of measures to evaluate if obstruction exists. These include through use of venous occlusion air plethysmography (venous drainage index, limb outflow resistance, limb outflow fraction), foot venous pressures (supine, upright, and ambulatory), femoral and caval venous pressures, hand foot pressure differential, and pressure response to hyperemia. Fig 1 depicts the venous occlusion air plethysmography (APG) device.

The venous drainage index (VDI) was postulated by Latimer and colleagues, and is based on the finding that venous collapse occurs with leg elevation, this leads to calf volume decrease, and the rate of calf volume decrease is dependent on the degree of proximal venous obstruction.[25] This can be quantified using an APG sensor cuff around the calf. Their work resulted in the generation of two variables, the VDI and the drainage reserve volume. The steps involved include calibration of the device with the heel elevated to 20 cm. This is followed by the drainage position where the leg is elevated, and a baseline volume trace is noted. The patient is then asked to stand upright with the weight on the contralateral leg, which enables generation of the venous filling index. The patient is then returned to the drainage position, which enables the calculation of the VDI (unobstructed). The patient is then made to stand again, and a circumferential pneumatic cuff is applied to obstruct the thigh veins, and tracing is allowed to reach a steady filling plateau. The cuff is then inflated again, the patient returned to the drainage position, and the VDI (obstructed) is calculated. The VDI equals 90% of the venous drainage volume/time it takes for the 90% of the volume to drain.[25] Venous drainage volume is the difference between the venous drainage volume unobstructed and the venous drainage volume obstructed. In their study, they were able to find that the greater the obstruction pressure, the less the venous drainage volume, and consequently, the higher the drainage reserve volume.[25] The authors also evaluated the role of VDI in patients undergoing stenting for CVI. They noted that VDI improved in 10 of 14 limbs that underwent stenting, recording a more than two-fold increase in drainage ($P = .02$).[26]

Adapting the thigh cuff occlusion technique[27-31] for APG, Nicolaides and colleagues were able to determine limb outflow resistance.[32] Steps involved include initial assessment of venous reflux through the venous filling index (VFI 90), followed by evaluation of the pressure-volume relationship for the leg through a stepwise deflation of the thigh cuff from 80 mm Hg in decrements of 10 mm Hg. The outflow curve is then plotted by sudden deflation of the thigh cuff (from 80 mm Hg) and allowing the plot to reach a plateau. The limb outflow resistance is then calculated as the ratio of the pressure to flow for a given thigh cuff (obstruction) pressure.[32] When resistance to flow at different pressures were studied, the authors found that the limb outflow resistance (LOR) was most discriminative for a thigh cuff pressure of 25 m Hg (LOR 25). A high LOR 25 was indicative of benefit with stenting and combined with VFI 90 it can give relative contribution of obstruction and reflux for the limb being studied.[32] However, evaluation of LOR 25 in a large sample with iliofemoral obstruction and response of the metric to stenting has not yet been studied.

Another hemodynamic metric that has been evaluated is outflow fraction, which was initially studied, using venous occlusion plethysmography, by Christopoulous and colleagues.[33] This involves the standard APG setup, with a circumferential pneumatic cuff applied to obstruct the thigh veins. The cuff was inflated to 80 mmHg and suddenly deflated. The outflow fraction is the ratio between the volume expelled in 1 second by the total venous volume × 100.[33] This metric has been evaluated in a publication by Kjurstens and colleagues, where they studied the role of hemodynamic measurements by APG in diagnosing venous obstruction of the lower limb.[34] They evaluated the relation between outflow fraction, ejection fraction, and residual volume fraction determined by APG and the presence of chronic deep venous obstruction. They found that outflow fractions of <28% and <38% were both found to have poor sensitivity but high specificity in determining obstruction.[34] A problem specific to the venous occlusion plethysmography technique is that the thigh cuff creates a reservoir that fills when the cuff is released, lending error to the calculations. Given the variation in the volume of this reservoir from limb to limb, it is hard to correct for.

Foot venous pressure has been evaluated in a few studies. It involves cannulation of a dorsal foot vein, and measurement of supine and upright foot venous pressures in the respective positions. Ambulatory foot venous pressure (AVP) is recorded at the end of 10 tiptoe movements.[35] Raju et al, in a recent study, found that supine foot venous pressure is associated with obstruction and does not worsen with reflux.[36] Upright foot venous pressure, on the other hand, worsens in severe reflux categories.[36] With regard to ambulatory venous pressure, although Welkie et al found that patients with deep venous obstruction had higher AVP,[37] Raju and colleagues found that AVP drop is normal in limbs with IVUS-defined iliofemoral obstruction without reflux.[38]

Femoral venous pressure gradient and femorocaval pressure gradients were evaluated by de Almeda and colleagues.[39] Although they found that there was correlation between venous pressure gradients and significant obstruction diagnosed on IVUS, this correlation did not translate into good diagnostic performance of the venous pressure gradients. Femoral venous pressure at rest and with reactive hyperemia and femoro-caval gradient after reactive hyperemia all had sensitivities that were quite low, ranging from 16% to 35%, whereas their specificities were high.[39] Femoral venous pressure measurements were also evaluated in a paper by Albrechtsson and colleagues, who found that the degree of obstruction to venous flow was best evaluated by measuring the pressure elevation and pressure difference after exercise and the time required for these parameters to return to pre-exercise levels.[40] Pressures during rest and exercise were less conclusive indicators of obstruction.[40] Kjurstens and colleagues noted a drop in the common femoral venous pressure with treadmill stress test that occurred at 3 months post stenting.[41] They observed that stenting of post thrombotic chronic iliofemoral venous obstruction significantly reduces venous hypertension and correlates with improvement in QoL.[41] As far as other hemodynamic metrics go, hand-foot pressure differential was found to be significant predictor of iliofemoral obstruction, whereas hyperemia pressure increase was not found to be a predictor of such obstruction.[1] With regard to determination of compensation of obstruction through collateralization, this can possibly be determined from limb outflow resistance; however, compensatory increase in lymphatic flow cannot be determined through use of hemodynamic testing.

Another hemodynamic modality that is being evaluated involves the use of magnetic resonance imaging. Chen and colleagues found that, in limbs with iliac vein stenosis, the presence of collateral vessels and decreased flow rate due to stenosis correlated significantly with lower limb symptom severity.[42] They found that a decreased iliac venous flow rate could indicate a better response to stent implantation.[42] The different hemodynamic tests are considered in Table I.

The shortcomings of hemodynamic testing include the inability to consistently diagnose obstruction due to lack of standardization, poor reproducibility, and patient-related factors (unexpected limb movement/difficulty in standing). Additionally, correlation between the APG-derived metrics and femoroiliocaval obstruction has been inconsistent. Hemodynamic testing is also unable to determine cause or location of obstruction. There is the problem of potential obstruction of lymphatic flow by the thigh cuff. Correlation of hemodynamic metrics with clinical assessment parameters including VCSS, visual analog scale pain score, QoL metrics, and IVUS-determined degree of obstruction also remains to be evaluated. Although no test is currently available that can reliably assess the hemodynamic impact of CIVO, alternative modalities, such as imaging tests, including IVUS, are unable to give any assessment of physiological significance of CIVO, or its impact on venous return and venous pressure changes. This is a fundamental challenge that needs to be addressed in the future.

Laboratory testing

This should focus on the evaluation of systemic problems, including but not limited to, those of cardiac, renal, or hepatic origin that could mimic the clinical manifestation of

Table I. Hemodynamic studies utilized in the diagnosis of chronic iliofemoral venous obstruction (CIVO)

Hemodynamic evaluation					
Study	**'n'**	**Patients**	**Metric evaluated**	**Comparator**	**Outcome**
Latimer et al[25]	21 limbs	Limbs without venous disease	Venous drainage tracings were obtained with APG using a dependency to elevation maneuver on limbs of 21 volunteers without venous disease APG thigh cuff inflation at 10, 20-, 30-, 40-, and 50-mmHg. VDI and DRV were obtained.	None	The VDI represents the gravitational venous drainage rate of the leg. The DRV is the undrained venous volume caused by the obstruction from an inflated thigh cuff. Both demonstrated a positive correlation with venous obstruction pressures.
Nicolaides et al[32]	30 limbs	15 limbs without and 15 limbs with iliac vein obstruction	LOR was measured at different venous pressures using occlusion APG. Reflux in ml/sec (VFI) and VCSS were measured in all limbs.	None	The combination of LOR_{25} with VFI enables determination of the relative contribution of reflux and obstruction in individual limbs.
Kjurstens et al[34]	312 limbs	Tertiary, outpatient clinic patients with chronic venous complaints	APG assessed OF, EF, and RVF. Diagnostic tests were assessed for obstructions at different levels of the deep venous system.	DUS and MRV	Poor correlation between OF, EF, or RVF, determined by APG, and the presence of chronic deep venous obstruction
Raju et al[36]	4291 limbs	Patients with CVD	Subset A limbs: mix of obstruction/reflux or neither (n = 4132). Subset B limbs: central obstruction (n = 159) and had IVUS-proven stenosis in the iliac veins corrected by stent placement. Reflux assessed by duplex ultrasound and APG (VFI 90). Foot pressure measurements included supine, erect, and AMVPs	IVUS	Supine venous hypertension associated with obstruction and does not worsen with reflux. Erect foot venous pressure worsens in severe reflux categories. Ambulatory venous hypertension worsens with increasing reflux and higher CEAP clinical classes and dominantly associated with reflux, not obstruction
Welkie et al[37]	330 limbs	274 limbs with CVD and 56 limbs in symptom-free volunteers	Each limb was assessed for functional venous volume, degree of valvular insufficiency, efficiency of the calf muscle pump, and noninvasive estimate of AMVP.	None	With progression of CVD venous volume expands, valvular function deteriorates, the calf muscle pump becomes inefficient, and ambulatory venous hypertension develops. Once extremities develop brawny edema or hyperpigmentation, further deterioration of limb hemodynamics does not occur. RVF offers a reliable noninvasive estimate of ambulatory venous pressure

(Continued on next page)

Table I. Continued.

Hemodynamic evaluation					
Study	**'n'**	**Patients**	**Metric evaluated**	**Comparator**	**Outcome**
de Almeda et al[39]	100 limbs	Patients with CVD	Venography and intravenous pressure measurements were performed in Group I, limbs with <50% (n = 49); Group II, limbs with >50% obstruction on IVUS (n = 51). Receiver operating characteristic curves compared the diagnostic performance of the VPGs. Logistic regression assessed the capacity of the VPGs to identify significant obstruction.	IVUS	There is a positive correlation between the VPGs and significant iliac vein obstruction. However, it does not translate to a good diagnostic performance. Only the femoro-caval gradient after reactive hyperemia added significant information to MRV in identifying significant caval-iliac vein obstructions when compared with IVUS.
Albrechtsson et al[40]	100 limbs	Post thrombotic limbs	Femoral vein pressure was measured in patients with post thrombotic venous disease with a duration of 6 months to 6 years. The examination was performed on a tiltable x-ray table. Intravenous pressure was recorded in the supine patient, at rest, during exercise consisting of 20 powerful contractions of the calf muscles and immediately after exercise	None	Good correspondence noted between femoral vein pressure and the severity of post-thrombotic symptoms. The degree of obstruction to venous flow was best evaluated by measuring the pressure elevation and pressure difference after exercise and the time required for these parameters to return to pre-exercise levels. Venography provided largely morphologic, rather than functional information.
Kjurstens et al[41]	12 limbs	Post thrombotic limbs	Treadmill stress test with invasive pressure measurements in the common femoral vein and dorsal foot veins of both affected and non-affected limbs, performed the day before and 3 months after stenting the obstructed tract	None	Stenting of post-thrombotic iliofemoral obstruction significantly reduces venous hypertension in the common femoral vein and correlates with an improvement in the QoL.
Chen et al[42]	69 limbs	Patients with CVD	Stenosis severity, the presence of collateral vessels, and FR differences between the CIV and EIV were measured using MRI and correlated with symptom severity including a subgroup of patients that underwent iliac vein stenting.	None	Iliac vein stenosis, collateral circulation, and decreased iliac vein flow correlated with the severity of lower limb venous symptoms in patients with decreased iliac vein flow as measured by MRI, possibly indicating a better response to iliac vein stenting in patients with MRI-measured decreased venous flow.

AMVP, Ambulatory venous pressure; *APG*, Air plethysmography; *CVD*, chronic venous disease; *CIV*, common iliac vein; *DRV*, drainage reserve volume; *DUS*, duplex ultrasound; *EF*, ejection fraction; *EIV*, external iliac vein; *FR*, flow rate; *IVUS*, intravascular ultrasound; *LOR*, limb outflow resistance; *MRI*, magnetic resonance imaging; *MRV*, magnetic resonance venography; *OF*, outflow fraction; *RVF*, residual volume fraction; *QoL*, quality of life; *VCSS*, Venous Clinical Severity Score; *VDI*, venous drainage index; *VFI*, venous filling index; *VPG*, venous pressure gradient.

CIVO. Details of such clinical evaluation and testing are, however, beyond the scope of this manuscript. If intervention is planned for the obstruction, then workup including a complete blood count and basic metabolic panel besides a coagulation panel would be indicated. In patients with a history of unprovoked venous thromboembolic event (VTE) and/or with a strong family history of VTE, a thrombophilia panel may be indicated per guidelines.

Diagnostic imaging

Duplex ultrasound. Duplex ultrasound (DUS) represents a noninvasive and readily available test for diagnosis of iliofemoral venous obstruction. However, it has some limitations, including lack of consistent visualization of the iliac segments on account of bowel gas and/or truncal obesity. Additionally, there is a learning curve associated with being able to perform an adequate evaluation of the iliocaval segment. A recent study had raised concern for dimensional disparity when compared with IVUS, the current gold standard for diagnosis of chronic iliofemoral venous obstruction. On comparing DUS-determined luminal diameters converted to area with IVUS-determined luminal area, Raju et al found that DUS measurements of common iliac vein (CIV) and external iliac vein (EIV) segments were smaller than IVUS-derived luminal areas by a mean of 54 mm^2 and 34 mm^2, respectively.[43] This would mean that DUS overestimated stenosis when compared with IVUS. However, on comparing DUS-derived minimum diameter to IVUS-derived minimum diameter of the CIV segment, Villalba and Larkin found moderate correlation between the two ($r = 0.383$; $P = .009$).[44] A problem with DUS, unrelated to the technology itself, is the diagnostic criteria used. Utilization of the 50% stenosis criterion for correction of stenosis is in common use.[45] The problem with this criterion is that venous stenosis, especially in post-thrombotic patients, can often be long, diffuse stenosis involving entire venous segments (ie, entire CIV or EIV). Focal lesions generally tend to be non-thrombotic in nature (non-thrombotic iliac vein lesions). Additionally, stenosis of the contralateral iliofemoral segment is not uncommon.[46] So, use of an adjacent or contralateral 'normal' segment to determine stenosis can lead to an erroneous diagnosis. Secondly, the 50% stenosis concept is carried over from the arterial system where there is a 'critical stenosis' beyond which compensatory mechanisms fail. However, in the venous system, there is continuous rise in venous pressure without a 'critical' stenosis set point.[47] Whether a given degree of stenosis leads to manifestation of symptoms/signs in a given individual depends on multiple mechanisms. These include compensatory mechanisms like collateral venous blood flow and lymphatic flow. Both vary from individual to individual. Additional factors that contribute to clinical manifestation include the status of the calf pump and the compliance/capacitance of the deep veins in the extremity. Quantification of each of these factors in terms of being able to prognosticate symptom/sign manifestation has not yet been possible, given the complex interactions between the four. So, for now, we are left with having to use the metric of significant QoL-impairing symptoms/signs that persist despite optimal conservative therapy to guide IVUS interrogation to confirm diagnosis and stenting. Suffice to note that the utilization of the 50% stenosis criterion does not have any validity in the venous system.

Computed tomography. Computed tomography venography (CTV) can define the location, degree, and extent of chronic iliofemoral venous obstruction,[48,49] in addition to determining presence of collaterals.[50] Current acquisition and postprocessing capabilities (multiplanar reconstruction evaluation and image processing, volume rendering, maximum intensity projection) can help determine and classify characteristics of the lesion. It can also identify extravascular structures that may be responsible for the compression and obstruction.[51-54] The modality can also identify the presence of congenital anatomical variations found in 20% of such patients.[55] Although multiple studies have compared CTV with IVUS, in the diagnosis of CIVO, there is wide variation in assessment of stenosis. Raju et al, making comparisons using luminal diameter stenosis in the CIV and EIV, noted a single-segment diagnostic sensitivity of 83% and 73% in the CIV and EIV, respectively. This sensitivity, however, increased to 97% when at least one of the two segments was considered diagnostic of iliac vein stenosis.[53] In another study, Rossi et al, using luminal diameter to determine stenosis, found that CTV had a sensitivity and specificity of 94% and 79.2% to detect stenosis of 50% or greater.[51] A study by Toh and colleagues, using planimetric area computations of both CTV and IVUS, found a correlation coefficient of 0.57 ($P < .005$), with area measurements on CTV being larger than those obtained from IVUS.[56] A similar result was obtained in the study by Shammas et al in 96 patients, where the authors noted that mean percentage stenosis on CTV and mean percentage stenosis on IVUS were not statistically different, despite an overestimation of minimal luminal area by CTV when compared with IVUS.[52] Jayaraj et al used three-dimensional CTV reconstructions utilizing center line measurements and planimetric area computations to determine diagnostic characteristics for CIVO and found a sensitivity of diagnosing stenotic lesions in the CIV, EIV, and common femoral vein (CFV) of 100%, 100%, and 80%, respectively. In their results, the authors noted an overall accuracy of three-dimensional CTV in determining stenosis of 91%, 86%, and 82% in the CIV, EIV, and CFV segments, respectively.[54] In essence, CTV diameter or luminal area measurements appear to have good correlation with IVUS. But given the discrepancy between studies, in patients with symptoms suggestive of CIVO not responding to conservative therapy, consideration should be given to IVUS evaluation even if the CTV is negative or equivocal.

Magnetic resonance imaging. Few studies have compared magnetic resonance imaging to IVUS, the gold standard for diagnosis of CIVO. Massenburg et al used subjective aspects (images were subjectively scored by a blinded physician as being normal, suspicious for obstruction, or definitely abnormal) to compare magnetic resonance venography (MRV) with IVUS and found that MRV had a sensitivity of 100% and specificity of 22.7% in the diagnosis of iliac vein stenosis.[57] Kusiak and Budyziksky evaluated 18 limbs with post thrombotic syndrome that underwent MRI and IVUS by comparing iliofemoral venous luminal areas on non-contrast-enhanced MR (NCE MR) and contrast-enhanced MR (CE MR) with IVUS. They noted strong correlation between luminal areas obtained on CE MR and NCE MR (r = 0.87-0.97; $P < .001$), but weak correlation between either CE MR or NCE MR and IVUS (correlation coefficient, −0.28 to 0.47; $P > .05$).[58] Saleem et al evaluated the EIV and CIV segments in 61 patients using luminal diameter conversion to area (πr^2), using the smallest diameter in these segments on MR and comparing it with IVUS luminal area. They found that MRV had a sensitivity of 93% and 100%, and a specificity of 0% and 50% for the CIV and EIV segments, respectively.[59] How et al, using a relaxation-enhanced angiography without contrast and triggering (REACT) protocol MR, obtained luminal areas of EIV and CIV and compared them with IVUS. The noted that REACT protocol MR had a sensitivity of 96.1% and a specificity of 78.8%.[60] It appears that the utility of MR imaging on the diagnosis of CIVO is dependent on the protocol utilized to image. Further study is clearly required to determine the appropriate protocol to be used.

Role of lymphoscintigraphy. In patients presenting with edema of the lower extremity and symptoms/signs of CIVO, a lymphoscintigram (LSG) should be pursued along with DUS/cross-sectional imaging, given the possibility of phlebolymphedema.[61,62] In limbs with LSG-positive lymphedema who continue to have persistent/residual leg edema with impairment of QoL, complex decongestive therapy can be pursued with likely benefit.[63] Thus, obtaining a LSG in patients presenting with leg edema has both diagnostic and prognostic significance.

Venography. Ascending venography (transfemoral or transpopliteal) serves as a good tool for determining vessel patency and focal stenosis. It is also able to define collaterals, and early collateral filling before the proximal ipsilateral iliac vein is a sign of proximal obstruction, but only in one-third of limbs undergoing such evaluation. It is less able to consistently determine presence of long segment stenosis that is frequently seen in post thrombotic obstruction. Additionally, even focal stenosis can sometime be missed with multiplanar venography. The presence of diffuse stenosis can be missed because the comparator (adjacent 'normal' area or contralateral side) may also be diseased. Multiple studies that compared venography with IVUS found that venography including multiplanar is not a reliable predictor of the location of the iliocaval confluence, presence/location of iliocaval stenosis, or its severity.[6-8]

Intravascular ultrasound. IVUS has become the gold standard for confirmation of diagnosis of femoroiliocaval obstruction with a sensitivity of 90%.[5,64] Its comparative advantages over DUS, cross-sectional imaging, and venography have been noted previously. Once CIVO is suspected in a patient based on clinical presentation and noninvasive diagnostic testing, then IVUS needs to be pursued to confirm the diagnosis. Such interrogation can be used to not only confirm the diagnosis, but also guide correction of the obstruction through stenting in the same session. Although diameters have been used on IVUS to guide the diagnosis, given that the vein lumen is typically not a circle, luminal area represents a better metric. Suggested criteria for diagnosis of iliofemoral venous obstruction is through use of normal minimal luminal areas in the CFV, EIV, and CIV venous segments (125 mm^2 in the CFV, 150 mm^2 in the EIV, and 200 mm^2 in the CIV).[65] Any luminal area below these cutoff areas in one or more segments is suggestive of stenosis and merits stenting in the symptomatic patient who has failed conservative treatment. As noted previously, there is no role for use of the 50% stenosis criterion to guide stenting. In fact, a recent study showed that the 50% stenosis criterion did not correlate with CEAP clinical class, VCSS, QoL, supine foot venous pressure, clinical or QoL improvement post stenting, or stent patency.[66] The different imaging modalities are considered in Table II.

DISCUSSION

Careful assessment of the patients presenting with symptoms/signs of CIVO is essential as the differential diagnoses for symptoms and signs are broad, involving multiple organ systems. It is essential to evaluate each limb using CEAP, VCSS, and the patient's venous disease-specific QoL. This not only helps determine the impact of the CIVO at presentation, but with the VCSS and venous disease-specific QoL metric, assess change over time. Appropriate workup to evaluate other etiologies is crucial if the suspicion for CIVO is low. When CIVO is suspected, then noninvasive imaging studies as a first step are appropriate. This can be DUS combined with a cross-sectional imaging study as long as no contraindications (allergy to contrast medium allergy, renal disease, etc) exist for the latter. Both CTV and MRV can be utilized. It is important to bear in mind the shortcomings of each of these studies as outlined previously. Although DUS can give anatomic information, its utility is more suited to understand flow

Table II. Diagnostic imaging tests used for chronic iliofemoral venous obstruction (*CIVO*)

Diagnostic tests					
Study	**No**	**Patient**	**Intervention**	**Comparator**	**Outcome**
DUS					
Raju et al[43] (Retrospective)	382 limbs	Limbs that had undergone IVUS interrogation for symptomatic CIVO	DUS (Stenotic luminal diameter converted to area)	IVUS (smallest luminal area of CIV and EIV segments)	Duplex yields a smaller cross-sectional image of CIV and EIV compared to IVUS.
Villalba and Larkin[44] (Retrospective)	47 patients	Patients who had undergone IVUS interrogation with intent to treat and DUS for iliac vein obstruction	DUS (% stenosis of L CIV - Comparison to 'normal' CIV diameter caudal to obstruction or contralateral 'normal' CIV diameter or normal minimum luminal diameters [16 mm in CIV])	IVUS (% stenosis based on CIV diameter)	89% agreement between DUS and IVUS for identification of L CIV stenosis of ≥50%. DUS had a PPV of 95.5%
CTV					
Rossi et al (Subgroup analysis of randomized clinical trial)[51]	100 limbs	Limbs undergoing IVUS interrogation for symptomatic CIVO	CTV (% stenosis based on diamet—r - Comparison to minimum iliac vein diameter caudal to obstruction or contralateral iliac vein minimum diameter or normal minimum luminal diameters [12 mm, 14 mm, 16 mm in CFV, EIV, and CIV, respectively])	IVUS (% stenosis based on area)	CTV has sensitivity, specificity, PPV, NPV, and accuracy of 94.0%, 79.2%, 94%, 79.1%, and 86.7%, respectively, to detect stenosis greater than 50%
Shammas et al[52] (Retrospective)	96 patients	Patients who had undergone treatment for iliofemoral venous compression	CTV (Minimal luminal area and % stenosis based on diameter - Comparison to 'normal' iliac vein diameter caudal to obstruction)	IVUS (Smallest luminal area and % stenosis based on diameter - Comparison to 'normal' iliac vein diameter caudal to obstruction)	Weak positive correlation (Spearman's rho, 0.27; P=.01) between minimal luminal area on CTV and IVUS. Moderate positive correlation (Spearman's rho, 0.327; $P < .01$) between % stenosis on CTV and IVUS
Raju et al[53] (Retrospective)	91 limbs	Limbs that had undergone IVUS interrogation for symptomatic CIVO	CTV (Stenotic luminal diameter converted to area)	IVUS (smallest luminal area of CIV and segments)	CTV has sensitivity, PPV and accuracy of 97%, 93%, and 91%, respectively, to detect stenosis when stenosis in at least one of two segments (EIV or CIV) was considered diagnostic of iliac vein stenosis

(Continued on next page)

Table II. Continued.

Diagnostic tests					
Study	**No**	**Patient**	**Intervention**	**Comparator**	**Outcome**
Jayaraj et al[54] (Retrospective)	22 patients	Patients who had undergone IVUS interrogation for symptomatic CIVO	CTV (Minimal luminal area computed from 3D reconstruction)	IVUS (smallest luminal area of CIV, EIV and CFV segments)	CTV has sensitivity of diagnosing CIVO in the CIV, EIV, and CFV of 100%, 100%, and 80%; Specificity of diagnosing CIVO in the CIV, EIV, and CFV of 67%, 57%, and 86%, respectively, and overall accuracy of 91%, 86%, and 82% in the CIV, EIV, and CFV segments.
MR imaging					
Massenburg et al[57] (Retrospective)	46 patients	Patients presenting with symptoms and/or signs of iliac vein obstruction	MR venography (Normal/ Suspicious/ Abnormal based on iliac vein – Stenosis/dilation/ discrepancy of diameter/ collaterals.	IVUS	MR venography had a sensitivity, specificity, PPV, NPV and a FPR of 100%, 22.7%, 58.5%, 100%, and 41.5%, respectively.
Kusiak and Budyziksky[58]	18 limbs	Limbs with post thrombotic syndrome	CE and NCE MR (iliofemoral venous luminal areas)	IVUS (luminal area)	Weak correlation between either CE or NCE MR and IVUS [$r = -0.28$ to 0.47 ($P > .05$)]. Strong correlation between luminal areas obtained on CE and NCE MR ($r = 0.87$ to 0.97, $P < .001$).
Saleem et al[59] (Retrospective)	61 patients	Patients who had undergone IVUS interrogation for symptomatic CIVO	MR venogram (minimum luminal diameter converted to area)	IVUS (smallest luminal area of CIV and EIV segments)	For CIV, sensitivity and specificity were of 93% and 0%, and for EIV sensitivity and specificity were 100% and 0%, respectively.
How et al[60] (Retrospective)	33 patients	Patients who had undergone REACT protocol MR venogram and IVUS	REACT protocol MR (smallest luminal area of CIV and EIV segments; Reference 'normal' iliac vein segment cranial or caudal to obstruction or contralateral iliac vein segment)	IVUS (separate comparison of smallest luminal areas and reference luminal areas of CIV and EIV segments obtained on MR to such areas on IVUS)	MR had a sensitivity of 96.1%, specificity of 78.8%, PPV of 91% and NPV of 90%. Good agreement ($\kappa = 0.779$; $P \leq .050$)

Table II. Continued.

Diagnostic tests					
Study	**No**	**Patient**	**Intervention**	**Comparator**	**Outcome**
Venography					
Gagne et al[6] (Prospective)	100 patients	C4 to C6 venous disease and suspected iliofemoral vein obstruction	MPV (% stenosis – luminal diameter and luminal area)	IVUS (% stenosis – luminal diameter and luminal area)	Compared with IVUS, the diameter reduction was on average 11% less for MPV ($P < .001$). IVUS identified significant lesions not detected with MPV in 26.3% of patients.
Lau et al[7] (Retrospective)	107 patients	C2 to C6 venous disease	Anterio-posterior venography (% stenosis by comparing smallest luminal diameters of CIV, EIV, and CFV segments to reference 'normal' iliofemoral vein segment cranial or caudal to obstruction)	IVUS (% stenosis by comparing smallest luminal diameters of CIV, EIV, and CFV segments to reference 'normal' iliofemoral vein segment cranial or caudal to obstruction)	Sensitivity by stenosis on venography was 4% and 21% in the L and R CIV, 44% and 46% in the L and R EIV, and 44% and 40% in the L and R CFV
Montminy et al[8] (Retrospective)	155 limbs	Patients who had undergone IVUS interrogation for symptomatic CIVO	Anterio-posterior venography (% diameter stenosis calculated by comparing diameter at the level of maximal stenosis of CIV, EIV, CFV, and IVC with the diameter of nearest normal vein in the same segment. Diameter stenosis converted to area $[A = \pi r^2]$ for comparison with IVUS area stenosis data)	IVUS (smallest luminal area of CIV, EIV, CFV, and IVC segments)	AP venography failed to identify stenosis in 19% of limbs. Ilio-caval confluence location on venography was higher with IVUS than with venography in 74% limbs. Median maximal area stenosis significantly higher with IVUS than with venography (69% vs 52%; $P < .0001$).

CE, Contrast-enhanced; *CFV*, common femoral vein; *CIV*, common iliac vein; *CTV*, computed tomography venography; *DUS*, duplex ultrasound; *EIV*, external iliac vein; *IVC*, inferior vena cava; *IVUS*, intravascular ultrasound; *L*, left; *MPV*, multiplanar venography; *MR*, magnetic resonance; *NCE*, non-contrast-enhanced; *NPV*, negative predictive value; *PPV*, positive predictive value; *R*, right; *REACT*, Relaxation-enhanced angiography without contrast and triggering.

characteristics across the iliofemoral venous segment. CTV or MRV can delineate the anatomy and provide information of the location and extent of the obstruction. In essence, the information provided by DUS and cross-sectional imaging tends to be complimentary.

Confirmation of CIVO. It is important to bear in mind that an ideal screening test for CIVO does not exist at this time. So, in patients with a strong clinical suspicion for CIVO who have failed conservative therapy, but in whom DUS and cross-sectional imaging are equivocal, IVUS should be pursued to rule out the diagnosis. Venography, including multiplanar venography, should not be used to replace IVUS as a test for confirmation of diagnosis due to its unreliability in diagnosing CIVO, determining its extent or severity. IVUS criteria for diagnosis of CIVO have to be based on normal minimal luminal diameters or areas in the CFV, EIV, and CIV. Any reduction in the luminal diameter or areas (12 mm/125 mm^2 in the CFV, 14 mm/150 mm^2 in the EIV, and 16 mm/200 mm^2 in the CIV) below these thresholds in a patient with QoL-impairing symptoms not responding to

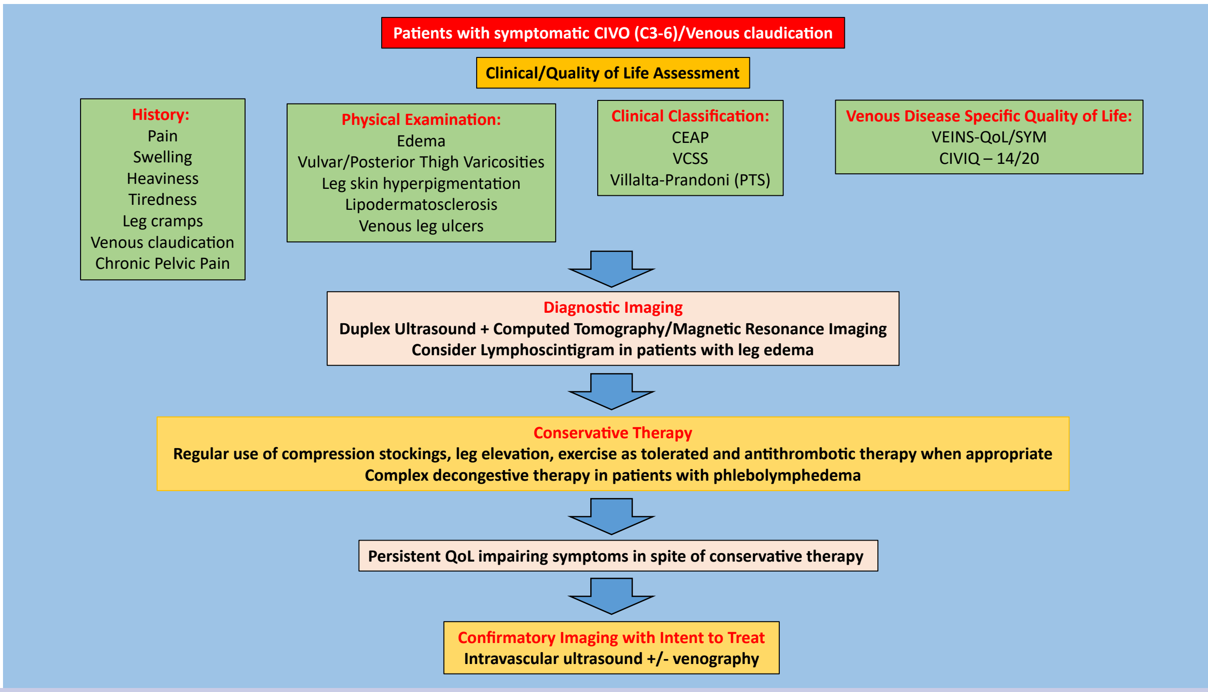

Fig 2. Algorithm for management of chronic iliofemoral venous obstruction (*CIVO*). *CEAP*, Clinical, Etiology, Anatomy and Pathophysiology; *CIVIQ*, Chronic Venous Insufficiency Questionnaire; *PTS*, post-thrombotic syndrome; *QoL*, quality of life; *VCSS*, Venous Clinical Severity Score; *VEINES-QoL/Sym*, Venous Insufficiency Epidemiological and Economic Study on Quality of Life/Symptoms.

conservative therapy requires stenting. There is no role for diagnosis of stenosis based on comparison to ipsilateral or contralateral "normal" segment(s). Nor is there any role for diagnosis of CIVO using the 50% stenosis criterion. As noted previously, there is a continuous rise in venous pressure with stenosis without a set cutoff point (no critical stenosis). So, venous hypertension and its clinical manifestations can develop even when the stenosis is less than 50%. Additionally, an individual can have 70% or 80% stenosis and be asymptomatic due to venous and lymphatic compensatory mechanisms. Thus, there is no role for stenting individuals who are asymptomatic (prophylactic stenting) or who are symptomatic but have not yet tried conservative measures.

An algorithm for the diagnosis of CIVO is suggested in Fig 2.

Future directions. It would be very useful to have a test that is simple, noninvasive, cost-effective, and can assess degree of obstruction, quantify compensatory mechanisms, and prognosticate improvement with intervention. Such a test would need comparisons with IVUS to determine its performance characteristics and represents a work in progress.

CONCLUSIONS

Diagnosis of CIVO involves careful evaluation of clinical manifestations, complimented by appropriate diagnostic testing. The interventionalist should be aware of the performance characteristics of individual diagnostic tests and utilize them to assess whether a patient merits IVUS assessment or not, the gold standard for diagnosis of CIVO. Such IVUS interrogation with the use of normal minimal luminal area should ultimately guide stenting in a patient with QoL-impairing presentation who has failed conservative therapy. There is no indication for IVUS interrogation and/or stenting in an asymptomatic patient (prophylactic) or even a symptomatic patient without QoL-impairing symptoms.

AUTHOR CONTRIBUTIONS

Conception and design: AJ
Analysis and interpretation: AJ, FR, FL, PM
Data collection: AJ, FR
Writing the article: AJ, FR, FL, PM
Critical revision of the article: AJ, FR, FL, PM
Final approval of the article: AJ, FR, FL, PM
Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: AJ

DISCLOSURES

None.

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Submitted Aug 10, 2023; accepted Dec 12, 2023.