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Evaluation of the diagnostic accuracy of contrast enhanced ultrasonography in chronic iliac venous obstruction

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ABSTRACT

Objective: The noninvasive diagnosis of chronic iliac vein obstruction can be challenging. Noninvasive modalities are available, but each has its own merits and drawbacks. Intravascular ultrasound (IVUS) is considered the diagnostic reference standard, but it is invasive. The role of contrast-enhanced ultrasonography in chronic iliac vein obstruction has so far not been studied.

Methods: This is a single-center retrospective study. Thirty-nine patients, suspected to have chronic iliac venous obstruction, underwent unenhanced ultrasonography, contrast-enhanced ultrasonography with Lumason, and IVUS on the same day.

Results: Most of the data set was female, had post thrombotic lesions, and belonged to CEAP Class C4 or higher. The intraclass correlation coefficient (kappa, average measures) between enhanced and unenhanced ultrasonography was 0.9 (95% confidence interval [CI], 0.87-0.92), indicative of very good agreement. However, the correlation coefficients between enhanced ultrasonography and IVUS and unenhanced ultrasonography and IVUS were 0.6 (95% CI, 0.16-0.67) and 0.5 (95% CI, 0.37-0.75), respectively, indicative of less optimal agreement. Considering IVUS as the reference standard, diagnostic accuracies for ultrasonography for external iliac vein with and without Lumason use were 71.3% and 71.4%, respectively. Diagnostic accuracies for ultrasonography for common iliac vein with and without Lumason use were 53.2% and 56.7%, respectively, when compared with IVUS.

Conclusions: The measures of diagnostic accuracy of contrast-enhanced ultrasonography and unenhanced ultrasonography are similar to each other in the diagnosis of chronic iliac vein obstruction when compared with a reference standard such as IVUS. Further studies are needed to delineate the complimentary value of contrast-enhanced ultrasonography in the diagnosis of chronic iliac vein obstruction. (J Vasc Surg Venous Lymphat Disord 2025;13:102001.)

Keywords: Chronic iliac vein obstruction; Contrast-enhanced ultrasonography; Intravascular ultrasound; Lumason; Noncontrast-enhanced ultrasonography

Chronic iliac vein obstruction (CIVO) plays an important role in the pathology of chronic venous disease. However, despite the advances in technology, the noninvasive diagnosis of CIVO remains challenging in some patients.[1] Several different noninvasive modalities can be utilized in the diagnosis of CIVO, but each modality has its own merits and drawbacks. These modalities include computed tomography venography (CTV), magnetic resonance venography (MRV), and duplex ultrasonography (DUS). Intravascular ultrasound (IVUS) is the reference standard in the diagnosis of CIVO.[2]

CTV has shown good dimensional parity with IVUS,[2-6] but its use involves contrast, time delay in scheduling, and radiation exposure. Additionally, the quality of the image is dependent on the timing of the contrast injection. Both MRV and DUS have shown dimensional disparity with IVUS in limited studies.[2,7-10] MRV is less readily available than CTV and DUS and often involves even more scheduling delays than CTV. MRV has a high sensitivity but low specificity when compared with IVUS examination and overestimates the severity of the stenosis in both the external iliac vein (EIV) and common iliac vein (CIV).[10]

DUS is noninvasive, inexpensive, and readily available. It is particularly well-suited to be a reasonable screening tool for CIVO. However, in our experience, DUS yields a smaller cross-sectional image of the CIV and EIV compared with IVUS.[7] Some of the other drawbacks with the use of DUS include operator dependence, difficulty in visualization due to body habitus, bowel gas, vessel depth, or tortuosity.[7]

Lumanson (sulfur hexafluoride lipid-type A microspheres) is an agent used in contrast-enhanced ultrasonography (CEUS). CEUS offers some advantages over conventional DUS, including narrow slice thickness and background subtraction of surrounding tissue. It also provides the ability to serially image, real-time image, and

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avoid radiation exposure.[11-14] However, the role of CEUS in the diagnosis of CIVO remains unclear. The aim of the current study is to examine the diagnostic accuracy of CEUS utilizing Lumason (Bracco Diagnostics Inc) and compare it with unenhanced ultrasonography in CIVO using IVUS as a reference standard.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective analysis of prospectively collected longitudinal data
- **Key Findings:** Considering intravascular ultrasound (IVUS) as the reference standard, diagnostic accuracies of ultrasonography for external iliac vein with and without Lumason use were 71.3% and 71.4%, respectively. Diagnostic accuracies for ultrasonography for common iliac vein with and without Lumason use were 53.2% and 56.7%, respectively, when compared with IVUS.
- **Take Home Message:** The measures of diagnostic accuracy of contrast-enhanced ultrasonography and unenhanced ultrasonography are similar to each other in the diagnosis of chronic iliac vein obstruction when compared with IVUS, a reference standard.

METHODS

Study design and setting. From August 2022 to August 2023, records of all patients who underwent IVUS and preoperative CEUS and unenhanced ultrasound in the evaluation of CIVO were included. This is a single-center study at a specialty venous clinic at a tertiary care hospital. Informed consent was obtained from all patients for the described procedures and imaging. Institutional review board permission was granted for publication of de-identified patient data from the study.

Inclusion criteria. Patients belonging to Clinical-Etiology-Anatomy-Pathophysiology (CEAP) class C3 or higher who had persistence of lifestyle limiting symptoms despite a 3- to 6-month trial of conservative therapy were selected to undergo further evaluation of CIVO with CEUS followed by IVUS.

Exclusion criteria. Patients with chronic total venous occlusions or a history of hypersensitivity to sulfur hexafluoride lipid microspheres or its components, such as polyethylene glycol, were excluded from the study.

Lumason. Lumason, also known as SonoVue, is approved for the CEUS of the heart, liver, and urinary tract. It can also be used for diagnosis of vesicoureteric reflux when applied intravesically.[15,16] Lumason is a true intravascular agent that is not nephrotoxic or hepatotoxic.[12] It can be used in patients who are allergic to iodinated contrast or gadolinium.[15,16] The half-life of Lumason is short (about 5 minutes). It is a pregnancy category B drug.[15,16]

Physiology of CEUS/lumason. Lumason is comprised of sulfur hexafluoride gas covered by a phospholipid shell. The mean diameter of the microspheres is 1.5 to 2.5 um. The microspheres exhibit a non-linear response to the ultrasound beam at a low mechanical index. This contrasts with the surrounding tissues, which exhibit a linear response.[15,16]

Ultrasound protocol. Unenhanced ultrasonography, CEUS, and IVUS were performed sequentially on the same day in supine position to minimize bias. All patients underwent overnight fasting to reduce bowel gas. A standard ultrasound examination was performed first with a color duplex instrument with B-flow feature (Logiq 9; GE Medical Systems) to locate and measure the iliac veins, followed by insertion of an IV (at least a 20-gauge) in the upper extremity. 2.4 mL of Lumason per dose was then injected, immediately followed by a 5-mL flush of normal saline. The iliac vein is then immediately scanned with CEUS after the injection (Fig). The diameter of the lumen of each vessel is measured at its narrowest point. Each scan takes about 10 to 15 minutes. At the conclusion of the study, the IV is discontinued.[1] The patient then proceeded with IVUS examination following the ultrasound.

IVUS and procedural details. Steps of IVUS examination have been described previously in detail.[17] Briefly, ultrasound-guided venous access was obtained via the femoral vein in the mid-thigh. Following venography, Visions PV 0.035 IVUS catheter (Phillips Volcano) was used to measure minimal luminal areas of the EIV and CIV. Venous stenosis was definitively diagnosed if the cross-sectional areas of EIV and CIV were <150 mm^2 (diameter, 14 mm) and <200 mm^2 (diameter, 16 mm), respectively.[18] These cross-sectional/diameter values correspond with the minimal sizes needed for optimal flow calculated from flow equations such as Poiseuille's equation and Young's scaling ratios, as well as IVUS observations of normal iliac vein segments. These values seem to correlate well with clinical improvement and have now been validated in multiple clinical series from our center.[17,18] In the context of appropriate symptoms with corresponding stenotic IVUS measurements, iliac stenting was performed.

Calculation of areas on IVUS and CEUS. Areas of <150 mm^2 (diameter, 14 mm) and <200 mm^2 (diameter, 16 mm) were considered as diagnostic of venous stenosis for EIV and CIV,[18] respectively, for CEUS, unenhanced ultrasonography, and IVUS.

Statistical analysis. Statistical analysis was performed using a commercially available statistics program (SPSS

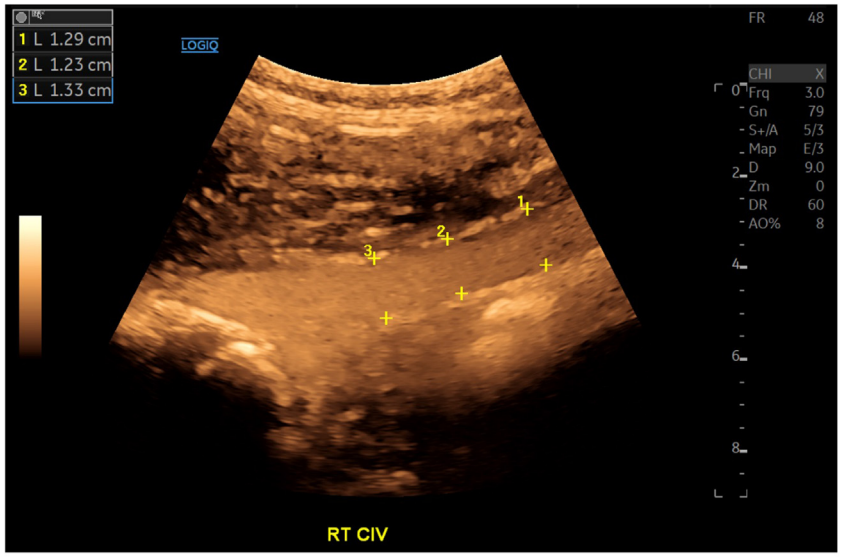

Fig. Contrast-enhanced ultrasonography (*CEUS*) of the common iliac vein (*CIV*) performed with agent Lumason.

version 26, IBM Corp). Correlation and Bland-Altman analysis were performed between unenhanced ultrasonography, CEUS, and IVUS. Measures of diagnostic assessment (sensitivity, specificity, positive predictive value, negative predictive value, and accuracy) were calculated. $P \leq .05$ was considered as significant.

RESULTS

Thirty-nine patients met the inclusion criteria. Demographics of the data set are shown in Table I. The majority of the subset was older (median age, 60 years), female, had left sided laterality, had post-thrombotic lesions, and belonged to CEAP class C4 or higher.

Table I. Demographics of patients who underwent contrast-enhanced ultrasonography (*CEUS*)

Parameter	N = 39
Age, years	60 (35-79)
Laterality (L:R)	3:2
Gender (M:F)	2:3
CEAP class	
C3	3 (8)
C4	23 (59)
C5	8 (20.5)
C6	5 (13)
PTS:NIVL	3:2

CEAP, Clinical-Etiology-Anatomy-Pathophysiology; *F*, female; *L*, left; *M*, male; *NIVL*, non-thrombotic iliac vein lesion; *PTS*, post thrombotic syndrome; *R*, right.
Data are presented as number (%) or median (range) unless otherwise indicated.

Pearson correlation test was computed for CEUS vs unenhanced ultrasonography and IVUS cross-sectional areas in the external and common iliac veins (Table II).

The intraclass correlation coefficient (kappa, average measures) between enhanced and unenhanced ultrasonography was 0.9 (95% confidence interval [CI], 0.87-0.92), indicative of very good agreement. However, the correlation coefficients between enhanced ultrasonography and IVUS and unenhanced ultrasonography and IVUS were 0.6 (95% CI, 0.16-0.67) and 0.5 (95% CI, 0.37-0.75), respectively, indicative of less optimal agreement. Enhanced ultrasonography had slightly better agreement with IVUS compared with unenhanced ultrasonography.

Measures of diagnostic accuracy (sensitivity, specificity, negative predictive value, and positive predictive value) are presented in Table III. Accuracies for ultrasonography for EIV with and without Lumason use were 71.3% and 71.4%, respectively, when compared with IVUS. Accuracies for ultrasonography for CIV with and without Lumason use were 53.2% and 56.7%, respectively, when compared with IVUS. Most of these measures appeared to be similar in CEUS and nonenhanced ultrasonography.

Bland-Altman plots of mean difference in segment caliber as measured by IVUS, CEUS, and non-contrast enhanced ultrasonography are shown in Table IV. Among patients with CIVO, CEUS exhibited a lower bias/difference (CIV, 10.2 mm; EIV, 9.3 mm) when compared with IVUS measurements of CIV and EIV. Non-contrast enhanced ultrasonography also exhibited a lower bias/difference (CIV, 14.4 mm; EIV, 12.4 mm) when compared with IVUS measurements of CIV and EIV. This suggested random rather than systematic differences between the two techniques.

Table II. Spearman correlation and *P*-values of data set (N = 39)

	Unenhanced ultrasound (without lumason)		Enhanced ultraound (with lumason)	
	Spearman correlation	*P* value	Spearman correlation	*P* value
EIV IVUS cross-sectional area	0.44	<.005[a]	0.48	.002[a]
CIV IVUS cross-sectional area	0.45	<.0005[a]	0.22	.21

CIV, Common iliac vein; *EIV*, external iliac vein; *IVUS*, intravascular ultrasound.
[a] *P*-value significant.

DISCUSSION

CEUS has been utilized in the arterial system, including the evaluation of endoleaks after endovascular aortic aneurysm repair[19] and transjugular intrahepatic portosystemic shunt follow-ups.[20] However, the use of CEUS has not been well-described in CIVO yet.[21] Veins, different than arteries, have a much larger lumen size. Also, the accuracy of CEUS compared with traditional (unenhanced) ultrasonography and IVUS is unknown.

The gold standard for the morphologic diagnosis of CIVO is IVUS, which provides a real-time image of the cross-sectional anatomy of the iliac vein. However, IVUS is invasive and may not be universally available. As such, it is not suitable as the initial modality to diagnose CIVO.

We have previously shown that DUS yields a smaller cross-sectional image of the CIV and EIV compared with IVUS.[7] Similarly, CEUS also yields smaller cross-sectional area of the imaged veins (CIV and EIV) when compared with IVUS. The measures of diagnostic accuracy and accuracy itself are very similar between CEUS and unenhanced ultrasonography. As such, it does not appear that the use of Lumason adds much discriminatory power or value to unenhanced ultrasonography alone.

There are some inherent deficiencies, including dimensional errors, with the use of unenhanced ultrasonography in the diagnosis of CIVO. It appears that CEUS shares these deficiencies as well. For instance, an orthogonal orientation is necessary for accurate B-mode measurement. However, the iliac vein frequently takes a tortuous three-dimensional pelvic course, making this measurement difficult to obtain accurately. Also, the vein can be accidentally compressed during ultrasonographic maneuvers, introducing error into the measurements.[7]

The diagnostic accuracy of CEUS may be dependent on its ability to completely fill, achieve wall to wall apposition, and opacify the organ completely. This may be difficult to achieve completely in a dynamic and expansile system such as the venous vasculature.

Overall, the clinical implication of the study is that the quest to find an optimal pre-IVUS test continues. CEUS and non-contrast enhanced ultrasonography both have their limitations. A diagnostic algorithm for the evaluation of patients with CIVO has been described previously in a prior publication and can be referred to for guidance.[2] CTV appears to perform well and should be considered in the workup of patients with CIVO who have failed conservative therapy before consideration is given to IVUS.

IVUS, used as the reference standard in this study, has its own limitations, which should be kept in mind. The study has inherent selection bias as only symptomatic patients were selected to undergo further interrogation with CEUS and IVUS.[7] Additional limitations include cost of Lumason, need for IV access, and cost for dedicated contrast software.[15,16] Additionally, other limitations of ultrasonography, as listed above, must be kept in mind. The study is limited by its design (prospective data collection, retrospective analysis) and sample size.

CONCLUSIONS

The measures of diagnostic accuracy of CEUS utilizing Lumason and unenhanced ultrasonography are similar in the diagnosis of CIVO when compared with IVUS, a reference standard. Further studies are required to ascertain the complementary value of CEUS in CIVO.

Table III. Measures of diagnostic accuracy of contrast-enhanced ultrasonography (*CEUS*) as compared with intravascular ultrasound (*IVUS*) in chronic iliac vein obstruction (*CIVO*)

	Sensitivity		Specificity		Negative predictive value		Positive predictive value	
CIVO								
Unenhanced (without Lumason)	76	87	70	37.5	0.5	0.4	0.8	0.8
Enhanced (with Lumason)	74	83	70	0	0.4	0	0.8	0.7

Table IV. Bland-Altman test for comparison of average bias in the data set (N = 39)

	Lumason, mm	No Lumason, mm
Iliac vein diameters		
CIV	10.2	14.4
EIV	9.3	12.4

CIV, Common iliac vein; *EIV*, external iliac vein.

AUTHOR CONTRIBUTIONS

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

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DISCLOSURES

SR reports ultrasound patent for intravascular ultrasound diagnostics and ultrasound patent for iliac vein stent design.

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