C-arm-based flat-panel detector cone-beam computed tomography venography in the diagnosis of iliac vein compression syndrome

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Abstract

Background: C-arm-based flat-panel detector cone-beam computed tomography (CBCT) venography has never been used in the management of iliac vein compression syndrome (IVCS). This study aimed to determine the technical feasibility and safety of CBCT venography in the diagnosis of IVCS compared with conventional venography (CV).

Methods: Twenty patients with clinical manifestations of lower extremity venous insufficiency were prospectively enrolled between May 2018 and December 2018. Each patient underwent both CV and CBCT venography. The feasibility and safety of CBCT venography were assessed by technical success rate and complication rate. The relationships between the clinical indexes and the results of CBCT venography and CV were analyzed with correlation analysis. The consistency of the diagnosis of IVCS using each modality was analyzed by the kappa test.

Results: The technical success rate was 100% for CBCT venography and for CV, without any complications. Compared with CV, CBCT venography was able to show more details of adjacent tissues which might be helpful for making etiological diagnosis. The stenosis rate under CBCT venography had excellent consistency with that under CV (kappa = 0.78, Chi-square test). The stenosis rate under CBCT venography was positively correlated with the presence of collateral veins (odds ratio 1.12, 95% confidence interval: [1.00, 1.26], P = 0.049), while the stenosis rate under CV was not. Unexpectedly, only one patient had a venous pressure gradient of more than 2 mmHg (1 mmHg = 0.133 kPa).

Conclusions: For the diagnosis of IVCS, C-arm-based CBCT venography was technically feasible, with good safety. The presence of collateral veins on CBCT was clinically significant. A C-arm fluoroscopy-based technique that combines CV and CBCT might be a promising protocol for the management of IVCS during a single session.

Keywords: May-Thurner syndrome; Diagnosis; Cone-beam computed tomography; Phlebography

Introduction

Cone-beam computed tomography (CBCT) is a new imaging modality that has recently been integrated into C-arm angiography. CBCT is based on the rotational movement around the patient of a C-arm equipped with a flat-panel detector. Post-processing of the acquired images results in CT-like images of vessels and soft tissues that provide additional information, especially three-dimensional (3D) images, for diagnosis and treatment guidance. CBCT has been applied in an increasing number of clinical circumstances, including intravascular procedures and image-guided therapy.

Iliac vein compression syndrome (IVCS) presents clinically as swelling or pain and edema in the lower extremities, and even deep vein thrombosis (DVT) of the leg. The condition is usually caused by the extrinsic compression of the left common iliac vein from the overlying right common iliac artery or other surrounding masses, and the subsequent pathophysiological changes of the vein. IVCS is also known as May-Thurner syndrome and Cockett syndrome. IVCS is rare, with an incidence of less than 1% in the general population, but the outcomes are substantial and debilitating. Accurate diagnosis of IVCS is required for prompt effective treatment to relieve symptoms and achieve long-term rehabilitation. Besides the clinical symptoms and signs, the diagnosis of IVCS depends on imaging tools. Among them, ultrasound is usually the first-choice screening tool due to its non-invasiveness and availability in almost every hospital. However, multidetector computed tomography with venography (CTV) or magnetic resonance imaging with...
venography (MRV) can create two-dimensional images of the vessels in almost any plane and create 3D images for overall perspectives; the status of the adjacent tissue is also shown in the axial plane, which greatly aids in ascertaining the causes of IVCS.[10] The gold standard for the diagnosis of IVCS is an invasive imaging examination via the femoral vein approach, including conventional venography (CV) techniques such as digital subtraction angiography (DSA) and intravascular ultrasound. The advantages of these invasive imaging techniques include diagnostic accuracy and good treatment support. However, these gold standard diagnostic techniques are not comprehensive enough to enable the consideration of all aspects of the etiology of IVCS, especially regarding factors outside of the iliac vein. Such etiological investigations can be done via CTV or MRV, but this requires the patient to wait for the application of another special radiological examination, and the process is time-consuming and inefficient.

C-arm CBCT is capable of performing almost real-time 3D imaging in the interventional suite, similarly to CTV or MRV. By allowing almost all interventional procedures, CT-guided or otherwise, to be performed in the interventional suite, the technology has the potential to significantly impact the practice of interventional radiology, with increased overall radiology department efficiency. [11] Therefore, we aim to use C-arm CBCT in the management of IVCS. As CBCT provides CT-like images, it may provide additional information for diagnosis, treatment guidance, and even modification of the IVCS management flowchart so that all IVCS management is performed in the interventional suite. This type of IVCS management performed all in the one session has not been well reported. The present study aimed to evaluate the technical feasibility of IVCS diagnosis using CBCT venography in comparison with DSA.

Methods

Ethical approval

This prospective study was conducted in the Department of Interventional Radiology and Vascular Surgery of Peking University Third Hospital from May 2018 to December 2018. The study was approved by the Ethics Committee of Peking University Third Hospital (registration number, IRB00006761-M2018105). Patients who fulfilled the inclusion criteria provided written informed consent before study enrolment.

Patients

Consecutive patients with signs of lower extremity venous insufficiency or DVT were assessed for study eligibility from May 2018 to December 2018. Patients aged 18 to 85 years with at least one of the following inclusion criteria were enrolled: (a) unilateral lower extremity varicose veins; (b) unilateral lower extremity edema; (c) unilateral lower extremity pigmentation or venous ulceration; (d) unilateral lower extremity DVT. Exclusion criteria were: (a) allergy to iodine contrast medium; (b) pregnancy or planning to become pregnant in the next 6 months; (c) heart, liver, or kidney insufficiency; (d) venous puncture site infection or systemic infection; (e) severe coagulopathy; (f) uncontrolled hyperthyroidism; (g) lower extremity venous insufficiency or DVT that was not related to iliac vein compression. The collected clinical data included medical history, especially related to venous insufficiency, such as lower extremity varicose veins, edema, pigmentation, eczema, and ulceration. Routine pre-operative workup was conducted, including routine blood tests, biochemistry, coagulation tests, tumor marker tests, electrocardiography, and chest radiography.

Technique for CV

The patient was in supine position in the interventional suite equipped with an angiographic fluoroscopy system (GE Innova 4100-Q, GE Healthcare, Fairfield, CA, USA). The groin area was routinely sterilized and dressed. Under local anesthesia, a skin incision was made above the femoral vein on the affected side. The Seldinger technique, sometimes ultrasound-guided, was used to achieve femoral vein access via the introduction of a 4F sheath (Terumo Corporation, Tokyo, Japan). Under X-ray guidance, a 4F pigtail catheter was introduced and positioned at the external iliac vein. The contrast agent lopamidol (diluted with normal saline to a concentration of 185 mg/150 mL) was injected using a high-pressure auto-injector at a pressure of 600 pounds per square inch, injection speed of 7 mL/s, and injection volume of 15 mL. The exposure field was extended from the third lumbar vertebra cephalically to the common femoral vein caudally. Anteroposterior (AP) and lateral projection venography images were obtained while the patient held their breath.

Technique for CBCT venography

The C-arm fluoroscopy mode was set at 3D-CT, and the other parameters were a spin speed of 20%/s, scan time of 9 s, frame number of 15 frames per second, and time delay of 0 s. The contrast agent was the same as for CV, but the injection speed of the high-pressure auto-injector was 8 mL/s and the total volume was 60 mL. Patients were asked to hold their breath during C-arm rotation. Anticoagulation therapy was initiated during the operation with intravenous unfractionated heparin (80 U/kg). The unfractionated heparin was continued intravenously for 24 h post-operatively to maintain the activated partial thromboplastin time (aPTT) at 70 to 90 s. Thereafter, low molecular weight heparin (100 U/kg every 12 h) was injected subcutaneously for 3 to 5 days. Oral warfarin was initiated 2 days post-operatively. The low molecular weight heparin was stopped when the international normalized ratio reached 2.0 to 3.0. The warfarin was continued to maintain the international normalized ratio at 2.0 to 3.0 for at least 6 months.

Observed indexes and calculation methods

Iliac vein stenosis rate

On the lateral view of DSA, the minimum distance between the anterior and posterior (AP) walls of the most compressed portion of the iliac vein was recorded as Distance a. The AP calibers of the iliac vein proximal and distal to the compressed area were recorded as Distance b and Distance c, respectively. On axial CBCT venography,
Distances $a$, $b$, and $c$ were recorded at locations corresponding to the three locations on DSA.

The iliac vein stenosis rate was calculated as $[(1-a/(b+c)) \times 100\%]$.

**Etiological diagnosis**

Multiplanar two-dimensional and 3D CBCT venography images were used to clarify the extrinsic and intrinsic details of the iliac vein to ascertain the etiology of iliac vein stenosis.

**Collateral veins**

The details of the collateral veins, especially distal to the stenotic area, were examined to aid in the establishment of the diagnosis and for the appraisal of treatment.

**Pressure gradient across the stenotic area of the iliac vein**

A gradient of $>2$ mmHg (1 mmHg = 0.133 kPa) at rest and $>3$ mmHg during exercise conveys hemodynamic significance. The pressure of the vein was measured through a pigtail catheter with the patient in supine position and breathing freely. Measurements were made at sites proximal and distal to the stenosis. Each measurement was repeated three times and the average value was recorded. The pressure gradient was calculated and expressed as cmH$_2$O (1 cmH$_2$O = 0.098 kPa).

**Radiation dosage**

The radiation dosage of each CV and CBCT venography procedure was recorded based on the fluoroscopy machine reports.

**Diagnostic criteria of IVCS**

The three clinical stages of IVCS are: (I) asymptomatic left common iliac vein compression; (II) venous spur formation; (III) left lower extremity DVT. Based on a previous report, the diagnostic criteria for IVCS in the present series were: (a) clinical presentations of lower extremity venous insufficiency, such as lower extremity varicose veins, edema, pigmentation, ulceration, or DVT; (b) iliac vein stenosis rate of more than 50%; and/or (c) the presence of collateral veins.

**Statistical analysis**

Statistical analyses were performed with SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov goodness-of-fit test was used to assess the normality of data distribution. Quantitative data that were normally distributed were expressed as mean $\pm$ standard deviation, and intergroup differences were analyzed with the Student’s $t$ test; non-normally distributed quantitative data were expressed as median (minimum, maximum) and analyzed by the Wilcoxon rank-sum test. For the diagnosis of IVCS, consistency between CBCT venography and DSA was assessed using the Kappa test. Kappa is calculated by following three steps: calculating observed agreement ($P_0$); calculating chance agreement ($P_c$); and calculating agreement beyond chance. Kappa = $[(P_0 - P_c)/(1 - P_c)] \times 100\%$.

The Pearson correlation coefficient was calculated for the correlation analysis of normally distributed data, while non-normally distributed data were assessed using Spearman rank correlation coefficient. The significance of collateral veins for the diagnosis of IVCS was assessed by logistic regression analysis. A value of $P < 0.05$ was considered statistically significant.

**Results**

**General data**

A total of 20 patients were included (12 males, eight females; mean age 57.3 $\pm$ 17.1 years). In accordance with the clinical-etiology-anatomic-pathophysiological classification system, there were two C2 cases, four C3 cases, three C4a cases, four C4b cases, two C5 cases, and five C6 cases. Both DSA and CBCT venography were uneventful intra- and post-operatively in all 20 patients. The technical success rate was 100%. The mean radiation dosage of each CBCT venography ($2.10 \pm 0.38$ milliSievert [mSv]) was significantly lower than the mean dosage of each DSA ($4.33 \pm 1.68$ mSv) ($t = 5.81, P < 0.001$).

**Diagnosis of IVCS on CBCT venography**

On CBCT venography, 14 of 20 patients fulfilled the diagnostic criteria and were diagnosed with IVCS. The mean iliac vein stenosis rate was 53.26% $\pm$ 19.30%. The mean minimum AP caliber of the most compressed iliac vein was significantly greater in the six patients without IVCS ($7.86 \pm 1.86$ mm) than in the 14 patients with IVCS ($4.23 \pm 1.67$ mm) ($t = 4.32, P < 0.001$).

**Imaging findings on CBCT venography**

In patients with IVCS, the axial view revealed a compressed iliac vein with a markedly decreased AP caliber and sometimes a collateral venous plexus; the coronal view revealed an iliac artery indentation on the vein and sometimes a “ridge” in the venous lumen; the sagittal view revealed the exact site of the most compressed segment of the vein [Figure 1].

The examination of tissues around the vein revealed that the main cause of IVCS was compression of the iliac vein by the right common iliac artery; in addition, the axial view revealed pathological changes of lumbar spine, such as disc herniation, osteophytes, and spondylolisthesis [Figure 2].

Spinal degeneration was common in patients with senility. Nine of the 14 patients with IVCS had such pathological changes, including local osteophytes (3/14), simple lumbar disc herniation (1/14), disc herniation and local osteophyte formation (4/14), and lumbar spondylolisthesis and osteophyte formation (1/14). Any of these lumbar pathological changes could significantly decrease the space between the lumbar spine and the right common iliac artery, which would aggravate the stenosis of the left common iliac vein.

CBCT venography revealed some rare causes of IVCS, such as compression from the left psoas major muscle and neoplasms [Figure 3].
Calci
cified atherosclerotic plaque in the right common iliac artery

Five of 20 patients had calcified atherosclerotic plaque in the right common iliac artery, where it crossed over the left common iliac vein. The average stenosis rate of the left common iliac vein in the 15 patients without calcified plaque (48.13% ± 18.25%) was significantly lower than the rate in the five patients with calcified plaque (68.11% ± 19.00%) (t = –2.17, P = 0.04).

CV results

IVCS was diagnosed in 12 of 20 patients using CV (compared with 14 of 20 patients using CBCT venography). The average iliac vein stenosis rate was 51.52% ± 16.73%. In the 12 patients diagnosed with IVCS using CV, the imaging findings in the AP projection were: (a) an enlarged caliber of the compressed area of the iliac vein; (b) poor contrast agent filling in the compressed area; (c) opening of collateral veins distal to the stenosis and visualization of the contralateral iliac vein. In the lateral projection, the arc compression sign of the common iliac vein was clearly manifested [Figure 4].

Consistency analysis of DSA and CBCT venography in the diagnosis of IVCS

Consistency analysis revealed an observed agreement of 90.0%, chance agreement of 54.0%, potential agreement beyond chance of 46.0%, and actual agreement beyond chance of 35.5%. The Kappa statistic value was 0.78, which indicates that CBCT venography and DSA had excellent consistency for the diagnosis of IVCS.

Venous pressure gradient

The venous pressure gradient at the sites distal and proximal to the compression was >2 mmHg in only one of 20 patients (the actual value in that one patient was 7.35 mmHg).

Correlation between the stenosis rate and the presence of a collateral venous plexus

Nine of 20 patients had an opening collateral venous plexus distal to the stenosis detected on both DSA and CBCT venography. Logistic regression analysis was performed using the stenosis rates determined by DSA and CBCT venography as dependent factors, and the existence of collateral veins as the covariant. The stenosis rate determined by CBCT venography was correlated with the presence of collateral veins (correlation coefficient 0.12, odds ratio 1.12, P = 0.049, 95% confidence interval: [1.00, 1.26]), while the stenosis rate determined by DSA was not.

Discussion

IVCS is not an uncommon disease among the general population. The estimated incidence of IVCS is 2% to 5%
in patients with venous disease. In particular, the incidence of IVCS is as high as 18% to 49% in patients with DVT.\textsuperscript{[16]} The diagnosis of IVCS is a prerequisite for effective treatment. However, in reality, the accurate diagnosis of IVCS is not straightforward due to the varied clinical symptoms and signs, especially the complex hemodynamics of the venous blood flow and its susceptibility to being influenced by the extrinsic environment.

At present, the most widely adopted gold standard method with which to diagnose IVCS and guide endovascular treatment is DSA with intravascular ultrasound.\textsuperscript{[14]} Although IVCS diagnosis also involves other modalities, such as CTV, MRV, and even angioscopy,\textsuperscript{[17]} these diagnostic tools are considered complementary in the clinical setting. To simplify the diagnostic flowchart of IVCS, especially to decrease the waiting time in the radiological department for CTV or MRV and improve the cost-effectiveness, we modified the current protocol by combining CV with CBCT venography to enable the diagnosis and treatment of IVCS to be performed in the interventional suite during one session. This modified protocol was attempted because CBCT is almost a standard procedure with C-arm fluoroscopy, while CV is easy to perform and provides good guidance for endovascular treatment.

Our initial experience in using this modified protocol in 20 patients indicated that CBCT venography was technically feasible for the diagnosis of IVCS. The 100% technical success rate and a 0% complication rate of CBCT venography indicated its safety and ease of performance. Furthermore, the average radiation dosage of CBCT was lower than that of DSA. The performance of CBCT venography by an experienced skilled operator avoids the need for repeated examinations, and so no extra cost is incurred by the patient.

In terms of diagnostic value, CBCT had excellent consistency with DSA. CBCT also has technical advantages that may aid in the etiological diagnosis of IVCS, especially the 3D observation of the targeted veins and the details of the tissue inside and outside of the vein. As CBCT was able to clearly show the surrounding tissue, especially the spine, the stenosis rate determined by CBCT was well correlated with the clinical presentations and the presence of collateral veins on imaging. Clinically, CBCT venography might be a good substitute for DSA for the diagnosis of IVCS. However, the image quality of CBCT venography was not as good as that of CTV. Thus, CTV is indispensable in some circumstances, such as for the detailed pathological diagnosis of adjacent tissues. The relatively poor image quality of CBCT may have been due to the scan time of 9 s, which may cause motion artifacts.

A venous pressure gradient of >2 mmHg at rest and >3 mmHg during exercise reportedly conveys hemodynamic significance for the diagnosis of IVCS.\textsuperscript{[12,13]} Unexpectedly, the venous pressure gradient was poorly correlated with

\begin{figure}
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\caption{Common cone beam computed tomography findings in a patient with spine degeneration aggravating the severity of IVCS. (A) Axial view of lumbar vertebral disc herniation (arrow) and vein compression. (B) Sagittal view of the herniated disc aggravating the vein stenosis (arrow). (C) An osteophyte of the lumbar spine in the axial plane (arrow). (D) The protruding osteophyte compressing the vein (arrow) in the axial plane. (E) The osteophyte decreasing the space between the artery and the spine in the axial plane. (F) Sagittal view of the lumbar spondylolisthesis (arrow) aggravating the severity of IVCS. IVCS: Iliac vein compression syndrome.}
\end{figure}
the clinical status in the present case series. In fact, most of the present patients had very low venous pressure that was easily affected by surrounding factors, such as the patient’s posture, breathing, and heart function. This suggests that the venous pressure gradient could potentially be neglected as one of the diagnostic standards. In contrast to the venous pressure gradient, the opening of collateral veins was strongly positively correlated with the venous stenosis rate determined by CBCT. The importance of the presence of collateral veins in the diagnosis of IVCS deserves further clinical study, and might be a good diagnostic criterion.

The present study revealed a close relationship between iliac vein stenosis and the presence of spinal degeneration and a calcified right common iliac artery. This suggests that the formation of vein stenosis is affected by both extrinsic causes and intrinsic causes, like “spur” formation. CBCT is currently a dependent complementary tool to CV for the diagnosis of some other rare causes of IVCS, such as compression due to the psoas major muscle and neoplasms. CV is the technological foundation for CBCT examinations, and is crucial for providing intravascular treatment guidance. As CBCT plays an important role in etiological diagnosis and CV plays an important role in treatment guidance, the combination of both techniques might be used in the future to effectively manage IVCS in one session in the interventional suite; this would lower costs and waiting times.

The limitations of the present study should be considered when interpreting the results. First, the sample size was small, as the present study describes the preliminary results of our ongoing study for the confirmation of the feasibility and safety of the technique. The preliminary findings of the present study need further investigation, especially regarding the use of the technique in clinics, since only two patients with IVCS underwent intravascular stenting after the imaging examinations in this group. The preliminary results of the study were; therefore, only diagnosis related. The second limitation was that only a single group of patients with suspected IVCS were analyzed with both CV and CBCT venography. Our study thus lacked a control group, as it is ethically impossible to perform both CV and CBCT venography on healthy subjects. The present findings require confirmation in further study with more patients.

In conclusion, C-arm-based CBCT venography was technically feasible and safe for the diagnosis of IVCS. The present preliminary findings suggest that the detection
of collateral veins on CBCT was clinically significant. The C-arm fluoroscopy-based technique, combining CV and CBCT, might be a promising protocol for the management of IVCS in one session. The preliminary findings of the present study require confirmation by large, randomized controlled trials.

Conflicts of interest

None.

References


Figure 4: Representative conventional venography images of iliac vein compression syndrome. (A) AP projection showing poor contrast agent filling of the left common iliac vein adjacent to its opening (arrow). (B) AP projection showing the appearance of large collateral veins (arrow) and an opacified contralateral iliac vein. (C) Lateral projection showing the stenotic area of the left common iliac vein (arrow). (D) AP projection showing that the left common iliac vein has an enlarged caliber but is only mildly filled with contrast agent (arrow). (E) AP projection showing the collateral venous plexus (arrow). (F) Lateral projection showing the notch (arrow) where the common iliac vein is compressed. AP: Anteroposterior.