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Thoracic Central Venous Evaluation: Comparison of First Pass Direct versus Delayed Phase Indirect Multidetector CT Venography

Baskaran Sundaram, M.D., Jean W. Kuriakose, M.D., Jadranka Stojanovska, M.D., M.S., Kuanwong Watcharotone, PhD, Robert A. Parker, ScD, and Ella A. Kazerooni, M.D., M.S.

Abstract

Purpose—To compare first pass and delayed phase thoracic Computed Tomography (CT) venography for the evaluation of suspected central thoracic venous pathology.

Material and methods—CT images and medical records of all patients who underwent thoracic CT venography over a five year period were retrospectively reviewed. Both first pass (18 seconds) and delayed phase (60 seconds) venous images were obtained in all patients. The images were reviewed in random order by three readers using a semi-quantitative visual grading scheme for image quality, including artifacts and the uniformity of venous enhancement. In addition, enhancement was quantitatively evaluated. The presence and type of venous pathology, and overall diagnostic confidence were recorded and compared. Reference verification was performed when available.

Results—18 patients formed the study group, mean age 49.5 years and 28% male. Dual arm injection was successful in 72% of exams. All readers reported more streak artifacts on first pass imaging than delayed imaging (72–94% vs. 27–44% respectively; $p < 0.05$). First pass imaging had significantly higher measured enhancement across all central venous segments than delayed imaging (mean HU range: 212–906 HU vs. 173–414 HU; $p < 0.05$), but also had significantly more heterogeneous enhancement (mean SD range 75–1058 HU vs. 67–378 HU; $p < 0.05$). For overall diagnosis, reader agreement, accuracy and confidence levels were higher for delayed phase images ($p < 0.05$).

Conclusion—Indirect thoracic CT venography using delayed phase imaging alone may be sufficient for evaluating clinically suspected central venous abnormality.

Keywords

superior vena cava; first pass; delayed phase; single phase; dual phase; CT venography; Superior Vena Cava syndrome

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Corresponding author: Baskaran Sundaram, M.D., Professor and Director of Cardiothoracic Imaging Division, Department of Radiology, Thomas Jefferson University Hospital, 132 S 10th St, Suite 1063 Main Bldg, Philadelphia, PA 19107.

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Introduction

Imaging plays a central role in the diagnostic evaluation of clinically suspected central thoracic venous pathology (1–9). While invasive catheter venography remains the reference standard for the diagnosis of upper extremity and thoracic central venous occlusions, is able to incorporate measurement of the pressure gradient when a stricture is found, and can be converted to concomitant intervention for treatment, as a diagnostic test alone it is invasive and associated with procedural complications, expensive compared to Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) techniques, and as a luminogram does not evaluate the surrounding structures. The latter is particularly important in patients with known or suspected malignancy. Doppler ultrasound of the central thoracic veins is limited due to poor transmission of sound waves into thorax. MRI can comprehensively evaluate the thoracic central veins (10); however limitations include claustrophobia, risk of nephrogenic systemic fibrosis in patients with renal impairment, lower spatial resolution than CT, longer exam times, inability to administer gadolinium during pregnancy, and contraindications in patients with ferromagnetic devices.

Among noninvasive tests, CT is generally preferred due to its lower cost, ease, widespread availability, higher spatial, temporal and contrast resolution, and the ability to comprehensively evaluate coexisting thoracic pathology. However, there is little data on the accuracy and performance of CT acquisition protocols for this purpose, including the timing of scanning following the peripheral intravenous administration of contrast and number of venous enhancement phases required for evaluating the central thoracic veins. First pass direct imaging is commonly performed using dual upper extremity intravenous lines, with image acquisition timed to the passage of contrast through the central veins (7). Delayed phase imaging 1–2 minutes after contrast injection can be performed alone or in addition to early phase imaging, and requires only a single upper extremity injection with imaging occurring during contrast recirculation through the heart, arterial system and capillary bed as it returns through the central thoracic veins back to the heart. The purpose of this study is to evaluate and compare the technical performance, quality and diagnostic performance of direct first pass and indirect delayed venous phase CT venography for evaluating suspected thoracic central venous abnormalities.

Materials and Methods

This retrospective review was approved by our Institutional review board (IRB) with a waiver of informed consent and is Health Insurance Portability Accountability Act (HIPAA) compliant. The electronic medical records of all patients who underwent central venous/superior vena cava CT protocol examinations over 5 years were reviewed and included in this study. No patients were excluded from this study. Patient characteristics are summarized in Table 1.

CT Technique

After anteroposterior and lateral scout images, helical CT images were obtained from four centimeter above the lung apices to immediately below the costophrenic angles at two time points. The first pass and delayed phase images were obtained 18 and 60 seconds

respectively after the initiation of intravenous contrast material injection. A total of 130 mL Iopamidol 300 mg iodine / ml (Bracco Diagnostics Inc., Princeton, New Jersey, New Jersey) was injected using a power injector with a Y-connector on the intravenous line tubing connected to bilateral 20 gauge antecubital fossa intravenous venous lines at 4 mL per second, followed by a mixture of 10 mL contrast material and 90 mL of 0.9% normal saline at 3 mL per second. CT examinations were acquired on a 64-detector CT scanner (VCT, General Electric Healthcare, Milwaukee, Wisconsin, USA) using 120 kVp, variable automated tube current (100 – 575 mA), gantry rotation of 0.5 second, detector coverage of 40 mm, pitch 1.375:1, slice thickness 1.25 mm, scan interval 0.625 mm, noise index of 26.4, and a standard image reconstruction algorithm for both phases.

Image Evaluation

The 36 total image series, 18 first pass and 18 delayed CT venography acquisitions were independently reviewed by three cardiothoracic radiologists. All 36 series were arranged in a different random order for each reader, who reviewed half of examinations at one time point, and the other half two months later. Radiologists reviewed the examinations in a blinded fashion using a commercially available workstation (General Electric Advantage Windows workstation; software version 4.6; General Electric Healthcare, USA), starting with standard axial, coronal and sagittal planes on soft tissue windows, with the ability to rotate the projection angle and the window width and levels to best suit the structures being analyzed during their interpretation.

Qualitative Evaluation

The vascular segments were divided into the right and left subclavian, jugular, and brachiocephalic veins, the Superior Vena Cava (SVC), right atrium, right ventricle, and main pulmonary trunk, right and left pulmonary arteries. The presence or absence of catheters/stents and streak artifacts were recorded. Contrast opacification homogeneity was graded for each segment on a 4-point scale: 0 = none, 1 = poor, 2 = moderate, 3 = excellent). Readers evaluated each segment for filling defects and vascular narrowing, and provided an overall diagnosis (Figures 1, and 2) with diagnostic confidence rating on a three point grading scale: 1 = high confidence, 2 = moderate confidence, 3 = low confidence. Identification of the collateral venous pathways and confidence in the ability to map the collateral venous pathways were also recorded.

Quantitative Evaluation of Contrast Enhancement

A different reader from the three qualitative readers performed a quantitative analysis of each venous segment. A region of interest (ROI) was placed on the first pass images, drawn to include the largest area for each specific anatomic segment in short. The ROI was copied and pasted onto the same anatomic venous location on the delayed phase (Figure 3). Any indwelling vascular devices were avoided when placing the ROIs. Mean CT attenuation Hounsfield values (HU) and standard deviation values were recorded. Background noise was measured and accounted for by measuring the Hounsfield unit attenuation values of mediastinal adipose tissue and the tracheal air column. Radiation exposure was recorded from the automatically generated dose report.

Reference Standard Verification and Clinical Follow Up

Digital subtraction catheter venography was performed on only five subjects (28%) within the subsequent 2 weeks of the CT examination; for these 5 subjects the CT and catheter venography findings were compared. The mean clinical follow-up after CT for all subjects was 1547 ± 718 days (range 21 – 2481 days) or 4.2 ± 2 years. During follow-up, three patients died from progressive malignancy, including one subject each with breast cancer, lung cancer and liposarcoma, 21, 178 and 204 days after the CT examination respectively. For the 13 patients who did not have catheter venography verification, available follow-up was 1738 ± 582 days (range 178 – 2481 days).

Statistical Analysis

For each subject there were a total of 24 anatomic segments evaluated, 12 for the first pass and 12 for the delayed phase, for a total of 432 anatomic segments evaluated for all subjects combined. Venous segments that did not opacify were excluded from comparative analysis. Anatomic segments were grouped for meaningful analysis of data. The qualitative reader evaluations for opacification, streak artifacts, filling defects, venous stenosis and overall diagnosis were compared between phases using McNemar's test. Cohen's Kappa statistic was used to evaluate the intra-reader agreement between the two phases. Fleiss' Kappa statistic was used to assess the inter-reader agreement. The mean of readers' diagnosis confidence levels between first pass and delayed phases were compared using Wilcoxon signed rank test. Subset analysis was done to test the reader accuracy against the reference standard. The paired quantitative ROI attenuation values between phases were compared using Wilcoxon signed-rank test to check the range (maximum minus minimum) of attenuation values and Brown and Forsythe's test was used to assess homogeneity of variances. Statistical analyses were performed using SAS software, Version 9.3 (SAS Institute Inc., Cary, NC, USA). A *p* value of less than 0.05 was considered statistically significant.

Results

Dual phase imaging was attempted on all patients. The dual arm injections were successfully performed in only 13 of 18 patients for a technical success rate for dual phase imaging of 72%. Unilateral arm injections were performed in five patients, two left side only and three right side only, including one breast cancer patient with unilateral post-treatment lymphedema, two patients with known contralateral central venous stricture and two patients in which one of the two upper extremity venous cannulation failed due to arm swelling. There were no immediate adverse events such as contrast extravasation, allergic-like contrast reaction or acute cardiovascular compromise following contrast material administration. The mean CT scan radiation exposure was 7.9 ± 2.1 mSv both the first pass and delayed phase acquisitions.

Qualitative Assessment

Streak artifacts in the subclavian veins, brachiocephalic veins and SVC were reported significantly more often on first phase images than delayed phase images by all three readers (94% vs. 44%, 72% vs. 27%, 77% vs. 27%; all *p* values < 0.05). There were no statistically

significant differences for any of the other 11 qualitative variables for any of the three readers.

Comparing the pattern of early vs. late results, reader 2 consistently found more abnormalities in the delayed than earlier images (7/7 variables in which there were differences, $p = 0.014$). Reader 1 showed a similar directional pattern (7/9 rates higher in the delayed than in the earlier phase images; $p > 0.4$), but reader 3 showed the opposite pattern (5/7 rates higher with earlier rather than delayed images; $p > 0.4$).

Intra-reader agreement between phases ranged from -0.17 to 0.86 . Intra-reader concordance between phases was substantial ($\kappa > 0.6$ for all three readers) for the presence of a catheter/stent and moderate ($\kappa > 0.4$ for all three readers) for filling defects in the SVC and overall diagnosis

The inter-reader agreement for the presence of a catheter or stent, homogenous opacification, streak artifacts, filling defects, venous narrowing, and diagnosis ranged from the Fleiss' Kappa values of -0.13 – 0.69 for the early phase, and -0.08 – 0.85 for the delayed phase. Concordance was substantial ($\kappa > 0.6$ for both phases) for the presence of catheter/stent and overall diagnosis for the SVC and moderate ($\kappa > 0.4$) for both for the presence of a filling defect and for venous narrowing in the left subclavian and innominate veins, and for overall diagnosis.

The overall inter-reader agreement for visualizing mediastinal / chest wall collateral pathways between phases was moderate (0.4 ; 95% CI $0.2 - 0.6$ versus 0.5 ; 95% CI $0.2 - 0.7$) with similar confidence levels (0.5 ; 95% CI $0.2 - 0.7$ versus 0.4 ; 95% CI $0.2 - 0.7$).

For first pass image sets, all 3 readers recorded 5 exams as normal, and 6 as abnormal they disagreed in seven examinations. Using delayed phase images, all 3 readers recorded 7 as normal and 8 as abnormal; they disagreed on three examinations. For overall diagnosis, inter-reader agreement for the early phase was 0.5 and late phase was 0.8 . Intra-reader agreement between phases ranged from 0.4 – 0.9 (Table 2). Readers trended towards higher diagnostic confidence with delayed phase images than first pass images (88–94% versus 76–89%; $P > 0.050$), as noted in table 3.

Agreement with reference standard

Five patients had catheter venography as part of a subsequent interventional procedure within 2 weeks of the CT examination, including one patient with central venous thrombus on CT, two patients with central venous occlusion on CT and two patients with both thrombus and venous narrowing on CT. For two readers the diagnostic accuracy was lower on the first pass images at 80% (95% CI $28.4 - 99.5$; $n=4/5$) than delayed phase images at 100% (95% CI $47.8 - 100$; $n=5/5$), and for one reader there was no significant difference with 100% agreement on both phases (95% CI $47.8 - 100$; $n=5/5$); however these differences were not statistically significant due to small sample size. Among the patients who did not receive catheter venography verification (13 patients), there were 4 exams in the early phase that were marked as normal and these patients had no symptoms of thoracic central venous pathology during the entire follow up period. There were 6 such patients in

the delayed phase in whom all readers agreed as normal exams and they had no features of thoracic central venous pathology during the follow up period. If we consider the exams that are regarded as normal CT thoracic vein studies by all readers with no subsequent diagnosis of any thoracic central venous abnormality or resolution of symptoms over the period of clinical follow up as true negatives together with the 5 patients who underwent catheter venography, the diagnostic accuracy in early phase images ranges from 88.9% to 100%, and in the delayed phase images it remains 100%.

Quantitative Assessment

The mean attenuation level range of attenuation values and variability of both levels across the set of images within vascular segments was generally higher for first pass images than for delayed phase images, as illustrated in Tables 4 and 5.

Discussion

Higher contrast enhancement is generally considered beneficial in non-invasive vascular imaging using CT, particularly for arterial imaging. For the central thoracic venous system, the trade-off is a higher frequency of streak artifacts that reduce image quality and reduce diagnostic agreement. One study of thoracic CT examinations using 75 ml of 370 mg I / ml @ 3 ml / seconds, streak artifacts were more frequent with mean SVC attenuation values of 459 $\pm$ 168 HU compared to when 60 ml of 370 mg I / ml plus 30 ml saline @ 3 ml / second was used with lower arterial attenuation values of 352 $\pm$ 125 HU (11). Another study found no significant difference in the frequency of streak artifacts with mean attenuation values of 299 $\pm$ 72 HU enhancement using 370 mg I / ml contrast material followed by 30 mL saline @ 2.5 mL / s compared to mean attenuation values of 155 $\pm$ 27 HU; 300 mg I / ml contrast plus 30 mL saline @ 2.5 mL / s (12). In our study, we note a higher frequency of streak artifacts when there was higher mean attenuation values during the first pass CT venograms at 1022 $\pm$ 883 HU in the SVC than on delayed phase imaging with mean SVC attenuation values of 377 $\pm$ 652 HU using 130 ml of 300 mg I / ml @ 4 ml / s followed by 100 ml of 10% contrast material plus 90% saline @ 3 ml / s) with acquisitions initiated at 18 and 60 seconds after the initiation of the contrast bolus respectively.

The more homogenous opacification found on delayed phase images than first pass images is a reflection of improved steady-state equilibrium over time with recirculation of contrast material from the venous injection through the heart, arterial system and capillary beds back into the venous system. Our finding is similar to a study that reported a higher frequency of homogenous lower extremity vein opacification on delayed phase imaging of calf veins imaged between 210–240 seconds and above the knee veins imaged at 180–300 seconds, compared to early phase imaging on indirect CT venography following CT pulmonary angiography (13). In our study, the brachiocephalic veins and SVC enhanced more homogeneously with less variability on delayed phase images than first pass images. While the homogeneity of internal jugular vein attenuation did not reach statistical significance in our study, this was most likely because they did not opacify in many cases on first pass images resulting in lower number of comparisons.

By only performing one phase instead of two for thoracic CT venography, a 50% reduction in radiation exposure can be achieved, only obtaining the delayed phase images. It also reduces by half the number of images for the reader to review, which should result in a gain in reader efficiency and work-flow.

The technical success rate of the dual arm injection protocol at our institution was 72% in our clinical cohort of patients with suspected central venous abnormality, representing the difficulty of obtaining dual arm intravenous access for simultaneous dual arm injection needed for first pass imaging of both the right and left sided central thoracic veins. In patients in whom the only available vascular access may be a small peripheral fragile vein that may not withstand the high pressure power injections, delayed phase imaging may be the only way to opacity both right and left sides of the thoracic veins. Even in patients with a central venous catheter, the tip of the catheter may be located in the lower SVC or at the cavoatrial junction, rendering the more peripheral thoracic veins unenhanced. In the event of central venous obstruction, opacification beyond the obstruction is possible more likely in delayed phased images as collateral pathways will have slow blood flow.

The primary limitation of our study is the small sample size reflecting the frequency of this clinical scenario in our institution, which is a quaternary care center with an National Cancer Institute designated cancer center and a large vascular access program. For purposes of scale, during the five-year time frame during in which the 18 CT examinations were collected, we performed approximately 600,000 thoracic CT examinations. During the same time period, there were only 2 thoracic MRI venograms and nine diagnostic thoracic central venous catheter venograms were obtained to specifically evaluate the central thoracic vein pathology. Additional limitations include the small number of patients who underwent catheter venography, including all of those reported to have a normal CT thoracic vein study, thereby lacking a gold standard reference verification for normal CT venography examinations. However when we consider normal CT thoracic vein studies with no subsequent diagnosis of venous abnormality or resolution of symptoms over the period of clinical follow up as true negatives with the 5 patients who underwent catheter venography, the diagnostic accuracy of delayed phase performs better than early phase images. We also did not evaluate the influence of patient characteristics, and contrast injection bolus shaping in this biphasic SVC CT injection protocol, which are beyond the scope of this study.

In conclusion, our results suggest that a single delayed phase for thoracic CT venous examination is appropriate for evaluating suspected central thoracic venous abnormality, due to better reader agreement, higher reader confidence, more homogenous venous enhancement, less streak artifacts and avoiding the technical challenges of a dual arm injection technique, reducing the radiation exposure by half compared to acquiring both first pass and delayed phase images.

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Figure 1.

A 53 year old female with metastatic breast cancer presented with swelling of the left upper extremity and neck.

(A) First pass phase thoracic CT venography demonstrates streak artifacts (arrow) emanating from the dense contrast material in the SVC.

(B) Delayed phase image demonstrates a filling defect (arrowhead) in the SVC adherent to the indwelling central venous catheter (curved arrow) and no streak artifacts.

Figure 2.

A 45 year old female with cystic fibrosis with a long-term right internal jugular venous catheter who presented with recurrent facial swelling.

(A) First pass and (B) delayed phase thoracic CT venography and (C) subsequent catheter venography demonstrate a filling defect (arrow) attached to the caudal end of the catheter, and focal SVC narrowing (curved arrow) at the cavoatrial junction. There was also a focus of heterogeneous enhancement (arrowhead in A) concerning for an additional thrombus present only on the first pass images and not confirmed on either delayed phase images or catheter venography, indicating a first pass venography false positive and most likely due to heterogeneity of venous enhancement with admixture of contrast from the bilateral upper extremity injections.

Figure 3.

A 51 year old male with a history of venous thromboembolic disease presented with two day history of increasing upper extremity pain, tingling and weakness. Bilateral upper extremity Doppler ultrasound excluded peripheral venous occlusion.

(A) Early phase thoracic CT venography demonstrates heterogeneous enhancement (arrow) with a mean attenuation value of 515 HU + / - 176 HU (132 to 1090 HU) that could be misinterpreted as a filling defect.

(B) Delayed phase images demonstrate homogenous opacification with a mean attenuation value of 198 HU + / - 21 (138 to 252 HU).

Tables 1

Study participant characteristics

CHARACTERISTICS OF STUDY PARTICIPANTS		
Total number of study participants	18	
Age	49.5 years +/- 10 years (range 28–68 years)	
Central venous catheter or stent	7 patients	
Gender	5 male	13 female
Clinical Indication for CT scan	Suspected SVC syndrome	11 patients
	Upper extremity swelling and/or pain	5 patients
	Road map prior to Vascular Intervention procedure	1 patient
	Cardiac nuclear medicine scan finding of SVC obstruction	1 patient
Relevant Clinical History	Malignancy	4 patients
	Cystic fibrosis	2 patients
	Fibrosing mediastinitis	1 patient
	Pneumonia	1 patient
	Chronic renal failure	1 patient
	Connective tissue disease	1 patient
	Trauma	1 patient
	Venous thromboembolic disorder	1 patient
	No pre-existing relevant diagnosis	6 patients

Table 2

Inter and Intra Reader Agreement For Overall Diagnosis

		Number*	Kappa values	95% CI
Inter-reader (between 3 readers)	First Pass	14	0.5	0.3–0.8
	Delayed phase	18	0.8	0.5–1
Intra-reader (between phases)	Reader 1	18	0.4	0.01–0.8
	Reader 2	14	0.9	0.6–1
	Reader 3	16	0.5	0.09–0.9

*
= Less than 18 due to exclusion of subjects with uninterruptable central venous segments.

Table 3

Reader Confidence Level for Overall Diagnosis

Reader	High/Moderate Confidence Level (%)		p-value *
	First Pass	Delayed Phase	
1	76% (13/17)	88% (15/17)	0.16
2	81% (13/16)	88% (14/16)	0.32
3	89% (16/18)	94% (17/18)	0.56

* McNemar's test.

Table 4

Mean enhancement of thoracic vasculature on CT venography

Anatomic Segment	First Pass			Delayed Phase		P-values	
	#	Mean (SD)	Median	Mean (SD)	Median	Median level between phases ^X	Variability between phases [*]
Right Subclavian Vein	18	788 (809)	599.5	414 (527)	189	0.18	0.02
Right Internal Jugular Vein	7	214 (368)	67	188 (98)	179	0.38	0.46
Right Brachiocephalic Vein	18	462 (521)	387.5	247 (125)	208	0.09	0.0032
Superior Vena Cava	18	615 (414)	512	231 (164)	189	0.0003	0.0037
Right Atrium	18	274 (155)	271	173 (53)	187.5	0.02	0.0003
Right Ventricle	18	223 (118)	212	182 (53)	180.5	0.22	0.0070
Main Pulmonary Artery	18	212 (121)	200	179 (52)	184	0.37	0.0009
Right Pulmonary Artery	18	216 (126)	210	175 (56)	174	0.46	0.0003
Left Pulmonary Artery	18	216 (124)	221	178 (51)	182	0.30	0.0004
Left Subclavian Vein	18	906 (1062)	274	249 (195)	177.5	0.04	0.0050
Left Internal Jugular Vein	7	817 (1058)	129	338 (318)	158	0.47	0.18
Left Brachiocephalic Vein	18	694 (694)	478.5	246 (145)	188	0.009	0.0003

^XWilcoxon Signed Rank test p-value for difference in median level between groups.^{*}Brown and Forsythe's test p-value for variability between the two phases;

Table 5

Range of enhancement of various thoracic vascular segments

Anatomic Segment	First Pass			Delayed Phase		P-values Median level between phases ^X
	#	Mean (SD)	Median	Mean (SD)	Median	
Right Subclavian Vein	18	740 (864)	245	358 (496)	131	0.21
Right Internal Jugular Vein	7	470 (982)	84	84 (56)	76	0.38
Right Brachiocephalic Vein	18	1058 (956)	998.5	364 (453)	100	0.0028
Superior Vena Cava	18	1022 (883)	698	378 (652)	83	0.0001
Right Atrium	18	213 (174)	132	92 (42)	82	0.0005
Right Ventricle	18	167 (247)	97.5	90 (38)	79.5	0.12
Main Pulmonary Artery	18	75 (32)	64	68 (25)	64	0.31
Right Pulmonary Artery	18	99 (78)	71	67 (19)	70	0.0258
Left Pulmonary Artery	18	98 (38)	94	71 (24)	63	0.0100
Left Subclavian Vein	18	722 (789)	304.5	216 (396)	108	0.0139
Left Internal Jugular Vein	7	874 (1037)	135	491 (1064)	71	0.58
Left Brachiocephalic Vein	18	818 (965)	248	100 (59)	88	0.0013

^X Wilcoxon Signed Rank test p-value for difference in median level between groups.