Advance Publication

Circulation Journal
doi:10.1253/circj.CJ-20-0416

ORIGINAL ARTICLE

Low Tube Voltage Computed Tomography Venography for Patients With Deep Vein Thrombosis of the Lower Extremities
— A Comparison With Venous Ultrasonography —

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Background: Low tube voltage computed tomography venography (CTV) can be expected to increase imaging contrast and decrease radiation exposure by using iterative reconstruction (IR). This study evaluated the diagnostic ability of low tube voltage CTV with IR for deep vein thrombosis (DVT), compared to ultrasonography (US).

Methods and Results: Two experienced radiologists retrospectively reevaluated the CTV data of 55 of 318 consecutive patients suspected of having DVT or pulmonary embolism between December 2015 and April 2017. The 55 patients had undergone both low tube voltage CTV and US (within 1 day before or after CTV). The lower extremity veins were divided into 10 segments. The DVT forms were categorized into 3 types: complete, concentric, and eccentric. We analyzed the 534 overall segments (16 segments excluded in US) measured using both CTV and US. The sensitivity-specificity was overall 73.3–90.0%, for femoropopliteal, it was 90.0–93.2%, and for the calf, it was 71.1–87.2%. The diagnostic accuracy between the 'eccentric only' and 'others' groups focusing on DVT forms was compared, and significant differences were revealed, especially in the muscular vein.

Conclusions: The DVT diagnostic ability above the knee was comparable between low tube voltage CTV with IR and conventional CTV, and the radiation dose was reduced. It was suggested that eccentric DVT measured by CTV tend to be a false-positive, especially in the calf muscular vein.

Key Words: Computed tomography venography; Deep vein thrombosis; Iterative reconstruction; Low tube voltage computed tomography venography; Ultrasonography

Venous thrombosis most commonly occurs in a deep vein in the leg or pelvis, and this type of thrombosis is known as a deep vein thrombosis (DVT). Compression ultrasonography (US) is the test of choice to diagnose symptomatic DVT.[1–5] Computed tomography pulmonary angiography (CTPA) combined with venous-phase imaging (CT venography: CTV) in the lower extremity is another option to evaluate a DVT in a patient with a suspected pulmonary embolism (PE) (**Table 1**).[6–14] To improve the prognosis of PE, it is important to assess the severity of PE and point out the sources of embolism, especially DVT above the knee, which can cause fatal PE. Both CTPA and CTV are useful to evaluate PE and DVT in a single examination.

CTV can provide information about the bilateral entire deep venous system; however, the main disadvantage of combined CTPA and CTV is the radiation exposure it provides. With technological advances in multi-detector computed tomography (MDCT), a reduced radiation dose from CT has been achieved in several ways. For example, the reduction of tube voltage using an iterative reconstruction (IR) algorithm has been reported and shown to be effective to reduce the radiation dose for lower-extremity CTV scans.[15–20] IR, which uses a correction loop in the reconstruction of an image from the raw image data to control noise on CT images, is a method to reduce image noise while maintaining image quality.

There are several reports of low tube voltage CTV with IR; however, to the best of our knowledge, no published study has evaluated the diagnostic ability between low tube voltage CTV with IR and US. We conducted the present study to evaluate the DVT diagnostic ability of low tube voltage CTV with IR compared to US.

Received April 30, 2020; revised manuscript received October 15, 2020; accepted October 22, 2020; J-STAGE Advance Publication released online January 13, 2021 Time for primary review: 25 days

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ISSN-1346-9843

Table 1. Studies Using Conventional Tube Voltage CTV Above the Knee

Author (Year)	N	Sensitivity (%)	Specificity (%)
Duwe et al (2000)[6]	74	89.0	94.0
Garg et al (2000)[7]	70	100.0	97.0
Loud et al (2000)[8]	71	100.0	100.0
Cham et al (2000)[9]	116	100.0	96.0
Peterson et al (2001)[10]	136	71.0	93.0
Loud et al (2001)[11]	308	97.0	100.0
Yoshida et al (2001)[12]	42	100.0	100.0
Begemann et al (2003)[13]	41	100.0	96.6
Lim et al (2004)[14]	26	100.0	100.0

CTV, computed tomography venography.

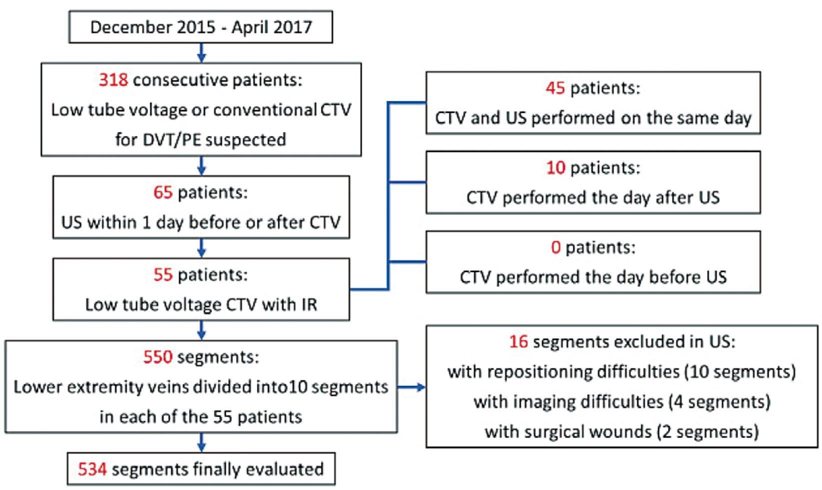

Figure 1. Patients selection and segments that were excluded. CTV, computed tomography venography; DVT, deep vein thrombosis; IR, iterative reconstruction; PE, pulmonary embolism; US, ultrasonography.

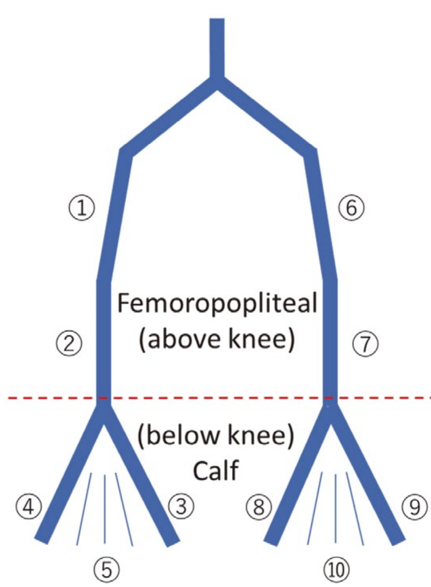

Figure 2. The 10 segments: ① right femoral vein; ② right popliteal vein; ③ right posterior-tibial vein; ④ right peroneal vein; ⑤ right muscular vein; ⑥ left femoral vein; ⑦ left popliteal vein; ⑧ left posterior-tibial vein; ⑨ left peroneal vein; ⑩ left muscular vein.

Methods

Patients

Our institutional review board (Niigata University) approved this retrospective study, and informed consent was waived. We adapted low tube voltage imaging with IR as our CT protocol for PE or DVT in December 2015 and started this study in May 2017.

We retrospectively reevaluated the CTV data of 55 of 318 consecutive patients suspected of having DVT or PE between December 2015 and April 2017 at our institute (Niigata University Medical & Dental Hospital). Sixty-five of the 318 patients had been examined by using US within 1 day before or after CTV, and 55 of these 65 patients had undergone low tube voltage CTV with IR. In the 55 patients, 45 patients had CTV and US performed on the same day, 10 patients had CTV performed the day after US, and no patients had CTV performed the day before US. The mean age of the 55 patients was 66.3 years (range 41–85 years). Eleven (20.0%) of the patients were male, and 44 (80.0%) were female.

The lower extremity veins were divided into 10 segments: right femoral vein; right popliteal vein; right posterior-tibial vein; right peroneal vein; right muscular vein; left femoral vein; left popliteal vein; left posterior-tibial vein; left peroneal vein; left muscular vein. We evaluated 10 segments in each of the 55 patients, and 16 of the total 550 segments

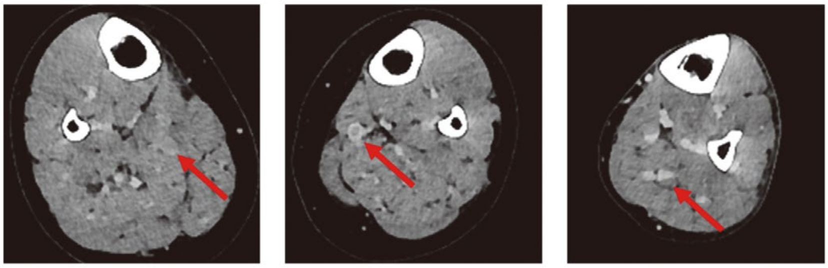

Figure 3. Three types of deep vein thrombosis (DVT) forms: Complete (left arrow); Concentric (center arrow); and Eccentric (right arrow).

were excluded as a result of US. The reasons for the 16 exclusions as a result of US were as follows: repositioning difficulties (10 segments), imaging difficulties (4 segments), and surgical wounds (2 segments). Finally, 534 segments of the 55 patients were evaluated (**Figures 1** and **2**).

MDCT Imaging Protocol

All patients underwent a combined CTPA and CTV of both lower limbs. All CTPA-CTV studies were performed on a 192-slice scanner (SOMATOM Force; Siemens Healthineers, Erlangen, Germany). All patients were examined while in the supine position with the bilateral ankles on a pillow to put the calf up. An automated power injector was used to administer 100 mL of 370 mgI/mL non-ionic contrast material (Iopamiron 370; Bayer HealthCare, Berlin, Germany) in all but one of the patients at a flow rate of 22.2 mgI/kg/s and an additional 40-mL bolus of 0.9% saline solution at the same flow rate through a 22-gauge. catheter in the antecubital vein. For the single patient, 100 mL of 350 mgI/mL non-ionic contrast material (Omnipaque 350; Daiichisankyo HealthCare, Tokyo) was used.

Automatic bolus tracking (CARE Bolus; Siemens) with a trigger attenuation threshold of 200 Hounsfield units (HU) within the pulmonary trunk was used, and the acquisition of CTPA started 10 s after the trigger. The acquisition of indirect CTV started 5 min after the completion of the CTPA to produce near-optimum enhancement in the veins of the lower extremities. CTV scanning was done from the abdomen to the calf in a craniocaudal direction during a single breath-hold; the patients were allowed to breathe during the leg scan.

The patients underwent CTV with the following parameters: tube voltage, 80 kVp; collimation, 192×0.6 mm; automatic tube current modulation (CARE Dose4D; Siemens) with a quality reference volume computed tomography dose index (CTDIvol) of 3 mGy; section thickness, 2.0 mm; slice interval, 2.0 mm; gantry rotation time, 0.28 s; and pitch, 0.85. The IR technique of the Sinogram Affirmed Iterative Reconstruction (SAFIRE; Siemens) was used with the strength level 4.

In most cases, sufficient contrast was obtained and no additional scan was performed. There were some segments with poor images due to postoperative vascular compression or metal artifacts, but even such segments were included in the CTV evaluation.

US Protocol

US was performed by medical technologists as routine work in accordance with the Japanese standard US protocol with a linear probe, color Doppler and the compression method,[21] and the saved image data were confirmed by a radiologist who was blinded to the CTV results.

Image Interpretation

All 55 examinations of the low tube voltage CTV with IR were anonymously evaluated by 2 experienced board-certificated radiologists (#1: 27 years' experience; #2: 15 years' experience) who were blinded to each patient's name, medical history, and report.

The diagnostic criterion for a DVT on CTV was a complete or partial intraluminal filling defect. We categorized the forms of DVTs as three types: complete, concentric, and eccentric (**Figure 3**). If there were different interpretations regarding the presence of DVTs or the forms of DVTs in a segment, a consensus decision was reached. The inter-observer variability was tested for the entire venous system, the proximal venous system, and the distal venous system.

Statistical Analysis

The statistical analyses were performed in the following order. We first analyzed the diagnostic ability of CTV for all segments, using US as a reference. We then analyzed the segments after dividing them into 2 groups: 'femoropopliteal' (femoral vein and popliteal vein) and 'calf' (posterior-tibial vein, peroneal vein, and muscular vein). Next, we analyzed the veins after dividing all segments into 5 groups per vein (femoral vein, popliteal vein, posterior-tibial vein, peroneal vein and muscular vein). Furthermore, we divided the CTV-positive segments into 2 groups according to the DVT forms: 'eccentric only' and 'others', and we used Fisher's exact test (2×2) to compare the true positives and false positives between the 2 groups. Finally, in addition to segment-based diagnostic ability, patient-based diagnostic ability was also calculated.

Cohen's kappa statistic was used to determine the differences of interpretations regarding the presence of DVTs. We defined κ values >0.80 as indicating excellent agreement, 0.61–0.80 as good agreement, 0.41–0.60 as moderate agreement, 0.21–0.40 as fair agreement, and ≤0.20 as poor agreement. Probability values <0.05 were considered significant. IBM SPSS Statistics version 25 was used for these analyses.

Results

Radiation Dose

The CTDI vol with the tube voltage set at 80 kVp was measured in the 55 patients, and the range was from

Table 2. Results of Low Tube Voltage CTV With IR vs. US, (A) 534 Segment-Based Results, (B) 55 Patient-Based Results

(A) Segment-based	n	CTV(+) US(+) (true positive)	CTV(+) US(–) (false positive)	CTV(–) US(+) (false negative)	CTV(–) US(–) (true negative)
Overall segments	534	63	45	23	403
Femoropopliteal segments	216	9	14	1	192
Calf segments	318	54	31	22	211
Femoral vein segments	108	4	5	1	98
Popliteal vein segments	108	5	9	0	94
Posterior-tibial vein segments	104	3	7	6	88
Peroneal vein segments	106	12	4	5	85
Muscular vein segments	108	39	20	11	38
(B) Patient-based	**N**	**CTV(+) US(+) (true positive)**	**CTV(+) US(–) (false positive)**	**CTV(–) US(+) (false negative)**	**CTV(–) US(–) (false negative)**
Overall	55	38	7	7	3
Femoropopliteal	55	6	8	1	40
Calf	55	35	8	9	3

Data are presented as (A) segment; (B) patient. CTV, computed tomography venography; IR, iterative reconstruction; US, ultrasonography.

Table 3. Results of DVT Diagnostic Ability Using Low Tube Voltage CTV With IR, (A) 534 Segment-Based Results, (B) 55 Patient-Based Results

(A) Segment-based	Sensitivity	Specificity	PPV	NPV	Accuracy
Overall segments	73.3	90.0	58.3	94.6	87.3
Femoropopliteal segments	90.0	93.2	39.1	99.5	93.1
Calf segments	71.1	87.2	63.5	90.6	83.3
Femoral vein segments	80.0	95.1	44.4	99.0	94.4
Popliteal vein segments	100.0	91.3	35.7	100.0	91.7
Posterior-tibial vein segments	33.3	92.6	30.0	93.6	87.5
Peroneal vein segments	70.6	95.5	75.0	94.4	91.5
Muscular vein segments	78.0	65.5	66.1	77.6	71.3
(B) Patient-based	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
Overall	84.4	30.0	84.4	30.0	74.5
Femoropopliteal	85.7	83.3	42.9	97.6	83.6
Calf	79.5	27.3	81.4	25.0	69.1

Data are presented as %. DVT, deep vein thrombosis; CTV, computed tomography venography; IR, iterative reconstruction; PPV, positive predictive value; NPV, negative predictive value.

2.39 mGy to 7.39 mGy, with a median of 3.78 mGy and an average of 3.99 mGy.

Sensitivity and Specificity

The results of the 534 segments from the 55 patients are summarized in **Tables 2A** and **3A**. Overall, the 534 segments had a sensitivity of 73.3% and a specificity of 90.0%; the 216 femoropopliteal segments had a sensitivity of 90.0% and a specificity of 93.2%, and the 318 calf segments had a sensitivity of 71.1% and a specificity of 87.2%. The femoral vein had a sensitivity of 80.0% and a specificity of 95.1%, the popliteal vein had a sensitivity of 100.0% and a specificity of 91.3%; the posterior-tibial vein had a sensitivity of 33.3% and a specificity of 92.6%; the peroneal vein had a sensitivity of 70.6% and a specificity of 95.5%; and the muscular vein had a sensitivity of 78.0% and a specificity of 65.5%.

In addition, the patient-based results of the 55 patients are presented in **Tables 2B** and **3B**. Overall, the patients had a sensitivity of 84.4% and a specificity of 30.0%, the femoropopliteal had a sensitivity of 85.7% and a specificity of 83.3%, and the calf had a sensitivity of 79.5% and a specificity of 27.3%.

False Positives and False Negatives

There were 14 false-positive segments and 1 false-negative segment above the knee (femoropopliteal). These actual images are shown in **Figure 4**. Of the 14 false-positive segments, 10 segments showed eccentric defects (**Figure 4A**) and 2 segments showed concentric defects (**Figure 4B**). The other 2 segments had poor contrast due to postoperative vascular compression in 1 patient (**Figure 4C**). False positives above the knee were often found in the saphenopopliteal junction or in the distal femoral vein. The only false-negative segment above the knee was noted on the US as a small eccentric thrombus (**Figure 4D**), but not on the CTV performed on the following day. No false negatives above the knee were found in the 45 patients who had undergone CTV and US on the same day. Therefore, the sensitivity above the knee in those 45 patients was 100%.

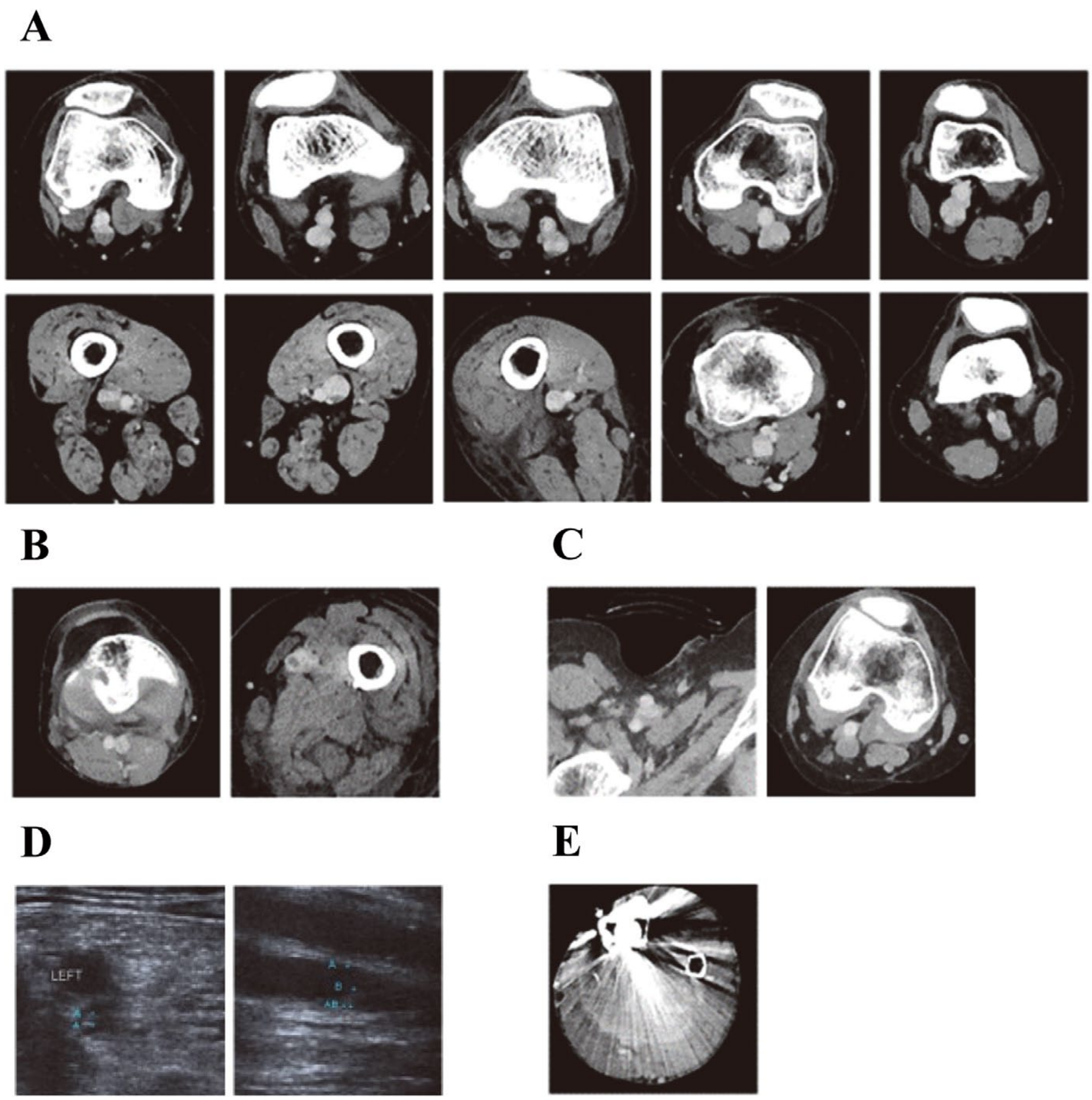

Figure 4. False-positive and false-negative images. (**A**) 10 false-positive segments with eccentric defects on CTV (above the knee). (**B**) 2 false-positive segments with concentric defects on CTV (above the knee). (**C**) 2 false-positive segments with poor contrast by postoperative vascular compression (above the knee in 1 patient). (**D**) 1 false-negative segment with eccentric DVT on US (above the knee). (**E**) 1 false-negative segment with poor image on CTV by metal artifact (below the knee). CTV, computed tomography venography; DVT, deep vein thrombosis; US, ultrasonography.

There were 31 false-positive segments and 22 false-negative segments below the knee (calf). More than half of these were found in the muscular veins, which had 20 false-positive segments and 11 false-negative segments. There was a false-negative segment in the muscular vein that was difficult to evaluate on CTV due to postoperative metal artifacts (**Figure 4E**).

Eccentric Only and Other Forms of DVTs

The results of the Fisher's exact tests (2×2) between 'eccentric only' – 'others' and 'true positives' – 'false positives' were as follows: overall segments, $P<0.001$; femoropopliteal segments, $P=0.013$; calf segments, $P<0.001$; femoral vein segments, $P=0.048$; popliteal vein segments, $P=0.266$; posterior-tibial vein segments, $P=1.000$; peroneal vein segments, $P=0.450$; and muscular vein segments, $P<0.001$ (**Table 4**).

Significant differences were found in overall segments, in femoropopliteal segments, in calf segments, in femoral vein segments and especially in muscular vein segments.

Inter-Observer Variability

There was good – moderate agreement between the 2 observers as to the presence of DVTs as follows: for overall segments, $\kappa=0.63$; for femoropopliteal segments, $\kappa=0.60$; for calf segments, $\kappa=0.63$. Of the segments with DVTs matched by 2 observers, the types of DVT forms matched 80.3% of the time.

Table 4. Results of CTV Accuracy Focusing on DVT Form by Using Fisher's Exact Test				
Fisher's exact test (2×2)	DVT form (on CTV)	True positive (US positive)	False positive (US negative)	P value
Overall segments	Eccentric only	7	29	<0.001*
	Others	56	16	
Femoropopliteal segments	Eccentric only	2	11	0.013*
	Others	7	3	
Calf segments	Eccentric only	5	18	<0.001*
	Others	49	13	
Femoral vein segments	Eccentric only	0	4	0.048*
	Others	4	1	
Popliteal vein segments	Eccentric only	2	7	0.266
	Others	3	2	
Posterior-tibial vein segments	Eccentric only	0	2	1.000
	Others	3	5	
Peroneal vein segments	Eccentric only	1	1	0.450
	Others	11	3	
Muscular vein segments	Eccentric only	4	15	<0.001*
	Others	35	5	

Probability values <0.05 were considered significant. *Considered significant. CTV, computed tomography venography; DVT, deep vein thrombosis; US, ultrasonography.

Discussion

Sensitivity and Specificity Above the Knee (Femoropopliteal)

Our present study analysis of 55 patients demonstrated that CTV with 80 kVp reconstructed with IR had a sensitivity 90.0% and a specificity of 93.2% in the femoropopliteal segments (i.e., the femoral vein and the popliteal vein).

The 90.0% CTV sensitivity above the knee was calculated from 9 true positives and 1 false negative. The only false-negative segment that missed DVT in the CTV had a localized mural thrombus in the US (**Figure 4D**). The possible reason for the false negative was the time lag; that the DVT had moved because of the CTV performed the day after the US. The additional analysis of the 45 patients who had undergone CTV and US on the same day showed a sensitivity of 100% (no false negatives) in the femoropopliteal segments. It is considered better to reduce the time lag between CTV and US as much as possible.

In contrast, the 93.2% CTV specificity above the knee was calculated from 14 false positives and 192 true negatives. Ten of the 14 false positives were eccentric defects and often found in the sapheno-popliteal junction or in the distal femoral vein (**Figure 4A**). Possible reasons for the false positives were as follows: laminar flow at the sapheno-popliteal junction, which might be observed as eccentric defects; or eccentric DVT in the distal femoral vein running deep on the dorsal side of the femur, which might be difficult to observe with US. In addition, there were 2 false positives with concentric defects, 1 of which (**Figure 4B Left**) was suspected to be overestimated for slight uneven imaging. The other (**Figure 4B Right**) was suspected of moving due to the time lag between CTV and US on the same day because there were multiple true positives below the knee. There were also 2 false positives (in 1 patient) with poor contrast because of postoperative vascular compression (**Figure 4C**).

In addition, the patient-based results above the knee (femoropopliteal) showed a slightly lower sensitivity and specificity than the segment-based results. As with the segment-based results, the only false negative due to time lag decreased the sensitivity, and some false positives, caused by the eccentric defects or the postoperative compression, decreased the specificity. Furthermore, the much lower number of true negatives due to no segmental divisions decreased the specificity.

Although there is room for improvement in these false positives and false negatives, the results in the femoropopliteal segments, with both sensitivity and specificity >90%, are considered comparable to the results of studies evaluating CTV using a conventional tube voltage.[6–14]

Sensitivity of PE

CT venography was reported by Loud et al in 1998.[22] According to a multicenter study using an above-knee CTV called PIOPED II, the sensitivity of PE was 83% in the CTPA single test, but the sensitivity of PE increased to 90% in the CTPA-CTV combination test.[23] In addition, the diagnostic ability of PE was equivalent in the combination test of CTPA-CTV and the combination test of CTPA-US.[24] Because the DVT diagnostic ability of conventional CTV and low tube voltage CTV (with IR) was shown to be equivalent above the knee in our study, it is estimated that the sensitivity of PE using low tube voltage CTV (with IR) is equivalent to that of PIOPED II. Further study is required on this point.

Reduction of Radiation Exposure by Low Tube Voltage CTV and IR

An increase in the patients' radiation exposure may be a problem due to the extensive coverage (including lower extremities) provided by the CTPA-CTV method. A low tube voltage protocol is a powerful method to reduce the radiation dose, especially for the vascular imaging. The image noise increases with the use of low tube voltage; however, as the energy of the X-rays decreases, the imaging effect of iodine increases. Thus, the contrast-to-noise ratio was maintained in low tube voltage CTV. The radiation dose at low tube voltage CTV has been reported at 10.3 mGy in CTDI vol and 1,163.3±73.6 mGy·cm in DLP.[15] The average CTDI vol value in our present study was 3.99 mGy, which is less than one-half the value of the previous study (10.3 mGy). A new reconstruction method using IR is being developed. IR is a reconstruction method capable of reducing image noise in CTV. It has been reported that the image quality obtained with IR is equal, whereas the radiation dose is reduced.[15] Compared to filtered back projection, IR has different image features. Images that are reconstructed with the use of IR show an oil painting appearance, and the diagnostic accuracy has not yet been evaluated. The present study demonstrates that the diagnostic accuracy of CTV was preserved when IR was used. To the best of our knowledge, this is the first study to evaluate the diagnostic accuracy of CTV using IR compared to US.

Sensitivity and Specificity Below the Knee (Calf)

Most reports of the CTV were targeted at the above-the-knee veins rather than the below-the-knee veins. In our study, there were many false negatives and significantly low sensitivity (71.1%) in the calf segments (i.e., the posterior-tibial vein, peroneal vein, and muscular vein). The specificity of the calf segments (87.2%) was also inferior to that of the femoropopliteal segments. Therefore, the overall sensitivity (73.3%) and specificity (90.0%) combining the femoropopliteal and calf results were relatively low. Among the calf veins, the diagnostic ability differed in the muscular vein compared to the posterior-tibial vein and the peroneal vein. Although the posterior-tibial vein and the peroneal vein both had >90% specificity, the muscular vein had particularly low specificity (65.5%).

We compared the diagnostic accuracy between the 'eccentric only' and 'others' groups, and significant differences were revealed in overall segments, femoropopliteal segments, calf segments, femoral vein segments and muscular vein segments; that is, the eccentric DVTs on the CTV tended to be false positive (US negative), especially in the calf muscular vein. One of the possible causes for the false positives is over-diagnosis of CTV, as mentioned in the case of the femoropopliteal. CTV has a potential limitation of incomplete mixing of contrast media. Muscular veins have underdeveloped vein valves and are affected by muscle contractions due to the angle of the ankle joint. As a result, stagnation of the blood flow or laminar flow may occur, and eccentric poor contrast regions may be formed on the CTV. Thus, CTV may overestimate the presence of eccentric DVTs, especially in muscular veins.

Loud et al included the lower leg when conducting CTV, but there has been no report showing the use of evaluating the lower leg veins in patients suspected of having a PE. The lower leg veins, in particular the muscular veins, are frequently the sites of thrombosis,[25] and further study is required to establish the use of CTV assessments of the lower leg veins.

Study Limitations

This study has several limitations: the retrospective design, the relatively low number of cases, the poor postoperative images and the time lag between CTV and US. Also, whether there was movement or a change of DVTs and therapeutic interventions between CTV and US was not investigated.

Conclusions

The DVT diagnostic ability above the knee was comparable between low tube voltage CTV with IR and conventional CTV, and the radiation dose was reduced. Our analyses suggest that eccentric DVT on CTV tend to be a false positive, especially in the calf muscular vein.

Acknowledgments

The authors gratefully acknowledge the work of past and present members of our laboratory.

Disclosures

The authors declare no conflicts of interest.

IRB Information

The Institutional Review Board of the Niigata University (2018-0422) approved this study. Our procedures were conducted in accordance with the Declaration of Helsinki and the ethical standards of the IRB of the Niigata University (responsible committee on human experimentation). Our studies on diagnostic accuracy conformed to STARD (Standards for Reporting of Diagnostic Accuracy Studies).

Data Availability

The deidentified participant data will not be shared.

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