Subtraction CT angiography for the diagnosis of iliac arterial steno-occlusive disease.

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Abstract:

Purpose. Accurate evaluation of stenosis in severely calcified arteries is a major challenge of conventional CT angiography (CTA) for peripheral arterial disease (PAD). The aim of this study is to evaluate the efficacy of subtraction CTA compared with conventional CTA and conventional angiography.

Materials and methods. 175 arterial segments of 31 consecutive patients with PAD who underwent CTA and subsequent digital subtraction angiography (DSA) were evaluated. The percentage stenosis of diseased arteries was measured in iliac arteries with caliper methods on conventional CTA and subtraction CTA, and concordance with DSA for identification of >50% stenosis were evaluated. Interpretation of CTA was always based on only maximum intensity projection (MIP).

Results. 174 (99%) segments were interpretable on subtraction CTA and had good correlation with DSA (R^2=0.844), although 55 (31%) segments were not evaluable on conventional CTA due to severe calcification. On subtraction CTA, segmental accuracy, sensitivity, specificity were 90.5%, 78.9%, 80.0%, respectively.

Conclusion. Subtraction CTA is an accurate diagnostic tool for the evaluation of PAD. It may be easier to interpret stenosis in the presence of calcifications as compared to the conventional CTA approach. Also, using only MIP, subtraction CTA allows similar evaluation with DSA.

Key words.

CT angiography; subtraction CT angiography; peripheral arterial disease; digital subtraction angiography; percentage stenosis.

Introduction:

Peripheral arterial disease (PAD) is a chronic and progressive health problem. The worldwide prevalence of PAD is 3-12% (1-6). The prevalence of PAD has been reported to increase from 8% in the age group 60 to 65 to 47% among the age group 85 to 90 years (7). Treatments of PAD are medical therapy, and revascularization with endovascular intervention or surgery. For revascularization, diagnosis of PAD needs not only the degree of stenosis but also the location. Therefore, evaluating the entire vascular tree is important. Traditionally, the diagnosis and pre-procedural assessment of PAD has been performed with invasive conventional angiography as the gold standard.

Contrast-enhanced computed tomography angiography (CTA) is an alternative to conventional angiography for the diagnosis of PAD. CTA is less invasive and easier to perform than conventional angiography. Many studies have already shown its high diagnostic accuracy with sensitivities and specificities of 83% up to 99% (8-11). However, extensive calcifications of the arterial wall hamper the correct assessment of the lumen for interpretation especially based on maximum intensity projection (MIP) and volume rendering (VR) that permit to evaluate the entire vascular tree. Such severe calcifications are common in patients with PAD who typically present with advanced age, diabetes mellitus or chronic renal failure requiring hemodialysis (12). Therefore, Interpretation of CTA is based on the axial images or curved planar reformation (CPR). These methods are more time-consuming work compared with DSA. Moreover, to evaluate the entire vascular tree, additional imaging for example MIP and VR is necessary.

Magnetic resonance angiography (MRA) could be a useful alternative, however, the usage of Gadolinium contrast medium is limited in patients with renal dysfunction. Gadolinium contrast medium is the contraindication for patients with severe renal dysfunction because of nephrogenic systemic fibrosis. Non-contrast MRA may be a promising solution but is still time-consuming (13). Also, widespread use remains hampered by limited scanner availability and expertise.

Recently, we developed subtraction CTA with orbital synchronized helical scan technique (OSHST) for the evaluation of PAD with severe arterial wall calcification. During this technique, the table movement and X-ray tube rotation are synchronized to identify the X-ray tube orbit for the repetition of helical scanning (14,15).

The aim of this study is to elucidate the efficacy of subtraction CTA compared with conventional CTA, using digital subtraction angiography (DSA) as the gold standard.

Materials and Methods:

Patient population

31 consecutive patients (Male 28: Female 3, mean age 70.8±8.6 years old) with PAD who underwent conventional CTA and subsequent digital subtraction angiography (DSA) prior to percutaneous transluminal angioplasty (PTA) were included. Risk factors and background of the patients are summarized in Table 1.

Patient characteristics are specified in Table 1. Briefly, 90% of the patients was male and mean age was 70.8±8.6 years. Diabetes was present in 39% of patients, while 10% of patients were on dialysis. Patients with estimated GRF below 45mL/min/1.73m^2 received intravenous hydration (500ml saline) pre and post procedure. Although three patients were asymptomatic, their ankle brachial index (ABI) showed low values during a regular medical checkup examination. Therefore, they underwent CTA examination to evaluate the presence of peripheral arterial disease.

Our institutional review board (IRB) approved this retrospective study and informed consent was waived.

Imaging protocol

320-row multi-detector CT (Aquilion ONE, Toshiba Medical Systems, Tochigi, Japan) was used in 16-row helical scanning mode. This approach, rather than wide volume scanning, was chosen as it results in better contrast enhancement at the distal lower extremities. The slice thickness, pitch factor, gantry rotation time, and tube peak voltage were 1mm, 0.843750, 0.5sec, and 120kVp, respectively. Also, adaptive dose reduction by tube current modulation was used (the range of tube current: 75 - 125mAs). For the acquisition of both pre-contrast and post-contrast images, OSHST was applied. Contrast medium (Iohexol 350, Daiichi Sankyou Company, Limited, Tokyo, Japan or Iopamidol 370, Bayer, Tokyo, Japan) was injected via the antecubital vein at 2mL/sec, total 65-75ml and immediately followed by 30mL saline flush. The start of the scan was triggered using the automatic bolus tracking technique with 200HU threshold at the upper limit of the abdominal aorta. The scan range was from the upper limit of the abdominal aorta to the ankle (Table 2). The lower extremities of the patients were fixed with Vac-Lok patient immobilization system (CIVIO Medical Solutions, Iowa, USA) to avoid patient motion and thus optimize the registration of pre-contrast and contrast-enhanced images (Fig. 1).

After the acquisition, datasets were reconstructed with a slice thickness of 1.0mm and 35cm of field of view, using reconstruction kernel of FC03 (moderate sharpness reconstruction kernel for general abdomen with beam hardening collection). The obtained images (both pre-contrast and contrast-enhanced images) were subsequently transferred to a dedicated workstation (Zio M900; Ziosoft, Tokyo, Japan) for generating subtraction CTA. Subtraction images were obtained by subtracting the pre-contrast images from the contrast-enhanced images. For this purpose, global automatic rigid registration was performed to obtain the subtraction images. In case of some remaining misregistration of calcium, rigid manual subtraction was performed by experienced radiological technologists (trained more than five years) with a dedicated application on CT scanner console. Subtraction CTA images were generated using MIP.

DSA was performed using a digital biplane system (Philips Medical System, Allura Xper FD20/10, Best, Netherlands) using a standard clinical protocol. Iodinated contrast material (Iopamidol 300, Bayer, Tokyo, Japan) was injected via a straight 4Fr catheter inserted with a femoral artery puncture using the Seldinger technique. In each series, 25-35mL of the contrast agent was administered at a rate of 7mL/sec.

Lesion analysis

For analysis the arterial tree was divided into the following 6 arterial segments: the common iliac arteries, the external iliac arteries, the internal iliac arteries (16-18). In one case with unilateral lesions, DSA was not performed on both sides. In seven cases, it was impossible to evaluate some segments for poor contrast enhanced DSA images. Therefore, a total of 11 segments were excluded for the evaluation. This resulted in a total of 175 evaluated arterial segments. In both conventional CTA and subtraction CTA, images were analyzed on the only anteroposterior MIP images. The percentage stenosis of each arterial segment was measured with caliper methods (Fig.2) in all three groups (conventional CTA, subtraction CTA, and DSA) (Fig.3) by two experienced radiologists independently. In the case of discordance, the final data was settled by consensus. When multiple stenoses were in the same segment, only the most severe lesion was evaluated. A significant stenosis was defined as ≥50% luminal narrowing. On conventional CTA, the segments deemed uninterpretable for severe calcifications were excluded.

Data and statistical analysis

The diagnostic accuracies (accuracy, sensitivity, specificity, positive predictive value, negative predictive value) of conventional and subtraction CTA were calculated against DSA findings as the reference standard.

The correlation between the percentage stenosis as determined on either conventional or subtraction CTA and DSA as the gold standard was assessed using regression analysis. To assess diagnostic accuracy, the area under the curve (AUC) of the receiver operating characteristic (ROC) was calculated for conventional CTA and subtraction CTA.

All statistical tests except ROC analysis were performed using a commercially available statistical package (SPSS version 11.5; SPSS, Chicago, Ill). ROC analysis was performed using R version 3.0.0 (The R Foundation for Statistical Computing) and pROC version 1.5.4 (20). Venkatraman method was used for the comparison of two ROC curves. All statistical analyses were done with 95% confidence level.

Results:

Conventional CTA

The average CT value of common femoral artery was 283±43 HU. The attenuation of the aortoiliac vasculature was enough for interpretation.

Fifty-five segments (31%) could not be evaluated due to severe calcification (Table 3). The AUC for conventional CTA excluding non-assessable lesions was 0.9701 (95% confidence interval [CI], 0.943 to 0.9897) for diagnosis of a segment with significant stenosis (≧50%) (Fig.4). Segmental accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 89.4%, 90.7%, 92.2%, 87.5%, and 90.0%, respectively (Table 4). When uninterpretable segments were scored as positive, the AUC for conventional CTA was 0.7446 (95% confidence interval [CI], 0.669 to 0.8162) (Fig.4). Segmental accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 92.9%, 53.8%, 65.0%, 89.1%, and 72.6%, respectively (Table 4). Interobserver kappa scores were 0.865 and 0.892 for conventional CTA without and with non-assessable lesions, respectively (Table 4).

Subtraction CTA

1 segments (1%) could not be evaluated due to residual calcifications (Table 3).

Subtraction CTA had a good correlation with DSA ($R^2=0.844$) (Fig. 5).

The corresponding ROC curve is shown in Fig.4. The AUC for subtraction CTA was 0.9444 (95% confidence interval [CI], 0.907 to 0.9728) for diagnosis of a segment with significant stenosis (≧50%), which was significantly higher than conventional CTA including uninterpretable segments scored as positive ($p<0.001$). Segmental accuracy, sensitivity, specificity, positive predictive value, negative predictive value were 90.5%, 78.9%, 80.0%, 89.9%, 84.5%, respectively. Interobserver kappa score was 0.838 (Table 4).

Discussion:

Endovascular treatment and surgery are beneficial in cases of severe PAD. For adequate decision making of treatment strategy, definitive diagnostic imaging is required. Treatment decisions depend not only on the degree of stenoses but also their locations, numbers, and distribution of lesions as well as their length as described in the TASC II guidelines (3).

Since PAD is a systemic disease the scan range should not be restricted to only the peripheral arteries but should also include the abdominal aorta and iliac arteries. The development of multidetector CT (MDCT) made it possible to scan these wide ranges with only one injection of contrast material. Also, as detectors increased, it became possible to scan with thin slices. Met et al. performed a meta-analysis for 20 studies comparing CTA with intra-arterial DSA. These studies included total 957 patients. Overall, the sensitivity of CTA for detecting more than 50% stenosis was 96% and specificity was 96%. Interpretation of CTA was always based on the axial images, although reading axial images represented a high workload. Other image reconstructions used were maximum-intensity projections (MIP), volume-rendered technique (VR), multiplanar reformation (MPR), curved-planar reformation (CPR) and virtual endoscopy (VE) (8). Schernthaner et al. and Ota et al. investigated the accuracy of CTA of PAD compared with DSA using primarily CPR images for the interpretation of CTA. Schernthaner et al. reported sensitivity and specificity of CTA in the detection of over 70% stenosis of 100% and 99.5% in the iliac arteries, 97.4% and 99.0% in femora-popliteal arteries. Ota et al. showed sensitivity, specificity, and accuracy of MDCT angiography of 99.2%, 99.1%, and 99.1% with regard to the detection of segments that had more than 50% stenosis (9, 10). Portugaller et al. demonstrated a sensitivity and specificity for depicting more than 70% stenosis of 84% and 78% using only semitransparent volume rendering technique (STVR). MIP reached values of 89% for sensitivity and 74% for specificity. MIP plus axial images reached values of 92% for sensitivity and 83% for specificity (11). Overall, many reports have confirmed the accuracy of CTA for the evaluation of PAD. However, interpretation of CTA was always based on the axial images and CPR. MIP and VR were used as additional tools. No investigations dedicated to the accuracy of CTA when using MIP and VR exclusively as compared to DSA are available.

MIP and VR have potential important advantages for diagnosing PAD compared with MPR, CPR and axial images. First, it is possible to evaluate the entire vascular tree based on TASC II guidelines similar to invasive angiography. Second, the time needed for reconstruction and diagnosis is considerably shorter as compared to other reading methods. Third, angiographic visualizations such as MIP and VR represent the lesions in an easier and more instinctive manner for physicians such as cardiologists and cardiovascular surgeons who are familiar to the (invasive) angiographic images. However, lesions with severe calcification remain difficult to evaluate by MIP and VR alone and thus still require the physician to revert to the more time-consuming use of MPR, CPR and axial images.

Commercially available software can rapidly perform removal of bone density using density thresholds. However, it is suitable for only uniform density. Density of arterial calcification is extremely various and partially overlaps the density of contrast enhanced vascular lumen. Therefore, simple removal of bone density have the nature of over- or under-estimation.

With subtraction CTA, theoretically, arterial calcifications could be removed with some artifacts including shading, partial volume, or undershooting that relate to severe calcifications. However, for subtraction CTA, perfect registration of the pre-contrast and post-contrast enhanced data sets is crucial. Nanbu, Imakita and Watanabe et al. used an orbital synchronized helical scan technique (OSHST) for evaluating intracranial aneurysms surgically treated with cobalt-alloy clips. OSHST was developed to permit 2 consecutive acquisitions along the same helical path, thereby reducing misregistration between the 2 scans and allowing acquisition of accurate subtraction images. For subtraction CT with OSHST, an initial scan was obtained followed by a second scan with the initial tube angle synchronized to the first scan, so that an essentially identical helical path was scanned. (14-16). We applied this method for diagnosis of PAD. However, for evaluating the peripheral vascular tree, it is necessary to move the CT table over a wide range, in contrast to cerebral CTA. Therefore, this examination is susceptible to patient movement during scanning. To overcome this problem, we applied the Vac-lok patient immobilization system (CIVCO Medical Solutions, Iowa, USA) which is a mat containing polystyrene beads. It gets hard and maintains its shape under vacuum. If despite these precautions patient movement still occurred, we used dedicated software for subtraction with rigid position matching technique to improve the registration.

In our study using DSA as the gold standard, arterial stenosis was evaluated accurately using subtraction CTA. Subtraction CTA had a good correlation with DSA ($R^2=0.844$). For the stenosis analysis (≧50%), subtraction CTA revealed a sensitivity and specificity of 78.9% and 80.0%, respectively. Interestingly, our study - in which MIP was used exclusively for evaluation of the subtraction CTA images - showed similar accuracy to evaluate arterial stenosis as seen in other articles in which axial images and CPR were used to evaluate CTA (8-11). MIP enables evaluation of the number and distribution of lesions as well as percent stenosis. Accordingly, treatment strategy of patients with PAD may be decided based on MIP images alone. Also, in the course of acquiring subtraction CTA, plain CT images are obtained. Pre-contrast CT provides important information of arterial calcifications that may influence treatment recommendations.

Dual energy acquisition has been proposed as an alternative technique for the evaluation of PAD. Dual energy CTA has the advantage of requiring images within a single acquisition and thus is considered less prone to motion artifacts as compared to subtraction CTA. Brockmann et al. performed a study comparing dual energy CTA with DSA. They found a sensitivity of 97.2% and specificity of 94.1% only using MIP (21). In a clinical routine setting, Kau et al. found somewhat lower accuracy with a sensitivity of 84% and a specificity of 67% for dual energy CTA also using only MIP (22). Based on their findings, the authors concluded that the performance of dual energy CTA was still limited in the presence of heavy calcifications. Subtraction CTA on the other hand may be better suited for calcium removal and thus facilitate the evaluation of such challenging cases (23).

Subtraction CTA requires dual (pre- and post-contrast) scanning and accordingly there is a concern of increased radiation dose. In this context, an important limitation of our current study is the fact that it was a retrospective feasibility study using data that were acquired prior to the introduction of iterative reconstruction techniques. Further optimization of the pre- and post-contrast acquisition parameters, including the use of iterative reconstruction and lower kVp, is likely to allow scanning at lower radiation doses similar to standard acquisition techniques (24,25).

Note that, in this case series, both the pre-contrast and contrast images were used for the diagnostic work-up; we used the pre-contrast images to determine the severity of arterial wall calcification which provided very important information for adequate decision-making of treatment strategy. And contrast enhanced images had enough contrast and image quality that enables conventional diagnostic work-up.

Second, during the percutaneous transluminal angioplasty procedure DSA was only performed in the iliac arteries. As a result, the target region in this study was from the common iliac artery to the common femoral artery. Extending the evaluation of diagnostic accuracy of subtraction CTA to the smaller arteries is therefore necessary.

In conclusion, subtraction CTA is an accurate diagnostic tool for the evaluation of PAD. Using only MIP, subtraction CTA allows evaluation of PAD with similar views as invasive angiography.

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Figure legends:

Fig.1

Vac-lok patient immobilization system (CIVCO Medical Solutions, Iowa, USA) is a mat containing polystyrene beads. It gets hard and maintains its shape under vacuum.

Fig.2

The percentage stenosis of each arterial segment was measured with caliper methods. The percent stenosis was calculated by $(b-a)/b \times 100$. The image on the left is subtraction CT angiography, image on the right is digital angiography,

Fig.3

Images of a 63-year-old man with right lower leg claudication (BMI= 20.0). On MIP of conventional CTA of iliac artery (a), the arterial lumen is not visible due to severe calcifications. However, MIP of subtraction CTA (b) visualizes the arterial lesions almost identical to digital angiography (c).

CTA of the distal arterial tree is shown (d, e). In subtraction CTA (e), the arterial lumen is clearly visible compared with conventional CTA (d), although the distal arterial tree is not evaluated in this study.

Fig.4

Area under the curve characteristics of subtraction CTA and conventional CTA without/with non-assessable lesions versus invasive angiography.

Abbreviations: Conv.CTA: conventional computed tomography angiography; Subtraction CTA: subtraction computed tomography angiography; NA: non-assessable lesions; ns: not significant; AUC: area under the curve

Fig.5

Correlation between subtraction CTA and DSA.

Abbreviations: SCTA: subtraction computed tomography angiography.

Table 1. Patient characteristics (*n* = 31)

Characteristic	Value
Age (years)	
Mean ± SD	70.8 ± 8.6
Range	49-86
Sex (*n*)	
Men	28 (90%)
Women	3 (10%)
Body measurements	
Height (cm)	161.7 ± 8.8
Weight (kg)	58.8 ± 12.2
Body mass index	22.5 ± 4.2
Renal function	
Serum creatinine level (mg/dL)	1.7 ± 2.9
Estimated glomerular filtration rate (mL/min/1.73 m^2)	67.1 ± 28.7
Risk factors of PAOD (*n*)	

Hypertension	26 (84%)
Diabetes mellitus	12 (39%)
Dyslipidemia	14 (45%)
Smoking	24 (77%)
Chronic renal insufficiency requiring dialysis	3 (10%)
Fontaine classification of disease (*n*)	
Ⅰ (asymptomatic)	3 (10%)
Ⅱ (claudication)	25 (81%)
Ⅲ (ischemic rest pain)	2 (6%)
Ⅳ (ulceration, tissue loss, gangrene)	1 (3%)

Values in parentheses are percentages. Abbreviations: PAOD: peripheral arterial occlusive disease; SD: standard deviation.

Table 2. Imaging protocol

Imaging protocol	
Scan parameters	
Slice mode	16 rows
Slice thickness	0.5 mm
Pitch factor	0.84375
Gantry rotation time	0.5 s/rot.
Tube peak voltage	120 kV
Tube current	75-125 mAs using volume EC with XY modulation
Scan range	From the upper limit of abdominal aorta to the ankle joints
Automatic bolus tracking	
Threshold value	200 HU
Location of ROI	the upper limit of abdominal aorta
Radiation Dose (DLP: mGy.cm)	

per examination	2809.9 +/- 114.2
per subtraction scanning (plain + CE)	2606.9 +/- 94.0
Contrast injection	
Iopamidol (370 mgI/mL) or Iohexol (350 mgI/mL)	65-75 mL
Injection	2 mL/sec via antecubital vein
Saline flush	30 mL

Abbreviations: EC: exposure control; HU: Hounsfield Unit; ROI: region of interest. CE: contrast enahncement

Table 3. Assessment of arterial stenosis (≥50%) with conventional CTA, subtraction CTA, and DSA.

CTA	DSA		Total
	<50%	≥50%	
Conventional CTA			
<50%	49	7	56
≥50%	5	59	64
Non assessable	37	18	55
Total	91	84	175
Subtraction CTA			
<50%	71	8	79
≥50%	19	76	95
Non assessable	0	1	1
Total	90	85	175

The parenthesis is a number except non assessable regions.

Table 4. Per segment diagnostic accuracy of conventional CTA and subtraction CTA to detect ≥50% stenosis.

Measure	**SCTA**	**Conv. CTA without NA**	**Conv. CTA with NA**
Accuracy (%)	90.5	89.4	92.9
Sensitivity (%)	78.9	90.7	53.8
Specificity (%)	80.0	92.2	65.0
Positive predictive value (%)	89.9	87.5	89.1
Negative predictive value (%)	84.5	90.0	72.6
Inter-observer kappa scores	0.838	0.865	0.892

Abbreviations: SCTA: subtraction computed tomography angiography; Conv. CTA: conventional computed tomography angiography; NA: non-assessable lesions