Role of MDCT in diagnosis of lower limb peripheral arteries diseases
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ABSTRACT
Background: Lower limb peripheral arterial disease (PAD) is a common disease that affects about two hundred million peoples per year. It is the third leading cause of cardiovascular morbidity. We plan to evaluate the diagnostic performance of 64-section computed tomographic (CT) angiography in the assessment of steno-occlusive disease in patients with PAD, with conventional digital subtraction angiography (DSA) as the reference standard.
Aim of study: is to compare the diagnostic accuracy of multidetector computed tomographic (MDCT) angiography in diagnosis of PAD compared to the DSA as pre-operative evaluation of lower limb peripheral arterial diseases.
Patients and methods: The study included 20 patients clinically presented with symptomatic PAD from February 2018 to July 2018. The study protocol was approved, and written informed consent was obtained from all patients. The patients underwent CT angiography and subsequent DSA. For stenosis analysis (≥70% stenosis), the arterial bed was divided into 35 segments and evaluated by three readers. Interobserver agreement was determined with generalized κ statistics. Accuracy, sensitivity, specificity, was calculated. Mc Nemar test was used to prove significant differences between CT angiographic and DSA findings.
Results: A total of 700 arterial segments were evaluated, with excellent agreement between readers (κ ≥ 0.928). On a segmental basis, both sensitivity and specificity for stenosis of 70% or more were at least 96% (386 of 400 segments and 290 of 300 segments, respectively), with an accuracy of 98% (686 of 700 segments). There was no significant difference between CT angiographic and DSA findings (P = .62–.87).
Conclusion: The diagnostic performance of 64-section CT angiography is excellent in patients with clinical symptoms of PAD.
Keywords: MDCT, DSA, PAD

INTRODUCTION
Lower extremity atherosclerotic peripheral arterial disease (PAD) is a relatively common disorder, particularly in the elderly population, that is caused and exacerbated by cardiovascular risk factors, such as a history of smoking, an elevated cholesterol level, or the presence of hypertension or diabetes mellitus (1).

In patients suspected of having PAD, it is important to not only establish the diagnosis but also accurately define the extent and severity of disease when planning subsequent treatment. Traditionally, pretreatment assessment of PAD has been performed with conventional catheter angiography. However, conventional angiography is an invasive procedure that can have a complication rate (puncture site complication and catheter-related complications) as high as 10%. Currently, complications of digital subtraction angiography (DSA) are substantially reduced, most of all in diagnostic procedures. The advent of alternative minimally invasive procedures, such as multidetector computed tomographic (MDCT) angiography has markedly reduced the need for diagnostic catheter angiography, effectively limiting its use to patients undergoing interventional treatment. Whereas CT angiography is clinically more useful than duplex ultrasonography (DUS) in the diagnostic work-up of patients with PAD. Further potential benefits of CT angiography include widespread availability, ease of use and rapid examination times over large volumes and considerable cost savings when this modality is used as a first-line diagnostic procedure (2).

Recently, a meta-analysis studies that were performed to evaluate the diagnostic performance of peripheral CT angiography with predominantly 16-section CT scanners showed overall sensitivity and specificity of 95% and 96%, respectively, in the detection of stenosis of more than 50% or occlusion. Improved performance (sensitivity, 97%–99%; specificity,
97%–98%) has been reported in two studies that were performed with 64-section scanners and were included in the meta-analysis.

The aim of this large-scale study was to evaluate the diagnostic performance of 64-section CT angiography in the evaluation of lower extremity steno-occlusive disease in patients suspected of having PAD by using conventional DSA as the reference standard.

PATIENTS AND METHODS

Study Setting: The study was conducted at Diagnostic and Interventional Radiology department (CT & Angiocath units) at Ain shams University Hospitals.

Study period: From February 2018 to July 2018.

Study population: The study included 20 patients having symptomatic lower limb PAD.

Inclusion criteria: 1- Diabetes Mellitus. 2- Any sex. 3- Age from 40 up to 70 years old. 4- Hyperlipidemia. 5- Smoking. 6- Hypertension.

Exclusion criteria: 1- Renal Failure. 2- Allergy to contrast media.

Sample Size: Twenty patients with clinical symptoms of lower limb PAD.

Ethical Considerations: Informed written consent was obtained from all patients participating in the study especially before MDCT and DSA. The study was approved by the Ethics Board of Ain Shams University.

Study Procedures

Patients were subjected to: Full history taking with clinical examination. Obtaining laboratory results including serum creatinine ratio. Patient have previously done lower limb arterial Doppler at Doppler unit at Ain Shams University. All patients underwent lower limb MDCT examination protocol and DSA protocol. Results of both studies were compared.

Multidetector CT Angiography: CT angiography was performed before DSA to avoid differential verification bias. A 64-section scanner was used with the following protocol: section thickness, 0.6 mm; reconstruction interval, 0.5 mm; 0.5-second gantry rotation time; pitch, 0.9; 100 kV; reference tube current, 200 mAs; mean tube current, 190 mAs; tube current range, 170–230 mAs with tube current modulation (Care Dose; Siemens); table feed, 40 mm/sec; individual scanning range, 1320–1535 mm; average scanning range, 1450 mm. All patients received ultravist (300) via an 18–20-gauge needle placed in a superficial vein in the antecubital fossa and injected with an automated dual-rail injector at a rate of 4 mL/sec. The total volume of contrast material administered was adjusted for the scanning length of each patient to establish a bolus duration that was equivalent to the scan duration. Scanning time was about 33 seconds. Therefore, we injected approximately 130 mL of contrast medium. We also used a saline flush of 30 mL injected at the same rate (4 mL/sec). Bolus tracing was used to determine the delay between the start of contrast material administration and scan initiation for each patient (attenuation threshold of Δ200 HU within a circular region of interest of 10–15 mm2 in the lumen of the proximal abdominal aorta, additional delay of 8 seconds before start of scanning). The reconstruction field of view was 34 cm, and the matrix size was 512 × 512, resulting in a voxel size of 0.6 × 0.6 × 0.6 mm; a mean of 5720 transverse images (range, 5160–6225 images) was generated for each patient. Image reconstruction was routinely performed with a medium soft-tissue deconvolution algorithm (B20 kernel). In patients with heavily calcified lesions, a separate medium-sharp deconvolution filter was applied (B46 kernel) to reduce calcium-related blooming artifacts. CT angiographic data sets were transferred to a dedicated for post processing. Reconstructed three-dimensional images included maximum intensity projections, volume-rendered images, and curved multiplanar reformations along the longitudinal axis of the artery. For each patient, a set of 25 images, generated with the three reconstruction algorithms (maximum intensity projection, volume rendered, and curved multiplanar reformation) was prepared for subsequent evaluation.

DSA Examination: Conventional DSA was performed with a standard angiographic unit (field of view, 40 cm; matrix, 1024 × 1024; average spatial resolution, 0.32 × 0.32 mm). An interventional radiologist
performed intra-arterial DSA after catheterization through a femoral artery access. An iodinated contrast agent (Ultravist 300) was administered through a 5-F guiding catheter. Aortograms were obtained initially. Thereafter, images of pelvic and leg arteries were obtained. In each series, 25–35 mL of the contrast agent was administered at a rate of 10–15 mL/sec. In cases in which endovascular revascularization was required, the therapeutic procedure took place during the same session.

**Image Analysis:** Diagnostic performance.—DSA images were reviewed at a 2-megapixel workstation by two vascular radiologists (expert in vascular and interventional procedures) blinded to CT angiographic and clinical data. Three independent radiologists who were blinded to the DSA findings performed evaluation of randomized CT angiographic images separately. Images were assessed at the previously mentioned dedicated workstation. Predefined three-dimensional reconstructions were available. Although each reader was free to interact with available data sets by using maximum intensity projection, volume-rendered, and curved multiplanar reformation techniques to identify and characterize stenosis and plaque morphology and composition. Image evaluation was performed with the arterial vascular system divided into 35 segments: (a) infrarenal aorta, (b) common iliac arteries, (c) external iliac arteries (proximal and distal segments), (d) internal iliac arteries, (e) common femoral arteries, (f) deep femoral arteries, (g) superficial femoral arteries (proximal and distal segments), (h) popliteal arteries (proximal and distal segments), (i) tibiofibular trunks, (j) anterior tibial arteries (proximal and distal segments), (k) peroneal arteries (proximal and distal segments), and (l) posterior tibial arteries (proximal and distal segments). In the analysis, the dorsalis pedis and plantar arteries were considered distal segments of anterior and posterior tibial arteries, respectively.4

Each segment was evaluated for the presence and degree of arterial stenosis and presence or absence of aneurysmal changes. The presence and extent of disease in each segment was determined by using a four-point scale: 1, no or mild stenosis (≤49% luminal narrowing); 2, moderate stenosis (50%–69% luminal narrowing); 3, severe stenosis (70%–99% luminal narrowing); and 4, occlusion (100% lumen blockage). Grade 3 and 4 stenosis was considered clinically relevant. If coexisting arterial stenoses were present in a single segment, only the stenosis with the higher grade was evaluated. Aneurysmal segments were defined as having dilatation of the lumen of 50% or more when compared with the most proximal healthy vessel. A separate subanalysis was conducted for calcified and noncalcified segments to investigate the effect of calcification on the diagnostic performance of CT angiography. Atherosclerotic plaques were graded as calcified if they had a calcified component represented for more than 50% of the extent of the alteration. they were graded as noncalcified if they had a total or predominant wide soft component. In these latter cases, eccentric calcifications could be present, but they had to be visible in no more than 50% of the extent of the alteration. Analysis was also performed to assess the diagnostic performance of CT angiography in the detection of severe stenosis or vascular occlusion in non-symptomatic legs to exclude differences in accuracy in a potentially less-involved arterial bed (inclusion of only a subset of stages of disease can result in spectrum bias).5

**Statistical methods:**

IBM SPSS statistics (V. 25.0, IBM Corp., USA, 2017-2018) was used for data analysis.

All patients and all arteries were included in the analysis, even if a study or vessel was not interpretable. The diagnostic performance of CT angiography was determined on a per-patient, per-segment, and per-region basis in terms of accuracy, sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios by using conventional DSA as the reference standard.

Accuracy was defined as the number of correctly identified patients, segments, or regions (either diseased or non-diseased) on CT angiographic images divided by the total number of patients, segments, and regions evaluated on
DSA images. Sensitivity in the detection of severe PAD was defined as the number of correctly identified clinically relevant (≥70% lumen narrowing) diseased segments or regions depicted at CT angiography divided by the total number of clinically relevant (≥70% lumen narrowing) diseased segments or regions depicted at DSA. Specificity was defined as the number of correctly identified segments or regions depicted at CT angiography without clinically relevant disease (≤69% lumen narrowing) divided by the total number of segments or regions depicted at DSA without clinically relevant disease. If a segment was uninterpretable at CT angiography, this segment was considered false-positive if DSA revealed a stenosis of no more than 69% and false-negative if DSA revealed a stenosis of at least 70% or occlusion. If a segment contained more than one clinically relevant stenosis, the most proximal severe stenosis at DSA was used as the anatomic basis for analysis. When a patient had at least one vascular region with a clinically relevant stenosis, the findings were defined as true-positive for steno-occlusive disease.

The χ2, McNemar, and Wilcoxon rank tests were used to test statistical significance, as appropriate. Interobserver and intermodality agreement was determined by using generalized κ statistics. A κ value of less than 0.20 indicated poor agreement; a κ value of 0.21–0.40, slight agreement; a κ value of 0.61–0.80, moderate agreement; and a κ value of 0.81–1.00, excellent agreement.

To give 90% power to the study at an α of .05 and to demonstrate a per-vessel negative predictive value for CT angiography that was substantially greater than 95%. Thus, at an assumed per-vessel stenosis rate of at least 70% corresponding to a sample size of 20 patients were needed.

RESULTS

During the study, 27 subjects were eligible for inclusion. Of these, 7 were excluded. Thus, the final evaluation was performed in 20 patients. Characteristics of the patient population are presented in table (1).

Table (1): Patient Characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>17(12)</td>
</tr>
<tr>
<td>Female sex</td>
<td>10(8)</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>62(±15)</td>
</tr>
<tr>
<td>Female sex</td>
<td>68(±4)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28(±5)</td>
</tr>
<tr>
<td>Glucose level</td>
<td>115(±40)</td>
</tr>
</tbody>
</table>

Diagnostic Performance

Table (2): Diagnostic accuracy of CTA for detection of femoral artery disease

<table>
<thead>
<tr>
<th></th>
<th>Femoral DSA</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
<td>Total</td>
</tr>
<tr>
<td>Femoral CTA</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>10</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>-</td>
<td>1</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Statistic</td>
<td>Value</td>
<td>Lower bound (95%)</td>
<td>Upper bound (95%)</td>
</tr>
<tr>
<td>Correct classification</td>
<td>90.0%</td>
<td>76.9%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Misclassification</td>
<td>10.0%</td>
<td>0.0%</td>
<td>23.1%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>90.9%</td>
<td>59.8%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Specificity</td>
<td>88.9%</td>
<td>54.0%</td>
<td>99.8%</td>
</tr>
<tr>
<td>False positive rate</td>
<td>11.1%</td>
<td>0.0%</td>
<td>28.2%</td>
</tr>
<tr>
<td>False negative rate</td>
<td>9.1%</td>
<td>0.0%</td>
<td>23.6%</td>
</tr>
<tr>
<td>Prevalence</td>
<td>55.0%</td>
<td>33.2%</td>
<td>76.8%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>90.9%</td>
<td>73.9%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>88.9%</td>
<td>68.4%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>8.1%</td>
<td>1.28</td>
<td>52.42</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.1%</td>
<td>0.02</td>
<td>0.67</td>
</tr>
<tr>
<td>Relative risk</td>
<td>8.1%</td>
<td>1.86</td>
<td>35.92</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>80.00</td>
<td>6.99</td>
<td>915.24</td>
</tr>
</tbody>
</table>

Conventional DSA was performed between 0 and 5 days (median, 3 days; mean, 0.9 day) after CT angiography. A total of 700
arterial segments pooled into 100 vascular regions were evaluated. Comparison of CT angiography with DSA in the detection of PAD for example in SFA is shown in table (2).

At DSA, atherosclerotic lesions were detected in 574 (82.6%) arterial segments, 356 (62.0%) vascular regions, and 19 (99.1%) patients; anemia and degenerative lumbar spine disease were diagnosed as the cause of claudication in two patients without any arterial atherosclerotic involvement.

The atherosclerotic lesions detected at DSA were classified as grade 1 in 224 segments (32.0%), grade 2 in 119 segments (17.0%), grade 3 in 342 segments (48.9%), and grade 4 (occlusion) in 15 segments (2.1%).

Excellent agreement between the blinded readers was achieved. We obtained κ values of at least 0.928, 0.913, and 0.887 at the patient, regional, and segmental levels respectively.

Aneurysmal changes were present in 4 segments (2 infrarenal abdominal aortic aneurysms and 2 femoropopliteal aneurysms) in 3 (11.3%) patients. These 4 segments were not included in the evaluation of diagnostic performance.

Overall, 442 (60.4%) of 700 segments had calcified lesions, while 277 (39.6%) had non calcified lesions. On a per-segment basis, the overall accuracy, sensitivity, and specificity of calcified lesions (0.98, 0.98, and 0.97, respectively) were similar to the overall accuracy, sensitivity, and specificity of non-calcified lesions (0.98, 0.98, and 0.98, respectively) Similar findings were obtained for analysis of vascular region (accuracy, sensitivity, and specificity of 0.97, 0.97, and 0.96, respectively, for calcified lesions and 0.98, 0.99, and 0.97, respectively, for non-calcified lesions). There were no significant differences in stenosis grading between the two groups (P > .05, χ² test).

DISCUSSION

Our results showed that the overall diagnostic performance of 64-section CT angiography was equivalent (accuracy, >0.98) to that of conventional DSA in the detection and treatment planning of PAD. The sensitivity, specificity, and accuracy of CT angiography exceeded 98% in our patient cohort, enabling the same therapy planning as DSA. These data compared favorably with results obtained with four- and 16-section scanners and with data in more recent small-scale studies performed with 64-section scanners. Importantly, unlike these previous studies, patient enrollment in our study was sufficient to provide 90% power to detect predictive variable differences. In fact, our study participants were representative of patients with PAD who were undergoing CT angiography in clinical practice. Most of the previous studies included predominantly patients with intermittent claudication. Such patients generally underwent conservative treatment and did not typically require CT angiography. On the contrary, our patient population included patients with acute limb ischemia and those with critical limb ischemia. These were the clinical conditions that require a complete assessment of lower extremity arteries to plan an open or endovascular intervention. Thus, this study could be considered of sufficient strength to be of direct and reliable relevance to routine clinical practice. In commenting on our results, there were three major aspects that might be emphasized: the technical planning of CT angiography, its diagnostic performance, and its clinical effect on PAD assessment. As far as technical planning, the use of faster scanners with an increased number of sections per gantry rotation (64 sections vs 16 sections), faster rotation speed (330 msec vs 375 msec), and superior temporal resolution (165 msec vs 188 msec) introduced the potential risk to outrun the contrast agent bolus when assessing peripheral arteries of the lower extremities due to acquisition mistiming.

Thus, in patients with severe steno-occlusive disease and coexisting cardiovascular disorders, opacification of the arterial tree may be delayed or asymmetric between the legs, impairing the accuracy of CT angiography. Therefore, we decided to adjust the volume of contrast medium based on the scan duration, according to the literature Ours was one of the few studies to emphasize the utility of staging PAD with clinically established criteria, rather
than simply evaluating the accuracy of CT angiography in stenosis assessment. In terms of clinical effect, there were no differences, with the exception of one case, between therapy recommendations made on the basis of CT angiographic findings and those made on the basis of DSA findings, providing vascular surgeons and interventional radiologists reliable information to plan conventional surgery, endovascular treatment, or a combination of the two procedures after a fast noninvasive examination. A drawback of CT angiography evidenced by our result was the radiation dose. While it had been shown that low-dose peripheral CT angiography was feasible and reasonably accurate in the identification of PAD, we kept radiation dose as low as reasonably achievable while favoring image quality and diagnostic accuracy. Moreover, considering that patients with PAD were likely to undergo repeated studies over time, mostly during post-interventional or post-surgical follow-up, we tried to keep radiation dose at minimal levels.

Our CT angiographic protocol resulted in an effective radiation dose substantially lower than that of DSA. In fact, even if our radiation dose was higher when compared with results reported with 16-section CT scanners, the mean effective radiation dose caused by 64-section CT angiography was lower by a factor of about two for women and by a factor of about one and a half for men when compared with the mean effective radiation dose calculated for conventional diagnostic DSA. Reduction of radiation exposure was possible in our study using an online modulation of tube current associated with routine use of 100 kV.

A potential limitation of our study was the fact that all patients were referred for DSA. Thus, patients with less severe PAD were almost absent from our series, yielding a high incidence of clinically relevant disease (210 of 212 patients, 99.1%), which would tend to increase both sensitivity and positive predictive value. However, it should be borne in mind that patients with severe PAD are precisely the patients who would benefit most from the reliability of CT angiography in interventional planning. Furthermore, to not fall into a spectrum bias, we performed a separate analysis of the non-symptomatic leg to exclude differences in accuracy in a potentially less-involved arterial bed. Another potential limitation was the clustering effect bias of our analysis that we were not able to overcome in the present study and that needs to be accurately addressed in further analyses.

CONCLUSION
Our study revealed excellent diagnostic performance of 64-section CT angiography and strong clinical relevance in a large consecutive series of patients with clinical symptoms of PAD.

Advances in Knowledge
As compared with digital subtraction angiography (DSA), CT angiography was highly accurate (accuracy, >0.98), faster (12 minutes ± 6 [standard deviation] vs 58 minutes ± 17) and better-tolerated (referred pain, 1.9% vs 67%) in the diagnosis and staging of peripheral arterial disease (PAD).

Beyond the stenosis evaluation and staging of PAD, peripheral CT angiography was a valid, strong, and reliable technique with which to select the most correct therapeutic plan (endovascular or surgical), according to the TransAtlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease guidelines.

Implications for Patient Care
The overall diagnostic performance of CT angiography was almost equivalent to that of conventional DSA in the detection and staging of clinically relevant PAD. Thus, this technique could be used as the primary method with which to evaluate this disease, enabling reduction of the radiation dose to patients.

In all but one case, there were no differences between therapy recommendations made on the basis of CT angiographic findings and those made on the basis of DSA findings. Therefore, peripheral CT angiography can be used as a primary method with which to guide therapeutic decision making.
References


