



Research article

Improving the diagnosis of peripheral arterial disease in below-the-knee arteries by adding time-resolved CT scan series to conventional run-off CT angiography. First experience with a 256-slice CT scanner



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ABSTRACT

Purpose: Run-off Computed Tomography Angiography (run-off CTA) of the lower extremities has become the method of choice for the diagnostic imaging of patients suffering from peripheral arterial disease (PAD). However, it remains a challenging radiological examination with a considerable risk of non-diagnostic image quality for the assessment of below-the-knee arteries. In this study, we investigate the diagnostic benefit of adding time-resolved CT scan series to the standard run-off CTA by performing repeated axial acquisitions over the calves of the patient during a second bolus of iodinated contrast injection.

Materials and Methods: This prospective study included 20 patients (9 male, 11 female; mean age 66.1 ± 14.9 years) who received a standard run-off CTA and an additional time-resolved CT scan series after a 10 min delay. The time-resolved series consisted of 18 repeated axial acquisitions over the calves directly below the knee with a 2 s interphase delay. For both series, two observers independently assessed the anterior tibial, posterior tibial and peroneal arteries of both legs for following criteria: arterial enhancement, presence and degree of stenosis, the confidence of grading, degree of stenosis and venous overlay. Quantitative assessment of arterial enhancement was performed by measuring the mean CT values (HU) in all arteries. Radiation exposure was quantified by the effective dose.

Results: A total of 118 arteries were assessed. The observer study showed that the additional time-resolved series improved both arterial enhancement (64% considered optimal enhanced versus 44%) and diagnostic confidence (59% considered as certain versus 33%) for the assessment of arterial stenosis (all $p < 0.05$). Venous overlay reduced from 15% to 6%. In all three arteries, the measured contrast enhancement by CT values (HU) was considerably higher (average 48%, $p < 0.05$) with the time-resolved series. The time-resolved series had an effect on stenosis classification ($p = 0.03$): a higher number of arteries were graded as having a non-significant stenosis (78.8% versus 71.2%). The interobserver variability in stenosis classification improved from $\kappa = 0.39$ to $\kappa = 0.61$. The mean effective dose was 5.1 ± 1.3 mSv for the run-off CTA and 0.2 ± 0.07 mSv for the time-resolved series. Per patient, a total volume of 140 mL contrast agent was injected.

Conclusion: A dynamic CT scan protocol with repeated axial series can be added to a standard helical run-off CTA sequence for the lower extremities within the same CT examination, and it increases image quality and diagnostic confidence for the assessment of presence and degree of arterial stenosis in below-the-knee arteries.

Abbreviations: PAD, Peripheral Arterial Disease; CTA, Computed Tomography Angiography; CTDI_{vol}, Computed Tomography Dose Index (mGy); DLP, Dose Length Product (mGy.cm); E, Effective dose (mSv); HU, Hounsfield Units; eGFR, estimated Glomerular Filtration Rate (mL/min/1.73m²); κ , Kappa statistic

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1. Introduction

Lower extremity peripheral arterial disease (PAD) is a common manifestation of atherosclerotic disease and is defined as a partial or complete obstruction of one or more arteries [1,2]. It is caused and exacerbated by cardiovascular risk factors, such as smoking, an elevated cholesterol level, or the presence of hypertension or diabetes mellitus [3]. Reported prevalence values range from 4.7% in patients aged between 60–69 years to 14.5% in patients aged over 69 years [4], and are expected to further increase worldwide as the population ages, cigarette smoking persists, and the epidemics of diabetes, hypertension, and obesity grow [5].

Both contrast-enhanced MR angiography (MRA) and Computed Tomography angiography (CTA) are highly accurate imaging modalities that reliably assess the presence, extent and severity of atherosclerotic disease [2,6,7]. In many centers, CTA of the peripheral arteries has replaced conventional diagnostic intra-arterial digital subtraction angiography (DSA) due to its minimally invasive nature, the availability of three-dimensional volumetric data acquisition, its high availability and short examination time [3,8,9].

The diagnostic value extracted from run-off CTA is undisputed for proximal, large caliber arteries (from the aorta to the popliteal artery). Contrary, the examination of below-the-knee arteries can prove extremely challenging for a myriad of reasons [8,10]: First, contrast concentration is physiologically reduced with time and distance passed, and arteries located further from the heart are most affected. Second, any hemodynamically significant lesion located up-stream will further decrease blood flow below the knee. Third, diameter size of below-the-knee arteries (2–3 mm) is considerably smaller than above-the-knee arteries (6–10 mm), and the ratio between lumen and external diameter of the vessel is likewise greatly reduced. Fourth, the presence of vessel wall calcifications hampers accurate assessment of residual lumen, particularly in diabetic patients or patients on hemodialysis that are prone to mediocalcinos. An optimal contrast timing should ensure sufficient arterial enhancement throughout the arterial tree: too early acquisition leads to insufficient enhancement, whereas delayed acquisition may result in a venous overlay. Sommer et al. introduced the concept of time-resolved CTA to overcome this by performing multiple helical CT acquisitions after contrast injection [10]. He reported that time resolved CTA could provide a higher diagnostic confidence than standard monophasic run-off CTA.

Fueled by the high technical demands in cardiac imaging, CT hardware technology is making rapid progress by improving gantry rotation speed and wider detectors to achieve motion-free volumetric data sets of the entire heart [11]. In theory, wide beam CT scanners could also allow a set of multiple axial acquisitions at high frame rate over the calves and, as such, obtain time-resolved run-off CTA at high temporal resolution. To the best of our knowledge, no publications exist that applies such wide detector acquisition to obtain time-resolved CTA data for imaging of PAD. Therefore, the purpose of this study was to investigate the feasibility of a time-resolved acquisition protocol with multiple 16 cm axial series over the calves and to assess its additional benefit to standard run-off CTA for the evaluation of PAD.

We set up a prospective study that targeted patients scheduled for standard run-off CTA. After the standard run-off CTA, an additional time-resolved CTA dataset was obtained during the same CT examination. Two observers independently assessed the anterior tibial, posterior tibial and peroneal arteries for the arterial enhancement, presence and degree of stenosis, their confidence of grading the degree of stenosis and presence of venous overlay. Quantitatively, the enhancement was measured by CT values, and patient radiation dose was calculated.

2. Materials and methods

2.1. Study design and patient collective

This prospective study was approved by the institutional review board (BUN 143201525091, local ethics committee, Vrije Universiteit Brussel) and included 20 (9 male, 11 female; mean age 66.1 ± 14.9 years) nonconsecutive patients who were referred for standard run-off CTA of the lower extremities because of suspicion of PAD. The following Rutherford classification [12] was attributed as a metric for clinical staging: 4 patients stage 0; 5 patients stage 1; 8 patients stage 3; 1 patient stage 4 and 2 patients stage 5. Standard exclusion criteria for contrast CT were applied: decreased kidney function ($eGFR < 60 \text{ mL/min/1.73m}^2$), known allergies to iodinated contrast-agent and hyperthyroidism. Within the same scan session, all patients underwent the standard run-off CTA and the additional time-resolved CTA after a 10 min delay.

2.2. CT scan and injection protocols

CT acquisition was performed with a 256-slice CT (Revolution CT, software version *revo_1.5_m3a.46*, GE Healthcare, Waukesha, WI) which has a maximal collimation of 16 cm ($256 \times 0.625 \text{ mm}$) per gantry rotation in axial scan mode. First, the standard run-off CTA was performed with a helical acquisition from the diaphragm to the toes. The scan parameters were: tube voltage 100 kV, auto mA with a noise index of 24, collimation 40 mm ($64 \times 0.625 \text{ mm}$), table feed 39.4 mm, pitch 0.98 and tube rotation 0.5 s. The reconstructed field of view (mm) was individually adapted to the anatomy of the patient. A biphasic injection protocol was used with 55 mL (flow 5.0 mL/s) + 35 mL (flow 3.0 mL/s) iodinated contrast (370 mg I/mL, Ultravist, Bayer Healthcare Pharmaceuticals), followed by a 40 mL saline flush (flow 3.0 mL/s). The CT acquisition was started by using automated bolus tracking software when a CT value threshold of 125 HU was reached in the suprarenal aorta. Secondly, after a 10 min delay, the time-resolved CTA series were performed with 18 repeated axial acquisitions over the calves directly below the knee with 2 s interphase delay. The scan parameters were: tube voltage 100 kV, auto mA with a noise index of 24, collimation 160 mm ($256 \times 0.625 \text{ mm}$), tube rotation 0.5 s and fixed field of view of 360 mm. Thirtyfive mL of the same iodinated contrast was injected using a flowrate of 5.0 mL/s + 15 mL (flow 3.0 mL/s), followed by a 40 mL saline flush (flow 3.0 mL/s). A fixed delay of 20 s after contrast injection was applied to start the time-resolved sequence in order to assess the wash in and wash out of the contrast bolus in the anterior tibial, posterior tibial, peroneal arteries at the level of the calves. The total scan duration was 45 s ($18 \times 0.5 \text{ s}$ passes with 2 s interphase delay).

2.3. Qualitative and quantitative image analysis

All patient data were de-identified prior to analysis. The CT data were processed on a clinical workstation (Advantage Workstation, GE Healthcare) in axial, coronal and sagittal planes, curved multiplanar reconstructions along each vessel of interest and maximal intensity projection (MIP) images. Standard rigid image registration of the 18 consecutive phases and bone removal was applied. In addition, movies were created from the time-resolved CT data that represent a loop of the 18 phases. Two board-certified radiologists with experience in run-off CTA (Y.D.B. and H.D., mean 4.5 years) participated in the observer study. The observers independently assessed the anterior tibial, posterior tibial and peroneal arteries of both legs for following criteria: arterial enhancement, presence and degree of stenosis, the confidence of grading, and venous overlay. Scoring was performed by an ordinal scale (Table 1). At first, the observers were only provided with the standard run-off CTA data. In a second session, both standard run-off CTA and the time-resolved series were provided for evaluation. In

Table 1
Image quality criteria and stenosis assessment for the observer study.

Criterion	Ordinal score
Arterial enhancement	Optimal – Average – Insufficient – None
Assessment of stenosis	Non significant (< 50%) – Significant (50-99%) – Occlusion (100%)
Confidence of stenosis grading	Confident – Average – Uncertain
Venous overlay	Yes – No

addition, quantitative assessment of arterial enhancement was performed by measuring the mean CT values (HU) in an ellipsoidal region of interest (ROI) in the three arteries of matching slices in the mid-segment for both legs.

2.4. Radiation dose evaluation

The additional radiation dose of the time-resolved series to the dose of the standard run-off CTA was considered. For all acquisitions, technical dose descriptors by Computed Tomography Dose Index (*CTDI_{vol}*) and dose length product (*DLP*) were documented from the Radiation Dose Structured Report RDSR of the studies [13]. Effective dose (*E*) was estimated following ICRP-103 guidelines [14] by using a CT patient dosimetry calculator (CT-Expo v1.7.1, G Stamm and H Nagel, Hannover). All CT acquisitions were simulated on a mathematical dosimetry phantom by applying the clinical scan protocol details (scan range and CT parameters).

2.5. Statistical analysis

Statistics were performed with SPSS (version 23, IBM Corporation, Armonk, NY). The differences in categorical image quality scoring and stenosis grading between the standard run-off and time-resolved series were assessed by a McNemar test (for venous overlay) and a Wilcoxon Sign Rank test (for arterial enhancement, stenosis grading and confidence of grading). The difference in enhancement by mean CT values (HU) between the standard run-off and time-resolved series and the difference between the reconstructed field of view was evaluated by a Wilcoxon Sign Rank test. For all tests, a *p*-value of less than 0.05 was considered to represent a statistically significant result. Inter-observer variability was evaluated by the Cohen kappa statistic with following levels of agreement: < 0.40 poor; 0.40-0.59 fair; 0.60-0.74 good; > 0.75 excellent [15,16].

3. Results

Image data of the standard run-off CTA and additional time-resolved CTA series were evaluated in a total of 118 arteries from 20 patients. For each patient, all three arteries of both legs were assessed, except for one patient who had an absent posterior tibial artery bilaterally, considered as a normal anatomical variant.

3.1. Effect of time resolved series on arterial classification for stenosis

Classification for significant stenosis was different (*p* = 0.03) between the standard run-off CTA and additional time-resolved CTA series (Table 2). Based on the time-resolved series, a higher number of arteries (78.8%) were graded as having a non-significant stenosis compared to standard run-off CTA (71.2%). We observed that the time-resolved series caused a shift towards a lower classification of stenosis degree (Table 3). From all arteries, 7.1% were reclassified from having a significant to non-significant stenosis and 3.6% from occlusion to significant. Only 1.5% were reclassified from significant to occlusion. The interobserver agreement in arterial classification increased on the brink of poor to fair (κ = 0.39) with standard run-off CTA to good (κ = 0.61) with the additional time series.

Table 2
Assessment of stenosis in the anterior tibial, posterior tibial and peroneal arteries for the standard run-off CTA and time resolved CTA. Reported values represent number of classified arteries out of total and frequency (%). Interobserver agreement by κ .

	Run-off CTA	Time resolved CTA
Non significant (< 50%)	84/118 (71.2%)	93/118 (78.8%)
Significant (50-99%)	28/118 (23.4%)	21/118 (17.9%)
Occlusion (100%)	6/118 (5.4%)	4/118 (3.2%)
κ	0.39	0.61

p = 0.03.

Table 3
Reclassification of stenosis gradation due to additional time resolved CTA series compared to standard run-off CTA alone. Reported values represent number of classified arteries out of total and frequency (%).

	Numbers and frequency
No change in grade	102/118 (86.7%)
Reclassified towards a lower grade	
Significant to non-significant	8/118 (7.1%)
Occlusion to significant	4/118 (3.6%)
Reclassified towards a higher grade	
Non-significant to significant	0/118 (0.0%)
Significant to Occlusion	2/118 (1.5%)

3.2. Effect of time-resolved series on enhancement, diagnostic confidence, radiation dose and contrast dose

Qualitatively, arterial enhancement was considered optimal in 64% of all evaluated arteries with the time-resolved CTA series compared to 44% with the standard run-off CTA (Table 4). Arteries with an insufficient enhancement for diagnosis reduced from 24% to 8% with the time-resolved CTA. In Fig. 1 an example is shown of a patient with insufficient enhancement of the lower leg arteries at standard run-off CTA and compared to a selected phase of optimal enhancement from the time-resolved CTA. Fig. 2 shows the dynamic evolution of arterial enhancement over all 18 phases of the anterior tibial artery, which reached a maximum enhancement in phase # 13. A CTA movie is provided as supplemental material that is derived from the time-resolved CTA series by subtracting the image data of the first non-enhanced pass from the consecutive contrast passes (see supplemental material). The diagnostic confidence of the observers in grading stenosis increased with the addition of the time-resolved CTA series, from 33% classified as certain to 59% (Table 4). Venous overlay reduced

Table 4
Observed arterial enhancement, observer confidence in stenosis assessment and presence of venous overlay in proximal, mid and distal segments of the anterior tibial, posterior tibial and peroneal arteries for the standard run-off CTA and time resolved CTA.

	Run-off CTA	Time resolved CTA
Arterial enhancement		
Optimal	52/118 (44%)	76/118 (64%)
Average	28/118 (24%)	30/118 (25%)
Insufficient	28/118 (24%)	9/118 (8%)
None	9/118 (8%)	3/118 (3%)
Confidence of grading stenosis		
Certain	39/118 (33%)	70/118 (59%)
Average	46/118 (39%)	42/118 (36%)
Uncertain	33/118 (28%)	6/118 (5%)
Venous overlay		
Present	18/118 (15%)	7/118 (6%)

All *p* < 0.05, Average κ = 0.42.

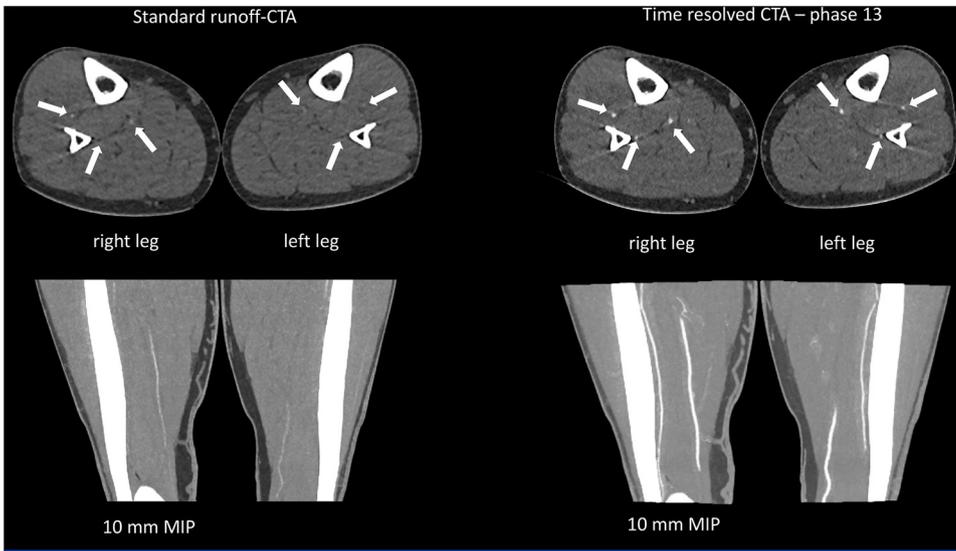


Fig. 1. Axial (top) and coronal maximum intensity projection (bottom) images of a 56 year old male patient. Images on the left are from the standard run-off CTA, images on the right represent the optimal phase of contrast (phase # 13) from the time resolved CTA series. Notice the increased enhancement in all three evaluated arteries (white arrows) with the time resolved CTA compared to standard run-off CTA.

from 15% to 6%. The average inter-observer agreement was fair ($\kappa = 0.42$).

In all three lower leg arteries, the measured contrast enhancement by CT values (HU) was considerably higher ($p < 0.05$) with the time-resolved CTA series by selecting the phase of optimal contrast (Table 5). The mean effective dose was 5.1 ± 1.3 mSv for the run-off CTA and 0.2 ± 0.07 mSv for the time-resolved series (Table 5). The administered contrast medium volumes for each patient were 90 mL for the standard run-off CTA and 50 mL for the additional time-resolved series. The axial (x,y) and z-axis resolution of the standard run-off CTA and additional time-resolved CTA series were comparable due to similar reconstructed field of views (respectively 374 ± 58 mm and 360 mm; $p = 0.52$) and detector element size (0.625 mm).

4. Discussion

Run-off CTA remains a challenging radiological examination regarding optimal scan acquisition parameters and timing after iodinated

Table 5

Arterial enhancement by CT values (HU) in the anterior tibial, posterior tibial and peroneal arteries for the standard run-off CTA and time resolved CTA, and radiation dose.

	Run-off CTA	Time resolved CTA
Arterial enhancement (HU)		
Peroneal a	167 (± 108)	257 (± 76)
Posterior tibial a	219 (± 125)	311 (± 76)
Anterior tibial a	198 (± 142)	294 (± 66)
Radiation dose		
<i>CTDI_{vol}</i> (mGy)	4.1 (± 0.9)	30.3 (± 6.1)
<i>DLP</i> (mGycm)	557 (± 163)	488 (± 97)
<i>E</i> (mSv)	5.1 (± 1.3)	0.2 (± 0.07)

Reported mean values with SD.

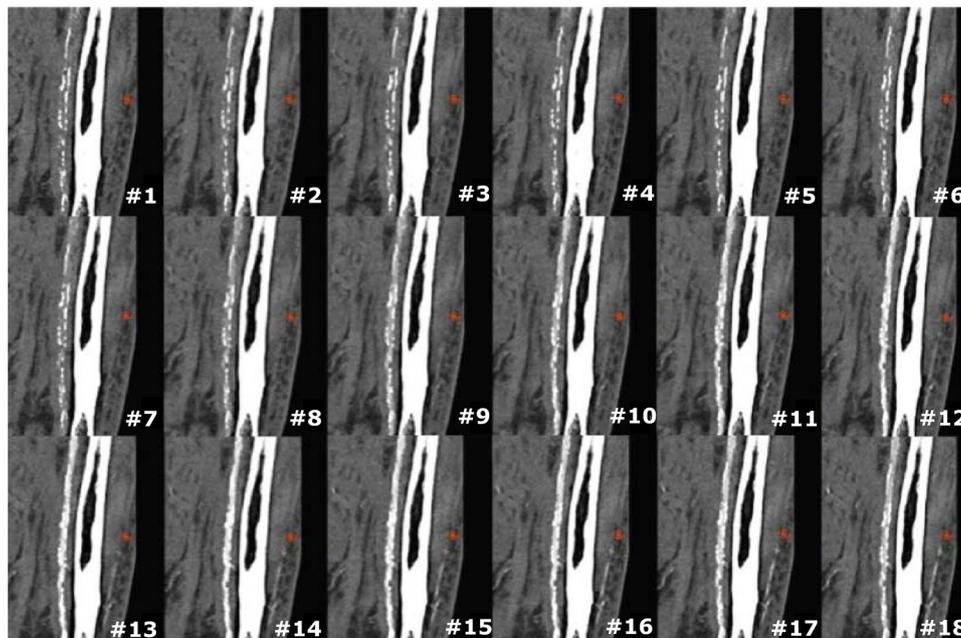


Fig. 2. Curved multiplanar reconstructions of the anterior tibial artery from the time resolved CTA. Each image represents a consecutive phase of the 18 repeated axial acquisitions with 2 s interphase delay. Notice the dynamic evolution of arterial enhancement with maximum intensity during phase # 13.

contrast injection. Its extended cranio-caudal coverage increases the risk of not having a sufficient arterial contrast enhancement in all vessel segments, in particular for small caliber vessels at the level of the calves. In addition, the actual speed at which an intravenously injected bolus of contrast medium propagates through the peripheral arterial tree is highly variable among patients [17].

Our study shows that a complementary dynamic acquisition with repeated axial passes over the calves improves arterial enhancement and diagnostic confidence in the assessment of occlusive disease for below-the-knee arteries. Dynamic time series allow the radiologist to select the optimal phase of enhancement for each arterial segment in both legs separately. Due to this, more arteries were classified as having optimal enhancement (64% versus 44%), and only 11% of the evaluated arteries were considered to have insufficient or no enhancement, compared to 32% with the standard run-off CTA alone (Table 4). The improved enhancement from the radiological observer study was confirmed by the recorded CT values (HU) in the vessels. Mean CT values increased by 52% in the peroneal artery, 42% in the posterior tibial artery and 48% in the anterior tibial artery (Table 5). Spatial resolution was similar between the dynamic series and the standard runoff series so it probably did not influence the qualitative assessment in favor or disfavor of a specific series.

The dynamic series also resulted in higher diagnostic confidence and a reclassification of the arterial segments for significant stenosis. With the addition of the dynamic series, certainty in reader confidence of grading stenosis increased from 33% to 59% (Table 4). Only 5% were classified as uncertain for the grading of stenosis, compared to 28% with standard run-off CTA alone. From all evaluated arteries for stenosis, 13.3% were reclassified, of which the majority were reclassified towards a lower category: 7.1% shifted from significant to non-significant and 3.6% from occluded to significant (Table 3). This information may have an important effect on the clinical management of the patient, including on the potential decision for revascularization. Only a small fraction (1.5%) was reclassified from significant to occluded.

Compared to the dosimetric data from the standard run-off CTA, the mean $CTDI_{vol}$ and DLP values of the dynamic scan are considerable, with in particular the $CTDI_{vol}$ of 30.3 mGy compared to 4.1 mGy (Table 5). However, the impact on the effective dose to the patient remains minimal, with an additional 0.2 mSv to the 5.1 mSv from the run-off CTA. This is caused by the fact that the dynamic series acquisition is limited to the level of the calves, which is a volume absent of important radiosensitive organs. Hence, the augmentation of the effective dose – or total body dose – due to the additional dynamic series remains limited (4%). The mean effective dose of the combined protocol in our study (5.3 mSv) is comparable to reported doses for standard run-off CTA 6.8 mSv [3]. However, large variabilities in dose are reported for run-off CTA. Some studies report doses in the range of 11.4 to 29.3 mSv [18], while others report doses as low as 1.9 mSv [19]. The difference in doses can be explained by the large variations in scan settings, in particular the kVp, and the availability of dose reducing techniques such as iterative reconstruction [2]. In addition, the applied methodology to estimate effective dose also plays an important role. Some authors [19] use a generic DLP to E conversion coefficient, while others – including our study – apply more detailed organ dose estimations [10]. The total administered contrast medium volume of the combined protocol in our study is 140 mL (90 mL for the run-off CTA + 50 mL for the dynamic series) which is comparable to reported literature values for single run-off CTA, varying between 100–160 mL [2,17,20,21].

The following limitations of our study merit consideration. First of all, additional invasive digital subtraction angiography (DSA) was not a part of this study and could have served as an external reference for the degree of stenosis as classified by the observers on CT. Secondly, current CT detector technology is limited to a scan volume of 16 cm. Hence, the dynamic series were limited to the region of the calves, and

a dynamic assessment of the entire lower leg vasculature was not possible. Finally, the sample size of 20 evaluated patients can be considered as a limitation. However, 118 arterial segments were assessed, and statistically significant results could be observed. Still, further evaluation of the proposed acquisition protocol and its use in clinical practice remains necessary.

In conclusion, our study demonstrates that a dynamic CT scan protocol with multiple time-resolved axial series can be performed over the calves at reasonable radiation and contrast agent dose. The dynamic sequence can be added to a standard helical run-off CTA sequence for the lower extremities within the same CT examination, and it increases diagnostic confidence for the assessment of presence and degree of arterial stenosis in below-the-knee arteries.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejrad.2018.11.030>.

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