European Journal of Radiology 146 (2022) 110080

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Computed tomography-based calcium scoring in cadaver leg arteries: Influence of dose, reader, and reconstruction algorithm

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ARTICLE INFO

Keywords:
Computed tomography
Lower extremities
Agatston method
Reconstruction methods
Vascular imaging

ABSTRACT

Purpose: Computed tomography (CT) might be a good diagnostic test to accurately quantify calcium in vascular beds but there are multiple factors influencing the quantification. The aim of this study was to investigate the influence of different computed tomography protocol settings in the quantification of calcium in the lower extremities using modified Agatston and volume scores.

Methods: Fresh-frozen human legs were scanned at different tube current protocols and reconstructed at different slice thickness. Two different iterative reconstruction protocols for conventional CT images were compared. Calcium was manually scored using modified Agatston and volume scores. Outcomes were statistically analyzed using Wilcoxon signed-rank tests and mean absolute and relative differences were plotted in Bland-Altman plots.

Results: Of the 20 legs, 16 had CT detectable calcifications. Differences between thick and thin slice reconstruction protocols were 129 Agatston units and 125% for Agatston and 78.4 mm^3 and 57.8% for volume (all $p \leq 0.001$). No significant differences were found between low and high tube current protocols. Differences between iDose^4 and IMR reconstruction protocols for modified Agatston were 34.2 Agatston units and 17.7% and the volume score 33.5 mm^3 and 21.2% (all $p \leq 0.001$).

Conclusions: Slice thickness reconstruction and reconstruction method protocols influenced the modified Agatston and volume scores in leg arteries, but tube current and different observers did not have an effect. This data emphasizes the need for standardized quantification of leg artery calcifications. Possible implications are in the development of a more universal quantification method, independent of the type of scan and vasculature.

1. Introduction

The presence of calcification in any vascular bed predicts ischemic cardiovascular, cerebral and peripheral artery disease [1–3]. For risk strategy purposes, quantification of these calcifications in vascular beds is of importance [4]. Especially quantification of coronary artery calcification has shown clinical relevance; using the Agatston method, the likelihood of a major adverse cardiac event can be assessed and the indication for preventative treatment can be fine-tuned [5,6]. The score is constituted by the amount and density of calcifications on unenhanced computed tomography (CT) [5].

Besides the coronary bed, there is growing interest in the quantification of calcium in other vascular beds [7,8]. For example, the quantification of calcium in the lower extremities of patients with peripheral artery disease affected by chronic limb-threatening ischemia [9,10]. Annual amputation and all-cause mortality rates of chronic limb-threatening ischemia are both around 20% [11]. Because of these adverse consequences, there is a need for a good diagnostic test to accurately quantify the amount of calcium in lower extremity peripheral artery disease and to better understand the process of chronic limb-threatening ischemia.

We aimed to quantify the degree of peripheral artery disease of the lower extremities using computed tomography (CT) and the Agatston method, which has proven to be useful for calcium quantification in the

Abbreviations: AU, Agatston units; CT, Computed tomography; HU, Hounsfield units; IMR, Iterative Model Reconstruction; IR, Iterative reconstruction; kV, Kilovoltage; mAs, Milliampere seconds; mm, Millimeters.

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https://doi.org/10.1016/j.ejrad.2021.110080
Received 8 June 2021; Received in revised form 25 November 2021; Accepted 27 November 2021
Available online 1 December 2021

coronary arteries. [6] Nevertheless, calcium quantification in the coronary arteries using CT has also shown its limitations with respect to reproducibility, including different CT types and vendors, different protocol settings (*e.g.,* radiation dose, slice thickness, and reconstruction methods), and different scoring platforms [12,13].

To the best of our knowledge, no studies have been conducted on the influence of different protocol settings for the quantification of calcium in peripheral artery disease of the lower extremities. Therefore, in our study, we evaluated the influence of dose settings, slice thickness, different raters, and the use of different types of reconstruction methods in the quantification of calcium in the lower extremities.

2. Materials and methods

Twenty human fresh-frozen legs were used for this study. The bodies had entered the anatomy department of the University Medical Center Utrecht through a donation program. During life, these people gave written informed consent for the use of their bodies for educational and research purposes after death. Before freezing, the legs had been amputated at approximately halfway the diaphysis of the femur.

3. Imaging protocols

CT scans were performed on the Philips iQon Spectral CT (Philips Healthcare, Best, the Netherlands). All scans were performed using 120 kV and two levels of tube current–time product (mAs): 40 mAs and 100 mAs. The two different slice thickness protocols were reconstructed at 3.0 mm and 0.9 mm. Iterative reconstruction was done with iDose^4 level 4. A convolutional soft kernel was used for reconstruction (Kernel B-Philips). An additional iterative reconstruction was computed at 1.0 mm slices using Iterative Model Reconstruction (IMR) routine level 1. There is a difference of 0.1 mm between the IMR and iDose^4 reconstructions as the standard image-reconstruction practices for IMR and iDose^4 are 1.0 mm and 0.9 mm thickness, respectively.

4. Data processing

Outcomes are described as modified Agatston and modified volume scores throughout the text as the original Agatston method has been developed for the coronary arteries. Besides the use in another vascular bed, no further changes were made between the Agatston method and the modified Agatston method. Modified Agatston and volume scores were off-label determined by two scorers (D.J.d.J. and S.v.d.S) for all different reconstruction protocols using the HeartBeat CS mode in IntelliSpace Portal version 10 (Philips Healthcare, Best, the Netherlands) [14] **[**Fig. 1**]**. The HeartBeat CS mode is based on the method by Agatston et al. [5] wherein calcifications measuring 130 Hounsfield Units (HU) or more were automatically detected and divided into groups based on the maximum attenuation (1 = 130HU – 200HU; 2 = 200 HU – 300 HU; 3 = 300 HU – 400 HU; and, 4 = 400 HU and higher). The volume score is the number of measured voxels with attenuation values of >130 HU multiplied by the volume of one voxel [15]. Volume scores are given in mm^3 and Agatston scores are given in Agatston units (AU).

The two scorers followed a previously agreed protocol, wherein the scorers selected all calcifications of 130 HU or higher in the large vessels of the lower extremities (i.e., superficial femoral artery, tibial-peroneal trunk, anterior and posterior tibial arteries, and peroneal artery, all to the start of the upper hock joint). No other branching arteries were included. Arteries that were directly adjacent to bone were included while carefully excluding the cortex of the bone.

4.1. Statistical analysis

Statistical analysis was performed using SPSS version 26.0 (IBM, Chicago, USA). The normality of distribution was checked using histograms, Q-Q plots, and the Shapiro-Wilk test. Parametric values were given as means with standard deviation. Nonparametric values were given as medians with an interquartile range. Firstly, an interscorer agreement was determined for modified Agatston and volume scores using a two-way mixed intra-class correlation coefficient (ICC) for consistency. Single measures ICC values of <0.50 were rated as poor, 0.50–0.75 as moderate, 0.75–0.90 as good, and values >0.90 were interpreted to have an excellent agreement [16]. Then, the paired values provided by the two scorers were averaged. Legs without visible calcifications in at least one of the used protocols were excluded for further analysis. To determine the differences in protocol settings, the high tube current and thin slice reconstruction protocols were compared to other protocols using Wilcoxon signed-rank tests. The differences in scan protocol settings are plotted and analyzed with Bland-Altman plots. Median absolute differences were calculated. Median relative differences were calculated by dividing the absolute difference by the highest score. P-values of ≤0.05 were considered statistically significant.

5. Results

Of the 20 legs, 16 had CT detectable calcifications. Between the two scorers, ICC values were good for the modified Agatston (ICC = 0.843 ($p \leq 0.001$)) and excellent for the volume scores (ICC = 0.998 ($p \leq 0.001$)).

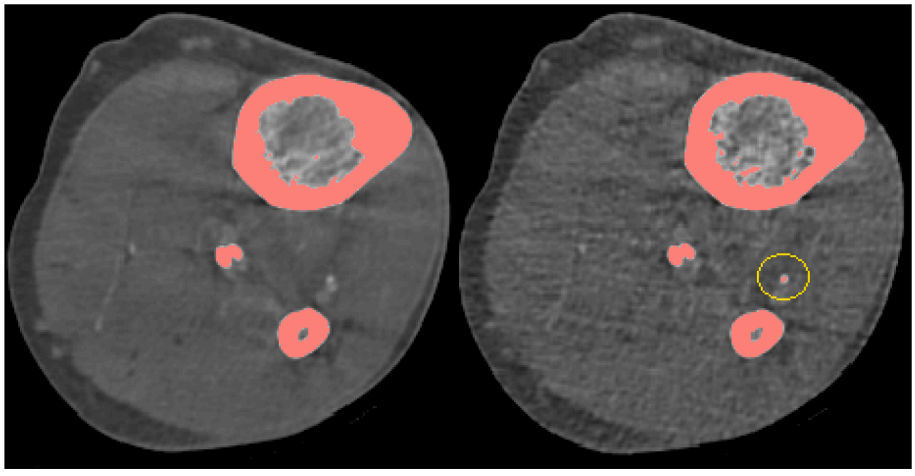

Fig. 1. Quantification of calcium. Illustrated are the same slices of the same leg in the calcium scoring program HeartBeat CS. Voxels of 130 HU and higher are automatically detected and rose-colored. In the yellow circle is a calcification scored in the protocol of the right leg with a thin slice and low tube current protocol, but not in the left leg with a thick slice and high tube current protocol.

The distribution of data was nonparametric ($p \leq 0.001$).

For the iDose^4 reconstructions of the low tube current protocols Agatston scores were 153.1 AU (IQR: 50.18–965.2) for the thin slice and 75.84 AU (IQR: 24.65 – 571.4) for the thick slice protocol. Agatston scores for high tube current protocols were 150.9 AU (IQR: 52.39–945.2) for the thin slice protocol and 72.48 AU (IQR: 26.02–577.7) for the thick slice protocol. The volume scores with low tube current protocols were 118.8 mm^3 (IQR: 40.11–724.0) and 106.2 mm^3 (IQR: 49.22–773.2) for thin and thick slices, respectively. With high tube current protocols, volume scores were 120.8 mm^3 (IQR: 41.78–708.9) for thin slices and 105.3 mm^3 (IQR: 41.60–776.8) for thick slices. The Agatston scores for the Philips iQon IMR reconstruction protocols were 138.7 AU (IQR: 39.27–913.5) for low tube current and 140.5 AU (IQR: 39.31–893.0) for high tube current. The volume scores were 121.3 mm^3 (IQR: 35.20–731.4) for low tube current and 117.4 mm^3 (IQR: 36.15–710.6) for high tube current protocols **[**Table 1**]**.

Regarding the slice thickness, the iDose^4 reconstructions produced significantly higher scores for the thin slice protocols compared to thick slice protocols. For the modified Agatston score, the median differences were 129 AU (IQR: 60.4 – 584) and 125% (IQR: 122 – 129) with a *p*-value of ≤0.001 **[**Table 2**]** **[**Figs. 2a and 2b**]**. For the modified volume score, the median differences were 78.4 mm^3 (IQR: 31.4 – 291) and 57.8% (IQR: 52.0 – 72.1) with a *p*-value of ≤0.001 **[**Table 2**]**. No significant differences were found between low and high tube current protocols for both the modified Agatston ($p = 0.950$) and volume scores ($p = 0.245$) **[**Table 2**]**. Mean absolute and relative differences are depicted in Figs. 2a and 2b.

Comparing the thin slice protocols of the iDose^4 reconstructions with the IMR reconstructions, median differences between modified Agatston scores were 34.2 AU (IQR: 14.3 – 114) and 17.7% (IQR: 15.5 – 20.8) with a *p*-value of ≤ 0.001, and differences between modified volume scores were 33.5 mm^3 (IQR: 10.8 – 186) and 21.2% (IQR: 15.0 – 28.3) with a *p*-value of ≤0.001 **[**Table 2**]**. Median differences for the low tube current protocols for the modified Agatston score were 29.0 AU (IQR: 15.2 – 109) and 17.0% (IQR: 12.8 – 21.6), with a *p*-value of ≤0.001. For the modified volume score, median differences were 32.0 mm^3 (IQR: 9.67 – 172) and 20.3% (IQR: 14.3 – 26.0), with a *p*-value ≤ 0.001. Overall, iDose^4 reconstruction protocols scored higher compared to the IMR reconstructions **[**Table 1**]**.

6. Discussion

Our study showed different outcomes for protocol settings in the quantification of calcium of the lower extremities. Slice thickness and reconstruction protocols influenced the outcome of the modified Agatston and volume scores significantly, but tube current protocols did not. Overall, the use of thin slice reconstruction protocols scored higher compared to the use of thick slice reconstruction protocols. iDose^4 reconstruction protocols scored higher than IMR reconstruction protocols. Since there is no reference standard to quantify the amount of calcium in the lower extremities, it is unknown to us what protocol settings most closely reflect the calcium load in these arteries.

Table 1
Calcium scores for different protocol settings.

	Agatston	Thin slices	Thick slices
Philips iQon iDose^4	Low mAs	153.1 (50.18–965.2)	75.84 (24.65–571.4)
	High mAs	150.9 (52.39–945.2)	72.48 (26.02–577.7)
	Volume	Thin slices	Thick slices
	Low mAs	118.8 (40.11–724.0)	106.2 (49.22–773.2)
	High mAs	120.8 (41.78–708.9)	105.3 (41.60–776.8)
	Agatston	Thin slices	
Philips iQon IMR	Low mAs	138.7 (39.27–913.5)	–
	High mAs	140.5 (39.31–893.0)	–
	Volume	Thin slices	
	Low mAs	121.3 (35.20–731.4)	–
	High mAs	117.4 (36.15–710.6)	–
		Median (IQR)	

Values are given as medians with an interquartile range (IQR). The volume scores are given in mm^3 and the Agatston scores are given in Agatston units.

We found that with the use of thin slice reconstruction protocols the modified Agatston and volume scores are significantly higher compared to the use of thick slice protocols. In the Bland-Altman plots, we observed that the higher the degree of calcification, the larger the difference between thick and thin slices reconstruction protocols for both the modified Agatston and volume score. This heterogeneity in calcium quantification for the use of slice thickness protocols has been reported by other authors before [17–21].

Studies of Vliegenthart et al. [20], Aslam et al. [17], and Mühlenburch et al. [18] match our findings, they also found higher Agatston and volume scores for thin slice protocols. Thin and thick slice protocols are believed to differ due to the influence of the partial-volume effect on the quantitative attenuation measurement of calcifications. There is a lower sensitivity for the detection of small calcifications with relatively low attenuation in thick slice protocols. Therefore, the authors suggest that the use of thin slice protocols will substantially improve the quantification of calcium by decreasing the partial volume effect and will improve the detection of smaller calcifications [22,23].

The use of thin slice protocols also influences the image noise. Image noise is inversely related to the slice thickness as thinner slice protocols generate more image noise. Thus, there is a balance between increased image noise and an increased spatial resolution [21].

To overcome the problem of increased image noise, iterative reconstruction (IR) was used [24]. IR has been proven to substantially reduce image noise [25,26] and to reduce blooming artifacts [27,28] resulting in higher image quality. However, IR is also known to influence the Agatston score. Gebhard et al. [27] used different levels of Adaptive Statistical Iterative Reconstruction (ASiR)) and found a reduction in Agatston score of 6.0% to 22.4% for higher levels (0.0% − 100%) of ASiR. Another study performed by Den Harder et al. [29], investigated the influence of different IR protocols (i.e., IMR level 1–3 and iDose^4 level 1–7) and decreased radiation dose for the Agatston, volume, and mass scores compared to traditional protocols using filtered back projection. They found that different IR protocols significantly influenced the quantification of calcium; lower Agatston scores were found using higher levels of IR protocols. A possible explanation proposed by Den Harder et al. is that with more advanced IR the borders of the calcification are smoothed, whereas the central area appears denser, causing decreased Agatston and volume scores.

We found higher Agatston and volume scores using iDose^4 level 4 reconstruction protocols compared to the use of IMR level 1 reconstruction protocols. This difference was also dependent on the degree of the calcium score; the higher the calcium score the higher the absolute differences. Possible explanations are the level of IR and the use of different IR methods [34]. In our study, we used IMR and iDose^4 to reconstruct images. These two methods have distinct mechanisms. IMR is a model- and knowledge based algorithm using forward and backward reconstructions [30,31] and iDose^4 is a hybrid IR algorithm [32]. The difference between IMR and iDose^4 is that IMR not only approaches the quantum noise statistics but also the non-random noise intrinsic to the geometry and optics of the imaging system [33]. IMR improves objective image quality most [33] and reduces artifacts such as beam hardening artifacts [34] more than iDose^4. The study of Suchá et al. [33], describes a comparison of the volume of artifacts between IMR and iDose^4. The volume of artifacts is higher for iDose^4 reconstructions compared to IMR and this may have caused a difference in the scores between the different reconstruction techniques in our study. Another possible explanation is that there was a minor difference in slice thickness of 0.1 mm in our study. We used 0.9 mm slices for iDose^4 and 1.0 mm slices for IMR level 1, and as we learned from previous findings on slice thickness, this may have influenced our results. The reason for this difference is that it is less time consuming to reconstruct IMR images in slices of 1.0 mm than slices of 0.9 mm. Moreover, it is common practice in our clinic to reconstruct

Table 2
Results of analysis.

Scanner		Comparison	Result (p-value)	(Absolute difference)	IQR	(Relative difference)	IQR
Philips iQon iDose[4]	Agatston	Slice thickness	**p ≤ 0.001***	**a = 129**	**60.4–584**	**r = 125**	**122–129**
		Tube current	p = 0.950	a = 5.19	1.53–9.91	r = 1.82	0.380–3.61
	Volume	Slice thickness	**p ≤ 0.001***	**a = 78.4**	**31.4–291**	**r = 57.8**	**52.0–72.1**
		Tube current	p = 0.245	a = 5.98	0.598–13.3	r = 1.43	0.426–2.51
Philips iQon IMR	Agatston	Tube current	p = 0.364	a = 2.22	0.674–13.6	r = 1.18	0.271–2.94
	Volume	Tube current	p = 0.478	a = 3.10	0.814–9.66	r = 1.48	0.282–3.21
	Agatston	Reconstruction method	**p ≤ 0.001***	**a = 34.2**	**14.3–114**	**r = 17.7**	**15.5–20.8**
	Volume	Reconstruction method	**p ≤ 0.001***	**a = 33.5**	**10.8–186**	**r = 21.2**	**15.0–28.3**
		P-value **A**bsolute median difference **R**elative median difference					

Results of the analysis were median absolute differences (a) and median percentage of relative differences (r). The differences in slice thickness were analyzed at low tube current. The differences in tube current were analyzed at thin slices. The iterative reconstruction methods iDose[4] and IMR were analyzed at low tube current and with thin slices. * Indicate statistically significant outcomes.

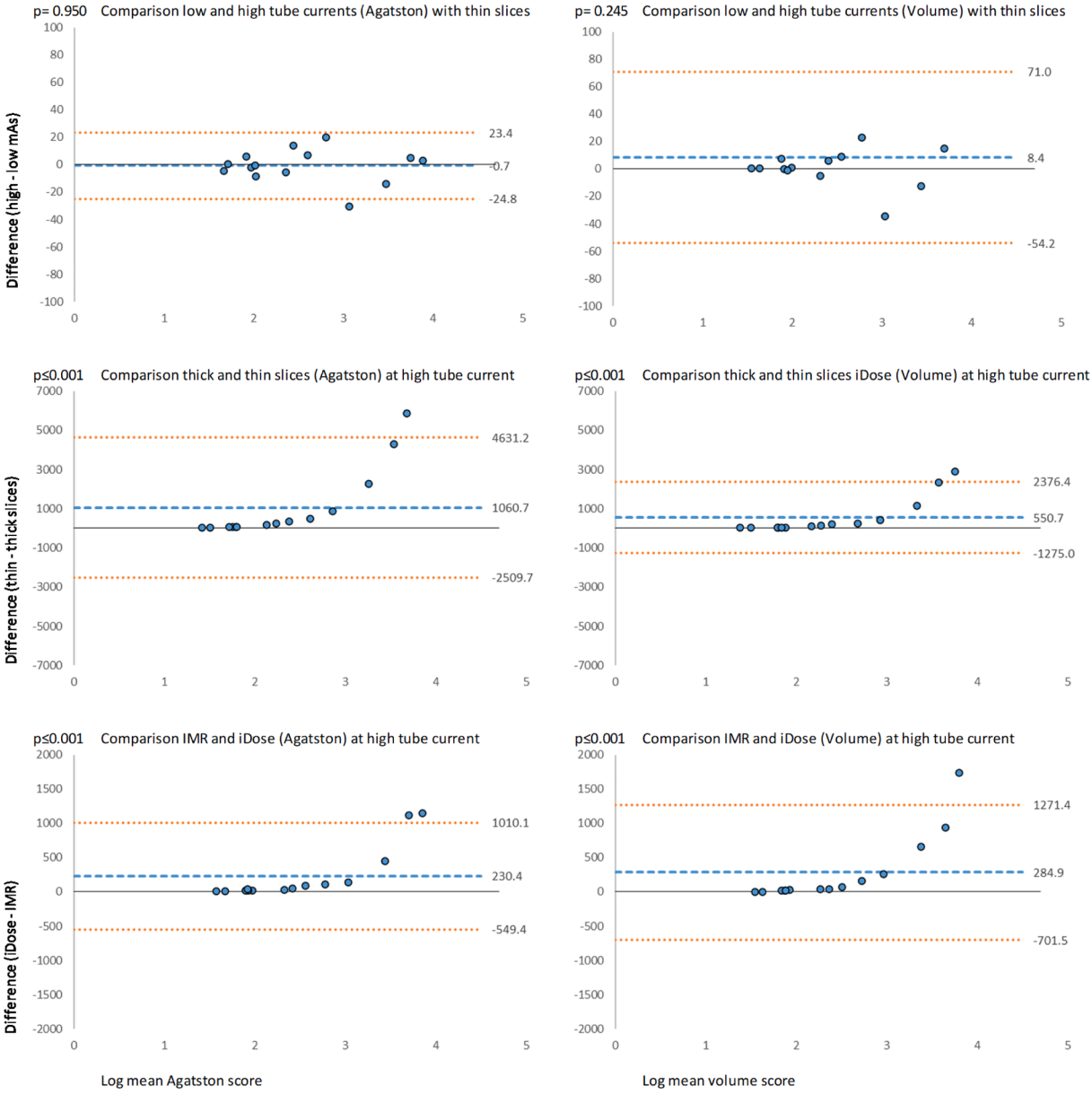

Fig. 2a. Bland-Altman plot of absolute differences in protocol settings.

IMR images in 1.0 mm and we decided to analyze the protocol as used in daily practice.

Furthermore, modified Agatston and volume scores were not influenced by tube current. The effect of differences in tube current settings on the outcome has been described more extensively in literature [35,36]. Dey et al. [35] compared different tube currents (i.e., 150

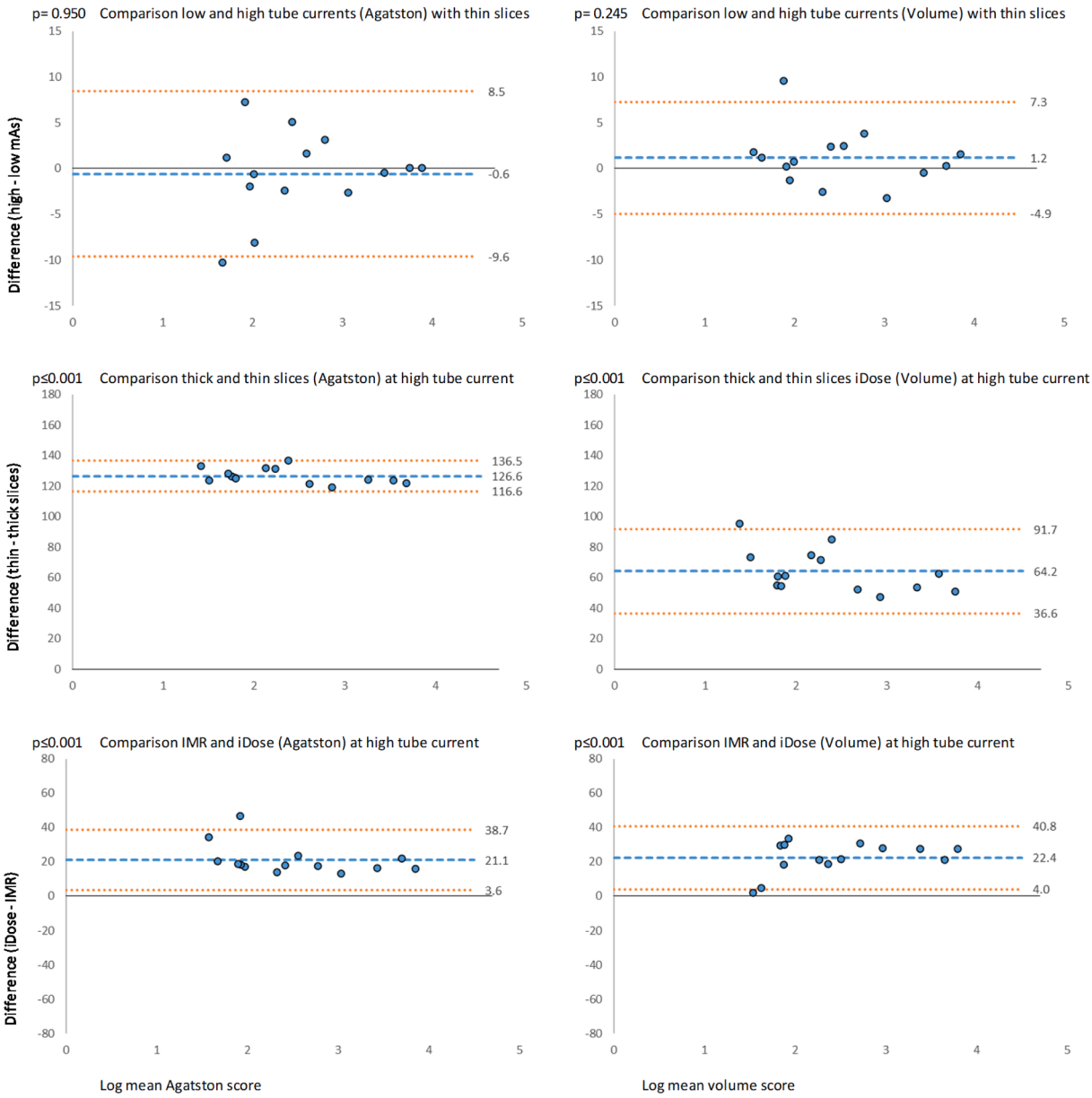

Fig. 2b. Bland-Altman plot of relative differences in protocol settings. Absolute and relative difference Bland-Altman plots of tube current, slice thickness reconstruction, and reconstruction method (iDose[4] or IMR) protocols for both the modified Agatston and volume scores. Depicted on the Y-axis is the difference between the protocol settings and on the X-axis a logarithmic scale mean calcium score. The orange dotted lines are 95% limits of agreement (±1.96 standard deviation of the difference). The blue dashed line is the mean difference.

mAs, 120 mAs, and 85 mAs) at 120 kV and found that there is no difference in accuracy for the quantification of coronary atherosclerosis using lower currents. They conclude that it is possible to reduce tube current without altering the outcomes of coronary calcium quantification. Although the image noise was higher in images using low tube currents, it was still acceptable. This is in line with our findings for the lower extremities. Likewise, Hong et al. [36] conducted a phantom study at extremely low tube currents (i.e., 20–160 mAs) and also found that there was a strong relationship between tube current and image noise, but not with the outcome of coronary calcium quantification. It is possible to use low tube currents, nevertheless, they argue that it might be better to use higher tube currents in obese patients in order to reduce image noise. In the lower extremities, we argue that compared to cardiac images image noise might be less due to surrounding tissue. On the other hand, image noise might also increase because the calcifications in the lower extremities are in the proximity of large bones, which pose the problems of beam hardening and scatter artifacts [37,38]. As described before, IR can be used to overcome these problems.

In this study, we use both the modified Agatston and volume scores to quantify the amount of calcium. However, a potential limitation of the Agatston score discussed in literature is the stepwise density scale of the weighting factor, consequently, the score might not capture changes or developments of calcifications accurately [39]. In our study, the modified volume score performed better than the modified Agatston score; the inter-scorer ICC was higher, and the relative differences of the volume score were half the differences of the modified Agatston score. In literature, it is theorized that due to the partial volume effect, the volume score will overestimate the size of larger lesions and underestimate the size of smaller lesions [4,40]. The calcium mass score has been reported as the score with the highest reproducibility. Unfortunately, we were not able to quantify the relative or absolute mass score in our study using IntelliSpace Portal because the program was not able to calculate a

(calibrated) mass score in non-coronary vasculature. This stresses the need for the development of a more universal quantification method, independent of the type of scan and vasculature.

There is limited data on the influence of protocol settings on the quantification of calcium of the lower extremities. Our findings might have implications for future CT applications in the quantification of calcium in non-coronary vascular beds. Moreover, we found a wider range in Agatston and volume scores in the lower extremities than in the coronary bed. This study attributes information on the quantification of calcium in vascular beds wherein calcium scores can be higher. Lastly, our results on tube current show that it is possible to quantify calcium in peripheral anatomy using low radiation doses. Therefore calcium quantification of the lower extremities can be performed in CT scans of low radiation dose in the future. A possible implication of our results is the use of CT in the diagnosis, risk stratification, and long-term follow-up of patients with peripheral artery disease.

This study also has some limitations. Firstly, we could not compare our results to a reference method, since no gold standard for calcium quantification in the lower extremities exists currently. Moreover, because this is a novel application of calcium quantification in the lower extremities, we can only compare our results to studies performed on other organs. Secondly, we were not able to cover all possible protocol settings, for example, we did not make use of post-processing methods such as mono-energetic reconstruction (mono-E) because this was beyond the scope of this study. Lastly, we could not analyze the mass score because it could not be generated for non-coronary beds.

In conclusion, different slice thickness reconstruction protocols and type of iterative reconstruction method influence the outcome of the modified Agatston score and to some extent also the modified volume score in the arteries of the leg, but tube current or different observers did not have an effect. This data emphasizes the need for a more standardized quantification method.

CRediT authorship contribution statement

Daan J. de Jong: Conceptualization, Methodology, Investigation, Writing – original draft, Formal analysis, Visualization. **Simone van der Star:** Conceptualization, Methodology, Investigation, Writing – review & editing, Resources. **Ronald L.A.W. Bleys:** Conceptualization, Resources. **Arnold M.R. Schilham:** Conceptualization, Methodology, Software, Writing – review & editing. **Hugo J. Kuijf:** Conceptualization, Software. **Pim A. de Jong:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Madeleine Kok:** Conceptualization, Methodology, Writing – original draft, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank the Elsemiek T. van Hulzen and the other radiology technicians of the UMC Utrecht for their work in collecting data. Daan J. de Jong is a medical student participating in the Honors program of the Faculty of Medicine, UMC Utrecht.

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