

Systematic analysis on the relationship between luminal enhancement, convolution kernel, plaque density, and luminal diameter of coronary artery stenosis: a CT phantom study

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Abstract To systematically investigate into the relationships between luminal enhancement, convolution kernel, plaque density, and stenosis severity in coronary computed tomography (CT) angiography. A coronary phantom including 63 stenoses (stenosis severity, 10–90 %; plaque densities, –100 to 1,000 HU) was loaded with increasing solutions of contrast material (luminal enhancement, 0–700 HU) and scanned in an anthropomorphic chest. CT data was acquired with prospective triggering using 64-section dual-source CT; reconstructions were performed with soft-tissue (B26f) and sharp convolution kernels (B46f). Two blinded and independent readers quantitatively assessed luminal diameter and CT number of plaque using electronic calipers. Measurement bias between phantom dimensions and CT measurements were calculated. Multivariate linear regression models identified predictors of bias. Inter- and intra-reader agreements of luminal diameter and CT number measurements were excellent (ICCs > 0.91, $p < 0.01$, each). Measurement bias of luminal diameter and plaque density was significantly ($p < 0.01$, each) lower (–12 % and 58 HU, respectively) with B46f as opposed to B26f, especially in plaque

densities >200 HU. Measurement bias was significantly ($p < 0.01$, each) correlated ($\rho = 0.37$ – 0.55 and $\rho = -0.70$ – 0.85) with the differences between luminal enhancement and plaque density. In multivariate models, bias of luminal diameter assessment with CT was correlated with plaque density ($\beta = 0.09$, $p < 0.05$). Convolution kernel ($\beta = -0.29$ and -0.38), stenosis severity ($\beta = -0.45$ and -0.38), and luminal enhancement ($\beta = -0.11$ and -0.29) represented independent ($p < 0.05$, each) predictors of measurement bias of luminal diameter and plaque number, respectively. Significant independent relationships exist between luminal enhancement, convolution kernel, plaque density, and luminal diameter, which have to be taken into account when performing, evaluating, and interpreting coronary CT angiography.

Keywords Coronary atherosclerosis · Coronary stenosis · Multisection computed tomography · Angiograph · Radiologic phantom

Introduction

Imaging assessment of coronary artery disease (CAD) has repetitively shown to have incremental prognostic value beyond the assessment of traditional risk factors, which is essential in selecting appropriate patient management [1, 2]. Both coronary artery stenosis and plaque composition therein represent independent predictors of major adverse cardiac events (MACE) in patients with known and suspected CAD [3–6].

The quantification of stenosis severity [7] and the classification of atherosclerotic plaques [8] has proven feasible with coronary computed tomography (CT) angiography and has gradually improved with new CT generations [9].

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Nevertheless, several factors have to be considered when performing, evaluating, and interpreting coronary CT angiography in order to prevent potential misinterpretation: calcified plaque components may lead to an overestimation of stenosis severity through an underestimation of the luminal diameter [7, 10]. Luminal enhancement affects the CT numbers of plaques [11]. To some extent, underestimation of the luminal diameter arising from high density plaque may be reduced by data filtering through sharper convolution kernels [12], the latter again is known to significantly impact on CT number of plaque assessment [13, 14].

All these relationships suggest systematic errors and thus may hamper accurate stenosis severity assessment and plaque characterization. There has been no study yet, to the best of our knowledge that investigated potential interactions factoring all of these aforementioned parameters in a standardized fashion.

The aim of this study was to investigate systematically into relationships of luminal enhancement, plaque density, convolution kernel, and luminal diameter of stenosis in coronary CT angiography.

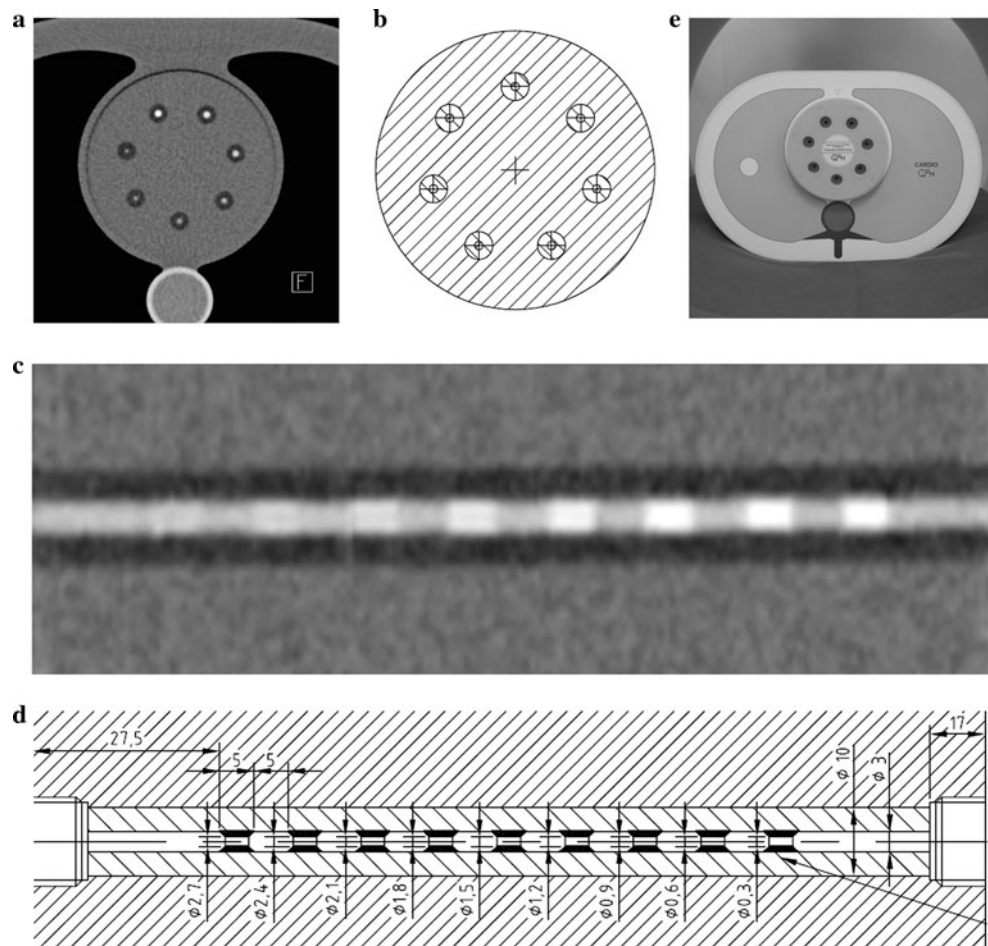
Materials and methods

Phantom set-up

For the purpose of this study, we designed a custom-made coronary artery phantom that was produced by a specialized manufacturer [Quality Assurance in Radiology and Medicine (QRM), Moehrendorf, Germany]. The phantom (Serial Number PP-02-02, QRM) comprises 7 equidistantly and circumferentially arranged tubes with an inner diameter of 3 mm. Each of these tubes is surrounded by a 1 mm layer of material with a fat equivalent CT number (-100 HU) to simulate pericoronary adipose tissue. Within the tubes, artificial plaque is arranged that concentrically narrows the lumen by $0.3 \text{ mm} \times n$ -steps simulating stenosis severity ranging from 10 % ($d = 2.7 \text{ mm}$) to 90 % ($d = 0.3 \text{ mm}$) (Fig. 1). In addition, plaque density varies with each of the tubes including seven different CT numbers (i.e., -100 , 0, 100, 200, 500, 750, and 1,000 HU at 120 kVp). CT numbers of the phantom body equal 35 HU.

Before imaging, the tubes were consecutively filled with different solutions of iodinated contrast material (iopromide,

Fig. 1 (a–e) Coronary artery phantom. **a** Axial CT image and **b** corresponding constructional drawing of the coronary artery phantom demonstrate 7 circumferentially arranged tubes. Each of the 7 tubes contains 9 concentric plaques ranging from 10 to 90 % stenosis severities as demonstrated by **c** multi-planar CT reformation along the course of a tube and **d** longitudinal constructional drawing. To simulate anthropomorphic condition and attenuation, **e** CT imaging was performed with the coronary artery phantom inserted into a commercially available chest [15]



Ultravist370[®], 370 mg I/ml, Bayer Schering Pharma, Berlin, Germany) diluted with variable parts of saline aiming for different levels of luminal enhancement (i.e., 0, 200, 300, 500, and 700 HU at 120 kVp). After each scan the tubes were washed intensively and drained three times with saline solution before reuse with another concentration of contrast material.

During CT imaging, the coronary artery phantom was placed into an anthropomorphic, commercially available chest (Pulmo Phantom[®], QRM; see Fig. 1). Both phantoms consist of materials made from epoxy resin and additives, such as calcium carbonate, magnesium oxide, hydroxyapatite and microspheres to obtain solid water, soft tissue, lung and bone equivalent structures, as well as different plaque densities [15].

CT imaging

All data was acquired with a first generation 64-section dual-source CT machine (Somatom Definition[®], Siemens Healthcare, Forchheim, Germany). Scans were performed with the following parameters: tube potential, 120 kVp; tube current–time product, 350mAs/rotation; detector collimation, $2 \times 32 \times 0.6$ mm; slice acquisition, $2 \times 64 \times 0.6$ mm by means of a z-flying focal spot; gantry rotation time, 330 ms. The scan was performed at a simulated heart rate of 60 bpm with a prospectively electrocardiography (ECG)-gated protocol; the latter being not different from retrospective gating neither in regards to stenosis measurement nor CT numbers [16].

Images were reconstructed at 70 % of the R–R interval with a slice thickness of 0.6 mm and an increment of 0.4 mm (field of view, 180; matrix, 512×512). Reconstructions were carried out with a soft tissue (B26f) and sharp convolution kernels (B46f) for data filtering.

Image analysis

All reconstructed images were transferred to an external workstation (Multi-Modality Workplace, Siemens Healthcare) for further analysis. One reader who was not involved in the data analysis reformatted, magnified (zoom factor, $10\times$), and saved one axial image (i.e., perpendicularly to the phantoms centerline and course of the tubes), each reconstructed with both convolution kernels ($n = 2$) of each plaque ($n = 63$) at different levels of luminal enhancement ($n = 5$) allowing for blinded analysis.

Then, two independent readers (LD and TP with 8 and 4 years of experience in reading coronary CT angiography—blinded for review) who were blinded to stenosis severity, plaque density, and convolution kernel analyzed each image ($n = 630$) quantitatively using electronic calipers provided with the software (Syngo Viewing, software

VE40A, Siemens Healthcare). The CT number of each plaque was assessed with a round region of interest (ROI) measurement that included as much plaque area as possible, respecting plaque borders and outer tube edges. In addition, a round ROI was manually drawn in the phantom body outside of the tubes to allow for determining image noise that was defined as the standard deviation of CT numbers. All images ($n = 630$) were analyzed twice by one reader (LD) to allow for intra-observer variability assessment. Second read-out session started after 4 weeks time interval in a different order to avoid recall bias.

Statistical analysis

Continuous variables are expressed as mean \pm SD and range. The intra-reader and inter-reader agreements regarding measurements of luminal diameter in stenosis, CT number of luminal enhancement, and CT number of plaque were analyzed by using intra-class correlation coefficients. According to Landis and Koch, ICC values of 0.61–0.80 were interpreted as substantial, and 0.81–1.00 as high agreement [17].

Measurement bias regarding luminal diameter (mbLD) was calculated by subtraction of luminal diameter as measured on CT images from the nominal diameter in stenosis. Measurement bias of CT number of plaque (mbNP) was calculated by subtracting plaque density from CT number of plaque, respectively. Difference between CT number of plaque and luminal enhancement (diffLP) was calculated by subtraction of measured intraluminal enhancement from nominal plaque density.

Regarding univariate analyses, image noise as well as measurement bias including mbLD and mbNP was compared among convolution kernels using repeated measures analysis of variances (ANOVA). Difference of mbLD between convolution kernels were also compared in plaque densities ≥ 200 HU using the *t* test for paired samples. To test for significant correlation of mbLD and mbNP with both diffLP and stenosis severity, Spearman's rank correlation was performed. We performed multivariate linear regression analyses to identify independent predictors of measurement bias.

Data analysis was performed using commercially available software (IBM SPSS Statistics Version 20, release 20.0.0, Chicago, IL, USA). A *p* value of $p < 0.05$ was considered statistically significant.

Results

Inter- and intra-reader agreements

For the reconstructions with the soft tissue convolution kernel (B26f), intra-reader and inter-reader agreements

($p < 0.001$ each) were excellent regarding luminal diameters (0.99 and 0.94), CT numbers of luminal enhancement (0.99 and 0.96), and CT numbers of plaques (0.97 and 0.99).

For the reconstructions with the sharp convolution kernel (B46f), intra-reader and inter-reader agreements ($p < 0.001$ each) were also excellent regarding luminal diameters (0.99 and 0.91), CT numbers of luminal enhancement (1.00 and 0.99), and CT numbers of plaques (0.98 and 0.99, respectively).

Hence, the mean of measurements was taken for further analysis (see Table 1).

Measurement bias of luminal diameter (mbLD)

Image noise was significantly ($p < 0.001$) higher with convolution kernel B46f (13 ± 1 HU) as compared with B26f (7 ± 0 HU). We found significant differences ($p < 0.001$) regarding the mbLD between convolution kernel B26f ($21 \pm 12\%$, -2 to 50%) and B46f ($13 \pm 11\%$, -17 to 47%). Difference of mbLD between convolution kernels were pronounced especially in plaque densities ≥ 200 HU (mean difference, $9 \pm 11\%$; $p < 0.001$). According to these results, subsequent univariate analyses were performed separately after clustering for convolution kernel.

We observed significant ($p < 0.001$, each) correlations of mbLD with diffLP regarding convolution kernels including B26f ($\rho = 0.55$) and B46f ($\rho = 0.37$; Fig. 2a). mbLD was smallest when diffLP was highly negative (i.e., luminal enhancement exceeding plaque density) and increased with positive values (i.e., plaque density exceeding luminal enhancement). This compares to a more pronounced underestimation of luminal diameter (i.e., overestimation of stenosis) with reduced luminal enhancement and higher plaque densities. Also, mbLD was negatively correlated

($p < 0.001$, each) with stenosis severity regarding both convolution kernels B26f ($\rho = -0.36$) and B46f ($\rho = -0.35$) separately. This represents a less pronounced underestimation of luminal diameter (i.e., reduced overestimation of stenosis) with increasing stenosis severity.

In a multivariate linear model, mbLD was dependent on convolution kernel, luminal enhancement, plaque density, and stenosis severity, all of which representing independent predictors (Table 2).

Measurement bias of CT number of plaque (mbNP)

Measurement bias of CT number of plaque was significantly ($p < 0.001$) reduced when B46f was used as opposed to B26f with a mean difference of 69 HU. According to these results, subsequent univariate analyses were performed separately for measurements taken on images reconstructed with either convolution kernel.

Measurement bias of CT number of plaque was negatively ($p < 0.001$, each) correlated with diffLP with respect to both convolution kernels including B26f ($\rho = -0.85$) and B46f ($\rho = -0.70$; Fig. 2b). This compares to an overestimation of plaque number by CT in plaque with densities smaller than that of luminal enhancement (diffLP of negative values) whereas an underestimation of CT number of plaque was found when the plaque density exceeded the luminal enhancement exceeded (diffLP of negative values). Also, mbNP was negatively correlated ($p = 0.001$) with stenosis severity regarding convolution kernel B26f ($\rho = -0.31$). This relationship was not found for the sharp convolution kernel B46f ($p = 0.71$).

In a multivariate linear model, mbNP was dependent on convolution kernel, luminal enhancement, and stenosis severity, all of which representing independent predictors (see Table 2).

Table 1 Descriptive statistics according to convolution kernel

	Soft tissue convolution kernel (B26f)			Sharp convolution kernel (B46f)		
	Mean	SD	Range	Mean	SD	Range
Luminal enhancement (HU)	475	176	200 to 751	439	170	195–711
Luminal diameter in stenosis (mm)	0.8	0.7	0 to 2.8	0.9	0.6	0–2.5
CT number of plaque (HU)	266	293	–108 to 906	286	318	–123 to 943
Measurement bias of luminal diameter (%)	21	12	–2 to 50	13	11	–17 to 47
Measurement bias of CT number of plaque (HU)	–110	182	–659 to 110	–41	134	–637 to 147

Discussion

In this study, we sought to systematically investigate into relationships of luminal enhancement, plaque density, convolution kernel, and stenosis severity in coronary CT angiography. Our results indicate that significant differences exist regarding the measurement bias of both luminal diameter and CT number of plaque between soft tissue (i.e., B26f) and sharp convolution kernels (i.e., B46f). Also, our study shows that the measurement bias of both assessment of luminal diameter and plaque density with CT is significantly correlated with the difference between luminal enhancement and plaque density as well stenosis severity. In multivariate analysis, bias of luminal diameter assessment with CT was dependent on plaque density. Also, convolution kernel,

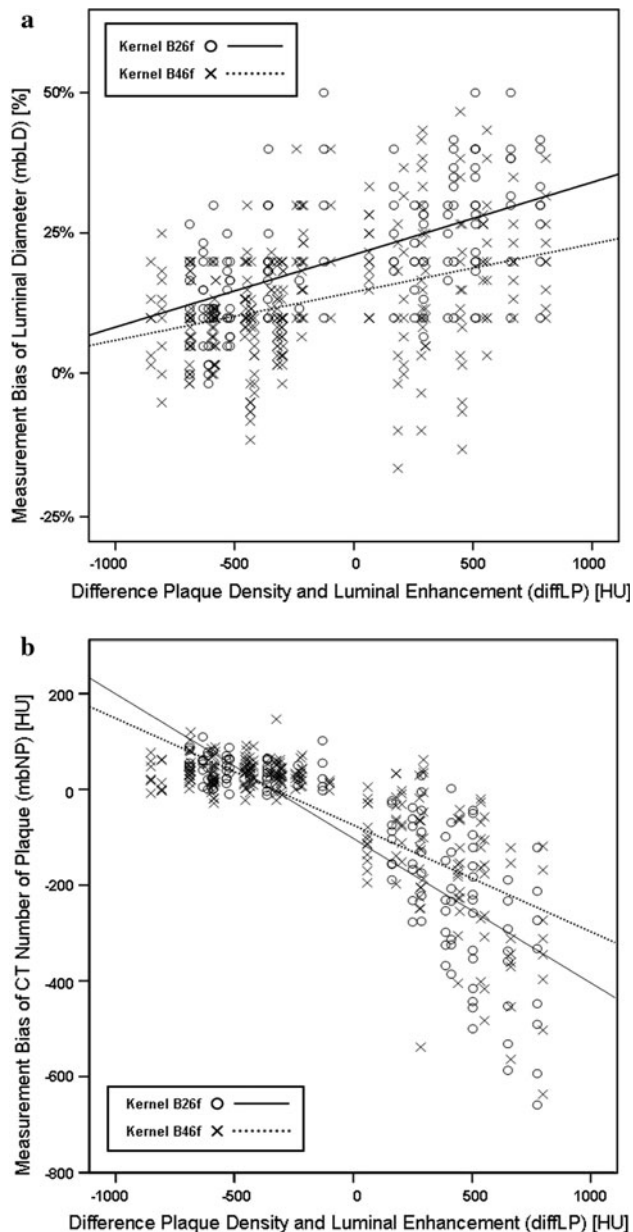


Fig. 2 **a** Measurement bias of luminal diameter plotted *versus* the difference between plaque density and luminal enhancement. Significant correlations ($p < 0.001$) were found for both soft tissue (i.e., B26f, $\rho = 0.56$) and sharp convolution kernels (i.e., B46f, $\rho = 0.37$) with a more pronounced overestimation of stenosis with increasing plaque densities and decreasing luminal enhancement. More accurate stenosis assessment with B46f may well be explained by the increase in spatial resolution with sharper convolution kernels. **b** Measurement bias of CT number of plaque plotted *versus* the difference between plaque density and luminal enhancement. Significant correlations ($p < 0.001$) were found for both soft tissue (i.e., B26f, $\rho = -0.85$) and sharp convolution kernels (i.e., B46f, $\rho = -0.70$). The scatter plot demonstrates increasing over- and underestimation of CT numbers when plaque densities were smaller (negative values on x -axis) or larger than luminal enhancement (positive values on x -axis), respectively

Table 2 Multivariate linear models including independent predictors of measurement bias

	β -Estimate	p value
(a) Model for measurement bias of luminal diameter		
Soft tissue versus sharp convolution kernel	-0.29	<0.001
Luminal enhancement (HU)	-0.11	<0.01
Plaque density (HU)	0.09	<0.05
Stenosis severity (%)	-0.45	<0.001
(b) Model for measurement bias of CT number of plaque		
Soft tissue versus sharp convolution kernel	-0.38	<0.001
Luminal enhancement (HU)	-0.29	<0.001
Stenosis severity (%)	-0.38	<0.001

stenosis severity, and luminal enhancement were found to be independent predictors of measurement bias regarding both luminal diameter and plaque density.

Convolution kernel

To increase the image sharpness during back projection of the CT attenuation profiles, each projection has to be convolved with a predetermined mathematical function, the convolution kernel [18]. This kernel represents a filtering procedure which influences image characteristics by the choice and design of the kernel. A soft tissue convolution kernel reduces spatial resolution as well as image noise, while a sharp convolution kernel increases spatial resolution as well as image noise [18]. Accordingly, our study shows a significantly increased image noise together with a reduced measurement bias regarding both luminal diameter and CT number of plaque with the use of a sharp convolution kernel (B46f) as compared with soft filtering (B26f).

More accurate stenosis assessment may well be explained by the increase in spatial resolution with sharper convolution kernels. There is wide agreement that in the presence of arterial wall calcifications, images should to be reconstructed with a sharp convolution kernel in order compensate for blooming and subsequent underestimation of luminal diameters [1]. This is in line with Maintz et al. [19] who demonstrated that the visualisation of coronary stents is improved with sharper convolution kernels. In small vessels without stents, there exists only little data that quantifies the effect of different convolution kernels on measurement bias [20], with neither stenosis severity nor plaque density being considered as potential influencing factors. Therefore, our study extends previous knowledge by demonstrating the use of sharp convolution kernels to be most beneficial for the accurate assessment of plaque numbers and luminal diameters especially in regards to stenoses with high CT numbers exceeding 200 HU.

Regarding the relationship of reconstruction kernel and plaque density assessment, we show that the use of a sharper convolution kernel significantly reduces measurement bias as compared with soft filtering. This is in line with an *ex vivo* study [18] which demonstrated that the use of sharper convolution kernels led to an increase in CT numbers of calcified plaque whereas a reduction was found in non-calcified plaques. Thus, this systemic error may hamper the characterization of coronary plaque on the basis of CT numbers only [13, 21].

Luminal enhancement and plaque density

In addition to convolution kernel, the level of luminal enhancement has to be taken into account when luminal diameters are quantitatively assessed. Our results demonstrate the measurement bias to be smallest when the plaque is of low density in the setting of high luminal enhancement. Vice versa, a more pronounced overestimation of stenosis severity was found in the setting of higher plaque densities and less luminal enhancement, being in line with the results from Suzuki et al. [20]. However, this study design did not allow for the assessment in vessels and/or luminal diameters falling below 3 mm nor into different plaque. In particular, coronary stenosis is known to be overestimated if caused by calcified plaque and associated with larger limits of agreement as compared to non-calcified plaque which was established using quantitative coronary angiography as the reference standard [22]. Although both effects were separately quantified in the former *in vitro* [20] and *in vivo* studies [22], our study elaborates on the combined assessment of plaque density and luminal enhancement.

The level of luminal enhancement has to be considered also when measuring the CT numbers of plaques [11, 13]. The results as presented herein are in good agreement with the latter studies and similarly show that CT numbers of plaque are progressively overestimated by up to 150 HU regarding coronary plaque with densities being lower than the luminal enhancement [11]. This collides with the high intraluminal enhancement desired for evaluation of degree of stenosis [23]. Today, the evaluation of stenosis is thought to be of a higher priority as compared to the sole evaluation of plaque composition and thus in clinical routine high intraluminal enhancement should be assured. Moreover, we show a significant underestimation of the CT number of plaque when its density exceeds the luminal enhancement (e.g. calcified plaque). Future studies should focus on determining an algorithm correcting for this measurement bias.

Stenosis severity

Our data suggests a more accurate luminal diameter assessment with increasing stenosis severity with both soft

tissue and sharp convolution kernels. An explanation for this finding may be that stenosis severity represents a procedural confound of measurement bias regarding the luminal diameter. This is because the dependent variables of plaque density and luminal enhancement changed along with the independent one.

Also in regards to plaque density, an increasing stenosis severity produced a decreasing CT number measurement bias but only when clustering for soft tissue convolution kernel reconstructions. This less pronounced underestimation of plaque density with soft filtering might be attributable to partial volume effects or different noise levels. The higher the stenosis severity, the higher the plaque area becomes which both simplifies ROI placement and renders CT number measurements to be less affected by partial volume artifacts [18]. This hypothesis is also underlined by the fact that the aforementioned correlation was found using the soft tissue convolution kernel only.

Study limitations

First, our phantom set-up excludes cardiac motion. However, this allows for imaging under ideal conditions being a prerequisite for accurate systematic analysis. Second, image reconstruction was carried out with the thinnest slice thickness possible (i.e., 0.6 mm) to improve the accuracy of quantitative stenosis assessment. CT numbers of coronary plaque however depend on the spatial resolution that comprises not only convolution kernels but slice thickness [13]. Finally, the experiment was conducted using filtered back projection and not using iterative reconstructions, which has been shown to reduce blooming artifacts from vessel wall calcifications [12].

In conclusion, our systematic analysis of measurement bias demonstrates luminal diameter and plaque density to be significantly correlated with each other. Significant relationships exist between all of the independent variables including luminal enhancement, convolution kernel, plaque density, and luminal diameter, all of which have to be taken into account when assessing for CAD by coronary CT angiography. Based on our findings, the use of a sharp convolution kernel, e.g. B46f, is recommended in the evaluation of stenosis caused by plaques with a density of >200 HU.

Conflict of interest None.

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