Received:
21 December 2018

Revised:
20 September 2019

Accepted:
09 November 2019

<https://doi.org/10.1259/bjr.20190003>

Cite this article as:

Misaka T, Sugitani Y, Asato N, Matsukubo Y, Uemura M, Ashikaga R, et al. Coronary artery to aortic luminal attenuation ratio in coronary CT angiography for the diagnosis of haemodynamically significant coronary artery stenosis. *Br J Radiol* 2020; **93**: 20190003.

FULL PAPER

Coronary artery to aortic luminal attenuation ratio in coronary CT angiography for the diagnosis of haemodynamically significant coronary artery stenosis

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Objective: This study aimed to assess and compare the diagnostic performance of the coronary artery to aortic luminal attenuation ratio (CAR), transluminal attenuation gradient (TAG), and corrected coronary opacification (CCO) difference on coronary CT angiography (cCTA) for detecting haemodynamically significant coronary artery stenosis.

Methods: 33 patients who underwent cCTA, gated SPECT myocardial perfusion imaging (MPI), and invasive coronary angiography within 3 months were included in this retrospective study. The degree of coronary stenosis on cCTA was visually assessed in all patients. Additionally, CAR, TAG, and CCO difference were analyzed and calculated in all patients. Haemodynamically significant coronary stenosis was defined as a vessel with $\geq 50\%$ luminal stenosis on invasive coronary angiography and an associated abnormal perfusion defect on MPI in the same territory. Diagnostic performance was assessed on a per-vessel basis by the area under the receiver operating characteristic (ROC) curve (AUC).

Results: Among 99 vessels, 12 were excluded and the remaining 87 were analyzed. 17 (19.5%) vessels were determined as haemodynamically significant coronary artery stenosis. On ROC analysis, the AUC was 0.71 for cCTA, 0.80 for CAR, 0.61 for TAG, 0.74 for CCO, 0.87 for combined CAR and cCTA, 0.77 for combined TAG and cCTA, and 0.75 for combined CCO and cCTA. The AUC for combined CAR and cCTA was significantly greater compared with cCTA alone ($p < 0.01$).

Conclusion: Non-invasive CAR derived from 64-detector row CT was feasible and might be helpful for the detection of haemodynamically significant coronary artery stenosis. Still, further investigations such as intra- and inter-reader correlation, evaluation of larger numbers in different settings, and time efficiency are required for applying CAR in various situations.

Advances in knowledge: CAR could be used as novel noninvasive technique to detect haemodynamically significant coronary artery stenosis.

INTRODUCTION

Coronary CT angiography (cCTA) is a non-invasive method for identifying obstructive coronary artery disease.^{1,2} However, cCTA has limited specificity for detecting haemodynamically significant coronary stenosis.^{3,4} Therefore, non-invasive functional imaging is required for identifying ischaemia.

Recently, several new techniques on CT images have been established, and these include the transluminal attenuation gradient (TAG),⁵⁻⁸ corrected coronary opacification (CCO) difference,⁹ stress CT myocardial perfusion imaging (MPI),^{10,11} and noninvasive fractional flow reserve (FFR)

derived from CT (FFR_{CT})^{12,13} to detect haemodynamically significant stenosis. Although each technique improves the diagnostic accuracy of haemodynamic significance of coronary stenosis, there are some limitations. Stress CT MPI requires additional radiation exposure and iodinated contrast medium. Although FFR_{CT} is a promising technique, it cannot be used in daily routine because it requires a few hours of analysis on a supercomputer and fees in a submission and assessment report. TAG and CCO difference can easily and rapidly assess haemodynamically significant stenosis with no additional radiation exposure or contrast medium.⁶ However, TAG may not be desirable for images acquired with multiple cardiac cycles on

narrow detector CT scanners because it can be influenced by contrast medium injection or the scan protocol.¹⁴ Although CCO has been developed to partially correct these factors, it can be affected by the coronary artery diameter in which the region of interest (ROI) is placed because intraluminal attenuation is decreased according to the reduction in vessel diameter.¹⁵

Coronary artery to aortic luminal attenuation ratio (CAR), which is a novel technique and has not been reported yet, can minimize the effect of multiple cardiac cycles and vessel diameter. We hypothesize that CAR improves detection of haemodynamic significance of coronary stenosis. This study aimed to assess and compare diagnostic performance of CAR, TAG, and CCO difference for detecting haemodynamically significant coronary artery stenosis.

METHODS AND MATERIALS

Patients

This retrospective study was approved by the institutional review board and the need to obtain informed consent was waived. Consecutive patients who underwent cCTA, gated SPECT MPI, and invasive coronary angiography within 3 months between September 2013 and November 2017 were included in this study. All patients underwent cCTA and gated SPECT MPI before invasive coronary angiography. Patients with a history of coronary artery bypass grafting, >50% stenosis in the left main coronary artery, multivessel disease, or myocardial infarction within 3 months were excluded. Vessels with a coronary stent, chronic total occlusions, or stenosis of a branch were also excluded.

Protocol of cCTA was performed using 64-detector row CT (Aquilion 64; Toshiba Medical Systems, Tochigi, Japan). On arrival, sublingual nitrates were administered to optimize coronary vasodilatation. Intravenous β -blockers were administered before scanning if the resting heart rate was >55 beats/min. The scan was acquired during injection of 24.5 mgI/kg/s of 100% iomeprol (Iomeron 350; Eisai, Bunkyo-ku, Japan), followed by 30 ml of saline at the same rate. The injection duration of contrast agent was 13 s, which was as long as (or slightly longer than) the estimated scan duration.¹⁶ Scans were manually triggered using bolus tracking when the contrast attenuation reached 150 HU in the ascending aorta. Retrospective electrocardiogram gating was used in all patients. Scan parameters were as follows: detector collimation: 64 $\times$ 0.5 mm; tube current: 500 mA; tube voltage: 120 kV; gantry rotation time: 350 or 375 ms; and helical pitch: 9.8, 11.2, or 12.0. Images were reconstructed from the diastolic phase period using the filtered back projection technique. Reconstruction slice thickness and slice gap were 0.5 and 0.3 mm, respectively.

Image analysis in cCTA

Images by cCTA were evaluated by two experienced radiologists with more than 9 years of experience in cardiac imaging, independently, who were blinded to the results of MPI and invasive coronary angiography. Image quality was determined by a 4-point scale as follows^{17,18}: score of 1 = non-diagnostic, with poor image quality; score of 2 = adequate, with reduced image quality; score of 3 = good, with a preserved ability to evaluate the

presence of luminal stenosis; and score of 4 = excellent, with the ability to evaluate luminal stenosis, as well as plaque characteristics. All segments $\geq$ 2 mm were analyzed using the 16-segment coronary model for modified American Heart Association classification.^{19,20} Each coronary segment was visually assessed for the degree of percent diameter stenosis, and any disagreement between two observers was resolved by consensus. When multiple stenoses were existed in one vessel, the maximum stenosis was applied. A vessel was considered significant if there was $\geq$ 50% luminal stenosis.^{1-3,6,9,10} The visual assessment with binary categorization on cCTA was denoted as cCTA50.

CAR analysis

Data with 0.5 mm slice thickness were analyzed in an offline workstation (AZE Virtualplace; AZE, Tokyo, Japan) by an experienced observer with >7 years of experience with analysis of cCTA. The overview of the CAR analysis is shown in Figure 1. The centerline of the vessel was automatically determined for each major coronary artery and manually corrected if necessary. Cross-sectional images perpendicular to the vessel centerline were reconstructed and the contours of the vessels were delineated automatically, then cross-sectional areas of the vessels were calculated. The circular ROI (diameter: 1 mm) was positioned on the center of the cross-sectional images at 1 mm intervals, from the proximal 7 mm² cross-sectional area to the distal 3 mm² cross-sectional area for measurement of luminal attenuation values. If the slice included a calcified area, it was excluded. The mean luminal attenuation value (HU) was then calculated from ROIs as the coefficient of specific distal coronary artery area. The circular ROI (area: as large as possible) was positioned on the center of the ascending aorta in the axial slice, where the left coronary artery was branched, as the coefficient of ascending aorta. CAR was expressed as the specific distal coronary artery to ascending aorta attenuation ratio. If all cross-sectional images from the proximal 7 mm² cross-sectional area to the distal 3 mm² cross-sectional area included calcifications, the vessel was excluded from further analysis.

TAG analysis

Data were analyzed using the same offline workstation as for CAR. The circular ROI (diameter: 1 mm) was positioned on the center of the lumen on cross-sectional images. The ROI was excluded if it included a calcified area. The mean luminal attenuation (HU) was measured at 5 mm intervals, from the ostium to a distal level where the cross-sectional area was <2.0 mm². TAG was determined from the change in HU per 10 mm length of coronary artery and defined as the linear regression coefficient between luminal attenuation (HU) and length from the ostium (mm).⁵

CCO difference analysis

CCO was defined as the quotient of mean luminal attenuation (HU) in circular ROIs, which were positioned on the coronary artery and descending aorta in the same axial slice, as previously described.⁹ In analysis of arteries with $\geq$ 50% luminal stenosis, at least two ROIs were positioned proximal to the stenosis and two ROIs were in the distal artery with a diameter $\geq$ 1.5 mm. Although the largest possible ROI was used, plaques or calcified areas were

Figure 1. Example of CAR analysis in the left anterior descending artery with haemodynamically significant stenosis. (a) Straight curved planar reconstruction image with the measurement range indicated by yellow lines from the proximal 7 mm² sectional area to the distal 3 mm² sectional area. (b) Representative cross-sectional images. The contours of the vessels indicated by blue ROIs for measurement of cross-sectional areas were delineated automatically. The circular ROI indicated by the yellow circle (diameter: 1mm) was positioned on the center of the cross-sectional for measurement of luminal attenuation. (c) Axial image of the ascending aorta with the ROI indicated by the yellow circle. CAR, coronary artery to aortic luminal attenuation ratio; ROI, region of interest

excluded. CCO difference was calculated as the change between the lowest CCO proximal to coronary stenosis and the lowest CCO distal to stenosis (CCO difference = pre-stenosis minimum CCO–post-stenosis minimum CCO). In normal arteries, CCO difference was calculated as the change between the highest CCO and the lowest CCO in the same distal artery segment (CCO difference = distal maximum CCO–distal minimum CCO). Concept of CAR, TAG, and CCO difference are shown in Figure 2.

^{99m}Tc gated SPECT MPI

Patients underwent exercise or adenosine stress–rest ^{99m}Tc gated SPECT MPI within the same day. First, rest gated SPECT MPI was performed with a dual-head SPECT camera system (Symbia E; Siemens Healthcare, Erlangen, Germany & Toshiba Medical Systems, Tochigi, Japan) 30 min after injection of ^{99m}Tc-tetrofosmin (296 MBq). Then, exercise or adenosine stress was given, and ^{99m}Tc-tetrofosmin (740 MBq) was injected at near-peak stress condition. Gated SPECT MPI was performed 30 min after injection of nuclear agent. Low-energy high-resolution collimators were used, and a 20% window was centered on the 140 keV energy peak of ^{99m}Tc. A total of 60 projections (step-and-shoot method, 30 s/projection; 64 × 64 matrix with a 1.45 zoom; total imaging time of 18 min) over a 360° acquisition orbit were

obtained. Data acquisition was performed with eight frames per cardiac cycle. Data were reconstructed by filtered back projection with a Butterworth filter (order 8, cut-off frequency of 0.80 cycles/cm in stress images; 0.73 at rest). No attenuation or scatter correction was used.

Image analysis in SPECT MPI

Perfusion defect areas were visually assessed by two expert observers (at least 8 years and 10 years of experience in MPI analysis and diagnosis, respectively) who were unaware of the cCTA or invasive coronary angiography results. Any disagreement was resolved by consensus. The presence of myocardial perfusion was divided into three patterns: (1) normal pattern with no defect at rest and stress images; (2) ischaemic pattern with a perfusion defect at stress that was no longer observed or partially improved at rest; and (3) infarcted pattern with a perfusion defect that was unchanged between rest and stress SPECT images.

To quantify the severity of perfusion defects in ischaemic and infarcted patterns, stress and rest SPECT images were scored by an automated scoring system (Heart Score View; Nihon Mediphsics, Tokyo, Japan). This system generates a polar-map from SPECT data using a 17-segment model, then mean % uptake in each segment is automatically scored on a 5-point scale (0,

Figure 2. Concept of CAR, TAG, and CCO difference. (a) CAR was expressed as the specific distal coronary artery to ascending aorta attenuation ratio. (b) TAG was determined from the change in HU per 10mm length of coronary artery and defined as the linear regression coefficient between luminal attenuation (HU) and length from the ostium (mm). (c) CCO was defined as the quotient of mean luminal attenuation (HU) in circular ROIs, which were positioned on the coronary artery and descending aorta in the same axial slice. CCO difference was calculated as the change between the lowest CCO proximal to coronary stenosis and the lowest CCO distal to stenosis. CAR, coronary artery to aortic luminal attenuation ratio; CCO, corrected coronaryopacification; HU, Hounsfield unit; ROI, region of interest; TAG, transluminal attenuation gradient.

normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; and 4, defect) by comparison with the normal stress and rest ^{99m}Tc SPECT MPI database developed for Japanese patients by the Japanese Society of Nuclear Medicine working group.^{21–25} Summed stress scores were defined as the sum of the scores of segments on stress images and summed rest scores were based on rest images. Summed difference scores were calculated as summed stress scores minus summed rest scores. SPECT with a normal pattern of myocardial perfusion was regarded as normal. An ischaemic or infarcted pattern and Summed difference scores = 0 in the same coronary artery territories were regarded

as non-conclusive. A normal pattern and Summed difference scores ≥ 1 were also regarded as non-conclusive. An ischaemic or infarcted pattern and summed difference scores ≥ 1 were regarded as abnormal.

Invasive coronary angiography

Invasive coronary angiography was performed in accordance with standard clinical practice within 90 days of cCTA and MPI. Catheterization was performed using the femoral or radial approach with standard 4- or 5F guiding catheters. At least two projections were obtained for assessing each major epicardial

vessel. An experienced cardiologist visually assessed the coronary angiographic images and was blinded to cCTA and MPI results because of the visual assessment's convenience, speed, wide use in clinical practice, and better diagnostic accuracy for prediction of haemodynamically significant coronary artery stenosis.^{26,27} Severity of stenosis was evaluated and a vessel with $\geq 50\%$ stenosis was regarded as significant.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation or median (quartiles) as appropriate. Categorical variables are expressed as percentages. Continuous and categorical variables were compared using the Mann–Whitney *U* test because of non-normal distribution. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of cCTA50, CAR, TAG, and CCO difference were calculated on a per vessel basis and expressed with 95% confidence intervals (CIs). Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic performance of cCTA50, CAR, TAG, and CCO for identifying haemodynamically significant coronary artery stenosis. A vessel with $\geq 50\%$ luminal stenosis on invasive coronary angiography and an associated abnormal perfusion defect on MPI in the same territory was defined as the reference standard. The incremental values in adding CAR, TAG, or CCO to cCTA50 in discriminating haemodynamically significant stenosis were assessed with the area under the ROC curve (AUC) based on a logistic regression model and the DeLong method.²⁸ The optimal cut-off values were determined by Youden index.²⁹ Statistical analysis was performed with statistical software (R Package v. 3.3.2; R Foundation for Statistical Computing, Vienna, Austria). A *p* value < 0.05 was considered statistically significant.

RESULTS

Patients' characteristics and acquisition results

Patients' characteristics and acquisition results are shown in Table 1. Median score of image quality was 3 (2–4). 41 consecutive patients were chosen, and 8 patients were excluded because of insufficient cCTA image quality of all 3 coronary arteries ($n = 5$) and $>50\%$ stenosis in the left main coronary artery ($n = 3$). Among 99 vessels in the remaining 33 patients, 12 vessels were excluded because of insufficient cCTA image quality ($n = 4$), branch vessel disease ($n = 1$), coronary stents ($n = 3$), or chronic total occlusions ($n = 4$). A total of 87 vessels were analyzed from 33 patients (mean age: 69.8 ± 7.4 years; 73% males). 17 (19.5%) vessels were determined as haemodynamically significant coronary artery stenosis.

Diagnostic accuracy of cCTA50, CAR, TAG, and CCO difference for detecting haemodynamically significant coronary artery stenosis

The diagnostic accuracy of cCTA50, CAR, TAG, and CCO difference are shown in Table 2. The mean CAR was significantly lower in vessels with haemodynamically significant coronary artery stenosis compared with nonsignificant vessels (0.66 ± 0.09 vs. 0.75 ± 0.07 , $p < 0.01$). The mean CCO difference was significantly higher in vessels with haemodynamically significant stenosis compared with nonsignificant vessels (0.40 ± 0.20 vs. 0.25 ± 0.18 , $p < 0.01$). The mean TAG was not significantly different between

Table 1. Patient characteristics and acquisition results ($n = 33$)

Characteristic	Value
Age (years)	69.8 ± 7.4
Male	24 (72.7%)
Body mass index (kg/m ²)	24.4 ± 3.1
Cardiovascular risk factors	
Diabetes	17 (51.5%)
Hypertension	20 (60.6%)
Hypercholesterolaemia	13 (39.4%)
Hyperlipidaemia	21 (63.6%)
Current smoker	4 (12.1%)
cCTA findings	
Heart rate during cCTA	59.0 ± 11.5
Image quality (using subjective 4-point scale)	3 [2–4]
Vessels with $\geq 50\%$ diameter stenosis on visual assessment	52 (59.8%)
Calcium score (Agaston Units)	580.2 ± 615.8
Agatston score ≥ 400	18 (54.5%)
MPI findings	
Summed stress scores	6.3 ± 5.7
Summed rest scores	3.6 ± 3.3
Summed difference scores	3.9 ± 4.5
Patients with MPI regarded as normal	4 (12.1%)
Patients with MPI regarded as non-conclusive	10 (30.3%)
Patients with MPI regarded as abnormal	19 (57.6%)
Invasive coronary angiography findings	
Vessels with $\geq 50\%$ diameter stenosis on visual assessment	40 (46%)
Vessels determined as functionally significant coronary artery stenosis	17 (19.5%)

MPI, myocardial perfusion imaging; SD, standard deviation; cCTA, coronary computed tomography angiography. Values are expressed as mean $\pm$ SD, median [interquartile range], or *n* (%).

vessels with haemodynamically significant stenosis and nonsignificant vessels (-19.6 ± 8.4 vs. -16.3 ± 7.2 , $p > 0.1$).

ROC curves of cCTA50, CAR, TAG, CCO difference, and combined cCTA50 and respective methods for identifying haemodynamically significant coronary artery stenosis

The ROC curves of cCTA50, CAR, TAG, CCO difference, and combined cCTA50 and respective methods for detecting haemodynamically significant coronary artery stenosis are shown in Figure 3. CAR showed higher AUC compared with cCTA50,

Table 2. Per vessel basis diagnostic performance of cCTA, CAR, TAG, CCO difference ($n = 87$)

	CCTA ($\geq 50\%$)	CAR (≤ 0.687)	TAG (≤ -13.2)	CCO difference (≥ 0.236)
Sensitivity (%)	94 (71–100)	71 (44–90)	88 (64–99)	94 (71–100)
Specificity (%)	49 (36–61)	83 (72–91)	39 (27–51)	53 (41–65)
PPV (%)	31 (19–45)	50 (29–71)	26 (15–39)	33 (20–48)
NPV (%)	97 (85–100)	92 (82–97)	93 (77–99)	97 (86–100)

CAR, coronary artery to aorta luminal attenuation ratio; CCO, corrected coronary opacification; NPV, negative predictive value; PPV, positive predictive value; TAG, transluminal attenuation gradient; cCTA, coronary computed tomography angiography.

TAG, and CCO difference, nevertheless there were no significant differences. The AUC for combined CAR and cCTA50 was 0.87 (0.78–0.96), which was significantly higher compared with

Figure 3. ROC curves of cCTA, CAR, TAG, CCO difference, cCTA + CAR, cCTA + TAG, and cCTA + CCO. The AUC for CAR was greater than that for cCTA, TAG, and CCO. The AUC for cCTA + CAR was significantly greater than that for cCTA alone (0.87 vs 0.71, $p < 0.01$). Although AUCs for cCTA + TAG and cCTA + CCO increased compared to that for cCTA alone, it was not statistically significant (0.77 vs 0.71, $p > 0.1$; 0.75 vs 0.71, $p > 0.1$, respectively). AUC, area under the ROC curve; CAR, coronary artery to aortic luminal attenuation ratio; CCO, corrected coronary opacification; cCTA, coronary computed tomography angiography; ROC, receiver operating characteristic; TAG, transluminal attenuation gradient.

cCTA50 alone (0.87 vs 0.71, $p < 0.01$) or CAR alone (0.87 vs 0.80, $p < 0.05$). The AUC for combined TAG and cCTA50 was 0.77 (0.66–0.88), which was not significantly higher compared with cCTA50 alone (0.77 vs 0.71, $p > 0.1$). Similarly, the AUC for combined CCO and cCTA50 was 0.75 (0.65–0.86), which was not significantly higher compared with cCTA50 alone (0.75 vs 0.71, $p > 0.1$).

DISCUSSION

In this study, we compared the diagnostic performance of cCTA50, CAR, TAG, and CCO difference in CT for detecting haemodynamically significant coronary artery stenosis. We found that CAR showed a superior diagnostic performance compared with the other methods. The diagnostic performance of adding CAR to cCTA50 was significantly greater than that with cCTA50 alone. CAR does not require any additional examination, and has relatively simple analysis that can be applied to any cCTA scan. Assessment of the diagnostic performance of CAR on CT has not been reported yet.

Previous studies have shown that diagnostic performance of TAG differs according to the longitudinal axis coverage of the CT scanner.^{6,13,30,31} Assessment of TAG320 with 320-detector row CT provides acceptable detection of invasive FFR.⁶ However, TAG derived from 64- or 256-detector row CT, which is limited for acquiring cCTA images with multiple cardiac cycles, shows relatively inferior diagnostic performance for detecting an FFR ≤ 0.80 and does not provide incremental diagnostic value over cCTA50 alone in assessing haemodynamic coronary stenosis.^{30,31,32} TAG can be affected by the condition of contrast agent injection, the scan timing, and the luminal attenuation values. Therefore, 320-detector row CT may be ideal for minimizing these features. Moreover, different scanner system such as dual-source CT may improve the diagnostic performance of TAG. Additionally, TAG shows a significant correlation with diameter and length of the vessels,¹⁵ which also may be related to the inferior diagnostic performance of TAG.

Our study also revealed that the AUC for CCO difference (0.74) was not superior to that for CAR (0.80). An explanation of the inferior diagnostic accuracy of CCO compared with CAR may be that pre-stenosis CCO depends on the area of segment stenosis. If coronary artery stenosis is present close to the coronary ostium, which has a larger diameter than the distal artery, pre-stenosis CCO has a relatively high value. Additionally, CCO uses at least two ROI measurements at each pre-stenosis and post-stenosis.

Although a few ROI measurements may be convenient, they may be more susceptible to image noise or motion artifacts.

In analysis of CAR, ROIs in the distal coronary artery were positioned on the specified area, which was ranged from the proximal 7 mm² sectional area to the distal 3 mm² sectional area. This process may minimize the effect of the coronary artery diameter. Additionally, in the process of calculation, the value of luminal attenuation in the distal coronary artery was divided by the attenuation value in the ascending aorta for correcting the effect of variability in coronary luminal attenuation values of each patient. These corrections may have resulted in acceptable diagnostic performance. Further study will be necessary to investigate whether CAR can serve regardless of various factors. Moreover, CAR added incremental value to the diagnostic performance of cCTA50 alone. In accordance with the fact that anatomical coronary artery stenosis cannot be precisely used to detect haemodynamic coronary artery stenosis, especially in lesions with moderate stenosis, CAR may have a potential role in functional assessment of the coronary artery. Specifically, applying the best cutoff value of CAR to the vessel with $\geq 50\%$ luminal stenosis on cCTA may help the decision of haemodynamic significant stenosis.

One limitation of this study is that our study was a retrospective, single-center study that involved 87 vessels in only 33 patients. Second, a reference standard of haemodynamically significant

coronary artery stenosis in this study was defined as a vessel with $\geq 50\%$ luminal stenosis on invasive coronary angiography and an associated abnormal perfusion defect on MPI in the same territory. However, several studies^{6,13,27–29} adopted an FFR ≤ 0.80 as a reference standard. Third, the utility of CAR in major vessels with a cross-sectional area $< 3.0 \text{ mm}^2$ or branch vessels is unknown. Fourth, cCTA was performed using 64-detector row CT, which is limited for acquiring images with multiple cardiac cycles. Finally, the effect of various factors, such as scanning techniques, scanning parameters such as tube voltage or tube current, injection protocols of contrast media, or reconstruction methods, has not been validated. These factors may influence not only CAR but also TAG or CCO difference.

In conclusion, the noninvasive CAR derived from 64-detector row CT was more feasible and offered opportunities for detecting haemodynamically significant coronary artery stenosis compared with TAG and CCO difference. Combination of CAR with cCTA assessment has incremental value over cCTA alone for detecting haemodynamically significant coronary artery stenosis. Still, further investigation is required for applying CAR in various scanning situations.

Still, further investigations such as intra- and inter-reader correlation, evaluation of larger numbers in different settings, and time efficiency are required for applying CAR in various situations.

REFERENCES

1. Vanhoenacker PK, Heijenbroek-Kal MH, Van Heste R, Decramer I, Van Hoe LR, Wijns W, et al. Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis. *Radiology* 2007; **244**: 419–28. doi: <https://doi.org/10.1148/radiol.2442061218>
2. Hamon M, Biondi-Zoccai GGL, Malagutti P, Agostoni P, Morello R, Valgimigli M, et al. Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography. A meta-analysis. *J Am Coll Cardiol* 2006.
3. Meijboom WB, Van Mieghem CAG, van Pelt N, Weustink A, Pugliese F, Mollet NR, et al. Comprehensive assessment of coronary artery stenoses. computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. *J Am Coll Cardiol* 2008; **52**: 636–43.
4. Koo HJ, Yang DH, Kim Y-H, Kang J-W, Kang S-J, Kweon J, et al. Ct-Based myocardial ischemia evaluation: quantitative angiography, transluminal attenuation gradient, myocardial perfusion, and CT-derived fractional flow reserve. *Int J Cardiovasc Imaging* 2016; **32**: 1–19. doi: <https://doi.org/10.1007/s10554-015-0825-5>
5. Choi J-H, Min JK, Labounty TM, Lin FY, Mendoza DD, Shin DH, et al. Intracoronary transluminal attenuation gradient in coronary CT angiography for determining coronary artery stenosis. *JACC: Cardiovascular Imaging* 2011; **4**: 1149–57. doi: <https://doi.org/10.1016/j.jcmg.2011.09.006>
6. Wong DTL, Ko BS, Cameron JD, Nerlekar N, Leung MCH, Malaiapan Y, et al. Transluminal attenuation gradient in coronary computed tomography angiography is a novel noninvasive approach to the identification of functionally significant coronary artery stenosis. *J Am Coll Cardiol* 2013; **61**: 1271–9. doi: <https://doi.org/10.1016/j.jacc.2012.12.029>
7. Peng K, Xu N, Zhang L, Xiao F, Indima N, Zhang J, et al. Transluminal attenuation gradient and corrected models in coronary CT angiography for determining stenosis severity: a primary study using dual-source CT. *Clin Radiol* 2017; **72**: 508–16. doi: <https://doi.org/10.1016/j.crad.2017.01.003>
8. Wen D, Li J, Zhao H, Li J, Zheng M. Diagnostic performance of two corrected transluminal attenuation gradient metrics in coronary CT angiography for the evaluation of significant in-stent restenosis by dual-source CT: a validation study with invasive coronary angiography. *Clin Radiol* 2018; **73**: 592.e1–592.e8. doi: <https://doi.org/10.1016/j.crad.2018.01.011>
9. Chow BJW, Kass M, Gagné O, Chen L, Yam Y, Dick A, et al. Can differences in corrected coronary opacification measured with computed tomography predict resting coronary artery flow? *J Am Coll Cardiol* 2011; **57**: 1280–8. doi: <https://doi.org/10.1016/j.jacc.2010.09.072>
10. Rochitte CE, George RT, Chen MY, Arbab-Zadeh A, Dewey M, Miller JM, et al. Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: the CORE320 study. *Eur Heart J* 2014; **35**: 1120–30. doi: <https://doi.org/10.1093/eurheartj/ehd488>
11. Williams MC, Newby DE. Ct myocardial perfusion imaging: current status and future

- directions. *Clin Radiol* 2016; **71**: 739–49. doi: <https://doi.org/10.1016/j.crad.2016.03.006>
12. Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, BS K, Ito H, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (analysis of coronary blood flow using CT angiography: next steps. *J Am Coll Cardiol* 2014; **63**: 1145–55.
 13. Ko BS, Wong DTL, Nørgaard BL, Leong DP, Cameron JD, Gaur S, BS K, Meredith IT, et al. Diagnostic performance of transluminal attenuation gradient and noninvasive fractional flow reserve derived from 320-Detector row CT angiography to diagnose hemodynamically significant coronary stenosis: an NXT substudy. *Radiology* 2016; **279**: 75–83. doi: <https://doi.org/10.1148/radiol.2015150383>
 14. Funama Y, Utsunomiya D, Oda S, Shimonobo T, Nakaura T, Mukunoki T, et al. Transluminal attenuation-gradient coronary CT angiography on a 320-MDCT volume scanner: effect of scan timing, coronary artery stenosis, and cardiac output using a contrast medium flow phantom. *Physica Medica* 2016; **32**: 1415–21 Available from. cited 2017 Jul 29. doi: <https://doi.org/10.1016/j.ejmp.2016.10.011>
 15. Park E-A, Lee W, Park SJ, Kim YK, Hwang HY. Influence of coronary artery diameter on intracoronary transluminal attenuation gradient during CT angiography. *JACC: Cardiovascular Imaging* 2016; **9**: 1074–83. doi: <https://doi.org/10.1016/j.jcmg.2015.10.028>
 16. Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the Society of cardiovascular computed tomography guidelines Committee: endorsed by the North American Society for cardiovascular imaging (NASCI. *J Cardiovasc Comput Tomogr* 2016; **10**: 435–49. doi: <https://doi.org/10.1016/j.jcct.2016.10.002>
 17. Pontone G, Bertella E, Mushtaq S, Loguercio M, Cortinovis S, Baggiano A, et al. Coronary artery disease: diagnostic accuracy of CT coronary angiography--a comparison of high and standard spatial resolution scanning. *Radiology* 2014; **271**: 688–94. doi: <https://doi.org/10.1148/radiol.13130909>
 18. Hausleiter J, Meyer TS, Martuscelli E, Spagnolo P, Yamamoto H, Carrascosa P, et al. Image quality and radiation exposure with prospectively ECG-Triggered axial scanning for coronary CT angiography. *JACC: Cardiovascular Imaging* 2012; **5**: 484–93. doi: <https://doi.org/10.1016/j.jcmg.2011.12.017>
 19. Hamdan A, Asbach P, Wellnhofer E, Klein C, Gebker R, Kelle S. . . A Prospective Study for Comparison of MR and CT Imaging for Detection of Coronary Artery Stenosis. 2011. Available from: http://ac.els-cdn.com/S1936878X10007357/1-s2.0-S1936878X10007357-main.pdf?_tid=bf244bb4-7469-11e7-8f2d-00000aab0f02&acdnt=1501338499_0466b9df6d17da39ad084ce09ce00e6b [cited 2017 Jul 29].
 20. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease. Report of the AD hoc Committee for grading of coronary artery disease, Council on cardiovascular surgery, American heart association. *Circulation* 1975; **51**(4 Suppl): 5–40. doi: <https://doi.org/10.1161/01.CIR.51.4.5>
 21. Nakata T, Hashimoto A, Matsuki T, Yoshinaga K, Tsukamoto K, Tamaki N. Prognostic value of automated SPECT scoring system for coronary artery disease in stress myocardial perfusion and fatty acid metabolism imaging. *Int J Cardiovasc Imaging* 2013; **29**: 253–62. doi: <https://doi.org/10.1007/s10554-012-0069-6>
 22. Kusuoka H, Nishimura S, Yamashina A, Nakajima K, Nishimura T. Surveillance study for creating the National clinical database related to ECG-gated myocardial perfusion SPECT of ischemic heart disease: J-ACCESS study design. *Ann Nucl Med* 2006; **20**: 195–202. doi: <https://doi.org/10.1007/BF03027430>
 23. Nishimura T, Nakajima K, Kusuoka H, Yamashina A, Nishimura S. Prognostic study of risk stratification among Japanese patients with ischemic heart disease using gated myocardial perfusion SPECT: J-ACCESS study. *Eur J Nucl Med Mol Imaging* 2008; **35**: 319–28. doi: <https://doi.org/10.1007/s00259-007-0608-x>
 24. Matsuo S, Nakajima K, Horie M, Nakae I, Nishimura T, The J-ACCESS Investigators. Prognostic value of normal stress myocardial perfusion imaging in Japanese population. *Circ J* 2007; **72**: 611–7. doi: <https://doi.org/10.1253/circj.72.611>
 25. Matsuo S, Nakajima K, Yamasaki Y, Kashiwagi A, Nishimura T. Prognostic value of normal stress myocardial perfusion imaging and ventricular function in Japanese asymptomatic patients with type 2 diabetes--a study based on the J-ACCESS-2 database. *Circ J* 2010; **74**: 1916–21. doi: <https://doi.org/10.1253/circj.CJ-10-0098>
 26. Arbab-Zadeh A, Hoe J. Quantification of coronary arterial stenoses by multidetector CT angiography in comparison with conventional angiography methods, caveats, and implications. *JACC Cardiovasc Imaging* 2011; **4**: 191–202. doi: <https://doi.org/10.1016/j.jcmg.2010.10.011>
 27. Adedji J, Xaplanteris P, Toth G, Ferrara A, Pellicano M, Ciccarelli G, et al. Visual and quantitative assessment of coronary stenoses at angiography versus fractional flow reserve. *Circulation* 2017; **10**. doi: <https://doi.org/10.1161/CIRCIMAGING.117.006243>
 28. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; **44**: 837–45. doi: <https://doi.org/10.2307/2531595>
 29. Youden WJ. Index for rating diagnostic tests. *Cancer* 1950; **3**: 32–5. doi: [https://doi.org/10.1002/1097-0142\(1950\)3:1<32::AID-CNCR2820030106>3.0.CO;2-3](https://doi.org/10.1002/1097-0142(1950)3:1<32::AID-CNCR2820030106>3.0.CO;2-3)
 30. Yoon YE, Choi JH, Kim JH, Park KW, Doh JH, Kim YJ, et al. Noninvasive diagnosis of ischemia-causing coronary stenosis using CT angiography: diagnostic value of transluminal attenuation gradient and fractional flow reserve computed from coronary CT angiography compared to invasively measured fractional flow reser. *JACC Cardiovasc Imaging* 2012; **5**: 1088–96.
 31. Stuijzand WJ, Danad I, Rajmakers PG, Marcu CB, Heymans MW, van Kuijk CC, et al. Additional value of transluminal attenuation gradient in CT angiography to predict hemodynamic significance of coronary artery stenosis. *JACC: Cardiovascular Imaging* 2014; **7**: 374–86. doi: <https://doi.org/10.1016/j.jcmg.2013.12.013>
 32. Wang R, Renker M, Schoepf UJ, Wichmann JL, Fuller SR, Rier JD, et al. Diagnostic value of quantitative stenosis predictors with coronary CT angiography compared to invasive fractional flow reserve. *Eur J Radiol* 2015; **84**: 1509–15. doi: <https://doi.org/10.1016/j.ejrad.2015.05.010>