Dynamic Coronary 320-Row CT Angiography Using Low-Dose Contrast and Temporal Maximum Intensity Projection: A Comparison with Standard Coronary CT Angiography

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Objective: The smallest diagnostically sufficient amount of contrast media (CM) should be used for coronary computed tomography angiography (CCTA) to minimize the risk of contrast-induced nephrotoxicity in elderly patients with coronary artery disease. The purpose of this study was to propose dynamic-CCTA using a low dose of CM and temporal maximum intensity projection (TMIP) and to investigate its image quality compared to standard-CCTA.

Materials and Methods: Participants comprised 30 patients with coronary artery disease who underwent dynamic-CCTA and standard-CCTA using 320-row CT. Dynamic-CCTA was continuously performed at mid-diastole throughout 15–25 cardiac cycles after bolus injection of CM [103 mg iodine/kg body weight (mgI/kg)]. TMIP-CCTA was reconstructed from three-phase dynamic-CCTA data, including a phase with peak enhancement of the ascending aorta. Standard-CCTA was performed using a standard CM dose (259 mgI/kg). Image quality of both TMIP-CCTA and standard-CCTA was analyzed.

Results: The amount of CM used in TMIP-CCTA and standard-CCTA was 16.2 ± 2.6 mL and 40.1 ± 7.3 mL, respectively. The mean effective radiation dose was not significantly different between the two methods. Mean coronary attenuation was significantly lower for TMIP-CCTA than standard-CCTA [346.9 ± 82.8 Hounsfield units (HU) vs. 455.4 ± 75.3 HU, $p < 0.05$]. Image noise was significantly lower for TMIP-CCTA than standard-CCTA (20.0 ± 3.2 HU vs. 28.1 ± 3.6 HU, $p < 0.05$). There were no differences in signal-to-noise ratio and visual assessment scores between the two methods.

Conclusion: TMIP-CCTA can be performed using more than 50% less CM with the same image quality as standard-CCTA.

Key words Computed tomography angiography · Contrast media · Coronary artery disease · Cardiac imaging technique.

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INTRODUCTION

Coronary computed tomography angiography (CCTA) is a well-known and reliable method for detecting coronary stenosis in patients with coronary artery disease (CAD) [1]. However, increased attention has been paid to the amount of injected contrast media (CM) for CCTA. Contrast-induced nephrotoxicity (CIN), an acute kidney injury caused by iodinated CM, is the third most common cause of hospital-acquired acute renal injury, representing about 12% of cases [2-4]. The smallest diagnostically sufficient amount of CM should be used, especially in patients with chronic kidney disease (CKD), because CIN is closely related to pre-existing renal insufficiency [5] and the delivered amount of CM [6]. As the rate of CKD is significantly higher in patients with CAD [7] and they may require repeated CT and conventional angiographic studies for clinical management, a reduction in CM dose is particularly important in these patients. However, CCTA protocols that deliver smaller amounts of CM do not provide sufficient and homogeneous enhancement of the coronary arteries [8].

In this study, we focused on temporal maximum intensity projection (TMIP) processing, which was used to reconstruct CT angiography images from CT perfusion data [9]. This processing method displays maximal enhancement over time [10]. Therefore, we hypothesized that TMIP combined with dynamic CCTA for the whole heart [heart-dynamic CT (DCT)] would reduce the CM dose and yield sufficient image quality. We postulated that this reconstruction protocol would increase contrast enhancement in the coronary artery and reduce image noise compared to DCT protocol for coronary evaluation only.

The purpose of this study was to propose dynamic-CCTA using low-dose CM and TMIP and to investigate image quality in comparison to standard-CCTA.

MATERIALS AND METHODS

Study population

Thirty patients who had undergone heart-DCT and standard-CCTA (SCCTA) with 320-row CT between February 2017 and July 2017 were prospectively enrolled as a part of routine care. All patients had been clinically referred for suspected CAD. The exclusion criteria were as follows: 1) previous coronary bypass surgery; 2) contraindications to nitroglycerin or CM; 3) heart rate >65 bpm; 4) body mass index (BMI) greater than 25 kg/m². The study protocol was reviewed and approved by the Institutional Review Board (28-283); the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients. Patient characteristics are summarized in Table 1. Body surface area (BSA) was estimated using the Mosteller formula [11].

Heart-DCT

CT examinations were performed using a 320-row CT scanner (Aquilion One Vision Edition; Canon Medical Systems, Tokyo, Japan). Heart-DCT was performed at 75% of the R-R interval (mid-diastole) for 15–25 cardiac cycles with prospective ECG-gating axial scanning for 20 s from 7 s after a 4-s CM

Table 1. Characteristics of 30 patients

Parameter	
Male: female ratio	15 : 15
Age (years)	61.5±12.1
Heart rate (bpm)	53.5±4.8
Body weight (kg)	60.2±11.9
Body mass index (kg/m ²)	21.3±3.3
BSA (m ²)	1.22±0.72

Data are presented as the mean±standard deviation, BSA was estimated with Mosteller formula [11]. BSA: body surface area

Fig. 1. Time chart of dynamic CCTA for whole heart DCT (heart-DCT). Heart-DCT was performed in mid-diastole for 15–25 cardiac cycles with prospective ECG-gating for 20 s beginning 7 s after a 4-s CM injection (25.9 mgI/kg/sec) (Iopamiron 370; Bayer HealthCare) through a 20-gauge cannula in the right antecubital vein. Contrast administration was followed by a 4-s injection of saline delivered at the same injection rate as the CM. The patients held their breath on inspiration during scanning. CM: contrast media.

injection (103 mgI/kg) (Iopamiron370; Bayer HealthCare, Osaka, Japan) through a 20-gauge cannula in the right antecubital vein (Fig. 1). Contrast administration was followed by a 4-s injection of saline solution delivered at the same injection rate as the CM. The patients held their breath on inspiration during scanning. Bae has reported that the time to peak aortic enhancement from the start of a 5-s injection is about 12 s in a porcine aorta [12]. Fleischmann reported that the time to peak aortic enhancement at an injection rate of 4 mL/s of 16 mL of CM is about 20 s [13]. The scan onset time and duration were determined on the basis of prior experimental studies so as not to miss out on the peak point for the ascending aorta during heart-DCT. All patients received sublingual nitroglycerin before the CT study. The scan parameters for heart-DCT were: collimation, 320×0.5 mm; gantry rotation time, 0.275 s; tube potential, 80 kVp; tube current, 100 mA; and z-coverage, 160 mm. The image reconstruction parameters for heart-DCT were: reconstructed field of view, 200 mm; slice thickness, 0.5 mm; section interval, 0.25 mm. Heart-DCT images acquired with half-scan were reconstructed with a forward projected model-based iterative reconstruction solution (FIRST) (“cardiac standard” setting).

SCCTA

SCCTA was performed using prospective ECG-triggered axial scans following heart-DCT. The phase window was limited to 70–80% of the R-R interval. Scan timing was determined by the peak time of attenuation in the ascending aorta obtained from heart-DCT data. Based on the theory of injection time [14], 259 mgI/kg of CM was administered for the 10-s CM injection, followed by a 30-mL saline flush during inspiratory breath hold. To align the injection speed, 103 mgI/kg was administered for TMIP [13]. The scan parameters for SCCTA were: collimation, 320×0.5 mm; gantry rotation time, 0.275 s; tube potential, 120 kVp; tube current, auto exposure control (540–750 mA); z-coverage, 160 mm. The image reconstruction parameters for SCCTA were: reconstructed field of view, 200 mm; slice thickness, 0.5 mm; section interval, 0.25 mm. SCCTA images acquired with half-scan were reconstructed with FIRST (“cardiac standard” setting).

TMIP-CCTA

The TMIP operation displays the maximal enhancement over time for each voxel from three-dimensional data [10]. Previous studies have reported that TMIP images reconstructed from cerebral CT perfusion data have excellent image quality for assessment of vascular morphology [15]. On the basis of this technique, TMIP images were used for heart-DCT data. TMIP-CCTA was reconstructed from three-phase dynamic-CCTA data, including the phase with peak enhancement of the ascending aorta (Fig. 2). To determine the optimal phase number of

Fig. 2. Selection phases for TMIP. The graph shows a time-curve of ascending aorta attenuation (HU) throughout all phases of heart-DCT. TMIP-CCTA was reconstructed from three-phase data as shown by the gray frame. These data were selected from the maximum enhancement phase of the ascending aorta to two phases behind. TMIP: temporal maximum intensity projection, HU: Hounsfield units, DCT: dynamic CT, CCTA: coronary computed tomography angiography.

TMIP-CCTA, we examined image quality at two, three, four, and five phases before this study. At two phases, artifact was reduced but image noise was increased; at four and five phases, image noise was reduced but artifact was increased. Consequently, we used three phases. TMIP-CCTA reconstruction was performed using a 320-row CT scanner.

Quantitative image analysis

The following parameters were measured on axial source images. 1) Mean CT attenuation of the ascending aorta, proximal right coronary artery (RCA), and left main trunk (LMT) were determined by placing a round region of interest of the ascending aorta (ROI_{Ao}) in the origin of the LMT. The area of the ROI_{Ao} was 400 mm² in the ascending aorta, which was not so small as to be affected by pixel variability and not so large as to include the vessel wall or perivascular fat [16]. The ROIs of the proximal RCA (ROI_R) and LMT (ROI_L) were as large as possible while carefully avoiding vessel wall inclusion to prevent partial volume effects. 2) Image noise was determined as the standard deviation (SD) of the attenuation value in ROI_{Ao}. We measured three ROIs in three different sequential slices. To minimize bias from single measurements, we calculated the mean of the measurements from all ROIs. 3) The signal-to-noise ratio (SNR) and the contrast-to-noise ratio (CNR) of the ascending aorta, proximal RCA, and LMT were calculated as SNR=the mean attenuation/image noise and CNR=contrast enhancement/image noise, respectively [16,17]. Contrast enhancement was calculated as the difference between mean attenuation in the lumen of each vessel and the adjacent perivascular fatty tissue. We compared these parameters between TMIP-CCTA and SCCTA.

Qualitative image analysis

All image data sets (30 patients×2 images) were presented in random order and were evaluated independently by two experienced radiologists (radiologist #1, 26 years of experience in cardiac radiology; radiologist #2, 9 years of experience in cardiac radiology). They evaluated image sharpness on a per-three main coronary arteries basis and overall image quality on a per-patient basis. They independently graded image sharpness on a 4-point scale by evaluating aortic wall sharpness (1=blurry, 2=poorer than average, 3=better than average, 4=sharpest). Overall image quality was graded on a 4-point scale (1=unacceptable, 2=acceptable, 3=good, 4=excellent) [16]. Adequate diagnostic image quality was defined as equal to or higher than a 3 for image sharpness and equal to or higher than a 2 for overall image quality.

Radiation dose of each image

The volume CT dose index (CTDI_{vol}) and the dose length product (DLP) were recorded to estimate the CT radiation dose. The effective dose (ED) at CCTA was derived from the product of DLP and a conversion coefficient for the chest according to European Commission Guidelines on quality criteria in CT (k=0.014 mSv m/Gy/cm) [18].

Statistical analysis

All numeric values are reported as the mean±SD. In terms of qualitative analysis, we averaged the visual scores of each item assessed by the two observers. The Wilcoxon signed-rank test was used for all comparisons of SCCTA and TMIP-CCTA, and p<0.05 was considered a statistically significant difference. Reader agreement was assessed using Cohen's kappa test. The following criteria were used: 0.21–0.40=fair agreement; 0.41–0.60=moderate agreement; 0.61–0.80=substantial agreement; and 0.81–1.0=almost perfect agreement [19]. All statistical analyses were conducted using JMP software (version 12.0.0; SAS, Cary, NC, USA).

RESULTS

Quantitative analysis results

The peak aortic enhancement time derived from 30 patients was 20.2±2.2 seconds. The mean attenuation values of the ascending aorta and coronary arteries were significantly higher in SCCTA than those in TMIP-CCTA (SCCTA vs. TMIP-CCTA: ascending aorta, 465.6±73.9 Hounsfield units (HU) vs. 382.8±87.7 HU, p<0.05; right coronary, 448.7±76.5 HU vs. 333.0±83.9 HU, p<0.05; left coronary, 462.1±74.1 HU vs. 360.7±81.7 HU, p<0.05, respectively). However, the mean image noise was significantly lower in TMIP-CCTA than in SCCTA (TMIP-CCTA vs. SCCTA: 20.0±3.2 HU vs. 28.1±3.6 HU,

p<0.05), leading to almost the same SNR between TMIP-CCTA and SCCTA (TMIP-CCTA vs. SCCTA: ascending aorta, 19.3±4.2 vs. 16.9±3.7, p<0.05; right coronary, 16.6±3.7 vs. 16.2±3.8, p=0.59; left coronary, 18.2±4.0 vs. 16.7±3.7, p=0.16, respectively) (Table 2). Results for CNR between TMIP-CCTA and SCCTA (TMIP-CCTA vs. SCCTA: ascending aorta, 19.0±4.2 vs. 15.8±3.2, p<0.05; right coronary, 16.1±3.8 vs. 15.1±3.1, p=0.24; left coronary, 18.2±3.8 vs. 15.8±3.2, p=0.07, respectively) were similar to those of SNR (Table 2).

Qualitative analysis results

The image sharpness of the RCA was not significantly different between TMIP-CCTA and SCCTA, but those of the LAD and LCX were significantly superior in SCCTA (TMIP-CCTA vs. SCCTA: RCA, 3.0±0.52 vs. 3.2±0.57, p=0.11; LAD, 3.1±0.45 vs. 3.5±0.45, p<0.05; LCX, 3.1±0.45 vs. 3.5±0.42, p<0.05, respectively) (Table 3). However, there was no significant difference between TMIP-CCTA and SCCTA in overall image quality (TMIP-CCTA vs. SCCTA: 3.2±0.55 vs. 3.2±0.46, p=0.59).

Table 2. Results of quantitative image analysis

	TMIP-CCTA	SCCTA	p value
CT attenuation (HU)			
Ascending aorta	382.8±87.7	465.6±73.9	<0.05
Proximal RCA	333.0±83.9	448.7±76.5	<0.05
LMT	360.7±81.7	462.1±74.1	<0.05
Image noise (HU)	20.0±3.2	28.1±3.6	<0.05
SNR			
Ascending aorta	19.3±4.2	16.9±3.7	<0.05
Proximal RCA	16.6±3.7	16.2±3.8	0.59
LMT	18.2±4.0	16.7±3.7	0.16
CNR			
Ascending aorta	19.0±4.2	15.8±3.2	<0.05
Proximal RCA	16.1±3.8	15.1±3.1	0.24
LMT	18.2±3.8	15.8±3.8	0.07

Data are presented as the mean±standard deviation. SNR: the signal-to-noise ratio, CNR: the contrast-to-noise ratio, RCA: right coronary artery, LMT: left main trunk, HU: Hounsfield units, CT: computed tomography, TMIP-CCTA: temporal maximum intensity projection-coronary computed tomography angiography, SCCTA: standard-CCTA

Table 3. Results of qualitative image analysis

	TMIP-CCTA	SCCTA	p value
Image sharpness			
RCA	3.0±0.52	3.2±0.57	0.11
LAD	3.1±0.45	3.5±0.45	<0.05
LCX	3.1±0.45	3.5±0.42	<0.05

Data are presented as the mean±standard deviation. RCA: right coronary artery, LAD: left anterior descending artery, LCX: left circumflex artery, TMIP-CCTA: temporal maximum intensity projection-coronary computed tomography angiography, SCCTA: standard-CCTA

Fig. 3. A 40-year-old female patient with suspected coronary artery disease. (A) Axial image. (B) MIP. (C) Curved MPR image with TMIP-CCTA. (D) Axial image. (E) MIP. (F) Curved MPR image with standard-CCTA. MPR: multiplanar reconstruction, TMIP: temporal maximum intensity projection, CCTA: coronary computed tomography angiography, CM: contrast media, MIP: maximum-intensity projection, CPR: curved multiplanar reconstruction, SCCTA: standard-CCTA.

Moreover, TMIP-CCTA achieved diagnostic image quality for all analysis items. The assessment of inter-observer agreement was excellent for image sharpness (weighted kappa=0.94, 0.97, and 0.92 for RCA, LAD, and LAD, respectively) and overall image quality (weighted kappa=0.94). A representative case is shown in Fig. 3.

Radiation and CM dose of each protocol

The CTDI_{vol}, DLP, and ED values and the amount of CM for each scan method are shown in Table 4. There was no significant difference between TMIP-CCTA and SCCTA (4.2 ± 0.68 mSv vs. 4.0 ± 1.9 mSv, $p=0.071$) in terms of ED. The amounts of CM used for TMIP-CCTA and SCCTA were 16.2 ± 2.6 mL and 40.1 ± 7.3 mL, respectively ($p<0.01$).

DISCUSSION

This study proposes TMIP-CCTA that combines smaller amounts of CM and dynamic scanning with a 320-row CT. Compared to SCCTA, TMIP-CCTA yielded almost the same SNR and overall image quality despite a 60% reduction in CM dose. This observation is of practical importance because use of CCTA with lower CM doses may reduce the risk of CIN with-

Table 4. Radiation and CM dose of each protocol

	TMIP-CCTA	SCCTA	p value
CTDI _{vol} (mGy)	20.4 ± 2.3	19.7 ± 9.8	0.065
DLP (mGy · cm)	300.0 ± 48.6	288.1 ± 142.0	0.071
ED (mSv)	4.2 ± 0.68	4.0 ± 1.9	0.071
CM (mL)	16.2 ± 2.6	40.1 ± 7.3	<0.001

Data are presented as the mean $\pm$ standard deviation. CTDI_{vol}: volume CT dose index, DLP: dose length product, ED: effective dose, TMIP-CCTA: temporal maximum intensity projection-coronary computed tomography angiography, SCCTA: standard-CCTA, CM: contrast media

out compromising the quality of diagnostic information, especially in patients with renal insufficiency. Furthermore, there was no significant difference between TMIP-CCTA and SCCTA with respect to radiation dose. Our findings suggest that, depending on the patient's renal function, heart rate, and pretest probability of CAD, TMIP-CCTA could be performed in place of SCCTA.

The image sharpness values of the LAD and LCX were significantly inferior in TMIP-CCTA compared to SCCTA. This was likely due to misregistration error. The left coronary artery system (LAD and LCX) is smaller in diameter than the RCA [20]. Therefore, the accuracy of non-rigid registration in the LAD

and LCX might be inferior to that in the RCA.

Image noise was significantly lower in TMIP-CCTA than in SCCTA. This was likely because of MIP algorithm, which displays the maximal enhancement for each voxel.

The mean attenuation of the ascending aorta and coronary arteries was significantly lower in TMIP-CCTA than in SCCTA. However, the mean coronary attenuation was 347 HU on TMIP-CCTA. This value satisfied the limit for optimal coronary attenuation (>300 HU) [21]. Oda et al. [8] reported that around 210 mgI/kg CM is appropriate for 320-row CCTA with a tube voltage of 80 kVp, while CCTA protocols with less than 210 mgI/kg CM cannot provide sufficient and homogeneous enhancement of the coronary arteries. On the other hand, our study found that TMIP-CCTA with a CM dose of 103 mgI/kg to be almost equivalent in overall image quality to CCTA with a CM dose of 259 mgI/kg. To our knowledge, a CM dose of 103 mgI/kg is the lowest of any published CCTA study.

CIN is associated with increased mortality rates, and there is a consensus that the most important risk factor for CIN is pre-existing renal insufficiency [22]. Invasive coronary angiography is also a known risk factor for CIN, and the risk for CIN is higher after coronary angiocardigraphy than after intravenous administration of CM [23]. TMIP-CCTA can be used to identify non-occlusive coronary artery in patients at high risk of CIN.

Heart-DCT can be used in the functional assessment of coronary arteries in that it calculates a novel coronary flow index (CFI). CFI can be used to detect myocardial ischemia derived from intermediate coronary stenosis [24]. Hybrid analysis of CFI and TMIP-CCTA enables functional and morphological assessment of the coronary arteries. Conventional dynamic myocardial perfusion imaging requires additional CCTA scans for coronary evaluation. If our reconstruction protocol is applied to DCT perfusion imaging, functional and anatomic imaging can be performed with a single contrast injection and CT exam.

This study has some limitations. First, the study population was small and from a single institution. Therefore, the incidence of significant coronary stenosis was low. As a result, we were not able to assess diagnostic performance for detection of coronary stenosis. Second, we included only patients with BMI less than 25 kg/m². CCTA images of obese patients tend to be poorer quality because of increased image noise. Therefore, low-tube-voltage and heart-DCT are not suitable for obese or even overweight patients. Validation studies are needed for obese patients. Third, this study excluded patients with heart rate (HR) >65 bpm. In the clinical setting, many patients have higher HR. There is concern that TMIP-CCTA image quality for patients with HR >65 will be degraded due to motion artifact. It is possible that registration error also arises in patients with high HR more often than in patients with low HR. However, in this study, heart-DCT was performed in mid-diastole for patients with lower HR.

Therefore, in patients with high HR >65, we infer that heart-DCT scanning at the end of systole might not degrade TMIP image quality.

In conclusion, TMIP-CCTA can decrease CM dose by more than 50% and still provide the same image quality as standard CCTA.

Conflicts of Interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008;52:1724-1732.
2. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis* 2002;39:930-936.
3. Katzberg RW, Haller C. Contrast-induced nephrotoxicity: clinical landscape. *Kidney Int Suppl* 2006;69:S3-S7.
4. Mohammed NM, Mahfouz A, Achkar K, Rafie IM, Hajar R. Contrast-induced nephropathy. *Heart Views* 2013;14:106-116.
5. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, et al. ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol* 1999;33:1756-1824.
6. Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existing chronic renal insufficiency. *J Am Coll Cardiol* 2000;36:1542-1548.
7. Utsunomiya D, Yanaga Y, Awai K, Oda S, Funama Y, Namimoto T, et al. Baseline incidence and severity of renal insufficiency evaluated by estimated glomerular filtration rates in patients scheduled for contrast-enhanced CT. *Acta Radiol* 2011;52:581-586.
8. Oda S, Utsunomiya D, Yuki H, Kai N, Hatemura M, Funama Y, et al. Low contrast and radiation dose coronary CT angiography using a 320-row system and a refined contrast injection and timing method. *J Cardiovasc Comput Tomogr* 2015;9:19-27.
9. Smit EJ, Vonken EJ, van der Schaaf IC, Mendrik AM, Dankbaar JW, Horsch AD, et al. Timing-invariant reconstruction for deriving high-quality CT angiographic data from cerebral CT perfusion data. *Radiology* 2012; 263:216-225.
10. Beier J, Buge T, Stroszczyński C, Oellinger H, Fleck E, Felix R. [2D and 3D parameter images for the analysis of contrast medium distribution in dynamic CT and MRI]. *Radiologe* 1998;38:832-840.
11. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987;317:1098.
12. Bae KT. Peak contrast enhancement in CT and MR angiography: when does it occur and why? Pharmacokinetic study in a porcine model. *Radiology* 2003;227:809-816.
13. Fleischmann D. Use of high concentration contrast media: principles and rationale-vascular district. *Eur J Radiol* 2003;45:S88-S93.
14. Tanaka R, Yoshioka K, Muranaka K, Chiba T, Ueda T, Sasaki T, et al. Improved evaluation of calcified segments on coronary CT angiography: a feasibility study of coronary calcium subtraction. *Int J Cardiovasc Imaging* 2013;29(Suppl 2):75-81.
15. Smit EJ, Vonken EJ, van der Schaaf IC, Mendrik AM, Dankbaar JW, Horsch AD, et al. Timing-invariant reconstruction for deriving high-

- quality CT angiographic data from cerebral CT perfusion data. *Radiology* 2012;263:216-225.
16. Nakaura T, Kidoh M, Sakaino N, Utsunomiya D, Oda S, Kawahara T, et al. Low contrast- and low radiation dose protocol for cardiac CT of thin adults at 256-row CT: usefulness of low tube voltage scans and the hybrid iterative reconstruction algorithm. *Int J Cardiovasc Imaging* 2013;29: 913-923.
 17. Maeda E, Tomizawa N, Kanno S, Yasaka K, Kubo T, Ino K, et al. The feasibility of forward-projected model-based iterative reconstruction solution (FIRST) for coronary 320-row computed tomography angiography: a pilot study. *J Cardiovasc Comput Tomogr* 2017;11:40-45.
 18. Oda S, Utsunomiya D, Funama Y, Awai K, Katahira K, Nakaura T, et al. A low tube voltage technique reduces the radiation dose at retrospective ECG-gated cardiac computed tomography for anatomical and functional analyses. *Acad Radiol* 2011;18:991-999.
 19. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-174.
 20. Park EA, Lee W, Park SJ, Kim YK, Hwang HY. Influence of coronary artery diameter on intracoronary transluminal attenuation gradient during CT angiography. *JACC Cardiovasc Imaging* 2016;9:1074-1083.
 21. Wong DT, Ko BS, Cameron JD, Nerlekar N, Leung MC, Malaipan 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: a comparison with fractional flow reserve. *J Am Coll Cardiol* 2013;61:1271-1279.
 22. From AM, Bartholmai BJ, Williams AW, Cha SS, McDonald FS, et al. Mortality associated with nephropathy after radiographic contrast exposure. *Mayo Clin Proc* 2008;83:1095-1100.
 23. Katzberg RW, Newhouse JH. Intravenous contrast medium-induced nephrotoxicity: is the medical risk really as great as we have come to believe? *Radiology* 2010;256:21-28.
 24. Nagao M, Yamasaki Y, Kamitani T, Kawanami S, Sagiya K, Yamanouchi T, et al. Quantification of coronary flow using dynamic angiography with 320-detector row CT and motion coherence image processing: detection of ischemia for intermediate coronary stenosis. *Eur J Radiol* 2016;85: 996-1003.