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Optimization of Coronary Attenuation in Coronary Computed Tomography Angiography Using Diluted Contrast Material

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Background: The purpose of this study was to evaluate a personalized protocol with diluted contrast material (CM) for coronary computed tomography angiography (CTA).

Methods and Results: One hundred patients with suspected coronary artery disease underwent retrospective electrocardiogram-gated coronary CTA on a 256-slice multidetector-row CT scanner. In the diluted CM protocol (n=50), the optimal scan timing and CM dilution rate were determined by the timing bolus scan, with 20% CM dilution (5 ml/s during 10 s) being considered suitable to achieve the target arterial attenuation of 350 Hounsfield units (HU). In the body weight (BW)-adjusted protocol (n=50, 222 mg iodine/kg), only the optimal scan timing was determined by the timing bolus scan. The injection rate and volume in the timing bolus scan and real scan were identical between the 2 protocols. We compared the means and variations in coronary attenuation between the 2 protocols. Coronary attenuation (mean ± SD) in the diluted CM and BW-adjusted protocols was 346.1±23.9 HU and 298.8±45.2 HU, respectively. The diluted CM protocol provided significantly higher coronary attenuation and lower variance than did the BW-adjusted protocol (P<0.05, in each).

Conclusions: The diluted CM protocol facilitates more uniform attenuation on coronary CTA in comparison with the BW-adjusted protocol. (*Circ J* 2014; **78:** 662–670)

Key Words: Computed tomography; Contrast material; Coronary attenuation; Injection protocol

In recent years, technological advances in multidetector-row computed tomography (MDCT) have produced increases in detector range and gantry rotation speed. Electrocardiogram (ECG)-gated data MDCT allows for the evaluation of cardiac anatomy and coronary artery stenosis without blurring, and has been widely available in clinical practice as coronary computed tomography angiography (CTA).[1–6]

In addition to coronary artery stenosis, coronary CTA can be used to evaluate the properties of coronary plaque. Many studies have reported the feasibility of coronary CTA for the accurate diagnosis and quantification of these 2 variables in patients with coronary artery disease (CAD),[7–13] but previous experimental and clinical studies have shown that coronary attenuation in coronary CTA affects the assessment of both coronary artery stenosis and plaque.[14–18] Lower coronary attenuation may decrease the diagnostic accuracy of coronary artery stenosis, whereas higher coronary attenuation may underestimate low-attenuation plaque.

Therefore, it is necessary to optimize coronary attenuation for the objective evaluation of coronary stenosis and plaque properties in case-control and cohort studies. The feasibility of the contrast-injection protocol with body weight (BW)-adjusted iodine dose has been confirmed in some studies, but unexpected contrast enhancement has been observed in clinical practice.[19,20] If robust contrast enhancement is achieved in coronary CTA, it would be considered a more reliable and less invasive diagnostic tool. The purpose of this study was to assess the feasibility of a personalized contrast-injection protocol using diluted contrast material (CM) to optimize coronary attenuation in coronary CTA.

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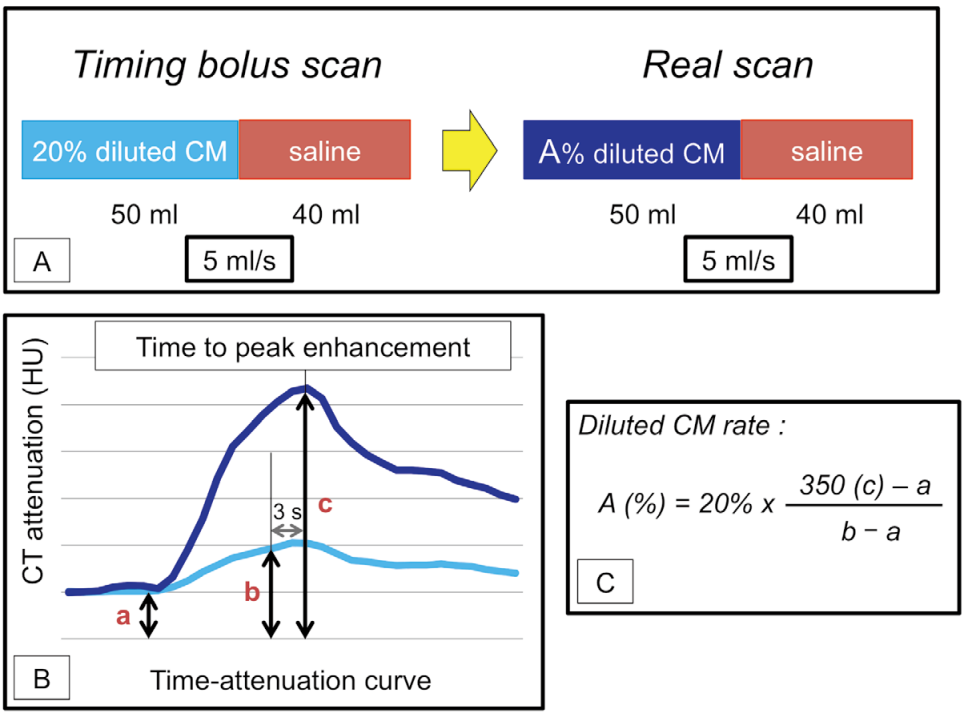

Figure 1. Contrast-injection protocol with diluted contrast material (CM). (**A**) Schematic diagram of contrast-injection with diluted CM. (**B**) Time-attenuation curve (TAC) of the timing bolus scan (light blue) and real scan (blue). (**C**) Formula used to determine the optimal CM dilution rate. The optimal scan timing and necessary CM dilution rate (A%) are determined by the TAC of the timing bolus scan with 20% CM dilution. a, Baseline attenuation; b, minimum guaranteed attenuation (3 s before peak enhancement of the TAC); c, estimated peak attenuation (target attenuation 350 HU). CT, computed tomography.

Methods

Patients

The institutional ethics committee approved the study protocol and all the patients provided written informed consent. From May 2010 to September 2011, 100 consecutive patients were prospectively enrolled in this study. The entry criteria were (1) age ≥20 years; and (2) suspected CAD based on chest symptoms and abnormal ECG and/or echocardiography. The exclusion criteria were as follows: (1) history of coronary artery bypass grafting; (2) history of myocardial infarction; (3) unstable angina (recent onset of angina within 1 month or severe and worsening clinical symptoms); (4) symptomatic congestive heart failure; (5) severe left ventricle dysfunction (left ventricular ejection fraction <30%); (6) greater than first-degree atrioventricular block; (7) compromised renal function (serum creatinine >1.5 mg/dl [114 mol/L]); (8) pregnancy, hyperthyroidism or a known allergic reaction to the CM; and (9) known history of bronchial asthma. All patients were randomly assigned to either the diluted CM or the BW-adjusted contrast-injection protocols.

CT Protocol

All patients received 0.6 mg of a nitroglycerin spray with 2 puffs (Myocor; Astellas Pharma, Tokyo, Japan) and 2–8 mg of a β-blocker (Inderal; AstraZeneca, London, UK) i.v. 5 min prior to the timing bolus scan to reduce the heart rate (HR), when the HR at rest was >70 beats/min. We used a 256-slice MDCT scanner (Brilliance iCT; Philips Healthcare, Cleveland, OH, USA) and an automatic dual injector (Stellant DualFlow; Nihon Medrad, Osaka, Japan). The CM was delivered via a 20-G catheter inserted into an antecubital vein. The examination included the timing bolus scan and real scan for coronary CTA. The mechanical parameters for CT were the same for the timing bolus scan and real scan.

The timing bolus scan was performed 6 s after the CM was injected, with axial data acquisition at 1-s intervals at the level of the ascending aorta (the upper level of scan range in the real scan) with the following parameters: gantry rotation time, 0.4 s/rotation; tube voltage, 120 kVp; tube current, 75 mA; and collimation, 2×16×0.625 mm. The real scan was performed with retrospective ECG gating; tube voltage, 120 kVp; effective tube current time-product, 800–1,300 mAs/rotation; gantry rotation time, 0.27 s/rotation; pitch factor, 0.14; collimation, 2×128×0.625 mm with a dynamic z-focal spot, 250-mm display field of view, 0.8/0.4-mm slice thickness/overlap, and 512×512 image matrix.

Contrast-Injection Protocol

Diluted CM Protocol Either iohexol (Omnipaque 350 mg iodine/ml; Daiichi Sankyo, Tokyo, Japan) or iopamidol (Iopamiron 370 mg iodine/ml; Bayer Yakuhin, Osaka, Japan) was randomly used for this protocol (**Figure 1**).

First, the timing bolus scan was performed with 20% CM dilution at the same injection rate and volume as that of the real scan (5 ml/s, 50 ml), followed by a saline chaser (5 ml/s, 40 ml) to estimate the optimal scan timing and the CM dilution rate required to achieve the target arterial attenuation (350 Hounsfield units; HU). Second, the time-attenuation curve (TAC) of the

Table 1. Clinical Patient Characteristics

Characteristics	Diluted CM protocol (n=50)	BW-adjusted protocol (n=50)	P-value
Age (years)	63.3±12.0	65.3±11.5	0.684
Male	32 (64)	27 (54)	0.309
Body weight (kg)	64.7±11.1	62.5±12.7	0.375
Body mass index (kg/m^2)	24.6±3.5	24.1±3.8	0.515
Hypertension	20 (40)	22 (44)	0.685
Diabetes mellitus	16 (32)	16 (32)	1
Hyperlipidemia	16 (32)	13 (26)	0.509
Smoking	19 (38)	15 (30)	0.398
Family history of CAD	9 (18)	6 (12)	0.401

Data given as mean±SD or n (%).
BW, body weight; CAD, coronary artery disease; CM, contrast material.

Table 2. CM Injection Parameters During the Real Scan

Variables	Diluted CM protocol (n=50)	BW-adjusted protocol (n=50)	P-value
Injection rate (ml/s)	5	3.7±0.7	<0.05
Scan delay (s)	20.0±2.5	19.9±2.4	0.568
Scan time (s)	5.6±0.5	5.5±0.3	0.235
Iodine dose (g iodine)	14.8±2.9	13.9±2.8	0.098
Iodine dose per BW (mg iodine/kg)	233.3±58.4	222.2±1.6	0.967
Scan heart rate (beats/min)	66.1±11.7	63.7±7.2	0.222

Data given as mean±SD.
Abbreviations as in Table 1.

arterial phase was created with a series of axial CT images at the region of interest (ROI) at the level of the ascending aorta. We measured aortic attenuation at the baseline (before the upslope) and 3 s before time to peak enhancement of the TAC in the timing bolus scan. Attenuation at 3 s before peak enhancement was taken as the "minimum guaranteed attenuation" if coronary CTA was initiated at this time using the timing bolus scan of 20% CM dilution. Third, for the target arterial attenuation of 350 HU, the optimal CM dilution rate for the real scan was calculated using the following formula: A(%)=20%×(350–baseline attenuation)/(minimum guaranteed attenuation in the timing bolus scan–baseline attenuation). Furthermore, the optimal scan timing for the real scan was also set as 3 s before peak enhancement of the TAC in the timing bolus scan. This calculation was automatically done using the formula fed into the coronary CTA database, and the optimal CM dilution rate for the real scan was adjusted on the monitor of a dual injector at intervals of 5% for clinical use within a few minutes. Finally, after setting the optimal CM dilution rate of the injector, the real scan was performed using an individually optimized CM injection profile (A%, 5 ml/s and 50 ml), followed by a saline chaser. If the CM dilution rate in the real scan was suggested to be above 100%, the injection duration was adjusted according to the increase in the necessary iodine dose (mg iodine) at the same injection rate of 5 ml/s.

BW-Adjusted Protocol Iopamidol was the CM used in this group. The injection volume of the CM (B ml) in the real scan was calculated using the formula: B(ml)=BW×0.6 (222 mg iodine/kg). The injection duration was fixed at 10 s in both the timing bolus scan and real scan, and the injection rate (0.1×B ml/s) was adjusted for each injection volume. First, the timing bolus scan was performed with 20% CM dilution (0.1×B ml/s, B ml), followed by a saline chaser (0.1×B ml/s, 40 ml). Then, the optimal scan timing was determined based on the TAC in the same manner as that for the diluted CM protocol. The real scan was performed with the regular (100%) CM, using the planned CM injection profile (0.1×B ml/s, B ml), followed by a saline chaser (0.1×B ml/s, 40 ml). The injection volume and rate in the timing bolus scan and real scan were also determined at intervals of 1 ml and 0.1 ml/s, respectively, for clinical use.

Data Analysis

Axial images with a slice thickness of 0.8 mm and a section interval of 0.4 mm were reconstructed with the beat-to-beat variable delay algorithm and multi-cycle reconstruction using a medium cardiac kernel (XCB). First, the mid-diastolic phases (70%, 75%, and 80% of the R-wave–R-wave interval) were reconstructed; data thus obtained were used for the coronary attenuation study if the image quality was good. In cases of inadequate image quality, image reconstruction was performed in 10% increments from 0% to 90% of the R-wave–R-wave interval to select the best phase with the highest image quality. All the CT datasets were analyzed with a commercially available program (Extended Brilliance Workspace, Philips Healthcare, Best, the Netherlands).

According to a standard 18-segment model (Society of Cardiovascular Computed Tomography Guidelines), the origin of the left main trunk (LM); proximal portion of the left anterior descending coronary artery (pLAD); proximal portion of the left circumflex artery (pLCX); and proximal, middle, and distal portions of the right coronary artery (pRCA, mRCA, and dRCA, respectively) were determined. We defined the mean coronary attenuation of 3 ROI in each coronary segment manually placed at the center of the coronary artery as the segmental attenuation. The mean aortic attenuation in the ascending aorta was also evaluated using 4 ROI in 3 sinuses of the Valsalva and sinotubu-

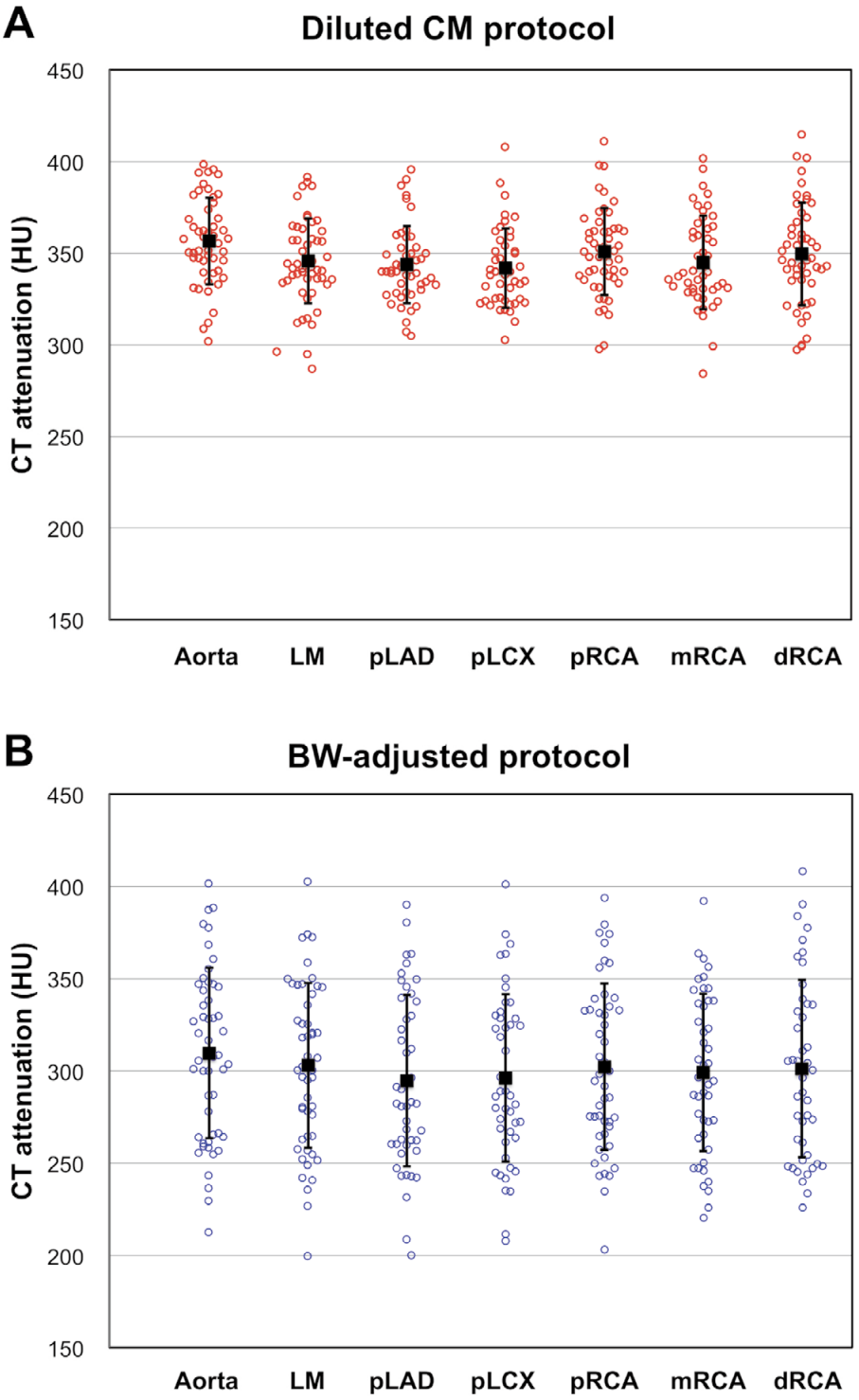

Figure 2. Aortic and coronary attenuations in the (**A**) diluted contrast material (CM) protocol and (**B**) body weight (BW)-adjusted protocol. Mean attenuation ± SD is given for the ascending aorta; origin of the left main trunk (LM); proximal portion of the left anterior descending coronary artery (pLAD); proximal portion of the left circumflex artery (pLCX); and proximal, middle, and distal portions of the right coronary artery (pRCA, mRCA, and dRCA, respectively). The mean attenuations of the aorta and all coronary segments in the diluted CM protocol were significantly higher with smaller variations (SD) than in the BW-adjusted protocol ($P<0.05$). CT, computed tomography.

Table 3. Coronary Attenuation vs. BW and Protocol

	Diluted CM protocol			BW-adjusted protocol		
	Lower BW (BW <63.0, n=25)	Higher BW (BW ≥63.0, n=25)	P-value	Lower BW (BW <59.5, n=25)	Higher BW (BW ≥59.5, n=25)	P-value
Body weight (kg)	55.6±5.3	73.7±7.4	<0.05	52.9±4.1	72.2±10.9	<0.05
Injection rate (ml/s)	5	5	–	3.2±0.2	4.2±0.5	<0.05
Iodine dose (g iodine)	13.5±2.8	16.2±2.4	<0.05	11.8±0.9	16.0±2.5	<0.05
Iodine dose per BW (mg iodine/kg)	246.3±74.5	220.2±32.3	0.187	222.5±1.6	222.0±1.6	0.297
Coronary attenuation (HU)	345.2±19.8	346.1±26.3	0.89	289.0±43.9	315.6±42.4	<0.05

Data given as mean±SD.
HU, Hounsfield units. Other abbreviations as in Table 1.

lar junction. All patients underwent measurement of aortic attenuation and of the 6 segments of coronary attenuation (LM, pLAD, pLCX, pRCA, mRCA, and dRCA).

Coronary segments with severe calcification, diffuse plaque, and diameter ≤2 mm were eliminated from analysis.

Statistical Analysis

Data are expressed as mean±SD or n (%). Continuous variables from among the patient characteristics, scan parameters, contrast-injection variables, and attenuation were compared using unpaired Student's t-test or Mann-Whitney U-test as appropriate, and categorical data were analyzed with the chi-squared test. The statistical significance of any difference among the coronary attenuations was assessed using the Tukey-Kramer method. Levene test was used to compare patient-to-patient variability among aortic and coronary attenuation between the 2 protocols. Pearson's correlation coefficient was used to assess the relationship between BW and iodine dose. All statistical analysis was done using SPSS version 21 (SPSS, Chicago, IL, USA); P<0.05 was considered statistically significant.

Results

The baseline patient characteristics are listed in Table 1. None of the variables was significantly different between the 2 protocols. The CM injection parameters are shown in Table 2. Iohexol (350 mg iodine/ml) and iopamidol (370 mg iodine/ml) were used in 26 patients and in 24 patients in the diluted CM protocol, and the mean CM volume was 38.6±7.6 ml and 43.9±6.9 ml, respectively. The mean CM volume of iopamidol was 37.6±7.6 ml in the BW-adjusted protocol. The mean iodine dose per BW in the diluted CM protocol was higher than that in the BW-adjusted protocol (233.3±58.4 mg iodine/kg vs. 222.2±1.6 mg iodine/kg), but the difference was not statistically significant (P=0.967). The mean CM dilution rate of iohexol and iopamidol was 77.1±15.2%, and 87.7±13.8, respectively. Three patients were considered to require the optimized CM dilution rate of >100%, based on the formula of the timing bolus scan (110% in 1 patient and 120% in 2 patients), and the injection duration was adjusted for each patient (11 s for 1 patient and 12 s for 2 patients).

Aortic and Coronary Attenuation

Ten coronary segments (pLAD, n=3; pLCX, n=5; mRCA, n=1; dRCA, n=1) in the diluted CM protocol and 20 segments (pLAD, n=4; pLCX, n=4; pRCA, n=2; mRCA, n=5; dRCA, n=5) in the BW-adjusted protocol were excluded from analysis because of severe calcification, diffuse plaque, and narrow segments. Only LM could be evaluated in both contrast-injection protocol groups (n=100); for the other segments intraluminal CT attenuation was unable to be measured because of motion artifact, massive calcification, smaller diameter, and anatomical variance. The total number of analyzed segments was 290 and 280 in the diluted CM protocol and BW-adjusted protocol, respectively. The aortic and mean coronary attenuation of all the coronary segments were 356.4±23.5 HU and 346.1±23.9 HU in the diluted CM protocol, and 308.9±46.3 HU and 298.8±45.2 HU in the BW-adjusted protocol, respectively. On segment-based analysis, in the diluted CM and BW-adjusted protocols they were as follows: 345.7±23.0 HU and 302.3±44.8 HU in LM, 343.7±21.0 HU and 294.0±46.6 HU in pLAD, 341.8±21.6 HU and 295.5±45.4 HU in pLCX, 350.7±23.6 HU and 301.6±45.2 HU in pRCA, 344.9±25.3 HU and 298.4±42.7 HU in mRCA, and 349.5±27.9 HU and 300.5±48.2 HU in dRCA, respectively (Figure 2). There was no significant difference among the coronary attenuations in both the 2 protocols. Aortic attenuation and all the coronary attenuations in the diluted CM protocol were significantly higher than those in the BW-adjusted protocol (P<0.05). Furthermore, both variations (SD×SD) in the aortic and all the coronary attenuations in the diluted CM protocol were significantly lower than those in the BW-adjusted protocol (P<0.05, for both). The diluted CM protocol provided more uniform coronary attenuations than the BW-adjusted protocol did.

CT attenuation in the LM segment was used as a representative of coronary arteries, because only the LM segment could be evaluated in all the patients. Analysis of subgroups according to median BW in the diluted CM and BW-adjusted protocols are listed in Table 3. There was no significant difference in coronary attenuation of the LM segment between the higher BW and lower BW subgroups in the diluted CM protocol, whereas coronary attenuation of the higher BW subgroup was significantly higher than that of the lower BW subgroup in the BW-adjusted protocol (P<0.05).

BW and Iodine Dose in the Diluted CM Protocol

The relationship between BW and iodine dose in the diluted CM protocol is shown in Figure 3. There was a moderate positive correlation between BW and iodine dose (r=0.421, P<0.05), even though it was calculated independently of BW. When BW was similar among patients, the CM dilution rate and iodine dose for the real scan were estimated to be different, and the diluted CM protocol could be successfully used to perform homogenous coronary CTA with lower patient-to-patient variation in aortic and coronary attenuation (Figure 4).

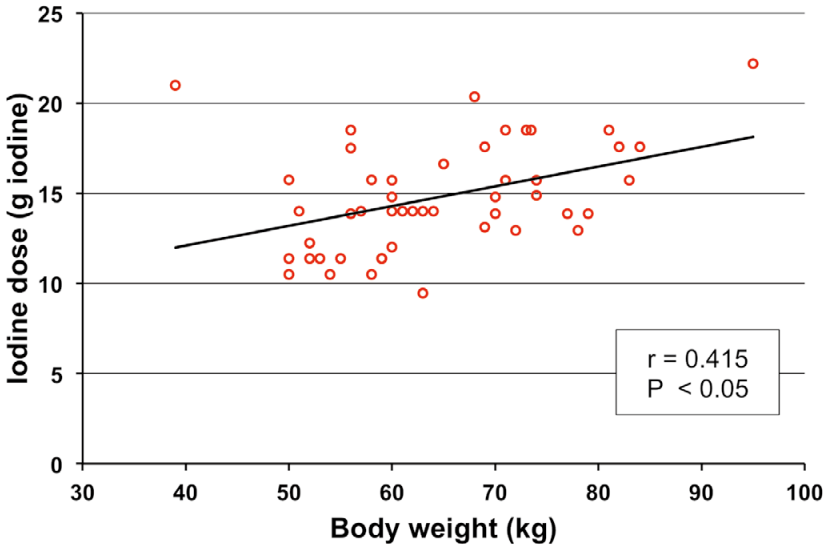

Figure 3. Relationship between body weight (BW) and iodine dose in the diluted contrast material protocol. A significant positive correlation is seen between BW and iodine dose (r=0.415, P<0.05).

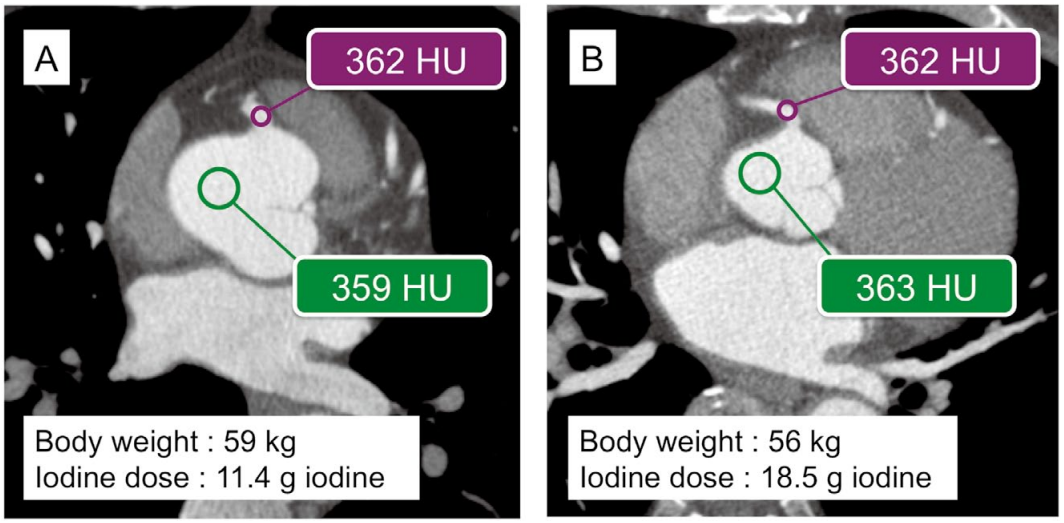

Figure 4. Representative examples of diluted contrast material (CM) protocol. Axial images at the level of the proximal right coronary artery (window level/width: 90/750). (**A**) Sixty-nine-year-old man (body weight, 59 kg; iodine dose, 11.4 g iodine). (**B**) A 68-year-old man (body weight, 56 kg; iodine dose, 18.5 g iodine). Using the customized CM protocol, the iodine dose per body weight differed between the 2 patients, but similar coronary and aortic attenuations, that is, close to the target attenuation, were achieved.

Discussion

In this study, we have shown that a personalized contrast-injection protocol using diluted CM achieved more homogenous coronary attenuation with lower patient-to-patient variation than did the conventional BW-adjusted protocol.

Rapid advances in CT technology have led to a considerable increase in the diagnostic accuracy of coronary CTA for detecting coronary artery stenosis.[21] The reproducibility and robustness of coronary CTA has been investigated in several studies. A few studies have suggested that a higher intracoronary attenuation of ≥326 HU on coronary CTA results in greater diagnostic accuracy for detection of coronary artery stenosis with 16- and 64-slice MDCT.[15,16] Furthermore, it has been reported that coronary attenuation should not be too high in order to allow for the detection of small calcified nodules with a density <500 HU.[18] For the assessment of coronary plaque on coronary CTA, the CT attenuation-based plaque characteristics and the prognostic values have been reported.[8,9,12,13,22,23]

At present, coronary CTA is performed using either the bolus-tracking method or timing bolus scan method. In general, the bolus-tracking method is simple, but it is difficult to reduce the iodine dose in this method, because of mechanical delay.[24] In contrast, the timing bolus scan method is slightly complicated

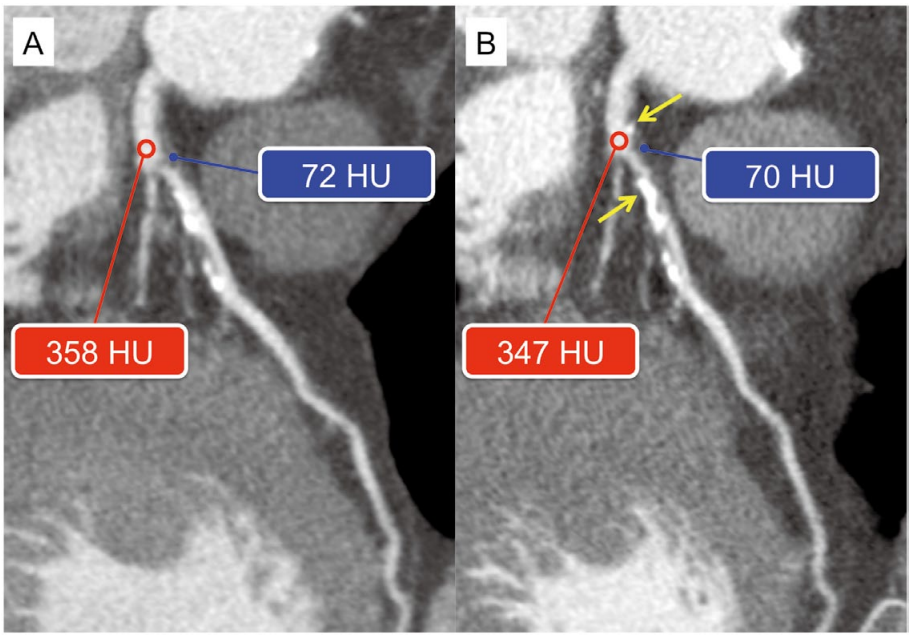

Figure 5. Follow-up using the diluted contrast material (CM) protocol. Curved multiplanar reformatted images at the left main trunk and left anterior descending coronary artery (window level/width: 90/750). A 75-year-old woman with suspected coronary artery disease underwent (**A**) coronary computed tomography angiography (body weight, 63 kg; iodine dose, 11.4 g iodine; dilution rate, 65%) and (**B**) a follow-up scan after 30 months of lipid-lowering therapy (body weight, 75 kg; iodine dose, 14.0 g iodine; dilution rate, 80%) using the same diluted CM protocol. (**A**) and (**B**) had almost equivalent coronary attenuations (red circles and lines). Coronary stenosis and the adjacent plaque attenuation were able to be evaluated (blue points and lines), which had not changed significantly. Some non-calcified plaques became calcified (yellow arrows).

but, in this method, it is easy to determine the time of CM arrival and to subsequently control the scan timing. The conventional timing bolus scan protocol, however, with different volumes for the timing bolus scan and the real scan, may not always result in the best scan timing in all patients. In this study, the timing bolus scan method using diluted CM further improved the scan timing in the real scan even in patients with low cardiac output, given that a similar TAC could be obtained although the peak was lower than that of the real scan.

In CT, contrast enhancement is affected by numerous interacting factors. These may be divided into 3 categories: CT scanning-, patient-, and CM-related factors, which are closely related.[25] Therefore, many scan protocols have been evaluated.[19,20,24,26–30] First, among CT scanning-related factors, tube voltage affects contrast enhancement in coronary CTA. MDCT coverage and ECG-gated scan mode determine the scan time of coronary CTA and influence the homogeneity of coronary attenuation. Second, the most important patient-related factor to be considered is BW. Some studies have indicated that the BW-adjusted injection protocols yield adequate enhancement of the coronary arteries.[19,20] Other studies have shown that coronary attenuation is affected by not only BW but also various other factors such as cardiac output, stroke volume, body surface area, and body mass index.[25,31,32] Finally, the CM-related factor that affects contrast enhancement is the iodine delivery rate, including injection rate, injection duration, and iodine dose.[27] Several studies support each of the CM-related variables, and it is difficult to determine the most important variable.[26,28,29,33]

The present protocol is based on simple assumptions that when the volume, injection rate, and injection duration of the CM are fixed, the time to peak enhancement is unaffected by the iodine dose and that a higher concentration of CM delivers a larger dose of iodine CM and results in a higher magnitude of peak contrast enhancement, as described by Bae.[25] We also confirmed this using a circulating pulsating cardiac phantom (**Figure 1**). In our clinical experience, the scan time of coronary CTA on 256-slice MDCT was approximately 8s; therefore, the injection duration was set at 10 s with a safety margin sufficient for the single-bolus geometry of the CM to reach the anatomical distal portion of the coronary arteries. The coronary target attenuation in this study was defined as 350 HU, in accordance with several previous reports.[14–16,18,33] Thus, we developed and applied a personalized protocol with diluted CM for retrospective ECG-gated coronary CTA using 256-slice MDCT.

In the present study, the diluted CM protocol allowed for homogenous coronary CTA close to the targeted attenuation (350 HU) with higher reproducibility, using a formula without any patient-related factors such as BW and cardiac function. Furthermore, the diluted CM protocol resulted in a smaller variation (SD) of aortic and coronary attenuations than did the BW-adjusted protocol, even though mean coronary attenuation was significantly different. Moreover, using median BW, there was no significant difference in coronary attenuation between the lower BW and higher BW subgroups in the diluted CM protocol; in contrast, coronary attenuation of the higher BW subgroup was significantly higher than that of the lower BW subgroup in the BW-adjusted protocol. This indicates that the reproducibility of coronary CTA using the BW-adjusted protocol may change with BW. Several studies have reported similar results[27,29] but,

in the present study, we speculate that the difference in the injection rate between the lower BW and higher BW subgroups is responsible for the results.

Recently, Kidoh et al reported a similar contrast-injection protocol using a formula based on the timing bolus scan.[34] They applied 64-slice MDCT, with the timing bolus scan using BW-based CM (0.3 ml/kg, 9-s injection) and a calculation formula with the target attenuation of 400 HU. They also achieved a good attenuation of coronary CTA similar to that obtained in the present study, but the variation (SD) of coronary attenuation in the present protocol was less than that in Kidoh et al protocol. The difference between the present results and that previous study may be attributed to several factors such as CT coverage (256-slice MDCT), fixed higher injection rate (5 ml/s), position of ROI on the timing bolus scan, sampling phase in the formula, and scan delay for the real scan, even when the target attenuation was different.

The diluted CM protocol involves 2 complexities. First, it is necessary to acquire data carefully during the timing bolus scan and to control HR during the scan. An error in TAC due to change in HR between the timing bolus scan and real scan may lead to unsatisfactory results of coronary CTA. The other is calculation of the optimal CM concentration for the real scan from the TAC of the timing bolus scan. The diluted CM protocol, however, has several important advantages over the previously reported contrast-injection protocols. First, it is characterized by high reproducibility, which enables a more reliable assessment of coronary artery stenosis and CT attenuation-based plaque analysis. The use of this protocol is promising for cross-sectional and follow-up studies in lipid-lowering therapy (**Figure 5**). Second, it is not necessary to collect patient information. Finally, this protocol has the flexibility to be used with other MDCT scanners and scan modes. For instance, it is possible to adjust the injection duration of the CM covering the scan time and to control the target attenuation, when the CT-scanning variables are altered, such as the type of MDCT, tube voltage, and ECG-gated scan mode. Thus, the diluted CM protocol promises better clinical use of coronary CTA.

Study Limitations

This study has several limitations. First, the sample size was relatively small. Second, the injection rate was fixed at 5 ml/s, but some patients may require a higher injection rate >5 ml/s for sufficient coronary attenuation. Third, the study assessed attenuation of the partial coronary segment only. Analysis of all the segments requires further evaluation, even though it is necessary to take into account variations in coronary anatomy and diameter in the distal segment. Finally, clinical application of this protocol to validate the diagnostic accuracy of coronary artery stenosis and atherosclerotic plaque is required for further evaluation.

Conclusions

The diluted CM protocol facilitates more uniform attenuation in coronary CTA in comparison with the BW-adjusted protocol. With an additional calculation of the optimal CM rate for the real scan from the TAC of the timing bolus scan, this protocol allows for a more reliable assessment of coronary artery stenosis and atherosclerotic plaque by facilitating coronary CTA with a higher reproducibility.

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References

1. Achenbach S, Ulzheimer S, Baum U, Kachelriess M, Ropers D, Giesler T, et al. Noninvasive coronary angiography by retrospectively ECG-gated multislice spiral CT. *Circulation* 2000; **102:** 2823–2828.
2. Nieman K, Oudkerk M, Rensing BJ, van Ooijen P, Munne A, van Geuns RJ, et al. Coronary angiography with multi-slice computed tomography. *Lancet* 2001; **357:** 599–603.
3. Funabashi N, Matsumoto A, Yoshida T, Watanabe S, Misumi K, Masuda Y. Usefulness of three-dimensional visualization of coronary arteries using electron-beam computed tomography data with volume rendering. *Circ J* 2000; **64:** 644–646.
4. Sato Y, Matsumoto N, Kato M, Inoue F, Horie T, Kusama J, et al. Noninvasive assessment of coronary artery disease by multislice spiral computed tomography using a new retrospectively ECG-gated image reconstruction technique: Comparison with angiographic results. *Circ J* 2003; **67:** 401–405.
5. Jinzaki M, Sato K, Tamami Y, Yamada M, Anzai T, Kawamura A, et al. Diagnostic accuracy of angiographic view image for the detection of coronary artery stenoses by 64-detector row CT: A pilot study comparison with conventional post-processing methods and axial images alone. *Circ J* 2009; **73:** 691–698.
6. Mollet NR, Cademartiri F, van Mieghem CA, Runza G, McFadden EP, Baks T, et al. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. *Circulation* 2005; **112:** 2318–2323.
7. Mollet NR, Cademartiri F, Nieman K, Saia F, Lemos PA, McFadden EP, et al. Multislice spiral computed tomography coronary angiography in patients with stable angina pectoris. *J Am Coll Cardiol* 2004; **43:** 2265–2270.
8. Schroeder S, Kopp AF, Baumbach A, Meisner C, Kuettner A, Georg C, et al. Noninvasive detection and evaluation of atherosclerotic coronary plaques with multislice computed tomography. *J Am Coll Cardiol* 2001; **37:** 1430–1435.
9. Leber AW, Becker A, Knez A, von Ziegler F, Sirol M, Nikolaou K, et al. Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: A comparative study using intravascular ultrasound. *J Am Coll Cardiol* 2006; **47:** 672–677.
10. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008; **359:** 2324–2336.
11. 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; **53:** 1724–1732.
12. Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol* 2007; **50:** 319–326.
13. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol* 2009; **54:** 49–57.
14. Becker CR, Hong C, Knez A, Leber A, Bruening R, Schoepf UJ, et al. Optimal contrast application for cardiac 4-detector row computed tomography. *Invest Radiol* 2003; **38:** 690–694.
15. Cademartiri F, Mollet NR, Lemos PA, Saia F, Midiri M, de Feyter PJ, et al. Higher intracoronary attenuation improves diagnostic accuracy in MDCT coronary angiography. *AJR Am J Roentgenol* 2006; **187:** 430–433.
16. Cademartiri F, Maffei E, Palumbo AA, Malagò R, La Grutta L, Meijboom WB, et al. Influence of intra-coronary enhancement on diagnostic accuracy with 64-slice CT coronary angiography. *Eur Radiol* 2008; **18:** 576–583.
17. Cademartiri F, Mollet NR, Runza G, Bruining N, Hamers R, Somers P, et al. Influence of intracoronary attenuation on coronary plaque measurements using multislice computed tomography: Observations in an ex vivo model of coronary computed tomography angiography. *Eur Radiol* 2005; **15:** 1426–1431.
18. Fei X, Du X, Yang Q, Shen Y, Li P, Liao J, et al. 64-MDCT coronary angiography: Phantom study of effects of vascular attenuation on detection of coronary stenosis. *AJR Am J Roentgenol* 2008; **191:** 43–49.
19. Nakaura T, Awai K, Yanaga Y, Nakayama Y, Oda S, Hatemura M, et al. Contrast injection protocols for coronary computed tomography angiography using a 64-detector scanner: Comparison between patient weight-adjusted and fixed iodine dose protocols. *Invest Ra-*

diol 2008; **43:** 512–519.
20. Isogai T, Jinzaki M, Tanami Y, Kusuzaki H, Yamada M, Kuribayashi S, et al. Body weighted-tailored contrast material injection protocol for 64-detector row computed tomography coronary angiography. *Jpn J Radiol* 2011; **29:** 33–38.
21. Schroeder S, Achenbach S, Bengel F, Burgstahler C, Cademartiri F, de Feyter P, et al. Cardiac computed tomography: Indications, applications, limitations, and training requirements: Report of a Writing Group deployed by the Working Group Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. *Eur Heart J* 2008; **29:** 531–556.
22. Fujimoto S, Kondo T, Kodama T, Orihara T, Sugiyama J, Kondo M, et al. Coronary computed tomography angiography-based coronary risk stratification in subjects presenting with no or atypical symptoms. *Circ J* 2012; **76:** 2419–2425.
23. Motoyama S, Sarai M, Inoue K, Kawai H, Ito H, Harigaya H, et al. Morphologic and functional assessment of coronary artery disease: Potential application of computed tomography angiography and myocardial perfusion imaging. *Circ J* 2013; **77:** 411–417.
24. Nakaura T, Awai K, Yanaga Y, Namimoto T, Utsunomiya D, Hirai T, et al. Low-dose contrast protocol using the test bolus technique for 64-detector computed tomography coronary angiography. *Jpn J Radiol* 2011; **29:** 457–465.
25. Bae KT. Intravenous contrast medium administration and scan timing at CT: Considerations and approaches. *Radiology* 2010; **256:** 32–61.
26. Funabashi N, Suzuki K, Terao M, Maeda F, Nakamura K, Mita Y, et al. New acquisition method to exclusively enhance the left side of the heart by a small amount of contrast material achieved by multislice computed tomography with 64 data acquisition system. *Int J Cardiol* 2007; **114:** 265–269.
27. Yanaga Y, Awai K, Nakaura T, Oda S, Funama Y, Bae KT, et al. Effect of contrast injection protocols with dose adjusted to the estimated lean patient body weight on aortic enhancement at CT angiography. *AJR Am J Roentgenol* 2009; **192:** 1071–1078.
28. Awai K, Hiraishi K, Hori S. Effect of contrast material injection duration and rate on aortic peak time and peak enhancement at dynamic CT involving injection protocol with dose tailored to patient weight. *Radiology* 2004; **230:** 142–150.
29. Kidoh M, Nakaura T, Nakamura S, Awai K, Utsunomiya D, Sakaino N, et al. Compact-bolus dynamic CT protocol with a test bolus technique in 64-MDCT coronary angiography: Comparison of fixed injection rate and duration protocol. *Int J Cardiovasc Imaging* 2012; **28:** 153–162.
30. Cademartiri F, de Monye C, Pugliese F, Mollet NR, Runza G, van der Lugt A, et al. High iodine concentration contrast material for noninvasive multislice computed tomography coronary angiography: Iopromide 370 versus iomeprol 400. *Invest Radiol* 2006; **41:** 349–353.
31. Bae KT, Seeck BA, Hildebolt CF, Tao C, Zhu F, Kanematsu M, et al. Contrast enhancement in cardiovascular MDCT: Effect of body weight, height, body surface area, body mass index, and obesity. *AJR Am J Roentgenol* 2008; **190:** 777–784.
32. Husmann L, Alkadhi H, Boehm T, Leschka S, Schepis T, Koepfli P, et al. Influence of cardiac hemodynamic parameters on coronary artery opacification with 64-slice computed tomography. *Eur Radiol* 2006; **16:** 1111–1116.
33. Yamamuro M, Tadamura E, Kanao S, Wu YW, Tambara K, Komeda M, et al. Coronary angiography by 64-detector row computed tomography using low dose of contrast material with saline chaser: Influence of total injection volume on vessel attenuation. *J Comput Assist Tomogr* 2007; **31:** 272–280.
34. Kidoh M, Nakaura T, Nakamura S, Awai K, Utsunomiya D, Yamashita Y, et al. Novel contrast-injection protocol for coronary computed tomographic angiography: Contrast-injection protocol customized according to the patient's time-attenuation response. *Heart Vessels* 2013 March 20, doi:20 10.1007/s00380-013-0338-x [Epub ahead of print].