

Coronary angiography using second-generation dual source computed tomography

Feasibility of low dose and low flow rate to achieve appropriate individual contrast enhancement using a test bolus-based contrast medium protocol—A CONSORT compliant article

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Abstract

Improved contrast enhancement consistency can be achieved using an individualized contrast media (CM) protocol. This study aimed to assess the feasibility of a low-dose, low-flow rate CM protocol to achieve appropriate individual contrast enhancement using a newly advocated individualized test bolus-based protocol for second-generation dual-source computed tomography angiography.

CM containing iodine (370 mg I/mL) was used in this study. A CM flow rate of 3.5 mL/s for patients with a body mass index (BMI) <25.0 kg/m², and 4.5 mL/s for those with BMI ≥25.0 kg/m² was used in group 1 (n=189). An individualized test-bolus based contrast injection protocol was then derived from the information gained from the test bolus and coronary enhancements in group 1. The proposed individualized test-bolus based CM injection protocol was applied in group 2 (n=219). Ascending aortic attenuations (AAo) were measured and compared with both groups.

The contrast enhancement consistency of AAo in group 2 improved significantly (31.8 vs 56.3 Hounsfield units [HU]; *P* < .001). The number of patients in group 2 with a contrast flow rate ≤3 mL/s was 63 (28.8%), with 77 (35.2%) using a contrast dose ≤40 mL. In group 2, no significant differences in mean AAo were found among subgroups with contrast flow rates ≤3.0, 3.1 to 4.0, 4.1 to 5.0 and >5.0 mL/s (351, 344, 346, and 348 HU, respectively), nor among subgroups with contrast doses ≤40, 41 to 50, 51 to 60, and >60 mL (349, 345, 344, and 350 HU, respectively).

Improved individual contrast enhancement uniformity can be achieved using an individualized CM protocol tailored to a test bolus. Approximately, one-third of patients received CM at a flow rate of no more than 3 mL/s and a total dose of no more than 40 mL.

Abbreviations: AAo = ascending aorta, BMI = body mass index, CM = contrast media, CT = computed tomography, CTA = computed tomography angiography, HU = Hounsfield units, LM = left main, PE_{DAo} = peak enhancement of descending aorta, PT_{AAo} = time to peak enhancement of ascending aorta, RCA = right coronary artery, ROIs = regions of interest, TB = test bolus.

Keywords: computed tomography, contrast media, coronary angiography, computed tomography angiography and timing bolus

1. Introduction

Coronary computed tomographic angiography (CTA) is a reliable, noninvasive imaging modality for evaluating coronary

heart diseases in appropriate clinical settings. The diagnostic performance of coronary CTA has improved with rapid advances in scanners and optimization of post-processing techniques.^[1–4] Among various factors, vessel enhancement during coronary CTA is one of the most important parameters for diagnostic purposes, and its effects on the accuracy of coronary stenosis detection have been extensively studied.^[5,6] An intracoronary CT value that is too low (<200 Hounsfield units [HU]) leads to a significant overestimation of stenosis, while higher intracoronary attenuation (>500 HU) leads to a significant underestimation of stenosis in smaller vessels.^[7] The optimal vascular attenuation for detection of coronary artery stenosis during coronary CTA is approximately 350 HU.^[7]

Optimization of contrast media (CM) injection protocols is mandatory to achieve state-of-the-art CTA at an appropriate kilovolt power, and can also reduce CM doses in certain patients.^[8–10] Determining the influence of different injection parameters and defining individualized optimal contrast injection protocols tailored to patient-related factors are recommended.^[11] The primary patient-related factors that affect the degree of arterial enhancement on coronary CTA include body weight, body mass index (BMI), heart rate, and cardiac output.^[12–14] One possible solution to the problem of variable enhancement response is CM adjustment using a timing bolus (TB) injection technique because the attenuation curve produced by the TB

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contains all the necessary information associated with patient-related factors.^[15,16] Additionally, some studies have reported notable correlations between various TB parameters and final enhancement in coronary CTA.^[16–18] A previous study by van Hoe et al.^[18] demonstrated that peak contrast enhancement of the TB served as a reliable predictor of the coronary enhancement in coronary CTA. Improved contrast enhancement consistency can be achieved using an individualized TB-based CM protocol.^[19]

For coronary CTA, contrast flow rates are generally no less than 5 mL/s, and an injection rate of 5 to 7 mL/s is recommended in most adults.^[20,21] Only a few studies, however, have applied contrast flow rates <4 mL/s in some patients.^[19] The present study aimed to assess the feasibility of a low-dose (no more than 40 mL), low-flow rate (no more than 3 mL/s), CM (370 mg I/mL) protocol to achieve appropriate individual contrast enhancement with a newly advocated, individualized test bolus-based CM protocol for second-generation dual-source computed tomography (DSCT).

2. Methods

The Institutional Ethics Committee of The Affiliated Jiangning Hospital of Nanjing Medical University (Nanjing, China) approved this study, and informed consent for treatment was obtained from all patients.

2.1. Patient selection for coronary CTA

From May 2015 to June 2016, a total of 417 patients were clinically scheduled for coronary CTA examinations in accordance with current guidelines and recommendations. Patients with impaired renal function ($n=3$), known hypersensitivity to iodinated CM ($n=1$), or a history of coronary artery bypass graft ($n=5$) were excluded. Thus, a total of 408 patients (218 men, 194 women; mean [\pm standard deviation]) age, 57.2 ± 11.0 years, with a mean BMI of 25.0 ± 3.2 kg/m² were enrolled in this study.

2.2. Scanning protocol

All examinations were performed using a second-generation DSCT instrument (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). Tube voltage selection criteria for data acquisition was 100 kV for patients with BMI <25 kg/m² and 120 kV for those with a BMI ≥ 25 kg/m.^[22] The tube current was auto-modulated by the scanner using a tube current modulation technique (care dose 4D). Coronary CTA was performed under retrospective electrocardiographic gating with electrocardiogram-based maximum tube current modulation using the following parameters: slice collimation, $2 \times 128 \times 0.6$ mm; gantry rotation time 280 ms/360°; and pitch adaptive to heart rates. Images were reconstructed using an iterative technique (Sonogram Affirmed Iterative Reconstruction, SAFIRE) with a strength factor of 2 in a 512×512 matrix, with a slice thickness of 0.75 mm and an increment of 0.6 mm using a medium smooth tissue convolution kernel (B26f).

2.3. CM protocols

Iodine-containing CM (Ultravist, 370 mg I/mL; Bayer Health Care, Berlin, Germany), followed by a 20 mL saline solution chaser was administered through the cubital vein using a 20-gauge needle and a dual-head power injector (Dual Shot, MedRad Inc. Indianola, PA). TB scanning at the level of the main

pulmonary artery was conducted to determine the contrast transit time. During the TB, 10 mL of CM at 3.5 mL/s for patients with a BMI <25.0 kg/m², and 13 mL at 4.5 mL/s for patients with a BMI ≥ 25.0 kg/m² were administered. In group 1, the contrast flow rates were identical to those of TB scanning during coronary CTA. In group 2, the contrast flow rates were individualized to peak enhancements of the descending aorta (PE_{DAo}) and times to the peak enhancements in the ascending aorta (PT_{AAo}), which were obtained from the TB (contrast flow rate = $1050 / [-135.995 + 15.413 * PT_{AAo} + 1.506 * PE_{DAo}]$ for patients with a BMI <25.0 kg/m², and contrast flow rate = $1350 / [-154.093 + 15.413 * PT_{AAo} + 1.506 * PE_{DAo}]$ for patients with a BMI ≥ 25.0 kg/m²). In both groups, the duration of CM injection was equivalent to the scanning time plus 8 seconds.

2.4. CT value measurement

Vascular enhancements for each patient were measured on axial imaging by 2 cardiovascular radiologists with 2 and 8 years' experience, respectively, who were fully blinded to the CM injection protocols. The measurements of all TB images were performed by manually drawing circular regions of interest (ROIs) positioned on the AAO and DAo. The measurements of AAO, left main (LM), and proximal segment of the right coronary artery (RCA) were also performed on coronary CTA images. All ROIs used for these measurements were placed within contrast-enhanced lumens and chosen to be as large as possible while carefully avoiding calcifications and plaques.

2.5. Statistical analysis

Data analysis was performed using SPSS version 24.0 (IBM Corporation, Armonk, NY). All continuous variables are expressed as mean \pm standard deviation. Patient characteristics, contrast injection protocols, and enhancements of AAO, LM, and RCA, were compared using the Student *t* test or analysis of variance (ANOVA), where appropriate; $P \leq .05$ was considered to be statistically significant. The uniformity of the enhancements of AAO and coronary arteries in the 2 phases was compared using Levene test for equality of variances. Inter-reader reproducibility of all quantitative measurements was assessed by calculating the intra-class correlation coefficient (ICC). An ICC >0.90 indicates excellent inter-reader agreement.

3. Results

3.1. Baseline characteristics of the 2 groups

Statistical analysis revealed that all ICCs were >0.90, which reflects excellent inter-reader agreement for all measurements. Comparisons of patient characteristics, including age, sex, height, weight, and BMI, indicated no statistically significant differences between the 2 groups. The mean heart rates in group 2, however, were higher than those in the group 1. Characteristics of both groups in the patient cohort are summarized in Table 1.

3.2. Uniformity of enhancements of the AAO and coronary arteries in the 2 groups

The mean value of CT attenuations in the AAO of group 1 was statically higher than 350 HU, while it reached the target value of 350 HU in group 2. Mean CT values of the AAO, LM, and RCA in group 1 were statistically higher than those in group 2. Compared with group 1, the uniformity of enhancements of the AAO, LM,

Table 1
Characteristics of patient cohort, scanning related parameters, and hemodynamic parameters.

Characteristics	100kV		P	120kV		P
	Group 1 (n=93)	Group 2 (n=119)		Group 1 (n=96)	Group 2 (n=100)	
Female/Male	47/46	59/60	.890	41/55	47/53	.546
Age, y	59.3±10.7	57.8±11.6	.197	56.2±10.2	55.3±10.8	.627
Height, m	1.62±0.07	1.63±0.08	.679	1.63±0.07	1.62±0.08	.529
Weight, kg	59.6±6.8	59.5±8.2	.920	73.1±8.8	73.7±9.2	.656
BMI, kg/m ²	22.6±1.7	22.4±1.9	.427	27.6±2.4	27.6±2.0	.855
HR	68.6±14.0	73.4±13.2	.029	65.6±12.0	71.4±11.5	.001

BMI=body mass index, HR=heart rate.

and RCA improved significantly with marked reduced inter-individual variations in group 2 (AAo: 31.8 vs 56.2 HU, $F=59.8$, $P<.001$; LM: 37.4 vs 70.7, $F=30.9$, $P<.001$; and RCA: 36.5 vs 59.9, $F=36.8$, $P<.001$). Clustered boxplots depicting mean attenuations of AAo, LM, and RCA in the 2 groups are shown in Fig. 1. In group 2, reduced variations in individual enhancements of AAo, LM, and RCA were also found in the separate BMI subgroups (i.e., $<25\text{ kg/m}^2$ and $\geq 25\text{ kg/m}^2$), which are summarized in Table 2.

3.3. CM protocols in the 2 groups

Compared with group 1, a reduced mean CM flow rate and dose was demonstrated in group 2. In group 2, the range of CM dose was 27 to 74 mL, and the range of CM flow rates was from 2.3 to 5.5 mL/s (Table 3). In group 2, the number of patients with CM flow rates ≤ 3 , 3 to 4, 4 to 5, and >5 mL/s were 63 (28.8%), 79 (36.1%), 64 (29.2%), and 13 (2.8%). Additionally, the number of patients with contrast doses ≤ 40 , 40 to 50, 50 to 60, and >60 mL were 77 (35.2%), 54 (24.7%), 64 (25.7%), and 21 (4.6%). In group 2, no significant differences in mean CT values of AAo, LM, or RCA were demonstrated among the subgroups with contrast flow rates ≤ 3.0 , 3.1 to 4.0, 4.1 to 5.0, and >5.0 mL/s, nor among the subgroups with contrast doses ≤ 40 , 41 to 50, 51 to 60, and >60 mL (Fig. 2). Representative images, acquired in 2 patients from group 2 with different CM flow rates (2.7 and 5.5 mL/s), demonstrated appropriate aortic enhancement, and are shown in Figs. 3 and 4.

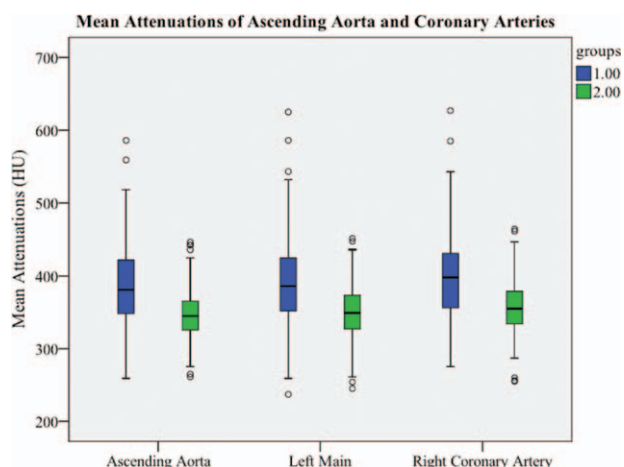


Figure 1. Clustered boxplots of mean attenuations of ascending aorta, left main and right coronary artery for both groups are presented in 2 groups.

3.4. Characteristics of patients in group 2 with flow rate $\leq 3\text{ mL}$ and dose $\leq 40\text{ mL}$

The mean body weight of patients with a flow rate $\leq 3\text{ mL}$ was 58.0 kg and the mean BMI was 22.1 kg/m^2 , which were statistically lower than the respective mean values in patients with flow rate $>3\text{ mL/s}$. Similarly, the mean body weight in patients with dose $\leq 40\text{ mL}$ was 57.8 kg and the mean BMI was 22.3 kg/m^2 , which were also statistically lower than the respective mean values in patients with a dose $>40\text{ mL}$. In contrast, there were no differences in mean heart rate or height between patients with a flow rate $\leq 3\text{ mL/s}$ and $>3\text{ mL/s}$, nor between patients with dose $\leq 40\text{ mL}$ and $>40\text{ mL}$.

4. Discussion

In this prospective cohort study investigating 408 patients, we successfully demonstrated that TB-based, individualized CM flow rate adaptation yielded improved uniformity of contrast enhancement for the AAo, LM, and RCA during dual-source coronary CTA. Approximately, one-third of all patients received CM at a flow rate of no more than 3 mL/s and a contrast dose no more than 40 mL, without affecting vessel enhancement.

Table 2
Aortic and coronary arterial attenuations of 100 and 120kV in the model building and validation phases.

Characteristics	Mean			Interindividual variation			
	Group 1	Group 2	P	Group 1	Group 2	P	
BMI ≤ 25	AAo	408.3	348.9	$<.001$	54.8	31.6	$<.001$
	LM	408.3	352.6	$<.001$	71.5	39.2	.001
	RCA	414.7	359.7	$<.001$	61.2	37.2	$<.001$
BMI ≥ 25	AAo	368.5	348.2	.001	50.6	32.4	$<.001$
	LM	365.2	354.3	.135	63.5	34.7	.007
	RCA	381.3	358.2	.001	54.1	35.7	$<.001$
All	AAo	388.1	348.6	$<.001$	56.2	31.8	$<.001$
	LM	386.4	353.3	$<.001$	70.7	37.4	$<.001$
	RCA	397.7	359.1	$<.001$	59.9	36.5	$<.001$

AAo=ascending aorta, LM=left main, RCA=right coronary artery.

Table 3
Contrast injection protocols in the groups.

Characteristics	Group 1 (n=189)	Group 2 (n=155)	P
Contrast dose, mL	53.6±7.3 (41–70)	46.0±10.1 (27–74)	$<.001$
Flow rate, mL/s	4.0±0.5 (3.5–4.5)	3.6±0.8 (2.3–5.5)	$<.001$
Duration, s	13.4±0.9 (11.3–16.0)	12.8±0.8 (10.8–15.4)	$<.001$

Values are ranges within parentheses.

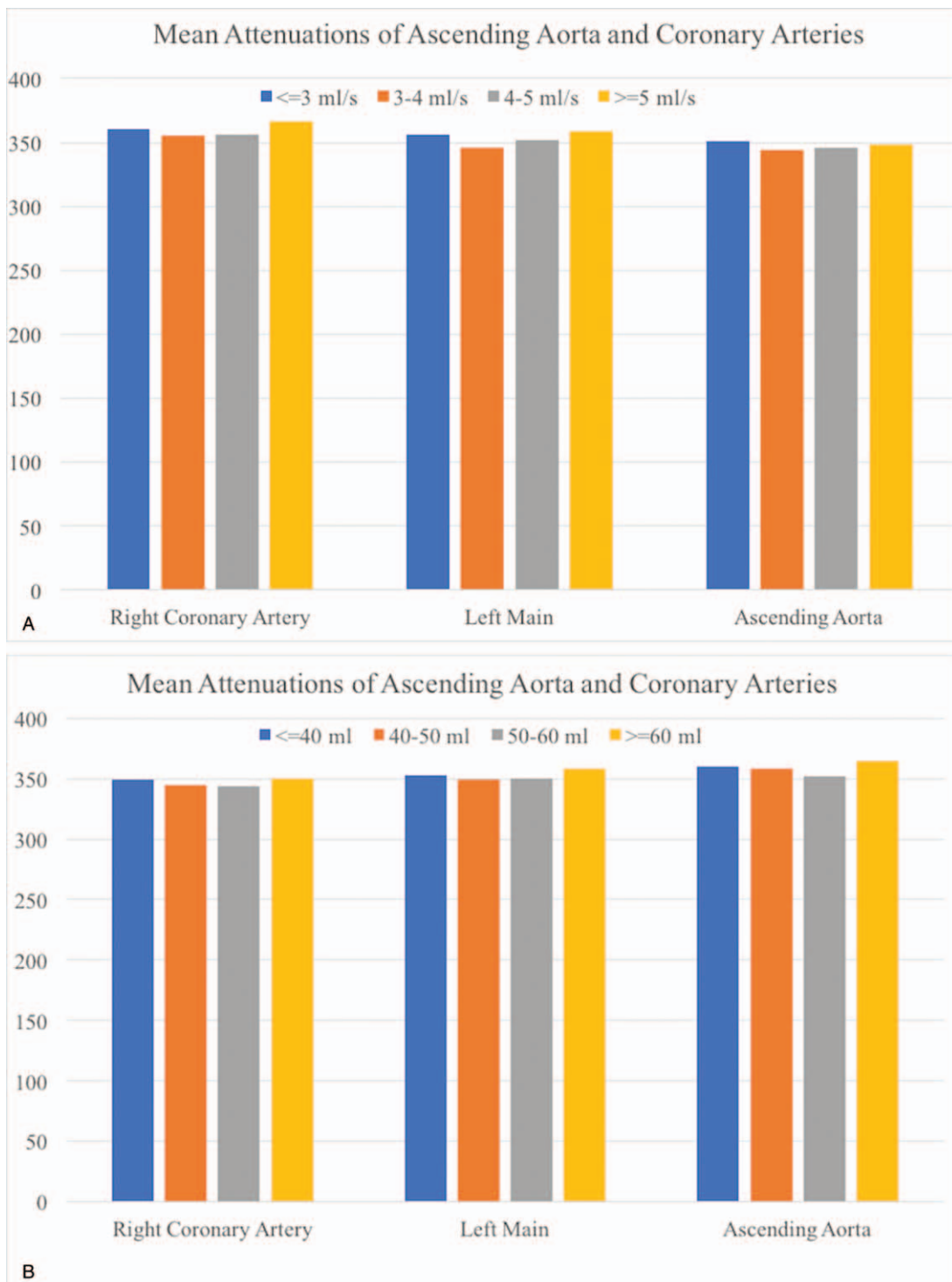


Figure 2. In the group 2, mean contrast enhancements of the ascending aorta (AAo), left main (LM) and right coronary artery (RCA) demonstrate no significant differences among subgroups of patients with contrast flow rates ≤ 3 , 3 to 4, 4 to 5 and >5 mL/s (A), nor among subgroups of patients with contrast doses ≤ 40 , 40 to 50, 50 to 60, and >60 mL (B).

With the development of technical aspects of CT, clinical practice and research are increasingly shifting toward defining the clinical implications of plaque morphology, myocardial perfusion, and patient outcomes.^[4,23] CT is regarded to be useful in evaluating coronary plaque quality and quantity to find high-risk, vulnerable plaques.^[24] The presence of positive vessel remodeling, low-attenuation plaques, napkin-ring sign, or spotty

calcification on coronary CTA could be useful information to identify high-risk, vulnerable plaques. However, the accuracy of density measurements of non-calcified plaques within coronary arteries has been found to be highly dependent on intracoronary contrast, which demonstrates a highly positive correlation with the intracoronary CT value.^[25,26] When CT is applied to separate non-calcified plaques into rupture-prone lipid-rich and stable

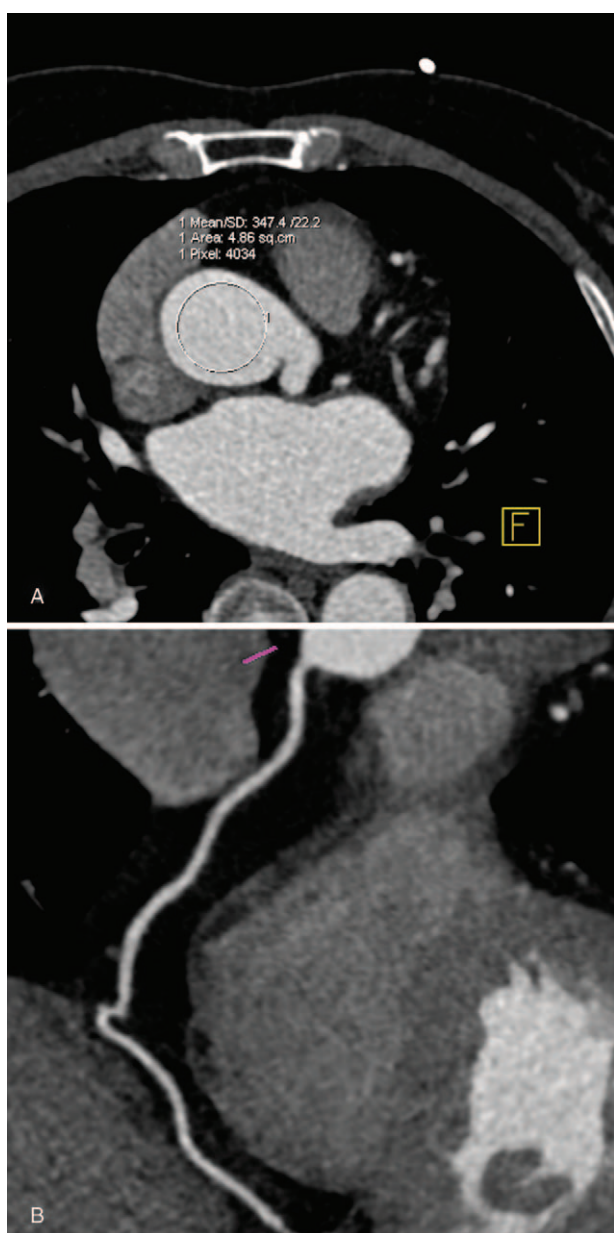


Figure 3. Representative images (window center: 200 HU and width: 600 HU) of a patient in the group 2. An axial image of the aortic root (A) with a CT value of 347 HU and a curved planar reconstructed image of right coronary artery (B) of a 74-year-old female patient (height 1.46 m and body weight 45 kg) with a contrast dose of 27 mL at a flow rate of 2.3 mL/s are presented.

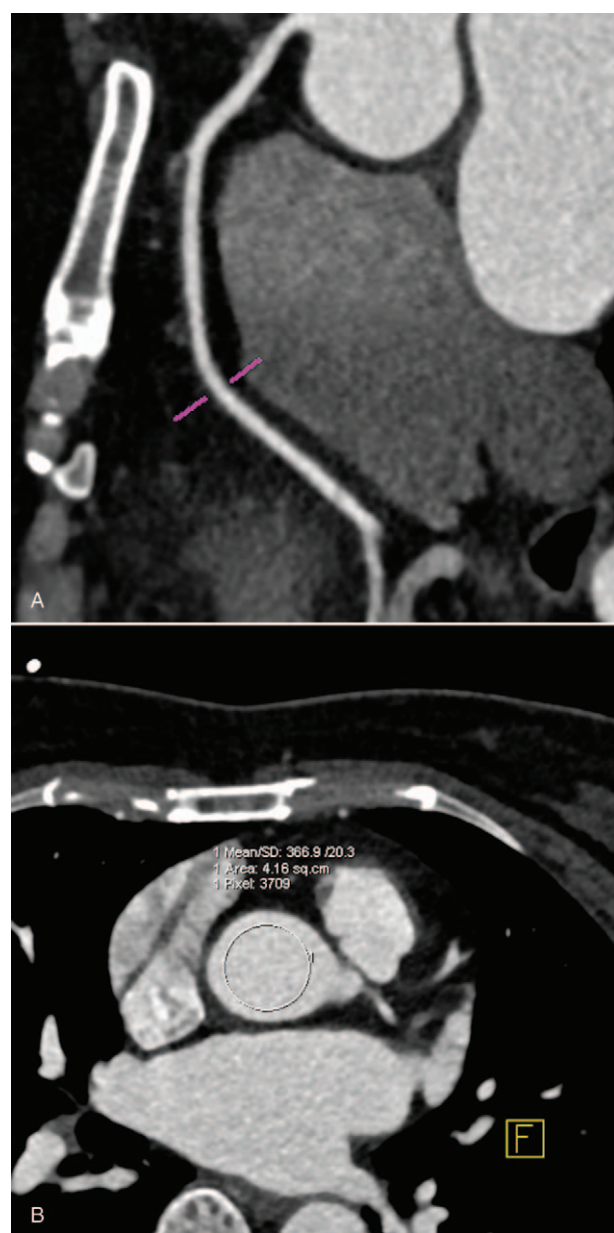


Figure 4. Representative images (window center: 200 HU and width: 600 HU) of a patient in the group 2. An axial image of the aortic root (A) with a CT value of 366 HU and a curved planar reconstructed image of right coronary artery (B) of another 75-year-old female patient (height 1.53 m and body weight 60 kg) with a contrast dose of 74 mL at a flow rate of 5.5 mL/s are demonstrated.

fibrous subtypes, higher intracoronary CT values may cause part of the plaques to change in subtype from lipid-rich to fibrotic.^[27] Characterization and classification of non-calcified plaques using absolute CT values, therefore, requires standardization of CM protocols. The optimal vascular attenuation for stenosis detection and plaque area measurement in coronary angiography is approximately 350 HU.^[7] In our study, the CM protocol tailored to TB resulted in mean aortic CT values of 348 HU, with remarkably reduced inter-individual variations, which is theoretically beneficial for the characterization and classification of non-calcified plaques.

The circulation of CM in the human body has been well studied and can be divided into 2 parts: “first pass” and “recirculation.”^[28,29] “First pass” indicates that the CM reaches the

arterial system for the first time, which is mainly affected by CM- and patient-related factors.^[28] CT values in the coronary arteries are influenced by patient body weight, BMI, heart rate, and cardiac output.^[12,14] To achieve optimal coronary artery enhancement, Zhu et al^[30] advocated that the CM dose should be tailored to body weight and BMI, with flow rate tailored to heart rate during dual-source coronary CTA, which results in a mean aortic CT value of 384.9 HU and an inter-individual variation of 42.2 HU. Meanwhile, a new test bolus-based contrast-enhancement prediction algorithm, which considers a human patient to be a linear time-invariant system, has no systematic errors in the amplitude of the predicted enhancement.^[31] In addition, Yang et al^[9] demonstrated that contrast optimization based on the peak value during TB is feasible in

high-pitch dual-source coronary CTA, with improved uniformity of coronary arterial enhancement (left coronary sinus: 335.8 ± 42.4 HU). Compared with CM dose tailored to body weight, a contrast-injection protocol customized according to patient time-attenuation response reduced the individual variations in peak aortic CT value, and achieved optimal coronary CT attenuation (250–350 HU) more frequently.^[10] In our study, with CM flow rates tailored to time to peak enhancement of the AAO and peak enhancement of the descending aorta, individual variations in AAO, LM, and RCA were all significantly reduced (31.8, 37.4, and 36.5 HU, respectively).

New CT technology, however, has introduced new challenges in clinical radiology practice, one of which is intravenous CM administration. Because of safety concerns and the pressure performance envelope of power injectors, lower CM injection flow rates with reasonable acceptance are preferred.^[28] During coronary CTA examinations in most institutions, CM injection rates ≥ 4 mL/s are applied.^[10,14,32] In group 1 in our study, with a CM flow rate of 3.5 mL/s for patients with BMI < 25.0 kg/m² and 4.5 mL/s for those with BMI ≥ 25.0 kg/m², 25% of patients with aortic enhancements > 400 HU were revealed, which indicated that lower CM flow rates could be applied in these patients. In group 2, mean CM flow rates of 3.2 mL/s for patients with BMI < 25.0 kg/m² and 4.6 mL/s for those with BMI ≥ 25.0 kg/m² were applied separately, and mean attenuation of aortic root reached 348 HU, with no significant difference from the target value of 350 HU. It is also worthwhile noting that CM with flow rates of no more than 4 mL/s were used in 64.9% of patients in group 2. In our study, after a CM flow rate was tailored to hemodynamic parameters, not only did individual uniformity of coronary arterial enhancement markedly improve, but nearly one-third of all patients with preserved coronary arterial enhancement received CM at flow rates of no more than 3 mL/s and a total CM dose of no more than 40 mL.

There were at least 3 limitations to our study. The first originated from the additional 10 to 13 mL of CM during TB that was needed to obtain hemodynamic parameters. Further research should be conducted to confirm the feasibility of this individualized TB-based CM protocol optimization with reduced CM doses for TB. Second, retrospective electrocardiogram gating was applied, which increased radiation doses. Third, this was a small, single-center study, which limits the generalizability of our results. Thus, further confirmation involving larger patient cohorts from multiple centers will be necessary.

In conclusion, improved individual CT value uniformity can be achieved with an individualized CM protocol tailored to TB during dual-source coronary CTA. To achieve aortic enhancement of 350 HU, more than one-half of patients received CM at a flow rate < 4 mL/s. Approximately, one-third of patients received CM at a flow rate no more than 3 mL/s, and doses no more than 40 mL without affecting coronary arterial enhancements.

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