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Minimizing individual variations in arterial enhancement on coronary CT angiographs using "contrast enhancement optimizer": a prospective randomized single-center study

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Abstract

Objectives To investigate the clinical utility of our newly developed contrast enhancement optimizer (CEO) software for coronary CT angiography (CCTA).

Methods We randomly assigned 295 patients (168 males, 127 females, median age 71 years) undergoing CCTA to one of two contrast media injection protocols. Group A ($n = 150$) was injected with a CEO-selected iodine dose based on patient factors. In group B ($n = 145$), we used our standard protocol (245 mg I/kg). We recorded the CT number in the ascending aorta and determined whether the CT number was equivalent in groups A and B. For the equivalence test, we adopted 75 Hounsfield units (HU) as the equivalence margin. The standard deviation in the CT number and the rate of patients with an acceptable CT number were compared using the *F* test and the chi-square test, respectively.

Results The iodine dose in group A was significantly smaller than that in group B (235.7 vs. 253.6 mg I/kg, $p < 0.001$). The CT number of the ascending aorta was 428.6 ± 55.5 HU in group A and 436.1 ± 68.7 HU in group B; the 95% confidence interval for the difference between the groups was -4.3 HU to 16.9 HU and within the range of the predetermined equivalence margins. In group A, the variance was significantly smaller than that in group B ($p = 0.009$). The number of patients with an acceptable CT number was significantly higher in group A than in group B (84.7% vs. 71.7%, $p = 0.007$).

Conclusions The use of our CEO for CCTA studies yielded optimal aortic contrast enhancement in significantly more patients than the standard protocol based on the body weight.

Key Points

- *With our contrast enhancement optimizer (CEO) software, optimal and stable aortic enhancement can be obtained on coronary CT angiography scans irrespective of patient factors.*
- *Management of contrast media becomes more appropriate by the CEO software.*
- *The CEO software can control contrast enhancement at different tube voltage levels.*

Keywords Diagnostic imaging · Computed tomography angiography · Cardiac imaging techniques · Contrast media · Cardiac output

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Abbreviations

CCTA	Coronary computed tomography angiography
CEO	Contrast enhancement optimizer
CTDIvol	Volume computed tomography dose index
DLP	Dose length product
HU	Hounsfield units
PBPK	Physiology-based pharmacokinetic
ROI	Region of interest
SD	Standard deviation

Introduction

Coronary CT angiography (CCTA) is the primary noninvasive imaging modality for diagnosing coronary artery disease [1, 2]. To fully exploit the diagnostic capabilities of CCTA, the coronary arteries must be optimally enhanced [3, 4]. For example, an intracoronary CT number below 350 Hounsfield units (HU) tends to result in significant overestimation of stenosis, while a CT number above 500 HU can lead to significant underestimation in smaller vessels [5]. However, optimal enhancement on CCTA scans is not easily obtained because patient, contrast media, and scanning factors [6] are involved. While contrast media and CT scanning factors can be controlled, patient factors such as the body habitus and cardiac function cannot. Efforts have been made to devise tailored contrast injection protocols that reduce the effect of individual variations [7–12]. However, to the best of our knowledge, no contrast media injection protocol that minimizes individual variations in the arterial enhancement on CCTA scans has been established.

Our newly developed software (contrast enhancement optimizer (CEO)) can select the optimal contrast enhancement protocol (contrast media dose and injection rate) based on patient, contrast media, and CT scanning factors. We hypothesized that our CEO software can minimize individual variations in arterial enhancement at CCTA. The purpose of this study was to investigate the clinical utility of the CEO for CCTA.

Materials and methods

This prospective randomized single-center study (No. E160926-7, Clinical study of CEO software for CCTA) was approved by our institutional review board; written informed consent was obtained from all patients.

Our contrast enhancement optimizer software

We developed simulation software for contrast enhancement [13] founded on the physiology-based pharmacokinetic (PBPK) model of Bae et al [14–16]. We modified the original PBPK model by adding organs that were not separately modeled in the PBPK model and by adding the diffusion of contrast media in the blood and the transmission of contrast media within an organ or vessel. Details of our simulation software are described elsewhere [13].

Based on that software, we developed our CEO software; it calculates the optimal contrast media injection protocol. The CEO outputs the contrast media volume and injection duration (or injection rate) for the optimal enhancement of the target organs at a specified time. The required input parameters to calculate the optimal contrast media injection protocol include the target organ, the target CT number, its sustained time, the admissible maximal contrast media dose, patient factors (patient body weight, height, and cardiac output), contrast media factors (contrast media brand, saline chaser), and CT scanning factors (tube voltage). We defined the target CT number as the minimal CT number necessary for the diagnosis of the target organ and the sustained time as the duration in which the CT number of the target organ is higher than the target CT number.

The CEO calculates the optimal contrast media protocol iteratively. The flowchart of the CEO algorithm is shown in Fig. 1. We set the initial contrast media dose to be consistent with the contrast media dose delivered in group B (245 mg I/kg body weight). Then, we compared the recorded sustained time with the targeted sustained time; when it did not match, the contrast media injection volume was updated using the following equation:

$$V_{n+1} = V_n + \alpha\left(T_{\text{targeted}} - T_{\text{measured}}\right)$$

where V_n is the contrast media injection volume, n the iteration number for optimization, and α the step-size coefficient for optimization. We applied $\alpha = 1.0$ in this study. T_{targeted} and T_{measured} are the targeted and the measured sustained time. The simulation is iteratively performed with the updated contrast media volume until a satisfactory condition is obtained. In all patients, the calculation results converged on one result.

In the actual process at examination of CCTA, the radiological technologist set the CEO in the following three steps: The first step is to input contrast media factors such as the type of contrast media, target CT number at the target organ, sustained time, and injection duration to the operation console of the CEO. The second step is to input scanning factors such as tube voltage. As all of these settings can be saved as preset values, the operator can set it with one click. The third step is to input patient factors such as body weight, height, and cardiac output. Radiological technologist can achieve these three steps within 1 min. The calculation time was about 10 s for one patient. The CEO software was installed into an independent computer.

Study population

We considered 300 outpatients who underwent CCTA for the evaluation of coronary artery disease between March 2017 and

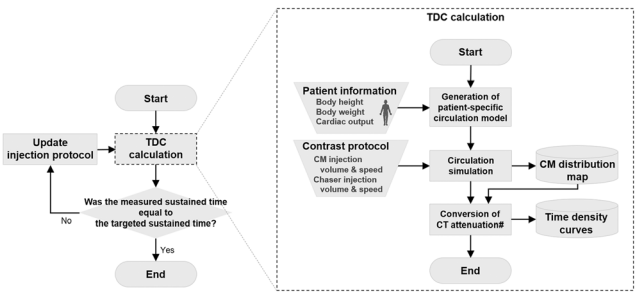

Fig. 1 Flowchart of the contrast media volume optimization algorithm. TDC, time density curve; CM, contrast media

January 2018 for inclusion in our study. Exclusion criteria were as follows: (1) known reduced cardiac function (ejection fraction of the left ventricle < 30%, $n = 1$), (2) severe renal failure without hemodialysis (estimated glomerular filtration rate < 45 ml/min/1.73 m^2, $n = 2$), and (3) history of hypersensitivity to iodinated contrast media ($n = 2$). Thus, our final study population consisted of 295 patients (168 males, 127 females, median age 71 years, range 32–95 years). They were randomly divided into two groups using a random number table. In group A ($n = 150$), we used the contrast media injection protocol selected by the CEO. Group B ($n = 145$) was assigned to our conventional contrast media injection protocol. The patient body weight, height, and cardiac output were recorded just before the CT examination. We measured cardiac output with a noninvasive cardiovascular monitor (Aesculon mini; Heiwa Bussan). The cardiac output obtained with the electrical velocimeter was continuously displayed on the monitor; the average value over 10 valid cardiac cycles was recorded.

Contrast media injection protocols

Iomeprol with an iodine concentration of 350 mg/ml (Iomeron 350; Eisai) was delivered via a 20-gauge catheter inserted into an antecubital vein using a power injector (Dual Shot GX; Nemoto Kyorindo). In both the groups (A and B), the contrast media volume was delivered in 12 s and followed by a 20 ml saline chaser at the same injection rate.

In group A, the contrast media dose was determined by the CEO and based on the body weight, height, and cardiac output. The patient habitus was recorded just prior to the CT study; the cardiac output was measured with a noninvasive cardiovascular monitor (Aesculon mini; Heiwa Bussan) [17, 18]. The ascending aorta was the target for contrast enhancement. The target CT number was 400 HU, and the sustained time was 8 s. The simulated scan tube voltage was 100 kVp.

In group B patients, we used our standard injection protocol for CCTA [5, 19–21]; an iodine dose of 245 mg I/kg was injected in 12 s and followed by a 20 ml saline chaser [22]. The minimum CT number of the ascending aorta was 400 HU [22]. As in group A, the habitus was recorded just prior to the CT study; cardiac output was measured with a noninvasive cardiovascular monitor (Aesculon mini; Heiwa Bussan) [17, 18].

CT scanning

All patients were scanned on a 64-detector row CT scanner (LightSpeed VCT; GE Healthcare); retrospective ECG-triggered helical scans were performed. The scan and reconstruction parameters were tube voltage, 100 kVp; beam width, 40 mm; detector collimation, 64 × 0.625 mm; pitch factor, 0.2 mm/rotation; gantry rotation, 0.35 s; slice thickness, 0.625 mm; scan field of view, 320 mm; display field of view, 180 mm; matrix, 512 × 512; reconstruction kernel, standard; and reconstruction method, filter back projection. Although we did not use a tube current modulation system, we changed the tube current from 240 to 770 mA according to patient body weight. All scans were from the top of the left atrial appendage to the level of the inferior margin of the cardiac apex in the craniocaudal direction. All patients were able to perform breath-holds during the examination. Each patient was given nitroglycerin sublingually (0.3 mg) 5 min before scanning; patients whose heart rate exceeded 65 beats per min thereafter additionally received landiolol hydrochloride (Corebeta; Ono Pharmaceutical Co., Ltd.). The scanning delay was determined using a bolus tracking method [5, 19]. A circular region of interest (ROI) of about 400 mm^2 was placed in the ascending aorta at the left main trunk level. Scanning was started automatically 5 s after contrast enhancement exceeded a predefined threshold of 150 HU. The median of volume CT dose index (CTDIvol) was 40.5 mGy (range, 16.4–77.9) and 39.7 mGy (12.3–77.9) for groups A and B, respectively. The median and range of dose length product (DLP) were 689.2 mGy/cm (268.0–1363.2) and 669.5 mGy/cm (212.9–1480.1) for groups A and B, respectively. There was no significant difference in CTDIvol and DLP between the two groups ($p = 0.58$ and $p = 0.51$, respectively; Student's t test).

Data analysis

A radiological technologist (Y.M. with 13 years of experience with CT studies and blinded to the injection protocol) measured the intravascular CT number of all patients on a CT workstation (Advantage Workstation ver. 4.4; GE Healthcare). To evaluate the stability of optimal enhancement, the CT number in a circular ROI placed in the ascending aorta at the left main trunk level on axial images was recorded. The sizes of the circular ROI cursors were set as big as possible according to the internal diameter of the aorta (approximately 5.0 mm^2 to 7.0 mm^2). Enhancement was classified as acceptable (350–500 HU) and unacceptable (< 350 HU or > 500 HU) based on the optimal CT number for the detection of coronary stenosis on CCTA scans [5], and intergroup comparisons were made.

We adopted the classification of the American Heart Association [19] for specification of the coronary artery segments and measured the CT number in the right coronary artery (segment 3), the left anterior descending artery (segment 7), and the left circumflex artery (segment 13). ROIs were placed on axial images of the segments with an easily identified lumen. And, we set the sizes of the circular ROI cursors at 1.5 mm^2 to 2.5 mm^2. Coronary artery stents and calcified and noncalcified plaques were carefully excluded from the ROIs [21, 23].

To investigate the reliability of the ROI measurements, we performed the Bland-Altman plot analysis between the two observers for 75 datasets randomly selected from each population (75 datasets from group A and 75 from group B).

We compared the number of patients with coronary artery disease between groups A and B. To evaluate stenosis of the coronary artery, CCTA images with volume rendering, maximum intensity projection, curved multiplanar reformat, and vessel cross sections were presented on a digital picture archiving and communication system using a diagnostic workstation (Advantage Workstation ver. 4.4; GE Healthcare). A board-certified radiologist with 31 years of experience who was blinded to the injection protocols evaluated the CCTA images. We defined significant coronary artery disease as a luminal narrowing ≥ 50% [24]. When more than one coronary segments were affected by coronary artery disease in one patient, the radiologist evaluated the most severe lesions and recorded the presence of stenosis and its location.

Statistical analysis

Continuous variables are expressed as the median and range or as percentages or counts. The Mann-Whitney *U* test was used to test intergroup differences in numerical and the chi-square test to assess differences in categorical data. The CT number of the ascending aorta and coronary arteries was expressed as the mean and the standard deviation (SD). To determine whether the CT number of the ascending aorta was equivalent in groups A and B, we performed the equivalence test [25]. As the SD of the CT number of the ascending aorta was 75 HU in our earlier study [22], we adopted 75 HU as the equivalent margin. To compare the SD of the CT number of the ascending aorta between the two groups we used the *F* test. To avoid statistical errors due to multiple observations per patient [26], we applied statistical tests only for the ascending aorta in both groups because its CT number and that of the coronary arteries might be correlated. To compare the number of patients in each group whose CT number of the ascending aorta was acceptable (350–500 HU) or unacceptable (< 350 HU or > 500 HU), we used the chi-square test. We investigated inter-observer agreement as to the ascending aorta to confirm the reliability of the measurement. Inter-observer agreement by the Bland-Altman plot analysis was to converge to 95% limits of agreement. Ninety-five percent limits of agreement were defined as mean difference ± 1.96 SD. We compared the number of patients with coronary artery disease between groups A and B using the chi-square test.

All statistical analyses except for calculation of patient number were performed with JMP 14 (SAS Institute, Inc.). Differences of $p < 0.05$ were considered statistically significant. We calculated the patient number for the *F* test based on 1.5 as the effect ratio (variance 1/variance 2), 0.80 as the desired power (1-beta), and alpha 0.05. As we hypothesized that the variance for the CT number of the aorta was smaller in group A than in group B, we used the one-sided (one-tailed) test. As a result, the minimum required number of patients per group was 153. The patient number was estimated using the free statistical software "G* Power 3.1" (http://www.gpower.hhu.de/).

Results

Patient demographic data

Patient demographic data are summarized in Table 1. There was no significant difference between the two groups for all items except body weight.

Contrast media dose and injection rate

The contrast media dose and scan parameters are summarized in Table 2. The iodine dose was significantly smaller in group A than in group B ($p < 0.001$). Although the contrast media

Table 1 Demographic data

	Group A[a]	Group B[b]	*p* value
No. of patients	150	145	
Age (years)	70 (40.0–95.0)	72 (32.0–89.0)	0.764
Male/female	87:63	81:64	0.726
Height (cm)	162.0 (144.0–184.0)	160.0 (135.0–180.0)	0.109
Body weight (kg)	62.5 (34.0–87.0)	60.0 (33.0–90.0)	0.047
Body mass index (kg/m^2)	23.4 (12.5–35.2)	23.1 (15.4–36.3)	0.229
Heart rate (beats/min)	61.0 (44.0–88.0)	59.5 (42.0–90.0)	0.176
Number of patients using landiolol hydrochloride, *n* (%)	104 (69.3%)	105 (72.4%)	0.609
Cardiac output (l/min)	3.4 (2.0–7.1)	3.3 (2.0–6.9)	0.730
Presence of coronary stenosis, *n* (%)	31 (20.7%)	32 (22.1%)	0.778

Landiolol hydrochloride was used to reduce heart rate before imaging

[a] Patients in whom the contrast media dose was determined with the contrast enhancement optimizer

[b] Patients in whom the contrast media dose was determined based on the body weight

Table 2 Comparison of contrast injection parameters

	Group A[a]	Group B[b]	*p* value
No. of patients	150	145	
Iodine dose (mg I/kg)	235.7 (163.6–465.2)	253.6 (231.0–265.7)	< 0.001
Injection rate (ml/s)	3.4 (2.4–5.3)	3.6 (2.0–4.7)	0.056
Scan delay (s)	23.0 (16.0–38.0)	23.0 (18.0–34.0)	0.168
Scan duration (s)	7.5 (6.1–10.3)	7.6 (6.6–10.1)	0.952

[a] Patients in whom the contrast media dose was determined with the contrast enhancement optimizer

[b] Patients in whom the contrast media dose was determined based on the body weight

injection rate tended to be lower in group A, the difference was not statistically significant ($p = 0.056$). There was no statistically significant intergroup difference in the scan delay and the injection duration ($p = 0.168$ and $p = 0.952$, respectively).

CT number in the ascending aorta and distal coronary arteries

The CT number in the ascending aorta of group A was 428.6 HU (SD 55.5); it was 436.1 HU (SD 68.7) in group B (Fig. 2, Table 3). The 95% confidence interval for intergroup differences was -4.3 HU to 16.9 HU and within the range of the predetermined equivalence margins (Fig. 3). Therefore, we concluded that the CT number of the ascending aorta in groups A and B could be regarded as equivalent. The intergroup difference in the SD was statistically significant ($p = 0.009$) (Fig. 2).

The number of patients with acceptable CT number was 127/150 (84.7%) vs. 104/145 (71.7%) in group A and group B, respectively, which was significantly greater in group A than in group B ($p = 0.007$).

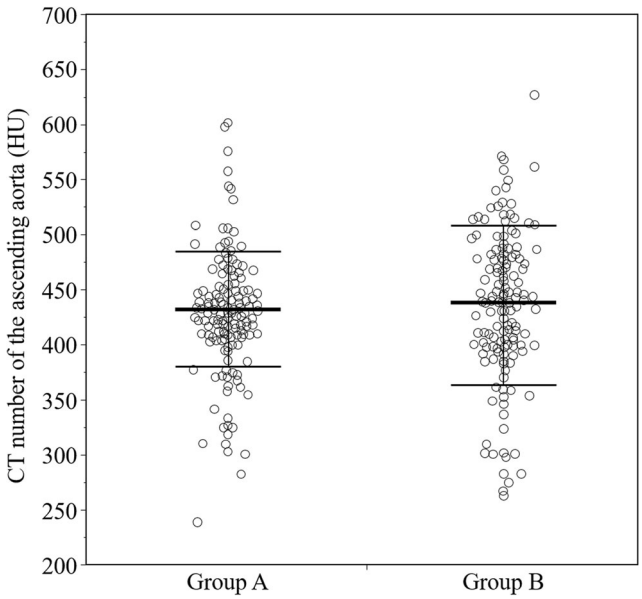

Fig. 2 Dot plots showing the CT number of the ascending aorta in group A (428.6 ± 55.5 HU) and group B (436.1 ± 68.7 HU). HU, Hounsfield units

The Bland-Altman plots between observers as to the ascending aorta at each site selected from each population are summarized in Fig. 4, respectively. The Bland-Altman plot almost converged within 95% limits of agreement at all sites in both populations.

The number of patients with coronary artery disease was 31 (20.7%) in group A and 32 (22.1%) in group B, respectively, and there was no significant difference between the two groups ($p = 0.778$).

Figure 5 shows our findings in patients with physical similarity who were examined using the CEO or the standard scanning protocol.

Discussion

Although we considered the CT number of the ascending aorta to be equivalent in groups A (CEO protocol) and B (standard protocol), its SD was significantly smaller in group A. Also, our CEO yielded optimal aortic contrast enhancement in significantly more patients than did the standard protocol. We thus concluded that our CEO obtained more robust contrast enhancement.

The body weight, height, and cardiac output were the patient factors for calculating the contrast media dose. Earlier studies reported that the primary patient-related factors affecting arterial

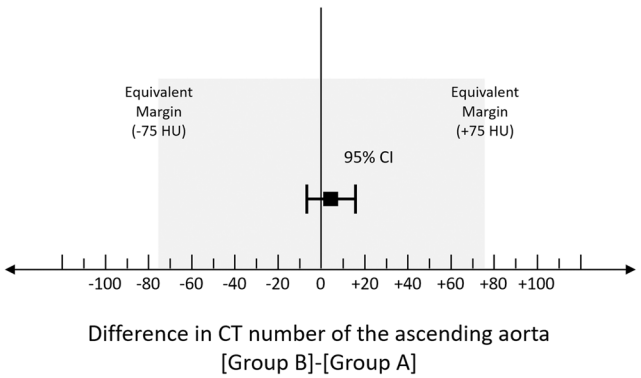

Fig. 3 The 95% confidence interval for the difference between the two groups in the CT number of the ascending aorta was -4.3 HU to 16.9 HU and within the range of the predetermined equivalence margins (75 HU). CI, confidence interval; HU, Hounsfield units

Table 3 Mean CT number of the ascending aorta and coronary arteries (segments 3, 7, and 13)

Artery	Group A[a]	Group B[b]
Ascending aorta	428.6 (55.5)	436.1 (68.7)
Coronary artery		
Segment 3	392.5 (74.1)	404.3 (84.6)
Segment 7	387.3 (65.1)	396.0 (76.9)
Segment 13	390.9 (65.2)	400.5 (80.3)

Parentheses show the standard deviation

[a] Patients in whom the contrast media dose was determined with the contrast enhancement optimizer

[b] Patients in whom the contrast media dose was determined based on the body weight

contrast enhancement at CT are the body size and cardiac output [14–16, 27–30]. At a given contrast media dose, enhancement of the arterial system and of parenchymal organs is inversely proportional to the body weight and cardiac output [31, 32]. Masuda et al [33] investigated the relationship between patient factors and aortic enhancement during arterial-phase hepatic dynamic CT. The standardized partial regression coefficient was much smaller between cardiac output and aortic enhancement [− 0.22] than between the body weight and aortic enhancement [0.74], suggesting that the contribution of cardiac output to aortic enhancement is relatively small. Although the cardiac output is not usually measured just prior to CT examinations, we recorded it just prior to scanning. As its contribution to aortic enhancement is relatively small, its assessment may not be necessary. However, this issue requires further study.

Our CEO can adjust the CT number of the target organ to within a diagnostically acceptable range. We considered 350–500 HU as an acceptable range for the CT number of the ascending aorta at CCTA. According to Fei et al [5], a higher CT number of the coronary arteries lead to significant underestimation of stenosis in smaller vessels, while a lower CT number result in stenotic overestimation. Yanaga et al [34] reported that setting a lower aortic enhancement limit (280 HU) during arterial-phase hepatic dynamic CT yields excellent depiction of hepatocellular carcinoma. Thus, adjusting the CT number of the target vessel or organ to within its optimal range is diagnostically important.

The application of our CEO reduces the interpatient variability in the CT number of the target vessels or organs. Comparison of groups A and B showed that the number of patients with an unacceptable CT number of the ascending aorta was lower in those subjected to the CEO protocol. Our earlier studies [31, 32] revealed that when the contrast media dose is based on the body weight and the injection duration is fixed, the variability in enhancement is lower than when a protocol with a fixed contrast media dose is used. Our CEO software calculates the optimal contrast enhancement protocol based on a pharmacokinetic model [13–15, 27]; adding the patient height and cardiac output to the body weight may yield a more accurate estimation of the extracellular fluid space volume, thereby contributing to a reduction in interpatient enhancement variations.

There was no statistical difference in the number of patients with significant coronary artery disease between groups A and B. We think this result was associated with equivalence of intravascular CT number between the two groups. As the interpatient variability in the CT number can be reduced by using the CEO, evaluation of coronary artery stenosis may be improved. However, it should be verified in larger population.

In our result, the iodine dose was significantly smaller in group A than in group B. This result suggests that overdosing of contrast media may be avoidable in each patient by using the CEO. This may be especially beneficial for patients with impaired renal function.

To investigate reproducibility in ROI measurement in both groups A and B, we performed the Bland-Altman plot analysis. The results showed that the reproducibility of ROI measurements between the two observers was high in both groups. Therefore, we think that the reliability of CT number measurement of the vessels in this study was reliable.

Our study has some potential limitations. As it was a single-institution study, multicenter investigations are needed to validate the use of our CEO. Also, the weight range of our study population was smaller than that of Westerners and the cardiac output range (2.0–7.1 l/min) may also be lower than that in Western populations (normal cardiac output range 4.0–8.0 l/min). Consequently, studies on Western populations are needed to validate the use of our CEO.

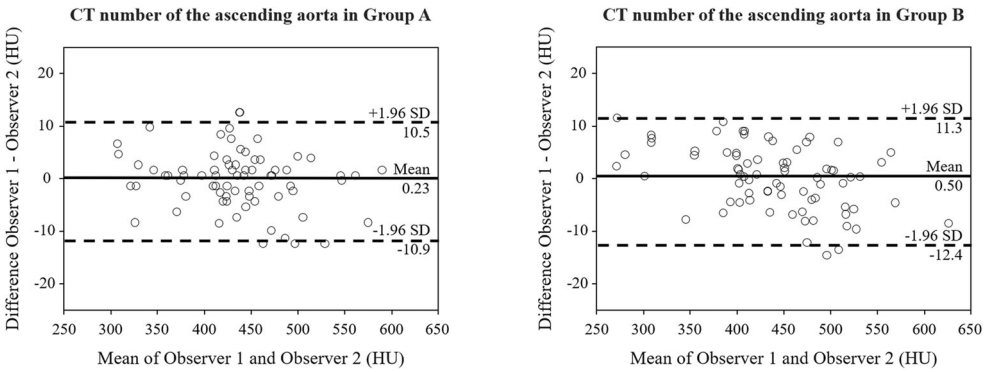

Fig. 4 Bland-Altman plot between observers 1 and 2 in the ascending aorta. The solid line represents the mean difference, and the dashed lines represent the 95% limits of agreement (mean difference ± 1.96 SD). SD, standard deviations; HU, Hounsfield units

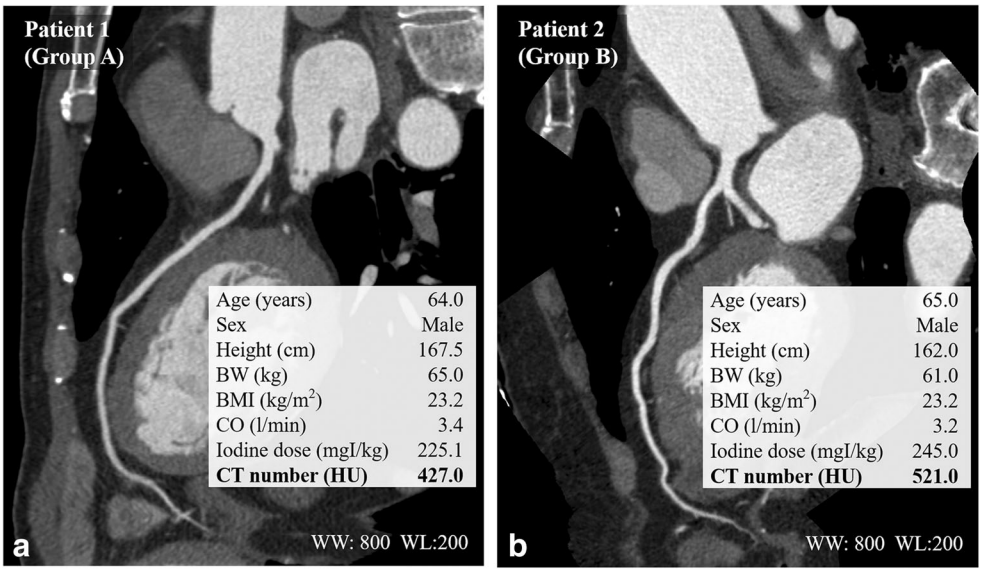

Fig. 5 Two representative, physically similar patients with suspected coronary artery disease. Both illustrations are curved maximum planar images of the left anterior descending artery. The window width and level were fixed at 800 HU and 200 HU, respectively. **a** CEO protocol. Patient 1, a 64-year-old man with a height, body weight, body mass index, and cardiac output of 167.5 cm, 65.0 kg, 23.2 kg/m^2, and 3.4 l/min, respectively. The iodine dose was 225.1 mg I/kg; the CT number obtained at the ascending aorta was 427 HU. **b** Standard protocol. Patient 2, a 65-year-old man with a height, body weight, body mass index, and cardiac output of 162.0 cm, 61.0 kg, 23.2 kg/m^2, and 3.2 l/min, respectively. The iodine dose (245 mg I/kg) was based on the body weight; the CT number obtained at the ascending aorta was 521 HU. BW, body weight; BMI, body mass index; CO, cardiac output; HU, Hounsfield units

In conclusion, with our CEO software, optimal and stable aortic enhancement can be obtained on CCTA scans, irrespective of patient variations.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Kazuo Awai.

Conflict of interest The authors declare that they have no competing interests.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval An institutional review board approval was obtained.

Methodology
- Prospective
- Randomized controlled trial
- Performed at one institution

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