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Influence of cardiac function on image quality in coronary computed tomography angiography☆

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ABSTRACT

Purpose: To evaluate the correlation between cardiac functional parameters and image quality in coronary computed tomography angiography (CCTA).

Material and methods: Sixty-six patients who underwent both CCTA and echocardiography were included. The coronary artery attenuation values and contrast-to-noise ratios (CNR) were measured in the proximal right coronary arteries (RCA) and left main (LM) trunk. Then, the averages of the mean values derived from RCA and LM were calculated. The cardiac output (CO), left atrial (LA) volume, and early mitral inflow velocity to mitral annular early diastolic velocity ratio (E/e′) were measured by echocardiography. The relationship of cardiac parameters with arterial attenuation and CNR were assessed by Pearson's correlation, Spearman's rank correlation and multivariable linear regression analysis adjusted for age, gender, body surface area and heart rate.

Results: The coronary artery attenuation value was negatively correlated with CO ($r = -0.30$, $p = 0.01$) and LA volume ($r = -0.37$, $p = 0.002$). CNR was negatively correlated with LA volume ($r = -0.4$, $p = 0.001$) and E/e′ ($r = -0.27$, $p = 0.03$). These associations remained significant in the multivariable analysis.

Conclusion: CO and diastolic function had an impact on image quality of CCTA. Adjusting CCTA protocol may improve image quality in patients with known diastolic dysfunction or reduced cardiac output.

1. Introduction

Cardiovascular diseases are a major cause of morbidity and mortality in the world [1,2]. Recent studies [3,4] showed that multi-detector computed tomography angiography (CCTA) had high diagnostic value for coronary artery disease (CAD), showing CCTA to be a non-invasive tool for diagnosis of CAD [5]. In CCTA, consistent vascular attenuation is essential to distinguish the coronary lumen from the vascular wall, to detect lesions in the coronary arteries, to assess the level of stenosis, and to detect vulnerable plaque [5–7]. Previous studies [8,9] suggested that the mean attenuation value for diagnostic image quality was above 326 Hounsfield Units (HU) for the proximal coronary arteries.

The coronary attenuation in CCTA imaging may be affected by many factors, including patient-related factors, such as total body weight (TBW) and body surface area (BSA) [10–13] and image acquisition-related factors, such as tube voltage and contrast material injection protocols [14–17]. Cardiac parameters may also play a role in

Abbreviations: TBW, total body weight; BSA, body surface area; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT, computed tomography; CNR, contrast-to-noise ratio; CO, cardiac output; CI, confidence interval; ICC, intra-class correlation coefficient; E/e′, early mitral inflow velocity to mitral annular early diastolic velocity ratio; HU, Hounsfield Unit; HR, heart rate; LA, left atrial; LM, left main; LVEF, left ventricular ejection fraction; RCA, right coronary artery; ROIs, regions of interest; SD, standard deviation

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the coronary attenuation. Previous studies have reported that cardiac hemodynamic parameters, such as cardiac output (CO), had an effect on the coronary attenuation value [18–22], but they did not mention other cardiac parameters, such as left atrial (LA) volume and early mitral inflow velocity to mitral annular early diastolic velocity ratio (E/e′) as measures for diastolic function. There has been no study showing the relationship between those cardiac parameters and coronary attenuation value. The purpose of the present study was to evaluate the association between cardiac hemodynamic parameters, including measures for diastolic function, and image quality represented as contrast enhancement in CCTA using 320-detector computed tomography (CT).

2. Materials and methods

This retrospective study was approved by the ethical review board for medical research involving human subjects in our institute, with waiver of informed consent.

2.1. Patient population

109 consecutive adult (≥20 years old) patients with clinical indications for CAD who underwent both coronary CT angiography and echocardiography between September 2015 and March 2017 at our institute were examined retrospectively. We included patients who were imaged using both of these modalities and had CO, LA volume, and E/e′ value in their echocardiography reports, regardless of presence of coronary artery disease or past history of cardiac surgery. Patients with more than one month between CCTA and echocardiography (n = 11) and patients who did not have information on CO, LA volume, E/e value in their echocardiography reports (n = 32) were excluded. A total of 66 patients were included in this study.

2.2. CT data acquisition

All CT examinations were performed with a 320-detector CT scanner (Aquillion One, Toshiba, Tochigi, Japan) with prospective ECG-gating axial scans. The parameters were: detector configuration, 320 × 0.5 mm; gantry rotation time, 275 ms; tube potential, 120 kV; and tube current, from 270 mA to 550 mA depending on patient's TBW. Atenolol was administered orally (Tenormin® 25 mg; AstraZeneca K.K Ltd., Osaka, Japan) 4 h before data acquisition, and Langiolol (Corebeta® 0.125 mg/kg; Ono Pharmaceutical Ltd., Osaka, Japan) was administered intravenously just before imaging to the patients who had heart rates (HR) exceeding 65 beat per minute (bpm). All patients received 0.3 mg nitroglycerin (Myocor spray® 0.3 mg, Toa Eiyo Ltd., Tokyo, Japan).

Patients were given an intravenous injection of iopamidol with 370 mgI/ml (Iopamiron 370, Bayer Yakuhin Ltd., Osaka, Japan) via an 18 or 20-gauge catheter in a right forearm vein using a power injector. To reduce the interpatient variability of contrast attenuation, we used a fixed contrast injection time of 12 s, and the flow rate was adjusted to the TBW of patient. The dose was tailored to the TBW of each patient by using the following formula: contrast dose (ml) = TBW × 0.84 (310 mg iodine/kg). This was immediately followed by a 25 ml saline flush delivered at the same rate as the contrast media. Bolus tracking in the ascending aorta with a threshold of 150 HU was performed, and image acquisition was automatically started 5 s after signal attenuation reached the threshold. For each patient, the reconstruction phase with minimum artifact was determined at the CT console by using cardiac-phase search software (Phase Navi, Toshiba, Tochigi, Japan). Using a medium soft-tissue convolution kernel (FC44), axial images for CNR calculations were reconstructed with the slice thickness of 0.5 mm and 0.25 mm increments.

2.3. CT data analysis

Coronary artery attenuation value measurements and CNR calculations were performed by placing round regions of interest (ROIs) in the coronary arteries and adjacent perivascular tissue [19]. The size of ROIs was selected to be as large as possible, avoiding plaque and obvious motion artifact. Measurements were performed in the RCA and LM. The average of coronary artery attenuation values was the mean of attenuation values of RCA and LM. Mean image noise was defined as the standard deviation (SD) of the CT attenuation of the aorta at level of the LM. The CNR of each coronary artery was calculated as the difference of the mean attenuation of the coronary lumen and perivascular tissue divided by image noise (Fig. 1). The average CNR was calculated as the mean of RCA CNR value and LM CNR value. All measurements were performed by a single reader: a radiologic technologist with 10 years of experience (T.N-C), with repeated measurements to assess intra-observer reproducibility. To assess inter-observer reproducibility, another reader, a radiologist with 10 years of experience (H.N-T), measured 30 patients in random order while blinded to the measurements made by the first reader.

2.4. Measurement of cardiac parameters

The echo parameters were taken from the clinical echo reports. Cardiac parameters were measured by two-dimensional (2D) and Doppler echocardiography, based on the American Society of Echocardiography recommendations [23]. Left ventricular ejection fraction (LVEF) was calculated by M-mode echocardiography using the Teichholz formula. LA volume was measured from the apical 4-chamber view. As diastolic functional parameters, the peak velocity of early phase (E) of the mitral flow using pulsed-Doppler echocardiography and the early peak diastolic mitral annular velocity (e′) at the septal and lateral mitral annulus were evaluated [24]. The e′ was calculated from the average of the septal and lateral mitral annulus. E/e′ was calculated as an index of LV filling pressures [24]. CO was calculated as the stroke volume multiplied by HR [24].

2.5. Statistical analysis

Continuous variables were presented as mean and SD for normally distributed data and median (25%ile, 75%ile) for non-normally distributed data. Kolmogorov-Smirnov test was used to test normal distribution of continuous variables.

Pearson's correlation coefficient or Spearman's rank correlation coefficient were used to assess the strength of the relationship between cardiac parameters and CT imaging parameters. Multivariate linear regression analysis was used to evaluate the effect of cardiac parameters on the coronary artery attenuation and CNR, adjusted for patient-related factors such as age, gender, BSA, and HR. Receiver operating characteristic (ROC) curves identified the threshold of cardiac parameters associated with low image quality, defined as a coronary artery attenuation of < 326 HU [8,9]. The best cutoff value was defined as the point at which the sum of sensitivity and specificity was highest.

Statistical analysis was performed using R software (R version 3.3.2, and EZR version 1.35, The R project for statistical analysis computing). Inter-observer reproducibility was performed using the intra-class correlation coefficient (ICC) by R software (irr package), where ICC < 0.4 represented poor reliability; ICC between 0.4 and 0.75, fair-to-good reliability; and ICC > 0.75, excellent reliability [25]. A two-tailed p-value < 0.05 was considered significant.

3. Results

3.1. Patients' characteristics

The patients' age was 69 ± 12 years (range, 37 to 88), and thirty-

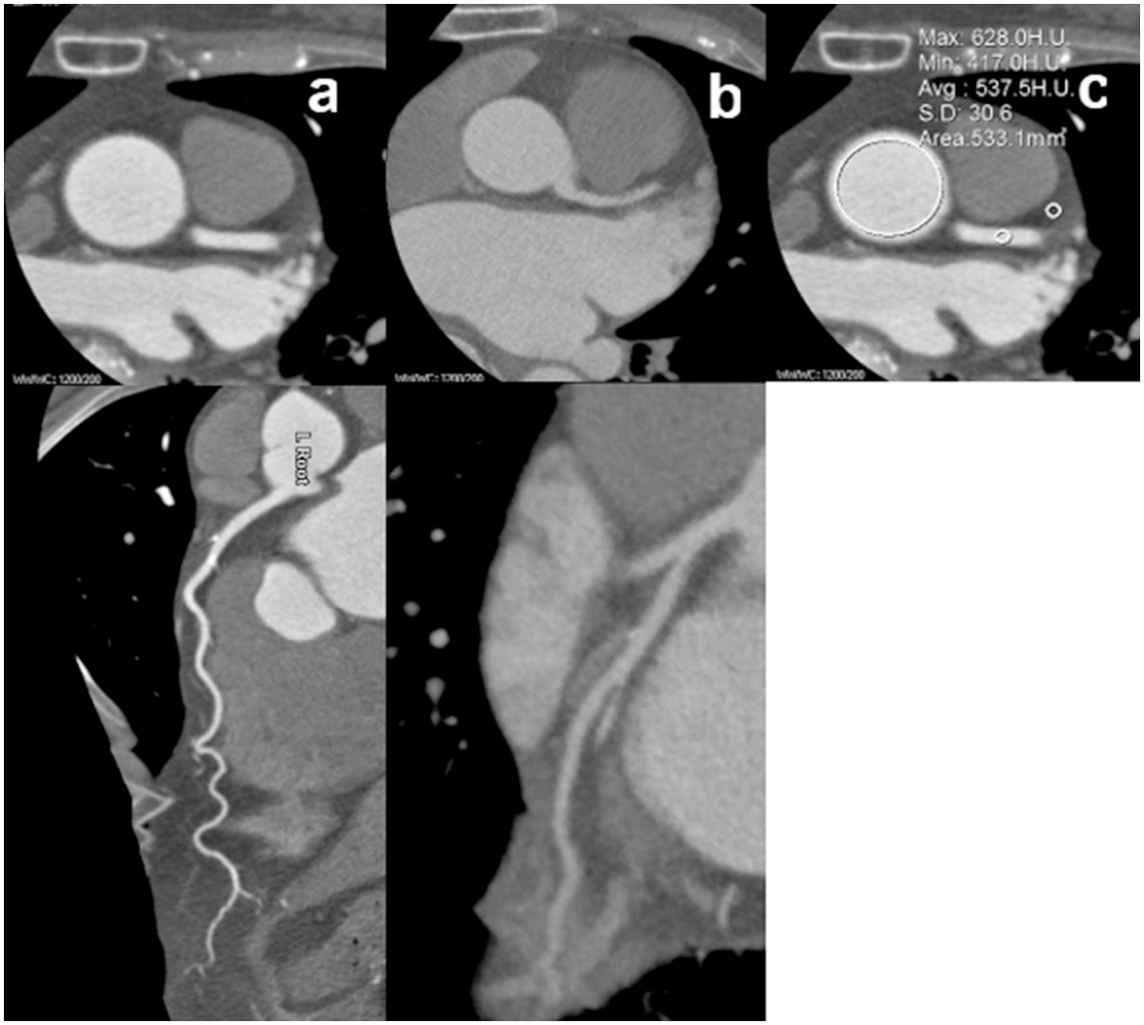

Fig. 1. Axial and curved multi-planar reconstruction (MPR) images of the left main trunk. Window level of 1.200 and width of 200 HU for all images. a. A 65 year-old female patient (TBW 57 kg) with CO of 3.75 l/min and LA volume of 26 ml. With 48 ml of contrast agent, the coronary arterial attenuation was 559 HU and coronary artery CNR was 22.7. b. A 59 year-old male patient (TBW 57 kg) with a CO of 2.96 l/min, LA volume of 138 ml. With 51 ml of contrast agent, the coronary arterial attenuation was 327 HU and coronary artery CNR was 16.7. c. An axial coronary CT angiography section illustrating region of the ROIs in the aorta, LM artery, and the adjacent perivascular fat. The ROIs were selected to be as large as possible, carefully avoiding calcifications, plaques, and stenosis.

six of the 66 patients (55%) were male. The mean patient body weight and BSA were 60 ± 13 kg (30 to 100) and 1.66 ± 0.21 m^2 (1.12 to 2.26), respectively. The median HR during acquisition was 62 bpm (56 to 67). The mean contrast dose during acquisition was 50 ± 8 ml (35 to 66). Thirty patients had CAD, including old myocardial infarction and angina pectoris, and thirty-six patients had no significant stenosis in CCTA finding (Table 1). Seven patients had atrial fibrillation (Af) and 4 patients had moderate or severe mitral regurgitation (MR).

3.2. Intra- and inter-observer reproducibility

Intra-observer reproducibility was excellent with ICCs of CNR and attenuation value were 0.817 (95% CI 0.687 to 0.891, $p < 0.001$) and 0.966 (95% CI 0.946 to 0.979, $p < 0.001$), respectively. Inter-observer reproducibility was also excellent between the two interpreters, with ICCs of CNR and of attenuation value being 0.878 (95% confidence interval 0.723 to 0.95, $p < 0.001$), and 0.974 (95% confidence interval 0.936 to 0.989, $p < 0.001$), respectively.

3.3. CT parameters

There was no significant difference between mean attenuation value

Table 1
The characteristics of patients.

	Value
Number of patients (n)	66
Old myocardial infraction patient n (%)	9/66 (13%)
Angina pectoris patient n (%)	21/66 (32%)
No significant stenosis on CT patient n (%)	36/66 (55%)
Male (%)	36/66 (55%)
Age (years)	69 ± 12
Body surface area (m^2)	1.66 ± 0.21
Body weight (kg)	60 ± 13
Contrast dose (ml)	50 ± 8
Cardiac output (l/m)	4.0 ± 1.2
Left atrial volume (ml)	53 (41–68)
Left ventricular ejection fraction (%)	63 (56–68)
E/e′ ratio	13 ± 4.3
Heart rate (bpm)	62 (56–67)
Attenuation value of RCA (HU)	438 ± 86
Attenuation value of LMT (HU)	443 ± 84
Average attenuation value of coronary arteries (HU)	440 ± 83
Contrast to noise ratio	23 ± 5.6
Interval time (days)	6 (2−12)

Value are mean ± standard deviation, number (%), median (25%iles–75%iles); CT indicates computed tomography; RCA, right coronary artery; LMT, left main trunk; E/e′, early mitral inflow velocity to mitral annular early diastolic velocity ratio.

of RCA (438 ± 86 HU [range, 256 to 621]) and of LM (443 ± 84 HU [249 to 657 HU], $p = 0.16$). Mean attenuation values of the coronary arteries and the adjacent perivascular tissue, and the image noise and CNR were 440 ± 83 HU (252 to 639), −102 ± 18 HU (−163 to −42), 24 ± 5.5 (14 to 40), and 23 ± 5.6 (14 to 39), respectively.

3.4. Echocardiography parameters

The mean values of CO and E/e′ were 4.0 ± 1.2 l/min (range, 2.1 to 7.6 l/min), 13 ± 4.3 (range, 6.6 to 22.5), respectively. The median values of LA volume and LVEF were 53 ml (42 to 68 ml), 63% (56 to 68%), respectively.

3.5. Correlations between the cardiac parameters and the attenuation values of coronary arteries

There were negative correlations between the attenuation value of the coronary artery and CO (r = −0.30, $p = 0.01$) or LA volume (r = −0.37, $p = 0.002$) (Fig. 2). No correlations were observed between the attenuation values and LVEF or E/e′.

Univariate linear regression analysis showed that higher CO and LA volume were associated with lower attenuation values. The association of the lower attenuation values with the higher CO (β = −17.6 [95% confidence interval, −32.6 to −2.6] HU per 1 l/min, $p = 0.02$) and LA volume (β = −1.1 [−1.79 to −0.4], $p = 0.002$) remained significant after being adjusted for age, gender, BSA, contrast dose, and HR (Table 2). These associations remained significant even after excluding patients with Af and moderate or severe MR (data not shown).

Table 2
Effect of cardiac parameters on the attenuation value in coronary artery

	Univariate		Multivariate	
	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value
CO (l/m)	−20 (−35.8 to −4.4)	0.01	−17.6 (−32.6 to −2.6)	0.02
LAV (ml)	−1.2 (−1.93 to −0.47)	0.001	−1.1 (−1.79 to −0.4)	0.002
LVEF (%)	0.69 (−1.04 to 2.4)	0.42		
E/e′	−0.37 (−5.12 to −4.3)	0.87		

β coefficient and 95% confidence interval were estimated using multivariate linear regression model to assess the relationship of cardiac parameters with the attenuation value in coronary artery as dependent variables. Multivariate model was adjusted for age, sex, body surface area, heart rate, and cardiac parameters. CO indicates cardiac output; LAV, left atrial volume; LVEF, left ventricular ejection fraction; E/e′, early mitral inflow velocity to mitral annular early diastolic velocity ratio; CI, confidence interval.

3.6. Correlations between the cardiac parameters and CNR

There was a negative correlation between the CNR and LA volume (r = −0.4, $p = 0.001$), or E/e′ (r = −0.27, $p = 0.03$), respectively (Fig. 3). No correlations were observed between the CNR and LVEF or CO.

Univariate linear regression analysis showed that higher LA volume and E/e′ were associated with lower CNR. The association of lower CNR with higher LA volume (β = −0.08 [95% confidence interval, −0.13 to −0.03] per 1 ml, $p = 0.002$), and higher E/e′ (β = −0.41 [−0.75 to −0.06], $p = 0.02$) remained significant after adjusted age, gender,

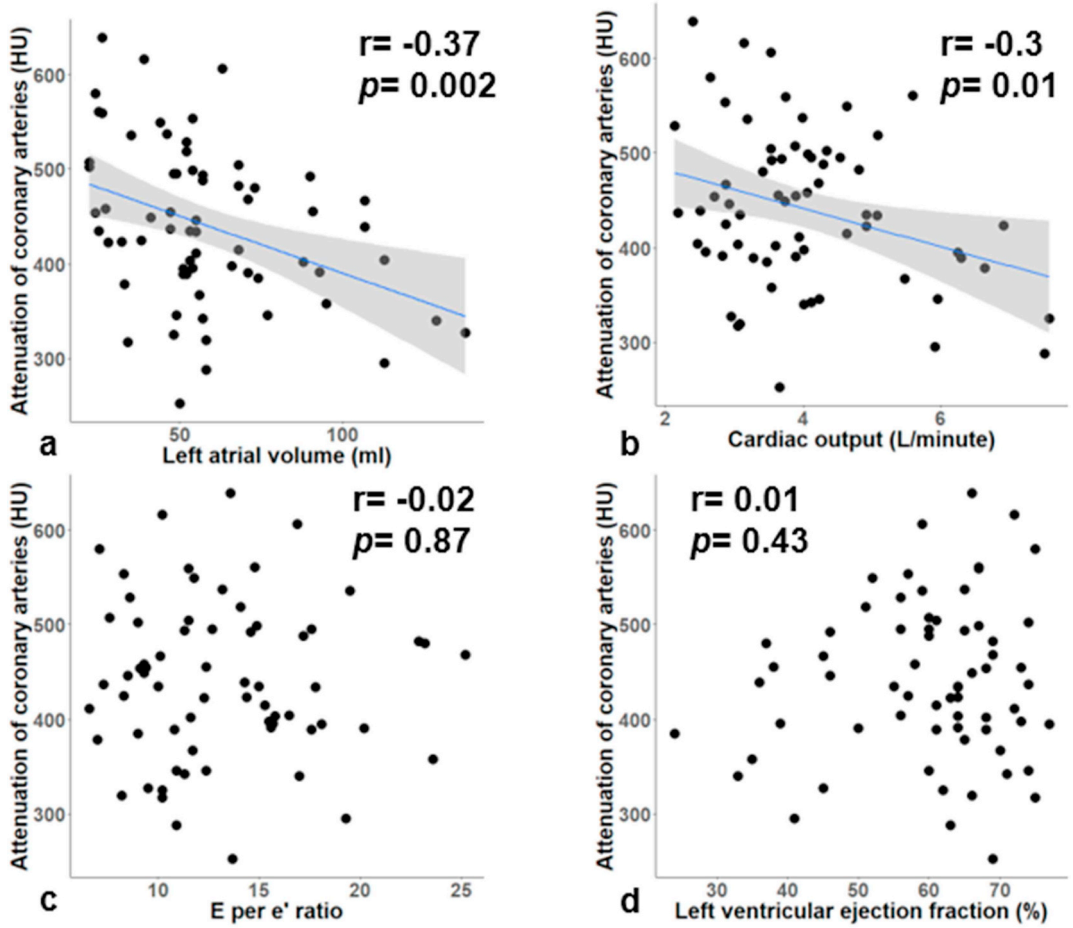

Fig. 2. Scattergrams of the relationship between the attenuation value and left atrial volume (a), cardiac output (b), E per e′ ratio (c), left ventricular ejection fraction (d). r, Pearson′ or Spearman′ correlation coefficient. Gray areas represent 95% CI.

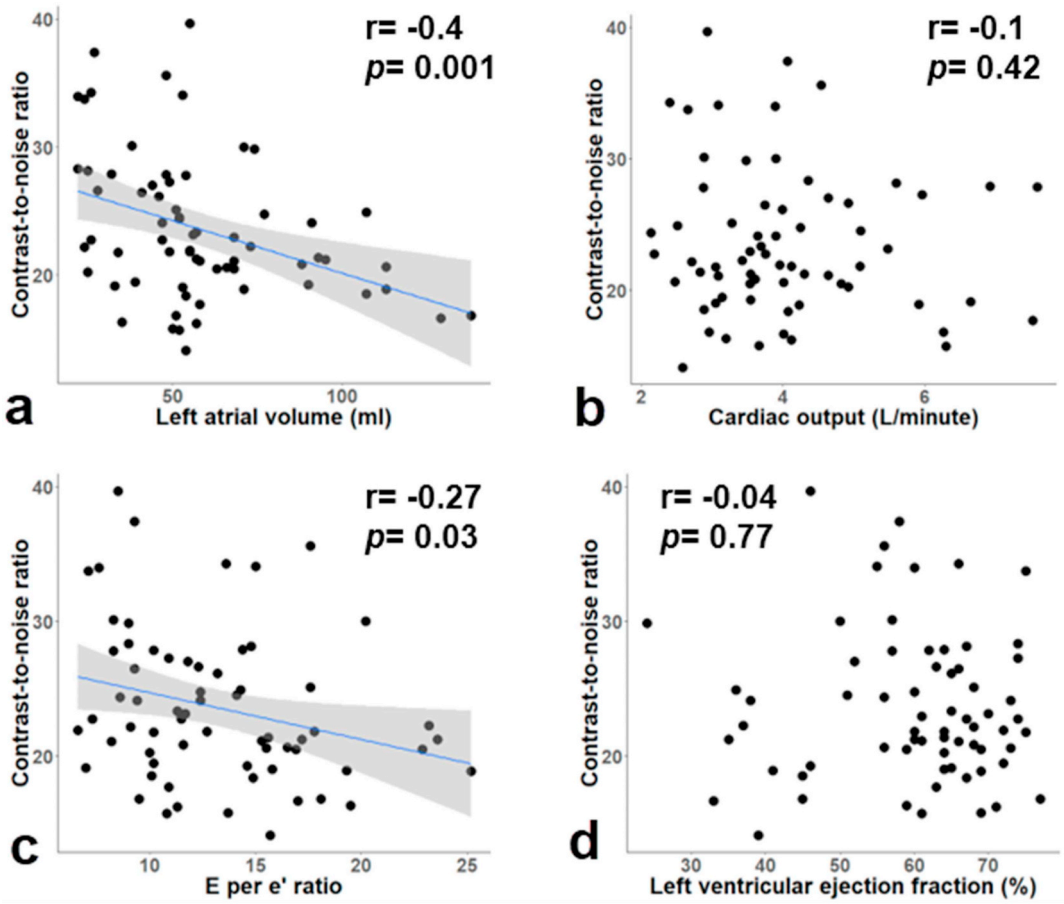

Fig. 3. Scattergrams of the relationship between the contrast to noise ratios and left atrial volume (a), cardiac output (b), E per e′ ratio (c), left ventricular ejection fraction (d). r, Pearson′ or Spearman′ correlation coefficient. Gray areas represent 95% CI.

Table 3
Effect of cardiac parameters on the contrast to noise ratio in coronary artery.

	Univariate		Multivariate	
	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value
CO (l/m)	−0.44 (−1.5 to 0.66)	0.42		
LAV (ml)	−0.08 (−0.13 to −0.03)	0.001	−0.08 (−0.13 to −0.03)	0.002
LVEF (%)	−0.01 (−0.13 to 0.1)	0.77		
E/e′	−0.34 (−0.65 to −0.03)	0.03	−0.41 (−0.75 to −0.06)	0.02

β coefficient and 95% confidence interval were estimated using multivariate linear regression model to assess the relationship of cardiac parameters with the contrast to noise ratio in coronary artery as dependent variables. Multivariate model was adjusted for age, sex, body surface area, heart rate, and cardiac parameters. CO indicates cardiac output; LAV, left atrial volume; LVEF, left ventricular ejection fraction; E/e′, early mitral inflow velocity to mitral annular early diastolic velocity ratio; CI, confidence interval.

BSA, contrast dose, and HR (Table 3). These associations remained significant even after excluding patients with Af and moderate or severe MR (data not shown).

3.7. Predictive value of cardiac parameters for image quality

The area under the ROC curve was 0.68 for LA volume to low image quality (coronary attenuation < 326 HU) (95% CI, 0.55 to 0.81). The optimal cutoff value of LA volume for prediction of low image quality was 48 ml (sensitivity of 91% and specificity of 43%) (Fig. 4). CO was a less accurate predictor than LA volume, with an area under curve of 0.63 (95% CI, 0.47 to 0.78).

4. Discussion

This study demonstrated that lower contrast enhancement in CCTA was associated with higher CO and LA volume. Lower CNR was associated with higher LA volume and E/e′. These associations remained significant after adjusting for other factors that may affect the coronary attenuation, such as BSA and contrast dose.

CO is the volume of blood pumped from the heart per minute. In this study, the attenuation value of the coronary artery was negatively correlated with CO. This result was consistent with previous experimental studies and clinical studies using CTs with different numbers of detectors [18–21,26]. Since the attenuation of vessels depends on the concentration of contrast material, that is, the number of contrast material molecules in a given vessel volume, it may be reasonable that CO had an impact on the attenuation values through dilution of contrast material molecules in coronary arteries. We suspect that prolonged circulation time, inducing the delay in washout of contrast material in lower CO, may contribute to the negative correlation of the attenuation value with CO in this study. Different timing of scanning or different dose/concentration of contrast material, which may be dependent on CO, may be needed to get adequate attenuation values in patients with different CO. As with previous studies [19], LVEF was not associated with attenuation values. LVEF is a relative value for systolic function-the fraction of blood ejected from heart with each heartbeat—so LVEF is independent of the absolute volume that affects attenuation value.

We found that the CNR was not associated with CO. This result was inconsistent with previous studies using 64-detector CT, which showed that higher CNR was associated with the lower CO [19]. In this study, as CO decreased, image noise (SD of attenuation value in aorta) tended to

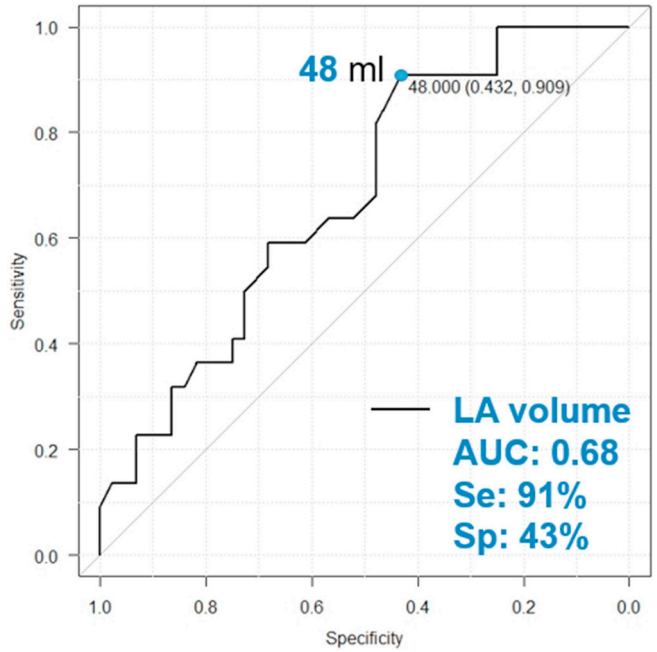

Fig. 4. Receiver operating curves (ROC) analysis of left atrial volume for prediction of low image quality.

increase ($r = -0.17$, $p = 0.12$) with increasing attenuation, resulting in a stable CNR (attenuation divided by noise). We cannot offer a good explanation as to how CO affected image-noise. The previous study used a 64-detector CT, while we used a 320-detector CT, and this difference may have contributed to the inconsistency.

Interestingly, we found that both attenuation values and CNR were negatively correlated with LA volume. Furthermore, CNR was also negatively correlated with E/e′. There has been no study showing the association of image quality with LA volume or E/e′. LA volume can be used as a surrogate for diastolic dysfunction because LA enlargement may reflect both severity and long-term effects of diastolic dysfunction better than diastolic filling patterns [27]. The ratio of E to e′ also has been reported to be comparable to invasive measures for assessment of diastolic function and to have utility in evaluating diastolic dysfunction [28]. Higher LA volume or E/e′ represents impaired diastolic function. LA volume may be more sensitive for cumulative effect of increased LV filling pressures [27], resulting in strong correlation between attenuation value or CNR and LA volume compared to E/e′. These negative correlations of attenuation value or CNR with LA volume or E/e′ may indicate that LV diastolic function may affect the image quality in CCTA. It was difficult to pursue the underlying mechanism for the lower attenuation with the impaired LV diastolic function represented as higher LA volume. One plausible explanation is higher dilution of the contrast materials in the pulmonary circulation in cases with LV diastolic dysfunction [29,30]. The increased end-diastolic pressure of LV causes increased pressure in the LA, pulmonary veins and pulmonary capillaries, resulting in increased pulmonary circulation and LA volume. If the contrast material is injected continuously, the concentration of contrast material in the aorta is affected by the contrast material in pulmonary circulation due to closed circulation. Increased blood volume in the pulmonary vascular bed with LA enlargement may potentially contribute to the dilution of the contrast material in pulmonary circulation, resulting in the lower attenuation values in the aorta.

ROC analysis demonstrated that LA volume was a good predictor of CCTA image quality, with an optimal cutoff value of 48 ml. This result indicated that the information of diastolic dysfunction, (such as LA volume) before acquiring images might be helpful in predicting the quality of CCTA images, and a modified protocol might be needed to obtain sufficient attenuation value in patients with known diastolic dysfunction. Increased injection speed might be needed to get a higher peak of contrast enhancement and shorter time to peak to overcome the dilution of contrast material. Further studies would be needed to establish a modified protocol for patients with diastolic dysfunction.

There were several limitations in this study. First, the coronary quality image depends on not only the attenuation but also other factors such as motion artifacts, so the attenuation and CNR may not exactly represent image quality, and attenuation values were measured only in the proximal RCA and LM, which may not be representative for whole coronary arteries. Second, echocardiography was not performed on the same day as the CCTA scan, so there was a possibility that echo parameters did not accurately represent the hemodynamic state at the time of the CT examination. However, none of the eligible patients had clinical events during the time between the two examinations (less than one month). Third, we did not evaluate hemodynamic factors using a thermodilution method. However, hemodynamic factors measured by echocardiography have been reported to have a strong relationship with hemodynamic factors evaluated by thermodilution methods [31]. Fourth, we used the Teichholz method to calculate EF instead of the modified Simpson's method, which is the preferred method in the current guidelines. In some cases, we could not use Simpson's method due to poor image quality, especially in the lateral wall. Fifth, we excluded 34 patients due to insufficient echocardiography data or a longer period between CT and echocardiography, resulting in potential selection bias. Sixth, this is a single center study that used a 320 detector machine, so it might be difficult to apply our findings to other facilities using a wide variety of CT scanners and different volumes of contrast. Seventh, all CT analyses were performed by a single reader. Further studies should be done to confirm the results of this study under different conditions.

5. Conclusion

Contrast enhancement of the coronary arteries in CCTA decreased with greater CO and impaired diastolic function demonstrated as higher LA volume and E/e′. CNR decreased with impaired diastolic function. Cardiac hemodynamic parameters, including measures for diastolic function had an impact on image quality of CCTA. Future studies are needed to elucidate the mechanism of the association of cardiac function with contrast enhancement, and to develop an adaptive protocol to obtain adequate image quality for CCTA.

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Conflict of interest

None of the authors have any conflicts of interest to declare.

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