Determining Whether Tube Voltages and Contrast Flow Rates have an Impact on a Test Bolus-Based Contrast-Enhancement-Prediction Algorithm during Coronary CT Angiography

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Objective: To assess whether tube voltages and contrast flow rates have an impact on a test bolus (TB)-based contrast-enhancement-prediction (CEP) algorithm during coronary computed tomographic angiography (CCTA).

Materials and Methods: A total of 188 anonymized CCTA examinations following TB scans were collected. During TB, a tube voltage of 100 kV and contrast flow rate of 3.5 mL/s were applied for Group 1 and 120 kV and 4.5 mL/s for Group 2. True aortic enhancements were extracted with a region of interest at the ascending aorta (AAo). TB signals and group information were used as independent variables in a stepwise linear regression analysis to predict aortic enhancement. For each patient, the errors in predicted aortic enhancements were calculated.

Results: Time to peak enhancement in the AAo (PT_{AAo}) and peak enhancement in the descending aorta (PE_{DAo}) during the TB study had significant correlations with AAo ($AAo = -125.627 + 1.619 \times PE_{DAo} + 16.236 \times PT_{AAo}$, $r = 0.782$, $p < 0.001$). The CEP algorithm without group information presented a minor systemic underestimation in Group 1 [-8 Hounsfield unit (HU)] and an overestimation in Group 2 (8 HU).

Conclusion: The TB-based CEP of aortic enhancement is feasible. The tube voltages and contrast flow rates during TB scanning were statistically significant, but resulted in a clinical negligible impact on the CEP algorithm.

Key words Tube voltage · Contrast agent · Coronary · Computed tomography angiography · Contrast enhancement prediction.

INTRODUCTION

Electrocardiographically gated coronary computed tomographic angiography (CCTA) is widely used in clinical practice as a robust non-invasive imaging modality with high spatial

and temporal resolution that enable accurate diagnosis or exclusion of coronary artery disease [1,2]. Technical improvements in computed tomography (CT) have contributed to higher contrast-to-noise ratios and lower radiation doses in CCTA [3,4]. However, improper intracoronary attenuation leads to misestimate of the degree of stenosis in smaller vessels and significantly modifies the attenuation of non-calcified plaques assessed with CT [5,6].

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To optimize the consistency in intracoronary attenuations in a particular scanning protocol, a prediction of contrast enhancement should be available before the CCTA scan. Many patient-related factors influence the magnitude of coronary contrast enhancement in CCTA scans [7-9], and one of the most important patient-related factors is cardiac output [10]. If one considers a patient as a linear time-invariant system, information about a patient's hemodynamic parameters can be obtained from a test bolus (TB) and could be used for enhancement prediction [11-13].

Intraarterial enhancement is influenced not only by patient-related factors, but also by contrast injection-related and CT scanning-related factors [14]. With technical improvements, a huge variety of contrast injection and CT scanning protocols have been introduced in CCTA practice [11,15]. Previous predictions of intracoronary attenuation were based on the same contrast injection and scanning protocols applied in the TB [10]. However, in the previous study, the contrast doses were approximately 20 mL with an injection duration of 5 seconds. The feasibility of the similar prediction algorithm propagating to the TB with reduced contrast doses and different scanning protocols needs to be investigated. Nevertheless, to our knowledge, limited investigations have been performed for this question. The purpose of this retrospective study was to assess whether the tube voltages and contrast flow rates have an impact on the TB-based contrast-enhancement-prediction (CEP) algorithm during CCTA by retrospectively quantifying the systematic and random errors between the predicted and true enhancements.

MATERIALS AND METHODS

Patient group

A total of 203 patients referred for clinically indicated CCTA were retrospectively included in a consecutive manner. Patients with coronary artery bypass ($n=2$) with premature ventricular contraction ($n=10$) or who could not follow the breathing instructions ($n=3$) were excluded from the study. Therefore, a total of 188 patients (101 men, 87 women; mean age, 57.9 ± 10.6 years) with a mean body mass index (BMI) of 25.2 ± 3.3 kg/m² were enrolled in this study. All local Institutional Review Boards approved this retrospective study using existing clinical data, and the need for patient informed consent was waived.

CT data acquisition

All CCTA examinations were performed in retrospective electrocardiogram gating during an end-inspiratory breath-hold using a second generation dual-source CT (Somatom Flash; Siemens Medical Systems, Erlangen, Germany). A tube voltage of 100 kV was selected for patients with BMI less than 25 kg/m²

(Group 1) and 120 kV for patients with BMI equal to or greater than 25 kg/m² (Group 2). The tube current was auto-modulated by a scanner with a tube current modulation technique (Care Dose 4D, Siemens Medical Systems). High concentration contrast (Ultravist, Iopromide, 370 mgI/mL; Bayer Health Care, Berlin, Germany) and saline were administered using a dual head power injector (Dual Shot, MedRad Inc., Indianola, PA, USA) through a 20-G needle preferably inserted into the right cubital vein.

Test bolus injection protocol

Contrast media of 10 mL at 3.5 mL/s was administrated for Group 1 and 13 mL at 4.5 mL/s for Group 2 during TB scanning. Dynamic monitoring scans were positioned at the level of the main pulmonary artery. Acquisition of the dynamic monitoring scans began 7 seconds after the initiation of contrast injection and terminated when attenuation of the descending aorta (DAo) began to decline. Sequential scans with a cycling time of 0.33 seconds and a repeated time of 1.18 seconds were acquired under end-inspiratory breath-hold. A region of interest (ROI) of 1-cm² was placed in the ascending aorta (AAo) to determine its time to peak enhancement (PT_{AAo}) using semi-automatic software (Dynamic Evaluation, Siemens Medical Systems).

Full bolus injection protocols

The remaining main bolus of contrast with the same flow rate as TB was applied. The injection duration of contrast was calculated as expected scanning time plus 8 seconds. An additional delay of 4 seconds was added to PT_{AAo} [16].

CT data analysis

Hemodynamic parameters were obtained from TB as follows: ROIs sized 75% of the corresponding artery areas in the DAo, AAo, and main pulmonary artery (MPA) were drawn, and three time-attenuation curves were obtained. The hemodynamic parameters including the peak enhancements and times to peak enhancement of the DAo (PE_{DAo} and PT_{DAo}), MPA (PE_{MPA} and PT_{MPA}), and AAo (PE_{AAo} and PT_{AAo}) were recorded. The enhancement of AAo in the full bolus scan was obtained by placing an ROI in the AAo at the same size as for the TB.

TB-based CEP

The TB-based CEP is based on a multivariable forward stepwise linear regression, and all the patients were considered in the line-time-invariant system. The aortic enhancement during CCTA was used as a dependent factor, and the parameters obtained during the TB study, as well as the group information, were considered independent variables. Formulae to predict aortic enhancement derived from the linear regression were generated, and systemic and random errors were calculated.

Statistical analysis

Continuous data are presented as mean±standard deviation. Patient demographic data, scanning, and contrast injection parameters between the two groups were calculated using Student's t-test or chi-square test where appropriate. Hemodynamic parameters obtained from the TB between the two groups were also calculated using Student's t-test. Linear regression of univariate analysis followed by forward stepwise linear regression of multivariate analysis including all covariates with $p < 0.10$ from the univariate analysis was used to investigate the influence of the hemodynamic parameters (PE_{DAo} , PT_{DAo} , PE_{MPA} , PT_{MPA} , PT_{AAo} , and PE_{AAo}) on the enhancement of AAo . To quantify the systematic and random errors of the CEP algorithm, a two-tailed paired Student's t test between the predicted and true aortic enhancements was assessed in Group 1, Group 2, and the entire patient group. Pearson's two-tailed bivariate correlation of the predicted and true aortic enhancements was performed. Analysis was performed using commercially available software (SPSS, Ver. 13.0, SPSS Inc., Chicago, IL, USA) and a two-tailed p-value < 0.05 was considered to indicate significance.

RESULTS

Patients

Patient demographic data, scanning, and contrast injection parameters are displayed in Table 1. Dose-length product and contrast medium (CM) volume in the 120 kV group were significantly higher than those in the 100 kV group ($p < 0.001$). There were no statistical differences of PT_{MPA} , PT_{AAo} , or PT_{DAo} between the two groups. In contrast, PT_{MPA} , PE_{AAo} , and PE_{DAo} in the 100 kV group were statistically higher than those in the 120 kV group (Table 2).

The TB-based algorithm of CEP

The linear regression of univariate analysis showed that the independent variables including PE_{MPA} , PT_{MPA} , PE_{AAo} , and PT_{DAo} had no influence on the attenuation of AAo . The PT_{AAo} and PE_{DAo}

Table 1. Demographic data and contrast injection parameters in the two groups

	100 kV (n=94)	120 kV (n=94)	P
Gender (male/female)	47/48	53/41	0.465
Age (years)	59.7±10.6	56.0±10.2	0.012
Height (m)	1.62±0.07	1.63±0.08	0.690
Weight (kg)	59.7±6.8	73.4±8.8	<0.001
Body mass index (kg/m ²)	22.6±1.65	27.7±2.29	<0.001
Heart rate (bpm)	66.2±11.6	64.3±9.9	0.242
Contrast flow rate (mL/s)	3.5±0	4.5±0	<0.001
Contrast dose (mL)	47.1±3.2	60.0±3.7	<0.001
Dose-length product (mGy·cm)	477±92.8	968±223.9	<0.001

obtained from the TB study, as well as the group information, had significant correlations with aortic enhancement during CCTA. The algorithm of CEP with the group information was as follows: $AAo = -67.897 + 1.506 \times PE_{DAo} + 15.413 \times PT_{AAo} - 18.098 \times \text{Group}$ ($r = 0.792$, $p < 0.001$; Group=1 for Group 1 and Group=2 for Group 2). The algorithm of CEP without the group information is as follows: $AAo = -125.627 + 1.619 \times PE_{DAo} + 16.236 \times PT_{AAo}$ ($r = 0.782$, $p < 0.001$).

The impact of group information on the CEP algorithm

For the entire patient cohort, the two-tailed paired Student's t-test revealed no significant differences (all $p > 0.9$) in true aortic enhancement or predicted enhancement from the CEP algorithm with group information, as well as without group information, as illustrated in Fig. 1. The two predicted enhancements had a high positive correlation ($r = 0.981$) without a significant difference in the mean values [387.4 ± 44.3 Hounsfield unit (HU) vs. 387.4 ± 43.5 HU, $p = 0.952$].

The CEP algorithm without group information presented a minor systemic underestimation in Group 1 (400 ± 44 HU vs. 408 ± 54 HU, $p = 0.031$) and an overestimation in Group 2 (375 ± 39 HU vs. 367 ± 49 HU, $p = 0.022$). The CEP algorithm with group information presented no significant systemic misestimation either in Group 1 or 2, as illustrated in the Bland-Altman plot (Figs. 2 and 3).

The average uncertainty in the predicted enhancement by the CEP algorithm without group information was -8 HU (2%) for the 100-kV group and 8 HU for the 120-kV group. The details of the systemic and random errors of the two CEP algorithms are listed in Table 3.

DISCUSSION

In this study, 188 patients with two different TB protocols (Group 1: $n = 94$; Group 2: $n = 94$) were analyzed. The PT_{AAo} and the PE_{DAo} obtained from the TB study had a high positive correlation with enhancement of AAo during CCTA. The multivariate stepwise linear regression analysis showed that different tube voltages and contrast flow rates had statically significant, but clin-

Table 2. Hemodynamic parameters from the test bolus in the two groups

	100 kV (n=94)	120 kV (n=94)	p
PT_{MPA} (s)	9.2±1.2	9.1±1.1	0.460
PT_{AAo} (s)	16.8±2.4	16.7±2.0	0.519
PT_{DAo} (s)	18.3±2.7	17.9±2.2	0.293
PE_{MPA} (HU)	251.1±60.0	224.3±46.2	0.001
PE_{AAo} (HU)	168.4±31.4	157.2±26.2	0.009
PE_{DAo} (HU)	156.3±29.3	142.0±24.6	<0.001

PT: time to peak enhancement, PE: peak enhancement, MPA: main pulmonary artery, AAo: ascending aorta, DAo: descending aorta

Fig. 1. Bland-Altman plots for the contrast enhancement prediction algorithm with group information (A) and without group information (C) in comparison with the true enhancement of the AAo. Scattergrams of the contrast enhancement prediction algorithm with group information (B) and without group information (D) against the true enhancement of the AAo. AAo: ascending aorta.

ical negligible impacts on predicting aortic enhancement.

Individualized medicine is gaining importance in the current health care system and adapting the contrast delivery protocols to the right dose and optimal scanning timing for each individual patient is very important for different CT scanning protocols. In clinical practice, TB and bolus tracking techniques provide patient-specific scan timing for a given injection protocol in every patient. Compared with the TB technique, the major advantage of bolus tracking is that no additional contrast agent is necessary. This helps reduce radiation exposure and procedure time. However, the bolus tracking technique also has some shortcomings. The same predefined post-trigger delay (PTD), which is usually used in all patients to allow for a simpler clinical workflow, may not be ideal. For example, patient-specific cardiovascular parameters such as blood circulation time and cardiac output may differ between patients, leading to different optimal

PTDs for the same injection and acquisition protocol. Despite these shortcomings, the use of a TB provides the advantage that the patients undergo a test procedure to practice breath-holding and to experience contrast infusion, and that hemodynamic parameters could be obtained before the real scan.

A previous study demonstrated that patient-related factors including body weight and heart rate had a negative correlation with coronary arterial enhancement during dual-source CT coronary angiography [7] since blood volume and cardiac output were partially determined by body weight and heart rate [8,17,18]. A clinical study [19] observed that the correlation between aortic peak enhancement and cardiac output was superior to the correlation with body weight. Cardiac output is closely related to the time-attenuation curve obtained from a TB injection [10,20]. Zhu et al. [10] held the view that cardiac output was inversely correlated to peak enhancement in the

Fig. 2. Bland-Altman plots for the contrast enhancement prediction algorithm with group information (A) and without group information (B) in comparison with the true enhancement of the ascending aorta in Group 1 (tube voltage of 100 kV and contrast flow rate of 3.5 mL/s).

Fig. 3. Bland-Altman plots for contrast enhancement prediction algorithm with group information (A) and without group information (B) in comparison with the true enhancement of the ascending aorta in Group 2 (tube voltage of 120 kV and contrast flow rate of 4.5 mL/s).

right ventricle and the time to peak enhancement in the left ventricle. They also recommend TB-based CM injection protocols for tube voltages of 100 kV and 120 kV to achieve consistent arterial enhancement. These proposed TB-based injection protocols achieved a desired preset and stable aortic enhancement during CCTA [16]. CM of 20 mL at 4 mL/s was administered during the TB in the study of Zhu et al. [16], which differed from the contrast flow rate and injection duration in this study.

Considering a patient as a linear time-invariant system, Korpmaal et al. [11] proposed another new TB-based CEP algorithm during CCTA, which incorporated population-averaged blood circulation characteristics. Their TB-based CEP algorithm had no systematic errors in the timing (-0.2 ± 2.0 seconds) and amplitude ($0.3 \pm 15.6\%$) of the predicted enhancements and was robust against coarser time-samples, incomplete TB scans, and different tube voltages. This CEP algorithm must be implanted in special software, and a population-averaged

Table 3. True and predicted ascending aortic enhancements without group information

	100 kV (n=94)	120 kV (n=94)	All-patients (n=188)
ENH _{true} (HU)	408.9 $\pm$ 54.6	366.0 $\pm$ 48.0	387.4 $\pm$ 56.6
ENH _{pred} (HU)	400.8 $\pm$ 44.4	374.2 $\pm$ 38.4	387.4 $\pm$ 43.5
Systemic error (HU)	-8.2 $\pm$ 34.8	8.1 $\pm$ 32.7	-0.0 $\pm$ 34.7

ENH_{true}: true enhancement, ENH_{pred}: predicted enhancement. Systemic error is calculated as ENH_{pred} minus ENH_{true}.

arterial impulse response of the patient (arterial input functions) should be inferred previously from other enhanced CT images [11], which makes it difficult to use in daily clinical practice. Our proposed TB-based CEP algorithm only requires the PE_{DAo} and PT_{AAo}, and yields simple formulae to predict arterial enhancement during CCTA. This TB-based CEP algorithm considering tube voltages and contrast flow rates demonstrated no systematic errors in predicting ascending aortic enhancement. This

proposed algorithm is slightly influenced by TB study protocols, but 8 HU mis-estimations in coronary enhancement are negligible during CCTA. We did not find that age or BMI had an influence on this TB-based CEP algorithm, which is consistent with the findings of TB-based CEP algorithms proposed by Zhu et al. [10] and Korporaal et al. [11]. This could be explained by the fact that PE_{DAo} and PT_{AAo} , which are partially determined by patient-related factors including age, body weight, BMI, and heart rate, had been accounted for in the CEP algorithms.

There were several limitations in this study. First, the random errors between the predictions and true enhancements were considered to be prediction algorithm errors. However, they reflect cardiovascular variations in the patient between the TB measurement and the computed tomographic angiography (CTA) scan and demonstrate that patients do not constantly behave as linear time-invariant systems. Second, an additional study to verify the performance of an individualized contrast injection protocol based on the recommended formulae must be performed. Finally, our study is retrospective and only included a relatively small number of patients.

In conclusion, the CEP algorithm on the basis of stepwise linear regression analysis demonstrates that the PE_{DAo} and PT_{AAo} obtained from the TB study correlate well to the aortic enhancement during CTA scanning. The tube voltages and contrast flow rates during TB scanning have a statistically significant, but clinically negligible impact on the CEP algorithm.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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