Personalized administration of contrast medium with high delivery rate in low tube voltage coronary computed tomography angiography

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Background: High delivery rate is an important factor in optimizing contrast medium administration in coronary computed tomography angiography (CCTA). A personalized contrast volume calculation algorithm incorporating high iodine delivery rate (IDR) can reduce total iodine dose (TID) and produce optimal vessel contrast enhancement (VCE) in low tube voltage CCTA. In this study, we developed and validated an algorithm for calculating the volume of contrast medium delivered at a high rate for patients undergoing retrospectively ECG-gated CCTA with low tube voltage protocol.

Methods: The algorithm for an IDR of 2.22 gIs^{-1} was developed based on the relationship between VCE and contrast volume in 141 patients; test bolus parameters and characteristics in 75 patients; and, tube voltage in a phantom study. The algorithm was retrospectively tested in 45 patients who underwent retrospectively ECG-gated CCTA with a 100 kVp protocol. Image quality, TID and radiation dose exposure were compared with those produced using the 120 kVp and routine contrast protocols.

Results: Age, sex, body surface area (BSA) and peak contrast enhancement (PCE) were significant predictors for VCE (P<0.05). A strong linear correlation was observed between VCE and contrast volume (r=0.97, P<0.05). The 100-to-120 kVp contrast enhancement conversion factor (E_c) was calculated at 0.81. Optimal VCE (250 to 450 HU) and diagnostic image quality were obtained with significant reductions in TID (32.1%) and radiation dose (38.5%) when using 100 kVp and personalized contrast volume calculation algorithm compared with 120 kVp and routine contrast protocols (P<0.05).

Conclusions: The proposed algorithm could significantly reduce TID and radiation exposure while maintaining optimal VCE and image quality in CCTA with 100 kVp protocol.

Keywords: Coronary computed tomography angiography (CCTA); contrast medium; image quality; radiation dose; total iodine dose (TID)

Introduction

The application of lower tube voltage (i.e., 100 kVp) protocol in coronary computed tomography angiography (CCTA) has been increasing over the past decade (1,2). It is mainly due to the benefit of radiation dose and total iodine dose (TID) reductions at lower tube voltage compared to the standard 120 kVp. Known as the "double low dose
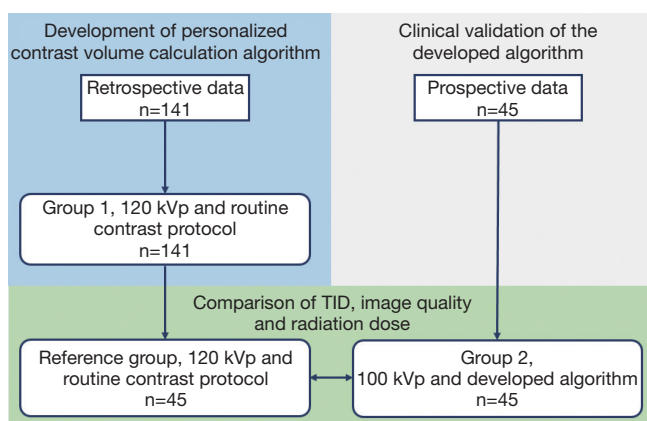
Figure 1 Flow diagram of patient assignment for development of a personalized contrast volume calculation algorithm, its clinical validation and retrospective comparison of TID, image quality and radiation dose. TID, total iodine dose.

strategy", it ensures safety as there will be less radiation exposure, in addition to reducing the risk of nephrotoxicity caused by the contrast medium (3,4).

When a lower tube voltage is applied, the mean photon energy (approximately half of the peak tube voltage) of the CCTA X-ray beam is reduced until it becomes close to the K-edge of iodine (33.2 keV). Photons with lower energies are more likely to be absorbed because of the K-edge of iodine, resulting in an increase of photoelectric effects. As the CT number of iodine is higher, a good vessel contrast enhancement (VCE) can be achieved while administering a lower TID to patients undergoing CCTA with low tube voltage protocol (5).

Initially, many studies have attempted to reduce TID by adjusting the contrast concentration or volume, and they mostly use a low iodine delivery rate (IDR) which was between 1.08 and 1.70 gIs^{-1} (6-12). IDR represents the rate at which iodine is delivered into the arterial system and is the main determinant of VCE in CCTA. At a given administered TID, the higher the iodine concentration and the injection rate, the greater the IDR and the VCE (13,14). Thus, a high delivery rate becomes an important factor when using low TID to optimize contrast medium administration (14-16).

Although IDR of 1.5 to 2.0 gIs^{-1} is usually recommended in CCTA (13,17,18), higher rate of more than 2.0 gIs^{-1} has been proven to be feasible in clinical practice (13,17-22). A personalized contrast volume calculation algorithm incorporating high IDR may accurately reduce TID and

produce optimal VCE in low tube voltage CCTA. To the best of our knowledge, no study has assessed the potential of using a "double low dose strategy" with a high IDR of more than 2.0 gIs^{-1} in terms of TID reduction, image quality and radiation exposure.

This study has two purposes: (I) development of a personalized contrast volume calculation algorithm using a high delivery rate and, (II) compare the developed algorithm in low tube voltage CCTA with the standard protocol ECG-gated CCTA scans in terms of reductions in iodine and radiation doses and assessment of image quality.

Methods

Patient and data sources

Data from 141 patients who underwent CCTA at the University of Malaya Medical Centre between January 2014 and December 2016 were retrieved to develop the personalized contrast volume calculation algorithm (thereafter referred to as "Group 1"). Subsequently, 45 patients with body mass index (BMI) of ≤30 kgm^{-2} who were scheduled to undergo CCTA at the same hospital from January 2017 to October 2017 were prospectively enrolled for validation of the algorithm (thereafter referred to as "Group 2"). This validation study was approved by the Medical Ethics Committee of the University of Malaya Medical Centre (Protocol No. 989.35) and informed consent was obtained from these patients. Lastly, another 45 patients with similar BMI to Group 2 subjects (thereafter known as "Reference Group") were chosen from Group 1 to compare their TID, image quality and radiation dose. *Figure 1* shows the assignment of subjects in the prospective and retrospective parts of this study.

All patients were referred for CCTA due to suspected coronary artery disease. Oral Lorazepam (1 mg, Lorans 1, Medochemie Ltd, Cyprus) was selectively given to patients with anxiety and for patients with systolic blood pressure of more than 90 mmHg, beta blocker, Metoprolol Tartrate (100–150 mg, Betaloc, AstraZeneca Pty Ltd., Australia) was given 60 minutes before the scanning to achieve a low and regular heart rate (less than 65 bpm). For asthmatic patients, an oral dose of Verapamil Hydrochloride (80–120 mg, Akilen 40, Medochemie Ltd., Malta) was given as an alternative to Metoprolol Tartrate. An 18 G intravenous cannula was inserted at the median cubital vein for contrast medium administration. Sublingual nitroglycerin (0.5 mg, Myonit Insta, Troikaa Pharmaceuticals Ltd., India) was
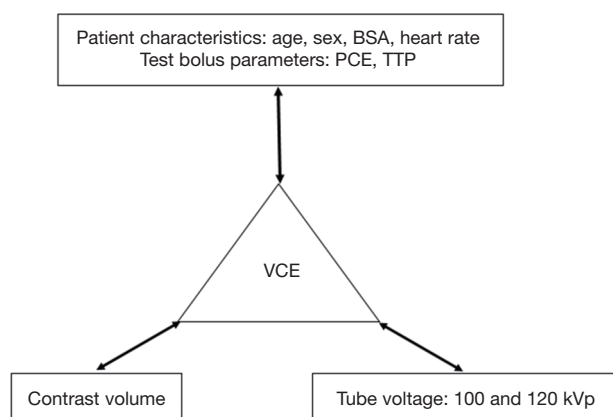
Figure 2 The development of personalized contrast volume calculation algorithm. BSA, body surface area; PCE, peak contrast enhancement; TTP, time-to-peak.

given, 5 minutes before data acquisition, to dilate the coronary arteries. Patient characteristics, such as sex, age, body weight and heart rate, were recorded.

CCTA image acquisition

Calcium score (non-contrast CT) was performed with sequential scans and the following scanning parameters: slice acquisition, 6×3.0 mm; tube potential, 120 kVp; reference mAs, 74 mAs; reconstructed slice thickness 3.0 mm.

All CCTA scans were performed with retrospectively ECG-gated protocol, using a 2×32 detector row dual-source CT scanner (Siemens Somatom Definition DS, Siemens Healthcare, Erlangen, Germany). A tube potential of 120 kVp and reference tube current-time product of 320 mAs were used for Group 1 and the Reference Group, whereas it was 100 kVp and 370 mAs for Group 2. Other scanning parameters were as follows: slice acquisition at 2×32×0.6 mm (19.2 mm z-axis coverage); full tube current for 20% to 75% of R-R interval; rotation time of 330 ms; temporal resolution at approximately 82.5 ms; and, reconstructed slice thickness of 0.6 mm. The scan length was set from the carina of trachea to the apex of the heart.

Contrast medium injection protocol

The contrast medium (Ultravist 370, Bayer HealthCare Pharmaceuticals, Berlin, Germany) was injected into the median cubital vein using a CT injection system (Medrad Stellant CT, Bayer HealthCare Pharmaceuticals, Berlin,

Germany). An injection rate of 6 mLs^{-1} was used to achieve high IDR of 2.22 gIs^{-1} for both test bolus and full bolus during the CCTA scan. A triphasic protocol recommended by the Society of Cardiovascular Computed Tomography (SCCT) was applied in the full bolus—an initial undiluted contrast bolus (first bolus), followed by a 20:80 mixture of contrast medium (10 mL) and saline (40 mL) before being completed with a 50 mL saline flush (23).

For Group 1 and the Reference Group, the contrast volume of the first bolus (50, 55 or 60 mL) was adjusted to a product of the estimated scan time and injection rate (thereafter referred to as "routine contrast protocol"). In this group, 75 patients (53.2%) received 60 mL, 24 patients (17.0%) received 50 mL and 42 patients (29.8%) received 55 mL of the first bolus. For Group 2, the contrast volume of the first bolus was calculated using the developed algorithm.

Development of personalized contrast volume calculation algorithm

The algorithm development consisted of three steps: establishing the relationship between VCE and contrast volume; establishing the relationship between VCE, patient characteristics and test bolus parameters; and, developing a 100-to-120 kVp contrast enhancement conversion factor (E_c). Details are summarized in *Figure 2*.

The VCE of scan images was calculated as the mean CT attenuation value (measured in HU). Using the RadiAnt DICOM Viewer software (Medixant, Poznan, Poland), a circular region of interest (ROI) was placed in the left main (LM) coronary artery and proximal right coronary artery (RCA). All ROIs were made as large as possible according to vessel size, but vessel walls, calcifications or metallic components were avoided to prevent partial volume effects.

Data from Group 1 was used to establish the relationship between VCE and contrast volume. Four contrast volumes were included, namely 0, 50, 55 and 60 mL. The VCE corresponding to 0 mL of contrast volume was measured in calcium score images, acquired prior to CCTA scan in every patient.

In establishing the relationship between VCE, patient characteristics and test bolus parameters, data from 75 patients that received 60 mL of the first bolus in Group 1 were used (thereafter referred as "Group 1a"). Mean VCE was compared with age, sex, body surface area (BSA), heart rate, and PCE and time-to-peak (TTP) of the test bolus.

The BSA was calculated from body weight, based on the equation derived by Livingston & Lee (24) in Eq. [1].

$$\text{BSA} = 0.1173 \times \text{body weight}^{0.6466} \quad [1]$$

Finally, a phantom study was conducted to construct the iodine attenuation curves for 100 and 120 kVp (Appendix I). The relative difference in the contrast enhancement between the two different tube voltages was used to develop the E_c.

Prospective clinical validation

The developed algorithm was applied to Group 2 with a targeted VCE of 350HU. The mean CT attenuation value was measured in the LM and proximal RCA arteries using the acquired axial images (thereafter referred to as "measured VCE").

The assessment of quantitative and qualitative image quality and radiation dose was performed in Group 2 and the Reference Group. The quantitative image analysis, including image noise, signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), and figure of merit (FOM) was performed on the axial images of both groups.

A circular ROI was placed in the ascending aorta (AA), RCA, LM, left anterior descending (LAD) and left circumflex (LCx) arteries. For measurements in AA, three ROIs were placed in the AA at the level of LM ostium and one slice above and below this level. For RCA, LM and LAD, three ROIs were placed at the proximal, middle and distal segments of the arteries. For LCx, only two ROIs were placed at the proximal and distal segments of the artery.

VCE was defined as the mean CT attenuation value (measured in HU) in each artery. The image noise was defined as the mean standard deviation of CT attenuation value for the ROIs placed in the AA. The SNR was calculated by dividing the VCE by the mean image noise measured in AA {Eq. [2]}. The CNR was calculated by subtracting the mean CT attenuation value (HU) measured in the chest wall muscle (HU_{cw}) from the VCE, and dividing this difference by the mean image noise measured in AA {Eq. [3]}.

FOM was defined as the ratio of CNR squared to effective dose (H_E) {Eq. [4]}. FOM reflects the relationship between image contrast, noise, and amount of radiation exposure.

$$\text{SNR} = \frac{\text{VCE}}{\text{Image noise}} \quad [2]$$

$$\text{CNR} = \frac{\text{VCE} - \text{HUcw}}{\text{Image noise}} \quad [3]$$

$$\text{FOM} = \frac{\text{CNR}^2}{H_E} \quad [4]$$

Qualitative image analysis was performed by two cardiovascular radiologists (Raja Aman RR and Mohamed Sani F, each with more than 10 years of experience in cardiac CT image reporting) using a post-processing and evaluation software (Centricity RIS-i Version 5, GE Healthcare, Chicago, USA). Using axial, multiplanar reformation (MPR) and thin-slab maximum intensity projection (MIP) images, the images were interpreted individually and in a random order. The evaluators were allowed to freely adjust the window settings. The VCE in the major coronary arteries (RCA, LM, LAD and LCx) were graded using a 5-point scale as follows: 1= poor opacification, insufficient for diagnosis; 2= suboptimal opacification, low diagnostic confidence; 3= acceptable opacification, sufficient for diagnosis; 4= good opacification of proximal and distal segments; and 5= excellent opacification of proximal and distal segments (*Figure 3*).

For radiation dose assessment, the H_E of each CCTA scan was estimated by multiplying the air-kerma length product (P_{KL}) to a P_{KL}-to-H_E conversion factor (E_{KL}) (25,26). The E_{KL} for chest, 0.014 mSv.mGy^{-1}cm^{-1} as recommended by the European Commission (EC) and Public Health England (PHE) (formerly NRPB) was used in this study (27,28).

Statistical analysis

Data analyses were performed using a statistical software (IBM SPSS Version 23, IBM Corporation, Armonk, USA). The Mann-Whitney U Test was used to compare patient characteristics (age, body weight, BMI, BSA, heart rate, PCE and TTP at test bolus, and measured VCE) between Group 2 and the Reference Group. Linear regression was used to determine the correlation between VCE and contrast volume, as well as contrast enhancement and iodine concentration during construction of the iodine attenuation curve. Multiple linear regression was used to correlate VCE with patient characteristics and test bolus parameters. Finally, the TID, quantitative and qualitative image quality scores, radiation dose of Group 2 were compared with the Reference Group using the Mann-Whitney U Test. For qualitative image quality analysis, the Wilcoxon Signed-
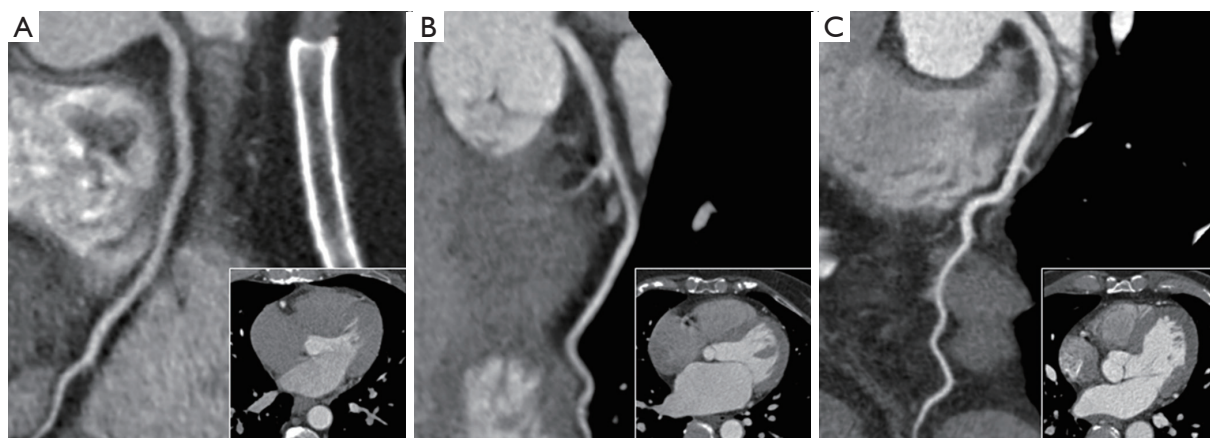
Figure 3 Curved MPR images of LM coronary artery to LAD artery and their corresponding axial images (inset). The images represent VCE scores of (A) Grade 3—acceptable opacification, sufficient for diagnosis; (B) Grade 4—good opacification of proximal and distal segments; and, (C) Grade 5—excellent opacification of proximal and distal segments. All images were displayed at a same window width of 800 and level of 300. MPR, multiplanar reformation; LM, left main; LAD, left anterior descending; VCE, vessel contrast enhancement.

Rank Test was used to assess interobserver variabilities in VCE scoring between the two groups. A P value less than 0.05 was considered statistically significant.

Results

Patient characteristics, test bolus and scanning parameters for Groups 1a, 2 and the Reference Group are shown in *Table 1*. The PCE at test bolus was the only significantly different parameter (P=0.017).

Development of personalized contrast volume calculation algorithm

The mean VCE for contrast volumes of 0, 50, 55 and 60 mL were 58.5, 450.1, 471.4 and 494.4 HU, respectively, as derived from *Figure 4*. These four points showed a linear correlation (r=0.97, P<0.05). The relationship between VCE, patient characteristics and test bolus parameters are shown in *Tables 2,3*. In *Table 2*, BSA showed the strongest inverse correlation with VCE (r=−0.61, P<0.05), whereas, age (r=0.52, P<0.05) and PCE at test bolus (r=0.60, P<0.05) showed significant positive correlation.

Multiple linear regression analysis in *Table 3* found that the strongest predictor for VCE is BSA (correlation coefficient −157.36, P<0.05), followed by sex (correlation coefficient 37.60, P<0.05), age (correlation coefficient 2.15, P<0.05) and PCE at test bolus (correlation coefficient 1.22, P<0.05). A linear relationship between iodine concentration

and contrast enhancement was observed for 100 and 120 kVp (*Figure 5*). The contrast enhancement at 100 kVp was higher by 19.6% compared to 120 kVp. The calculated E_c was (29.089/35.862)=0.81.

In multiple linear regression analysis, the relationship between patient characteristics and test bolus parameters with VCE could be described in Eq. [5]. Under sex parameter, male patients were labelled as "0" while females were labelled as "1".

$$VCE = (2.15 \times Age) + (37.60 \times Sex) - (157.36 \times BSA) + [1.22 \times PCE\ (120)] + 512.19 \quad [5]$$

As PCE(120) in Eq. [5] was meant for a 120 kVp tube voltage, it was necessary to convert the PCE at 100 kVp [PCE(100)] by multiplying its value with the calculated E_c derived from the iodine attenuation curve as shown in Eq. [6].

$$PCE\ (120) = PCE\ (100) \times 0.81 \quad [6]$$

The correlation between VCE and contrast volume is positively linear as described in Eq. [7],

$$VCE = m \times contrast\ volume + VCE^0 \quad [7]$$

where m is the constant and VCE_0 is the Y-intercept when contrast medium has not been administered.

The VCE in Eq. [7] was estimated using patient characteristics and test bolus parameters derived from Eq. [5]. Then, m in Eq. [7] was determined by filling in the VCE_0 measured from calcium scoring images, the contrast volume of 60 mL and the estimated VCE from

Table 1 Patient characteristics, test bolus parameters, scanning parameters and measured VCE for Group 1a, 2 and the Reference Group

Parameters	Group 1a	Group 2	Reference Group	P value (Group 2 vs. Reference Group)
Patient (n)	75	45	45	
Male/female ratio	34:41	19:26	22:23	
Age (years)	56.5±10.6	57.7±14.4	59.6±12.2	0.611
Body weight (kg)	67.2±9.5	64.7±11.2	66.1±9.0	0.684
BMI (kgm^{-2})	25.9±4.1	24.9±3.3	25.0±2.8	0.824
BSA (m^2)	1.8±0.2	1.7±0.2	1.8±0.2	0.432
Heart rate (bpm)	63.9±7.2	67.7±9.4	65.8±4.0	0.373
PCE at test bolus (HU)	100.4±28.5	114.8±44.9	96.6±29.5	0.017*
TTP at test bolus (s)	16.2±2.5	15.6±3.2	15.0±1.8	0.453
Tube voltage (kVp)	120	100	120	
Reference mAs (mAs)	320	370	320	

*, $P<0.05$. BMI, body mass index; BSA, body surface area; mAs, tube current-time product; PCE, peak contrast enhancement; TTP, time-to-peak; VCE, vessel contrast enhancement.
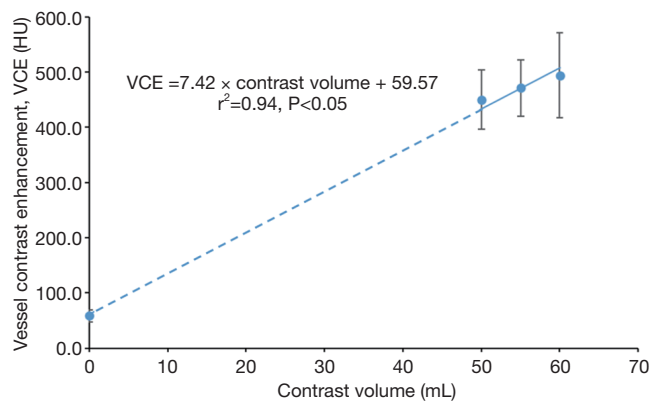

Figure 4 The relationship between VCE and contrast volume. VCE, vessel contrast enhancement.

Eq. [5]. Once m was determined, the algorithm was used to calculate the contrast volume to achieve a VCE of 350 HU at 100 kVp {Eq. [8]}. The value of 280 HU was obtained by multiplying 350 HU with the calculated E_c.

$$\text{Contrast volume} = \frac{280\,\text{HU} - \text{VCE}_0}{m} \qquad [8]$$

Prospective clinical validation

Table 4 shows the comparison of measured VCE, TID, radiation dose, quantitative and qualitative image analysis

Table 2 Relationship between VCE, patient characteristics and test bolus parameters

Parameters	r	P value
Age (years)	0.52	0.0001*
BSA (m^2)	−0.61	0.0001*
Heart rate (bpm)	0.60	0.616
PCE at test bolus (HU)	0.60	0.0001*
TTP at test bolus (s)	0.17	0.148

*, $P<0.05$. BSA, body surface area; PCE, peak contrast enhancement; TTP, time-to-peak; VCE, vessel contrast enhancement.

for Group 2 and the Reference Group. All scans for Group 2 were successfully performed with a mean measured VCE of 393.5±33.0 HU (314.5 to 444.0 HU). The measured VCE was significantly lower (P=0.0001) in Group 2 compared with the Reference Group.

When TID of Group 2 was compared with the Reference Group, which used a tube voltage of 120 kVp and the routine contrast protocol, a significant reduction (P=0.0001) was achieved. The H_E was significantly lower (P=0.0001) in Group 2 compared to the Reference Group. By using the 100 kVp, the radiation dose was reduced by 38.5%.

For quantitative image analysis, comparable image noise and FOM were observed in Group 2 and the Reference

Table 3 Multiple linear regression analysis of patient characteristics and test bolus parameters associated with VCE

Variables	Correlation	Coefficient standard error	P value	95% confidence interval
Age (years)	2.15	0.49	0.0001*	1.33 to 2.97
Sex	37.60	10.29	0.0001*	20.45 to 54.75
BSA (m²)	−157.36	33.86	0.0001*	−213.80 to −100.95
PCE at test bolus (HU)	1.22	0.18	0.0001*	0.92 to 1.53

*, $P<0.05$; BSA, body surface area; PCE, peak contrast enhancement; VCE, vessel contrast enhancement.

Group. The SNR and CNR in Group 2 were significantly lower ($P<0.05$) compared to the Reference Group. Image quality was considered sufficient for diagnosis by the evaluators in all examinations in Group 2 and the Reference Group. In Group 2, the VCE was graded as acceptable to excellent (3.5 to 5.0) for LM and LCx and good to excellent (4.0 to 5.0) for RCA and LAD. In Reference group, the VCE was graded as acceptable to excellent (3.5 to 5.0) for LCx and good to excellent (4.0 to 5.0) for RCA, LM and LAD. There was no significant difference in VCE scores in the major coronary arteries between both groups. The Wilcoxon Signed Rank Test demonstrated no significant interobserver variabilities in VCE scores made by the two evaluators for both groups.

Discussion

CCTA with lower tube voltage is a widely used protocol to reduce the radiation dose. However, it also drastically increased the VCE. Although there was no consensus on the upper limit of VCE, an optimal range should be between 250 and 450 HU based on the detection of coronary stenosis, quantitative analysis of atherosclerotic plaque and diagnostic performance of CCTA (23,29-34). The developed algorithm in this study used 350 HU as a targeted VCE, which was within this optimal range, while achieving TID reduction with high IDR.

There were several advantages in using the personalized contrast volume calculation algorithm. First, it reduced the risk of nephropathy induced by the contrast medium (35). Second, it helped to keep the VCE within optimal range for quantitative analysis of coronary artery disease and plaques (34). Third, it helped to reduce the radiation exposure to the contrast-enhanced organs (36). Several studies have reported that using contrast medium during a CT examination would increase the organ dose by 17% to 74% (36-38). The increase of X-ray photon absorption
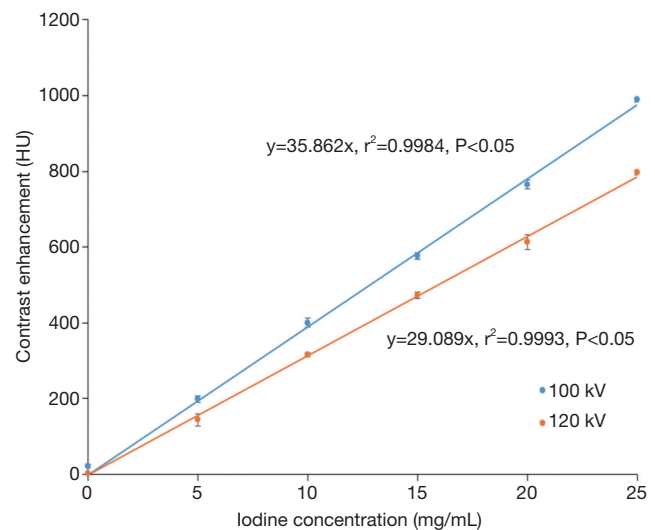

Figure 5 Iodine attenuation curves for tube voltages of 100 and 120 kVp.

in contrast-enhanced organs might lead to unnecessary biological effects (38). In an *in vitro* study conducted by Grudzenski *et al.* (39), the use of iodinated contrast medium during CT examination has been reported to cause 30% increase in DNA double-strand breaks in peripheral blood lymphocytes, compared to the unenhanced CT examination. This finding was supported by another *in vivo* study conducted by Wang *et al.* (40) which reported a 38% increase in DNA double-strand breaks in the peripheral blood lymphocytes during contrast-enhanced CT. Furthermore, the injection of iodinated contrast medium before a CT examination had been observed to cause more DNA damage (90%) compared with injection after examination (40).

In analyzing the relationship between VCE and contrast volume, although no data were available for VCE with contrast volume of between 10 and 40 mL, a linear fit was chosen to correlate the VCE at 0, 50, 55 and 60 mL. The

Table 4 Comparison of measured VCE, TID, radiation dose, quantitative and qualitative image analysis

Parameters	Group 2	Reference Group	P value
Measured VCE (HU)	393.5±33.0	465.0±50.8	0.0001*
TID (g)	19.5±2.7	28.7±1.4	0.0001*
H_E (mSv)	4.8±0.8	7.8±2.0	0.0001*
Quantitative image quality analysis			
Image noise (HU)	26.0±4.5	24.6±3.3	0.070
SNR			
RCA	15.1±2.9	19.1±4.0	0.0001*
LM	15.9±3.4	19.0±3.3	0.0001*
LAD	15.9±3.0	18.1±3.5	0.001*
LCx	15.6±2.9	18.2±3.8	0.001*
CNR			
RCA	12.1±2.6	16.4±3.7	0.0001*
LM	12.9±2.6	16.4±3.0	0.0001*
LAD	12.7±2.4	15.4±3.2	0.0001*
LCx	12.6±2.6	15.6±3.5	0.0001*
FOM (mSv^{-1})			
RCA	33.1±17.9	38.8±19.8	0.201
LM	37.4±16.9	36.9±14.9	0.888
LAD	36.0±15.9	33.2±14.9	0.485
LCx	35.8±15.6	33.9±15.6	0.586
Qualitative image quality analysis			
VCE			
RCA	4.8 (4.0–5.0)	4.9 (4.5–5.0)	0.130
LM	4.7 (3.5–5.0)	4.8 (4.0–5.0)	0.186
LAD	4.7 (4.0–5.0)	4.9 (4.0–5.0)	0.169
LCx	4.8 (3.5–5.0)	4.9 (3.5–5.0)	0.191

*, P<0.05. CNR, contrast-to-noise ratio; FOM, figure of merit; H_E, effective dose; SNR, signal-to-noise ratio; TID, total iodine dose; VCE, vessel contrast enhancement; LAD, left anterior descending; LCx, left circumflex; LM, left main; RCA, right coronary artery.

linear relationship between VCE and contrast volume has been reported by Burbank *et al.* (41) by doubling the contrast volume, the peak iodine concentration in the blood and VCE are doubled.

From the multiple linear regression analysis between VCE, patient characteristics and test bolus parameters, the best predictor for VCE was BSA, which were negatively correlated with each other. A similar result was reported by Komatsu *et al.* (34), and the inverse relationship between BSA and VCE had also been reported (15,42,43). Using a BSA-adapted contrast medium protocol, Pazhenkottil *et al.* (43) had successfully reduced TID by 11% compared with the fixed-contrast medium protocol.

Two other patient characteristics, age and sex were also significant predictors. The association between VCE and age could be explained by the reduction in cardiac output

among older patients, which caused a higher PCE (44-46). The inverse relationship between PCE and cardiac output (L.min^{-1}) and cardiac index (L.min^{-1}m^{-2}) had been demonstrated by Sakai *et al.* (47). In their study, every reduction in cardiac index led to a 38% increase in PCE. There was a difference in blood volume between men and women, therefore, a slight difference in PCE and TTP could be expected in different sexes. For a given BMI, men had 5% to 10% more blood compared with women. Thus, a higher VCE would be observed in women when they were given the same TID per body weight as men (48).

The PCE at test bolus was found to be a significant predictor for VCE. Previous studies also concurred with this result (49-51). Every increment of 1.0 HU in PCE at test bolus was found to lead to an increment of 1.2 HU in the VCE of our study. This is comparable to the results by Komatsu *et al.* (34), who observed an increment of 1.3 HU in VCE with every increment of 1.0 HU in PCE at test bolus.

As TTP increases with the decrease in cardiac output, TTP was reported to be directly correlated with PCE in several studies (34,47). However, there was no significant relationship found between TTP at test bolus and VCE. This could be due to the less variation of cardiac output in Group 1a, that can be indicated by the narrow range of TTP at test bolus (12 to 22 s), compared to the wider range between 15 to 36 s in the other study (47). From the iodine attenuation curves, there was an increase of contrast enhancement by 19.6% at a tube voltage of 100 kVp compared with 120 kVp, and this was comparable with those observed by Higashigaito *et al.* (52).

When applying the personalized contrast volume calculation algorithm in the Group 2 patients, the resulting images had significantly lower VCE than the Reference Group, but the quality was still acceptable as it fell within the optimal VCE range. This study achieved a higher TID reduction of 32.1% when using the personalized contrast volume calculation algorithm compared with other studies, which reported a reduction of between 14.9% and 27.3% (6,7,10,12). Those studies also used a tube voltage of 100 kVp and tried to maintain a similar VCE value as 120 kVp, but their IDR was lower, resulting in a TID of 18.9 to 20.9 g (6,7,10,12).

Although contrast concentration had been reported as an important factor affecting PCE, a higher concentration of iodine contrast medium would not necessarily produce a better image. Mihl *et al.* (53) observed that IDR, and not contrast concentration, was the determinant factor in

VCE. Thus, unlike the previous studies, a higher IDR of 2.22 gIs^{-1} was applied in our study, which was achieved with an injection rate of 6 mLs^{-1} and contrast concentration of 370 mgmL^{-1}. As PCE increases proportionally with IDR, a higher IDR results in more TID reduction (54,55).

A personalized contrast protocol based on automatic tube voltage selection was developed in a recent study conducted by Eijsvoogel *et al.* (19). The authors have focused on only one patient factor, which is the calculated blood volume to tailor the contrast medium administration to individual patient (19). While in our study, we have presented a personalized contrast volume calculation algorithm based on parameters which are closely associated with the patient's cardiovascular and contrast pharmacokinetic response during CCTA scanning, including the patient's age, sex, BSA and PCE at test bolus.

The radiation dose was lowered by 38.5% in the 100 kVp protocol. This finding was consistent with the findings from the other studies, where the H$_E$ was lowered by 30% to 53% in 100 kVp compared with 120 kVp (10,56-58).

Despite lower SNR and CNR, the images produced by combining the developed algorithm and 100 kVp protocol were rated as sufficient for diagnosis by the evaluators. As the image noise increases at lower tube voltage, a higher reference mAs (370 mAs) was used at 100 kVp and successfully produced similar image noise compared to routine protocol. The comparable FOM in Group 2 and the Reference Group indicated that the dose efficiency achieved by combining the developed algorithm and 100 kVp protocol was similar to the routine protocol.

This study had several limitations. First, it did not evaluate the diagnostic accuracy of the developed algorithm and 100 kVp protocol in the detection of coronary stenosis as not all patients had undergone invasive coronary angiography for confirmation of the stenosis. Since there would be changes in contrast protocol and tube voltage, the diagnostic accuracy might be affected. Second, the comparison of TID, image quality and radiation dose were performed on two groups of patients rather than scanning the same patients with two protocols. However, the effects of comparing different groups of patients were minimized by matching their features (such as BMI) as close as possible. We deemed it unethical to repeatedly expose a single group of patients to CT radiation by sending them for a second examination. Third, the clinical applicability of the developed algorithm using a lower tube voltage of 80 and 70 kVp could not be performed due to technical limitations

of the current scanner. This could be investigated when the latest models, such as third generation dual-source CT scanners, become available.

Conclusions

The combination of developed personalized contrast volume calculation algorithm using high IDR and 100 kVp significantly reduced TID and radiation dose while maintaining optimal VCE and acceptable image quality, compared with standard 120 kVp and routine contrast protocol.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Medical Ethics Committee of the University of Malaya Medical Centre (Protocol No.: 989.35) and informed consent was obtained from patients involved in prospective study.

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Appendix I

A phantom study was conducted to construct the iodine attenuation curves for 100 and 120 kVp. Five polyethylene vials were filled with 2 mL of iodinated contrast medium (Ultravist 370, Bayer HealthCare Pharmaceuticals, Berlin, Germany) at different concentrations: 5, 10, 15, 20 and 25 mgmL^{-1}, respectively. One control vial was filled with 2 mL of saline (*Figure S1A*). The vials were then placed in a plug location for heart, in a female adult anthropomorphic phantom (702-G, CIRS Inc., Norfolk, Virginia, USA) *Figure S1B*.

CCTA scan was performed with sequential mode for 100 and 120 kVp, using a 2×32 detector row dual-source CT scanner (Siemens Somatom Definition DS, Siemens Healthcare, Erlingen, Germany). To avoid the influence of different noise level on the contrast enhancement, 250 and 138 mAs were used for 100 and 120 kVp, respectively, to achieve the same CTDI volume (CTDI$_{vol}$) of 28.0 mGy.

Images were reconstructed with a medium smooth reconstruction kernel (B26f), at slice thickness of 0.75 mm and pixel matrix of 512×512. The mean CT attenuation value (HU) for saline and each concentration of iodine was measured in axial images by placing a circular region of interest (ROI) in the control and contrast-containing vials *Figure S1C* and determined as contrast enhancement.

The iodine attenuation curves for both 100 and 120 kVp were constructed and relative difference in the contrast enhancement between the two different tube voltages was used to develop a 100-to-120 kVp contrast enhancement conversion factor (E$_c$).
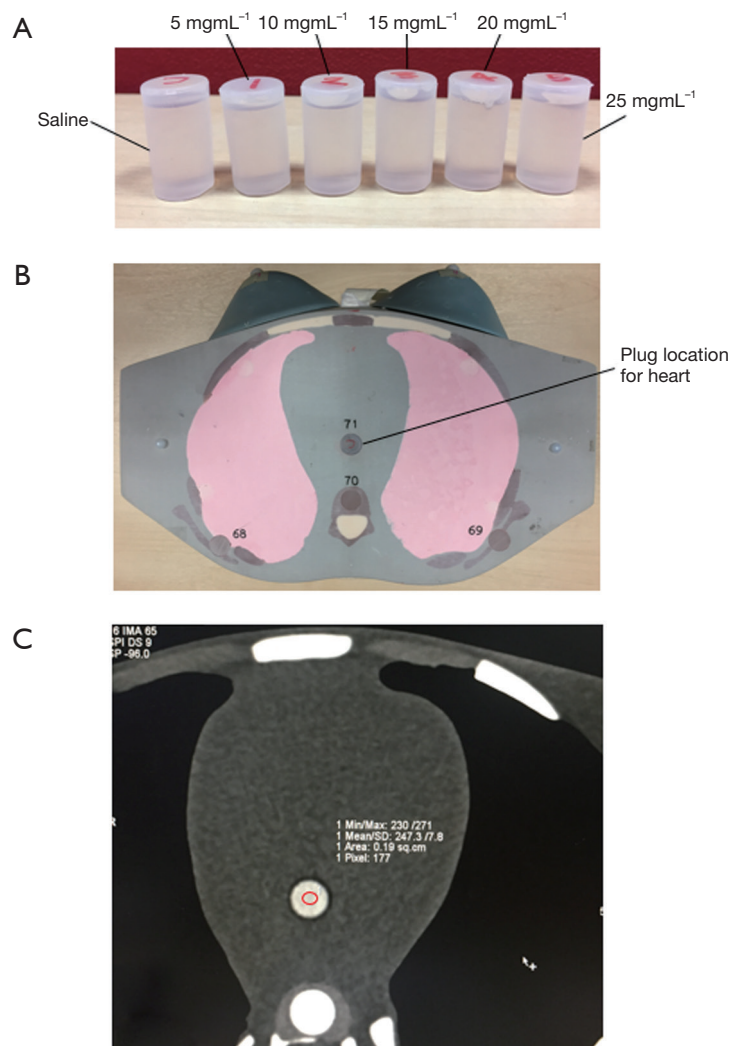

Figure S1 (A) Six polyethylene vials of 2 mL in volume that has been filled with saline and different concentrations of iodinated contrast medium: 5, 10, 15, 20 and 25 mgmL^{-1}; (B) placement of polyethylene vial in female adult anthropomorphic phantom; (C) ROI for contrast enhancement measurement. ROI, region of interest.