Coronary CT Angiography Using Low Iodine Delivery Rate and Tube Voltage Determined by Body Mass Index: Superiority in Clinical Practice*

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Summary: To explore the feasibility and superiority of iodine delivery rate (IDR) and tube voltage determined by patients' body mass index (BMI) in coronary CT angiography (CCTA), a total of 1567 patients undertaking CCTA during Feb. and Dec. 2016 were enrolled and divided into two groups. In the control group, the IDR and tube voltage were fixed, while in the experimental group, the IDR and tube voltage were determined by patients' BMI. The volume of iodinated contrast media (ICM), extravasation rate, extravasation volume, extravasation recovery interval, incidence rate of adverse reactions, effective dose (ED) and image quality of the two groups were compared. The experiments demonstrated that the ICM volume, extravasation rate, extravasation volume, extravasation recovery interval, incidence of adverse reactions and ED were lower or shorter in the experimental group than in the control group, and the differences were statistically significant (all $P<0.05$). However, there were no significant differences in the mean CT value, image noise, signal to noise ratio and contrast to noise ratio between the two groups (all $P<0.05$), which were consistent with the diagnosticians' subjective evaluation outcomes. Our findings suggested that in CCTA, it is feasible to determine the IDR and tube voltage based on patients' BMI; low tube voltage and IDR are superior to the fixed tube voltage and IDR and are worthy of clinical promotion.
Key words: iodinated contrast media; iodine delivery rate; tube voltage; ICM extravasation; adverse reactions

Coronary CT angiography (CCTA) as a minimally invasive, fast and accurate examination of coronary arteries, has been widely used in clinical practice. The specificity and sensitivity of CCTA in detecting coronary stenosis has been widely recognized. Iodinated contrast media (ICM) are the most frequently utilized contrast agents in CCTA worldwide. It is estimated that ICM are administered at least 100 million times each year worldwide[1]. To guarantee the quality of images, the amount of ICM used in CCTA is quite large. In recent years, it was revealed that ICM could cause contrast-induced nephropathy (CIN), which is the third leading cause of hospital acquired renal failure, accounting for 11% to 12% of the incidence of renal injury and 6% of hospital mortality[2, 3]. As nephrotoxicity caused by ICM is related to the ICM volume[4], it is meaningful to reduce ICM volume while ensuring the quality of CCTA images. Therefore, how to use the minimal ICM volume to guarantee high-quality coronary artery images is a very important issue in CCTA research and application.

ICM extravasation means in the process of CCTA examination, ICM leak through the veins, and cause clinical manifestations such as skin blisters, ulcers, gangrene, or even fascia compartment syndrome due to the physical and chemical properties of contrast[5]. ICM extravasation can also cause local symptoms such as pain, numbness, skin blisters, ulcers of the injection site, and systemic symptoms such as allergy (pruritus and urticaria), headache, nausea, vomiting, acute kidney injury, and so on[1, 6]. Severe reactions may progress to life-threatening emergencies if not managed appropriately and efficiently[7]. Besides

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bringing physical and mental discomfort to patients, ICM extravasation and the adverse reactions also increase the workload and psychological burden of the nurses. As a result, the extravasation and adverse reactions caused by ICM in CCTA should arouse proper concern.

As the severity of extravasation and adverse reactions of ICM is positively correlated with the flow rate and volume of extravasation, nurses may first determine the iodine delivery rate (IDR) and tube voltage based on patients' BMI, and then calculate the injection velocity, so as to conduct individualized CCTA. This study will explore the feasibility and superiority of low tube voltage and low IDR in CCTA while ensuring the quality of images.

1 SUBJECTS AND METHODS

1.1 Research Subjects

A total of 1567 patients undertaking CCTA in the Department of Medical Imaging of the First Hospital of Xi'an Jiaotong University were enrolled. The inclusive criteria were as follows: heart rate 50–80 beats/min; regular heart rhythm; being able to hold breath for at least 15 s; normal cardiac function. Exclusive criteria were as follows: patients with hyperthyroidism under treatment; patients who used ICM before and developed severe adverse reactions, and those with irregular heart rhythm.

The subjects were divided into the control group and experimental group. The control group enrolled 748 patients who underwent CCTA during Feb. 1 and July 15, 2016, including 436 males and 312 females, average 53 years. The experimental group involved 819 patients who received CCTA during Aug. 20 and Dec. 31, 2016, including 498 males and 321 females, average 49 years. In the control group, the IDR and tube voltage were fixed, while in the experimental group, the IDR and tube voltage were determined based on each patient's BMI. The experiment was approved by the Ethics Committee of the Medical Center of Xi'an Jiaotong University. All the patients signed the informed consent before CCTA examination.

1.2 Preparations before CCTA

Before CCTA, the nurses interviewed both groups of patients, assessing the absolute contraindications, asthma, drug history, allergy history, the liver, kidney and cardiac functions. All patients had sound heart function and heart rate (50–80 beats/min). The nurses provided adequate drinking water and dietary guidance to patients. Besides, the patients received respiratory training, holding breath for 15 s without inhaling or exhaling, and the chest and abdominal wall remained undulated. Spiral CT scans of the coronary arteries were performed using a 128-row 256-sclice conventional CT scanner (Brilliance iCT, Royal Philips, Netherlands). Contrast medium with an iodine concentration of 370 mg/mL (iopamidol, Shanghai Bracco Sine Pharmaceutical Corp. Ltd, China) was used for all patients. After being warmed to body temperature (37°C), ICM was injected into the antecubital vein using a standard CT power injector (XD 8018, Ulrich GmbH & Co. KG, Buchbrunnenweg, Germany), a 3-way stopcock extension tube and a standard 20G needle (BD Company, Franklin Lakes, USA). Before ICM injection, 30 mL saline at 5 mL/s was injected to assess patients' blood vessels. After ICM injection, 40 mL saline at 5 mL/s was injected to wash the pipe.

1.3 Injection Protocol and ICM Volume

For the control group, the IDR, tube voltage and injection velocity were 1.9 gI/s, 120 kV, and 5 mL/s, respectively. For the experimental group, the IDR and tube voltage were determined by patients' BMI. During scanning, the tube voltage was 80–120 kV. The injection velocity was assessed based on IDR (IDR/ICM concentration) as shown in table 1. The formula of ICM injection volume was:

$$\text{Injection volume} = (\text{Scanning time} + \text{Delay time}) \times \text{Flow velocity}$$

Table 1 The injection protocol of ICM for the experimental group

BMI	IDR (gI/s)	Tube voltage (kV)	Flow velocity (mL/s)
BMI<18.5	1.2	80	3.2
18.5≤BMI<24.9	1.3	100	3.5
BMI≥25	1.6	120	4.3

1.4 ICM Extravasation and Adverse Reactions

ICM extravasation refers to the leakage of ICM outside the vein in the process of image enhancement. Due to the physical and chemical characteristics of ICM such as hyperosmosis, extravasation may cause skin blisters, ulcers, tissue necrosis and even fascial septal syndrome[5].

ICM extravasation was observed in both groups and the extravasation rate was calculated. The extravasation volume was estimated by referring to the methods mentioned in literature, the injection volume of the CT power injector and ICM displayed in the images. The severity of extravasation was classified as mild, moderate and severe. Mild extravasation was limited, and the skin swelling around the puncture site was less than 4 cm. Moderate extravasation caused 4–6 cm swelling, but the swelling did not cross the joints. Severe extravasation caused more than 6 cm swelling, and the swelling significantly crossed the joints[8]. Both groups received telephone interview. The information about the time needed for recovery was collected, and the extravasation recovery interval was calculated. Data were compared between the two groups. Adverse

reactions such as allergy, headache, nausea, vomiting, and injection site pain were observed, and the incidence rate of adverse reactions was calculated.

1.5 Effective Volume (ED)

As radiation is harmful to human body, reducing radiation dose can reduce the risk to patients. This study examined the radiation dose during the CCTA examination. The ED was calculated as follows: ED=dose-length product (DLP) × transfer coefficient k of the test site. According to the criteria issued by the International Commission on Radiological Protection, the chest k=0.014mSv/(mGy·cm). The ED calculation formula was as follows:

ED= DLP(mGy·cm)×0.014[mSv/(mGy·cm)]

1.6 Image Quality Evaluation

1.6.1 Objective Evaluation The CT value of the coronary lumen, image noise, signal to noise ratio (SNR), and contrast to noise ratio (CNR) were measured and evaluated. According to the definition of coronary segments issued by New York Heart Association[9], the CT values were measured, including the right coronary artery, left anterior descending branch, proximal segment of the cyclotron branch (1 cm from the initial point), middle segment, distal segment of the coronary artery and the aortic root (the initial point of the left coronary artery). The fixed window width was 800 HU and the window position was 100 HU. The area of the region of interest (ROI) on the aortic root was (50±5) mm^2. The ROI was best placed in the middle of arteries to avoid calcification and plaque areas. SNR was the ratio of average coronary CT value to the background noise. CNR was the ratio of the difference between the average CT value of coronary artery and chest wall muscle to the background noise.

1.6.2 Subjective Evaluation The image quality was evaluated by two radiographers independently and all images were scored subjectively[10]. The scoring system was as follows: 4 points, good vascular enhancement, smooth, clear and sharp edge, no artifacts, no obvious noise; 3 points, good vascular enhancement, relatively smooth edge, few artifacts, slight noise that did not affect the diagnosis of coronary artery diseases; 2 points, poor vascular enhancement, many artifacts, strong noise that somewhat affected the diagnosis; 1 point, very poor vascular enhancement, severe artifacts, very strong noise that seriously affected the quality of images.

1.7 Statistical Analysis

Data collected were analyzed with SPSS18.0 (SPSS Inc, China). The variables were expressed as means±standard deviation. $P<0.05$ was considered statistically significant. The basic indexes (age, height, weight and BMI), ICM dose, extravasation volume, ED, CT value, image noise, SNR and CNR were compared with *T*-test. The gender composition ratio, extravasation rate and incidence of adverse reactions were compared with Chi-square test. The extravasation recovery interval was compared with Kaplan-Meier analysis. Subjective score of image quality was compared with Rank-Sum test.

2 RESULTS

2.1 Comparison of the Demographic Data of Patients

All patients successfully completed CCTA. There were no statistical differences in gender, age, height, weight and BMI between the two groups ($P>0.05$). The results are shown in table 2.

Table 2 Comparison of demographic data of the control and experimental groups

Basic indexes	Control group (*n*=748)	Experimental group (*n*=819)	χ^2 or *t* value	*P* value
Gender (male)	436 (58.3%)	498 (60.8%)	7.16	0.216
Age (years)	53.2±9.6	49.8±11.4	–5.56	0.543
Height (cm)	169.3±8.8	168.5±9.1	–3.24	0.897
Weight (kg)	68.3±10.6	70.8±7.8	5.60	0.550
BMI ($kg·m^{-2}$)	24.8±3.5	24.2±3.1	–3.12	0.782

2.2 ICM Volume

The qualities of CCTA images of both groups were satisfactory. As indicated in fig. 1, the ICM volume was 57.87±5.97 mL in the control group, which was statistically higher than that in the experimental group, 38.59±4.32 mL ($t= –72.64$, $P<0.001$).

2.3 ICM Extravasation and Adverse Reactions

Fig. 2 showed the ICM extravasation and adverse reactions. Extravasation occurred in 26 (3.48%) and 8 (0.98%) cases in the control group and experimental group, respectively, ($\chi^2=11.50$, $P=0.001$). Adverse reactions occurred in 22 (2.94%) and 6 (0.73%) cases in the control group and experimental group ($\chi^2=10.87$,

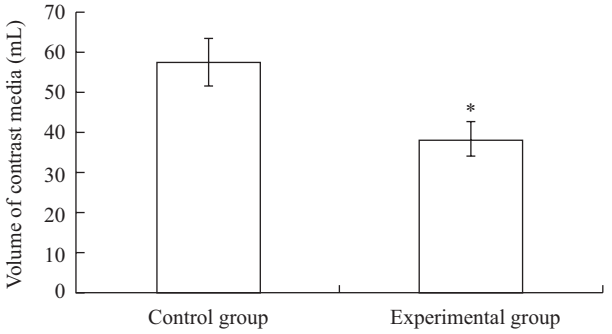

Fig. 1 ICM volume in the control and experimental groups
*$P<0.05$ *vs.* control

P=0.001).

As shown in fig. 3, the extravasation volume was 31.08±5.59 mL in the control group, and 11.50±4.69 mL in the experimental group, with significant difference between the two groups (t= –8.96, P<0.001).

It was indicated in fig. 4 that the median extravasation recovery interval was 24 h in the control group, (95% CI: 19.00–29.00 h), while it was 6 h in the experimental group (95% CI: 3.23–8.77 h). There was statistical difference between the two groups (χ^2=30.22, P=0.001).

2.4 ED Results

Fig. 5 showed the comparison of ED between the control and experimental groups. ED was 8.24±3.08 mSv in the experimental group, which was statistically lower than that in the control group (10.04±3.18 mSv) (t= –11.33, P<0.001).

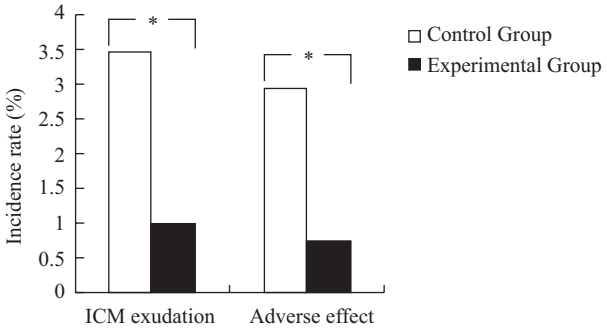

Fig. 2 Incidence rates of ICM extravasation and adverse reactions in the control and experimental groups. *P<0.05 *vs.* control

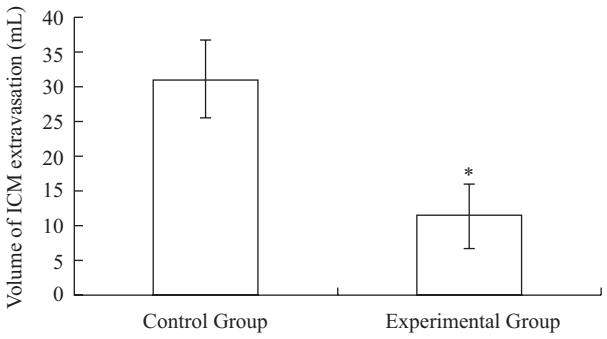

Fig. 3 Volume of ICM extravasation in the control and experimental groups. *P<0.05 *vs.* control

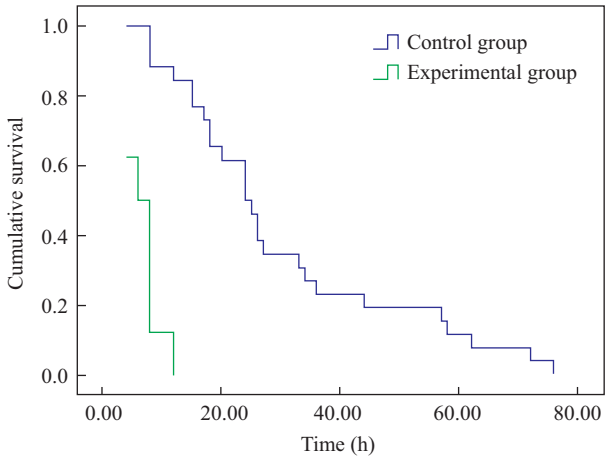

Fig. 4 Extravasation recovery intervals in the control and experimental groups

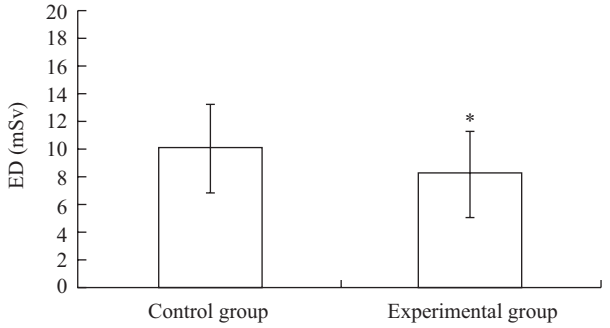

Fig. 5 ED in the control and experimental groups. *P<0.05 *vs.* control

2.5 Image Quality Evaluation

As indicated in table 3, there were no statistical differences in the CT values of the aortic root, main branch, left anterior descending branch, proximal segment of the cyclotron branch, middle segment, and distal segment of the right coronary artery between the two groups (all P>0.05). Table 4 showed that there were no significant differences in the subjective scores

Table 3 Comparison of CT values of target vessels, image noise, SNR and CNR between the two groups

Parameter	Control group (n=748)	Experimental group (n=819)	t value	P value
Aortic sinus (HU)	389.7±51.2	408.6±60.8	12.86	0.264
Proximal segments (HU)	365.0±35.4	385.3±25.5	10.71	0.397
Middle segments (HU)	358.3±45.4	374.5±26.3	16.65	0.319
Distal segments (HU)	328.7±38.5	343.3±22.5	17.84	0.291
Image noise (SD)	34.9±7.2	38.8±4.5	9.13	0.632
SNR	28.5±5.3	25.6±7.0	–8.31	0.774
CNR	36.6±7.3	34.9±9.4	–9.46	0.805

Proximal segments: average values of main branch of right coronary artery, left anterior descending branch and cyclotron branch; Middle segments: average values of main branch of right coronary artery, left anterior descending branch and cyclotron branch; Distal segments: average values of main branch of right coronary artery, left anterior descending branch and cyclotron branch.

Table 4 Comparison of subjective scores of image quality between the two groups

Subjective score	Control group (n=748)	Experimental group (n=819)
4	688	776
3	54	38
2	6	5
1	0	0

of image quality between the two groups (Z=5.67, P>0.05). In both groups, the image quality could ensure accurate diagnosis.

3 DISCUSSION

The aim of this study was to optimize ICM delivery parameters in CCTA. Although previous studies have concluded that low IDR and low tube voltage were feasible in CCTA examination[11–13], in most of these studies, the IDR and tube voltage were determined by researchers in a subjective manner. In our experiment, the IDR and tube voltage were determined by the patients' BMI; therefore, they were individually based and relatively lower than those used in the traditional method. As was shown in fig. 1, the ICM volume was significantly lower in the experimental group than in the control group (P<0.001), which indicated that low IDR based on patients' BMI is not only feasible, but also superior to the traditional fixed IDR. As is known, the amount of iodine within the blood at a dedicated tube voltage is considered to be the key determinant of vessel attenuation[14–16], and low tube voltage yields stronger contrast enhancement for a given injection protocol[11, 12, 14, 17, 18]. It is explained that the resulting photon energy is closer to the K-edge of iodine (33 keV), resulting in higher intravascular enhancement[13, 19]. Therefore, low tube voltage allows us to use low IDR while maintaining the image quality. Consequently, it is safer for patients and can reduce the rates of ICM extravasation and adverse reactions. In the present study, although the tube voltage was lower in the experimental group (except for those whose BMI≥25), the quality of images was not affected.

At present, there have been few large-sample studies on ICM extravasation. Some studies confirmed that extravasation rate was closely related to ICM injection velocity. When the ICM injection velocity increased from 0.5 mL/s to 1.0–1.5 mL/s, the incidence of extravasation rose from 0.10% to 0.24%[20]. Hou *et al* also stated that extravasation rate was positively correlated with injection velocity[21]. Our study indicated that the extravasation rate in the experimental group was significantly lower than that in the control group (P<0.05, fig. 2), and the extravasation volume was smaller too (P<0.05, fig. 3). In our experimental scheme, the ICM injection velocity in the experimental group was lower than that in the control group, indicating that our findings were consistent with the results of previous studies. The extravasation recovery interval in the experimental group was significantly shorter than that in the control group (P<0.05, fig. 4), which might be explained that, because the dose of ICM in the experimental group was lower than that in the control group, the incidence of adverse reactions was lower.

The adverse reactions induced by ICM fall into two categories, immediate adverse reactions and delayed allergic reactions. The former occur within 1 h after ICM are administered, while the latter manifest 1 h to 7 days after ICM are used. Immediate adverse reactions include urticaria, sweating, nausea, vomiting, syncope, laryngeal edema, bronchospasm, low blood pressure shock, convulsions, pulmonary edema, or even respiratory or cardiac arrest[22]. Delayed allergic reactions involve the identification of ICM by T lymphocytes proliferation[23]. Therefore, such reactions are generally rashes, pleomorphic erythema, epidermal necrosis, vasculitis, and so on. According to previous studies, the overall incidence rate of adverse reactions induced by ICM was 3%–13%, and serious adverse reactions accounted for 0.04%–0.2%[24]. In our study, the incidence rate of adverse reactions in the experimental group was 0.73%, which was significantly lower than that in the control group (P<0.05), and significantly lower than the rate obtained from previous studies. This might be due to that the dose of ICM injected in the experimental group was low.

Fig. 5 showed that the ED in the experimental group was significantly lower than that in the control group, which might be related to the decrease of tube voltage in the experimental group. As is known to all, the radiation dose of X ray is proportional to the square of the tube voltage, so the reduction of tube voltage is beneficial to the reduction of radiation dose. In addition, after the tube voltage is lowered, the CT value of endovascular ICM relatively increases, thus the concentration of ICM is reduced, and risk of the CIN is reduced accordingly[25].

Studies have shown that reducing the tube voltage can increase the image noise and lead to decrease of SNR and CNR in the images[26]. Our study obtained similar results. As shown in table 3, compared with the control group, the experimental group had increased CT value and background noise, and slightly decreased SNR and CNR, but there were no statistical differences between the two groups. Referring to the results of subjective image quality evaluation indicated in table 4, we believe that the increase of image noise in the experimental group is acceptable, and the image quality can meet the diagnostic requirements.

In conclusion, this study provides a tentative approach to ICM injection optimization at low iodine

flow rate and tube voltage determined by BMI. Low IDR and tube voltage based on patients' BMI in CCTA is feasible and superior compared with traditional approach. The ICM volume, extravasation rate, extravasation volume, extravasation recovery interval, incidence rate of adverse reactions and ED are lower or shorter than those in the traditional approach. The image quality can meet the diagnostic requirements. The injection protocol of ICM in the present study is worth wide clinical application.

Conflict of Interest Statement

The authors declare no competing financial interests.

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