Received:
28 June 2018

Revised:
27 October 2018

Accepted:
31 October 2018

<https://doi.org/10.1259/bjr.20180572>

Cite this article as:

Masuda T, Funama Y, Nakaura T, Sato T, Tahara M, Matsumoto Y, et al. Usefulness of diluted contrast medium for test-scanning of infants scheduled for contrast-enhanced cardiovascular computed tomography angiography. *Br J Radiol* 2019; **91**: 20180572.

FULL PAPER

Usefulness of diluted contrast medium for test-scanning of infants scheduled for contrast-enhanced cardiovascular computed tomography angiography

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Objective: To compare the ability of test scans with undiluted and diluted contrast medium (CM) to predict contrast enhancement (CE) on cardiovascular CT angiography (CCTA) images of infants.

Methods: We divided 120 consecutive infants who had undergone CCTA on a 64-MDCT scanner into two equal groups. In one group, the test bolus consisted of undiluted CM [protocol 1 (P1): injection volume = total body weight $\times$ 1.2 ml, injection time 5 s], in the other (P2) it was total body weight $\times$ 4.0 ml (CM 15%, saline 85%, injection time 16 s). CE on the test scans was recorded on a 3-point visual scale. We investigated the relation for CE in the pulmonary artery and ascending aorta between the P1 or P2 test scans and CCTA images.

Results: While peak CE was observed on all test scans performed with P2, in approximately 10 % of test scans obtained under P1, peak CE was not visualized. There was a strong positive linear correlation for CE of the pulmonary artery and ascending aorta on P2 images ($r = 0.61$ and $r = 0.63$, $p < 0.01$); under P1 the correlation was weak ($r = 0.26$ and $r = 0.33$, $p < 0.01$).

Conclusion: Test-scanning with diluted CM revealed the optimal CE peak time and was useful for predicting CE on CCTA scans of the pulmonary artery and ascending aorta in infants with congenital heart disease.

Advances in knowledge: Diluted test scans help to select the optimal scan parameters for the CCTA study of infants by using contrast-to-noise-based scanning.

INTRODUCTION

CT and cardiovascular CT angiography (CCTA) are widely used to evaluate congenital heart disease (CHD).¹⁻³ For the assessment of CHD on CCTA scans, the optimal contrast material (CM) injection protocol yielding sufficient vascular contrast enhancement (CE) must be used; the CE peak time (PT) is most important for the diagnostic quality of CCTA scans.

Test injection with diluted CM has been reported as useful for obtaining the optimal PT and for predicting CE on CCTA images.⁴⁻⁷ However, it remains unclear whether undiluted or diluted CM is preferable in infants with CHD.

In this retrospective study, we compared test bolus scans performed with undiluted and diluted CM to investigate

their usefulness for predicting CE on CCTA scans of infants.

METHODS AND MATERIALS

This retrospective study received institutional review board approval. The publication of our findings was approved by the legal representatives of all infants.

Patients

Between May 2013 and November 2016, 130 consecutive infants aged from 0.1 to 12 months were considered for inclusion in this study. We subsequently excluded 10 because the amount of contrast medium (CM) that can be used in infants with severe heart failure is limited.⁸ All included infants underwent CCTA for the evaluation of cyanotic- ($n = 44$) or acyanotic heart disease ($n = 41$), aortic

coarctation ($n = 32$), and vascular ring ($n = 3$). Their serum creatinine level was obtained within 3 months prior to CCTA studies; their estimated glomerular filtration rate was calculated using the modified isotope-dilution mass spectrometry formula. The infants were divided into two equal, non-randomized groups. For test scanning, one group was injected with undiluted between May 2013 and December 2014 and the other with diluted CM between January 2015 and November 2016 [protocol 1 (P1) and protocol 2 (P2), respectively]. The sex, age, body height, body weight (BW), and heart rate during the examinations are shown in Table 1.

CT scanning

Helical scans were acquired on a 64-detector-row CT instrument (Lightspeed VCT; GE Healthcare, Milwaukee, WI). The CT scanning parameters with non-gated CT were 0.4 s rotation, 0.625 mm detector row width, 1.375 helical pitch (beam pitch), 137.5 mm table movement per rotation, 50 cm scan field of view (FOV), 80 kVp, and 40–300 mA. All patients were sedated before CT examination and all patients were free-breathing during the

examination. All scans were from the top of the apical portion of the lung to the level of the inferior margin of the cardiac apex in the craniocaudal direction. Image reconstruction was in a 10- to 15 cm display FOV depending on the patient body size.

CM injection protocols

The injection protocols for the test- and CCTA scans are shown in Table 2. We injected undiluted (P1) or diluted CM (P2) (Omnipaque-300; Daiichi-Sankyo, Tokyo, Japan) through a 24-gauge catheter into the antecubital vein using a power injector (Dual Shot; Nemoto-Kyorindo, Tokyo, Japan). The administered iodine dose was 600 mg kg^{-1} totalbody weight (TBW) for P1 and P2. Under P1, the CM dose was total BW $\times 1.2 \text{ ml}$ delivered in 5 s; under P2 it was TBW $\times 4.0 \text{ ml}$ (15% CM, 85% saline) injected in the course of 16 s. CM delivery was followed by flushing with 5 ml of physiological saline at the CM injection rate. To monitor the ascending aorta at the level of the main pulmonary artery, we obtained dynamic low-dose (80 kVp, 10 mAs) scans; the inter-scan interval was 1.0 s. The acquisition of dynamic monitoring scans began 5.0 s after the start of CM injection. A region of

Table 1. Characteristics of patients undergoing test scanning with undiluted and diluted contrast medium

	P1	P2	<i>p</i> -value
	Undiluted contrast medium	Diluted contrast medium	
Number of patients	60	60	
Sex (male/female)	34/26	37/23	0.71
Age (months)	3.0 (0.1–12.0)	4.0 (0.1–12.0)	0.69
Body height (cm)	56.0 (40.0–72.0)	55.0 (41.0–75.0)	0.55
Body weight (kg)	5.0 (2.0–12.0)	4.0 (2.0–12.0)	0.11
Body mass index (kg cm^{-2})	15.3 (4.1–25.5)	14.9 (7.4–29.8)	0.34
Heart rate (bpm)	125.0 (89.0–154)	123.0 (91.0–152)	0.89

Values are given as median (minimum and maximum)

Table 2. Contrast medium injection protocols

	Parameter	P1	P2
		Undiluted contrast medium	Diluted contrast medium
Test scans	Iodine dose (mgI kg^{-1})	200	200
	Injection volume (ml)	TBW (kg) $\times 1.2$	TBW (kg) $\times 4.0$
		CM: 50%, saline: 50%	CM: 15%, saline: 85%
	Injection rate (ml/s)	TBW (kg) $\times 0.25$	TBW (kg) $\times 0.25$
	Injection duration (s)	5	16
	Saline chaser (ml)	5	5
CCTA	Iodine dose (mgI kg^{-1})	600 (TBW $\times 2.0$)	600 (TBW $\times 2.0$)
	Injection volume (ml)	TBW $\times 4.0$	TBW $\times 4.0$
		CM: 50%, saline: 50%	CM: 50%, saline: 50%
	Injection rate (ml s^{-1})	TBW (kg) $\times 0.25$	TBW (kg) $\times 0.25$
	Injection duration (s)	16	16
	Saline chaser (ml)	5	5

CCTA, cardiovascular CT angiography; CM, contrast medium; TBW, total body weight.

Figure 1. Measurement position and location on the axial image. The CT number of the pulmonary artery (blue circle) and ascending aorta (red circle) was measured using a 10 mm diameter circular round ROI in the each patient. ROI, region of interest.

interest (ROI) was placed inside the ascending aorta to obtain a time-attenuation curve for PT measurements. We recorded peak contrast enhancement (CE) in the ascending aorta by constructing time-enhancement curves that connected all time points. The arrival time at the ascending aorta was defined as the interval between the start of test scan injection and the time of peak CE. For CCTA scanning, the injection volume was 4.0 ml (CM: TBW $\times$ 2.0 ml; saline TBW $\times$ 2.0 ml) delivered in 16 s. CM delivery was followed by flushing with 5 ml of physiological saline at the same injection rate.

Data analysis

Median CE (in Hounsfield units, HU) of the pulmonary artery and ascending aorta was recorded on undiluted and diluted test scans and on CCTA images. Using a CT console monitor, 10 mm diameter circular ROIs were placed on unenhanced test scans and on CCTA scans (Figure 1). Areas with streak artifacts were carefully excluded from the ROI. The degree of CE was expressed as the difference in the CT number, calculated by subtracting the HU on unenhanced test scan images from the HU on CCTA scans.

Qualitative assessment

A diagnostic radiologist and a pediatric cardiologist with 30 and 25 years of experience, respectively, recorded CE of the test scans. Each reader inspected 60 randomized test scans acquired under P1 or P2 and recorded the findings on a 3-point visual scale where 3 = excellent peak enhancement of the pulmonary artery and ascending aorta, 2 = marginal enhancement, and 1 = not evaluable (Figure 2). When their initial assessment differed, the images were inspected again and the final score was assigned by consensus. All images were presented on a digital picture archiving and communication system using a diagnostic workstation (Advantage windows workstation v. 4.2; GE Healthcare, Milwaukee, WI).

Statistical analysis

To compare the male-to-female ratio under the two test scan protocols, we used the χ^2 test. To compare the age, body height, body weight, body mass index, and heart rate we used Mann–Whitney *U* test. For the comparison of arrival time, start scan, injection rate, and M volume under the two test scan protocols, we used the Mann–Whitney *U* test. To compare CE on the test- and CCTA scans, we applied the Mann–Whitney *U* test. For analysis of the results obtained with both test scan protocols, we obtained the Pearson product-moment correlation coefficient (*r*) and investigated the relationship between CE obtained with P1 and P2 and compared our findings with CE on CCTA images. To determine the strength of association, we took “*r*” as the absolute value of the normal data distribution; *r* = 0–0.19 was recorded as very weak, 0.2–0.39 as weak, 0.40–0.59 as moderate, 0.6–0.79 as strong, and 0.8–1.0 as very strong correlation. We compared the correlation coefficients using the method of Meng et al.⁹ Differences of *p* < 0.05 were considered statistically significant. Statistical analyses were with free statistical software (v. 3.2.2, the R project for statistical computing; <http://www.rproject.org/>).

RESULTS

Visualization of the CE score on test scans

On test scans acquired under P1, the visualization scores were of 3, 2, and 1, respectively, for 68, 13, and 10% of the pulmonary artery; these scores were assigned to 73, 17, and 10% of images of the ascending aorta. With P2, the visualization scores were 3, 2, and 1, respectively, for the visualization of 85, 15, and 0% of the pulmonary artery; these scores were assigned to 88, 12, and 0% of P1 images of the ascending aorta. There was a significant

Figure 2. Differences in the visualization scores assigned to axial image of the test scans for the pulmonary artery and the ascending aorta. A-3 = excellent peak enhancement, B-2 = marginal enhancement, and C-3 = not evaluable.

Table 3. Contrast administration parameters

	P1	P2	<i>p</i> -value
	Undiluted contrast medium	Diluted contrast medium	
Test scans:			
Arrival time (s)	15.0 (11.0–21.0)	17.0 (13.0–25.0)	0.11
Injection rate (ml s ⁻¹)	1.3 (0.5–3.0)	1.0 (0.5–3.3)	0.11
Contrast medium volume (ml)	2.8 (1.2–7.2)	3.0 (1.2–7.2)	0.65
CCTA scan:			
Start scan (s)	15.0 (11.0–21.0)	17.0 (13.0–25.0)	0.11
Injection rate (ml s ⁻¹)	1.3 (0.5–3.0)	1.0 (0.5–3.3)	0.11
Contrast medium volume (ml)	20.0 (8.0–48.0)	16.0 (8.0–48.0)	0.13

CCTA, cardiovascular CT angiography.

Values are given as median (minimum and maximum)

difference between images acquired with P1 and P2 in the visualization scores of the pulmonary artery ($p < 0.01$) and of the ascending aorta ($p < 0.01$). Under P1, the Cohen κ -value for interobserver agreement on CE of the pulmonary artery and aorta was 0.68 and 0.69, respectively; with P2, these values were 0.64 and 0.71, respectively.

Comparison of CE obtained with P1 and P2

Under P1, the arrival time at the ascending aorta was 15 s; it was 17 s with P2 ($p = 0.11$, Table 3). Mean CE in the pulmonary artery and ascending aorta was significantly higher under P2 than P1 (231.2 and 234.6 HU, respectively, vs 164.7 and 179.8 HU, respectively, $p < 0.01$). There were also significant differences in the correlation between CE on test scans of the pulmonary artery and ascending aorta and their correlation on CCTA images ($p < 0.01$). Under P2, it exhibited a strong positive linear relationship for the pulmonary artery and ascending aorta ($r = 0.61$ and $r = 0.63$, respectively, $p < 0.01$) (Figure 3). With P1, the positive linear correlation was weak ($r = 0.26$ and $r = 0.33$, respectively ($p < 0.01$)) (Figure 4).

DISCUSSION

CCTA is important for the accurate pre-operative evaluation of the morphology of the heart and blood vessels,^{10,11} especially in infants with complex CHD.¹² It facilitates the pre-operative assessment of the shape of and the spatial relation among the great arteries, the pulmonary artery and its branches, of anomalous pulmonary venous connections, and of shunts and anomalous coronary arteries.^{12,13}

We compared CE in the pulmonary artery and ascending aorta of infants using test scans obtained with undiluted (P1) or diluted (P2) CM and compared the results with CCTA images. We found that P2 test scans yielded accurate PT results that could be used to predict CE on CCTA images.

Dilution makes it possible to deliver the total amount of CM required for diagnostic imaging scans. As small volumes of CM administered via the brachial vein are retained for some time in the dead space between the brachial vein and the superior

Figure 3. Correlation between CE of the pulmonary artery on test scans and CCTA images. (a) undiluted (P1)- and (b) diluted (P2) CM. There was a strong positive linear correlation with diluted contrast medium and a weak positive linear relationship with undiluted contrast medium ($r = 0.61$ and $r = 0.26$, $p < 0.01$). CCTA, cardiovascular CT angiography; CE, contrast enhancement; CM, contrast medium; HU, Hounsfield unit.

Figure 4. Correlation between CE of the ascending aorta on test scans and CCTA images. (a) undiluted (P1) and (b) diluted (P2) CM. There was a strong positive linear correlation with diluted contrast medium and a weak positive linear relationship with undiluted contrast medium ($r = 0.63$ and $r = 0.34$, $p < 0.01$). CCTA, cardiovascular CT angiography; CE, contrast enhancement; CM, contrast medium; HU, Hounsfield unit.

vena cava,¹⁴ it is unavailable immediately after the termination of contrast injection.^{14,15} In neonates and small children, the CM osmolality is of particular importance⁸ because they are thought to be especially susceptible to fluid shifts and have a lower tolerance for intravascular osmotic loads than adults. The intravascular administration of hyperosmolar CM can result in fluid migration from extravascular soft tissues into blood vessels, thereby eliciting expansion of the blood volume.^{16,17} The sequelae of large fluid shifts are cardiac failure and pulmonary edema and children with significant pre-existing cardiac dysfunction are particularly at risk. Therefore, diluted CM is useful for the acquisition of preoperative imaging studies in infants with CHD.

Earlier studies revealed that the time-density curve of the test bolus can be used to predict CE on CCTA scans. Others^{7,18} reported that test scans with a small amount of CM were useful for predicting and controlling time-dependent aortic enhancement. To increase the accuracy of our test injection results, we delivered a volume of diluted CM (P2) that consisted of 15% CM and 85% saline (TBW $\times$ 4.0 ml) rather than the smaller amount of undiluted CM that is injected in infants under conventional test bolus protocols.^{7,19} Our findings document that CE of the ascending aorta and pulmonary artery on CCTA scans can be predicted on P2 test-bolus images of infants with CHD.

P2 test scans help to select the optimal scan parameters for the CCTA study of infants. The contrast-to-noise ratio (CNR), defined as the vessel enhancement value (in HU), divided by the background image noise, can be controlled by optimizing the diagnostic image quality and radiation dose.¹⁹ As higher enhancement yields a better CNR, the radiation dose can be

decreased. To maintain the image quality of test scans with lower enhancement, the image noise must be decreased by increasing the radiation dose. This can be achieved by applying the CNR index of the image noise to lower tube-voltage CTA scans.²⁰ For the application of the “as low as reasonably achievable” radiation concept and to obtain the optimal scanning parameters, CNR-based scanning may be preferable for CCTA scanning of infants.

Our study has some limitations. First, we investigated the value of test scanning with diluted or undiluted CM for predicting CE on CCTA images only in infants with CHD. The findings may be different in older patients. Second, our investigation was a non-randomized retrospective study and randomized prospective studies are needed to validate our findings. Lastly, we did not confirm the relationship between the CM and image quality.

In conclusion, test scans with diluted CM were useful for obtaining the optimal PT and for predicting CE of the pulmonary artery and ascending aorta on CCTA scans of infants with CHD.

DISCLOSURE

The authors have no conflicts of interest directly relevant to the content of this article.

PATIENT CONSENT

This retrospective study received institutional review board approval. The publication of our findings was approved by the legal representatives of all infants.

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