Low Iodine Dose is Related with Overestimation of Extracellular Volume Derived from Cardiac CT

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Objective: To assess the relationship between the amount of injected contrast medium and the extracellular volume (ECV) value during cardiac CT and to propose a minimum amount of contrast medium necessary to correctly calculate ECV.

Materials and Methods: A total of 95 patients who underwent comprehensive cardiac CT were included. Patients first underwent myocardial CT perfusion (CTP) with a contrast medium dose determined by the body weight (<70 kg: 50 mL; 70–89 kg: 55 mL; ≥90 kg: 60 mL). Coronary CT angiography (CTA) scan followed with a contrast medium dose of 0.8×body weight (kg). We defined the ECV value calculated after CTP as ECV_{CTP}, and we used the ECV value calculated after the CTA exam as the reference standard (ECV_{ref}). We calculated the difference in ECV values (ECV_{diff}) as ECV_{CTP}-ECV_{ref}.

Results: The injected iodine doses during CTP and the entire exam were 284±50 and 559±69 mg iodine/kg, respectively. There was a weak but significant negative relationship ($R^2=0.07$, $p=0.01$) between the injected iodine dose during CTP and ECV_{diff}. The ECV_{diff} of patients who received an injected iodine dose of <285 mg iodine/kg during CTP was significantly higher (2.7±4.1 vs. 0.8±3.4%, $p=0.02$) than that of the remaining patients.

Conclusion: ECV derived from cardiac CT might be overestimated when a small amount of contrast medium is injected. Injection of ≥285 mg iodine/kg is adequate to calculate the ECV value using cardiac CT.

Key words Contrast agents · Extracellular space · Multidetector computed tomography.

INTRODUCTION

Delayed enhancement of the myocardium is related to increased risk of cardiovascular events [1]. Diagnosis of delayed enhancement has been well established using MRI, but recent improvements in CT technology now allow delayed enhancement analysis of the myocardium using CT [2]. However, the contrast between diseased and normal myocardium in CT is inferior to that in MRI [3,4]. Moreover, when diffuse myocardial fibrosis is present, delayed enhancement might not be detectable [5]. Calculation of extracellular volume (ECV) can be used to detect focal or diffuse myocardial damage [4-6]. ECV derived from CT is in good relationship with ECV derived from MRI [4,7]. Therefore, ECV evaluation using CT could be used to diagnose myocardial disorders.

Previous MRI studies showed that ECV could be overestimated when the injected dose of contrast medium was small [8,9]. A similar concern remains when a small amount of contrast medium is injected for an ECV evaluation using CT. Contrast medium is injected twice during a typical comprehensive cardiac CT protocol [a combination of dynamic myocardial CT perfusion (CTP) under stress and coronary CT angiography (CTA)]. ECV is clinically calculated using a delayed enhancement image...
after the full dose of contrast medium has been injected. ECV can also be calculated using an image acquired between the CTP and CTA, when only the contrast medium for CTP has been injected. We hypothesized that ECV derived using a small dose of contrast medium might overestimate the ECV value. Therefore, our purpose in this study was to assess the relationship between the amount of injected contrast medium and the ECV value and propose a minimum amount of contrast medium necessary to correctly calculate ECV.

MATERIALS AND METHODS

Patients undergoing comprehensive cardiac CT entered a prospective registry under the protocol registration system of the UMIN clinical trials registry (UMIN000024245). In brief, the main objective of this registry is to test whether microvascular dysfunction, estimated as the calculated stress myocardial blood flow, has additive value over coronary stenosis in predicting the prognosis of patients. The inclusion criteria are a history of type 2 diabetes regardless of symptoms, suspected coronary artery disease due to multiple risk factors, or evaluation of coronary stenosis after a percutaneous coronary intervention. Patients who met the inclusion criteria and did not have severe renal dysfunction (estimated glomerular filtration rate >40 mL/min/1.73 m²) were invited to participate at the outpatient department. The study protocol was approved by the local ethics committee (IRB No. 0085), and all patients gave written informed consent.

Patients

The records of 100 patients in the registry from August 2017 to August 2018 were initially included. The exclusion criteria were as follows: delayed enhancement visually present (n=2), unable to hold breath (n=2), and allergy to contrast medium (n=1). Thus, the final group included 95 patients. All patients were asked to discontinue caffeine intake for at least 12 hours before the exam. Hematocrit was measured at the time of the CT exam.

CT acquisition

All patients underwent cardiac CT using a single-source CT (Somatom Definition AS+; Siemens Healthineers, Forchheim, Germany) with a collimation of 64×0.6 mm and flying-focal spot, resulting in 128 slices. All scans were performed at the fastest gantry rotation time of 300 ms. Two intravenous lines were placed, one in each antecubital vein, to administer contrast medium and adenosine triphosphate (ATP). We used a self-monitoring device to allow patients to visually control their respiration (Ableches; APEX Medical, Tokyo, Japan). We trained each patient before the scan to keep the end-inspiratory position at the same position. We used iopamidol (370 mg iodine/mL; Iopamiron 370; Bayer, Osaka, Japan) when the body weight was <70 kg; otherwise we used iomeprol (350 mg iodine/mL; Iomeron 350; Eisai, Tokyo, Japan). We used iomeprol in patients who weighed ≥70 kg because the amount of contrast medium included was 135 mL for iomeprol and only 100 mL for iopamidol.

First, a baseline non-enhanced image of the myocardium was acquired (Fig. 1A). The scanning parameters were as follows: tube potential, 100 kVp; reference mAs, 190 mAs; scan coverage, 68.5 mm; acquisition window, 30–40% of the R-R interval. One slice at the mid-level of the myocardium was reconstructed with half reconstruction, a slice thickness of 10 mm, and a convolution kernel of B36f (Fig. 1A). These parameters were used throughout except for the scan before the coronary CTA, as described later.

Myocardial CTP was initiated 3 min after the administration of ATP (Adetphos; Kowa Company, Tokyo, Japan) at 0.14 mg/kg/min. The amount of contrast medium was determined by the body weight (<70 kg: 50 mL; 70–89 kg: 55 mL; ≥90 kg: 60 mL). The contrast medium was injected for 12 s, followed by a saline chaser. Although we adjusted the contrast medium amount during CTP by body weight, the amount of contrast medium in patients who weighed ≥70 kg was smaller than in lean patients for the following reasons. First, the upper limit of the injection speed using an intravenous catheter was 5.0 mL/s; thus, the maximum amount of contrast medium that could be delivered during a 12 s injection time was 60 mL. Second, we did not use a longer injection time than 12 s during the CTP because streak artifacts from the right heart system might negatively influence the image quality of the myocardium of the left ventricle during the dynamic CTP scan. ATP infusion was discontinued after the acquisition was completed.

Before the coronary CTA was performed, a single slice image of 10 mm was scanned to identify a region of interest (ROI) for the bolus tracking method of coronary CTA. The scanned level, reconstruction thickness, and convolution kernel were the same as the baseline image (Fig. 1B). We used this image to calculate ECV when only the contrast medium for the CTP had been injected (ECV_{CTP}).

Coronary CTA was performed using a contrast medium dose determined by the body weight [0.8×body weight (kg)]. The contrast medium was injected for 14 s followed by a saline flush. The bolus tracking method was used to determine the scan timing. The scan started 6 s after the descending aorta reached 60 Hounsfield units (HU) above the initial value. If the heart rate was more than 65 beats/min, a maximum dose of 12.5 mg of lantiodol (Corebeta; Ono Pharmaceutical, Tokyo, Japan) was given intravenously [10]. All patients received 0.3 mg of sublingual nitroglycerin (Nitropen; Nippon Kayaku, Tokyo, Japan).

Finally, a delayed enhanced image was scanned with the same parameters as the baseline image. One slice at the mid-
The level of the myocardium was reconstructed (Fig. 1C). We used this image to calculate the reference ECV using the full dose of contrast medium (ECV_ref).

For processing, images were transferred to a workstation (Synapse Vincent Ver 5.2; Fujifilm Medical, Tokyo, Japan).

**ECV calculation**

Two ROIs were placed at the left ventricle and the septum (Fig. 1). The ROIs were made as large as possible without including the adjacent structures. The non-enhanced image, enhanced image after CTP, and enhanced image after CTA were placed side-by-side, and the ROIs were copied on the workstation. The ECV was calculated using the following formula:

$$ECV = \frac{100 - Hct}{\Delta Myo} \times \frac{\Delta LV}{\Delta LV}$$

where Hct is hematocrit, ΔMyo is myocardial enhancement, and ΔLV is left ventricular enhancement. We defined ECV_{CTP} as the ECV value calculated with contrast medium injection after CTP (Fig. 1A and B). The ECV calculated using the delayed enhancement image with a full dose of contrast medium was used for reference (ECV_{ref}) (Fig. 1A and C). The difference in ECV (ECV_{diff}) was calculated as ECV_{CTP} - ECV_{ref}.

All measurements were performed by a single cardiovascular radiologist with 13 years of experience. A second radiologist with 5 years of experience evaluated 20 randomly selected patients to investigate interobserver variability.

**Statistical analysis**

Continuous variables are shown as mean±standard deviation, and categorical variables are given as number unless otherwise indicated. Student’s t-test was used to compare continuous variables. Fisher’s exact test or the chi-square test was used to compare categorical and skewed variables. Pearson correlation analysis was used to investigate the relationship between ECV_{diff} and injected iodine dose. The agreement between ECV_{CTP} and ECV_{ref} was assessed using Bland-Altman plots. Intraclass correlation coefficients (ICC) was used to investigate interobserver variability. We performed a sub-group analysis based on the median iodine injection dose during CTP of 285 mg iodine/kg. All statistical analyses were performed using JMP software (ver 12.2.0; SAS Institute, Cary, NC, USA). In all analyses, p<0.05 was taken to indicate statistical significance.

**RESULTS**

**Patient characteristics**

The patients were dominantly male with a mean age of 62.4±12.0 y and a body mass index of 25.6±4.4 kg/m² (Table 1). The mean contrast medium dose injected for CTP was 52.4±4.6 mL with a total dose of 104.5±14.3 mL during the entire exam. The mean scan timing of early and delayed phase scans used to calculate ECV was 5.0±1.8 and 15.0±3.9 min, respectively, after initial injection of contrast medium. The mean scan delay between coronary CTA and delayed phase scan was 8.4±3.4 min. The injected iodine dose during CTP and the entire exam were 284±50 (range, 178 to 430) and 559±69 (range, 386 to 817) mg iodine/kg, respectively. Sub-group analysis based on injected iodine dose during CTP showed that patients who received smaller iodine doses were significantly heavier than those who received larger doses (80.2±10.2 kg vs. 56.2±8.5 kg, p<0.01). The total injected contrast medium dose of heavier patients was significantly larger (114.7±10.1 mL vs. 92.2±7.3 mL, p<0.01) than in lighter patients, but the iodine dose per body weight was significantly smaller.
Hiroaki Arakawa, et al

ECV value

The mean attenuation of the left ventricle and septum was 86.6±10.2 and 67.5±5.7 HU, respectively, in the post-CTP images and 107.0±11.4 and 76.2±7.2 HU in the delayed phase images (Table 2). The mean hematocrit and ECV_ref were 42.7±4.1% and 28.5±4.4%, respectively. ECV_CTP (29.9±5.9%) was significantly higher than ECV_ref (p=0.02). Subgroup analysis showed significantly lower (p<0.01) attenuation of the left ventricle and septum in the post-CTP and delayed phase images in patients who received iodine dose <285 mg iodine/kg during the CTP scan than in the remaining patients. ECV_CTP was higher in the low-iodine dose group than in the remaining patients (30.5±6.5% vs. 29.2±5.1%, p<0.01), but ECV_ref did not differ between the groups (28.7±4.0% vs. 28.3±5.0%, p=0.65).

Table 1. Patient and scan characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>CTP iodine dose (mg iodine/kg)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>285</td>
<td>285</td>
</tr>
<tr>
<td>Number of patients</td>
<td>95</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td>Male</td>
<td>66 (69)</td>
<td>44 (46)</td>
<td>22 (23)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>62.4±12.0</td>
<td>58.8±11.8</td>
<td>66.7±11.0</td>
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<td>Body weight (kg)</td>
<td>69.3±15.9</td>
<td>80.2±10.2</td>
<td>56.2±8.5</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>25.6±4.4</td>
<td>28.0±4.0</td>
<td>22.6±3.0</td>
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<td>Coronary risk factors</td>
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<tr>
<td>Diabetes mellitus</td>
<td>71 (75)</td>
<td>43 (45)</td>
<td>29 (31)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61 (64)</td>
<td>32 (34)</td>
<td>30 (32)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>74 (78)</td>
<td>45 (47)</td>
<td>30 (32)</td>
</tr>
<tr>
<td>Smoking, current/ex</td>
<td>31 (33)/33 (35)</td>
<td>20 (21)/18 (19)</td>
<td>11 (12)/15 (16)</td>
</tr>
<tr>
<td>Family history</td>
<td>15 (16)</td>
<td>8 (8)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Contrast medium (mL)</td>
<td></td>
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<tr>
<td>CTP</td>
<td>52.4±4.6</td>
<td>55.4±3.1</td>
<td>48.7±3.2</td>
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<tr>
<td>Total</td>
<td>104.5±14.3</td>
<td>114.7±10.1</td>
<td>92.2±7.3</td>
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<tr>
<td>Iodine dose (mg iodine/kg)</td>
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<td></td>
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<tr>
<td>CTP</td>
<td>284±50</td>
<td>247±24</td>
<td>328±30</td>
</tr>
<tr>
<td>Total</td>
<td>559±69</td>
<td>509±35</td>
<td>619±50</td>
</tr>
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</table>

Numbers are reported as mean±standard deviation or n (%). *statistically significant, p<0.05. CTP: CT perfusion

Table 2. Enhancement and ECV

<table>
<thead>
<tr>
<th>Attenuation (Hounsfield units)</th>
<th>All patients</th>
<th>CTP iodine dose (mg iodine/kg)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>285</td>
<td>285</td>
</tr>
<tr>
<td>Plain</td>
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<td></td>
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<tr>
<td>Left ventricle</td>
<td>43.7±6.5</td>
<td>44.8±6.6</td>
<td>42.3±6.1</td>
</tr>
<tr>
<td>Septum</td>
<td>45.2±6.1</td>
<td>45.4±6.4</td>
<td>44.8±5.8</td>
</tr>
<tr>
<td>Post-CTP</td>
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<td></td>
<td></td>
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<tr>
<td>Left ventricle</td>
<td>86.6±10.2</td>
<td>83.0±9.7</td>
<td>90.9±9.3</td>
</tr>
<tr>
<td>Septum</td>
<td>67.5±5.7</td>
<td>66.0±5.6</td>
<td>69.1±5.3</td>
</tr>
<tr>
<td>Delayed phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle</td>
<td>107.0±11.4</td>
<td>103.2±11.9</td>
<td>111.7±9.1</td>
</tr>
<tr>
<td>Septum</td>
<td>76.2±7.2</td>
<td>74.3±8.0</td>
<td>78.4±5.4</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>42.7±4.1</td>
<td>43.7±4.3</td>
<td>41.5±3.4</td>
</tr>
<tr>
<td>ECV_CTP (%)</td>
<td>29.9±5.9</td>
<td>30.5±6.5</td>
<td>29.2±5.1</td>
</tr>
<tr>
<td>ECV_ref (%)</td>
<td>28.5±4.4</td>
<td>28.7±4.0</td>
<td>28.3±5.0</td>
</tr>
</tbody>
</table>

Numbers are reported as mean±standard deviation. *statistically significant, p<0.05. ECV_CTP: ECV calculated after CTP; ECV_ref: reference ECV; CTP: CT perfusion, ECV: extracellular volume

(509±35 mg iodine/kg vs. 619±50 mg iodine/kg, p<0.01) in patients with smaller iodine dose during CTP.
Minimum Contrast Medium for CT-ECV

Relationship between iodine dose and ECV\textsubscript{diff}
There was a weak but significant negative relationship ($R^2=0.07$, $p=0.01$) between iodine dose injected during CTP and ECV\textsubscript{diff} (Fig. 2A). The ECV\textsubscript{diff} of patients with an injected iodine dose $<285$ mg iodine/kg during CTP was significantly higher than that of the remaining patients (B). Dotted lines indicate 95% confidence intervals. ECV\textsubscript{diff}: difference of ECV between ECV calculated after CTP and reference ECV. CTP: CT perfusion, ECV: extracellular volume.

Reproducibility of measurements
The mean ECV\textsubscript{CTP} and ECV\textsubscript{ref} of observers 1 and 2 were $30.4\pm6.2\%$ vs. $31.1\pm6.5\%$ and $28.3\pm4.1\%$ vs. $28.8\pm4.9\%$, respectively. These values did not differ significantly ($p>0.05$). The ICC for ECV\textsubscript{CTP} and ECV\textsubscript{ref} were 0.86 and 0.74, respectively, indicating good interobserver agreement.

DISCUSSION
The present study showed that ECV\textsubscript{CTP} had a negative relationship with injected iodine dose. ECV\textsubscript{CTP} overestimated the ECV value when the iodine dose was $<285$ mg iodine/kg. There-
fore, we recommend a minimum value of 285 mg iodine/kg to correctly calculate ECV.

ECV calculations using MRI overestimate the value when a small amount of contrast medium is injected. ECVs calculated with an injection amount of 0.1 mmol/kg were 2.3% higher than ECV values with an injection amount of 0.2 mmol/kg [8]. Another study reported that an injection amount of 0.1 mmol/kg led to 1.9% higher ECV values than 0.15 or 0.20 mmol/kg injection protocols [9]. Because iodine and gadolinium are small aqueous molecules, their dispersion to the myocardium might be faster than the renal clearance, which could lead to overestimation of ECV values with a small injected amount of contrast medium. We acknowledge that the total number of contrast molecules injected during CT is much higher than during MRI. However, the following factors are important. First, although iodine and gadolinium are extracellular contrast agents, the ingredients are not the same. Second, the relationship between amount of contrast medium and enhancement is different in CT and MRI. Therefore, the minimum number of contrast molecules required for accurate quantification of ECV differs between the modalities.

ECV values might vary when the injection is performed by bolus only or by infusion. ECV rises slightly with time when the contrast medium is injected by bolus, but the difference between 2- and 20-minute postcontrast acquisitions was within 1% [9]. ECV might also be overestimated when ECV is >40% using a bolus only injection [11]. ECV calculation relies on the assumption of a 2-compartment model when a steady state exists between the compartments. This model might be limited when the equilibrium is incomplete [12]. To overcome that limitation, the amount of contrast medium should not be too small when the injection is performed by bolus only.

ECV derived from cardiac CT correlates well with ECV measured by cardiac MRI [5,7,13]. The injected iodine dose ranged from 580 to 670 mg iodine/kg, which is enough to calculate ECV according to our results. The benefits of CT over MRI in measuring the ECV is that the total examination time is shorter [5] and patients with cardiac devices can undergo CT exams [14]. The ECV calculation could be performed by just adding a delayed acquisition after a coronary CT scan. However, we need to be cautious when using advanced scanners, because coronary CT can be performed with an iodine dose lower than 285 mg iodine/kg [15].

We acknowledge that this study has the following limitations. First, the proposed cutoff of 285 mg iodine/kg is the value needed to calculate the ECV. Because the contrast between diseased and normal myocardium in CT is inferior to MRI, this amount might not be enough to visually diagnose delayed enhancement. Second, we used a tube voltage of 100 kVp in all patients. The results might vary when another tube voltage is used. Third, we used ECV values derived from delayed scans as a reference standard. We did not validate the ECV values using another modality such as cardiac MRI. Fourth, the scan interval after contrast medium injection might affect the ECV value because the equilibrium phase might not be achieved if the interval is too short. The mean scan timing to calculate $E_{CV_{CTP}}$ was 5.0 min, which is compatible with a previous study that recommended that a 5 min interval (minimum) is feasible for calculating the ECV [16]. Fifth, patients who received <285 mg iodine/kg were heavier than the remaining patients. Image noise might influence the accuracy of the ECV calculation; however, noise appears randomly, so although the ECV value might not be precise, the average value should not be influenced if the number of patients is large enough. Finally, the vasodilative effect of the ATP might increase the myocardial enhancement. However, the ECV calculated when the injected contrast medium was $\geq$285 mg iodine/kg did not differ significantly from the reference value. Therefore, the effect of ATP is probably small.

In conclusion, ECV values derived from cardiac CT might be overestimated when a small amount of contrast medium is injected. An iodine injection $\geq$285 mg iodine/kg is adequate to correctly calculate the ECV value using cardiac CT.

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

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