

RESEARCH ARTICLE

# Risk of Contrast-Induced Nephropathy after Repeated Contrast Medium Administration

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**Objective:** Non-invasive coronary computed tomography angiography is frequently used to exclude coronary artery disease in patients with low-to-intermediate pre-test probability because of the high negative predictive value. The strategy of coronary computed tomography angiography and subsequent invasive coronary angiography in case of positive findings has risks owing to repeated contrast medium administration and the possibility of contrast-induced nephropathy. **Methods:** We retrospectively evaluated the changes in the serum creatinine level and estimated glomerular filtration rate (at baseline, 24 h, and 48 h after contrast administration) in patients with repeated contrast medium administration in order to evaluate contrast-induced nephropathy development. All patients were intravenously hydrated with 1000 ml sodium chloride (0.9%) per day during hospitalization. **Results:** The study included 17 patients. Of these patients, 7 (41.2%) had prior impaired renal function (estimated glomerular filtration rate <60 ml/min/1.73 m<sup>2</sup>). The mean coronary computed tomography angiography contrast medium (iopromide 769 mg/ml) volume was 114.11 ± 7.75 ml and the mean invasive coronary angiography contrast medium (iohexol 755 mg/ml) volume was 129.7 ± 19.24 ml. The serum creatinine level was significantly higher and the estimated glomerular filtration rate was significantly lower at 48 hours after the second contrast medium administration than at baseline (p = 0.05 and p = 0.03, respectively). None of the patients had contrast-induced nephropathy. **Conclusion:** Repeated contrast medium administration was not associated with contrast-induced nephropathy development at 48 hours after the second contrast medium administration, even in patients with prior impaired renal function.

**Keywords:** contrast-induced nephropathy, contrast medium administration, renal function

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## Introduction

The rapid evolution of cardiovascular imaging during the last few decades has resulted in an increase in the use of intra-venous/intra-arterial iodinated contrast agents. Conventional invasive coronary angiography (ICA) is the gold standard approach for the evaluation of coronary artery disease (CAD), and non-invasive coronary computed tomography angiography (CCTA) is frequently used to exclude CAD in patients with low-to-intermediate pre-test probability. However, the strategy of CCTA and subsequent ICA in the case of positive findings has some risks owing to repeated contrast exposure and the possibility of subsequent contrast-mediated renal injury. Contrast-induced nephropathy (CIN) was first described in the 1950s [1], and it remains one of the leading causes of hospital-acquired acute renal injury [2]. Several studies have mentioned the incidence of CIN after single administration of radiocontrast medium [3,4]. However, in real life, repeated contrast medium administration (CMA) is not infrequent. The present study aimed to assess the change in renal function after two consecutive imaging procedures involving intra-venous and intra-arterial CMA in order to evaluate CIN development. To our knowledge, the risk of CIN development after CCTA followed by ICA has not been investigated previously.

## Methods

We reviewed the records of patients admitted to our institution for CCTA followed by ICA between January and December 2015. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board.

Renal function was evaluated according to changes in the serum creatinine (sCr) level and eGFR 24 hours after each CMA and 48 hours after the last CMA compared with baseline values (before CMA). The diagnostic criterion for CIN was a rise in the sCr level by 25% or more or an absolute increase in the sCr level by 0.5 mg/dl or more compared with the baseline value. The eGFR was calculated using the Cockcroft–Gault formula (creatinine clearance [CrCl] = [140–age] × weight / sCr × 72; CrCl<sub>female</sub> = CrCl × 0.85 [female sex adjustment]). The results are expressed as mean ± standard deviation (SD), and the data were compared using one-way ANOVA for repeated measurements. All statistical analyses were performed using STATA 14.0 (Stata Corporation, College Station, TX, USA). A p-value ≤0.05 was considered significant.

## Results

The study included 17 patients. Prior impaired renal function (eGFR <60 ml/min/1.73 m<sup>2</sup>) was noted in 41.2% of the patients, and a history of ST-elevation myocardial infarction (STEMI) was noted in 41.2% of the patients.

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The demographic and clinical characteristics of the study patients are presented in Table I.

**Table I. Demographic and clinical characteristics of the patients**

Parameter	Number (%)
Male	16 (94.1)
Age (mean $\pm$ SD), years	61.41 $\pm$ 9.007
Hypertension	15 (88.2)
Diabetes mellitus	4 (23.5)
Hypercholesterolemia	6 (35.2)
Smoking history	5 (29.4)
Obesity	4 (23.5)
Prior STEMI	7 (41.2)
Prior non-STEMI	2 (11.8)
eGFR < 60 ml/min/1.73 m <sup>2</sup>	7 (41.2)

eGFR: estimated glomerular filtration rate; STEMI: ST-elevation myocardial infarction

The time interval between procedures was 24 hours. In patients with a prior eGFR <60 ml/min/1.73 m<sup>2</sup>, ICA was performed after an additional 24-hour period. All patients were intravenously hydrated with 1000 ml sodium chloride (0.9%) per day during hospitalisation. Oral fluid intake was not assessed. Iopromide (769 mg/ml) was used for CCTA, and iohexol (755 mg/ml) was used for ICA.

The mean contrast volume received was 114.11  $\pm$  7.75 ml for iopromide and 129.7  $\pm$  19.24 ml for iohexol.

The sCr levels and eGFRs at baseline, 24 hours after the first CMA (CCTA), and 24 and 48 hours after the second CMA (ICA) are shown in Table II.

There were no significant differences in the mean sCr level and mean eGFR between baseline and 24 hours after ICA (sCr: 0.92  $\pm$  0.28 vs. 0.92  $\pm$  0.33 mg/dl,  $F(2.32) = 1.6$ ,  $p = 0.21$ ; eGFR: 95.43  $\pm$  26.69 vs. 94.48  $\pm$  23.3 ml/min/1.73 m<sup>2</sup>,  $F(2.32) = 1.22$ ,  $p = 0.29$ ). The sCr level was significantly higher and the eGFR was significantly lower 48 hours after ICA than at baseline (sCr: 0.95  $\pm$  0.08 vs. 0.92  $\pm$  0.28 mg/dl,  $F(3.48) = 3.08$ ,  $p = 0.05$ ; eGFR: 91.82  $\pm$  21.84 vs. 95.43  $\pm$  26.69 ml/min/1.73 m<sup>2</sup>,  $F(3.48) = 4.13$ ,  $p = 0.03$ ). None of the patients met the diagnostic criterion for CIN.

## Discussion

CIN affects up to 50% of patients at high risk [3], and it is a clinical reality with high health and economic burdens [5]. In a previous large meta-analysis, James et al. found that the presence of CIN following coronary angiography was associated with increased patient mortality and major cardiovascular events [6].

The risk of CIN after a second contrast exposure has been investigated in a few studies. Trivedi et al. reported a CIN incidence of 14.3% after repeated CMA, even in patients with preserved renal function [7]. On the other

hand, Winther et al. performed a study on the effect of repeated CMA in patients with end-stage kidney disease and found a low risk of post-contrast acute kidney injury and long-term complications [8].

In the present study, we investigated the impact of both intra-venous and intra-arterial CMA on renal function assessed according to the sCr level and eGFR. The important finding of our study was the complete absence of CIN, even in patients with prior impaired renal function. Only 1 patient showed a significant decrease in the eGFR, resulting in a change in the classification of kidney disease from 3a to 3b. However, this patient had other risk factors for kidney disease, such as hypertension and insulin-dependent diabetes mellitus. Interestingly, several patients showed better values of sCr and eGFR at 24 hours after the first CMA, supporting the hypothesis of the correction of pre-renal dysfunction after the initial procedure by intravenous administration of sodium chloride (0.9%). It is known that oral hydration can improve renal function after CMA [9,10]. However, data on the extent of oral fluid intake before and after CMA were not available.

Our findings appear to confirm previous results indicating the lack of kidney injury after CMA [11,12]. Sinert et al. compared contrast-exposed patients with contrast-unexposed patients and did not find significant kidney injury after CMA in patients with previously normal renal function. In fact, the incidence of acute kidney injury was greater among patients without CMA than among those with CMA (8.9% vs. 5.7%) [13]. Additionally, McDonald et al. did not find a greater risk of nephropathy development in contrast-exposed patients than in contrast-unexposed patients, irrespective of baseline renal function [14]. These findings question whether CMA or other pathological conditions actually cause degradation of renal function.

The present study had several limitations. First, this study had a small sample size. Second, this retrospective study had a possible selection bias (oral hydration status and other prophylactic treatments to prevent CIN). Third, the sCr level and eGFR at 72 hours or more after the second CMA were not assessed. Renal function might decline late after CMA. Thus, further studies with a large sample size and long assessment period are needed.

In conclusion, although the sCr level was high and eGFR was low 48 hours after the second CMA, repeated CMA was not associated with CIN development at this point, even in patients with impaired renal function prior to CMA. Intravenous administration of sodium chloride (0.9%) might help improve renal function before and after CMA.

**Table II. Evolution of serum creatinine (sCr) level and estimated glomerular filtration rate (eGFR)**

Parameter	Baseline	24 hours after CCTA	24 hours after ICA	48 hours after ICA
sCr (mean $\pm$ SD), mg/dl	0.92 $\pm$ 0.28	0.89 $\pm$ 0.25	0.92 $\pm$ 0.33	0.95 $\pm$ 0.08
eGFR (mean $\pm$ SD), ml/min/1.73 m <sup>2</sup>	95.43 $\pm$ 26.69	97.68 $\pm$ 23.95	94.48 $\pm$ 23.3	91.82 $\pm$ 21.84

CCTA: coronary computed tomography angiography; ICA: invasive coronary angiography

### Author's contribution

VD - Conceptualization, data curation, formal analysis, methodology, supervision, validation, visualization, writing original draft, writing review and editing

MD - Data curation, investigation, methodology, validation, writing review and editing

CM - Conceptualization, formal analysis, methodology, validation, writing original draft

IVS - Data curation, formal analysis, methodology, supervision, writing review and editing

MB - Conceptualization, formal analysis, methodology, supervision, validation, writing review and editing

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### Conflict of interest

None to declare.

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