European Radiology (2019) 29:5314–5321
https://doi.org/10.1007/s00330-019-06138-3

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Immediate and delayed hypersensitivity after intra-arterial injection of iodinated contrast media: a prospective study in patients with coronary angiography

Kyoung-Hee Sohn[1,2] · Gun-Woo Kim[2,3] · Suh-Young Lee[2,4,5] · Hyo-Soo Kim[6] · Sang-Heon Cho[2,4,5] · Jung-Kyu Han[6] · Hye-Ryun Kang[2,4,5]

Received: 11 January 2019 / Revised: 18 February 2019 / Accepted: 7 March 2019 / Published online: 1 April 2019

Abstract

Objectives While hypersensitivity reactions (HSR) to intravenously administered iodinated contrast media (ICM) have been well studied, not much is known about HSR to intra-arterially administered ICM.

Methods A prospective observational study was performed to evaluate coronary angiography (CAG)-induced ICM hypersensitivity in patients who underwent CAG using ICM including ioversol, a low-osmolar non-ionic monomer, and iodixanol, an iso-osmolar non-ionic dimer. The HSR were investigated through in-patient monitoring after CAG and telephone interview after discharge.

Results A total of 714 patients were enrolled during the observation period, of whom 26 (3.6%) showed immediate HSR and 108 (15.1%) showed delayed HSR. With regard to severity, proportion of immediate HSR grades 1, 2, and 3 was 57.7%, 38.5%, and 3.8%, respectively, whereas that of delayed HSR grades 1, 2, and 3 was 85.2%, 13.9%, and 0.9%, respectively. Multivariate analysis revealed that previous intra-arterial exposure to ICM was an independent risk factor for immediate HSR (odds ratio (OR) 2.92, 95% confidence interval (CI) 1.22–6.96; $p = 0.015$). Iodixanol was a significant risk factor for delayed HSR (OR 1.61, 95% CI 1.07–2.43; $p = 0.024$) and correlated with a higher incidence of delayed HSR within 24-h post-ICM administration compared to ioversol.

Conclusion The incidence rate of immediate and delayed HSR in intra-arterially administered ICM was 3.6% and 15.1%, respectively. Previous exposure to intra-arterially administered contrast media was a significant risk factor for immediate HSR. Compared to ioversol, iodixanol was associated with relatively earlier and more frequent delayed HSR.

Key Points

- *In this prospective study, the incidence of immediate and delayed hypersensitivity in intra-arterial injection of contrast media during coronary angiography was 3.6% and 15.1%, respectively.*
- *Delayed hypersensitivity reactions were more common but less severe than immediate hypersensitivity reactions during coronary angiography.*
- *Previous exposure to ICM* via *intra-arterial route was a significant risk factor for immediate hypersensitivity to intra-arterial contrast medium.*

Keywords Coronary angiography · Hypersensitivity · Contrast media · Prospective studies

✉ Jung-Kyu Han
hpcrates@gmail.com

✉ Hye-Ryun Kang
helenmed@snu.ac.kr

[1] Department of Internal Medicine, Kyung Hee University Medical Center, Seoul, South Korea

[2] Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul, South Korea

[3] Department of Internal Medicine, St. Carollo General Hospital, Suncheon, South Korea

[4] Division of Allergy and Clinical Immunology, Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Chongno-gu, Seoul 110-744, South Korea

[5] Seoul National University Hospital Regional Pharmacovigilance Center, Seoul, South Korea

[6] Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, 101 Daehak-ro, Chongno-gu, Seoul 110-744, South Korea

Abbreviations

CAG	Coronary angiography
CI	Confidence interval
CT	Computed tomography
HSR	Hypersensitivity reactions
IA	Intra-arterial
ICM	Iodinated contrast media
IV	Intravenous
OR	Odds ratio

Introduction

With recent advancements in medical-imaging equipment and the wide use of imaging for diagnostic purposes, the use of iodinated contrast media (ICM) is constantly increasing. As a result, adverse reactions, classified as toxic reactions and hypersensitivity to ICM are also increasing [1]. Adverse reactions to ICM can be further classified as immediate adverse reactions or delayed adverse reactions according to time of onset and symptoms [2]. Hypersensitivity reactions (HSR) are either immediate reactions occurring within 1-h post-ICM administration, or delayed HSR, which become apparent 1 h to 2 weeks post-ICM administration [3, 4].

The incidence of immediate HSR to contrast ranges from 0.2 to 3% for mild-to-moderate cases and 0.004 to 0.04% for severe cases [5–7]. The incidence of delayed HSR is unclear because of limitations in post-ICM monitoring, as adverse reactions often occur after the patient has been discharged; some studies have reported an incidence between 0.01–9.5% [8, 9]. Transient erythema is the most common delayed HSR; however, drug reactions with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, and toxic epidermal necrolysis have also been reported [3, 10].

The increase in elderly population and incidence of cardiocerebrovascular diseases has led to the widespread use of coronary angiography (CAG) or cerebral angiography. In CAG, the contrast medium is administered through the intra-arterial (IA) route instead of the intravenous (IV) route; hence, the pattern of adverse reactions might differ from that observed with ICM delivered through the IV route. However, the incidence, onset, and severity of adverse reactions to ICM administered through the IA route based on prospective observational studies have not been reported. Previous studies on the use of contrast media through IA route have indicated an incidence of immediate adverse reactions between 2.7–4.0% [11, 12] and of delayed adverse reactions, 24.8–45.8%, which is higher than that reported in studies involving use of ICM through IV route [13–15]. However, since these studies were based on voluntary reporting by discharged patients, there is a probability that cardiac symptoms, related to underlying cardiovascular disease or coronary procedure (e.g., chest pain), were being reported [15]. In this prospective study, we aimed to determine the incidence and severity of immediate and delayed hypersensitivity related to IA administration of contrast in patients undergoing CAG and analyze the risk factors for immediate and delayed hypersensitivity.

Methods

Study participants

Patients who received underwent CAG from February 2015 to October 2015 at the Department of Internal Medicine of Seoul National University Hospital were included in the study. Demographic information and presence of pre-existing conditions were obtained through retrospective analysis of electronic medical records. The study was approved by the Institutional Review Board of Seoul University Hospital (IRB No. 1412-052-632); all patients provided written informed consent to participate in this study.

Study methods

CAG with or without percutaneous coronary intervention was performed through the radial or femoral artery per protocol at the Cardiovascular Center of Seoul National University Hospital. Ioversol (Optiray 320®) and iodixanol (Visipaque®) were used as contrast media; ioversol is a second-generation, low-osmolar, non-ionic monomer (osmolarity, 710 mOsm/kg·H_2O; viscosity at 37 °C: 5.8 mPa/S) and iodixanol is a third-generation, iso-osmolar, non-ionic dimer (osmolarity, 290 mOsm/kg·H2O; viscosity at 37 °C: 6.3 mPa/S). The patients were alternatively assigned in the order of procedure.

To determine the presence of immediate HSR after CAG, a nurse observed patients in the recovery room for 1 h; for delayed HSR, four nurses affiliated with the Pharmacovigilance Center conducted phone interviews at 6- to 12-h and 1-, 3-, 7-, and 14-days post-examination to investigate the occurrence of following reactions: cutaneous (rash, urticaria, erythema, pruritus, or heat sensation), cardiovascular system (chest discomfort or palpitations), respiratory system (dyspnea or wheezing), digestive system (nausea or vomiting), nervous system (dizziness), urinary system (urinary symptoms), musculoskeletal system (pain), upper airway system (epistaxis), and fever. Patients who experienced immediate HSR were classified according to grading of ESUR guideline 10.0 (http://www.esur-cm.org/index.php/en/) and delayed HSR were graded as mild in patients with no treatment requirement, moderate in patients showing immediate response to appropriate treatment with no need for hospitalization, and severe in patients with a reaction requiring hospitalization or was life-threatening. Serum creatinine was measured before examination (1 week before

the CAG to day 0) and on days 2 or 3. Acute kidney injury (AKI) was defined as an increase in serum creatinine > 0.3 mg/dL, or > 1.5 times baseline, within 48–72 h.

Statistical analysis

The sample size was determined to investigate delayed HSR. Assuming the delayed HSR ratio was 30%, the estimated sample size was calculated as 559 with a 5% type 1 error and 99% confidence level. Mean differences between continuous variables in the adverse reactions group and the control group was analyzed using *t* test and the results represented as mean ± standard deviation. As the immediate HSR did not follow the normal distribution, the Kruskal-Wallis test was performed. Comparison of the frequency between the three groups (no exposure to contrast, previous IA exposure, and previous IV exposure) was performed using chi-square test and Fisher's exact test, and the correlation between patient age and the amount of contrast media was analyzed using Pearson's correlation. We conducted logistic regression to evaluate risk factors. First, we conducted univariate logistic regression; variables with $p < 0.1$ in univariate analysis were included as candidate variables in multiple logistic regression. For the onset time of delayed HSR, each contrast media was analyzed using Fisher's exact test. Statistical analyses were performed using SPSS version 23.0 (IBM Corp.), and results with $p < 0.05$ were considered statistically significant.

Results

Patient characteristics

During the study period, 726 CAGs were conducted, of which 714 patients were enrolled in this study. The mean age was 62.9 ± 10.3 years, and 71.0% (507/714) of the patients were male. There were 428 (59.9%) patients with previous IV exposure to ICM and 343 (48.0%) patients with previous history of CAG. Seventy-two patients (10.1%) reported presence of allergic disease, including bronchial asthma, allergic rhinitis, atopic dermatitis, drug allergy, or food allergy (Table 1).

Characteristics of patients with immediate and delayed HSR

Of the 714 patients who received CAG, 26 (3.6%) patients had immediate HSR, and 108 (15.1%) had delayed HSR. Twenty patients had a history of previous HSR to ICM; all of whom were pre-medicated with anti-histamines, and three patients were administered steroids in addition to anti-histamines. Among these 20 patients, one (5.0%) showed immediate HSR, and three (15.0%) showed delayed HSR. However, there was no statistically significant difference as compared to the control group (without previous adverse reaction).

Patients in the immediate HSR group had a higher proportion of males (71.0%) and a history of previous exposure to ICM via intra-articular route. With regard to the development of delayed HSR, iodixanol was associated with an incidence of 18.8% (56/298), whereas was associated with an incidence of 12.5% (52/416) ($p = 0.02$).

Clinical symptoms and severity of immediate and delayed HSR

The incidence of immediate HSRs differed among the groups based on previous ICM exposure: those with no exposure to ICM reported a lower incidence of HSR (2.4%) compared to those in the IV and IA exposure groups; however, this difference was not statistically significant. The incidence of immediate HSR was 3.3% with previous IV exposure and 5.2% with previous IA exposure, which indicated that IA exposure was related to a higher risk of immediate HSR (p value = 0.04). On the other hand, there were no significant differences in the incidence of delayed HSR across the three groups (no exposure group 17.5%, previous IV exposure group 14.5%, previous IA exposure group 14.3%; Fig. 1a).

Among the 26 patients with immediate HSR, grade 1 was observed in 15 (57.7%) patients, grade 2 in 10 (38.5%), and grade 3 in one (3.8%); in delayed HSR, mild, moderate, and severe reactions were observed in 92 (85.2%), 15 (13.9%), and one (0.9%) patient(s), respectively (Fig. 1b). Among these, the patient with severe immediate HSR experienced symptoms of anaphylaxis, such as hypotension, angioedema, and dyspnea, whereas the patient with severe delayed HSR experienced whole-body maculopapular eruption with mucositis.

Among the patients with immediate HSR, 17 (65.4%) patients showed skin symptoms, followed in order by gastrointestinal (19.2%), cardiovascular (11.5%), CNS (11.5%), and respiratory (3.8%) symptoms. Among the patients exhibiting delayed HSR, 81 (75.0%) patients showed cutaneous reactions, 15 patients (13.9%) showed reactions involving the CNS, including dizziness, and 13 (12.0%) patients showed cardiovascular symptoms, such as chest pain and palpitations. Reactions related to the digestive system were observed in 8.3% of patients, those related to the respiratory system in 3.7%, those involving fever in 1.8%, and those involving the urinary system, musculoskeletal system, or upper airway symptoms in 0.9% of patients (Table 2).

Five of 711 patients with pre- and post-renal function test results showed > 1.5 times baseline and/or an increase in serum creatinine > 0.3 mg/dL (incidence 0.7%), and there was no difference according to contrast type.

Table 1 Baseline characteristics of the study

	Total	Immediate HSR		*p* value	Delayed HSR		*p* value
	(*n* = 714)	Absence (*n* = 688)	Presence (*n* = 26)		Absence (*n* = 606)	Presence (*n* = 108)	
Age (years)	62.9 ± 10.3	63.1 ± 10.2	58.5 ± 10.8	0.026*	63.0 ± 10.3	62.9 ± 10.4	0.920
Male gender	507 (71.0%)	490 (71.2%)	17 (65.4%)	0.520	437 (72.1%)	70 (64.8%)	0.124
Previous IV exposure to ICM	428 (59.9%)	414 (60.2%)	14 (53.8%)	0.518	366 (60.4%)	62 (57.4%)	0.595
1	225	216	9	0.663	190	35	0.822
≥ 2	203	198	5	0.378	176	27	0.420
Previous IA exposure to ICM	343 (48.0%)	325 (47.2%)	18 (69.2%)	0.028*	294 (48.5%)	49 (45.4%)	0.547
1	184	176	8	0.648	156	28	0.968
≥ 2	159	149	10	0.043*	138	21	0.444
Allergic disease[a]	72 (10.1%)	68 (9.9%)	4 (15.4%)	0.361	62 (10.2%)	10 (9.3%)	0.757
CKD	51 (7.1%)	50 (7.3%)	1 (3.8%)	1.000	47 (7.8%)	4 (3.7%)	0.157
Bun (mg/dL)	16.7 ± 8.2	16.7 ± 8.3	16.1 ± 6.1	0.700	16.9 ± 8.6	15.6 ± 5.3	0.126
Cr (mg/dL)	1.1 ± 1.1	1.1 ± 1.1	1.1 ± 1.3	0.912	1.1 ± 1.1	1.0 ± 0.7	0.286
DM	40 (5.6%)	40	0		36 (5.9%)	4 (3.7%)	0.614
Contrast media							
Ioversol (Optiray®)	416 (58.3%)	405	11	0.093	364	52*	0.021*
Iodixanol (Visipaque®)	298 (41.7%)	283	15	0.093	242	56*	0.021*
Radiation dose (mg)	137.2 ± 92.3	136.2 ± 92.5	163.5 ± 85.9	0.140	137.6 ± 94.8	135.0 ± 77.1	0.788
Previous ICM hypersensitivity[b]	20 (2.8%)	19 (2.8%)	1 (3.8%)	0.529	17 (2.8%)	3 (2.8%)	1.000

[a] Allergic disease is defined as if patients have one of following alone or in combination: bronchial asthma, allergic rhinitis, atopic dermatitis, urticaria, drug allergy (antibiotics, NSAID, sulfa, or pyrine), or food allergy

[b] Among 20 patients, 17 patients were administered anti-histamines, and three patients were administered anti-histamines and steroids as pre-medications

* *p* value < 0.05

HSR, hypersensitivity reactions, *ICM* iodinated contrast media, *IA* intra-arterial, *IV* intravenous, *CKD* chronic kidney disease, *DM* diabetes mellitus

Risk factors for immediate and delayed HSR

We used multivariate logistic regression analysis to determine risk factors for development of immediate and delayed HSR in patients who underwent CAG. The patients' age, previous exposure to contrast media through IV and/or IA route, history of allergic disease, cumulative dose of contrast agent, and ICM type were considered dependent variables. A history of previous exposure to ICM through IA was a significant risk factor for immediate HSR (OR 2.92, 95% CI 1.22–6.96; $p = 0.015$; Table 3). The use of iodixanol was a significant factor in the development of delayed HSR, compared to the use of ioversol (OR 1.61, 95% CI 1.07–2.43; $p = 0.024$) (Table 3).

Subgroup analysis of immediate and delayed HSR based on the contrast media type

Since the incidence of delayed HSR was different based on the type of contrast media used, subgroup analysis based on ICM type used in CAG was conducted. For immediate HSR, the iodixanol group demonstrated a slightly higher incidence, which did not reach statistical significance compared to the ioversol group (5.3% vs. 2.7%, $p = 0.092$, Fig. 2). The incidence of delayed HSR was 12.5% in the ioversol subgroup and 18.8% in the iodixanol subgroup ($p = 0.022$). With regard to the incidence of delayed HSR by onset time, the iodixanol subgroup showed an earlier occurrence, with significant differences between the two ICM types for incidence within 24 h ($p = 0.002$). There was no difference between the two groups in severity or clinical manifestations both immediate and delayed HSR (data not shown).

Discussion

The present prospective study examined the incidence and severity of immediate and delayed HSR to contrast administered through the IA route, reporting on 714 patients who underwent CAG. The results indicated an incidence rate of 3.6% for immediate HSR and 15.1% for delayed HSR. Immediate HSR occurred at a 2.9-fold higher frequency in patients with previous history of IA route of contrast administration; delayed HSR occurred at a 1.6-fold higher frequency in patients administered iodixanol versus ioversol.

Since the development of low-osmolar, non-ionic contrast media in the 1970s, the use of contrast media has continued to

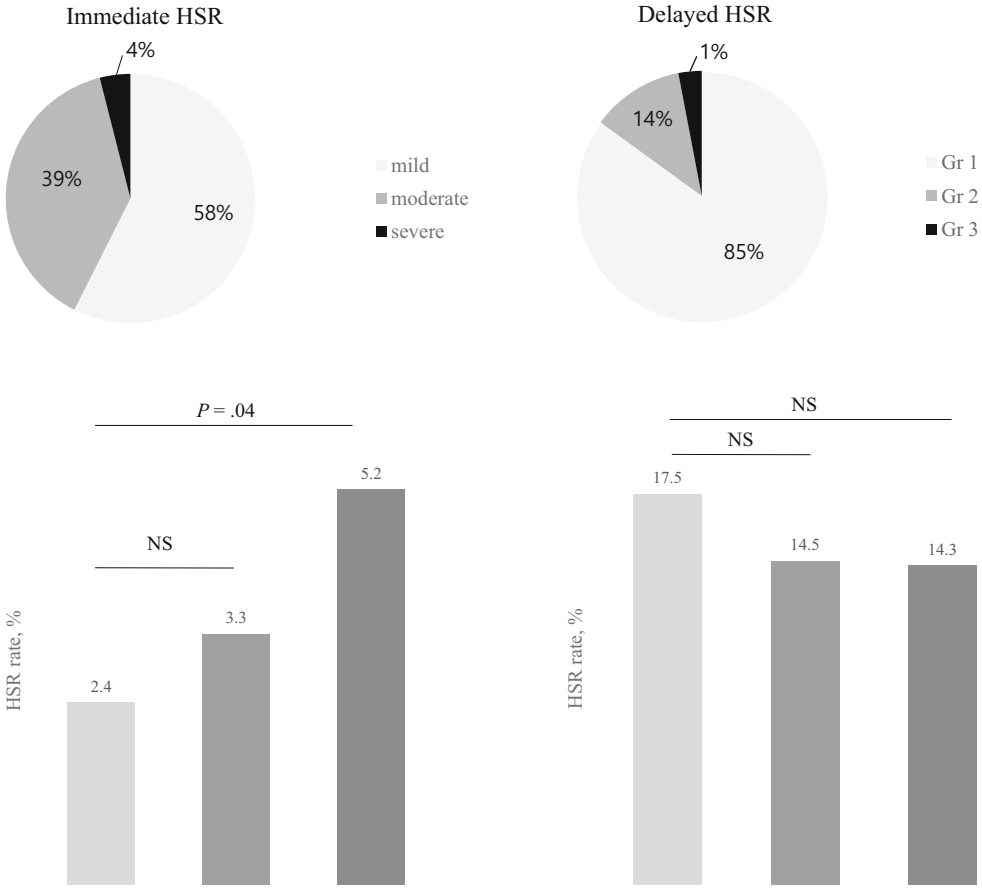

Fig. 1 **a** Rate of hypersensitivity reactions according to previous exposure to intravenous and intra-arterial contrast agents: Previous exposure to ICM via intra-arterial route increased the incidence of immediate HSR. **b** Pie-chart showing severity of immediate and delayed hypersensitivity reactions in immediate and delayed HSR. HSR hypersensitivity reactions, ICM iodinated contrast media

expand. Unlike conventional CT scan, CAG involves the injection of contrast media into an artery, resulting in maintenance of high concentration media through systemic circulation. For the IV route of contrast exposure, immediate HSR was reported in 0.7 to 15% of cases [16, 17], and delayed HSR was reported in 0.1 to 10.7% of cases [9, 18]. The incidence of immediate HSR via IA to contrast was similar; however, the incidence of delayed HSR was slightly higher in the IA route, compared to intravenous injection. In a survey of 118 patients who underwent CAG, Sakai et al [14] reported that 45.8% of patients experienced delayed adverse reactions; whereas Sutton et al [15] reported that 24.8% of 2001 patients undergoing CAG, showed delayed HSR to non-ionic contrast media. In our study, the incidence of delayed HSR to contrast media following CAG was 15.1%, which was lower than the previously reported data. Because previous studies were based on retrospective self-reporting, there is a possibility that these studies overestimated adverse reactions by reporting cardiovascular disease-specific or procedure-related symptoms (e.g., chest pain) as adverse reactions to ICM. To reduce such background noise in this study, trained pharmacovigilance nurses conducted follow-up surveys through telephone interview for 2 weeks and reviewed patient medical records related to HSR. Sutton et al [15] reported female sex as a risk factor; however, sex-related differences were not observed in this study.

Through this study, we confirmed a higher incidence of contrast-induced immediate HSR with previous IA exposure compared to previous IV contrast administration. Hemodynamically, IA contrast administration differs from IV in that a similar contrast enhancement is achieved with less contrast because of the high velocity of blood flow in the artery; in addition, the artery has a thick smooth-muscle cell layer, fibroblasts, and vascular stem cells, which increases the likelihood of immune activation through structural interactions with leukocytes and mast cells. Additionally, antigen-presenting dendritic cells, which are keys to the sensitization underlying immediate HSR, are often found in atherosclerotic vascular lesions [19]. Because of these immunological concepts, we speculated that intra-articular exposure to contrast was likely to increase the risk for immediate HSR.

Moreover, a different pattern of delayed HSR according to the contrast used was observed. Iodixanol induced delayed HSR more frequently and at a relatively earlier time-point than ioversol. Previous study also showed a higher incidence of delayed cutaneous reactions with iodixanol than with ioxaglate or iopamidol [20]. The involved pathophysiological mechanisms were not clearly identified; however, an in vivo study conducted by Speck et al [21] reported that non-ionic dimers, when administered through IV injection, are retained for longer time-periods (over 72 h) in organs, such as the skin,

Table 2 Clinical manifestations of immediate and delayed hypersensitivity reactions to intra-arterially administered iodinated contrast media

	Immediate[a] ($n = 26$)	Delayed[a] ($n = 108$)
Cutaneous symptom	17 (65.4%)	81 (75.0%)
Cardiovascular symptom	3 (11.5%)	13 (12.0%)
CNS symptom	3 (11.5%)	15 (13.9%)
GI symptom	5 (19.2%)	9 (8.3%)
Respiratory symptom	1 (3.8%)	4 (3.7%)
Urinary symptom	–	1 (0.9%)
Musculoskeletal symptom	–	1 (0.9%)
Upper respiratory symptom	–	1 (0.9%)
Fever	–	2 (1.8%)

[a] If patients experience any of the following symptoms, multiple responses were available

CNS central nervous system, *GI* gastrointestinal

liver, lungs, lymph nodes, and spleen. Delayed HSR developing within 1 to 6 h is defined as an "accelerated reaction," and our study showed a higher incidence of hypersensitivity reactions occurring with 24 h following administration of the dimeric ICM, iodixanol.

Most delayed HSR to contrast are cutaneous reactions: maculopapular rash, itching, or local edema [4]. However, generalized systemic effects, including vomiting, headache, myalgia, and fever may also be observed. Similar to drug-related delayed HSR, CD4 T cell–mediated reactions have been observed in skin biopsy specimens in cases of delayed reactions to contrast [22, 23]. In case of non-immediate HSR, the results indicate 38 to 79% positivity for delayed skin tests and patch test [24, 25], with 96–100% specificity for intradermal tests performed within 24 h [24]. This suggests that delayed HSR may result from possible exposure during the sensitization period. Therefore, the role of allergy in delayed HSR to contrast remains unclear and large-scale studies evaluating the pathogenic mechanisms using skin tests are required.

Four factors determine the adverse reactions to contrast media: ionicity, osmolarity, viscosity, and chemotoxicity. According to previous studies, osmolarity significantly affects renal toxicity, with viscosity also reportedly involved in this response [26]. For patients receiving CAG, older age and poor renal function are considered as risk factors for cardiovascular disease. Therefore, a dimer-type contrast media with an osmolarity similar to blood plasma is preferred to prevent renal toxicity [27]; however, dimer ICMs tend to increase the probability of delayed HSR [20]. Iodixanol, a non-ionic dimer, exhibits low hemodynamic effect and is considered advantageous for cardiovascular function [11]. In this study, iodixanol caused a higher incidence of delayed HSR compared with ioversol in patients during CAG, although there was no difference in severity. Therefore, if iodixanol is used for patients with poor cardio-renal function, the patient should be carefully monitored for symptoms of delayed HSR.

Along with HSR, nephrotoxicity following the administration of ICM remains a clinically important concern in contrast-enhanced CT and angiography [24, 28, 29]. The incidence of AKI varied depending on the definition of AKI, ranging from 0.7 to 50% [30–32]. In the current study, the incidence of AKI was 0.7% and there was no difference according to ICM types while a previous study demonstrated that iodixanol was beneficial to protect against AKI in high risk patients during CAG [32].

This is the first prospective study focused on HSR following contrast exposure through IA route; however, there are some limitations. First, only two ICMs, iodixanol and ioversol, were studied; therefore, these observations are not representative of all available contrast media. Second, sensitization status evaluated through skin test was not available;

Table 3 Multiple logistic regression analysis according to immediate and delayed hypersensitivity reactions

	Immediate HSR ($n = 26$) vs. control ($n = 688$)			
	Unadjusted OR (95% CI)	p value [a]	Adjusted OR (95% CI)	p value
Previous IA exposure (−)	Reference		Reference	
Previous IA exposure (+)	2.51 (1.08–5.86)	0.028	2.92 (1.22–6.96)	0.015
	Delayed HSR ($n = 108$) vs. control ($n = 606$)			
	Unadjusted OR (95% CI)	p value [b]	Adjusted OR (95% CI)	p value
Ioversol	Reference		Reference	
Iodixanol	1.62 (1.07–2.44)	0.021	1.61 (1.07–2.43)	0.024

[a] The p values were determined by multivariate logistic regression analysis with adjustments for age, previous exposure to contrast via IV and IA route, previous hypersensitivity to contrast, history of allergic disease, cumulative dose of contrast and type of contrast media

[b] The p values were determined by multivariate logistic regression analysis with adjustments age, previous exposure to contrast via IA and IA route, history of allergic disease and type of contrast

IA intra-arterial, *CI* confidence interval, *OR* odds ratio

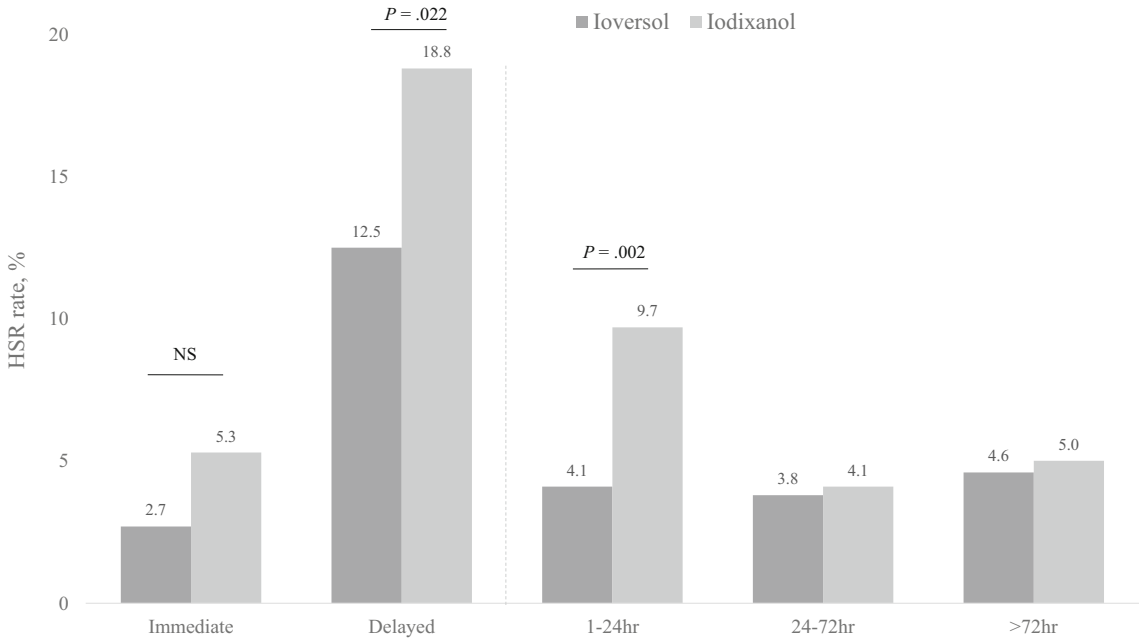

Fig. 2 Immediate and delayed hypersensitivity reactions according to onset time, based on type of contrast media. HSR hypersensitivity reactions

therefore, limitations exist in identification of the mechanism associated with delayed HSR. Third, since our study was originally designed to investigate delayed HSR, the statistical power was not sufficient to reach a general conclusion of immediate HSR. Lastly, the use of ICM was similar to a random assignment but it was not strictly randomized. Therefore, the possibility of unknown bias affecting the choice of ICM cannot be completely ruled out although there was no intentional bias in the selection of ICM. Nevertheless, the present study has several strengths based on largest prospective design and comprehensive analysis using structured questionnaires.

In conclusion, our study was conducted to determine the incidence and clinical patterns associated with immediate and delayed HSR to contrast exposure via IA route, in patients who underwent CAG. Our findings showed that intra-arterial injection of contrast media resulted in an incidence rate of 3.6% and 15.1% for immediate and delayed HSR, respectively. Although delayed HSR occurred at a higher rate compared with that of immediate HSR, severe reactions were rare, at 0.0014%. Further studies are needed to investigate the efficacy of skin test and pre-medication in patients with delayed HSR to iodinated contrast.

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Hye-Ryun Kang.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all patients in this study.

Ethical approval Institutional Review Board approval was obtained (the Institutional Review Board of Seoul National University Hospital (IRB No. 1412-052-632).

Methodology
- prospective
- observational
- performed at one institution

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