

Iodinated Contrast Media Allergy in Patients Hospitalized for Investigation of Chest Pain



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What is already known about this topic? Iodinated contrast media (ICM) allergy is often considered as a significant contraindication for percutaneous coronary intervention (PCI), thus causing delays in the treatment of subjects with chest pain and compromising patient management.

What does this article add to our knowledge? PCI does not appear to induce clinically significant allergic reactions, regardless of the presence or absence of a previous diagnosis of ICM allergy. This study could not demonstrate any advantage for premedication, and future prospective trials should determine whether it is still indicated.

How does this study impact current management guidelines? This study advocates reconsideration of premedication administration in subjects with ICM allergy.

BACKGROUND: Iodinated contrast media (ICM) allergy may entail severe adverse events in patients who undergo percutaneous coronary intervention (PCI). Premedication protocols and low-osmolality contrast media have been thought to improve the outcomes of these individuals.

OBJECTIVE: The objective of this study was to assess the prevalence and severity of allergic reactions during PCI in patients admitted for investigation of chest pain.

METHODS: This is a retrospective analysis of 13,652 patients who were hospitalized with chest pain during the years 2010-2016, at the Department of Internal Medicine, Meir Medical Center. Patient records were screened for diagnosis of prior ICM allergy. Primary outcomes were: (1) records of previous allergy to ICM, (2) administration of antiallergic premedication, and (3) allergic reactions to the ICM during the procedure.

RESULTS: Nine hundred thirty-one individuals without prior ICM allergy were referred for PCI, of whom 2 had minor allergic reactions. Previously diagnosed ICM allergy was recorded for 216 subjects (mean age 65.5 ± 10 years, 42% males). Of these, 32 were referred to in-hospital PCI. Premedication was

administered in 10 cases only with no documented rationale for not treating the other 22. Only one of the pretreated patients experienced a reaction attributed to allergy, showing no statistical advantage for premedication. No mortality was documented in the 30 days after PCI among the patients with known ICM allergy.

CONCLUSIONS: PCI did not induce substantial allergic reactions to ICM in patients with a previously diagnosed allergy. This study did not demonstrate an advantage for premedication. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:2059-64)

Key words: Iodine allergy; Chest pain; Percutaneous coronary intervention; Allergic reaction; Mortality

Primary percutaneous coronary intervention (PCI) is considered as the definitive management for ischemic heart disease. PCI requires injection of iodinated contrast media (ICM) to enable imaging of the coronary arteries. Adverse reactions to ICM that are associated with PCI are rare, but potentially fatal.¹ Possible underlying mechanisms for hypersensitivity reactions to ICM include immediate and nonimmediate reactions, immune complex disease, and cytotoxic reaction.²⁻⁴ Hypersensitivity responses are thought to involve mast cells,⁵ serotonin release,⁶ and IgE antibodies.⁷ Increased osmolality of the injected agent has been suggested to play a role in direct mast cell activation. The rate of severe hypersensitivity reactions to ICM has been reported to be as low as 0.03% to 0.16%.⁴ However, in patients with a prior adverse reaction, the incidence may be increased by 5-fold.⁸ Premedication has been suggested to decrease the risk for recurrence by 50%.⁹ Recommended protocols mostly include corticosteroids and H1 and H2 blockers,³ while specific drug types and doses vary across medical centers. The currently common use of low-osmolality ICM further decreases the risk of an allergic reaction.^{3,10}

Individuals with chest pain, who are candidates for nonemergency PCI, are occasionally suspected of having ICM

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*Abbreviations used**ACS- Acute coronary syndrome**ICM- Iodinated contrast media**PCI- Percutaneous coronary intervention*

allergy. This may be due to a previous reaction, but may also be attributed to the erroneous diagnosis of “iodine allergy.” The latter is an entity that does not exist, and is frequently confused with seafood or fish allergy, hypersensitivity to antiseptic solutions, or other conditions that are unrelated to ICM allergy. It remains unclear whether ICM allergy invariably requires preparation for nonemergency PCI, and how important it is to recommend a premedication regimen. In this study, we examined the impact of ICM allergy in patients who had been hospitalized because of chest pain. We also assessed the significance of a previous diagnosis of ICM allergy.

METHODS

Patients and study design

This study was based on a retrospective cohort of patients with chest pain, compiled at the Meir Medical Center. Data were retrieved from the medical records of the Emergency Room, Department of Medicine, and the Intensive Cardiac Care Unit, from January 1, 2010, through June 31, 2016. The compilation of this cohort was focused on nonemergency PCI, and therefore patients with an established diagnosis of acute coronary syndrome (ACS) or angina equivalent symptoms (such as dyspnea) were excluded.

Records were screened for the complete list of diagnoses, demographic data, laboratory values, and medical procedures (including PCI). Mortality data were collected through the hospital medical record system, which is interfaced with the Ministry of Health database, thus allowing access to post-hospitalization documentation. Death events were considered to be likely related to the procedure only if they occurred within the following 30 days, according to the accepted definition.¹¹

Definition of ICM allergy

Prior ICM allergy was determined in patients who had a documented diagnosis of a personal history of allergy to radiographic dye on their admission. Specific details of a prior allergic event were derived from screening of community and hospitalization medical records. The absence of further verification to this diagnosis was not regarded as an exclusion criterion.

Contrast media and premedication regimen

During the study period, all PCI procedures were carried out with the nonionic iodinated radiographic contrast medium ULTRAVIST 370 (iopromide injection 77% w/v, 370 mg I/mL, Bayer, Whippany, NJ). The standard premedication protocol comprises oral prednisone 50 mg given 13 and 7 hours before the procedure, and intravenous promethazine 12.5 mg at the beginning of the procedure.

Outcomes

Primary outcomes were: (1) records of allergy to ICM before PCI, (2) premedication according to the protocol, and (3) subsequent allergic reaction to contrast media. The secondary outcomes were 30-day all-cause mortality.

Ethical considerations

The study was approved by the local Institutional Ethics Committee in keeping with the principles of the Declaration of Helsinki (application number 0160-17-MMC).

Statistical analysis

Data are presented as numbers and percentages for nominal parameters and as means and standard deviations for continuous parameters. Differences between the groups were analyzed with the χ^2 or Fisher's exact test, as appropriate. Continuous variables were examined for normality (Shapiro-Wilk test) and data were analyzed accordingly. The *t*-test was used for normally distributed variables and the Mann-Whitney *U* test for nonparametric variables. *P* < .05 was considered statistically significant. Data were analyzed using SPSS Version 21 (IBM Corporation, Armonk, NY).

RESULTS

Patient characteristics

A total of 13,652 subjects were hospitalized and, therefore, included in this analysis. The study design is depicted in [Figure 1](#). The mean age of the study population was 58 ± 13 years, with a 62% male predominance. A prior diagnosis of ICM allergy was recorded for 216 (1.6%) ([Table I](#)). Patients with allergy were relatively older than nonallergic subjects (65.2 ± 10.0 years vs 58.3 ± 12.7 years), with a 58% female predominance. The prevalence of most of the coexisting conditions, including hypertension, dyslipidemia, chronic obstructive pulmonary disease, and diabetes mellitus, was higher among patients with a known allergy. ICM-sensitive patients had a higher prevalence of atrial fibrillation (12% vs 5.6%), congestive heart failure (10.2% vs 4.5%), and prior stroke (16.2% vs 5.4%).

No significant differences were noted in ICM allergic patients, between those who underwent PCI and those who did not, except for hypertension ([Table I](#)).

PCI in patients with ICM allergy

Thirty-two patients with ICM allergy were referred for PCI during the index hospitalization. Twenty-seven of them were suspected, after admission, of having ACS, and 5 were considered to have nonspecific chest pain. Seven additional patients with ACS and ICM allergy were managed without PCI. This decision was due to various reasons (eg, transfer to another hospital) but not related to ICM allergy. Confirmation of ICM allergy was sought in patient medical records and attained in 15 of the 32 subjects with reported ICM allergy who underwent PCI ([Table II](#)). Of these, 10 were documented to have had a severe reaction, manifested as anaphylactic shock, dyspnea, or hypotension. The remaining 5 had experienced rash, pruritus, and dizziness.

A premedication protocol was prescribed for only 10 of the 32 individuals with a preexisting diagnosis of ICM allergy who were referred for PCI ([Figure 1](#); [Table II](#)). There was no documented explanation for not administering premedication in the remainder of the patients. The severity of prior allergy events was not greater in those who were given premedication compared with those who did not ([Table II](#)). Only 1 patient had a response that could be reasonably attributed to an allergic reaction. This was a 59-year-old woman who had previously experienced ICM-induced anaphylaxis. Despite receiving intravenous corticosteroids prior for PCI, she had hypotension, which resolved

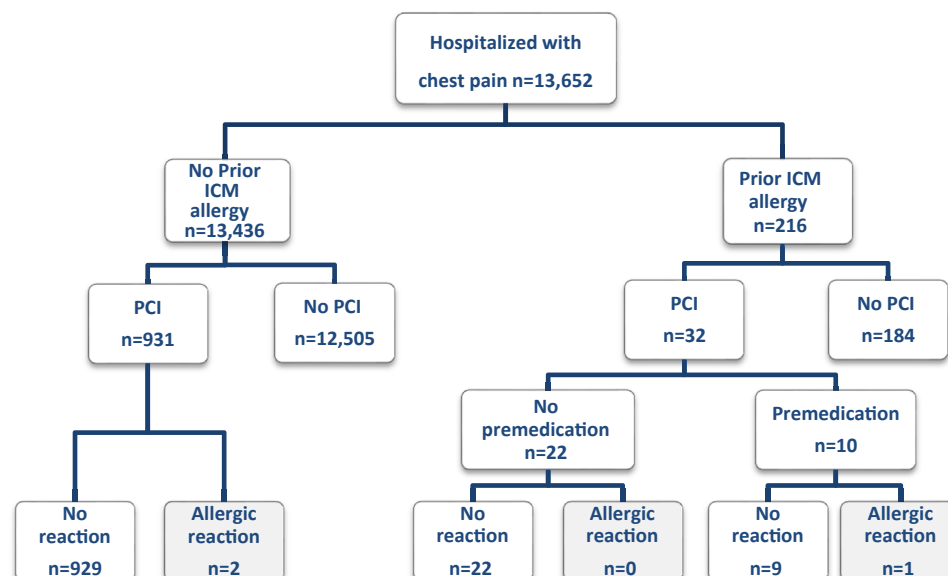


FIGURE 1. Study flowchart. ICM, iodinated contrast media; PCI, percutaneous coronary intervention.

TABLE I. Clinical characteristics of patients admitted for investigation of chest pain

Characteristic	All hospitalized patients (n = 13,652)		P value	ICM-allergic patients (n = 216)		P value
	ICM allergy (n = 216)	No allergy (n = 13,436)		In-hospital PCI (n = 32)	No PCI (n = 184)	
Age (y)	65.2 ± 10.1	58.3 ± 12.7	<.001	65.4 ± 9.1	65.2 ± 10.4	.91
Male sex	90 (41.7)	8281 (61.6)	<.001	18 (56.3)	72 (39.1)	.07
Hypertension	87 (40.3)	3737 (27.8)	<.001	7 (21.9)	80 (43.5)	.03
Current smoker	42 (19.4)	2634 (19.6)	.95	8 (25.0)	34 (18.5)	.47
Dyslipidemia	132 (61.1)	5259 (39.1)	<.001	23 (71.9)	109 (59.2)	.24
COPD	22 (10.2)	700 (5.2)	.001	4 (12.5)	18 (9.8)	.75
Diabetes mellitus	92 (42.6)	2797 (20.8)	<.001	17 (53.1)	75 (40.8)	.19
Prior cardiovascular disease						
Atrial fibrillation	26 (12.0)	747 (5.6)	<.001	4 (12.5)	22 (12.0)	1.0
Congestive heart failure	22 (10.2)	560 (4.5)	<.001	1 (3.1)	21 (11.4)	.21
Myocardial infarction	11 (5.1)	389 (2.9)	.06	1 (3.1)	10 (5.4)	1.0
Prior stroke	35 (16.2)	716 (5.4)	<.001	7 (21.9)	28 (15.2)	.43
Prior TIA	4 (1.9)	107 (0.8)	.09	0 (0)	4 (2.2)	1.0

COPD, Chronic obstructive pulmonary disease; ICM, iodinated contrast material; PCI, percutaneous coronary intervention; TIA, transient ischemic attack. Data are presented as mean ± standard deviation, or as number (%).

promptly. Mortality was not documented in any of the ICM allergic patients during the 30 days after PCI.

Among patients with a prior record of ICM allergy who underwent PCI, no differences were found in baseline characteristics, cardiovascular risk factors or associated diseases, between those who received prophylactic premedication and those who did not (Table III). Accordingly, the ACS index was similar in the 2 groups. Premedication did not yield any significant difference in the patient outcome (Table III).

PCI in patients without ICM allergy

Nine-hundred thirty-one patients who were admitted with chest pain and no previous ICM allergy were referred for PCI during the index hospitalization (Figure 1). Two patients (0.2%) had minor allergic reaction: a 59-year-old female patient developed a rash and

was treated successfully with intravenous corticosteroids and antihistamines; a 63-year-old male had low blood pressure requiring administration of intravenous fluids (Table II).

DISCUSSION

We investigated the characteristics, treatment, and outcomes of patients with diagnosed ICM allergy who were admitted to internal medicine wards for investigation of chest pain. Our analysis yielded several findings: (1) the prevalence of documented ICM sensitivity was 1.6%, (2) only one-third of patients with reported allergy received premedication prior for PCI, (3) the rate of allergic reaction in patients with prior allergy was low, regardless of premedication (1 patient), (4) the overall rate of new-onset allergic reaction was remarkably low (0.2%), and (5)

TABLE II. Characteristics and outcomes of patients who were referred for PCI with prior or new-onset ICM allergy

Patient	Sex	Age (y)	Prior ICM allergy	Type of prior allergic reaction	Pre-PCI medication	Post-PCI adverse reaction	Type of allergic reaction	30-d mortality
1	F	72	+	Rash	+	—		—
2	M	44	+	Dyspnea	+	—		—
3	M	75	+	NA	+	—		—
4	F	69	+	NA	+	—		—
5	M	55	+	Hypotension	+	—		—
6	F	68	+	NA	+	—		—
7	F	76	+	NA	+	—		—
8	M	67	+	NA	+	—		—
9	F	58	+	Anaphylaxis	+	+	Hypotension	—
10	M	53	+	NA	+	—		—
11	M	73	+	NA	—	—		—
12	M	67	+	NA	—	—		—
13	F	77	+	Rash	—	—		—
14	M	63	+	Dyspnea	—	—		—
15	M	71	+	Dyspnea	—	—		—
16	F	77	+	Dyspnea	—	—		—
17	M	70	+	NA	—	—		—
18	F	56	+	NA	—	—		—
19	M	58	+	NA	—	—		—
20	M	40	+	Rash	—	—		—
21	M	73	+	NA	—	—		—
22	F	64	+	NA	—	—		—
23	F	71	+	NA	—	—		—
24	F	70	+	Dizziness	—	—		—
25	M	68	+	Dyspnea	—	—		—
26	M	64	+	Dyspnea	—	—		—
27	F	71	+	Dyspnea	—	—		—
28	M	75	+	NA	—	—		—
29	F	58	+	Pruritus	—	—		—
30	M	68	+	NA	—	—		—
31	M	58	+	NA	—	—		—
32	F	65	+	Anaphylaxis	—	—		—
33	F	59	—	—	—	+	Rash	—
34	M	63	—	—	—	+	Hypotension	—

ICM, Iodinated contrast material; PCI, percutaneous coronary intervention.

there was no mortality during the following 30 days among the patients with known ICM allergy who were referred for PCI.

Our hypothesis was that the real-life significance of ICM allergy is obscure to many cardiologists who perform PCI. Although it is generally accepted that low-osmolality ICM and premedication increase patient safety, some have claimed that breakthrough reactions may occur.^{12,13} Furthermore, for the past 3 decades, PCI has been the definitive treatment for coronary artery disease, and reports of major adverse reactions due to ICM have increased accordingly.^{14,15} In a Korean study that investigated 30 patients with prior adverse ICM reactions, all of whom were premedicated with corticosteroids and H1 antihistamines, hypersensitivity reactions occurred in 5 patients, constituting 17% of this cohort.¹² However, 4 subjects experienced cutaneous manifestations only, including 3 events of facial flushing, which is usually not considered as an allergic response.¹⁶ This may account for their observation that the recurrence rate after premedication was higher in patients with mild previous reactions than in those with severe previous reactions.

We report an exceedingly low adverse reaction rate among patients with or without prior ICM allergy undergoing PCI, implying that low-ionic PCI is safe even in patients with an alleged or proven diagnosis of ICM allergy. These findings concur with those of another single-center study of 501 patients with ST-elevation myocardial infarction who underwent emergency PCI.¹⁷ Six patients had a prior ICM reaction and received urgent premedication; none of the patients had complications or evidence of allergy.

We propose a number of possible explanations for our findings. First, the mean age of the patients with ICM allergy was more than that of the patients without allergy. This raises the possibility that their ICM sensitivity was initially diagnosed after exposure to older generation ICM, while a low-osmolality agent was used in the subsequent PCI. Second, PCI occasionally requires a low volume of ICM, which may be below the threshold of some individuals for an allergic response. Third, allergy may have been diagnosed incorrectly in some patients.

Previous studies have shown that most reactions initially described as drug allergies are not true immunological

TABLE III. Characteristics of individuals who received premedication and those who did not, among ICM allergic patients who underwent PCI

Characteristic	Premedication		RR (95% CI)	P value
	Yes (n = 10)	No (n = 22)		
Age (y)	63.0 ± 10.5	66.1 ± 8.1	0.97 (0.89-1.05)	.35
Male sex	5 (50.0)	13 (59.1)	0.69 (0.15-3.11)	.71
Hypertension	3 (30.0)	4 (18.2)	1.93 (0.34-10.91)	.65
Current smoker	3 (30.0)	5 (22.7)	1.46 (0.27-7.82)	.68
Dyslipidemia	6 (60.0)	17 (77.3)	0.44 (0.09-2.21)	.41
COPD	1 (10.0)	3 (13.6)	0.70 (0.06-7.74)	1.0
Diabetes mellitus	3 (30.0)	14 (63.6)	0.24 (0.05-1.22)	.13
Prior cardiovascular disease				
Congestive heart failure	1 (10.0)	0 (0)	0.90 (0.73-1.11)	.31
Myocardial infarction	0 (0)	1 (4.5)	1.05 (0.96-1.15)	1.0
Prior stroke	1 (10.0)	6 (27.3)	0.30 (0.03-2.87)	.39
Outcomes				
Index ACS	8 (80.0)	19 (86.4)	0.63 (0.09-4.53)	.64
Allergic reaction	1 (10.0)	0 (0)	0.90 (0.73-1.11)	.32

ACS, Acute coronary syndrome; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICM, iodinated contrast material; PCI, percutaneous coronary intervention; RR, risk ratio.

allergies^{18,19} and some have even questioned the validity of allergy to ICM.^{20,21} A recent study showed that the diagnosis of ICM allergy is unsubstantiated in the majority of patients,²² and that relevant information is lacking. Misdiagnosis may increase the risk of unnecessary premedication, including corticosteroids, with their ensuing adverse effects. Furthermore, even in cases of confirmed allergy, data supporting premedication are lacking¹ and it remains unclear whether premedication with corticosteroids can alter the outcome of adverse reactions.¹³ Interestingly, a survey conducted among radiologists showed that nearly 40% refrain from corticosteroid administration to patients with a history of mild reactions when repeating elective procedures.²³ The administration of premedication to only 10 of the 32 patients in the current cohort appears to be random rather than a validated medical decision. Furthermore, we could not detect a difference between of the 2 groups, although this may have been influenced by the limited sample size. Therefore, avoidance of premedication probably reflects a low level of awareness to prior ICM allergy. This is likely explained by the fact that severe systemic reactions are rare in a real-life setting.

Study limitations

The main limitations of this study are due to its retrospective design. Diagnosis was defined by the documented history of ICM allergy, and further verification was restricted to data already existing in medical records. The subjects that are included in our cohort did not complete formal allergic evaluation with testing of the suspected media and therefore ICM allergy may have been over- or underdiagnosed. Nevertheless, this study screened a large unselected population and thus provides insights regarding the real-life significance of ICM allergy.

CONCLUSIONS

Taken together, we propose several conclusions and recommendations for subjects with a diagnosis of ICM allergy. We show that in more than half of the subjects there is no

documented justification for the diagnosis of allergy. Therefore, all patients with a history of ICM allergy should undergo a formal allergic evaluation to rule out misdiagnosis. Furthermore, premedication can probably be avoided in patients with mild allergic reactions and, if administered, should not cause considerable delays in imaging and medical procedures. This practice appears to be already adopted by some radiologists.²³ Finally, randomized controlled trials are warranted to define the role of premedication and to compare its benefit compared with corticosteroid adverse effects. We believe that our study provides convincing evidence that such prospective trials are expected to be feasible and safe.

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