

Hypersensitivity Reactions to Radiocontrast Media: The Role of Complement Activation

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Although intravenous use of radiocontrast media (RCM) for a variety of radiographic procedures is generally safe, clinically significant acute hypersensitivity reactions still occur in a significant percentage of patients. The mechanism of these anaphylactoid, or “pseudoallergic,” reactions is complex, involving complement activation, direct degranulation of mast cells and basophils, and modulation of enzymes and proteolytic cascades in plasma. In this review, basic information on different RCMs and their reactogenicity is summarized and updated, and the prevalence, pathomechanism, prediction, prevention, treatment, and economic impact of hypersensitivity reactions are discussed. Particular attention is paid to the in vitro and in vivo evidence supporting complement activation as an underlying cause of RCM reactions.

Introduction

Radiographic procedures using water-soluble radiocontrast media (RCM) represent routine medical practice today in all developed countries. In the United States, for example, more than 10 million tests are performed yearly with various RCM [1•,2••]. Nevertheless, intravenous (IV) use of RCM still carries a significant risk for hypersensitivity reactions (HSRs) manifested in a broad range of cutaneous, gastrointestinal, cardiopulmonary, and other symptoms (Table 1). These reactions, also referred to as “RCM reactions,” are usually not IgE-mediated and, therefore, belong to the category of “pseudoallergic” or anaphylactoid reactions. Nevertheless, true IgE-mediated acute reactions and nonacute, delayed-type HSRs to RCM have also been reported [3,4].

The symptoms listed in Table 1 are similar with all RCM and essentially correspond to the acute allergic or pseudoallergic reactions caused by numerous drugs, including antimicrobial and antineoplastic agents, non-

steroidal anti-inflammatory drugs (NSAIDs), certain analgesics, liposomal drugs, and water-insoluble drugs that are dissolved with the help of Complement (C)-activating emulgents (*eg*, Cremophor EL) [5,6••]. However, some symptoms are more frequent with RCM compared with other reactogenic drugs, and there are also differences among different opaque agents in the spectrum of the hypersensitivity symptoms they cause.

Radiocontrast media can be classified according to their iodine content, osmolality (hyper-, low-, and iso-osmolar), level of ionization (ionic and nonionic), and level of polymerization (monomeric and dimeric). Earlier RCM preparations were mono- or diiodinated compounds (*eg*, pyridines); however, the structure of current RCM is based on fully substituted benzoic acid with three iodines at positions 2, 4, and 6 on the benzene ring. The ionic monomers are sodium or meglumine salts of the anionic triiodinated benzene ring; these are the high osmolality RCMs (>1400 mOsm/kg). Their dimerized derivatives have lower osmolality (*eg*, 600 mOsm/kg), and further derivatization with hydroxyl groups or other hydrophilic conjugates results in nonionic, lower-osmolality (500–700 mOsm/kg) or iso-osmotic RCM [2••].

Hypersensitivity reactions have been a concern since the first organic, iodinated compound was used for IV pyelography in 1928 by Swick, an American urologist [7••]. Subsequent development of new-generation RCM, characterized by a transition from hyperosmolar to iso-osmolar, ionic to nonionic, and monomeric to dimeric preparations, was driven by the need to reduce the reactogenicity while maintaining or improving the opacity of products. Therefore, the initial hyperosmolar, ionic, monomeric class of RCM (*eg*, diatrizoate, iothalamate) was outdated in the early 1980s by lower-osmolar, ionic, dimeric RCM (*eg*, ioxaglate). Progress then continued with the introduction of nonionic, monomeric, lower-osmolar RCM (iopamidol, iohexol, ioversol, iopromide, ioxilan), and finally, in 1996, the US Food and Drug Administration (FDA) approved iodixanol, the nonionic, dimeric, iso-osmolar RCM [2••]. Table 2 lists the best-known RCM, with specification of their above-discussed physicochemical properties. It should be noted that in addition to categorization according to molecular and physico-

Table 1. Symptoms of RCM reactions

Category	Symptom
Common allergic	Angioedema, chill, choking, conjunctivitis, coughing, diaphoresis, edema, fever, headache, nausea, rhinitis, sneezing, wheezing
Cutaneous	Erythema, urticaria, flushing, rash, dermatitis, skin eruptions, pruritus
Gastrointestinal	Emesis
Cardiovascular and hemodynamic	Hypertension, hypotension, cardiac arrhythmias, cardiac arrest
Respiratory	Tachypnea, dyspnea, bronchospasm, asthma attack, cyanosis, pulmonary infiltration
Vegetative/neural	Chest, low back and lumbar pain, confusion, sensation of warmth,* tingling, panic of imminent death
Delayed (days)	Generalized maculopapular exanthema

*Particularly characteristic of RCM reactions.
RCM—radiocontrast media.

Table 2. Physicochemical properties of RCM that influence hypersensitivity reactions

Generic name	Osmolarity	Ionization	Polymerization
Diatrizoate	Hyper-	Ionic	Monomeric
Iodixanol	Iso-	Nonionic	Dimeric
Iohexol	Low-	Nonionic	Monomeric
Iopamidol	Low-	Nonionic	Monomeric
Iopromide	Low-	Nonionic	Monomeric
Iothalamate	Hyper-	Ionic	Monomeric
Ioversol	Low-	Nonionic	Monomeric
Ioxaglate	Low-	Ionic	Dimeric
Ioxilan	Low-	Nonionic	Monomeric

RCM—radiocontrast media.
Adapted from Hong *et al.* [2••].

chemical properties, earlier classifications also considered the severity and clinical manifestations of HSRs (nonreactogenic, mildly or severely reactogenic RCM; anaphylactoid, vasomotor RCM); the diagnostic procedure for which they were used (*eg*, myelography, angiography, arteriography, venography, urography, arthrography, CT); and the pathogenesis of HSRs (C activation, IgE-binding, direct degranulation of mast cells and basophils) [8–10].

The goal of this review is to briefly summarize and update basic information on different RCM and their reactogenicity, discussing the pathomechanism, prediction, prevention, treatment, and economic impact of HSRs. C activation is one of the most thoroughly studied causes of RCM reactions. In this review, particular attention is devoted to the *in vitro* and clinical studies attesting to this mechanism.

Prevalence and Critical Factors Influencing Radiocontrast Media Reactions

In addition to the physicochemical properties of RCM, the main factors influencing the rate and extent of RCM reactions include the amount of agent infused; route (site) and speed of administration; premedication status of patients; and criteria for positive reaction. With all these variables, it is perhaps not surprising that the reported incidence rate of different types of RCM reactions span a range as broad as

0.0004% to 60%. According to comprehensive estimates applied for all kinds of symptoms with all procedures and all types of RCM, the overall incidence rate of RCM reactions is 2.1% to 12.7% [2••]. The frequency of severe anaphylactoid reactions is estimated to be up to 1% to 2% [2••], whereas that of nonsevere, cutaneous, vasomotor, pulmonary, cardiovascular, or gastrointestinal symptoms is in the 5% to 8% range [1•]. However, to illustrate the critical dependence of these statistics on details, life-threatening RCM reactions during coronary angiography occur only in 0.0004% to 0.002% of patients [11].

As for the relationship between RCM properties and HSRs, it has been proposed in several studies that nonionic, low-osmolarity RCM (LO-RCM) are safer than ionic, high-osmolarity agents (HO-RCM) [2••,11–14]. Barrett *et al.* [13], for example, enrolled 1856 patients to compare the reactogenicity of LO- versus HO-RCM used in cardiac angiography. The overall incidence of HSRs requiring treatment was 9% versus 29% in these groups, respectively, and hemodynamic deterioration and severe or prolonged reactions also occurred more frequently in the HO group (2.9 % vs 0.8%) [13].

Pathomechanism

The pathogenesis of RCM-related immediate HSRs cannot be explained by a unique mechanism. As illustrated by the

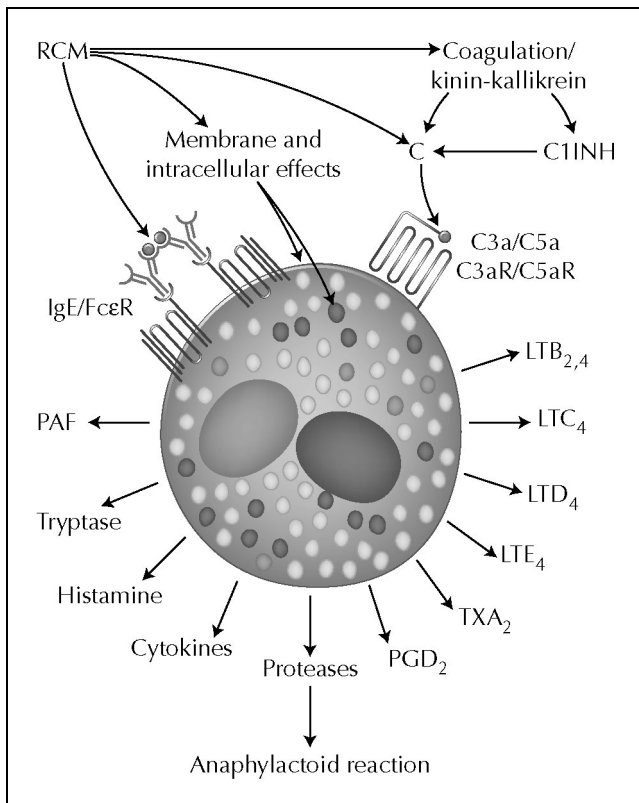


Figure 1. Mechanisms of RCM reactions. This schematic illustrates the various triggering mechanisms and secretory products of mast cells and basophils during RCM reactions. C—complement; C1INH—C1-esterase inhibitor; LT—leukotriene; PAF—platelet-aggregating factor; PG—prostaglandin; RCM—radiocontrast media; TXA—thromboxane.

scheme in Figure 1, major triggering factors implicated are 1) activation of the C system with consequent activation of mast cells and basophils via C5a and C3a receptors; 2) activation of mast cells and basophils via IgE receptors; 3) direct secretory effects on mast cells and basophils due to local changes in osmolarity and ion (mainly sodium and calcium) concentrations; and 4) activation of plasma proteolytic systems, in particular the coagulation and kinin-kallikrein systems, entailing additional C activation by various crossover amplifications and depletion of C1-esterase inhibitor (C1INH) [6••,15].

As for the effector arm, the best known secondary mediators of anaphylaxis are histamine, tryptase, platelet-activating factor (PAF), leukotriene (LT)_{B2}, LT_{B4}, LTC₄, LTD₄, LTE₄, thromboxane (TX)_{A2}, prostaglandin (PG)_{D2} and TXD₄ [6••,8–10,12] (Fig.1). The pathophysiologic effects of the best-known mediator, histamine, are mediated both by H1 and H2 receptors. Specifically, H1 receptors contribute to the cardiovascular and cutaneous symptoms via inducing vasoconstriction and vascular leakage, whereas H2 receptors cause vasodilation, increased heart rate and pulse pressure, and basophil degranulation via rising cellular cyclic AMP levels [16].

Direct secretory effects on mast cells and basophils involves non-receptor-mediated stimulation of mast cells

and basophils for immediate release of preformed allergic mediators, such as PAF, histamine, and tryptase, but not those that are de novo synthesized in response to activation of these cells via IgE or C5a receptors (LT_{B1}, LTC₄, LTD₄, LTE₄, TXA₂, and PGD₂). The release reaction was shown to be Ca⁺⁺-dependent and similar to the effects of Ca⁺⁺ ionophores; however, RCM (diatrizoate) had a more complex effect on cell function as it rendered basophils refractory to subsequent release reactions [17]. Another important detail concerning the secretory response of mast cells and basophils is that these cells display differential response to different RCM or other stimuli. For example, mast cells from the skin might not respond to certain RCM, whereas pulmonary and cardiac mast cells are triggered for strong release reaction [18]. Likewise, mannitol, an osmotic stimulus, might induce the release of histamine from human basophils, but to a lesser extent from mast cells [18].

Complement Activation As an Underlying Cause of Radiocontrast Media Reactions

Activation of the C system as the main underlying cause of RCM reactions has been studied since the 1970s via numerous in vitro, in vivo, and clinical studies. Nevertheless, the picture that has emerged is far from consistent, and the question of whether C activation is the major cause of HSRs, a contributing factor, or only an epiphenomenon, is still open. In reviewing the in vitro data, it is clear that RCMs have several different effects, both within the C cascade and in its regulatory system, and that charge, viscosity, iodine number, hydrophilicity, and osmotic pressure are all critical variables in these interactions [10,19]. C activation by RCM was demonstrated to proceed via both the classic and the alternative pathways [10,19], as well as via unusual mechanisms, such as: 1) nonspecific, nonsequential cleavage of C proteins [20]; 2) suppression of natural inhibitors of C, such as factor H and I [10]; and 3) direct action on the thioester bonds of C4 and C3. However, another activation mechanism implicated is an electrolyte imbalance in serum [21].

Some of the in vitro studies contradict theories indicating C activation as the underlying cause of HSRs, or, at least, the authors interpret their data as contradicting the C concept. Vik *et al.* [21], for example, found no increase in serum SC5b-9 levels following the addition of iodixanol to serum, leading to the conclusion that it was unlikely that C activation was responsible for iodixanol-induced anaphylactoid reactions in humans. Lieberman [10] suggested that depletion of C proteins in human serum was not due to true C activation but rather to nonspecific binding of C proteins to RCM, without anaphylatoxin liberation. At the extreme, Mikkonen *et al.* [22] suggested inhibition of C activation by RCM on the basis that iohexol, ioxaglate, iodixanol, and meglumine amidotriz solutions effectively blocked insulin-induced generation of C3a-desArg in normal human serum. The authors claimed that these mol-

ecules, particularly the ionic ones, inhibited the binding of factor B to surface-associated C3b, interfering with alternative-pathway amplification.

Considering these C activation–opposing data and the technical intricacies and possible conceptual pitfalls in interpreting C assays [23], many data in this field require a close scrutiny with regard to conclusiveness and biologic relevance.

Several animal studies attested to a causal role of C activation in RCM reactions. Lasser *et al.* [24] reported severe “idiosyncratic” responses in dogs to the injection of sodium iothalamate, manifested in vomiting, hypotension, and hyperreflexia. The authors found significant depletion of C during the symptoms, suggesting that C activation was causally involved in the reaction. In further dog studies by Lang *et al.* [25], serial daily injections of RCM (metrizamide, iothalamate, diatrizoate, acetrizoate, iodipamide, and iopanoate) caused substantial declines of serum C over several days. Napolovlu *et al.* [19] proved that various RCM in the 0.5- to 2.0-g iodine/kg range activated the C system in rats via the alternative pathway, with efficacy in the following order: triombrast > hexabrics > ultravist ≥ melitracast = omnipac.

Human data on C activation during RCM reactions include case reports—for example—on a severe anaphylactoid reaction to a pyelographic RCM, manifested in a precipitous fall in plasma hemolytic C, C3, C4, and C1INH levels, with a rise of C3 conversion products [26]. This patient also developed consumption coagulopathy [26]. Vandenplas *et al.* [27] reported the case of a 29-year-old woman who developed fulminant pulmonary edema following IV administration of RCM. The study showed a slight decrease of several C components (C3, C4, and factor B) and a transient consumption coagulopathy. Of particular interest in the latter paper, the authors presented direct hemodynamic and laboratory evidence for pulmonary capillary leakage as the underlying cause of edema, a process known to arise as a consequence of C activation–related sequestration of granulocytes and platelets in the pulmonary microcirculation [28–30]. Another case report postulated that C activation was responsible for the death of a patient undergoing IV pyelography with diatrizoate [10]. Consistent with the key role of anaphylatoxin liberation, the autopsy showed a picture typical of acute respiratory distress syndrome (ARDS), including the presence of granulocytic aggregates in the pulmonary microcirculation [10]. As is known, C activation plays a key role in the development of ARDS [31–36].

Among the more extensive clinical studies examining the role of C activation in RCM reactions, Small *et al.* [37] analyzed HSRs and C activation in 220 patients undergoing IV pyelography. Nineteen percent of patients displayed HSRs, whereas depressed serum CH₅₀ levels, indicating C activation, occurred in 49%. The RCM-induced decline of CH₅₀/mL was apparent within 90 seconds after the start of the infusion and returned to normal after approximately 30 minutes. This study highlighted an important fact regarding the rela-

tionship between C activation and HSRs, namely, that more people display signs of C activation reactions than HSRs. Hence, C activation might be present in patients without a clinically manifested reaction, suggesting that anaphylatoxin liberation does not necessarily cause HSRs. C activation might, therefore, be a precondition, or contributing factor to HSRs, but it does not solely explain the phenomenon. Other factors or preconditions might also need to be present in people who develop HSRs. This point was reinforced in the studies by Westaby *et al.* [38], who demonstrated significant elevation of the anaphylatoxin C3a in the peripheral blood of seven of 11 patients receiving RCM for coronary angiography. In three of seven patients, C3a was increased between four- and 10-fold, but only one of these patients developed symptoms, which were mild.

It should be noted that C activation has not been a consistent finding in all clinical studies reporting C measurements in patients given RCM. Kolb *et al.* [20], for example, found no significant changes in CH₅₀ and hemolytic C3 activity in serum samples obtained from 40 patients before and 30 minutes after undergoing IV pyelography with methylglucamine diatrizoate or iothalamate.

Modulation of Enzymes and Proteolytic Cascades in Plasma

One major confounding factor in assessing the role of C activation in RCM reactions is that C is not the only homeostatic plasma enzyme system in blood that is activated during these reactions. It has been described that RCM reactions correlate with diminished concentrations of C1INH in plasma, a protein that inhibits the activation of all four proteolytic cascades in blood—that is, the C, coagulation, fibrinolytic, and kinin-kallikrein systems. This explains the association of HSRs and C activation with accelerated conversion of prekallikrein to kallikrein [10,39,40] as well as the occasional coagulopathy observed in reactor patients. Therefore, one potential cofactor to HSRs might be a proteolytic scission product liberated by the activation of proteolytic chains in blood other than the C system. In fact, some studies claimed that activation of coagulation or the kinin system might play a more important role in the HSRs than C activation, at least in rabbits [41] and guinea pigs [25].

Radiocontrast media–induced, nonspecific proteolysis without participation of the multicomponent C3/C5 convertases might deserve particular attention, because it explains the concurrent activation of coagulation, fibrinolysis, and the kinin-kallikrein systems in humans. This mechanism was proposed by Kolb *et al.* [20] on the basis that C activation by RCM was not inhibited by ethylenediaminetetraacetic acid (EDTA), which normally suppresses C activation via both the classic and the alternative pathways. The nonspecific lysis resulted in a reduction of CH₅₀ as well as a loss of C4, C2, C3, and C5 hemolytic activities, whereas C6, C8, and C9 were not affected. The parallel

production of C3 proteolytic cleavage products and the fact that purified C3 was unaffected by RCM [20] showed that the loss of C3 hemolytic activity was not due to direct alteration of the C3 molecule. Other studies also showed that the C3 and C4 cleavage products that arose as a consequence of RCM-induced, nonspecific proteolysis were different from the C3b and C4b formed during normal C activation, but they formed functional C3 and C5 convertases [10].

Risk Factors, Prevention, and Treatment

Radiocontrast media reactions have several risk factors, including tendencies toward allergy (atopic constitution) and asthma, and a history of previous reactions to RCM or other drugs. Severe reactions are largely confined to patients with coronary heart disease [13]. The treatment of acute RCM reactions is largely empiric and supportive. Resuscitation, if necessary, usually involves intubation and infusion of a plasma expander and IV medication with epinephrine, methylprednisolone, diphenhydramine, ranitidine, and atropine sulfate. Vital signs, electrocardiogram, and respiratory functions are continuously monitored until the patient is stabilized. Supportive drugs might be needed for 72 hours [2••,42]. High-risk patients should receive prophylaxis before any diagnostic procedure involving RCM. Treatment of organ dysfunctions induced by RCM reactions might require special attention.

Economic Implications of Radiocontrast Media Reactions

Considering that the cost of relatively low-reactogenic, low-osmolality RCM is substantially higher than that of high-osmolality RCM, some studies addressed the economic sense of switching from universal to selective use of low-osmolality contrast media. Therefore, Michalson *et al.* [43] compared the cost of RCM and treatment of adverse reactions with the use of low or high osmolality RCM. Based on a total of 42,598 radiocontrast studies over 3.5 years, giving an overall reaction rate of 1.2%, the authors pointed out that the incremental cost using low-osmolality RCM was approximately US\$79 per procedure, a figure very close to the estimate of Barrett *et al.* [13] (\$89) a few years before. Because the cost of treating adverse reactions associated with selective use of low-osmolality RCM was minimal compared with the cost of total conversion to low-osmolality RCM, the authors concluded that selective use of low-osmolality RCM meant a savings to their institution of approximately \$1 million per year [43].

Conclusions

The introduction of low-osmolality RCM has greatly reduced the threat of HSRs; however, the economic burden associated

with universal use of these nonreactogenic contrast media will most likely keep the problem alive for a long time, at least in radiologic centers unable to switch to universal use of these "modern" agents. Future solutions for improved prevention and treatment of RCM reactions include individualized prediction of the reactions—for example, by using in vitro pseudoallergy tests, or application of selective inhibitors of C-mediated HSRs, such as blockers of C activation or action [6••].

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