Systemic Reactions to Intravascular Contrast Media

A Guide for the Anesthesiologist

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Millions of radiologic examinations using intravascular contrast media (ICM) are performed yearly in the United States.1 Approximately 5% of these studies are complicated by an adverse systemic reaction to ICM2,4; of these reactions, one-third are severe and call for immediate treatment. Fortunately, most severe reactions respond well to treatment, but an estimated 500 fatalities per year in the United States follow ICM examinations.

Adverse reactions to contrast media during general anesthesia have not been reported yet; however, except for those done in children, relatively few contrast studies require general anesthesia.

Anesthesiologists may be consulted urgently for assistance during a reaction but more commonly are asked to "stand by" for a patient who has a high risk of undergoing a reaction. This review will survey the incidence of such reactions, the physical properties of the contrast media that produce them, current theories of their pathogenesis and prophylaxis, and the treatment of acute reactions.

Incidence of Reactions

Five to eight per cent of all ICM examinations are complicated by systemic reactions.1,5 Shehadi and Toriolo compiled case reports of 302,083 ICM studies in the United States and Italy.1 For statistical purposes, they divided reaction syndromes into four categories, based primarily on their severity and the type of treatment that was needed (table 1): mild, moderate, severe, and fatal. The overall incidence of reactions in this review was 4.7%.

Other studies find similar incidences of reactions.3,4,6 These studies consider all types of ICM examinations and all types of reactions. However, Shehadi found that different radiographic studies had different incidences of reactions. The rate for excretory urography was twice that for arterial examinations,2,3 and the rate for iv cholangiography was twice as high as urography.

The manner of dye injection also influences risk. Intravenous urography performed by single bolus injection has a lower reaction incidence (5.4%) than when performed by slow infusion (7.1%). Following single bolus injection for iv cholangiography, the risk of reaction (12.7%) is higher than the risk conveyed by slow infusion (8.2%). Other high-risk studies include cerebral and coronary angiography.

Many factors influence the risk of reaction. A history of any allergy or atopic disease may increase the risk of reaction 1.5-16-fold.1,4,7 Patients allergic to seafood or shellfish have a 15% incidence of reaction; patients with asthma have an 11.2% incidence.8 Although a history of previous ICM reaction increases the risk of subsequent reaction to 17-35%,6,7 many patients undergo repeated ICM examinations without any sign of reaction.

Anaphylactoid reactions have been reported in all age groups, including infants.8 A disproportionately high number of ICM reactions occur in the third and fourth decades of life.2,4 Younger patients tend to have milder reactions than older patients. There is no gender bias in the risk of reaction. Patients with cardiac disease are four to five times more likely to have a systemic reaction; they also tend to have more severe reactions.

Ansell et al. found that the dose of iodinated ICM is an important risk factor. Distinctly fewer reactions occur at a dose of less than 20 g iodine,7 which, depending on the particular contrast compound, is approximately 50

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ml. Ansell's survey is the only one to find a difference in incidence between ethnic groups, with an eightfold higher incidence in Indians living in England than in native Britons.4

Physical Properties of Contrast Media

Compounds that have a density greater than soft tissue and bone are termed positive contrast media.† Density is related to molecular weight of a compound, and the difference in contrast effect (increased contrast effect giving better radiographic visualization) increases with the fourth power of atomic number.9 The density of soft tissue is approximately equal to the density of water and is 0.92–1.06 g/cm.3 The density of iodine is 4.94 g/cm.3

Several representative contrast media molecules are shown in figure 1. Iodine is a universal component of contrast media because it has both high density and low toxicity. In addition, it is attached easily to organic compounds that are filtered freely and not absorbed by the glomeruli and tubules. The iodine is strongly covalently bound to complex benzoic acid or pyridone derivatives, and only traces (0.1%) of free iodine or iodide ion are found in contrast media solutions.

Contrast media are prepared as salts; iodine containing anions such as diatrizoate and metrizoate are formulated with various cations such as methylglucamine, calcium, or magnesium. Dahl et al. examined the effects of different cations on the incidence of ICM reactions and concluded that the species of cation is unimportant in determining the likelihood of a reaction.10

For some studies, the exact cationic concentration is important. If the sodium to meglumine ratio is beyond a narrow range during coronary angiography, for example, ventricular fibrillation may be precipitated.

The iodine content of different ICM varies from 20 to 45%. More than 99% of this iodine is organically bound, with only traces of iodine or iodide ion in free solution. This high iodine content has several physiologic effects. Thyroid function tests that rely on estimation of iodine uptake, such as the protein bound iodine (PBI) and radioactive iodine uptake (RAI), may be invalidated.

Contrast media are also hypertonic relative to plasma. For example, meglumine iothalamate (Conray 400®) has an osmolarity of approximately 2,100 mOsm/l;4 and many ICM have osmolarities above 1,000 mOsm/l. Hemodynamic alterations may result from the administration of hypotonic solutions to patients and are not related to other systemic effects of contrast media such as histamine release. Coté et al. studied the hypotensive response to hypertonic solutions such as mannitol 25% (1,600 mOsm/l) and glucose 50% (2,523 mOsm/l).11 Infusion of these solutions in humans and in rabbits causes cardiovascular changes similar to those found on injection

<table>
<thead>
<tr>
<th>Type of Reaction*</th>
<th>Number of Reactions</th>
<th>Percentage of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>14,301</td>
<td>3.3</td>
</tr>
<tr>
<td>Moderate</td>
<td>9,943</td>
<td>1.4</td>
</tr>
<tr>
<td>Severe</td>
<td>216</td>
<td>0.07</td>
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<tr>
<td>Fatal</td>
<td>19</td>
<td>0.000</td>
</tr>
<tr>
<td>Total number of studies</td>
<td>302,082</td>
<td></td>
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</tbody>
</table>


* Mild—Nausea, vomiting, flushing. No treatment was needed. Moderate—Facial edema, bronchospasm, mild hypotension. These required treatment in the radiology department, but the patient was discharged following the examination. Severe—Prolonged hypotension, angina, ventricular fibrillation, convulsions. These reactions required hospitalization for treatment. Fatal—Hypotension, cyanosis, pulmonary edema, ventricular fibrillation, convulsions, and anoxia preceding death.

† Negative contrast media, such as air and helium, are associated with different types of toxicity than intravascular contrast media and will not be discussed in this review.

‡ Conray® iothalamate package insert, Mallinkrodt Diagnostic Products Division, 1981.

![Generalized Anion Structure](image1)

**Cation Structures**

- Na⁺
- Ca++
- Mg**

![Representative Anions](image2)

**Diatrizoate Acid**

![Iothalamic Acid](image3)

**Ipodate Sodium**

![Iodipamide](image4)

**FIG. 1.** Several commonly used intravascular contrast media compounds, along with the structures of common cations used in the formulation of the contrast media. As commercially prepared, more than one cation may appear in a particular contrast medium. For example, Hyqouxe® 75% contains 25% sodium diatrizoate and 75 percent meglumine diatrizoate.
of intravenous contrast media. There is an initial brief hypertensive response, followed by mild hypotension in most patients. Central venous, right ventricular, and pulmonary artery pressures increase, as does cardiac output. Hyperosmolar solutions also decrease systemic vascular resistance. Hemoglobin and hematocrit levels may fall 10–15%, and serum osmolality may rise 10–12%. Equilibration with the extracellular fluid compartment is reached in 10 min postinjection, with a fall to normal osmolality occurring with excretion of the contrast medium.

High osmolality may cause shrinkage and clumping of erythrocytes resembling an agglutination–thrombosis effect. Hemoglobin SS containing erythrocytes may become deformed permanently when exposed to hypertonic solutions, causing a sickle cell crisis. Patients who have sickle cell disease must be well hydrated during ICM examinations.

The increase in osmolality also causes a diuresis, which after 10–15 minutes may reverse the initial increase in blood volume and lead to hypovolemic cardiovascular compromise. This rapid initial increase in blood volume and subsequent decrease is particularly dangerous in patients who have a history of congestive heart failure. Patients with renal or hepatic dysfunction may have impaired excretion of contrast media.

Contrast media also compete with other drugs for protein binding sites. Lasser et al. demonstrated potentiation of pentobarbital anesthesia following injection of sodium diatrizoate in a rat model. This effect is attributed to displacement of pentobarbital from albumin–binding sites by the contrast medium, as observed in in vitro competitive equilibrium dialysis studies.

Patients taking highly protein bound drugs such as warfarin or isoniazid may have temporary alterations in plasma concentrations of these drugs following ICM examinations. Relative binding affinities of contrast media for albumin also have been studied; an inverse relationship between the degree of binding of albumin and the LD₅₀ was found in several species. In more clinically applicable doses of ICM, binding to and activation of proteins of the complement or coagulation systems may interfere with their normal function.

Types of Reactions

The properties of contrast media that make them useful diagnostic agents, especially high density and stability of iodine–organic binding, cause certain adverse reactions in all patients. Decreased hematocrit, increased osmolality, and an osmotic diuresis occur in almost all patients who undergo ICM examinations. The clinical significance of these changes depends on the cardiovascular status of the patient and the dose of the contrast medium used. Some patients, however, seem to have idiosyncratic reactions to certain contrast media but not others. These reactions range from nausea and flushing to anaphylactoid shock and death.

Lalli retrospectively studied over 200 fatal and near-fatal ICM reactions, attempting to correlate the first manifestation of a reaction with later outcome. Nausea or vomiting occurs as the prodromal symptom in 20% of anaphylactoid and fatal reactions. Usually the onset is within 2 min of ICM injection, and the duration of discomfort is short. Urticaria is another important early symptom; it is caused by histamine release and by disruption of normal capillary permeability. Many ICM injections are performed in darkened rooms, and, therefore, this sign of ICM reaction must be sought actively by the radiologist. Urticaria is an important symptom of a reaction primarily because of patient discomfort, since urticaria alone rarely progresses to more serious reactions. Eruption of urticaria may increase patient anxiety, which has been linked causally to more serious reactions.

Chills, fever, and facial flushing occur commonly. Lalli speculates that these are due to increased cutaneous blood flow and the effects of contrast media on the hypothalamus. These symptoms do not indicate invariably progression to a more serious reaction. Another possible prodromal reaction is a change in mental status, including expressions of anxiety, restlessness, attempts to move, and reporting of a "peculiar feeling." These are also symptoms of hypoxia. Most radiologists inform their patients that they may feel flushing, itching, nausea, or lightheadedness and ask the patient to speak out when these sensations occur. A minority of radiologists, believing that anxiety increases the incidence of ICM reactions, advocate not warning the patient of possible prodromal reactions nor actively questioning the patient about their occurrence. Because of drapes, room darkness, or preexamination medications, reactions often are unreported or unnoticed.

A more serious physiologic manifestation of an ICM reaction is a decrease in systemic vascular resistance, with resultant hypotension and compensatory tachycardia. Vascular collapse and markedly decreased cardiac filling pressures after ICM, with prompt response to fluid resuscitation, was noted in two cases reported by Obeid et al.

Decreased blood pressure and cardiac dysrythmias are the first sign of intravascular contrast media toxicity in 10–13% of fatal reactions.

The third and potentially most harmful manifestation of an ICM reaction is anaphylactoid shock. Oral, lingual, and pharyngeal edema may progress quickly to upper airway obstruction and bronchospasm and may severely limit ventilation and oxygenation. This reaction may occur within 1 min of the administration of as little as
0.1 ml contrast material or may take several hours to develop. Respiratory distress was the first symptom to develop in 20% of patients who progressed to fatal ICM reactions.

There is a gradation of severity of ICM reactions, and minor reactions do not necessarily progress to more severe physiologic alterations. Clearly, though, a prolonged period of patient observation during and after the ICM examination is warranted. Monitoring blood pressure and electrocardiogram are not standard procedures for all ICM examinations. Verbal contact with the patient and a technician's 'finger on the pulse' is a common method of assessing patient status. Perhaps electrocardiographic monitoring and frequent determinations of blood pressure should be routine procedures. Several cases of anaphylactoid reaction 6–8 h after ICM administration have been reported. Early observation of reactions allows prompt treatment, with the expectation of decreased morbidity and mortality.

Pathogenesis of ICM Reactions

The diversity of reactions and their idiosyncratic appearance have led to the formulation of many different proposals of pathogenic mechanisms. A list of proposed etiologies of ICM mediated systemic reactions appears in Table 2.

Many components of the anaphylactoid reactions to contrast media are similar to the effects of systemic histamine release by other drugs or mechanisms. These allergic-like reactions include urticaria or other rashes, rhinitis, oral, laryngeal and epiglottic edema, bronchospasm, and systemic hypotension. Studies have demonstrated that contrast media can cause marked histamine release and degranulation of basophils and mast cells in vitro. Until recently, though, human studies have failed to demonstrate a significant increase in serum histamine levels during ICM examinations in either reactive or non-reactive patients. Failure to find evidence of histamine release probably was due to either insensitive assay techniques or to inactivation of histamine during passage through the lung. With current radioimmunoassay and microenzymatic assays sensitive to 1–2 ng/ml histamine, Cogen et al. studied histamine release during cardiac catheterization with meglumine and sodium diatrizoate (Renografin 76). They inject ICM into the pulmonary artery for left ventriculography and sample aortic root blood at 1, 3, 5, and 7 min following ICM administration. Prior to injection, no histamine was detected in aortic root plasma. After injection in five of six patients, histamine levels of up to 80 ng/ml were detected. Despite these high levels of histamine, no patients had allergic or anaphylactoid reactions or significant hypotension. Cogen speculates that the extent of histamine release may depend on the particular organ system perfused by ICM. Patients who have profound anaphylactoid reactions to ICM may have a predisposition to excessive histamine release, less rapid inactivation, or increased end-organ sensitivity to histamine or other vasoactive substances released by contrast media.

Simon et al. studied histamine release, complement hemolytic activity, and fibrin split products (FSP) in patients undergoing intravenous pyelography. Rises in histamine and FSP occurred in 40% of patients, and complement activity increased in 63%. Six of 43 patients had immediate generalized reactions to ICM, but measured changes in histamine, complement, and FSP did not correlate with presence or absence of reaction. Although histamine certainly is released by ICM infusion, it cannot be the major factor in the development of ICM reactions, or these reactions would be much more common. Even patients who have a history of allergy or ICM reaction do not predictably have high histamine levels during a repeat ICM study.

Histamine is not the only vasoactive substance released by contrast media. Serotonin, bradykinin, SRS-A (slow reactive substance of anaphylaxis), and various components of the complement activating and inhibiting systems have been implicated in ICM mediated reactions.

The complement system of serum proteins is a complex set of biochemical mediators activated via immunogenic, hemolytic, fibrinolytic, and possibly osmotic interactions with other plasma components. Activation of the complement cascade can cause:

1. Degranulation of mast cells and basophils, with release of histamine and, indirectly, kallikrein activation
2. Increased vascular permeability
3. Release of anaphylotoxin and chemotactic activators
4. Cell membrane disruption and thrombin activation
5. Enhanced phagocytosis by binding to cell membranes ("immune adherence")

The classical pathway of complement activation begins when the C1 complement protein molecule combines with the Fc portion of an immunoglobulin molecule (IgG
or IgM) that already has combined with antigen. This activates the C-1 protein complex, changing it from a proesterase to an esterase, which initiates the complement cascade. The alternate pathway of complement activation is initiated by various complex compounds, including polysaccharides, lipopolysaccharides, and cobra venom factor.26

As mentioned, complement activation can cause important alterations in the coagulation, fibrinolytic, and kinin systems, related to the cardiovascular instability, disseminated intravascular coagulation, and anaphylactoid reactions seen during some contrast media reactions. Contrast media are capable of activating the complement system, but the precise method or location of entry into the cascade are unknown.16 Activation of complement by contrast media probably is mediated by other plasma factors liberated by contrast media, such as plasminogen or FSP. Lasser et al. first demonstrated activation of the complement system by contrast media in vitro and then in dogs in vivo.29,30 Two years later, Arroyave et al. demonstrated complement activation in humans in response to contrast media.31 Gonsette et al. studied levels of C1q, C3 activator, C3c, and C4 after intravenous injection of seven different contrast media compounds in humans and noted a drop of 30–40% of complement activity.32 However, there is no correlation between ICM reactions and decreases in complement level; two of Gonsette’s patients had urticaria develop without any drop in complement level. There was no correlation in vivo between activation of complement and the degree of hypotension, ionic or nonionic formulation, or degree of protein binding of the contrast compounds. However, there is a positive correlation between the amount of complement activation and the lipid solubility of the contrast media. In addition, if calcium gluconate is added to the most activating ICM compound, ioxallic acid, much less complement activation occurs.

Why then do some patients manifest reactions to ICM-mediated release of histamine and complement, whereas most do not? Siegle et al. found that the blood of atopic patients released more histamine when incubated in vitro with contrast media than the blood of nonatopic patients.33 Transfer of serum from atopic patients to nonatopic leukocytes did not cause a similar histamine release. They also compared the in vitro levels of total hemolytic complement (CH50) of patients who did and did not have a reaction to contrast media. CH50 was lower in reactive patients in this study; the inference is that complement activation occurred in patients who had reactions. Lasser et al. found that there is a critical difference in C1 esterase inhibitor levels between patients who react to contrast media and those who do not.16 Lower levels of C1 esterase inhibitor, which interrupts the complement cascade early in its course, may predispose a patient to complement-mediated ICM reactions. Lasser measured significantly lower baseline and postcontrast values for CH50 in reactors versus nonreactors; presumably more complement activation occurred in reactors. In a rabbit model, 3 days of pretreatment with prednisolone 50 mg/kg markedly increased the levels of C1 esterase inhibitor and raised the LD50 of methylglucamine iopamidol.

In a case study, Lasser et al. reported that a 29-year-old woman suffered a severe anaphylactoid response to sodium diatrizoate concurrent with marked depletion of CH50 and C1 esterase inhibitor.34 The patient had had a protracted pelvic Klebsiella infection and had a preexisting low level of complement before the ICM examination. The reaction to diatrizoate began with conjunctivitis and periorbital edema and progressed over 15 minutes to hypotension, pulmonary edema, metabolic acidosis, ventricular fibrillation, and, eventually, successful resuscitation. The authors suggest that patients who will react to contrast media with severe anaphylactoid symptoms may be predisposed to react because of preexisting low levels of CH50 and C1 esterase inhibitor. This hypothesis was tested in a dog model; the animal had been given methylglucamine or sodium iothalamate often over a period of 2 years. It did not exhibit a profound anaphylactoid reaction until its CH50 and C1 esterase inhibitor levels had declined significantly.35

Lasser’s patient also exhibited signs of consumptive coagulopathy, with decreased fibrin and platelets and increased FSP. This has been demonstrated repeatedly in vitro and in vivo. Patients with hypercoagulability syndromes, such as multiple myeloma and Waldenstrom’s macroglobulinemia, have been noted to have severe anaphylactoid and consumption coagulopathic reactions to contrast media.36 Schulze suggests that contrast media are capable of binding with serum proteins that normally control the coagulation, fibrinolytic, and complement systems.37 His group found no change in hemolytic complement activity, Hageman factor or plasminogen concentration in nonreactive humans after ICM administration and concluded that there was no evidence of direct activation of these regulatory systems in normal patients by ICM.

Contrast media may alter protease activity by protein binding or by binding to platelet or erythrocyte membranes. This binding then would alter enzyme function or induce abnormal antigenicity, leading to activation of the complement and the thrombosis–fibrinolysis cycles. Thus, there is substantial evidence that contrast media cause activation of the complement system and also that activation of the complement system can cause reactions similar to those seen with contrast media. Unfortunately,
current evidence precludes a cause-and-effect relationship. Further investigation into the mechanism of contrast media activation of complement activation is needed.

There is substantial evidence both for and against an antibody-antigen explanation of severe contrast media reactions. Early attempts to prove an antibody-mediated basis for ICM reactions were unsuccessful because neither circulating antibody–antigen complexes nor isolated anti-ICM antibodies could be detected. Individual case reports demonstrating an IgE-induced reaction and an IgM antithrombale have been published in recent years.

Contrast media compounds have a relatively small molecular weight and, therefore, must function as haptens to induce antibody formation. Antibodies to contrast media compounds have been induced in experimental animals. Brash attached contrast media compounds to carrier protein, emulsified the protein in Freund’s adjuvant, and immunized rabbits with the haptene–protein combination. IgG anti-ICM antibodies developed in the rabbits. When aluminum hydroxide was used instead of Freund’s adjuvant, IgE antibodies were produced. Lymphocyte transformation, a necessary precursor to antibody formation, has been demonstrated to occur after ICM exposure to lymphocytes in vitro.

Brash notes several other factors that favor the allergic explanation of severe ICM reactions. Allergic patients have a four times greater incidence of reaction than non-allergic patients. Atopic patients may have a greater tendency toward the production of antibodies to foreign substances. In the “advanced technologic environment” we live in, there is constant exposure to halogenated benzene compounds, similar to those used for ICM examinations. This may represent the previous exposure needed for antibody formation, which explains why patients may have ICM reactions the first time they are exposed to ICM.

Evidence against antibody mediation of ICM reactions is also strong. Attempts to correlate the potential for reactions with standard tests for IgE-mediated anaphylaxis, the measurement of histamine and hypersensitivity skin testing, have failed to show a consistent relationship. Attempts to detect circulating immune complexes during acute reactions have not been successful. The fact that reactions occur after the first exposure to ICM and sometimes fail to occur after repeat ICM examinations (without prophylactic pretreatment) also casts doubt on an antibody-mediated basis to ICM reactions. Perhaps a more universal phenomenon occurs after ICM administration that leads to systemic reactions in some patients.

ICM infusions produce several deleterious side effects on the heart and cardiovascular system, which, with appropriate monitoring, can be detected in many patients. Pfister et al. closely monitored the electrocardiogram of a large series of patients during intravenous urography. (ECG monitoring during ICM studies is not a routine procedure.) Patients with New York Heart Association Class II through IV cardiac disease have a 24% incidence of dysrhythmias (primarily premature ventricular contractions) and ischemia during the ICM examination. Even 5% of patients with “normal” cardiovascular systems by history experience dysrhythmias and ischemia. Other serious rhythm disturbances, such as electromechanical dissociation, have been reported during coronary angiography.

Several mechanisms may operate to produce these dysrhythmias. Vasodilatation and hypotension may cause a reflex tachycardia, and possibly ischemia; ICM may cause altered origination and conduction of electrical activity, and there may be a direct negative inotropic effect of ICM on the myocardium.

Histamine release during ICM administration may cause decreased coronary perfusion, either by direct vascular constriction or by producing A-V conduction disturbances that impair coronary filling. Alterations of calcium availability caused by ICM may be a source of negative inotropy. Several ICM are formulated with disodium ethylenediamine tetracetate (disodium edetate) or citrate. Wolpers et al. examined several different ICM with regard to their in vitro calcium binding abilities. They used a calcium-sensitive, flow-through electrode to measure ionized calcium, and found that with or without calcium-binding additives, there was an intrinsic effect of calcium chelation with a 20% decrease in ionized calcium levels by ICM.

Fischer et al. examined this issue in an in vitro study in dogs using a right coronary injection of sodium methylglucamine diatrizoate. This compound contains sodium citrate 0.32% and disodium edetate 0.04%. Either adding calcium chloride 24 mmol/l to the compound or changing the additive to calcium disodium edetate decreased the incidence of ventricular fibrillation.

Fischer et al. also studied pulmonary artery (PA) and left atrial (LA) pressures during ICM administration in dogs. During high doses of ICM, 16 ml/kg, PA pressures rose 284%, LA pressures rose 43%, and left ventricular end-diastolic pressure (LVEDP) rose 28%. Serum osmolality rose to 465 mOsm/l. During coronary angiography in humans with Renografin 76, 12 Morissette found that a 16.2% fall in COP occurred, along with a 32% rise in LVEDP. This decreased the COP-LVEDP gradient by 8.7 mmHg to -0.3 mmHg, a level at which there is a significant danger of pulmonary edema. Using radiiodinated human serum albumin for determination of plasma volume, they found a 17% increase in plasma volume. These changes occurred within 2 min, and values returned to baseline within 30 min. It is not clear whether
these pressure changes are the primary factor causing pulmonary edema in ICM reactions or whether the release of histamine and other vasoactive mediators is more important.

Thus, contrast media have been shown to induce major alterations in cardiac conduction, contractility, filling pressures, and pulmonary alveolar fluid gradients. Although these investigations have been performed primarily during arteriographic contrast studies (since invasive hemodynamic monitoring already has been established), it is reasonable to assume that similar changes would occur during any contrast study if enough hypertonic dyes were used.

In addition, several animal studies have found a synergistic toxicity (a decrease in LD₅₀) between contrast media and commonly used cardiac glycosides. Addition of calcium to ICM, as suggested by some authors, has not been studied. One might speculate, however, that it may either be ineffectual or harmful for patients who are known to have coronary artery spasm and are taking drugs such as verapamil and nifedipine.

These potentially harmful effects of ICM partially explain the four times greater incidence of ICM reactions noted in patients with cardiac disease, and may explain some of the nonanaphylactoid reactions to ICM that are seen.

Another vital organ system affected by ICM is the central nervous system. ICM have been shown to penetrate the blood–brain barrier in a dose-dependent manner in doses similar to those used clinically and have appeared in the cerebrospinal fluid following urography in dogs. Intracerebral ICM is approximately 1000 times more lethal than intravenous ICM, with the cause of death being pulmonary edema and cardiac arrest. When delivered into the CSF, sodium diatrizoate is particularly noxious, causing seizures in very low doses. It is not likely that this toxicity is due to hypertonicity alone, as similarly hypertonic sodium chloride does not produce this reaction. Lalli has formulated a "unified theory of intravascular contrast media reactions," based on CNS toxicity. Patients who have ICM reactions may have less well developed choroid plexuses than normal patients; these plexuses may allow more ICM to enter the third and fourth ventricles. Here, contact with the hypothalamus may cause fever or chills and via reticular connections with the respiratory center, cause respiratory arrest. Direct stimulation of the chemoreceptor trigger zone may induce nausea and vomiting. Neurogenic pulmonary edema may occur, directly from hypothalamic stimulation or indirectly by strong sympathetic outflow. Sympathetic stimulation also may explain cardiac dysrhythmias and cause splenic contraction and release of Factor VIII producing consumption coagulopathy.

Hypothalamic induced vagal stimulation through the medulla and vagus nerves often has been implicated in ICM reactions, including bronchospasm and bradycardia. Cholinesterase inhibition was seen to some degree with now obsolete contrast media and has been discredited as a source of increased vagal tone causing ICM reactions. Andrews reported six cases of ICM-mediated vagal reactions. All patients had severe bradycardia, apnea, pallor, and hypotension. He attributed these reactions to pain from pinprick, sensation of ICM injection, rectal distention, and fear. These reactions occurred despite atropine 0.4 mg intramuscularly.

Another common ICM reaction, urticaria, may be provoked by emotion and increased body temperature. These are mediated by CNS alterations.

Lalli’s theory is attractive and is supported by several case reports of mental disturbances and autopsy findings of cerebral edema after ICM examinations. It is also supported by his analysis of the influence of anxiety on the incidence of ICM reactions. He found that preexamination hypnotic suggestion significantly reduced the incidence of nausea, vomiting, and urticaria. His series was too small to assess changes in the incidence of the more serious reactions. Many radiologists believe that high patient anxiety increases the likelihood of an ICM reaction. Several sedative drugs administered prior to the radiographic examination, such as diazepam, Innovar, and droperidol alone, commonly are used to diminish this anxiety.

**Treatment of Contrast Media Related Reactions**

There are five classes of drugs used to treat ICM reactions. Drugs and dosages are listed in table 3. Radiologists will treat more than 90% of all systemic reactions without requesting the assistance of an anesthesiologist. Most reactions (flushing, nausea, and urticaria) can be treated with only patient reassurance and continued observation. Only severe bronchospasm and anaphylactoid reactions will necessitate help from an anesthesiologist.

<table>
<thead>
<tr>
<th>Table 3. Treatment of Contrast Media Reactions</th>
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<tbody>
<tr>
<td><strong>Adrenergic agonists</strong></td>
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<tr>
<td>Epinephrine 3–5 mcg/kg iv bolus</td>
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<tr>
<td>Epinephrine 1–4 mcg/min iv infusion</td>
</tr>
<tr>
<td>Aminophylline 5–6 mg/kg/20 min, initial dose</td>
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<tr>
<td>Aminophylline 0.5–0.9 mg·kg⁻¹·hr⁻¹, maintenance dose</td>
</tr>
<tr>
<td>Atropine 0.5–2.0 mg iv</td>
</tr>
<tr>
<td>Diphenhydramine 25–50 mg iv</td>
</tr>
<tr>
<td>Methylprednisolone 100–1,000 mg iv</td>
</tr>
<tr>
<td>Dexamethasone 4–20 mg iv</td>
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<tr>
<td>Normal saline (infuse to maintain normal blood pressure)</td>
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Downloaded From: http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=data/journals/jasa/931426/ on 06/22/2017
Skills in airway management and familiarity with the following drugs only rarely, but then urgently, will be required.

Adrenergic agonists cause bronchodilation, increase cardiac contractility and heart rate, and shift blood volume from the muscular compartment to the central compartment. They also may decrease histamine release by increasing concentrations of intracellular cyclic-AMP of mast cells and basophils. Choice of a particular drug depends on the manifestation of the ICM reaction. If bronchospasm is the primary problem, an isoproterenol infusion may be the drug of choice. If upper airway edema and hypotension predominate, an epinephrine bolus followed by an infusion iv is preferable.

Proper treatment of serious ICM reactions requires a reliable intravenous access route, and this should be assured as soon as any ICM reaction is suspected. Because ICM reactions may progress rapidly and cutaneous blood flow may be decreased, the iv route is more effective than subcutaneous drug administration.

Since epinephrine or isoproterenol may cause tachycardia or dysrhythmias, the ECG should be monitored during ICM reactions. Primarily alpha agonists such as methoxamine or phentolamine only should be used if severe hypotension is present. Alpha agonists decrease c-AMP production in mast cells and basophils, which stimulates release of histamine and SRS-A. They are therefore not drugs of choice in the treatment of anaphylactoid hypotension.

Methylxanthines are used in the treatment of bronchospasm. Aminophylline causes bronchial smooth muscle relaxation and airway dilation. Tachycardia and dysrhythmias are not uncommon, and ECG monitoring is warranted. Patients who have not taken aminophylline preparations previously need to have an appropriate loading dose, followed by a maintenance infusion. For asthmatic patients already on a theophylline preparation, the loading dose to treat an acute episode of bronchospasm is halved, and the maintenance dose is the same. Therapeutic levels of aminophylline range from 10 to 20 mcg/ml.

Anticholinergics can relax bronchial smooth muscle slightly, decrease troublesome secretions, and possibly decrease the release of histamine and SRS-A. Relatively high doses of atropine are needed to cause complete vagal blockade. If atropine is given during bradycardia, its onset of action may be delayed because of slow distribution. Dysrhythmias also may occur when atropine is given during strong vagal stimulation.

Antihistamines are probably of little value during severe ICM reactions. Their weak antinociceptive and bronchodilating actions may be insufficient if unsupplemented. Specific receptors blocked by antihistamines already may have been activated. Nevertheless, these drugs are relatively harmless, and most authors empirically recommend their use. Diphenhydramine (Benadryl) is the most commonly used antihistamine.

Finally, steroids often are employed in the treatment of ICM reactions, although their use is empiric. Proposed actions of steroids include stabilization of mast cell and basophil membranes with decreased histamine release, decreased capillary permeability, decreased edema formation, and modification of antibody-antigen reactions.

Supplemental oxygen (if possible, cool mist) and patient reassurance are helpful. Intravenous fluid resuscitation is essential for replacement of fluid lost from the intravascular space during anaphylactoid reactions. Intravenous cannulae should remain in place during the period of observation after a suspected reaction. Expertise in airway management also is needed, because airway obstruction may develop rapidly. Early intervention by an anesthesiologist may prevent a more heroic intervention later. Radiologists should not hesitate to ask for assistance as soon as a more than mild ICM reaction becomes evident.

Radiology suites often have atropine, diphenhydramine, and epinephrine available. A common practice is to tape these drugs and syringes to a wall. Both suction and ECG monitors usually are available, though not in each radiology room. Other resuscitation equipment such as laryngoscopes and endotracheal tubes may arrive only with the anesthesiologist.

Anesthesiologists should visit radiology suites periodically to learn exactly which resuscitation drugs and equipment are available. Recommendations then can be made about resuscitation planning; these suggestions otherwise might be unfamiliar to radiologists. Anesthesiologists should urge radiologists to become certified in Advanced Cardiac Life Support or be available for practice resuscitation drills for new radiology personnel. Finally, anesthesiologists actively should make known their availability and willingness to help treat severe ICM reactions.

**Prophylaxis against ICM Reactions**

Prevention of systemic ICM reactions is, of course, highly desirable. For patients who have a history of a reaction to ICM, various preexamination drug regimens have been advocated for prophylaxis. For patients who never have had an ICM examination but have a high risk of reaction based on allergic, atopic, or cardiac history, a variety of *in vitro* and *in vivo* tests to assess likelihood of a reaction have been proposed. The anesthesiologist may suggest them if consulted to evaluate the risk of an ICM examination.

Intradermal and subcutaneous skin testing is considered useless by most authorities. There is no correlation
between patient reactions via these routes and subsequent reaction with intravascular administration of ICM. This is because these routes are only useful in detecting IgE-mediated anaphylactic reactions of antigen challenges; as noted, very few, if any, ICM reactions are documented to occur via this mechanism.

The preponderance of clinical opinion is that intravenous pretesting also is of little benefit. Severe anaphylactoid reactions have occurred in response to as little as 1 ml ICM. However, some investigators have found IV pretesting to have useful predictive value. Yocum et al. prospectively studied intravenous pretesting in patients with either suspected or documented past ICM reaction. Their technique was to administer, at 15-min intervals, serial dilutions of ICM starting with 0.1 ml of 1:10,000 concentration of full strength solution and to observe for reactions. They studied 142 patients who had a well-documented history of ICM reaction. Of these, 18 had a positive pretest, manifesting pruritis, urticaria, conjunctivitis, rhinitis, or angioedema. Fifteen of these patients received pretreatment with diphenhydramine and/or prednisone; none had more than a mild reaction to a full dose of ICM. Three pretest-positive patients unintentionally did not receive the ordered premedication; all three had anaphylactoid reactions within 5 min of injection of 1–5 ml ICM. Of the 124 patients who had a history of a reaction but a negative pretest, 53 received no premedication and had a reaction incidence of 21%. The other 71 patients received premedication, which decreased the incidence to 4%. They also studied 41 patients with a vague history of ICM reaction. All 41 had negative pretests and had a reaction incidence of 5%, which was no different than the general population. The conclusion was that serial dilution pretesting was useful in identifying a high-risk group of patients and in allaying anxiety about the potential for ICM reactions in patients who had only a vague history of reaction.

Raising the issue of pretesting may have other benefits. When Yocum et al. requested permission to enter patients into their study, the primary physician cancelled the study in 10% of the cases because the risks versus the benefit of the study were reconsidered.

The optimum pretest for ICM reactions would use an in vitro serum marker to avoid patient exposure to even miniscule doses of ICM. Several such tests have been proposed. Arroyave incubated diatrizoate with peripheral leukocytes of patients with a positive history of reaction and patients with a history of atopy, and normal volunteers. There was a significant increase in histamine release induced by ICM in atotics and patients with a history of reaction. This increased tendency to release histamine was not transferrable by serum. Lasser et al. evaluated the rate of conversion of prekallikrein to kallikrein in reactors versus nonreactors. The theoretic basis of this test as a predictor of ICM reaction is that the Cl esterase inhibitor in part controls the prekallikrein–kallikrein conversion in vivo; low levels of Cl esterase inhibitor have been linked to an increased incidence of reaction. They found retrospectively that in the presence of dextran sulfate as an activating agent that plasma of patients with a history of reaction did convert prekallikrein to kallikrein faster than nonreactors. They retrospectively calculated that this test had a sensitivity of 88%, a specificity of 82% and a predictive value of 79%.

If one cannot predict which patients will have an ICM reaction, many studies have demonstrated the benefit of pretreating all patients who are at high risk for these reactions. Zweiman et al. studied patients with a history of reaction. As Yocum noted, the investigation caused a significant number of ICM studies (approximately 40%) to be cancelled by the referring physician. Sixty-nine patients with a history of rash or anaphylactoid reaction were given prednisone 150 mg in divided doses from 18 hours before to 12 hours after the study. No patient experienced more of a reaction to ICM than urticaria or mild oral mucosal swelling. Greenberger et al. reported a series of 142 patients at high risk (history of reaction or allergy to iodine or shellfish) who received prednisone 50 mg po every 6 h for three doses and diphenhydramine 50 mg im 1 h before the ICM examination. No serious reactions occurred, and the overall incidence of minor reactions was 6.8%, one-third the incidence expected in these high-risk patients. Greenberger’s series extended a series reported by Kelly, who found a similar benefit to premedication. Diphenhydramine or atropine alone given as sole premedications are reported to increase the incidence of minor reactions, such as rashes or mental status disturbances. Therefore, the best recommendation for prophylaxis seems to be a course of steroids and antihistamines together at least 18 hours prior to ICM examination. The benefit of H2 antagonists (cimetidine, ranitidine) for prophylaxis against ICM reactions has not been documented yet.

Other drugs may have some protective value. Harnish et al. studied the effect of several drugs on the LD90 of sodium diatrizoate. Significant decreases in mortality were found by pretreatment with quindine, diazepam, and lidocaine. Neither the mechanisms of protection (membrane stabilization?) nor the clinical relevance of this high-dose contrast study in mice is known with certainty.

Summary

 Intravascular contrast media reactions are not uncommon. They occur frequently in relatively young and healthy patients, and are more likely to occur in patients with strong allergic, atopic, asthmatic, or cardiac histories. Five different types of reactions occur: Vasomotor, va-
sovagal, dermal, osmotic, and anaphylactoid. These different manifestations are seen both individually and in various combinations. The seriousness of a reaction depends not only on the extent of the reaction, but also upon the patient's cardiovascular status. Most severe reactions are idiosyncratic, and the history of reaction to contrast media always will not predict the current response to contrast media.

ICM reactions occur commonly enough so that most anesthesiologists will at some time be asked to help prevent or treat them. Knowledge about their incidence, risk factors, mechanisms of pathogenesis, treatment, and prevention should decrease the morbidity and mortality of these unfortunate occurrences.

Anesthesiologists should actively seek out radiologists to suggest the following:

1. Increased use of routine blood pressure and ECG monitoring
2. Routine visits by anesthesia staff to the radiology suite to review available drugs and equipment
3. Regularly scheduled cardiopulmonary resuscitation drills for new radiology personnel
4. Availability of emergency respiratory care equipment, oxygen, suction, atropine, diphenhydramine, and epinephrine in every radiology suite.

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