What Every Cardiologist Should Know About Intravascular Contrast

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Contrast-enhanced x-ray imaging remains essential to the diagnosis and treatment of many types of cardiac and vascular disease. Despite the rapid advancements in less invasive imaging techniques, only traditional angiography provides a high-resolution, real-time, dynamic view of vascular structures. Cardiologists have become concerned about contrast selection since the introduction of new agents over the last 2 decades. This concern has sparked three sequential debates within our community: the cost effectiveness of low osmolal contrast; whether nonionic agents are prothrombogenic; and whether the potential for nephrotoxicity differs between contrasts. Following is a summary of clinically relevant aspects of the cost effectiveness of low osmolal contrast and the prothrombogenicity of nonionic agents. These issues are important not only to those who perform angiography, but also to those who refer patients to, or follow them after, the procedure.

[Rev Cardiovasc Med. *2003;4(suppl 5):S19–S27*]

Key words: Contrast toxicity • Low osmolal contrast • Nonionic agents

Contrast-enhanced x-ray imaging remains essential to the diagnosis and treatment of many types of cardiac and vascular disease. Despite the rapid advancements in less invasive imaging techniques, only traditional angiography provides a high-resolution, real-time, dynamic view of vascular structures. Iodinated contrast is ideally suited for such imaging because of the degree to which it absorbs x-radiation and its relative safety. Historically, cardiac

angiographers viewed the traditional, high osmolal contrast agents as relatively inert substances that were generally well tolerated by patients except those "predisposed" to what were considered the two major adverse reactions to "dye:" allergy and nephrotoxicity. The latter events were rarely severe and other manifestations of contrast toxicity were either not problems for cardiologists (eg, pain accompanying peripheral arterial injection) or not considered significant (eg, nausea, vomiting, transient rhythm, and blood pressure changes). Cardiac toxicity (arrhythmia and hypotension) was not attributed to contrast per se but, rather, to the invasive nature of catheterization in a compromised patient. There appeared to be little difference between the available high osmolal contrast agents in terms of safety or efficacy. Cardiologists have become concerned about contrast selection since the introduction of new agents with lower osmolality over the last 2 decades. This concern has sparked three sequential debates within our community: the cost effectiveness of low osmolal contrast; whether nonionic agents are prothrombogenic; and whether the potential for nephrotoxicity differs between contrasts. Investigation into these controversies has greatly increased our overall knowledge of contrast and the extent to which it perturbs normal (and abnormal) physiology. Following is a summary of clinically relevant aspects of the cost effectiveness of low osmolal contrast and the prothrombogenicity of nonionic agents; other papers in this symposium address nephrotoxicity. These issues are important not only to those who perform angiography, but also to those who refer patients to, or follow them after, the procedure.

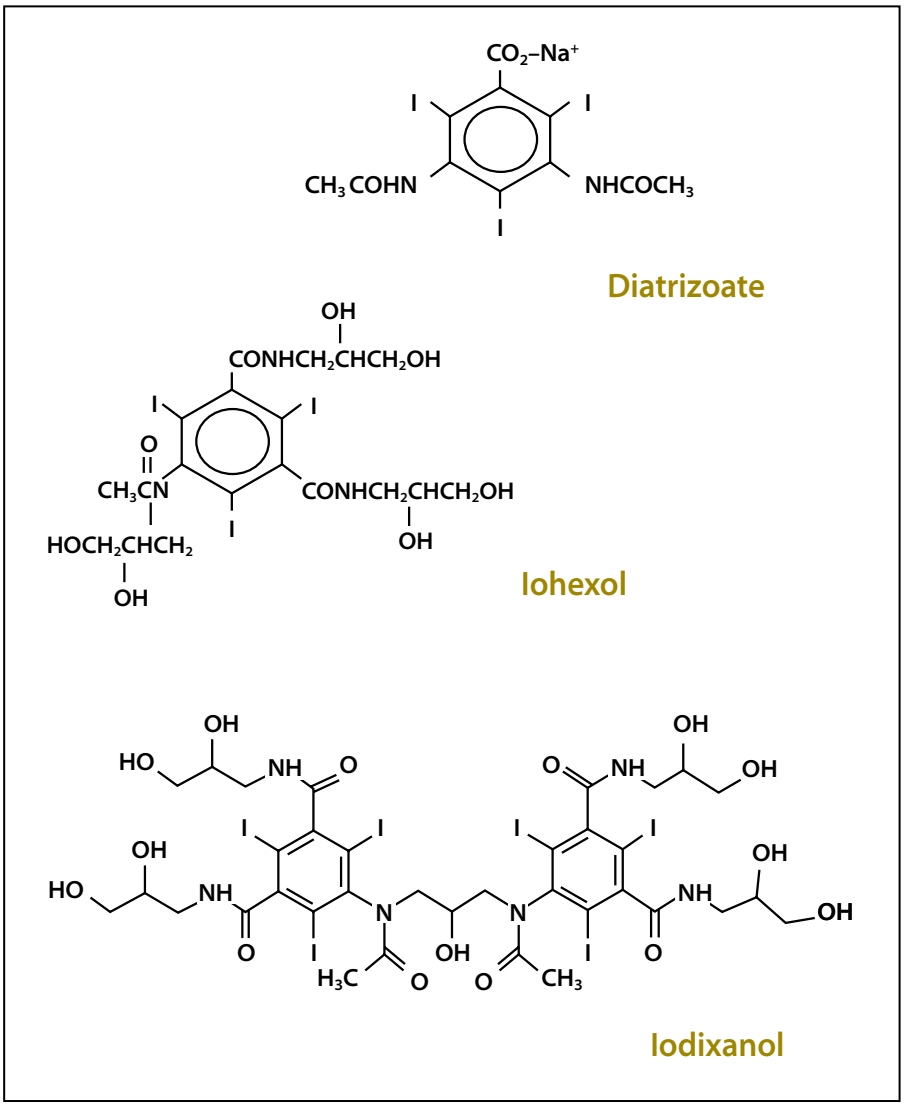

Figure 1. *Structural formulae for three common radiocontrast agents.*

History

Shortly after the discovery of x-ray imaging by Roentgen, the ability to delineate blood vessels was demonstrated by ex-vivo injection of a variety of noxious materials into the vessels of cadaveric specimens. In-vivo angiography was accomplished using potassium iodide, but this and other agents, such as strontium bromide, thorium, lipoidal, and sodium iodide, were found to be too toxic for general use.

The evolution of modern intravascular contrast began with attempts at developing urographic agents. The first organic iodinated compounds were pyridones, introduced in the late 1920s. Bi-iodinated pyridones appeared in the early 1930s; however, it wasn't until the mid-1950s that a tri-iodinated benzoate, diatrizoate, was produced. This ionic agent, using a combination of the cations sodium and N-methylglucamine (meglumine), became the

Table 1
Representative Contrast Media

Brand Name	Compound	mOsm/kg H_2O	Viscosity	Iodine (mg/mL)	Sodium (mEq/L)	gI/kg	LD50 (mouse)
Hypaque®-76*	Sodium-meglumine	2,160	13.3	9.0	370	160	7.5
Renografin®-76†	Diatrizoate meglumine/sodium	1,940	10.0	8.4	370	190	7.5
Hexabrix®	Ioxaglate meglumine/ioxaglate	600	15.7	7.5	320	150	11.2
Isovue®	Iopamidol	796	20.7	9.4	370	2	21.8
Omnipaque®	Iohexol	844	20.4	10.4	350	5	24.2
Opitray®	Ioversol	702	9.9	5.8	320	2	17
Visipaque®‡	Iodixanol	290	26	11.8	320	19	>21

*Formulated with the additives of calcium disodium EDTA.
†Originally formulated with the additives of sodium citrate, sodium EDTA.
‡Formulated with the addition of a "balanced" sodium and calcium salts to bring to isotonicity.
All nonionic contrasts have additives of tromethamine and calcium disodium EDTA.
Hypaque-76: Sanofi Winthrop; Renografin-76: Squibb Pharmaceuticals; Hexabrix: Mallinckrodt Inc., Hazelwood, MO; Isovue: Squibb Pharmaceuticals; Omnipaque: Amersham Health, Princeton, NJ; Opitray: Mallinckrodt Inc., Hazelwood, MO; Visipaque: Amersham Health, Princeton, NJ.

standard intravascular contrast in the United States for coronary angiography until the mid-1980s. These "dyes" had high osmolality that was thought to relate to toxicity, especially pain, when injected peripherally. A nonionic agent, metrizamide, was designed to reduce osmolality and was introduced in the 1970s. Metrizamide was not stable in aqueous solution and was supplied as a freeze dried powder requiring reconstitution just prior to use. It was also expensive and, although it had potential benefits compared to the ionic agents, it was not generally used for coronary angiography. By the late 1970s and early 1980s, second-generation nonionic agents and the ionic dimer ioxaglate were in clinical use. The nonionic dimers were introduced in the late 1980s.

Classifying Contrast

There are a number of ways in which contrast media may be distinguished from each other (Table 1, Figure 1). Because much of the toxicity associated with these agents is related to osmolality, this parameter has been most frequently used. By convention, the ratio of iodine atoms to osmotically active particles of the compound is used to characterize this property. The traditional high osmolal contrast agents have osmolalities of about 2000 mOsm/kg water and were thus considerably hyperosmolal compared to plasma. Because these ionic agents dissociate into two osmotically active particles (the tri-iodinated anion and a cation) for each 3 iodine atoms, they are termed ratio 1.5 agents (3/2). In order to decrease osmolality, one must either increase the number of iodine atoms or decrease the number of osmotically active particles of a compound. The nonionic monomers (eg, iohexol, iopamidol, ioversol, etc.) have 3 iodine atoms for each osmotically active particle and are termed ratio 3 agents. A ratio 3 agent can also be created by the formation of an ionic dimer (ie, ioxaglate) in which there are 6 iodine atoms for each 2 osmotically active particles. Ratio 3 agents have osmolalities of about 600 mOsm/kg water – 900 mOsm/kg water. A ratio 6 compound can be achieved by the formation of a nonionic dimer (eg, iodixanol) in which each osmotically active particle is associated with 6 iodine atoms. As noted above, the ratio 1.5 agents are referred to as high osmolal contrast material while ratio 3 agents are termed low osmolal contrast material and the ratio 6 agents are considered iso-osmolal. Iodixanol is actually hypo-osmolal and is brought to iso-osmolality by the addition of a small amount of a sodium and calcium salts.

The viscosity and the iodine concentration of contrast media are influenced by osmolality. The viscosity of the ratio 3 and 6 agents tends to be greater than that of the high osmolal contrast agents, especially at room temperature. Because of this, the former agents are usually formulated in solutions of lower concentration. Most of the lower osmolal contrasts are dispensed with lower iodine concentrations (eg, 320–350 mgI/mL) than the typ-

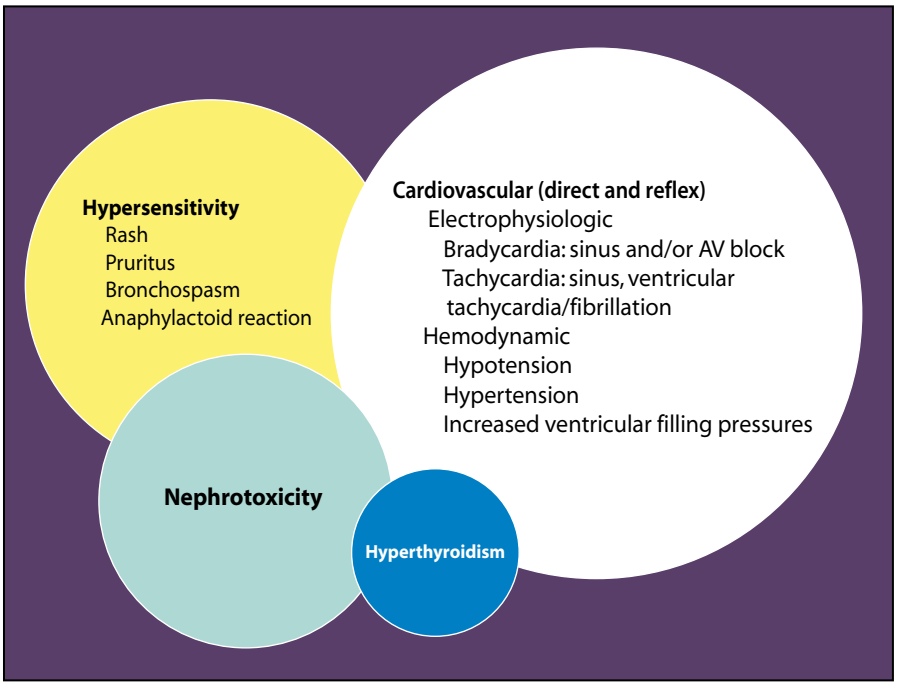

Figure 2. *Overlapping symptoms of contrast toxicity.*

ical high osmolal contrast agents (370 mgI/mL). It is important to note that warming contrast to body temperature significantly decreases viscosity, which may be an important consideration when small catheter systems are used.

While the traditional high osmolal contrast agents were ionic, most of the low osmolal compounds are nonionic; the only exception is ioxaglate, which is a ratio 3 agent. Ionic agents must have a critical concentration of sodium as one of the cations to prevent cardiac arrhythmia upon coronary injection.[1,2] Ionic contrasts cause more physiologic perturbation than the nonionics. This is not generally desirable although it has been argued that there may be some advantages to ionic contrast (vide infra).

All contrasts are formulated with buffers and stabilizers that are usually considered inert. Some of the high osmolal contrast agents utilized sodium citrate and sodium EDTA for these purposes. These additives bind calcium avidly and produce more arrhythmia and myocardial depression than identical contrast using calcium disodium EDTA.[3,4] One of the most frequently used high osmolal contrast agents was formulated with calcium binding additives, increasing toxicity. Unfortunately, this was a frequent comparator to ratio 3 contrasts in randomized trials magnifying the difference between ratio 1.5 and 3 agents.

The toxicity of contrast has been expressed as the dose of intravenously administered contrast that results in the death of 50% of the animal population exposed to it. While the LD50 for mice has little direct relationship to man, it has been used to extrapolate suggested maximum dosages of contrast for any single procedure. The commonly accepted value for high osmolal contrast agents of 3 mL/kg to 5 mL/kg of body weight has been perpetuated for the newer contrasts. While it is wise to use as little contrast as is clinically necessary, large dosages of the ratio 3 and 6 agents have been given in complex situations and appear to be well tolerated.[5] We have given in excess of 1 L of iodixanol at a single sitting in over 50 patients without adverse effect. Because the volume of contrast administered is considered a risk factor for contrast-mediated nephrotoxicity, patients at increased potential for this event (especially those with pre-existing renal dysfunction) should receive as little contrast as possible. It is important to ensure adequate hydration when a large dose of contrast is used.

Contrast Toxicity

The sole function of a contrast agent is to absorb x-radiation; any other effect may be reasonably considered undesirable. There are many potential adverse reactions to contrast (Figure 2) which range in degree of severity from annoying to life threatening. The manifestation of these effects depends on the specific agent administered and its route and dose, as well as the patient's physiologic state.

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Hypersensitivity Reactions

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Table 2
Incidence of Adverse Events: Ionic vs Nonionic Contrast

	Number of Patients		Overall Reactions		Severe Reactions	
Reference	Ionic	Nonionic	Ionic	Nonionic	Ionic	Nonionic
Katayama[11]	169,284	168,363	12.7%	3.1%	0.22%	0.04%
Palmer[12]	79,278	30,268	3.8%	1.2%	0.1%	0.01%
Wolf[13]	6,006	7,170	4.2%	0.7%	0.4%	0.0%

Rates of adverse events encountered in large registries comparing ionic and nonionic contrast given intravenously.
Adapted with permission from Stacul.[14]

and range from a mild rash to bronchospasm and anaphylactoid shock. The incidence of death resulting from a hypersensitivity reaction to high osmolal contrast agents is approximately 1 in 40,000 exposures, which could account for an annual death toll in the United States as high as 500 patients.[6,7] Hypersensitivity reactions to contrast are generally considered pseudo-allergic because most are unrelated to an antigen-antibody reaction. They appear to result from the release of vasoactive mediators such as histamine, serotonin, and bradykinin upon exposure to contrast.[8] The incidence of this type of reaction is higher in individuals with a history of hypersensitivity to a variety of inciting factors, including those with food allergies and asthma. While patients who are allergic to shellfish do have an increased propensity to contrast reaction, it is no greater than patients who are allergic to peanuts, eggs, or strawberries.[9]

Hypersensitivity reactions appear more common when contrast agents are administered intravenously,[10] which may be related to the presence of cells in the lung capable of releasing vasoactive peptides and amines. The concept that a hyperosmotic insult induces release of these substances in the lung and elsewhere is supported by the reports from large registries[11–13] comparing predominantly intravenously administered high osmolal contrast agents and nonionic contrast (Table 2). It is important to note that the ratio 3 and 6 agents reduce the incidence of immediate hypersensitivity reactions but do not abolish them. Lasser and colleagues[15] demonstrated that pretreatment of patients with corticosteroids prior to high osmolal contrast agent exposure could reduce the incidence of reaction. The benefit was seen when the steroids were dosed 12 and 2 hours prior to contrast, but not when only the 2 hour dose was given. The decrease in the incidence of reactions to high osmolal contrast agents brought about by steroid pretreatment is less than that achieved by use of nonionic agents. Recently, it has been suggested that pretreatment with steroids prior to administration of a low osmolal contrast may further reduce the incidence of adverse events in patients at increased risk for hypersensitivity reactions.[16,17]

Delayed Hypersensitivity

While the typical hypersensitivity reaction occurs within minutes of exposure to contrast, attention has more recently been directed at reactions that occur hours to days after contrast exposure. These late reactions usually occur within 3 days of contrast exposure, but may be delayed for as long as a week. A maculopapular rash is the most common manifestation but urticaria, erythema, and angioedema may also occur. There is a wide range in the reported incidence of delayed reactions, with most large studies reporting an occurrence of less than 4%.[18,19] A recent study compared the incidence of immediate and late contrast reactions encountered with cardiac angiography using ioxaglate, iopamidol, and iodixanol. Early contrast reactions occurred in 22%,

Table 3
Severe Adverse Events Associated with High Osmolal Contrast During Diagnostic Angiography at The Johns Hopkins Hospital

Number of Procedures	1144
Severe Complications (%)	33 (2.8)
Contrast Related (%)	17 (1.5)
Hypotension → Death	3
Prolonged Hypotension → Resuscitation	3
Ventricular Arrhythmia → DC conversion	7
Acute Nephropathy	4*

*One patient had cholesterol embolization
Modified with permission from Brinker.[23]

9% and 8%, respectively, while late reactions were noted in 4%, 4%, and 12%, respectively.[20] There has been a suggestion that late reactions are more common with ratio 6 agents. This seems to be true of iotrolan, which was withdrawn from intravascular use for this reason.[21] It does not appear to be the case with iodixanol; there was no difference in the frequency of delayed reactions between this contrast and the ratio 3 agent iohexol.[22]

Unlike acute hypersensitivity reactions, the delayed reactions appear to be frequently mediated by an antigen-antibody reaction and display a positive immunoglobulin E skin test. Most delayed reactions resolve spontaneously, although symptomatic treatment may occasionally be needed. Recognition of delayed contrast reaction is especially important in patients having undergone coronary stenting, as physicians may mistakenly consider these symptoms to be related to thienopyridine treatment, which may be inappropriately discontinued.

Cardiovascular Toxicity

Contrast toxicity associated with noncardiac angiography is usually defined by the hypersensitivity events described above. It has long been known that contrast delivered directly into the coronary artery or chambers of the heart can have profound effects that are more frequent and potentially more severe than hypersensitivity reactions. The injection of high osmolal contrast agents into a coronary artery is consistently associated with slowing of the heart rate and depression of blood pressure. These effects usually last only about 5 seconds to 10 seconds and therapy is rarely required.[23] In some patients, especially those with heart failure, pulmonary hypertension, critical valvular disease, or severe coronary obstructions, these transient changes can initiate a cycle of myocardial ischemia, more severe hypotension, further ischemia, and eventually death. Over one half of the severe complications associated with cardiac catheterization at The Johns Hopkins Hospital during 1980–1981[23] could be attributed to high osmolal contrast agents (Table 3). None were due to hypersensitivity.

In some patients, the transient changes in heart rate and blood pressure caused by injecting a high osmolal agent into a coronary artery can initiate a cycle of myocardial ischemia, more severe hypotension, further ischemia, and eventually death.

Randomized trials comparing high osmolal contrast agents with nonionic contrast for cardiac angiography demonstrated that three times as many adverse reactions requiring treatment occurred with the former. Severe or prolonged life-threatening reactions occurred in 2.9% of high osmolal contrast agent patients versus 0.8% of nonionics.[24] Hill and coworkers[25] found similar results using Renografin as the ionic comparator. Our own study demonstrated a 3-fold greater incidence of overall adverse events with high osmolal contrast agents, but we found no difference in the incidence of severe events between the two groups.[26] This study used an ionic comparator that is not formulated with calcium binding additives.

The ionic dimer ioxaglate produces less hemodynamic and electrophysiologic perturbations than high osmolal contrast agents, but slightly more than nonionic ratio 3 agents. It would appear that even low osmolal ionic agents can bind calcium to a degree. Hypersensitivity reactions, as well as nausea and vomiting, appear to be more frequent with ioxaglate than nonionics.[27,28] One might anticipate that the ratio 6 contrasts would be associated with even less physiologic perturbation than ratio 3 nonionics. In a randomized study comparing iodixanol and iohexol in relatively low-risk patients, there appeared to be no significant differences in hemodynamic or electrophysiologic parameters between the two agents.[29] Bergstra and colleagues,[30] however, found a lessened increase in left ventricular end diastolic pressure after ventriculography with iodixanol compared to iohexol in patients with decreased ejection fraction, suggesting that there may be some clinical benefit of the ratio 6 above that of the nonionic monomer in compromised patients. Most recently, a benefit with regard to nephrotoxicity has been demonstrated with iodixanol compared to iohexol.[31]

Contrast and Coagulation

That clots can form on catheters and guidewires and potentially embolize into the systemic circulation has been self-evident since the beginning of angiography. While there was a time when anticoagulation was given for coronary arteriography performed by the Judkins technique, it was found that the practice of meticulous technique in handling catheters and guidewires obviates this need. Shortly after the introduction of nonionic contrast, reports of clot-like material appearing in contrast syringes and angiographic evidence of embolization appeared.[32] The issue of whether nonionic agents were prothrombotic was hotly debated[33] until the publica-

tion of a large prospective study of patients undergoing diagnostic angiography found that the 0.18% incidence of thrombotic events encountered with nonionic agents was no different than that seen with ionic contrast regardless of systemic anticoagulation or antiplatelet therapy.[34] Shortly thereafter a number of papers appeared suggesting that while diagnostic angiography with nonionic agents might not be associated with thrombo-embolic phenomena, angioplasty, especially in the setting of acute coronary syndromes, was.[35–38]

A large, multicenter randomized trial was performed comparing the nonionic dimer, iodixanol, to the ionic dimer, ioxaglate.[39] The Randomized Trial of Contrast Media Utilization in High-Risk PTCA (COURT) enrolled patients considered to be at increased risk for an ischemic complication of coronary intervention. The primary endpoint, a composite of in-hospital major clinical adverse events possibly related to thrombus, occurred significantly more often in the ioxaglate group (9.5% vs 5.4%, $P = .027$). The advantage of iodixanol over ioxaglate occurred primarily in those patients who did not receive abciximab during their procedure. This trial suggests that iodixanol has less of a potential for thrombus-mediated complications than does ioxaglate. A similar multicenter study enrolling patients at less risk for intervention was performed in Europe.[40] While no difference in a composite of in-hospital or 2-month major adverse coronary event was found, there was an increased risk of hypersensitivity and adverse drug reactions in the ioxaglate-treated patients.

Based on these and other recent clinical trials, it appears that nonionic contrast is not a risk factor for thrombo-embolism when used in the performance of coronary intervention. In fact, iodixanol may be advantageous in patients at increased risk for these events. Whether all of the benefits associated with iodixanol can be extended to other nonionics as a class effect is uncertain because the former is a ratio 6 agent and is formulated with small amounts of sodium and calcium additives.

Hyperthyroidism

Both clinical and chemical hyperthyroidism has been detected in elderly patients after undergoing intravascular contrast studies with nonionic contrast.[41,42] In most cases, the disorder was self-limited but a few patients required thyroid suppression. The cases occurred in a non-iodine deficient population and are thought to be due to autonomous thyroid nodules. Certainly patients with overt hyperthyroidism should be treated prior to exposure to iodine-containing contrast. A degree of suspicion of this diagnosis should be held for patients exhibiting subtle signs compatible with hyperthyroidism after angiography.

Cost:Benefit Ratio

Upon their introduction, the low osmolal contrasts were 10–15 times more expensive than the traditional high osmolal agents. While it was clear that the former were better tolerated than the latter, there was controversy as to whether the degree of benefit justified the expense. Most studies addressing this issue excluded patients at high risk of serious adverse events, for whom low osmolal agents were assumed to be safer. There has been no evidence demonstrating a decreased mortality with the routine use of low osmolal agents. Realizing the financial burden that would be placed on many high vol-

Main Points

- Because much of the toxicity associated with contrast is related to osmolality, this parameter has been most frequently used to distinguish them from eqach other.
- Acute allergy-like phenomena occur in as many as 10% – 15% of patients receiving contrast agents and range from a mild rash to bronchospasm and anaphylactoid shock.
- Recognition of delayed contrast reaction is especially important in patients having undergone coronary stenting, as physicians may mistakenly consider these symptoms to be related to thienopyridine treatment, which may be inappropriately discontinued.
- While patients who are allergic to shellfish do have an increased propensity to contrast reaction, it is no greater than patients who are allergic to peanuts, eggs, or strawberries.
- It appears that nonionic contrast is not a risk factor for thrombo-embolism when used in the performance of coronary intervention.
- The primary endpoint in the COURT trial, a composite of in-hospital major clinical adverse events possibly related to thrombus, occurred significantly more often in the ioxaglate group (9.5% vs 5.4%, $P = .027$).

ume centers, professional organizations avoided endorsing universal low osmolal contrast.[43] While some suggested guidelines for risk stratifying patients, the medicolegal ramifications of this is problematic for many centers. Over the years, the cost of low osmolal contrast has significantly decreased, easing transition to the routine use of these agents (although there remains a cost differential, especially between high osmolal contrast agents and the nonionic dimer). At this time, about 90% of all cardiac angiography in the United States is performed with low osmolal contrast, of which 95% is nonionic (industry data).

Alternatives to Iodinated Contrast

Gadolinium is a rare earth element that is highly toxic unless chelated. Contrasts utilizing gadolinium are important for magnetic resonance imaging and have been used for about 20 years. The first report of gadolinium as a radiographic contrast appeared in 1993.[44] This agent, in the relatively low doses approved for intravascular use, has little nephrotoxic potential, which underlies its use by radiologists primarily in the performance of renal angiography and intervention. Because of the relatively poor radio-opacification achieved by available formulations, the contrast is generally used for digital subtraction angiography. Its availability has led to the performance of other arteriographic procedures, including coronary angiography.[45] It has been suggested recently that a mixture of gadolinium and iodinated contrast may increase radiographic opacification and allow a higher total volume to be given while still being protective of the kidneys.[46] An argument has been made that the relative lack of nephrotoxicity of gadolinium is the result of the small volume of drug given (about 40 mL to 60 mL). An equal x-ray attenuating dose of iodinated contrast would be as little as 10 mL to 13 mL of iodinated contrast having 350 mg/mL of iodine.[47] Although there may be a small niche for these agents, it would appear that the role of the gadolinium chelates in coronary angiography is limited.

Conclusion

The introduction of nonionic contrast has had considerable impact on the performance of cardiac angiography and intervention. While these agents are most vital for patients at high risk—those with severe aortic stenosis or a hemodynamically unstable coronary event—their benefits extend, to a degree, to all patients. There are no longer concerns about the occurrence of nausea and vomiting; the angiographer needn't worry about having to "cough the patient" through an episode of asystole accompanying a right coronary injection; and a serious anaphylactoid reaction is now extremely unlikely, even if the patient is thought to be at increased risk for such an event. The controversies surrounding the evolution of contrast over the last 25 years (ie, cost:benefit, thrombogenicity, nephrotoxicity) have correctly refocused attention on these agents as drugs with the potential for serious toxicity. While we may not have resolved every issue (and others are likely to arise), our knowledge base has certainly been expanded. New contrasts[48] are sure to be introduced and subjected to the same scrutiny as their forbearers, with the goal of making angiography safer and more comfortable. ■

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