

Frequently Asked Questions: Iodinated Contrast Agents¹

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Although iodinated contrast agents are safe and widely used, adverse events occur and questions remain about their use, safety, and interactions. Some questions are easily answered and others still require extensive investigation. For one frequent question—is informed consent necessary before all contrast media injections—the simple answer is no. Another question concerns use of contrast media in patients with prior reactions or allergies. Contrast agents can be safely used in such patients, but special care must be taken to be aware of what the previous reaction was and to be ready to treat any reaction. The protective role of pre-treatment with steroids is well established for minor reactions, but they may not prevent major reactions. It is important to realize that even life-threatening, anaphylactoid reactions are not the result of a true allergy to contrast media. Many questions arise about contrast agent-induced nephropathy. Baseline serum creatinine values should be obtained in patients who are at risk, not all patients. The incidence and natural history of contrast agent-induced nephropathy remain unclear. It occurs only in patients with compromised renal function before contrast agent injection, but even patients with normal serum creatinine levels can have renal dysfunction. Calculated creatinine clearance is a better way to determine risk and to follow this complication. The outcome in almost all patients is benign, with progression to end-stage renal disease being rare. The major risk factors, in addition to renal dysfunction, are long-standing diabetes mellitus, dehydration, and use of other nephrotoxic medications. Recent work in preventing and ameliorating contrast agent-induced nephropathy with *N*-acetyl cysteine, substitution of an isosmolal nonionic contrast agent, and various hydration regimens has been promising. Another common concern is use of iodinated contrast agents in pregnant or breast-feeding women. In both cases, there is no evidence of harm to the fetus or infant, but it is prudent to weigh the theoretical risks and benefits and avoid contrast agent administration unless it is truly necessary.

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Abbreviation: n-AC = *N*-acetyl cysteine

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Introduction

Every radiologist is intimately familiar with contrast agents, and, with the increasing use of computed tomography (CT), the number of patients receiving these medications continues to increase. This widespread use has helped engender improved understanding of contrast agents, but many questions and misunderstandings remain. The intent of this article is to pragmatically address some of the main concerns that arise with the day-to-day use of iodinated contrast agents. These include the need for informed consent and for measurement of renal function, definition of risk factors that may predict adverse events, how to deal with patients who have had a prior reaction, and how to assess for and deal with contrast nephrotoxicity.

Do I Have to Obtain Consent before Contrast Material Injection?

The simple answer is no, but that is probably too simple. If there were no risks associated with injection of contrast agents, or if the risks were vanishingly small, there would be no need for consent. Conversely, if there were high risk, perhaps risk of death in one of 100 or even one of 1,000 exposures, informed consent would be mandatory. The actual risk of death, however, is very low, less than one in 130,000 at most (1,2). The risk of other severe adverse events, such as renal failure or stroke, is also very low. An additional major consideration is that it is becoming almost physically impossible for a physician to obtain consent for every contrast agent injection, given the increasing number of CT examinations being performed.

If a lawyer were asked the above question, the answer would almost invariably be yes. The definition of malpractice, however, is based on usual and customary practice, and clearly many radiologists, probably a majority, do not obtain formal informed consent. As with many areas in the practice of medicine, there are no absolute guidelines that pertain. The compromise that is often used is an "information sheet" (3). It is important to remember that informed consent is a process, one that is intended to provide information to both the patient and the physician. To this end, most such information sheets ask the patient to answer certain questions that help define a patient's risk, such as diabetic and renal function status, prior reaction to contrast agents (if any had been administered previously), and history of allergies. The questions are followed by a short

paragraph that explains the risks that may be associated with contrast agent injection, including the very small risk of death or cerebrovascular accident. The patient is also informed that if he or she has any questions related to contrast agent use, a radiologist will be made available to provide further information.

In summary, the injection of an iodinated contrast agent is very safe, particularly in comparison to other situations in which consent is usually obtained, such as surgery or angiography. "Usual and customary practice"—the practice of at least a reasonable minority of responsible radiologists—is to not obtain informed consent. The purpose of consent is to gather and impart relevant information to allow the procedure to be as safe and comfortable as possible. A straightforward, one-page information sheet is a practical, reasonable, and widely used approach.

How Should I Deal with a Patient Who Is "Allergic" to Contrast Agents?

First, although typical adverse reactions encountered after the administration of an iodinated contrast agent resemble allergic reactions, with signs ranging from urticaria to an anaphylactoid process, such reactions are not allergies. Contrast agent molecules are small, with a molecular weight of about 850 kD, and are probably too small to be able to act as antigens. Second, despite extensive investigations, no antibodies to contrast agents have been reliably identified in patients who have had systemic, allergylike reactions. Finally, there is extensive experience indicating that a patient who had an allergylike adverse event after contrast agent injection is unlikely to experience a similar or more severe reaction if contrast agent were injected again (1). In fact, although a prior reaction remains the best predictor of a future adverse event, the likelihood of a recurrent reaction is in the range of 8%–25% (1). If the previous reaction were caused by a true allergy, the risk would approach 100%.

If the Patient Had a Prior Reaction to a Contrast Agent, Should I Ignore It, Begin a Pre-Treatment Regimen, or Avoid Any Further Contrast Agent Injection?

There is no simple answer. Many different approaches have been suggested. It is not necessary to avoid any further contrast agent injection in most cases. A very small number of patients, anecdotally, have recurrent reactions, which seem to occur after various types of contrast agents and which are not preventable with a pre-treatment regimen. In most cases, these adverse effects are

delayed cutaneous reactions (discussed later) that may be severe but are not life threatening. Very rarely, recurrent life-threatening reactions are reported to occur, but these cases are both rare and poorly documented.

Use of a different contrast agent is a reasonable approach, although it is often impossible to define either the specifics of a prior reaction or the specific contrast agent used. Obtaining a careful patient history is helpful in this regard. If the patient's reaction occurred in the United States before 1985, a nonionic, low-osmolality agent could not have been used, so one could be used now. If the reaction occurred before 1997, iodixanol, the nonionic isotonic dimer, was not available, so it could be substituted. Regardless, the two crucial factors are the awareness of a prior reaction and the ready availability of equipment and expertise to treat any reaction that may occur.

The use of a pre-treatment regimen, including administration of corticosteroids with or without antihistamines or other medications, has been proved safe (4,5). It has also been proved effective, but with the major caveat that it is effective in preventing only minor adverse events. Prospective studies of pre-treatment have been too small to be able to determine whether pre-treatment with steroids prevents the life-threatening reactions (4,6). There is evidence from a large prospective registry, however, that they do not (1). If pre-treatment is to be used, the crucial points to remember are that it almost certainly won't hurt, that steroid use must begin about 12 hours before contrast agent injection to prevent even minor adverse events (4), and that the attending radiologist and other personnel must still be ready to treat a reaction.

In summary, unless the patient has a clearly documented history of multiple significant prior reactions—and this is *very* rare—there is no need to refrain from injecting iodinated contrast media in a patient who has had a prior reaction. Pre-treatment with steroids almost certainly won't harm the patient, but it will delay the procedure at least 12 hours, and it is unlikely to prevent a severe reaction. Use of a contrast agent that the patient has not been exposed to previously may help, but being ready and able to treat a life-threatening reaction is the crucial element (7).

If a Patient Has Other Allergies or Asthma, Does It Predict an Increased Risk of an Adverse Event?

It does, but minimally. The presence of a history of multiple severe allergies does increase the risk of a reaction following contrast agent injection, but only by a very small percent (1). Further, most such reactions will be minor, as are most

reactions in general. A strong history of allergies should increase awareness of the possible risks of a reaction, but there is no need to avoid injection of contrast media. A history of asthma has also been thought to be a good predictor of increased risk. Empirically, asthma appears to increase the risk only of bronchospasm, not other adverse events. The risk, again empirically, seems to be particularly high in patients with active asthma. Fortunately, such patients are generally familiar with the use of β -agonist inhalers and have one with them. Nevertheless, such inhalers should always be available where contrast media are being administered.

In the past, many thought that an allergy to shellfish was a predictor of an increased risk of a reaction to a contrast agent, presumably because both shellfish and contrast agents contain iodine. Such a relationship is clearly not true. Organic iodide as found in shellfish is an essential element, so individuals cannot be allergic to it.

Should I Obtain Serum Urea Nitrogen and Creatinine Values for Every Patient before I Inject Contrast Media?

Not every patient is at risk of developing contrast agent-induced nephropathy, so recent values of serum urea nitrogen (ie, BUN) and creatinine are not needed in every patient. As will be discussed, the risk is confined to patients with underlying compromise of normal renal function (8). If a patient has known renal dysfunction, it is important to have recent measurements of serum urea nitrogen and creatinine (eg, within the preceding month) to make sure that the patient's renal function is stable. For all other patients, it is important to find out if they have risk factors for renal problems. These factors include diabetes mellitus; history of recurrent renal stones or recurrent urinary tract infections; history of bladder outlet obstruction (eg, benign prostatic hypertrophy or bladder prolapse); recent history of an event known to cause a risk of renal damage, such as major surgery, dehydration, or cardiogenic shock; and use of nephrotoxic medications such as gentamycin, high-dose nonsteroidal anti-inflammatory drugs, or certain chemotherapeutic drugs. It is not clear whether the risk related to diabetes mellitus is different for types 1 and 2. The risk is probably more a function of the duration of the diabetes and the ongoing control of blood sugar level. In general, it is better to err on the side of caution and obtain a serum urea nitrogen value (as a rough guide to the level of hydration) and a creatinine value (as an indicator of whether there

is true renal dysfunction). The frequency with which contrast agent–enhanced examinations must be delayed because this information is missing clearly depends on the patient population, the usual approach of the referring doctors, and the protocols of the radiology department. If patients are well screened and if referring physicians are properly informed, contrast-enhanced imaging studies most likely will need to be delayed infrequently.

What about Patients Who Take Metformin?

Patients who take metformin or metformin-containing medications present a different challenge for radiologists. If a patient's blood levels of metformin are high, the patient has a risk of developing lactic acidosis, which has been reported to be fatal in about 50% of cases (9). Metformin is excreted unchanged by the kidney; therefore, people with compromised renal function will have higher than expected serum levels and are at risk of developing lactic acidosis. In addition, individuals with very poor cardiac function or acute hepatic compromise have increased lactate production or impaired lactate breakdown and also are at risk of developing lactic acidosis. For all such patients, the use of metformin is contraindicated.

Because contrast agents are associated with nephrotoxicity, it was postulated that the concomitant use of metformin and an iodinated contrast agent could lead to an increased risk of lactic acidosis. This hypothesis has been disproved empirically, and the package insert approved by the U.S. Food and Drug Administration has been altered accordingly. Although the package insert is perhaps overly cautious, it states that metformin use should be stopped at the time an iodinated contrast agent is administered and that the patient should wait 48 hours before resuming use of metformin. There is no mandate to measure serum creatinine levels at that time. Rather, the patient should be reevaluated clinically, and a creatinine value should be obtained if there are any other reasons that the patient's renal function may have been compromised, such as major surgery or cardiogenic shock (7). The major point to remember is that metformin is contraindicated in patients with any compromise in renal function. It is surprising how often patients who take metformin and who have elevated serum creatinine levels are referred for a contrast agent study. In these patients, the imaging study should be delayed and the referring physician should be notified.

How Should I Deal with a Woman Who Is Pregnant or Breast-Feeding?

These concerns have been addressed by the American College of Radiology in its recently released fifth edition of the *Manual on Contrast Media* (10). Because contrast media are small molecules that are rapidly distributed throughout the extracellular space, they must be assumed to readily cross the placental barrier. Further, contrast media molecules are most likely present in breast milk shortly after parenteral administration to a breast-feeding patient. There is no evidence suggesting that iodinated contrast agents are teratogenic in humans. On the other hand, the experience is too limited to conclude that they are safe. It is, therefore, wise to avoid administering them in women who are pregnant (particularly in the first trimester) when possible. It is appropriate, however, to use contrast agents when the procedure requiring them is thought to be essential. That is, the risks, as always, must be balanced against the possible benefits. Overall, the theoretical risks of radiation exposure are most likely greater than those incurred from contrast agents.

In breast-feeding women as well, the risks to the patient and to her infant must be weighed against any possible benefits. If an iodinated contrast agent is administered, the infant is likely to receive a small amount orally and then to absorb a small amount. There is no real evidence of contrast agent–induced toxicity in newborns, but on the other hand there is little concrete information confirming the safety of these medications in infants. A further concern regarding the use of iodinated contrast agents in both pregnant and breast-feeding women is the theoretical effect of these agents on the fetal or neonatal thyroid. Although in theory all of the iodine in contrast agents is organically bound rather than free, it is not clear that no free iodide is present or to what extent there is thyroid uptake in the fetus or newborn and what the effect on thyroid function might be. The consensus recommendation is that a breast-feeding mother should use a pump to remove breast milk before contrast agent administration, and then afterward, she should use the pump and discard breast milk for 12–24 hours before resuming normal breast-feeding. Since the biologic half-life of iodinated contrast agents is less than 60 minutes, the amount remaining in the mother (assuming her renal function is normal) after 12 hours is essentially undetectable.

What Is Contrast Agent–induced Nephropathy? How Is It Defined and How Often Does It Occur?

In the most general terms, contrast agent–induced nephropathy is the occurrence of renal failure, as indicated by an increase in serum creati-

nine level or a fall in calculated creatinine clearance, after the administration of an iodinated contrast agent. For several reasons, there is no widely accepted definition of contrast agent–induced nephropathy. First, such nephropathy occurs essentially only in those patients who have abnormal renal function before contrast agent injection. Second, the parameters used clinically are imprecise. That is, serum creatinine levels vary with age, muscle mass, and gender. A serum creatinine value of 1.2 mg/dL in a healthy 20-year-old man or woman is normal and indicates that the glomerular filtration rate is in the normal range of 60–120 mL/min, most likely close to or above 100 mL/min. The same serum creatinine value in a 50-kg, 80-year-old woman, however, likely correlates with a significantly decreased glomerular filtration rate, perhaps even less than 40 mL/min. This difference is because glomerular filtration rate decreases with increasing age, and creatinine production, a function of muscle mass, also decreases. In short, the serum creatinine value is a reasonable screening parameter, since it is inexpensive and readily available, but it is not particularly accurate. It is not practical to measure true creatinine clearance, but it is helpful to use a formula, such as that of Cockcroft and Gault (11) or Levey et al (12), to calculate creatinine clearance. In fact, some institutional laboratories routinely report calculated creatinine clearance with serum creatinine levels.

Most studies of contrast agent–induced nephropathy have used serum creatinine values, at baseline and after contrast agent administration. Because of the limitations of serum creatinine, these studies have shown widely varying results. Contrast agents have been cited as one of the most frequent causes of in-hospital renal failure (13,14), which is probably a valid impression, but many other factors must be considered. These factors include not only real glomerular filtration rate, but also concomitant risk factors such as dehydration, surgery, and use of additional nephrotoxins (eg, gentamycin, nonsteroidal anti-inflammatory drugs, certain chemotherapeutic drugs). At this time, it is impossible to define the true incidence of contrast agent–induced nephropathy.

What Are the Risk Factors for Contrast Agent–induced Nephropathy?

As previously implied, the major risk factor is underlying renal dysfunction. Contrast agent–induced nephropathy essentially never occurs if a patient’s renal function is truly normal. The presence of diabetes, particularly if long standing, is probably not an independent risk factor, but it is a major contributing factor in the presence of renal dysfunction (8,15). Additional concerns, as

noted, are dehydration, poor renal perfusion (as occurs with severe congestive heart failure), and the presence of other factors that may be nephrotoxic, such as certain medications or major surgery. The volume of contrast agent administered is another dependent risk factor: If renal function is truly normal (the 20-year-old healthy patient with a serum creatinine level of 1.2 mg/dL), then a high volume of contrast agent will not lead to nephropathy. If the patient has underlying renal dysfunction, however, increasing the volume of contrast agent injected will increase the likelihood of worsening renal function (16).

What Is the Natural History of Contrast Agent–induced Nephropathy?

In the vast majority of cases, contrast agent–induced nephropathy will be manifest by a transient increase in serum creatinine level, which usually peaks at 4–7 days and gradually returns to baseline. A persistent elevation of serum creatinine level is unusual, as is progression to end-stage renal disease (8,17). The risk of either of these endpoints increases as a direct function of the severity of a patient’s underlying renal failure; that is, most patients who require dialysis after contrast agent injection had very poor renal function at baseline. In one study of over 600 patients with elevated serum creatinine levels who underwent cardiac catheterization, only seven patients required dialysis, and permanent dialysis was necessary in only three of these (8).

How Can Contrast Agent–induced Nephropathy Be Prevented?

First, nephropathy is not really a worry in patients with truly normal renal function, regardless of the volume of contrast agent injected. For patients at risk, the first step in preventing nephropathy is adequate hydration (18). In practical terms, adequate hydration is usually achieved by instructing patients to drink several liters of fluid over 12–24 hours before contrast agent injection. When such hydration isn’t possible because an imaging study is urgent, because the patient cannot take oral fluids, or because sedation or anesthesia will be needed and thus oral fluids are contraindicated, intravenous hydration can be given and may actually be more effective. Intravenous hydration should consist of at least 1 mL of normal saline per kilogram of body weight per hour, beginning 12 hours before contrast agent injection and continuing for 12 hours afterward. It is also important to remember that, invariably, patients do not adequately hydrate themselves; thus,

for patients at risk of nephropathy and if it is feasible, intravenous hydration should be used, beginning at least 12 hours before contrast agent injection (19). There is evidence that normal saline is more effective than is half-normal saline (20). Recently, the use of sodium bicarbonate for hydration, as compared with sodium chloride (normal saline), has been reported as being effective in decreasing the incidence of contrast agent–induced nephropathy (21). This approach is appealing because of its low cost and relative ease of use, but further proof of efficacy is necessary. One concern with the Merten et al study (21) is that hydration consisted of a 7-hour infusion begun 1 hour before contrast agent injection. Other studies have shown that hydration with an infusion of normal saline that begins at least 12 hours before contrast agent injection is more effective than either short infusions or random oral hydration (19).

Many other approaches for preventing contrast agent–induced nephropathy have been investigated. It is logical to think that administration of either a diuretic such as furosemide or dialysis during or immediately after contrast agent injection would help. Furosemide has been shown to be not helpful (18). Results of studies with dialysis do not agree, but most suggest that dialysis also is not helpful (22,23). Use of fenoldapam mesylate, a selective dopamine α_1 -receptor agonist (thus a post-glomerular renal vasodilator), has been advocated, but the bulk of the evidence suggests it does not have any protective or ameliorating effect (24), and its use requires close monitoring. Various other vasoactive agents have been investigated, mainly in small clinical studies, without any real proof of efficacy. Two agents that have been considered promising, although neither has been conclusively proved to be effective, are *N*-acetyl cysteine (n-AC) and iodixanol (Visipaque; GE Healthcare Group, Princeton, NJ), the only available nonionic, isosmolal, iodinated contrast agent. N-AC acts as both a vasodilator and as a free radical scavenger. Contrast agent nephrotoxicity was believed to be caused by a prolonged decrease in glomerular flow, so enhancing flow (as with n-AC or fenoldapam) might be protective. These hemodynamic changes have been demonstrated repeatedly in animal studies, but in humans, injection of contrast agent does not lead to a significant decrease in renal blood flow. It is well known, however, that the renal medulla is poorly oxygenated and is close to hypoxic under normal conditions. If hypoxia occurs, reactive oxygen species that are toxic to cells are

produced. In theory, then, n-AC may be effective because it is a free radical scavenger (25). The studies performed to date and analyses of them reach conflicting conclusions (26–28). Most but not all studies that used either oral administration with four doses twice daily starting on the day before contrast agent injection or intravenous administration starting 30 minutes before injection have shown a protective effect. In addition, n-AC is safe, readily available, and inexpensive.

Iodixanol has been shown to have a protective effect in two relatively small studies (29,30) and in other empiric reports. The reason why iodixanol should be effective is not entirely clear. To step back a step, or a generation of contrast agents, the bulk of the evidence suggests that there is a difference, probably minor, in the incidence of contrast agent–induced nephropathy when high-osmolality versus low-osmolality contrast agents are used, but no difference between them in the need for dialysis (8). It may be that the same holds true for iodixanol: The likelihood of a rise in serum creatinine level may be decreased, but the outcome for patients may not be different. Thus, iodixanol is promising, but further studies are needed to prove that it is effective in preventing or limiting contrast agent–induced nephropathy. Many additional approaches have been used to prevent or at least to minimize the incidence and severity of nephropathy, and other larger studies are necessary to answer the persistent and clinically important questions that remain.

Is There a Level of Serum Creatinine above Which a Patient Should Not Receive an Iodinated Contrast Agent?

The short answer is no. In all patients, regardless of whether renal function is normal, the potential risks must be balanced against the possible benefits. A serum creatinine level of 2.0 mg/dL, or 3.0 or 1.8, does not by itself indicate what the glomerular filtration rate is, although it is clearly reduced, nor does it accurately predict the risk of increased morbidity or mortality after injection of iodinated contrast media.

From a practical point of view, the radiologist should first calculate the creatinine clearance and then determine whether the relevant diagnostic question can be as adequately answered with another examination that does not require injection of an iodinated contrast agent. For example, if a patient is strongly suspected of having pulmonary embolism and has a mildly elevated creatinine level, but cannot undergo magnetic resonance angiography because of a pacemaker, what is the risk of performing CT angiography, which is likely to yield definitive results, versus a ventila-

tion perfusion lung scan? If the patient is stable and at low risk for anticoagulation, it is reasonable to do a ventilation perfusion scan, at least initially. If, however, a rapid and definitive answer is needed (eg, if the patient is hemodynamically compromised), CT pulmonary angiography should be performed. It is likely to cause no more than a transient increase in creatinine level while providing a definitive answer. In such a situation, it is probably better to start hydration (with normal saline or perhaps with sodium bicarbonate), start intravenous n-AC, and perform CT angiography. Remember, the risks related to contrast agent-induced nephropathy primarily depend on the baseline renal function and concomitant factors that place the patient at risk, such as dehydration, congestive heart failure, and recent major surgery. In most cases in which the patient has an elevated serum creatinine level (even if it is fairly markedly elevated), his or her renal function, as reflected in serum creatinine values, will likely worsen but then return to baseline.

What about Delayed Reactions to Contrast Agents?

Delayed reactions have been reported, with a low frequency, for many years (31,32). The reports have increased with the use of nonionic dimeric contrast media (33). Such reactions are almost invariably cutaneous, with a maculopapular, erythematous eruption occurring 12–48 hours after contrast agent administration. Although the rash is usually self-limited and only mildly symptomatic, it can be very uncomfortable and can spread over the entire body over the course of a few days. If the rash is localized and mildly pruritic, a topical steroid can be used. If it continues to spread and is more bothersome, the patient should be referred to a dermatologist. Such reactions have been reported to recur, even when a different contrast agent is used (34), but usually they do not. They also do not appear to presage other contrast agent reactions.

Summary

Contrast agents continue to cause concern among patients, referring physicians, and radiologists because of their widespread use and the rare but potentially important adverse events associated with them. The questions that arise concerning contrast agents have changed over time, with changes in the formulations and consequent improvement in safety. Mortality still occurs after injection of contrast agents of all types, but it is very rare. The major questions associated with use of contrast media currently concern practical matters, such as how to appropriately inform patients about the risks and benefits of contrast

agent use, how to deal with patients who have particular risk factors for an adverse event (eg, prior reaction, strong history of allergies, compromised renal function, diabetes mellitus), and how to deal with concerns of nephrotoxicity. Obtaining formal informed consent is both impractical and unnecessary, but it is imperative that radiologists get information from patients before contrast agent injection and supply information to them regarding the nature of the contrast media. Anaphylactoid reactions are not true allergies and are fortunately rare, but unfortunately can occur unpredictably. The crucial factor in dealing with them is to be prepared to treat them whenever and wherever they occur. Such preparation requires the presence of appropriate resuscitation equipment and medications and the availability of fully trained personnel. Contrast agent nephrotoxicity is a topic of interest currently because of the aging population, the associated increase in the number of patients with compromised renal function, and the increasing use of contrast-enhanced examinations. It is encouraging that there are several promising approaches to decreasing the incidence and severity of this problem, although neither the efficacy of these treatments nor the natural history of contrast agent-induced nephropathy is yet clear. The most important measure currently is ensuring that hydration is adequate. At this time, the approach that is best documented as effective is intravenous normal saline infused at 1 mL/kg/hr for 12 hours before and 12 hours after contrast agent injection. A 7-hour infusion of sodium bicarbonate beginning 1 hour before injection is promising, but the method has not yet been conclusively proved to be effective. It is encouraging that contrast agents have become safer and more thoroughly understood over the past few years, but many questions and concerns remain.

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