Contrast Media: Procedural Capacities and Potential Risks

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Contrast media are known to have transient hemodynamic properties that can influence a patient's clinical status, including heart rate variability and blood pressure. These changes have the potential to impact the diagnostic quality of CT scans. Although most patients are able to receive contrast media without significant adverse reactions, events occur in a minority of cases. These reactions range from mild discomfort (injection-associated pain and heat sensation) to more significant cardiac, renal, and hypersensitivity reactions. The incidence of adverse reactions varies with the type of contrast media used, and several randomized trials have elucidated the cardiac and renal differences among agents. Risk factors for contrast-induced acute kidney injury (CIAKI) have been established, with baseline kidney disease amplified by the presence of diabetes constituting the highest-risk patient group. Strategies for preventing CIAKI include antioxidant therapy, hydration regimens, and choice of contrast agents. Enhanced knowledge on the part of physicians and medical personnel regarding the properties and potential side effects of iodinated contrast agents should lead to improved patient safety and efficacy when performing radiologic examinations.
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With advances in technology, the diagnosis and treatment of cardiovascular disease is benefitting from improved imaging modalities and techniques. Cardiac CT is playing an increasingly important role in this arena. Similar to other procedures in cardiology and radiology, this technique relies on the use of iodinated contrast media. There are currently more than 70 million procedures utilizing contrast media performed in the world every year, the majority used for CT studies.[1] Most patients are able to tolerate contrast media without significant sequelae; however, adverse effects do occur

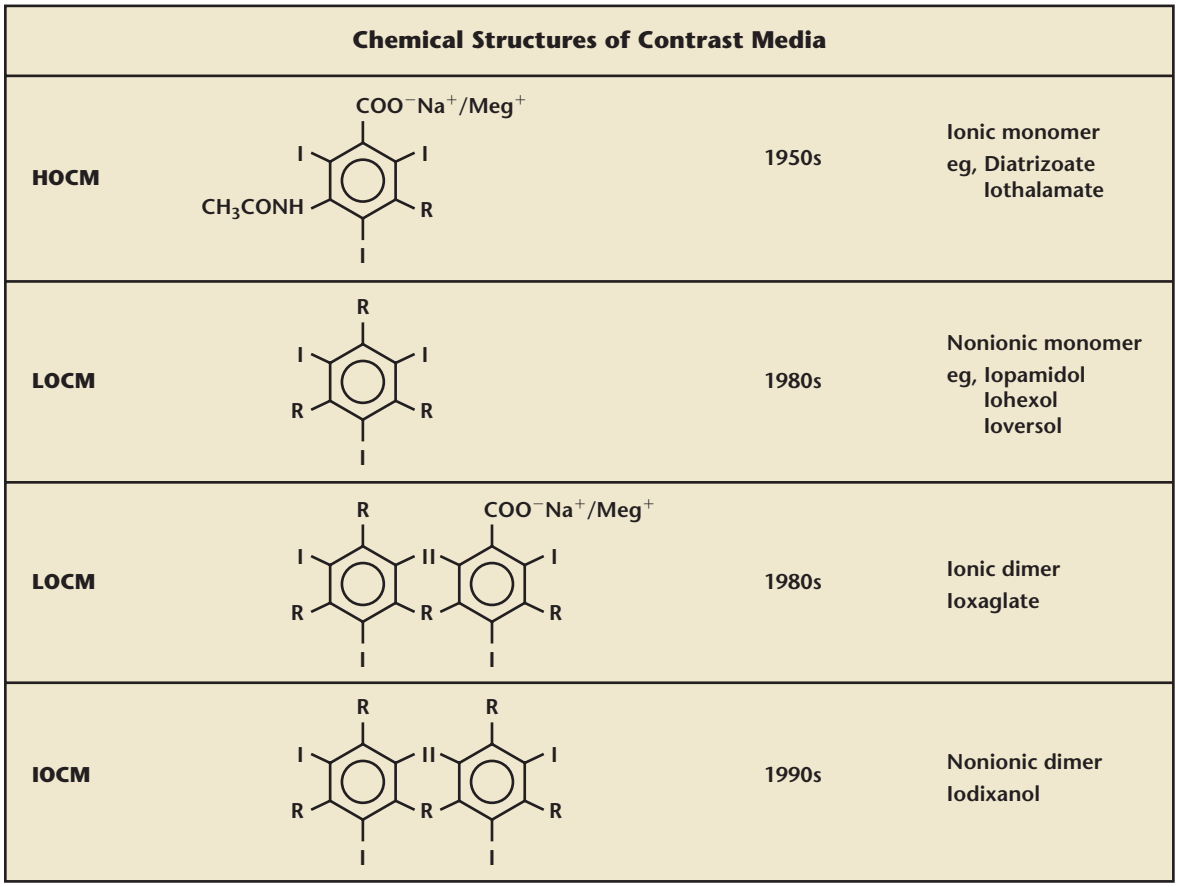
in a minority of cases. Contrast media are known to have transient vasodilatory properties that can influence a patient's hemodynamic status and heart rate. Although these variations usually cause only minor clinical effects, they can impact the diagnostic quality and sensitivity of cardiac scans. Patient comfort can also vary with different contrast media, with certain agents causing greater injection-associated pain and heat sensation. Finally, more severe adverse reactions can occur, and generally are classified into the categories of cardiovascular, renal, and hypersensitivity (allergic) reactions.

Cardiovascular reactions include thrombotic, arrhythmic, and volume overload. Hypersensitivity reactions are mild cutaneous eruptions, although they can range in severity to anaphylactoid reactions with a rare occurrence of life-threatening events (mortality $< 1/100000$). The primary renal complication is contrast-induced acute kidney injury (CIAKI). The incidence of CIAKI in the general population has been estimated at less than 2%. However, in high-risk patients (eg, those with chronic kidney disease and particularly those with diabetes mellitus), it has been reported to be approximately 20% to 30%.[2]

Pharmacology

The chemical structure of contrast agents consists of a benzoic acid molecule, with 3 atoms of iodine replacing the hydrogen atoms at positions 2, 4, and 6 of the benzene ring. Agents are further classified based on the charge of the iodinated molecules (ionic vs nonionic), their molecular structure (monomeric vs dimeric), and their osmolality (Figure 1). The osmolality of contrast agents is related to the number of particles in solution. The original contrast agents were ionic monomers and were hypertonic compared with human serum (approximately 1500-1800 mOsm/kg). This was due to the 3:2 iodine to particle ratio that conferred the high osmolality. These agents included diatrizoate, and were associated with a relatively high incidence of adverse cardiorenal effects.

Figure 1. *Chemical structures of contrast media. HOCM, high osmolal contrast media; IOCM, isomolal contrast media; LOCM, low osmolal contrast media. Reprinted from Davidson C et al,[49] with permission from Elsevier.*



This led to the development of newer agents that had lower osmolality and were less chemotoxic. These second-generation low osmolal contrast agents were either nonionic monomers of iodinated benzene rings (eg, iohexol, iopamidol, and ioversal), or an ionic dimer ioxaglate. These agents possess a 3:1 or 6:2 iodine to particle ratio, respectively. Although their osmolality was lower than that of high osmolal ionic agents, they remain hyperosmolal relative to plasma (approximately 600-850 mOsm/kg).

The most recent class of contrast media is the nonionic dimer iodixanol. It is iso-osmolal to plasma at all iodine concentrations (approximately 290 mOsm/kg). Iso-osmolal nonionic contrast agents reduce osmolality by linking 2 molecules of iodinated benzene rings together, creating a dimer with a 6:1 iodine to particle ratio. This is done through the use of a common side chain, and results in 1 large molecule in solution.

Hemodynamic Effects

Contrast media has been shown to impact hemodynamic parameters such as heart rate, blood pressure, left ventricular pressure, and stroke volume. High osmolal ionic contrast agents were found to decrease both systolic and diastolic blood pressure, depress myocardial contractility, and increase blood volume.[3] The decrease in blood pressure was largely due to systemic vasodilation secondary to the high osmolality of these early contrast media (in addition to factors such as sodium concentration and chemotoxicity). Subsequent animal and clinical studies demonstrated that low osmolal and iso-osmolal contrast agents had fewer hemodynamic effects than high osmolal agents.[4,5]

Bergstra and colleagues[6] compared the iso-osmolal agent iodixanol with the low osmolal agent iohexol in 48 patients with reduced cardiac function (mean ejection fraction 33%) undergoing ventriculography. They found that left ventricular end-diastolic pressure (LVEDP) increased in both contrast medium groups 30 seconds after injection. After iohexol injection, however, it remained elevated for a longer period, and the maximum increase (19%) was higher than was achieved with iodixanol (14%; $P = .0018$). Left ventricular systolic pressure decreased (the minimum value occurring 10 sec after injection for both contrast media) and then increased to a level higher than at baseline. It was felt that all of these hemodynamic effects were likely due predominantly to an increase in circulating blood volume and reflex sympathetic stimulation.

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Effect of Contrast on CT Imaging

Early trials of 4-detector row and 16-detector row coronary CT angiography showed that overall image quality was dependent on patient heart rate. A higher heart rate led to a shorter R-R interval, and subsequently a shorter end-diastolic portion of the cardiac cycle. Acquiring images during diastole was an important issue, particularly for early generation multidetector CTs with a gantry rotation time of 500 msec and a temporal resolution of 250 msec. Giesler and colleagues[7] examined 100 patients (400 coronary arteries) with 4-detector row CT, and found that as the heart rate increased, the number of arteries that could be evaluated decreased, and the overall sensitivity for stenosis detection decreased from 62% (heart rate $\leq$ 70 beats per minute [bpm]) to 33% (heart rate $>$ 70 bpm). Using 16-detector row CT and a gantry rotation time of 420 msec, Hoffmann and coworkers[8] found that motion-free depiction of 97% of the coronary segments was attained in patients with heart rates below 80 bpm, whereas the best image quality was obtained with heart rates below 75 bpm.

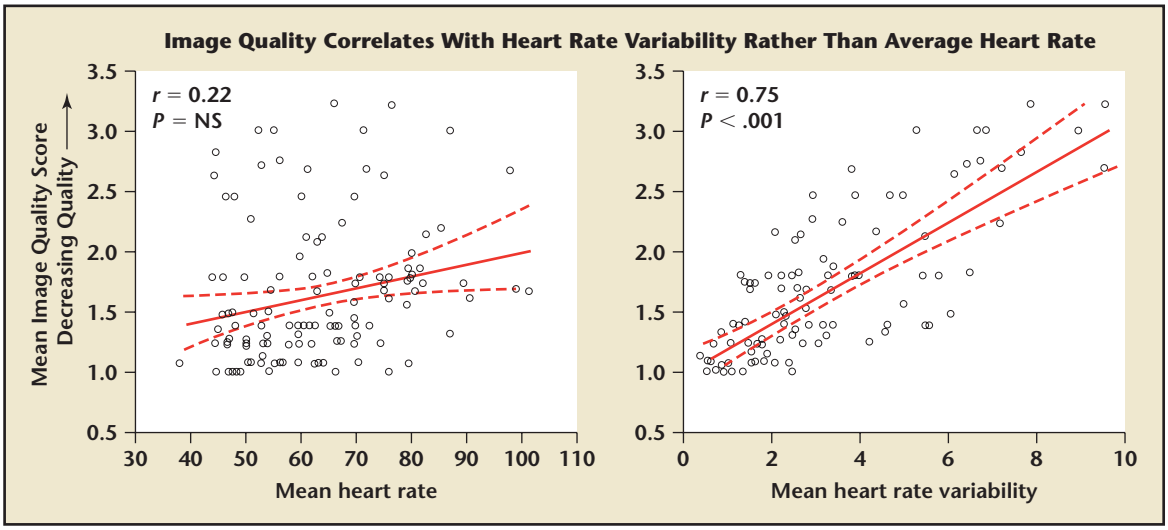
The development of 64-section CT coronary angiography improved temporal resolution even further with a gantry rotation time of 370 msec. A recent trial by Leschka and colleagues[9] examined the role of both average heart rate and heart rate variability for optimum image quality with 64-section cardiac CT studies. They found that there was no correlation between mean heart rate and image quality for all segments of the right coronary artery (RCA) ($r = 0.15$; P = NS) and left anterior descending (LAD) arteries ($r = 0.16$; P = NS), but there was a significant, albeit weak, correlation for the left circumflex artery (LCX) ($r = 0.33$; $P < .05$). When all segments were analyzed together, no significant correlation was found between average heart rate (mean 63.3 bpm $\pm$ 13.1, range 38-102 bpm) and image quality. Possible explanations offered for the decreased dependency of 64-section CT on average heart rate were improved temporal resolution, the larger volume coverage of 32 $\times$ 0.6 mm per rotation with the decrease in scanning time to approximately 12 seconds, and the improved longitudinal resolution.

Although average heart rate may not be as critical for image quality

with 64-section cardiac CT as it was for earlier-generation scanners, heart rate variability does appear to play a significant role. With intercycle variability in heart rate, the commonly applied technique of using retrospective electrocardiograph-gated image reconstruction (based on using a certain percentage of the R-R interval to match images) may not generate images corresponding to identical cardiac phases. Leschka and colleagues[9] did find a strong correlation between heart rate variability (assessed by standard deviation of heart rate) and the mean image quality of all coronary segments ($r = 0.75$; $P < .001$) (Figure 2). These correlations were slightly higher for the RCA ($r = 0.77$; $P < .001$) and similar for the left main and LAD ($r = 0.68$; $P < .001$) and LCX ($r = 0.69$; $P < .001$) arteries. They also studied the effects of β-blocker therapy on heart rate variability. The variability in heart rate was significantly lower in patients who were receiving β-blockers than in those who were not (2.45 bpm ± 1.53 vs 4.29 bpm ± 2.25; $P < .05$). Consequently, they found that image quality was also better ($P < .05$).

Several trials have examined the impact of different contrast media on average heart rate. Tveit and coworkers[10] compared the vital signs of 102 patients receiving iso-osmolal iodixanol versus low osmolal ioxaglate (ionic dimer) during cardiac angiography. They found that there was a slight but significant increase in mean heart rate in the ioxaglate group compared with the iodixanol group (4.8 ± 4.6 bpm vs 1.8 ± 4.6 bpm; $P = .002$). Manninen and coworkers[11] compared the heart rates of 120 patients receiving iodixanol versus low osmolal iopromide in cardiac angiography. They also found a slight but statistically significant increase in heart rate in the iopromide group (6.9 ± 4.1 bpm) when compared with the iodixanol group (3.3 ± 3.6 bpm; $P < .001$) following left ventriculography. Finally, Schmid and colleagues[12] examined the effects on heart rate of 216 patients undergoing cardiac angiography or peripheral intra-arterial (IA) digital subtraction angiography with iodixanol versus low osmolal iomeprol. No significant differences were noted between iomeprol and iodixanol in terms of mean changes in heart rate during left coronary arteriography ($P = .8$), right coronary arteriography ($P = .9$), and left ventriculography ($P = .8$). In patients undergoing IA injections for digital subtraction angiography, there again were no significant differences between contrast media noted for effects on mean heart rate after the first injection ($P = .6$) or across the first 4 injections ($P = .2$). These studies all indicate that both iso-osmolal and low osmolal contrast media have a low to negligible impact on patient heart rate during angiographic examinations. These studies are limited in that they do not directly assess the effects of bolus intravenous (IV) contrast media injection in the setting of gated cardiac CT scanning. Given that average heart rate is less important for diagnostic accuracy with newer generation 64-section CT scanners, these minor changes are unlikely to be clinically significant. The impact of different contrast media on heart rate variability on the other hand may be clinically relevant and as of yet has not been studied. This should be an area of future investigation with regard to improving the diagnostic accuracy of cardiac CT.

Figure 2. *Image quality correlates with heart rate variability rather than average heart rate. Reprinted with permission from Leschka S et al.[9]*



Chemotactic Effects

In addition to hemodynamic consequences, the osmolality of various contrast agents impacts the extent to which patients experience injection-associated pain and heat sensation. This issue is important both in terms of patient comfort and again diagnostic accuracy (eg, pain may cause patients to move, leading to artifacts). Prior studies had established that low osmolor contrast agents caused less injection-associated pain than high osmolal agents.[13] As the degree of pain experienced by patients was considered to be proportional to the osmolality, it was theorized that an iso-osmolal contrast agent would be even better tolerated. This was studied by Pugh and colleagues[14] in a double-blind clinical trial comparing iso-osmolal iodixanol with low osmolal iopromide in femoral arteriography. One hundred patients were randomized and evaluated for radiographic quality, discomfort, adverse events, femoral blood flow, and renal function. Radiographic quality was found to be similar in both groups. Forty-six patients (97%) in the iodixanol group and 45 patients (100%) in the iopromide group experienced a sensation of warmth/discomfort in connection with the injections. There was no statistically significant difference in the frequency of discomfort in the 2 groups, but the intensity of warmth was significantly milder following iodixanol injection than after iopromide injection ($P = .003$). The mean percentage increase in blood flow was found to be less with iodixanol (43.4%) than with iopromide (96.3%) ($P < .05$). They concluded that both contrast agents were safe and effective, and the main difference was an increase in femoral blood flow seen with iopromide.

These findings were subsequently confirmed in 2 larger trials by Justesen and coworkers[15] and Manke and coworkers,[16] again comparing injection-associated pain with iodixanol and a low osmolal agent in femoral arteriography. Justesen and co-workers[15] examined 2452 patients in a multicenter, double-blind, randomized trial comparing iodixanol with iopromide. They found that the iodixanol group reported significantly less injection-associated pain (0.9%) than the iopromide group (9.5%) ($P < .001$). When severe heat sensation was evaluated in addition to pain, this affected 4.1% in the iodixanol group compared with 19.8% in the iopromide group ($P < .001$).

There are now sufficient data to suggest that iso-osmolal contrast causes less injection-associated pain and heat sensation than low osmolal agents.

Manke and coworkers[16] also examined injection-associated pain and heat sensation with iodixanol, but they used iomeprol as the comparative low osmolal agent. Similar to the findings noted above, they found that the iodixanol group reported significantly less injection-associated pain after the first injection (7.4% vs 17.6%; $P = .007$), and after all injections (11% vs 19.4%; $P = .045$). Iodixanol also caused less heat sensation after the first injection ($P = .007$), and after all injections ($P = .029$). Heat sensations in the iodixanol group were less intense after all injections ($P < .001$). There were no differences between the contrast media groups with respect to overall image quality or diagnostic utility.[15] There are now sufficient data to suggest that iso-osmolal contrast causes less injection-associated pain and heat sensation than low osmolal agents. This likely is due to a relative decrease in the extent of blood flow augmentation due to decreased osmolality with iso-osmolal media.

Electrophysiologic Effects

The injection of contrast media systemically can also lead to alterations in electrolyte concentrations. Changes in these parameters have been shown to impact cardiac contractility and electrophysiologic effects. Animal studies from the 1970s showed the importance of sodium concentration when preparations of meglumine diatrizoate (hypertonic ionic monomer) that were low in sodium were shown to increase the risk of ventricular fibrillation (VF) in coronary angiography.[17] It was believed that the normal sodium value in serum would be the ideal level for a contrast medium. Further studies with nonionic contrast media would reveal that there is a critical balance between sodium and calcium ions, and that the addition of these electrolytes in the optimal ratios could reduce the incidence of VF. Adding proper concentrations of sodium to nonionic contrast media decreased the incidence of VF and reduced adverse effects on contractile force, whereas adding too much sodium decreased contractile force. This latter effect could be counteracted by the addition of calcium. Chai and associates[18] studied the electrolyte and hemodynamic effects of contrast media by injecting the left coronary artery of pigs with isotonic solutions that varied in electrolyte balance, viscosity, and chemotoxicity. All of the test solutions were roughly isotonic to plasma. They found that the addition of a balanced electrolyte solution (19 mmol/L NaCl and 0.3 mmol/L $CaCl_2$) to iodixanol reduced the fibrillatory propensity of the contrast agent. Furthermore,

solutions with the highest viscosity and an electrolyte composition that most closely resembled the physiologic normal range of myocardial interstitial fluid had the lowest fibrillatory propensities.

Thrombotic Effects

The cardiovascular complications of iodinated contrast media (aside from their hemodynamic and electrophysiologic effects discussed above) mainly involve thrombotic events (including coronary embolus, coronary occlusion, transient ischemic attack and stroke). Some in vitro studies suggested that nonionic low osmolal contrast agents could be more thrombogenic than ionic agents; however, this was not proven in larger clinical trials. In a prospective study of 8517 consecutive patients undergoing diagnostic cardiac catheterization with low osmolal contrast media (either iopamidol [n = 6293] or iohexol [n = 2224]), thrombotic events occurred in 15 patients (0.18%), a rate that was comparable with that seen previously with ionic contrast.[19] Other cardiovascular complications were similarly low with an incidence of ventricular tachycardia/VF of 0.1%, profound bradycardia of 0.2%, and prolonged angina of 0.3%.

Schrader and colleagues[20] prospectively evaluated the outcomes of 2000 patients undergoing percutaneous coronary intervention (PCI) with low osmolal contrast. According to a randomized, double-blind protocol, they received either iomeprol (nonionic low osmolal monomer; n = 1001) or ioxaglate (ionic low osmolal dimer; n = 999). The rate of major ischemic complications was found to be comparable after both agents (emergency bypass surgery, 0.8% vs 0.7%; myocardial infarction [MI], 1.8% vs 2.0%; cardiac death during hospital stay, 0.2% vs 0.2%).

The incidence of major adverse cardiac events (MACE) during PCI in patients receiving a nonionic isoosmolal contrast agent (iodixanol) or an ionic low osmolal agent (ioxaglate) was compared in a prospective, randomized, double-blind trial of 856 high-risk patients undergoing PCI for acute coronary syndromes.[21] The composite MACE endpoint was less frequent in those receiving iodixanol compared with those receiving ioxaglate (5.4% vs 9.5%, respectively; $P = .027$), primarily related to the lower incidence of periprocedural MI and abrupt closure of the target vessel.

Hypersensitivity Reactions

The rate of any hypersensitivity reaction has been reported in the 6% to 8% range.[22] Reactions are more common with IV than IA injections. This is likely due to activation of vasoactive substances such as bradykinin, serotonin, and histamine upon passage through the lung. These reactions typically are idiosyncratic, largely independent on the rate of infusion, and can occur in response to even small amounts of contrast. As opposed to true anaphylactic reactions which are mediated by IgE, contrast reactions appear to result from direct complement activation and/or mast cell activation, and are typically categorized as anaphylactoid. With this type of reaction, vasoactive substances are released from circulating basophils and tissue mast cells, causing characteristic symptoms. The severity of the reactions have been classified as mild (grade I: single episode of emesis, nausea, sneezing, or vertigo), moderate (grade II: hives, multiple episodes of emesis, fevers, or chills), or severe (grade III: clinical shock, bronchospasm, laryngospasm or edema, loss of consciousness, hypotension, hypertension, cardiac arrhythmias, angioedema, or pulmonary edema).[23] The risk of reaction is highest in patients with a history of prior contrast reactions, but is also elevated in individuals with atopic conditions such as asthma, allergic rhinitis, or eczema.

Immediate Versus Delayed Reactions

Reactions can be further divided into early hypersensitivity reactions (developing within 24 hours of administration) and delayed reactions (developing from 24 hours to 1 week after administration). Sutton and colleagues[24] examined the incidence of skin reactions with 3 different contrast agents: iopamidol (nonionic monomer), ioxaglate (ionic dimer), and iodixanol (nonionic dimer). They found that early reactions occurred in 22.2% of those receiving ioxaglate, 7.6% of those receiving iodixanol, and 8.8% of those receiving iopamidol ($P < .0001$). Late skin reactions occurred in 12.2% of those receiving iodixanol, 4.3% of those receiving ioxaglate, and 4.2% of those receiving iopamidol ($P < .0001$). Therefore, ionic contrast agents were associated with a significantly higher incidence of early reactions, whereas the nonionic dimer (iodixanol) was associated with a higher incidence of late skin reactions.

Shellfish Allergies

It is a misconception that patients allergic to shellfish are at increased risk for adverse reactions to contrast media beyond that of any atopic individual or patients with other food allergies.[25] The association between seafood allergies and contrast reactions has been attributed mistakenly to a common iodine allergy because there is a high iodine content in seafood. Iodine and iodide, however, are small molecules that typically do not cause allergic reactions. The culprit behind shellfish allergies is

thought to be tropomyosin proteins, which are structurally unrelated to iodine.

Prophylaxis

Given that recurrence rates of allergic reactions approach 50% on re-exposure to contrast agents, premedication to block the anaphylactoid reaction is indicated. Patients with a prior history of a contrast reaction should receive premedication with steroids and antihistamines. A variety of regimens for prophylaxis are utilized. One common and effective regimen, adopted from a study by Greenberger and colleagues,[26] involves the administration of 50 mg of prednisone at 13 hours, 7 hours, and 1 hour prior to the procedure, together with 50 mg of diphenhydramine 1 hour prior to the procedure. Another study demonstrated that treatment with methylprednisolone 12 hours and 2 hours preprocedure was superior to 2 hours only.[27] The consistent message is that multiple preprocedure doses starting at least 12 hours prior to the procedure are required to prevent recurrent allergic reactions.

Contrast-Induced Acute Kidney Injury

CIAKI is defined as the new onset or exacerbation of renal dysfunction after contrast administration without other identifiable causes. The risk is directly related to baseline renal function.[28,29] Most studies define CIAKI as either a relative increase in serum creatinine of 25% or more above the baseline value, or an absolute increase greater than 0.5 mg/dL ($>$ 44.2 μmol/L). CIAKI typically develops about 24 to 48 hours after contrast exposure, with serum creatinine peaking 3 to 5 days later and generally returning to baseline within 7 to 10 days.

Epidemiology and Pathophysiology

The frequency of CIAKI appears to have decreased over the past decade from a general incidence of approximately 15% to less than 7%.[30] This is, in part, due to greater awareness of the problem, improved preventive strategies, and newer contrast media with fewer adverse renal effects. Despite these improvements, the use of iodinated contrast media remains the third most common cause of hospital-acquired renal failure, and the leading cause among cardiac patients. The mortality rate in cases of CIAKI requiring dialysis is estimated to be approximately 14%.[31]

Although the exact mechanism is unclear, studies in experimental animals have postulated that renal vasoconstriction (possibly mediated by endothelin and adenosine), direct toxic effects of the molecule (exposure to high osmotic loads leading to characteristic histopathologic changes known as *osmotic nephrosis*), and oxidative stress (generation of oxygen free radicals) are possible explanations.

Risk Factors

The primary risk factor for the development of CIAKI is pre-existing renal insufficiency.[32] This is amplified by concomitant diabetes mellitus. Other risk factors include congestive heart failure (left ventricular ejection fraction $<$ 40%), uncontrolled hypertension, anemia, dehydration, advanced age ($>$ 75 years), use of diuretics, other nephrotoxic drugs, and volume of contrast used.

Assessment of Patients at Risk

A recent advisory statement by the American Heart Association (AHA) and the National Kidney Foundation recommended the use of the glomerular filtration rate (GFR), as opposed to standard creatinine measurements, to most accurately detect kidney function in patients with cardiovascular disease.[33] Inferring GFR from the serum creatinine level alone can be misleading because of the differing rates of creatinine production between persons, mainly due to variations in muscle mass. Women and the elderly often have the appearance of normal serum creatinine levels, despite substantial reductions in GFR. The 2 formulas that are widely used to estimate GFR are the Modification of Diet in Renal Disease (MDRD) equation, and the Cockcroft-Gault equation. The MDRD equation (Table 1) is generally considered to be the more accurate equation, and has received a Class I recommendation for use by the AHA. There are 2 forms of the MDRD equation, with the abbreviated version being simpler and appearing to be just as accurate. Values below 60 mL/min per 1.73 square

Table 1
MDRD Study Equations for Calculating GFR

MDRD 1
$GFR = 170 \times [SCr]^{-0.999} \times [Age]^{-0.176} \times [0.762 \text{ if patient is female}] \times [1.18 \text{ if patient is black}] \times [BUN]^{-0.170} \times [Alb]^{0.318}$
MDRD 2 (Abbreviated)
$GFR = 186 \times [SCr]^{-1.154} \times [Age]^{-0.203} \times [0.742 \text{ if patient is female}] \times [1.21 \text{ if patient is black}]$

Alb, serum albumin; BUN, blood urea nitrogen; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; SCr serum creatinine.
Adapted with permission from Brosius FC et al.[33]

meters of body surface area should be regarded as abnormal.

Choice of Contrast Agents

The properties of contrast media that may contribute to their renal effects include ionicity, iodine content, osmolality, viscosity, and other physiochemical properties. It is widely acknowledged that the high osmolality of the first-generation agents was primarily responsible for their adverse renal effects. The clinical evidence supporting the role of other chemical properties (eg, viscosity) is lacking, and thus their relative contribution to the risk of toxicity is debatable.

Low Osmolal Contrast Media Versus High Osmolal Contrast Media

A meta-analysis compared the relative nephrotoxicity of high osmolal with low osmolal contrast media demonstrating that low osmolal agents are significantly less nephrotoxic than high osmolal agents (P = .02).[28] The pooled odds ratio for the prevalence of CIAKI events (rise in serum creatinine of > 0.5 mg/dL) was 0.61 (95% CI, 0.48-0.77).

Studies published since this meta-analysis further support these same findings. The largest prospective randomized study was the Iohexol Cooperative Study.[32] This study compared iohexol (nonionic low osmolal) with sodium-meglumine diatrizoate (ionic high osmolal) in 1196 patients undergoing cardiac angiography. The overall incidence of nephrotoxicity was 3.2% in the iohexol group compared with 7.1% in the diatrizoate group (P = .002). Most of the benefit was confined to patients with chronic kidney disease, particularly those with diabetes.

Iso-Osmolal Contrast Media Versus Low Osmolal Contrast Media

The Nephrotoxic Effects in High-Risk Patients Undergoing Angiography (NEPHRIC) study[34] was a prospective, double-blind, randomized, placebo-controlled trial that compared iodixanol with iohexol in patients at high risk for developing CIAKI. In 129 patients who had diabetes and renal impairment undergoing coronary or aortofemoral angiography, the mean serum creatinine concentration increased significantly less in patients who received iodixanol compared with iohexol (0.13 mg/dL vs 0.55 mg/dL; P = .001). Using an increase in creatinine of 0.5 mg/dL as the definition of CIAKI, 3% of the iodixanol group versus 26% of the iohexol group developed this complication (P = .002).

The Cardiac Angiography in Renally Impaired Patients (CARE) study[35] compared low osmolal and iso-osmolal contrast media in high-risk patients. The low osmolal agent used for comparison was iopamidol rather than iohexol. This prospective, double-blind, randomized trial enrolled 414 patients with chronic kidney disease (170 with concomitant diabetes mellitus). The primary endpoint was a serum creatinine increase greater than or equal to 0.5 mg/dL, and occurred in 4.4% (9 of 204 patients) after iopamidol and 6.7% (14 of 210 patients) after iodixanol (P = .39). Subgroup analysis revealed that in patients with diabetes and renal insufficiency, serum creatinine increases of 0.5 mg/dL or more were 5.1% (4 of 78 patients) with iopamidol and 13% (12 of 92 patients) with iodixanol (P = .11). This trial found no statistically significant difference in the incidence of CIAKI following the administration of low osmolal or iso-osmolal contrast media, whereas the NEPHRIC trial did. One key difference between the 2 trials was that all of the patients enrolled in CARE received hydration with sodium bicarbonate (as opposed to normal saline in NEPHRIC), and many received N-acetylcysteine (NAC), which as discussed later are also protective strategies. Another explanation is that iopamidol may have a different profile than other low osmolal agents.

A recent meta-analysis examined 16 double-blind comparative trials of IA contrast media, in which iodixanol was compared with low osmolal contrast media.[36] This analysis included a total of 2727 patients, 1382 who received iodixanol and 1345 who received low osmolal contrast (iohexol, iopromide, iopamidol, or ioxaglate). CIAKI occurred significantly less often following iodixanol administration than after use of a low osmolal agent. This was most evident in the subgroups of patients with renal impairment, and with both renal impairment and diabetes. It should be noted that most of the studies included in the meta-analysis used iohexol as the low osmolal contrast agent. The only study in the meta-analysis that compared iopamidol and iodixanol did show a favorable trend with iopamidol.[37] Recent American College of Cardiology/AHA guidelines for unstable angina and non–ST-segment elevation MI state that the use of iodixanol is a class I indication for patients with chronic kidney disease undergoing contrast procedures.[38]

CIAKI occurred significantly less often following iodixanol administration than after use of a low osmolal agent.

Strategies for Prevention of CIAKI

Volume Expansion

Intravascular volume expansion is protective by increasing renal blood

flow, decreasing vasoconstriction, and improving tubular filtration, in addition to having possible neurohormonal benefits. One suggested protocol to reduce the risk for CIAKI is administration of 1 to 1.5 mL/kg/h of IV isotonic crystalloid initiated 12 hours before the procedure and continued for 6 to 24 hours. Outpatients should receive IV crystalloid for up to 3 hours before the procedure and up to 12 hours after. However, these recommendations are also dependent on the volume status and left ventricular function of the patient prior to the procedure. A comparison of saline, saline plus mannitol, or saline plus furosemide demonstrated a potentially harmful effect of forced diuresis with mannitol or furosemide.[39]

Recent studies have reported on the benefit of isotonic sodium bicarbonate compared with sodium chloride for hydration in the high-risk patient. Merten and colleagues[40] randomized 119 patients with stable creatinine values of at least 1.1 mg/dL to receive a 154 mEq/L infusion of either sodium chloride (n = 59) or sodium bicarbonate (n = 60) for 1 hour before and 6 hours after iopamidol administration. The primary endpoint of CIAKI occurred in 8 patients (13.6%) infused with sodium chloride but in only 1 (1.7%) of those receiving sodium bicarbonate (mean difference, 11.9%; 95% CI, 2.6-21.2; $P = .02$).

A subsequent study by Briguori and colleagues[41] found that the strategy of volume supplementation by sodium bicarbonate plus NAC was statistically superior to the combination of normal saline with NAC alone or with the addition of ascorbic acid in preventing CIAKI in patients at medium to high risk (serum creatinine > 2 mg /dL). Both of these studies suggest that the incidence of CIAKI can be lowered to less than 5%, even in high-risk patients. Another advantage of the sodium bicarbonate regimen is that prehydration can be accomplished in 1 hour (as opposed to 12 hours), which can logistically improve compliance with hydration regimens.

Pharmacologic Agents

Many pharmaceutical agents have been evaluated for reduction in the risk of CIAKI, yielding some positive but mostly negative or conflicting results. A recent CIAKI Consensus Working Panel divided pharmaceutical agents into 3 categories. Agents that were judged to be potentially beneficial, but needed further evaluation included theophylline/aminophylline (adenosine antagonists), statins (due to beneficial effects on endothelial function and decreased oxidative stress), ascorbic acid (antioxidant), and prostaglandin E_1(vasodilator). Agents found to be neutral in their role included NAC (antioxidant), fenoldopam (dopamine receptor agonist), dopamine (vasodilator), calcium channel blockers, atrial natriuretic peptide (vasodilator), and L-arginine (substrate for nitric oxide synthesis). Agents that were concluded to be potentially detrimental included furosemide (diuretic), mannitol (diuretic), and dual endothelin receptor antagonists.[42]

Another review of preventive measures was recently reported, and made similar recommendations on the efficacy of these pharmaceutical agents.[43] Agents were classified as either possibly beneficial, or not proven beneficial. These recommendations are summarized in Table 2.

Theophylline/Aminophylline

These medications are adenosine antagonists, and have been postulated to reduce renal vasoconstriction. A meta-analysis of 7 trials (480 patients) showed that the administration of theophylline or aminophylline appeared to protect against contrast-induced declines in renal function.[44] Several oral and IV dosage regimens have been evaluated, with a single IV dose preprocedure appearing to be the most convenient and effective.

Ascorbic Acid

This widely-available antioxidant has been evaluated for its role in the possible reduction of oxidative stress and free radical production. In a

Table 2
Approach to Prevention of Contrast-Induced Nephropathy Based on Possible Etiologic Mechanisms

Hemodynamic-vascular	Cytoxic-free radical	Other
Possibly beneficial		
Aminophylline/theophylline	N-Acetylcysteine	Statins
Prostaglandin E_1	Sodium bicarbonate	
	Ascorbic acid	
Not proven beneficial		
Angiotensin II		
Fenoldopam		
Dopamine		
Calcium channel blocker		
Endothelin antagonists		
Adenosine		

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double-blind, placebo-controlled trial of 231 patients undergoing cardiac catheterization, the incidence of CIAKI was significantly lower in the patients receiving ascorbic acid.[45] In this trial 3 g ascorbic acid was administered at least 2 hours preprocedure, followed by 2 g in the night and the morning after the procedure.

N-acetylcysteine

There are conflicting data on the role of NAC in preventing CIAKI. The most comprehensive meta-analysis reviewed 20 of the published trials involving 2195 patients.[46] There was a nonsignificant trend toward decreased CIAKI in patients treated with NAC. Another recent study of patients with acute MI undergoing primary PCI demonstrated benefit to high-dose NAC (1200 mg IV preprocedure and 1200 mg orally twice daily for 48 hours after PCI).[47] A large prospective randomized trial is needed before NAC can be routinely recommended for CIAKI prevention. Although the benefit of NAC is uncertain, it is safe, inexpensive, and has few reported side effects.

Hemofiltration

Hemodialysis has been shown to remove contrast media and in small studies to reduce the risk of CIAKI in high-risk patients with chronic renal failure.[48] Hemofiltration allows for increased hemodynamic stability compared with hemodialysis while permitting 10 to 15 times the usual hydration without adding intravascular volume. The drawbacks to hemofiltration are that it is invasive and logistically complex. Further analysis in larger clinical trial is needed before it can be widely recommended.

Other Measures

In addition to the preventative strategies, potentially nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs, cyclosporine, vancomycin, amphotericin) should be withdrawn at least 24 hours before in at-risk patients. Although not implicated in CIAKI, metformin (which is predominantly renally excreted) should be withdrawn on the day of the procedure to avoid the risk that lactic acidosis might occur during a postprocedure decline in renal function. It is recommended that metformin continue to be withheld for 48 hours following the contrast injection, and that the patient's renal function be reassessed prior to resuming this medication.

Conclusions

With newer formulations of iodinated contrast media, significant adverse reactions have become less common. When reactions do occur, however, they can be serious, and appropriate preventive strategies need to be implemented to minimize the incidence. Patients at greater risk for contrast-induced reactions (history of diabetes or renal insufficiency, underlying cardiac disease, allergy of any kind, dehydration, metabolic abnormalities) should be identified prior to undergoing any IV or IA contrast administration. Hospitals should adopt screening forms and protocols to assist with this process. Patients at greater risk should be treated with the described preventive measures to minimize their risk of an adverse contrast-related event. If an adverse reaction occurs, it should be recognized and treated promptly. Enhanced knowledge on the part of physicians and medical personnel regarding the properties and potential side effects of iodinated contrast agents should lead to improved patient safety and efficacy. ■

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Main Points

- Although most patients are able to receive contrast media without significant adverse reactions, events occur in a minority of cases; these reactions range from mild discomfort (injection-associated pain and heat sensation) to more significant cardiac, renal, and hypersensitivity reactions.
- Data suggest that iso-osmolal contrast causes less injection-associated pain and heat sensation than low osmolal agents, likely due to a relative decrease in the extent of blood flow augmentation as a result of their decreased osmolality.
- Contrast-induced acute kidney injury (CIAKI) typically develops about 24 to 48 hours after contrast exposure; the frequency of CIAKI appears to have decreased over the past decade, in part due to newer contrast media with fewer adverse renal effects.
- There are numerous strategies that can be employed to reduce the risk of or to prevent CIAKI, including but not limited to volume expansion, administration of pharmacologic agents, and hemofiltration.

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