Contrast Nephropathy

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With the increasing use of radiographic contrast media in diagnostic and interventional procedures, contrast-induced nephropathy (CN) has become an important cause of iatrogenic acute renal impairment. In fact, CN is the third leading cause of new acute renal failure in hospitalized patients (1). The pathophysiology and risk factors for this complication are becoming better understood, but there is still controversy surrounding many aspects. The purpose of this article is to review recent developments in the area of CN. Particular emphasis will be placed on means of minimizing the risk or preventing this important problem.

Definition and Clinical Features

Many different definitions of CN appear in the literature, but it is commonly defined as an acute decline in renal function following the administration of intravenous contrast in the absence of other causes. For research purposes, a definition such as a rise in serum creatinine ≥25 or 50% above the baseline value is often used. Patients with CN typically present with an acute rise in serum creatinine anywhere from 24 to 48 h after the contrast study. Serum creatinine generally peaks at 3 to 5 d and returns to baseline value by 7 to 10 d (2–4). The acute renal failure is nonoliguric in most cases (5,6). Urinalysis often reveals granular casts, tubular epithelial cells, and minimal proteinuria, but in many cases may be entirely bland. Most, but not all, patients exhibit low fractional excretion of sodium (5,7). The diagnosis of CN is frequently obvious if the typical course of events follows the administration of contrast. However, other causes of acute renal failure, including atheromatous embolic disease, ischemia, and other nephrotoxins should always be considered. This is particularly true if significant renal impairment should occur in patients without risk factors for CN.

Pathogenesis

CN appears to be the result of a synergistic combination of direct renal tubular epithelial cell toxicity and renal medullary ischemia (8). Direct cytotoxicity in CN is suggested by histologic changes of cell injury and enzymuria after contrast administration (9). The nature of the contrast, associated ions, concentration, and concomitant hypoxia are all important to the degree of cellular damage, while the osmolality of the solution seems to be of secondary importance (8). The injection of contrast induces a biphasic hemodynamic change in the kidney, with an initial, transient increase and then a more prolonged decrease in renal blood flow (2). The mediators of these changes are still unknown. Alterations in the metabolism of prostaglandin, nitric oxide, endothelin, or adenosine may play a role.

Risk Factors and Epidemiology

Mild, transient decreases in GFR occur after contrast administration in almost all patients (10). Whether a patient develops clinically significant acute renal failure, however, depends very much on the presence or absence of certain risk factors (Table 1). A multivariate analysis of prospective trials has shown that baseline renal impairment, diabetes mellitus, congestive heart failure, and higher doses of contrast media increase the risk of CN (8). Other risk factors include reduced effective arterial volume (e.g., due to dehydration, nephrosis, cirrhosis) or concurrent use of potentially nephrotoxic drugs such as nonsteroidal anti-inflammatory agents and angiotensin-converting enzyme inhibitors. Multiple myeloma has been suggested as a potential risk factor for CN, but a large retrospective study failed to demonstrate an increased risk in these patients (11). Of all these risk factors, preexisting renal impairment appears to be the single most important; patients with diabetes mellitus and renal impairment, however, have a substantially higher risk of CN than patients with renal impairment alone (12,13).

Prospective studies have produced extremely varied estimates of the incidence of CN. These discrepancies are due to differences in the definition of renal failure as well as differences in patient comorbidity and the presence of other potential causes of acute renal failure. A recent epidemiologic study reported a rate of 14.5% in a series of approximately 1800 consecutive patients undergoing invasive cardiac procedures (14). Patients without any significant risk factors have a much lower risk, averaging about 3% in prospective studies (9). On the other hand, the risk of renal failure after contrast rises with the number of risk factors present. In one study, the frequency of renal failure rose progressively from 1.2 to 100% as the number of risk factors went from zero to four (15).

Clinical Outcomes

The clinical importance of CN may not be immediately obvious given the high frequency of recovery of renal function,
but it is by no means a benign complication. Dialysis is infrequently required (16,17). Some degree of residual renal impairment has been reported in as many as 30% of those affected by CN (18). Other comorbid events such as hypotension, sepsis, and atheroembolic disease certainly contribute. The occurrence of acute renal failure can prolong the hospital stay (19). Finally, there is some evidence that mortality may be increased in patients with CN. In a retrospective study, Levy et al. compared the outcomes of hospitalized patients with CN to a control group of patients matched for age, baseline serum creatinine, and type of diagnostic procedure that received contrast but did not develop CN. The mortality in the CN group was 34% compared with 7% in the control group ($P < 0.001$, odds ratio 5.5), even when severity of comorbid illness was controlled by matching patients by APACHE II scores (20).

CN is no different from acute renal failure of any other etiology in terms of the complications that may ensue. The possibility that patients who are receiving the oral antidiabetic agent metformin may develop lactic acidosis as a result of CN has received particular attention. This rare complication can occur only if the contrast causes significant renal failure and the patient continues to take metformin. In a recent review of this subject, no conclusive evidence was found to indicate that the use of contrast precipitated metformin-induced lactic acidosis in patients with a normal serum creatinine ($<1.5 \text{ mg/dl or 130 } \mu\text{mol/L}$). The complication was almost always observed in non-insulin-dependent diabetic patients with decreased renal function before injection of contrast media (21). There is really no justification to discontinue metformin before the day of the contrast-requiring procedure. It seems prudent, however, to instruct patients not to take this drug for 48 h or so after contrast administration and resume taking the drug only if there are no signs of nephrotoxicity. This is especially true for patients in high-risk subgroups.

**Strategies for the Prevention of CN**

Contrast administration, more often than not, is a planned procedure, and patients at particularly high risk can often be identified before the investigation. Much effort has therefore been directed at avoiding or minimizing the risk of this complication. This process begins with the selection of the procedure. Contrast agents should not be administered without a clear indication. Methods not requiring iodinated contrast such as magnetic resonance imaging, ultrasound, nuclear medicine techniques, or carbon dioxide angiography are becoming more widely available and should be used preferentially if they will provide the required information. The decision to give contrast should reflect a risk-to-benefit ratio established for an individual patient. In most patients, the risk factors for CN can be identified with a routine history and physical examination. Renal impairment may be asymptomatic until advanced, but it is impractical to measure renal function before contrast administration in all cases. If no other risk factors for renal impairment are present, it is probably not necessary to determine renal function. When contrast administration is deemed appropriate, the lowest dose of contrast possible should be used. Optimally, any risk factors for CN should be corrected before contrast administration. If contrast must be administered in the presence of an uncorrectable or uncorrected risk factor, it is advisable to monitor renal function by serum creatinine before and at 48 to 72 h after the procedure.

A variety of specific measures have been used in an attempt to decrease the risk of CN, particularly in high-risk patients. The following is a discussion of the evidence supporting the use of some of the more common practices.

**Nonionic and Low-Osmolality Media**

These alternative forms of contrast media, which have approximately one-half to one-third the osmolality of standard agents, were developed at great expense in an attempt to reduce the incidence of complications associated with radiocontrast agents. Unfortunately, they are also capable of inducing CN, although perhaps less frequently than high-osmolality contrast agents. Because of their high cost relative to the standard agents, however, considerable debate has taken place regarding the role of low-osmolality media in clinical practice. There have been numerous studies addressing this question, but few individual studies had the power to determine the relative clinical nephrotoxicity of high- and low-osmolality agents. For this reason, Barrett and Carlisle performed a meta-analysis of all the randomized trials available before the end of 1991 comparing the nephrotoxicity of high- and low-osmolality contrast in humans by serial measurement of GFR or serum creatinine. Pooling the $P$ values from the trials suggested a reduction in nephrotoxicity with low-osmolality media, which was of borderline statistical significance ($P = 0.02$). In a subgroup analysis, low-osmolality media were only statistically significantly less nephrotoxic in patients with renal impairment (22). Data from a study by Rudnick et al., the largest randomized trial to date, was included in this meta-analysis despite the fact that the final report was published several years later. This trial involved 1196 patients, 192 of whom had some degree of renal impairment before contrast administration. In patients with normal renal function, low-osmolality contrast was not found to confer any benefit. In patients with a serum creatinine $>1.6 \text{ mg/dl (141 } \mu\text{mol/L})$ before contrast administration, however, the use of high-osmolality contrast was associated with a risk of CN that was 3.3 times greater than that in the low-osmolality contrast group (17). Because of the large

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**Table 1. Risk factors for contrast nephropathy**

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<td>Preexisting renal impairment</td>
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successful as inpatient hydration in preventing CN (26). 0.45% saline for 6 h afterward has been shown to be as using oral hydration before the procedure and intravenous seems to be developing. For outpatient procedures, a protocol flexible to allow an increase in rate if a negative fluid balance the duration of the attendant diuresis. The protocol should be 2 h before contrast and continuing for up to 24 h, depending on venous 0.45% saline at a rate of 1 ml/kg per h, beginning 1 to taken, carries minimal risks of adverse effects if appropriate care is modestly beneficial, however, this approach is simple and carries minimal risks of adverse effects if appropriate care is taken, i.e., close monitoring of the patient’s fluid balance and clinical status. A reasonable starting protocol might use intravenous 0.45% saline at a rate of 1 ml/kg per h, beginning 1 to 2 h before contrast and continuing for up to 24 h, depending on the duration of the attendant diuresis. The protocol should be flexible to allow an increase in rate if a negative fluid balance seems to be developing. For outpatient procedures, a protocol using oral hydration before the procedure and intravenous 0.45% saline for 6 h afterward has been shown to be as successful as inpatient hydration in preventing CN (26).

**Fluid Administration**

The administration of intravenous fluids has long been used to reduce the likelihood of CN for high-risk patients. The rationale for this approach is that giving fluids before the study may correct subclinical dehydration, whereas hydration for a period of time afterward may counter an osmotic diuresis resulting from the contrast. Some benefits of this approach have been suggested by uncontrolled and retrospective studies (23,24), but there has never been a randomized, controlled trial of deliberate hydration versus no intervention for the prevention of CN. It is clear that even vigorous fluid administration does not afford complete protection from CN for high-risk patients. In a recent study by Solomon et al., for example, 11% of patients with chronic renal insufficiency developed CN despite saline administration beforehand (25). Even if only modestly beneficial, however, this approach is simple and carries minimal risks of adverse effects if appropriate care is taken, i.e., close monitoring of the patient’s fluid balance and clinical status. A reasonable starting protocol might use intravenous 0.45% saline at a rate of 1 ml/kg per h, beginning 1 to 2 h before contrast and continuing for up to 24 h, depending on the duration of the attendant diuresis. The protocol should be flexible to allow an increase in rate if a negative fluid balance seems to be developing. For outpatient procedures, a protocol using oral hydration before the procedure and intravenous 0.45% saline for 6 h afterward has been shown to be as successful as inpatient hydration in preventing CN (26).

**Furosemide**

The use of furosemide as prophylaxis for CN has been controversial. It has been hypothesized that loop diuretics might reduce the potential for ischemic injury by interfering with active transport and decreasing the oxygen demands of medullary tubular segments (27). Recent studies, however, suggest that furosemide may actually be detrimental in certain patients. In a randomized trial of patients with renal insufficiency undergoing cardiac catheterization, Solomon et al. found that acute renal impairment was more common in a group treated with saline and furosemide compared with a group given saline alone. Serum creatinine rose even in those patients who gained weight, making it unlikely that dehydration alone accounted for the adverse effects of the diuretic (25). Weinstein and colleagues also found an increase in the mean serum creatinine for a group of patients given furosemide, while a control group given fluids alone had no change in serum creatinine following contrast (28). In this study, the patients in the furosemide-treated group did lose weight, suggesting that dehydration may have played a role. Most recently, Stevens et al. reported the results of a randomized trial in which high-risk patients undergoing cardiac catheterization were treated with a combination of fluid therapy, furosemide, mannitol, and low-dose dopamine and compared with a control group treated with hydration alone (29). The investigators attempted to ensure that each patient maintained extracellular volume by replacing urine output with intravenous saline. Although the authors concluded that this regimen of forced diuresis provided a modest benefit in preventing CN, there was no statistical difference in the mean rise in serum creatinine at 48 h between the groups. Because CN occurred in 41% of patients with a urine output ≤150 ml/h in the first 24 h compared with 16.2% of those with urine output greater than this, the authors suggest that high urine output may be protective against CN. An alternative explanation is that patients who developed renal impairment had reduced urine output. Thus, there is currently more evidence arguing against rather than for the use of furosemide for the prophylaxis of CN, and its use for this purpose is not recommended.

**Mannitol**

Infusions of mannitol have also been widely used to prevent CN, but again its use is controversial. Mannitol exhibited no protective effect in the study by Solomon et al. In fact, patients with chronic renal insufficiency treated with saline and mannitol had a higher incidence of CN than those treated with saline alone (25). Another recent trial found that while mannitol did increase the risk of CN in diabetic patients with renal insufficiency, it was found to reduce the risk in azotemic nondiabetic patients (30). Overall, however, there is not enough evidence to recommend mannitol as a means to reduce CN.

**Dopamine**

Low-dose dopamine is a renal vasodilator and is effective even in patients with chronic renal insufficiency. This property has made it very attractive as a potential means for preventing CN, but clinical studies thus far have shown mixed results. Hans and colleagues conducted a randomized trial of 55 patients with chronic renal insufficiency undergoing abdominal aortography or arteriography of the lower extremities, 40% of whom were diabetic. Patients were randomized to receive either dopamine 2.5 mcg/kg per min beginning 1 h before arteriography and continuing for 12 h afterward or an equal volume of saline over the same time period. Serum creatinine rose linearly in both groups over time, and there was no statistical difference between the groups except on the first day after the procedure. In a subgroup of 20 patients with a baseline serum creatinine ≥2.0 mg/dl (175 μmol/L), however, there was a significantly greater rise in creatinine in the control group over the 4 d of follow-up. Creatinine clearance did not change in the patients receiving dopamine, whereas it declined significantly in the control group (31). Hall and coworkers
reported that dopamine reduced the risk of CN in azotemic patients, but there were few diabetic patients in this study (32). Weisberg et al. randomized patients undergoing cardiac angiography to either low-dose dopamine or fluids alone. Patients with diabetic nephropathy had lower renal blood flow than nondiabetic patients with a similar degree of renal impairment and only the diabetic patients had a rise in renal blood flow in response to dopamine. Paradoxically, dopamine was associated with an increased rate of CN in the diabetic patients but seemed to protect the nondiabetic patients (33). Finally, Abizaid et al. recently reported no difference in the rate of CN in high-risk patients undergoing coronary angiography randomized to receive either saline or saline plus dopamine (19). About half of the patients in this study were diabetic, but subgroup analysis of the effect of dopamine in diabetic patients versus nondiabetic patients was not performed. Although it appears that dopamine may be of some benefit in preventing CN in nondiabetic patients, more evidence is required before it can be recommended for routine use. Dopamine should not be used to prevent CN in diabetic patients.

**Atrial Natriuretic Peptide**

Atrial natriuretic peptide (ANP) may theoretically interfere with the pathogenesis of CN by increasing renal blood flow, but clinical studies have not yet shown such a benefit. Kurnik and colleagues showed that prophylactic ANP was associated with an increase in renal blood flow in diabetic patients with renal insufficiency, but this agent was worse than mannitol and probably deleterious for such patients (34). Similar results were found in a study by Weisberg et al., in which ANP, dopamine, and mannitol all caused an increase in global renal blood flow in diabetic patients with renal failure, but increased the risk of CN compared to patients given saline alone. ANP was superior to saline alone in nondiabetic patients, in whom mannitol and dopamine proved equally beneficial (30). Recently, a randomized, double-blind, placebo-controlled trial of ANP was reported by the same group, in which 247 patients were given either saline or one of three doses of ANP infusions starting 12 h before and lasting 12 h after contrast administration. About half of the patients were diabetic. ANP treatment did not reduce the risk of CN overall or in the subgroups defined by diabetic status (35). Based on this evidence ANP cannot be recommended for prophylaxis of CN.

**Calcium Channel Blockers**

Drugs of this class have been shown to blunt the decreases in renal blood flow induced by contrast in laboratory studies. Several randomized trials of calcium-blocking agents for the prevention of CN have been published. Neumayer et al. gave 20 mg of nifedipine once a day for 3 d beginning before contrast to 16 patients and matching placebo to another 19 cases. The patients had close to normal baseline renal function. Inulin clearance fell by 27% at 2 d in the control group, whereas it was unchanged in the nifedipine-treated patients (36). Russo et al. gave 10 mg of nifedipine sublingually just before high-osmolality contrast for intravenous pyelography in 10 nondiabetic patients. Two control groups were given high- or low-osmolality contrast without a calcium channel blocker. Nifedipine caused an acute increase in renal plasma flow and GFR over a 2-h period, whereas these parameters both decreased with high- and were unchanged with low-osmolality contrast (37). Khoury and colleagues randomly assigned 111 patients having mainly nonionic contrast with prophylactic fluids to a single dose of 10 mg of nifedipine, or no treatment before contrast. Only 85 patients (76%) were evaluable and there were more diabetic patients in the group not given nifedipine (37 versus 24%). The proportion with renal dysfunction was not stated, but the average serum creatinine before contrast was in the normal range. There was little change in serum creatinine within 48 h in either group (38). These studies are all quite small and do not include high-risk patients with renal insufficiency. Additional large-scale randomized trials are necessary, particularly in high-risk patients, before calcium channel blockers can be recommended for the prevention of CN. Patients taking calcium channel blockers for other indications, however, should continue their therapy uninterrupted.

**Theophylline**

Because adenosine has been suggested as having a role in the pathogenesis of CN, theophylline, an adenosine antagonist, has been investigated as a means to reduce the risk of this complication. In one of the first studies, Erley et al. compared placebo to 5 mg/kg theophylline given intravenously before nonionic contrast in 39 patients. Half of the subjects had a GFR <75ml/min and about 15% were diabetic. There were no clinically important changes in renal function in either group, although theophylline prevented the small fall in creatinine, inulin, and para-aminohippurate clearances seen in the placebo group (39). Katholi and colleagues compared placebo with 2.88 mg/kg theophylline given orally every 12 h for four doses starting before coronary angiography in 93 patients. This trial used a factorial design with patients concomitantly randomized to high-osmolality or low-osmolality contrast. Another group received nonionic contrast with dipyridamole, an adenosine reuptake inhibitor. All patients had a serum creatinine of <2.0 mg/dl (175 μmol/L) and about 20% were diabetic, although none had > 1+ proteinuria. Almost all were receiving calcium channel blockers, and all were given deliberate hydration. Theophylline completely prevented the fall in creatinine clearance seen within 24 h after nonionic contrast and reduced that after ionic contrast by about half. Serum creatinine was not significantly changed in any group. Dipyridamole enhanced the rise in urinary adenosine and the fall in creatinine clearance after nonionic contrast (10). More recent studies have focused on higher risk patients. Abizaid et al. randomized patients with serum creatinine ≥1.5 mg/dl undergoing coronary angioplasty to saline hydration alone, saline hydration plus dopamine infusion, or saline hydration plus 4 mg/kg aminophylline followed by a drip of 0.4 mg/kg per h starting 2 h before the intervention. Twenty patients were enrolled in each group, with more than half of them being diabetic. All patients were hydrated with 0.45% saline and received nonionic contrast. Neither dopamine nor aminophylline reduced the incidence of CN compared with saline hydration alone (19). Erley and...
colleagues studied 80 patients with serum creatinine ≥1.5 mg/dl receiving contrast media. All patients were hydrated, and patients were randomized to 810 mg of theophylline daily or placebo. Sixty-four patients completed the entire protocol. Serum creatinine and creatinine clearance measured at baseline and for 3 d after contrast administration did not change significantly in either group, suggesting that theophylline provided no benefit over hydration alone in these patients. Theophylline, however, did prevent the increase in N-acetyl-beta-glucosaminidase enzymuria seen in the placebo group (40).

These studies suggest that theophylline prevents some of the contrast-associated changes in renal function, but a benefit over saline hydration alone has not been convincingly demonstrated. This is particularly true with respect to patients with preexisting renal impairment. Nevertheless, there may be some value to the use of theophylline for reduction of CN in those at risk. Although the dose, duration, and route of administration of theophylline differed in each study, it seems likely that a dose of <5 mg/kg for less than 2 d, starting before contrast, would suffice.

**Management of Acute Renal Failure Resulting from Contrast Nephrotoxicity**

In most cases the injury resulting from CN is mild and renal impairment reverses within a week or so. Avoidance of further nephrotoxic insults and careful control of fluid and electrolyte balance is generally all that is required. In more severe cases, dialysis may be necessary to treat the consequences of renal failure. To date, no specific therapy has been found to be of benefit in the treatment of CN. A randomized trial of ANP as a treatment for acute renal failure did not demonstrate an overall reduction in the need for dialysis in a subgroup of 65 patients with CN (41). Abizaid et al. randomized 72 patients who developed CN after coronary angioplasty to receive either 0.45% saline or saline plus dopamine 1 ml/kg per h until serum creatinine returned to its baseline value. Dopamine treatment proved to be detrimental, as patients in this group had higher peak serum creatinine and required dialysis more frequently than patients in the control arm (19).

**Summary**

CN is an important cause of iatrogenic acute renal failure and carries significant risks for affected patients. The most effective strategy for the prevention of this complication is careful procedure selection and patient assessment. Patients with risk factors for CN who require contrast administration should have the risks corrected before exposure to a contrast agent if possible. Patients with noncorrectable risk factors should receive the minimal necessary dose of contrast, and should have their renal function checked by serum creatinine before and at 48 to 72 h after contrast administration. No intervention has been convincingly shown to prevent CN in high-risk patients, with the possible exception of intravenous hydration and the use of low-osmolality contrast in select patients. Furosemide and mannitol should not be used as a means to reduce CN.

**References**
