The prevention of contrast-induced nephropathy in patients undergoing percutaneous coronary intervention

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Contrast-induced nephropathy (CIN) is a leading cause of morbidity and mortality in high-risk patients undergoing percutaneous coronary intervention (PCI) or other radiocontrast procedures. Approximately 25% of all patients selected for these procedures are at risk for its development. Patients who experience this complication have higher rates of mortality, longer hospital stays and poorer long-term outcomes. The occurrence of CIN is directly related to the number of co-existing clinical risk factors. Among the many risk factors, preexisting renal impairment, advanced age, the presence of diabetes mellitus and both the volume and type of the contrast agent administered are among the most important. While the precise pathophysiological mechanisms responsible for this condition are complex and incompletely understood, experimental studies suggest that the pathogenesis involves a combination of renal ischemia and direct tubular epithelial cell toxicity. At the present time, adequate periprocedural hydration and the selection of low-osmolar and, more recently, iso-osmolar contrast agents are the only available tools to the operator for reducing the risk of this complication. Several other modalities, such as the use of NaHCO₃ and hemofiltration, also appear promising in preventing the development of this complication. This article reviews the epidemiology, pathophysiology, and consequences of CIN. It also reviews the risk factors for the development of CIN, as well as the history of the various modalities studied in its prevention.

Key words: Contrast media - Angiography - Kidney diseases, chemically induced.

Contrast-induced nephropathy (CIN) is a leading cause of morbidity in high-risk patients undergoing percutaneous coronary intervention (PCI) or other radiocontrast procedures. It is estimated that approximately 5-10% of all patients selected for these procedures are at risk for the development of CIN. Those who develop this complication suffer higher rates of mortality, longer hospital stays and poorer long-term outcomes. Experimental studies suggest that the pathogenesis of contrast media nephrotoxicity involves a combination of renal ischemia and direct tubular epithelial cell toxicity. At the present time, adequate periprocedural hydration and the selection of low-osmolar and, more recently, iso-osmolar contrast agents are the only available tools to the operator for reducing the risk of this complication. There are cur-
Currently no US Food and Drug Administration approved medications that reduce the rates of this complication. This article reviews the epidemiology, pathophysiology, and consequences of CIN. It also reviews the risk factors for the development of CIN, as well as the history of the various modalities studied in its prevention.

### Definition, incidence, and diagnostic features

The use of iodinated contrast media is central to the performance of diagnostic and therapeutic radiologic procedures for both cardiac and peripheral vascular disease. The growing use of these procedures in recent years has resulted in an increase in the incidence of renal dysfunction caused by the exposure to contrast material: an iatrogenic disorder known by a variety of terms as radiocontrast nephropathy (RCN), CIN or contrast-associated nephropathy (CAN). The extent of renal dysfunction required to define this state has varied widely among different studies, making it difficult to gauge the true incidence of this condition. In the current era, the most widely accepted definition is an absolute increase in serum creatinine >0.5 mg/dL, or a relative increase in serum creatinine >25% from baseline after systemic contrast administration in the absence of another underlying etiology. Using this strict definition, the overall incidence of contrast nephropathy in the general population is reported to be 1.2% to 1.6%. It is important to note, however, that in selected populations (especially those undergoing PCI), the incidence of CIN is much higher. In their retrospective analysis of 7,586 patients from the Mayo Clinic PCI registry, Rihal et al. found the overall incidence of CIN to be 3.3%. Patients with diabetes mellitus and those with baseline renal insufficiency were at greatest risk. In a smaller study of 1,826 patients by McCullough et al., CIN occurred in 14.5% of the patients. CIN has a very predictable time course, as it typically presents with an acute rise in serum creatinine within 24 to 48 hours of contrast exposure. Serum creatinine generally peaks after 3 to 5 days and returns to baseline or near baseline in 1 to 3 weeks. Although the diagnosis of CIN becomes obvious if these typical events occur after administration of contrast media, the differential diagnosis includes other causes of acute renal failure after percutaneous intervention such as atheroembolism, aortic dissection, renal ischemia from angiotensin-converting enzyme inhibitors, and postrenal obstruction from prostatism or anticholinergic drug administration, especially in patients without significant risk factors.

### Risk factors

The occurrence of RCN is most strongly related to the presence of risk factors (Table I). A mild, transient decrease in glomerular filtration rate (GFR) after contrast administration occurs in almost all patients. It is the presence or absence of risk factors that determines the occurrence of CIN. Based on numerous studies, the 3 most important risk factors for the development of CIN are preexisting renal impairment, the presence of diabetes mellitus, and the volume of contrast agent used. Other risk factors include advanced age, reduced effective arterial volume secondary to dehydration or congestive heart failure, and the concurrent use of nephrotoxic drugs such as ACE inhibitors and/or NSAIDs. Prospective studies have shown that in patients without any significant risk factors the risk of developing acute renal failure is approximately <1%. In one study the incidence of acute renal failure rose from 1.2% to 100% as the number of risk factors went from 0 to 4. Patients with both preex-

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**Table I.** Risk factors for the development of CIN.

| 1) Preexisting renal impairment |
| 2) Diabetes mellitus |
| 3) Volume of contrast used |
| 4) Age >70 years |
| 5) Reduced effective arterial volume |
| - Dehydration |
| - Congestive heart failure |
| 6) Concurrent use of nephrotoxic drugs such as ACE-inhibitors and NSAIDs |
existing renal impairment and diabetes have the highest risk of developing CIN. Some of the most important risk factors are discussed below.

**Baseline renal insufficiency**

Preexisting renal insufficiency is perhaps the most important risk factor for the development of CIN. In this group of patients, the incidence has been reported to be as high as 55% in some series. Furthermore, the risk for the development of CIN increases in proportion to the extent of baseline insufficiency. In one study, compared to patients with a baseline serum creatinine level <1.2 mg/dL, those with creatinine values ranging from 1.4 to 1.9 mg/dL had a 5-fold increase in the risk of CIN (from 2% to 10.4%). For those patients with a baseline serum creatinine >2 mg/dL, the risk increased to 62%. In another study by Rudnick et al., the frequency of CIN increased in the presence of compromised renal function in proportion to the severity of baseline insufficiency: it ranged from 5% in patients with mild renal insufficiency to >50% in those with severe renal dysfunction and diabetes.

In addition to its effect in predicting the development of CIN, baseline renal insufficiency has also been recently shown to be predictive of subsequent mortality. In one of the largest studies in this regard, Sadeghi et al. analyzed the CADILLAC trial data and found preexisting moderate renal insufficiency in 18% of 2082 patients undergoing primary percutaneous cardiac intervention for acute myocardial infarction. In patients with that level of renal insufficiency, mortality was significantly higher at 30 days and at 1 year compared to patients without baseline renal insufficiency. Furthermore, there was an incremental increase in mortality for each 10-mL/min decrement in baseline creatinine clearance.

**Diabetes mellitus**

Along with baseline renal insufficiency, diabetes mellitus is one of the most important risk factors for the development of CIN. Given the increased incidence of vascular disease in this patient population, along with the growing prevalence of diabetes in the general population, diabetics clearly represent a substantial proportion of patients who undergo radiologic procedures that require the use of contrast agents. The reported incidence of CIN in this population has varied widely, ranging from 5.7% to 29.4%. It is particularly noteworthy that in diabetics without evidence of renal insufficiency, albuminuria or the absence of other risk factors, the incidence of CIN is comparable to that of a healthy population. Also noteworthy is the deletriously synergistic combination of diabetes mellitus and renal insufficiency. Indeed, the combination of diabetes and renal insufficiency presents a greater risk for the development of CIN than either one alone.

**The volume of contrast agent**

The volume of contrast agent is an important risk factor for the development of contrast nephropathy. Both the use of large amounts of contrast dye as well as the performance of closely-spaced repetitive studies have been associated with the development of CAN. Unfortunately, no clear consensus appears in the literature with regards to the definition of low dose. Different studies have defined low dose in different ways, ranging from less than 70 mL to less than 140 mL. Since the development of CIN is multifactorial, it is unlikely that a uniform cutoff value can be applicable to all patients. Indeed, such cutoff values do not apply to patients with baseline renal insufficiency, in whom toxicity can occur with as little as 20 to 30 mL of contrast.

**Age**

The elderly are clearly at increased risk for the development of CIN for a variety of reasons: age-related diminution of renal function, the presence of renovascular disease, and the presence of complex anatomy requiring prolonged procedures and more contrast. In a prospective study of 183 patients greater than age 70, the overall incidence of CIN was 11%.
Pathophysiology

The mechanisms by which contrast-induced renal toxicity occurs are complex and incompletely understood. However, basic science studies implicate several pathophysiological mechanisms, including direct tubular toxicity, as well as hemodynamic and osmotic effects resulting in renal medullary ischemia.

Contrast media have a direct cytotoxic effect on renal structures, including reduction of transepithelial resistance, insulin permeability, polarized cellular enzyme release and other parameters of renal tubular cell viability. The direct renal tubular cytotoxicity is suggested by histologic changes of cell injury and the presence of enzymuria following contrast administration. Patients who have received radiocontrast material have been noted to have an increased urinary excretion of lysosomal enzymes and small molecular weight proteins, which are nonspecific indicators of tubular damage.

In addition to these direct tubular effects, radiocontrast agents also appear to induce a biphasic hemodynamic response with deleterious consequences. This response is characterized by an initial brief period of vasodilation, followed by a variable period of renal vasoconstriction. Weisberg et al. demonstrated that all patients have an early initial increase in renal blood flow after radiocontrast administration. Surprisingly, patients with diabetes, who have a lower baseline renal blood flow, manifest an earlier, more sustained, and more pronounced increase in renal blood flow after contrast injection as compared to their nondiabetic counterparts.

The mechanism by which contrast medium causes subsequent vasoconstriction is still not clearly understood. Alterations in the metabolism of prostaglandin, nitric oxide, endothelin, or adenosine are thought to play a role. The renal medulla is extremely vulnerable to ischemic injury because of its low perfusion at baseline, and the vasoconstriction induced by the contrast media is now believed to be the most likely cause of CIN.

In addition to hemodynamic and direct tubular effects, contrast media also exert osmotic effects on the renal bed. The large contrast-induced osmotic load results in an increase in renal oxygen consumption. The osmotic diuresis leads to an increase in renal metabolic activity, which further aggravates medullary hypoxia. In addition, the release of endothelin and vasopressin, along with a reduction in prostacyclin synthesis and/or release, further reduces blood flow to the nearly anoxic medulla.

Clinical course and outcome

While the recovery from CIN is very likely and dialysis is infrequently required, some degree of residual renal impairment has been reported in as many as 30% of patients who developed CIN. The acute renal failure seen in CIN is generally nonoliguric and reversible. In high-risk patients, oliguria may develop within 24 hours of contrast medium administration, with the peak increase in creatinine often exceeding 5 mg/dl (440 µmol/L) and sometimes even necessitating dialysis. The urinalysis is often compatible with acute tubular necrosis, demonstrating renal tubular epithelial cells and coarse granular casts.

In cases of a delayed onset of renal failure after contrast administration (i.e., >1 week), acute renal failure secondary to atheroembolic disease should be suspected, particularly in patients with known atherosclerotic disease. Compared with CIN, the clinical course of atheroemboli-induced acute renal failure is prolonged and is associated with a much lower recovery rate.

The development of CIN has been associated with an increase in morbidity and both in-hospital and long term mortality. In a study by Aronow et al., the development of CIN in patients following coronary stenting was shown to significantly increase the hospital length of stay. Levy et al., in a retrospective study, concluded that patients who developed CIN had higher mortality (34%) compared to patients (7%) who did not develop CIN after contrast administration. In a study by McCullough et al., acute renal failure requiring dialysis after coronary angioplasty...
was <1%, and creatinine clearance, diabetes, and contrast dose were shown to be independent predictors of acute renal failure requiring dialysis. The in-hospital mortality for those who developed acute renal failure was 35.7% and the 2-year survival was 18.8%. Similarly, in the Mayo series, 22% of patients with acute renal failure died during the index hospitalization compared with only 1.4% of patients without acute renal failure. Furthermore, among hospital survivors with acute renal failure, 1- and 5-year estimated mortality rates were 12.1% and 44.6%, respectively. These rates were much higher than the 3.7% and 14.5% mortality rates in patients without acute renal failure. In yet another study, Gruberg et al. studied the effects of contrast administration on morbidity and mortality in 439 patients with a baseline creatinine >1.8 mg/dL. The in-hospital mortality rate was 22.6% for those requiring hemodialysis as a result of contrast administration. The cumulative 1-year mortality rate was 45.2% for those who required dialysis. Thus, taken together, these data would suggest that the development of acute renal failure following contrast administration is highly correlated with death during the index hospitalization as well as during long-term follow-up. What remains unknown is whether CIN contributes directly to mortality or whether it is merely a marker for more severe underlying disease that is itself the cause of higher mortality.

**Prevention**

The prevention of CIN begins with the identification of risk factors for its development, and the attempt to control or modify them prior to the administration of contrast media. All of the risk factors discussed earlier can be identified from a routine medical history and baseline blood tests. While many risk factors are non-modifiable, their early identification can lead to changes in the approach to such patients undergoing these procedures. These changes may take the form of cancelling procedures deemed not absolutely essential, limiting the quantity of contrast material administered, avoiding the simultaneous performance of diagnostic and interventional procedures, and most importantly, hydrating the high-risk patient prior to the performance of angiography. The development of other prevention strategies remains in evolution but has been hampered by an incomplete understanding of the underlying pathophysiology of this condition. As such, numerous strategies (reflecting this incomplete understanding) have been studied through the years (Figure 1). With the exception of hydration and the use of low osmolar contrast agents, none of these therapies have been convincingly and consistently shown to be effective, while a few are very promising. Some of the most important studied strategies are discussed below.

**Hydration**

Hydration is currently the only universally accepted measure for the prevention of CAN. By improving urine output, hydration prevents crystallization of contrast dye in the renal tubules. In addition, hydration administered following the procedure counters any osmotic diuresis caused by the contrast agent. Many studies have demonstrated the benefits of hydration in preventing CIN. However, prior to the mid-1990s, mannitol and furosemide were the agents of choice for preventing contrast nephrotoxicity. In a classic study, Solomon et al. were able to demonstrate that in patients with chronic renal insufficiency who were undergoing cardiac angiography, hydration with 0.45% saline provided better protection against acute decreases in renal function induced by radiocontrast agents than did hydration with 0.45% saline plus mannitol or furosemide. Importantly, this study also established a regimen consisting of both 12 hours of precatheterization and 12 hours of postcatheterization intravenous hydration as an appropriate prophylaxis for patients with mild-to-moderate renal insufficiency undergoing diagnostic angiography. In an attempt to maintain the benefit of this hydration regimen but decrease the length of hospitalization it obligatorily mandates, Taylor et al. tested an outpatient oral
precatheterization hydration strategy in comparison with overnight intravenous hydration. They found that an outpatient hydration protocol including precatheterization oral hydration (1,000 mL clear liquid over 10 h) followed by 6 h of i.v. hydration (0.45 normal saline solution at 300 mL/h) beginning just before contrast exposure was as effective as the traditional pre- and postcatheterization intravenous hydration protocol but was associated with a decrease in hospital length-of-stay.

More recently, Mueller et al. performed a randomized comparison of 2 hydration regimens (isotonic versus half-isotonic) in 1,620 patients undergoing coronary angioplasty. Contrast media-associated nephropathy was significantly reduced with isotonic versus half-isotonic hydration (0.7% vs 2%, respectively). Three predefined subgroups benefited in particular from isotonic hydration: women, persons with diabetes, and patients receiving 250 mL or more of contrast. Importantly, the incidence of cardiac and peripheral vascular complications was similar between the 2 hydration groups. Based on their large randomized and controlled study, the authors concluded that isotonic hydration is superior to half-isotonic hydration in the prevention of contrast media-associated nephropathy.

**Forced diuresis**

The data with regards to forced diuresis with either furosemide or mannitol in the prevention of contrast nephropathy has been controversial. As stated, prior to the mid-1990s, mannitol and furosemide were the agents of choice for preventing contrast nephrotoxicity. In the study by Solomon et al. discussed earlier, saline alone was better therapy than saline coupled with forced diuresis. In that study, serum creatinine rose even in patients who gained weight, making it
unlikely that dehydration alone accounted for the adverse effects of the diuretic. However, the study by Solomon et al. has been criticized for not controlling for the intravascular volume status of the patients before and after the contrast exposure. To address this particular concern, Stevens et al. performed the PRINCE study, which was designed to test the hypothesis that forced diuresis with maintenance of intravascular volume would result in less contrast-induced renal injury. 42 To this end, they randomized 98 patients with baseline renal impairment to 1 of 2 regimens: forced diuresis with intravenous crystalloid, furosemide, mannitol (if pulmonary capillary wedge pressure <20 mmHg), and low-dose dopamine versus intravenous crystalloid and matching placebos. They demonstrated that patients with a low urine flow rate (<150 mL/h) experienced a much higher incidence of renal failure compared to those with a high urine flow rate (>150 mL/h) (45.9% vs 21.6%). Their results led these authors to conclude that, hemodynamics permitting, forced diuresis with intravenous crystalloid, furosemide, mannitol and low-dose dopamine provides a modest benefit against CIN provided a high urine flow rate can be achieved.

**Type of contrast agent**

The use of low-osmolar agents (compared with high osmolar agents) are associated with a lower risk of the development of renal toxicity – but probably only in those with baseline renal insufficiency and/or diabetes mellitus. In a large randomized study by Rudnick et al., 10 patients with baseline renal impairment (defined as a serum creatinine >1.6 mg/dL) were 3.3 times more likely to develop CIN when they were administered high osmolality contrast agents as opposed to low osmolality agents. Importantly, however, this benefit was not seen in those patients with baseline normal renal function. Similarly, in a meta-analysis of 14 trials by Barrett et al., only patients with preexisting renal impairment benefited from the use of low-osmolality contrast agents. 40 More recently, Aspelin et al. extended these observations to the use of iso-osmolar contrasts, which are iso-osmolar to blood and associated with even lower toxicity than that of low-osmolar contrast medium. They performed a randomized multicenter study comparing the nephrotoxicity of iodixanol (an iso-osmolar non-ionic contrast agent) with that of iohexol (a low-osmolar non-ionic contrast agent) in patients with stable diabetes mellitus and impaired renal function who underwent coronary or aortofemoral angiography. 35 In this randomized and double-blind prospective study, iodixanol induced significantly less increase in serum creatinine concentration than the low-osmolar agent iohexol. Thus, in high-risk patients (especially those with baseline renal insufficiency), the use of low and iso-osmolar contrast medium substantially reduces the risk of nephropathy compared with the use of high-osmolar contrast medium.

**Atrial natriuretic peptide**

Atrial natriuretic peptide (ANP) is a potent vasodilator whose levels increase following the administration of contrast, especially in patients with preexisting renal impairment. ANP is known to increase renal blood flow and thus mitigate the development of CIN. 50 Despite this sound pathophysiologic rationale, however, clinical studies to date have failed to establish a role for this agent in the prevention of CIN. In one of the earlier studies, Kurnik et al. randomized 20 consecutive patients with chronic renal failure (60% with diabetes) in a prospective, double-blind fashion to receive either ANP (50 µg bolus, then 1 µg/min infusion) or mannitol (15% at 100 ml/h) for 2 hours before and during cardiac catheterization with diatrizoate. Despite beneficial effects on renal blood flow (especially in patients with diabetes), acute renal failure occurred to a similar extent in both groups. More recently, Kurnik et al. performed a multicenter, prospective, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of intravenous ANP to prevent CIN. Two hundred and forty-seven patients with stable chronic renal failure (serum creatinine greater than 1.8 mg/dL or serum creatinine between 1.5 and 1.8 mg/dL
with estimated creatinine clearance of < or = 65 mL/min) were assigned to receive either placebo or 1 of 3 doses of ANP (0.01 µg/kg/min, 0.05 µg/kg/min, or 0.1 µg/kg/min) for 30 minutes before and continuing for 30 minutes after radiocontrast administration. All patients were given intravenous 0.45% saline for 12 hours before the radiocontrast procedure and continuing for 12 hours after the last dose of radiocontrast. They found that the administration of intravenous ANP before and during a radiocontrast study did not reduce the incidence of CIN in patients with preexisting chronic renal failure, whether or not they had diabetes mellitus. Thus, based on these unsatisfactory results, ANP has not been recommended for use in the prophylaxis of CIN.

**Endothelin blockers**

Endothelin is a potent endogenous vasoconstrictor that has been implicated in the pathogenesis of CIN. Endothelin has been proposed as one of several possible mediators responsible for the reduction in renal blood flow seen after contrast administration. Indeed, endothelin synthesis is increased and renal cortical nitric oxide synthesis decreased following the administration of contrast media. There are 2 receptors for endothelin, endothelin-A and endothelin-B. Endothelin-A mediates vasoconstriction and is found in smooth muscle, while endothelin-B mediates vasodilation through the release of nitric oxide and prostacyclin and is found in endothelial cells.52 In a rat model of RCN,53 a highly selective endothelin-A receptor antagonist was partly protective of GFR and prevented medullary necrosis as determined by histopathologic examination. However, blockade of endothelin-B receptors in the same rat model yielded no additional protection. In a clinical study by Wang et al.,55 158 patients with chronic renal insufficiency and undergoing cardiac angiography were randomized to receive either a mixed endothelin A and B receptor antagonist or placebo. All patients received intravenous hydration with 0.45% saline before and after radiocontrast administration. Patients receiving the mixed endothelin receptor antagonist had a greater mean increase in serum creatinine 48 hours after angiography, a higher incidence of radiocontrast nephrotoxicity, and suffered from more adverse effects such as hypotension. This negative effect of the mixed endothelin receptor antagonist was apparent in both diabetic and nondiabetic patients. Based on the results of this clinical trial, there has been a diminution in the enthusiasm for further studies with this agent in the prevention of CIN.

**Calcium-channel blockers**

Calcium channel blockers are believed to prevent CIN by increasing renal blood flow. Several relatively small studies have demonstrated preservation of renal blood flow and GFR in patients treated with these agents compared to those given placebo.54, 55 In one of the larger studies with calcium channel blockers,56 Khoury et al. randomized 85 patients to receive either 10 mg of nifedipine with saline hydration or saline hydration alone before the administration of contrast. The trial demonstrated that there was little change in serum creatinine levels within 48 hours in either group. Thus, the data in the literature do not support the use of calcium channel blockers for the prevention of CIN.

**N-acetylcysteine**

N-acetylcysteine (NAC) is believed to be renoprotective via renal vasodilatory and antioxidative properties.57, 58 In animal models, NAC ameliorates radiocontrast-induced renal vasoconstriction by mechanisms that are independent of prostaglandins and nitric oxide. Numerous small clinical studies have demonstrated a beneficial effect of this medication when used in the protection against contrast-induced acute renal failure. Three meta-analyses have assessed the efficacy of prophylactic NAC administration when used in this context.39, 59, 60 The NAC and control groups had a total of 444 and 441 patients, respectively. Collectively, these meta-analyses demonstrated a large and statistically significant risk reduction in the incidence of contrast-induced acute renal failure in patients.
treated with NAC (RR = 0.37 to 0.66). Therefore, in order to prevent 1 case of CIN, 8 to 9 patients need to be treated with NAC. Two recent randomized studies of oral NAC for prevention of contrast nephropathy have also been performed, with conflicting results. One study showed that the prophylactic oral administration of NAC provided no additional benefit beyond saline hydration in patients with mild to moderate renal insufficiency undergoing coronary angiography, especially if relatively low doses of contrast agent were used. The other study demonstrated that a double dose of NAC (1 200 mg twice daily for a total of 2 days) was more effective in preventing CIN, particularly if a large amount (>140 mL) of a non-ionic low osmolality contrast dye was utilized.

**Theophylline**

In patients with normal renal function, the administration of contrast medium leads to renal vasodilation as a result of the activation of adenosine A2 receptors. In the setting of impaired renal function, however, the administration of contrast medium leads to the activation of both adenosine A1 and A2 receptors. The A2 receptor is associated with initial renal vasodilation while the A1 receptor is responsible for the sustained aggravation of renal hemodynamics that is potentially related to the development of CIN. Theophylline is an adenosine antagonist that is believed to prevent the vasoconstrictive effect of A1 receptors. Some studies have shown that theophylline prevents the decline in GFR and creatinine clearance seen after contrast administration. However, other studies have not been able to demonstrate a beneficial effect of this agent when used in this setting. In a randomized study consisting of 80 patients, Erley et al. were unable to demonstrate a benefit for the use of theophylline above and beyond that of hydration alone in patients with impaired renal function undergoing angiography. Abizaid et al. studied a similar group of patients with baseline renal insufficiency undergoing angioplasty and randomized them to 1 of 3 arms: saline hydration alone, saline hydration plus dopamine infusion, or saline hydration plus aminophylline. Following the administration of non-ionic contrast media, neither aminophylline nor dopamine reduced the incidence of CIN compared to saline hydration alone. Based on the available evidence, it can be concluded that the administration of theophylline does not provide any additional benefit beyond hydration alone for the prevention of CIN.

**Fenoldopam**

Renal medullary ischemia secondary to contrast-induced medullary vasoconstriction contributes to the development of CIN. Fenoldopam is a specific agonist of the dopamine-1 receptor that has been shown to increase both renal medullary and renal cortical blood flow. For this reason, it has been evaluated as a therapeutic modality for the prevention of CIN. Indeed, many small studies have have demonstrated that fenoldopam decreases the incidence of CIN. Based on these encouraging investigations a large-scale multicenter, prospective, double-blind, placebo-controlled randomized trial was conducted to determine the safety and efficacy of fenoldopam mesylate to prevent CIN in patients with chronic renal insufficiency undergoing invasive cardiac procedures. Three hundred and fifteen patients at 28 centers in the United States were randomized to receive either fenoldopam mesylate (n=157) or placebo (n=158). NAC was administered prior to the procedure in 49.6% of patients in the fenoldopam group and 54.1% of patients in the placebo group. Patients were randomized 1:1 to receive fenoldopam or matching placebo, stratified by the presence or absence of pharmacologically treated diabetes. Disappointingly, the incidence of CIN, using 2 different definitions, was no different between the 2 groups. Importantly, the lack of efficacy of fenoldopam was independent of diabetic status, baseline renal function, NAC use, hydration status, or the amount of contrast administered. Based on the results of this landmark CIN study, fenoldopam is no longer marketed for use in the prevention of CIN.
**Hemofiltration**

Hemofiltration (HF) refers to the use of a hydrostatic pressure gradient to induce the filtration (or convection) of plasma water across the membrane of the hemofilter. The process removes smaller solutes (such as urea and electrolytes) in a concentration similar to that of plasma. A recent study prospectively randomized 114 patients with renal insufficiency (mean serum creatinine concentration of 3±1 mg per deciliter) scheduled to undergo elective PCI to treatment with either HF or saline hydration for the prevention of contrast agent-induced nephropathy.34 HF and saline hydration were initiated 4 to 8 hours before the coronary intervention and continued for 18 to 24 hours after the completion of the procedure. A nonionic, low-osmolality contrast agent was used in all patients. CIN occurred less frequently among the patients in the HF group compared to those in the control group (5% vs 50%). In-hospital mortality was 2% in the HF group and 14% in the control group, and the cumulative 1-year mortality was 10% and 30%, respectively. All of these differences reached statistical significance. In this study, the use of preemptive continuous venovenous HF in the manner described resulted in a significant reduction in CIN in a cohort of patients known to be at considerable risk (mean baseline creatinine level, 3 mg per deciliter [265.2 µmol per liter]). The apparent benefit of this intervention was greater than that observed for all other therapeutic interventions that have been studied to date. These findings are particularly noteworthy because the benefit with continuous venovenous HF was evident despite the large volumes of contrast agent administered (mean, 247 ml) in this study.71

**NaHCO3**

Pretreatment with sodium bicarbonate is protective in animal model of acute ischemic renal failure.72 A recent study prospectively randomized 137 patients with renal insufficiency scheduled to undergo diagnostic or interventional procedures requiring radiographic contrast to treatment with either sodium bicarbonate or sodium chloride infusion for the prevention of CIN (defined as a 25% change in serum creatinine).76 The study was terminated early due to an overwhelming benefit of sodium bicarbonate infusion as compared to saline. One hundred and nineteen patients completed the study protocol and were included for interim analysis. The group receiving sodium bicarbonate treatment had a 1.7% (1 of 60) incidence of CIN compared to an incidence of 13.6% (8 of 59) in patients who had received sodium chloride. When results were analyzed using another common definition of contrast nephropathy (a change of at least 0.5 mg/dL in serum creatinine), 7 of 59 patients (11.9%) who were treated with sodium chloride developed contrast nephropathy compared with only 1 of 60 (1.7%) who received sodium bicarbonate. When patients undergoing cardiac catheterization were analyzed separately, the benefit of sodium bicarbonate treatment was even larger (incidence of CIN, 16.7% for sodium chloride vs 2% for sodium bicarbonate). These results suggest that hydration with sodium bicarbonate is efficacious and practical, requiring pretreatment only 1 hour before contrast injection. Although confirmation in a larger multi-center study is necessary, infusion of sodium bicarbonate may provide a safe, simple and inexpensive means of preventing contrast-induced renal failure.

**Dopamine**

Selective stimulation of renal DA1 receptors by low-dose dopamine has been shown to increase renal blood flow. However, studies using low-dose dopamine for the prevention of CIN have been negative, particularly in diabetic patients.13, 44, 73, 74 Dopamine’s effects on multiple receptors (DA1, DA2, α and β receptors) and the lack of a true separation of receptor activation by dose make it difficult to selectively activate only the DA1 receptors.6, 75 Because of these reasons and also because of its potentially detrimental effect in diabetic patients, dopamine has not been recommended for routine use for CIN prophylaxis.
Management

There is no specific therapy of benefit for CIN once it has occurred. Fortunately, in the majority of cases, the functional impairment is reversed within 1 week or 2 and the need for dialysis is rare. Care should be taken to prevent further injury to the kidneys by avoiding the administration of nephrotoxic drugs (e.g., NSAIDs, ACE inhibitors). In addition, patients should be adequately hydrated so as to maintain adequate renal blood flow and glomerular filtration. Such patients should not be exposed to repeat contrast administration unless it is deemed absolutely essential.

Conclusions

Contrast induced nephropathy is an iatrogenic disorder, resulting from exposure to contrast media. With the growing number of diagnostic and interventional radiologic procedures in recent years, the prevalence of this order can be expected to increase. While the precise pathophysiological mechanisms responsible for this condition are complex and incompletely understood, it appears that contrast-induced renal hemodynamic and cytotoxic effects play a major role in its development. Once it occurs, CIN is associated with an increase in morbidity and both in-hospital and longterm mortality. There are a number of patient-related risk factors which increase the probability of its occurrence. The most important of these risk factors are the presence of diabetes mellitus, baseline renal insufficiency, advanced age and the amount of contrast material administered. Importantly, risk factors are synergistic in their ability to produce CIN. Primary prevention is the most effective way of decreasing its incidence. Although there are many new promising modalities in the prevention of CIN, such as NaHCO₃ and HF, hydration remains the most effective method of prevention. In addition, the use of low- or iso-osmolar agents and acetylcysteine are also beneficial in selected high-risk patients. Figure 2 provides an algorithm for the management of the high-risk patient scheduled to undergo a contrast-requiring angiographic procedure.

Hydration

Normal saline 0.5-1 mL/kg/h for 3-12 h before and after procedure or

NaHCO₃ hydration: mix 3 ampule in 1 L of D5W and infuse @ 3.5 mL/kg bolus for 1 h before and 1.18 mL/kg for 6 h after

(For congestive heart failure patients – use clinical judgement)

NAC

600 mg b.i.d. for 2 days
Use 1 200 mg b.i.d. if creatinine >2.5 mg/dL or anticipated use of contrast volume is high

Use lowosmolar non-ionic contrast agent (iso-osmolar non-ionic agent for diabetic patient)

Figure 2.—Algorithm for the management of the high-risk patient undergoing coronary angiography and/or percutaneous coronary intervention.

Riassunto

La prevenzione della nefropatia da mezzo di contrasto nei pazienti sottoposti a intervento di rivascolarizzazione coronarica percutanea

La nefropatia da mezzo di contrasto rappresenta una delle principali cause di morbilità e di mortalità nei pazienti ad alto rischio sottoposti a intervento di rivascolarizzazione coronarica percutanea o ad altre procedure che utilizzano mezzi di contrasto radiopachi. Approssimativamente il 25% di tutti i pazienti selezionati per queste procedure sono a rischio di sviluppare una nefropatia da mezzo di contrasto. I pazienti che presentano questa complicanza hanno un rischio di mortalità più elevato, una degenza ospedaliera più prolungata e una prognosi a lungo termine peggiore. L’incidenza della nefropatia da mezzo di contrasto è direttamente correlata al numero di fattori di rischio clinico coesistenti. Tra i fattori di rischio, i più importanti sono rappresentati dalla pregressa
compromissione della funzionalità renale, dall’età avanzata, dalla presenza di diabete mellito e dal volume e dal tipo del mezzo di contrasto somministrato. I precisi meccanismi fisiopatologici responsabili di questa patologia sono complessi e non sono ancora stati completamente chiariti, tuttavia alcuni studi sperimentali suggeriscono che il processo patogenetico comprende una combinazione di ischemia renale e di tossicità cellulare diretta a livello dell’epitelio tubulare. Al momento attuale, un’adeguata idratazione periprocedurale e l’utilizzo selettivo di mezzi di contrasto a bassa osmolarità e, più recentemente, di mezzi di contrasto isosmolari, rappresentano gli unici strumenti a disposizione dell’operatore per ridurre il rischio di questa complicanza. Diverse altre modalità, come l’utilizzo di NaHCO₃ e l’emofiltrazione, sembrano essere ugualmente promettenti nel prevenire lo sviluppo di questa complicanza. Questo articolo presenta una review dell’epidemiologia, della fisiopatologia e delle conseguenze della nefropatia indotta da mezzo di contrasto e viene fornita una rassegna cronologica delle strategie utilizzate per la sua prevenzione.

Parole chiave: Mezzo di contrasto - Angiografia coronarica - Patologia renale.

References

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