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Prevention of radiocontrast-induced nephropathy

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Radiocontrast-induced nephropathy (RCIN) is a common and important complication of coronary angiography and percutaneous coronary intervention (PCI). RCIN is the third most common cause of hospital-acquired acute renal failure and is associated with increased morbidity, mortality, and length of hospitalization.[1,2] The single most important risk factor for development of RCIN is underlying renal insufficiency, particularly if it is caused by diabetic nephropathy.[3] Other important risk factors include reduced effective circulating volume, high volume contrast administration, and concomitant use of cardiovascular drugs with renal effects. Given the prevalence of these risk factors in patients with coronary artery disease (CAD) and the increasing use of PCI, there is considerable interest in exploring strategies to prevent RCIN in this population. This issue of *Cardiology Rounds* comprehensively reviews recent studies and outlines recommended strategies for preventing RCIN in patients with chronic renal insufficiency prior to coronary angiography and PCI.

Definition and diagnostic features

RCIN is defined as a worsening of renal function following radiocontrast exposure in the absence of other identifiable causes. Most commonly, RCIN is defined as an acute increase in serum creatinine (sCr) concentration to >44 µmol/L or an increase of >25% above baseline within 48 hours of contrast exposure.[4] RCIN has a very predictable time course: sCr typically increases within 24-48 hours after exposure, peaks at 3-5 days, and resolves within 7-10 days.[5] Alternative diagnoses should be entertained in patients who present with later onset and a longer course of acute renal insufficiency following contrast exposure.

RCIN is usually non-oliguric and urinalysis typically shows evidence of coarse granular casts and low-grade proteinuria in the absence of hematuria and heme-granular casts. Urate and calcium oxalate crystals may be present and the fractional excretion of sodium may be <1%.

The differential diagnosis of acute renal failure in patients with CAD after coronary angiography and PCI includes atheroembolic disease, which is associated with considerable morbidity and mortality. This is usually distinguished from RCIN because of the more persistent time course of renal impairment and the presence of associated peripheral findings on physical examination. Saklayen et al prospectively evaluated 267 elderly patients undergoing coronary angiography with a mean sCr of 106 µmol/L at baseline.[6] Only 5 of 263 patients at follow-up had persistent renal insufficiency above baseline, 2 of which later died of renal failure. In this high-risk population, atheroembolic renal failure was an important, but relatively uncommon complication of coronary angiography.

Other diagnoses that should be considered following coronary angiography and PCI include aortic dissection, drug-related causes (diuretics and angiotensin-converting enzyme [ACE] inhibitors), low-output states resulting in compromised renal perfusion, and post-renal causes including prostatism and anticholinergic drug administration.

Risk factors and incidence

The incidence of RCIN following contrast exposure depends largely on the population studied and varies with each study due to differences in the definition of RCIN and the co-morbidities of the study population. A mild and transient decrease in glomerular filtration rate (GFR) following contrast exposure occurs in almost all patients. While the overall risk of developing RCIN in unselected patients is <3%,[4] the incidence in patients undergoing PCI is higher. McCullough et al reported an incidence of 14.5% as defined by a 25% increase in sCr following PCI in 1826 unselected patients.[2]

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Davidson et al prospectively studied 1144 patients undergoing angiography with a mean baseline sCr of 90 µmol/L.[7] RCIN occurred in 6% as defined by a rise in sCr to >44 µmol/L. They identified baseline renal insufficiency and age as risk factors for RCIN. Rudnick et al prospectively studied 1196 patients undergoing coronary angiography and grouped them according to the presence of chronic renal insufficiency (sCr ≥132 µmol/L) and an underlying history of diabetes.[3] Patients were prehydrated and randomized to either low-osmolar (LOCM) or high-osmolar contrast media (HOCM). The incidence of RCIN was greatest in those with both baseline renal insufficiency and diabetes mellitus. While chronic renal insufficiency alone was associated with a higher incidence of RCIN, patients with diabetes mellitus and normal renal function did not have higher rates of RCIN. In fact, there is no convincing evidence that patients with diabetes in the absence of renal insufficiency are particularly at risk.[5]

Numerous studies have shown a gradient of risk in patients with chronic renal insufficiency exposed to contrast agents. The incidence of RCIN and associated serious outcomes (eg, need for dialysis) increases exponentially as baseline sCr rises.[2,8,9]

Modifiable risk factors shown to increase RCIN risk include reduced effective circulating volume secondary to either dehydration or congestive heart failure and the volume of contrast administered.[2,4] Rudnick et al also demonstrated an increased incidence of RCIN in patients exposed to HOCM versus LOCM.[3] Addressing these modifiable risk factors is the first step in preventing RCIN in patients undergoing coronary angiography and PCI.

Pathophysiology of RCIN

Although the precise mechanisms underlying RCIN are unclear, it is generally accepted that radiocontrast agents exert their toxic effects through a combination of ischemic injury to the renal medulla and direct tubular toxicity.

Ischemic injury to the renal medulla is thought to be related to both decreased oxygen supply (due to contrast-mediated renal vasoconstriction) and increased demand (due to increased solute delivery to the distal tubules). The renovascular response to radiocontrast agents has been shown to be biphasic, with an initial period of vasodilatation and augmented renal blood flow, followed by a period of prolonged vasoconstriction. The subsequent fall in renal blood flow correlates with the development of RCIN.[10] Potential mediators of contrast-induced vasoconstriction include prostaglandins, nitric oxide, endothelin-1, calcium ions, and adenosine.[11]

The renal medulla functions normally on the verge of hypoxia and is therefore particularly susceptible to alterations in oxygen balance. Medullary blood flow is low at baseline and represents only 5%-10% of the total renal blood flow (RBF). It is further compromised by radiocontrast-mediated shunting of blood to the cortex and by red blood cell aggregation, resulting in medullary congestion. A decrease in blood flow or an increase in solute delivery can result in a negative oxygen balance and ultimately, ischemic necrosis of the outer medullary tubule, the histologic hallmark of RCIN.

Direct tubular toxicity is thought to be primarily mediated by reactive oxygen species that cause toxic, ischemic, and immune-mediated cell injury.[12,13] Evidence of direct tubular injury is suggested by increased urinary excretion of tubular enzymes and failure of the proximal tubules to reabsorb small molecular-weight proteins after contrast exposure.[14]

Table 1: Strategies for preventing RCIN

- **Preventing vasoconstriction with vasodilators**
  - Calcium channel blockers
  - Atrial natriuretic peptide
  - Angiotensin receptor blockade
  - Dopamine and dopamine receptor agonists (fenoldopam)
  - Adenosine antagonists – theophylline and aminophylline
  - Endothelin receptor antagonists
- **Forced diuresis and avoidance of volume depletion**
  - Saline hydration and forced diuresis with mannitol and furosemide
- **Reducing osmotic injury**
  - High-osmolar vs. low-osmolar and iso-osmolar agents
- **Contrast elimination – prophylactic hemodialysis**
- **Use of N-acetylcysteine**

Prevention of RCIN

Studies evaluating agents for prophylaxis against RCIN have targeted a variety of proposed mechanisms of contrast-induced injury. Strategies include:

- prevention of vasoconstriction and maintenance of renal blood flow
- prevention of osmotic injury through avoidance of volume depletion and the use of non-ionic low and iso-osmolar contrast media
- elimination of contrast media following exposure
- prevention of renal injury secondary to oxygen free-radicals using N-acetylcysteine (Table 1).

While many studies demonstrate reductions in contrast-related renal insufficiency following intervention, none to date have demonstrated improvement in hard clinical outcomes such as mortality or need for dialysis.

Vasodilator strategies

Calcium channel blockers: These agents attenuate the effects of most vasoconstrictors implicated in RCIN, reduce vasoconstriction, and maintain RBF and GFR following contrast exposure in animal and human studies.[15,16] Neumayer et al randomized 35 patients with normal renal function to either nitrendipine or placebo prior to radiocontrast exposure.[17] GFR measured at 48 hours post-exposure was significantly higher in the nitrendipine-compared to the placebo-group. Khoury et al demonstrated no difference in the sCr (at 48 hours post-contrast exposure) between nifedipine and placebo pretreated patients.[18] Cacoub et al prospectively studied 27 patients with moderate renal insufficiency randomized to receive nifedipine or placebo.[19] No difference was seen between groups, with 36% in the nifedipine group and 37.5% in the control group developing RCIN, defined as a 20% increase in sCr at 48 hours post-contrast exposure. Therefore, there is insufficient evidence to support the use of calcium channel blockers in the prevention of RCIN.

Atrial natriuretic peptide: Atrial natriuretic peptide (ANP) is a potent vasodilator thought to increase RBF. ANP levels have been observed to increase in patients after contrast exposure. Small studies have shown improved RBF and maintenance of GFR in patients treated with intravenous (I.V.) ANP; however,

they failed to show a reduction in RCIN.[20,21] A single, randomized, double-blind, placebo-controlled trial failed to show a reduction in RCIN in patients treated with I.V. ANP.[22]

Renin-angiotensin system: Animal studies have shown that interruption of the renin-angiotensin system reduces radiocontrast-induced renal vasoconstriction.[23] Russo et al showed attenuation of radiocontrast-induced reductions in GFR and RBF with the ACE-inhibitor, captopril in humans.[10] Gupta et al prospectively randomized 71 patients with chronic renal insufficiency and diabetes mellitus to captopril 25 mg 3 times daily for each of 3 days prior to coronary angiography.[24] There was a 79% reduction in RCIN in captopril-treated patients compared to placebo in those not pretreated with saline hydration. These dramatic results have not been reproduced; therefore, at present, the use of ACE inhibitors to prevent RCIN is not recommended.

Adenosine: Adenosine acts as a vasodilator in most vascular beds. In patients with impaired renal function, however, adenosine can cause sustained renal vasoconstriction via activation of adenosine receptors, an effect that can be countered by the adenosine antagonist, theophylline.[25] In 2 randomized-controlled trials, theophylline significantly attenuated GFR decline at 48 hours post-contrast exposure.[26,27] However, a recent trial by Erley et al using oral theophylline in prehydrated patients with impaired renal function showed no benefit over saline hydration alone.[28] Similarly, Abiziad et al demonstrated that aminophylline had no benefit over saline hydration alone.[29] Due to conflicting results, therefore, there is insufficient evidence for using adenosine antagonists to prevent RCIN.

Endothelin-1: Endothelin-1 is a potent vasoconstrictor thought to play a role in contrast-induced renal vasoconstriction. One randomized-controlled trial used a nonselective endothelin receptor blocker for pretreatment in patients with mild to moderate renal impairment; however, there was a higher incidence of RCIN in the endothelin receptor blocker-treated patients compared to controls.[30]

Dopamine and dopamine receptor agonists: Dopamine is an endogenous catecholamine shown to increase GFR and RBF through activation of dopamine-1 (D1) receptors. However, it is nonselective even at low doses and interacts with D2 receptors and adrenergic receptors to induce vasoconstriction. Various studies with low-dose I.V. dopamine have been largely negative with no clear benefit in preventing RCIN.[20,29,31-32] Fenoldapam is a selective D1 receptor agonist shown to increase RBF in hypertensive patients[33] and cortical and medullary blood flow in animal studies.[34] Unlike dopamine, it remains selective even at high doses with no stimulation of D2 or alpha- and beta-adrenergic receptors. In a study by Bakris et al, fenoldopam infusion protected against contrast-related reductions of both RBF and GFR in volume-depleted anesthetized dogs.[35] Several human studies suggest that fenoldopam prevents RCIN; however, all were nonrandomized, and historic cohorts served as controls.[36-38] The largest, by Kini et al, prospectively studied 150 adequately hydrated patients with mild-to-moderate renal insufficiency undergoing PCI.[38] Fenoldopam infusion led to an incidence of RCIN (sCr increase of 25%) of 4.5%, significantly lower than the 19% in the historical control group with similar baseline demographics. Tumlin et al recently published a pilot study of fenoldopam in 45 patients with moderate-to-severe renal insufficiency (baseline sCr 176 to 440 µmol/L).[39] Patients were randomized to a 0.45% NaCl solution versus a 0.45% NaCl solution plus a fenoldopam infusion (0.1 µg/kg/min at least 1 hour pre-contrast exposure). With fenoldopam, RFB was 15.8% above baseline versus 33.2% below in controls. There was also a nonsignificant trend toward decreased RCIN at 48 hours (21% with fenoldopam versus 41% in controls) and a significant decrease in peak sCr at 72 hours post-contrast exposure.

A large, randomized, double-blind, placebo-controlled trial, The Evaluation of Corlopam in Patients at Risk for Renal Failure – A Safety and Efficacy Trial (CONTRAST), evaluating dopamine receptor agonists in the prevention of RCIN has been initiated. Currently, however, there is insufficient evidence to support fenoldopam use to prevent RCIN.

Forced diuresis and avoidance of volume depletion

I.V. hydration may be helpful in preventing RCIN by improving urine output and thereby preventing crystallization of dye in the renal tubules. Although it is currently the standard of care, I.V. hydration has not been compared to usual preprocedure fasting in a randomized controlled trial. However, its superiority over forced diuresis with furosemide or mannitol was established in a randomized-controlled trial by Solomon et al who reported an 11% incidence of RCIN in saline-treated patients (0.45% NaCl solution 12 hours pre- and post-contrast exposure), versus 28% in saline and mannitol-treated patients, and 40% in saline- and furosemide-treated patients.[40] A recent study using oral pre-hydration prior to contrast exposure followed by I.V. hydration with 0.45% NaCl solution for 6 hours after angiography showed no difference in the incidence of RCIN.[41]

Reducing osmotic injury

Contrast media contain iodine atoms that provide opacification. Nephrotoxicity is thought to be related to the number of dissolved particles in solution. Higher osmolarity of the media induces a greater osmotic diuresis and increases distal sodium delivery, which in turn increases medullary work and oxygen demand, leading to hypoxia. Therefore, the ideal contrast agent has a high iodine atom-to-dissolved particle ratio; this is achieved with non-ionic LOCM and iso-osmolar contrast media. In a meta-analysis of 25 trials, Barrett et al examined the incidence of RCIN in patients receiving LOCM versus HOCM.[42] The odds ratio of a rise in sCr to >44 µmol/L with LOCM was 0.61, suggesting that it was superior to HOCM. Rudnick et al also demonstrated an increased incidence of RCIN in patients exposed to HOCM versus LOCM.[3]

In a recently published randomized-controlled trial by Aspelin et al, 129 patients with moderate-to-severe renal insufficiency and diabetes mellitus undergoing coronary or aortofemoral angiography were randomized to either the LOCM *iohexol* or the iso-osmolar contrast agent *iodixanol.*[43] Those receiving *iodixanol* had a significantly lower increase in sCr at 72 hours post-contrast exposure and a significantly lower incidence of RCIN defined by an increase in peak sCr to >44 µmol/L (17 in the *iohexol* group versus 2 in the *iodixanol* group). Therefore, LOCM and iso-osmolar contrast media with the highest iodine atom-to-dissolved particle ratio should be used in patients with pre-existing renal insufficiency. Ionic contrast media are best avoided and the dose of contrast media should be limited to <2 mL/kg in these patients, and, if available, iso-osmolar agents should be considered.

Contrast elimination – hemodialysis

Lehnert et al studied the role of prophylactic hemodialysis following contrast exposure as a rapid and efficient method

of removing contrast media.[44] Thirty patients with moderate-to-severe renal insufficiency were randomized to receive either hemodialysis or conservative therapy after contrast exposure. The overall incidence of RCIN in this high-risk group was 47% with no difference between the 2 groups. Despite initial enthusiasm, contrast elimination with hemodialysis is currently not recommended.

N-acetylcysteine

The nephrotoxic effects of radiocontrast agents may be mediated, at least in part, by reactive oxygen species. This is supported by animal studies revealing that oxygen-derived free radical (OFR) production increases following exposure to radiocontrast media[45] and that administration of allopurinol and superoxide dismutase (agents that decrease OFR levels) results in preservation of GFR.[12] Animal studies have also shown that dehydration increases renal susceptibility to OFR species.[46]

Because of its antioxidant properties, there has been considerable recent interest in the use of the oxygen-free radical scavenger N-acetylcysteine (NAC) as a prophylactic agent in patients at risk for RCIN. In addition to its role as an antioxidant, NAC is a potent vasodilator that increases expression of nitric oxide synthase (NOS).[47] Unfortunately, results from numerous trials of NAC in the prevention of RCIN have been inconsistent and difficult to interpret due to differences in patient demographics and design.

Tepel et al published the first major trial of NAC in the prevention of RCIN; 83 patients with moderate renal insufficiency (baseline sCr 211 µmol/L) were randomized to saline hydration (1 mL/kg/h of 0.45% NaCl solution for 12 hours pre- and post-procedure) versus saline hydration and NAC (600 mg twice daily on the day before and on the day of the procedure).[48] Patients received approximately 75 mL of a non-ionic low-osmolar dye during contrast-enhanced computed tomography. The incidence of RCIN (increase of 44 µmol/L in sCr at 48 hours) was significantly lower in the NAC group (2%) versus controls (21%). There were, however, a number of concerns. Despite the low dose of contrast, the control group had an incidence of RCIN of 21%, raising the possibility of a Type I error, whereby the authors may have demonstrated a difference in study groups that did not represent a true drug effect. Alternatively, it has been suggested that NAC is only effective in preventing RCIN in patients who are well-hydrated and exposed to low volumes of contrast (<100 mL), considerably lower than what would usually be encountered during PCI. Further criticisms relate to the timing and frequency with which NAC was administered. As a drug with a half-life of 2.7 hours (6.25 hours for its major metabolite), it is unclear why it was administered on a b.i.d. schedule on the day prior to contrast exposure. Regardless, Tepel demonstrated a sizeable reduction in the incidence of RCIN in NAC-treated patients and set the stage for numerous follow-up studies.

In contrast to the study by Tepel, with volumes of contrast, Diaz-Sandoval et al[49] subsequently published a randomized, double-blind, placebo-controlled trial of NAC versus saline hydration in patients exposed to higher doses of non-ionic LOCM (mean volume186 mL) during coronary angiography (the APART Study). Fifty-four patients with mild-to-moderate renal insufficiency (mean sCr 140 µmol/L) were randomized to receive saline (1 mL/kg/h of 0.45% NaCl solution for 2-12 hours before and 12 hours post-procedure) versus saline and NAC. The incidence of RCIN (increase in sCr of >44 µmol/L at 48 hours) was 8% in the NAC group versus 45% in the saline control group. Again, the incidence of RCIN in the control group was considerably higher than previously reported and, in this case, presumed secondary to inadequate pre-hydration. In fact, there were no data on the exact duration and volume of pre-hydration administered to the 2 groups. Given the particularly high doses of contrast used, differences in pre-hydration in the 2 groups may have accounted for the significant difference in event rates and for the unusually high event rate in the control group.

The benefit of NAC over saline hydration alone was also demonstrated by Shyu et al in a randomized placebo-controlled trial of 121 patients with moderate to severe renal insufficiency (mean sCr 246 µmol/L) undergoing coronary angiography or PCI.[50] A lower dose of NAC was administered on the same schedule (400 mg) as Tepel. The incidence of RCIN was 3.3% in NAC-treated patients versus 24.6 % in controls following moderate volumes of contrast exposure (mean of 120 mL). In this case, the benefit of NAC over simple saline hydration was demonstrated in patients who received adequate pre-hydration and a moderate contrast challenge.

Interestingly, 3 subsequent trials failed to demonstrate NAC benefit over saline hydration alone.

- Durham et al randomized 79 patients with moderate renal insufficiency (mean sCr 200 µmol/L) to saline versus saline and NAC.[51] The major difference in this study was the dose and schedule of NAC. Patients received 1200 mg of NAC 1 hour before and 3 hours after coronary angiography. The saline hydration protocol, volume, and type of contrast agent were similar to Tepel.[48] There was no difference in the incidence of RCIN between the 2 groups (saline 24% versus saline plus NAC 26.3%).
- Briguori et al randomized 183 patients with mild-to-moderate renal insufficiency (mean sCr 132 µmol/L) to saline versus saline and NAC (saline hydration and NAC dosing same as Tepel).[52] There was no difference in the incidence of RCIN between groups (6.5% NAC versus 11.2% saline). However, in a subgroup of patients receiving lower doses of non-ionic LOCM (<140 mL), NAC-treated patients had a significantly lower incidence of RCIN. The results of this study, taken together with the results of Tepel et al, suggest that NAC may be protective when the volume of contrast administered is small, ie,<100 mL.
- A recent nonrandomized trial by Boccalandro et al also failed to show that NAC benefited patients exposed to moderate-to-high doses of contrast media.[53]

The largest randomized-controlled trial of oral NAC was recently published by Kay et al in Hong Kong.[54] They randomized 200 patients with mild-to-moderate renal insufficiency (median sCr 110 µmol/L; mean 24 hour sCr clearance of 46 mL/min) undergoing elective coronary angiography or PCI to saline versus saline and NAC (saline hydration and NAC dosing the same as in Tepel et al). All patients received non-ionic LOCM

Table 2: Recommendations for preventing RCIN

In all patients prior to coronary angiography and PCI

- Obtain a stable sCr concentration prior to contrast exposure (in elderly patients, estimate creatinine clearance using the Cockcroft-Gault formula)
- Avoid contrast agents in volume-depleted patients
- Avoid prolonged fluid deprivation prior to procedure
- Discontinue potentially harmful medications:
  - Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Metformin
  - Diuretics and ACE inhibitors (unclear)

In patients with normal renal function with and without diabetes mellitus (DM)

- These patients are low risk and do not require further preparation or treatment

In patients with mild-to-moderate chronic renal insufficiency with/without DM

- **Elective**
  - Ideally, avoid day-case investigation
  - Provide I.V. saline hydration unless contra-indicated, either 0.45% or 0.9% NaCl solution at a rate of 1 mL/kg/h for 12 hours prior to procedure and at least 6 hours following procedure
  - Use non-ionic low-osmolar or iso-osmolar contrast media (preferred)
  - Limit volume of contrast media used
  - Fenoldopam – currently insufficient data to support its use (not available in Canada)
  - Oral N-acetylcysteine – standard dosing (Tepel et al[48]) – safe, inexpensive, balance of data suggest benefit in reducing RCIN.
- **Urgent or emergent**
  - Manage the same as elective cases except for rapid pre-hydration if not contraindicated – minimum 500 cc saline pre-procedure and 1L post-procedure over 12 h
  - Rapid protocol of NAC and saline hydration (Baker[55]) – potential harmful effects may outweigh benefit
- **In patients with severe chronic renal insufficiency or ESRD on dialysis**
  - Management as in patients with mild-to-moderate renal impairment
  - No benefit with prophylactic HD
  - Contrast exposure may decrease residual renal function
  - Patients with ESRD – no studies support the need for adjustment of hemodialysis scheduled to prevent fluid overload and congestive heart failure
- **Agents that are not recommended**
  - Calcium channel blockers
  - Atrial natriuretic peptide
  - Theophylline
  - Endothelin receptor antagonists
  - Low-dose dopamine infusion
  - Forced diuresis with mannitol or furosemide

ESRD= end-stage renal disease; HD = hemodialysis

(mean volume 120 mL). The incidence of RCIN (increase in sCr >25% above baseline at 48 hours after contrast exposure) was significantly lower in NAC-treated patients (4%) compared to controls (12%). Treatment with NAC was also associated with a small, but significant decrease in length of hospitalization (3.4±0.9 days for NAC versus 3.9±2.0 days for controls).

The recently published RAPPID Study demonstrated that a rapid protocol of I.V. NAC and saline infusion was superior to standard saline hydration alone in preventing RCIN.[55] This study randomized 80 patients with mild-to-moderate renal insufficiency (sCr of 160 µmol/L) undergoing elective coronary angiography or PCI to saline (saline hydration was the same as in Tepel) versus 150 mg/kg I.V. NAC in 500 mL normal saline over 30 minutes prior to contrast administration followed by 50 mg/kg NAC in 500 mL of normal saline over 4 hours after angiography). The incidence of RCIN (defined as an increase in sCr by 52 µmol/L at 48 hours) was significantly lower in the NAC group (5% NAC; 21% saline control). Infusion of NAC was prematurely discontinued in 7% of patients due to nonserious adverse effects. In addition, 4 patients (2 in each group) undergoing elective procedures with no pre-existing evidence of heart failure developed acute pulmonary edema, a complication that was expected to be considerably higher in CAD patients at risk for RCIN who required urgent or emergent procedures, the population for whom this protocol was initially designed.

In summary, the balance of data suggests that NAC is beneficial in the prevention of RCIN. The incidence of RCIN, as defined in most studies, can be reduced with oral NAC in patients with chronic renal insufficiency undergoing elective coronary angiography and PCI, and the use of a rapid protocol for I.V. NAC and saline administration in patients undergoing urgent and emergent procedures. Although the study by Kay et al showed a small decrease in the length of hospitalization in NAC-treated patients, there is still no direct evidence that NAC results in decreased morbidity and mortality.[54] It is therefore unclear whether its effects extend beyond simply limiting minor exacerbations in sCr concentrations following radiocontrast exposure. In contrast to oral NAC, which has been shown to be safe, convenient, and inexpensive, the potential gains associated with use of the rapid protocol of hydration and I.V. NAC administration (outlined in the RAPPID study) in patients requiring urgent or emergent procedures may be outweighed by the potential harmful effects.

Management strategies for RCIN

Recommendations for managing patients with chronic renal insufficiency undergoing coronary angiography or PCI, including the use prophylactic interventions aimed at the prevention of RCIN, are summarized in Table 2.

References

1. D'Elia JA, Gleason RE, Alday M, et al. Nephrotoxicity from angiographic contrast material; a prospective study. *Am J Med* 1982;72:719-725.
2. McCullough P, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention. *Am J Med* 1997;103:368-375.
3. Rudnik MR, Griffiths SM, Barrett BJ, et al. Nephrotoxicity of ionic and non-ionic contrast media in 1196 patients: A randomized trial – the Iohexol Cooperative Study. *Kidney Int* 1995;47:254-261.
4. Soma VR, Cavusoglu E, Vidhun R, et al. Contrast-associated nephropathy. *Heart Disease* 2002;4:372-379.
5. Baker CSR. Prevention of radiocontrast-induced nephropathy. *Cathet Cardiovasc Intervent* 2003;57:532-538.
6. Saklayan MG, Gupta S, Suryaprasad A, Azmeh W. Incidence of atheroembolic renal failure after coronary angiography. A prospective study. *Angiology* 1997;48(7):609-613.
7. Davidson CJ, Hlatky M, Morris KG, et al. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization: A prospective trial. *Ann Intern Med* 1989;110:119-124.
8. Moore RD, Steinberg EP, Powe NR, et al. Nephrotoxicity of high-osmolarity vs low-osmolarity contrast media: randomized clinical trial. *Radiology* 1992; 182:649-655.
9. Barrett BJ, Parfrey PS, Vasasour HM, et al. Contrast nephropathy in patients with impaired renal function: high versus low osmolar media. *Kidney Int* 1992;41:1274-1279.

10. Russo D, Minutolo R, Cianciaruso B, et al. Early effects of contrast media on renal hemodynamics and tubular function in chronic renal failure. *J Am Soc Nephrol* 1995;6: 1451-1458.
11. Murphy SW, Barrett BJ, Parfrey PS. Contrast nephropathy. *J Am Soc Nephrol* 2000;11: 177-182.
12. Bakris GL, Lass N, Gaber AO. Radiocontrast medium-induced decline in renal function: a role for oxygen free radicals. *Am J Physiol* 1990;258:F115-120.
13. Baiga R, Ueda N, Walker PD, et al. Oxidant mechanisms in toxic acute renal failure. *Am J Kidney Dis* 1997;29:465-477.
14. Parvez Z, Ramamurthy S, Patel NB, et al. Enzyme markers of contrast media-induced renal failure. *Invest Radiol* 1990;25(Suppl 1):S133-S134.
15. Bakris GL, Burnett JC Jr. A role of calcium in radiocontrast-induced reduction in renal hemodynamics. *Kidney Int* 1985;27:465-468.
16. Russo D, Testa A, Volpe LD, et al. Randomized prospective study on renal effects of two different contrast-media in humans: Protective role of a calcium channel blocker. *Nephron* 1990;55:254-257.
17. Neumayer HH, Junge W, Kufner A, et al. Prevention of radiocontrast-media-induced nephrotoxicity by the calcium channel blocker nitrendipine: A prospective randomized clinical trial. *Nephrol Dial Transplant* 1989;4:1030-1036.
18. Khoury Z, Schlicht JR, Como J, et al. The effect of prophylactic nifedipine on renal function in patients administered contrast-media. *Pharmacotherapy* 1995;15:59-65.
19. Cacoub P, Deray G, Baumelou A, et al. No evidence for protective effects of nifedipine against radiocontrast-induced acute renal failure. *Clin Nephrol* 1998;29(4):215-216.
20. Weisburg LS, Kurnik PB, Kurnik BR. Dopamine and renal blood flow in radiocontrast-induced nephropathy in humans. *Ren Fail* 1993;15:61-68.
21. Weisberg LS, Kurnik PB, Kurnik BR. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. *Kidney International* 1994;45:259-265.
22. Kurnik BRC, Allgren RL, Genter FC, et al. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis* 1998;31:674-680.
23. Caldicott WJ, Hollenberg NK, Abrams HL. Characteristics of response of renal vascular bed to contrast media: evidence for vasoconstriction induced by renin-angiotensin system. *Invest Radiol* 1970;5:539-547.
24. Gupta RK, Kapoor A, Tewari S, et al. Captopril for the prevention of contrast-induced nephropathy in diabetic patients: a randomized study. *Ind Heart J* 1999;51: 521-526.
25. Arend LJ, Bakris GL, Burnett JC, Jr. Role of intrarenal adenosine in the renal hemodynamic response to contrast media. *J Lab Clin Med* 1987;110:406-411.
26. Erley CM, Duda SH, Schlepekow S, et al. Adenosine antagonist theophylline prevents reduction of glomerular filtration rate after contrast media application. *Kidney Int* 1994;45:1425-1431.
27. Katholi RE, Taylor GJ, McCann WP, et al. Nephrotoxicity from contrast media; attenuation with theophylline. *Radiology* 1995;195:17-22.
28. Erley, CM, Duda SH, Rehfuss D, et al. Prevention of radiocontrast-media-induced nephropathy in patients with pre-existing renal insufficiency by hydration in combination with the adenosine antagonist theophylline. *Nephrol Dial Transplant* 1999;14: 1146-1149.
29. Abizaid AS, Clark CE, Mintz GS, et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with pre-existing renal insufficiency. *Am J Cardiol* 1999;83:260-263.
30. Wang A, Bashore T, Holcslaw T, et al. Randomized prospective double-blind multicentre trial of an endothelin receptor antagonist in the prevention of contrast nephrotoxicity. *J Am Soc Nephrol* 1998;9:37A.
31. Kapoor A, Sinha N, Sharma RK, et al. Use of dopamine in prevention of contrast induced acute renal failure-a randomized study. *Int J Cardiol* 1996;53:233-236.
32. Hans SS, Hans BA, Dhillon R, et al. Effects of dopamine on renal function after arteriography in patients with pre-existing renal insufficiency. *Am Surg* 1998;64:432-436.
33. Elliott WJ, Weber RR, Nelson KS, et al. Renal and hemodynamic effects of intravenous fenoldopam versus nitroprusside in severe hypertension. *Circulation* 1990;81: 970-977.
34. Kien N, Moore P, Jaffe R, et al. Blood flow distribution during controlled hypotension induced by fenoldopam in anaesthetized dogs. *Anesth Analg* 1990;70:S203.
35. Bakris GL, Lass NA, Glock D. Renal hemodynamics in radiocontrast medium-induced renal dysfunction: a role for dopamine-1 receptors. *Kidney Int* 1999;56:206-210.
36. Hunter DW, Chamsuddin A, Bjarnason H, Kowalik K. Preventing contrast-induced nephropathy with fenoldopam. *Tech Vasc Interv Radiol* 2001;4:53-56.
37. Maydoon H, Croushore L, Weaver D, et al. Use of fenoldopam to prevent radiocontrast nephropathy in high-risk patients. *Catbet Cardiovasc Intervent* 2001;53:341-345.
38. Kini AS, Mitre CA, Kim M, et al. A protocol for prevention of radiographic contrast nephropathy during percutaneous coronary intervention: effect of selective dopamine receptor agonist fenoldopam. *Catbet Cardiovasc Intervent* 2002;55:169-173.
39. Tumlin JA, Wang A, Murray PT, et al. Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: A pilot trial in the prevention of contrast nephropathy. *Am Heart J* 2002;143:894-903.
40. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994;331:1416-1420.
41. Taylor AJ, Hotchkiss D, Morse RW, McCabe J. PREPARED: Preparation for Angiography in Renal Dysfunction. A randomized trial of inpatient versus outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. *Chest* 1998;114:1570-1574.
42. Barrett BJ, Carlisle EJ. Meta-analysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology* 1993;188:171-178.
43. Aspelin P, Aubry P, Fransson S, et al. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003;348:491-499.
44. Lehnert T, Keller E, Gondolf K, et al. Effect of haemodialysis after contrast medium administration in patients with renal insufficiency. *Nephrol Dial Transplant* 1998;13: 358-362.
45. Parvez Z, Rahman MA, Moncada R, et al. Contrast media-induced lipid peroxidation in the rat kidney. *Invest Radiol* 1989;24:697-702.
46. Yoshioka T, Fogo A, Beckman JK. Reduced activity of antioxidant enzymes underlies contrast media-induced renal injury in volume depletion. *Kidney Int* 1992;41:1008-1015.
47. Safirstein R, Andrade L, Vieira JM. Acetylcysteine and nephrotoxic effects of radiographic contrast agents – a new use for an old drug. *N Engl J Med* 2000;343;210-212.
48. Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* 2000;343: 180-184.
49. Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury. (the APART Trial). *Am J Cardiol* 2002;89:356-358.
50. Shyu KG, Chang JJ, Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. *J Am Coll Cardiol* 2002;40:1383-1388.
51. Durham JD, Caputo C, Dokko J, et al. Randomized-controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. *Kidney Int* 2002;62: 2202-2207.
52. Briguori C, Manganelli F, Scarpato P, et al. Acetylcysteine and contrast agent-associated nephrotoxicity. *J Am Coll Cardiol* 2002;40:298-303.
53. Boccalandro F, Amhad M, Smalling RW, et al. Oral acetylcysteine does not protect renal function from moderate to high doses of intravenous radiographic contrast. *Catbet Cardiovasc Intervent* 2003;58:336-341.
54. Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention. *JAMA* 2003;289(5):553-558.
55. Baker CSR, Wragg A, Kumar S, et al. A rapid protocol for the prevention of contrast-induced renal dysfunction: The RAPPID Study. *J Am Coll Cardiol* 2003;41:2114-2118.

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