Contrast-induced nephropathy: A cardiologist’s perspective

Hassan Ismail, MD MPH
Cardiology fellow

Contrast-induced nephropathy
CIN – Definition

• Absolute increase in serum creat of at least 0.5 mg/dL

OR

• Relative increase of at least 25% from baseline

CIN – 2 key points

• No current treatment can reverse or ameliorate contrast-induced nephropathy once it occurs, but prophylaxis is possible

• Many preventive measures have failed to show benefits in well-designed randomized trials

CIN – Burden of the problem

• Common cause of hospital acquired acute renal failure

• Its incidence is low in patients with normal renal function at baseline but much higher in patients with baseline renal insufficiency
CIN - Burden of the problem

- Patients undergoing PCI procedures have a higher mortality rate if nephropathy develops. The risk is even higher if dialysis is required.
- McCullough et al. found the risk of in-hospital mortality was 1.1% compared with 7.1% for those with nephropathy and 35.7% for those with nephropathy requiring dialysis.

(Am J Med 1997; 103:368-375)

- About 1,500,000 diagnostic LHC and 500,000 PCI procedures are performed annually in the US.

Historic perspective and types of contrast media
Historic perspective and types of contrast media

Ionic, high-osmolar agents

• The earliest contrast agents (containing sodium atom that dissociates from the molecule in aqueous solution) - Two active molecules are required to deliver 3 iodine atoms – extremely high osmolality 2,000 mOsm/L
  • Monomers
  • Predominant agents until the 1980's
  • Iothalamate, Diatrizoate, Mitrizoate

Nonionic or ionic, low-osmolar agents

• Introduced in the 1980's
  • The predominant contrast agents being used –
  • Monomers – requiring only one osmotically active particle to produce 3 iodine particles – osmolality is about 600-900 mOsm/L - Iohexol
  • Dimers – 2 benzene ring – osmolality of 600 mOsm/L - Ioxaglate and Hixabrix

Historic perspective and types of contrast media

Nonionic, iso-osmolar agents

• The newest contrast agent
  • Nonionic dimer
  • Low osmolality at # 300 mOsm/L
  • Iodixanol

Risk factors for CIN

• Pre-existing renal insufficiency
• Diabetes mellitus
• Volume of contrast media
Pre-existing renal insufficiency

- The single greatest risk factor
- Sixty percent of CIN have preexisting renal insufficiency
- The more severe the renal insufficiency the greater the risk for CIN
- An approximate estimation or percent risk of CIN is calculated by multiplying the serum creatinine concentration by 10

Diabetes mellitus

- The risk is related to coexisting renal insufficiency
- Patients with diabetes and normal renal function have similar risk of CIN to those with no diabetes
- Patients with renal insufficiency and diabetes have a greater risk for CIN than patients with the same level of renal insufficiency with no diabetes

Volume of contrast media

- Studies have shown correlation between the volume of contrast media and the risk of CIN
- Cigarroa et al used a predetermined formula based on body weight and baseline renal function to limit the volume of contrast media in patients undergoing coronary angiography:
  - 3 ml of contrast/kg of body weight to a maximum of 300 ml divided by serum creatinine
- Nephropathy developed in 21% of patients with contrast volume exceeding the formula amount compared with 2% of patients with contrast within the formula amount

Pathophysiology of CIN

- Renal ischemia
- Direct toxicity to tubular epithelial cells
Pathophysiology of CIN - Renal ischemia

- Renal flow increases transiently then decreases over a longer time
- Pathologic ischemic changes: necrosis of the medullary thick ascending limbs, tubular collapse and casts
- Decrease in medullary oxygenation measured with oxygen microelectrodes: active transport of sodium in the ascending limb of Henle is increased, endothelin is increased, and blockade of vasodilatory compounds such as NO and PG


J Clin Invest 1988; 82:401-412

Pathophysiology of CIN Vasoconstriction

- Vasoconstriction mediate hypoxic injury and enhance CIN: adrenergic stimulation and RAAS don’t seem to be involved in CIN. PG with vasodilatory properties may counter the vasoconstriction induced by contrast media since treatment with indomethacin is necessary to induce experimental CIN

Kidney Int 2000; 57:1675-1680

Pathophysiology of CIN Endothelin

- Potent renal vasoconstrictor
- Multiple experimental observations suggest that it may play a role in CIN
- Clinical trial: Patients with CRF undergoing LHC were randomized to receive endothelin receptor antagonist SB290670 or placebo - CIN was more common in the treatment group 56% vs. 29% (P=0.002)

Semin Nephrol 1997; 17:15-26

Kidney Int 2000; 57:1675-1680

Pathophysiology of CIN Adenosine

- Adenosine causes vasodilatation in the efferent arterioles and medullary capillaries and vasoconstriction in the afferent arterioles leading to decreased renal blood flow
- Theophylline inhibits contrast media induced vasoconstriction and decreased GFR

Pathophysiology of CIN
Role of osmolality
- Hypertonic solutions reduce glomerular filtration rate and renal blood flow
- Hyperosmolality activates tubuloglomerular feedback and increases tubular hydrostatic pressure leading to decrease in glomerular filtration
- Osmotic diuresis result in increased active transport of sodium in the thick ascending limb and in vasoconstriction leading to worsened medullary hypoxemia

Pathophysiology of CIN
Reactive oxygen species
- Post ischemic oxidative stress leads to formation of oxygen-free radicals which may lead to apoptotic cell injury
- Adenosine role in CIN may be related to increased generation of oxygen-free radicals
- N-acetylcysteine and sodium bicarbonate

Pathophysiology of CIN
Direct cellular toxicity
- Direct toxicity to renal cells
- Proximal cell vacuolization, interstitial inflammation, cellular necrosis, enzymuria
- Markers of cellular injury- potentiated with hypoxia and are more pronounced with high-osmolar agents than with low-osmolar agents

Preventive measures
- Many tried, few succeeded
Preventive measures

Hydration

- Reduces the activity of RAS
- Reduces the levels of other vasoconstrictive hormones such as endothelin
- Increases sodium diuresis
- Decreases tubuloglomerular feedback
- Prevent tubular obstruction
- Protect against reactive oxygen species
- Dilute contrast media in the tubules

Does Mannitol or Furosemide help?

- Seventy-eight patients with chronic renal insufficiency -- mean SCR 2.1 -- undergoing cardiac angiography
- Randomly assigned to receive 0.45% saline alone for 12 hours before and 12 hours after angiography, saline plus mannitol, or saline plus furosemide
- Among the 28 patients in the saline group, 3 (11%) had such an increase in serum creatinine as compared with 7 of 25 (28%) in the mannitol group and 10 of 25 (40%) in the furosemide group (P = 0.05)

In patients with chronic renal insufficiency who are undergoing cardiac angiography, hydration with 0.45 percent saline provides better protection against acute decreases in renal function than does hydration with 0.45 percent saline plus mannitol or furosemide.

CIN- Hydration – What regimen?

Oral vs. IV fluids

- Prospective study randomized patients undergoing coronary angiography to receive IV saline for 12 hours before and after catheterization or oral fluid only
- CIN occurred in 34.6% of those who received oral fluid only and 3.7% of those who received IV saline

Nephron Clin Pract 2003; 93:C29-34

CIN- Hydration – What regimen?

- Preparation for angiography in Renal Dysfunction (PREPARED) trial
- Patients with CRF undergoing coronary angiography
- Hydration on an outpatient basis coupled with brief period of IV hydration is equivalent to overnight IV hydration

Chest 1998; 114:1570-1574
CIN - Hydration - What regimen?

- Randomized patients undergoing CT studies or angiography to receive 2000 ml of IVF over 24 hours or 300 ml during the procedure
- GFR rate fell by 34.6 ml/minute in the bolus infusion group compared with a 18.3 ml/minute fall in the continuous infusion group (P<0.05)

Clin Nephrol 2004; 62:1--77

- The Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE)
- The incidence of CIN in patients with urine flow > 150 ml/hr was 21.6% vs. 45.9% in those with lower urine flow rate (P=0.03). But patients undergoing forced diuresis revealed no improved risk of CIN

J Am Coll Cardiol 1999; 33:403--411

CIN - Hydration - What regimen?

- Randomized trial compared the use of isotonic (0.9%) saline in 685 patients with half-isotonic (0.45%) saline in 698 patients
- The incidence of CIN was significantly lower in the isotonic saline group (0.7%) than with half-isotonic saline (2%) P=0.04

Arch Intern Med 2002; 162:329-336
Preventive measures
N-acetylcysteine – Tepel et al, 2000

- Animal studies
- Potential mechanisms
- Study of 83 patients with CRF (serum creat > 1.2 or creat cl < 50) - 32.5% with diabetic nephropathy
- CT with contrast
- All received 24 hour 0.45% saline – randomized to N-acetylcysteine 600 mg bid one day before and the day of the procedure or placebo
- CIN occurred in 2% in the N-acetylcysteine group compared with 21% in the placebo group (P=0.01)


Preventive measures
N-acetylcysteine – Durham et al, 2002

- Study of 79 patients with CRF (serum creat > 1.7)
- Cardiac angiography with or without PCI
- All received IVF – randomized to N-acetylcysteine 1200 mg po one hour before angiography and a second dose 3 hours after the procedure or placebo
- No sig difference in the rate of renal failure in the 2 groups, N-acetylcysteine group 10 of 38 (26.3%) compared with 9 of 41 (22%) in the placebo group (P=NS)

Kidney Int 2002; 62:2202-2207

Preventive measures
N-acetylcysteine – Diaz-Sandoval et al, 2002

- Study of 54 patients with CRF (serum creat > 1.4 or CrCl < 50)
- Cardiac angiography
- All received 0.45% saline – randomized to N-acetylcysteine 600 mg po bid the day before and the day of procedure or placebo
- CIN occurred in 45% of the control group compared with 8% of the N-acetylcysteine group (P= 0.005)

Am J Cardiol 2002; 89:356-358
Preventive measures
N-acetylcysteine – Shyu et al, 2002

- Study of 200 patients with CRF (Scr > 2 or CrCl < 40)
- Cardiac angiography
- All received 0.45% saline – randomized in single blind fashion to N-acetylcysteine 400 mg po bid for 2 days or placebo
- CIN occurred in 24.6% of the control group compared with 3.3% of the N-acetylcysteine group (P < 0.001)

J Am J Cardiol 2002; 40:1383–1388

Preventive measures
N-acetylcysteine – Kay et al, 2003

- Study of 200 patients with CRF (CrCl < 60)
- Cardiac angiography
- All received 0.9% saline – randomized to N-acetylcysteine 600 mg po bid the day before and the day of procedure or placebo
- CIN (25% increase in Scr) occurred in 12% of the control group compared with 4% of the N-acetylcysteine group (P= 0.03)
- Benefit was greater in diabetics

JAMA 2003; 289:553–558
Preventive measures
N-acetylcysteine – Baker et al., 2003

- Study of 80 patients with CRF (Scr > 2 or CrCl < 40)
- Cardiac angiography
- Randomized to IV hydration with or without IV
  acetylcysteine – IV acetylcysteine was given at a dose of 150 mg/kg in 500 ml of NS over 30
  minutes before the procedure and 50 mg/kg in 500 ml over 4 hours after the procedure
- CIN occurred in 21% of the control group compared with 5% of the N-acetylcysteine group
  ($P=0.045$)

J Am J Cardiol 2003; 41:2114-2118

Preventive measures
N-acetylcysteine – Allaqaband et al., 2002

- Study of 123 patients with CRF (Scr > 1.6 or CrCl < 60)
- Cardiac angiography
- Unblinded study
- Randomized to IV hydration alone, fenoldapam + IV
  hydration, or N-acetylcysteine + IV hydration –
- N-acetylcysteine was given at 600 mg po bid the day before and the day of procedure
- There was no sig difference in CIN among the 3 groups
  15.3%, 15.7%, 17.7% ($P=0.919$)

Catheter Cardiovasc Interv 2002; 57:279-283
Preventive measures
N-acetylcysteine – Briguori et al, 2002

- Study of 183 patients with CRF (Scr > 1.2 or CrCl < 70)
- Cardiac or peripheral angiography
- No placebo
- All received IV hydration - randomized to N-acetylcysteine 600 mg po bid the day before and the day of procedure or IV hydration alone.
- There was no sig difference in CIN (>25% increase in Scr 48hrs after procedure) among the 2 groups 11%, 6.5% (P=0.22)


Preventive measures
N-acetylcysteine – Vallero et al, 2002

- Study of 100 consecutive patients with CRF (Scr > 1.2)
- Cardiac angiography
- All received IV hydration - randomized to N-acetylcysteine 600 mg po bid the day before and the day of procedure or placebo.
- There was no sig difference in CIN among the 2 groups 0 patients, 2 patients (P=NS)

Ital Nefrol 2002; 19:529-533

Preventive measures
N-acetylcysteine – Boccalandro et al, 2003

- Study of 73 patients consecutive patients with CRF (Scr > 1.2 or CrCl < 50)
- Cardiac angiography
- No placebo
- All received IV hydration - randomized to N-acetylcysteine 600 mg po bid the day before the day of procedure or IV hydration alone.
- There was no sig difference in CIN among the 2 groups 12%, 13% (P=0.84)

Catheter Cardiovasc Interv 2003; 58:336-341
Preventive measures
N-acetylcysteine – Goldenberg et al, 2003

- Study of 80 patients with CRF (Scr > 1.5)
- Cardiac angiography
- All received 0.45% saline – randomized to N-acetylcysteine 600 mg po bid for 2 days or placebo
- There was no sig difference in CIN among the 2 groups 3/39, 4/41 (P=NS)

J Am Coll Cardiol 2002; 41: 537A

Preventive measures
N-acetylcysteine – Loutriakis et al, 2003

- Study of 47 patients with CRF (Scr > 1.5)
- Cardiac angiography
- All received IV hydration – randomized to N-acetylcysteine 600 mg po bid the day before and the day of procedure or placebo
- There was no sig difference in CIN (increase in Scr by 0.5 or 25%) among the 2 groups 13.1%, 25% (P=NS)

J Am Coll Card 2003; 146:E23

Preventive measures
N-acetylcysteine – Oldemeyer et al, 2003

- Study of 96 patients with CRF (Ccr < 50)
- Cardiac angiography
- All received 0.45% for 12 hours before and after procedure – randomized to N-acetylcysteine 1500 mg po q 12 hrs for 4 doses or placebo
- There was no sig difference in CIN (increase in Scr by 0.5 or 25%) among the 2 groups 6.4%, 8.2% (P=0.74)

Am J Heart 2003; 146:E23
Preventive measures

N-acetylcysteine – negative studies

- Meta-analysis of 20 studies involving 2,195 patients – RR of CIN was 0.73 (95% confidence interval 0.52-1.0; P=0.08)
- Meta-analysis of 15 studies involving 1,776 patients – RR of CIN was 0.65 (95% confidence interval 0.43-1.0)

One more positive study

- 354 undergoing primary angioplasty for acute MI
- Placebo, 600 bolus IV followed by 600 po bid for 4 days, or 1200 bolus IV followed by 1200 po bid for 4 days
- Marked dose dependent reduction in CIN, 35% in control compared with 15% (standard dose), and 8% (high dose) 
P<0.0001


Author | N | % Placebo | Criteria RF | Dosing | Procedure | Country
--- | --- | --- | --- | --- | --- | ---
Baker | 90 | 21 | 2.0/40 | IV | LHC + PCI | UK
Diaz | 54 | 45 | 1.4/50 | TP | LHC + PCI | US
Kay | 200 | 12.2 | 2.0/40 | TP | LHC + PCI | China
Shih | 121 | 24.6 | 2.0/40 | 400 bid x 2d | LHC + PCI | Taiwan
Total | 93 | 21.4 | 1.2/50 | TP | CT | Germany

Studies

- Allaqaband 85 15 >1.6/60 TP LHC + PCI | US
- Boccalandro 179 12.3 >1.2/50 TP LHC + PCI | US
- Briguori 183 11 >1.2/70 TP LHC + PCI | Italy
- Durham 79 22 >1.7 1200 bid x 1d TP LHC + PCI | US
- Goldenberg 80 7.7 >1.5 600 bid x 2d LHC + PCI | US
- Loutrialis 47 13 >1.5 TP LHC + PCI | US
- Loutrialis 96 6.4 <50 1500 bid x 2d LHC + PCI | US
- Valero 20 0 >1.2 TP LHC + PCI | Italy

Preventive measures

Theophylline

- Adenosine antagonist
- Erley et al randomized 39 patients receiving contrast media to IV theophylline or placebo – GFR dropped from 88 to 75 4 hours after contrast administration in the placebo group but remained unchanged in the theophylline group
- Other several small studies revealed theophylline given orally or intravenously prevented the decline in Ccl but – Studies included low risk patients and CIN was not observed in any groups
- Small number in the studies
- Theophylline is not recommended for standard prophylaxis against CIN

Kidney Int 1994; 45:1425-1431
Preventive measures
Low-osmolar vs. high-osmolar

- Animal studies
- Clinical studies revealed no difference in the risk for CIN when dealing with average risk population
- A large prospective randomized DB study of 1,196 (509 azotemic, 213 diabetics & 483 average risk patients)
  - No difference in average risk patients
  - No difference in diabetics with NL renal fx
  - Small difference in renal failure non-diabetic pts, 4% vs. 7%
  - More pronounced difference in renal failure patients with diabetes, 12% vs. 27%
- Subsequent meta-analysis revealed that low-osmolar agents reduced CIN by 50%  
  Kidney Int 1995; 47:254-261

Preventive measures
Low-osmolar vs. iso-osmolar

- Animal studies
- Small randomized DB study from UK of 124 with renal impairment (30% diabetics) patients revealed ioxaglate was less than half as nephrotoxic as iohexol
- NEPHRIC trial: Small prospective randomized DB multicenter trial of 129 patients with azotemia and diabetes revealed – iso-osmolar agent led to lower incidence of CIN 3% vs. 26% (P=0.002)  
  Br J Radiol 1999; 72:701-703

Other CM CV complications
High vs. low osmolar non-ionic

- Compared with high osmolar ionic contrast agents, low osmolar nonionic contrast agents have revealed decreased incidence of major complications associated with diagnostic cardiac catheterization

Other CM CV complications
Ionic vs. nonionic

- A nonionic LOCM (Omnipaque) caused profound platelet degranulation in nearly 80% of platelets compared with 2 to 3% of platelets in the control. Conversely, an ionic HOCM (Urografin) caused only 25% degranulation, whereas an ionic LOCM (Hexabrix) caused no platelet activation
- Blood from patients anticoagulated with heparin and pretreated with standard-dose aspirin in preparation for PTCA showed the same pattern of contrast media-induced platelet activation as normal subjects

Invest Radiol, 1989; 24: 379-374
Cardiology, 1989; 5:6-10
Circulation, 1989; 80(pt 1):3035-3044
Thrombotic events occurred in 15 patients (0.18%). Coronary thrombus or embolus were defined as coronary embolus, coronary occlusion, transient ischemic attack, or stroke occurring at the time of catheterization. Hemofiltration was randomized controlled single center trial of 114 patients, randomized to hemofiltration. Several studies have failed to demonstrate the effectiveness in HD in reducing CIN risk. Six hours of HD removes 60–90% of contrast medium. Although the clinical thrombotic events associated with nonionic contrast have an unusual temporal clustering and may result in major complications, the overall incidence (0.18%) of these thrombotic complications with nonionic contrast agents is quite similar to that reported with ionic contrast media.

Other CM CV complications

**Ionic vs. nonionic**
- Cardiovascular complications, especially thrombotic events, were prospectively evaluated in 8,537 consecutive patients undergoing diagnostic cardiac catheterization with either iopamidol (n = 6,293) or iohexol (n = 2,224).
- Thrombotic events were defined as coronary embolus, coronary occlusion, transient ischemic attack, or stroke occurring at the time of catheterization.
- Thrombotic events occurred in 15 patients (0.18%). Coronary thrombus or embolus occurred in 7 patients, a thromboembolus from the ventricular catheter occurred in 1 patient, and transient ischemic attack or stroke occurred in 7 patients. Six of 15 patients with thrombotic events were premedicated with heparin.
- Although the clinical thrombotic events associated with nonionic contrast have an unusual temporal clustering and may result in major complications, the overall incidence (0.18%) of these thrombotic complications with nonionic contrast agents is quite similar to that reported with ionic contrast media.

**Sodium bicarbonate lowered the risk of CIN 1.7% vs. 13.6% (P=0.02),**

**Mortality was lower in the hemofiltration group 2% vs. 14% (P=0.02).**

**Comparing iodixanol (n=405) with ioxaglate (n=410)**

**Primary end point MACE- 5.4% vs. 9.5% P=0.027.**

**Preventive measures**

**Hemodialysis vs. hemofiltration**
- 2-3 hours of HD removes 60-90% of contrast medium.
- Sodium bicarbonate lowered the risk of CIN 1.7% vs. 13.6% (P=0.02).
- The infusion rate was 3 ml/kg/hr for 1 hr before procedure, followed by 1 ml/kg/hr during the procedure and continued for 6 hrs afterwards.
- Sodium bicarbonate lowered the risk of CIN 1.7% vs. 13.6% (P=0.02).

**Preventive measures**

**Sodium bicarbonate**
- Reducing the formation of oxygen free radicals.
- Merten et al. randomized controlled single center trial comparing hydration with sodium bicarbonate vs. sodium chloride in 119 azotemic patients receiving low-osmolar contrast medium.
- Both infusions contained 154 meq in 1 L of 5% dextrose and water.
- The infusion rate was 3 ml/kg/hr for 1 hr before procedure, followed by 1 ml/kg/hr during the procedure and continued for 6 hrs afterwards.
- Sodium bicarbonate lowered the risk of CIN 1.7% vs. 13.6% (P=0.02).
Preventive measures

Sodium bicarbonate

- 502 patients undergoing coronary angiography with or without angioplasty with renal insufficiency randomized to sodium bicarbonate infusion vs saline alone. All patients received NAC and iso-osmolar CM
- There was no difference in the 2 groups in the risk of CIN


Recommendations

Strategies that do not work

- Mannitol
- Furosemide
- Dopamine
- Atrial natriuretic factor
- Fenoldopam
- Prostaglandin

Strategies that may work

- N-acetylcysteine
- Sodium bicarbonate
- Furosemide
- Dopamine
- Hemofiltration
- Prostaglandin
- Theophylline
- CCB

Currently recommended strategies

- Parenteral hydration
- Minimize contrast volume
- Low or iso-osmolar contrast
- Adequate time between contrast studies
- Avoid NSAID

Take home message

- The risk of CIN is directly proportional to the severity of preexisting renal insufficiency
- Hydration with normal saline is the most effective preventive intervention
- N-acetylcysteine may be effective in high-risk diabetic patients
- Sodium bicarbonate may be of value but may not provide more benefit beyond N-acetylcysteine
- Contrast agents that are nonionic and of lower osmolality are less nephrotoxic but can still cause nephropathy
- There is evidence that ionic LOCM compared with nonionic LOCM render platelet activation in patients undergoing angiography
- Due to high cost and logistical effort associated with hemofiltration, larger randomized trials should be performed before it could be recommended for high-risk patients
- Theophylline is not recommended as standard prophylaxis against CIN

Remember...

Mortality from CIN requiring HD > Mortality from acute MI with no revascularization