The pathophysiology of contrast medium induced nephropathy

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Background

- Contrast medium-induced nephrotoxicity (CIN) still remains one of the most clinically important complications following the use of iodine contrast media.
Why?

Is CIN a clinical problem in spite of the use of less toxic contrast media?
Increased use of contrast media

- Higher volumes and concentrations to sicker patients
- Increased use of CT and interventional vascular techniques
Reasons for Concern

• With 60 million CM doses/yr, even a low incidence of CM complications affects a large number of patients

• Patients exposed to CM are increasingly elderly, with multiple co-morbidities that increase their risk

• The most common form of CM-induced injury, contrast-induced nephropathy (CIN) can have serious renal and nonrenal consequences
CIN Consensus Panel Statement

CIN is a common and potentially serious complication following the administration of CM in patients at risk for acute renal injury.
Before *intravenous administration* of an iodinated agent...all patients should be questioned about potential renal dysfunction at the time of referral....
How to avoid ..........

“Luck favours a prepared mind”

Louis Pasteur
How do you prepare your mind

• What is CIN
• Is CIN dangerous
• Who is the risk patient
• What is the pathophysiology of CIN
How do you prepare your mind

• What is CIN
Contrast-Induced Nephropathy (CIN)

Definition

• New onset or exacerbation of renal dysfunction after contrast administration without other identifiable causes:

  Increase by >25%

  or

  Absolute $\uparrow$ of $>0.5$ mg/dL or $\geq 44.2$ μmol/L


Occurs 24–48 hours post contrast exposure, with creatinine peaking 5–7 days later and normalizing within 7–10 days in most cases.
CIN is replaced by CM-AKI

• Contrast Medium Induced Acute Kidney Injury
Clinical & cellular phases of ARF

How do you prepare your mind

• What is CIN
• Is CIN dangerous
• Who is the risk patient
• How do I manage the risk
Contrast-induced nephropathy

- What does a rise in serum creatinine >0.5mg/dL (>44µmol/L) within 48 hours mean?
- ... a reasonable surrogate for more relevant outcomes such as need for dialysis, increased length of hospitalization.
- ... a marker for outcome (1-year mortality).
Incidence of CIN

- Third most common cause of hospital-acquired renal failure
- Occurs in less than 1% of general population
- Occurs in 5.5 – 12 % of patients with renal insufficiency
- But, occurs in 50% of patients with both renal insufficiency and diabetes mellitus

## Review of Death Certificates (1999)

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure or nephropathy</td>
<td>58</td>
</tr>
<tr>
<td>Anaphylactic shock and allergic reactions</td>
<td>19</td>
</tr>
<tr>
<td>Cardiopulmonary arrest</td>
<td>10</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>8</td>
</tr>
<tr>
<td>Stroke and cerebral hypoxia</td>
<td>4</td>
</tr>
</tbody>
</table>

- 48 certificates collected, 46 did not state the CM name
- 60% women
- Median age 73 y
- Variety of contributing conditions mentioned

_Wysowski DK, Nourjah P. AJR. 2006 Mar;186(3):61_
Kaplan Meier 1-year Survival Rates Following CIN

% Event-free Survival

Cumulative 1-year Mortality
CIN: 37.7%
No CIN: 19.4%
P=0.001

The Pathophysiology of CIN
Pharmacokinetics

• Distributes extracellular space
• Insignificant metabolization
• Half-life 2 hours
• Excreted by glomerular filtration
• No tubular reabsorption
• 98% excreted within 24 hours
• Ecretion: bile, sweat, saliva, tears


Nephrotoxicity of contrast media

• Plausible causes

  – Vascular effect - Cytotoxic effect

• Osmotoxicity
• Chemotoxicity
• Viscosity toxicity
• Ion toxicity
Pathophysiology

• Hemodynamic effects

• Toxic tubular damage

• Formation of reactive oxygen species (ROS)

Site for action for CIN

- General – vascular?
- Local (kidney)
  - vascular, direct cell toxicity
  - blocking of distal tubules
  - ?

NOT ONE SINGLE CAUSE
Figure 1: Proposed Pathophysiological Mechanisms

PRE-RENAL
- Intravascular volume
- Hypotension
- Diabetes
- Uric acid
- Ca^{2+}
- Cholesterol
- Contrast agent
- Nephrotoxic drugs
- Hypertension
- Sepsis

-RENAL
- Adenosine
- Endothelin
- Vasoconstriction
- NO
- Prostaglandins
- Vasodilatation
- Interstitial Pressure

RENAL BLOOD FLOW

DIRECT TUBULAR TOXICITY

MEDULLARY HYPOXIA

TUBULAR OBSTRUCTION

O_2 CONSUMPTION

CONTRAST-INDUCED NEPHROPATHY

Gleeson, AJR
Primary prevention

• Select the least nephrotoxic CM
  – What types of CM are there?
Nephrotoxicity of contrast media

• Plausible causes
  
  – Vascular effect
  
  • Cytotoxic effect

• Osmotoxicity
• Chemotoxicity
• Viscosity toxicity
• Ion toxicity
CM Classification 300-400 mg I/ml

Osmolarity (mOsm/kg H₂O)

Ionicity

Name

# Benz. rings

Viscosity at 37°C (cP)

Diatrizoate
Iothalamate
≈4.0-9.0

Iodixanol

Iotrolate

Dimer


CM Osmolality

HOCM, high-osmolar CM; LOCM, low-osmolar CM; IOCM, isosmolar CM
• Is there a difference between low-osmolar and high-osmolar CM

• Is there a difference between iso-osmolar and low-osmolar CM

• Is there a difference between low-osmolar CM with regard to nephrotoxicity
Pathophysiology

- Hemodynamic effects
- Toxic tubular damage
- Formation of reactive oxygen species (ROS)

Hemodynamics: mediators

- Adenosine
- Endotheline
- ANP
- Dopamine
- NO
- Prostaglandines
- Rest: Serotonin, bradykinin, leukotrienes, histamine, catecholamines, vasopressin
- Receptor subtypes

Hemodynamics

$pO_2$ 25mmHg

$pO_2$ 10-15mmHg

$pO_2$ 40mmHg

$pO_2$ 20-30mmHg
Pathophysiology

- Hemodynamic effects
- Toxic tubular damage
- Formation of reactive oxygen species (ROS)

Tubular toxicity

- Reduced proliferation of tubular cells
- Impairment of mitochondrial enzymes
- Apoptosis
- Affect polarity of the epithelium
- Reduce tubular transport

Pathophysiology

- Hemodynamic effects
- Toxic tubular damage
- Formation of reactive oxygen species (ROS)

Reactive oxygen species (ROS)

- CM enhance ROS generation
  - Decline in renal medullary blood flow
  - Increase in tubular transport
- Increased ROS formation
  - Endothelial dysfunction
  - Reduced NO
  - Increased AT-II and endothelin-I

Nephrotoxicity of contrast media

• Plausible causes
  
  – Vascular effect
  – Cytotoxic effect
  
  • Osmotoxicity
  • Chemotoxicity
  • Viscosity toxicity
  • Ion toxicity
The role of osmolality
CM Osmolality

HOCM, high-osmolar CM; LOCM, low-osmolar CM; IOCM, isosmolar CM
**Contrast Media Properties and CIN**

Viscosity vs CIN

\[ y = -0.1466x + 13.38 \]

\[ R^2 = 0.002 \]

Significance F = 0.887

Viscosity at 37° C

CIN Incidence (%)

Os molality vs CIN

\[ y = 0.0077x + 5.2833 \]

\[ R^2 = 0.389 \]

Significance F = 0.030

mOsm/kg H₂O

CIN Incidence (%)

*Viscosity and osmolality data taken from Davidson C et al. *Am J Cardiol.* 2006;98(suppl):42K-58K.*
Osmotoxicity

• High osmolality is bad
• Iso-osmolality is good

- How is “low osmolality” in clinical studies?
Osmotoxicity

- We know hypertonicity is ”bad” – osmolality matters
- But does it matter between HOCM, LOCM and IOCM – Contrast Media?
Hemodynamics effects of osmolality

- ↑ Renal plasma flow
- ↑ Natriuresis and diuresis
- ↑ Tubular Na reabsorption
- ↑ Oxygen demand tubular cells
- Red blood cell aggregation

Osmolar effects on human red blood cells

Iodixanol 320
290 mOsm/kg H₂O

Iohexol 350
844 mOsm/kg H₂O

Images courtesy of G. Nash, Department of Physiology, University of Birmingham Medical School, Birmingham, UK
Relationship between toxic effect and contrast media and clinical outcome studies

• Osmolality – yes
• Viscosity – no

Chemotoxicity - yes
The role of viscosity
The role of viscosity

- Studies in rats have suggested a role, but no CIN have been reported.
- Studies in pigs have shown no role of viscosity.
- Studies in humans have shown no role of viscosity.
Hemodynamic effects of viscosity

- ↑ Renal tubular viscosity
- ↑ Tubular obstruction
- ↑ Increase interstitial pressure
- ↓ Perfusion
- Hypoxia

Contrast Media Properties and CIN

Viscosity vs CIN

\[ y = -0.1466x + 13.38 \]

\[ R^2 = 0.002 \]

Significance F = 0.887

Viscosity at 37°C vs CIN Incidence (%)

Osmolality vs CIN

\[ y = 0.0077x + 5.2833 \]

\[ R^2 = 0.389 \]

Significance F = 0.030

OSMOLALITY vs CIN

mOsm/kg H₂O vs CIN Incidence (%)

*Viscosity and osmolality data taken from Davidson C et al. *Am J Cardiol.* 2006;98(suppl):42K-58K.
Comparison between different CM

1. Only randomized controlled studies
2. Only peer reviewed journals
3. Only more than 50 patients/per arm
4. Only head-to-head comparisons
5. Intra-arterial injection
6. Intra-venous injection
RCT

- Statistical difference is superior to no difference
- “No difference” does not automatically imply equality
  “Absence of evidence not equal to evidence of absence”

Limitations
Number of and level of risk-patients, sample size, time for measuring Scr and timing and number of postdose SCR measures etc
Conclusions

• Intuitively, expressing the CM dose in gram iodine and renal function in estimated GFR seems more appropriate than present standards.

• It may provide the examiner with a simple numerical relationship to assess the risk of CIN.
• Is there a difference between low-osmolar and high-osmolar CM
  YES, High osmolar are more nephrotoxic

• Is there a difference between iso-osmolar and low-osmolar CM
  Yes, Intraarterially it is shown and i.v.Iso-osmolar is either better or equal

• Is there a difference between low-osmolar CM
  Not shown

With regard to nephrotoxicity
Take home message

Iodinated Contrast Medium
(Contrast-Induced Renal Failure)

- Hemodynamic effects
- Direct CM molecule toxicity
- Endogenous biochemical disturbance

Pre-renal
- dehydration
- hypotension
- Medullary ischemia
- Red blood cell sludging
- Adenosine increases
- Endothelin increases
- NO decreases

↑ Oxygen free radicals
↓ Antioxidant enzyme activity

Acute Renal Failure

How do you prepare your mind

- What is CIN
- Is CIN dangerous
- **Who is the risk patient**
- How do I manage the risk
CIN: Patient-related Risk Factors

**Established**
- Pre-existing renal impairment with DM
- Pre-existing renal impairment without DM
- Dehydration
- Congestive heart failure
- Old age
- Administration of nephrotoxic drugs

**Questionable**
- DM without renal impairment
- Hypertension
- Hyperuricemia
- Proteinuria
- Multiple myeloma
- Gender

_CIN, contrast-induced nephropathy; DM, diabetes mellitus_


ESUR, Guidelines on Contrast Media version 5.0
## Classic and Possible Risk Factors for CIN

<table>
<thead>
<tr>
<th>Modifiable risk factors</th>
<th>Nonmodifiable risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classic risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Low effective circulatory volume</td>
<td>Pre-existing renal failure</td>
</tr>
<tr>
<td>Use of nephrotoxic drugs</td>
<td>DM with pre-existing renal failure</td>
</tr>
<tr>
<td>Increased dose of CM</td>
<td>Older age</td>
</tr>
<tr>
<td>Short duration of 2 CM admins</td>
<td>Class III-IV CHF and decreased LVEF</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Possible risk factors</th>
<th></th>
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<tbody>
<tr>
<td>Hypertension</td>
<td>African-Americans and nonwhites</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Prior kidney surgery</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>AIDS</td>
</tr>
<tr>
<td>Periprocedural hypotension</td>
<td>Polyarteritis nodosa</td>
</tr>
</tbody>
</table>

Diabetes Amplifies the Risk of CIN

McCullough PA et al. *Am J Cardiol*. 2006;98(suppl):27K-36K.
A Risk Score for Prediction of CIN in PCI Patients

Multivariate Predictors

- Hypotension: 5 pts
- IABP use: 5 pts
- CHF: 5 pts
- SCr >1.5 mg/dL (>132 umol/L): 4 pts
- Age >75 yr: 4 pts
- Anaemia: 3 pts
- Diabetes mellitus: 3 pts
- Contrast volume mL: 1 pt/100 mL

Risk score:

- < 5
- 6 to 10
- 11 to 15
- >16

Risk group:

- Development dataset
- Prediction dataset

Mehran et al, J Am Coll Cardiol 2004; 44:1393
Prevention

Primary prevention
- Alternative imaging
  - Use the least nephrotoxic CM and adapt dose to renal function (ALARA)

Secondary prevention
- Identify risk-patients, plasma volume expansion, pharmacological, withdraw nephrotoxic drugs, RRT—dialysis, hemo-filtration, etc.
Minimising the Risk of CIN In Patients at Risk

• Withdrawal of nephrotoxic medications
• Use of adequate hydration
• Pharmacological interventions
• Appropriate selection and use of CM
Minimising the Risk of CIN In Patients at Risk

• Withdrawal of nephrotoxic medications
• Use of adequate hydration (plasma expansion)
• Pharmacological interventions
• Appropriate selection and use of CM
Prophylaxis

*Hydration!! (plasma expansion)*

- Sodium chloride (0.9% NaCl)
  - ESUR: 100 ml/h 4h before and 24h after
  - SFMR: 1 ml/kg/h 6h prior 12-24h after taking into account cardiac and renal status
- Intravenous better than per oral
- Fluid list
- Cave forced diuresis
Minimising the Risk of CIN
In Patients at Risk

• Withdrawal of nephrotoxic medications
• Use of adequate hydration
• Pharmacological interventions
• Appropriate selection and use of CM
Pharmacological Interventions and the Prevention of CIN

- Strategies that do not work
  - Mannitol
  - Furosemide
  - Dopamine
  - Atrial natriuretic peptide
  - Fenoldopam

- Strategies that may work
  - Calcium channel blockers
  - Theophylline
  - Ascorbic acid
  - Prostaglandins
  - N-acetylcysteine

Conclusion

I. Always consider alternative imaging method

II. Identify risk patients

III. The incidence of CIN may be reduced by:
   - Using the lowest dose of CM possible
   - Correlating dose to renal function
   - Using adequate hydration and interventions
   - Discontinuing use of nephrotoxic drugs
   - Choosing a low-osmolar or iso-osmolar contrast
### Society Recommendations for High-risk Patients

<table>
<thead>
<tr>
<th>Society</th>
<th>Iso-osmolar</th>
<th>Low-osmolar</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA 2007 (UA/NSTEMI)</td>
<td>✓</td>
<td>–</td>
</tr>
<tr>
<td>ACC/AHA 2008 (PCI)</td>
<td>✓</td>
<td>–</td>
</tr>
<tr>
<td>ESUR 2005</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>French Radiologic Society 2004</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>German Cardiac Society 2004</td>
<td>✓</td>
<td>–</td>
</tr>
<tr>
<td>Hungarian Society of Nephrology 2007</td>
<td>✓</td>
<td>–</td>
</tr>
<tr>
<td>National Kidney Foundation (K/DOQI) 2005</td>
<td>✓</td>
<td>–</td>
</tr>
<tr>
<td>Norwegian Society of Nephrology 2004</td>
<td>✓</td>
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</table>
Summary

• More patients are undergoing CT procedures as the technology improves and becomes more widely available

• CIN is a safety issue associated with contrast-enhanced CT

• Patients with CIN experience more in-hospital complications and have higher mortality rates than patients without CIN

• At-risk patients should be identified through the use of risk assessment protocols, prior to contrast-enhanced CT procedures