

Contrast Nephropathy – Too Much or Too Little Concern?

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 - C.R. Bard
 - Humacyte
 - Vascular Therapies, Inc.
 - W L Gore
- None of this pertinent to this presentation

Please note

WE WILL NOT BE DISCUSSING GADOLINIUM OR NEPHROGENIC SYSTEMIC FIBROSIS, JUST IODINATED CONTRAST

Contrast Nephropathy – What is it?

- Acute Kidney Injury occurring after exposure to iodinated radiocontrast media*
- Usually reversible (but not always)**

*Davidson CJ, Hlatky M, et al. Ann Intern Med 1989; 110(2):119.

*Parfrey PS, Griffiths SM, et al. NEJM 1989; 320(3):143.

**Rich MW, Crecelius CA. Arch Int Med 1990; 150(6):1237

Contrast Nephropathy – Possible Etiology

- Actual cause not well understood
 - Tubular hypoxia and injury*
 - Viscosity**
 - Vasoconstriction d/t endothelial factors***
 - Direct toxicity to tubular cells****

*Heyman SN, Rosenberger C, et al. Nephrol Dial Transplant 2005; 20 Suppl 1:i6.

**Persson PB, Hansell P, Liss P. Kidney Int 2005; 68(1): 14.

***Cantley LG, Spokes K, et al. Kidney Int 1993; 44(6): 1217.

****Zager RA, Johnson ACM, et al. Kidney Int 2003; 64:128.

Tubular Hypoxia and Injury

- Inhibit mitochondria activity*
 - Increase adenosine by hydrolysis of ATP
 - Adenosine + Medullary Hypoxia generates “Oxygen Radicals”
 - These radicals “scavenge” Nitric Oxide

*Wong PC, et al. Int J Cardiol 158(2): 186-192, 2012

Tubular Hypoxia and Injury

- Increased oxygen consumption via Endothelin-A receptor*,**
- Possible direct cytotoxicity d/t altered integrity of membranes***

*Heyman SN, et al. J Amer Soc Neph 3:58-65. 1992

**Wang A, et al. KI 57:1675-1680. 2000

***Zager RA, et al. KI 64:128-139, 2003

Viscosity / Osmolality

- Other substances like Mannitol or Hypertonic Saline cause similar histology*
- Contrast enters tubule and, especially with any volume depletion, becomes more concentrated affecting tubular flow / fxn**
- Increased blood viscosity affecting red cell deformability and increasing resistance to blood flow***

*Detrenis S, et al. Nephrol Dial Transplant 20:1452-1550. 2005

**Seeliger E, et al. Radiol 256(2):406-414. 2010

***Basu a, et al. (Jul 3, 2017) [emedicine.Medscape.com](http://emedicine.medscape.com). Retrieved Aug 18, 2017 from <http://emedicine.medscape.com/article/246751-overview#a5>

Vasoconstriction – Direct and Indirect

- Direct release endothelin and prostaglandins*
 - With adenosine activates A₁ receptor constricting afferent arteriole
 - But also medullary vasodilatation vs constriction due to multiple mediators
- Direct action of contrast on vascular smooth muscle cells**
- Makes any pre-existing vascular pathology worse***

*Wong PC, et al. Int J Cardiol 158(2): 186-192, 2012

**Basu a, et al. (Jul 3, 2017) emedicine.Medscape.com. Retrieved Aug 18, 2017 from <http://emedicine.medscape.com/article/246751-overview#a5>

***Lameier NG. Nephrol Dial Transplant. 21(6):i11-23, 2006

Direct Tubular Toxicity

- Direct effect of contrast on tubular cells*, **
- Cytotoxicity causes apoptosis of tubular cells***
 - Cellular casts obstruct

*Sendeski MM. Clin Exp Pharm & Physio. 38:292-299, 2011

**Humes HD, et al. Am J Physio. 252:F246-F255, 1987

***Caiazza A, et al. Biomed Research Int Vol 2014 Article ID 578974. 2014

Radiocontrast Nephrotoxicity – Major Risks

- **Decreased GFR**
- Proteinuria
- Age
- Presence of DM
- Dose of Contrast
- Type of Contrast
- ACEI / ARB Use
- Volume Status
- PG Inhibition
- Hyperviscosity Syndromes

Radiocontrast Nephrotoxicity – Major Risks

- Decreased GFR
 - In absence of CKD, risk $\leq 1\%$ *
 - For those with decreased renal function, incidence after contrast study is 10 to 30% **
 - Incidence of Contrast AKI increases proportional to baseline decrease GFR***

*Wilhelm-Leen E, et al. JASN 28(2):653. 2017

**Rudnick MR, et al. KI 47:254-261. 1995

***Thomas T, et al. JACC Cardiovasc Interv 7(1):1-9, 2014

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Radiocontrast Nephrotoxicity – Major Risks

- Proteinuria
 - Additional risk factor for contrast nephropathy*
 - May be an independent risk **

*Piskinpasa S, et al. Ren Fail 35(1):62, 2013

**Tao Y, et al. J Neurointerv Surg 9(5):455, 2017

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Radiocontrast Nephrotoxicity – Major Risks

- Age
 - GFR tends to decrease with aging even in normal
 - Association between age ≥ 65 and AKI from contrast*
 - Age > 75 associated with 1.5 to 5x increased risk with increased incremental risk with each additional year of age**
 - BUT another retrospective review of 5006 patients did not find age to be a risk factor***
- Perhaps age, by itself is not the issue but co-morbidity is

*Palli E, et al. Oxid Med Cell Longev, Jan 28, 2014

**Mardani S, et al. J Nephrofarm, 2(2):27-30, 2013.

***Traub SJ, et al. Academ Emerg Med, 20:40-45, 2013

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Radiocontrast Nephrotoxicity – Major Risks

- Presence of DM
 - Increased oxygen consumption in DM kidney*
 - Increased snGFR in diabetic kidney**
 - Often see micro and macro vascular disease in DM***
- Diabetic status associated with bloodflow issue, increased snGFR, hampered antioxidant capacity, altered sensitivity to chemical mediators ****

*Hansell P, et al. Clin Exp Pharm and Physio 40(2):123-137, 2013

**Bak M, et al. JASN 11(7):1287-1292, 2000

***Heyman SN, et al. CJASN 3(8):288-296, 2008

****Heyman SN, et al. Biomed Res Int, Nov 21, 2013

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Radiocontrast Nephrotoxicity – Major Risks

- Dose of Contrast
 - More contrast amount leads to more AKI*
 - Safety demonstrated with <10mL fistula study in CKD population**
 - Safety demonstrated with IV vein mapping in CKD (<20 mL contrast)***

*Marenzi G, et al. Ann Int Med 150(3):170, 2009

**Kian K, et al. KI 69(8):1444, 2006

***Asif A, et al. Semin Dial 18(3):239-242, 2005

Radiocontrast Nephrotoxicity – Major Risks

- Type of contrast*
 - New lower osmolar agents possibly less risk BUT data not conclusive*
 - Iodixanol may have a unique benefit over others BUT AGAIN, conflicting data and studies exist**

*Lautin EM, et al. AJR 157(1):59, 1991

**Eng J, et al. Ann Int Med 164(6):417, 2016.

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Radiocontrast Nephrotoxicity – Major Risks

- ACEI / ARB Use
 - May be an independent risk factor for contrast AKI*
 - Significant increase (11.4 vs 6.3%) in patients on ACEI/ARB**
 - BUT, other data suggests no association***

*Umrudin Z, et al. J Nephrol 25(5):776-781, 2012

**Rim MY, et al. Am J Kid Dis 60:576, 2012.

***Zhou L and Duan S. Kidney Blood Press Res 38:165-171, 2013.

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Radiocontrast Nephrotoxicity – Major Risks

- Volume Status
 - May be relative issue (decreased cardiac, etc)
 - Can adversely affect GFR increasing risk
 - Can lead to more avid re-absorption and even higher osmotic forces in tubules
 - Some conflicting data but most accept as a risk factor*

*Pakfetrat M, et al. IJKD 4(2):116-122, 2010

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Radiocontrast Nephrotoxicity – Major Risks

- PG Inhibition
 - NSAIDs can adversely affect renal function especially with dehydration or decreased effective renal bloodflow*
 - Any decrease GFR can increase risk of contrast nephropathy
 - Prostaglandins involved in response to contrast**
 - Not clear that NSAIDs increase risk of contrast nephropathy independently**

*Huerta C, et al. Am J Kidney Dis 45(3):531, 2005

**Heyman SN, et al. Invest Radiol 45:188-195, 2010

***Diogo LP, et al. Arg Bras Cardiol 95(6):726-731, 2010

Radiocontrast Nephrotoxicity – Major Risks

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- **Hyperviscosity Syndromes**

Radiocontrast Nephrotoxicity – Major Risks

- Hyperviscosity Syndromes
 - Can cause pre-existing issues with microscopic bloodflow
 - Incidence 0.6 – 1.25% in MM patients compared to normal*
 - Subsequent review showed little correlation in MM patients with normal GFR but correlation to b2-macroglobulin levels**
- Risk may be due to the effect of the disease and not the viscosity

*McCarthy CS and Becker JA. Radiology 183(2):519-521, 1992

**Pahade JK, et al. AJR 196:1094-1101, 2011

Contrast Toxicity – Is it so bad?

- Acute
 - Transient decrease renal function 3 to 7 days after exposure
 - Most recover after 5 to 7 days from peak
 - Some may have persisting decrease GFR compared to baseline
 - Length of stay and short term mortality higher*
 - More likely to require renal replacement therapy**

*Alderson S, et al. Critical Care 18(Suppl 1):374, 2014

**Kim SM, et al. AJKD 55(6):1018-1025, 2010

Contrast Toxicity – Is it so bad?

- Long term
 - Risk of cardiovascular, cerebrovascular, and all cause mortality increased*
 - Worse “event-free” outcomes in those with contrast nephropathy**
 - Even in those that recover, long term mortality increased
- But, effect of nephropathy or of co-morbidities?

*Saito A, et al. IJ Card 227:424-429, 2017

**Cho JY, et al. Jour Card 56(3):300-306, 2010

Contrast Toxicity – Is it so bad?

- The water is muddy*
 - Contrast?
 - Atheroembolic disease?
 - Co-morbidities?
 - “Selection bias?”
- Which patients get these studies?



*Rudnick M and Feldman H. CJASN 3(1):263-272, 2008

Contrast Toxicity – Can we prevent?*

- Mannitol / Lasix
- Ca⁺⁺ Blockers
- Dopamine / Fenoldopam
- Endothelin Receptor Antagonist (Ambrisentan)
- Prostacycline
- Atrial Natriuretic Peptide
- Adenosine Agonists (Theophylline, Aminophylline)
- Bicarbonate
- Statins
- Acetylcysteine
- Fluids
- Limit exposure

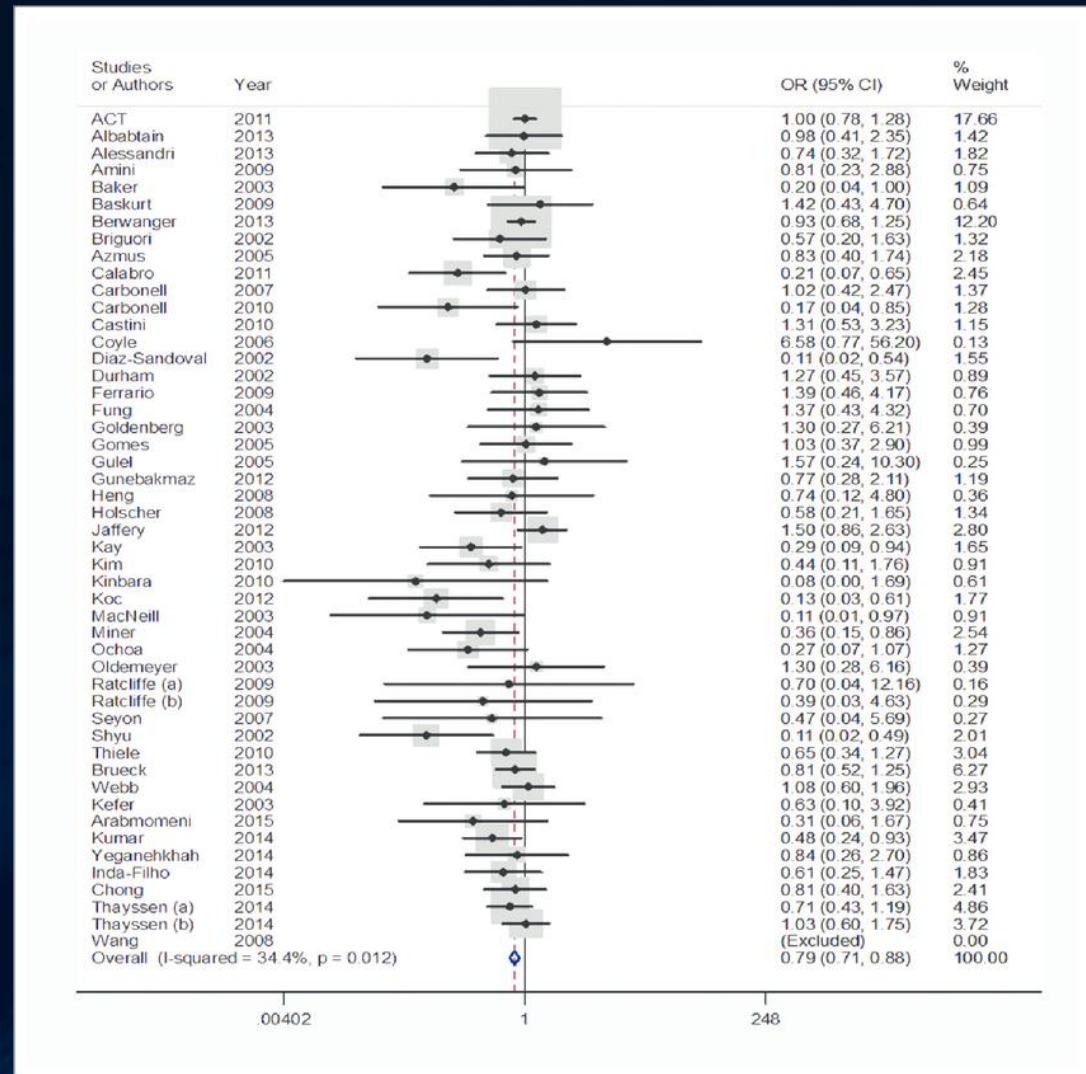
*Wong PC, et al. Int J Cardiol 158(2): 186-192, 2012. ; Bakris GL, et al. KI 56:206-210, 1999. ; Kini AS, et al. Am J Cardiol 89:999-1002, 2002. ; Lewis JB, et al. JASN 9:134A, 1998. ; Gleeson TG, et al. Am J Roentgen 183:1673-1689, 2004. ; Shammass NW et al. J Invasive Cardiol 13:738-740, 2001

N-Acetylcysteine?

“The only well established treatment for the prevention of CIN is intravenous hydration”

Steven Fishbane

CJASN 3(1):281-287, 2008



From Ali-Hassan-Sayegh S, et.al. Angiology 2016

Contrast Toxicity - Treatment

- Avoid further insult
- Fluids
- Bicarb?
- Diuretic?
- Dialysis

Contrast Nephrotoxicity - Perspective

- Avoid – No Contrast, No Toxicity
 - Find alternate diagnostic study
- Use less
 - Angiography in CKD
 - Vein mapping in CKD

Contrast Nephrotoxicity - Perspective

- Avoid
- Use less
- Hydrate
- Bicarb?

Contrast Nephrotoxicity - Perspective

- Avoid
 - Find alternate diagnostic study
 - Use less
- Hydrate
- Bicarb?
- Acetylcysteine?

Contrast Nephrotoxicity - Perspective

- Avoid
 - Find alternate diagnostic study
 - Use less
- Hydrate
- Low ionic dye
- Bicarb?
- Acetylcysteine?
- Be afraid! (Dry, DM, GFR, Hyperviscosity, NSAIDs)

Contrast Nephrotoxicity - Perspective