Kontrast Madde Nasıl Böbrek Hasarına Yol Açıyor

Dr. Hasan Micozkadıoğlu
Başkent Üniversitesi Tıp Fakültesi
Nefroloji Bilim Dalı
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Results: 1 to 20 of 5693

1. Effects of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Contrast-Induced Nephropathy.
   Zhou L, Duan S.
   PMID: 24686005 [PubMed - as supplied by publisher]

2. Can Full-Dose Contrast-Enhanced CT Be Omitted From an FDG-PET/CT Staging Examination in Newly Diagnosed FDG-Avid Lymphoma?
   van Hamersvelt HP, Kwee TC, Fijnheer R, Beek FJ, de Klerk JM, Niewelstein RA.
   J Comput Assist Tomogr. 2014 Mar 27. [Epub ahead of print]
   PMID: 24681861 [PubMed - as supplied by publisher]

3. Lower Blood Vitamin D Levels Are Associated With an Increased Incidence of Contrast-Induced Nephropathy in Patients Undergoing Coronary Angiography.
   PMID: 24680172 [PubMed - in process]
Acute Kidney Injury in the Critically Ill: Is Iodinated Contrast Medium Really Harmful?*

Stephan Ehrmann, MD¹; Julie Badin, MD¹; Laurent Savath, MD²; Olivier Pajot, MD³; Denis Garot, MD¹; Tài Pham, MD⁴; Xavier Capdevila, MD, PhD²; Dominique Perrotin, MD¹; Karim Lakhal, MD²

Objectives: To assess whether the use of iodinated contrast medium increases the incidence of acute kidney injury in ICU patients, compared with patients not receiving iodinated contrast medium.

Design: Prospective observational matched cohort study.

Setting: Two ICUs in two tertiary teaching hospitals.

Patients: A total of 380 adults were included (20% more than once), before an iodinated contrast medium infusion (contrast inclusions, n = 307) or before an intrahospital transfer without iodinated contrast medium infusion (control inclusions, n = 170).

Interventions: None.

Measurements and Main Results: Among contrast inclusions, iodinated contrast medium–associated acute kidney injury occurred after 23 administrations (7.5%) according to the Acute Kidney Injury Network definition (stage ≥ 1, over 48 hr). As expected, a broader definition (≥ 25% increase in serum creatinine over 72 hr) yielded a greater incidence (16%). In 146 pairs of contrast and control inclusions, matched on propensity for iodinated contrast medium infusion, the incidence of acute kidney injury was similar (absolute difference in incidence, 0%; 95% confidence interval, −5.2; 5.2%), Acute Kidney Injury Network definition). Hospital mortality was also similar in 71 contrast and 71 control patients included only once and matched the same way. Contrary to iodinated contrast medium infusion (odds ratio, 1.57; 95% confidence interval, 0.69–3.53), the Sequential Organ Failure Assessment score at inclusion (odds ratio, 1.18; 95% confidence interval, 1.07–1.31) and the number of other nephrotoxic agents (odds ratio, 1.38; 95% confidence interval, 1.03–1.85) were independent risk factors for acute kidney injury.

Conclusions: The specific toxic effect of monomeric nonionic low-osmolar iodinated contrast medium in ICU patients with multiple renal aggressions seemed minimal. Severity of disease and the global nephrotoxic burden were risk factors for acute kidney injury, regardless of iodinated contrast medium infusion. (Crit Care Med 2013; 41:1017–1026)

Key Words: contrast medium/adverse effects; intensive care units; kidney diseases/chemically induced; kidney disease/epidemiology; tomography/x-ray computed
Intravenous Contrast Material–induced Nephropathy: Causal or Coincident Phenomenon?¹

Robert J. McDonald, MD, PhD
Jennifer S. McDonald, PhD
John P. Bida, PhD
Rickey E. Carter, PhD
Chad J. Fleming, MD
Sanjay Misra, MD
Eric E. Williamson, MD
David F. Kallmes, MD

Purpose: To determine the causal association and effect of intravenous iodinated contrast material exposure on the incidence of acute kidney injury (AKI), also known as contrast material–induced nephropathy (CIN).

Materials and Methods: This retrospective study was approved by an institutional review board and was HIPAA compliant. Informed consent was waived. All contrast material–enhanced (contrast group) and unenhanced (noncontrast group) abdominal, pelvic, and thoracic CT scans from 2000 to 2010 were identified at a single facility. Scan recipients were sorted into low- (<1.5 mg/dL), medium- (1.5–2.0 mg/dL), and high-risk (>2.0 mg/dL) subgroups of presumed risk for CIN by using baseline serum creatinine (SCR) level. The incidence of AKI (SCR = 0.5 mg/dL above baseline) was compared between contrast and noncontrast groups after propensity score adjustment by stratification, 1:1 matching, inverse weighting, and weighting by the odds methods to reduce intergroup selection bias. Counterfactual analysis was used to evaluate the causal relation between contrast material exposure and AKI by evaluating patients who underwent contrast-enhanced and unenhanced CT scans during the study period with the McNemar test.

Results: A total of 157,140 scans among 53,439 unique patients associated with 1,510,001 SCR values were identified. AKI risk was not significantly different between contrast and noncontrast groups in any risk subgroup after propensity score adjustment by using reported risk factors of CIN (low risk: odds ratio [OR], 0.93; 95% confidence interval [CI]: 0.76, 1.13; P = .47; medium risk: odds ratio, 0.97; 95% CI: 0.81, 1.16; P = .76; high risk: OR, 0.91; 95% CI: 0.66, 1.24; P = .58). Counterfactual analysis revealed no significant difference in AKI incidence between enhanced and unenhanced CT scans in the same patient (McNemar test: χ² = 0.63, P = .48) (OR = 0.92; 95% CI: 0.75, 1.13; P = .46).

Conclusion: Following adjustment for presumed risk factors, the incidence of CIN was not significantly different from contrast material–independent AKI. These two phenomena were clinically indistinguishable with established SCR-defined criteria, suggesting that intravenous iodinated contrast media may not be the causative agent in diminished renal function after contrast material administration.

¹From the Clinician Investigator Training Program (R.J.M.), Department of Radiology (R.J.M., J.S.M., C.J.F., S.M., E.E.W., D.F.K.), Department of Health Sciences Research (E.E.W.), and Department of Neurosurgery (D.F.K.), College of Medicine, Mayo Clinic, 200 1st St SW, Rochester, MN 55905; and Department of Biochemistry, Stanford University School of Medicine, Stanford, Calif (J.P.B.). From the 2012 RSNA Annual Meeting. Received August 12, 2012; revision requested October 1; revision received October 16; accepted October 25; final version accepted October 31. Address correspondence to R.J.M. (e-mail: mcdonald.robert@mayo.edu). ©RSNA, 2013.

Tarihçə
Tarihçe

Moses Swick, MD
“father of intravenous urography”

• 1930, proposed using an organic nucleus as iodine carrier
• Benzoic acid is metabolized to hippuran
• Hippuran is excreted by the kidneys
• Lead to the development of sodium diatrizoate in 1950s
Dr. Torsten Almén is a pioneer in the development of modern nonionic contrast media.
Tarihçe

• İyodlu kontrast ajanlarla anjiyografi 1920’lere kadar uzanıyor
• İlk ajan sodyum iodid kötü görüntüleme ve yüksekтокsisite
• Triiiodo benzoik asit halkalı ajan 1950’lär
• Noniyonik ve dimerik ajanlar 1970’lär
• Tüm dünyada yılda 75 milyondan fazla intravenöz kontrast ajan kullanımı mevcut

Kontrast Ajanlar

- İyonik monomerik
- Noniyonik monomerik
- İyonik dimerik
- Noniyonik dimerik

İyodlu ajanlar 4 kategorkiye ayrılıyor:

- İyonik monomerik: İyod/total atom
- Noniyonik monomerik: Ozmolarite
- İyonik dimerik: Viskozite
- Noniyonik dimerik

Thomsen HS et al. BJU Int 2000;86(Suppl 1):1–10
Pathophysiology of renal tissue damage by iodinated contrast media

Mauricio M Sendeski

Institute of Vegetative Physiology, Charité Medical University, Berlin, Germany

Fig. 1 The structure of three types of contrast media (CM), with benzene rings and iodine atoms shown in bold. (a) Diatrizoic acid, a ionic monomeric CM. The arrow points to the carboxyl group of ionic CM. (b) Iopromide, a non-ionic monomeric CM. (c) Iodixanol, a non-ionic dimeric CM. Note the presence of six iodine atoms and two benzene rings.
Pathophysiology of contrast-induced nephropathy

Philip Ching Yat Wong *, Zicheng Li, Jun Guo, Aidong Zhang
Department of Cardiology, First Affiliated Hospital of Jinan University, Shipai, Guangzhou 510630, China

Table 1
Features of some contrast media.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Type (Ionicity)</th>
<th>Iodine content (mg/mL)</th>
<th>Osmolality (mOsm/kg H₂O)</th>
<th>Viscosity at 37 °C (mPa.s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diatrizoate</td>
<td>HOCM (Ionic)</td>
<td>140–462</td>
<td>550–2938</td>
<td>1.4–19.5</td>
</tr>
<tr>
<td>Iothalamate</td>
<td>HOCM (Ionic)</td>
<td>141–480</td>
<td>600–2400</td>
<td>1.5–9.0</td>
</tr>
<tr>
<td>Ioxithalamate</td>
<td>HOCM (Ionic)</td>
<td>120–380</td>
<td>610</td>
<td>1.1–8.5</td>
</tr>
<tr>
<td>Ioxaglate</td>
<td>LOCM (Ionic)</td>
<td>160–350</td>
<td>295–680</td>
<td>1.7–10.5</td>
</tr>
<tr>
<td>Iohexol</td>
<td>LOCM (Nonionic)</td>
<td>180–350</td>
<td>~410–780</td>
<td>2.2–10.6</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>LOCM (Nonionic)</td>
<td>150–370</td>
<td>300–832</td>
<td>1.5–9.5</td>
</tr>
<tr>
<td>Iopromide</td>
<td>LOCM (Nonionic)</td>
<td>150–400</td>
<td>340–880</td>
<td>1.2–12.3</td>
</tr>
<tr>
<td>Iobitridol</td>
<td>LOCM (Nonionic)</td>
<td>250–350</td>
<td>585–915</td>
<td>4.0–10.0</td>
</tr>
<tr>
<td>Iomeprol</td>
<td>LOCM (Nonionic)</td>
<td>150–400</td>
<td>301–730</td>
<td>1.4–12.6</td>
</tr>
<tr>
<td>Iodixanol</td>
<td>IOCM (Nonionic)</td>
<td>150–320</td>
<td>290**</td>
<td>1.7–11.1</td>
</tr>
</tbody>
</table>

* Pure solution in water. ** After adjustment for use. Source: Davidson et al. [9].
Predispozan Faktörler

- Böbrek hastalığı
- Diyabetes Mellitus
- Yaş (>75)
- Sepsis, şok
- Kontrast ajan miktarı (>100 ml)
- Hipotansiyon
- Dehidrataşyon
- Nefrotoksik ajan
- Anemi
- EF < %40
FIGURE 1: Pathogenesis of contrast-induced nephropathy. Abbreviations: CM, contrast media; EF, ejection fraction; CIN, contrast-induced nephropathy.
Pathophysiology of renal tissue damage by iodinated contrast media

Mauricio M. Sendeski
Institute of Vegetative Physiology, Charité Medical University, Berlin, Germany

Table 1  Findings from cell culture studies on the toxic effects of contrast media

<table>
<thead>
<tr>
<th>Finding</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphological changes of apoptosis and/or necrosis</td>
<td>25, 28, 32, 41, 44</td>
</tr>
<tr>
<td>Caspase activation</td>
<td>36, 51</td>
</tr>
<tr>
<td>↓↓Cell viability quantified with:</td>
<td>25, 27, 29, 30, 32–35, 35–37, 41, 45, 47, 48, 51, 52</td>
</tr>
<tr>
<td>lysosomal dye uptake, MTT uptake,</td>
<td></td>
</tr>
<tr>
<td>Trypan blue uptake, TUNEL staining,</td>
<td></td>
</tr>
<tr>
<td>MTS reduction and chromium-51 release</td>
<td></td>
</tr>
<tr>
<td>DNA fragmentation and damage</td>
<td>28, 31, 41, 44</td>
</tr>
<tr>
<td>↑↑ATF2 expression (a gene involved in apoptosis by oxidative stress)</td>
<td>52</td>
</tr>
<tr>
<td>↑↑Translocation of phosphatidylserine (an early sign of apoptosis)</td>
<td>51</td>
</tr>
<tr>
<td>↑↑Intracellular calcium</td>
<td>44</td>
</tr>
<tr>
<td>↓↓Cellular ATP</td>
<td>44</td>
</tr>
<tr>
<td>↓↓Cellular cAMP</td>
<td>49</td>
</tr>
<tr>
<td>↓↓NO production</td>
<td>43, 50</td>
</tr>
<tr>
<td>Impairment of store-operated Ca^{2+} entry</td>
<td>46</td>
</tr>
<tr>
<td>Activation of phospholipase A</td>
<td>49</td>
</tr>
<tr>
<td>↑↑Intracellular peroxide</td>
<td>48</td>
</tr>
<tr>
<td>↑↑Endothelin release</td>
<td>39, 40</td>
</tr>
<tr>
<td>↑↑Histamine release</td>
<td>49</td>
</tr>
<tr>
<td>↑↑Endothelial cell permeability</td>
<td>43</td>
</tr>
<tr>
<td>Loss of polarity in tubular cells</td>
<td>27</td>
</tr>
<tr>
<td>Damage of tight junctions and/or monolayer disruption</td>
<td>27, 29</td>
</tr>
<tr>
<td>Cytoplasmic vacuolization, loss of microvilli</td>
<td>25</td>
</tr>
<tr>
<td>↑↑Release of lactate dehydrogenase</td>
<td>33, 42, 45</td>
</tr>
</tbody>
</table>

MTT, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide; TUNEL, terminal deoxynucleotidyltransferase-mediated dUTP–digoxigenin nick end-labelling; MTS, 3-[4,5-dimethylthiazol-2-yl]-5-3-carboxymethoxyphenyl]-2-[4-sulphophenyl]-2H-tetrazolium; ATF2, activating transcriptional factor 2; NO, nitric oxide.
Pathophysiology of renal tissue damage by iodinated contrast media

Mauricio M Sendeski
Institute of Vegetative Physiology, Charité Medical University, Berlin, Germany

Table 2  Functional effects of contrast media on blood vessels *in vitro*

<table>
<thead>
<tr>
<th>Effect</th>
<th>Vessel (species)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraction</td>
<td>Descending vasa recta (rat)</td>
<td>64,65</td>
</tr>
<tr>
<td></td>
<td>Renal artery (human, rat, rabbit)</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Carotid, aorta, renal, iliac, mesenteric, celiac arteries (rabbit)</td>
<td>67*</td>
</tr>
<tr>
<td></td>
<td>Aorta (rabbit)</td>
<td>68,69</td>
</tr>
<tr>
<td>Dilation</td>
<td>Renal artery (pig)</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Ear artery (dog)</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Mesenteric, celiac arteries (rabbit)</td>
<td>67*</td>
</tr>
<tr>
<td>Dilation ⇒ Constriction</td>
<td>Pulmonary artery (rat)</td>
<td>71</td>
</tr>
<tr>
<td>↑AngII contraction, ↓NO production</td>
<td>Descending vasa recta (rat)</td>
<td>64</td>
</tr>
<tr>
<td>↓ACh dilation</td>
<td>Aorta (rabbit)</td>
<td>70</td>
</tr>
<tr>
<td>↓ET contraction, ↓NO dilation</td>
<td>Renal artery (rat)</td>
<td>72</td>
</tr>
<tr>
<td>↑PE contraction, ↓NO dilation</td>
<td>Iliac artery (rabbit)</td>
<td>46*</td>
</tr>
</tbody>
</table>

*Different contrast media had different effects.

AngII, angiotensin II; ACh, acetylcholine; ET, endothelin; NO, nitric oxide; PE, phenylephrine.
Hücre hasarına yol açan nedenler

- İyod sekonder toksisite
  - Hücrelere ve bakterilere toksik
  - Fotoliz (Saklama, Işık maruziyeti)
  - Miktar
  - İyonik
- Ozmolarite
- Viskozite
- Elektrik yükü
Figure 4 Dose-dependent association of volume of administered contrast media with the incidence of contrast media-induced acute kidney injury in 185 patients. Patients who received the lowest quartile of contrast media volume (mean ± SD in parenthesis below) were seven-fold less likely to develop contrast media-induced acute kidney injury compared with those with the highest quartile of contrast volume; the risk of contrast media-induced acute kidney injury doubles with every 20 mL of contrast administered. Reprinted with permission from...
Hücre hasarına yol açan nedenler

- Ozmolarite
  - >800 mosmol
  - Ozmotik nefrozis
  - Anizositoz
  - Tamm-Horsfall
  - Bence-Jones
  - Ürik Asid

Tumlin J et al. Am J Cardiol 2006;98(suppl):14K-20K
Hücre hasarına yol açan nedenler

- Viskozite
  - İntratubuler basınç↑, GFR↓
  - Maruziyet süresi↑
  - Ozmotik Nefrozis
  - İnterstisyel basınç↑, DVR kompresyon
INVITED REVIEW

Pathophysiology of renal tissue damage by iodinated contrast media

Mauricio M Sendeski

Institute of Vegetative Physiology, Charité Medical University, Berlin, Germany

Fig. 2 Functional effects of contrast media (CM) on isolated perfused descending vasa recta: all types of CM caused significant constriction (data indicate the degree of constriction from rest). Owing to the low, equalized iodine concentration used, all CM solutions tested are comparable to the control solution in terms of the iodine concentration used, osmolarity and viscosity. Data are the mean ± SEM. *P < 0.05 compared with control. Reproduced with permission from Sendeski et al.65
Figure 3 Renal retention of iopromide 300 mg l/mL and ioxixanol 320 mg l/mL, respectively, following intravenous administration in minipigs. Representative CT scans (64-slice scanner) 1 h (upper row) and 6 h (lower row) post-injection at dosages of 1 and 2 g iodine/kg BW, respectively. Reprinted with permission from Ref.68
Clinical update

Contrast-induced kidney injury: mechanisms, risk factors, and prevention

Erdmann Seeliger, Mauricio Sendeski, Charanjit S. Rihal, and Pontus B. Persson

1Institute of Physiology, Center for Cardiovascular Research, Charité—Universitätsmedizin Berlin, CCM, Hessische Str. 3-4, Berlin D-10115, Germany; and 2Cardiac Catheterization Laboratory, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

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A

Urine volume (mL)

- Iodixanol
- Iodixanol + NaCl
- Iodixanol + NaHCO₃
- Iodixanol + MannitGluc
- half dose iodixanol

* +
Clinical update

Contrast-induced kidney injury: mechanisms, risk factors, and prevention

Erdmann Seeliger¹*, Mauricio Sendeski¹, Charanjit S. Rihal², and Pontus B. Persson¹

¹Institute of Physiology, Center for Cardiovascular Research, Charité—Universitätsmedizin Berlin, CCM, Hessische Str. 3-4, Berlin D-10115, Germany; and ²Cardiac Catheterization Laboratory, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

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![Graph showing urine viscosity (mm²/s) with asterisks indicating significance levels.](image_url)
Clinical update

Contrast-induced kidney injury: mechanisms, risk factors, and prevention

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¹Institute of Physiology, Center for Cardiovascular Research, Charité—Universitätsmedizin Berlin, CCM, Hessische Str. 3-4, Berlin D-10115, Germany; and ²Cardiac Catheterization Laboratory, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA.

Received 30 September 2011; revised 2 December 2011; accepted 15 December 2011; online publish-ahead-of-print 19 January 2012
Hemodinamik Değişiklikler ve Hipoksi

- Kortikal vazokonstrüksiyon, GFR ↓
- Dış Medulla hipoksik
  - Hiperozmolar çevre
  - Arteriovenöz shunt
  - Aktif Transport, Oksijen ihtiyacı ↑
  - DVR vazokonstriksiyonu
CALL FOR PAPERS | Pathophysiology of Acute Kidney Injury

Iodinated contrast media cause endothelial damage leading to vasoconstriction of human and rat vasa recta

Mauricio M. Sendeski, Anja Bondke Persson, Zhi Zhao Liu, Jonas F. Busch, Steffen Weikert, Pontus B. Persson, Stefan Hippenstiel, and Andreas Patzak

1Institut für Vegetative Physiologie, Charité Universitätsmedizin-Berlin, Berlin, Germany; 2Klinik für Urologie, Charité Universitätsmedizin-Berlin, Berlin, Germany; and 3Medizinische Klinik m.S. Infektiologie und Pneumologie, Charité Universitätsmedizin-Berlin, Berlin, Germany

Submitted 21 August 2012; accepted in final form 10 October 2012

Fig. 1. A: representative image of an isolated perfused human descending vasa recta (DVR). The typical appearance of rat pericytes is also found in human DVR. Pericytes have contractile properties that enable DVR to react to vasoactive substances and thus take part in the control of medullary blood flow (19). B–D: close up of a region where contraction of pericytes leads to a diminution of DVR luminal diameter.
Fig. 2. Behavior of isolated human DVR perfused with contrast medium (CM). CM caused significant constriction of human DVR. Concomitant intra- and extraluminal application of adrenomedullin (AM) prevented the pronounced DVR constriction by CM. Adrenomedullin alone did not cause significant changes in DVR diameter (*P < 0.05).

Fig. 3. Behavior of isolated rat DVR perfused with CM. CM caused significant constriction of rat DVR. Concomitant intra- and extraluminal application of adrenomedullin prevented the pronounced DVR constriction by CM. Adrenomedullin alone did not cause significant changes in DVR diameter (*P < 0.05).
Fig. 5. Morphology of the endothelial cell layer of rat interlobar arteries investigated with scanning electron microscopy (SEM) following administration of CM alone or in combination with adrenomedullin compared with controls. Control endothelia show a slight, physiological nuclear bulging and alignment in the direction of flow (A, ×6,000). Endothelia of CM-treated vessels show massive cell bulging, widened irregular intercellular spaces (B, ×6,000) (C, ×12,000), and massive shedding of membrane blebs (D, ×12,000). Adrenomedullin alone (E, ×6,000) caused no visible changes of the endothelial cell layer compared with controls (A, ×6,000). Adrenomedullin, however, attenuated endothelial cell bulging, retraction, and blebbing in CM-treated vessels (F, ×6,000) compared with CM alone.
Fig. 4. Effects of CM on the reactivity of isolated perfused DVR to ANG II. DVR that were perfused with CM had an increased reactivity to ANG II. Concomitant intra- and extraluminal treatment with adrenomedullin prevented the increased ANG II response (*P < 0.05).
Review Article

Reactive Oxygen Species and the Pathogenesis of Radiocontrast-Induced Nephropathy

Samuel N. Heyman, MD,* Seymour Rosen, MD,† Mogher Khamaisi, MD, PhD,‡ Jean-Marc Idée, PhD,§ and Christian Rosenberger, MD¶

Abstract: Experimental findings in vitro and in vivo illustrate enhanced hypoxia and the formation of reactive oxygen species (ROS) within the kidney following the administration of iodinated contrast media, which may play a role in the development of contrast media-induced nephropathy. Clinical studies indeed support this possibility, suggesting a protective effect of ROS scavenging or reduced ROS formation with the administration of N-acetyl cysteine and bicarbonate infusion, respectively. Furthermore, most risk factors, predisposing to contrast-induced nephropathy are prone to enhanced renal parenchymal hypoxia and ROS formation.

In this review, the association of renal hypoxia and ROS-mediated injury is outlined. Generated during contrast-induced renal parenchymal hypoxia, ROS may exert direct tubular and vascular endothelial injury and might further intensify renal parenchymal hypoxia by virtue of endothelial dysfunction and dysregulation of tubular transport. Preventive strategies conceivably should include inhibition of ROS generation or ROS scavenging.

Key Words: reactive oxygen species, hypoxia, kidney, radiologic contrast media, kidney failure, acute

(Invest Radiol 2010;45: 188–195)
<table>
<thead>
<tr>
<th>TABLE 2. Putative Adverse ROS Effects Participating in the Pathogenesis of CIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct renal parenchymal oxidative injury</strong></td>
</tr>
<tr>
<td>Affecting cell membranes, cytosolic and nuclear systems</td>
</tr>
<tr>
<td><strong>Mitochondrial dysfunction</strong></td>
</tr>
<tr>
<td>Leading to feed-forward loop of enhanced ROS formation</td>
</tr>
<tr>
<td><strong>Enhanced tubular oxygen consumption and energy expenditure</strong></td>
</tr>
<tr>
<td>Leading to hypoxia and depleted energy stores</td>
</tr>
<tr>
<td>Due to enhanced transport activity in mTALs</td>
</tr>
<tr>
<td>Due to the activation of energy-consuming reparative processes (PARP)</td>
</tr>
<tr>
<td><strong>Altered endothelial function</strong></td>
</tr>
<tr>
<td>Leading to hypoxia</td>
</tr>
<tr>
<td>Due to defective nitrovasodilation</td>
</tr>
<tr>
<td>Due to the formation of vasoconstrictive isoprostanes</td>
</tr>
<tr>
<td>Due to the induction of or synergism with ET-1 and angiotensin II</td>
</tr>
<tr>
<td><strong>Altered cellular stress response</strong></td>
</tr>
<tr>
<td>Inhibition of HIF—upregulation</td>
</tr>
</tbody>
</table>

CIN indicates contrast media-induced nephropathy; ROS, reactive oxygen species; PARP, poly-(ADP-ribose) polymerase; HIF, hypoxia inducible factors.
Contrast-induced nephropathy (CIN) is the third leading cause of acute renal failure in hospitalized patients. Endothelial dysfunction, renal medullary ischemia, and tubular toxicity are regarded as the most important factors in the pathogenesis of CIN. Mannose-binding lectin (MBL), a pattern recognition protein of the lectin pathway of complement, has been found to aggravate and mediate tissue damage during experimental renal ischemia/reperfusion (I/R) injury which was alleviated by inhibition with Cl inhibitor, a potent MBL, and lectin pathway inhibitor. In this paper, we highlight the potential role of MBL in the pathogenesis of human CIN. In experimental I/R models, MBL was previously found to induce tubular cell death independent of the complement system. In addition, after binding to vascular endothelial cells, MBL and its associated serine proteases were able to trigger a proinflammatory reaction and contribute to endothelial dysfunction. In humans, urinary MBL was increased after administration of contrast media and in individuals with CIN. Moreover, individuals with normal/high MBL levels were at increased risk to develop radiocontrast-induced renal dysfunction. Hence, MBL and the lectin pathway seem to be a promising target given that a licensed, powerful, human recombinant inhibitor exits to be added to the scarce armamentarium currently available for prophylaxis of CIN.
Nefrojenik Sistemik Fibrozis
Scleromyxoedema-like cutaneous diseases in renal-dialysis patients

Shawn E Cowper, Howard S Robin, Steven M Steinberg, Lyndon D Su, Samardeep Gupta, Philip E LeBoit

15 renal dialysis patients have been identified with a skin condition characterised by thickening and hardening of the skin of the extremities and an increase in dermal fibroblast-like cells associated with collagen remodelling and mucin deposition. The disease closely resembles scleromyxoedema, yet has significant enough clinical and histopathological differences to warrant its designation as a new clinicopathological entity.
Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee guidelines

Henrik S. Thomsen • Sameh K. Morcos • Torsten Almén • Marie-France Bellin • Michele Bertolotto • Georg Bongartz • Olivier Clement • Peter Leander • Gertraud Heinz-Peer • Peter Reimer • Fulvio Stacul • Aart van der Molen • Judith AW Webb

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Fig. 1 Number of publications listed under “nephrogenic systemic fibrosis” in PubMed from 2001 to 2011. The decreasing number of papers probably reflects the fact that the incidence of NSF has been reduced to zero or almost zero after change to more stable agents.
Gadolinium-enhanced cardiovascular magnetic resonance: administered dose in relationship to United States Food and Drug Administration (FDA) guidelines

Figure 2 (A) Weighted mean contrast dose (mmol/Kg) from 2004 to 2010. (B) No change in mean gadolinium contrast dose before versus after FDA black box warning. Dashed horizontal lines represent minimum contrast dose and horizontal lines represent maximum contrast dose.
Nefrojenik Sistemik Fibrozis

• Gadolinium içeren kontrast ajanlar 4 kategori’ye ayrılıyor
  - İyonik lineer
  - İyonik makrosiklik
  - Non-iyonik lineer
  - Non-iyonik makrosiklik
Fig. 4. European Medicines Agency categorization of gadolinium-containing contrast agents by nephrogenic systemic fibrosis risk* [93–95]. *Based on thermodynamic and kinetic properties. Reproduced with permission from Bernstein E.J., Kay J. Nephrogenic systemic fibrosis: A fibrosing disorder induced by gadolinium exposure. Int J Adv Rheumatol 2011;9(4):123–33.
Risk Faktörleri

- KBH
- Non-iyonik, lineer
- Miktar
- Maruziyet süresi
Risk Faktörleri

- EPO
- IV demir
- Hiperkalsemi
- Hiperfosfatemi
- Asidoz
- KC yetmezliği
- Artmış inflamasyon
Cumulative risk factors

- Impaired renal function
- Systemic inflammation
- Vascular injury
- Increased body iron
- High erythropoietin dose
- Hyperparathyroidism
- Hypothyreoidism

Cumulative dose of Gd

Risk factors:

- Non-ionic linear Gd chelates
- Ionic linear Gd chelates
- Macrocyclic Gd chelates

Cumulative Risk of NSF
Table 3. Potential role of EPO in the pathogenesis of NSF

<table>
<thead>
<tr>
<th>Endothelial dysfunction increases</th>
<th>endothelin-1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>asymmetric dimethyl arginine</td>
</tr>
<tr>
<td>Proinflammatory increases</td>
<td>monocyte chemoattractant protein-1</td>
</tr>
<tr>
<td>Cell proliferation increases</td>
<td>endothelial cells</td>
</tr>
<tr>
<td></td>
<td>smooth muscle cells</td>
</tr>
<tr>
<td></td>
<td>endothelial progenitor cells</td>
</tr>
</tbody>
</table>
Advanced kidney disease, gadolinium and nephrogenic systemic fibrosis: the perfect storm
Mark A. Perazella

Section of Nephrology, Yale University School of Medicine, New Haven, Connecticut, USA
Correspondence to Mark A. Perazella, Section of Nephrology, Yale University School of Medicine, BB 114, 330 Cedar Street, New Haven, CT 06520-8369, USA
Current Opinion in Nephrology and Hypertension 2009, 18:519–525

Purpose of review
Studies of a rare systemic fibrosing condition-entitled nephrogenic systemic fibrosis (NSF) are linked to gadolinium-based contrast (GBC) agent exposure in patients with advanced kidney disease. However, many patients with kidney disease are exposed to GBC agents, yet they do not develop this devastating disorder.

Recent findings
NSF appears more likely to develop when the combination of advanced kidney disease,

Figure 1 Process of transmetallation of GBC agent

A nonionic linear chelate binds Gd\(^{3+}\) less tightly than other chelates, allowing endogenous cations such as Cu\(^{2+}\), Fe\(^{3+}\), Zn\(^{2+}\), and Ca\(^{2+}\) to compete with Gd\(^{3+}\) for chelate binding. This allows free Gd\(^{3+}\) to be released into the circulation when it may ultimately deposit in tissues. Gd\(^{3+}\), gadolinium; Cu\(^{2+}\), copper; Fe\(^{3+}\), iron; Zn\(^{2+}\), zinc; Ca\(^{2+}\), calcium (original material). GBC, gadolinium-based contrast.
# Table 2. Potency of various endogenous cations in inducing transmetallation of gadolinium-DTPA-BMA

<table>
<thead>
<tr>
<th>Cation-DTPA-BMA</th>
<th>$\log K_{\text{therm}}$</th>
<th>Transmetallation Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>$10^{7.2}$</td>
<td>+</td>
</tr>
<tr>
<td>Zinc</td>
<td>$10^{12}$</td>
<td>++</td>
</tr>
<tr>
<td>Copper</td>
<td>$10^{13}$</td>
<td>++</td>
</tr>
<tr>
<td>Gadolinium</td>
<td>$10^{16.9}$</td>
<td>–</td>
</tr>
<tr>
<td>Iron</td>
<td>$10^{21.9}$</td>
<td>+++</td>
</tr>
</tbody>
</table>

*K_{therm} is a thermodynamic stability constant. The plus and minus symbols refer to the degree of potency. +, mild; ++, moderate; ++++, strong; –, n/a.*

A patient with underlying kidney disease is exposed to a linear GBC agent. Due to an increased half-life, retained GBC (which has a low binding stability) undergoes transmetallation with endogenous cations (Fe$^{3+}$, Ca$^{2+}$, etc.) allowing free Gd$^{3+}$, intact GBC, or Gd$^{3+}$ bound to phosphate to enter tissues. Underlying inflammation and endothelial injury enhance leakage of Gd$^{3+}$ and GBC through the vasculature and entry into tissues. Once in tissues, Gd$^{3+}$ may be engulfed by macrophages, which produce local and systemic cytokines (and other mediators) that attract circulating fibrocytes (CF) to the tissues. The fibrocytes then become spindle cells that promote fibrosis through the production of various factors, particularly TGF-β1. GBC, gadolinium-based contrast; NSF, nephrogenic systemic fibrosis; TGF-β1, transforming growth factor-beta 1 (original material).
Gd compounds signaling through Toll-like receptors 4 and 7 in normal human macrophages: establishment of a proinflammatory phenotype and implications for the pathogenesis of Nephrogenic Systemic Fibrosis

Peter J. Wermuth and Sergio A. Jimenez
Jefferson Institute of Molecular Medicine. Thomas Jefferson University. Philadelphia. PA. USA
TEŞEKKÜRLER