Canadian Journal of Cardiology 32 (2016) 247–255

Review

Contrast-Induced Nephropathy: From Pathophysiology to Preventive Strategies

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ABSTRACT

Contrast-induced nephropathy (CIN) is a frequent cause of acute kidney injury in hospitalized patients. CIN is most commonly defined as either an absolute (≥ 0.5 mg/dL; ≥ 44 μmol/L) or relative (≥ 25%) increase in serum creatinine levels at 48-72 hours after exposure to iodinated contrast media (CM). Its occurrence is associated with worsened clinical outcomes. Patients undergoing cardiac catheterization and percutaneous coronary intervention are particularly vulnerable to CIN. The complex pathophysiology of CIN involves different mechanisms, such as vasoconstriction, oxidative stress, medullary ischemia, and the direct toxic effects of CM. In CIN pathophysiology, both patient-related and procedure-related risk factors have been identified. The risk for CIN can be reliably estimated with clinical scores such as that proposed by Mehran. Because no definitive treatment exists for CIN, the most effective strategy remains prevention. Several interventions have been investigated—from hydration to various pharmacologic agents and mechanical devices. In this state-of-the-art article, we review the pathophysiology, diagnosis, risk stratification, and preventive strategies for CIN.

RÉSUMÉ

La néphropathie induite par les produits de contraste est une cause fréquente de lésion rénale aiguë chez les patients hospitalisés. On la définit habituellement comme une élévation absolue (≥ 0,5 mg/dl; ≥ 44 μmol/l) ou relative (≥ 25 %) de la créatinémie dans un délai de 48 à 72 heures suivant l'exposition à un produit de contraste iodé. Elle est associée à une dégradation de l'état clinique du patient. Les patients qui doivent subir un cathétérisme cardiaque et une intervention coronarienne percutanée sont particulièrement vulnérables à cette complication. La physiopathologie de la néphropathie induite par les produits de contraste est complexe et est associée à plusieurs mécanismes, notamment la vasoconstriction, le stress oxydatif, l'ischémie médullaire et les effets toxiques directs du produit de contraste. Divers facteurs de risque ont été dénombrés – certains liés au patient et d'autres liés à l'intervention – et il est possible d'estimer avec précision le risque de survenue de cette complication à l'aide d'outils d'évaluation comme celui proposé par Mehran. Puisqu'il n'existe pas à l'heure actuelle de traitement clairement défini pour la néphropathie induite par les produits de contraste, la prévention demeure la meilleure solution. Plusieurs types d'interventions, allant de l'hydratation à l'administration de divers agents pharmacologiques en passant par l'utilisation de certains dispositifs mécaniques, ont été étudiés en vue de contrer cette complication. Dans cet article à la fine pointe des connaissances actuelles, nous examinons la physiopathologie, le diagnostic, la stratification du risque et les stratégies préventives de la néphropathie induite par les produits de contraste.

Epidemiology and Disease Burden

Contrast-induced nephropathy (CIN) has been defined as the occurrence of acute renal impairment within 2-7 days after administration of iodinated contrast media (CM).[1,2] After surgery and hypotension, CIN is the leading cause of acute renal failure during hospitalization (11%).[3] Half of the cases of CIN are reported in patients undergoing cardiac catheterization and percutaneous coronary intervention (PCI).[3,4]

The incidence of CIN in individuals with normal renal function who undergo PCI is low (< 3%).[5] Moreover, in the majority of patients who are actually diagnosed with CIN, this condition manifests exclusi1vely as an increase in serum creatinine (SCr) levels, which resolves spontaneously in a few days. However, the incidence of CIN rises dramatically (up to 40%) in patients with chronic kidney disease (CKD).[5-7] In these patients, CIN is associated with in-hospital need for dialysis (< 1%), long-term kidney failure, and overall mortality (7%-31%).[7-9] Finally, 13% of those requiring in-hospital dialysis may depend on dialysis permanently.[10] As such, CIN is associated with a longer length of stay and increased costs.[11] Therefore, CIN represents a significant

Received for publication March 29, 2015. Accepted May 19, 2015.

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See page 253 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.05.013

Table 1. Definitions of contrast-induced nephropathy

Definition	Author
Increase of ≥ 0.5 mg/dL (44 μmol/L) or ≥ 25% in serum creatinine at 48 h	Mehran et al.[12]
Increase of > 0.5 mg/dL (44 μmol/L) or > 25% in serum creatinine within 72 h	European Society of Urogenital Radiology[13]
Increase of ≥ 0.3 mg/dL (27 μmol/L) or ≥ 50% in serum creatinine with oliguria (< 0.5 mL/kg/h for > 6 h)	Acute Kidney Injury Network[14]
Increase of > 50% in serum creatinine or decrease of > 25% in glomerular filtration rate with oliguria (< 0.5 mL/kg/h for > 6 h)	RIFLE (**R**isk, **I**njury, **F**ailure, **L**oss of Kidney Function and **E**nd-Stage Kidney Disease) Classification[15]
Increase of > 100% in serum creatinine with oliguria (< 0.5 mL/kg/h for > 12 h)	Kidney Disease Improving Global Outcomes[16]
Increase of > 0.5 mg/dL (44 μmol/L) or > 25% in serum creatinine at 72 h	Canadian Association of Radiologists[17]

problem in current practice, and prevention strategies need to be optimized.

Variations in Definitions

Unfortunately, there is a lack of consensus on how to define CIN (Table 1), which hampers comparisons across studies. CIN has traditionally been diagnosed with 2 measurements of SCr levels (before and after CM exposure).[2,12-15,17,18] The most recognized definition is an absolute (≥ 0.5 mg/dL; ≥ 44 μmol/L) or relative (≥ 25%) increase in baseline SCr concentration at 48-72 hours.[2,18,17,19] This definition has been shown to correlate well with major adverse events and mortality on follow-up.[12,19]

Pathophysiology

The pathophysiology of CIN involves a complex interaction of several mechanisms (Fig. 1). CKD (defined as a baseline estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) plays a central role in the pathophysiology of CIN: a significant reduction in functional nephrons is the *milieu* in which CM exerts its toxic effects.[17,18]After a transient phase of vasodilation, CM induces intense vasoconstriction mediated by endothelin, inhibition of nitric oxide–mediated vasodilation, changes in the intracellular calcium concentration of smooth muscle cells, and adenosine (in contrast to its effects on the heart, adenosine causes prolonged vasoconstriction in the kidney).[20-22] The subsequent sustained reduction in renal blood flow contributes to renal injury in several ways: (1) release of reactive oxygen species; (2) "osmotic nephrosis" or vacuolization from direct toxic effects of CM on tubular cells, leading to acute tubular necrosis; and (3) ischemia of the outer regions of the medulla, further increasing tubular cell injury.[20-23] Moreover, the route of administration is important in determining the risk of CIN, because CM seems to be less nephrotoxic when injected intravenously than when given intra-arterially.[17,24] Finally, also the chemical properties of CM play a role in the pathophysiology of CIN (see next section).[23,25]

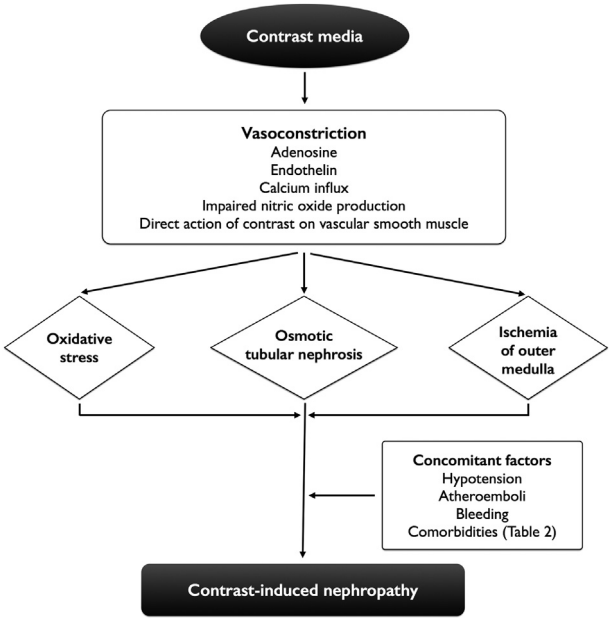

Figure 1. Pathophysiology of contrast-induced nephropathy.

It must be underscored that additional factors might confound the relationship between CM exposure and the development of acute kidney injury (AKI), such as hypotension, microembolization of atheromatous debris, or bleeding complications, which can lead to ischemic acute tubular necrosis.[18] In light of this, it is important to carefully analyze procedural events (eg, difficulty navigating an atheromatous aorta, persistent hypotension, and overt or nonovert bleeding), the baseline risk of certain procedures (balloon aortic valvuloplasty, aortic dilation and stenting), and patient characteristics (peripheral artery disease, anticoagulation, bleeding diathesis, and shock) to promptly address such complications. Imaging studies (eg, computed tomography) are valuable tools in ruling out embolic and bleeding complications, further refining clinical assessment.

Type of CM and CIN

Intravascular CM are tri-iodinated benzene derivatives that rely on iodine for their radio-opacity.[23] CM can be classified according to 2 properties: osmolality and viscosity. Osmolality expresses the ratio between the number of iodine atoms and the number of CM particles. A higher ratio (ie, a lower osmolality) will lead to improved attenuation of x-rays (and hence visualization), because there are more iodine atoms per particle in the CM.[26] Iodine, released from CM by photolysis, is 1 of the factors determining the cytotoxic effects of CM.[22,23]

High-osmolar CM (HOCM; 1000-2500 mOsm/kg) are ionic monomers with a ratio of 1.5:1, which ensures good visualization and water solubility.[20,23] Such compounds have been associated with pseudoallergic reactions and a high incidence of nephrotoxicity.[20] Therefore, low-osmolar CM