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Contrast-induced nephropathy: Basic concepts, pathophysiological implications and prevention strategies☆

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ABSTRACT

Contrast-induced nephropathy (CIN) is reversible acute renal failure observed following administration of iodinated contrast media (CM) during angiographic or other medical procedures such as urography. There are various mechanisms through which CM develop their nephrotoxic effects, including oxidative stress and apoptosis. CIN is a real-life, albeit not very rare, entity. Exact pathophysiology remains obscure and no standard diagnostic criteria apply. The Acute Kidney Injury Network criteria was recently employed but its incidence/clinical significance warrants further clarification based on recent methodological advancements, because most published studies to date were contaminated by bias. The current study is a comprehensive review conducted to provide an overview of the basic concepts of CIN and summarize recent knowledge on its pathophysiology and the evidence supporting potential prevention strategies. CIN is expected to increase morbidity, hospital stay and mortality, while all patients scheduled to receive CM should undergo risk assessment for CIN and high-risk patients may be considered candidates for prevention strategies. The value of using compounds with antioxidant properties other than sodium bicarbonate, remains controversial, warranting further clinical investigation.

Contents

Abbreviations: AKI, Acute kidney injury; BUN, Blood urea nitrogen; CIN, Contrast-induced nephropathy; CM, Contrast medium/media; GFR, Glomerular filtration rate; KIM-1, Kidney injury molecule-1; L-NAME, (N^{w}-nitro-L-arginine methyl ester); MDA, Malondialdehyde; NGAL, Neutrophil gelatinase-associated lipocalin; ROS, Reactive oxygen species; sCr, Serum creatinine; SOD, Superoxide dismutase.

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1. Introduction

Contrast-induced nephropathy (CIN) is reversible acute renal failure observed after administration of iodinated contrast media (CM) during angiographic or other medical procedures such as urography. The expected increase of serum creatinine (sCr) generally appears within 48 h after CM exposure, reaching a peak within the following 5 days. Increased morbidity, hospital stay and mortality is often associated with CIN (Golshahi, Nasri, & Gharipour, 2014; Rewa & Bagshaw, 2014). CIN has a considerable prevalence that reaches 15% in high-risk patients (see below; Section 6. Risk factors of CIN), whereas in ordinary patients the incidence does not exceed 1% (Rancic, 2016).

CM are non-reabsorbable solutes of high-, low- or isoosmolality, which act as osmotic diuretics, reducing electrolyte re-absorption along the nephron and thereby causing an increase in urine output (Solomon, 2014). Iodinated CM can be ionic or non-ionic, depending on their solubility in water. First generation CM have really high osmolalities (around 1000–2500 mOsm/kg) compared to plasma (290 mOsm/kg), due to the fact that osmolality, molar concentration and ionic strength are directly proportional quantities (Pannu, Wiebe, Tonelli, & Alberta Kidney Disease, 2006). The second generation CM were mainly characterised by lower solution osmolality of around 400–800 mOsm/kg, through formation of ionic dimers (ioxaglate) or non-ionic monomers (iopromide, iopamidol, iohexol, ioversol) (Pannu et al., 2006). The final step in evolution was the development of isoosmolar CM, such as iodixanol and iotrolan, which are non-ionic dimeric compounds. Pure low-osmolar CM solutions are actually hypoosmolar. Therefore, in order to reach plasma osmolality electrolytes are added (Jost et al., 2011).

The osmotic properties of CM could account for numerous hemodynamic alterations, including vasodilatation, increases in circulating blood volume and peripheral blood flow, and decreases in systemic resistance (hypotension) (McClennan, 1990). Hemodilution effects result from extravascular water shifts into the bloodstream that contribute to some of the hemodynamic perturbations associated with high-osmolar CM administration. Red blood cell changes (crenation and rigidity) and endothelial damage directly at the injection site accompanied by release of vasoactive substances, such as serotonin, histamine, prostaglandins, fibrinolysins, kallikreins, leukotrienes, bradykinin etc., may lead to hemodynamically altered microcirculation or other physiologic changes that may cause side effects. Some hemodynamic effects can be related to osmolality and to a lesser degree to the chemotoxic properties of the CM. These include negative inotropic effects and decrease in myocardial contractility after intra-cardiac injections. Decreased cardiac output and increased pulmonary artery pressure may occur along with plasma volume changes noted previously. Effects on the cardiac conduction system may result in abnormal electrocardiogram patterns, some of which may be clinically significant depending on the underlying cardiovascular status.

Reduction of osmolality in modern CM has ameliorated their safety profile (Caiazza, Russo, Sabbatini, & Russo, 2014) at the expense of increased viscosity (Jost et al., 2011). Viscosity strongly depends on iodine concentration of the solution, increasing exponentially (Seeliger et al., 2007) and strongly influences renal side-effects. CM with higher viscosity increase urine viscosity leading to higher tubular pressure that causes low urine flow rate and clearance, which in their turn prolong bioavailability, leading to a more pronounced tubular injury (Seeliger et al., 2010; Ueda, Nygren, Hansell, & Ulfendahl, 1993). High osmolality could actually reduce exposure through osmotic diuresis and in vitro dilution (Lenhard et al., 2012). Animal studies have shown that during administration of high viscosity isoosmolar CM, osmotic diuresis is missing and the dwelling time of CM in the urinary tubules and thus their bioavailability is higher (Jost, Pietsch, Lengsfeld, Hutter, & Sieber, 2010) (Fig. 1).

To mitigate this effect, current practice mandates a) right choice of the agent, b) heating of low-osmolar/isoosmolar CM before use because viscosity is inversely proportional to temperature and c) aggressive hydration around the time of exposure to dilute the agents and decrease their viscosity (Dorval et al., 2013). Most medical centres no longer use intravascular, high-osmolar CM to avoid various adverse effects associated with their use (ACR Committee on Drugs and Contrast Media, 2016). A meta-analysis showed that in patients with underlying renal insufficiency, nephrotoxicity of CM with low-osmolality is lower compared to high-osmolar CM (Barrett & Carlisle, 1993). It is not clear yet whether intravenous low-osmolar or isoosmolar CM (iodixanol) are less detrimental regarding CIN (Dong, Jiao, Liu, Guo, & Li, 2012; McCullough & Brown, 2011). According to the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines (Authors/Task Force members, 2014), for patients with moderate-to-severe chronic kidney disease undergoing coronary angiography or multi-detector computed tomography, CM volume should be minimized and isoosmolar should be considered over low-osmolar

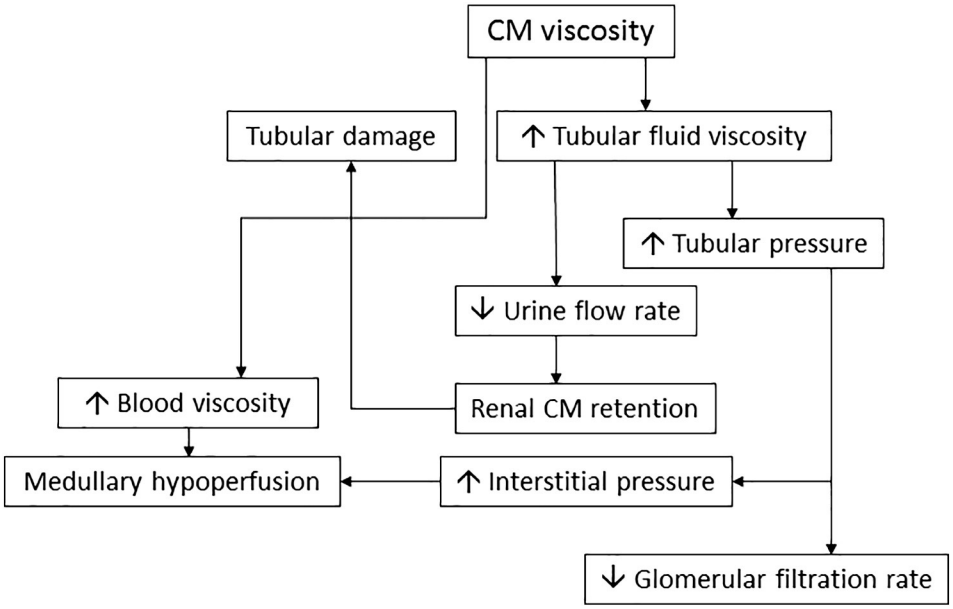

Fig. 1. Simplified scheme depicting the basic mechanism of CM viscosity-induced damage (Seeliger et al., 2012).

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