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Contents

Bimonthly Volume 6 Number 3 May 6, 2017

## REVIEW



## MINIREVIEWS



## ORIGINAL ARTICLE

### Case Control Study



### Retrospective Study

*World Journal of Nephrology*
**Volume 6 Number 3 May 6, 2017**

# Contents



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REVIEW

# Contrast-induced acute kidney injury: A review of practical points

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## Abstract

Contrast-induced acute kidney injury (CI-AKI) is one of the most common causes of AKI in clinical practice. CI-AKI has been found to be strongly associated with morbidity and mortality of the patients. Furthermore, CI-AKI may not be always reversible and it may be associated with the development of chronic kidney disease. Pathophysiology of CI-AKI is not exactly understood and there is no consensus on the preventive strategies. CI-AKI is an active research area thus clinicians should be updated periodically about this topic. In this review, we aimed to discuss the indications of contrast-enhanced imaging, types of contrast media and their impact on nephrotoxicity, major pathophysiological mechanisms, risk factors and preventive strategies of CI-AKI and alternative non-contrast-enhanced imaging methods.

**Key words:** Angiography; Nephrotoxicity; Computed tomography; Contrast-induced acute kidney injury; Contrast media; Cholesterol embolization syndrome; Hemodialysis; Contrast nephropathy



**Core tip:** The best preventive measure of contrast-induced acute kidney injury is to avoid unnecessary contrast administration which requires a good knowledge of indications and risk factors of contrast-enhanced imaging. Recently, alternative non-contrast-enhanced imaging modalities have been developed which may help us to decrease the frequency of contrast administration. In this review, these alternative modalities are discussed concisely. Type, osmolality, molecular structure and viscosity of contrast media (CM) are important determinants of nephrotoxicity. Major studies and meta-analyses comparing CM in terms of renal safety are also discussed.

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## INTRODUCTION

Medical imaging has become an important diagnostic and therapeutic tool in clinical medicine in the era of great technological advances. Contrast media (CM) are increasingly used for better imaging in a broad spectrum of areas such as diagnostic computed tomography (CT) and magnetic resonance imaging (MRI), procedures of interventional radiology and percutaneous transluminal coronary angioplasty (PTCA). There are several adverse effects of CM including nausea, vomiting, thyroid dysfunction and hypersensitivity reactions such as urticaria, laryngeal edema, bronchospasm, hypotension and anaphylactoid shock[1].

Contrast-induced acute kidney injury (CI-AKI) is one of the most important adverse effects of CM. In the past, CI-AKI was considered to be a mild state with asymptomatic and transient elevations in serum creatinine values however recent studies have demonstrated that both short term and long-term mortality rates have been found to be significantly higher in patients with CI-AKI compared to patients without CI-AKI[2]. Furthermore, a history of CI-AKI may be associated with development of chronic kidney disease (CKD) and progression to end-stage renal disease (ESRD) in long term[3,4].

In this review, we aimed to discuss the indications of contrast-enhanced imaging, types of CM and their impact on nephrotoxicity, major pathophysiological mechanism of CI-AKI, risk factors and preventive strategies of CI-AKI and alternative non-contrast-enhanced imaging methods.

## DEFINITION OF CM

CM is a chemical substance which is used to improve the image quality of various body parts, to differentiate pathological from healthy tissues and to better delineate vascular structures. CM may be used by the way of oral route, intravascular or also through other luminal organs however absorption and nephrotoxic effects of CM used other than intravascular route may be negligible. In this review, the effects of intravascular administration of CM will be discussed.

## DEFINITION OF CI-AKI

Various definitions of CI-AKI have been used in the literature. The most widely used definition is the increase in serum creatinine $\geqslant$ 0.5 mg/dL or 25% increase of serum creatinine from the baseline value at 48 h after CM administration. However timing of serum creatinine analysis after CM-enhanced imaging is controversial. Measurement as early as 12 h after the procedure (% change of creatinine from baseline) was found to significantly predict CI-AKI and furthermore it was associated with the development of renal damage after 30 d[5]. Serum cystatin C levels have also been evaluated as an early marker of CI-AKI. In the study by Briguori *et al*[6] performed on CKD patients undergoing PTCA, increase of cystatin C levels $\geqslant$ 10% at 24 h after the procedure was found to reliably predict the patients with high risk of CI-AKI.

## EPIDEMIOLOGY OF CI-AKI

Incidence of CI-AKI in patients undergoing elective, non-emergent contrast-enhanced CT has been found to be very low, < 1%[7]. In CKD patients, incidence of CI-AKI after intravenous CM administration was found to be 4%[8]. However incidence of CI-AKI following contrast-enhanced CT performed in an emergency setting was found to be higher, > 10% which might reflect the underlying severe clinical status of the patient[9]. Critically ill patients seem to be much more vulnerable to CI-AKI. In a study performed on critically ill patients without pre-existing renal disease, serum creatinine levels were elevated $\geqslant$ 25% from the baseline in 18% of the patients after CM-enhanced CT[10].

Incidence of CI-AKI in patients undergoing PTCA with normal baseline renal function was reported to be < 3%[11]. However, the incidence of CI-AKI was found to be as high as 40% in CKD patients undergoing PTCA[12,13].

## NEPHROTOXICITY OF MRI CONTRAST AGENTS

Until recently, MRI contrast agents also called gadolinium-based contrast agents (GBCA) have been considered to be safe in terms of nephrotoxicity. However GBCA has also been reported to cause AKI especially at high doses used for angiography in patients with pre-existing CKD and diabetic nephropathy[14-16]. In an *in vitro* study, cytotoxicity of GBCA was compared to that of iodinated CM in renal tubular cells at angiographic concentrations and GBCA was not less cytotoxic compared with iomeprol[17]. In another study, urinary interleukin-18 and N-acetyl-glucosaminidase levels were found to increase transiently after administration of GBCA in patients with normal renal function[18]. These results suggest that GBCA also induces cytotoxicity in renal tubular cells. Another important adverse effect of GBCA is the specific clinical entity called nephrogenic systemic fibrosis (NSF) which occurs especially in patients with CKD. NSF is a potentially mortal complication associated with GBCA. Recently, a relationship between previous gadolinium administrations and high signal intensity in the several parts of the brain has been suggested independent of renal function[19,20]. Gadolinium concentration in tissue was found to be strongly associated with cumulative gadolinium dose[21]. Currently, clinical significance of gadolinium deposition in tissues is unclear, further studies are needed to clarify this issue.

In clinical practice, although GBCA are considered to

**Table 1 Common indications for contrast media use in medical imaging**

| |
|---|
| Diagnosis and treatment of vascular diseases such as coronary artery disease, pulmonary thromboembolism, arteriovenous malformations, aneurysms, arterial dissections and thrombosis |
| Diagnosis and staging of neoplastic diseases and mass lesions |
| Diagnosis of inflammatory and infectious diseases such as multiple sclerosis, meningitis, pancreatitis, diverticulitis |

be relatively safer than iodinated CM, risks of AKI, NSF and brain deposition should be kept in mind[14,16].

## CLINICAL ISSUES NECESSITATING CM USE

It is important for clinicians to know the indications of contrast-enhanced imaging to avoid unnecessary contrast administration and its related complications. Common indications of CM use in clinical medicine are presented in Table 1. Accordingly, vascular, neoplastic and inflammatory diseases necessitate contrast-enhanced imaging. However CM is not usually suitable for the imaging of intracranial hemorrhages, cervical trauma, simple bone fractures, interstitial lung diseases and urinary system stones.

## TYPES OF IODINATED CM AND THEIR IMPACT ON NEPHROTOXICITY

Type, osmolality, molecular structure and viscosity of CM are important determinants of nephrotoxicity associated with these agents (Table 2). Hyperosmolal CM (HOCM) was shown to more frequently cause CI-AKI compared with low-osmolal CM (LOCM)[22]. However HOCM are no more used in clinical practice. There are controversial results in studies comparing iso-osmolal CM (IOCM) and LOCM as seen in Table 3. In most of these studies, no difference was found between IOCM and LOCM in terms of renal safety. Meta-analyses comparing IOCM and LCOM are presented in Table 4. In the meta-analysis by Reed *et al*[23], iodixanol (IOCM) was found to be associated with a reduced risk of CI-AKI compared to iohexol (LOCM) however risk of CI-AKI was not significantly different between iodixanol and other LOCM. In a very recent meta-analysis by Eng *et al*[24], a modest decrease in the risk of CI-AKI was found with iodixanol (IOCM) when compared to other LOCM however no difference was found between the groups in terms of risk of renal replacement therapy, cardiovascular outcomes or death. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommended to use LOCM or IOCM instead of HOCM however due to lack of reliable evidence, no recommendation was made about the preference of IOCM or LOCM[25].

IOCM has lower osmolality compared with LOCM, however since IOCM has dimeric structure, it has higher viscosity than that of monomeric LOCM. Viscosity rather than osmolality determines the resistance to blood flow, thus IOCM may impair renal medullary blood flow to a greater extent compared to LOCM[26]. Lack of clear superiority of IOCM over LOCM in terms of renal safety may be caused by higher viscosity of IOCM.

## MAJOR PATHOPHYSIOLOGICAL MECHANISMS OF CI-AKI

Exact pathophysiological mechanism of CI-AKI is not known and includes complex cascades of events. Proposed mechanisms of CI-AKI are presented in Table 5. The most important elements of pathophysiological mechanism of CI-AKI seem to be the medullary hypoxia due to CM-induced medullary vasoconstriction[27-29] and direct renal tubular cytoxicity[30-33]. CM-induced vasoconstriction is not exactly understood but it is probably caused by an imbalance between vasoconstrictive (endothelin, adenosine) and vasodilatatory mediators (nitric oxide and prostocyclin)[28,32,34]. The contribution of oxidative stress seems to be an important and complementary event that further exacerbates CI-AKI[32,35,36].

In normal physiological state, renal medullary blood flow and oxygen tension are relatively lower than those of the renal cortex. Furthermore, thick ascending limb located in the outer part of the renal medulla has a high-rate of ion transport with increased oxygen consumption exacerbating the relative hypoxia of the renal medulla. The most susceptible part of the nephron to hypoxia is well-known to be the renal medulla. CM is shown to decrase the oxygen tension of the renal medulla and simultaneously CM - induced osmotic diuresis causes increased sodium delivery to thick ascending limb leading to increased oxygen demand[27,37].

CM is known to cause direct mesangial and tubular cell toxicity. Proposed mechanisms of CM-induced cytotoxicity include oxidative stress, cellular energy failure, impaired cellular calcium homeostasis and increased apoptosis[33,38-40]. In the study by Peer *et al*[33], iodinated CM at different concentrations was found to induce apoptosis in both mesangial and tubular cells. The relationship between hypoxia, oxidative stress and direct cytotoxicity is not well-understood in the context of CI-AKI. Previously, a mismatch between the metabolic demands and the perfusion of renal medulla, in another words "relative hypoxia" was suggested to cause increased oxidative stress leading to further cytotoxicity[36]. However, recently, in the study by Liu *et al*[32], CM-induced direct cytotoxicity has been shown to cause increased oxidative stress even in the absence of hypoxia. Oxidative stress seemed to be a consequence not a cause of renal tubular injury. Furthermore, in this study CM was found to increase tubuloglomerular feedback which might contribute to disturbances of renal perfusion and filtration[32]. It may suggested that direct cytotoxicity of CM may be the primary event that pull the trigger rather than hypoxia, hypoperfusion or oxidative stress in the pathophysiological mechanism of CI-AKI.

**Table 2 Types, osmolalities and molecular structures of iodinated-contrast media**

| Osmolality | High osmolal (> 1400 mosm/kg) | Low osmolal (500-850 mosm/kg) | | Iso-osmolal (290 mosm/kg) |
|---|---|---|---|---|
| Molecular structure | Ionic/monomer | Ionic/dimer | Non-ionic/monomer | Non-ionic/dimer |
| Name of molecule | Diatrizoate (Hypaque) | Ioxaglate (Hexabrix) | Iohexol (Omnipaque)<br>Iopamidol (Isovue)<br>Ioversol (Optiray)<br>Iopromide (Ultravist)<br>Iopentol (Imagopaque)<br>Iomeprol (Iomeron) | Iodixanol (Visipaque) |

**Table 3 Major studies comparing low-osmolal and iso-osmolal contrast media in terms of renal safety**

| Ref. | Baseline renal functions/patient population | Procedure/ administration route | Compared drugs | Aim of the study/primary end points | Results |
|---|---|---|---|---|---|
| Feldkamp *et al*[94] | Normal GFR | PTCA (intra-arterial) | Iodixanol (IOCM) *vs* Iopromide (LOCM) | ⩾ 25% increase in SCr at 48 h | No difference |
| Hardiek *et al*[95] | Normal GFR, diabetic patients | PTCA (intra-arterial) | Iodixanol (IOCM) *vs* Iopamidol (LOCM) | ⩾ 25% increase in SCr days 1, 3 and 7 | No difference |
| Aspelin *et al*[96] (NEPHRIC) | CKD, diabetic patients | PTCA (intra-arterial) | Iodixanol (IOCM) *vs* Iohexol (LOCM) | Peak increase in SCr day 0–3 | Iso-osmolal safer than low-osmolal CM |
| Jo *et al*[97] (RECOVER) | CKD | PTCA (intra-arterial) | Iodixanol (IOCM) *vs* Ioxaglate (LOCM) | Increase in SCr ⩾ 25% or ≥ 0.5 mg/dL within 2 d | Iso-osmolal safer than low-osmolal CM |
| Solomon *et al*[98] (CARE) | CKD | PTCA (intra-arterial) | Iodixanol (IOCM) *vs* Iopamidol (LOCM) | Increase in SCr > 0.5 mg/dL at 45-120 h | No difference |
| Rudnick *et al*[99] (VALOR) | CKD | PTCA (intra-arterial) | Iodixanol (IOCM) *vs* Ioversol (LOCM) | Increase in SCr > 0.5 mg/dL within 72 h | No difference |
| Barrett *et al*[8] (IMPACT) | CKD | CT (intravenous) | Iodixanol (IOCM) *vs* Iopamidol (LOCM) | Increase in SCr > 0.5 mg/dL or ⩾ 25% at 48–72 h | No difference |
| Kuhn *et al*[100] (PREDICT) | CKD | CT (intravenous) | Iodixanol (IOCM) *vs* Iopamidol (LOCM) | Increase in SCr > 0.5 mg/dL within 48-72 h | No difference |
| Thomsen *et al*[101] (ACTIVE) | CKD | CT (intravenous) | Iodixanol (IOCM) *vs* Iomeprol (LOCM) | Increase in SCr > 0.5 mg/dL at 48-72 h | Low-osmolal safer than iso-osmolal CM |
| Nguyen *et al*[102] | CKD | CT (intravenous) | Iodixanol (IOCM) *vs* Iopromide (LOCM) | Peak rise in SCr days 1-3 | Iso-osmolal safer than low-osmolal CM |
| Wessely *et al*[103] | CKD | PTCA (intra-arterial) | Iodixanol (IOCM) *vs* İomeprol (LOCM) | Peak increase in SCr | No difference |

CM: Contrast media; CKD: Chronic kidney disease; LOCM: Low-osmolal contrast media; CT: Computed tomography; PTCA: Percutaneous transluminal coronary angioplasty.

CM - induced increase in blood and renal tubular viscosity may lead to resistance to blood flow and further exacerbate the medullary hypoxia[41]. Another important mechanism may be the mitochondrial dysfunction, especially ionic CM was found to impair the mitochondrial functions and membrane potentials in proximal tubular cells[42].

## RISK FACTORS FOR CI-AKI

Patients who are scheduled to have a contrast-enhanced diagnostic or interventional procedure should be evaluated for risk factors of CI-AKI (Table 6). Most important risk factors for CI-AKI are pre-existing CKD (GFR < 60 mL/min per 1.73 $m^2$) and diabetes mellitus which may have additive effects on each other. In a study performed on patients undergoing contrast-enhanced CT, incidence of CI-AKI was found to be higher in diabetic CKD patients compared with non-diabetic CKD patients[43].

### *Impacts of the type of imaging procedure and administration route of CM on CI-AKI*

Type of the contrast-enhanced procedure seems to be an important determinant of CI-AKI. As aforementioned in this review, risk of CI-AKI with invasive PTCA seems to be higher compared to that of contrast-enhanced CT. This difference of the risk of CI-AKI between the two procedures may be caused by two reasons: (1) clinical status and comorbidities of the patients; and (2) administration route of the CM. Patients undergoing PTCA usually have significant ischemic heart disease and advanced atherosclerosis. During PTCA, significant hypotension may occur leading to ischemic nephropathy in addition to CI-AKI. Another important adverse event that may occur with invasive angiographic procedures is the cholesterol embolization syndrome (CES) which is sometimes hard to differentiate from CI-AKI. Administration route of the CM may also be important in the occurrence of CI-AKI. For contrast enhanced CT, CM is given intravenously, however

**Table 4 Meta-analyses comparing iso-osmolal and low-osmolal contrast media in terms of renal safety**

| Metaanalyses | Baseline renal functions | Procedure/administration route | Compared drugs | Results |
|---|---|---|---|---|
| McCullough *et al*[104] (16 trials) | Both normal GFR and CKD | PTCA (intra-arterial) | Iodixanol (IOCM) *vs* various LOCM | Iodixanol safer than LOCM, *e.p.* in patients with CKD or CKD + diabetes mellitus |
| Reed *et al*[23] (16 trials) | Both normal GFR and CKD | PTCA + CT (intra-arterial + intravenous) | Iodixanol (IOCM) *vs* various LOCM | Overall, no difference. However, iodixanol safer than ioxaglate and iohexol |
| Heinrich *et al*[48] (25 trials) | Both normal GFR and CKD | PTCA + IV urography + CT (intra-arterial + intravenous) | Iodixanol (IOCM) *vs* various LOCM | Overall, no difference. However, iodixanol safer than iohexol in CKD patients when CM used *via* intra-arterial route |
| From *et al*[105] (36 trials) | Both normal GFR and CKD | PTCA + CT (intra-arterial + intravenous) | Iodixanol (IOCM) *vs* various LOCM | Overall, no difference. Iodixanol safer than iohexol |
| Eng *et al*[24] (29 trials) | Both normal GFR and CKD | PTCA + IV urography + CT (intra-arterial + intravenous) | Iodixanol (IOCM) *vs* various LOCM | Iodixanol slightly safer than LOCM but the lower risk did not exceed a minimally important clinical difference |

CM: Contrast media; CKD: Chronic kidney disease; LOCM: Low-osmolal contrast media; CT: Computed tomography; PTCA: Percutaneous transluminal coronary angioplasty.

**Table 5 Proposed pathophysiological mechanisms of contrast-induced acute kidney injury**

| |
|---|
| Medullary vasoconstriction and hypoxia[27-29] |
| Direct cytotoxicity to renal tubular cells[30-33] |
| Release of vasoconstrictive mediators: Endothelin, adenosine, angiotensin Ⅱ, vasopressin[28] |
| Reduction of vasodilatatory mediators: Nitric oxide, prostocyclin[28,32,34] |
| Increased oxidative stress[32,35,36] |
| Impairment of tubulo-glomerular feedback[32] |
| Increased blood and renal tubular viscosity[41] |
| Impairment of mitochondrial function and mitochondrial membrane potential[42] |

**Table 6 Patient-related and contrast media-related risk factors for contrast-induced acute kidney injury**

| |
|---|
| Patient-related risk factors |
| Pre-existing CKD |
| Diabetes mellitus and diabetic nephropathy |
| Older age |
| Simultaneous use of nephrotoxic drugs |
| Multiple myeloma |
| States of reduced kidney perfusion |
| Dehydration |
| Congestive heart failure |
| Hemodynamic instability |
| Contrast-media related risk factors |
| High volume of CM |
| Use of hyperosmolal CM |
| Multiple exposure to CM in short-term |
| Intra-arterial administration |

CKD: Chronic kidney disease; CM: Contrast media.

in PTCA, CM is given intra-arterially. Risk of CI-AKI has been found to be higher with intra-arterial CM compared to intravenous CM administration especially when CM is used suprarenally[44,45]. With suprarenal intra-arterial administration of CM, peak CM concentration within the kidney was found to be higher[46]. In the meta-analysis by Dong *et al*[47], risk of CI-AKI with intra-arterial iodixanol was found to be significantly lower when compared with intra-arterial LOCM. However no difference was found between IOCM and LOCM in terms of renal safety when CM was used intravenously. Similarly, in another meta-analysis by Heinrich *et al*[48], iodixanol was found to be safer than iohexol in CKD patients undergoing a procedure with intra-arterial CM administration. Iodixanol (IOCM) may be suggested to be a better choice for patients in the interventional cardiology setting[47].

### *Volume of CM*

Lower doses of CM (definitions of low dose are variable: < 30-125 mL) were found to be less nephrotoxic[49,50]. In a study by Manske *et al*[49], low dose of CM was defined as < 5 mL/kg per serum creatinine. Recently, newer CT modalities have been developed using low tube voltage and low CM volume to reduce radiation exposure and the risk of CI-AKI without sacrificing image quality[51-53]. However it should be kept in mind that even very low doses of CM may lead to CI-AKI in patients with high risk factors.

## RISK SCORING FOR CI-AKI

Several risk scoring systems have been developed to predict the CI-AKI. In the study by Mehran *et al*[54], CI-AKI was defined as an increase ⩾ 25% and/or ⩾ 0.5 mg/dL in serum creatinine at 48 h after PCI and they proposed a CI-AKI risk stratification score based on 8 readily available variables including (1) patient-related features such as age > 75 years, diabetes mellitus, chronic congestive heart failure (CHF), acute pulmonary edema, hypotension, anemia, and CKD; (2) procedure-related features such as the use of IABP or increasing volumes of CM. Integer scores of these risk factors were determined as: Hypotension, 5; IABP, 5; CHF, 5; age > 75 years, 4; anemia, 3; diabetes mellitus, 3; each 100 mL of CM, 1; serum creatinine > 1.5 mg/dL, 4; eGFR = 40-60 mL/min per 1.73 $m^2$, 2; eGFR = 20-40 mL/min per 1.73 $m^2$, 4; eGFR < 20 mL/min per 1.73 $m^2$, 6. These scores are summed up and total risk score is obtained. For example, if total risk score is ⩽ 5, risk of CI-AKI is 7.5% and risk of

**Table 7 Strategies to reduce the risk of contrast-induced acute kidney injury**

| |
|---|
| Assess the risk of CI-AKI |
| Assess the need of contrast-enhancement, avoid unnecessary contrast administration |
| Avoid concomitant use of other nephrotoxic drugs |
| Hydrate the patient with isotonic saline and/or sodium bicarbonate before and after the procedure |
| N-acetyl-cysteine 1200 mg orally twice daily |
| Prefer iso-osmolal or hypo-osmolal CM |
| Use minimum amount of CM |
| Check renal functions within 1 wk of the procedure |

CI-AKI: Contrast-induced acute kidney injury; CM: Contrast media.

dialysis is 0.04%. However risk of CI-AKI is 57% and risk of dialysis is approximately 13% with a total risk score of ⩾ 16. In conclusion, in this study, increasing total risk score was found to exponentially predict increased risk of CI-AKI. Another simple risk scoring for CI-AKI in patients undergoing PTCI is composed of age, creatinine and ejection fraction (ACEF score) which has been found to be an independent and useful predictor of CI-AKI defined as a rise in serum creatinine ⩾ 0.5 mg/dL[55,56].

## TREATMENT OF CI-AKI

There is no specific treatment for CI-AKI. There is no evidence that any of the preventive strategies are helpful once the CI-AKI develops. Similar to the management of other types of AKI, stabilization of hemodynamic parameters and maintenance of normal fluid and electrolyte balance is crucial. Thus, prevention may be the only treatment modality for CI-AKI.

## PREVENTION OF CI-AKI

Preventive strategies of CI-AKI are presented in Table 7. First things first, to prevent CI-AKI, avoid unnecessary contrast administration which requires good communication between the clinician and the radiologist. Clinicians should be informed about the medical imaging techniques alternative to contrast-enhanced medical imaging. If contrast use is inevitable, every patient should be evaluated for the risk factors for CI-AKI. Re-evaluation of concomitant use of other nephrotoxic drugs is of the utmost importance. Non-steroid anti-inflammatory drugs and nephrotoxic antibiotics such as aminoglycosides, colistin and antifungals such as amphotericin B should not be used if clinically possible.

### *Intravenous hydration*

Various strategies and drugs have been tried to prevent CI-AKI in the literature (Table 8), however intravascular hydration seems to be the best preventive measure against CI-AKI[57-59].

In a prospective randomized study, hydration with isotonic (0.9% saline) and half-isotonic (0.45% sodium chloride plus 5% glucose) solutions were compared in terms of efficiency in prevention of CI-AKI in patients undergoing coronary angioplasty. Hydration was performed before, during and after the procedure and total amount of hydration was approximately 2000 mL. In this study, isotonic hydration was found to be superior to half-isotonic hydration in the prevention of CI-AKI[57]. In a study performed on patients undergoing nonemergency cardiac catheterization, saline hydration starting from 12 h before the procedure was compared to unrestricted oral fluid intake[59]. Patients in the first group received normal saline for 24 h (at a rate of 1 mL/kg per hour). Intravenous saline hydration was found to decrease the both incidence and severity of CI-AKI. In contrast, in a very recent prospective, randomized, non-inferiority study performed on CKD patients (eGFR: 30-59 mL/min per 1.73 $m^2$) undergoing an elective procedure with CM, patients were randomly assigned to receive intravenous 0.9% NaCl or no prophylaxis[60]. No prophylaxis group was found to be non-inferior to prophylaxis group and furthermore it was found to be cost-effective. However, despite the results of this study, we still strongly recommend hydration especially in patients with high risk of CI-AKI. Hypervolemia should be avoided during hydration of the patients. Monitorization of left ventricular end diastolic pressure was found to be a useful and effective way of guiding fluid replacement in a randomized controlled trial[61]. Further studies are needed to prove the efficacy of hydration in prevention of CI-AKI.

**Table 8 Experimental drugs and procedures to prevent contrast-induced acute kidney injury**

| |
|---|
| Drugs |
| Hydration with isotonic saline[57-59] |
| N-acetyl-cysteine[69,106-110] |
| Sodium bicarbonate[58,68,108,109,111] |
| Theophylline[112-114] |
| Mannitol[115] |
| Furosemide[115-117] |
| Ascorbic acid (vitamin C)[118] |
| Tocopherol (vitamin E)[119] |
| Statins[120-124] |
| Mesna[125] |
| Dopamine[126] |
| Fenoldopam (dopamin agonist)[127] |
| Calcium channel blockers (verapamil, diltiazem)[128] |
| Adenosine[129] |
| Endothelin receptor antagonists[130] |
| Atrial natriuretic peptide[131] |
| Iloprost ($PGI_2$ analogue)[132] |
| Misoprostol ($PGE_1$ analogue)[133] |
| Trimetazidine[134] |
| Erythropoetin[135,136] |
| Nebivolol[137] |
| Sodium citrate[138] |
| Procedures |
| Remote ischemic preconditioning[72,73] |
| Prophylactic hemodialysis/hemofiltration/hemodiafiltration[71,139,140] |

### *Sodium bicarbonate*

There is controversy about the efficacy of sodium bicarbonate to prevent CI-AKI, several studies found

sodium bicarbonate as protective against CI-AKI[62,63] while others found no beneficial effect[64-66]. In a meta-analysis, sodium bicarbonate was found to be protective against CI-AKI but with a borderline significance[63]. In another 2 meta-analyses, no difference was found between bicarbonate and saline in terms of prevention from CI-AKI[67,68].

There is no standard dose of sodium bicarbonate for the prevention of CI-AKI. In a study, bicarbonate solution was prepared by adding 154 mL of 1000 mEq/L sodium bicarbonate to 846 mL of 5% dextrose in $H_2O$[62]. In this study, hydration with sodium bicarbonate before contrast exposure is more effective than hydration with sodium chloride for prophylaxis of CI-AKI. In another study, bicarbonate solution was prepared with 75 mL of 8.4% sodium bicarbonate added to 1 L of isotonic saline[65]. In this study, no difference was found between sodium bicarbonate plus saline group and hyration with only saline group in terms of prevention from CI-AKI. Since sodium bicarbonate contains high amount of sodium, risk of hypervolemia should be taken into consideration especially in patients with congestive heart failure and CKD and dose of the bicarbonate should be individualized.

#### *N-acetylcysteine*

N-acetylcysteine (NAC) did not decrease the risk of CI-AKI in patients undergoing PTCA in a large randomized trial[69]. There are several meta-analyses about the efficacy of NAC against CI-AKI with both non-significant[70] and significant results[67]. Although the strength of the evidence is low, NAC is a well tolerated, inexpensive drug and it has a relatively good profile of adverse effects. Thus, in 2012, KDIGO suggested NAC for patients with high risk of CI-AKI[25]. There is no consensus on the dose of the NAC however it is usually used at a dose of 600-1200 mg orally twice daily.

#### *Prophylactic hemodialysis/hemofiltration*

Prophylactic hemodialysis (HD) and hemofiltration (HF) were not found to be protective against CI-AKI. In the meta-analysis including 8 studies of HD and 3 studies of HF, no beneficial effects of these treatment modalities was found against CI-AKI[71]. Furthermore, HD was found to increase the risk of CI-AKI. Thus prophylactic renal replacement treatments are not recommended.

#### *Remote ischemic preconditioning*

Remote ischemic preconditioning (RIP) is an interesting procedure that has been evaluated as a potential protective mechanism of CI-AKI. RIP depends on a hypothesis that a transient ischemia of an organ may protect against an ischemic injury of another distant organ. Mostly, RIP has been induced by arm ischemia performed by inflation of blood pressure cuffs. In preliminary studies, RIP has been found to decrease the risk of CI-AKI[72,73]. However further randomized clinical trials are needed before a recommendation can be made.

#### *Should we stop ACEI/ARB treatments before the contrast-enhanced imaging?*

Some clinicians may prefer to stop angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) before the contrast administration because ACEI/ARB are considered to increase the risk of CI-AKI. Supporting these concerns, in a retrospective study, use of ACEI/ARBs during PTCA was found to be independently associated with increased risk of CI-AKI[74]. However in a prospective randomized trial, discontinuation of ACEI/ARB treatments 24 h before PTCA did not influence the incidence of CI-AKI in patients with CKD[75]. We think that, cessation of ACEI/ARB treatments for only 1 d before the procedure might not be adequate because renal hemodynamic effects of these drugs might last longer. In a very recent meta-analysis, ACEI use was not found to have a significant effect on the CI-AKI in patients undergoing PTCA[76]. In summary, there is not enough evidence to recommend withholding or continuing ACEI/ARB treatments before contrast-enhanced imaging.

#### *Should we stop metformin treatment before the contrast-enhanced imaging?*

Metformin is not a nephrotoxic drug however it is excreted by the kidney. Metformin is known to cause severe lactic acidosis in patients with renal impairment. About 8% of cases reporting metformin induced lactic acidosis were found to be associated with CI-AKI[77]. Cessation of metformin at least 48 h before the contrast administration is a common but controversial clinical practice[78]. According to other researchers, the risk of metformin induced lactic acidosis is extremely low in patients with normal renal function thus discontinuation of metformin is considered unnecessary in non-uremic patients[79]. We think that it will be appropriate to discontinue metformin especially in CKD patients who are planned to have a contrast-enhanced procedure.

## ALTERNATIVE NON-CONTRAST ENHANCED IMAGING TECHNIQUES

In the era of rapidly evolving technology, new non-contrast-enhanced imaging modalities have been developed (Table 9). Most of these modalities are MRI-based techniques. Knowledge of these new techniques may be beneficial for the renal health of the patients needing contrast-enhanced imaging and interventions. Preference of these imaging modalities may be discussed between the clinician and radiologist.

## CONTRAST USE IN END-STAGE RENAL DISEASE

There are two concerns about the use of iodinated CM in patients with ESRD; risk of loss of residual renal function (RRF) and CM-induced hypervolemia.

**Table 9 Alternative non-contrast enhanced imaging techniques**

| Name of the technique | Clinical indications | Notes |
|---|---|---|
| TOF MR angiography | Cerebral aneurysm<br>Stroke<br>Atherosclerotic carotid disease<br>Arteriovenous malformation<br>Peripheral artery disease (less frequently) | No contrast agent is required |
| ECG-gated fast spin echo MR angiography | Peripheral artery disease<br>Thoraco-abdominal aortic aneurysm | No contrast agent is required.<br>Higher image quality compared to TOF MR angiography in peripheral arterial imaging |
| SSFP MR imaging | Coronary artery disease<br>Myocardial viability and function<br>Pericardial diseases<br>Renal artery stenosis<br>Congenital heart diseases | No contrast agent is required |
| Arterial spin labeling with/without SSFP | Native and transplanted renal renal artery stenosis<br>Renal perfusion<br>Cerebral blood flow<br>Characterization of masses | No contrast agent is required.<br>Evaluation of organ perfusion<br>When combined with SSFP, it can be used as an angiographic imaging |
| Phase contrast MR imaging | Imaging of major thoroco-abdominal vascular structures<br>Congenital heart disease<br>Renal artery stenosis | No contrast agent is required.<br>Quantification of blood flow and velocity |
| Carbon-dioxide angiography | Peripheral artery disease (mostly infra-diaphragmatic) | No contrast agent is required.<br>Non-allergenic, non-nephrotoxic, inexpensive.<br>Neurotoxic, risk of air trapping and distal ischemia |

TOF: Time-of-flight; MR: Magnetic resonance; ECG: Electrocardiography; SSFP: Steady-state free precession.

RRF is associated with better outcome and survival in patients with ESRD[80]. Thus it should be preserved by avoiding unnecessary use of CM and nephrotoxic drugs. HD treatment after iodinated CM exposure was not shown to preserve RRF in patients with ESRD[81].

Another concern about the contrast administration is the hypervolemia that may be induced by the CM. Sometimes clinicians may prefer to perform HD immediately after contrast enhanced imaging. However as reported by Hamani *et al*[82], new non-ionic LOCM does not seem to increase serum osmolality, arterial blood pressure and it does not cause hypervolemia. Thus immediate HD may not be warranted to prevent hypervolemia in stable chronic HD patients.

GBCA should be better avoided in ESRD patients because of the risk of potentially mortal complication: NSF which is a systemic fibrosing disease that occurs due to exposure to GBCA especially in patients with GFR < 30 mL/min[83]. If it is inevitable to use GBCA in ESRD patients, immediate HD after the imaging procedure should be considered because GBCA has been shown to be effectively removed by HD[84]. However no proof exists that HD after GBCA exposure reduces the risk of NSF.

In HD patients without urine output (no RRF), if contrast-enhanced imaging is required, CT is clearly preferred over MRI to avoid the risk of NSF.

## PROGNOSIS OF CI-AKI

Short and long term mortalities of patients with CI-AKI have been shown to be higher compared with patients without CI-AKI[85-87]. However there are few studies about the long-term renal prognosis of patients who developed CI-AKI. In a prospective study performed on patients with symptomatic peripheral artery disease undergoing PTCA, patients with CI-AKI were found to be at increased risk of long-term loss of renal function, cardiovascular events, and death[88]. In this study, one year after the procedure, decline in eGFR was significantly higher in patients with CI-AKI compared with patients without CI-AKI (12.4 mL/min *vs* 6.2 mL/min). In another observational study on CKD patients undergoing PTCA, persistent renal dysfunction was defined as the decrease of creatinine clearance ⩾ 25% of baseline values at 3 mo[3]. In this study, overall incidence of CI-AKI was found to be 12%, and persistent renal dysfunction was found in 18.6% of CI-AKI patients. Similarly, in another study performed on patients undergoing PTCA, continuous deterioration of kidney function (CDKF) was defined as > 25% increase in serum creatinine or serum creatinine > 0.5 mg/dL above baseline at 6 to 8 mo after PTCA[4]. In this study CDFK was found in 16% of the study population and this group of patients was found to have significantly higher 5-year mortality rate. In a large study performed to find the incidence of CKD onset after PTCA, incidence of new-onset CKD within 6 mo of the procedure was found to be 0.9%[89]. Furthermore, in this study trans-radial access site was found to be associated with less CKD than the femoral approach.

## CES

The most important alternative diagnosis of AKI after

contrast-enhanced imaging especially PTCA is the CES which is rarer than CI-AKI however long-term renal survival is significantly worse than CI-AKI[90]. CES manifests later than CI-AKI, usually 1-2 wk after the procedure. Dislodgement of cholesterol crystals from the atherosclerotic plaques leads to embolization of the small peripheral arterioles causing a multisystemic disease with allergic-immunological features including eosinophilia, hypocomplementemia, livedo reticularis, distal gangrenes with palpable pulses (blue-toe syndrome) and pathognomonic Hollenhorst plaques on ophthalmologic examination[91]. Renal biopsy reveals empty clefts within the obliterated lumens of the arterioles[90]. Differentiation of CI-AKI and CES is important because these two diseases may have different types of treatment modalities. Once developed, CI-AKI necessitates only supportive measures. However since CES is a type of allergic-immunological disease, anti-inflammatory treatments such as corticosteroids and cyclophosphamide may be considered[92,93]. But there is no proof of efficacy of these anti-inflammatory treatments on CES.

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