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Contrast-induced acute kidney injury in interventional cardiology: Emerging evidence and unifying mechanisms of protection by remote ischemic conditioning☆

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ABSTRACT

Contrast-induced acute kidney injury (CI-AKI) is a common complication of many diagnostic and therapeutic cardiovascular procedures. It is associated with longer in-hospital stay, more complicated hospitalization course, and higher in-hospital morbidity and mortality. With increasing use of contrast media in various diagnostic and interventional procedures, the prevalence of CI-AKI is expected to rise. Although pre-hydration with intravenous normal saline is recommended in patients with elevated risk of CI-AKI, this approach is often not feasible in many clinical settings. Remote ischemic conditioning (RIC), elicited by application of one or more, brief, non-injurious episodes of ischemia and reperfusion of a limb, is a promising therapy for preventing or attenuating the deleterious effects of contrast media on the kidney. Although the mechanisms of protection by RIC have not been completely defined, complex humoral, neural, and inflammatory pathways have been hypothesized to be in play. Given that RIC is non-invasive and cheap, it is attractive from clinical and economic perspective as a therapy to protect the kidney from CI-AKI. In this succinct review, we highlight the unifying mechanisms of CI-AKI and provide an overview of proposed biological mechanisms of renal protection by RIC. Emerging pre-clinical and clinical evidence in interventional cardiology is also discussed.

Contents

1. Introduction

Contrast-induced acute kidney injury (CI-AKI) defined as relative increase in serum creatinine within 48–72 h is a common complication of intravenous, iodinated contrast medium that is widely used for

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diagnostic and therapeutic cardiovascular interventions [1–10]. CI-AKI predicts elevated risk of heart attack, longer in-hospital stay, more complicated hospitalization course, and higher in-hospital morbidity and mortality [2,6–8]. It is one of the leading causes of hospital-acquired AKI, and the third most common cause of AKI after hypovolemia, and nephrotoxic medications [11]. The incidence of CI-AKI varies substantially (14.8 to 55%) among studies depending on how CI-AKI is defined, and the presence of risk factors such as chronic renal insufficiency, diabetes mellitus and heart failure [1–10,12]. The risk of CI-AKI is especially high in the setting of emergent cardiac procedures such as primary percutaneous coronary intervention (PCI) for acute myocardial infarction [2,12]. In the US, approximately 1.4 million cardiac catheterization procedures are performed each year, and other contrast-enhanced diagnostic imaging studies are performed for various purposes [13,14]. With increasing use of contrast medium in diagnostic and interventional procedures, the incidence of CI-AKI may rise in the next few decades. Although pre-hydration with intravenous normal saline is recommended in patients with elevated risk of CI-AKI, this approach is often not feasible in many clinical settings including patients with heart failure and acute ST elevation myocardial infarction (STEMI) requiring emergent primary PCI.

Emerging evidence suggests that remote ischemic conditioning (RIC), elicited by brief episodes of ischemia and reperfusion at a distant vascular bed, may protect vital organs including the kidney from subsequent injury [15–19]. This strategy appears to be protective when applied prior to ischemic injury (pre-conditioning), during ischemic injury (peri-conditioning) or at the onset of reperfusion (post-conditioning) [17]. Classically, RIC is performed in humans by inflating a blood pressure (BP) cuff placed around one limb to a pressure above systolic BP for 5 min followed by deflation for another 5 min to allow reperfusion; this cycle is usually repeated 3–4 times [16,17]. Given that RIC is non-invasive and cheap, it is attractive from clinical and economic perspective as a therapy to protect the kidney from CI-AKI. In this succinct review, we highlight the unifying mechanisms of CI-AKI and provide an overview of proposed biological mechanisms of renal protection by RIC. Emerging pre-clinical and clinical evidence is also discussed.

2. Contrast media and contrast-induce acute kidney injury risk

Iodinated contrast medium is a substance used to enhance the visibility of vascular structures and organs during radiographic procedures. As detailed in Table 1, contrast media may be either ionic or non-ionic; or be of high or low osmolarity. Evidence indicates that type of contrast agents plays a role in the development CI-AKI [20–22]. In one study, for example, administration of a nonionic, low-osmolality contrast agent led to an 18% reduction in creatinine clearance [20]. In comparison, an ionic high-osmolality contrast medium produced a greater reduction in creatinine clearance (42%) [20]. Among patients with normal or mildly depressed renal function, use of a non-ionic, low-osmolality contrast medium minimized nephrotoxicity as measured by reductions in creatinine clearance after coronary angiography [21]. In the meta-analysis of 45 trials, greater increase in serum creatinine after administration of high- compared with low-osmolality contrast medium was seen in patients with pre-existing renal failure [22]. Thus, nonionic and low osmolality contrast media are preferred in patients at high risk for developing CI-AKI. The volume of contrast medium is another major modifiable risk factor for CI-AKI [12,23,24]. Although minimizing contrast volume is the preferred strategy for the prevention of CI-AKI, some studies have shown that relatively low volume of contrast (less than 100 ml) can still induce permanent renal injury and the need for dialysis in patients with diabetes and pre-existing chronic kidney disease [25,26].

Table 1
Commonly used iodinated contrast media.

Name	Type	Iodine content	Osmolality	
Nonionic				
Iohexol (Omnipaque 350)	Monomer	350 mgI/ml	884	Low
Iopamidol (Isovue 370)	Monomer	370 mgI/ml	796	Low
Iopromide (Ultravist 370)	Monomer	370 mgI/ml	774	Low
Ioxilan (Oxilan 350)	Monomer	350 mgI/ml	695	Low
Iodixanol (Visipaque 320)	Dimer	320 mgI/ml	290	Low
Ionic				
Metrizoate (Isopaque 370)	Monomer	370 mgI/ml	2100	High
Diatrizoate (Hypaque 50)	Monomer	300 mgI/ml	1550	High
Ioxaglate (Hexabrix)	Dimer	320 mgI/ml	580	Low

Many risk factors predict increased risk for developing CI-AKI including: pre-existing kidney disease, older age, female gender, diabetes, heart failure, use of nephrotoxic drugs, renal artery stenosis, nephrotic syndrome, multiple myeloma, and renal transplant [4–6,12]. Diabetes mellitus increases the risk of CI-AKI in patients undergoing cardiac catheterization partly because of impaired nitric oxide generation [25,27]. Also, older age is an independent predictor of CI-AKI for multiple reasons including age-related changes in renal function such as diminished glomerular filtration rate, tubular secretion, and concentrating ability of the kidneys [5,12]. Periprocedural hypotension is also a major risk factor for the development of CI-AKI, and even a relatively short period of hypotension is hazardous [12,28]. Detailed analyses of these risk factors have been previously published [12]. Mehran et al. combined these risk factors to develop a risk classification system for prediction of CI-AKI in patients undergoing coronary angiography [12].

3. Mechanism of contrast-induced acute kidney injury

The pathogenesis of CI-AKI has been proposed to include vascular and tubular pathways. A detailed review of pathophysiological mechanisms of CI-AKI is outside the scope of this review, and has been extensively reviewed [29–33]. Of the various proposed pathways, the major pathophysiological concepts of CI-AKI are: 1) contrast medium–induced vasoconstriction and reduction in renal blood flow resulting in renal ischemic injury; 2) iodinated contrast agent and oxygen free radical–mediated direct renal tubular toxicity [29–33].

3.1. Vasoconstriction and renal ischemic injury

It is well established in the literature that contrast agents induce natriuresis and diuresis, which activate the tubuloglomerular feedback response, resulting in vasoconstriction of the glomerular afferent arterioles causing a decrease in glomerular filtration rate [33–36]. The best data related to the pathogenesis of contrast-induced vasoconstriction come from animal models. Studies have shown evidence of acute tubular necrosis (ATN) following contrast agent infusion in animal models, though the mechanisms are still not completely understood [34–36]. The most favored theory is that ATN is caused by renal vasoconstriction resulting in medullary hypoxia, possibly mediated by alterations in nitric oxide, endothelin, and/or adenosine. Given that the renal medullary vascular bed is composed of long vessels of small diameter, reduction in renal medullary blood flow may also be due to increased viscosity of contrast agent and enhanced tubular interstitial pressure. The outer medulla, in particular appears to be susceptible to injury due to reductions in renal blood flow [35]. This increased susceptibility results from baseline borderline hypoxic conditions in the outer medulla, which are due in part to the high oxygen requirements for active sodium transport and countercurrent flow [36].

3.2. Direct renal tubular cytotoxicity

Direct tubular injury, due to direct cytotoxic effects of contrast medium or in association with the generation of oxygen free radicals, contributes to CI-AKI [37,38]. Importantly, direct cytotoxicity may also be exacerbated by and act in concert with renal artery vasoconstriction. Sustained reduction in renal blood flow, because of vasoconstriction,