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Contrast-Induced Nephropathy in Coronary Angiography and Intervention

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1. Introduction

Since the advent of coronary angioplasty more than 3 decades ago, the volume of percutaneous coronary interventions (PCI) has been rising progressively, with relative decrease in amount of coronary artery bypass graft (CABG) surgery. Roughly 1.4 million of catheterization procedures are performed in U.S. each year.[1] Contrast medium is widely used in both diagnostic coronary angiography and PCI, and intravenous use of iodinated contrast medium is a common precipitator of contrast-induced nephropathy (or contrast-induced acute kidney injury [AKI]). [2, 3] With the trend of increasing PCI use in the modern era, expectedly more patients will develop contrast-induced AKI in the future. Currently contrast-induced nephropathy has been the third most common cause of hospital-acquired AKI in the large registry studies. [4] This phenomenon is worthy of our attention, since past researchers have identified that contrast-induced AKI can be associated with increased late incidence of acute myocardial infarction (AMI) and target vessel revascularization [5], longer in-hospital stay [6], a more complicated hospitalization course (bleeding episodes requiring transfusion, vascular complications) [7], and higher in-hospital mortality and morbidity [8-10]. More importantly, contrast induced AKI correlates with higher healthcare resource utilization including hospitalization cost [11]. The economical spending increases even further if the episodes of contrast-induced AKI are dialysis-requiring.

We have witnessed significant advancement in the development of contrast medium within the past 7 decades. [8] The structure, osmolality and its inherent chemotoxicity have also changed tremendously, and are the focuses of experiments involving various animal models, cell culture systems, and human subjects. [12] In addition, knowledge of the pathogenesis and the relevant risk factors of contrast-induced AKI is also expanding, and this progress contributes significantly to our planning of strategies to prevent this

adverse event after contrast medium injection. In this sense, a thorough understanding of the epidemiology, pathophysiology, clinical manifestations, diagnosis, prevention strategy and management of contrast-induced AKI is of critical importance for both primary care physicians and intervention cardiologists.

2. Epidemiology of contrast induced acute kidney injury (AKI)

The reported incidence of contrast-induced AKI varies widely among the existing literature, ranging from 2% to 25% after contrast medium injection [2, 13-15]. The estimations differ according to the cohort being studied, the definition used to identify patients with contrast-induced AKI, the distinction of the baseline risk factors of the population studied, and the intervention administered for prevention. [2] Maioli and coworkers, in a randomized controlled trial (RCT) to evaluate the effectiveness of various preventive strategies, identified a 2~2.5 fold difference in the incidence of contrast-induced AKI (control group, 12%; intervention group, 27.3%). [16] Weisbord and colleagues, in another study, demonstrated the importance of the AKI definition to the estimated incidence (ranging from 0.3% if stringently defined by serum creatinine [sCr] change of 1.0 mg/dL, to 13.7% if loosely defined by sCr change of 0.25 mg/dL). [3] Consequently, a consistent definition of contrast-induced AKI is vital for both clinical and research interest in this field.

2.1. Definition of contrast-induced acute kidney injury (AKI)

The definition of contrast-induced AKI can be divided into 2 main components, the pre-defined time frame and the change of renal function markers (Table 1). Typically contrast-induced AKI is defined by the current literature as an increase in sCr within the first 24 or 48 hours after contrast injection. [2, 14] There are arguments, however, that a period of 24 hours best captures the group of patients who develop contrast-induced AKI and carry the most favorable outcome; others claim that the elevation of sCr for clinical diagnosis of contrast-induced AKI takes at least 48 hours. [17] The European Society of Urogenital Radiology (ESUR) has produced guidelines on contrast-induced AKI in 1999, and updated the content in 2011. [18, 19] Contrast-induced AKI (then termed contrast-induced nephropathy [CIN]) is defined as “a condition in which an impairment in renal function (an increase in sCr by more than 25% or 0.5 mg/dL) occurs within 3 days following intravascular administration of a contrast medium, in the absence of an alternative etiology”. [18] Recently, the threshold of sCr change for diagnosis of AKI has been challenged, since minor sCr change has been shown to correlate with outcome measures. [20] In 2007, Acute Kidney Injury Network (AKIN) group has proposed a further fine-tuned classification scheme for staging AKI. [21] Milder AKI was staged as an elevation of sCr of 0.3 mg/dL within 48 hours. This concept further enhances the diagnostic probability of contrast-induced nephropathy, but there concerns that this criteria might be over-sensitive and leads to false positive diagnosis. [22] The researchers are now gradually adopting this scheme in categorizing contrast-induced AKI.

<i>Potential Serum markers</i>	<i>Time frame</i>		
	<i>Within 2-4 hours after procedure</i>	<i>Within 24 hours after procedure</i>	<i>Within 48 hours after procedure</i>
Serum creatinine		0.5 mg/dL ↑	0.5 mg/dL ↑
Serum creatinine		1.0 mg/dL ↑	
Serum creatinine		25% ↑ from baseline	25% ↑ from baseline
Serum creatinine		50% ↑ from baseline	
Serum cystatin C [#]	? 25% ↑ from baseline		
Urinary NGAL [#]	↑ >100-150 ng/mL		

Abbreviations: NGAL, Neutrophil gelatinase-associated lipocalin

[#] Still under investigation

Table 1. The currently available definition of contrast-induced nephropathy

Other rapidly-responsive serum markers aiming at earlier detection of renal function change also are under investigation. Cystatin C is a cationic low molecular weight cysteine protease, produced at a constant rate by all nucleated cells.[23] It is not metabolized in the serum, and is freely filtered by glomeruli, thus serving as a good marker for assessing glomerular filtration rate (GFR).[24] A Japanese study utilizing cystatin C and sCr in evaluating post-computed tomographic coronary angiography AKI concluded that serum cystatin C at day one after examination significantly correlates with change of sCr, indicating AKI. [25] Cystatin C is particularly useful in patients with diabetic history. On the other hand, Ribichini et al, in another study comparing sCr and cystatin C for detecting AKI after PCI within 12 hours, found that serum cystatin C performed significantly worse than sCr, with an area under curve (AUC) value of 0.48 only. [26] Neutrophil gelatinase-associated lipocalin (NGAL) is a small stress protein released from injured tubular cells after various stimuli. [27] A multitude of studies have documented its role in earlier detection of AKI, with excellent sensitivity and fair specificity.[28-30] Hirsch and coworkers first demonstrated in pediatric population that, with a cut-off value of 100 ng/mL and timeframe of 2 hours, urinary NGAL predicts contrast-induced AKI well, with 73% sensitivity and 100% specificity. [31] Another study from Austria reached similar findings, with additional benefit of improving renal outcome, possibly due to earlier detection. [32] Besides, there are other potential candidate biomarkers implicated as possessing a role in contrast-induced AKI, including kidney-injury molecules -1 (KIM-1), urinary L type fatty acid-binding protein (L-FABP), but few human studies are available currently.[33] Finally, the exact diagnostic modality of choice for contrast-induced nephropathy remains uncertain. A recent study by Erselcan and colleagues discovered that sCr-based diagnosis can in fact differ substantially from radionuclide-based GFR estimation method. [34] Consequently, the reported incidence of contrast-induced nephropathy in the literature might contain certain degree of deviation. Nonetheless, a close monitor-

ing of sCr change and other markers of renal function change after contrast exposure is still crucial and necessary to detect any evidence of contrast-induced nephropathy after PCI.

3. Risk factors for contrast induced acute kidney injury (AKI)

Identification of patients potentially susceptible of developing contrast-induced AKI before their exposure is important, since modification of the ways we administer contrast medium can lead to a decrease in AKI. [4] Risk factors for developing such injury can be divided into 2 parts: patient-related factors and procedure-related factors. We will give a brief overview of these factors in the following sections.

3.1. Patient-related risk factors

There are several factors identified in the literature that enhances the susceptibility of developing contrast-induced AKI (Table 2).

Patient-related risk factors	Procedure-related risk factors
Advanced age	Higher contrast medium volumes
Diabetes (especially with nephropathy)	Higher contrast medium osmolality
Pre-existing CKD	Intra-arterial (vs. intravenous) route
Arterial hypotension	
Absolute intravascular volume depletion status	
Relative intravascular volume depletion status	
Diuretic use	
NSAID use (?)	
ACE inhibitor/ARB use (?)	

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory agent

Table 2. Factors associated with increased risk of contrast-induced acute kidney injury

3.1.1. Diabetes mellitus (DM)

DM has been established as an independent factor for patients developing contrast-induced AKI. Presence of DM is associated with a 1.5 ~ 3 fold higher risk of renal injury after contrast exposure, and it potentially amplifies the risk incurred by pre-existing chronic kidney disease (CKD) alone (see below). [13, 15, 35] DM putatively predisposes host kidneys to ischemic injury (from macro- or micro-vascular stenosis), increases oxidative stress and free radical damage, as well as endothelial dysfunction.[36] The accompanying co-

morbidities such as coronary artery diseases also contribute to the increased susceptibility. [37] Fluid retention in DM patients also increases the use of diuretics, which is also reportedly a risk factor for contrast-induced AKI. [38] In addition to the impact of a baseline DM, pre-procedural glucose level higher than 200 mg/dL is also a risk factor for contrast-induced AKI (2-fold risk). [39]

3.1.2. *Advanced age*

Advanced age is another risk factor that enhances the probability of developing contrast-induced AKI. The definition of advanced age differs between the reported studies, but generally a range of 65-75 year-old is adopted. [15] Age higher than 75 can associate with a 1.5-5 fold elevated risk, while every one-year increment carries a 2% increased risk. [7, 15, 35] Aging *per se* denotes the physiologic degeneration of the kidney, both structurally and functionally, and the ability of recovery after various nephrotoxic insults also dampens in this population. [40] Most experts agree that a baseline renal function should be measured in older patients before their exposure to contrast medium. [2, 19]

3.1.3. *Pre-existing chronic kidney disease (CKD)*

Probably the most important risk factor for contrast-induced AKI is a baseline comorbidity of CKD. Almost all clinical trials and scoring models for predicting and stratifying risk of contrast-induced AKI have shown that CKD independently leads to more contrast-induced AKI episodes. [6, 7, 9, 13, 15, 35] The risk of renal dysfunction is directly proportional to the baseline sCr value, and further amplified by the presence of DM. [7, 15] Rihal et al, in a large PCI cohort, identified that patients with pre-procedural sCr 1.2-1.9, 2.0-2.9, >3 mg/dL, had a graded increment in risk of developing contrast-induced AKI (odds ratio [OR] 2.4, 7.4 and 12.8, respectively). [35] One-third of patients with sCr level higher than 2.0 mg/dL receiving contrast medium for radiographic studies will develop contrast-induced AKI. [41, 42]

The definition of CKD seems to vary somewhat between studies. It is generally agreed that patients with CKD should be classified by the stages proposed by the Kidney Disease Outcome Quality Initiative (KDOQI) according to their GFR values. [19] (Table 3) CKD is usually defined as renal function within stage 3 or higher level based on the KDOQI scheme, but there are some controversy about this. [43] GFR can be estimated by the Modification of Diet in Renal Disease (MDRD) formula, which takes account of each patient's sCr, age, ethnicity and gender. [44] However, this equation might be flawed when applied in patients with unstable or changing renal function. Patients with special dietary preference such as vegetarians and high protein diets, and ones with extreme body stature (very obese or lean) may be unsuitable by MDRD formula, too. [44] Recently, Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) creatinine equation is found to outperform MDRD formula in these situations, but this equation, too, does not apply during changing renal function. [45] Nonetheless, sCr-based estimation of GFR is currently still the most valuable and timely method of grading patients' baseline renal function. Patients with estimated GFR (eGFR) higher than 60 ml/min/1.73m² should be treated as normal unless they have other renal diseases. [46]

3.1.4. Arterial hypotension

Hemodynamic instability has been quoted as a risk factor for contrast-induced AKI. [6, 13, 15] This can be demonstrated in certain parameters like hypotension and placement of intra-aortic balloon pump (IABP). [47] Gruberg and coworkers identified that use of IABP is linked to a 2 fold increase of developing contrast-induced AKI in patients receiving PCI. [48] In addition, anemia *per se* can also be treated in this regard as a factor that reduces tissue oxygenation and predisposes to CIN. [49]

3.1.5. Absolute intravascular volume depletion (dehydration)

Dehydration is commonly cited as a risk factor for contrast-induced nephropathy. [35, 50, 51] However, few clinical trials actually prove this risk, possibly owing to the fact that dehydration status is difficult to demonstrate and quantify.

3.1.6. Relative intravascular volume depletion

Statuses such as congestive heart failure (CHF) also potentiate the development of contrast-induced AKI, through mechanisms similar to dehydration and absolute intravascular volume depletion. [2, 15] CHF is also a risk factor for AKI in critically ill patients. [2] Most clinical trials have shown that CHF (with a New York Heart Association [NYHA] grade 3-4) is associated with elevated risk of contrast-induced AKI (OR around 1.5-2.0). [13, 15, 35] There are also studies showing that AMI within 24 hours of PCI with a low left ventricular ejection fraction (LVEF) independently predicts occurrence of CIN, with a 80% higher risk. [6, 35]

3.1.7. Drugs (Angiotensin-converting enzyme inhibitors [ACEI], angiotensin-receptor blockers [ARB], Non-steroidal anti-inflammatory agents [NSAID])

ACEI and ARB, by virtue of their glomerular hemodynamic effect, have been implicated in predisposing patients to contrast-induced AKI. [42] However, minimal data exists regarding their actual role in the development of such renal injury. Currently, most available results are retrospective in nature, and case numbers are low. Umrudhin and colleagues, in a small case control study, demonstrated that use of ACEI or ARB is associated with 2.5-3.0 fold higher risk of developing CIN after coronary angiography. [52] On the contrary, withdrawal of ACEI or ARB before coronary procedures does not seem to reduce the risk of contrast-induced AKI. [53]

NSAIDs are commonly prescribed for analgesic and anti-pyretic purposes, and are notorious for their adverse impact on cardiovascular outcomes after AMI. [54] Through the interruption of intrarenal prostaglandin production, these drugs impede the hemodynamic regulation of kidney during nephrotoxic insults. Intuitively, they should contribute significantly to contrast-induced nephropathy, but there are very few clinical data currently. A Brazilian group identified no obvious increase in risk of CIN in patients taking NSAIDs before they receive coronary procedures, but the case number was low. [55] Further study is

warranted before we can conclude that NSAID is neutral or potentially promoting contrast-induced AKI at this time.

Other nephrotoxic agents such as cyclosporin, tacrolimus, platinum-based chemotherapeutic regimen can theoretically enhance the susceptibility of the kidney to the insult of contrast medium. [56] Likewise, few clinical data exists concerning this issue, but physicians and cardiologists are still advised to refrain from these drugs in patients preparing for coronary procedures.

3.1.8. *Miscellaneous*

Elevated high sensitivity CRP has recently been reported as a risk factor for contrast-induced AKI. [57] The mechanism is putatively related to higher inflammatory status and the cytokine effect, but this remains speculative. Some researchers also claimed that multiple myeloma elevates the risk of CIN, but this association is inconsistent among recent studies. [56, 58, 59] Multiple myeloma by itself might not increase the inherent risk, but patients with myeloma is frequently dehydrated, and such dehydration could underlie the basis of the heightened risk. [19]

3.2. Procedure-related risk factors

Procedure-related risk factors include the volume, the osmolality, and the route of contrast medium administration.

3.2.1. *Osmolality of contrast medium*

Iodinated contrast media are structurally composed of carbon-based skeletons and iodide atoms, which render the molecules radiopaque. Contrast media are classified according to their osmolality into 3 types: high-osmolal (HOCM) (ex. diatrizoate), with an osmolality of ~2000 mOsm/kg; low-osmolal (LOCM)(ex. Iohexol, iopamidol, ioxaglate), with an osmolality of 600~800 mOsm/kg; and isosmolal (IOCM) (iodixanol), with an osmolality similar to serum. [2] When the contrast media were first introduced decades ago, only HOCM are available for imaging purposes. LOCM/IOCM were later developed in 1980s and 1990s, in order to reduce the accompanied toxicity incurred by high osmolality. [8] Earlier meta-analysis before 1990 demonstrated that the pooled OR for developing CIN decreased substantially after the introduction of LOCM. [60] High osmolality contrast medium is now an established risk factor for contrast-induced AKI. [2, 8, 14, 19] IOCM has been shown to possess the lowest risk for contrast -induced AKI in patients with CKD, but different IOCM agents do not seem to display clinically different effect. [61-64] A systemic review performed several years ago found that IOCM possess the lowest risk of contrast-induced AKI. [64] However, several clinical trials done in recent years yielded conflict results, with similar CIN rates between IOCM and LOCM agents. [65, 66] Despite these controversies, the American College of Cardiology (ACC) /American Heart Association (AHA) guidelines for the management of patients with acute coronary syndrome (ACS) list IOCM as a class I recommendation. [67]

3.2.2. *Volume of contrast medium*

The volume of administered contrast medium can be another important factor regarding the risk of contrast-induced AKI. Multiple studies have identified that the mean contrast volume is an independent predictor of CIN. [5, 9, 15] Even small volumes of contrast medium (~30ml) might trigger renal injury in high-risk patients. [68] For every 100ml increase in the amount of contrast medium used, there is a concomitant 12% increase of the risk. [35] Several groups proposed that the volume of contrast administered should not exceed twice the number of a given patient's baseline eGFR value (in milliliter), while others found that adjustment of the contrast volume to one's body weight and sCr level could minimize the risk. [2, 69]

3.2.3. *Route of contrast medium administration*

Circumstantial evidence has pointed out that intra-arterial injection of contrast medium carries a higher risk of contrast-induced AKI than intravenous use. [15, 70] However, no mechanisms have been provided to explain this phenomenon. [2] Some speculative reasons are as follows: the dose used in intravenous enhancement for computed tomography (CT) is usually lower than that for arteriography; patients who received contrast-enhanced CT are usually less hemodynamically unstable than ones receiving intra-arterial studies; intra-arterial angiography may incidentally incur atheroembolism, which would not be expected to happen in intravenous studies. [2, 19] There are also reports suggesting that patients who were at-risk for intra-arterial procedures might not be at-risk for intravenous studies. [3] Nonetheless, based upon the available evidence, it is prudent to evaluate patients regarding the exact necessity, risk and benefit for intra-arterial or intravenous procedures. If both indications exist with equal risk-benefit ratio, a choice of intravenous administration of contrast medium might be better.

4. **Clinical course and pathophysiology of contrast-induced AKI**

The norm of contrast-induced nephropathy is that sCr begins to rise within 24 hours after contrast medium administration, peaks at 3-5 days, and returns to baseline level or near baseline within 1-3 weeks. [71] It has been shown that even transient rise of sCr can associate with longer hospital stay. [42] Most patients developing contrast-induced AKI do not require dialysis; however, they do have poorer short-term and long-term survival. [9, 48] Gruberg et al, in a large cohort of patients with CIN after coronary angiography, reported that only 0.4% require hemodialysis after AKI occurs, but those necessitating dialytic support have particularly higher mortality (12-35%). [42, 48]

The pathophysiologic sequence of contrast-induced AKI includes a pre-existing impaired renal function, and the superimposed acute events consisting of vasoactive mediator-related vasoconstriction, triggered by iodinated contrast medium. [2] Besides, experimental studies also suggest that contrast-induced nephropathy can be a combination of both: renal ischemia and the direct tubulotoxicity exerted by contrast medium. [42]

4.1. Renal ischemia

Animal studies showed that contrast medium intravascular injection can increase the activity of a variety of vasoactive substances, including vasopressin, angiotensin II, dopamine-1, endothelin and adenosine, while decrease the activity of renal vasodilators such as nitric oxide and prostaglandins. [72, 73] Other mechanisms include high osmolality-related renal blood flow decrease, and the enhanced erythrocyte aggregation induced by contrast medium. [74, 75] This decrease in renal blood flow and GFR after exposure to contrast medium is frequently severer in dehydrated animals than euvolemic ones. [76] In particular, renal medulla is more susceptible to ischemic insult than renal cortex, and contrast medium has been reported to cause shunting of blood flow to the cortex. [77]

4.2. Direct tubulotoxicity

The tubulotoxicity of contrast medium can be demonstrated in the pathological changes it induces, including epithelial vacuolization, cellular necrosis or apoptosis and interstitial inflammation. [78] Contrast medium can additionally reduce antioxidant enzyme activity within the kidney of experimental animals, and free radical mediated cytotoxicity of the renal tubular cells has been detected in these models. [78] The higher osmolality of contrast medium can also contribute to its epithelial cell toxicity. The osmolar-driven solute diuresis with subsequent tubuloglomerular feedback activation can theoretically reduce GFR, and increased tubular hydrostatic pressures might cause compression of surrounding microvasculatures, leading to a decrease in GFR. [42] In an in vitro cell model, apoptosis (presenting as DNA fragmentation) was found to increase in cells exposed to hyperosmolar contrast media, with the degree of fragmentation proportional to the osmolality of contrast media. [79] Consequently, contrast medium possesses direct tubulotoxicity not only through the induction of oxidative stress and cellular injury, but also through the hyperosmolality it carries. It would be interesting to speculate whether the available isosmotic contrast media can reduce the renal abnormality displayed by exposure to their high osmolar and low osmolar counterparts, but there seems to be no difference. [80] A plausible reason is that isosmolar contrast medium still has increased viscosity and might cause more tubular cell vacuolization and cessation of renal microcirculation. [81]

5. Risk prediction and modeling

Many research groups have strived to devise predictive models for patients with high risk of developing contrast-induced AKI. Mehran and colleagues developed a simple scoring method that integrates 8 baseline clinical variables to evaluate the risk of CIN after PCI. These variables include advanced age (defined as age > 75), hypotension, CHF, anemia, DM, CKD (defined as sCr > 1.5 mg/dL), use of IABP and procedural factors (volume of contrast medium), each with different score. [15] Risk categories are divided into low, moderate, high, and very high. They found that the incidence of contrast-induced AKI ranges from 7.5% in the low risk category, to 57.3% in the very high risk category. Bartholomew and

coworkers, in another large cohort of post-PCI CIN patients, derived a risk scoring scheme composed of DM, CHF, hypertension, peripheral vascular disease, IABP uses, CKD (defined as creatinine clearance < 60 ml/min), and procedural factors (urgent or emergency procedures, contrast volume ≥ 260 ml). [13] Incidence of CIN ranged from 0.5% in the lowest risk category, to 43% in the highest risk category. These studies did prove that the risk factors identified previously are mutually additive, and the risk of contrast-induced AKI increases prominently as risk factors accumulate. However, none of the reported studies have been prospectively applied to different populations, and the utility in real-world is still in question. It is currently inappropriate to recommend the routine use of these models in risk stratification of specific population [2], but we should bear in mind that the more risk factors our patients possess, the higher risk he/she might develop AKI after receiving PCI.

6. Strategies of prevention for contrast-induced AKI

6.1. Modification of risk factors

Some of the patients' baseline comorbidities cannot be changed (eg. DM, CHF, etc.), but others are potentially modifiable to reduce the risk of developing CIN. First, the selection of the patients for PCI can be important. Patients with unstable hemodynamic status or circulatory collapse are at high-risk of developing contrast-induced AKI, and the risk/benefit ratio needs to be carefully weighed for these patients. [42] The clinical need for PCI should be scrutinized, and the in-charge cardiologist or hospitalist should consider whether another procedure without the use of iodinated contrast media can act as a substitute. [59] Nonetheless, in the setting of emergency procedures (like primary PCI), where the benefit of very early intervention outweighs the risk of waiting for the results of the blood test, it is still necessary to proceed without available sCr. [2] When possible, it is still desirable to obtain a pre-procedural blood sample for sCr, since the likelihood of impaired renal function pre-procedurally can increase the subsequent risk of developing CIN and other adverse events. Second, patients with DM, HTN, CHF or potentially changing renal function should receive a pre-procedural baseline renal function testing (if they have not received one before), and if possible, a nephrology/radiology specialist consultation could be obtained. [2] Hyperglycemic status should be properly managed before procedure. Agents such as NSAIDs, diuretics (if feasible), and possibly ACEIs should be discontinued 1-2 days before administration of contrast media. [42] Finally, if PCI or diagnostic coronary angiography is warranted, the amount of contrast medium volume should be as little as possible, and the choice of contrast medium should be iso-osmolar or low osmolar agents, especially in patients with high risk. [2, 8, 14, 42] Repeated exposure should be delayed for 48 hours in patients at-risk of developing contrast-induced AKI, and an even longer delay if patients are diabetic or have pre-existing CKD. [42] Ideally, the interval between procedures should be 2 weeks, the expected recovery time for kidney after an acute insult, but frequently this is not possible, especially in patients with AMI and complicating courses. [19] In this situation, the interval should still be as long as clinically acceptable.

6.2. Volume expansion

There is broad consensus that volume expansion (through isotonic saline hydration) is capable of reducing the risk of contrast-induced nephropathy. The putative benefit of adequate volume expansion includes improving renal blood flow, inducing diuresis with dilution of contrast medium within renal tubules, suppression of the renin-angiotensin-aldosterone system, lowering the secretion of arginine vasopressin, and less reductions in the renal production of endogenous vasodilators (nitric oxide, prostaglandin). [82] However, firm evidence regarding the benefit of volume expansion is not available and not expected to exist, since randomized, double-blinded trials comparing hydration and a control group without hydration cannot be performed for lack of ethical acceptability.

6.2.1. Route of volume expansion

The route of volume expansion has been debated. Earlier expert group consensus suggested that intravenous hydration is more favorable than oral hydration [18], but clinical evidence seemed conflicting. Trivedi and coworkers prospectively evaluated the efficacy of unrestricted oral fluids or intravenous normal saline for 24 hours (at a rate of 1ml/kg/hr, 12 hours before and 12 hours after procedures) in a small group of elective PCI patients. [83] Contrast-induced AKI occurred significantly less frequently in the intravenous hydration group than the oral fluid group (3.7% vs. 34.6%). Dussol et al performed another study comparing intravenous normal saline (at a rate of 15 ml/kg for 6 hours before procedure) to oral salt tablet (1g/10kg body weight for 2 days before procedure) in a moderately-sized cohort receiving various radiologic studies. [84] Oral salt supplement was found to be as effective as intravenous saline hydration for the prevention of contrast-induced AKI. However, the pre-procedural fasting policy routinely instituted in some groups might make oral salt tabley not feasible. Nonetheless, most groups currently use intravenous hydration for volume expansion purposes in clinical practice.

6.2.2. Formula of hydration

Currently the most popular and effective solution for preventing CIN is isotonic saline (0.9%). Earlier studies comparing saline and other solutions including mannitol or mannitol with furosemide have demonstrated the superiority of saline infusion. [85, 86] The strategy of forced diuresis is also not favored by existing evidence. In the PRINCE study (Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation), Stevens and coworkers found no benefit from forced diuresis with intravenous crystalloid, furosemide, mannitol or low-dose dopamine therapy, compared with hydration alone in at-risk patients. [86] The lack of benefit of mannitol and furosemide might come from their renal untoward effects, including osmotic diuresis-related increase of renal oxygen consumption, vasoconstrictor effect of mannitol and diuretic-induced hypovolemia. [42] In addition, Mueller et al, in a large group of patients receiving PCI, compared the strategy of isotonic saline (0.9%) infusion to half-isotonic saline infusion (0.45%, + plus 5% glucose) starting one day before procedures. [87] Isotonic hydration is superior to half-isotonic hydration in the efficacy for prevention of contrast-induced AKI.

The issue of sodium bicarbonate for preventing contrast-induced AKI is also controversial. It is suggested that sodium bicarbonate might result in urine alkalinization and reduce the generation of free radical through scavenging reactive oxygen species. [19] Bicarbonate can also increase urine flow, while on the contrary, the large amount of chloride from isotonic saline infusion may lead to constriction of the renal vasculature. [88] Merten and colleagues first performed a pilot study comparing sodium bicarbonate (154 mEq/L in dextrose 5% water at a rate of 3ml/kg/hour) started one hour before procedure and continued for six hours after (at a rate of 1ml/kg/hour), to infusion of sodium chloride at a similar rate. [89] The more favorable effect of sodium bicarbonate prophylaxis inspired multiple follow-up studies focusing on similar issues, with more-or-less similar results. Several metanalysis concluded that sodium bicarbonate is more effective than sodium chloride in protecting against CIN, but the heterogeneity of included studies exist, with even publication bias in some studies. [88, 90] Besides, the lower risk of contrast-induced AKI does not seem to translate into lower mortality or less need for dialytic support. [91] The potential risk of alkalemia induced by sodium bicarbonate infusion in patients with CHF and electrolyte disturbance (hypocalcemia, hypokalemia) is another concern. Nonetheless, based upon existing evidence, sodium bicarbonate serves as an equal or even better choice for prevention of contrast-induced AKI, compared with sodium chloride. [19]

6.2.3. Amount and rate of volume expansion

There is currently no clear evidence for the optimal rate and duration of volume expansion. Correlation with patients' body weight seems reasonable, and expert consensus agrees that 1.0-1.5 ml/kg/hour of infusion is appropriate. [19] However, there are clinical trials comparing overnight hydration before elective procedures to bolus hydration immediately before the procedures, and continuous hydration seems to provide better protection. [92] It is recommended now that intravenous hydration should start 12 hours before PCI or coronary angiography and continue for 12 hours after, at a rate provided above. [19]

6.3. Pharmacological prophylaxis

Other than intravenous hydration, pharmacologic prophylaxis for at-risk patients against CIN has been tested with multiple drugs, but currently no single agent is approved specifically for this purpose. [19] Several candidate drugs have been attempted, with conflicting results. We will briefly review these drugs in the following section.

6.3.1. N-acetylcysteine (NAC)

NAC has been the center of investigation during the last decade. It possesses antioxidant and potentially vasodilatory properties. [8] Usually NAC is given orally but intravenous formula is also available, and owing to its low price, the availability is also high. NAC has minimal side effects and is generally considered safe. The most common protocol of NAC is to give this agent orally 600mg twice a day for 24 hours on the day before and the day of procedure. [19]

More than 30 randomized controlled trials have been performed regarding the efficacy of NAC for preventing contrast-induced AKI, and most studies involve patients receiving PCI or diagnostic coronary angiography. The results are conflicting, with some displaying lower incidence of CIN, while others demonstrating no significant benefit. [93-95] Some researchers proposed that higher dose NAC might be more effective than standard dose NAC [96], but we should remind ourselves that intravenous NAC at higher doses might be associated with significant side effects (hypotension, bronchospasm, etc.) Meta-analysis of existing studies also display conflicting results, depending on the studies included. [97-99] However, most studies are under-powered, and the beneficial effect of NAC is mostly deducted by earlier studies, with small size and lower quality. [19] Furthermore, there have been observations that NAC might lower sCr without affecting GFR, devoid of benefit to renal function. [100] In conclusion, the benefit of NAC in preventing contrast-induced AKI remains unproven, and the use of NAC should be carefully weighed against the potential side effects listed above.

6.3.2. *Fenoldopam*

Fenoldopam mesylate is a selective dopamine-1 receptor agonist that produces systemic and renal artery vasodilatation. [42] It is found to exhibit desirable renal effects including decrease in renal vascular resistance and increase in renal blood flow, GFR, with natriuresis. Small-group studies have identified potential benefit of fenoldopam with normal saline in the amelioration of renal blood flow reduction caused by contrast media, but this is not validated in a subsequent large, multicenter, double-blind randomized placebo-controlled trial. [101] It is also found to perform inferiorly to NAC in several controlled trials. [102] Currently, the routine use of fenoldopam to protect against contrast-induced AKI could not be recommended.

6.3.3. *Theophylline*

Theophylline, through cyclic AMP generation, is found to relieve the renal vasoconstrictive response to contrast media injection potentially mediated by adenosine in animal models. [103] Multiple investigators have evaluated the competitive adenosine antagonists, theophylline and aminophylline as candidate agents for reducing the risk of CIN. A meta-analysis concluded that prophylactic theophylline use appears to protect against contrast-induced AKI, but the included trials are few, and publication bias is likely. [103] There are also studies suggesting the superiority of theophylline over NAC. [104] Further evaluation is needed in this regard. Significant side effect resulting from use of theophylline is rarely observed during short-term use and if serum concentration being kept low.

6.3.4. *Ascorbic acid*

Ascorbic acid is a potent, water-soluble antioxidant capable of scavenging reactive oxygen species that potentially introduces damage to vital macromolecules. Ascorbic acid has been shown to attenuate renal damage from various types of insult, including post-ischemic stress, cisplatin-related and aminoglycoside-related injury in animal models. [105] It also

possesses extensive safety record as a harmless dietary supplement. Randomized controlled trials utilizing oral ascorbic acid as a prophylactic strategy for reducing CIN have been performed, and the results appear to be positive. [106] Boscheri et al, in a small cohort, failed to display benefit of ascorbid acid. [107] In this sense, definite conclusion also can not be made at this time, owing similarly to low case numbers and somewhat flawed study design.

6.3.5. *Statin*

Statin, also hydroxymethylglutaryl coenzymeA reductase (HMG-CoA) inhibitor, improves the lipid profiles of patients, and has reportedly pleiotropic effects on vasculature, including decreasing low-density lipoprotein (LDL), lipid peroxidation, improving inflammation, lowering risk of cellular necrosis and elevated collagen content in human plaques. [108] Statin therapy significantly reduces cardiovascular mortality and morbidity in patients with hyperlipidemia, and post-procedural statin also is shown to reduce cardiovascular events in patients receiving PCI. [109] Although the exact mechanism by which statin reduces iodinated contrast media-induced AKI is still unclear, it is likely that one of the anti-oxidation, anti-inflammatory, and anti-thrombotic effects can be the principle reason. [110] In a large group of PCI patients, statin use was found to reduce incidence of CIN (OR 0.87). [110] Patti et al further demonstrated that pre-procedural statin use not only prevents against contrast-induced AKI but also leads to a better long-term survival after 4 years of follow-up. [111] Several recent meta-analyses yielded conflicting results, and some researchers proposed that statin might be helpful mostly in patients with more advanced CKD. [112, 113] Thus, it remains unknown whether statins is beneficial for preventing contrast-induced AKI at present, and further clinical trials are awaited to determine the specific group of patients that acquire the most benefit from statin use.

6.3.6. *Iloprost*

Iloprost is a stable prostaglandin I₂ (prostacyclin) analogue, which exerts renal vasodilatory effect and has been shown to protect animal kidneys against ischemic and toxic insults. [114] Development of contrast-induced AKI might partially originate from attenuation of the renal prostacyclin response, and thus iloprost is theoretically beneficial for the prevention of CIN. Spargias and coworkers first conducted a pilot study on iloprost, with a regimen of 1-2 ng/kg/min infusion from 30-90 minutes before procedures and continuing until 4 hours after procedures, for prevention of CIN. [115] The result was promising. Subsequent larger confirmatory trials yielded similarly positive findings. [116] However, these results were all produced by a single group, and other researchers have not been able to replicate their findings. The other drawbacks of iloprost are its tolerability issues. [116] Further studies are needed to affirm the role of iloprost in our armamentarium against contrast-induced AKI.

6.3.7. *Miscellaneous*

There is limited evidence regarding low-dose dopamine, calcium channel blockers, atrial natriuretic peptides, L-arginine, endothelin antagonists in their roles in the prevention of contrast-induced nephropathy. [19]

7. Conclusion

Contrast-induced AKI, or contrast-induced nephropathy, is a growing issue in the contemporary field of intervention cardiology and also in fields like diagnostic radiology. Although the definitions of contrast-induced AKI are still changing with the advancement of new biomarkers reflecting renal function and injury, the most popular and cost-effective method is still serum creatinine. As the understanding of the pathogenesis of CIN also progresses, more and more strategies for prevention of contrast-induced AKI are being developed and tested clinically. It will be vital for primary care physicians and cardiologists to carefully select their patients as candidates of contrast medium containing procedures, knowledgeably stratify the risk, and implicate evidence-based prophylactic means to reduce the incidence of contrast-induced AKI.

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