Device-Based Therapy in the Prevention of Contrast-Induced Nephropathy

Dion Stub, MBBS, PhD, Stephen J. Duffy, MBBS, PhD, David M. Kaye, MBBS, PhD

INTRODUCTION

Acute kidney injury after exposure to radiographic contrast media, contrast-induced nephropathy (CIN), is a major cause of acute renal failure associated with significant morbidity and mortality. The incremental presence of predisposing factors, including preexisting chronic kidney disease (CKD), contrast volume, diabetes, and advancing age, contributes significantly to the risk of CIN, which may exceed 30% in the highest-risk patients. Given the frequent coexistence of some of these risk factors in patients with atherosclerosis, individuals undergoing coronary angiography or coronary intervention represent a particularly high-risk group. The development of CIN has major clinical implications, with associated higher procedural mortality, longer hospitalization, and risk of permanent renal injury requiring long-term renal replacement therapy. In this context, there has been considerable interest in the development of strategies to reduce the risk of CIN, including a range of pharmacologic and device-based approaches. As reviewed elsewhere, pharmacologic approaches have yielded somewhat variable effects of the incidence of CIN, leading to increasing interest in other techniques that may be more efficacious in the prevention of CIN.

Importantly, the applicability of the various preventive interventions must also be considered in light of the specific clinical scenario. For example, the development of CIN in patients presenting with ST elevation myocardial infarction is associated with a particularly poor outcome. Given the time imperative in this patient group, only effective strategies that can be rapidly implemented and do not require a period of precontrast exposure will be practical in order to avoid any delay in the time interval.

KEYWORDS

- Device-based therapy
- Prevention
- Contrast-induced nephropathy
- Coronary angiography

KEY POINTS

- Comprehensive strategies are required to reduce the risk of contrast-induced nephropathy in high-risk populations and in scenarios whereby patients are undergoing coronary angiography and intervention.
- Simple medical devices have been developed to reduce radiographic contrast dose and renal exposure and to optimize hydration.
- Ongoing studies are being conducted to investigate the efficacy of these devices and to examine the practicalities of their incorporation in routine clinical practice.

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to coronary intervention. Similarly, the use of other strategies, such as aggressive volume loading, is limited by the presence of left ventricular dysfunction or other causes of significantly elevated left ventricular end-diastolic pressure.

In this article, the authors review the various device-based approaches that have been evaluated as interventions to reduce the risk of CIN. From a conceptual standpoint, a range of device-based strategies has been developed to potentially mitigate the risk of CIN by addressing one or more of several key targets, including the minimization of contrast volume, removal of radiographic contrast to limit renal exposure, and the direct mitigation of contrast-induced renal injury (Fig. 1, Table 1).

Reducing Radiographic Contrast Volumes

It is well established that the volume of contrast injected during a procedure is a major risk factor for the development of CIN, particularly when repeat delivery of contrast is performed early after the index procedure. Within some high-risk patient populations, the risk of CIN may increase up to 40% with every additional 5 mL of contrast media used. In this context, however, progress in interventional cardiology has seen the use of increasingly complex coronary interventions that require large contrast volumes; this is often coupled with the increasing prevalence of well-established risk factors for CIN in the interventional population, including preexisting CKD, aging, diabetes, heart failure, and ST elevation myocardial infarction (STEMI). Therefore, the limitation of contrast volumes should be a key objective in at-risk individuals; however, this may come at the cost of image quality. One potential source for mitigation of largely wasted contrast volume is that attributable to excess coronary ostial reflux. Although the exact amount of contrast reflux has not been precisely determined, it has been previously shown to be present in more than 60% of contrast injections. Recently, a device designed to attenuate the loss of contrast caused by reflux by altering the contrast injection pressure profile (AVERT, Osprey Medical, Minneapolis, MN) was shown to reduce contrast volumes by approximately 40% without significant loss of image quality. The influence of this approach on the incidence of CIN is currently being evaluated in a randomized clinical trial (AVERT Clinical Trial, NCT01976299).

The use of automated contrast injection systems has also been proposed as a means of limiting the volume of radiographic contrast and possibly the incidence of CIN. Recently, however, Gurm and colleagues, in a large registry study, demonstrated that automated injection systems reduced contrast volumes by less than 3%, and there was no impact on the rate of CIN.

REMOVAL OF CONTRAST MEDIA

Following coronary delivery of iodinated radiographic contrast, the possibility of removing

Limit Contrast Use & Systemic Exposure

- Reduce contrast use by decreasing reflux
- Direct contrast removal

Renoprotection
- dialysis/CVVH
- vasodilation
- cooling
- RIC

Promote balanced diuresis

Fig. 1. General schema of potential device-based approaches for the prevention of CIN. CVVH, continuous veno-veno hemofiltration; RIC, remote ischemic conditioning.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Primary End Point</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct removal of contrast media</strong></td>
<td></td>
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<tr>
<td>Hemodialysis</td>
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<tr>
<td>Lehnert et al, 1998</td>
<td>Randomized</td>
<td>30 Patients 212 ± 14 μmol/L</td>
<td>Contrast removal</td>
<td>Average removal of 32% of contrast media; but increased rates of CIN (53% vs 40%)</td>
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<tr>
<td>Vogt et al, 2001</td>
<td>Randomized</td>
<td>113 Patients 316 ± 112 μmol/L</td>
<td>CIN and MACE</td>
<td>Nonsignificant increase in event rate (24% vs 14%)</td>
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<tr>
<td>Hsieh et al, 2005</td>
<td>Case control</td>
<td>40 Patients 216 ± 11 μmol/L</td>
<td>Short- and long-term renal function</td>
<td>No significant change in renal function between both groups</td>
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<tr>
<td><strong>Continuous hemofiltration</strong></td>
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<tr>
<td>Marenzi et al, 2003</td>
<td>Randomized</td>
<td>114 Patients 265 ± 88 μmol/L</td>
<td>CIN</td>
<td>Significant reduction in CIN with hemofiltration (5% vs 50%)</td>
</tr>
<tr>
<td>Marenzi et al, 2006</td>
<td>Randomized</td>
<td>92 Patients 205 ± 50 μmol/L</td>
<td>CIN</td>
<td>Significant reduction with 2 doses of hemofiltration compared with control (3% vs 26% vs 40%)</td>
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<td><strong>Removal of contrast from coronary sinus</strong></td>
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<tr>
<td>Danenberg et al, 2008</td>
<td>Pilot study</td>
<td>7 Patients 262 ± 56 μmol/L</td>
<td>Contrast removal</td>
<td>Able to perform in 4 patients, with average removal of 44% of contrast media</td>
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<tr>
<td>Duffy et al, 2010</td>
<td>Case control</td>
<td>41 Patients eGFR &lt;60 mL/min</td>
<td>Change in eGFR</td>
<td>Able to perform in 31 of 41 patients; significant improvement in change in eGFR -0.7 vs -2.5 mL/min</td>
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<td><strong>Automated balanced hydration system</strong></td>
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<tr>
<td>Briguori et al, 2011</td>
<td>Randomized</td>
<td>294 Patients 99 IQR (70–216) μmol/L</td>
<td>CIN</td>
<td>Significant reduction in rate of CIN (11% vs 21%)</td>
</tr>
<tr>
<td>Marenzi et al, 2012</td>
<td>Randomized</td>
<td>170 Patients 94 ± 20 μmol/L</td>
<td>CIN</td>
<td>Significant reduction in rate of CIN (5% vs 18%)</td>
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<td><strong>Remote ischemic conditioning</strong></td>
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<tr>
<td>Er et al, 2012</td>
<td>Randomized</td>
<td>100 Patients 90 IQR (81–100) μmol/L</td>
<td>CIN</td>
<td>Significant reduction in rate of CIN (12% vs 40%)</td>
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<tr>
<td>Deftereos et al, 2013</td>
<td>Randomized</td>
<td>225 Patients 55 IQR (50–72) μmol/L</td>
<td>CIN</td>
<td>Significant reduction in rate of CIN (12% vs 30%)</td>
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<td><strong>Dual intrarenal drug infusion</strong></td>
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<tr>
<td>Talati et al, 2012</td>
<td>Retrospective case control</td>
<td>104 Patients eGFR 31 ± 12 mL/min</td>
<td>CIN</td>
<td>Significant reduction in CIN (12% vs 30%)</td>
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</table>

*Abbreviations: eGFR, estimated glomerular filtration rate; IQR, inter quartile range; MACE, major adverse cardiac events.*
contrast before its exposure to the kidneys has also been an appealing target. In broad terms, 2 approaches have been applied in the context of coronary imaging involving either the removal of radiographic contrast from the coronary sinus (CS) before exit from the heart to the general circulation or, alternatively, the removal of contrast from the general circulation by hemodialysis (HD) or continuous veno-veno hemofiltration.

**HD and Continuous Veno-Veno Hemofiltration**

Although it is well established that HD is effective in eliminating contrast agent from the blood, this has not translated to a reduction in rates of CIN or improved clinical outcomes. In a small randomized trial of 30 patients with CKD, Lehnert and colleagues found that prophylactic HD started 63 minutes after radiocontrast procedures could effectively remove contrast agent but had no significant benefit on the postprocedural change in creatinine or incidence of CIN. In a larger randomized trial of 113 patients with significant baseline CKD (creatinine >200 μm/L), Vogt and colleagues found that prophylactic HD started 60 minutes after low-osmolality radiocontrast administration did not show any short-term beneficial effect compared with conservative measures, with actually a deterioration in renal function in the HD group. Furthermore, patients who received prophylactic HD were more likely to have procedure-related complications. The lack of efficacy of HD in the prevention of CIN has been further confirmed in another case control study of patients undergoing coronary angiography.

In contrast to hemodialysis, continuous veno-veno hemofiltration (CVVH) is a continuous form of renal-replacement therapy that constitutes an alternative strategy for extracorporeal removal of contrast following radiological procedures. Hemofiltration is associated with hemodynamic stability and may allow for significantly increased volumes of hydration, without an associated risk of fluid overload and lung congestion, and can be safely performed following percutaneous coronary intervention (PCI).

In an initial single-center randomized study, Marenzi and colleagues studied the effects of CVVH and saline hydration initiated 4 to 8 hours before the coronary intervention and continued for 18 to 24 hours after the procedure was completed. An increase in the serum creatinine concentration of more than 25% from the baseline value after the coronary intervention occurred less frequently among the patients in the hemofiltration group than among the control patients (5% vs 50%, \( P<.001 \)), although the rate of increase in creatinine in the CVVH group seemed to parallel that in the control group after the cessation of CVVH. Significant effects on the incidence of in-hospital events and cumulative 1-year survival were also observed. In a further randomized trial, the same group randomized patients to CVVH beginning before or after the coronary intervention. This study showed that although CVVH commencing before the procedure was effective, the effect of CVVH initiated after the procedure was more modest. Taken together, although these results are encouraging, confirmation with larger multisite studies is required. Perhaps most importantly, the cost and resource implications of CVVH are a major limitation in the widespread adoption of such an approach, perhaps with the exception of very-high-risk patients.

**Removal of Contrast via the CS**

Prevention of contrast release from the heart to the general circulation by CS blood collection is another approach that has been recently tested by several groups. The CS receives blood from most of the left ventricular myocardium and drains much of the left coronary circulation while receiving a more variable distribution from the right coronary artery. Since the inception of cardiac resynchronization therapy in particular, experience in CS cannulation has grown considerably, building on the prior experience of electrophysiologists and invasive cardiovascular physiologists.

Movahed and colleagues first illustrated the concept of removing contrast via CS in an animal proof-of-concept study. In this study, the CS of 5 pigs undergoing coronary angiography were cannulated, and 50 mL of blood was collected immediately after coronary contrast injection. An average of 51% of the injected contrast was recovered by this method. In the same year, Meyer and colleagues used a balloon-tipped through lumen catheter introduced via the superior vena cava in dogs. The balloon was inflated during the injections, and the venous blood from the CS was collected. An average of 70% of the injected contrast was recovered by this method.

Another system involves a dual-contrast detection/aspiration system (Catharos Medical Systems, Los Gatos, CA, USA). The catheter has an expanding tip and integrated fiber optics using a
light-reflection technology for endovascular contrast detection. The catheter system monitors CS blood for contrast presence and provides signals for CS evacuation. A peristaltic pump that evacuates contrast-laden CS blood through the catheter’s central lumen facilitates aspiration. A preclinical study reported approximately 60% retrieval of injected contrast.

These preliminary preclinical models have subsequently been translated into several differing CS contrast collecting systems used in the clinical setting. Danenberg and colleagues cannulated the CS with a double-lumen, balloon-tipped catheter; however, they were unable to maintain an adequate position of the Reverse Berman catheter (Arrow International, Reading, PA, USA) in the CS reliably; but in the 3 remaining patients, 44% of the injected contrast material was retrieved.

The contrast removal system with the largest clinical experience is the CINCOR removal system (Osprey Medical, Minnetonka, MN, USA). In the initial clinical report, Duffy and colleagues performed a safety and efficacy study using a purpose-designed 11-F CS aspiration catheter and CS support device placed via a 14-F right internal jugular vein sheath. The CS was successfully cannulated with the aspiration catheter in 31 of 41 patients, and there were no device-related serious adverse events. In this nonrandomized study, patients with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min had no change in eGFR at 72 hours after the procedure compared with a matched comparator cohort in which eGFR decreased significantly after the procedure despite similar demographics and contrast volumes. CS contrast aspiration resulted in the recapture of 32% +/- 3% of the delivered contrast, ranging from 6% to 64%. A CINCOR removal catheter for CS cannulation via the femoral vein has been developed and successfully implemented in small patient series.

Together these studies demonstrate that CS collection of contrast is feasible; however, the more complete collection of injected contrast seems more challenging perhaps because of the initial loss caused by coronary reflux as described earlier.

DEVICE-MEDIATED RENAL PROTECTION

Automated Balanced Hydration

Data from the prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy (PRINCE trial) highlighted that increasing urine flow rate (>150 mL/h) may potentially reduce the nephrotoxic effect of contrast media. The postulated mechanism of benefit being that high urine output would lower the concentration of contrast in the kidneys, reducing transit time of contrast through the kidneys and improved flow in renal tubules. The evidence for hydration per se and the composition of the administered fluids are addressed elsewhere in this series.

The combined use of diuretics and hydration to reduce CIN have in general been associated with worse clinical outcomes, possibly because of the difficulty in matching hydration, intravascular volume, and urine volume. In this context, an automated system consisting of a closed-loop fluid management system comprising a high-volume pump, a dual-weight measuring system, single-use intravenous set, and urine collection system that interfaces with a urinary catheter and real-time display of urine and replacement fluid volume was developed to optimize hydration and urinary flow (RenalGuard System, PLC Medical Systems, Inc, Milford, MA, USA) supported with the use of intravenous diuretics.

Two phase-3 multicenter randomized trials of the RenalGuard system have subsequently been performed. The first was the Renal Insufficiency Trial After Contrast Media Administration Trial II (CIN-RG trial, NCT01456013). This study randomized patients with an eGFR less than 30 mL/min/1.73 m² and/or a Mehran risk score greater than 11 to either sodium bicarbonate solution and n-acetylcysteine or system-guided hydration in an open-label study. The primary end point of an increase of greater than 0.3 mg/dL in serum creatinine at 48 hours was significantly reduced in the RenalGuard group (11.0% vs 20.5%, p = .025) supported by a significant attenuation of the postcontrast cystatin C increase. The second trial, MYTHOS, was a single-center Italian study. This study randomized 174 elective patients or patients with non-STEMI, most of whom had CKD stage 3 renal disease, to matched hydration with the RenalGuard system extending from 90 minutes before to 4 hours after the procedure compared with control hydration for at least 12 hours before and 12 hours after the procedure. The primary end point of CIN, defined as a more than 25% or 0.5-mg/dL increase in serum creatinine at 72 hours, was significantly reduced in the matched hydration group compared with controls (4.6% vs 18.0%, P = .005), with a trend toward a reduction in a composite outcome of clinical cardiac events. Further studies of this system are presently underway (CIN-RG trial, NCT01456013).

Renal Cooling

Driven by interest in the potential protective effects of cooling on oxidative tissue injury in other
organs, the possibility that systemic cooling may prevent CIN has also been addressed. The systemic hypothermia to prevent radiocontrast nephropathy (COOL RCN trial) investigated whether systemic hypothermia is effective in preventing CIN in patients with CKD. Patients at risk for CIN were randomized to standard care versus intravascular catheter-induced systemic hypothermia as a preventive strategy. The study showed that the therapy could be used safely in patients undergoing angiography; however, there was no net effect on rates of CIN.36

**Intrarenal Drug Infusion**

The influence of various pharmacologic interventions on the incidence of CIN has been discussed elsewhere. In an attempt to enhance the potential effectiveness of such strategies, the effect of direct intrarenal infusion of various agents has been investigated. Among these, a bifurcated catheter (Benephit catheter, AngioDynamics, Latham, NY, USA) has been used for dual direct renal infusion of fenoldopam, a drug that has been shown to improve renal blood flow but not CIN rates when used intravenously. A recent retrospective observational nonrandomized study showed that dual intrarenal infusion was associated with lower CIN rates than a matched control group.37 Further studies would be required to establish the practicality and efficacy of this approach.

**Remote Ischemic Conditioning**

Remote ischemic conditioning (RIC) is a therapeutic strategy by which protection can be afforded to one vascular bed by ischemia to another bed in the same or different organ. Although the precise mechanism of organ protection in RIC is not entirely understood, it has been reported that brief episodes of nonlethal ischemia and reperfusion preserve adenosine triphosphate during ischemia38; induce production of endogenous autacoids, such as adenosine, opioids, and bradykinin that activate protein kinases so as to inhibit the opening of the mitochondrial permeability transition pore that plays a critical role in tissue necrosis38,40; reduce the generation of deleterious reactive oxygen species31,42; and attenuate inflammation.43

Although most RIC research has focused on myocardial protection, some studies have investigated the benefit of RIC in the reduction of acute kidney injury in the setting of cardiac and major noncardiac surgery, with varying results.44-48 This paradigm has also led to the evaluation of RIC as a potential renoprotective strategy against CIN. A randomized control trial performed by Er and colleagues49 studied the effects of RIC in patients undergoing elective coronary angiogram. One hundred patients with CKD (eGFR <60 mL/min) were randomized to receive RIC (4 cycles of alternating 5-minute inflation and 5-minute deflation of a standard upper arm blood pressure cuff to 50 mm Hg +systolic blood pressure) or a sham RIC (blood pressure cuff inflated to diastolic pressure and then deflated to 10 mm Hg). The primary end point of CIN at 48 hours was significantly reduced in the RIC group compared with the control (12% vs 40%, \( P = .002 \)), albeit perhaps with a surprisingly high incidence of CIN in controls. Using a different approach, the effects of myocardial rather than skeletal muscle ischemia was examined in another study. Following PCI, the effect of four 1-minute cycles each consisting of a 30-second stent balloon inflation to nominal pressure with 30 seconds deflation was performed in a single-blind study.50 The primary end point of CIN at 96 hours was significantly reduced in the RIC group (12.4% vs 29.5%, \( P = .002 \)). Larger studies with increased power are needed in these populations to confirm the effects of RIC on renal protection and its clinical sequelae.

**SUMMARY**

CIN is a common condition that is associated with short- and, likely, long-term adverse outcomes. Although periprocedural intravenous hydration is the simplest and most widely used technique to prevent CIN, the limited ability of this approach to mitigate CIN risk in high-risk populations, such as those patients with established advanced CKD and patients with STEMI, has provided an impetus to develop new preventive strategies. A range of potentially useful device-based approaches offers new preventive techniques. Well-designed and adequately powered randomized studies of these device-based therapies are urgently needed to determine the expanding role they will play in future clinical practice.

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Prevention of Contrast-Induced Nephropathy


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