REVIEW ARTICLE

# Percutaneous Coronary Interventions are Vital to the Heart, But What About the Kidneys?

**Onur Akhan**

*Department of Cardiology, Bilecik Training and Research Hospital (liked with Bilecik Seyh Edebali University), Bilecik, Turkey*

**ABSTRACT**

Contrast-induced nephropathy can be defined as the development of transient or permanent renal dysfunction due to use of nephrotoxic contrast agents like in coronary angiography. Vasomotor irregularity, increased glomerular permeability, tubular damage, and medullar ischemia are among the possible etiology. Advanced age, amount of contrast, use of other nephrotoxic drugs, and some accompanying diseases increase this risk. Negative consequences can be listed as need for dialysis, prolonged hospital stay, and increase in in-hospital mortality. Risk analysis should be done first to prevent the development of contrast nephropathy. Decreasing the amount of contrast, hydration, regulation of the type of contrast used are the main points to be considered.

**Key words:** Coronary interventions, contrast nephropathy, contrast agents, cardiology

## INTRODUCTION

Contrast-induced nephropathy (CIN) can be defined as the development of transient or permanent renal dysfunction after coronary angiography. Non-oliguria and an increase in serum creatine values (0.5 mg/dl or 25% increase) are seen in contrast nephropathy (CN). In general, these values reach the highest value in 2–3 days and regress to basal values on the 7$^{th}$ day. Chronic hemodialysis is rarely seen in these patients.[1,2]

CIN can also be seen in imaging methods using nephrotoxic contrast, but we will talk about the situation after coronary interventions with related studies.

## PATHOPHYSIOLOGY

The pathophysiology of CIN includes vasomotor irregularity, increased glomerular permeability (loss of protein), direct tubular damage, tubular obstruction, and medulla ischemia. Medulla ischemia is associated with an increase in adenosine, endothelin, and free radical-induced vasoconstriction and a decrease in nitric oxide and prostaglandin-induced vasodilatation.[3]

## RISK FACTORS

Advanced age, congestive heart failure, existing renal dysfunction, multiple myeloma, hypovolemia, use of other drugs (such as gentamicin, ACE inhibitor, and NSAIDs), and increased amount of contrast may increase the risk by 50%.[3,4] It is also more common in women.

In 2004, a risk score was mentioned to determine the risk of CIN after percutaneous interventions.[5] The risk-related calculation and subsequent score-related risks are shown in Tables 1 and 2.

Although it was stated that the score could be used for clinical and research purposes after the study, it could not be used in the pre-procedure risk assessment because it was affected by variables related to procedural events (affected by the amount of contrast, and intra-aortic pump use).[5]

**Address for correspondence:**
Dr. Onur Akhan, Department of Cardiology, Bilecik Training and Research Hospital (liked with Bilecik Seyh Edebali University), Bilecik, Turkey.

**Table 1:** Risk calculator

| | |
|---|---|
| Hypotension (SBP < 80 mmHg + 1 h inotrop use) | 5 |
| Intra-aortic Balloon Pump (IABP) | 5 |
| CHF (NHYA 3-4 or pulmonary edema) | 5 |
| Age > 75 | 4 |
| Anemia (Man: Htc < 39/Woman: Htc < 36) | 3 |
| Diabetic Mellitus | 3 |
| Amount of Contrast | 1/100 cc |
| Kreatinin >1.5 mg/dl GFR< 60 ml/dk/1.73 $m^2$ | 4 Every 20 units drop in GFR value → 2 |

**Table 2:** Score-related risks

| | | |
|---|---|---|
| ≤5 | 7.5% | 0.04% |
| 6–10 | 14% | 0.12% |
| 11–16 | 26.1% | 1.09% |
| ≥16 | 57.3% | 12.6% |

## NEGATIVE OUTCOMES

In a study by McCullough *et al*., the incidence of CIN was reported to be between 1.1% and 7.1% and 35% needed dialysis. In addition, hospital stay and in-hospital mortality rates (up to 5 times) were increased due to CIN.[6]

## WHAT CAN BE DONE?

To prevent CN, limitation of the amount of contrast (maximum 3 ml/kg or 5 ml/kg/serum creatinine), hydration and arteriolar vasodilation were planned. In the studies, it was found that the amount of contrast was related to CIN, and in one study it was stated that the ratio of contrast amount to glomerular filtration rate (GFR) above 3.7 was predictive for CIN.[7]

## CONTRAST SUBSTANCES

The osmolarity, viscosity, and chemotoxicity of the contrast agent used are seen as determinants of toxicity.[3]

In randomized, controlled studies, it was found that the incidence of CIN decreases when low osmolar substance is used compared to high osmolar substance use. In comparison of nonionic isoosmolar substances and low osmolar substances, non-ionic isoosmolar substances were found to be superior.[2]

## HYDRATION

Hydration is particularly important in patients with existing renal dysfunction. In a study by Solomon *et al*., which included 78 patients with mean creatine values of 2.1, contrast-enhanced nephropathy was found at a rate of 26% and 11% in the saline (0.45%) treated group. In addition, saline administration alone was superior to the use of mannitol or furosemide in combination with saline.[8]

In a study published in 2002 and involving 1620 patients who underwent coronary angioplasty, 0.9% saline were found to be superior to 0.45% sodium chloride in terms of CN, although it did not provide significant advantage in terms of mortality. In the study, female gender, diabetes status, and presence of more than 250 ml of contrast were considered significant risk factors.[9]

In studies published in in 2004 and 2008, sodium chloride and sodium bicarbonate infusions were compared before and after the procedure (1 h 3 ml/kg) and after (6 h 1 or 1.5 ml/kg) and sodium bicarbonate was not superior to sodium chloride.[10,11]

When the studies on how hydration should be performed, it is stated that iv hydration may be superior to oral hydration, but some studies did not find a significant difference. However, periprocedural infusion administration was superior to bolus administration during the procedure.[12,13]

## HEMOFILTRATION

Hemofiltration method can be used to remove the contrast agent directly and reduce the effect of contrast agents on the kidney.

In a study conducted in Italy, 114 patients with a mean basal creatine level of 3 mg/dl and a mean GFR of 26 ml/min were included. 58 patients underwent hemofiltration for 4–6 h before the procedure, hemofiltration was discontinued during the procedure and saline infusion was given and after the procedure hemofiltration was continued for 18–24 h. During the process saline infusion was applied at a rate of 1 lt/h and heparin was applied. The remaining 56 patients received saline infusion at a rate of 1 ml/kg/h starting 6–8 before the procedure and continuing until 24 h after the procedure. At the end of the study, although it was found to be superior in terms of contrast-associated nephropathy, in-hospital mortality, 1-year mortality and hemofiltration in all clinical events, it was stated that hemofiltration is not a cost-effective method. It has also been shown to cause adverse conditions such as the need for heparin use and delaying percutaneous intervention time. In addition, it was also stated that the high-risk group that required repetitive intervention was included

in the study and therefore it may not be appropriate to use the application in simple interventional applications.[14]

In another study involving the chronic renal failure group, it was stated that prophylactic hemofiltration after contrast agent administration may cause hypovolemia, increase renal ischemia, and prolong treatment time.[3]

## N-ACETYL CYSTEIN (NAC)

In a prospective randomized trial published in 2000, the use of NAC at doses of 600 mg twice a day before the procedure showed significant benefit in CIN, but in later years, prospective randomized trials no significant benefit. (In these studies, 1200 mg twice a day was given for 2 days before and after the procedure).[15-17] In a retrospective study evaluating approximately 90000 patients, no clinical significance was observed also.[18]

## ARTERIOLAR VASODILATATION

Use of dopamine in renal doses has been shown to worsen the severity and course of renal failure.[19]

In studies with the selective dopamine A1 receptor agonist fenoldopam, contradictory results were obtained. In a placebo-controlled study which assessing 45 patients, co-infusion of saline and phenoldopam compared to 0.45% saline infusion showed significant positive effects on CN, creatine values, and renal blood flow.[20]

However, in prospective, placebo-controlled, and randomized study which assessing 315 patients (CONTRAST Trial), there was no significant difference in primary outcome CIN.[21] Other studies have shown that simultaneous selective phenoldopam infusion into renal arteries causes more pronounced vasodilatation and that the use of phenoldopam can reduce the need for dialysis up to 4%.[22]

## ASCORBIC ACID

In a randomized double-blind placebo-controlled trial of 241 patients with mean creatine values of 1.2 mg/dl or more, creatinine progression was found to be significantly less in ascorbic asid using group (with doses per oral 3 g ascorbic acid use before the procedure and 2 g twice a day use after the procedure) compared to the control group.[23] In a meta-analysis of nine randomized controlled trials in 2013, it was shown that ascorbic acid had significantly positive effects over placebo or alternative therapies.[24]

## STATINS

The PLOS ONE meta-analysis, which was conducted with data from nine randomized trials in 2012, showed that statins significantly reduced the risk of CN, but there was no significant difference in the need for dialysis.[25]

According to the 2019 dyslipidemia guidelines for chronic renal injury patients, statin use is recommended for non-dialysis-dependent stage 3–5 chronic kidney injury with Class I indication, and for patients with atherosclerotic cardiovascular disease is recommended for 2a indication.[26]

**Table 3:** Agents and their beneficial situations

| Harmful | Ineffectıve | Need for advanced trıals |
|---|---|---|
| Furosemide | Fenoldopam | Theophylline |
| Mannitol | Dopamine | Statins |
| Endothelin receptor antagonist | Calcium channel blocker | Ascorbic acid |
| | Atrial natriuretic peptide | Prostaglandin E1 |
| | L- Arjinine | |

## OTHER AGENTS

The agents investigated in studies to reduce and prevent the frequency of CN in patients undergoing percutaneous coronary intervention and benefit status as a result of the data obtained from the studies are shown in Table 3.[27,28]

## CURRENT GUIDELINES

In the 2018 ESC myocardial revascularization guideline, the assessment of the risk of CIN in all patients and the provision of adequate hydration was indicated with a Class 1 indication. It has also been suggested with Class 1 indication that the contrast agent to be used in interventional procedures should be low osmolar or isoosmolar and the use of contrast agent should be reduced as much as possible.

In cases where the expected contrast agent usage is more than 100 ml, it is recommended that the hydration should be started 12 h before procedure at a rate of 1 ml/kg/h (half dose if GFR value is 35 and below) and continued for up to 24 h. This hydration advice and preprocedural statin use (with doses 80 mg atorvastatin or 20/40 mg rosuvastatin) advice are given with Class 2a indication.

Alternative hydration regimens (adjustment according to central venous pressure measurement, addition of furosemide) and prophylactic hemofiltration 6 h before complex intervention were indicated by Class 2b indication. The use of hemodialysis as a preventive agent is not recommended.

In the AHA guidelines, risk assessment, limitation of hydration and use of contrast agents are shown at the same recommendation levels. In addition, the use of isoosmolar contrast agent was recommended with a Class 1 indication and it was stated that the use of NAC was not beneficial.[14]

## CONCLUSION AND SUMMARY

Risk factors should be evaluated before percutaneous intervention. As the risk factors increase, the risk of CN may increase and for this purpose hydration should be started in these conditions.

Attention should be paid to the amount of contrast during the procedure, and if possible, isoosmolar or low osmolar agent should be used.

Hydration should be continued during the procedure and renal functions (especially on day 2 and 3 when CN occurs) should be monitored in risky patients.

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