ABSTRACT: Background. Percutaneous coronary intervention (PCI) requires the use of iodinated contrast medium and consequently poses the risk of contrast-induced nephropathy (CIN), which can negatively impact on outcome. Patients with chronic kidney disease (CKD) are at particularly high risk of CIN. In this study, we investigated the role of continuous renal replacement therapy (CRRT) performed before and after versus only after PCI in patients with CKD. Methods. We studied 46 consecutive patients with CKD (mean creatinine >2 mg/dL) submitted to PCI: 21 (mean creatinine 2.7 ± 1.6 mg/dL) treated with CRRT only after PCI (CRRTpost) and 25 (mean creatinine 3.0 ± 1.3 mg/dL) with CRRT before and after PCI (CRRTpre-post). CRRT was performed with hemofiltration (creatinine <3 mg/dL) or hemoafiIltration (creatinine >3 mg/dL); initiated 6-8 hours before PCI and re-started immediately post PCI for 18-24 hours. Results. Creatinine showed a greater reduction in CRRTpre-post (2.4 ± 1.0 vs 3.0 ± 1.3 mg/dL; P<0.02) with respect to CRRTpost (2.6 ± 1.3 vs 2.7 ± 1.6 mg/dL; P=0.67). At median 14.7-month follow-up, CKD worsened in 3 patients (12%) of CRRTpre-post and in 9 (43%) of CRRTpost (P=0.042). Kaplan-Meier analysis at 18 months showed a significantly higher overall mortality in patients treated with CRRTpre-post vs CRRTpost (P=0.041), which became even more significant during the entire follow-up period (P=0.026) and an increase in cardiovascular deaths (5 vs 0, respectively). Conclusions. Our results suggest that in CKD patients undergoing PCI, CRRT performed before and after is more effective in preventing a further deterioration of renal function and is associated with an improved long-term outcome when compared to CRRT performed only after. J INVASIVE CARDIOL 2013;25(2):80-84

Key words: contrast-induced nephropathy, CRRT

Contrast-induced nephropathy (CIN) is the third most common cause of hospital-acquired renal failure and accounts for approximately 11% of cases. The prevalence of CIN reported in the literature ranges between 1% and 45% and depends largely on the comorbidities of patients analyzed in each single study and on the parameters used to define CIN.1-3 Percutaneous coronary intervention (PCI) requires the use of iodinated contrast medium and consequently poses the risk of CIN; the clinical relevance of CIN derives not only from kidney impairment, but also from its negative prognostic impact. Several studies have reported a significantly higher in-hospital and long-term mortality in patients developing CIN after PCI.4-9 Most cases of CIN occur in patients with chronic kidney disease (CKD), for whom a preventive renal strategy is mandatory.

Currently available prophylactic measures consist of hydration, antioxidant agents (acetylcysteine, ascorbic acid), and use of low-osmolar and iso-osmolar contrast agents; these strategies have been shown to provide some protection, reducing the incidence of CIN.10-13 However, their efficacy in patients with severe CKD is still controversial and their impact on clinical outcome is a matter of debate. According to Marenzi, a preventive hemofiltration, a modality of continuous renal replacement therapy (CRRT) started 4 to 8 hours before exposure to a contrast agent and continued for 18 to 24 hours after the procedure, resulted in a significant reduction in CIN incidence, also improving in-hospital and long-term outcomes in patients with severe CKD undergoing PCI.14 Nevertheless, CRRT performed before contrast medium administration is invasive, can be associated with complications and is a time and money consuming procedure; for these reasons, it can be mandatory to evaluate if its employment is really beneficial in this setting.

The aim of the present study was to analyze outcome and incidence of CIN in patients with severe CKD undergoing invasive cardiovascular procedures and treated with two different preventive strategies: CRRT performed before and after contrast agent exposure and CRRT performed only after contrast medium administration.

Methods

We studied 46 consecutive patients admitted to the cardiac step-down unit of the University of Florence with CKD (serum creatinine >2 mg/dL or estimated glomerular filtration rate [eGFR] less than 30 mL/min) who needed to be submitted to PCI. These patients were treated according to two different protocols: 21 patients (mean serum creatinine level 2.7 ± 1.6 mg/dL) were treated with CRRT only after contrast medium exposure (CRRTpost group); 25 patients (mean serum creatinine 3.0 ± 1.3 mg/dL) were submitted to CRRT at least 6 hours before and 24 hours after contrast medium administration (CRRTpre-post group). The choice of the timing of CRRT depended on logistic reasons or attendant physician judgment, usually based on CIN risk profile.

CIN was defined as an increase in serum creatinine concentration of more than 25% from baseline value after contrast medium administration.12,15 Pre-existing CKD was defined as baseline serum creatinine >1.5 mg/dL (eGFR <45 mL/min). Creatinine clearance was calculated with the Cockcroft-Gault formula.16
Venous access for blood withdrawal and return for CRRT was obtained using a standard femoral vein catheter connected to the PRISMA system (Hospal Gambro Dasco). In patients with serum creatinine <3 mg/dL, CRRT was performed as continuous venovenous hemofiltration (CVVH). In patients with serum creatinine >3 mg/dL, CRRT was performed as continuous veno-venous hemodiafiltration (CVVHDF). Unfractionated heparin was used as anticoagulant to maintain an activated partial thromboplastin time between 65 and 85 seconds in both CRRT modalities.

In the CRRTpre-post group, CRRT was initiated at the same time as hydration with saline from 6 to 8 hours before the PCI, re-started as soon as the procedure ended (usually within 30 minutes) and continued for 18 to 24 hours; in the CRRT post group, hydration with saline was begun 6-8 hours before PCI, re-started as hydration with saline from 6 to 8 hours before the PCI, re-started after PCI, and continued for 18 to 24 hours. CRRT was performed using predilution technique with an M 100 PRESET PRISMA filter.

According to CVVH protocol, blood was driven through the circuit by means of a peristaltic pump at a rate of 150 mL/min; the flow of isotonic replacement fluid was set at 1000 mL/h and was exactly matched with the rate of ultrafiltrate production so that no net fluid loss resulted.14 In CVVHDF protocol, we employed a blood flow of 150 mL/min, a saline containing dialysate of 1000 mL/h, and replacement fluid rates of 1000 mL/h, without any volume loss.16

Creatinine serum level and eGFR values were measured at baseline and 6, 12, and 24 hours after PCI. Urine output was measured daily during hospital stay. We conducted an ambulatory follow-up during which creatinine levels were also assessed.

Worsening of renal function was defined as an increase in serum creatinine levels >25% of basal value; we finally evaluated how many patients underwent chronic dialytic treatment and mortality for both overall and cardiovascular causes.

Overall mortality was evaluated at the following time periods: at 1 year, at 18 months, and during the entire median 14.7 months of follow-up.

Informed consent was obtained from each patient enrolled in the study. The study was approved by the Institutional Committee on human research.

For statistical analysis, data were stored in a dedicated database and analyzed using the Statistical Package for Social Sciences for Windows release 13.0 (SPSS Inc). Data were expressed as frequencies and percentages for categorical data and mean ± standard deviation or median (25th-75th percentile, that is, interquartile range [IR]) for continuous data, according to normality of distribution, assessed by means of one-sample Kolmogorov-Smirnov test. Comparisons were made by means of chi-square (or Fisher's exact test when the expected value in at least one cell was less than 5) and student's t-test or Mann-Whitney U-test when needed, respectively. Survival was assessed with Kaplan-Meier curves; log-rank test has been reported. In all cases, a two-tailed P-value <.05 was taken as significant.

**Results**

Clinical and instrumental characteristics of patients investigated are reported in Tables 1 and 2. Median CRRT duration was significantly lower in the CRRT pre-post group versus the CRRT post group (Table 2). Serum creatinine levels at discharge showed a greater significant reduction in the CRRT pre-post group (2.4 ± 1.0 mg/dL vs 3.0 ± 1.3 mg/dL at admission; P = .002) with respect to CRRT post (2.6 ± 1.3 mg/dL vs 2.7 ± 1.6 mg/dL; P = .667) and parallel to this GFR values significantly increased in the CRRT pre-post group (49.5 ± 27.7 vs 24.6 ± 8.3; P < .001) while in the CRRT post group this increase was not significant (41.0 ± 17.6 vs 33.0 ± 23.0; P = .072) (Table 3).

Trends of serum creatinine and eGFR are shown in Figure 1. Creatinine values after PCI remained stable in patients treated with CRRTpre-post, while there was a significant increase creatinine levels in those treated with CRRTpost. Moreover, serum creatinine

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### Table 1. Baseline characteristics of patients investigated.

<table>
<thead>
<tr>
<th>Demographic Features</th>
<th>Overall Population</th>
<th>CRRTpre-post n = 25 (54.3%)</th>
<th>CRRTpost n = 21 (45.7%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.7 ± 10.4</td>
<td>73.0 ± 11.4</td>
<td>74.0 ± 8.3</td>
<td>.740</td>
</tr>
<tr>
<td>Male gender</td>
<td>35 (76%)</td>
<td>21 (84%)</td>
<td>14 (66.7%)</td>
<td>.298</td>
</tr>
<tr>
<td>Chronic kidney injury</td>
<td>46 (100%)</td>
<td>25 (100%)</td>
<td>21 (100%)</td>
<td>1</td>
</tr>
<tr>
<td>Mean creatinine (mg/dL)</td>
<td>2.9 ± 1.4</td>
<td>3.0 ± 1.3</td>
<td>2.7 ± 1.6</td>
<td>.536</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19 (41%)</td>
<td>10 (40%)</td>
<td>9 (42.9%)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31 (67%)</td>
<td>16</td>
<td>15</td>
<td>.754</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>16 (35%)</td>
<td>9</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Overweight</td>
<td>14 (30.4%)</td>
<td>7</td>
<td>7</td>
<td>.755</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (32.6%)</td>
<td>9</td>
<td>6</td>
<td>.754</td>
</tr>
<tr>
<td>Cancer</td>
<td>4 (8.7%)</td>
<td>3</td>
<td>1</td>
<td>.614</td>
</tr>
<tr>
<td>COPD</td>
<td>5 (10.9%)</td>
<td>4</td>
<td>1</td>
<td>.357</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>9 (19.6%)</td>
<td>4</td>
<td>5</td>
<td>.711</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>8 (17.4%)</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>4 (8.7%)</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Main diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>14 (30.4%)</td>
<td>8</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>7 (15.2%)</td>
<td>3</td>
<td>4</td>
<td>.686</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>22 (47.8%)</td>
<td>12</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>STEMI</td>
<td>3 (6.5%)</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; CABG = coronary artery bypass graft; NSTEMI = non-ST segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.
levels after 48 and 72 hours showed a significant reduction only in the CRRT pre-post group. On the other hand, urine output evaluated after contrast medium administration and at the end of CRRT showed a significant increase in both groups (1.7 ± 0.4 vs 2.2 ± 0.6 mL/kg/h in the CRRT pre-post group; \( P < .001 \) and 0.4 ± 0.1 vs 1.2 ± 0.4 mL/kg/h in the CRRT post group; \( P < .001 \)) (Table 3).

No patient in the CRRT pre-post group developed CIN, while 13 patients (61.9%) in the CRRT post group showed this complication (Table 3).

During a median follow-up period of 14.7 months (range, 4.9-29.1 months), we observed a worsening of CKD in 3 patients (12%) of the CRRT pre-post group and in 9 patients (43%) of the CRRT post group (\( P = .042 \)) (Table 3).

Kaplan-Meier analysis at 18-month follow-up showed, in patients treated with CRRT post vs CRRT pre-post, a significantly higher overall mortality (\( P = .041 \)), which became even more significant during the entire follow-up period (\( P = .026 \)) (Figure 2) and an increase in cardiovascular deaths (5 vs 0, respectively).

The complications related to CRRT observed in both groups of patients investigated were anemia and bleeding at the insertion site in 4 patients (2 in each group); in-hospital mortality occurred in 1 patient of the CRRT post group.

Discussion

These preliminary data suggest that in patients with CKD undergoing PCI, CRRT performed before and after procedures requiring contrast medium administration is more effective in preventing a further worsening of renal function and is associated with an improved long-term outcome when compared to CRRT performed only after these procedures.

In our study, patients treated with CRRT before and after the administration of contrast medium did not develop CIN, while more than 60% showed this complication in the other group.

The mechanisms through which hemofiltration prevents a further deterioration in renal function and the need of a CRRT session before contrast medium administration to obtain a full clinical benefit in patients with severe CKD are not fully understood. However, our results suggest that the potential capability of hemofiltration to remove contrast medium from blood seems to play a minor role when this procedure is performed only after PCI. The lack of a significant preventive effect of post-hemofiltration alone is in agreement with previous studies in which prophylactic hemofiltration or hemodiafiltration started during or as soon as possible after contrast medium administration, did not determine any significant advantage when compared with saline hydration.17-20

The need for a hemofiltration treatment before contrast agent exposure suggests that, among other possible mechanisms, a controlled high-volume hydration plays a major role in kidney protection. In fact, dehydrated patients are at risk of developing CIN possibly for a higher concentration of toxic substances arriving in the renal tubule and for a reduction in the antioxidant defense mechanisms during volume depletion.21 Moreover, an adequate hydration could prevent the osmotic diuretic effect of contrast agents and may increase the effective circulating volume, the renal perfusion pressure, and the glomerular filtration without vasoconstriction, which is typical of volume-depleted patients.22,23
It is supposable that CRRT before procedures requiring contrast medium can remove some proteins or other unknown factors that could interact with contrast, thus resulting in CIN. With regard to this, there is some evidence on the role of CRRT in removing inflammatory cytokines (TNFα, IL-6, and IL-8) from the circulation of septic patients, suggesting that hemofiltration could prevent CIN also by interrupting the TNF-mediated inflammatory cascade.

Even though the employment of a mild contrast agent dose remains the major prophylactic measure, hydration with saline solution represents a cornerstone of CIN prophylaxis. However, effective hydration before PCI is logistically difficult and poorly tolerated, in particular when CKD coexists with a reduced cardiac function. Hence, the removal by convective filtration of toxic mediators, as by the absorption to the filter membrane of toxic mediators, may further contribute to the additional protective effect of hemofiltration before contrast medium administration.

It is also supposable that heparin infusion, required for CRRT performed before contrast exposure, may have protected these patients from renal ischemia-reperfusion injury, induced by contrast agents, but no data are available to confirm this issue.

Moreover, we cannot exclude that patients submitted to CRRT only after PCI, although the treatment was performed as early as possible, have been already exposed to a contrast-induced damage, which can also influence long-term outcome. In fact, in the present study, the evaluation at follow-up showed that a smaller number of patients in the CRRT pre-post group presented a further worsening of renal failure as well as an increase in both global and cardiovascular mortality.

The results obtained in the CRRT pre-post group are also supported by the recommendations of recent guidelines on myocardial revascularization, which suggest in class IIa LOE B a prophylactic hemofiltration 6 hours before and 24 hours after complex PCI for patients with severe CKD.

Finally, in our population, CRRT performed before and after contrast medium administration in patients with CKD was associated with a significant reduction in the median duration of CRRT, a parameter which is also important for its impact on global costs and complications related to these treatments.

**Study limitations.** This study has some limitations concerning its retrospective analysis and the limited number of patients investigated. Despite the lack of randomization, the two groups analyzed showed similar demographic characteristics. Moreover, it is noticeable that patients with higher creatinine levels at admission were treated with CRRT pre-post and showed better short- and long-term outcomes with respect to the others.

**Conclusion**

In conclusion, our data suggest that CRRT performed before and after PCI is more effective for CIN prevention in patients with severe CKD in comparison to CRRT performed only after and, in particular, is capable of significantly reducing serum creatinine levels and increasing eGFR values and is associated with a lower mortality rate during follow-up. Therefore, although a CRRT pre-post protocol appears to be more time and money consuming, in our experience it should be adopted as a first-line strategy for these patients.

### References


**Figure 1.** Timeline indicating variations in creatinine serum levels and estimated glomerular filtration rate from baseline to 24, 48, and 72 hours after percutaneous angioplasty. CRRT = continuous renal replacement therapy; BL = baseline; PCI = percutaneous coronary intervention.

**Figure 2.** Kaplan-Meier survival curves for patients treated with the two continuous renal replacement therapy (CRRT) protocols evaluated during the entire follow-up period, at 1 year, and at 18 months. BL = baseline; PCI = percutaneous coronary intervention.