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CLINICAL RESEARCH STUDY

Comparison of Two Hemofiltration Protocols for Prevention of Contrast-induced Nephropathy in High-risk Patients

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ABSTRACT

PURPOSE: Contrast-induced nephropathy is a complication of contrast medium administration during diagnostic and interventional procedures, with important prognostic relevance. Patients with chronic kidney disease have a higher risk for contrast-induced nephropathy and poorer outcome. In patients with chronic kidney disease, hemofiltration reduces contrast-induced nephropathy incidence and improves long-term survival. We assessed the mechanisms involved in the prophylactic effect of hemofiltration and of the most effective hemofiltration protocol to prevent contrast-induced nephropathy in patients with chronic kidney disease.

SUBJECTS AND METHODS: We randomized 92 patients with chronic kidney disease (creatinine clearance ≤30 mL/min) to three different prophylactic treatments: intravenous hydration with isotonic saline (1 mL · kg · h for 12 hours before and after contrast exposure, control group; n = 30); intravenous hydration for 12 hours before contrast exposure, followed by hemofiltration for 18 to 24 hours after contrast exposure (post-hemofiltration group; n = 31), and hemofiltration performed for 6 hours before and for 18 to 24 hours after contrast exposure (pre/post-hemofiltration group; n = 31). The incidence of contrast-induced nephropathy (>25% increase in creatinine) and the in-hospital clinical course were compared in the three groups.

RESULTS: Twelve patients (40%) in the control group, 8 patients (26%) in the post-hemofiltration group, and 1 patient (3%) in the pre/post-hemofiltration group experienced contrast-induced nephropathy (P = .0013); hemodialysis was required in 9 (30%), three (10%), and zero (0%) patients, respectively (P = .002). In-hospital mortality was 20%, 10%, and 0%, respectively (P = .03).

CONCLUSIONS: Hemofiltration is an effective strategy for contrast-induced nephropathy prevention in patients with chronic kidney disease who are undergoing cardiovascular procedures. Pre-hemofiltration is required to obtain the full clinical benefit, suggesting that, among different mechanisms possibly involved, high-volume controlled hydration before contrast media exposure plays a major role.

KEYWORDS: Hemofiltration; Contrast-induced nephropathy; Chronic kidney disease

Contrast-induced nephropathy, defined as an absolute or relative increase in serum creatinine concentration (Cr) occurring 48 to 72 hours after contrast media administration, is a possible complication of diagnostic imaging and interventional procedures.[1-3] The clinical relevance of contrast-induced nephropathy derives not only from the transient or permanent kidney impairment but also from the associated prognostic implications. Several studies have reported a significantly higher in-hospital and long-term mortality in patients developing contrast-induced nephropathy after percutaneous coronary interventions.[2-7]

Most cases of contrast-induced nephropathy occur in patients with preexisting renal insufficiency. Therefore, in patients with chronic kidney disease a preventive renal strategy is mandatory. Among currently available prophy-

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lactic measures, only hydration, antioxidant agents (acetylcysteine, ascorbic acid), and use of low-osmolar and isoosmolar contrast agents has been shown to provide some protection, reducing the incidence of contrast-induced nephropathy.[8-12] However, their efficacy in patients with severe chronic kidney disease is still controversial, and their impact on clinical outcome is completely unknown. Nevertheless, there is an increase in the use of contrast agents for diagnostic and therapeutic procedures even in patients with nondialysis-dependent severe chronic kidney disease. Unfortunately, these patients may have an overall mortality rate of 30% within 1 year when they undergo coronary angiography or percutaneous coronary procedures.[13] Thus, in the decision-making process, the mortality risk associated with the diagnostic and therapeutic value of invasive procedures should be weighed against the poor natural outcome of patients with chronic kidney disease whose coronary artery disease is managed conservatively by medical therapy alone.[14]

We recently demonstrated that use of preemptive hemofiltration initiated 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 of contrast-induced nephropathy incidence and improved in-hospital and long-term outcome in patients with severe chronic kidney disease undergoing percutaneous coronary interventions.[15] Several aspects regarding hemofiltration remain unknown and need to be investigated, such as the mechanism(s) involved in the prophylactic effect, the definition of patients with the best cost-benefit profile, and the identification of hemofiltration protocols that are easier to perform and less time consuming. In particular, performing hemofiltration after contrast exposure only as a contrast-induced nephropathy preventive strategy is an attractive concept that offers two practical advantages. First, it allows the extension of the implementation of hemofiltration in patients with chronic kidney disease undergoing primary angioplasty for acute myocardial infarction. This is a population at high risk for contrast-induced nephropathy, given the large amount of contrast that may be required in complex cases, the frequently associated hemodynamic instability, and the preclusion for contrast-induced nephropathy prophylaxis measures before contrast exposure.[16] Second, it offers the possibility to assess, at the end of the cardiovascular procedure, the real need for hemofiltration on the basis of the patient's risk factors, procedural complications, and contrast volume used. Contrast load, in effect, cannot be predicted in a significant proportion of cases, given the widespread use in recent years of ad hoc coronary procedures among patients undergoing initial coronary angiography. In this context, the capability of performing hemofiltration after contrast agent administration only, if demonstrated efficacious, may increase the clinical applicability of this effective contrast-induced nephropathy preventive strategy.

We therefore conducted a prospective, randomized study to compare the incidence of contrast-induced nephropathy in patients with severe chronic kidney disease undergoing invasive cardiovascular procedures and treated with three different prevention protocols: hydration, hemofiltration performed before and after contrast agent exposure, and hemofiltration performed only after contrast agent administration.

CLINICAL SIGNIFICANCE

- Hemofiltration performed before and after percutaneous coronary interventions prevents contrast-induced nephropathy and improves outcome in chronic kidney disease patients.
- We evaluated whether hemofiltration after contrast exposure only was equally effective.
- Contrast-induced nephropathy was prevented only in patients undergoing hemofiltration before and after percutaneous coronary interventions (3% vs 26%; $P = .0013$).
- Hemofiltration is an effective strategy for contrast-induced nephropathy prevention. However, pre-procedural treatment is required to obtain the full clinical benefit.

METHODS

Study Population

In this study, we enrolled 92 consecutive patients with severe chronic kidney disease who were scheduled for invasive diagnostic and therapeutic cardiovascular procedures at our institute between January 1, 2002, and May 31, 2004. Included were patients with an estimated creatinine clearance less than 30 mL/min.[17,18] Excluded were patients with acute coronary syndromes, cardiogenic shock, acute renal failure, chronic peritoneal or hemodialysis treatment, overt congestive heart failure, recent major bleeding, and contraindications to anticoagulation. A nonionic, low-osmolality contrast agent (Iopentol, Nycomed Imaging AS, Oslo, Norway) was used in all patients. The ethical committee of our institution approved the protocol, and written informed consent was obtained from all patients.

Study Protocol

Patients were randomized in a 1:1:1 ratio to receive 1 of the following 3 prophylactic treatments: intravenous hydration with isotonic saline, performed for 12 hours before and for 12 hours after contrast agent exposure (control group); intravenous hydration with isotonic saline, performed for 12 hours before contrast agent administration, followed by hemofiltration treatment for 18 to 24 hours after contrast agent exposure (post-hemofiltration group); and hemofiltration treatment performed for 6 hours before and for 18 to 24

hours after contrast agent exposure (pre/post-hemofiltration group). Group assignment was accomplished with the use of a computer-generated randomization scheme. Patients randomized to hemofiltration (post-hemofiltration and pre/post-hemofiltration groups) were admitted to the intensive care unit for the duration of treatment; those allocated to the control group were admitted to the contiguous subintensive care unit, followed by the same medical and nursing staff of the former, and transferred to the intensive care unit in case of major complications. In the pre/post-hemofiltration group, hemofiltration treatment was stopped during the invasive procedure, and the circuit was temporarily filled with a saline solution and short-circuited to exclude the patient without interruption of the flow. The control group and post-hemofiltration group (the latter only during the pre-hemofiltration period) received a continuous intravenous infusion of isotonic saline at a rate of 1 mL · kg · h. The infusion rate was reduced to 0.5 mL · kg · h when poorly tolerated because of concomitant left ventricular dysfunction. Serum Cr was evaluated at baseline, immediately before the invasive procedure, each day for the following 3 days, and at hospital discharge. Creatinine clearance was calculated by applying the Cockcroft-Gault formula to the Cr.[18] Contrast-induced nephropathy was defined as a greater than 25% increase in Cr from baseline.[15] According to our clinical protocol, renal replacement therapy (hemofiltration or hemodialysis) was performed in case of acute renal failure and prolonged (>48 hours) oligoanuria despite more than 1 g of intravenous furosemide per 24 hours. It was performed earlier in the case of concomitant overt heart failure.[19]

The primary end point of the study was the incidence of contrast-induced nephropathy in the 3 study groups. The secondary end point included in-hospital adverse clinical events.

Hemofiltration

Hemofiltration was performed according to a protocol described previously in detail.[15,19] Briefly, a double lumen catheter was introduced into the femoral vein for blood withdrawal and reinfusion and connected with an extracorporeal circuit. Blood was driven through the circuit by means of a peristaltic pump (B. Braun Diapact CRRT, Mirandola, Italy, or Prisma, Hospal, Mirandola, Italy) at a rate of 100 mL/min. Isotonic replacement fluid (post-dilution hemofiltration) was set at a rate of 1000 mL/h, and was exactly matched with the rate of ultrafiltrate production so that no net fluid loss resulted. A loading heparin bolus of 5000 IU was administered intravenously before hemofiltration initiation and followed by a continuous heparin infusion of 500 to 1000 IU/h through the inflow side of the circuit.

Statistical Analysis

We based calculation of the sample size on a power analysis that assumed an expected reduction in the absolute incidence of contrast-induced nephropathy of 30% in the 2 hemofiltration groups, pooled together, compared with the control group. The inclusion of 30 patients in each group allowed for an 80% power with an α error of 0.05. Descriptive statistics are presented as the mean value ± standard deviation or frequency (%). The clinical characteristics of the three groups were compared using analysis of variance for continuous variables and the chi-square test for categoric variables. A multivariable logistic regression model was applied including all the potential confounding factors: age, gender, baseline creatinine clearance, and contrast agent volume. A P value of less than .05 was considered to indicate statistical significance. All calculations were computed with the aid of the SAS software package (Version 8.02; SAS Institute Inc, Cary, NC).

RESULTS

Of the 92 patients included in the study, 30 were randomized to the control group, 31 were randomized to the post-hemofiltration group, and 31 were randomized to the pre/post-hemofiltration group. Baseline clinical characteristics were similar in the three groups (Table 1). By inclusion criteria, all patients had severe (stage 4) chronic kidney disease.[16] The average Cr value was 3.6 ± 0.8 mg/dL in the control group, 3.6 ± 0.7 mg/dL in the post-hemofiltration group, and 3.7 ± 0.9 mg/dL in the pre/post-hemofiltration group (P = not significant). The average estimated creatinine clearance was 20 ± 5 mL/min, 20 ± 4 mL/min, and 18 ± 4 mL/min, respectively (P = not significant). The number of additional risk factors for contrast-induced nephropathy, in particular diabetes mellitus and left ventricular dysfunction, was also similar among groups. Table 2 shows the type of procedures involving contrast agents in the 3 study groups.

The time course of Cr in the three treatment groups is reported in Figure 1. In patients undergoing hemofiltration, Cr decreased during the treatment as a consequence of its removal by ultrafiltration and simultaneous blood dilution by fluid replacement. The Cr reduction in pre/post-hemofiltration was greater because of the more prolonged duration of the treatment compared with the post-hemofiltration group. After the end of the hemofiltration treatment, Cr progressively returned toward baseline value in the pre/post-hemofiltration group. On the contrary, it significantly increased, as an average, in the other 2 groups, and this increase was greater in control patients than in hemofiltration-treated patients. At discharge (9.3 ± 5 days after the angiographic procedure; median 8 days, range 4-21 days), Cr was significantly increased in the controls and post-hemofiltration group compared with baseline levels, with a higher value in controls. Conversely, no significant difference was observed in the pre/post-hemofiltration group between baseline and discharge values.

Only 1 patient (3%) of the pre/post-hemofiltration group experienced contrast-induced nephropathy after the invasive procedure compared with 12 patients (40%) of the control group, and 8 patients (26%) of the post-hemofiltration group (P = .0013). When contrast-induced

Table 1 Baseline characteristics of the study patients

	Controls (n = 30)	Post-hemofiltration (n = 31)	Pre/post hemofiltration (n = 31)	*P* value
Age (y)	71 ± 6	72 ± 8	72 ± 7	.86
Men	22 (73%)	23 (74%)	20 (65%)	.65
Weight (kg)	71 ± 8	73 ± 9	68 ± 7	.12
Diabetes	12 (40%)	9 (29%)	7 (23%)	.86
Hypertension	18 (60%)	21 (68%)	23 (74%)	.50
Prior MI	8 (27%)	13 (42%)	10 (32%)	.44
Prior CABG	3 (10%)	5 (16%)	4 (13%)	.77
Prior PCI	2 (7%)	2 (6%)	1 (3%)	.80
Prior CHF	5 (17%)	9 (29%)	6 (19%)	.47
Mean LVEF (%)	47 ± 10	46 ± 12	48 ± 12	.66
LVEF < 40%	9 (30%)	12 (39%)	8 (26%)	.24
Peripheral arterial disease	9 (30%)	9 (29%)	10 (32%)	.96
Cerebral vascular disease	4 (13%)	4 (13%)	5 (16%)	.92
COPD	5 (17%)	4 (13%)	4 (13%)	.89
Chronic atrial fibrillation	4 (13%)	3 (10%)	2 (6%)	.66
Aspirin	15 (50%)	19 (61%)	13 (42%)	.31
ACE inhibitor or ARB	9 (30%)	10 (32%)	8 (26%)	.85
Diuretics	17 (57%)	20 (64%)	18 (58%)	.80
Indication for angiography				
Stable angina	10 (33%)	8 (26%)	9 (29%)	.81
Recent MI	4 (13%)	7 (23%)	6 (19%)	.64
Unstable angina	9 (30%)	10 (32%)	8 (26%)	.85
Other	7 (23%)	6 (19%)	7 (23%)	.92
Serum creatinine (mg/dL)	3.6 ± 0.8	3.6 ± 0.7	3.7 ± 0.9	.85
Creatinine clearance (mL/min)	20 ± 5	20 ± 4	18 ± 4	.12

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

nephropathy was defined as an absolute increase in baseline Cr of at least 0.5 mg/dL, 1 patient (3%), 14 patients (47%), and 13 patients (42%), respectively, developed contrast-induced nephropathy ($P < .001$) (Fig. 2). After adjustment for possible confounding factors (age, gender, baseline creatinine clearance, and contrast volume), the relative risk of contrast-induced nephropathy in the pre/post-hemofiltration group, compared with the control group, was 0.05 (95% confidence interval 0.006-0.41; $P = .0004$). In the pre/post-hemofiltration group, compared with the post-hemofiltration group, the relative risk was 0.096 (95% confidence interval 0.01-0.82; $P = .026$). In the post-hemofiltration group, compared with the control group, the relative risk was 0.52 (95% confidence interval 0.17-1.56; $P = .28$).

Table 3 shows the major adverse clinical events occurring after the invasive cardiovascular procedure in the 3 study groups. Emergency hemodialysis or hemofiltration for

Table 2 Radiocontrast procedures

	Controls (n = 30)	Post hemofiltration (n = 31)	Pre/post hemofiltration (n = 31)	*P* value
Coronary angiography	28 (93%)	28 (90%)	27 (87%)	.71
PCI	8 (27%)	9 (29%)	9 (29%)	.97
Single vessel	6 (20%)	7 (23%)	8 (26%)	.86
Multivessel	2 (7%)	2 (6%)	1 (3%)	.80
Associated procedures	9 (30%)	10 (32%)	11 (35%)	.90
Aortic angiography	3 (10%)	3 (10%)	4 (13%)	.90
Peripheral angioplasty	1 (3%)	1 (3%)	2 (6%)	.78
Renal angioplasty	2 (7%)	3 (10%)	4 (13%)	.71
Others	3 (10%)	3 (10%)	2 (6%)	.87
Contrast volume (mL)	232 ± 144	237 ± 122	223 ± 131	.92

PCI = percutaneous coronary intervention.

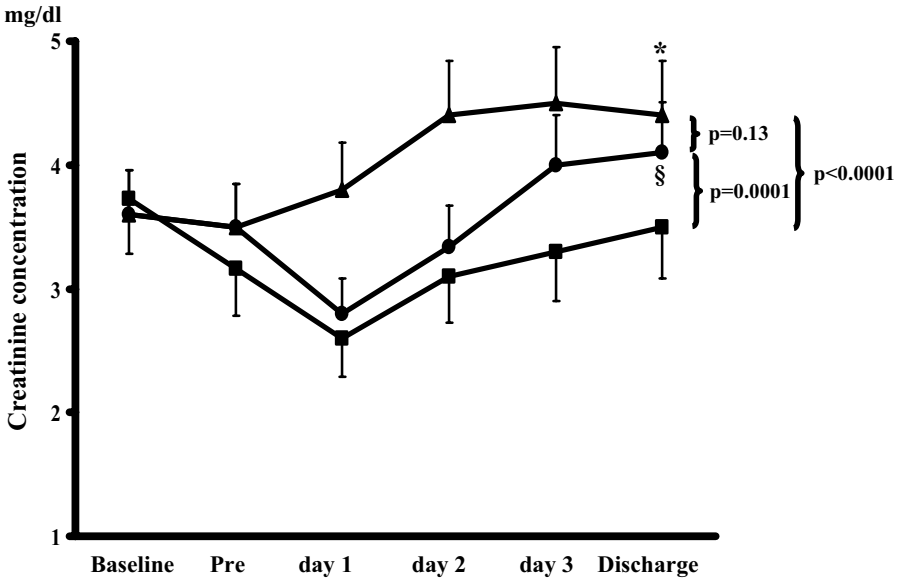

Figure 1 Serum creatinine concentration at baseline, before contrast medium administration (Pre), in the following 3 days (days 1, 2, and 3), and at hospital discharge in patients treated with hydration (control group = *triangles*) and in the two groups undergoing hemofiltration before and after contrast administration (pre/post-hemofiltration group = *squares*) or after contrast administration only (post-hemofiltration group = *circles*). *$P < .0001$ versus baseline; §$P = .001$ versus baseline.

contrast-induced nephropathy-related acute renal failure was required in 9 patients (30%) in the control group, 3 patients (10%) in the post-hemofiltration group, and none in the pre/post-hemofiltration group ($P = .002$). Nine patients (10%) died during the hospitalization period: six (20%) in the control group, 3 (10%) in the post-hemofiltration group, and none (0%) in the pre/post-hemofiltration group ($P = .03$). All deaths were attributable to cardiovascular causes (cardiogenic shock in 3 patients, multiorgan failure in 3 patients, refractory heart failure in 2 patients, and cardioembolic stroke in 1 patient).

DISCUSSION

The results of this study confirm our previous observation that prophylactic hemofiltration is effective in preventing contrast-induced nephropathy in patients with severe chronic kidney disease receiving contrast media for diagnostic and interventional procedures.[15] In addition, the present investigation provides further information on the clinical application of hemofiltration and the most effective protocol, and offers new insights into the mechanism(s) involved in its beneficial effect. In this study the indication to hemofiltration was limited to patients with severe chronic kidney disease, defined by a less than 30 mL/min value of estimated creatinine clearance, as proposed by the National Kidney Foundation.[18] This represents a population at high cardiovascular risk. Evidence now suggests that the incidence of atherosclerotic vascular disease is three times greater in patients with severe chronic kidney disease compared with the general population.[20] These patients combine atherogenic risk factors related to the uremic state, including hyperfibrinogemia, dyslipoproteinemia, and hyperhomocisteinemia, with those predisposing to chronic renal failure, such as diabetes mellitus, hypertension, hypercolesterolemia, and advanced age.[21,22] In addition to severe renal insufficiency, most of our patients had associated important risk factors for contrast-induced nephropathy. In such a high-risk population, hemofiltration was confirmed to be a very effective strategy. Only 3% of the patients treated with hemofiltration before and after contrast administration developed contrast-induced nephropathy, an incidence similar to that observed in patients with normal renal function undergoing percutaneous coronary interventions.[1,23] As previously reported, the in-hospital clinical outcome was favorably influenced by hemofiltration. Although the sample

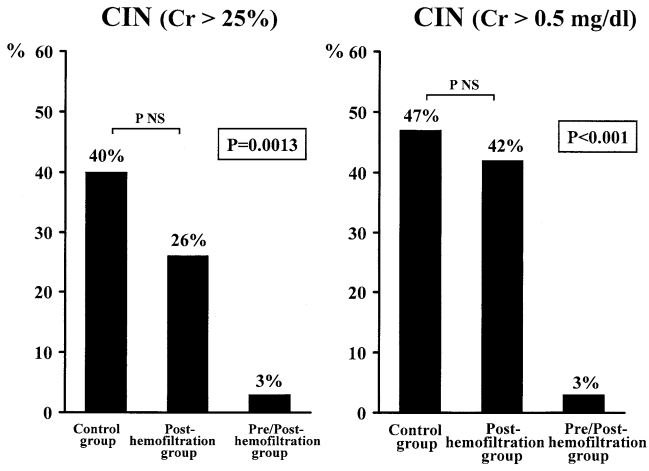

Figure 2 Incidence of contrast-induced nephropathy (CIN) defined as a relative (>25%; *left*) or an absolute (>0.5 mg/dL; *right*) increase in baseline serum creatinine (Cr), in the control group and in the two groups undergoing hemofiltration before and after contrast administration (pre/post-hemofiltration group) or after contrast administration only (post-hemofiltration group).

Table 3 Postprocedural complications

	Controls (n = 30)	Post hemofiltration (n = 31)	Pre/post hemofiltration (n = 31)	*p* value
Acute myocardial infarction	5 (17%)	4 (13%)	1 (3%)	.21
Emergency CABG	0 (0%)	0 (0%)	0 (0%)	-
Pulmonary edema requiring MV	1 (3%)	1 (3%)	0 (0%)	.59
Cardiogenic shock requiring IABP	1 (3%)	0 (0%)	0 (0%)	.35
Blood transfusion	4 (13%)	6 (19%)	5 (16%)	.81
ARF requiring RRT	9 (30%)	3 (10%)	0 (0%)	.002
≥2 clinical complications	6 (20%)	2 (6%)	0 (0%)	.019
In-hospital mortality	6 (20%)	3 (10%)	0 (0%)	.02

ARF = acute renal failure; CABG = coronary artery bypass graft surgery; IABP = intra-aortic balloon pump; MV = mechanical ventilation; RRT = renal replacement therapy (hemodialysis, hemofiltration).

size of our study population was not powered to detect any difference in mortality among the study groups, a significantly lower in-hospital mortality was observed in patients undergoing pre/post-hemofiltration. On the other hand, the present study confirms that when prophylaxis with saline solution infusion only is carried out, as in our control group, the incidence of contrast-induced nephropathy, as well as the need for an emergency renal replacement therapy, is very high, and the clinical implications, in terms of unfavorable in-hospital outcome, are of major relevance. Up to now, when taking care of a patient with coronary artery disease and severe chronic kidney disease, the cardiologist had to choose between the adverse prognosis related to a conservative approach of the cardiovascular pathology and the serious prognostic implication of contrast-induced nephropathy associated with invasive procedures.[13-15] Hemofiltration, by preventing contrast-induced nephropathy and its associated poor outcome, may extend the range of patients with severe renal disease in whom it is possible to perform coronary procedures safely, thus shifting the balance toward the interventional approach.

The mechanisms through which hemofiltration prevents further renal function deterioration in patients with severe chronic kidney disease are not fully understood. However, our results may help in clarifying some of them. We compared 2 different hemofiltration protocols to define the relative role of pre- and post-hemofiltration treatment in producing the observed beneficial effect. A clear advantage of a post-hemofiltration protocol is the possibility to treat patients with acute myocardial infarction and underlying chronic kidney disease who are subjected to primary angioplasty, and to more appropriately define the indications for hemofiltration use in more selected patients, namely, those with the highest risk profile who can benefit the most.[15] It has been disappointing, however, to not observe a reduction of the contrast-induced nephropathy rate when post-hemofiltration only was performed. This finding indicates that a pre-hemofiltration session is required to obtain a full clinical benefit. Thus, the results of the present study suggest that the potential capability of hemofiltration to remove contrast media from the circulation, thus reducing the dye concentration to which the kidneys are exposed, seems to play, if any, a minor role.[24] The lack of a significant preventive effect of post-hemofiltration alone is in agreement with previous studies in which prophylactic hemodialysis or hemodiafiltration, started during or soon after contrast media administration, did not result in any significant reduction in the degree of renal function deterioration when compared with saline hydration alone.[25-28]

The need for a session of hemofiltration before contrast agents exposure suggests that, among other possible mechanisms, controlled high-volume hydration plays a major role in kidney protection. Undoubtedly, dehydrated patients are more prone to develop contrast-induced nephropathy.[1,2] This is likely because of the higher concentration of toxic substances in the renal tubules and the increased susceptibility to contrast-induced nephropathy caused by a reduction of the antioxidant defense mechanisms during volume depletion.[29] Proper hydration may counterbalance the osmotic diuretic effect of contrast agents and may increase effective circulating volume, renal perfusion pressure, and glomerular filtration. Moreover, it may decrease vasoconstriction in volume-depleted patients and enhance dye elimination. Finally, it also reduces sodium reabsorption, makes contrast more diluted in the tubules, and decreases residence time of contrast within the tubules.[30,31] Hydration with saline solution still represents the mainstay of contrast-induced nephropathy prophylaxis.[8,9] However, vigorous hydration before invasive procedures is difficult logistically and poorly tolerated, in particular in the presence of impaired cardiac and renal function. A substantial fluid administration and the consequent intravascular volume expansion without a parallel fluid removal increase the risk of vascular congestion and pulmonary edema. Conversely, when patients are treated with hemofiltration, fluid infusion and elimination are exactly matched, allowing infusion rate to be markedly and safely increased compared with intravenous hydration (from 10 to 15 times with our protocol). This results in a magnification of the beneficial effect of hydration without the risk of hypervolemia and extravascular fluid accumulation. It can also be speculated that, in addition to high-volume controlled hydration, removal by con-

vective filtration and by adsorption to the filter membrane of mediators of contrast-induced toxicity, such as endothelin, angiotensin, prostaglandins, and adenosine, or uremic toxins may play an additional protective role during the hemofiltration session preceding contrast exposure.[32,33] Another renal protective effect may also derive from the alkalinizing bicarbonate-based solution, which was used in our protocol as the replacement fluid during hemofiltration, as recently suggested by Merten et al.[34] Because bicarbonate-based solution may be more efficacious than sodium solution in reducing contrast-induced nephropathy, further studies that compare this type of hydration protocol with hemofiltration are warranted. Finally, heparin has been shown to attenuate ischemia-reperfusion injury and to inhibit acute inflammation and oxidative stress.[35-37] Thus, heparin infusion before contrast exposure in the pre/post-hemofiltration group may have protected, at least in part, these patients from renal ischemia-reperfusion injury induced by the contrast agents.

Study Limitations

Our study does not address the question of whether pre-hemofiltration only is sufficient to prevent contrast-induced nephropathy. However, it must be considered that post-hemofiltration treatment does not require a significant additional increase of the procedural cost (the same circuit, filter, and venous catheter were used in our study). Furthermore, the clinical advantage of excluding the post-hemofiltration session is modest, in comparison with the possibility to avoid the pre-hemofiltration treatment. Finally, although patients treated with post-hemofiltration had a contrast-induced nephropathy rate not significantly different from that observed in controls, they showed a reduced incidence of clinical complications. In particular, fewer patients required additional renal replacement therapies (10% vs 30%; $P = .046$) and in-hospital mortality was lower than that observed in controls (10% vs 20%; $P = .25$). Thus, postprocedural hemofiltration treatment seems justified and may further improve the efficacy of this therapy in protecting against contrast-induced nephropathy, particularly in high-risk patients undergoing complex cardiovascular interventions.

Another limitation of this study is the lack of accurate evaluation of renal function. We used Cr value to assess renal function changes. Because hemofiltration artificially lowers Cr, renal function deterioration may have been concealed by this therapy. However, the hemofiltration-related Cr reduction and the typical Cr increase caused by contrast-induced damage have different time courses. The former occurs during the first 24 hours after contrast administration, whereas the latter generally starts 48 to 72 hours after contrast administration and peaks a few days later. Thus, it is unlikely that acute renal dysfunction may have been missed because of hemofiltration treatment. Additional evidence of this is the fact that 26% of the patients in the post-hemofiltration group (42% when an absolute increase of at least 0.5 mg/dL in baseline Cr was considered) showed a significant Cr increase during the hospital stay, despite the initial Cr decrease.

Furthermore, the unblinded nature of the study may have influenced in part our result. As patients undergoing hemofiltration were admitted to the intensive care unit, they had more vigilance by the staff than controls, and thus possible lower complication rates. However, all patients undergoing hemofiltration (pre- and pre/post-hemofiltration groups) were treated in the intensive care unit for a similar period of time, so that our results cannot be explained by a different standard of care between the 2 groups.

CONCLUSION

Our data confirm that hemofiltration is a highly effective strategy for the prevention of contrast-induced nephropathy in patients with severe chronic kidney disease who are undergoing invasive diagnostic and interventional procedures. Moreover, this study demonstrates that hemofiltration before contrast media administration is needed to obtain the full beneficial effect. Finally, it suggests that high-volume controlled hydration is likely the major prophylactic mechanism of hemofiltration for the prevention of contrast agent-induced kidney injury.

References

1. Rich MW, Crecelius CA. Incidence, risk factors and clinical course of acute renal insufficiency after cardiac catheterization in patients 70 years of age or older. A prospective study. *Arch Intern Med*. 1990; 150:1237-1242.
2. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors and relationship to mortality. *Am J Med*. 1997;103:368-375.
3. Gruberg L, Mintz GS, Mehran R, et al. The prognostic implications of further renal function deterioration within 48 hours of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol*. 2000;36:1542-1548.
4. Rubenstein MH, Harrell LC, Sheynberg BV, et al. Are patients with renal failure good candidates for percutaneous coronary revascularization in the new device era? *Circulation*. 2000;102:2966-2972.
5. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;105:2259-2264.
6. Best PJM, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol*. 2002;39:1113-1119.
7. Gruber L, Mehran R, Dangas G, et al. Acute renal failure requiring dialysis after percutaneous coronary interventions. *Catheter Cardiovasc Interv*. 2001;52:409-416.
8. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol, and furosemide on acute changes in renal function induced by radiocontrast agents. *N Engl J Med*. 1994;331:403-411.
9. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med*. 2002;162:329-336.
10. Briguori C, Manganelli F, Scarpato P, et al. Acetylcysteine and contrast agent-associated nephrotoxicity. *J Am Coll Cardiol*. 2002;40:298-303.
11. Spargias K, Alexopoulos E, Kyrzopoulos S, et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation*. 2004;110:2837-2842.
12. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. A double-blind randomized multicenter study of iso-osmolar and low-osmolar non-ionic contrast media. *N Engl J Med*. 2003;348:491-499.

13. Hemmelgarn BR, Ghali WA, Quan HQ, et al. Poor long-term survival after coronary angiography in patients with renal insufficiency. *Am J Kidney Dis*. 2001;37:64-72.
14. Keith DS, Nichols GA, Gullion CM, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*. 2004;164:659-663.
15. Marenzi G, Marana I, Lauri G, et al. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med*. 2003; 349:1331-1338.
16. Marenzi G, Lauri G, Assanelli E, et al. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol*. 2004;44:1780-1785.
17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.
18. National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) Advisory Board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(Suppl 2):S17-S31.
19. Marenzi G, Bartorelli AL, Lauri G, et al. Continuous veno-venous hemofiltration for the treatment of contrast-induced acute renal failure after percutaneous coronary interventions. *Cathet Cardiovasc Intervent*. 2003;58:59-64.
20. Jungers P, Massy ZA, Khoa TN, et al. Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study. *Nephrol Dial Transplant*. 1997; 12:2597-2602.
21. Parfrey PS, Foley RN, Harnett JD, et al. Outcome and risk factors of ischemic heart disease in chronic uremia. *Kidney Int*. 1996;49: 1428-1434.
22. London GM, Drueke TB. Atherosclerosis and arteriosclerosis in chronic renal failure. *Kidney Int*. 1997;51:1678-1695.
23. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both: a prospective controlled study. *N Engl J Med*. 1989;320:143-149.
24. Schindler R, Stahl C, Venz S, et al. Removal of contrast media by different extracorporeal treatments. *Nephrol Dial Transplant*. 2001;16: 1471-1474.
25. Vogt B, Ferrari P, Schonholzer C, et al. Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. *Am J Med*. 2001;111:692-698.
26. Sterner G, Frennby B, Kurkus J, Nyman U. Does post-angiographic hemodialysis reduce the risk of contrast medium nephropathy? *Scand J Urol Nephrol*. 2000;34:323-326.
27. Lehnert T, Keller E, Gondolf K, et al. Effect of hemodialysis after contrast medium administration in patients with renal insufficiency. *Nephrol Dial Transplant*. 1998;13:358-362.
28. Gabutti L, Marone C, Monti M, et al. Does continuous venovenous hemodiafiltration concomitant with radiological procedures provide a significant and safe removal of the iodinated contrast ioversol? *Blood Purif*. 2003;21:152-157.
29. Yoshioka T, Fogo A, Beckman YK. Reduced activity of antioxidant enzymes underlies contrast media-induced renal injury in volume depletion. *Kidney Int*. 1992;41:1008-1015.
30. Heyman SN, Rosen S. Dye-induced nephropathy. *Semin Nephrol*. 2003;23:477-485.
31. Persson PB, Patzak A. Renal haemodynamic alterations in contrast medium-induced nephropathy and the benefit of hydration. *Nephrol Dial Transplant*. 2005;20:i2-i5.
32. Cantley LG, Spokes K, Clark B, et al. Role of endothelin and prostaglandins in radiocontrast-induced renal artery constriction. *Kidney Int*. 1993;44:1217-1223.
33. Caldicott WJ, Hollenberg NK, Abrams HL. Characteristics of response of renal bed to contrast media: evidence for vasoconstriction induced by renin-angiotensin system. *Invest Radiol*. 1970;5:539-547.
34. Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate. A randomized controlled trial. *JAMA*2004;291:2328-2334.
35. Hisama N, Yamaguchi Y, Okajima K, et al. Anticoagulant pre-treatment attenuates production of cytokine-induced neutrophil chemoattractant following ischemia-reperfusion of rat liver. *Dig Dis Sci*. 1996; 41:1481-1486.
36. Derhaschnig U, Pernerstorfer T, Knechtelsdorfer M, Hollenstein U, Panzer S, Jilma B. Evaluation of anti-inflammatory and antiadhesive effects of heparins in human endotoxemia. *Crit Care Med*. 2003;31:1108-1112.
37. Sela S, Shurtz-Swirski R, Shapiro G, et al. Oxidative stress during hemodialysis: effect of heparin. *Kidney Int*. 2001;78:S159-S163.