

## ORIGINAL ARTICLE

# The Prevention of Radiocontrast-Agent-Induced Nephropathy by Hemofiltration

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## ABSTRACT

**BACKGROUND**

Nephropathy induced by exposure to radiocontrast agents, a possible complication of percutaneous coronary interventions, is associated with significant in-hospital and long-term morbidity and mortality. Patients with preexisting renal failure are at particularly high risk. We investigated the role of hemofiltration, as compared with isotonic-saline hydration, in preventing contrast-agent-induced nephropathy in patients with renal failure.

**METHODS**

We studied 114 consecutive patients with chronic renal failure (serum creatinine concentration,  $>2$  mg per deciliter [ $176.8$   $\mu\text{mol}$  per liter]) who were undergoing coronary interventions. We randomly assigned them to either hemofiltration in an intensive care unit (ICU) (58 patients, with a mean [ $\pm$ SD] serum creatinine concentration of  $3.0 \pm 1.0$  mg per deciliter [ $265.2 \pm 88.4$   $\mu\text{mol}$  per liter]) or isotonic-saline hydration at a rate of 1 ml per kilogram of body weight per hour given in a step-down unit (56 patients, with a mean serum creatinine concentration of  $3.1 \pm 1.0$  mg per deciliter [ $274.0 \pm 88.4$   $\mu\text{mol}$  per liter]). Hemofiltration (fluid replacement rate, 1000 ml per hour without weight loss) and saline hydration were initiated 4 to 8 hours before the coronary intervention and were continued for 18 to 24 hours after the procedure was completed.

**RESULTS**

An increase in the serum creatinine concentration of more than 25 percent from the baseline value after the coronary intervention occurred less frequently among the patients in the hemofiltration group than among the control patients (5 percent vs. 50 percent,  $P < 0.001$ ). Temporary renal-replacement therapy (hemodialysis or hemofiltration) was required in 25 percent of the control patients and in 3 percent of the patients in the hemofiltration group. The rate of in-hospital events was 9 percent in the hemofiltration group and 52 percent in the control group ( $P < 0.001$ ). In-hospital mortality was 2 percent in the hemofiltration group and 14 percent in the control group ( $P = 0.02$ ), and the cumulative one-year mortality was 10 percent and 30 percent, respectively ( $P = 0.01$ ).

**CONCLUSIONS**

In patients with chronic renal failure who are undergoing percutaneous coronary interventions, periprocedural hemofiltration given in an ICU setting appears to be effective in preventing the deterioration of renal function due to contrast-agent-induced nephropathy and is associated with improved in-hospital and long-term outcomes.

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N Engl J Med 2003;349:1333-40.

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**R**ADIOCONTRAST-AGENT-INDUCED nephropathy is a common cause of acute renal failure,<sup>1-3</sup> which can range from a transient elevation of the serum creatinine concentration to permanent renal failure necessitating dialysis. When contrast-agent-induced nephropathy complicates percutaneous coronary interventions, it is associated with significant in-hospital and long-term morbidity and mortality, as well as with a prolonged hospital stay.<sup>1-8</sup> In addition, the clinical outcome of patients who require emergency dialysis after a percutaneous coronary intervention is very poor, with a reported in-hospital mortality rate as high as 62 percent.<sup>9,10</sup>

Most patients in whom contrast-agent-induced nephropathy develops have risk factors for it.<sup>1-3,11,12</sup> It has been reported that 90 percent of such nephropathy occurs in patients with preexisting renal failure.<sup>3,11</sup> Nevertheless, an increasing number of patients with chronic renal failure are being referred for percutaneous coronary interventions, owing to the greater prevalence of cardiovascular disease among patients with renal failure, combined with the prolongation of their life span.<sup>13</sup>

Contrast-agent-induced nephropathy is a potentially preventable condition. However, currently available strategies, such as hydration and the use of acetylcysteine, mannitol, furosemide, calcium antagonists, dopamine, fenoldopam, or other renoprotective drugs, have been shown to have no benefit or to reduce the incidence of such nephropathy only in patients with mild renal impairment and exposure to a low volume of contrast agent.<sup>14-19</sup> Moreover, prophylactic hemodialysis, started immediately after the administration of a contrast agent in patients with reduced renal function, has demonstrated no net benefit.<sup>20</sup>

In contrast to hemodialysis, hemofiltration is a continuous form of renal-replacement therapy that constitutes an alternative strategy for the prevention of contrast-agent-induced nephropathy in high-risk patients.<sup>21,22</sup> Hemofiltration is associated with hemodynamic stability<sup>21-23</sup> and can exert a beneficial effect through other mechanisms as well. First, since periprocedural hydration has been proved to be an efficacious and well-tolerated strategy, the potential benefit of hemofiltration can be markedly amplified by administering a volume of fluid per hour that is 10 to 15 times that delivered by standard hydration, without an associated risk of fluid overload and lung congestion. Second, like glomerular filtration, hemofiltration is able to remove con-

trast agents from the circulation.<sup>24</sup> This mechanism, along with the dilution of contrast agents through the infusion of replacement fluid, lowers the concentration of the contrast agent in the blood and may reduce the exposure of the kidneys to the nephrotoxic effects of these agents. We performed a prospective, randomized study comparing hemofiltration with saline hydration for the prevention of contrast-agent-induced nephropathy in patients with renal insufficiency who were to undergo elective percutaneous coronary interventions.

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## METHODS

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### STUDY POPULATION

We enrolled 114 consecutive patients with chronic renal failure who were scheduled for coronary angiography or an elective percutaneous coronary intervention at our institution, Centro Cardiologico Monzino in Milan, Italy, between January 1, 2000, and October 31, 2001. Eligible patients were those with a serum creatinine concentration exceeding 2 mg per deciliter (176.8  $\mu$ mol per liter) and a creatinine clearance rate of less than 50 ml per minute. Patients with an acute coronary syndrome, cardiogenic shock, long-term peritoneal dialysis or hemodialysis treatment, overt congestive heart failure, recent major bleeding, or contraindications to anticoagulant therapy were excluded. A nonionic, low-osmolality contrast agent (Iopentol, Nycomed Imaging) was used in all patients. Renoprotective drugs were not administered to any patient during the study. The ethics committee of our institution approved the protocol, and written informed consent was obtained from all patients.

### STUDY PROTOCOL

On the basis of computer-generated random numbers, patients were assigned to receive either hemofiltration therapy in an intensive care unit (ICU) (hemofiltration group) or intravenous hydration with isotonic saline given in a step-down unit (control group). Patients randomly assigned to hemofiltration were admitted to the ICU for the duration of treatment; those assigned to the control group were admitted to the contiguous step-down unit, where they were followed by the medical and nursing staff of the ICU, and were transferred to the ICU if there were major complications. The intensity of monitoring was lower in the step-down unit than in the ICU: there was a ratio of patients to staff members of approximately 2:1 in the ICU and 4:1 in the

step-down unit. For patients in the hemofiltration group, a treatment session was started 4 to 6 hours before the scheduled coronary procedure; treatment was resumed after the procedure was completed and continued for 18 to 24 hours. Hemofiltration treatment was stopped during the coronary procedure, and the hemofiltration circuit was temporarily filled with a saline solution and was "short-circuited" to exclude the patient without interruption of the flow through the circuit. Patients in the control group received a continuous intravenous infusion of isotonic saline at a rate of 1 ml per kilogram of body weight per hour (0.5 ml per kilogram per hour if the ejection fraction was less than 40 percent) for 6 to 8 hours before and 24 hours after the coronary procedure.

Blood urea nitrogen and serum creatinine were measured at base line, immediately before angiography, at the end of either treatment, daily for the following three days, and at hospital discharge. Urine output was measured daily during the hospital stay. The creatinine clearance was calculated by applying the Cockcroft–Gault formula to the serum creatinine value.<sup>25</sup> Contrast-agent–induced nephropathy was defined as an increase of more than 25 percent from the base-line value in the serum creatinine concentration. According to our clinical protocol, emergency renal-replacement therapy (hemofiltration or hemodialysis) was performed if there was oligoanuria for more than 48 hours despite the administration of more than 1 g of intravenous furosemide per 24 hours. Emergency renal-replacement therapy was performed earlier in the event of concomitant overt heart failure.<sup>22</sup> Twelve-month clinical follow-up was conducted by office visit or by telephone.

#### CONTINUOUS VENOVENOUS HEMOFILTRATION

The extracorporeal circuit, which included a hemofilter (Renaflow HF700), originated from and terminated in a Y-shaped double-lumen catheter, which was percutaneously inserted in a femoral vein (with use of a 12-French catheter, Arrow International). Blood was driven through the circuit by means of a peristaltic pump (Diapact CRRT, B. Braun) at a rate of 100 ml per minute. The flow of isotonic replacement fluid was set at a rate of 1000 ml per hour 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 before the initiation of hemofiltration and was followed by a continuous heparin infusion of 500 to 1000 IU per hour through the inflow side of the circuit. Hep-

arinization was monitored by measurement of the activated partial-thromboplastin time.

#### STATISTICAL ANALYSIS

For the calculation of the sample size, we assumed an incidence of contrast-agent–induced nephropathy of 40 percent in the control group and a 25 percent reduction with hemofiltration (an incidence of 30 percent); the inclusion of 50 patients in each group allowed for 80 percent power with an alpha error of 0.05. All data are presented as means  $\pm$  SD or as percentages. Comparisons of base-line variables between the two treatment groups were performed with Fisher's exact test for categorical variables and with Student's unpaired t-test for continuous variables. Changes during hemofiltration and hydration treatment were assessed with the use of repeated-measures analysis of covariance. A P value of less than 0.05 was considered to indicate statistical significance. All calculations were computed with the aid of the SAS software package (SAS Institute).

## RESULTS

Of the 114 patients included in the study, 58 were randomly assigned to the hemofiltration group and 56 to the control group. Base-line characteristics and biochemical values were similar in the two groups (Table 1). All patients had severe chronic renal failure. The average calculated creatinine clearance rate was  $26 \pm 9$  ml per minute in the hemofiltration group and  $26 \pm 8$  ml per minute in the control group ( $P = 0.63$ ). The frequency of additional risk factors for contrast-agent–induced nephropathy was also similar in the two groups. Tables 2 and 3 indicate the types of procedures involving contrast agent and the postprocedural complications. There were no instances of treatment-associated hypotension in the hemofiltration group (although shock developed in one patient in this group two days after the end of hemofiltration treatment), and the other complications in this group were minimal. Three patients in this group had bleeding at the site of vascular access; in one case, blood transfusion was required. Two patients in the hemofiltration group required a two-stage percutaneous coronary intervention — because of the complexity of the procedure in one patient and because of the onset of high-rate atrial fibrillation with hemodynamic instability in the second patient. Hemofiltration was prolonged for three days in both of these patients.

Figure 1 shows the time course of renal-function

**Table 1. Base-Line Characteristics of the Study Patients.\***

Characteristic	Hemofiltration Group (N=58)	Control Group (N=56)	P Value
<b>Clinical characteristics</b>			
Age — yr	69±10	69±11	0.75
Male sex — no. (%)	46 (79)	43 (77)	0.74
Diabetes — no. (%)	17 (29)	17 (30)	0.90
Hypertension — no. (%)	40 (69)	38 (68)	0.90
Prior myocardial infarction — no. (%)	18 (31)	16 (29)	0.77
Prior CABG — no. (%)	6 (10)	7 (12)	0.71
Prior PTCA — no. (%)	2 (3)	2 (4)	1.00
Left ventricular ejection fraction — %	50±13	49±12	0.67
Left ventricular ejection fraction <40% — no. (%)	14 (24)	14 (25)	1.00
<b>Medications</b>			
ACE inhibitors — no. (%)	7 (12)	8 (14)	0.72
Aspirin — no. (%)	25 (43)	29 (52)	0.35
Diuretics — no. (%)	32 (55)	32 (57)	0.83
<b>Laboratory measures†</b>			
Serum creatinine — mg/dl	3.0±1.0	3.1±1.0	0.84
Creatinine clearance — ml/min	26±9	26±8	0.63
Blood urea nitrogen — mg/dl	58±21	63±21	0.18

\* Plus-minus values are means ±SD. CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, and ACE angiotensin-converting enzyme.

† To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for urea nitrogen to millimoles per liter, multiply by 0.357.

values and urine output in the two treatment groups. During hemofiltration in the ICU, the serum creatinine and blood urea nitrogen concentrations decreased as a consequence of the removal of these solutes by ultrafiltration and simultaneous dilution of the blood through fluid replacement. Thereafter, values for these two measures progressively returned to their base-line levels. No significant changes from base line in renal function were observed at discharge. Urine output remained stable throughout the study period. In the control group, the mean creatinine and blood urea nitrogen values increased significantly after the coronary procedures and were still higher than base-line values at hospital discharge. A transient reduction in urine output was observed after the coronary intervention in the control patients. Only 3 patients in the hemofiltration group (5 percent) had contrast-agent-induced nephropathy after the coronary procedure, as com-

pared with 28 patients in the control group (50 percent,  $P<0.001$ ).

Emergency hemodialysis was required in 10 control patients (18 percent) but in no patients in the hemofiltration group. Four control patients (7 percent) were treated with hemofiltration because of pulmonary edema that occurred after the coronary intervention. Four patients in the hemofiltration group (7 percent) and five in the control group (9 percent) underwent elective surgical coronary revascularization before discharge.

In-hospital mortality was significantly lower in the hemofiltration group. Only one patient in the hemofiltration group died (because of cardiogenic shock), whereas eight deaths occurred in the control group (three due to acute myocardial infarction complicated by cardiogenic shock, two due to multiorgan failure, two due to refractory heart failure, and one due to ischemic stroke). Thus, the in-hospital mortality rate was 2 percent in the hemofiltration group, as compared with 14 percent in the control group ( $P=0.02$ ).

All enrolled patients completed the study according to the protocol. In 24 patients (14 in the control group and 10 in the hemofiltration group), one-year follow-up was conducted through direct telephone contact, with the use of reports from the patient's general practitioner, or through contact with relatives, whereas the remaining 81 patients were evaluated at an office visit. During the one year of follow-up, permanent dialysis was required in three patients in the control group and one patient in the hemofiltration group. Fourteen additional patients died during follow-up (five in the hemofiltration group and nine controls), resulting in a cumulative one-year mortality rate of 10 percent in the hemofiltration group and 30 percent in the control group ( $P=0.01$ ). The cause of death could not be determined in five cases. The remaining nine patients died from acute cardiovascular events: myocardial infarction in two patients, sudden death in two patients, and pulmonary edema, cardiac tamponade, stroke, pulmonary embolism, and intestinal infarction in one patient each.

The relative risk of death within one year in the control group, as compared with the hemofiltration group, was 1.16 (95 percent confidence interval, 0.96 to 1.40;  $P=0.11$ ) among patients with a base-line serum creatinine concentration of less than 4 mg per deciliter ( $353.6 \mu\text{mol per liter}$ ) and 3.53 (95 percent confidence interval, 1.08 to 11.20;  $P=0.002$ )

among those with a base-line serum creatinine concentration of 4 mg per deciliter or higher.

## DISCUSSION

Prophylactic hemofiltration in the ICU appears to be an effective and safe strategy for the prevention of contrast-agent-induced acute renal dysfunction in patients with chronic renal failure who are undergoing percutaneous coronary interventions. Furthermore, in-hospital and one-year clinical outcomes were also significantly improved in the hemofiltration group, as compared with the control group.

Patients with chronic renal failure now live longer and have a predisposition toward accelerated atherosclerosis; they thus represent an increasing percentage of the patients undergoing percutaneous coronary interventions.<sup>26</sup> The clinical outcome of patients in whom contrast-agent-induced nephropathy develops after percutaneous coronary interventions is particularly poor, with a reported in-hospital mortality rate of more than 20 percent and a cumulative one-year mortality rate of more than 35 percent.<sup>1-10,27</sup> In two studies, mortality increased to 45 percent and 62 percent, respectively, when dialysis was required.<sup>4,9</sup>

Our study patients were at very high risk for acute deterioration of renal function and poor clinical outcomes.<sup>1-10</sup> All had marked renal insufficiency (range of serum creatinine concentrations, 2.1 to 6.3 mg per deciliter [185.6 to 556.9  $\mu$ mol per liter]) and exposure to a high volume of contrast agent; most also had one or more additional risk factors for contrast-agent-induced nephropathy. Despite this high-risk profile, contrast-agent-induced nephropathy developed in only 5 percent of the patients treated with hemofiltration in the ICU, whereas such a deterioration of renal function occurred in 50 percent of the control patients treated with saline hydration. The average amount of contrast agent used was greater than that reported in other studies, because many of our patients underwent coronary angiography and coronary intervention during the same session. Indeed, in approximately 30 percent of the cases, multiple procedures were performed. These factors probably contributed to the high incidence of contrast-agent-induced nephropathy in the control group.

When the in-hospital and one-year follow-up periods were considered, the mortality rate in the control group was significantly higher than that ob-

**Table 2. Procedures Involving Radiocontrast Agent.\***

Variable	Hemofiltration Group (N=58)	Control Group (N=56)	P Value
Coronary angiography — no. (%)	58 (100)	56 (100)	1.00
PTCA and stenting — no. (%)	51 (88)	48 (86)	0.94
Single-vessel	45 (78)	42 (75)	0.92
Multivessel	6 (10)	6 (11)	0.81
Associated procedures — no. (%)	18 (31)	15 (27)	0.77
Aortic angiography	10 (17)	8 (14)	0.86
Peripheral angioplasty	2 (3)	2 (4)	1.00
Renal angioplasty	6 (10)	5 (9)	0.80
Other	4 (7)	3 (5)	0.73
Volume of contrast agent used — ml	247 $\pm$ 125	258 $\pm$ 132	0.70

\* Plus-minus values are means  $\pm$ SD. PTCA denotes percutaneous transluminal coronary angioplasty.

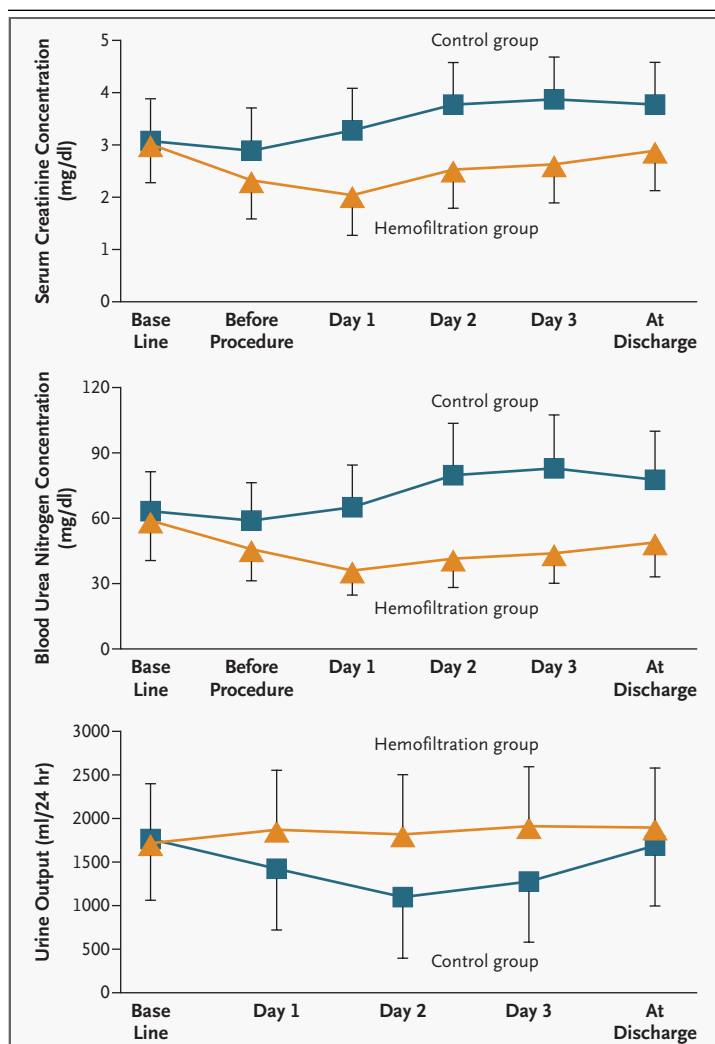
**Table 3. Postprocedural Complications.\***

Complication	Hemofiltration Group (N=58)	Control Group (N=56)	P Value
	no. (%)		
Myocardial infarction			
Q-wave	0	2 (4)	0.24
Non-Q-wave	1 (2)	1 (2)	1.00
Emergency CABG required	0	0	1.00
Pulmonary edema	0	6 (11)	0.02
Hypotension or shock	1 (2)	3 (5)	0.36
Blood transfusion required	1 (2)	3 (5)	0.36
Renal-replacement therapy required	2 (3) <sup>†</sup>	14 (25)	<0.001
All clinical events	5 (9)	29 (52)	<0.001

\* CABG denotes coronary-artery bypass grafting. Renal-replacement therapy consisted of hemodialysis or hemofiltration.

<sup>†</sup> These two patients underwent prolonged prophylactic treatment with hemofiltration.

served in the hemofiltration group and was similar to that reported in previous studies involving patients with chronic renal failure who were exposed to contrast agents.<sup>4,5,8</sup> The rates of all the primary end points (complications and death, either in the hospital or during follow-up) in patients treated with hemofiltration in the ICU were markedly lower than those in the control group and were no different from those reported for patients without chronic renal failure or with chronic renal failure that was not complicated by contrast-agent-induced nephropathy.<sup>5-7</sup> Although we attribute most of the benefit to hemofiltration, the general intensity of the



**Figure 1. Serum Creatinine Concentration, Blood Urea Nitrogen Concentration, and Urine Output before the Percutaneous Coronary Intervention, at the End of Treatment (Day 1), on the Following Two Days (Days 2 and 3), and at Hospital Discharge.**

For the interaction between time and treatment in terms of the serum creatinine concentration,  $F$  statistic=45.5 ( $P<0.001$ ). Changes from base line in the serum creatinine concentration were significant ( $P<0.01$ ) before the procedure and on days 1, 2, and 3 in the hemofiltration group and at day 2, day 3, and discharge in the control group; the difference between the two groups was significant beginning on day 1. For the interaction between time and treatment in terms of the blood urea nitrogen concentration,  $F$  statistic=53.6 ( $P<0.001$ ). Changes from base line in the blood urea nitrogen concentration were significant ( $P<0.01$ ) before the procedure and on days 1, 2, and 3 in the hemofiltration group and beginning on day 1 in the control group; the differences between the two groups were significant beginning on day 1. For the interaction between time and treatment in terms of urine output,  $F$  statistic=13.5 ( $P<0.001$ ). Changes from base line in the urine output were significant ( $P<0.01$ ) on day 2 and day 3 in the control group but at no time point in the hemofiltration group; the differences between the two groups were significant on day 2 and day 3. To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for urea nitrogen to millimoles per liter, multiply by 0.357.

care rendered or the use of an infusion of heparin during hemofiltration — in addition to the two different renal-treatment strategies — could have accounted for some of the differences in clinical outcomes between the two groups.

Several strategies have been evaluated for the prevention of contrast-agent-induced nephropathy. Among these strategies, only hydration with saline,<sup>15,28</sup> the use of low-osmolality contrast agents,<sup>29</sup> and treatment with acetylcysteine<sup>14,19,30</sup> or fenoldopam<sup>18,31</sup> have been shown to provide some protection and to reduce the incidence of contrast-agent-induced nephropathy. However, the efficacy of these measures is still controversial in patients with severe renal failure who are undergoing radiographic procedures requiring a high volume of contrast agent,<sup>19</sup> and their effect on the clinical outcome is unknown. Recently, Vogt et al. evaluated prophylactic hemodialysis started soon after the administration of the contrast agent and continued for an average of three hours.<sup>20</sup> The rationale for the study was to remove the contrast agent efficiently by hemodialysis, thus reducing the concentration of contrast agent to which the kidneys would be exposed. However, this strategy did not show any beneficial effect as compared with saline hydration alone, and patients who were treated with hemodialysis were more likely to have a decline in renal function and to require additional hemodialysis treatment.<sup>20</sup>

A possible explanation for these results is that hemodialysis can induce hypovolemia and consequently may worsen renal ischemic injury, delay recovery of renal function, and result in a need for prolonged treatment.<sup>32</sup> On the other hand, hemofiltration is associated with hemodynamic stability and, by preserving the volume of circulating blood, safeguards against renal hypoperfusion.<sup>23</sup> This effect is particularly useful when coronary procedures are performed in patients with critical conditions such as myocardial infarction or acute cardiovascular events such as pulmonary edema or severe left ventricular dysfunction. In addition to hemodynamic stability, hemofiltration provides controlled high-volume hydration and removal of contrast agent from the circulation, with a resultant reduction in the kidneys' exposure to the agent.<sup>21-23</sup> The interplay of these mechanisms may explain the positive effect of hemofiltration on outcomes among our patients with preexisting renal failure. The preservation of renal function had a positive effect on clinical outcome, as demonstrated by the significant

reduction in in-hospital and one-year morbidity and mortality.

A limitation of hemofiltration delivered in the ICU is its relatively high cost as compared with that of saline infusion delivered in less intensive treatment settings. However, it must be emphasized that our positive results were obtained in a group of patients at very high risk who were undergoing multiple interventions requiring a larger volume of contrast agent than that used during simple diagnostic radiographic procedures. Indeed, our patients represent a population in which a preventive strategy with hemofiltration appears to be justified and cost effective, given the high risk of contrast-agent-induced nephropathy, with its attendant high medical costs. However, the results of this study are not directly applicable to all high-risk patients who are exposed to contrast agents for simpler procedures.

In our study, patients with the higher base-line serum creatinine concentrations ( $\geq 4$  mg per decili-

ter) had the greatest positive effect, in terms of long-term survival, from hemofiltration. Hence, a more selective criterion than that used in our study (serum creatinine concentration,  $>2$  mg per deciliter) may identify patients who could obtain the maximal benefit from hemofiltration, and its use should result in greater cost effectiveness for this treatment. It is also possible that, in higher-risk patients, additional renal prophylaxis could be achieved by combining hemofiltration with drugs such as acetylcysteine and fenoldopam that may have a renoprotective role. In conclusion, our data suggest that, in patients with chronic renal failure who are undergoing percutaneous coronary interventions, periprocedural treatment with hemofiltration results in a significant reduction in the incidence of contrast-agent-induced nephropathy and improvement of in-hospital and long-term outcomes.

Supported by the Centro Cardiologico Monzino and by a grant (ICS030.6/RC2001) from the Italian Ministry of Health.

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