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Post-coronarography Application of Continuous Veno-Venous Hemofiltration in the Prevention of Contrast Nephropathy in Patients with Complex Multisystem Deficiency

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Abstract. *Background: An increased admission of high-risk patients to diagnostic and interventional radiological procedures with contrast medium has resulted in an increase of contrast-induced nephropathy, which now represents the third main cause of hospital-acquired acute renal failure. The pathogenic mechanism of contrast-induced nephropathy (CN) is unclear, but there is much evidence which indicated an interaction between direct tubular cytotoxicity and osmotic/hemodynamic effects. Continuous veno-venous hemofiltration (CVVH) has shown possible benefits in preventing CN. It is not understood when and how prophylactic strategies should be used either in pharmacological therapies or in continous renal replacement therapy (CRRT) approaches. The aim of this study was to evaluate the efficiency of the CVVH technique in preventing CN secondary to emergency radiological procedures in very high-risk patients. Patients and Methods: Twelve patients with severe chronic renal impairment (serum creatinine concentration >2 mg/dl with an estimated glomerular filtration rate (eGFR) <40 ml/min) in association with at least two severe comorbidities (such as previous acute myocardial infarction in hypertensive or diabetic patients, obesity, cardiac failure with ejection fraction <40%, severe hypotension) were treated with CVVH after coronarography using an iso-osmolar contrast medium (Visipaque, Iodixanol), with or without percutaneous transluminal coronary angioplasty. Adverse events and their association with the interventional radiological procedure were investigated after hemofiltration. Results: Statistically significant differences were observed for both eGFR and serum creatinine at different time points (pre-, post- and 7 days after the procedure) at $p<0.05$. Statistical analysis of all the variables related to the radiological procedure and the hemofiltration technique did not cause any modification of renal function between the pre- and post-procedure values. No patient showed signs of cardiovascular instability, nor were any episodes of marked hypotension reported during the dialysis session. No patient showed any adverse effects related to the interventional radiological procedure or to the CVVH technique. Renal function, according to serum creatinine concentration and the e-GFR calculation (Cockcroft), did not worsen but had improved when the patients left hospital, with function rates statistically significantly better compared to that on hospital admission, even 7 days after the radiological procedure. Conclusion: The present study suggests the efficiency of the CVVH technique in preventing CN in high-risk patients who need to undergo interventional radiological cardiovascular procedures involving the administration of an iodine-based contrast medium.*

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The prevalence of contrast-induced nephropathy (CN) has increased over the last decade and it has now become the third main cause of hospital-acquired pharmacologically induced acute renal failure (1, 2). This situation is due to both the increased use of contrast medium in diagnostic and interventional radiological procedures and an increased number of patients at risk of developing this type of nephropathy. In fact, specific factors increase the risk for developing CN, such as pre-existing impaired renal function,

congestive heart failure, hypotension, obesity, the administration of high doses of the contrast medium, the use of nephrotoxic drugs (including non-steroidal anti-nflammatory drugs and ACE inhibitors) which render the kidney more vulnerable to the effects of the iodine-based contrast medium, above all for the effect that they have on renal hemodynamics (3-9).

The pathogenic mechanism responsible for CN is still not totally clear even if various studies have demonstrated that this type of nephropathy results from an interaction between direct cytotoxicity toward the renal tubular cells, osmotic effects and effects on renal hemodynamics (10). The oxidative stress produced by the increase in intratubular osmolarity, determined by the presence of the contrast medium, causes apoptosis of the renal tubular cells (11). The osmotic effect also produces an osmotic diuresis, an increase in sodium and water excretion with the activation of the tubulo-glomerular feedback mechanism which contributes to the reduction of the glomerular filtration rate (GFR) (12). All these factors increase metabolic activity and renal oxygen consumption, increasing hypoxia in the renal medulla with possible subsequent ischemia and cell necrosis (13).

In animal models a biphasic renal blood flow effect has been demonstrated after exposure to the contrast medium, with a short initial increase and a following prolonged decrease induced by activation of transforming growth factor and increased endothelin synthesis, adenosine and calcium ions, reduced nitric oxide production and the increased release of oxygen free radicals (14).

The onset of CN, as well as causing an acute reduction in renal function, is associated with an increase in morbidity and mortality (15). The prevention strategy involves the correct stratification of risk factors in patients assigned to radiological procedures requiring the use of contrast medium; it also implicates the evaluation of prophylactic strategies and pharmacological therapeutic and procedural approaches that, in any case, have often produced contrasting results in the various studies performed. Saline or sodium bicarbonate solution infusion and pre- and post-procedure *N*-acetylcysteine administration are reported as the most frequent tools to prevent CN in daily clinical practice (16-22). Various studies have also evaluated the efficiency of hemodialysis and hemofiltration. But hemodialysis, in contrast with hemofiltration (23-24), has not been shown to be of any benefit in preventing CN (25-32). Continuous veno-venous hemofiltration (CVVH) is a form of renal-replacement therapy that permits an infusion of a large volume of isotonic replacement fluid exactly matched with the ultrafiltration rate. This procedure allows iodine-contrast medium to be partially removed from the circulation, therefore providing high volume hydration with dilution of contrast agents without causing fluid overload and preserving the volume of the circulation by ensuring hemodynamic stability.

Patients and Methods

The first aim of our study was to evaluate the efficiency of CVVH technique in preventing CN secondary to emergency radiological procedures in patients with severe chronic renal impairment in association with severe comorbidity. The indicator of contrast-induced renal nephropathy was considered to be an absolute increase of ≥0.5 mg/dl in serum creatinine and/or a relative increase of ≥25% in blood creatinine levels within 48-72 hours after the administration of the iodine-based medium (33-34). Then we investigated the incidence of adverse events and their association with the interventional radiological procedure and the hemofiltration technique.

In this light, patient inclusion criteria were defined as follows: the presence of chronic renal impairment with blood creatinine levels of >2 mg/dl and with an eGFR of <40 ml/min; the presence of at least two of the following co-morbidities: insulin dependent diabetes mellitus (IDDM) complicated by at least one previous myocardial infarction, hypertension with at least one episode of previous myocardial infarction, obesity with a body mass index (BMI) of >35 kg/m^2, an ejection fraction (EF) of d40%, a chronic hypotensive state with average arterial blood pressure (ABP) of <80 mm Hg, one or more cardiovascular procedures performed that require the administration of an iodine-based contrast medium. The interval between the end of the procedure and the beginning of the CVVH was set to <180 minutes.

Patients receiving dialysis were excluded from the study, as they are often affected by acute congestive heart failure, cardiogenic shock, recent hemorrhagic episodes or contraindications to the use of anticoagulation therapies. Distributions of comorbidities for the patients included in the study are given in Table I. The inclusion criteria used in the present study were also confirmed by the application of the Mehran Score (MS) (35), a risk score for predicting CN that is calculated by the attribution of a number score according to a different value for a set of risk factors such as hypotension, intra-aortic balloon pump, congestive heart failure, anemia, age >75 years, diabetes, contrast media volume and renal dysfunction defined as serum creatinine >1.5 mg/dl or an eGFR of <60 ml/min. A global score between 11 and 16 indicates a high risk for developing CN, a score >17 indicates a very high risk. According to this method, in our study 4 patients were classified as high-risk (MS=11-16), while 8 as very high-risk (MS>17).

A cardiovascular surgical procedure was indicated for 5 patients with stable angina with recurring episodes after light exercise, in two cases following recent myocardial infarction with persistent ventricular disfunction and in 5 for the presence of acute coronary syndrome due to unstable angina. Three patients underwent a coronarography and it was not necessary to perform angioplasty or position stents due to the presence of subcritical stenosis. In 9 patients, however, it was necessary to perform percutaneous transluminal coronary angioplasty (PTCA) with the positioning of stents. All patients received an iso-osmolar contrast medium (Iodixanol, Visipaque) at an average dose of 190.6±76.27 ml. The average length of the interventional radiological procedure was 53±38 minutes per patient. At the end of the radiological procedure all the patients underwent CVVH.

Vascular access was obtained using a temporary central venous double lumen catheter inserted into the femoral vein and connected to the extra-corporeal circuit. The protocol suggested a 24-hour long CVVH session with blood flow at 120-150 ml/min.

Table I. *Distribution of comorbidities considered as inclusion criteria for the patients studied.*

Distribution of comorbidities										
Patient	Age (years)	Gender	$[creat]_p$[1] pre (mg/dl)	eGFR[2] pre (ml/min)	IDDM[3] + AMI[4]	HY[5] + AMI[4]	EF[6] ≤40%	ABP[7] average <80 mmHg	BMI[8] >35 kg/m^2	Mehran score
1	64	M	**2.3**	**32.10**	**Yes**		50	126	**36**	**13**
2	70	F	**2**	**25**		**Yes**	**40**	103	23	**14**
3	66	M	**2.1**	**27.90**	**Yes**		**40**	113	20,9	**16**
4	78	M	**2.1**	**31.60**	**Yes**		**40**	100	30	**20**
5	65	M	**2.4**	**26**	**Yes**		50	**66**	22	**17**
6	74	F	**2.3**	**31.20**	**Yes**		**35**	110	**40.8**	**16**
7	66	M	**2.1**	**39.20**		**Yes**	**35**	103	29.4	**13**
8	85	M	**3.1**	**24.90**			**40**	103	**37.1**	**19**
9	84	M	**5.4**	**15**	**Yes**		60	**71**	**38.2**	**22**
10	79	M	**2.2**	**23.50**		**Yes**	60	**70**	22.4	**18**
11	78	M	**2.2**	**28.60**		**Yes**	55	103	**38.1**	**13**
12	74	M	**2.4**	**24.3**	**Yes**		50	**70**	27.3	**16**
MEAN±SD	73±7	M/F=10/2	2.56±0.98	27.73±6.1	7/12	4/12	46±9	98±19	30.8±7	16±3

Bold letters and numbers indicate pathological alterations according to the inclusion criteria. [1]Serum creatinine; [2]estimated glomerular filtration rate; [3]insulin dependent diabetes mellitus; [4]acute myocardial infarction; [5]hypertension; [6]ejection fraction; [7]arterial blood pressure; [8]body mass index.

The re-infusion, during the dialytic hemofiltration session, occurred at a flow of 1000±200 ml/h. Infusion of 10-12 UI/kg/h heparin into the circuit was maintained continuously.

The nephrological laboratory parameters and cardiac test results were evaluated before the radiological procedure, at the end of hemofiltration and 7 days after the patient left the hospital, and they were analysed by using descriptive and interferential statistical techniques (Student's *t*-test, ANOVA for repetitive measurements, Bonferroni test and Fisher test). The statistical analyses were performed using the statistics software STATVIEW (Abacus Concepts, Berkeley, CA, USA). The value of $p<0.05$ was considered to be statistically significant.

Table II. *CVVH characteristics.*

CVVH Characteristics	Prescribed	Effected
Interval (end of procedure/ start of CVVH)(min)	<180	160±57
Duration CVVH (h)	24	18.5±7.4
Blood flow (ml/min)	120-150	122±24
Re-infused solutions (ml/h)	800-1250	931±170

Results

The parameters of treatment with CVVH are shown in Table II. Statistical analysis of all the variables related to the radiological procedure and the hemofiltration technique did not cause any modification of the renal function curve between the pre- and post- procedure values.

No patient showed signs of cardiovascular instability, nor were any episodes of marked hypotension reported during the dialysis session. Figure 1 shows the renal function according to the eGFR and blood creatinine levels before, immediately after and then 7 days after the procedure. Statistically significant differences were observed for both GFR and serum creatinine at different time points (pre-, post- and after 7 days) with $p<0.05$. The mean value of the eGFR at the end of the procedure was 32.51±6.5 ml/min, the estimated mean values for the time before the interventional radiological procedure and for 7 days after leaving hospital were 27.72±6.14 ml/min and 31.07±6.56 ml/min respectively. The mean value for serum creatinine was 2.56±0.98 mg/dl pre-procedure, 2.2±0.9 mg/dl post-procedure and 2.22±0.57 mg/dl after 7 days.

Six out of the twelve patients treated showed an EF calculated before the interventional radiological procedure of ≥50%, (mean 56±4.4%), while 6 presented a reduced systolic function, <50% (mean EF 8.3±2.5%). The study of the renal function in these two groups of patients highlighted the results shown in Figure 1 regarding eGFR (A) and blood creatinine (B) in the two groups of patients. No substantial variations in haemoglobin levels nor plasmatic osmolarity were observed. By considering the results in Figure 2, the study of renal function in patients with an EF of <50% did not show any difference from those with an EF of >50%. Considering the absolute increase of ≥0.5 mg/dl in serum creatinine and/or a relative

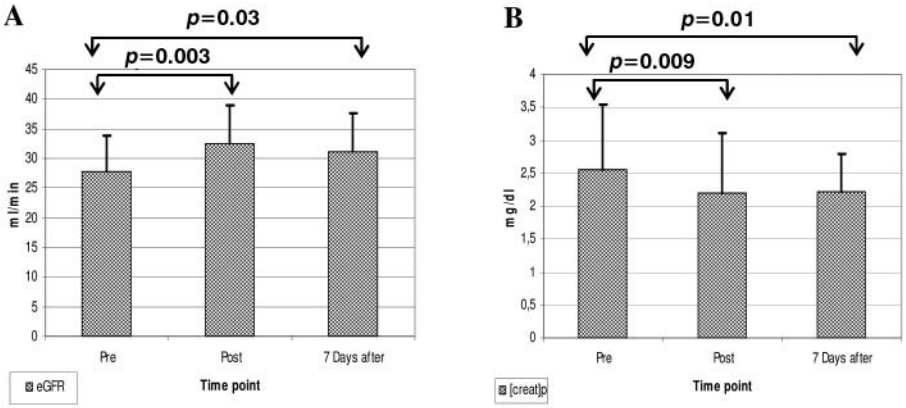

Figure 1. *Mean values of eGFR (A) and serum creatinine (B) in all patients evaluated at the time points pre-, post- and 7 days after the CVVH procedure.*

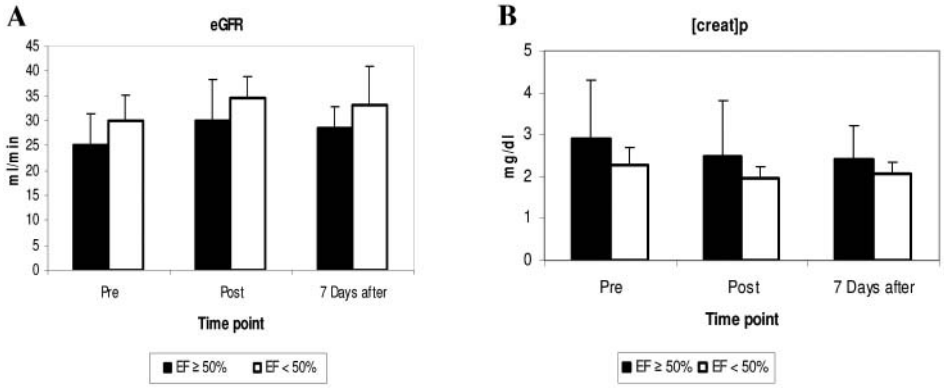

Figure 2. *Mean values of eGFR (A) and blood creatinine (B) in two groups of patients first with ejection fraction (EF) ≥50% and the other with EF <50% evaluated at the time points pre-, post- and 7 days after the CVVH procedure.*

increase of ≥25% in blood creatinine within 48-72 hours after the administration of the iodine-based medium as an indicator and extending the evaluation up to 7 days after the execution of the procedure, no statistically significant decline in renal function was reported.

No patient showed any adverse effects related or not to the interventional radiological procedure and the hemofiltration technique, such as marked hypotension, new myocardial infarction, thrombocytopenia, hemorrhagic episodes or other signs of cardiovascular instability or disequilibrium syndrome.

In two patients the prescribed treatment was not concluded for technical reasons with an anticipated reduction in time of 22% of the initial prescription. In one case in particular, it was necessary to interrupt the session because of a malfunction in the CVVH monitor during the session and in the other case the session was interrupted due to filter clotting. As a result, the total duration of the dialytic sessions was 17 and 14 hours, respectively.

Discussion

The present study confirms the efficiency of CVVH technique in preventing CN in high-risk patients who need to undergo interventional radiological cardiovascular procedures involving the administration of an iodine-based contrast medium.

The increased risk of CN was evaluated by using strictly codified inclusion criteria, as reported above. These criteria required that all the patients were diagnosed with impaired renal function, eGFR <40 ml/min, in association with at least two comorbidity factors that notably increase the risk of developing CN.

Consistent with this, among the 318 patients admitted to hospital and who underwent interventional radiological cardiovascular procedures over a 6-month period, 12 (3.8%) were included in the study.

Despite the limited number of cases considered, our results highlighted the fact that even though the patients were at high-risk, none of them developed direct and/or

indirect signs of CN as the data show in Figures 1 and 2. Interestingly, according to serum creatinine concentration and the e-GFR calculation (Cockcroft), renal function had improved when the patients left hospital.

In particular, this study highlighted the importance of hemodynamic stability parameters (*e.g.* quantity of contrast medium administered, actual duration of the interventional radiological procedure, actual duration of CVVH, re-infusion effectively performed, actual blood flow maintained) as main indicators in the evaluation of the role of CVVH in CN. Even though there is a protocol prescription to follow, the clinical scenario can influence the development of the extracorporeal procedure.

The quantity of contrast medium, the length of the procedure, the volumes of solution re-infused, the flow maintained during the technique and the general parameters (*e.g.* age, gender) did not have statistically significant effects on renal function regarding the pre- and post-interventional procedure values.

In addition our study confirmed that intra-CVVH cardiovascular stability had positive effects on renal function (36). This was confirmed by the analysis of both ABP and cardiac frequency and the absence of modifications on biochemical markers such as hematocrit, haemoglobin and main serum electrolytes values.

Even when taking into consideration patients with a considerably reduced EF (dilatative cardiopathy) before the contrastographic procedure, no differences were found in the renal function of the two groups (Figure 2).

It is still controversial if CVVH reduces the risk of contrast medium nephropathy and its outcome. Some authors reported a beneficial use of CVVH even before the interventional-radiological procedure (25, 26), while others did not observe any advantage in using the hemofiltration technique to prevent CN (37-40) versus infusion and pharmacologic treatment alone. Our study showed that the well-defined criteria for each patient should be defined in performing artificial substitutive techniques, even at low flows. In fact, the overlapping of one or more conditions able to determine the development of CN is the real "trigger" element that needs to be focused on in future studies.

In spite of the good results obtained in some studies (25, 26), the distribution of complications within the different groups of patients is not always easy to understand from the extensive use of CVVH and this does not allow the exact identification of how many and what type of comorbidities are detectable in a single patient undergoing the different treatments.

Most of the studies reported preliminary protocols but they did not investigate the parameters related to CVVH treatment effectively obtained by clinical monitoring, such as duration of the session, blood flow, average re-infusion flow and eventual complications connected to the hemofiltration technique (*e.g.* filter clotting, hemodynamic instability, thrombocytopenia purpura): which consequently does not allow for any comparison between the prescribed parameters and the ones actually obtained (21-24).

Furthermore, if the removal of iodine composites and the benefits connected with the re-infusion solution is well known, the hypothesis about the possible benefits coming from the removal and absorption of molecules with a pro-inflammatory and oxidating action are less clear. We can argue that this is firstly because they are difficult to detect and secondly because of a simultaneous removal of anti-inflammatory and antioxidating molecules (41, 42).

On the other hand, when using extra-corporeal circulation techniques in the prevention of CN in a cardiopathic patient, some potential "disturbing" factors need to be considered. In particular, the blood/artificial membrane contact is able to determine an *acute phase reaction*, inducing the activation of both the platelet-coagulative and the immunological systems, necessitating the use of a highly biocompatible membrane (43, 44).

In addition, the risk of cardiovascular instability related to extra-corporeal circulation, the re-infusion volumes and both electrolyte and osmotic disequilibrium that always occur and modify the fluid distribution within the organism, need to be evaluated. It is also necessary to account for the fact that the setting up of conditions favourable for immunological/platelet-coagulative activation and cardio-vascular instability increase the risk of renal ischemia and the oxygen free radical production, which are involved in the pathogenesis of CN (10, 13, 43).

Finally, it is well known that the use of extra-corporeal removal techniques has to comply with specific indications and should be proposed for a limited number of patients with multiple, real comorbidity factors. Collectively, our data suggested the following conclusions. Firstly, partial removal of the contrast medium can reduce the tubular damage in the kidney. Secondly re-infusion during the hemofiltration technique represents a valid alternative to endovenous hydration which, if performed under the "standard" conditions, brings an increased risk of water overload in patients with cardio-renal dysfunction. Lastly, alkalinization (determined by bicarbonate solutions) reduces the free radical production (45) and "normalizes" tubular re-absorption of bicarbonates.

Even though our study involved a limited number of cases, it indicates some accurate criteria for CVVH treatment in patients who could otherwise only be treated with conservative therapy because of their ischemic cardiopathy.

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