Original article

Kardiologia Polska
2011; 69, 9: 891–896
ISSN 0022–9032

Early implementation of continuous venovenous haemodiafiltration improves outcome in patients with heart failure complicated by acute kidney injury

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Abstract

Background: Acute kidney injury (AKI) is a serious complication of heart failure (HF). Continuous venovenous haemodiafiltration (CVVHDF) is a widely accepted method for treating this complication. However, the optimal time of its initiation has not been established.

Aim: To compare the outcome of patients with HF treated with CVVHDF which was implemented late (the first two years of our experience) or early (the next two years of our experience).

Methods: Thirty seven patients, mean age 65 years, were hospitalised between April 2006 and January 2010 with the diagnosis of HF complicated by AKI. The primary cardiovascular diseases were: valvular heart disease (30%), acute coronary syndrome (27%), dilated cardiomyopathy (16%), exacerbation of chronic HF (11%), and others (16%). The inclusion criteria for CVVHDF therapy were: symptoms of HF including cardiogenic shock with high levels of creatinine (≥ 300 μmol/L) and/or oliguria and/or symptoms of septic shock. The exclusion criteria were: serious coagulation disturbances or inability of placing a catheter in a central vein. Group A consisted of 12 patients treated from April 2006 to the end of 2007. In group B, there were 25 patients treated from the beginning of 2008 to January 2010. Before treatment, mean ejection fraction, left ventricular diastolic diameter and mean blood pressure in both groups were comparable. Renal replacement therapy in group B was started earlier than in group A (mean 2.0 ± 2.0 days *vs* 4.0 ± 4.3 days from the onset of symptoms of AKI; NS).

Results: The day after the beginning of CVVHDF, renal failure parameters improved in both groups, but the improvement was much more significant in group B. In group A, 11 (92%) patients died. The mean CVVHDF duration was six days and all patients required mechanical ventilation. In group B, 17 (68%) patients died (NS). The mean CVVHDF duration was shortened to four days. Seventeen (68%) patients were ventilated mechanically and this parameter was significantly different between the groups ($p = 0.03$)

Conclusions: An early introduction of CVVHDF significantly diminished the need to use mechanical ventilation and indicated a positive trend in the reduction of in-hospital mortality in patients with HF complicated by AKI.

Key words: heart failure, kidney injury, renal replacement therapy, continuous venovenous haemodiafiltration

Kardiol Pol 2011; 69, 9: 891–896

INTRODUCTION

Acute kidney injury (AKI) is a common complication observed in severely ill patients who require hospitalisation in Intensive Care Units (ICU). The reported incidence of AKI in ICU settings ranges from 1% to 25% depending on AKI definition and the population studied [1–4]. Uncomplicated AKI can usually be managed outside the ICU setting and is associated with a good prognosis, with mortality rates of 5% to

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Received: 06.11.2010 **Accepted:** 06.07.2011

10% [5, 6]. In contrast, the mortality in AKI complicating non-renal organ system failure in patients admitted to ICU approaches 70%, a figure which has not changed for decades [7–9]. It has been shown that an increase in the serum creatinine level, even as small as 0.2 mg/dL, has an adverse impact on AKI patient survival [10]. For this reason, it is very important to diagnose AKI more promptly, especially in critically ill patients.

About 70% of patients who exhibit AKI in ICU require renal replacement therapy (RRT) [7]. Haemodialysis and continuous venovenous haemodiafiltration (CVVHDF) are well-established treatment methods in patients with AKI. The CVVHDF, as a method of continuous RRT (CRRT), is particularly promising in treating such patients. It is an efficient method in removing solutes over the course of 24 to 48 hours, just as conventional haemodialysis is. A slower rate of solute removal prevents an abrupt fall in plasma osmolality that induces extracellular volume depletion with further reduction in blood pressure, which is especially unfavourable in hypotensive patients. Compared to haemodialysis, CVVHDF, in addition to being better tolerated haemodynamically, has several advantages such as possibility of unlimited alimentation, optimal fluid balance and gradual urea removal without fluctuations [11]. The CVVHDF eliminates proinflammatory substances, free radicals, endotoxins and cytokines, and this seems to be particularly beneficial in septic patients [12].

Soubrier et al. [7] found that the negative predictive factors of survival after CVVHDF initiation included mechanical ventilation at the time of CVVHDF initiation, ischaemic acute tubular necrosis and septic shock requiring vasoactive treatment at CVVHDF initiation. In contrast, urine output of more than 1 L/day and, surprisingly, creatinine level exceeding 300 mmol/L at CVVHDF initiation predicted favourable outcomes [7]. In survivors, time delay to CVVHDF initiation was shorter than in non-survivors (3.5 ± 3.0 and 5.4 ± 5.7 days, respectively) [7].

In our department, we started treatment with CVVHDF in 2006. At the beginning of our experience with this type of RRT therapy, especially in patients with heart failure (HF), we used CVVHDF as a second line therapy after full treatment for HF and unsuccessful pharmacological treatment of complicating AKI. From 2008 onwards, we decided to start CVVHDF earlier i.e. as soon as AKI was diagnosed. The aim of the present report was to compare the outcome of patients treated early *vs* late with CVVHDF.

METHODS

Of 5,816 patients hospitalised in our ICTC between April 2006 and January 2010, HF was diagnosed in 1,001 (17%) patients. In this group, 37 patients (mean age 65 ± 15 years, 14 women) suffered from HF complicated by AKI which required RRT. The primary cardiovascular diseases are shown in Table 1.

Table 1. Primary cardiovascular disease complicated by acute kidney injury in patients who required renal replacement therapy

Cardiovascular disease	N (%)
Valvular heart disease	11 (30)
Acute coronary syndrome with acute HF	10 (27)
Dilated cardiomyopathy	6 (16)
Exacerbation of chronic HF	4 (11)
Cardiac arrest	2 (5)
Coronary artery disease post-CABG	2 (5)
Constrictive pericarditis	1 (3)
Congenital heart disease	1 (3)

HF — heart failure; CABG — coronary artery bypass grafting

The inclusion criteria for CVVHDF therapy (Prismaflex®, Gambro) were symptoms of left or right ventricular failure including cardiogenic shock with concomitant high levels of creatinine (≥ 300 μmol/L) and/or oliguria (urine output < 400 mL/day), and/or symptoms of septic shock. The exclusion criteria were serious coagulation disturbances or impossibility of placing a catheter in a central vein. The severity of HF was categorised according to the Killip classification. The diameters of heart chambers and ventricular systolic/diastolic function were estimated echocardiographically before RRT.

The patients were divided into two groups: 12 patients treated from April 2006 to the end of 2007 (group A), and 25 patients treated from the beginning of 2008 to January 2010 (group B). A detailed comparison between both groups before starting CRRT is presented in Table 2. Patients from group A significantly more often received norepinephrine and had lower systolic blood pressure compared to patients from group B. Renal function and compensation of metabolic acidosis tended to be better in group B than group A, but the differences did not reach statistical significance.

The central venous pressure was measured before CVVHDF and, if necessary, adjusted with fluids infusion according to the patient's haemodynamic status. A high level of potassium (> 6 mmol/L) was observed very rarely. It was quickly diminished to normal level by pharmacological treatment and was not an indication for CRRT.

In group A, time elapsed from occurrence of symptoms indicating the need for RRT to the beginning of RRT was 0–16 days (mean 4.0 ± 4.3 days). In group B, this time ranged from 0–7 days, (mean 2.0 ± 2.0 days, NS). All patients underwent CVVHDF with unfractionated heparin anticoagulation. In both groups, the blood flow, fluid replacement, dialysate flow rates and removal of fluid were set individually depending on the patient's weight, magnitude of fluid overload, blood creatinine and potassium levels. The blood flow rate was between 100 mL/min and 210 mL/min. The diagram of CVVHDF therapy with fluids flow rate preferred in our department is presented in Figure 1.

Table 2. Parameters of cardiac dysfunction and heart failure treatment in both study groups before start of continuous renal replacement therapy (group A — treated late; group B — treated early)

Parameters of heart failure	Group A (n = 12)	Group B (n = 25)	P
EF [%]	33 ± 19	36 ± 18	NS
LVDD [mm]	56 ± 11	60 ± 17	NS
4th stage of Killip classification	11 (92%)	15 (60%)	NS
Treatment:			
Furosemide [mg]	757 ± 385	765 ± 315	NS
Dobutamine	12 (100%)	25 (100%)	NS
Dopamine < 5 μg/kg/min	11 (92%)	23 (92%)	NS
Epinephrine	10 (83%)	16 (64%)	NS
Norepinephrine	11 (92%)	13 (52%)	< 0.05
IABP	7 (58%)	5 (20%)	NS
Mean blood pressure [mm Hg]	67 ± 14	78 ± 15	0.04
Creatinine concentration [mmol/L]	477 ± 554	372 ± 241	NS
GFR (mL/min/1.73 m²)	17 ± 10	20 ± 12	NS
Metabolic acidosis	11 (92%)	14 (56%)	NS

EF — ejection fraction; LVDD — left ventricular diastolic diameter; IABP — intraaortic balloon pump; GFR — glomerular filtration rate

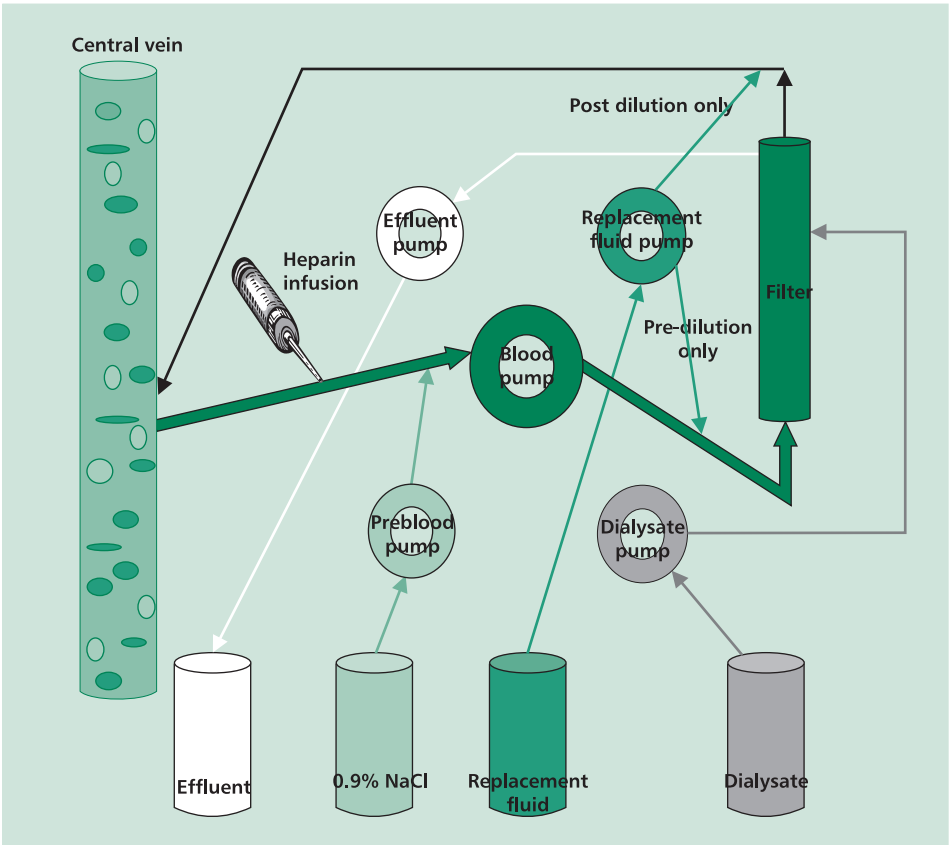

Figure 1. Diagram of continuous venovenous haemodiafiltration with unfractionated heparin (UFH) anticoagulation. Blood and fluid rates were set individually in each case and we cannot create one set of standard fluid flow parameters. We usually used set: (1) Blood rate: 100–210 mL/min; (2) UFH infusion rate titrated to maintain a value of 1.5 to 2 times prolonged activated partial thromboplastin time (aPTT — was controlled before start of CVVHDF therapy and every 4–6 h during continuation of treatment). Due to risk of thrombocytopenia, the number of platelets was checked each day of treatment; (3) 0.9% NaCl used for blood pre-dilution: 150–300 mL/h; (4) Replacement fluid flow rate (Hemosol): 300–1500 mL/h, mostly as post-dilution; (5) Dialysate flow rate (Hemosol or Dialisan): 500–2000 mL/h; (6) Ultrafiltration (fluid removal rate): 0–500 mL/h

Table 3. Comparison of analysed parameters after implementation of CVVHDF therapy in patients treated late (group A) or early (group B)

Parameters	Group A (n = 12)	Group B (n = 25)	P
Mechanical ventilation	12 (100%)	17 (68%)	0.03
Mean blood pressure [mm Hg]*	69 ± 14	74 ± 15	NS
Creatinine concentration [μmol/L]	387 ± 280	210 ± 121	0.0442
GFR [mL/min/1.73 m^2]*	20 ± 14	34 ± 18	0.015
Furosemide [mg]	845 ± 294	705 ± 300	NS
In-hospital deaths	11 (92%)	17 (68%)	NS
CVVHDF duration (mean) [days]	2–13 (5.7 ± 3.8)	1–10 (3.8 ± 2.4)	NS

*Results at the second day of treatment; GFR — glomerular filtration rate; CVVHDF — continuous venovenous haemodiafiltration

The CVVHDF was continued: (1) until recovery of kidney function was achieved i.e. when normalisation of creatinine level, reduction of fluid overload, and urine output ≥ 400 mL/day were present; or (2) until definite therapy such as cardiac surgery, heart transplantation, implantation of artificial ventricles or conventional haemodialysis implementation; or (3) until death.

Statistical analysis

The results are expressed as the mean value ± SD. The significance of the differences between analysed parameters was verified by Student's t-test. The exact Fisher test was used to check differences between the groups. The level of significance was set at $p < 0.05$. The Kaplan-Meier survival curves were plotted for both study groups.

RESULTS

One day after the beginning of CVVHDF, creatinine concentration decreased in both groups, although the improvement was more significant in group B ($p = 0.0442$). Simultaneously, glomerular filtration rate increased much more in group B than in group A ($p = 0.015$). In group A, the mean time of CVVHDF duration was six days and all patients required mechanical ventilation. In group B, the mean time of CVVHDF duration was shortened to four days. Seventeen (68%) patients were ventilated mechanically and this parameter was significantly different between the groups ($p = 0.03$). In group B, fewer patients died (68%) than in group A (92%), but the difference was not significant. Diuretics administration was continued during CVVHDF therapy and doses of furosemide did not change significantly during RRT (Table 3).

The probability of survival in time in both studied groups is presented by Kaplan-Meier curve (Fig. 2). The difference between groups was of borderline significance value ($p = 0.0551$).

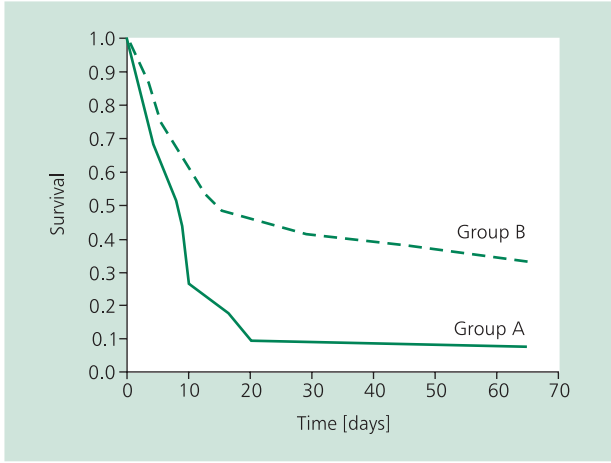

Figure 2. Kaplan-Meier curves showing the probability of survival in groups A and B

DISCUSSION

Kidney injury is a major contributor to progressive cardiac damage, whereas HF is often associated with a rapid deterioration of renal function [13, 14]. Continuous RRT is an increasingly used method of therapy in severely ill patients. Indications for RRT include huge fluid overload, pulmonary oedema, manifestations of uremic encephalopathy and pericarditis or the presence of purpura as well as several metabolic abnormalities. In patients with heart diseases, especially HF, an additional indication for RRT is unsuccessful treatment of HF. Even if all necessary types of therapy, including mechanical support of left or biventricular function for haemodynamic stabilisation, were used in patients and the systolic blood pressure reached 90 mm Hg, such symptoms as oedema, pulmonary congestion and ascites required RRT institution in some cases.

Patients with AKI are particularly resistant to conventional HF therapy. Even high doses of diuretics are unable to reduce fluid overload and moreover can negatively affect kidney function. In our opinion, starting RRT should be considered in patients with constant urine output reduction despite increased doses of diuretics with concomitant pulmonary congestion or increasing oedema. Another important indication for RRT is the necessity of performing diagnostic tests with the use of nephrotoxic contrast administration or cardiothoracic surgery.

In patients with severe cardiac diseases complicated by AKI, CRRT seems beneficial. Elahi et al. [15] showed that early and aggressive use of CVVHDF was associated with better than expected survival in severe AKI after cardiac operations. This excellent result (22% mortality) was achieved in patients in whom CVVHDF was started when urine output was less than 100 mL within eight hours of cardiac surgery despite furosemide infusion [15]. Mean time to CVVHDF initiation was 0.78 days, while in patients classified to a group of late haemofiltration, this time was 2.55 days [15].

Our results, especially those obtained in group A showed no improvement in survival rate. The parameters of kidney injury were corrected very quickly, but patients died due to primary cardiac causes. The CRRT therapy was applied in severely ill patients, which explains our results. Looking for better results, according to some suggestions from the literature, we tried to shorten the time to CRRT initiation. During the first two years of CVVHDF therapy, patients were referred to CRRT after a rather lengthy pharmacological treatment. We hoped that a high dose of diuretics in association with inotrope positive treatment would help to achieve an adequately high urine output. Norepinephrine was administered in hypotensive patients who did not respond to treatment with dobutamine and intraaortic balloon pump (IABP) support, or had contraindications to IABP. The higher number of patients treated with norepinephrine in group A than in group B also confirmed that in these patients, CVVHDF was a second line therapy.

Since the beginning of 2008, we have shortened the time between the indication for CRRT and the beginning of the therapy to two days. Although haemodynamic status, type of HF treatment and creatinine concentration in group B were comparable with those observed in group A, CVVHDF resulted in a significantly better improvement in the parameters of kidney function. Although a 24% reduction in the in-hospital mortality was not significant, this outcome is very promising and, probably, essentially associated with the early therapy with CVVHDF.

Our study also confirmed something already reported in the literature: the unfavourable effects of mechanical ventilation on mortality in patients with AKI. The observed 32% reduction in the need for mechanical ventilation was, in our opinion, also closely associated with the early implementation of CVVHDF therapy.

CONCLUSIONS

Early introduction of CVVHDF significantly reduced the need for using mechanical ventilation and resulted in a positive trend towards reducing in-hospital mortality rates in patients with HF complicated by AKI.

Conflict of interest: *none declared*

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Wczesne zastosowanie ciągłej żylno-żylnej hemodiafiltracji poprawia rokowanie u chorych z niewydolnością serca powikłaną ostrym uszkodzeniem nerek

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Streszczenie

Wstęp i cel: Celem pracy była ocena rokowania u chorych z niewydolnością serca (HF) powikłaną ostrym uszkodzeniem nerek (AKI), leczonych za pomocą ciągłej żylno-żylnej hemodiafiltracji (CVVHDF). Badanych podzielono na 2 grupy. Do grupy A zaliczono pacjentów leczonych w pierwszych 2 latach od początku stosowania CVVHDF, a do grupy B — chorych poddanych terapii w późniejszym okresie.

Metody: W okresie od kwietnia 2006 do stycznia 2010 r. w Klinice Intensywnej Terapii Kardiologicznej hospitalizowano 37 chorych z HF powikłaną AKI. Wada serca była przyczyną HF u 30% osób, ostry zespół wieńcowy — u 27% chorych, kardiomiopatię rozstrzerzeniową stwierdzono u 16% pacjentów, a zaostrzenie przewlekłej HF u 11%. U pozostałych 16% chorych rozpoznano inne przyczyny HF. Kryteriami włączenia do leczenia za pomocą CVVHDF były: objawy lewo- i/lub prawokomorowej HF, w tym wstrząs kardiogenny i stężenie kreatyniny we krwi ≥ 300 μmol/l i/lub skąpomocz, i/lub objawy wstrząsu septycznego. W przypadku istotnych zaburzeń krzepliwości krwi lub niemożności założenia dostępu żylnego do żyły centralnej nie stosowano CVVHDF. W grupie A było 12 chorych leczonych od kwietnia 2006 do końca 2007 r., a w grupie B — 25 osób leczonych od początku 2008 do stycznia 2010 r. Przed terapią badane grupy nie różniły się pod względem wartości frakcji wyrzutowej, wymiaru rozkurczowego lewej komory i średniego ciśnienia tętniczego krwi. U chorych z grupy B CVVHDF rozpoczęto wcześniej niż u pacjentów z grupy A (średnio 2,0 ± 2,0 *v.* 4,0 ± 4,3 dni; NS).

Wyniki: W drugiej dobie leczenia za pomocą CVVHDF w obu grupach parametry niewydolności nerek poprawiły się, ale w istotnie większym stopniu w grupie B. W trakcie pobytu w szpitalu zmarło 11 (92%) chorych z grupy A; terapia za pomocą CVVHDF trwała średnio 6 dni, a 12 (100%) osób wymagało wentylacji mechanicznej. W grupie B zgony szpitalne wystąpiły u 17 (68%) chorych, a średni czas trwania CVVHDF wynosił 4 dni. W porównaniu z grupą A istotnie rzadziej zastosowano wentylację mechaniczną (17 chorych, 68%; p = 0,03).

Wnioski: U chorych z HF powikłaną AKI wcześnie rozpoczęte leczenie nerkozastępcze za pomocą CVVHDF ogranicza konieczność stosowania wentylacji mechanicznej i pozytywnie wpływa na redukcję śmiertelności wewnątrzszpitalnej.

Słowa kluczowe: niewydolność serca, ostre uszkodzenie nerek, terapia nerkozastępcza, ciągła żylno-żylna hemodiafiltracja

Kardiol Pol 2011; 69, 9: 891–896

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Praca wpłynęła: 06.11.2010 r. **Zaakceptowana do druku:** 06.07.2011 r.