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THE FACTORS INFLUENCING RENAL RECOVERY IN CARDIAC SURGERY ASSOCIATED ACUTE KIDNEY INJURY

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ФАКТОРИ, ЩО ВПЛИВАЮТЬ НА ВІДНОВЛЕННЯ ФУНКЦІЇ НИРОК У КАРДІОХІРУРГІЧНИХ ПАЦІЄНТІВ З ГОСТРИМ ПОШКОДЖЕННЯМ НИРОК

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Keywords: *acute kidney injury, cardiac surgery, continuous renal replacement therapy, intermittent renal replacement therapy, multiorgan failure, renal recovery.*

Ключові слова: гостре пошкодження нирок, кардіохірургія, тривала ниркова замісна терапія, інтермітуюча ниркова замісна терапія, синдром поліорганної недостатності, відновлення ниркової функції.

Abstract. *Background. In-hospital mortality of cardiac surgery patients with AKI is 3-7 times higher than those without AKI. This prospective observational study was dedicated to evaluate a differential approach of applying continuous and intermittent modalities in CS-AKI patients on the rate and grade of renal function recovery.*

Methods. One hundred and six adult cardiac surgery patients admitted hospital in 2008-2011 years, who had AKI and met inclusion criteria were allocated in CRRT or IRRT group.

Results. Sixty eight cardiac surgery with AKI patients who needed RRT were discharged from hospital. Among them, recovery of renal function was observed in 54 patients (79,4%) and 14 patients (20,6%) remained RRT-dependant. Complete recovery of renal function was reached in 33 patients (48,5%), while partial was observed in 21 patients (30,9%). Univariate analysis showed that complete recovery of renal function in CS-AKI significantly associated with reducing of dopamine dose during the first day of RRT (p=0,01) and long-term use of dobutamine (p=0,009). Partial recovery was associated with early dobutamine withdrawal (p=0,005) and absence of MOF (p=0,016), while RRT-dependence at discharge was associated with absence of MOF (p=0,006) and escalation of dopamine dose on the first day of RRT (p=0,025). The rate of renal recovery was statistically significantly higher in patients with CS-AKI with MOF than in patients with CS-AKI without MOF. In univariate analysis RRT-dependance at discharge of patients with CS-AKI with MOF was statistically significantly associated with arising of dopamine dose during the first day of RRT (p=0,006) and no-use of dobutamine at RRT start (p=0,006). Partial recovery was associated with early withdrawal of dobutamine (p=0,038).

Discussion. Frequency of renal recovery in presented study was higher than in VA/NIH Acute Renal Failure Trial Network study because of differences in patients` population and corresponds to other studies of CS-AKI patients.

Conclusions. Recovery of renal function in CS-AKI patients associated with decreasing dose of dopamine, prolonged use of dobutamine, illness severity and does not associated with specific RRT modality.

Резюме. *Госпітальна летальність пацієнтів кардіохірургічного профілю з ГПН в 3-7 разів вища ніж у пацієнтів без ГПН. Це проспективне оглядове дослідження присвячено диференційному застосуванню та впливу тривалої (ТНЗТ) та інтермітуючої ниркової замісної терапії (ІНЗТ) у пацієнтів кардіохірургічного профілю на частоту та ступінь відновлення ниркової функції.*

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Методи. 106 кардіохірургічних пацієнтів, госпіталізованих в 2008-2011 роках та які мали ГПН та критерії включення, були розподілені у групи ТНЗТ та ІНЗТ.

Результати. 68 кардіохірургічних пацієнтів з ГПН, які потребували НЗТ, були виписані. Серед них відновлення ниркової функції спостерігалось у 54 пацієнтів (79,4%), 14 пацієнтів (20,6%) потребували лікування НЗТ. У 33 пацієнтів (48,5%) повністю відновилась функція нирок, у 21 пацієнта (30,9%) спостерігалось часткове відновлення ниркової функції. За даними однофакторного аналізу повне відновлення ниркової функції у кардіохірургічних пацієнтів з ГПН достовірно пов'язане зі зниженням дози допаміну в першу добу НЗТ (p=0,01) та тривалим застосування добутаміну (p=0,009). Часткове відновлення було асоційоване з ранньою відміною добутаміну (p=0,005), відсутністю СПОН (p=0,016), у той час як залежність від НЗТ при виписці була асоційована з відсутністю СПОН (p=0,006) та збільшенням дози допаміну в перший день НЗТ (p=0,025). Частота відновлення ниркової функції виявилась статистично достовірно вищою серед кардіохірургічних пацієнтів з ГПН у складі СПОН ніж серед пацієнтів з ГПН без СПОН. За даними однофакторного аналізу залежність від НЗТ серед кардіохірургічних пацієнтів з ГПН у складі СПОН на момент виписки статистично достовірно пов'язана зі збільшенням дози допаміну в першу добу НЗТ (p=0,006) та невикористанням добутаміну на початку НЗТ (p=0,006). Часткове відновлення було пов'язане з ранньою відміною добутаміну (p=0,038).

Обговорення. Частота відновлення ниркової функції в даному дослідженні була вище ніж у дослідженні VA/NIH Acute Renal Failure Trial Network за рахунок різниці у популяції пацієнтів та відповідає іншим дослідженням кардіохірургічних пацієнтів з ГПН.

Висновки. Відновлення ниркової функції у пацієнтів кардіохірургічного профілю з ГПН асоційоване зі зниженням дози допаміну, тривалим застосуванням добутаміну, важкістю захворювання та не пов'язане з модальністю НЗТ.

INTRODUCTION. Incidence of acute kidney injury (AKI) is growing and associated with adverses outcomes, particularly in critically ill patients. Depending on the definition frequency of AKI can reach 30% of patients after cardiac surgery [7] with renal replacement therapy (RRT) requirement of 2,6% of all patients or up to 22,5% of patients with AKI [4].

In-hospital mortality of cardiac surgery patients with AKI is 3-7 times higher than those without AKI [4, 1]. In case of AKI that needs RRT further deterioration of in-hospital mortality is observed with figures as high as 47-76% [2, 7].

Today, several modalities of RRT could be applied for AKI treatment and include continuous or intermittent extra-corporeal methods (hemodialysis, hemofiltration and hemodiafiltration) and peritoneal dialysis. Numerous clinical trials conducted last years could not demonstrate clear benefit of specific RRT modality in treatment of AKI in terms of in-hospital mortality nor recovery of renal function. Moreover, the frequency and the grade of renal recovery in patients with cardiac surgery associated AKI (CS-AKI) are poor investigated.

This clinically-based prospective observational study was dedicated to evaluate a differential approach of applying continuous and intermittent modalities of RRT in CS-AKI patients on the rate and grade of renal function recovery.

MATERIALS AND METHODS. Adult patients admitted National Institute of Cardio-Vascular Surgery NAMS of Ukraine for cardiac surgery during 2008-2011 years and met inclusion criteria were allocated in group of continuous modalities (CRRT) or in group of intermittent modalities (IRRT) of renal replacement therapy (RRT). Inclusion criteria: age ≥ 18 years old, cardiac illness with indications for surgical intervention and AKI, which needed RRT before or after surgical operation. Exclusion criteria: age < 18 years old; chronic kidney disease (CKD) V.

AKI was defined and staged according with RIFLE criteria ascribed by Bellomo et al., as well as complete and partial recovery of renal function [8]. Defining and staging of CKD was performed according with K/DOQI Guideline (2002) [5]. Glomerular filtration rate (GFR) was calculated using MDRD equation [5].

Sepsis, severe sepsis and septic shock were diagnosed according and multiple organ failure (MOF) was defined according to Consensus Conference (1991) as the presence of altered organ functions of two or more organs systems in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Surgical intervention, management before and after surgical treatment were conducted according to the local protocols of National Institute of Cardio-Vascular Surgery NAMS of Ukraine. Indications for RRT were determined according to the local protocol of Institute of Nephrology NAMS of Ukraine.

IHD was conducted with Innova (Gambro Dasco S.p.A., Italy) and AK-200 Ultra S (Gambro Lundia AB, Sweden) dialysis machines and Polyflux 17L (Gambro Dialyzatoren GmbH, Germany) dialyzers. Bicarbonate dialysis fluid was used with flow rate 500 ml/min and blood flow rate - 250 — 350 ml/min. The duration of sessions was 4-8 hours.

CVVH was performed in pre-dilution mode with Prisma machine (Gambro Dasco S.p.A., Italy) throughout 24 hours per day. HF1000 sets and Gambrosol 2 and Gambrosol 4 solutions were used (Gambro Dasco S.p.A., Italy). Blood flow rate was set up at 180 ml/min and prescribed substitution fluid rate was 35 ml/kg/hr.

SLEDD was performed with with Innova (Gambro Dasco S.p.A., Italy) and AK-200 Ultra S (Gambro Lundia AB, Sweden) dialysis machines and Polyflux 17L (Gambro Dialyzatoren GmbH, Germany) dialyzers. Sessions` duration was 8-12 hours and blood flow rate was 100 ml/min, meanwhile dialysis fluid rate was 350 ml/min.

HVHF was carried out in pre-dilution mode with AK-200 Ultra S (Gambro Lundia AB, Sweden) machine, Polyflux 14S (Gambro Dialyzatoren GmbH, Germany) hemofilters and durability 4-8 hours. Bicarbonate substitution fluid was used with flow rate 75-100 ml/kg/hr and blood flow rate was set up at 250 ml/min.

Vascular access in all cases was central venous catheter for hemodilaysis 12 Fr, 20 cm (Arrow International Inc., USA), which was introduced in right jugular or subclavian vein or left subclavian vein. For anticoagulation unfractioned heparin was used in loading dose 10-25 IU/kg and maintain dose 10-20 IU/kg/hr (IHD and HVHF) or 3-20 IU/kg/hr (CVVH and SLEDD). RRT for patients with active bleeding, INR ≥ 4 or APTT ≥ 120 sec was performed without anticoagulation.

Patients treated with CRRT could be switched to the intermittent HD after three days of treatment and in the case all of followed: vasopressors withdrawal, weaning from mechanical ventilation and urine output about 1 ml/kg/hr, which provides zero or negative water balance.

Statistical analysis included descriptive statistics and non-parametric tests (Mann-Whitney) for comparison. Kaplan-Mayer estimator was used for survival analysis). Preliminary correlation analysis was performed using Kendall tau-b and factors statistically significantly associated with outcome were included in multivariate and univariate analysis. All calculations were performed with SPSS for Windows v. 17.0 software.

RESULTS. One hundred and six adult cardiac surgery patients (74 males and 32 females), who needed RRT due to AKI development in perioperative period were prospectively included in the study. Forty nine patients were treated with continuous RRT modalities (CVVH - 43, SLEDD - 6) were allocated in the group of continuous RRT (CRRT), meanwhile 57 patients assigned group of intermittent RRT (IRRT) (IHD - 40, HVHF – 17) (tables 1, 2).

Table 1

Baseline clinical patients` characteristic at RRT initiation

	Continuous RRT (n=49)	Intermittent RRT (n=57)	P
Male, n (%) Female, n (%)	39 (79,6) 10 (20,4)	35 (61,4) 22 (38,6)	0,043
Age, years (Mean±SD)	51,9±15,4	57±13,3	0,085
CKD-I, n (%)	2 (4,1)	1 (1,8)	0,292
CKD-II, n (%)	6 (12,2)	3 (5,3)	0,292
CKD-III, n (%)	2 (4,1)	11 (19,3)	0,292
Diabetes mellitus, n (%)	8 (16,3)	7 (12,3)	0,499
MOF, n (%)	40 (81,6)	34 (59,6)	0,014
Sepsis, n (%)	17 (34,7)	8 (14)	0,013
Oligouric, n (%)	40 (81,6)	40 (70,2)	0,174
Mechanical ventilation, n (%)	26 (53,1)	18 (31,6)	0,026

Table 2

Baseline laboratory patients` characteristic at RRT initiation

	Continuous RRT (n=49)	Intermittent RRT (n=57)	P
Weight, kg (Mean±SD)	79,4±19,8	78,1±15	0,934
Height, cm (Mean±SD)	171,6±8,7	169,7±10,3	0,393
BMI (Mean±SD)	26,7±5,6	26,9±4,4	0,577
BSA, м2 (Mean±SD)	1,9±0,3	1,92±0,22	0,967
APACHE II (Mean±SD)	23,2±6	20,8±5,6	0,041
MODS (Mean±SD)	7±3,4	5,8±3,3	0,045
SOFA (Mean±SD)	8,8±3,9	6,9±4,1	0,007
GFR (MDRD) (Mean±SD)	15,6±6,3	14,2±4,9	0,378
Blood urea, mmol/l (Mean±SD)	30,7±11,1	31,2±10,5	0,738
Blood creatinine, μmol/l (Mean±SD)	378,7±136,6	407,1±222,6	0,938
Urine output, ml/kg/hr. (Mean±SD)	0,4±1,6	0,5±2,4	0,061

There were no significant differences between groups in types of cardiac surgery.

Sixty eight cardiac surgery with AKI patients who needed RRT were discharged from hospital. Among them, recovery of renal function was observed in 54 patients (79,4%) and 14 patients (20,6%) remained RRT-dependant. Complete recovery of renal function was reached in 33 patients (48,5%), while partial was observed in 21 patients (30,9%).

There were no statistical difference between patients treated with CRRT or IRRT in frequency of complete (51,4% vs 45,5%, respectively) or partial (31,4% vs 30,3%, respectively) renal recovery nor RRT-dependance (17,2% vs 24,2%, respectively) at discharge.

Multivariate analysis demonstrated statistically significant association of renal function recovery of CS-AKI patients and changes of dopamine dose for the first day of RRT, terms of dobutamine usage, presence of MOF (table 3).

Table 3

Multivariate analysis of renal function recovery of CS-AKI patients

Effect		Value	F	Hipothesis df	Error df	P
Mean urine output for the first 3 days of RRT	Pillai's Trace	,427	2,609	2,000	7,000	,142
Changes in dopamine dose for the first day of RRT	Pillai's Trace	,647	6,419	2,000	7,000	,026
Dopamine dose at RRT start	Pillai's Trace	,512	3,665	2,000	7,000	,081
Total dopamine dose for the first 3 days of RRT	Pillai's Trace	,374	2,089	2,000	7,000	,194
Blood creatinine at RRT start	Pillai's Trace	,285	1,397	2,000	7,000	,309
Duration of dobutamine use	Pillai's Trace	,648	6,453	2,000	7,000	,026
Mechanical ventilation at RRT start	Pillai's Trace	,303	1,522	2,000	7,000	,283
Presence of MOF	Pillai's Trace	,742	10,085	2,000	7,000	,009
Presence of respiratory failure	Pillai's Trace	,266	1,271	2,000	7,000	,338
Dobutamine dose at RRT start	Pillai's Trace	,273	1,316	2,000	7,000	,327
Presence of heart failure	Pillai's Trace	,181	,773	2,000	7,000	,497
Pre-operative RRT	Pillai's Trace	,125	,502	2,000	7,000	,626

Univariate analysis showed, that complete recovery of renal function in CS-AKI significantly associated with reducing of dopamine dose during the first day of RRT (p=0,01) and long-tern use of dobutamine (p=0,009). Partial recovery was associated with early dobutamine withdrawal (p=0,005) and absence of MOF (p=0,016), while RRT-dependence at discharge was associated with absence of MOF (p=0,006) and escalation of dopamine dose on the first day of RRT (p=0,025) (table 4).

Table 4

Univariate analysis of renal function recovery of CS-AKI patients

Source	Dependent variables	Type III Sum of Squares	df	Mean Square	F	P
Changes in dopamine dose for the first day of RRT	RRT-dependence	,090	1	,090	7,604	,025
	Complete recovery	1,575	1	1,575	11,081	,010
	Partial recovery	,912	1	,912	6,969	,030
Duration of dobutamine use	RRT-dependence	,006	1	,006	,503	,498
	Complete recovery	1,664	1	1,664	11,704	,009
	Partial recovery	1,869	1	1,869	14,284	,005

Continue Table 4

Source	Dependent variables	Type III Sum of Squares	df	Mean Square	F	P
Presence of MOF	RRT-dependence	,166	1	,166	14,012	,006
	Complete recovery	,475	1	,475	3,342	,105

There was statistically significant difference between cardiac surgery patients with CS-AKI with MOF and with CS-AKI with-out MOF regarding frequency of complete recovery of renal function and RRT-dependence at discharge (table 5).

Table 5

Recovery of renal function in CS-AKI patients with or without MOF

Grade of renal function recovery	CS-AKI with MOF n (%) n=38	CS-AKI with-out MOF n (%) n=30	P
Complete recovery	25 (65,8%)	8 (26,7%)	0,001
Partial recovery	8 (21,1%)	13 (43,3%)	0,05
RRT-dependance at discharge	5 (13,2%)	9 (30%)	0,044

Subsequently, separate analysis of patients with CS-AKI with MOF was undertaken and multivariate analysis showed that complete recovery of renal function in patients with CS-AKI with MOF had statistically significant association with withdrawal of dopamine during the first day of RRT (p=0,026) and long-term use of dobutamine (p=0,005). Meanwhile, univariate analysis failed to demonstrate any significant association with complete recovery in this group of patients.

In univariate analysis RRT-dependance at discharge of patients with CS-AKI with MOF was statistically significantly associated with arising of dopamine dose during the first day of RRT (p=0,006) and no-use of dobutamine at RRT start (p=0,006). Partial recovery was associated with early withdrawal of dobutamine (p=0,038).

During the first day of RRT the increasing of dopamine dose among CS-AKI patients with MOF, who remained RRT-dependant at discharge was 0,85±1,7 mcg/kg/min, while the reduction of dopamine dose among patients with partial or complete recovery was 0,44±0,81 mcg/kg/min and 1,02±1,74 mcg/kg/min, respectively (p=0,046). Dobutamine was withdrawn at 1,2±0,8 days after RRT initiation in patients who established partial recovery of renal function and at 5,1±3 days in those who had complete recovery. No-one among CS-AKI patients with MOF who was RRT-dependant at discharge was treated with dobutamine (p=0,006).

DISCUSSION. The major limitations of our study are conjuncted with its observational nature and relatively small population size. On the other hand, the aim of this study was to evaluate different RRT modalities in real-life environment.

Frequency of renal recovery in cardiac surgery patients with AKI was 79,4% (48,5% - complete and 30,9% - partial) in our study. In VA/NIH Acute Renal Failure Trial Network study the frequency of complete recovery of renal function was 15,4% in intensive treatment group and 18,4% - in less-intensive care group. The rate of partial recovery in this study was 8,9% and 9%, respectively [8]. The large difference (24,3-27,9% and 79,4%) in the rate of renal function recovery between VA/NIH study and our results can be explained by differences in patients` population that included, because C. Hobson et al. Reported 36% frequency of complete recovery of renal function in cardiac surgery patients and 50% - partial recovery, that is quite similar to our results [3].

Meta-analysis conducted by Karvellas et al., found out that “early” initiation of RRT is associated with higher rate of renal recovery in comparison with “late” initiation. However, our study was not designed to define the influence of timing RRT start to renal recovery and RRT was initiated according to the local protocol uniformly to all patients [5].

Our results suggest that RRT modality per se does not influence renal recovery and are cohered with others investigations [6].

Renal recovery in patients with CS-AKI is related to pharmacological treatment (mostly) and severity of the illness. Beneficial effect of dobutamine in this cohort of patients can be explained by the fact that deterioration of pump function of the heart is the most frequent cause of the CS-AKI. Especially, when that deterioration reaches failure degree and form multiorgan failure (coupling heart failure with AKI).

The deterioration of heart pump function as the major cause of CS-AKI can explain the fact, that patients with CS-AKI with MOF have higher in-hospital mortality rate and higher renal recovery rate. Successful treatment of heart failure in patients who have MOF (heart failure resulted in renal failure and sometimes in other organ failure) results in reconvalescence from MOF and, as a consequence, renal recovery, when unsuccessful treatment of acute heart failure (which is not uncommon) leads to the death. In the case of CS-AKI without MOF, the cause of AKI mostly is not related to the heart

failure - drug induced, including contrast-induced, associated with prolonged cardio-pulmonary bypass, septic or related unrecognized previously kidney disease. These conditions are, in most cases, less lifethreating, but associated with worsened renal recovery.

Negative association of dopamine use with renal function recovery obtained in our study corresponds to results of numerous studies showed that dopamine use in AKI has no beneficial effects and even can be harmful. Current KDIGO recommendation not using dopamine for treatment nor prevention of AKI is reflection of these studies` results [6]. In our study dopamine was used according to hemodynamic indications (not as AKI treatment) and, on the other hand, can serve as indicator of illness` severity, because, in general, patients who need dopamine infusion have more unstable hemodynamic compare to those who need dobutamine.

CONCLUSION. Recovery of renal function in CS-AKI patients associated with decreasing dose of dopamine, prolonged use of dobutamine, illness severity and does not associated with specific RRT modality.

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