



Tsyrenov D.D., Tabakyan E.A., Merzhin K.V., Buldakova N.A., Akchurin R.S.

# THE HEMODYNAMICS AND RENAL FUNCTION BEFORE AND AFTER PULMONARY THROMBOENDARTERECTOMY

*Federal State Budgetary Institution «National medical research center of cardiology» of Ministry of health of Russia, Moscow, Russia*

## SUMMARY

**Objective:** to study the pulmonary hemodynamics and kidney function in patients with chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary thromboendarterectomy (PTE). To analyze the main results of PTE.

**Material and methods:** among 51 patients with CTEPH undergoing PTE, the group with chronic kidney disease (CKD) was identified. The main parameters of hemodynamics, such as cardiac output (CO), cardiac index (CI), pulmonary arterial pressure (PAP), pulmonary vascular resistance (PVR), were determined. The cases of acute kidney injury (AKI) after PTE were identified. The correlation

between hemodynamics and renal function was analyzed.

**Results:** there was decrease of mean PAP, PVR and increase of CO and CI after PTE. In cases of AKI 1–2, the complete recovery of renal function were observed. Glomerular filtration rate (GFR) increased before discharge in patients with CKD and in other patients.

**Conclusion:** the positive dynamics of renal function in patients with CTEPH after PTE is more probably associated with an increase in the CI and renal perfusion.

**Key words:** *pulmonary thromboendarterectomy, hypothermic circulatory arrest, glomerular filtration rate, acute kidney injury.*

## Information about authors:

<b>Tabakyan Evgeniy Avedikovich</b>	clinical research of laboratory of artificial circulatory support of department of cardiovascular surgery, National medical research center of cardiology, e-mail: tabakyan@mail.ru, 121552, Russia, Moscow, st. 3rd Cherepkovsky, 15 a.
<b>Merzhin Kirill Vyacheslavovich</b>	surgeon of department of cardiovascular surgery, National medical research center of cardiology, e-mail: kirill_merzhin@mail.ru, tel.8-495-414-66-20, 121552, Russia, Moscow, st. 3rd Cherepkovsky, 15 a.
<b>Buldakova Nadezhda Anatolievna</b>	postgraduate student of department of cardiovascular surgery, National medical research center of cardiology, e-mail: lyhil_zolotoi@mail.ru, тел. 8-495-414-72-85, 121552, Russia, Moscow, st. 3rd Cherepkovsky, 15 a.
<b>Akchurin Renat Suleymanovich</b>	The head of department of cardiovascular surgery, National medical research center of cardiology, e-mail: rsakchurin@list.ru, tel. 8-495-414-61-43, 121552, Russia, Moscow, st. 3rd Cherepkovsky, 15 a.
<b>Corresponding author: Tsyrenov Damba Damdinovich</b>	postgraduate student of department of cardiovascular surgery, National medical research center of cardiology, e-mail: damba-tit@mail.ru, tel. 8-495-414-72-85, 8-916-064-25-48, 121552, Russia, Moscow, st. 3rd Cherepkovsky, 15 a.

✉ damba-tit@mail.ru

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## INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) – the precapillary form of pulmonary hypertension, in which chronic obstruction of large and medium branches of the pulmonary arteries, as well as secondary changes in the microcirculatory bed of the lungs, lead to a progressive increase in pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP) with the development of right ventricular failure (RVF). CTEPH is a remote complication of acute thromboembolic event with a development rate of up to 9.1% during the first 2 years after the episode [1].

Hemodynamic disorders in patients with CTEPH contribute to the development and progression of chronic kidney disease (CKD), which should be considered as cardiorenal syndrome (CRS) [2]. Pulmonary thromboendarterectomy (PTE) is the method of choice

in the treatment of CTEPH patients [1,3-5]. Distinctive features of operation are long-term cardiopulmonary bypass (CPB), deep hypothermic circulatory arrest (DHCA), a long rewarming phase. Under such conditions of artificial circulation, we can assume a higher incidence of acute kidney injury (AKI) compared with operations without circulatory arrest and deep hypothermia.

Acute kidney injury (AKI) is a dangerous condition that causes adverse outcomes, mortality and morbidity [6]. The incidence of acute kidney injury (AKI) after operations with CPB reaches 30%. The need for renal replacement therapy is observed in no less than 1% of patients [7]. However, there is no detailed analysis of the development of acute kidney injury (AKI) in stages after the PTE. In this article, the state of hemodynamics and the function of the kidneys before and after PTE are analyzed.

**Purpose of the study:** to study the parameters of pulmonary hemodynamics and renal function in patients with CTEPH before and after PTE. Analyze the main results of PTE.

## MATERIAL AND METHODS

The study included 51 patients (32 men and 19 women) with CTEPH, operated from 2010 to 2018. Prior to surgery, patients were divided into two groups according to the presence or absence of CKD of II-III st. After the operation, we identified groups with acute kidney injury (AKI) and without acute kidney injury (AKI) according to the RIFLE 2004 classification [8,9]. The glomerular filtration rate (GFR) was estimated by the formula CKD EPI 2009 in ml / min. Instrumental support for PTE, features of artificial circulation and intensive care have been described previously [10]. Pulmonary arterial pressure (PAP) were controlled by Swan-Ganz catheter in the pulmonary artery, cardiac output (CO) was measured by the thermodilution method, cardiac index (CI) and pulmonary vascular resistance (PVR) were obtained by the calculation method. Nonparametric statistical methods were used. To assess inter-group differences, the Mann-Whitney U-test was used, and to assess the dynamics of intra-group differences – the Wilcoxon T-test. Results are presented in the form of median, lower and upper quartiles, a percentage of the total, reliability  $p < 0,05$ .

## RESULTS

From 2010 to 2018, in our department, PTE were performed to 51 patients with CTEPH. In 10 cases, combined operations were performed: coronary bypass surgery – 5, closure of an open foramen

ovale window (OFO) – 3, thrombectomy from the right atrium – 1, cavotricuspid isthmus cryoablation – 1. Before surgery, chronic kidney disease (CKD) II-III st. was diagnosed in 29.4% of patients.

The results of examination are presented in Table 1.

Due to the too early mortality, 2 patients were excluded from the study. The woman of 59 years old with CKD of the third stage: the lethal outcome was a result of pulmonary intraoperative bleeding. Male 28 years old: PTE was not performed due to the impossibility of separating the thrombotic material, that led to pulmonary hypertensive crisis, polyorganic insufficiency (PI) and death, on the 6th day in the intensive care unit. In 49 patients, perioperative parameters were analyzed, their relationship with the development of AKI was evaluated.

The main results are shown in Table 2.

After PTE in 13 cases, the development of acute kidney injury (AKI) was observed on 1-2 postoperative days, which was 26.5% of the total number of patients; the need for renal replacement therapy – 2%; First-stage acute kidney injury (AKI) – in 8 cases (16.3%), stage 2 AKI – in 3 cases (6.1%), stage 3 – in 2 cases (4.1%). Twelve of them had complete restoration of kidney function. In one patient with catastrophic antiphospholipid syndrome (CAPS) the 3rd stage of AKI progressed, thrombocytopenia and polyorganic insufficiency developed. Intensive therapy, plasma exchange procedures and renal replacement therapy did not have an effect; death was fixed on day 10. The prevalence of preoperative risk factors of AKI after operations of PTE is analyzed. There were no significant differences between the groups. Patients with CKD of the 2nd stage – 4 (30.7%) in the presence of AKI and 10 (27.7%) without AKI. Diabetes mellitus type 2 was diagnosed in 2 (15.3%)

**Table 1. Results of preoperative examination of patients with CTEPH**

Variables (units of measure)	Group of CKD 2-3 (n = 15; w-7)	Group without CKD (n = 36; w-12)
Age (years)	56 (50; 62)	54 (35; 63)
Anamnesis of pulmonary hypertension (years)	5 (3; 8)	4 (2; 6,5)
Diabetes mellitus type 2 (n/%)	3/20	2/5,5
FC of Chronic Heart Failure by NYHA	3 (3; 4)	3 (3; 4)
The hemoglobin (g / l)	136 (128;150)	142 (135; 157)
Serum creatinine (μmol / L)	110 (94; 122)	76 (69; 92) *
Serum urea (mmol/l)	6,5 (6,1; 7,1)	5,8 (4,6; 6,3) **
CKD before surgery (CKD EPI 2009): (ml/min)	69 (61; 78)	101 (94; 111) *
Hereditary thrombophilia (n/%)	5 /33,3	16/44,4
Antiphospholipid syndrome (n/%)	2/13,3	7/19,4
Average PAP before surgery (mmHg)	47 (45; 57)	45 (40; 52)
CI (l / min / m <sup>2</sup> )	2 (1,5; 2,1)	1,78 (1,6; 2)
PVR (dynes×s×cm-5)	1035 (777;1254)	917 (753; 1131)

The Mann-Whitney U-test:  $p = 0,00003$  \*;  $p = 0,005$  \*\*

**Table 2. Results of perioperative examination of groups with and without AKI**

Indicators (units of measure)	AKI (n = 13)	Without AKI (n = 36)
Age (years)	62 (50; 66)	53,5 (38,5; 59)
CTEPH anamnesis (years)	8 (3; 13)	4 (2; 6) #
Artificial circulation time CPB (min)	245 (214; 284)	246 (222; 276)
DHCA total time (min)	45 (31; 51)	40 (28;48)
DHCA number amount (n)	3 (2; 3)	2,5 (2;3)
Minimal Hb artificial circulation (g / l)	76 (63; 83)	73 (66,5; 83,5)
Dose of Lasix Furosemid per Day 1 (mg)	40 (30; 60)	20 (20; 40) ***
Max. serum creatinine after surgery (μmol / L)	174 (148; 207)	93 (84; 118) *
Max. Serum urea after surgery (mmol / L)	15,7 (9,1; 19,2)	7,1 (6,3; 8,4) **
Max. Lactate 1st day (mmol / l)	5,1 (3,6; 7,8)	2,9 (2,6; 3,9) ****
Volume of diuresis for the first day (ml)	1950 (1350;2500)	2425 (1775;3175)
number of days in the intensive care unit	4 (3;10)	3 (2; 4)
number of days in hospital after surgery	14 (13; 24)	13,5 (12;16,5)

Mann-Whitney U-test:  $p = 0,000002$  \*,  $p = 0,00003$  \*\*,  $p = 0,014$  \*\*\*,  $p = 0,0005$  \*\*\*\*,  $p = 0,024$

**Table 3. Hemodynamic parameters and kidney function before and after pulmonary thromboendarterectomy (PTE)**

Indicators (units of measure)	AKI (n =13)	Without AKI (n = 36)
Mean PAP before operation (mmHg)	45 (41; 60)	47 (41;53)
Mean PAP – 1st day. after surgery (mmHg)	31 (24; 36) p=0,001	27 (23,5;30) p=0,000001
PVR before surgery (dynes×s×cm-5)	909 (817; 1244)	917 (753; 1131) *
PVR 1st day. after surgery (dynes×s×cm-5)	267 (223; 486) ** p=0,0033	288 (240; 377) * p=0,000001
CO before operation (l / min)	3,5 (2,8; 4,8) **	3,56 (3,2;3,9) *
CO 1st day. after the operation (l / min)	4,25 (3,9; 5,2) ** p=0,06	4,65 (4,4; 5,2) * p=0,000001
CI before operation (l / min / m <sup>2</sup> )	1,8 (1,3; 2,4) **	1,78 (1,6; 2,1) *
CI – 1st day after the operation (l / min / m <sup>2</sup> )	2,2 (2,1; 2,3) ** p=0,06	2,48 (2,2; 2,7) * p=0,000001
Mean serum creatinine level before surgery (μmol / L)	89 (75; 95)	83 (69; 98)
Mean serum creatinine level max after operation (μmol / L)	174 (148; 207) p=0,0014	93 (84; 118) p=0,000039
Mean serum creatinine level before discharge (мкмоль/л)	76,5 (69; 89) *** p=0,18	65,5 (60; 73) p=0,000002
GFR before surgery (ml / min)	97 (88; 99)	93,5 (77; 109)
GFR before discharge (ml / min)	98,5 (88; 105) *** p=0,36	113,5 (95;120) p=0,000001

Reliability based on the Wilcoxon T-test, (n = 34) \*, (n = 11) \*\*, (n = 12) \*\*\*

patients in AKI group and in 3 (8.3%) patients in the group without AKI. Among the patients with AKI, there were 3 (23%) women, without AKI – 15 (41.6%). Among intraoperative risk factors, combined operations were recorded in the group with AKI in 3 cases (23%), without AKI – in 7 (19.4%); transfusion of 1-2 doses of blood at CPB in patients with AKI in 4 cases (30.7%), without AKI – in 10 (27.7%), there were no significant differences. We observed a significant decrease in PVR, an increase in CO and CI for the first day after PTE compared with preoperative data.

The parameters of hemodynamics and kidney function before and after the operation are presented in Table 3.

In the AKI group, in the first day after the operation, 8 patients showed an increase in CO and CI, in 2 cases a decrease and in 1 there were no change. 1 patient had acute reduction of CO during the first hours after surgery which required correction of volemia, contractility, heart rate. In her case, an increase in plasma creatinine more than 2 times from the baseline was observed 24 hours after the operation with a decrease to preoperative values by the 5th day.

In the non-AKI group in the 1st case there was a slight decrease in CO and CI, a lack of dynamics in 1 patient; in other cases – an increase in CO and CI in the first day after the operation. The increase in GFR before discharge from the hospital was observed in 32 patients, the absence of the dynamics – in 4 patients without AKI.

In the analysis of the general group, the following results were obtained: in 14 patients with CKD, the level of preoperative creatinine decreased from 107 (94; 116) to 77 (65, 88) μmol / L

and an increase in GFR from 69 (61, 78) to 99 (86; 112) ml / min before discharge (p = 0.0012).

Among complications after PTE, the development of neurologic symptoms were observed in 8 cases: chorea, posthypoxic encephalopathy, paranoid behavior, extrapyramidal symptoms. A specialized treatment was carried out together with a neurologist, a psychiatrist. All neurologic symptoms were resolved: in 6 cases during the in-hospital period, in 2 – up to 14 days after discharge. Two cases of were observed after discharge from the hospital: in the first case it was due to the development of residual pulmonary hypertension and hemothorax on 45 postoperative days, in the second – pleural empyema complicated by sepsis, death – on 34 postoperative days.

## DISCUSSION

Low CO, typical for patients with CTEPH, is likely to lead to chronic kidney hyperperfusion and development of CKD. Obviously, an increase in the duration of an anamnesis of pulmonary hypertension increases the risk of developing CKD and AKI. We observed a significantly longer history of CTEPH in patients with AKI compared with patients without AKI. According to the results of the international registry in patients who underwent PTE (n = 404), the median time from the onset of symptoms to the diagnosis was 15 months; in 0.5% of cases in the preoperative period, stage 5 CKD was diagnosed, the percentage of patients with CKD of other stages was not indicated [11]. According to Kuniyama T and co-authors, during examination of 276 patients with CTEPH, the mean level of serum creatinine before surgery was  $97.2 \pm 26.5$  μmol / L [12]. In our study, the mean serum creatinine level in patients with CKD was equal to 110 μmol / L, without CKD – 76 μmol / L.

Execution of the PTE requires a bloodless surgical field for accurate search and maximum removal of obstructive material. Oblecleration of the operating field is maximally achievable under conditions of circulation arrest [13]. Surgery with long-term artificial circulation, DHCA in addition to neurological complications, carries potential risk of AKI. Intraoperative risk factors for AKI development are haemolysis, low hemoglobin level, microcirculatory disturbances during artificial circulation, systemic inflammatory response syndrome, ischemia in DHCA. At the same time, compliance with the protocol of perfusion, including the maximum time of circulatory arrest, the rate of warming, etc., helps to avoid potential complications.

According to our results, the need for renal replacement therapy (RRT) in AKI was 2%, the DHCA median in the AKI group was 45 min. KasperKorsholm and co-authors in the analysis of 239 patients who underwent PTE under conditions of DHCA describe 40 (16.8%) cases of development of AKI, requiring RRT. The median duration of DHCA was 38 minutes [14].

Now many studies describe the effects of various methods of perfusion on the central nervous system, lung function and kidney function. In a randomized controlled study PEACOG 2011 compared the results of PTE between the group with antegrade cerebral perfusion (ACP) – n = 39 and the DHCA group lasting less than 20 min-n = 35. Nine patients switched from ACP to DHCA to ensure complete endarterectomy. In the DHCA group, one case of AKI, requiring RRT, was registered in the ACP group – 0. There were 3 deaths: two in the DHCA group, one in the ACP group. There was no statistically significant difference in adverse events between the two groups. The authors recommend DHCA as an optimal condition for the implementation of PTE [13]. In our clinic we share similar position, we did not use ACP method for PTE operations.



Kalinin R.A. and co-authors in the study divided 17 patients into two groups by blind randomization. The first group consisted of 7 patients who had PTE under moderate hypothermia with ACP, the second group consisted of 10 patients operated under the conditions of DHCA. In the early postoperative period, one case of AKI was observed in both groups, each of them required a substitution renal therapy [15]. Madani M. and al. in work 2016 write that the most important aspect of PTE is the maximum possible endarterectomy that minimizes residual thromboses in order to reduce the risk of residual pulmonary hypertension. To ensure complete endarterectomy, additional DHCA can be safely used within 20 minutes with reperfusion periods of at least 10 minutes. Over the past 10 years, authors from Europe have published a number of publications with changes in this technique in the form of a decrease in the degree of hypothermia, duration or failure of a complete stop of blood circulation. At present, it is known that these modifications are not necessary and could potentially jeopardize the completeness of endarterectomy [16].

Control of hemodynamic parameters before stabilization of the patient's condition allows to react in a timely manner to changes in CO, PAP, and preventing the development of complications. Optimization of the parameters of pulmonary hemodynamics, in our opinion, leads to an increase in oxygenation of the blood, improvement of renal perfusion and their function in the majority of patients. So, according to own experience, the developed cases of AKI were completely reversible in 12 out of 13 cases, maximally by 5th day after the operation. According to foreign authors, rapid recovery of kidney function in patients after cardiac surgery improves long-term survival [17]. The percentage of patients with AK, the need for substitution renal therapy in our study is not higher than in other cardiac operations with artificial circulation without deep hypothermia [18,19].

The in-hospital mortality with PTE is from 4 to 8.5-10% [14, 20-23]. With the combined operations of PTE and coronary bypass, PTE and valve operations, this indicator increased to 9.6% and 16.7%, respectively [22]. In the Department of Cardiothoracic Surgery in San Diego, which has the largest experience in the world in conducting operations of PTE, the death rate decreased to 2.2% [24]. Currently, our hospital has an internal hospital mortality rate of 5.8%.

## CONCLUSION

A longer history of PH is one of the factors in the development of CKD and one of the predictors of AKI. It is necessary to diagnose and operate patients with CTEPH at early stages, before decompensation of RVF and a significant decrease in CI to minimize the risk of developing CKD and AKI. DHCA is the optimal method for perfusion of PTE. In the early postoperative period, an urgent correction of hemodynamic disturbances is important to prevent PI. Positive dynamics of kidney function in patients with CTEPH after PTE is most likely associated with an increase in CI and renal perfusion.

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