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PATHOGENETIC MECHANISMS, EPIDEMIOLOGY AND CLASSIFICATION OF ACUTE KIDNEY INJURY IN HEART TRANSPLANT RECIPIENTS

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Kidney injury in heart transplant recipients is of a complex nature and bears the features of all types of cardiorenal interaction impairment. Pre-transplant renal dysfunction, perioperative acute kidney injury, as well as factors associated with graft and immunosuppression, determine the prevalence and severity of kidney pathology in this group of patients. This review examines the pathophysiology of kidney dysfunction in heart failure, the epidemiology, and criteria for acute kidney injury.

Keywords: cardiorenal syndrome, heart transplantation, epidemiology, criteria for acute kidney injury.

Heart disease and renal dysfunction are often interrelated. When the heart and kidneys are affected simultaneously, mortality, morbidity, as well as the complexity and cost of treatment increase significantly [1]. Mutual heart-kidney interaction syndrome has been known for a long time. However, until 2008 it had no clear definition and classification. This situation was corrected at an international conference facilitated by ADQI (Acute Dialysis Quality Initiative), where the opinions of leading experts in the field of nephrology, intensive care, cardiac surgery, cardiology, and epidemiology were reconciled.

Five types of cardiorenal syndrome (CRS) have been identified, which reflect all possible interdependent heart and kidney injury [2, 3]. At the same time, different types of CRS can be manifested at different stages of the disease in one patient. In some cases, there may be a vicious circle, where there is simultaneous or combined heart and kidney damage. A unique example of such a situation is kidney injury in heart transplant recipients, since at different stages of treatment, before and after transplantation, there could be manifestations of all CRS types: impaired kidney function with long-term heart failure (HF) at the preoperative stage; acute kidney injury (AKI) in the perioperative period against the background of cardiopulmonary bypass (CPB), heart graft dysfunction, use of cardiotonic drugs, mechanical support of the contractile function of the heart, immunosuppression; in some cases, renal damage has an outcome in the terminal stage with a continuing need for dialysis replacement therapy and persistence of such pathological mechanisms as suburemia, overhydration, chronic inflammation, bone and mineral disorders, anemia, and others, leading to the development in a heart graft characteristic of a chronic kidney disease (CKD) in the final, dialysis-dependent stage, changes in the form of cardiofibrosis, myocardial hypertrophy, calcification of heart valves and blood vessels.

MECHANISMS OF KIDNEY INJURY IN IMPAIRED CARDIAC FUNCTION

The pathophysiology of kidney injury in HF is complex, involving multiple pathological factors acting simultaneously (Fig.). Although a fall in cardiac output and renal perfusion has traditionally been considered as the main cause of HF-related renal dysfunction, the results of a number of major clinical trials do not support this position. For example, using an analysis of data from 118,465 patients with acute decompensated HF, Heywood et al. could not demonstrate an association between left ventricular systolic dysfunction and deterioration of kidney function [4]. According to the results of a study by K. Damman et al., in 2557 patients who underwent right heart catheterization, increased central venous pressure (CVP) was a predictor of mortality and was associated with low estimated glomerular filtration rate (eGFR), regardless of the cardiac index (CI) [5]. A number of studies suggest the presence of other pathophysiological mechanisms of renal dysfunction, particularly the effect of high right atrial pressure on venous congestion and venous hypertension. The same authors confirmed previously published data in a study of 2647 patients with systolic HF, in whom a decrease in the eGFR and mortality were associated with such manifestations of

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venous stasis as ascites and increased pressure in the jugular vein [6]. According to the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) study, which enrolled patients with decompensated HF, renal function depended neither on cardiac index, nor on pulmonary capillary wedge pressure, nor on systemic vascular resistance. However, it was associated with right atrial pressure [7].

Based on database analysis of a branch of the same study, Hanberg et al demonstrated that there is a statistically significant inverse correlation between CI and eGFR in patients with HF who underwent pulmonary artery catheterization [8].

In a study by Guglin et al. in 178 HF patients, eGFR correlated with high CVP and low renal perfusion pressure. EchoCG found that deterioration of renal function was associated with tricuspid regurgitation peak velocity, but not with left ventricular systolic function [9]. Maeder et al. reported that in patients with HF, tricuspid regurgitation severity was independently associated with the degree of impaired renal function [10]. At the same time, many studies that have analyzed right atrial pressure in HF have two shortcomings complicating interpretation of these data: severity of preexisting parenchymal renal disease and degree of reduction of left ventricular systolic function are not considered. It is possible that increased right atrial pressure becomes clinically significant for the onset of renal venous congestion only when the cardiac index is decreased. In an animal experiment simulating acute renal venous congestion (13 mm H_2O), renal dysfunction (decreased blood flow, eGFR, sodium and free water clearance) became less pronounced when systemic hemodynamics were restored to control values by transfusion [11]. Damman et al. report that in potential lung recipients with HF, due to pulmonary hypertension, right atrial pressure (RAP) and renal blood flow were independently correlated with radioisotope-measured eGFR. Moreover, the association with RAP was more pronounced in patients with reduced renal blood flow [12]. For instance, Uthoff et al. report that in patients with acute HF, the combination of arterial hypotension and high CVP was significantly associated with lower eGFR [13]. Thus, therapeutic measures aimed at reducing renal congestion will be most effective in patients with arterial hypotension.

The hemodynamic response to reduced systemic arterial pressure depends on endothelial function, which is impaired in both chronic kidney disease and heart failure. Reduced renal perfusion pressure stimulates the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). Angiotensin II and catecholamines cause glomerular arteriolar vasoconstriction that

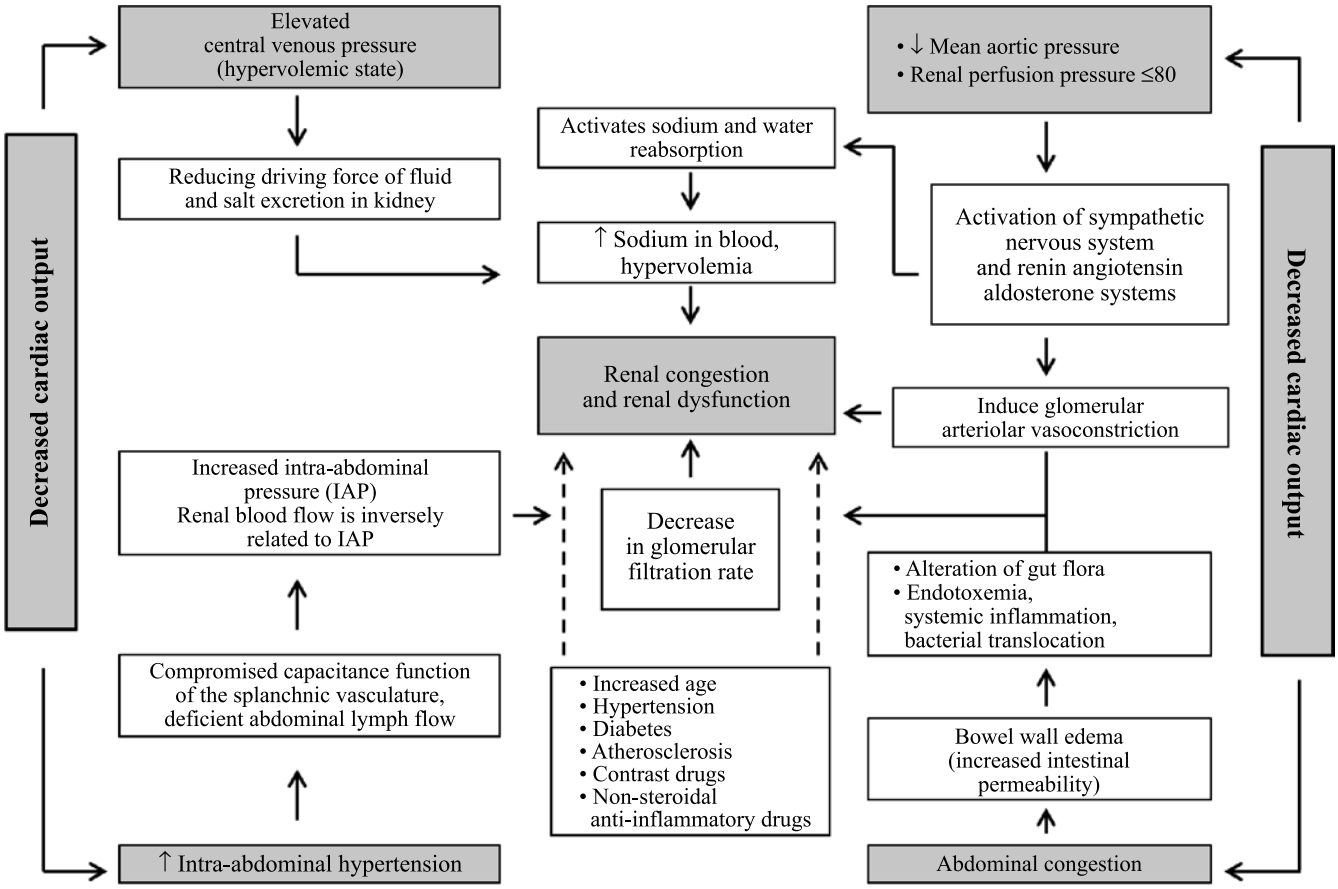

Fig. Pathophysiology of renal venous stasis and Impaired kidney function in heart failure (adapted from B. Afsar et al., 2016 [28])

reduces renal plasma flow [14]. Angiotensin II exerts a disproportionate vasoconstrictor effect on efferent arterioles, maintaining eGFR despite reduced renal plasma flow [15]. Thus, initially, the filtration fraction and eGFR were preserved, then the increase in angiotensin II and catecholamine production proves inadequate, which entails an even greater preglomerular vasoconstriction and reduction in eGFR [16]. This, in turn, activates sodium and water reabsorption in the proximal tubule, leading to even greater systemic and renal congestion; renal interstitial pressure increases; all capillary bed and tubules are compressed; local hypoxia develops. Increased pressure in the tubule lumen leads to a decrease in the transglomerular pressure gradient and exacerbates the decrease in eGFR [17].

In people without HF, the transient state of hypervolemia results in increased renal excretion of salt and fluid; this reduces the blood volume and cardiac output, normalizing blood pressure. However, in patients with HF, despite the hypervolemic state, elevated right atrial pressure and CVP negatively affect renal sodium excretion, creating a vicious cycle of sodium and fluid retention and HF build-up, which leads to even greater renal congestion [18].

Increased intra-abdominal pressure, blood congestion in the abdominal organs and interstitial space also play a role in impaired renal function. There is a negative correlation between the magnitude of renal blood flow and intra-abdominal pressure [19, 20]. According to a study by P.K. Harman et al., when the intra-abdominal pressure was elevated to 20 mmHg, GFR decreased to <25% of normal in experimental animals; when the intra-abdominal pressure was elevated to 40 mmHg, GFR fell to 7% of normal, while cardiac output was reduced to 37% of normal [21]. Compromised capacitance function of the abdominal organs and deficient abdominal lymph flow also contribute to elevated pressure in the right heart, which might additionally imply the occurrence of renal dysfunction [22]. In addition, disturbed intestinal microcirculation and barrier function, characteristic of HF, stimulate the production of cytokines that aggravate myocardial dysfunction, which in turn contributes to disturbed microcirculation [23]. Proinflammatory cytokines TNF and interferon-γ can disrupt the epithelial barrier function [24]. Subsequent entry of bacterial lipopolysaccharides into the bloodstream activates macrocytes and macrophages to produce proinflammatory mediators [24].

Inflammation can both contribute to the onset and be a consequence of renal venous stasis [25]. Inflammation causes vascular dysfunction through endothelial factors and increased arterial stiffness, decreased myocardial contractility due to functional suppression of contractility and myocardial cell death. P.C. Colombo et al. evaluated the effect of peripheral venous stasis induced by venous stress test on inflammation and endothelial activation. Venous arm pressure was increased to ~30 mmHg above the baseline level by inflating a tourniquet cuff around the dominant arm. Plasma interleukin-6 (IL-6), endothelin-1 (ET-1), angiotensin II, vascular cell adhesion molecule-1, and chemokine ligand 2 were significantly increased in the congested arm [26]. In HF and venous congestion, activation of RAAS and the sympathetic nervous system exacerbates the inflammatory response. According to experimental data from K. Iwata et al., RAAS activation leads to stimulation of nicotinamide adenine dinucleotide phosphate oxidase by angiotensin II, which leads to formation of reactive oxygen species.

All these processes promote progression of renal dysfunction and development of renal fibrosis [27].

Fibrosis is a common pathophysiological mechanism of cardiorenal syndrome. Disease-related injury to any organ triggers a complex cascade of cellular and molecular response, which culminates in tissue fibrosis. Although this fibrogenic response can be restrained for some time by adaptive mechanisms; in the case of prolonged damaging effects, sclerotic parenchyma, cellular dysfunction and, ultimately, functional insufficiency develop [29]. The cause of fibrotic processes, both in the heart and in the kidneys, is endothelial dysfunction arising from inflammation and oxidative stress, associated, in turn, with aging, arterial hypertension, diabetes mellitus and obesity, and leading to cardiovascular disease, HF and CKD [30]. Myocardial remodeling occurs after heart damage and involves the secretion of extracellular matrix proteins by myofibroblasts. This promotes cardiac fibrosis and preserves myocardial structure and function, but such a condition leads to chamber dilatation, cardiomyocyte hypertrophy, and apoptosis, and ultimately leads to the progression to heart failure [30]. In the kidney, tubulointerstitial fibrosis and dysfunction can be caused by differentiation of tubular epithelial cells into myofibroblasts through an epithelial-mesenchymal transition phenotype, leading to the cells losing their polygonal shape and epithelial markers and acquisition of a fibroblast phenotype with increased extracellular matrix synthesis (e.g. collagen I, III, fibronectin). Aldosterone can trigger a cascade of processes leading to cardiac, vascular, and renal fibrosis, mutually involving them in the development of cardiorenal syndrome. Experimental studies have supported such pathogenetic mechanisms. For example, in an experiment on rats, with AKI induced by bilateral renal ischemia/reperfusion, treatment with a mineralocorticoid receptor antagonist spironolactone prevented the activation of fibrotic and inflammatory processes, preventing the development of CKD [31, 32]. Of interest in this regard are the results obtained in the study of living kidney donors, who, 12 months after nephrectomy, developed a decrease in eGFR, accompanied by significant increase in left ventricular mass, confirmed by MRI, without development of arterial hypertension. Changes in eGFR were independently associated

with changes in left ventricular mass. Compared with the control group, the donors had a significantly increased concentration of fibroblast growth factor-23 and high-sensitivity C-reactive protein. However, the clinical relevance of these findings is unclear, as observational studies have shown favorable long-term outcomes for living kidney donors [33]. Nevertheless, studies of living kidney donors compared with controls suggest an increased risk of cardiovascular events and end-stage CKD [34, 35]. Elevated concentrations of highly sensitive cardiac troponin T and microalbuminuria were much more common in donors than in the control group [35]. Meanwhile, Paoletti et al. suggested that in 100 kidney transplant recipients, regression of left ventricular hypertrophy portends better long-term combined clinical outcome (death, any cardiovascular or renal event) [36].

In addition to these factors, activation of mineralocorticoid receptors through a number of mechanisms (inflammation; increased potassium levels in the blood, which has a proarrhythmic effect) promotes fibrotic changes in the heart, arteries, and kidneys. This process involves such mediators of inflammation and fibrosis as galectin-3 [31, 37], NGAL [38], stimulating growth factor ST2 [39] and cardiotropin-1 [40].

The pathophysiology of kidney injury after cardiac surgery with CPB is even more complex and multifactorial. Additional mechanisms affecting renal function in patients with chronic heart failure after such operations may include microembolization, metabolic and hemodynamic disorders, ischemia–reperfusion injury, and oxidative stress [41]. These mechanisms of injury may be interrelated and synergistic. The use of CPB has been associated with an alteration of vasomotor tone and a reduction in the renal parenchymal oxygen tension, and consequently, decreasing the renal perfusion pressure up to 30% and, hence, increasing the ischemia–reperfusion injury [42]. In addition, the formation of microemboli may be increased by the use of CPB. It is well known that emboli smaller than 40 μm are not effectively filtered by CPB-system filters and can damage renal capillaries directly. The release of free hemoglobin secondary to hemolysis is associated with renal tubular damage and coagulation activity dysfunction [41].

In cardiac recipients, nephrotoxic calcineurin inhibitors and risks associated with the use of organs from extended criteria donors are added to all of the described factors contributing to the onset of renal injury.

AKI EPIDEMIOLOGY AND CLASSIFICATIONS

AKI is a common complication occurring in more than 50% of patients within the first week after admission in the intensive care unit (ICU) [42]. According to M. Ostermann and J. Cerda, AKI-related mortality in the acute period is 24% in adults and 14% in pediatric patients [43]. Thus, it is 7 times higher than mortality in the non-AKI group of patients. Consequences of AKI include the need for renal replacement therapy (RRT), chronic kidney damage in about 20% of patients, and reduced quality of life. The additional cost of treating 1 patient with AKI requiring RRT in the United States averages $42,077 [44]. According to B.J. Moore and C.M. Torio, AKI accounts for 8–16% of all hospital admissions in the United States, which is about 13 million patients annually. The duration of hospitalization with a secondary diagnosis of AKI almost tripled from 2005 to 2014 [45]. According to Kerr et al., hospitalizations in 2014 for AKI patients in the UK incurred a cost of $1.3 billion, which was more than 1% of the total NHS budget [46].

Data on the incidence of AKI varies widely. In the past, more than 30 definitions of acute renal failure could be found in the literature. The diagnosis of acute renal failure was based on urine output and urea and creatinine as markers of eGFR reduction. The criteria for assessing the degree of renal dysfunction varied considerably among different authors. All these necessitated the development of a generally accepted classification of acute renal failure. For this purpose, the Acute Dialysis Quality Initiative (ADQI) expert group was formed in 2003. In 2004, ADQI presented the RIFLE classification, in which 5 stages of renal damage impairment were identified – Risk, Injury, Failure, Loss, End-stage kidney disease [47].

In 2007, members of the Acute Kidney Injury Network (AKIN) working group coined the term AKI (Acute Kidney Injury) to define a wide range of acute renal dysfunction from the earliest and mildest forms to cases where replacement therapy is required. The term AKI is intended to express the reversible nature of kidney injury in most cases. AKIN proposed a modification of RIFLE, which drew attention to the minimal increase in blood creatinine levels in a shorter period of time [48]. Finally, in 2012, in the clinical guidelines for the treatment of AKI, KDIGO, in turn, proposed again to increase the time period for assessing the degree of renal injury and drew attention to the delayed increase in blood creatinine levels in relation to renal dysfunction [49]. According to the KDIGO (Kidney disease: Improving Global Outcomes) clinical guidelines, AKI is a sudden decrease in kidney function in a period not exceeding 7 days, and CKD is pathological changes in the renal structure or function that last more than 90 days [49]. AKI should be considered as a systemic disease with long-term pathological effects on the heart, lungs, central nervous system, and especially the kidneys. The time interval between the onset of AKI and the development of CKD has been suggested to be called acute kidney disease. This term defines the course of the disease after AKI in patients with ongoing pathophysiological processes in the kidney. The main AKI classifications are shown in Table.

The addition of urine output as a criterion increases the incidence of AKI compared to a situation where se-

rum creatinine alone is assessed [50, 51]. Xuying Luo et al. analyzed the data of 3,107 patients who were consecutively admitted at the ICU over a 6-month period [52].

AKI was determined according to the RIFLE, AKIN and KDIGO classifications. KDIGO was the most sensitive for AKI detection (KDIGO 51%, RIFLE 46.9%, AKIN 38.4%). Meanwhile, the major limitation of these classifications is the use of serum creatinine levels as a marker of renal function. It is known that creatinine concentration can be influenced by factors not associated with glomerular filtration, such as gender, age, race, body surface area, diet, intake of certain drugs, as well as diabetes and liver disease [49]. Besides, a change in serum creatinine levels does not allow to identify the localization of renal injury, tubular or glomerular. To increase creatinine levels in the blood, a loss of about 50% of renal function is required.

As a consequence, it is detected 24–72 hours later than the concentration of a number of new biomarkers of kidney injury. These limitations facilitate the research of new substances that allow not only to predict and diagnose AKI, but also to identify the localization, type and etiology of injury, predict outcomes, and determine when to start treatment and ensure that it is monitored.

The currently known biomarkers make it possible to assess renal function (cystatin C [53], galectin-3 [54], proenkephalin [55]), predict AKI progression (interleukin-18 (IL18) [56]), neutrophil gelatinase-associated lipocalin (NGAL) [57], microRNA [58]), determine renal injury (NGAL, hepatic form of fatty acid binding protein (L-FABP) [59], microRNA, IL18, kidney injury molecule-1 (KIM-1) [60]), detect cell cycle inhibition (tissue inhibitor of metalloproteinase-2 and protein-7, which binds insulin-like growth factor (TIMP-2 and IGFBP-7) [61]) and, finally, determine the nephrotoxic effect of drugs (N-acetyl-glucosaminidase, gamma-glutamyl transpeptidase, alanine aminopeptidase) [62]. Although the use of most of the new biomarkers of kidney injury is still under study, their introduction into broad clinical practice is inevitable in the future. L-FABP is approved for use in Japan, NGAL is present in the European guidelines, and the TIMP-2 + IGFBP-7 combination is FDA approved in the United States [63].

Meanwhile, Klein et al. conducted a meta-analysis of 63 studies of new biomarkers in order to explore the possibility of using them in determining the onset of RRT in AKI. Unambiguous results were not obtained [64]. Biomarkers, which, according to the analysis, seem useful for predicting the use of RRT, are actually markers of kidney stress, damage and decreased glomerular filtration rate. From a clinical point of view, a decision to initiate RRT is not based on the severity of kidney injury, but on the presence of metabolic, electrolyte and volumetric disorders in the patient, as well as concomitant pathological conditions.

ACUTE KIDNEY INJURY IN HEART RECIPIENTS

Heart transplantation remains the only true "cure" for end-stage heart failure. Since 1967, when K. Barnard first performed a successful heart transplant (HTx), the number of such operations has been steadily increasing. By June 30, 2018, over 146,975 heart transplantations were performed in patients of all ages worldwide. According to the register of the International Society for

Table

Comparison of acute kidney injury scales

RIFLE		AKIN		KDIGO		Amount of urine
Stage	SCr	Stage	SCr	Stage	SCr	
RISK	1.5-fold increase or decrease in GF by >25%	1	Increase ≥26.5 μmol/L or 1.5–2-fold increase of baseline	1	Increase by 1.5–1.9 times or by ≥26.5 μmol/L of the baseline	<0.5 mL/kg/hour for 6–12 hours
INJURY	2-fold increase or decrease in GF by >50%	2	Increase by >2–3 times of the baseline	2	Increase by 2–2.9 times of the baseline	<0.5 mL/kg/hour for ≥12 hours
FAILURE	3-fold increase or SCr >354 μmol/L with rapid increase >44 μmol/L or GF decrease >75%	3	Increase by >3 times of baseline or SCr ≥354 μmol/L with rapid increase ≥44 μmol/L or RRT initiation	3	Increase by 3.0 times of the baseline or SCr ≥354 μmol/L or RRT initiation, or a decrease in GF to <35 mL/min/1.73 m^2 in patients <18 years of age	<0.5 mL/kg/hour for 24 hours or anuria for ≥12 hours
LOSS	Complete absence of renal function for >4 weeks					
END-STAGE KIDNEY DISEASE	Complete absence of renal function for >3 months					

RIFLE and KDIGO assess changes in SCr levels within 7 days, AKIN within 48 hours.

Heart and Lung Transplantation 2019, the 1- and 5-year survival rates of heart recipients were 81% and 69%, respectively [65].

Kidney injury is one of the most serious complications in both the early and late postoperative period, directly affecting treatment outcomes. According to numerous authors, the development of AKI and CKD is associated with longer ICU and hospital stay, higher incidence of infectious complications, acute graft rejection, and, in general, higher mortality rate [66, 67]. According to the results of a meta-analysis of 27 cohort studies with data from 137,201 heart recipients, the average incidence of AKI was 47.1% (4.5%–72.3%), the need for RRT was 12% (2.1%–39.06%). The incidence of AKI and severe AKI requiring RRT has increased in recent years. AKI after heart transplantation was associated with increased short-term and 1-year mortality (3.5 and 2.3-fold, respectively). AKI and AKI requiring a RRT were unfavorable prognostic factors in heart transplantation and were associated with a 13-fold increase in the risk of death within 90 days after surgery. Despite advances in transplantology in recent years, the risk of in-hospital mortality (and/or mortality within 90 days after surgery) and mortality within 1 year after transplantation has not changed over the past 20 years. This situation is probably due to liberalization of HTx indications and the use of organs from extended criteria donors [66]. Other results were published by Zijlstra et al, who analyzed data from 580 heart recipients who received transplants in Rotterdam from 1984 to 2013. The patients were divided into groups A (1984–1999) and B (2000–2013). Despite a significantly higher number of older donors in group B compared to group A (mean age 43 versus 29 years, donors over 50 years old 33% versus 2%, respectively), long-term survival was higher among group B recipients (90%, 86%, 81% and 68% by 30 days, 1 year, 5 years and 10 years, respectively, against 93%, 89%, 78%, and 53% in the same period in group A). In heart recipients who survived within 1 year after surgery, the 10-year survival was significantly higher in group B than in group A (80% versus 60%, respectively, $p < 0.0001$). In particular, this decrease was associated with a reduced incidence of kidney injury (14% in group A versus 4% in group B). According to the authors, such outcomes were achieved thanks to the use of new immunosuppression protocols, early prescription of statins regardless of cholesterol levels, active treatment of arterial hypertension and preemptive myocardial revascularization of the graft [68]. Since there are still no effective targeted pharmacotherapeutic for AKI, prevention, and early identification of patients at risk of AKI can potentially play an important role in improving treatment outcomes. Risk factors for AKI in heart transplantation have been studied by many authors. Preoperative ones include preexisting renal dysfunction, diabetes mellitus, older age of both donor and recipient, previous heart transplantation; Intra- and postoperative ones include graft ischemic time, surgery and CPB, large blood loss and much blood transfusions, mechanical circulatory support, functional heart graft failure [69–71]. According to Wang et al., who retrospectively analyzed heart transplants at 8 UK centers from 1995 to 2017, there was a steady increase in RRT use in the 30-day postoperative period – from 12% in 1995–2000 to 47.7% in 2011–2017. More frequent use of RRT was associated with older age of donors, higher number of recipients with urgent status, and more frequent use of mechanical (intra-aortic balloon pump, extracorporeal life support, assisted circulation) and inotropic support. Statistical analysis revealed RRT predictors in the post-transplant period: male gender, the need for left ventricular bypass and inotropic support before transplantation, intraoperative kidney dysfunction, and development of severe graft dysfunction after surgery. The use of organs from older donors increased the risk of requiring RRT. Besides, repeated surgical interventions and infectious complications were significantly associated with the need for RRT. As for the survival of recipients in this study, this indicator in the group of recipients with a need for RRT was lower than in other recipients only within 3 months after surgery. This difference was particularly pronounced in the early post-transplant period (71.6% and 94.7%, respectively) [72]. Meanwhile, according to Boyle et al., in the group of heart recipients with AKI requiring RRT, in-hospital mortality was 50% versus 1.4% in the group of recipients without AKI [73]. Guven et al. reported that the need for RRT within 30 days after transplantation was associated with higher mortality at 1 year after surgery (22% versus 8% in the group of recipients who did not require RRT) [74]. In a study by Romeo et al., this indicator in the group of heart recipients who received RRT within a month after surgery was also significantly higher than in other recipients (59.2% versus 5.8%) [75]. In all these studies, AKI requiring RRT served as a unifying risk factor for high mortality, but a common factor was also right ventricular failure – graft dysfunction [73–75].

Heart transplant recipients represent a unique population of patients in whom all types of cardio-renal syndrome can be observed at different stages of the pathological process. Over the past two decades, studies conducted among patients with severe heart failure have shown that venous congestion is a major damaging mechanism leading to the onset and progression of renal dysfunction, along with decreased cardiac output. It also activates the renin-angiotensin-aldosterone system with further sodium and water retention, inflammation with production of pro-inflammatory cytokines, endothelial dysfunction, fibrosis activation, and increased intra-abdominal pressure. In the meantime, clear data on the effect of such a mechanism in donor heart recipients are fragmentary. For example, several publications report that right ventricular failure in the early postoperative period is combined with

a high incidence of AKI requiring RRT with increased mortality. Introduction of precision methods for assessing and correcting hydration and volemic status in patients awaiting HTx and in cardiac recipients, would most likely reduce AKI incidence and improve transplantation outcomes. However, this requires further study.

The authors declare no conflict of interest.

REFERENCES

1. *Dasta JF, Kane-Gill S.* Review of the Literature on the Costs Associated With Acute Kidney Injury. *J Pharm Pract*. 2019 Jun; 32 (3): 292–302. doi: 10.1177/0897190019852556.
2. *Ronco C, House AA, Haapio M.* Cardiorenal syndrome: refining the definition of a complex symbiosis gone wrong. *Intensive Care Med*. 2008; 34 (5): 957–962. doi: 10.1007/s00134-008-1017-8.
3. *Ronco C, Bellasi A, Di Lullo L.* Cardiorenal Syndrome: An Overview. *Adv Chronic Kidney Dis.* 2018; 25 (5): 382–390. doi: 10.1053/j.ackd.2018.08.004.
4. *Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J et al.* High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail.* 2007; 13: 422–430. doi: 10.1016/j.cardfail.2007.03.011.
5. *Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL.* Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol*. 2009; 53: 582–588. doi: 10.1016/j.jacc.2008.08.080.
6. *Damman K, Voors AA, Hillege HL, Navis G, Lechat P, van Veldhuisen DJ et al.* Congestion in chronic systolic heart failure is related to renal dysfunction and increased mortality. *Eur J Heart Fail.* 2010; 12: 974–982. doi: 10.1093/eurjhf/hfq118.
7. *Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M et al.* Cardiorenal interactions: insights from the ESCAPE trial. *J Am Coll Cardiol.* 2008; 51: 1268–1274. doi: 10.1016/j.jacc.2007.08.072.
8. *Hanberg JS, Sury K, Wilson FP, Brisco MA, Ahmad T, Ter Maaten JM et al.* Reduced Cardiac Index Is Not the Dominant Driver of Renal Dysfunction in Heart Failure. *J Am Coll Cardiol*. 2016; 67 (19): 2199–2208. doi: 10.1016/j.jacc.2016.02.058.
9. *Guglin M, Rivero A, Matar F, Garcia M.* Renal dysfunction in heart failure is due to congestion but not low output. *Clin Cardiol.* 2011; 34: 113–116. doi: 10.1002/clc.20831.
10. *Maeder MT, Holst DP, Kaye DM.* Tricuspid regurgitation contributes to renal dysfunction in patients with heart failure. *J Card Fail.* 2008; 14: 824–830.
11. *Priebe HJ, Heimann JC, Hedley-Whyte J.* Effects of renal and hepatic venous congestion on renal function in the presence of low and normal cardiac output in dogs. *Circ Res.* 1980; 47: 883–890. doi: 10.1161/01.res.47.6.883.
12. *Damman K, Navis G, Smilde TD, Voors AA, van der Bij W, van Veldhuisen DJ et al.* Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. *Eur J Heart Fail*. 2007; 9: 872–878. doi: 10.1016/j.ejheart.2007.05.010.
13. *Uthoff H, Breidthardt T, Klima T, Aschwanden M, Arenja N, Socrates T et al.* Central venous pressure and impaired renal function in patients with acute heart failure. *Eur J Heart Fail.* 2011; 13: 432–439. doi: 10.1093/eurjhf/hfq195.
14. *Blankstein R, Bakris GL.* Renal hemodynamic changes in heart failure. *Heart Fail Clin.* 2008; 4 (4): 411–423. doi: 10.1016/j.hfc.2008.03.006.
15. *Sambandam KK.* Effective use of loop diuretics in heart failure exacerbation: a nephrologist's view. *Am J Med Sci.* 2014; 347: 139–145. doi: 10.1097/MAJ.0b013e31828a2962.
16. *Ruggenenti P, Remuzzi G.* Worsening kidney function in decompensated heart failure: treat the heart, don't mind the kidney. *Eur Heart J.* 2011; 32: 2476–2478. doi: 10.1093/eurheartj/ehr242.
17. *Schrier RW.* Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? *J Am Coll Cardiol.* 2006; 47: 1–8. doi: 10.1016/j.jacc.2005.07.067.
18. *Guazzi M, Gatto P, Giusti G, Pizzamiglio F, Previtali I, Vignati C, Arena R.* Pathophysiology of cardiorenal syndrome in decompensated heart failure: role of lung-right heart-kidney interaction. *Int J Cardiol.* 2013; 169: 379–384. doi: 10.1016/j.ijcard.2013.09.014.
19. *Cheatham ML, White MW, Sagraves SG, Johnson JL, Block EF.* Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. *J Trauma.* 2000; 49: 621–626; discussion 626–627. doi: 10.1097/00005373-200010000-00008.
20. *Bloomfield GL, Blocher CR, Fakhry IF, Sica DA, Sugerman HJ.* Elevated intraabdominal pressure increases plasma renin activity and aldosterone levels. *J Trauma.* 1997; 42: 997–1004; discussion 1004–1005. doi: 10.1097/00005373-199706000-00002.
21. *Harman PK, Kron IL, McLachlan HD, Freedlender AE, Nolan SP.* Elevated intra-abdominal pressure and renal function. *Ann Surg*. 1982 Nov; 196 (5): 594–597. doi: 10.1097/00000658-198211000-00015.
22. *Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WHW, Mullens W.* Abdominal contributions to cardiorenal dysfunction in congestive heart failure. *J Am Coll Cardiol.* 2013; 62: 485–495. doi: 10.1016/j.jacc.2013.04.070.
23. *Sandek A, Rauchhaus M, Anker SD, von Haehling S.* The emerging role of the gut in chronic heart failure. *Curr Opin Clin Nutr Metab Care. 2008*; 11: 632–639. doi: 10.1097/MCO.0b013e32830a4c6e.
24. *Sandek A, Anker SD, von Haehling S.* The gut and intestinal bacteria in chronic heart failure. *Curr Drug Metab.* 2009; 10 (1): 22–28. doi: 10.2174/138920009787048374.
25. *Ross EA.* Congestive renal failure: the pathophysiology and treatment of renal venous hypertension. *J Card Fail.* 2012; 18: 930–938. doi: 10.1016/j.cardfail.2012.10.010.

26. *Colombo PC, Onat D, Harxhi A, Demmer RT, Hayashi Y, Jelic S et al.* Peripheral venous congestion causes inflammation, neurohormonal, and endothelial cell activation. *Eur Heart J.* 2014; 35: 448–454. doi: 10.1093/eurheartj/eht456.
27. *Iwata K, Matsuno K, Murata A, Zhu K, Fukui H, Ikuta K et al.* Up-regulation of NOX1/NADPH oxidase following drug-induced myocardial injury promotes cardiac dysfunction and fibrosis. *Free Radic Biol Med.* 2018; 120: 277–288. doi.org/10.1016/j.freeradbiomed.2018.03.053.
28. *Afsar B, Ortiz A, Covic A, Solak Y, Goldsmith D, Kanbay M.* Focus on renal congestion in heart failure. *Clin Kidney J*. 2016; 9 (1): 39–47. doi: 10.1093/ckj/sfv124.
29. *Rockey DC, Bell PD, Hill JA.* Fibrosis: a common pathway to organ injury and failure. *N Engl J Med.* 2015; 372: 1138–1149. doi: 10.1056/NEJMra1300575.
30. *Travers JG, Kamal FA, Robbins J, Yutzey KE, Blaxall BC.* Cardiac fibrosis: the fibroblast awakens. *Circ Res*. 2016; 118: 1021–1040. doi: 10.1161/CIRCRESAHA.115.306565.
31. *Calvier L, Martinez-Martinez E, Miana M, Cachofeiro V, Rousseau E, Sádaba JR et al*. The impact of galectin-3 inhibition on aldosterone-induced cardiac and renal injuries. *JACC Heart Fail*. 2015; 3: 59–67. doi: 10.1016/j.jchf.2014.08.002.
32. *Lattenist L, Lechner SM, Messaoudi S, Le Mercier A, El Moghrabi S, Prince S et al*. Nonsteroidal mineralocorticoid receptor antagonist finerenone protects against acute kidney injury-mediated chronic kidney disease: role of oxidative stress. *Hypertension*. 2017; 69: 870–878. doi: 10.1161/HYPERTENSIONAHA.116.08526.
33. *Segev DL, Muzaale AD, Caffo BS, Mehta SH, Singer AL, Taranto SE et al*. Perioperative mortality and long-term survival following live kidney donation. *JAMA*. 2010; 303: 959–966. doi: 10.1001/jama.2010.237.
34. *Mjøen G, Hallan S, Hartmann A, Foss A, Midtvedt K, Øyen O et al.* Long-term risks for kidney donors. *Kidney Int*. 2014; 86: 162–167. doi: 10.1038/ki.2013.460.
35. *Moody WE, Ferro CJ, Edwards NC, Chue CD, Lin EL, Taylor RJ et al*. CRIB-Donor Study Investigators. Cardiovascular effects of unilateral nephrectomy in living kidney donors. *Hypertension*. 2016; 67: 368–377. doi: 10.1161/HYPERTENSIONAHA.115.06608.
36. *Paoletti E, Bellino D, Signori A, Pieracci L, Marsano L, Russo R et al.* Regression of asymptomatic cardiomyopathy and clinical outcome of renal transplant recipients: a long-term prospective cohort study. *Nephrol Dial Transplant.* 2016; 31: 1168–1174. doi: 10.1093/ndt/gfv354.
37. *Shevchenko OP, Ulybysheva AA, Gichkun OE, Mozheiko NP, Stakhanova EA, Kvan VS, Shevchenko AO*. Galectin-3 in heart transplant rejection and fibrosis. *Russian Journal of Transplantology and Artificial Organs*. 2019; 21 (3): 62–68. doi: 10.15825/1995-1191-2019-3-62-68.
38. *Tarjus A, Martínez-Martínez E, Amador C, Latouche C, El Moghrabi S, Berger T et al*. Neutrophil gelatinase-associated lipocalin, a novel mineralocorticoid biotarget, mediates vascular profibrotic effects of mineralocorticoids. *Hypertension.* 2015; 66: 158–166. doi: 10.1161/HYPERTENSIONAHA.115.05431.
39. *Martínez-Martínez E, Cachofeiro V, Rousseau E, Álvarez V, Calvier L, Fernández-Celis A et al.* Interleukin-33/ST2 system attenuates aldosterone-induced adipogenesis and inflammation. *Mol Cell Endocrinol.* 2015; 411: 20–27. doi: 10.1016/j.mce.2015.04.007.
40. *López-Andrés N, Rousseau A, Akhtar R, Calvier L, Iñigo C, Labat C et al.* Cardiotrophin 1 is involved in cardiac, vascular, and renal fibrosis and dysfunction. *Hypertension.* 2012; 60: 563–573. doi: 10.1161/HYPERTENSIONAHA.112.194407.
41. *Vives M, Hernandez A, Parramon F, Estanyol N, Pardina B, Muñoz A et al.* Acute kidney injury after cardiac surgery: prevalence, impact and management challenges. *Int J Nephrol Renovasc Dis.* 2019; 12: 153–166. doi: 10.2147/IJNRD.S167477.
42. *Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM et al.* Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol*. 2017; 13 (4): 241–257. doi: 10.1038/nrneph.2017.2.
43. *Ostermann M, Cerda J*. The burden of acute kidney injury and related financial issues. In: Ding X, Rosner MH, Ronco C, eds. Acute Kidney Injury – Basic Research and Clinical Practice. Basel, Switzerland: Contrib Nephrol, Karger; 2018: 100–112.
44. *Hoste EAJ, Kellum JA, Selby NM, Zarbock A, Palevsky PM, Bagshaw SM et al.* Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol*. 2018; 14 (10): 607–625. doi: 10.1038/s41581-018-0052-0.
45. *Moore BJ* (IBM Watson Health), *Torio CM* (AHRQ). Acute Renal Failure Hospitalizations, 2005–2014. HCUP Statistical Brief #231. Rockville, MD: Agency for Healthcare Research and Quality; 2017. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb231-Acute-Renal-Failure-Hospitalizations.jsp.
46. *Kerr M, Bedford M, Matthews B, O'Donoghue D.* The economic impact of acute kidney injury in England. *Nephrol Dial Transplant.* 2014; 29 (7): 1362–1368. doi: 10.1093/ndt/gfu016.
47. *Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettila V.* Acute renal failure after cardiac surgery: evaluation of the RIFLE classification. *Ann Thorac Surg.* 2006; 81: 542–546.
48. *Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A.* Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care.* 2007; 11: R31. doi: 10.1186/cc5713.
49. Kidney disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Inter Suppl*. 2012; 2: 1–138. doi: 10.1038/kisup.2012.1.
50. *Kellum JA, Sileanu FE, Murugan R, Lucko N, Shaw AD, Clermont G.* Classifying AKI by urine output versus serum creatinine level. *J Am Soc Nephrol.* 2015; 26 (9): 2231–2238.
51. *Salgado G, Landa M, Masevicius D, Gianassi S, San-Román JE, Silva L et al*. Acute renal failure according to the RIFLE and AKIN criteria: a multicenter study. *Med Intensiva.* 2014; 38 (5): 271–277. doi: 10.1016/j.medin.2013.04.007.

52. *Luo X, Jiang L, Du B, Wen Y, Wang M, Xi X.* Beijing Acute Kidney Injury Trial (BAKIT) workgroup. A comparison of different diagnostic criteria of acute kidney injury in critically ill patients. *Critical Care.* 2014; 18: R144. doi: 10.1186/cc13977.
53. *Yong Z, Pei X, Zhu B, Yuan H, Zhao W.* Predictive value of serum cystatin C for acute kidney injury in adults: a meta-analysis of prospective cohort trials. *Sci Rep.* 2017; 7: 41012. doi: 10.1038/srep41012.
54. *Shevchenko OP, Ulybysheva AA, Mozheiko NP, Gichkun OE, Stakhanova EA, Vasilieva VP, Shevchenko AO.* Diagnostic value of galectin-3 in heart transplant recipients with myocardial complications. *Russian Journal of Transplantology and Artificial Organs*. 2020; 22 (1): 8–15. doi: 10.15825/1995-1191-2020-1-8-15.
55. *Schulz C-A, Christensson A, Ericson U, Almgren P, Hindy G, Nilsson PM et al.* High level of fasting plasma proenkephalin-a predicts deterioration of kidney function and incidence of CKD. *J Am Soc Nephrol.* 2017; 28: 291–303. doi: 10.1681/ASN.2015101177.
56. *Lin X, Yuan J, Zhao Y, Zha Y.* Urine interleukin-18 in prediction of acute kidney injury: a systemic review and meta-analysis. *J Nephrol.* 2015; 28: 7–16. doi: 10.1007/s40620-014-0113-9.
57. *Hošková L, Franekova J, Málek I, Kautzner J, Szárszoi O, Jabor A et al*. Comparison of Cystatin C and NGAL in Early Diagnosis of Acute Kidney Injury After Heart Transplantation. *Ann Transplant*. 2016; 21: 329–245. doi: 10.12659/aot.896700.
58. *Velikiy DA, Gichkun OE, Shevchenko OP.* MicroRNAs in heart transplant recipients. *Russian Journal of Transplantology and Artificial Organs.* 2017; 19 (2): 126–132. (In Russ.) https://doi.org/10.15825/1995-1191-2017-2-126-132.
59. *Parr SK, Clark AJ, Bian A, Shintani AK, Wickersham NE, Ware LB. et. al.* Urinary L-FABP predicts poor outcomes in critically ill patients with early acute kidney injury. *Kidney Int.* 2015; 87: 640–648. doi: 10.1038/ki.2014.301.
60. *Bonventre JV.* Kidney injury molecule-1 (KIM-1): a urinary biomarker and much more. *Nephrol Dial Transpl.* 2009; 24: 3265–3268. doi: 10.1093/ndt/gfp010.
61. *Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M et al.* Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care.* 2013; 17: R25. doi: 10.1186/cc12503.
62. *Teo SH, Zoltán, Endre ZH.* Biomarkers in acute kidney injury (AKI). *Best Pract Res Clin Anaesthesiol.* 2017; 31 (3): 331–344. doi: 10.1016/j.bpa.2017.10.003.
63. *Pickering JW, Endre ZH.* Bench to bedside: the next steps for biomarkers in acute kidney injury. *Am J Physiol – Ren Physiol.* 2016; 311: F717–721. doi: 10.1152/ajprenal.00268.2016.
64. *Klein SJ, Brandtner AK, Lehner GF, Ulmer H, Bagshaw SM, Wiedermann CJ, Joannidis M.* Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. *Intensive Care Med.* 2018; 44: 323–336. doi: 10.1007/s00134-018-5126-8.
65. *Khush KK, Cherikh WS, Chambers DC, Harhay MO, Hayes D Jr, Hsich E et al.* The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report – 2019; focus theme: Donor and recipient size match. *J Heart Lung Transplant*. 2019; 38 (10): 1056–1066. doi: 10.1016/j.healun.2019.08.004.
66. *Thongprayoon C, Lertjitbanjong P, Hansrivijit P, Crisafio A, Mao M, Watthanasuntorn K et al*. Acute Kidney Injury in Patients Undergoing Cardiac Transplantation: A Meta-Analysis. *Medicines (Basel)*. 2019; 6 (4): 108. doi: 10.3390/medicines6040108.
67. *Goltz AM, Zakharevich VM.* Retransplantatsiya serdtsa. *Transplantologiya: itogi i perspektivy*. Pod red. S.V. Gautier. M.–Tver': Triada, 2019: 271–290.
68. *Zijlstra LE, Constantinescu AA, Manintveld O, Birim O, Hesselink DA, van Thiel R et al*. Improved long-term survival in Dutch heart transplant patients despite increasing donor age: the Rotterdam experience. *Transpl Int*. 2015; 28: 962–971. doi: 10.1111/tri.12503.
69. *Tjahjono R, Connellan M, Granger E.* Predictors of Acute Kidney Injury in Cardiac Transplantation. *Transplant Proc*. 2016; 48 (1): 167–172. doi: 10.1016/j.transproceed.2015.12.006.
70. *García-Gigorro R, Renes-Carreño E, Peiretti MAC, López PA, Vela JLP, Rodríguez JG et al.* Incidence, Risk Factors and Outcomes of Early Acute Kidney Injury After Heart Transplantation: An 18-year Experience. *Transplantation*. 2018; 102 (11): 1901–1908. doi: 10.1097/TP.0000000000002293.
71. *Wang T-J, Lin C-H, Wei H-J, Wu M-J.* Long-Term Outcomes and Risk Factors of Renal Failure Requiring Dialysis after Heart Transplantation: A Nationwide Cohort Study. *J Clin Med*. 2020, 9 (8), 2455; https://doi.org/10.3390/jcm9082455.
72. *Wang L, Wang T, Rushton SN, Parry G, Dark JH, Sheerin NS.* The impact of severe acute kidney injury requiring renal replacement therapy on survival and renal function of heart transplant recipients – a UK cohort study. *Transpl Int*. 2020 Jun 16. doi: 10.1111/tri.13675.
73. *Boyle JM, Moualla S, Arrigain S, Worley S, Bakri MH, Starling RC et al*. Risks and outcomes of acute kidney injury requiring dialysis after cardiac transplantation. *Am J Kidney Dis.* 2006; 48 (5): 787–796. doi: 10.1053/j.ajkd.2006.08.002.
74. *Guven G, Brankovic M, Constantinescu AA, Brugts JJ, Hesselink DA.* Preoperative right heart hemodynamics predict postoperative acute kidney injury after heart transplantation. *Intensive Care Med*. 2018; 44: 588–597. doi: 10.1007/s00134-018-5159-z.
75. *Romeo FJ, Varela CF, Vulcano N, Pizarro R, Greloni G, Posatini R et al*. Acute Kidney Injury After Cardiac Transplantation: Foe or Common Innocent Bystander? *Transplant Proc*. 2018; 50 (5): 1489–1495. doi: 10.1016/j.transproceed.2018.03.106.

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