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RENAL REPLACEMENT THERAPY IN HEART TRANSPLANT RECIPIENTS

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Kidney injury in cardiac transplant recipients is one of the most severe complications affecting both short- and long-term transplant outcomes. The need for renal replacement therapy (RRT) is determined not only and not so much by the degree of renal dysfunction, as by the need for correction of fluid balance and metabolic disorders. These circumstances are associated with the specificity of extracorporeal renal replacement therapy in donor heart recipients. In this review, we discuss the problems of early versus delayed initiation of RRT, anticoagulation and vascular access, advantages and disadvantages of continuous and intermittent techniques. Special attention is paid to chronic kidney injury and peculiarities of kidney transplantation in heart recipients.

Keywords: heart transplantation, acute kidney injury, hemodialysis, kidney transplant after heart transplant.

Heart transplantation (HTx) is currently the most effective treatment for end-stage heart failure. Acute kidney injury (AKI), whose incidence has been increasing in recent years due to liberalization of indications for HTx and the use of organs obtained from expanded criteria donors, is one of the major complications prolonging hospital stay and worsening the prognosis in heart transplant recipients. According to some transplant centers, the need for renal replacement therapy (RRT) reaches 40%. However, the literature data concerning specific problems of RRT use in heart recipients are few, and considering issues, such as optimal timing of RRT initiation, comparison of efficiency of permanent and intermittent techniques, anticoagulation regimens, choice of optimal vascular access and others, we have to focus on the results of studies evaluating RRT use in intensive care units (ICU).

RRT IN CRITICALLY ILL PATIENTS

Timing of RRT initiation: early vs delayed initiation

Despite the significant increase in the frequency of RRT use in AKI or multiple organ failure in ICU, many aspects of such treatment remain a subject of debate. This applies particularly to the timing of RRT initiation. Early initiation allows to manage fluid balance and rapidly correct electrolyte and metabolic disorders. At the same time, RRT itself can cause a number of complications, particularly hemodynamic, metabolic, and hemorrhagic disorders, catheter-associated infection (CAI), unwanted removal of drugs and their metabolites [1]. To date, a large number of studies have been published in favor of both early and late initiation of RRT in AKI [2–6].

Of the randomized clinical trials (RCTs) that found statistically significant improvements in survival and renal function recovery with early vs. late initiation of RRT, ELAIN (Early vs LAte INitiation of RRT) was the most telling. This single-center trial enrolled 231 patients with AKI after surgery. In the early initiation group, RRT was initiated within 8 hours of diagnosis of KDIGO (AKI Kidney Disease: Improving Global Outcomes) stage 2; in the delayed initiation group, within 12 hours of stage 3 AKI or when absolute indications for RRT arose, which included blood urea elevations greater than 100 mg/dL (16.65 mmol/L), hyperkalemia above 6.0 mEq/L, and edema resistant to diuretic therapy. Mortality was significantly lower in the first group than in the second (39.3% vs. 54.7%, p = 0.03). Of the 119 patients randomized to the delayed-initiation group, 11 did not receive RRT due to restoration of renal function [2].

At the same time, multicenter RCT AKIKI (Artificial Kidney Initiation in Kidney Injury) showed no statistically significant differences in patient survival in the early and delayed RRT initiation groups. The study included 620 patients with AKI from 31 ICUs, which were divided into 2 equal groups. In the delayed-initiation group, RRT initiation criteria were oligo or anuria for more than 72 hours, blood urea concentration greater than 40 mmol/L, hyperkalemia greater than 6.0 mmol/L or 5.5 mmol/L after glucose solution infusion with insulin; a pH below 7.15 and acute pulmonary edema due to fluid overload. Sixty-day survival did not differ between the groups; half of those patients who were assigned a

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delayed strategy did not receive RRT. The mortality rate in both groups was nearly 50%. CAI was less common in the delayed strategy group, which can be attributed to the shorter duration of RRT. The authors conclude that the delayed strategy avoided RRT in a significant number of patients [3].

Most studies have used the AKI KDIGO stages as criteria for patient selection. In practice, however, these criteria are rarely the only basis for initiating RRT, with most AKI patients with KDIGO stage 3 not receiving RRT [7]. Some authors, comparing outcomes among patients with AKI depending on whether they received RRT or not, demonstrate a better survival rate associated with the absence of RRT [8]. For objective results, it is necessary to form beforehand groups of patients for early and delayed initiation of RRT. However, for the patients included in the group of delayed initiation, there is a risk not to receive RRT as a result of an unfavorable outcome. A recent meta-analysis of RCTs, devoted to the timing of RRT initiation in severe AKI, taking into account individual data of patients, has not revealed dependence of mortality on timing of initiation of RRT, provided that delayed initiation of RRT is carried out at close observation of patients and RRT is initiated at occurrence of appropriate clinical indications [9].

Vascular access for RRT

It is advisable to use ultrasound guidance when implanting the RRT central venous catheter (CVC) in an ICU setting. According to results of a meta-analysis by Rabindranath et al., implantation of RRT catheters in the jugular vein allows to avoid installation defects in the vast majority of cases, reduce manipulation time and significantly reduce the complication rate [10]. According to Prabhu et al., this tactic also provides better results for femoral access [11]. According to clinical guidelines [12, 13], placing temporary catheters into subclavian veins should be avoided to avoid stenosis and to preserve the possibility to implant permanent CVC in the event of chronic renal injury. According to a multicenter RCT conducted by Parienti et al., subclavian vein catheterization is associated with a lower risk of CAI and thrombotic complications and a higher incidence of pneumothorax compared with jugular or femoral catheter localization [14].

Another multicenter RCT indicates that with respect to catheter dysfunction or RRT effectiveness, there were no differences for catheter localization in the internal jugular vein and femoral vein. Catheters located in the right internal jugular vein were associated with a significantly lower incidence of dysfunction compared with the left internal jugular vein. While the same 16 cm jugular catheters were used in both positions, the right position provided the shortest route to the superior vena cava. Femoral access was associated with a significantly lower risk of catheter dysfunction compared with the left jugular access. It was recommended for use when there was no possibility to insert the catheter into the right jugular vein and when the patient's body mass index was less than 28.4. This approach allowed to reduce the incidence of catheter dysfunction without increasing the risk of CAI. For optimal RRT efficiency in case of femoral access, it was recommended to use catheters 25 cm long reaching the inferior vena cava. If it is necessary to continue RRT for a long time, the use of tunneled jugular catheters is considered to be preferable [15].

According to Coupez et al., the incidence of dysfunction in catheter replacement by guidewire is significantly higher than that in new catheter placement (37.6% vs. 15.7%, $p < 0.01$), with the risk of infection not significantly different [16]. Chua et al. report similar results, noting that the risk of catheter infection is higher in older and more massive patients, especially in the femoral position [17]. Heparin lock is traditionally used to maintain catheter patency; citrate-based solutions in various concentrations, antibiotics or other drugs with antibacterial properties are used less frequently. Sungur et al. report that "leakage" of catheter-filling solution into the vascular channel can reach 20% and depends on catheter design. This amount may be clinically significant in increasing the risk of bleeding and antibiotic toxicity [18]. According to reports by Correa Barcellos et al., the use of citrate-based solutions does not reduce the risks of infection and dysfunction [19]. Landry et al. indicate that the use of antibacterial solutions as a lock reduces the risk of infection but may contribute to the development of bacterial resistance and should be considered in cases with a high probability of CAI [20]. Since the risk of catheter infection directly correlates with the duration of its stay in the vessel, the need for continued RRT should be assessed daily, and if there is no need, the catheter should be removed [12, 13].

RRT techniques, continuous and intermittent

A number of techniques are used for RRT in an ICU setting, namely intermittent hemodialysis, sustained low-efficiency dialysis (SLED), extended daily dialysis, prolonged intermittent renal replacement therapy (IRRT), and continuous renal replacement therapy (CRRT) techniques (hemofiltration, hemodiafiltration). CRRT and IRRT methods are usually considered to be complementary; neither of them has obvious advantages over the other [21, 22]. As a rule, the choice of the optimum method is made at a certain stage of treatment in the given patient, and also in view of traditions and possibilities of ICU. According to the literature, CRRT and IRRT can achieve correction of metabolic and water-electrolyte disorders. At the same time, the studies did not reveal the advantages of any method in terms of improving patient survival [21–23]. Schneider et al. performed a

meta-analysis of 23 studies (7 randomized and 16 observational studies) to identify the preferred method of treatment. A pooled analysis of the observational studies showed a higher incidence of dialysis dependence among surviving patients initially treated with IRRT compared to CRRT. However, analysis of the results of randomized trials did not confirm these findings [24]. Wald et al. reported that in critical patients with AKI, the use of CRRT, compared to IRRT, was associated with a lower likelihood of chronic dialysis [25]. In contrast, in a retrospective study using data from 1,338 patients receiving RRT at the University of Pittsburgh Medical Center ICU, Liang et al. reported no statistically significant differences in risks of or causes for non-recovery of renal function (death or esCRF) after 90 and 365 days from treatment initiation with IRRT versus CRRT methods [23]. However, in a retrospective study, it can be difficult to determine why a given patient was started on CRRT or IRRT. For example, CRRT to control volemia was initiated in patients with expected hemodynamic instability, and IRRT was initiated in patients with low-dose vasopressors due to electrolyte disturbances without the need for high volume UV. Nash et al. performed a meta-analysis of 21 randomized clinical trials comparing different RRT methods used to treat AKI patients in ICU. The authors found no statistically significant differences in 30-, 90-day, 2-year survival, and the occurrence of dialysis dependence in patients initially treated with CRRT, IRRT, and SLED [26]. The use of different RRT methods in one patient during treatment depending on clinical indications is a common practice, which is one of the main limitations of such analysis. According to KDIGO clinical practice guidelines, "no RRT is ideal for all patients with AKI. Clinicians should be aware of the pros and cons of different RRTs, and tailor RRT on the basis of the individual and potentially changing needs of their patients" [12].

Efficacy of RRT methods

The efficacy of IRRT is traditionally calculated on the basis of urea kinetics. Fractional clearance of urea for 1 procedure is expressed as Kt/V index, which should reach 1.2–1.4, and the number of sessions to 3–7 times a week [27]. In CRRT, due to the high screening ratio for low molecular weight compounds, almost equal to one, the volume purified from substances such as urea is approximately equal to the ultrafiltration volume for CVVH, and also includes the dialysate volume for CVVHD and CVVHDF. The recommended replacement volume for post-dilution is 20–40 ml/hr/kg patient weight [27, 28] and should provide correction of metabolic, electrolyte and acid-base disorders [29]. The adequacy of RRT is not limited to effective elimination of uremic compounds. Treatment should also provide adequate correction of metabolic, electrolyte and acid-base disorders, as well as water balance. According to Sutherland et al. and Teixeira et al., an increase in fluid accumulation of more than 10–20% from ICU admission to RRT is significantly associated with increased risk of death [30, 31]. The main task is to maintain a neutral fluid balance, and in case of hyperhydration, to achieve gradual removal of excess fluid, avoiding related complications [31–33]. Tolerability of ultrafiltration depends on the rate of intravascular volume replenishment from interstitial space. Devices based on non-invasive hematocrit control are effective for UV management to optimize vascular replenishment [33].

Anticoagulation in RRT

Two main methods of anticoagulation are used to prevent extracorporeal thrombosis – systemic administration of unfractionated or low molecular weight heparin and regional citrate anticoagulation (RCA) [34]. According to a meta-analysis of 11 RCTs performed by Bai et al. in CRRT, RCA significantly reduced the risk of extracorporeal thrombosis compared to regional and systemic heparinization. The RCA group had a significantly lower bleeding risk than the systemic heparin group and a similar bleeding risk to the regional heparin group. No significant survival difference was observed between the groups [35].

At the same time, a number of complications can be associated with the use of RCA, in particular calcium loss and citrate accumulation. The calcium citrate complex has a molecular weight of about 300 Da and easily passes through the dialysis membrane. To maintain a neutral calcium balance, calcium must be administered throughout the procedure. When blood calcium levels fall, parathyroid hormone (PTH) levels rise rapidly, mobilizing calcium from bone tissue. According to Klingele et al., such bone demineralization can lead to fractures during prolonged RRT [36]. When citrate metabolism in the liver is impaired, it accumulates in the blood, ionized calcium is not released from the citrate-calcium complex, and the Ca/Ca^{++} ratio exceeds 2.5. Due to citrate accumulation, bicarbonate concentration decreases, and metabolic acidosis develops. In a retrospective study by Khadzhynov et al., 32 patients out of 1070 (2.99%) who received CRRT with RCA had metabolic signs of citrate accumulation against a background of marked hyperlactatemia. Although this complication occurred in a small number of patients, it was associated with 100% mortality [37]. Thus, in patients with metabolic disorders, RCA requires careful laboratory monitoring.

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The choice of an RRT technique usually depends on the patient's hemodynamic status. Convection-based CRRT techniques avoid rapid changes in blood osmolarity and homeostasis indices, as well as occurrence of

disequilibrium syndrome. Prolonged procedure helps to distribute the necessary volume of UV over a long period of time, thus reducing the intensity of fluid removal and improving hemodynamic tolerance. Continuous methods are used for hemodynamic instability, intermittent methods replace them when the patient's condition stabilizes [38]. This approach corresponds to KDIGO guidelines [12].

Most publications on AKI in cardiac recipients have little or no description of the RRT techniques used [39–43].

The recently published results of a retrospective observational study by Shen et al. provide a detailed description of the approach to RRT in cardiac recipients at Shanghai Zhongshan Hospital [44]. In the process of data analysis, the recipients were divided into 2 groups. In the early targeted RRT group, the indications for RRT were changed from traditional to anticipatory. In group 2 patients, the onset of RRT was determined by traditional indications. There was an agreement between cardiovascular surgeons, intensive care specialists and nephrologists to determine the early onset of RRT. Early initiation of RRT after orthotopic heart transplant often occurred in the absence of traditional indications, such as accumulated fluid overload ≥5%, persistent low cardiac output, high central venous pressure (CVP), arterial hypotension requiring high doses of inotropic support, and initiation of ECMO. Targeted RRT included hemodialysis, hemofiltration, hemodiafiltration, and isolated UV. Target was established by the time RRT was initiated and assessed every 6 hours. The technique, dose, duration, and frequency of RRT sessions were determined according to the patient's need and tolerability to achieve the target. The targeted RRT protocol included the following parameters.

1. RRT method. Hemodialysis was used in the presence of hyperkalemia, metabolic acidosis and persistent azotemia. Hemofiltration or hemodiafiltration was used in the presence of marked signs of inflammation. If the patient had no metabolic and electrolyte disturbances, isolated UV was used.
2. Duration. If the patient was hemodynamically stable and the goal could be achieved within a day, IRRT or extended IRRT was used. If the target could not be achieved during the day, continuous methods were used.
3. Intensity. Intensity depended on the needs for fluid removal, detoxification and hemodynamic stability.

All procedures were performed on IRRT devices, highly permeable polysulfone membranes with 25–30 ml/hr/kg replacement volume and 150–250 ml/min blood flow. Anticoagulation was performed mainly by low heparin doses. When analyzing the data, the authors obtained the following results. After 72 hours from initiation of treatment, the amount of urine and renal perfusion pressure were significantly higher in Group 1 patients, while creatinine and blood lactate levels, degree of fluid overload, CVP and vasoactive drug doses were significantly lower than those in Group 2 patients. In-hospital mortality (39.1% versus 63.3%, $p = 0.039$), ICU length of stay (26 ± 18 versus 38 ± 20 days; $p = 0.008$), and hospitalization (38 ± 33 versus 64 ± 45; $p = 0.005$) were significantly lower in the early- versus late-RRT group. At the same time, the cost of RRT in group 1 patients was significantly lower than in group 2 (0.54 ± 0.10 vs. 0.63 ± 0.11 \$10,000, $p < 0.001$).

Such an approach to RRT seems to be the most appropriate, as it allows not only to optimally use the capabilities of each technique, but also to maximally adapt them to the specific clinical situation.

Chronicity of renal injury in heart recipients

According to the International Society for Heart and Lung Transplantation registry, the incidence of chronic kidney disease (CKD) in heart recipients reaches 50% by 5 years after surgery, and by the 10-year milestone, 6% of patients need RRT, including 3.7% who become kidney recipients [45]. Despite the fact that AKI is a frequent complication and a probable risk factor for chronic renal damage and mortality after non-transplant cardiovascular surgery, reports on short-term and long-term consequences of renal dysfunction after heart transplantation are quite controversial. For instance, according to some authors, the development of AKI in the early period after HTx was not a predictor of esCRF development in the long term [45–47]. Jokinen et al. even showed an improvement in renal function in heart recipients who required RRT in the early postoperative period by the end of year 1 after transplantation [48]. At the same time, according to Ivey-Miranda et al., the need for RRT in the early postoperative period was a predictor of worse long-term survival in heart recipients [46].

Garcia-Gigorro et al. report a trend toward worse survival by 10 years after HTx, which, however, did not reach statistical significance [40]. Other authors suggest that cardiac recipients who required RRT in the early postoperative period and survived within the first 3 months after transplantation did not have a worse prognosis for long-term survival compared to other recipients [47, 49]. At the same time, according to Wang et al. and Fortrie et al., the need for RRT in the early post-HTx period was an independent predictor of esCRF in the long term [42, 50]. However, Fortrie et al. report significantly worse long-term survival in recipients who required RRT early after HTx [50]. In contrast, the results obtained by Wang et al. suggest that recipients who survived within the first 3 months after surgery had no higher risk of death compared to other recipients [42].

One possible explanation for these contradictions is the different approaches to conducting RRT. For example, preventive initiation of RRT and the use of the

most modern techniques are likely to contribute to better outcomes and, consequently, a better long-term prognosis. However, further research is needed to obtain reliable results.

Kidney transplantation to heart recipients

In heart recipients, the risk of developing CKD increases every year after transplantation. Some degree of renal impairment occurs in about half of heart recipients by 5 years postoperatively [51]. End-stage renal failure requiring RRT develops in 5% of patients by 5 years and in up to 12% by 10 years after transplantation [52]. Kidney transplantation significantly improves survival and quality of life in this category of patients.

Between 1995 and 2008, the number of heart recipients on the waiting list for subsequent kidney transplantation increased by 307%. During the same period, the number of primary patients with end-stage CKD on the donor kidney waiting list increased by only 74%, and the number of kidney recipients waiting for retransplantation increased by 70% [53]. According to Cassuto et al., the relative risk of death for heart recipients after kidney transplantation was significantly lower than for heart recipients on the waiting list (HR = 0.73, CI = 0.58–0.93, p = 0.011). At the same time, delisting of heart recipients due to death or deterioration was 15.8% annually for pre-dialysis CKD patients and 20.3% for dialysis patients [54]. Such data suggest the benefit of earlier kidney transplantation in heart recipients with renal failure.

According to Grupper et al., the median long-term survival of heart recipients with stage 5 CKD after renal transplantation was not significantly different from that of heart recipients without renal failure (17.5 versus 17.1 years, p = 0.27) and was significantly higher than that of heart recipients who remained on dialysis (17.5 versus 7.3 years, p < 0.001) [55]. The study by Roest et al. shows similar results. Kidney transplantation contributed to better survival of heart recipients with esCRF compared with those who remained on dialysis and with those who received conservative therapy (median 6.4 years, 2.2 years, and 0.3 years, respectively, p < 0.0001). Significantly better survival was observed in those who received a kidney from a living donor compared with a deceased donor and in those who received a kidney from a related donor compared with an unrelated donor (p = 0.02) [56].

A separate group is represented by patients suffering from a combination of end-stage renal insufficiency and end-stage renal failure who require simultaneous heart and kidney transplant (SHKTx). According to a number of studies, heart and kidney recipients have a lower rate of rejection of both cardiac and renal transplants compared with heart or kidney recipients alone [57, 58]. According to Hermsen et al. data, the time that elapsed before the development of the first cardiac transplant rejection crisis was significantly longer in heart and kidney transplant recipients than in heart recipients only (p = 0.011). A similar trend, though not reaching statistical significance, was observed in heart-kidney transplantation compared to kidney transplantation from living donors. The authors also found a lower incidence of cardiac allograft vasculopathy in SHKTx than in HTx [59]. Lower incidence and severity of rejection crises, as well as greater efficacy in controlling these crises, has been noted in heart-lung transplantation compared with lung transplantation; in simultaneous liver and kidney transplantation [60] compared with liver or kidney transplantation alone [61]. To date, the mechanisms of such immune tolerance remain unclear, but there are several possible explanations for this phenomenon. They are suppression of the immune response associated with chimerism of hematopoietic cells of the donor [62]; a state of anergy resulting from implantation of a large mass of foreign tissue into the recipient's body, as well as "diversion of the immune response" towards another transplanted organ [63].

In the case of SHKTx, there are simultaneous and staged heart and kidney transplants. In this case, organs from the same donor are used. In simultaneous transplantation, both operations are performed simultaneously. In the staged method, after heart transplantation, the patient is sent to the intensive care unit for a period usually not exceeding 24 hours, and after hemodynamic stabilization, the patient returns to the operating room for kidney transplantation [63]. In some cases, subsequent kidney to heart recipient transplantation (SKTx) is used, with considerably longer time between heart and kidney transplantation. To date, there are no recommendations as to when a single-stage or a staged technique should be used. Despite the increased duration of cold ischemia for the renal graft, many authors have advocated two consecutive operations [64, 66]. In this case, having a recovery period for the new transplanted heart allows to optimize the hydration status before kidney transplantation and to reduce the negative influence of such factors as low perfusion pressure and unstable hemodynamic conditions on the kidney graft. In addition, it is believed that warming the patient and hemostasis is more appropriate prior to kidney transplantation (KTx). Several authors have suggested that the indication for SHKTx in a potential heart recipient is a decrease in estimated glomerular filtration rate (eGFR) to <37–40 mL/min [67, 68], while eGFR ≤30 mL/min is considered a relative contraindication for isolated heart transplantation [69].

According to an analysis of the United Network for Organ Sharing (UNOS) Registry, mortality rates did not differ significantly between heart and kidney donor waiting lists, while the 5-year survival rate of kidney heart recipients was higher than that of heart recipients with renal insufficiency, regardless of the need for dialysis prior to transplantation [70]. Similar results are reported

by Kilic et al. and Schaffer et al. They also note that the appropriateness of using two organs from the transplant pool simultaneously for one recipient is justified by the fact that heart recipients with renal failure who are on the kidney waiting list have more than twice the mortality by the end of 3 years after HTx than patients with isolated esCRF (40% versus 14–18%) [71, 72]. At the same time, Melvinsdottir et al. and Gallo et al. report benefits of SKTx over SHKTx [73, 74]. According to an analysis of the UNOS database from 2007 to 2016, the risk of death for SHKTx recipients was 4.7 times higher than for SKTx recipients when calculated from the HTx date and 2.6 times higher when calculated from the KTx date. It was also shown that although the vast majority of patients with end-stage heart failure and stage 4 and 5 CKD received SHKTx, 17% of patients who received SHKTx had an eGFR of 45 ml/min/1.73 m^2, whereas 38% of patients who received SKTx had an eGFR of 45 ml/min/1.73 m^2. The authors consider one of the advantages of SKTx to be the possibility of kidney transplantation from a living donor [73]. These data are at odds with many previously published results reporting that cardiac recipients with postoperative renal failure have a significantly lower survival rate than recipients without renal failure, and SHKTx can offset this difference. Another analysis of the UNOS database (2000–2015), carried out by a group of authors, which aimed to determine the indications for SHKTx or SKTx based on the severity of renal dysfunction of a potential heart recipient, can only partially explain these contradictions. Patients with an eGFR of 30 mL/min/1.73 m^2 who underwent SHKTx were found to have significantly better survival at 5 years post-transplant compared with those who underwent SKTx (75% and 59%, respectively, $p = 0.04$). For patients with eGFR between 30 and 44 ml/min/1.73 m^2, the differences in survival did not reach statistical significance [74].

Despite the increasing number of simultaneous heart and kidney transplants, to date, there are no guidelines on when to choose a single-stage, staged or subsequent approach. It is clear that if the recipient has systemic hemodynamic disorders and cardiac graft dysfunction, it is advisable to perform kidney transplantation after the clinical condition has been stabilized, which is confirmed by reports from Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow [75, 76].

Thus, all varieties of renal replacement therapy, including kidney transplantation, are widely used in heart transplant recipients. Given the complexity and versatility of pathological processes that lead to the need for RRT at all stages of heart transplantation and the heterogeneity of the literature devoted to this problem, it is difficult to expect the appearance of clinical guidelines clearly regulating the tactics of this type of treatment in heart recipients. Timely initiation, careful selection of optimal RRT method taking into account prevailing pathogenetic mechanisms, and assessment of risks of complications are the factors that make it possible to achieve optimal treatment outcomes in this patient cohort.

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