

IRREVERSIBLE ACUTE KIDNEY INJURY AFTER HEART TRANSPLANTATION-CARDIORENAL SYNDROME TYPE 1

Katerina Ristoska¹, Ninoslav Ivanovski^{1,5}, Fljamure Zeqiri-Keka²,
Ilina Hamamdzieva^{3,5}, Biljana Gerasimovska-Kitanovska^{3,5}, Ognen Ivanovski^{4,5}, Zivko Popov^{5,6}

¹ Zan Mitrev Clinic, Skopje, RN Macedonia

² PHI Institute for general health, Skopje, RN Macedonia

³ University Clinic of Nephrology, Skopje, RN Macedonia

⁴ University Clinic of Urology, Skopje, RN Macedonia

⁵ University "Ss. Cyril and Methodius" – Skopje, RN Macedonia

⁶ Macedonian Academy of Sciences and Arts, Skopje, RN Macedonia

Corresponding author: Dr Katerina Ristovska, Zan Mitrev Clinic – Skopje, North Macedonia, Bledski dogovor No 8, e-mail: katerina.ristoska@zmc.mk, Telephone: +38970324445

ABSTRACT

We report on a case of 55-year-old woman with diabetes, dilatative cardiomyopathy and end-stage heart failure (NYHA IV and ejection fraction of 26%) who underwent orthotopic heart transplantation and subsequently developed irreversible acute kidney injury (AKI) requiring permanent dialysis. Postoperatively she endured multiple problems associated with the orthotopic heart transplant: opportunistic infections, septic shock, and malnutrition. This culminated in anuric renal failure. A cardiorenal syndrome type 1 was diagnosed. Our patient's course illustrates diabetes, pre-existing chronic kidney disease (CKD) and early AKI as identified risk factors for irreversible AKI after heart transplant. The deterioration of renal function after the heart transplantation is associated with high risk of hospitalization, cardiovascular events and death. The authors analyze the possible pathophysiologic mechanisms and preventive and curative measures.

Keywords: Cardiac Transplantation, Acute kidney Injury, Cardioneurology Chronic hemodialysis

INTRODUCTION

Cardiac transplantation is life-saving for advanced heart failure. But kidney injury is a well-known complication. [1, 2, 3] As survival has improved after transplant, chronic kidney dysfunction has become increasingly prevalent in this population. In published cohorts, the cumulative incidence of End Stage Renal Disease (ESRD) after heart transplant ranges from 4% after 5 years to 20% after 10 years. [4, 5] But AKI is even more common: one registry found 28.4% of heart-transplant recipients required dialysis during a 5 year follow-up, yet re-

nal dysfunction with a usual increase of creatinine is much higher. [6] This highlights the serious impact of renal injury among heart transplant patients.

The mechanism of renal injury after cardiac transplant is multifactorial. Transplant-specific factors include nephrotoxic immunosuppressants (notably calcineurin inhibitors) [7, 8] and graft-related phenomena, superimposed on perioperative insults (hypotension, ischemia-reperfusion) and systemic events (sepsis, inflammation, microemboli). [9, 10] Although "cardiorenal syndrome" concepts em-

phasize heart–kidney interactions in chronic heart failure, post-transplant AKI primarily reflects direct renal insults. The risk factors that contribute to post-transplant AKI are diabetes mellitus, body weight, hypertension, age of recipients. We review a case of irreversible AKI, requiring HD after heart transplant. We analyze the existing literature on the incidence, risk factors, and pathophysiology.

Table 1. *Cardiorenal syndrome – Types*

Type 1	Acute heart failure leading to Acute Kidney Disease (AKD)
Type 2	Chronic heart failure leading to kidney failure
Type 3	AKD leading to uremic cardiomyopathy and heart failure
Type 4	Chronic kidney disease leading to heart failure
Type 5	Systemic disease leading to heart and kidney failure

CASE PRESENTATION

A 55-year-old woman with long-standing insulin-dependent diabetes mellitus and ischemic cardiomyopathy (NYHA Class IV, left ventricular ejection fraction 26%) underwent orthotopic heart transplantation for end-stage heart failure. Her pre-transplant course was complicated by progressive dilated cardiomyopathy. The preoperative evaluation noted a moderately reduced baseline renal function (GFR 65 ml/min/ 1.73 m²) but no serious or advanced stage kidney disease. The transplant procedure itself was uneventful except for prolonged graft ischemia time (low-flow hypothermia during cardiopulmonary bypass).

In the early postoperative period, the patient developed severe systemic illness. She suffered opportunistic infections (cytomegalovirus, fungal pneumonia and toxoplasmosis) under immunosuppression, followed by septic shock syndrome, requiring high-dose vasopressors. Nutritional status declined (prolonged parenteral nutrition), and she experienced episodes of hypotension. Creatinine began rising by day 3 post-transplant, and during the following several weeks she became partially anuric. Despite maximal medical management (fluid resuscitation, pressor support, and avoidance of further nephrotoxins), renal function did not recover. A renal ultrasound showed normal-size kidneys without obstruction. Therefore, no biopsy

was performed. By six months post-transplant she required continuous renal replacement therapy, later converted to intermittent hemodialysis. She never became dialysis-independent during follow-up, establishing irreversible renal failure. Notably, her pre-transplant diabetes and perioperative AKI were recognized risk factors for graft nephropathy. In published series, pre-existing diabetes and acute kidney injury before or early after transplant strongly predict post-transplant renal failure. Her immunosuppressive regimen included tacrolimus (calcineurin inhibitor) and mycophenolate mofetil. The cumulative calcineurin exposure over these weeks was high. This clinical course – diabetes plus intense immunosuppression plus septic hypotension – closely matches factors identified by others as predispositions to severe post-transplant AKI.

DISCUSSION

This patient's irreversible AKI highlights several transplant-specific injury mechanisms, on top of general ICU/AKI insults. Key contributing factors include *diabetes and pre-operative kidney function, prevalence of congestion, calcineurin-inhibitor nephrotoxicity, perioperative hemodynamic injury, ischemia–reperfusion injury, systemic inflammation/sepsis, and microvascular embolic injury*. Figure 1 conceptually summarizes these overlapping pathways leading to persistent AKI after heart transplant.

Diabetes and preoperative kidney condition. The general state of the kidneys before the cardiac transplantation are very important for the appearance of the AKI or development of ESRD requiring dialysis. Insulin dependent diabetes, under which the patient was suffering, is one of the more frequent conditions which might contribute to AKI in the early and late periods after cardiac surgery or cardiac transplantation. [11,12] The mechanism could be explained with the renal perfusion during the cardiac surgery. Only slight deterioration of renal function (GFR was 66 ml/min) and diabetes might be sufficient for AKI. Microvascular and microembolic injury during the cardiac surgery may play a significant role in renal damage in the diabetic condition. Our patient's risk factors, such as diabetes and post-operative AKI, are important when we discuss the kidneys, but the role of cardiac surgery

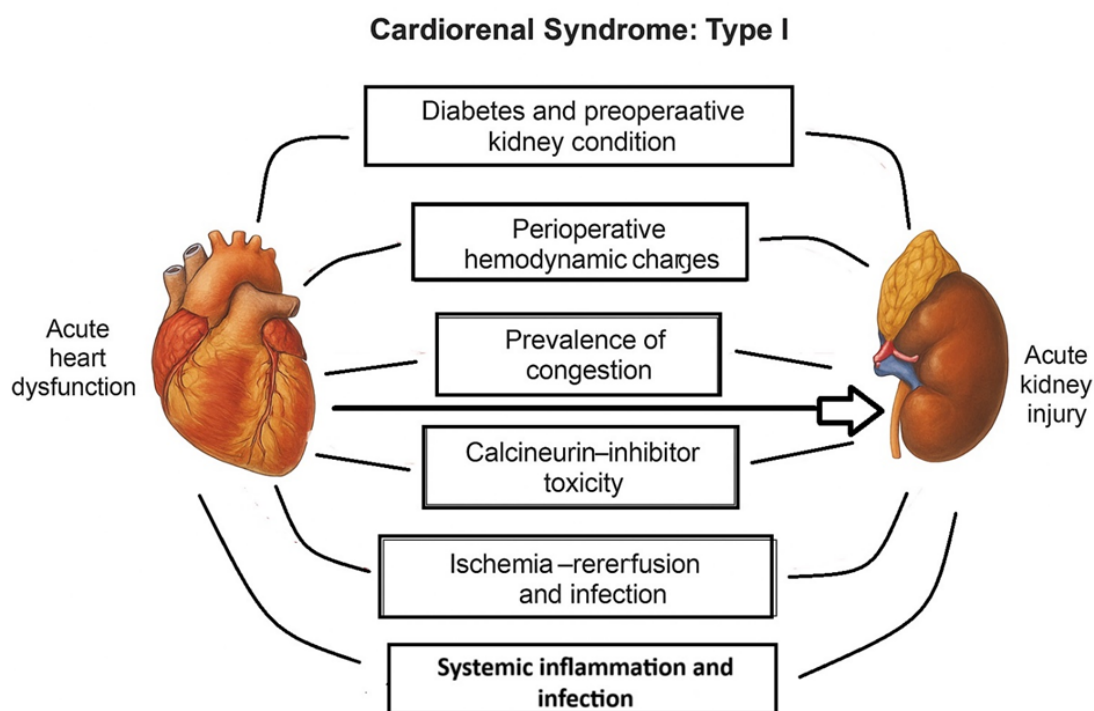


Figure 1. Pathophysiologic contributions to irreversible AKI after cardiac transplantation

and the complications we noted during the whole effect of cardiac transplantation are the other side of the equation.

Perioperative hemodynamic changes and importance of AKI. This heart transplant is performed under cardiopulmonary bypass, with a possible insufficient perfusion. Intraoperative hypotension, pump-related shear stress, and vasopressor use can all reduce renal blood flow. Prolonged low cardiac output during surgery causes global renal ischemia. In our patient, episodes of intraoperative or early postoperative hypotension (during septic shock) likely produced AKI. Postoperative renal damage (even brief) predicts worse renal outcomes. Any severe hemodynamic event (cardiogenic shock or sepsis) after transplant can precipitate AKI by tubulo-interstitial injury. The ADQI consensus on cardiovascular surgery-associated AKI notes that hypotension and low perfusion during and after CPB are major modifiable factors in AKI pathogenesis. Although we lack direct hemodynamic monitors here, it is plausible that renal hypoperfusion during septic shock irreversibly damaged the transplanted patient's kidneys. [13, 14]

Prevalence of congestion. It is very well known that one of the main consequence of acute cardiac failure is a congestion of the kidneys. As

a predominantly vascularized organ the kidney is susceptible to every change in perfusions or of congestion. The acute and chronic heart failure change the renal hemodynamic and increase renal venous hypertension. The ESCAPE study showed that right atrial pressure is the only hemodynamic parameter associated with the baseline kidney dysfunction. Therefore, congestion was a dominant reason for kidney disturbances after heart transplantation. [15, 16] In addition, neurohormonal pathways are also important in the whole pathophysiology of Cardiorenal syndrome. Activation of sympathetic nervous system and renin-angiotensin system as well as imbalance of reactive oxygen species/nitric oxide production are usual processes who finalize the syndrome. [17]

Calcineurin-inhibitor toxicity. Most cardiac transplant patients receive calcineurin inhibitors (cyclosporine or tacrolimus) to prevent rejection, but these drugs are potently nephrotoxic. Calcineurin inhibitors, especially Cyclosporin A, induces afferent arteriolar vasoconstriction and chronic arteriolar hyaline sclerosis, causing a sustained drop in GFR. In one classic study of heart-transplant survivors on cyclosporine, mean creatinine clearance fell ~40% within 6 months, and 6.5% developed ESRD requiring dialysis over

6–9 years. The investigators noted a one-third decrease in clearance by 6 months on CNI therapy. Consistent with this, tacrolimus (a more modern CNI) has been associated with lower ESRD risk than cyclosporine. For example, Roest et al. found that tacrolimus-based immunosuppression reduced ESRD incidence (HR ~0.4) while any AKI requiring . Minimizing CNI exposure and the introduce of other immunosuppressant like mTOR inhibitors as Everolimus and/or Sirolimus. Switching to CNI-sparing regimens has been proposed to mitigate this risk, but requires balancing rejection versus nephrotoxicity . [18, 19]

Ischemia–reperfusion injury. The transplanted heart experiences warm ischemia during procurement and reperfusion in the recipient. Reperfusion triggers systemic inflammatory mediators and free radicals that can damage distant organs, including kidneys. Ischemia–reperfusion injury is known to induce AKI in transplant and cardiovascular settings. For example, after donor brain death and organ reperfusion, cytokine release can impair renal microcirculation. While few studies have isolated this effect in heart transplants, it is reasonable that our patient's kidneys suffered a second hit when the new heart was reperfused, amplifying inflammatory cascades. [20, 21, 22, 23]

Systemic inflammation and infection. Post-transplant patients are immunocompromised and prone to severe infections. Sepsis and systemic inflammatory response (SIRS) independently cause AKI via intrarenal vasoconstriction, cytokine storm, and tubular apoptosis. Our patient had documented opportunistic infections and septic shock – classic precipitants of sepsis-associated AKI. Indeed, any AKI requiring RRT has been associated with high mortality and poor recovery. The combination of surgical stress and infection likely prolonged inflammation. Heightened cytokines (TNF- α , IL-6) and endotoxins in sepsis can persistently impair renal autoregulation, reinforcing irreversible injury. [24, 25, 26]

CONCLUSION

Irreversible AKI after heart transplantation is a serious and multifactorial complication. In our patient, preexisting diabetes, septic shock, and calcineurin-inhibitor exposure

synergized to produce acute renal failure that never recovered. The prognosis of post-transplant AKI is poor: patients requiring RRT face high mortality and progression to CKD/ESRD. Published series demonstrate that even transient post-transplant AKI strongly predicts later dialysis or death. Recognizing high-risk features (e.g. diabetes, baseline CKD, perioperative hypotension) should prompt aggressive prevention. When AKI occurs, supportive RRT and consideration of renal-sparing protocols are key. Ultimately, co-management by transplant cardiology and nephrology teams is crucial. Further research into renal-protective strategies in the transplant setting is needed to reduce the burden of this complication.

REFERENCES

1. Ronco C, Chang-Yin Chionh, Haapio M, Anavekar N. The Cardiorenal Syndrome. *Blood Purif* 2009; 27: 114-126
2. Jose P, Skali H, Anavekar N, et al. Increase in Creatinine and Cardiovascular Risk in Patients with Systolic Dysfunction after Myocardial Infarction. *J Am Soc Nephrol* 2006; 17: 2886-2891.
3. Fedele F, De Luca L, Gheorghiadu M. The cardiorenal syndrome: recognition and treatment. *Ital Heart J* 2005;6(12); 941- 945
4. Roest S, Hesselink D, Klimczak-Tomaniek D, Kardys I, Caliskan K, Brugts J, Maat P.V.M. A, Cizek M, Constantinescu A and Manintveld O. Incidence of end-stage renal disease after heart transplantation and effect of its treatment on survival. *ESC Heart Failure* 2020; 7: 533-541
5. Wang TJ, Lin CH, Wei HJ, Wu MJ. Long-Term Outcomes and Risk Factors of Renal Failure Requiring Dialysis after Heart Transplantation: A Nationwide Cohort Study. *J. Clin. Med.* 2020; 9: 2455
6. Nadim M, Forni L, Bihorac A, et al. Cardiac and Vascular Surgery – Associated Acute Kidney Injury : the 20th International Consensus Conference of the ADQI (Acute Disease Quality Initiative) Group. *J Am Heart Assoc* 2018;7: e008834
7. Goldstein DJ, Zuech N. Sehgal V et al. Cyclosporine –n associated end-stage nephropathy after cardiac transplantation: incidence and progression. *Transplantation* 1997; 63: 664-668
8. Rossi A, and Vella J. Acute Kidney Disease after Liver and Heart Transplantation. *Transplantation* 2016; 100: 506-514

9. Alonson S, Nisbet P and Bunke M. Fluid resuscitation practices in cardiac surgery patients in the USA: a survey of health care providers. *Perioperative Medicine* 2017; 6: 15
10. Sueyoshi K, Watanabe Y, Inoue T et al. Predictors of long-term prognosis in acute kidney injury survivors who require continuous renal replacement therapy after cardiovascular surgery. *Plus One* 2019; 14(1): e0211429.
11. Mitsas A, Elzawawi M, Boekels M, et al. Heart Failure and Cardiorenal Syndrome: A Narrative Review on Pathophysiology, Diagnostic and Therapeutic Regimens-From a Cardiologist's View. *J Clin Med* 2022; 11: 7041
12. Kalantari K, Chang J, Ronco C and Rosner M. Assessment of intravascular volume status and volume responsiveness in critically ill patients. *Kidney International* 2013; 83: 1017-1028
13. Ding X, Cheng Z, Qian Qi. Intravenous Fluids and Acute Kidney Injury. *Blood Purif* 2017; 43: 163-172
14. Liang K, Sileanu F, Clermont G et al. Modality of RRT and Recovery of Kidney Function after AKI in Patients Surviving to Hospital Discharge. *Clin J Am Soc Nephrol*, 2016; 11: 30-38
15. Gnanaraj J, Haehling S, Anker S, ERaj D, and Radhakrishnan J. The relevance of congestion in the cardio-renal syndrome. *Kidney International* 2013; 83: 384-391
16. Llacer P, Marcos MC, Espriella R et al. Congestion as a crucial factor determining albuminuria in patients with cardiorenal disease. *Clinical Kidney Journal* 2024;17:sfae 140
17. Bryan K and Rangaswami J. Mechanistic Insights in Cardiorenal Syndrome. *NEJM Evid* 2022;1(9).
18. Friedman SB. Immunosuppression after Cardiac Transplantation: What is the Best Approach? *The Science Journal of the Lander College of Arts and Sciences* 2023; 17(1): 98-106
19. Alyz A, Abbas S, Moore E, et al. The natural history of renal function following orthotopic heart transplant. *Clin Transplant* 2005; 19(5): 683-689
20. Wald R, Kitchlu A, Harel Z, Silver S. Care of Acute Kidney Injury Survivor. *Nephron* 2017; 137: 306-309
21. Nakamura Y, Saito Sh, Miyagawa Sh, et al. Perioperative ischemic reperfusion injury and allograft function in the early post-transplantation period. *Inter act Cardiovasc Thorac Surg*, 2019; 29:230-236
22. Rangaswami J, Bhalla V, Blair J, Chang T, Costa S, Lengtine K, Lerma E, Mezue K, Molitch M, Mullens W, Ronco C, Tang W, McCullough P. Cardiorenal Syndrome: Classification , Pathophysiology, Diagnosis and Treatment Strategies: A Scientific Statement from the American Heart Association. *Circulation* 2019; 139: issue 16: 1-67.
23. Olivero JJ, Olivero JJ, Nguyen P, Kagan A. Acute Kidney Injury After Cardiovascular Surgery: An Overview. *MDCVJ* 2012;VIII: 31-36
24. Taiwo A, Khush K, Stedman M et al. Longitudinal Changes in Kidney Function Following Heart Transplantation: Stanford Experience. *Clin Transplant* 2018; Kenneally LF, Lorenzo M, Romero-Gonzales G et al. Kidney function in acute heart failure: a practical approach to interpretation and management . *Clinical Kidney Journal* 2023;16: 1587-1588
25. Kenneally LF, Lorenzo M, Romero-Gonzales G et al. Kidney function in acute heart failure: a practical approach to interpretation and management . *Clinical Kidney Journal* 2023;16: 1587-1588
26. Tomiyama H and Yamashina A. Vascular Dysfunction: A Key Player in Chronic Cardio-renal Syndrome. *Intern Med* 2015; 54: 1465-1472

Резиме**ИРЕВЕРЗИБИЛНО БУБРЕЖНО ОШТЕТУВАЊЕ
ПО ТРАНСПЛАНТАЦИЈА НА СРЦЕ – КАРДИОРЕНАЛЕН СИНДРОМ ТИП 1**

**Катерина Ристовска¹, Нинослав Ивановски^{1,5},
Фљамуре Зекири-Кека², Билјана Герасимовска-Китановска^{3,5},
Илина Хамамџиева^{3,5}, Огнен Ивановски^{4,5}, Живко Попов^{5,6}**

¹ Клиника Жан Митрев, Скопје, РС Македонија

² ЈЗУ Институт за јавно здравје на РСМ, Скопје, РС Македонија

³ Универзитетска клиника за нефрологија, Скопје, РС Македонија

⁴ Универзитетска клиника за урологија, Скопје, РС Македонија

⁵ Универзитет „Свети Кирил и Методиј“, Скопје, РС Македонија

⁶ Македонска академија на науките и уметностите, Скопје, РС Македонија

Известуваме за пациент на 55 години со дијабетес и со дилатативна кардиомиопатија со срцева слабост од крајни размери (NYHA IV, EF 26%), која помина ортотопична трансплантација на срце и разви иреверзибилно бубрежно оштетување, кое бараше вклучување дијализа. Постоперативно таа разви акутно бубрежно оштетување како последица на опортунистички инфекции, септичен шок, малнутриција и дејство на калциннеурински инхибитор како имуносупресор. Се постави дијагноза на кардиоренален синдром тип 1. Нашата пациентка покажа дијабетес како основна болест и слабо оштетување на бубрежната функција, но далеку од состојба на потешко оштетување. Појавата на бубрежни оштетувања доведуваат до висок ризик од чести хоспитализации, кардиоваскуларни настани и смрт на болниот. Авторите ги анализираат можните патофизиолошки причини за настанување на овој тежок синдром, кој може да ја компромитира трансплантацијата на срцето.

Клучни зборови: срцева трансплантација, акутно бубрежно оштетување, кардионефрологија, хронична хемодијализа