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Deepak Jain^{1*}, HK Aggarwal², Promil Jain³ and Pulkit Chhabra⁴

¹Associate Professor, Department of Medicine, India

²Senior Professor and Head, Department of Medicine III, India

³Assistant Professor, Department of Pathology, India

⁴Resident, Department of Medicine, India

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***Corresponding author:** Deepak Jain, Doctor, Department of Medicine, PGIMS, Rohtak-124001 (Haryana), India, Tel: +91-9416147887; E-mail: jaindeepakdr@gmail.com

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Case Report

Cardiorenal Syndrome: A Physician Perspective

Abstract

Cardiac diseases are associated independently with decrease in kidney function and progression of existing kidney diseases. Conversely, chronic kidney disease (CKD) represents an independent risk factor for cardiovascular events and outcomes. Renal dysfunction frequently accompanies cardiac failure and that cardiac dysfunction frequently accompanies renal failure. This interdependent relationship has come to be known as the “cardiorenal syndrome”. Direct and indirect effects of each organ that is dysfunctional can initiate and perpetuate the combined disorder of the two organs through a complex combination of neurohormonal feedback mechanisms. In this review pathophysiology and management of five different subtypes of cardiorenal syndrome is discussed.

Introduction

Cardiac diseases are associated independently with decrease in kidney function and progression of existing kidney diseases. Conversely, chronic kidney disease (CKD) represents an independent risk factor for cardiovascular events and outcomes. Acute decompensated heart failure, cardiac ischemia, and arrhythmia may lead to acute impairment of kidney function through renal arterial under filling and a drop in renal blood flow secondary to low cardiac output. Investigative and therapeutic procedures such as percutaneous coronary intervention, coronary artery bypass surgery, or fibrinolytic therapy can also lead to impaired kidney function. Data from the Acute decompensated Heart Failure National Registry (ADHERE) of over 100,000 patients admitted with acute decompensated heart failure (ADHF) revealed that almost one third of patients have a history of renal dysfunction [1]. An acute increase in serum creatinine level accompanies 21%–45% of hospitalizations for ADHF, depending on the time frame and magnitude of creatinine level increase. In patients with ADHF, an acute increase in serum creatinine level > 0.3 mg/dl is associated with increased mortality, longer hospital stay and more frequent readmissions. 39% patients in New York Heart Association (NYHA) class 4 and 31% of patients in NYHA class 3 had severely impaired renal function (creatinine clearance <30 ml/minute) [2]. Decreased kidney function also present as a significant comorbid condition in approximately 50% of patients with chronic heart failure. Renal failure is clearly linked with increased adverse cardiovascular outcomes. Almost 44% of deaths in patients with end-stage renal disease (ESRD) are due to cardiovascular diseases [3]. Meta-analysis

indicated that patients with ESRD are more likely to die from cardiovascular causes than from renal failure itself. Death from cardiovascular causes is 10–20 times more common in patients with chronic renal failure than in matched segments of the general population [4]. It should therefore come as little surprise that renal dysfunction frequently accompanies cardiac failure and that cardiac dysfunction frequently accompanies renal failure. This interdependent relationship has come to be known as the “cardiorenal syndrome”. Cardiorenal syndrome (CRS) is thus defined as “disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other”. The mechanism underlying the interplay of cardiac failure and kidney dysfunction is still not completely understood.

Cardiorenal Connection

Both heart and the kidneys are richly vascular (the kidneys are more vascular than the heart) and both organs are supplied by sympathetic and parasympathetic innervations. These two organs act in tandem to regulate blood pressure, vascular tone, diuresis, natriuresis, intravascular volume homeostasis, peripheral tissue perfusion and oxygenation. They have endocrine functions with interdependent physiological hormonal actions regulated by arterial natriuretic peptide, a vasodilator secreted from the heart and renin-angiotensin-aldosterone system (RAAS). Dysfunction of either of the two organs can cause dysfunction of the other. Changes in the RAAS, the imbalance between nitric oxide (NO) and reactive oxygen species (ROS), the sympathetic nervous system (SNS) and inflammation are the cardiorenal connectors to develop CRS [2].

Previous terminology did not allow physicians to identify and fully characterize the chronology of the pathophysiological interactions that characterize a specific type of combined heart/kidney disorder. A diseased heart has numerous negative effects on kidney function but, at the same time, renal insufficiency can significantly impair cardiac function. Thus, direct and indirect effects of each organ that is dysfunctional can initiate and perpetuate the combined disorder of the 2 organs through a complex combination of neurohormonal feedback mechanisms. For this reason, a subdivision of CRS into 5 different subtypes seems to provide a more concise and logically correct approach [5]. The various subtypes of cardio renal syndrome are depicted in Table 1

Pathophysiology

Recent advances in basal and clinical sciences have improved our understanding of organ crosstalk and help to establish therapies based on pathophysiology of CRS. A reduced cardiac output in CHF resulting in decreased renal perfusion could be an easy explanation for the worsening renal function but worsening renal function has been demonstrated in patients with ADHF with preserved left ventricular EF. The most common underlying risk factors that account for renal dysfunction in the setting of heart failure or cardiac dysfunction include hypertension, diabetes mellitus, severe atherosclerotic disease, elderly age and a prior history of renal insufficiency or heart failure. This decline in renal function, despite a presumed preservation of blood flow to the kidneys, has led to the search for other mechanisms of CRS, including the role of the renin-angiotensin-aldosterone system (RAAS), oxidative stress, sympathetic over activity and various chemicals like nitric oxide [NO], prostaglandins, natriuretic peptides, endothelin, etc.

The low-Flow-State hypothesis

Progressive decline in GFR observed in HF primarily reflects inadequate renal perfusion secondary to reduced cardiac output. Inadequate renal blood flow or perfusion pressure prompts renin release by the juxtaglomerular cells of the afferent arterioles through low-flow states in the ascending limb of the loop of Henle and pressure-sensing baroreceptors. Renin release and RAAS activation confer extreme sodium avidity, volume retention, decreased glomerular perfusion (i.e.

afferent arteriolar constriction), and profibrotic neurohormone increases, leading to ventricular remodeling and thus worsening pump failure [6]. However recent work especially ESCAPE trial founding no correlation between improvement of cardiac index with renal functions lead to conclusion that there is much more than simply reduced blood flow to explain the pathophysiology of CRS [7].

Elevated central venous pressure and intra-abdominal hypertension

Heart failure is marked by an elevation in central venous pressure which reduces the perfusion gradient across the renal capillary bed. This rising renal venous pressures reduce or even abolish urine production by collapsing renal tubules and hence reducing GFR. Patients with baseline renal dysfunction or worsening renal function after admission have significantly elevated central venous pressure compared to those with less or no renal dysfunction [8]. Intra-abdominal pressure (IAP) is said to be elevated when >8 mmHg and intra-abdominal hypertension is defined as pressure >12 mmHg. Patients with elevated IAP have significantly lower baseline GFR compared with those with normal IAP, and the degree of reduction in IAP after diuresis correlates with an improvement in renal function.

Renin-Angiotensin-Aldosterone axis and oxidative injury

The extreme sodium and water retention along with ventricular remodeling conferred by RAAS elaboration in HF are a maladaptive response to altered hemodynamics, sympathetic signaling, and progressive renal dysfunction. System in heart failure patients, increasing both preload and afterload and thus myocardial oxygen demands. Ang II activates the enzyme NADPH oxidase in endothelial cells, vascular smooth muscle cells, renal tubular cells, and cardiomyocytes [9-11]. This leads to the formation of ROS, mostly superoxide. A growing body of evidence suggests that ROS are responsible for the processes of aging, inflammation, and progressive organ dysfunction. Nitric oxide (NO) is responsible for vasodilation and natriuresis and assists in renal control of ECFV. Superoxide antagonises these effects but also reduces bioavailability of NO. 8 Oxidative stress damages DNA, proteins, carbohydrates, and lipids and also shifts cytokine production towards pro inflammatory mediators such as interleukin-1, interleukin-6, and tumour necrosis factor alpha. Interleukin-6 also stimulates fibroblasts leading

Table 1: Classification of cardiorenal syndrome.

Type	Name	Mechanism	Clinical conditions	Markers
Type I	Acute cardiorenal syndrome	Abrupt worsening of cardiac function leading to acute kidney injury	Acute cardiogenic shock and acutely decompensated congestive heart failure	ET-1, troponin, CPK-MB
Type II	Chronic cardiorenal syndrome	Chronic abnormalities in cardiac function causing progressive and potentially permanent kidney disease	Chronic congestive heart failure	ET-1, BNP
Type III	Acute renocardiac syndrome	Abrupt worsening of kidney function causing acute cardiac disorder	Acute kidney ischemia and glomerulonephritis	TNF- α , IL-1, IL-6, IL-8
Type IV	Chronic renocardiac syndrome	Chronic kidney disease contributing to decline in cardiac function	Chronic glomerular and interstitial disease	PTH, CPP product, cystatin C
Type V	Secondary cardiorenal syndrome	Systemic condition causing both cardiac and kidney dysfunction	Diabetes mellitus, sepsis	–

Abbreviations: ET-1, Endothelin-1; CPK-MB, Creatine phosphokinase-MB; BNP, B-type natriuretic peptide; TNF, Tumor-necrosis factor; IL, Interleukin; PTH, Parathyroid hormone; CPP, Calcium-phosphate product; Ellipses indicate not applicable.

to increased cardiac and renal fibrosis [12]. These cytokines play a crucial role in the pathophysiology of atherosclerosis, have negative inotropic effects, assist in cardiac remodeling and even cause thrombotic complications

The benefits of angiotensin- converting enzyme (ACE) inhibition and aldosterone antagonism through blockade of the intracardiac RAAS, reduction in adrenergic tone, improvement in endothelial function, and prevention of myocardial fibrosis are well described in cardiac failure; RAAS inhibition has been a main focus of therapy in HF for the last 2 decades and has led to improved outcomes for many patients. Unfortunately, little is known about the long-term benefits or adverse effects of RAAS inhibition on kidney function in HF.

The sympathetic servous system

SNS activation is initially a protective mechanism in congestive cardiac failure (CCF) patients as like RAAS activation, to maintain cardiac output by positive chronotropic and inotropic effect on myocardium. However the adverse consequences of sympathetic nervous system activity are well known. Sustained elevated adrenergic tone causes a reduction in β adrenergic receptor density, particularly β_1 within the ventricular myocardium, as well as uncoupling of the receptor from intracellular signaling mechanisms⁶. Less well appreciated are the systemic effects of renal sympathetic stimulation. As left ventricular systolic failure progresses, diminished renal blood flow and perfusion pressure lead to baroreceptor-mediated renal vasoconstriction, activation of the renal sympathetic nerves, and release of catecholaminergic hormones. This problem is compounded in patients with HF with advanced renal insufficiency because there is reduced clearance of catecholamines by the kidneys [13]. SNS activation also increase the release of neuropeptide Y which is a vascular growth promoter.it causes neointimal proliferation, leading to atherosclerosis, vasoconstriction and interfere with normal immune system function [14].

Endothelin effects

The release of endothelin has some adverse effects because it causes vasoconstriction and induces hypertrophy of cardiac myocytes. Moreover, it stimulates and potentiates noradrenaline, angiotensin II and aldosterone [15].

Arginine vasopressin effects

Arginine vasopressin (AVP), too, has adverse effects on CRS progression by fluid retention and potentiation of angiotensin II and noradrenaline actions. It also stimulates myocardial hypertrophy [16].

Drugs and Toxins

Some drugs may have harmful effects in the progression of CRS. Inotropic drugs augment neurohormonal activation. High-dose diuretics produce hypovolemia, and intravenous vasodilators cause hypotension. Contrast agents also found to have same effects and enhance progression of CRS.

Biomarkers of cardiorenal syndromes

For decades, the rise in serum creatinine has been the only detectable sign of a reduction in glomerular filtration. Creatinine has had the disadvantages of being linked to creatine and the overall body muscle mass, hence, differing according to body size in addition to the rate of renal elimination. Furthermore, the kidney both filters and secretes creatinine. Hence, there is a clear need for better laboratory markers of renal filtration unlike cardiac biomarkers indicating myocardial injury and overload (troponin, creatine kinase myocardial band, and natriuretic peptides), the field of nephrology has been devoid of approved blood or urine markers of AKI. Thus, the current paradigm is that when renal injury occurs, clinicians must wait to observe a reduction in GFR before AKI is inferred. The concept of measuring makers of the acute injury process is crucial to the early upstream identification of AKI before there is serious loss of organ function. Some emerging novel biomarkers are useful in the setting of both cardiac and renal dysfunction are depicted in Table 2 [17].

Prevention and Management

Acute cardiorenal syndrome: type 1

Avoidance of volume depletion, removal of superimposed renal toxic agents, minimization of the toxic exposure (iodinated contrast, time on cardiopulmonary bypass) and the use of antioxidant agents such as N-acetylcysteine and BNP in the perioperative period after cardiac surgery can act as a preventive measure. Use of continuous renal replacement therapy (CRRT) can also be useful as it ensures euvolemia and avoids hypo- or hypervolemia and provides sodium and solute (nitrogenous waste products) removal.

In case of acute decompensated heart failure or cardiogenic shock, diuretics should be used to deplete the extracellular fluid

Table 2: Biomarkers of Cardiorenal Syndromes.

Biomarkers	Predictors
Neutrophil gelatinase associated lipocalin (NAGL)	Biomarker for ischemic and nephrotoxic renal injury; early AKI in both adults and children - Value of >170ng/ml predicts the development of type 1 cardiorenal syndrome within 48-72 hours
CystatinC	Proximal tubuleinjury Predict AKI earlier then creatinine
Kidney injury molecule -1 (KIM-1)	Renal proximal tubule injury following Ischemia andnephrotoxins - Combined with NGAL, important marker in phases of AKI
Sodium hydrogen exchanger (NHE3)	Ischemia, pre-renal, post-renalAKI
Cytokines (IL-6, IL-8,IL-18)	Nephrotoxic, delayed graftfunction
N Acetyl β glucosaminidase	Early AKI
α -Glutathione S-transferase	Proximal tubular injury, acuterejection
π -Glutathione S-transferase	Distal tubule injury, acuterejection
L-type Fatty acid binding protein	Ischemia andnephrotoxins
Netrin-1	Ischemia and nephrotoxins,sepsis
Keratin-derivedchemokine	Ischemia and delayed graftfunction

volume at a rate that allows adequate time for intravascular refilling from the interstitium. To achieve adequate diuresis, infusions of loop diuretics have been demonstrated to have greater efficacy than intermittent dosing [18]. Vasodilators such as nitroglycerin and nitroprusside can be used to relieve symptoms and improve hemodynamics for patients with preserved or elevated blood pressure. Positive inotropes such as dobutamine or phosphodiesterase inhibitors are required for patients with low blood pressure and poor renal perfusion. If kidney function continues to worsen, angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) should be avoided in order to maintain the GFR.

Chronic cardiorenal syndrome: type II

Use of RAAS antagonists, beta-adrenergic blocking agents and statins used in chronic heart failure have been proved to be beneficial to kidneys in Type II CRS. Glycaemic control in diabetic and blood pressure control in hypertensive patients has also a preventive role.

Interruption of the RAAS is the primary aim in the management of Type II CRS as it stabilizes creatinine, and in many instances leads to improvement over the course of the time but can lead to significant decrease in kidney function and/or elevated potassium. Aldosterone antagonists, such as spironolactone and eplerenone are important adjuncts to therapy in patients with severe heart failure. Both CHF and CKD are associated with anaemia, which is commonly treated with erythropoiesis stimulating agents which may reduce apoptosis, fibrosis and inflammation in heart. Hence, there has been intense interest in using erythropoiesis-stimulating agents in heart failure patients [19].

Acute renocardiac syndrome: type III

In patients with pre-existing CKD, diabetes, older age or volume contraction undergoing coronary and other angiographic procedures leading to contrast nephropathy, prevention provides the best opportunity to “treat” or avoid Type III CRS. Preventive strategies have been studied, including parenteral hydration (hypotonic or isotonic saline or bicarbonate), diuretics, mannitol, natriuretic peptides, dopamine, fenoldopam, theophylline and N-acetylcysteine [20]. Treatment of primary kidney diseases such as acute glomerulonephritis or kidney allograft rejection may potentially lessen the risk of Type III CRS. Management should focus on intra and extravascular volume control with either use of diuretics and forms of extracorporeal volume and solute removal (CRRT, ultrafiltration, haemodialysis).

Chronic renocardiac syndrome: type IV

Treatment of CKD with blood pressure and glycaemic control, RAAS blockers and disease-specific therapies are the best means of preventing this syndrome.

Complications in CKD patients such as anaemia, hypertension, altered bone and mineral metabolism, dyslipidaemia, albuminuria and malnutrition should be managed properly [21]. There should multifaceted approach

focusing on the decline of cardiovascular risk factors and complications common to CKD patients as observational studies have demonstrated the association between adverse cardiovascular events and these conditions.

Secondary cardiorenal syndromes: type V

There are no proven methods to prevent or ameliorate this form of CRS at this time. Supportive care with a judicious intravenous fluid approach and the use of pressor agents as needed to avoid hypotension are reasonable but cannot be expected to avoid AKI or cardiac damage [22].

It is difficult to formulate a common treatment strategy, as type V CRS includes a heterogeneous group of disorders such as sepsis, SLE, amyloidosis and diabetes mellitus. Therapies directed to the improvement in function of one organ need to consider the interaction with, and role of the other, as injury to one organ is likely to influence or injure the other organ and vice versa.

Future directions in treatment of cardiorenal syndrome

Potentially promising pharmacological approaches include selective adenosine A1 receptor blockers as adenosine lowers cortical blood flow, resulting in anti-natriuretic responses. A1 receptor antagonists have been shown to cause diuresis and natriuresis while minimally affecting potassium excretion or glomerular filtration [23]. Vasopressin antagonists (V2 receptor antagonists “vaptans”, e.g. conivaptan and tolvaptan) have also been proved useful [24]. Other interventions include the earlier use of dialysis and ultrafiltration, and ultimately, left ventricular assist devices to manage these patients effectively, at least in the short-term.

Conclusion

The various subtypes of CRS present unique challenges because therapies directed at one organ may have beneficial or detrimental effect on the other. Better understanding of the bidirectional pathways by which the heart and kidneys influence each other's function is necessary to tailor therapy appropriate to the situation. A multi-disciplinary approach that includes the nephrologist, cardiologist, and intensive care specialist is preferred.

References

1. Adams KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, et al. (2005) Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 149: 209-216. [Link: https://goo.gl/h73s6Q](https://goo.gl/h73s6Q)
2. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW (2004) Armstrong, “Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 109: 1004-1009. [Link: https://goo.gl/IRQpUa](https://goo.gl/IRQpUa)
3. National Institutes of Health (1997) National Institute of Diabetes and Digestive and Kidney diseases. Annual Data Report, USRDS, Bethesda USA.
4. Raine AE, Margreiter R, Brunner FP, Ehrich JH, Geerlings W, et al. (1992) Report on management of renal failure in Europe XXII. *Nephrol Dial Transplant* 2: 7-35. [Link: https://goo.gl/e7ovCQ](https://goo.gl/e7ovCQ)

5. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R (2008) Cardiorenal syndrome. *J Am Coll Cardiol* 52: 1527-1539. [Link: https://goo.gl/N1dS6y](https://goo.gl/N1dS6y)
6. Bock JS, Gottlieb SS (2010) Cardiorenal Syndrome -New Perspectives. *Circulation* 121: 2592-2600. [Link: https://goo.gl/VgL7W0](https://goo.gl/VgL7W0)
7. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, et al. (2008) Cardiorenal interactions: insights from the ESCAPE trial. *J Am Coll Cardiol* 51: 1268 -1274. [Link: https://goo.gl/VAGXn9](https://goo.gl/VAGXn9)
8. Shah B N, Greaves K. The Cardiorenal Syndrome: A Review *International Journal of Nephrology* Volume 2011, Article ID 920195, 11 pages doi:10.4061/2011/920195. [Link: https://goo.gl/iADxs5](https://goo.gl/iADxs5)
9. Ushio-Fukai M, Zafari AM, Fukui T, Ishizaka N, Griendling KK (1996) p22(phox) is a critical component of the superoxide-generating NADH/NADPH oxidase system and regulates angiotensin II-induced hypertrophy in vascular smooth muscle cells. *J Biol Chem* 271: 23317-23321. [Link: https://goo.gl/P5QVix](https://goo.gl/P5QVix)
10. Chabrashvili T, Kitiyakara C, Blau J, Karber A, Aslam S, et al. (2003) Effects of ANG II type 1 and 2 receptors on oxidative stress, renal NADPH oxidase, and SOD expression. *Am J Physiol Regul Integr Comp Physiol* 285: 117-124. [Link: https://goo.gl/uRRwBq](https://goo.gl/uRRwBq)
11. Nakagami H, Takemoto M, Liao JK (2003) NADPH oxidase-derived superoxide anion mediates angiotensin II-induced cardiac hypertrophy. *J Mol Cell Cardiol* 35: 851-859. [Link: https://goo.gl/f1xbkd](https://goo.gl/f1xbkd)
12. Hill MF, Singal PK (1996) Nitioxidant and oxidative stress changes during heart failure subsequent to myocardial infarction in rats. *Am J Pathol* 148: 291-300. [Link: https://goo.gl/ZbEZJU](https://goo.gl/ZbEZJU)
13. Laederach K, Weidmann P (1987) Plasma and urinary catecholamines as related to renal function in man. *Kidney Int* 31: 107-111. [Link: https://goo.gl/tqfuOr](https://goo.gl/tqfuOr)
14. Li L, Lee EW, Ji H, Zukowska Z (2003) Neuropeptide Y-induced acceleration of postangioplasty occlusion of rat carotid artery. *Arterioscler Thromb Vasc Biol* 23: 1204-1210. [Link: https://goo.gl/CLOYOk](https://goo.gl/CLOYOk)
15. Moe GW, Rouleau JL, Nguyen QT, Cernacek P, Stewart DJ (2003) Role of endothelins in congestive heart failure. *Can J Physiol Pharmacol* 81: 588-597. [Link: https://goo.gl/NnwNx6](https://goo.gl/NnwNx6)
16. Lee CR, Watkins ML, Patterson JH, Gattis W, O'Connor CM, et al. (2003) Vasopressin: A new target for the treatment of heart failure. *Am Heart J* 146: 9-18. [Link: https://goo.gl/YqW9rx](https://goo.gl/YqW9rx)
17. Peter AMC (2011) Cullough. Cardiorenal Syndromes: Pathophysiology to Prevention. *International Journal of Nephrology* 1-10. [Link: https://goo.gl/VD5M02](https://goo.gl/VD5M02)
18. Salvador DR, Rey NR, Ramos GC, Punzalan FE (2004) Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. *Cochrane Database Syst Rev* 20: 31-78. [Link: https://goo.gl/oGQuIR](https://goo.gl/oGQuIR)
19. Fu P, Arcasoy MO (2007) Erythropoietin protects cardiac myocytes against anthracycline-induced apoptosis. *Biochem Biophys Res Commun*. 354: 372-378. [Link: https://goo.gl/1dvubB](https://goo.gl/1dvubB)
20. Jasuja D, Mor MK, Hartwig KC, Palevsky PM, Fine MJ, et al. (2009) Provider knowledge of contrast-induced acute kidney injury. *Am J Med Sci* 338: 280-286. [Link: https://goo.gl/h5ndoj](https://goo.gl/h5ndoj)
21. Manley HJ (2007) Disease progression and the application of evidence-based treatment guidelines diagnose it early: a case for screening and appropriate management. *J Manag Care Pharm* 13: S6-12. [Link: https://goo.gl/XXu1Rz](https://goo.gl/XXu1Rz)
22. Prowle JR, Bellomo R. (2010) Continuous renal replacement therapy: recent advances and future research. *Nat Rev Nephrol* 6: 521-529. [Link: https://goo.gl/Py4RJV](https://goo.gl/Py4RJV)
23. Gottlieb SS, Brater DC, Thomas I, Havranek E, Bourge R, et al. (2002) BG9719 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. *Circulation* 105: 1348-1353. [Link: https://goo.gl/cmngx4l](https://goo.gl/cmngx4l)
24. Gheorghade M, Gattis WA, O'Connor CM, Adams KF, Elkayam U, et al. (2004) Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA* 291: 1963-1971. [Link: https://goo.gl/9BH3HI](https://goo.gl/9BH3HI)