



## CASE REPORT

# Fixing a Broken Heart: Two for the Price of One

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### Abstract

Although widely recognized and with increasing incidence, cardiorenal syndrome management remains a challenging topic. We report the case of a 49-year-old man with progressive chronic heart failure of ethanolic and valvular aetiology, further complicated by kidney disease, admitted with cardiogenic shock which resulted in acute kidney injury evolving into renal replacement therapy dependency. After 3 months on dialysis, the patient was submitted to a bioprosthetic mitral valve implantation and tricuspid valvuloplasty with positive improvement of acute heart failure signs and symptoms, overall health and quality of life. Moreover, renal function gradually recovered with a total independence of dialysis.

### Keywords

Cardiorenal syndrome, Acute kidney injury, Acute decompensated heart failure, Chronic heart failure

tial underlying mechanisms [2]. Acute CRS, recently re-named CRS type 1, is characterized by acute worsening of cardiac function leading to acute kidney injury (AKI) in the setting of active cardiac disease such as acute decompensated heart failure (ADHF) [3]. Emerging therapeutic options, including new drugs and devices, have been improving clinical outcome of CRS patients. However, their overall prognosis remains unacceptably poor and the two organ disease is associated with increased morbidity, mortality and health costs.

### Case Report

We present a case of a 49-year-old male, with past medical history of alcoholic cardiomyopathy complicated by tricuspid valve severe regurgitation and permanent atrial fibrillation. An implantable cardioverter defibrillator was placed for secondary prophylaxis in 2017 due to monomorphic ventricular tachycardia. He was an active smoker (84 pack-year) and abstinent from alcohol since April 2017. His current medications included apixaban, enalapril, bisoprolol, torasemide, spironolactone and metolazone. His kidney function was normal (Table 1).

In June 2018 he was admitted with fatigue, (New York Heart Association class III, peripheral edema and worsening ascites and management included augmented intravenous diuretics and paracentesis. Underlying etiology of aggravated congestive heart failure was culture-negative endocarditis of the mitral valve and gen-

### Introduction

The heart and kidney interaction is increasingly being recognized as a complex bidirectional axis with several interfaces which includes predominantly the effect of detrimental hemodynamic stress and neurohormonal activation, but also structural cardiac changes secondary to renal disease and the impact of anemia, bone mineral and atherosclerotic diseases, among many others [1]. The term cardiorenal syndrome (CRS) refers to a pathophysiological disorder in which cardiac dysfunction can result in or be caused by renal dysfunction. It is classified into five subtypes according to the poten-

**Table 1:** Serum creatinine (Scr) and serum urea (Sur) evolution.

Date	10/04/18	07/06/18	04/07/18	30/07/18	07/08/18	11/11/18	10/12/18	27/11/19
Scr (µmol/L)	70.7	168	302.4	163.6	740	141.47	161.8	156.5
Sur (mmol/L)	7.1	16.2	20	14.7	40.9	9.3	7	18



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tamicin combined with ampicillin was administered for 6 weeks. During this admission, kidney function deteriorated, with serum creatinine (Scr) peaking at 302.4  $\mu\text{mol/L}$ , without urinalysis or immunologic blood tests alterations. Multifactorial etiology for kidney dysfunction was considered, including infection, diuretics, gentamicin toxicity and CRS. Once better from infectious and congestive state, he was discharged with Scr 163.6  $\mu\text{mol/L}$ .

A week later, he presented to the cardiology clinic with worsening ascites and fatigue despite the increase of his diuretics dosage. He was admitted to an intensive care unit with cardiogenic shock and acute kidney injury [serum urea (Sur) 40.9 mmol/L and Scr 740  $\mu\text{mol/L}$ ]. He was started on noradrenaline, dobutamine and furosemide perfusions and even though his blood pressure stabilized, he remained anuric and hemodialysis (HD) was needed shortly after. After several days, he was hemodynamically stable and was able to come off both the vasopressor and inotropic agents, although still dialysis-dependent, and was transferred to the nephrology ward. Heart ultrasound showed de novo severe mitral regurgitation of organic nature, without any signs of endocarditis, with an ejection fraction of 35% (previously 40%).

During the initial transition, the patient became increasingly overloaded and there was a need to increase his HD plan to six times weekly, that was slowly tapered during the following month during which the patient regained partial diuresis (500 mL/day). Renal ultrasound was performed and was unremarkable, with normal corticomedullary differentiation. Urine sediment was bland. Assuming that the kidney injury was most likely caused by CRS type 1, we presented the case to cardiology, who agreed that the patient was eligible for heart surgery. The patient was then discharged, still HD dependent, awaiting surgery.

A month later, he was admitted for bioprosthetic mitral valve implantation and tricuspid valve repair, after which he required ICU monitoring and vasopressor and inotropic support for 72 hours. After three weeks, he was discharged, maintaining dialysis treatment. Over the course of two months, a slowly but steady improvement of his renal function was noted and eventually, HD was stopped, with a Scr 161.8  $\mu\text{mol/L}$  and Sur 7 mmol/L. A year later, his creatinine remains within the same values, without any peripheral edema nor ascites and no complaints of shortness of breath.

## Discussion

An effective classification of CRS has been proposed in a Consensus Conference by the Acute Dialysis Quality Group [2] in 2008. This classification divides CRS in 2 main groups, cardiorenal and renocardiac CRS, based on the *primum movens* of disease (cardiac or renal). Both groups are then divided into acute and chronic types

according to the onset and duration of the underlying organ dysfunction. Type 5 CRS integrates all cardiorenal involvements induced by systemic diseases [2].

In this case, it is clear that, although we have a long standing heart failure (HF), it was an acute event, namely, de novo severe mitral regurgitation that was the primary cause for the CRS. CRS type 1 is characterized by acute worsening of cardiac function leading to AKI in the setting of active cardiac disease [3]. In these patients, underlying chronic kidney disease (CKD) is fairly frequent and contributes to AKI in 60% of all cases studied, which represents an independent mortality risk factor in ADHF patients. Pathophysiology includes hemodynamic mechanisms, leading to decreased renal arterial flow and a consequent fall in glomerular filtration rate (GFR). There are different hemodynamic profiles, such as “cold” [with reduction in effective circulation fluid volume related to the renin angiotensin-aldosterone system (RAAS) and systemic nervous system activation causing afferent vasoconstriction] and “wet” (pronounced increase in central venous pressure with increased pulmonary and/or systemic congestion which is responsible for the decrease in renal vein and kidney perfusion pressure and progressive decline in GFR), with the former representing the main hemodynamic change [3].

Non-hemodynamic mechanisms also play a part, including chronic inflammation and asymmetry in the proportion of reactive oxygen species/nitric oxide production. Oxidative stress is a hallmark of type 1 CRS, as showed by a marked increase in circulating reactive oxygen species and reactive nitrogen species, coupled with increased expression of interleukin-6. Renal tubular epithelium is particularly vulnerable to ischemic injury resulting in cell death by apoptosis and necrosis with consequent loss of epithelial cell structure and function [4].

The management of CRS can be challenging. The importance of primary prevention cannot be stressed enough for both cardiac and renal disease as they share common risk factors. This includes blood pressure, cholesterol and glucose management as well as physical activity and smoking cessation [5]. Treatment strategies should focus on managing the predominant underlying condition, whether that is cardiac or renal. In this case, therapy should focus predominantly on managing chronic HF and preventing, decreasing and treating decompensation episodes, mainly by improving cardiac function, decreasing volume overload and increasing ejection fraction [5].

Regarding treatment options, intravascular and extravascular volume control should be reached primarily with diuretics, as prevention of left ventricular volume overload is mandatory to maintain adequate cardiac output and systemic perfusion. Diuretics, especially loop diuretics, are the gold standard in ADHF and CRS type 1 therapy and while they succeed in reducing flu-

id overload and improving symptoms (such as shortness of breath and edema), they can also worsen the ongoing kidney injury, while having no benefit in its recovery [3]. Nevertheless, aggressive diuresis improves survival despite worsening renal function and remains the mainstay of management in fluid overload in both HF and renal failure, although careful use is warranted [5]. Adding distal tubule-acting diuretics (thiazides, thiazide-like and aldosterone antagonists) to loop diuretics are sometimes needed to try to overcome diuretic resistance (defined as the attenuation of the maximal diuretic effect that ultimately limits sodium and chloride excretion). The use of inhibitors of aldosterone receptors in patients with chronic HF leads to significant improvement in survival and hospitalization rates [5]. The RALES trial, conducted with spironolactone, showed a reduction in mortality compared with the placebo group [6]. Additionally, daily sodium and fluid intake restriction needs to be reinforced [5].

As explained before, RAAS antagonism is an essential part of therapy for acute and chronic HF and renal failure. Angiotensin-converting enzyme (ACE) inhibition and angiotensin receptor blockers (ARBs) are known to aggravate renal function prompting hesitation to prescribe and a low threshold for stopping. They should not be discontinued as such patients have decreased mortality despite deterioration in GFR [5].

Although beta-blockers should be avoided in acute HF, they are a hallmark of the management of chronic HF. When coupled with either ACE inhibitors or ARBs, they are associated with better cardiovascular and renal outcomes not only in elderly patients, but also in those with advanced CKD [3].

Nepriylsin is an enzyme that contributes to the breakdown of several endogenous vasoactive peptides (natriuretic peptides, bradykinin and adrenomedullin), opposing the neurohormonal activation that leads to vasoconstriction, sodium retention and maladaptive remodeling. Its inhibition was a potential therapeutic strategy to delay the development or progression of both cardiovascular and kidney disease, achievable by neprilysin inhibitor sacubitril. A new combination drug, sacubitril/valsartan, became a new cornerstone in the management of chronic HF, after a recent study showed an overwhelming benefit in terms of hospitalization for HF, death from cardiovascular causes and their composite as well as all-cause mortality [7]. Sacubitril/Valsartan is recommended by NICE as an option for treating symptomatic chronic HF with reduced ejection fraction, only in people with 1) NYHA class II to IV symptoms; 2) Left ventricular ejection fraction of 35% or less and; 3) Who are already taking a stable dose of ACE inhibitors or ARBs.

Recently, levosimendan, a calcium sensitizer inodilator agent, has been proven to provide benefits in ADHF

by increasing ejection fraction and diuresis [3], although its use is only possible with inpatient admission. Other positive inotropic agents, such as dopamine or dobutamine, are also used for ADHF with low cardiac output, improving and maintaining systemic perfusion and preserving endorgan function in patients with severe systolic dysfunction or symptomatic hypotension [7].

Given the high prevalence of CKD in patients with HF and vice versa, implantable device therapy is part of the therapeutic options in this population [4]. Cardiac resynchronization (CRT) or left ventricular assist devices can improve hypoperfusion in HF patients [8]; in fact, a systematic review by Garg, et al. [9] demonstrated that CRT in patients with CKD led to an improvement in left ventricular ejection as well as GFR, which suggests a degree of reversibility in CRS 1 and 2 [4], although additional studies are required to evaluate this further.

Once pharmacological treatment fails in both AKI and CKD patients and oligo-anuric renal failure is established, renal replacement therapy has to be started [3]. Similarly, ultrafiltration may be considered for patients with refractory congestion not responding to medical therapy [4].

Despite recent advances in perioperative cardiovascular care, due to their fragile condition and high mortality risk, dialysis patients are often excluded of major cardiac surgeries, such as mitral valve replacement and tricuspid repair. However, intervention of valvular defects might be of potential beneficial value in the presence of CRS, allowing optimization of hemodynamics and potentially improving renal perfusion [9]. This case validates that even if we are presented with a dialysis dependent patient, if the kidney dysfunction is of an acute setting and if the patient is stable enough without any life threatening condition, a surgical approach should always be sought as a viable option, as long as the underlying condition has the potential of being corrected. As such, end stage renal failure should not be regarded as an absolute contraindication to cardiac surgery. For our patient, this meant a dramatic improve in both his heart and kidney function with dialysis independence and an extremely positive impact in his quality of life.

## Conclusion

The pathophysiology and clinical impact of the various subtypes of CRS exemplify the intricate cross talk between the heart and the kidney. Given the huge morbidity and mortality of the dual burden of these organ system afflictions, early recognition of the clinical phenotype of CRS and interventions to slow down end organ damage are crucial in positively influencing the burden of this pathological symbiosis. We hereby present a report in which renal function improved dramatically after identification and correction of the CRS' culprit, avoiding renal replacement therapy and, mostly, having a powerful impact on patient's life.

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