Cardiorenal syndromes and their role in water and sodium homeostasis

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Water, sodium and cardiorenal syndromes

Summary

Sodium is the main osmotically active ion in the extracellular fluid and its concentration goes hand in hand with fluid volume. Under physiological conditions, homeostasis of sodium and thus amount of fluid is regulated by neural and humoral interconnection of body tissues and organs. Both heart and kidneys are crucial in maintaining volume status. Proper kidney function is necessary to excrete regulated amount of water and solutes and adequate heart function is inevitable to sustain renal perfusion pressure, oxygen supply etc. As these organs are bidirectionally interconnected, injury of one leads to dysfunction of another. This condition is known as cardiorenal syndrome. It is divided into five subtypes regarding timeframe and pathophysiology of the onset. Hemodynamic effects include congestion, decreased cardiac output, but also production of natriuretic peptides. Renal congestion and hypoperfusion leads to kidney injury and maladaptive activation of renin-angiotensin-aldosterone system and sympathetic nervous system. In cardiorenal syndromes sodium and water excretion is impaired leading to volume overload and far-reaching negative consequences, including higher morbidity and mortality of these patients.

Key words

cardiorenal syndrome, renocardiac syndrome, volume overload, sodium retention

Introduction

The function of the heart and kidneys is tightly, bidirectionally connected and both organs are crucial in maintaining water and electrolyte homeostasis. Because of this, damage to one organ often leads to injury of the other. This is mediated by different neurohormonal pathways, triggering a vicious cycle. This situation is called cardiorenal syndrome (CRS), where impaired cardiac function has negative effect on kidney functions and vice versa. CRS classification helps the medical professionals to understand the etiology and to direct appropriate therapy [1]. Moreover, patients with CRS also have worse prognosis than patients with single organ lesion. It has been classified into five subtypes (CRS 1-5, see **Table 1**) regarding pathophysiology and timeframe [2]. Heart and kidney dysfunction results in fluid retention, electrolyte disbalance etc.

Volume overload manifests as congestion and oedemas, with many negative effects on different organs [3]. In heart, volume overload induces dilation or hypertrophy of the heart chambers, which worsen heart function and predispose to heart failure, arrythmias etc. [4]. The consequence of gastrointestinal mucosal oedema is decreased absorption not only of nutrients, but also of medication, resulting in deficient effect of pharmacotherapy [5]. Pulmonary congestion and oedema manifest as dyspnea [6]. In systemic circulation, volume overload is characterized by increased central venous pressure that is transmitted into organs (including kidneys) and decrease the perfusion pressure. Specific responses of crucial organs will be described below.

Water and sodium homeostasis

Maintenance of water homeostasis is a complex process ensured by neural and humoral interconnection of body tissues and organs. Extracellular fluid volume is controlled by changes in blood pressure, blood osmolality and by variation of blood viscosity and velocities [7].

Kidneys

Adequate renal and heart functions are crucial for preservation of adequate volume status. Apart from water loss by breathing or sweating, the only possibility to excrete regulated volume of fluids is through kidneys. As about 150-200 l of primary urine is created daily, effective regulatory mechanisms are necessary [8]. Tubular system of the nephron passes through highly concentrated medullary interstitium, creating osmotic gradient which allows water reabsorption [9]. As the osmotic gradient wouldn't be sufficient without adequate blood flow and filtration pressure, proper

heart function is necessary. Under physiological conditions about 25 % of the resting cardiac output flows into the kidneys [10]. To prevent washout of the medullar concentration gradient, only 2 % of blood supply flow through deep medullar glomeruli and a mechanism called countercurrent exchange exists [11].

To maintain water homeostasis ability to create urine either more concentrated or more diluted than plasma is necessary. This is possible thanks to different permeability of nephron segments and specialized channels, especially by aquaporin channels (AQP) [10]. Seven types of AQP are present in specific regions of nephron´s tubular system, enabling transcellular water movement. Majority of these channels is present constitutively, but AQP 2 presence is administrated by vasopressin (mentioned below) and tightly regulate amount of excreted water [12, 13]. Intercellular water and solutes passageway is controlled by tight junction proteins. Expression of some of these proteins is dependent directly on medullar tonicity changes [14].

Heart

Both cardiac atria and ventricles include different types of receptors. In atria, particularly in pulmonary venous and cavo-atrial junctions [15], there are two types of vagal afferent nerves (A and B) [16]. Type A receptors sense heart rate and as a response, they modulate systolic function. In higher heart rate they increase contractility and vice versa [17]. Type B receptors are stretch receptors sensing atrial volume [18]. As response to atrial distension heart rate and urine flow increases [19]. In situations when atrial pressure rises slowly, these receptors have ability to adapt [18]. Third type of atrial receptors include unmyelinated afferent fibers also sensitive to stretch. In case of atrial distension both cardiovascular and renal functions are affected. Distension especially of the left atrium causes tachycardia, hypotension and lowers the systemic vascular resistance [20]. In kidneys urine flow increases and discharge of renal sympathetic nerve decreases.

Ventricular reflexes are mediated by vagal and sympathetic afferent fibers. Two types of unmyelinated vagal fibers were described. The first, mechanoreceptors, are stimulated by increased end-diastolic volume and by increased end-diastolic and end-systolic pressure [21], but also have the ability to sense situations as ischemia etc., where myocardial motion is altered [22]. The second, chemoreceptors, react to hypoxia, probably thanks to released bradykinin and prostaglandins [23]. As a result, distension of ventricles, especially the left, leads to reflex vasodepression, peripheral vasodilation and bradycardia. In kidneys reflex renal vasodilation occurs [22]. Sympathetic ventricular afferent fibers are also both unmyelinated and myelinated. Myelinated fibers respond to

blood pressure and coronary flow, especially in patients with heart failure [24]. Unmyelinated fibers are rapidly adapting, innervating mechano- and chemoreceptors sensitive to changes in intracardiac volume, wall motion, bradykinin, and prostaglandins [25, 26]. Their stimulation leads to excitatory or pressor reflex [27-29].

In congestive heart failure vagal afferents control plasmatic antidiuretic hormone level, renal nerve activity and plasma renin activity. As left atrial receptors have the ability of adaptation, in chronic state level of antidiuretic hormone remains inappropriately high, contributing to oedemas, ascites and hyponatremia [20].

Heart participates on maintaining fluid balance also by releasing atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) as a response to sensing myocardial stretching. Most important effects of natriuretic peptides include decrease in vascular tone and increase of natriuresis and water excretion via kidneys [30].

Humoral pathway

Important mechanism leading to sodium and water retention is triggering of renin-angiotensin-aldosterone system (RAAS), often activated in heart failure [31] **(Figure 1)**. This system participates in regulation of both intravascular volume and systemic vascular resistance but have also other effects e.g. pro-inflammatory, pro-apoptotic, etc. [32]. Decreased renal blood flow, decreased sodium content or beta-activation directly or indirectly result into renin flush out of specialized cells in afferent arterioles [33]. This triggers cascade of events as renin cleaves angiotensinogen produced in liver into inactive angiotensin I, which is converted into physiologically active angiotensin II. The last process takes place mostly in lungs and is catalyzed by angiotensin converting enzyme [34]. Angiotensin II has several effects including increased sodium reabsorption, vasoconstriction of systemic arterioles, potentiation of feeling of thirst, stimulation of neurohypophysis to vasopressin releasement and stimulation of aldosterone releasement from adrenal cortex leading to further sodium retention [35]. Acting in renal tubules, aldosterone increases reabsorption of both sodium and water by different transporters (e.g. Na+/Cl-symporter) [36]. Studies showed that increased levels of aldosterone have deleterious effect on kidney function and glomerular filtration rate [36, 37]. Vasopressin, released from hypothalamus, regulates sodium concentration in serum by balancing renal water excretion and urine concentration. Under the vasopressin effect, AQP 2 is inserted into luminal membrane in kidney, letting water flow from the filtrate into medullary interstitium, creating more concentrated urine [38].

ANP and BNP are parts of natriuretic peptide family secreted by the heart, acting as cardiac hormones [39]. In healthy organism proANP outbalances in healthy atrial tissue and is proteolytically processed into final bioactive α-ANP and side product β-ANP [40]. On the other side proBNP is processed within ventricular myocytes with active BNP and inactive N-terminal proBNP being final products [41]. Levels of all these proteins are increased in patients with heart failure. Their main effects include decrease in vascular tone and increase of natriuresis and thus also water excretion via kidneys, but antifibrotic and antihypertrophic effects are also present [42]. Both ANP and BNP decrease systemic blood pressure. They acutely act as vascular smooth muscle cells relaxants and in chronic state they also regulate endothelial permeability [30].

In some patients with advanced stages of kidney disease or HF the only possibility of treatment is organ transplantation. The changes in humoral pathways haven´t been clearly described in this group of patients, however few studies exist. In work of Issa et al. plasma renin activity and plasma aldosterone levels were measured five years after kidney transplantation, and their levels stayed in the normal range. In this study it was also proven, that blockage of angiotensin II is effective in the RAAS suppression [43]. Heart transplantation often leads to normalization of heart endocrine function, however levels of BNP remain high even in the good graft function and rather level change than absolute value should be considered [44].

Neural pathway

Apart from neural fibers mediating connection between tissues and organs as mentioned above, several brain areas contain specialized neurons able to sense plasma osmolality and volume change [45]. In situation of decreased plasma volume vasopressin is secreted from hypothalamus and the feeling of thirst arises [46, 47].

As mentioned above, neural connections between tissues and organs, namely sympathetic nervous system (SNS) is overreactive in both HF and CKD [48]. Parasympathetic vagal nerve may inhibit SNS and norepinephrine release at presynaptic level. Under physiological conditions at rest parasympathetic tone predominates over SNS [49]. In both HF and kidney disease vagal activation is attenuated [50, 51]. It was proven that regular dialysis halts parasympathetic damage [52].

Vagal nerve stimulation was tested on animal models with optimistic findings such as slower left ventricular dilation with improved ejection fraction [53], improvement of hemodynamic measures, decreased risk of arrythmias and death [54]. However, these positive effects were not proved in clinical studies [55]. On the other side, blunting SNS by betablockers showed as

advantageous and is a basic part of HF treatment [56]. Trials with moxonidin (central sympatholytic agent) were prematurely terminated due to higher morbidity and mortality [57].

Kidneys play an important feedback role in in SNS activation and modulation of the axis of heart - brain - vasculature. In recent years the effect of renal denervation in patients with poorly controlled hypertension and HF was proven in several studies where ejection fraction and diastolic parameters improved, hypertrophy and maladaptive remodeling regressed [58-60].

Sodium and water shifts in the body

Body is composed by two main compartments, separated by semipermeable membrane, i.e., intracellular, and extracellular, which comprises both intravascular and interstitial compartment. Solute concentration in these compartments differs and creates concentration gradients and osmotic pressure, which is equilibrated by water movement through semipermeable membrane [61]. Sodium and water contents are responsible for cell volume. Specific situation occurs in brain to prevent brain oedema. Tight junctions in brain capillaries create blood barrier which sodium can´t pass. This is important as brain swelling or shrinkage may be a life-threatening condition [62].

As sodium is one of the main osmotically active ions in the extracellular fluid, its concentration goes hand in hand with fluid volume. Human body have precise osmoregulatory mechanisms, which under healthy conditions maintain sodium concentration within physiologic range [63]. Sodium shifts are primarily mediated by Na+/K+ATPase, an active transporter that exchange sodium from the cell for extracellular potassium (primarily intracellular cation) [64].

In study of Titze et al. it was proven that skin serves as “osmotically inactive” sodium storage by increasing glycosaminoglycan production and sulfatation. It was concluded that also monocyte phagocytes system contributes to the control of interstitial sodium and blood pressure homeostasis [65]. This mechanism was studied in patients with heart failure (HF), CKD and dialysis population and the levels of skin sodium in HF population was comparable to dialysis patients, and significantly higher than in CKD patients [66].

Other important mechanisms regulating water and sodium excretion as RAAS or role of hypothalamus are mentioned above.

Rapid sodium changes causing hyponatremia occur in case of excess water intake or other pathologic conditions, when kidneys are not capable adequately dilute urine and to excrete free water. Sodium concentration increases in case of insufficient urine concentration in large amount of

sodium ingestion/infusion or if there is inadequate loss of electrolyte-free water [67]. Significantly worse ability of urine dilution or concentration was proven in patients with advanced CKD (e-GFR<60 ml/min) [68].

Cardiorenal syndromes

Cardiorenal syndrome type 1

Acute heart failure (AHF), cause of CRS1, is a syndrome comprising several pathophysiologic entities, developing like de novo heart failure or as an acute decompensated chronic heart failure [69]. The most common AHF etiologies include acute coronary syndromes, severe arrhythmias, uncontrolled hypertension, severe valvular disease, pulmonary embolism etc. [70]. Symptoms may also vary depending on the predominant involvement of the left or right heart compartments. Acute failure of the left heart function is represented on one side by decreased cardiac output (CO) with peripheral hypoperfusion, on the other side by congestion, which transmits through the lung circulation, with the development of pulmonary congestion/oedema and pleural effusions, into the right heart. Since the right compartments are normally relatively low-pressure, an acute pressure overload leads to their failure with signs and symptoms of right heart failure [71]. This manifest as systemic congestion, including renal congestion, increased intra-abdominal pressure and in advanced stage also pleural effusions. Forward failure of the right heart results in underfilling of left ventricle with inadequate cardiac output or even in cardiogenic shock [72].

As about 25% of the cardiac output flows into the kidneys to eliminate a sufficient amount of fluid, decrease in CO and decreased mean arterial pressure lower perfusion pressure [71], leading to kidney hypoperfusion [72]. On the contrary, renal congestion leads to distension of renal venules with their obliteration, further reducing renal perfusion pressure and causing fluid extravasation generating increased renal interstitial pressure. All these conditions cause hypoxic state of renal parenchyma with glomerular and tubular dysfunction and water retention. Symptoms as dyspnea, lower limb swelling, weight gain etc. occur [73]. Acute decrease in renal blood flow activates renin-angiotensin-aldosterone system (RAAS), SNS and reduces nitric oxide in the endothelium with releasement of inflammatory mediators [71] **(Figure 2).**

Cardiorenal syndrome type 2

CRS 2 is a syndrome where hemodynamic changes of chronic heart failure (CHF) cause impairment of kidney functions [74]. CHF affects about 1-2 % of adult population, but its' prevalence

in people over 70 years is more than 10 % [75]. It is characterized by elevated brain natriuretic peptides and by functional and/or structural changes of the heart accompanied by typical signs and symptoms of HF [76]. In patients with long-term stable CHF dependency between underlying CHF and worsening of renal function was proved [75, 77]. However, the reverse is also possible, and potential improvement of renal functions was proved after appropriate non-pharmacological therapy and pharmacological therapy, especially guideline-mediated therapy of HF, including gliflozins [78].

Among patients with CHF, the "backward" effects are much more common. They lead to venous congestion and increase of the renal venous pressure, which lowers the renal perfusion pressure. Chronic renal congestion induces structural kidney injury, including glomerulosclerosis and tubulointerstitial fibrosis [79]. Laboratory tests prove elevated renal injury biomarkers, mild to moderate proteinuria, and a progressive decline of glomerular filtration rate [80]. In "forward" HF, where cardiac output is decreased, the state of renal arteries underfilling leads to maladaptive activation of the RAAS and the SNS [81]. Angiotensin II, part of RAAS, has various effects, including vasoconstriction with increased systemic vascular resistance, increased venous tone, and leads to congestion. In kidneys, vasoconstriction affects predominantly the efferent arteriole. This exceeds glomerular filtration fraction and increases tubular sodium and water reabsorption. Further excess of body water is caused by its central effect increasing thirst [82] **(Figure 3)**.

Cardiorenal syndrome type 3

In CRS 3, acute kidney injury causes heart dysfunction and may be also described as acute renocardiac syndrome. Renal impairment may arise on different sites, i.e. prerenal, renal and postrenal, so proper fast evaluation of etiology and treatment is necessary [83]. Most common etiology, especially in elderly patients, is prerenal including hypovolemia or hypotension. About 50% of causes are renal, caused by diseases of glomeruli, tubules or interstitium, and by vascular diseases. Nephrotoxic medication plays an important role and due to the availability of contrast examinations, the frequency of contrast-induced nephropathy increases [84]. Indirect effects of AKI are caused by different pathways including sodium and water retention, electrolyte imbalance, acidemia and uremic toxins [85]. Electrolyte imbalance may manifest itself as hyperkalemia, hyperphosphatemia, hypocalcemia etc. also varying due to primary cause of renal failure [86]. Hyperkalemia, as one of the most common, not only increases susceptibility to life-threatening arrythmias [87], but rapid changes in potassium levels result in muscle weakness, paralysis or change in mental status [88]. Decreased pH disturbs energy metabolism of cardiomyocytes and have

negative inotropic effect, but also potentiate pulmonary vasoconstriction and increases afterload of the right ventricle [88]. Uremic toxins increase microvascular permeability, reduce cardiac contractility [89], and are associated with more frequent occurrence of myocardial infarction, or can cause pericarditis [90, 91]. All of this can trigger vicious circle, activation of SNS and RAAS with further organ dysfunction.

Cardiorenal syndrome type 4

This type of CRS, which may also by described as chronic renocardiac syndrome is caused by chronic kidney disease (CKD). CKD affects more than 13% of worldwide population with rising tendency, especially due to rising prevalence of comorbidities as diabetes mellitus and hypertension, causing higher morbidity and mortality of afflicted patients [92]. It is a slowly progressing and irreversible syndrome reflecting functional and/or structural kidney changes. It is divided into five stages regarding glomerular filtration rate (GFR) and into three stages according to amount of albuminuria [93].

As kidneys lose their function, sodium and water excretion is impaired, and RAAS is activated [94]. Fluid overload often occurs, with far-reaching hemodynamic consequences. As kidneys' blood flow is normally relatively high, approximately 400 ml/100 g of tissue per minute, and dependent on adequate intra- and transglomerular pressure [95], both appropriate inflow and outflow are inevitable. In these patients with systemic congestion and heart failure, renal functions further worsen due to hypoxia and ischemia. Ronco et al. described renal impairment as "Congestive kidney failure" and in this situation without adequate treatment vicious circle starts [96]. As mentioned, CKD is associated with increased SNS and RAAS activity, so not surprisingly angiotensin-convertin enzyme inhibitors, angiotensin receptor blockers or betablockers were proven profitable for this group of patients [97, 98]. Usage of gliflozins was also proven beneficial [99]. In patients with autosomal dominant polycystic kidney disease, tolvaptan was documented to prevent progression of CKD [100]. In end-stage kidney disease the use of hemodialysis is often necessary. Thanks to advances in technology the dialysis was proven to improve both mortality and morbidity [101]. Accelerated atherosclerosis in patients with decreased GFR results in coronary artery disease including myocardial infarctions with further hemodynamic impairment conditioned by calcifications in both vessels and heart, by increasing arterial stiffness and by decreased aortic compliance. Left ventricular hypertrophy develops or further worsens in advanced renal disease [102]. In addition, malnutrition and inflammation are often present [103] **(Figure 4)**.

Cardiorenal syndrome type 5

Pathophysiology of this type of CRS encounters different systemic disorders causing simultaneous impairment of heart and kidneys. It can also be caused by a chronic disease, for example liver cirrhosis. Common etiologies include particularly acute sepsis, but also connective tissues disorders such as lupus erythematosus or drug toxicity [104].

Pathophysiology of this syndrome varies by cause. In sepsis hemodynamic and microvascular changes lower flow velocities [105], leading to septic cardiac dysfunction caused by alteration in coronary blood flow, ischemia, inflammatory mediators and changes in myocardial metabolism [106]. Studies on septic kidney injury differ, however metanalyses showed that in about 30% of studies renal blood flow (RBF) was preserved or increased. In this situation acute tubular apoptosis was main cause of renal injury [107]. In other studies RBF decreased, resulting into acute tubular necrosis. Other changes include changes in central nervous system in order to preserve blood supply to vital organs [108].

In all cardiorenal syndromes water and sodium homeostasis is impaired due to dysfunction of crucial organs - kidneys and heart. Although the pathophysiology of CRS types differs, without adequate treatment they all lead to vitious circle causing fluid retention with further consequences, including higher morbidity and mortality of these patients. Deleterious effects of heart failure include direct hemodynamic effects as congestion or decreased cardiac output, but also other effects connected with natriuretic peptides production described above. Renal congestion has a direct effect on tubules as tubular injury, apoptosis, or necrosis. Impaired renal functions have on one hand direct effect on kidney sodium and water excretion, on the other hand maladaptive activation of RAAS and SNS occurs.

Prevention

Type 2 diabetes mellitus (DM 2) is the most frequent cause of both CKD and heart failure with preserved ejection fraction (HFpEF) in developed countries [109]. Obesity is the predisposing factor to DM 2, therefore adequate management of obesity and diabetes is the most important measure for preventing CKD and HFpEF and therefore also the development of CRS. Other general influenceable risk factors include dyslipidemia, hypercholesterolemia, hypertension and smoking [110-112]. In all CRS types, the maintenance of normovolemia and avoidance of kidney ischemia is important and the usage of nephrotoxic and cardiotoxic medication should be minimized [113]. Regular medical check-ups with proper both non-pharmacological and pharmacological treatment

are inevitable. In the prevention of CRS 2 positive effect of RAAS inhibitors, betablockers, statins and gliflozins was proved [113, 114], and so was the effect of pharmacological agents as RAAS blockers and gliflozins in CRS 4 [113, 115, 116]. Prevention of iodine contrast-induced nephropathy is important especially in patients with established CKD and included adequate hydration and, according to some, but not all studies also the administration of N-acetylcystein (CRS 3), especially if high dosed [116].

Gaps in the current knowledge and further research possibilities

There are still some blind spots giving us the opportunity for further research. In patients with ESRD on hemodialysis there is much unknown. The diagnosis of HFpEF in this group of patients remains the most frequently underdiagnosed entity in clinical practice of hemodialysis patients [117]. Hemodialysis induces a lot of changes, some of which are reversible, however we do not know how to avoid CKD- mineral and bone disorder, pathological hypertrophy of left ventricle etc. [118-121]. If arteriovenous access for hemodialysis is created, there is still the question of safe access flow [122].

In recent years, probably the biggest progress was in the study of biomarkers. It showed that NGAL may predict both renal and cardiovascular outcomes in myocardial infarction patients, but further research is needed [123, 124]. Newly also microRNA are used [125-128] and creation of multivariable panel of microRNAs in combination with conventional biomarkers is the next goal [128].

Another possibility for further research is represented by animal models. So far animal model usage in CRS study includes especially rat and mouse models [129, 130], however translation of these results to human is limited, so there is effort to use also larger animal models as canine, porcine or ovine models. Lately, dog models were used by Szczepankiewicz et al. while studied urine podocin/creatinine ratio which was higher in dogs with heart or kidney impairment [131]. Orieux et al. proved origin of CRS in porcine models with pulmonary hypertension [132]. Interesting option in recent years represents advanced in vitro models with control of cellular component and environment [133].

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Table 1. Classification of cardiorenal syndromes (CRS) [1]

Cardiorenal subtype	Description	Examples/Etiology
CRS Type 1 (acute CRS)	Rapid worsening of cardiac function leading to acute kidney injury	Acute myocardial infarction with cardiogenic shock, acute valvular insufficiency, acute decompensated heart failure
CRS Type 2 (chronic CRS)	Chronic abnormalities in cardiac function leading to chronic kidney disease	Chronic inflammation, long-term renin-angiotensin-aldosterone system and sympathetic nervous system activation, chronic hypoperfusion
CRS Type 3 (acute renocardiac syndrome)	Acute worsening of renal function leading to worsening cardiac function	Uremia causing impaired contractility, hyperkalemia causing arrythmias, volume overload causing pulmonary oedema

CRS Type 4 (chronic renocardiac syndrome)	Chronic worsening of renal function leading to worsening cardiac function	CKD leading to LVH, coronary disease and calcification, diastolic dysfunction, etc.
CRS Type 5	Acute or chronic systemic disease leading to both cardiac and renal dysfunction	Sepsis, diabetes mellitus, amyloidosis, vasculitis

Figure 1. Blood volume and pressure control of renal water and sodium excretion
RBF - renal blood flow, GFR - glomerular filtration rate, ACE - angiotensin converting enzyme, ACTH - adrenocorticotropic hormone, ADH - antidiuretic hormone

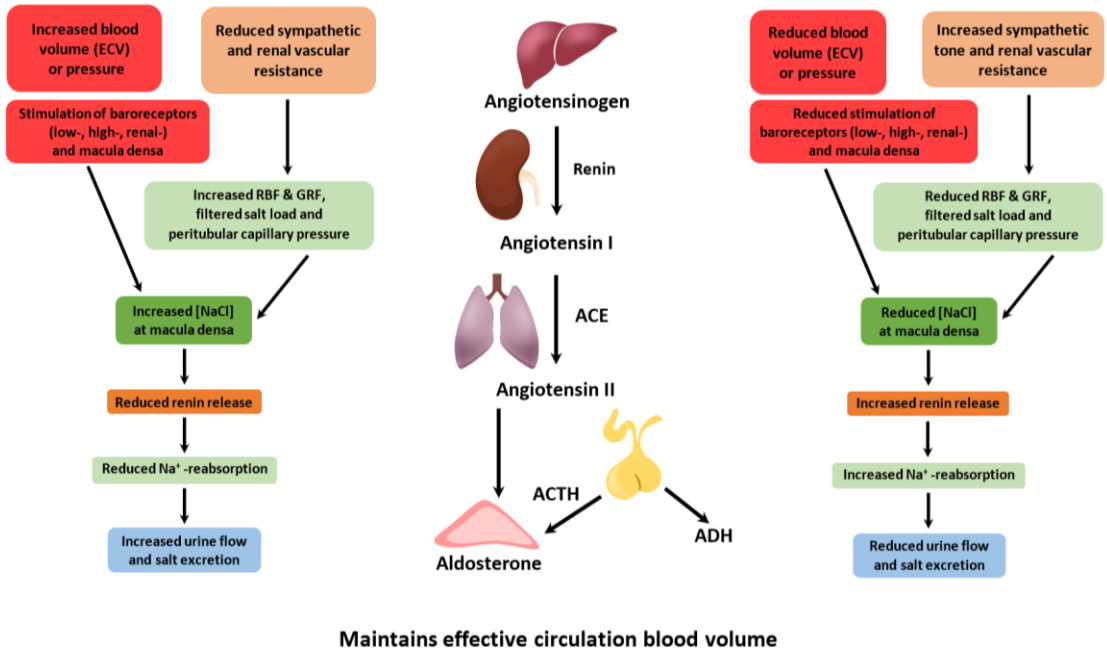


Figure 2. Pathophysiology of cardiorenal syndrome type 1
ADHF - acutely decompensated heart failure, RAAS - renin-angiotensin-aldosterone system, AKI - acute kidney injury, CKD - chronic kidney disease

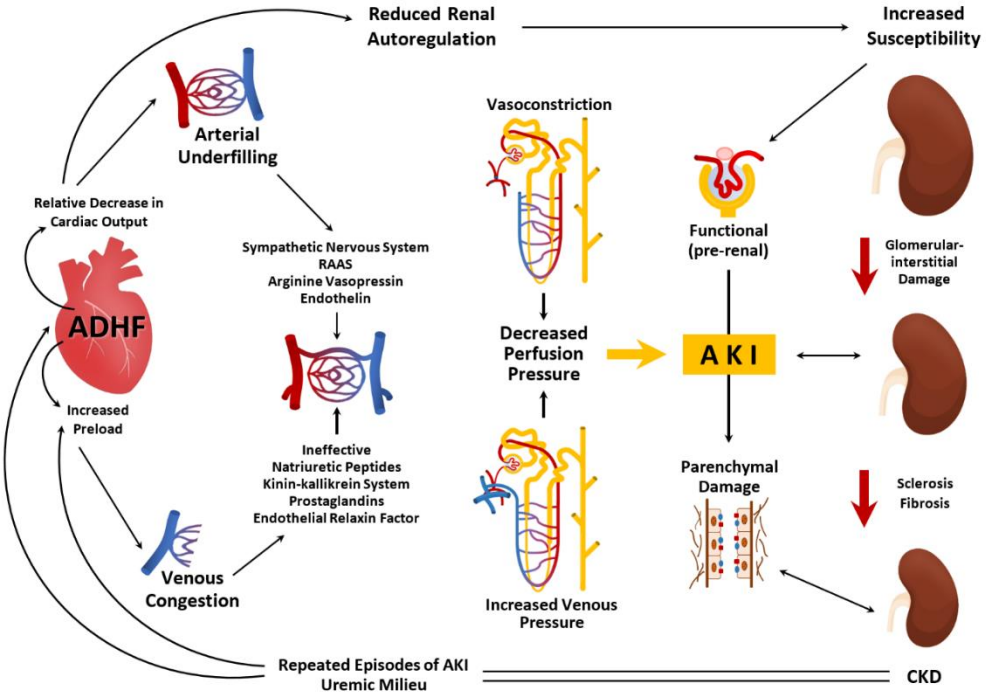


Figure 3. Pathophysiology of cardiorenal syndrome type 2

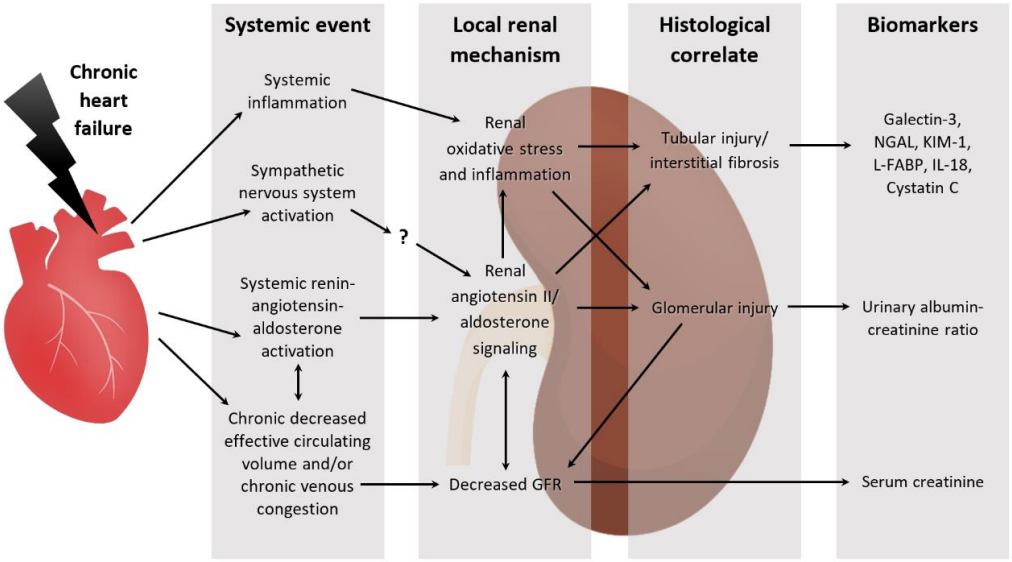
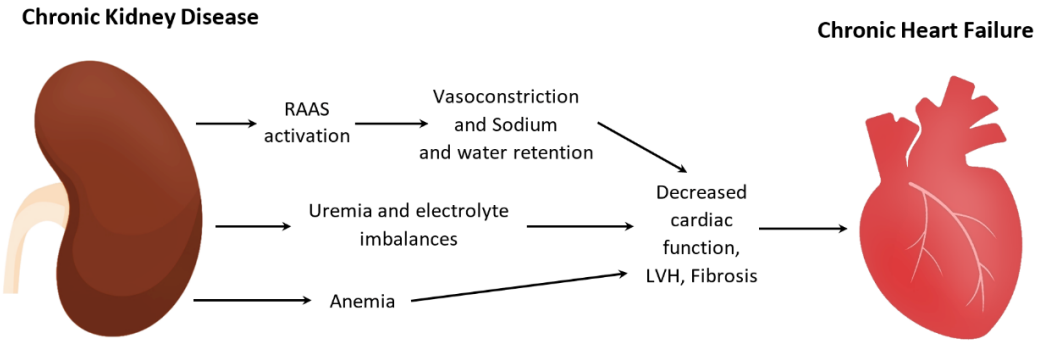


Figure 4. Pathophysiology of cardiorenal syndrome 4

RAAS - renin-angiotensin-aldosterone system, LVH - left ventricle hypertrophy


Chronic Kidney Disease
Chronic Heart Failure
RAAS activation
Vasoconstriction and Sodium and water retention
Uremia and electrolyte imbalances
Anemia
Decreased cardiac function, LVH, Fibrosis