Cardiorenal syndrome: long road between kidney and heart

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Abstract

Almost 200 years ago, the first evidence described by Robert Bright (1836) showed the strong interaction between the kidneys and heart and, since then, the scientific community has dedicated itself to better understanding the mechanisms involved in the kidney–heart relationship, known in recent decades as cardiorenal syndrome (CRS). This syndrome includes a wide clinical variety that affects the kidneys and heart, in an acute or chronic manner. Moreover, it is well established in the literature that the immune system, the sympathetic nervous system, the renin–angiotensin–aldosterone, and the oxidative stress actively play a strong role in the cellular and molecular processes present in CRS. More recently, uremic molecules and epigenetic factors have been also shown to be key mediators in the development of syndrome. The present review intends to present the *state of the art* regarding CRS and to show the paths known, until now, in the long road between the kidneys and heart.

Keywords Cardiorenal syndrome · Renal diseases · Cardiovascular diseases · Inflammation · Immune system

Abbreviations

ACE	Angiotensin-converting enzyme
ACEIs	Angiotensin-converting enzyme inhibitors
ADHF	Acute decompensated heart failure
AKI	Acute kidney injury
Ang	Angiotensin
ANS	Autonomic nervous system
ARB	Angiotensin receptor blockers
ASC	Apoptosis-associated speck
AT1	Angiotensin II type 1 receptor
AT2	Angiotensin II type 2 receptor
ATP	Triphosphate adenosine
β-ARs	β-Adrenergic receptors
CaMKII	$Ca2^+$/calmodulin-dependent protein kinase II
CAT	Catalase
CCL	(C–C motif) ligand
CCR	(C–C) chemokine receptor
CH	Cardiac hypertrophy
CKD	Chronic kidney disease
CRP	C-reactive-protein
CRS	Cardiorenal syndrome
CVD	Cardiovascular disease
CXCL	CXC chemokine ligands
DAMPs	Damage-associated molecular patterns
DCs	Dendritic cells
DRI	Direct renin inhibitors
EC	Endothelial cell
eNOS	Endothelial NOS
ESKD	End-stage kidney disease
ERK	Extracellular signal-regulated kinases
EVs	Extracellular vesicles
FGF23	Fibroblast growth factor 23
GFR	Glomerular filtration rate
HMGB1	High mobility group box 1
HF	Heart failure
HOCl	Hypochlorous acid

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HSPS	Heatshock proteins
ICAM-1	Intercellular adhesion molecule 1
IFM	Interfibrillar mitochondria
IFN	Interferon
IL	Interleukin
IRI	Ischemia and reperfusion injury
IS	Indoxyl sulfate
LV	Left ventricle
MAPK	Mitogen-activated protein kinase
MBD	Mineral bone disorder
MC	Mast cell
MCO	Medium cut-off
MDA	Malondialdehyde
MHC	Major histocompatibility complex
MI	Myocardial infarction
MiR or MiRNA	MicroRNA
MMPs	Matrix metalloproteases
MPs	Mononuclear phagocytes
NF-κB	Nuclear factor kappa B
Nfr2	Nuclear factor erythroid 2
NLR	NOD-type intracytoplasmic receptor
NO	Nitric oxide
NOS	Nitric oxide synthase
NOX	NADPH oxidase
PAMPs	Pathogen-associated molecular patterns
PBUT	Protein-bound uremic toxin
PCS	P-Cresyl sulfate
PMNs	Polymorphonuclear neutrophils
PRA	Plasma renin activity
PTH	Parathyroid hormone
RAAS	Renin-angiotensin-aldosterone system
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
SOCS	Suppressor of cytokine signaling
SOD	Superoxide dismutase
SNS	Sympathetic nervous system
TAC	Transversal aortic constriction
TGF-β	Transforming growth factor beta
TLR	Toll-like receptors
TNF-α	Tumor necrosis factor-alpha
Tregs	Regulatory T cells
UT	Uremic toxins
VCAM1	Vascular cell adhesion protein 1
VSMC	Vascular smooth muscle cells

Cardiorenal syndrome: general considerations

The relationship between the heart and kidneys has been studied since 1836, starting with the connection between proteinuria and cardiac alterations [1]. The first study concerning this subject was published by Robert Bright (1836),

who observed that the prevalence of cardiovascular diseases (CVD) in patients with renal disease was accompanied by the secretion of urinary albumin [1]. Although the connection between the two organs has been studied for almost two centuries, it was only in 2004 that the National Heart, Lung, and Blood Institute formally attempted to define cardiorenal syndrome (CRS) as an increase in systemic volume by the kidneys that is aggravated by the progression of heart failure (HF). In 2008, the definition of CRS became considerably broader when the Acute Dialysis Quality Initiative reached a consensus of two major CRS groups, cardiorenal and reno-cardiac, based on the initial pathology, and then further subdivided into five types of CRS [2, 3]. The results are summarized in Table 1.

It is notable that all CRS types have crosstalk, and all can develop into a cycle that worsens both the primary and secondary conditions, further aggravating the pathology shown in Fig. 1 and Table 1. In general, patients with CRS usually exhibit systemic congestion (45% of patients, and for those who present, 80% of cases present with severe congestion), hyperkalemia, hypertension, elevation of creatinine (< 30% in relation to baseline), and resistance to diuretics and others [3]. It is important to observe that all CRSs share the same mechanisms to maintain (or attempt to maintain) homeostasis. These are the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system (SNS), inflammation, and oxidative stress. The first are principal mechanisms of regulation with respect to volume and pressure to stabilize CRS; therefore, these are the main targets of pharmacological treatments.

Different studies have shown distinct alterations in response to CRS, such as the loss of renal blood flow self-regulation, abnormalities in renovascular reactivity, intermittent activation of renin–angiotensin (increasing angiotensin II type 1, AT1 and AT2), and sympathetic systems, decreasing aorta responsivity, uremia, and metabolic acidosis. All of these changes elicit endothelial dysfunction that is detected by the loss of endothelial sensitivity to acetylcholine [15–18]. Direct damage to the endothelium is also recognized by the immediate inhibition of endothelial nitric oxide synthase (eNOS), leading to the known vasoconstrictor profile of inflamed arteries and an increase of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), IL- (interleukin) 1, and IL-6 in the renovasculature [19]. Additionally, Casas et al. detected a pro-inflammatory environment due to an increase in C-reactive protein, fibrinogen, and IL-1β markers in the blood of patients with chronic renal dysfunction and consequent coronary disease [20].

Although vascular effects of CRS mainly concern the renovasculature, many authors have also investigated vascular alterations in distinct models of renal failure in other vascular beds. In 1981, Ueda et al. showed that aortas from attached ureter rats were less responsive to norepinephrine

Table 1 Classification of the cardiorenal syndrome types

| Type	Group	Classification	Description	Clinical implications	Consequences	Ref
1	Cardiorenal	Acute	Initial and acute damage of cardiac function, generating an acute kidney injury (AKI) mainly caused by hemodynamic mechanisms	Decompensated heart failure (ADHF) Decrease in glomerular filtration rate (GFR) Congestion	ADHF alters renal perfusion and systemic blood pressure (BP). Renal function decreases given the decay of cardiac output. Activation of sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS) to repair the arterial flow and the reduced GFR due to ADHF. Increasement of blood pressure (BP) and sodium retention. Excessive elevations of cytokines	[4–11]
2		Chronic	Pre-existing or chronic damage of cardiac function, generating an chronic kidney disease (CKD) mainly caused by long-term hemodynamic mechanisms	Congenital heart disease Atrial fibrillation Chronic heart ischemia Constrictive pericarditis Increase of glomerular and arteriolar resistance Hypertension	Chronic heart patients have impaired GFR, creating an increasement of the capillary hydrostatic pressure implying the environment of overactivated RAAS and SNS, presenting an over circulation volume, resulting in CKD progression	[7, 12–15]
3	Renocardiac	Acute	Initial and acute damage in the kidneys (AKI), generating an acute heart injury, mainly by hemodynamic, inflammation and oxidative stress mechanisms	Decrease of GFR Congestion Arrhythmia Acute heart failure Cardiac hypertrophy	As renal function is compromised, sodium and water are retained, creating a volume overload, hypertension, and myocardial injury. An acidemia condition can worsen the vasoconstriction and increase arterial pressure	[16–21]
4		Chronic	Pre-existing or chronic renal damage, generating an chronic heart, mainly caused by long-term uremia	Chronic inflammation Hypertension Anemia Electrolyte imbalance and volume overload Accumulation of uremic toxins Dialysis	Endothelial tissue calcification and erythropoietin resistance can be observed. Hyperphosphatemia and secondary hyperparathyroidism can lead to mineral bone disorder (MBD) increasing the FGF23 that has a direct mechanism in promoting directly hypertrophy, remodeling, and contractile alterations	[22–25]
5	Secondary	Systemic	Systemic diseases, simultaneously compromising renal and cardiac function mainly for inflammatory mechanisms	Decrease of GFR Increasement of inflammation Compromised myocardial contractility	Renal blood flow decreases during sepsis, resulting in tubular necrosis, decrease of GFR, and severe kidney injury. Once affecting the renal and heart tissue, sepsis also modulates the RAAS and SNS systems as well as inflammatory cytokines. Systemic conditions directly affect the contractile apparatus (actin, myosin, and associated proteins)	[7, 14, 26, 27]
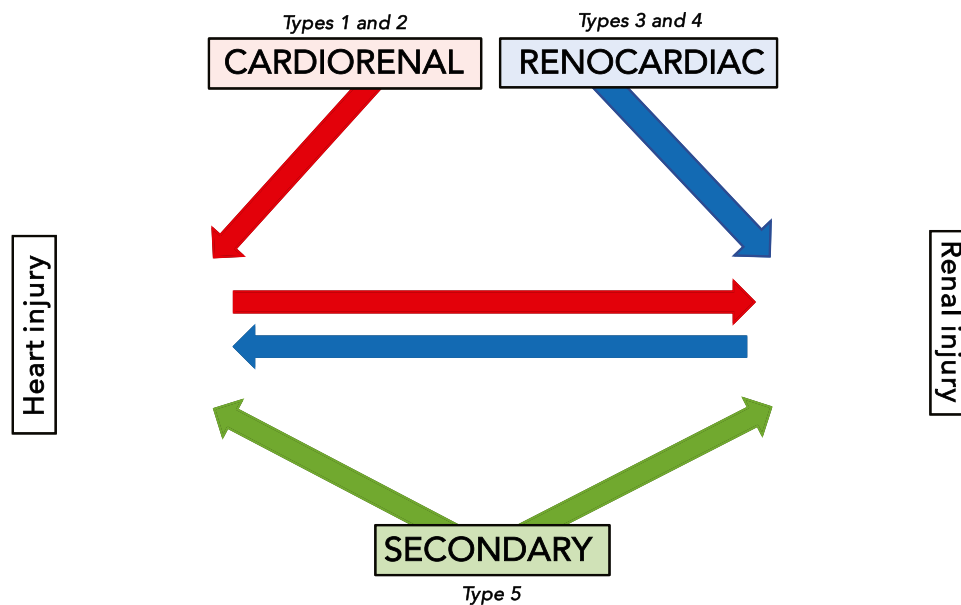
Fig. 1 Flowchart describing the sequence of organ involvement during the five types of cardiorenal syndrome (CRS). The red arrows indicate CRS types 1 and 2, which are considered cardiorenal; the first injury occurs in the heart as acute decompensated heart failure (ADHF) which is type 1 and chronic heart failure (CHF) which is type 2. The blue arrows indicate CRS types 3 and 4, which are considered renocardiac; the first injury occurs in the kidneys as AKI which is type 3 and CKD which is type 4. The green arrows indicate CRS type 5 which is considered secondary; when a secondary dis- ease such as sepsis or diabetes impairs the heart and kidney function concomitantly, the primary and secondary injuries occur due to the systemic disease, that simultaneously induces both cardiac and renal dysfunction, as if it were bi-directional. The physiological disturbances shared by all CRS types are imbalance of hemodynamics (increase of sodium and water retention), congestion, inflammation, oxidative stress, activation of renin–angiotensin–aldosterone (RAAS), and sympathetic nervous system (SNS)

and angiotensin II (Ang II) in comparison to control animals, although no significant histological lesions were observed [21]. Using a model of renal failure due to subtotal nephrectomy, Amann et al. reported an increase in aortic wall thickness provoked by secretion of factors stimulating proliferation of vascular smooth muscle cells. This resulted in an increased matrix deposition [22]. In a 5/6 nephrectomy rat model, Nesher et al. showed a reduction of the aortic contraction in response to KCl, while acetylcholine vasodilation was impaired in animals with chronic renal failure. Such effects were prevented by administration of L-arginine in the rats' drinking water [23].

The vehicles traveling along the highway: classical cellular mechanisms in CRS

RAAS in CRS

One of the most impressive systems in the control of cardiovascular function is RAAS. Until the 1980s, only Ang II was studied as an active peptide of this system. It was produced by an enzymatic cascade from the action of renin on its angiotensinogen substrate and then by the action of the angiotensin-converting enzyme (ACE) (Fig. 2). Until then,

this vasopeptide acted through the AT1 receptor, promoting vasoconstriction, water intake, and Na^+ retention. In the early 1990s, new components of this system were discovered through an independent ACE pathway [24]. These components formed from angiotensin (Ang) I and are referred to as Ang 1–7. Pharmacological blockade of RAAS occurs through the inhibition of ACE or angiotensin receptor blockers (ARB) and has been used widely in the control of renal and cardiac injury, such as chronic kidney disease (CKD) and HF [25, 26].

It is well known that increased Ang II levels in the heart can lead to myocardial necrosis [90], whereas RAAS stimulation can cause coronary cell death due to intense coronary vasoconstriction [91–93]. It is also known that high levels of Ang II act through several physiological mechanisms, resulting in myocardial damage (e.g., apoptosis of coronary endothelial cells (EC) or cardiac myocytes).

Several studies have reported increased cardiac expression of AT1 over the course of cardiac development and the progression of cardiac failure after myocardial infarction (MI) and other cardiac diseases [27–29], demonstrating that the increase in AT1 expression mediates the hypertrophic role of Ang II [30–32]. Considering these results, the RAAS blockade prevents excessive sodium reabsorption and adverse cardiac remodeling, as well as

Fig. 2 Flowchart describing the action of the renin–angiotensin–aldosterone system (RAAS) in CRS. Activation of the RAAS system occurs after renin release in the kidneys that catalyzes the synthesis of angiotensinogen to form angiotensin I (Ang I). Ang I is converted to Ang II by ACE produced in the lungs. Ang II binds to AT1 receptors in the smooth muscle cells of the peripheral blood vessels causing vasoconstriction and increasing vascular resistance and blood pressure in the heart. It can also cause hypertrophy, fibrosis, and heart failure (HF). In the figure, it is possible to see the therapies involved in the RAAS blockage: AT1 antagonists, ACR blockers, and renin inhibitors
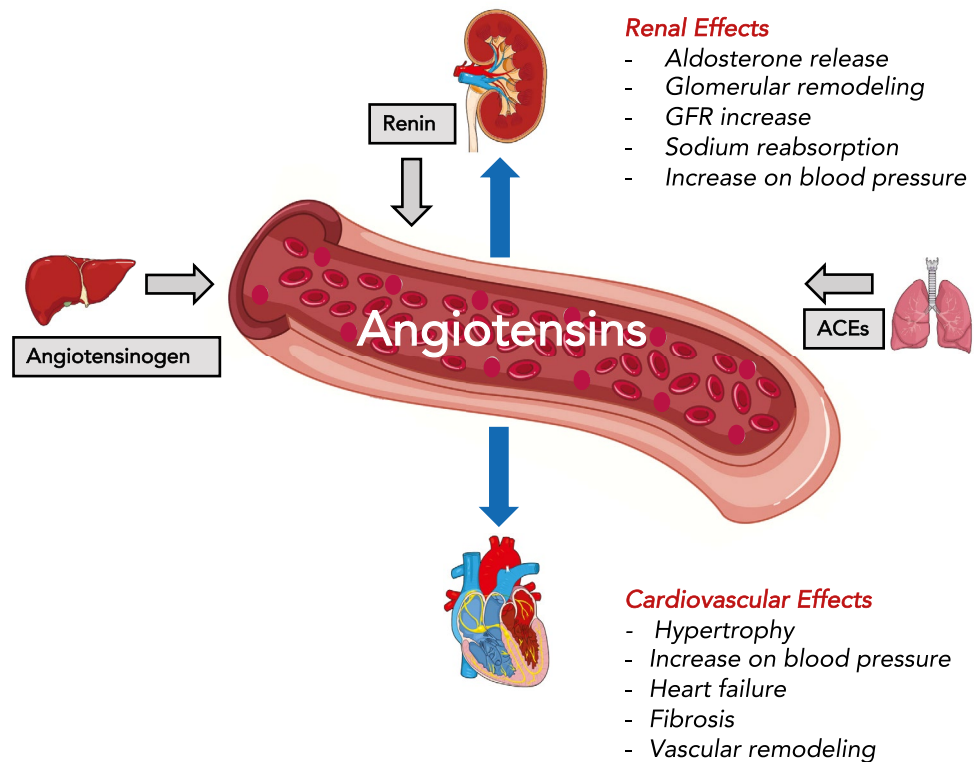
myocardial ischemia and reperfusion injury (IRI) lesions and post-infarction remodeling [33, 34]. Recent studies on pharmacological approaches are discussed further.

Panico et al. demonstrated that the pharmacological manipulation of RAAS suggests that Ang II formation is also important in attenuating CRS in mice after renal IRI [35]. In the same study, the authors showed that acute kidney injury (AKI) induced by unilateral IRI did not change plasma levels of Ang II, but cardiac RAAS seemed to be important in avoiding the worsening observed in this model [35]. The beneficial effects of Ang II may be related to vasoconstrictor effects, which decrease the inflow of inflammatory mediators and maintain endothelial nitric oxide (NO) levels in the renal tissue. Furthermore, cardiac Ang II could stimulate the ACE2/Ang 1–7/ MAS receptor axis, which is responsible for inflammation during renoprotection [36–38].

Despite the described and known benefits of RAAS blockade in the isolated heart or kidney and its cardioprotective and renoprotective effects, the role of this system and its implications in cardiorenal patients requires further examination. Recently, worldwide researchers have focused their attention on the regulatory axis of SARS-CoV-2, which highlights the protective action of ACE2/ Ang 1–7 on the cardiovascular system [39–41].

Neurohumoral control in CRS

The autonomic system (ANS) plays an important role in several biological processes, from behaviors and emotions to immune system functions [42]. It operates through catecholamines, epinephrine, and noradrenaline. These chemicals belong to large families of α-and β-adrenergic receptors (adrenoceptors, β-ARs) that are distributed in different tissues, with the most varied levels of expression performing similar functions in the pathway activation that modulates calcium transport for muscle contraction [43].

The ANS is fundamental to BP control, whether continuously (long-term) or moment-to-moment. These adjustments are responsible for hemodynamic stability. Thus, we can highlight a study in patients with end-stage kidney disease (ESKD) that had an increased risk of CVD and sudden death with increased SNS activity [44].

Renal IRI leads to the development of cardiac hypertrophy (CH). In many other models, AKI can directly or indirectly induce acute cardiac dysfunction by increasing angiotensin levels (AT1, AT2, and ACE), local and systemic cytokines (TNF-α, ILs, and IFN-γ), arrhythmias, and other components [45, 46], such as increasing the presence of local norepinephrine and increasing sympathetic activity [35, 47].

Some vasomotor sympathetic activity is a common characteristic of HF [48]. Therefore, the SNS is a relevant therapeutic target [47]. During HF, renal sympathetic nerve activity increases and causes renal norepinephrine accumulation and renin release, which induces renal vasoconstriction that may contribute to CRS. Additionally, RAAS is induced, which interrupts the balance between reactive oxygen species (ROS), NO, and inflammation. In combination with decreased renal perfusion and increased pressure of the renal vein, these factors contribute to the pathogenesis of CRS [48].

A study of myocardial infarction (MI) induced by thoracic aortic coarctation (TAC) demonstrated an increase in norepinephrine levels in the plasma and urine, which was reduced with concomitant renal denervation. This treatment showed an improvement in renal injury induced by aortic regurgitation and decreased expression levels of KLF5, S100A8, S100A9, TNF, CSF2, and Ly6Clo macrophages. There was also a decrease in left ventricle (LV) systolic function, CH, fibrosis, and survival after infarction, indicating the importance of sympathetic activity in the kidneys and heart. Additionally, renal denervation was performed. Inhibition of cardiac afferent nerve signaling through the administration of epicardial capsaicin and/or resection of the spinal dorsal horn, which also reduced the expression of CSF2 in the kidneys after thoracic aortic coarctation, indicates that cardiac afferent nerves have an intrinsic interaction between the heart and the brain [49].

Among the conditions that raise the hemodynamic levels for both the heart and kidneys, we highlight inflammatory factors (Fig. 3). An important role for IL-6 is documented in the mechanisms involved in the development of CH [50], which precedes HF. This is a process that also involves the presence of the SNS, where catecholamines that are present in the immune cells can play a crucial role in the SNS interface and immune system [51]. An association between changes in levels of Ang II and cytokines, with increased cardiac mass and cardiac remodeling, increases SNS activity in the heart [52–54].

Gueguen et al. and Vieira-Rocha et al. demonstrated the role of the RAAS and SNS in the pathogenesis of hypertension in different models of hypertension, comparing BPH/2 J (hypertensive) and BPN/3 J (normotensive) mice and neuromodulation of the vascular angiotensin AT1 in fetal programming of hypertension, respectively. The elevated renal levels of norepinephrine contributed to the evolution of hypertension via expression of renin or the occurrence of hypersympathetic activation. This activation involved tonic facilitation, through endogenous Ang II, of pre-junctional AT1 receptors, resulting in the development of hypertension in these animals [55, 56].
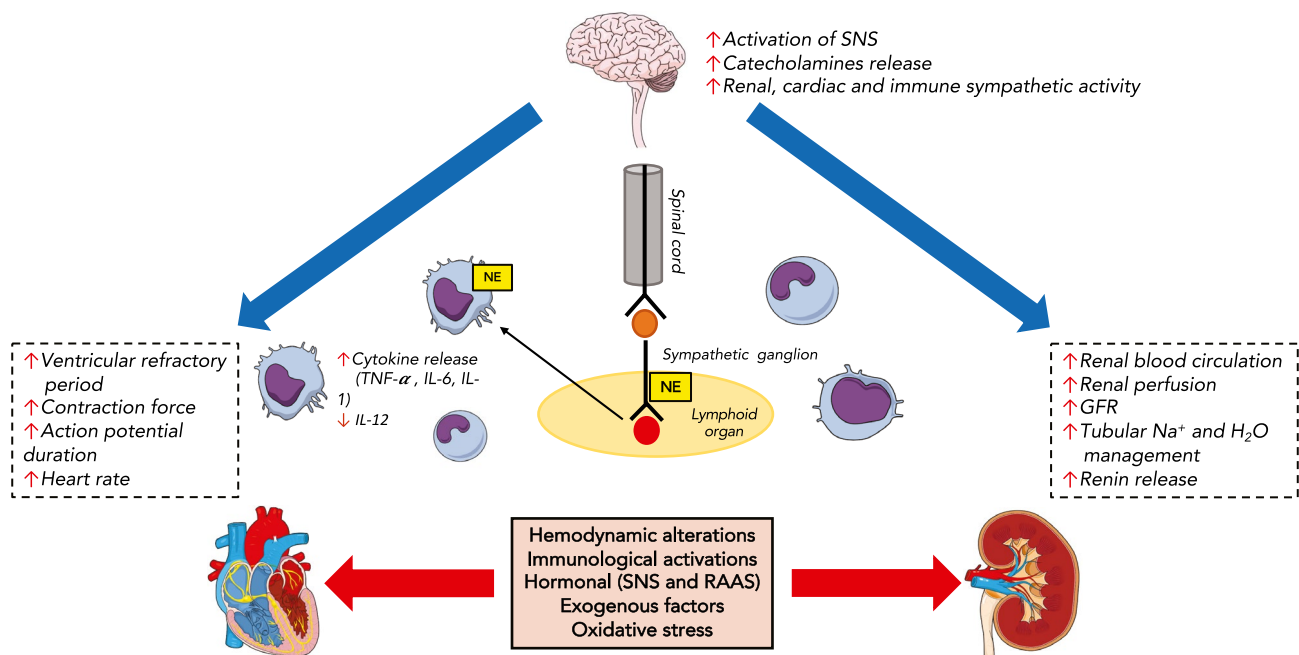

Fig. 3 Flowchart describing the action of the neuronal control of the sympathetic nervous system (SNS) in CRS. The SNS acts through the catecholamines, noradrenaline, and epinephrine. This system has direct interference in the immune system, and is the main connector between the heart–kidney axis, promoting the movement of the involved immune cells from the kidney that reach the heart through the bloodstream (cytokines: IL-1, TNF-α, IL-6), leading to both cardiac and renal dysfunction

The development and progression of CRS occurs through feedback activation of neurohormonal pathways. Both β-adrenergic blockade and inhibition of RAAS, among other methods, can act as new therapeutic strategies to mitigate the deleterious processes linked to HF and CRS. This will be discussed further in the following sections.

Inflammation in CRS

During the inflammatory phase, immune cells, such as mature phagocytes, are recruited to the infarcted area to clean the dead cells and matrix debris. The elimination of dead cells and matrix debris stimulates anti-inflammatory pathways and targets the transition to the proliferative phase, accompanied by immune cell infiltration, activated fibroblasts, and an increase in angiogenic processes. Concomitantly, toll-like receptors (TLRs) are activated in response to damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) present in many cell types, including resident cardiac macrophages, fibroblasts, cardiomyocytes, mast cells (MCs), vascular cells, and infiltrating leukocytes [57, 58]. Both the innate and adaptive immune responses are induced by TLR stimulation [59]. In Fig. 4, we observed the activation of signaling pathways in white cells (mainly macrophages). Two signals are activated by CRS DAMP during stress. (1) The first is through the classical TLR2/4 pathway that releases IL-1β. This cytokine is fundamental to the maintenance of cardiac alterations during CRS type 3, for example, (2) NLRP3 signaling. This signal begins with the phagocytosis of DAMP,
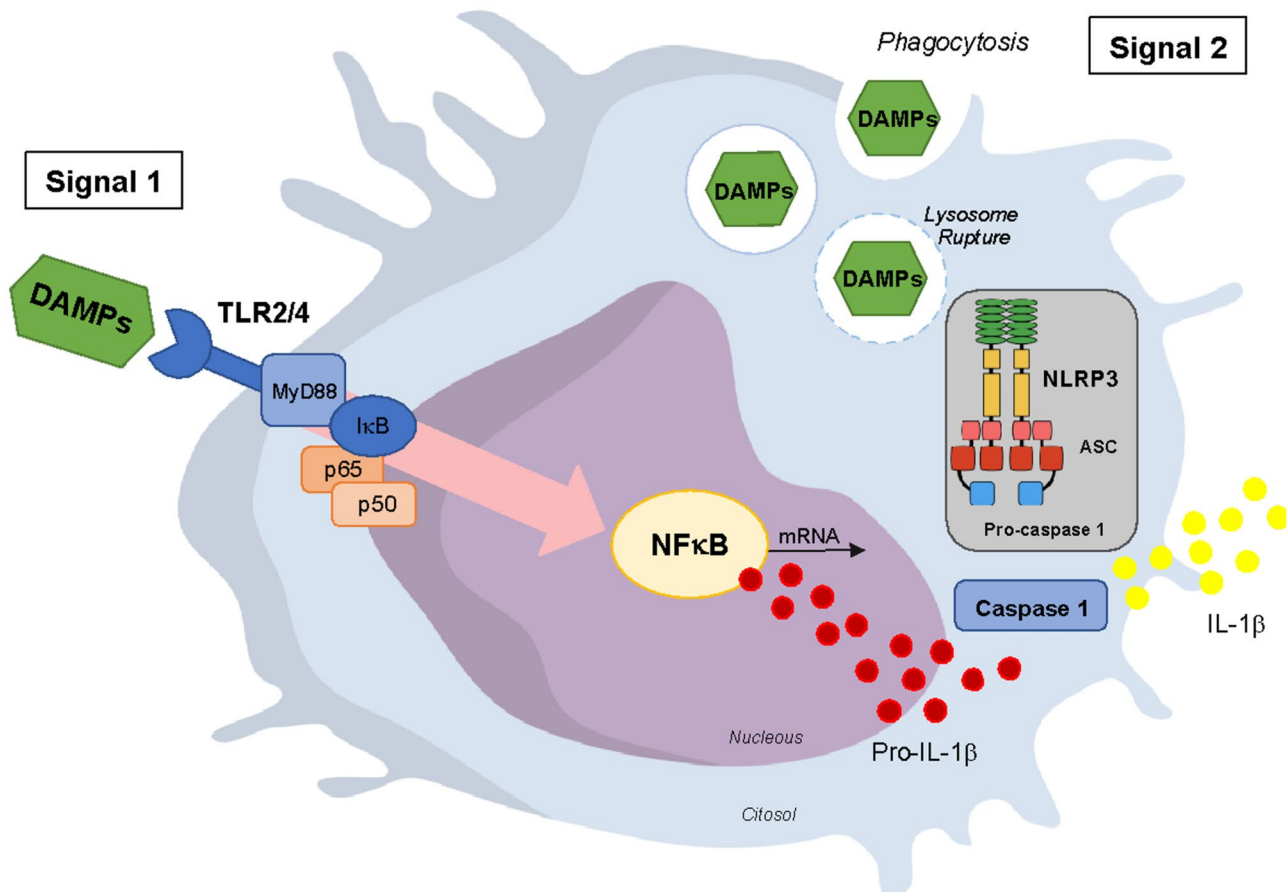

Fig. 4 Principal mechanisms evoked by damage-associated molecular patterns (DAMPs) during CRS. Two signals are activated by DAMPs during the CRS. The DAMPs can be inflammatory factors, oxidative stress components, uremic toxins accumulated during renal failure, sepsis, and diabetes. Signal 1: the classical TLR2/4 pathway. When connected with the receptor, the DAMPs promote the activation of MyD88 and the release of the transcription factor, NF-kB, that synthetizes pro-inflammatory mRNA expression, like the pro-IL-1β. When activated, this cytokine is fundamental to the maintenance of cardiac alterations during CRS. Signal 2: the NLRP3 signal. This signal starts by the phagocytosis of the DAMP, activating the signal though lysosomal damage. Activation of the NOD-type intracytoplasmic receptor (NLR) family can lead to the formation of protein complexes called inflammasomes, including the NLRP3 inflammasome, formed by three basic structures: NOD-type receptors, adapter protein (ASC), and pro-caspase 1. These active caspases are capable of inducing proteolytic maturation of interleukin-1 beta (IL-1β), which are then released into the extracellular environment stimulating other cells such as the cardiomyocytes and podocytes

activating the signal through lysosomal damage. Activation of the NOD-type intracytoplasmic receptor (NLR) family can lead to the formation of protein complexes called inflammasomes, including the NLRP3 inflammasome. NLRP3 is formed by three basic structures: NOD-type receptors, adapter protein (ASC), and pro-caspase 1. These active caspases are capable of inducing proteolytic maturation of IL-1β and IL-18, which are released into the extracellular environment and stimulate other cells, such as cardiomyocytes and podocytes [60]. Both signaling pathways were studied in renal IRI and diabetic mice, respectively, and in both models, signal 2 showed great importance for the maintenance of cardiac alterations and was shown to be a potential therapy for CRS [46, 61].

In the HF setting, there is increased expression of TLR4 in the cardiac myocytes of both humans and rodents. In the heart, TLR signaling stimulates two downstream pathways. In the acute phase of ischemia, it is cytoprotective and may increase the function of cardiac myocytes. In contrast, chronic activation of TLRs (TLR4 and TLR2) leads to left ventricular dysfunction [59]. The leukocyte-specific activation of TLR2- or complement-mediated signaling in bone marrow transplantation experiments was associated with marked injury after infarction, suggesting that innate immune activation may extend ischemic injury [57]. Another role for innate immunity in HF is the process by which apoptotic polymorphonuclear neutrophils (PMNs) attract macrophages to the site of injury to limit neutrophil activity. If PMN infiltration remains unmarked or if there is a prolonged persistence of inflammatory triggers at the site of injury, a negative feedback loop is created, inducing chronic inflammation that does not resolve [62].

Under conditions of myocardial ischemia in experimental mouse models, myocardial cells undergo necrosis, thus releasing DAMPs, such as triphosphate adenosine (ATP) and high mobility group box 1 (HMGB1). These DAMPs culminate with the release of cytokines such as IL-1β, IL-18, and TNF-α by cardiac resident cells, in turn activating ECs. In this scenario, the uptake of cell debris by cardiac macrophages induces a type I interferon (IFN) response that initiates inflammation post-MI. After ischemia (within 12–24 h post-MI), neutrophils are the first inflammatory cells recruited through the chemoattractant chemokine (C-X-C motif) ligands (CXCL) 1, CXCL2, and CXCL8. Neutrophils produce IL-6, which activates ECs and induces the C–C motif ligand (CCL) and vascular cell adhesion protein 1 (VCAM1) for subsequent monocyte recruitment. They also release matrix metalloproteases (MMPs) to break down the extracellular matrix and dead cells within the infarcted area. Splenic Ly6C^{hi}CCR2^{hi}CX3CR1^{lo}CD62L^{+} monocytes are recruited via C–C motif chemokine ligand 2 (CCL2) chemokine receptor (CCR) 2 chemoattraction. These cells scavenge debris and release inflammatory cytokines and MMPs at the infarct site. Thus, the inhibition of the CCL2-CCR2 pathway has been effective in avoiding monocyte recruitment, improving infarct healing, and attenuating LV remodeling post-MI [63, 64].

On the other hand, inflammatory cytokines such as IL-4, IL-6, and TNF-α are important agents that promote CH, fibrosis, and dysfunction, as evidenced in anterior studies using a pressure overload experimental model. Increased myocardial expression of TNF-α, IL-1β, and IL-6 was observed in patients with pressure overload [65]. In cardiac fibroblasts, increased production of these three cytokines has been associated with reduced collagen synthesis and infarct expansion [66]. In pressure overload-induced HF, innate immune cells, including monocytes, mononuclear phagocytes (MPs), dendritic cells (DCs), and macrophages provide an inflammatory response by delivering proteases and cytokines. Additionally, macrophages promote efferocytosis and phagocytosis, and activate myofibroblasts and immune cells, indicating that MPs participate in pressure overload-induced HF [65]. At the same time, activation of the nuclear factor kappa B (NF-κB) signaling pathway, an important regulator of cellular inflammation that is related to an increase in renal expression of IL-6 and TNF-α, causes a decrease in renal function [4].

DCs are another example of immune cell involvement in CRS and may be involved in the connection between heart and kidney diseases. Virzì et al. demonstrated in an Ang II-induced renal damage model, renal DCs expressed major histocompatibility complex (MHC) class II and CD86 (markers of DC maturation), causing CD4 + and CD8 + T cells to infiltrate the kidney. This demonstrates the performance of DCs as connectors of innate and adaptive immunity [67]. Additionally, Bansal et al. reported on the role of DCs as antigen-presenting cells in T lymphocytes, inducing their activation.

Under the scenario of a reduced left ventricular ejection fraction and increased volume of the diastolic and final systolic areas in the LV, elevated circulating levels of these cytokines have been observed to have direct cardio-depressive effects. In renal ischemia, systemic inflammation and not AKI plays an immediate role in myocardial damage and dysfunction, as evidenced in rat hearts, where there is higher expression of ICAM-1 (intercellular adhesion molecule 1) and apoptosis in the myocardium. Additionally, 48 h after kidney injury, damage such as increased diastolic and systolic diameters at the end of the LV decreased fractional shortening, left ventricular dilation, and increased relaxation times were observed [68]. During the progression of HF in humans, increased circulating levels of TNF-α and IL-6 have been found, which are associated with increased mortality [69]. Castillo-Rodriguez et al. compared these inflammatory cytokines with uremic toxins (UTs), suggesting that their accumulation contributes to CKD

manifestations and fulfills the criteria to be considered as UTs [69].

Another example is the generation of an early immune response consisting of the activation of DCs and the activation of signaling pathways dependent on IL-23/IL-17 and IL-12/IFN-γ. Due to kidney damage caused by IRI, neutrophils, macrophages, and lymphocytes (particularly CD4$^+$ T cells and B cells) are elevated. The activation of antigen-dependent T cells has also been demonstrated in experimental models of renal IRI. T cells undergo early activation and become a bridge between the adaptive and innate immune systems after antigen activation or in the presence of chemokines. This specific immune response during AKI leads to a cardiorenal connection [8].

The activation of TLR2 and TLR4 followed by an increase in inflammatory cytokines, immunosuppressive cytokines, DCs, and T cell activation was observed in an acute myocardial ischemic injury renal IRI model, confirming that ischemia/reperfusion rapidly activates the innate immune response. In contrast, post-injury renal TNF-α levels were significantly reduced due to the depletion of DCs before IRI [67]. TLRs can also be activated by heat shock proteins (HSPs) that interact with both kidney cells and cardiomyocytes. This family of proteins are important mediators involved in the control of gene transcription and intracellular signaling, in addition to being important connectors of the immune system, mainly HSP60, 70, and 90 [70].

Higher levels of IL-18 expression lead to the production of IL-1β, which has negative inotropic effects on the myocardium in both in vitro and in vivo models. Additionally, IL-18 induces cardiac fibrosis and hypertrophy. During AKI, elevated levels of TNF-α have been found to cause direct depressant effects on the myocardium by reducing the sensitivity of the β-ARs to catecholamines, altering calcium signaling, and inducing apoptosis. Inhibition of TNF-α led to decreased cardiac apoptosis in rat models. In experimental models, renal ischemia for 30 min led to abrupt increases in IL-1 and TNF-α levels in the systemic circulation, with concomitant detection in cardiac tissues. The increased expression of ICAM-1 in ECs and infiltration of leukocytes into the myocardium were accompanied by an increase in the cardiac activity of IL-1 and TNF-α [71].

In acute coronary syndrome, IL-6 may induce anti-apoptotic pathways, thereby restricting tissue damage. On the other hand, sustained IL-6 levels might also lead to deleterious effects via reduced expression of suppressors of cytokine signaling (SOCS)-3 and increased neutrophilic recruitment. This cytokine, together with IL-1β, stimulates C-reactive protein (CRP) production. Overproduction of IL-1β has been shown to be due to AKI and is produced by ECs and macrophages in the coronary arteries in ischemic heart disease [71]. When using an IL-1β antagonist as treatment, the duration and amplitude of calcium transience were rescued, thus preventing ventricular arrhythmias [46].

Oxidative stress in CRS

ROS are produced at controlled and physiological levels that may exert beneficial cellular functions, such as a second messenger in cellular signaling pathways, cognitive function, yield of thyroid hormone, and participation in immunological responses [72]. However, excessive production of ROS or reactive nitrogen species (RNS) leads to detrimental effects, disrupting cellular homeostasis by damaging cellular proteins, lipids, and DNA, which results in dysfunction and cellular death [73, 74].

The generation of ROS and RNS occurs in the kidneys under physiological and pathological conditions, and the major sources of ROS in the kidneys are NADPH oxidase (NOX) 4 and [75, 76]. Through pathological stimuli, such as Ang II, TNF-α, high glucose, and even superoxide anion (O_2^-) from NADPH oxidase, mitochondrial increases of O_2^- release and the complementary reduction of Mn-SOD worsens make the production of O_2^-, inducing oxidative stress [77, 78].

It is thought that the key role of oxidative stress in various types of AKI and CKD diseases both directly and indirectly affects all kidney hemodynamic functions, such as glomerular filtration, tubular reabsorption, and secretion, leading to cellular apoptosis, fibrosis, and impaired function. Meng et al. demonstrated that NOX4 overexpression in the toxic AKI model confirmed the significance of this overexpression by leading the kidneys to programmed cell death and inflammation. They highlighted its depletion as a potent therapeutic agent [79]. Other studies involving cisplatin-AKI indicated increased lipid peroxidation and impaired antioxidant enzyme activity [80]. Choi et al. observed the same lipid peroxidation through malondialdehyde (MDA), which occurred simultaneously with apoptosis of renal tubule cells and inflammatory infiltration in an AKI model using Sprague–Dawley rats [80]. Other groups using a renal bilateral IRI model in Wistar rats showed the same increase in MDA levels [40].

During the progression of CKD, an alteration in nuclear factor erythroid 2 (Nfr2), which is responsible for encoding many enzymatic antioxidants, modulates activity of enzymatic antioxidants superoxide dismutase (SOD), enhances activity of NOX, and exhibits characteristics of carbonyl stress [81]. In CKD that results from diabetes and hypertension, it is well established that Ang II also enhances oxidative stress and inflammation. Similarly, so does the AT1 receptor, which stimulates NADPH oxidase and mitochondria to generate O_2^-, and reduces glutathione cycle activity by inhibiting Nrf2 [82, 83].

In healthy hearts, the generation of ROS and RNS comes from ECs, phagocytes, and cardiomyocytes. In cardiomyocytes, the peroxisomes, xanthine oxidase, and xanthine are the principal sources of ROS O_2^- and H_2O_2, whereas NOS enzymes release NO. In ECs, only xanthine oxidase produces O_2^-, and NOS generates NO. In phagocytes, NOX and prostaglandin hydroperoxidases are involved in releasing O_2^-, and when activated, these cells are capable of releasing hypochlorous acid (HOCl) [84]. However, several studies have indicated the importance of oxidative stress in the development of heart diseases, including MI, CH, and HF. Many clinical studies have revealed that MDA levels are increased in the plasma of patients with chronic HF [85, 86].

In LV remodeling, mitochondrial and cytosolic oxidative stress are important, although NADPH oxidases are crucial for the activation of MMPs [87]. CH is also observed in diabetes, and one study indicated that protein kinase C beta is the major moderator of oxidative stress in the diabetic heart, which stimulates NOX [88]. One mouse model of LV hypertrophy induced by Ang II and atrial natriuretic peptide (ANF) indicated the detrimental role of NOX2 activity in Ang II-induced hypertrophy [89].

CRS oxidative stress may occur due to ischemic injury, venous congestion, and inflammation [90]. A human study of CRS type 1 evaluated the contribution of oxidative stress in 11 patients who developed AKI due to acute HF, showing a remarkable increase in ROS and RNS in the circulation [91]. Our previous study characterized oxidative stress in CRS type 3 by induction of renal IRI in mice. Eight days after kidney injury induction, lipid oxidation and increased NO levels in the heart were observed [92]. In contrast, at the same time point in the left kidney, catalase (CAT) activity decreased, but SOD activity increased [92]. Taken together, it is possible to use the evidence of oxidative stress and redox balance in CRS to approach new therapies and improve the clinical conditions observed in CRS patients.

The setback along the highway: emerging mechanisms in CRS

Uremic toxins in CRS

To unveil possible new interactions and causes of CRS, studies on the accumulation of UTs and endocrine dysregulation (as mineral bone disorder (MBD)) have been one of the main non-traditional mechanisms of CRS development. The proposed analogy for this review is that the accumulation of UTs can be considered as accidents on highways that lead to traffic on long roads.

UTs are defined as molecules that are incapable of being filtered that accumulate in the bloodstream, causing severe problems to the body's systems, especially the cardiovascular system. The toxicity caused by the accumulation of these molecules lead to the loss of considerable biological functions, and as dilapidation progressed, the uremic retention became more grave due to increasing loss of kidney function (reducing the glomerular filtration rate, GFR) [93–95]. The accumulation of UTs occurs in all types of CRS, especially types 3 and 4, which have a primary renal injury. Renal impairment contributes to gradual structural damage, leading directly to a reduction in GFR and/or subsequent proteinuria [96]. The most notable molecules in the class of water-soluble compounds that play an important role in CRS are urea, creatinine, uric acid, and inorganic phosphorus. The renal injury markers creatinine and urea are related to cardiomyocyte contractile injury and lead to an increase in cardiac oxygen consumption by lowering norepinephrine and causing insulin resistance [97]. Uric acid is also correlated with atrial fibrillation, HF, and hypertension [98]. Furthermore, uric acid was previously associated with negative cardiovascular effects, such as endothelial dysfunction, increased RAAS activity, inflammation, and oxidative stress [99]. Some studies have even linked the progression of CKD in type 2 diabetes and hypertension to high levels of uric acid. Inorganic phosphorus is responsible for the progression of CVD and renal dysfunction. Studies of patients with CKD have associated hyperphosphatemia with a substantially higher incidence of mortality from CVD and peripheral and visceral vascular calcification [100, 101]. The relationship between Pi and cardiovascular diseases, such as coronary disease, ventricular hypertrophy, and HF, increases the mortality rate, ranking these UTs with the largest toxic effect on the cardiovascular system [11, 102, 103]. Pi has been identified in several studies as a UT that causes cardiovascular calcification [56].

High levels of medium toxins, such as fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH), contribute to progressive renal injury, substantially intervening in the continuous diminishment of GFR and cardiac function. It is important to highlight that these toxins are naturally synthesized by the organism and are crucial for preserving mineral balance. It was observed that after the decline of GFR in patients with CKD stage 5, FGF23 levels increased 1000-fold above normal [104]. FGF23 elevation also impairs the heart tissue in a kidney-independent mechanism, as cardiomyocytes treated with FGF23 develop CH [105] and dysfunctional contraction [106].

The most studied protein-bound (PB) UTs during CRS are indoxyl sulfate (IS) and p-cresyl sulfate (PCS). They cause the direct loss of renal function [45] and increase the mortality of HF patients [107], which are associated with CKD progression. Inflammation has already been studied as one of the factors responsible for the retention of these substances, as well as oxidative stress [108]. Increased levels of

these toxins are observed in patients with chronic inflammation through the examination of pro-inflammatory cytokines, such as IL-6, TNF-α, and IL-1β, which lead to LV hypertrophy, cardiac fibrosis, and dysfunction [109]. The ROS release (as H_2O_2 and nitrite) from the accumulation of PB UTs directly induces cardiac injury, with urinary IS excretion reported as having a positive linear correlation with oxidative stress in the heart [108].

The consequences of UT accumulation in blood vessels are always present in renal failure and greatly affect vascular function. As reported by Brunet et al. uremia induces vascular dysfunction mainly due to four aspects: (1) acceleration of atherosclerosis, (2) arterial stiffness, (3) vascular calcification, and (4) intimal hyperplasia [110]. UTs are involved in all these aspects, and their action is closely associated with cardiovascular mortality. Importantly, the overload of PB UTs generated from renal impairment has been associated with a non-traditional risk factors for renal, cardiac, and vascular dysfunction due to distinguished albumin-binding properties, making these solutes non-dialysable under the state of irreversible renal dysfunction [24]. In the vasculature, PB UTs have a range of effects on vascular smooth muscle cells, ECs, immune cells, and erythrocytes. In this way, IS, which is one of the main UTs studied and of a higher concentration compared to other UTs, increases the proliferation, oxidative stress, inflammation, and senescence of vascular smooth muscle cells (VSMCs). Additionally, it increases oxidative stress (observed as H_2O_2 and reactive nitrogen isoforms), apoptosis (p53, p21, and p16 proteins), and inflammation, and decreases cell–cell contact of ECs [111]. The mechanisms underlying the effects of PB UTs on the vasculature are the most distinct; however, the imbalance of ROS and inflammation seems to be most prevalent [111].

Epigenetic in CRS

Emerging data indicates that epigenetic modifications occur due to CKD and CVD development. Among them, smoking, mitochondrial dysfunction, hypertension, and nephron numbers are significantly influenced by in utero environment programming [112]. Many of these modifications are directly involved in setting the five types of CRS; however, the role of histone modification, methylation, and RNA interference directly affecting CRS is unclear. There are new findings concerning cardiorenal physiopathology. Histone H3 epigenetics undergo strong acetylation, dimethylation, and phosphorylation during renal injury [113]. Induction of cardiomyopathy-related genes is modulated by H3 modifications [113]. Phosphorylation of H3 histone was already observed to be controlled by $Ca2^+$/calmodulin-dependent protein kinase II (CAMKII) δ, suggesting that H3 is related to cardiomyocyte hypertrophy [114]. Once DNA methylation of renal cells is affected by uremia, and this can be a

consequence of CRS, the epigenetic implications involving the syndrome have been suggested [115].

Non-coding RNAs, such as short microRNAs, are also part of the epigenetic environment once they work via epigenetic mechanisms. MicroRNAs (miRNAs) can be secreted from cells and reflect the interaction of long-distance organs [116], making them powerful biomarkers of HF or kidney injury, and consequently, CRS. A significant part of these miRNAs are released in the form of extracellular vesicles (EVs). They serve as a "witness" of this crossing on the long road, and every EV has specific membrane proteins from the sender cell, for example, the kidney podocytes [117, 118]. Intriguingly, some EVs containing miRNA have been found in the plasma of dialysis patients (chronic kidney patients or ESKD) [119, 120]. The literature contains more than 2500 microRNAs that have been isolated or inhibited in some way in experimental models. Here, we report the main discoveries related to microRNAs in CRS, specifically.

The most relevant and studied miRNA in CRS is miR-21, which has been reported in all five CRS types. It is overexpressed in the heart and kidneys after injury and leads to the progression from acute to chronic primary organ dysfunction in CRS [121]. Some studies have shown the cardioprotective and renoprotective roles of miR-21 inhibition during MI, AKI, and diabetes [121]. In the heart, MiR-21 works by enhancing extracellular signal-regulated kinase (ERK)-mitogen-activated protein kinase (MAPK) activity, leading to fibrosis and remodeling after cardiomyocyte injury [122]. In the kidneys, miR-21 contributes to the progression of AKI to CKD and is activated by inflammation, apoptosis of EC, and fibrosis [123]. During renal inflammation, IL-6 and extracellular vesicles secreted by macrophages induce miR-21 in renal fibroblasts [122]. MiR-21 can interact with other miRNAs, such as miR-29b, which acts in myocardial fibrosis during infarction after treatment with IS in a CRS model. Rana et al. demonstrated that the elevation of serum concentrations of IS were associated with an increase in miR-21 and a reduction in miR-29b [124]. MiR-21 is also related to the proliferation of tubular epithelial cells, where the knockdown of this miRNA promotes apoptosis of these cells after renal IRI [125].

In the heart, miRNAs are involved in basic mechanisms, including hypertrophy, contraction, and fibrosis [126]. In the blood of patients with HF, miR-423–5, miR320a, miR22, and miR92b were observed, which were related to the severity of CVD [127–130]. MiR-29 is highly expressed in cardiomyocytes after injury and is related to myocardial fibrosis through alterations in TGF-β mRNA expression [130]. CH is another phenomenon that appears to be controlled by miRNAs. The roles of miR23a, miR1, miR133, miR199b, and miR208 have been observed [131]. Alterations in miR21, miR199a, miR210, and miR494 were observed after injury,

associated with cardiomyocyte survival after injury [131], and can be involved in the progression of CRS.

In contrast, in renal tissue, miRNAs are involved in the proliferation and migration of renal tubule cells [132]. In a model of diabetes, MiR-192 is responsible for regulating TGF-β in proximal tubule cells by reducing the GFR [133]. Knockdown of the miR-30 family is key to vascular damage and fibrosis in renal cells after injury and is decreased in podocytes of AKI patients [134]. Renal IRI alters the expression of many miRNAs, including miR-687, miR-489, miR-494, miR-24, miR-21, and miR-126 [135].

Maintenance of the highway and vehicles: theranostic approaches

CRS treatments and therapies focus on symptom management through pharmacological methods (Table 2). Pharmacological treatments are mainly aimed at decongestion. Considering that many CRS patients present with congestion, decongestive measures are essential to revert the increased volume overload. The main mechanism proposed to relieve congestion is diuretic use [136].

Type 1 and 2 CRS patients with diuretic resistance, as acute decompensated heart failure (ADHF) and HF, have imbalances in the hemodynamics and activate many mechanisms, which can prolong the time to maximize the concentration of drugs. Additionally, as most diuretics are protein-bound, the volume of distribution increases, reducing diuretic availability [137]. Consequently, CRS types 1 and 2 require higher doses of diuretics than others [138]. Diuretics decrease circulation fluid volume, enhance electrolyte imbalances, and disturb the neurohormonal balance [138]. About 90% of HF

Table 2 The main management strategies used in each type of cardiorenal syndrome. RAAS, renin–angiotensin–aldosterone system; CKD, chronic kidney disease; MBD, mineral bone disorder; PTH, parathyroid hormone

CRS	Management strategies
1	Congestive relives: vasodilators and diuretics RAAS blockers Inotropics
2	RAAS blockers Beta-blockers Erythropoiesis-stimulator agents
3	Congestive relives: vasodilators and diuretics Isotonic fluids Anti-inflammatory drugs
4	Hemodialysis Management of CKD-MBD: vitamin D therapies, PTH inhibitors (cinacalcet), phosphate binders
5	Management of the primary disease Norepirephrine (sepsis), dopamine, vasopressin

patients take diuretics to prevent short-term mortality and rehospitalization in CRS cases [139].

Inotropics are solutions that are used to treat hypotension and low cardiac output in patients with CRS [140]. The use of dopamine, dobutamine, and milrinone have improved the cardiac index, as well as renal blood flow, easing patient congestion, and improving the mortality rate during CRS, especially for types 1 and 2 [141]. The combination of both dopamine (at low doses) and diuretics seems to be the answer to short-term/acute CRS (types 1 and 3).

Vasodilators can also be used to decongest the central venous pressure as they decrease ventricular filling pressure and myocardial oxygen consumption [142]. Many vasodilators have shown significant results in CRS. The most studied are nesiritide, nitroglycerine, and sodium nitroprusside. They have been shown to be a renal-protective therapy in patients with ADHF [143, 144]. Despite their benefits, these drugs have not been associated with the prevention of CRS, being more effective when used for short-term treatments and conjugated to diuretics [144].

The drugs most commonly used to treat CRS are β-AR blockers and RAAS inhibitors. β-AR blockers have been shown to promote an improvement in flow, alleviating BP, and renoprotection, resulting in decreased hospitalization and mortality due to CRS [139]. They block epinephrine and are not recommended for the treatment of type 1 CRS, as they are potentially hypotensive and bradycardic drugs [141]. Interrupting the SNS response is fundamental for the treatment of CRS. The most indicated β-blockers are propranolol, metoprolol, bisoprolol, and nebivolol in patients with HF, and carvedilol in patients with end-stage renal disease [139].

The process of binding to β-ARs is a common mechanism shared by all β-blockers, which compete with agonists for the binding site at the receptor. β-Blockers activate the coupling of Gi-proteins, inhibiting AC activation. The Gβγ subunit of Gi induces both the inhibition of apoptosis (via stimulation of MAPK and the AKT pathway) and prevents Gs-mediated deleterious effects, leading to cardioprotection. In HF, β-blockers might lead to cardioprotection and a reduction in cardiac remodeling via NOS activation, which in turn controls the heart rate [145].

RAAS inhibitors are considered the first pharmacological HF therapy and have been extended to the treatment of kidney and cardiorenal diseases, showing efficiency when controlling CRS. In patients with CRS, outstanding activation of AT1 receptors by Ang II contributes to the enhancement of aldosterone from the adrenal glands. Aldosterone promotes water and sodium retention in nephron cells, resulting in increased BP [146]. The RAAS is targeted at different locations during CRS therapies, mostly to control hypertension. RAAS therapies can be divided into angiotensin-converting enzyme inhibitors (ACEIs), ARBs, and direct renin inhibitors (DRIs).

ACEIs inhibit the conversion of Ang I to Ang II and reduce Ang II in the bloodstream. There is a class of ACEIs, selenium analogs, pharmacologically developed and studied to have an ACE inhibitory effect and to prevent the oxidative stress product, peroxynitrite. The most commonly used ACEI is captopril [147]. ARBs prevent Ang II binding to the AT1 receptor. Studies on the blockade of RAAS with ARBs show a reduction of inflammation and improvement of endothelial function in heart injury and CRS models. Both ACEIs and ARBs display a feedback loop that increases the plasma renin activity (PRA). This happens after the drop-in stimulus to AT1 receptors in the kidney, leading to a compensatory increase in renin release [147].

Finally, DRI use the mechanism of reducing PRA, and the production of Ang I also decreases, leaving less substrate for Ang II conversion by ACE. Furthermore, functional renin is very important to Ang II production and cellular responses to renin. The rapid activation of MAPKs, caused by the binding of renin, triggers intracellular signals responsible for cell survival, gene expression, mitosis, differentiation, and apoptosis [147]. The use of RAAS blockers improves the survival rates in HF patients, while decreasing renal injury and creatinine levels; however, it can cause hyperkalemia. This shows the cardio and renal protection; however, at first use and low doses, the RAAS blockers can decline the GFR once it constricts the arteries, causing what the authors call, the transient and reversible worsening of renal function [148]. This is the reason for the contraindication of RAAS blockers with nonsteroidal anti-inflammatory drugs, as indicated only after addressing volume depletion [148]. Despite being the subject of studies for decades, RAAS blockers are still the target of biotechnological improvements to mitigate the adverse effects observed in chronic treatments.

Concerning CRS caused by the accumulation of UTs, high-flux membranes were created to clear medium molecules; however, the elimination was not efficient in molecules with a molecular mass > 15 kDa, such as FGF23 (32 kDa), IL-6 (25 kDa), and myoglobulin (17 kDa) [149, 150]. Sevinc et al. compared patients undergoing high-flux hemodialysis followed by medium-cut-off (MCO) membrane hemodialysis or vice versa. The authors demonstrated that the levels of middle compounds, such as β2-microglobulin and myoglobulin, were decreased in the first and last sessions with MCO dialyzers compared to high-flux dialyzers, indicating that it is a possible way to reduce UT levels. Moreover, MCO membrane was capable of significantly reducing serum albumin levels over 3 months of usage [151].

General conclusions

The purpose of this review was to contribute to the detailing of the main aspects involved in the crosstalk between the kidneys and heart. Only in the 2000s was CRS systematically described and characterized, contributing to the advances observed in the diagnosis and treatment currently present. However, the molecular and cellular mechanisms involved in the different types of CRS are not yet fully understood. Thus, medicine 4.0 has been seeking new tools and strategies to combat different pathologies, and therefore, the understanding of all agents involved in the kidney–heart connection remains urgent.

Declarations

Conflict of interest The authors declare no competing interests.

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