Chapter 14

Free Radicals and Biomarkers Related to the Diagnosis of Cardiorenal Syndrome

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Additional information is available at the end of the chapter

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Abstract

The National Heart, Lung, and Blood Institute Working Group has postulated the cardiorenal syndrome (CRS) as an interaction between the kidneys and the cardiovascular system in which therapy to relieve congestive heart failure (HF) symptoms is limited by the further worsening renal function. CRS is classified from type I to V, taking into account the progression of the symptoms in terms of mechanisms, clinical conditions, and biomarkers. Experimental and clinical studies have shown the kidney as both a trigger and a target to sympathetic nervous system (SNS) overactivity. Renal damage and ischemia, activation of the renin angiotensin aldosterone system (RAAS), and dysfunction of nitric oxide (NO) system are associated with kidney adrenergic activation. Indeed, the imbalances of RAAS and/or SNS share an important common process in CRS: the activation and production of free radicals, especially reactive oxygen species (ROS). The present chapter addresses connections of the free radicals as potential biomarkers as the imbalances in the RAAS and the SNS are developed. Understanding the involvement of free radicals in CRS may bring knowledge to design studies in order to develop accurate pharmacological interventions.

Keywords: Cardiorenal syndrome, renin angiotensin aldosterone system, sympathetic nervous system, reactive oxygem species, free radicals

1. Introduction

Cardiorenal syndrome (CRS) refers to multiple abnormalities characterized by a cluster of concurring symptoms related to cardiac and renal damage. The syndrome is commonly initiated by renal insufficiency secondary to heart failure (HF) [1]. However, the term CRS is

also used to describe the negative effects of reduced renal function on the heart and the circulation [2].

A lack of a precise definition to CRS has been pointed out by recognized authors [3]. Based on epidemiologic data, the primary failing organ [4] can be either the heart or the kidney. Therefore, it is accepted that CRS can begin and perpetuate due to a merge in neurohormonal feedback mechanisms involving cardiac and renal dysfunctions. This concept expanded the comprehension about its pathogenesis and treatment.

Ronco et al. and the National Kidney Foundation [5] address CRS as a heart and kidney disorder where acute or chronic dysfunction in one of these organs may induce acute or chronic dysfunction in the other. In addition, Ronco et al. [6] presented a concept that interchanges cardio and renal functions causing CRS and classified it from type I to V, as following:

- Type I (acute cardiorenal syndrome): acute decline in heart function causing kidney dysfunction.
- Type II (chronic cardiorenal syndrome): chronic abnormalities in heart function causing kidney dysfunction.
- Type III (acute renocardiac syndrome): acute decline in kidney function causing heart dysfunction.
- Type IV (chronic renocardiac syndrome): chronic abnormalities in kidney function causing heart dysfunction.
- Type V (secondary cardiorenal syndromes): coinciding heart and kidney dysfunction secondary to systemic conditions.

In the next paragraphs each type of CRS will be described, whose injuries are linked to inflammation and to other deleterious processes connected to free radicals generators. Giving its main classification, the key-systems involved in CRS are the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS).

Type I—acute CRS characterized by a rapid worsening of cardiac function that leads to acute kidney injury (AKI). Sudden worsening of cardiac function (due to, e.g., acute cardiogenic shock, acute decompensation of chronic heart failure, procedures like coronary angiography, or cardiac surgery) triggers acute renal dysfunction, which consequently leads to humorally mediated damages that involves the activation of both SNS and RAAS systems, as well as to sodium and water retention, and to vasoconstriction. This process enhances the initial impairment in cardiac function, creating, therefore, a snowball effect.

The acute decline in renal function in CRS type I presents a diagnostic challenge since the activation of inflammatory pathways is involved in the acute impairment and acceleration in cardiovascular pathobiology [4, 7].

Diuretic responsiveness is decreased in CRS type I. In a congestive state, decreased response to diuretics may result from the physiological phenomenon of diuretic braking (diminished diuretic effectiveness secondary to postdiuretic sodium retention) [8].

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Type II—chronic CRS. The progressive chronic kidney disease (CKD) is linked to chronic cardiac abnormalities; the main example is congestive heart failure. In fact, reduced renal perfusion is related to the mechanism underlying the long-term aggravation of the renal function in chronic heart failure, which has micro-and macrovascular disease as predisposing factors [9, 10].

Frequently, there can be excessive production of vasoconstrictive mediators (epinephrine, angiotensin, and endothelin) and altered sensitivity and/or release of endogenous vasodilators (natriuretic peptides and nitric oxide—NO) [2].

Among the causes of chronic heart disease that increase susceptibility to kidney impairments toward CKD is low cardiac output, an important cause of chronic kidney hypoperfusion and of apoptosis. Initially, kidney damage begins with the development of sclerosis and fibrosis, related to the low cardiac output, subclinical inflammation, endothelial dysfunction, and accelerated atherosclerosis; these main changes, then, progress to CKD. The most important features of chronic heart disease involved are chronic hypoperfusion, increased renovascular resistance, increased venous pressure, and embolisms.

Regarding the kidney, the main alterations that feed chronic heart disease are anemia, sodium and water retention, calcium and phosphates abnormalities, uremic solute retention, left ventricular hypertrophy, hypertension, and activation of SNS and RAAS.

Type III—acute renocardiac syndrome, which has the abrupt worsening of kidney function as the primary cause (e.g., AKI, ischemia, or glomerulonephritis), being responsible for acute cardiac dysfunction (e.g., heart failure, arrhythmia, and ischemia). Although AKI can affect the heart [6], the cause and effect relationship has not been well established. It is known, nonetheless, that pulmonary edema occurs due to fluid overload, that elevated serum potassium levels could culminate in arrhythmias and cardiac arrest, that uremia builds up myocardial depressant factors affecting negatively the inotropism [11] and could cause inflammatory processes in the pericardium [12], and that high hydrogen ion serum concentration leads to pulmonary vasoconstriction [13], a strong contributor to right-sided heart failure. In addition, low blood pH (acidemia) decreases myocardial contractility [14], and when combined with electrolyte imbalance, heightens the risk of irregular heart rhythms [15]. Ultimately, compromised kidney perfusion alone can initiate inflammatory and apoptotic processes in the heart [3].

Type IV—chronic renocardiac syndrome, in which primary CKD, is the main condition (e.g., chronic glomerular disease) that decreases cardiac function and causes ventricular hypertrophy, diastolic dysfunction, and/or increases the risk of adverse cardiovascular events. According to the National Kidney Foundation [5], CKD is subdivided in five stages based on the severity of kidney damage and glomerular filtration rate.

Type V—secondary CRS characterized by the presence of both cardiac and renal dysfunction is due to acute or chronic systemic disorders. Although systematic information on CRS type V is limited, there is a notorious increase in mortality as more organs fail. Comprehension is limited in terms of how simultaneous renal and cardiovascular failure may affect differently an outcome when compared to simultaneous pulmonary and renal failure, for example.

Nonetheless, it is clear that several acute and chronic diseases can affect both organs concurrently and that once started, one organ can affect the other. An example of a very common and serious condition affecting the heart and the kidney is severe sepsis. Other examples include diabetes, amyloidosis, systemic lupus erythematosus, and sarcoidosis. Several chronic conditions such as diabetes and hypertension may contribute to CRS types II and IV.

As seen earlier, an imbalance in the components of the SNS and the RAAS contributes to CRS. Generally, a reduced cardiac output in cardiac heart failure resulting in decreased renal perfusion is thought to be an easy explanation for the worsening renal function [16]. Interestingly though, worsening renal function has been demonstrated in patients with acute decompensated heart failure with preserved left ventricular ejection fraction [17, 18]. This decline in renal function, despite presumed blood flow preservation, has led to an investigation for other mechanisms of CRS, including the role of the renin-angiotensin-aldosterone system (RAAS), of various chemicals (nitric oxide [NO], prostaglandins, natriuretic peptides, endothelins, etc.), of oxidative stress, and of sympathetic overactivity.

The following sections in this chapter aim to conclude that the lack of balance between the RAAS and the SNS triggers deleterious effects in CRS due to processes associated with free radicals production and excessive oxidative stress. Before reaching this conclusion, however, free radical concepts must be addressed.

2. Biomarkers, free radicals, and oxidative stress: basic concepts

A *Biomarker* is a biological marker that reveals medical signs, in other words, it is an objective indicator of a medical state that can be measured accurately and reproducibly without being invasive [19]. The National Institute of Health Biomarkers Definitions Working Group [20], as well as heads in the field of clinical trials and biostatistics from the US National Institute of Health and the US Food and Drug Administration, developed consistent and comprehensive definitions of terms relating to the use of biomarkers. According to them, a biomarker is *objectively measured and evaluated as an indicator of normal biological and pathogenic processes, or pharmacologic responses to a therapeutic intervention.* The use of biomarkers in basic and clinical research as well as in clinical practice has become so conventional that it is now accepted almost without question.

A free radical is a molecular species that contains an unpaired electron in an atomic orbital resulting in high reactivity and instability, yet it is capable of independent existence. These molecules can either donate or accept electrons, therefore, behaving as oxidizing or reducing agents [21]. Among the most important free radicals in cardiovascular disease, especially in CRS, are the reactive oxygen species (ROS) composed of: hydroxyl radical ($OH\bullet$), superoxide anion radical ($O\bullet^-$), hydrogen peroxide (H_2O_2), oxygen singlet ($^1O_2$), hypochlorite (ClO^-), NO radical ($NO\bullet$), and peroxynitrite radical ($ONOO^-$). As other highly reactive species, they are potentially capable of disrupting homeostasis in the nucleus and in the cellular membrane by damaging DNA, proteins, carbohydrates, and lipids [22].

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ROS are derived either from normal essential metabolic processes in the human body or from external sources such as exposure to X-rays, ozone, cigarette smoke, air pollutants, and industrial chemicals [23]. Free radical formation occurs continuously in the cells due to enzymatic and nonenzymatic oxygen reactions with organic compounds. Enzymatic reactions that produce free radicals include those involved in the respiratory chain, in phagocytosis, in prostaglandin synthesis, and in the cytochrome P450 system [24].

The term "oxidative stress" describes the oxidative damage resulting from unfavorable antioxidant defenses against free radical generation [25, 26]. Short-term oxidative stress may occur in tissues injured by trauma, infection, heat, hypertonia, toxins, or excessive exercise. Injured tissues produce higher levels of radical generating enzymes (e.g., xanthine oxidase, lipogenase, and cyclooxygenase), increase phagocyte activation and free iron and copper release, and produce an excess of ROS by disrupting the electron transport and oxidative phosphorylation. The initial mutation and progression of cancer, as well as the side effects of radiation and chemotherapy, have all been linked to the imbalance between ROS and the antioxidant defense system.

In addition, ROS has been implicated in the induction and in the complications of cardiac and renal [27] dysfunctions related to CRS [28] through the SNS and the RAAS [29].

3. RAAS and SNS: renal and cardiovascular systems

This section attempts to explain basic concepts about the signaling transductions of the RAAS and the SNS involved in CRS progression.

The RAAS plays an important role in systemic blood pressure regulation as well as in fluid and in electrolyte balance [30]. Angiotensin II (Ang II), the main effector peptide, is involved in cardiovascular and renal physiological and pathological effects, with inflammatory aspects [31] of different diseases present in CRS.

3.1. Ang II and its main signaling pathways to produce cardio and renal injuries

AT1 and AT2 are the main receptors activated by Ang II, being the first prominent receptor involved in harmful consequences of RAAS activation.

The main effect of Ang II is vasoconstriction by [32–34] increasing sympathetic tone [35] and arginine vasopressin (AVP) release [36–38] through stimulation of AT1 receptors mainly present in the vasculature. Activation of Ang II receptors and even nonreceptor pathways has been presented in a review by Touyz and Berry [39]. Briefly, ligand-receptor binding leads to activation of G proteins through an exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP), releasing α and β-γ complexes, which mediate downstream actions. AT1 receptors can be interacted with various heterotrimeric G proteins including Gq/11, Gi, Gα12, and Gα13. Different G protein isoforms lead to distinct signaling cascades. Gq activation results in the activation of phospholipase C (PLC), whereas GαI leads to cGMP formation. Although G protein-coupled receptors do not contain intrinsic kinase activity, the members of the G

protein receptor kinase family phosphorylate the G protein-coupled receptors on serine and threonine residues. AT1 receptors are phosphorylated in response to Ang II stimulation. Several tyrosine kinases, including Janus kinases (JAK and TYK), Src family kinases, and focal adhesion kinase (FAK) can phosphorylate AT1 receptors [40].

Angiotensin II has a long-term control over blood pressure through various mechanisms: direct stimulation of AT1 kidney receptors [10] and indirect adrenal gland aldosterone releasing regulate renal reabsorption of sodium and water [41], and acts on the hypothalamus causing thirst [36, 37].

The renin activity on the α2-globulin angiotensinogen produces the decapeptide angiotensin I (Ang I), which is then cleaved by an angiotensin-converting enzyme (ACE) to produce the octapeptide Ang II [42].

In mammals, there are two isoforms of ACE: somatic ACE, abundant on the surface of pulmonary endothelial cells, and testicular ACE. Both isoforms are found as soluble enzymes in the plasma and in seminal fluid [43]. Production of Ang II from Ang I also occurs through an ACE-independent way by the activity of other enzymes such as cathepsin G, a chymostatin-sensitive Ang II-generating enzyme, and chymase [36].

Besides its primary vasoconstrictor effects, Ang II also presents growth factor and cytokine-like properties [44]. The different forms of intracellular signaling processes explain its varied effects. In VSMC and also in renal cells, including glomerular endothelial and mesangial cells, Ang II induces chemokines such as monocyte chemoattractant protein-1 (MCP-1) [45–48].

AT1 signaling through phospholipids involves phospholipase C (PLC), phospholipase D (PLD), and phospholipase A_2 (PLA_2).

PLC signaling results in rapid production of the second messengers 1,4,5-inositol triphosphate (IP_3) and diacylglycerol (DAG). While IP_3 stimulates Ca^{2+} mobilization from the sarcoplasmic reticulum, DAG causes Ca^{2+} influx from extracellular space after protein kinase C (PKC) stimulation [49]. The increased cytoplasmic calcium concentration ([Ca^{2+}] c) leads to Ca^{2+}-dependent, calmodulin-activated phosphorylation of the myosin light chain, which, in turn, leads to cellular contraction. This is the main mechanism involved in the vascular smooth muscle cell (VSMC) contraction. PKC activation by this process regulates intracellular pH through the Na+/H+ exchanger [49, 50] and also activates both the nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) signaling as well as the ROS production.

PLD signaling is related to the phosphatidylcholine hydrolysis. The AT1 receptors mediating PLD activation involve Gβ-γ, Gα12, Src, and RhoA [51]. The pathways associated with Ang II-induced activation of PLD in VSMC are PKC independent, but involve intracellular Ca^{2+} mobilization and Ca^{2+} influx that is tyrosine kinase-dependent. Ang II-induced PLD signaling has been implicated in cardiac hypertrophy, VSMC proliferation, and vascular contractility [52, 53]. Among the PLD-mediated responses, there are vascular generation of superoxide anions by stimulating NADPH oxidase, and, under long-term stimulation of AT1 receptors, growth and remodeling in the cardiovascular system [54].

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The PLA2 activation due to Ang II binding on AT1 receptors is responsible for arachidonic acid release from cell membrane phospholipids [55], and its consequent metabolism by cyclooxygenases, lipoxygenases, or cytochrome P450 oxygenases results in various different eicosanoids influencing vascular and renal mechanisms that are important in blood pressure regulation. The main PLA2-derived eicosanoids resultants from cyclooxygenases include prostaglandin (PG) H2, which is then converted to thromboxane (Tx), PGI2 (prostacyclin), or to PGE2, PGD2, or PGF2α, by different enzymes (22). Lipoxygenases-derived molecules are the leukotrienes [55]. Cytochrome P450 oxygenases leads to the production of the hydroxy-eicosatetraenoic acids (HETE)—acids derived from epoxidation and allylic oxidation.

In VSMC, AT1 receptor stimulation by Ang II interconnects all phospholipases (PLA_2, PLD, and PKC) activation to initiate NADPH oxidase activity. DAG and Ca^{2+}, from the sarcoplasmic reticulum by IP3, activate PKC, which leads to phosphorylation of p47phox and initial activation of the NADPH oxidase [56, 57]. PLD also mediates PKC activation; phosphatic acid (PA) is produced, serving as a source of DAG [58–60]. Furthermore, PLA2 is activated by calcium cleaving phosphatidylcholine to products that heightens NADPH oxidase action, lysophosphatidylcholine (LPC) and arachidonic acid (AA) [61].

AT1-mediated tyrosine phosphorylation leads to mitogen-activated protein kinase (MAPK) activation associated with growth factors and cytokine activity, which corroborate to mitogenic and inflammatory consequences of Ang II. Moreover, AT1 receptor activation may be mediated by the activation of receptor tyrosine kinases (RTK) to bring about the Ang II stimuli on epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and insulin growth factor receptor (IGFR) [62, 63].

Furthermore, Ang II stimulates phosphorylation of several nonreceptor tyrosine kinases such as PLC-γ, Src family kinases, Janus kinase (JAK), focal adhesion kinase (FAK), Ca^{2+}-dependent tyrosine kinases, p130Cas, and phosphatidylinositol 3-kinase (PI3K) [64]. Altered VSMC function in hypertension is associated with increased activation of c-Src by Ang II. Vascular and cardiac growth, remodeling, and repair are assumed to involve Janus kinase, and the signal transducers and activators of transcription from early growth response genes mediated by Ang II [65]. FAK-dependent signaling pathways triggered by Ang II are related to cell migration and changes in cell shape and volume [66]. p130Cas mediated-Ang II effects regulate α-actin expression, cellular proliferation and migration, and cell adhesion, playing a relevant role in cardiovascular disease and actin filament assembly [67]. PI3K in Ang II signaling in VSMC may control the balance between mitogenesis and apoptosis [68].

Ang II activates the three major members of the mitogen-activated protein kinases (MAPK) family [69, 70]: ERK1/2 (related to enhanced proto-oncogene expression, and activation of the transcription factor, cell cycle progression, and protein synthesis in VSMC [71]), JNKs (regulation of cell growth, and vascular damage associated with cardiovascular disease [72]), and p38 MAPK (inflammatory responses, apoptosis, and inhibition of cell growth [73]).

Finally, by signaling through heterotrimeric G proteins, AT1 receptors activate monomeric small (21 kDa) guanine nucleotide-binding proteins (small G proteins) in VSMC. Activation of Ang II via AT1 receptor is coupled with Rho subfamily (RhoA, Rac1, and Cdc42), whose

Ang II effects are associated with increased Ca^{2+} sensitization, VSMC contraction, cytoskeletal organization, cell growth, inflammation, and regulation of NADPH oxidase [74]. In general Ang II, as other Gq coupled receptors, effectively activates NADPH oxidase in the cardiovascular system, enhancing production of ROS, whose effects majorly contribute to the pathogenesis of cardiovascular and kidney disease [75].

The integration of all the concepts above leads to the comprehension that important deleterious effects of Ang II could contribute to features observed in the CRS. This is supported by therapeutic involvement of angiotensin-converting enzyme inhibitors (ACEi) and of angiotensin receptor inhibitor, which have proven to be effective in the CRS therapy (for pharmacotherapy guidance we suggest reading the guideline organized by Dickstein et al. [76]). The activation of the RAAS determines renal hypoxia, vasoconstriction, intraglomerular hypertension, glomerulosclerosis, tubulointerstitial fibrosis, and proteinuria [77]. Similarly, the activation of the SNS involves proliferation of smooth muscle cells and adventitial fibroblasts in the intrarenal vascular walls [78]. Ang II increases renal vascular resistance in animal models, and the addition of an α_2-adrenoceptors agonist enhances this response. NADPH oxidase inhibition, as well as Rho kinase inhibition, or the presence of a superoxide dismutase (SOD) mimetic attenuates this interaction between Ang II and α_2-adrenoceptors agonist. Furthermore, in preglomerular VSMCs, the α_2-adrenoceptors agonist enhanced Ang II-induced intracellular O_2^- production and activation of RhoA, responses which were prevented by inhibition of phospholipase C (PLC), PKC, c-Src, NADPH oxidase, and by a SOD mimetic.

3.2. Free radicals: key biomarkers in experimental models to explain RAAS and SNS in CRS

Excessive and inappropriate activation of the RAAS [79] is directly implicated in many ways in the progression of renal disease due to heart failure. In parallel to the heart failure, the ongoing, uncontrolled activation of the RAAS is indicative of renal failure.

The model proposed by Guyton [80] describes a heart–kidney connection regarding extracellular fluid volume (ECFV), cardiac output, and mean arterial pressure. In this arrangement, the pathophysiological basis of CRS is structured on the combined renal and cardiac disease invoking a number of specific factors that synergistically aggravate the disease.

In Guyton's model [80], the kidney is placed as a regulator of extracellular fluid volume and the RAAS is placed with its corresponding extensions (aldosterone and endothelin) and its antagonists (natriuretic peptides and NO). The model explains changes in extracellular fluid volume, blood pressure, and cardiac output in merged heart and renal failure. An extension to this model, however, was projected by Bongartz et al. [29] to explain the accelerated atherosclerosis, the cardiac remodeling and hypertrophy, and the progression of renal disease observed in the severe CRS. When the heart or the kidney fails, a vicious cycle, called the cardiorenal connection [81, 82] in a scheme depicted by Bongartz et al. [29], progresses: the RAAS, the NO-ROS balance, the sympathetic nervous system, and inflammation interact and synergize.

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The reduction in circulating arterial blood volume triggers arterial baroreceptors and activates neurohormonal pathways resulting in compensatory mechanisms in order to restore physiological tissue perfusion to correct the relative hypovolemia, such as in hemorrhage [83].

Indeed, not only the RAAS is activated but also the SNS. The endothelin and arginine-vasopressin systems are triggered by low renal function as protection mechanisms. Additionally, sodium-retentive vasoconstriction can counterbalance the activation of vasodilatory natriuretic hormone (natriuretic peptide) systems and cytokines (prostaglandins, bradykinin, and NO) [84].

These pathways lead to an outcome of heart failure, an impairment involving volume retention due to hemodynamics and reabsorptive actions of angiotensin II (Ang II) [86].

In addition to the imbalance of extracellular fluid volume (ECFV) and vasoconstriction, the activation of NADPH-oxidase by Ang II harms the cardiorenal connection by generating ROS [87].

Ang II not only stimulates NADPH oxidase-dependent O_2^- production in VSMCs but also in endothelial cells and adventitial fibroblasts [88, 89]. Additionally, stretch of the vasculature could enhance O_2^- and hydrogen peroxide (H_2O_2) production by NADPH oxidase during a relatively short period of time [90, 91].

Mohazzab and Wolin [92] and Rajagopalan et al. [93] have identified NADPH oxidase as a major site of O_2^- generation in intact arteries (endothelial cells and vascular smooth muscle cells [94]) besides renal tubular cells [95] and cardiomyocytes [96]. Interestingly, constituents of phagocyte NADPH oxidase were found in many different tissues, like in mesangial cells [97], vascular smooth muscle cells [98, 99], endothelial cells [100], glomerular epithelial podocytes [101], kidney proximal tubular epithelial cells [102], and fibroblasts [103].

The multimolecular enzyme NADPH oxidase has the following components: a membrane-associated 22-kDa α-subunit (p22phox) and a 91-kDa β-subunit (gp91phox) with cytoplasmic constituents (p47phox, p67phox, and p40phox) [104].

The severity of CRS is positively associated with oxidative damage to renal tubular or interstitial cells due to interference with feedback systems involved in renin secretion and angiotensin formation. Chronic inhibition of NO synthesis causes upregulation of cardiac ACE and Ang II receptors, possibly mediating inflammatory changes [105]. It has been demonstrated [105] a complete NADPH oxidase system along the luminal membrane of the macula densa, suggesting that O_2- generated at this site forms a barrier and limits the actions of NO locally generated to reach targets on the luminal membrane. Thus, local NADPH oxidase impairs the bioavailability of NO, which is implicated by the regulation of sodium reabsorption in distal nephrons and activation of macula densa cells of hypertensive rats.

Renal blood flow reduction due to activation of the RAS leads to stimulation of the macula densa and subsequent secretion of renin; in critical kidney impairment (such as in hypoxia), this vicious cycle of RAAS starts or maintains the development of CRS [27].

Ang II may produce cell changes in the glomerular epithelium [106]. Local expression of the RAS in podocytes has been recently confirmed in human podocytes [107, 108]. Direct injury

to podocytes of transgenic rat models with overexpression of the human Ang II Type 1 receptor, developed substantial selective proteinuria (albuminuria) without an increase in blood pressure. This model's glomerular injury led to nephron loss through the classic pathway present in focal segmental glomerulosclerosis [109]. Also, aldosterone, an end product of Ang II, directly injures podocytes [110, 111].

Therefore, added to these direct consequences of tubulointerstitial damages, present mainly in CRS type II, activation of this system can induce glomerulosclerosis and anatomical damage to glomerular tufts, with a subsequent decrease in postglomerular capillary perfusion.

Beswick et al. [112] identified ROS production in a model of mineralocorticoid (deoxycorticosterone acetate [DOCA]-salt) hypertensive rats. NADPH oxidase activity is increased in the aortic wall of the DOCA-salt rat, and such an increase is associated with elevated O_2^- production; long-term inhibition of NADPH oxidase significantly decreased O_2^- production and systolic blood pressure, but treatment of DOCA-salt rats with the losartan (Ang II inhibitor) does not significantly alter blood pressure, suggesting that locally produced Ang II does not contribute to the elevated peripheral vascular resistance. This calls into question the role of Ang II in O_2^- generation in this model. On the other hand, NADPH-oxidase mediated ROS release in glomeruli of Dahl [113] salt-sensitive rats with heart failure, which was attenuated by ACEi [114]. In human beings, similarly, NADPH-oxidase is active in the hearts of patients with end-stage heart failure [115]. Inhibition of ACE possibly decreases vascular oxidative stress and/or improves extracellular SOD activity in patients with coronary artery disease due to higher NO bioavailability [116].

Ang II has a role in vascular inflammation via the nuclear factor kappa B (NF-kB) pathway, responsible for producing chemotactic and adhesion molecules [117, 118].

Complicated mechanisms link the RAS to the SNS [119]. The rise of sympathetic hyperactivity detected in kidney failure has been attributed to the failing organ [120], and ACEi could control this outflow in chronic failure [121, 122]. Blocking Ang II signaling transduction causes reduced SNS hyperactivity after myocardial infarction in rats, attenuating ensuing development of heart failure [123].

Oxidative stress induced by hydrogen peroxide presented higher activation of preganglionic sympathetic neurons both in vivo and in vitro in rats, culminating in a greater mean blood pressure and pulse [124]. Moreover, spontaneously hypertensive rats were found to have sympathetic renal activity controlled by vascular superoxide concentrations [125].

4. Oxidative stress in target CRS organs

Considering the RAAS and the SNS and that the impaired functions of the target organs (kidney and heart) can conjointly trigger and intensify diseases related to the syndrome's development, this section aims to provide the reader with molecular/cellular explanations about why free radicals and consequent oxidative stress are feasible to act as CRS biomarkers.

4.1. Heart and oxidative stress

ATP is constantly demanded in physiologic cardiac functioning. So mitochondria organelles, as major sources of ATP, must be in prompt activity to keep homeostasis [126]. When the balance between cardiac cells and mitochondria is lost, there is cardiac damage due to increased oxidative stress as can be observed in heart failure.

In a normal heart, most of the ATP is produced by fatty acid oxidation, while the remaining part is due to oxidizing pyruvate, an end product of glycolysis or derived from lactate [127]. On the other hand, with decreasing ATP concentrations, there is a metabolic shift from fatty acid oxidation to glycolysis in cardiomyocytes under heart failure progression [128–130]. Indeed, the decrease in mitochondrial oxidative metabolism is reduced by a compensatory increase in glucose uptake and glycolysis [131, 132].

The main cause of the damage affecting the cardiomyocytes is the self-perpetuation of the oxidative stress as the reduced oxidative metabolism leads to an accumulation of free fatty acid in cardiomyocytes.

The PKC activation and consequent sarcoplasmic reticulum stress are the main intracellular mechanisms explaining both contributors to mitochondrial oxidative stress: lipotoxicity of circulating fatty acid and intracellular lipid accumulation [133].

Independent of the heart failure stage, changes in mitochondrial electron transport chain components were described [134–137]. Indeed, the progressive decrease of ATP production is linked to both a decrease of fatty acid oxidation and a reduction of mitochondrial respiration due to electron transport chain defects [138].

The disruption of the mitochondrial electron transport chain homeostasis is a well-established source of ROS that forms a vicious cycle by amplifying the electron transport chain dysfunctions. In heart failure, the decreased mitochondrial respiratory activity leads to a further drop in oxidative phosphorylation, associated with an increased electron leakage and superoxide generation.

As already mentioned, ROS are produced by nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX). There are seven NOX isoforms that function primarily as ROS-generating enzymes, being important sources of O_2^- and H_2O_2 in the cardiovascular system [139]. When physiological functioning of NOXs is disrupted, the production of ROS increases.

Overactivation of the RAAS and the SNS are essential to maintain and amplify the oxidative stress in heart failure, as previously explained. NADPH oxidase activated by Ang II is the primary source of ROS that produces mitochondrial dysfunction [140]. The effects are due to both NOX4 and NOX2, which are upregulated by Ang II in a mitochondrial ROS-independent and dependent manner, respectively [141].

ROS accounts for the damage observed in heart failure, such as cardiac remodeling, cardiomyocyte contractility, ion transport, and Ca^{2+} handling. ROS act on multiple intracellular signaling pathways for transcriptional activation of selected nuclear genes and finally eliciting transcriptional reprogramming [142]. In response, the most prominent adaptive processes

accompanying HF are an increase in sympathetic tone. Increased adrenergic activity causes a reduction on the physiological role of respirasomes, and consequently mitochondrial dysfunction, and a gradual decrease in the cardiac performance [28]. The excessive sympathetic activity can induce cardiomyocyte apoptosis, hypertrophy, and focal myocardial necrosis [85].

The lack of energy in cardiomyocytes is an important result of the oxidative stress observed in decompensated HF, explained by reduced Ca^{2+} sensitivity in response to oxidative impairment of myofibrillar proteins [143].

ROS were shown to activate matrix metalloproteinase (MMP) in cardiac fibroblasts [144]. MMP are a large family of Ca^{2+}-dependent zinc-containing endopeptidases that are responsible for tissue remodeling and degradation of extracellular matrix (ECM), including collagens, elastins, gelatin, matrix glycoproteins, and proteoglycan. Overexpression of MMPs results in imbalance between its activity and the activity of TIMPs and can lead to a variety of disorders [145–149]. Since MMP plays a central role in organ development and subsequent tissue remodeling in inflammation and in injury, they are relevant HF biomarkers, especially in CRS [150].

4.2. Kidney and oxidative stress

Oxidative stress and inflammation are progressively enhanced in progressing stages of kidney diseases directly related to CRS such as CKD [151–153]. This section describes mechanisms that link RAAS and its components to the increased oxidative stress and inflammation within the kidneys [154–156].

Ang II acts preferentially in tubular epithelial cells, whereas aldosterone acts in podocyte injury [157]. As previously said, NOX enzymes (NADPH oxidases) are the primary source of ROS. Under Ang II and aldosterone stimuli, cytosolic subunits of NADPH oxidase can translocate into the mitochondrial membrane and increase ROS production and affect the NO function. It is the balance between NO and Ang II rather than their absolute concentration that determines the physiological/pathophysiological effects on multiple organ systems including cardiovascular and renal systems. Ang II systematically decreases regional blood flows, impairs renal function, and causes cardiac hypertrophy [158].

In the kidney, NOX are active in vascular smooth cells in both cortex and medulla [159, 160]. NOX4, NOX2, and NOX1 are expressed in the kidney cortex, being NOX4 the most abundantly expressed renal isoform, primarily not only located in renal tubular cell [161–163] but also found in glomerular mesangial cells [164, 165].

A critical role played by NOX-produced ROS is the uncoupling of NO synthase (NOS). Considering its physiological role, NO produced by endothelial cells causes vasodilatation of the afferent arteriole, consequently increasing renal blood flow, attenuating tubuloglomerular feedback, and promoting pressure natriuresis [166]. NO stimulates soluble guanylyl cyclase (sGC) and increases cGMP production that triggers cGMP-dependent protein kinases, phosphodiesterases, and ion channels [167]. On the other hand, NO is activated in a non-cGMP-dependent process and causes covalent proteins changes [168]. NO reacts with O_2^- to form $ONOO^-$ [169], therefore, limiting its physiological activity of afferent arteriole relaxation [170,

171], which leads to reduced renal blood flow. Vasoconstriction, inflammation, and impaired vascular and renal functions [172] are the main results of $ONOO^-$ accumulation.

O_2^- and $ONOO^-$ are the main free radicals that start proinflammatory and profibrotic cascades [55]. In the absence of or in a low concentration of NO, the cyclooxygenases (COX) activity is amplified, so vasoconstriction is enhanced due to TxA2, yet the vascular relaxation is impaired due to reduced PGI2 production [172, 173].

Mesangial cell apoptosis [174] and cellular hypertrophy, respectively, due to MAP kinase and ERK1/ERK2 pathways [175], explain the development of epithelial-mesenchymal transition (EMT) [176, 177] caused by NOX-derived ROS. EMT of tubular epithelial cells is characterized by loss of epithelial properties and gain of excessive deposition of extracellular matrix-producing characteristics of myofibroblast [178, 179]. The transforming growth factor β (TGF-β) induces EMT and is assumed to be one of the major causes of renal fibrosis [180–182].

According to Yang and Liu [183], and to Rubattu et al. [28], EMT regulates the loss of epithelial cell adhesion, the *de novo* α-smooth muscle actin (α-SMA) expression and reorganization, the disruption of tubular basement membrane, and the enhanced cell migration and invasion into the interstitium. Increased expressions of PLA2, MCP-1, CSF-1, and COX-2 promote fibrosis and inflammation on renal interstitium, all due to NOX activation under oxidative stress progression [184–187]. The main transcription factors involved are NF-kB [74] and c-jun [188].

Second, free radicals' inflammatory effects can be related to uncoupling proteins (UCPs) [189, 190]. UCPs are mitochondrial transporters present in the inner membrane; they belong to the family of anion mitochondrial carriers including adenine nucleotide transporters. There are three UCPs (1–3). In comparison to the established uncoupling and thermogenic activities of UCP1, UCP2, and UCP3 appear to be involved in the limitation of free radical levels in cells rather than in physiological uncoupling and thermogenesis.

UCP2 gene variants are positively associated with kidney diseases, being considered as a predictor of genetic risk for CKD [191, 192].

5. Oxidative stress: biomarkers and therapeutic strategies in CRS

The main proposal of biomarkers is an early diagnosis of CRS allowing early therapeutic intervention. The continuance of mitochondrial biogenesis against cardiac insult and the reduction of mitochondrial ROS production are the two most promising approaches that may soon yield effective treatments for HF [193].

The action of ROS and their products in organs, such as heart, kidney, and the entire cardiovascular system, turn them into promising biomarkers for predicting cardiovascular risk in CRS and also for therapeutic responses. Important investigations have characterized new oxidation byproducts in specific circumstances, however, oxidized lipoproteins, including low-density lipoproteins (LDL) have a long track record as biomarkers and appear to be among the most promising oxidation markers to potentially impact clinical practice in the near future

[194]. Nonetheless, this biomarker is more appropriate for atherosclerosis than for HF related to CRS. Biomarkers such as MMP and mitochondrial function may be more adequate.

Concerning clinical evaluation of cardiovascular and renal dysfunctions, ROS is examined due to the association between plasma and urine markers of oxidative stress. There are several clinical studies where biomarkers were and are being tested [195]. The following sections attempt to cover potential biomarkers related to oxidative stress.

5.1. Heart biomarkers of oxidative stress

The main molecules approached in this section are the ones involved in HF since this is the main cardiac disease in CRS linked to kidney dysfunction.

The molecules are matrix metalloproteinase (MMP), myeloperoxidases (MPO), and mid-regional proadrenomedullin (MR-proADM).

Although HF, but not myocardial infarction, is the main cardiac disease related to CRS, studies have shown that increased MMP production is a biomarker related to both. Since dramatic reduction in the incidence of rupture and reduction in heart size and development of heart failure is observed when MMP activation is reduced, it can predict CKD present in CRS [196].

Considering the role of MMP in stem cell mobilization following cardiac injury, in the very active field of cell-based therapy following myocardial infarction, MMP-9 was found in bone marrow; its function is to release mononuclear cells into the blood flow. After ischemic injury, there seems there to be local formation of inflammatory cytokines, such as tumor necrosis factor (TNF), platelet-derived growth factor, and vascular endothelial growth factor [197]. A significant component of regulation of MMP production following myocardial infarction is induced by the local inflammatory cytokines, which is practically what is observed in HF. Excess TNF in the myocardium has direct relation to an elevated formation of local MMP-9 and MMP-2, and this is associated with modifications in integrin isoform transition [196]. The consequence is aggressive collagen dissolution with possible acute myocardial rupture. If the dissolution goes on without rupture, the heart becomes expressively dilated, with decreased function and poor survival [196]. On the other hand, if the gene for TNF is removed, there is a significant reduction in the levels of the inflammatory cytokines associated with the reduction in MMP activation.

Once MMP are formed, they stay as proenzymes in the ground substance of the extracellular space. However, if met by other activation signals like oxygen free radicals and ischemic triggers such as thrombin or chymase or angiotensin-converting enzyme (ACE) from mast cells, then propeptides are unconfined, liberating the enzyme's active site [198]. A membrane type MMP can also catalyze this process or other proteolytic agents such as plasminogen activators (urokinase-type plasminogen activator) or plasmin. Plasmin's activation is due to inflammation and coagulation cascades. Reduction in cardiac rupture after myocardial infarction could be reached by inhibiting MMPs, plasminogen activators, or cytokines [196, 198].

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Taking into account the kidney and the heart to explain the role of the free radicals, Rubattu et al. [28] published a review about pathogenesis of CRS and oxidative stress. The information is addressed briefly in the next paragraphs. Myocardial MMP activity is also increased in the failing heart [199]. Sustained MMP activation causes structural changes due to an abnormal extracellular environment for myocytes. Dimethylthiourea, a hydroxyl radical scavenger, inhibits matrix metalloproteinase 2 (MMP2) activation parallel to left ventricular remodeling and failure [200]. Additionally, release of mitochondrial intermembrane proteins crucially triggers apoptotic pathways: cytochrome c, endonuclease G (EndoG), apoptosis-inducing factor (AIF), and second mitochondria-derived activator of caspase (Smac) lead to caspase activation, nuclear DNA fragmentation, and cell death [201]. Release and nuclear translocation of EndoG and AIF stimulate DNA degeneration, independent of caspase activation [202]. Stress kinases, such as c-Jun N-terminal kinase (JNK) and p38-mitogen activated protein kinase (MAPK), are activated by increase in ROS levels [203]. The link between hypertrophy mitochondrial dysfunction seen in HF could be due to JNK. Actually, in addition to the induction of hypertrophic cardiomyocytes, JNK promotes autophagy through Bcl-2 and 19-KDa interacting protein-3 (BNIP3), eventually leading to mitophagy [204, 205]. In turn, higher mitophagy rates ends in MMP activation [206].

Besides the MMP, there are the myeloperoxidases (MPO) considered a key player in the initiation and maintenance of chronic heart failure (CHF) by contributing to intracellular NO depletion. NO consumption through MPO activity may lead to protein chlorination or nitration and to tissue damage.

As revised by Anatoliotakis et al. [207], the principal mechanism by which MPO exerts its effects on the human heart and vessels is thought to be by direct effects of oxidative products on the arterial wall causing endothelial dysfunction, as well as by affecting the function and distribution of cholesterol in the form of LDL and HDL. MPO is the main molecule responsible for lipid peroxidation and conversion of LDL to an atherogenic form that is subsequently taken up by macrophages, a step crucial for the formation of foam cells [208]. Additionally, MPO acts as an enzymatic sink for NO, thus impairing NO-dependent blood vessel relaxation and guanylate cyclase activation [209].

La Rocca et al. [210] demonstrated that human endocardial endothelial cells can express MPO after oxidative stress through the buildup of the end product, 3-chlorotyrosine. Abnormalities in endothelial functions may lead to many cardiovascular issues, including CHF. The authors concluded that the endothelium suffers the consequences as well as plays an important role in cardiovascular stress due to oxidation.

Considering what was the earlier approach about CRS, a positive association can be made with an MPO increase and disease progression. MPO, a marker of oxidative stress [211, 212], maintained a modest association with HF in this cohort when combined with each of the established and emerging biomarkers.

MR-proADM shows great promise as an independent prognostic tool for cardiac diseases. Although it has been shown as a strong predictive marker for a variety of cardiac disease, it is also a biomarker for other diseases including chronic obstructive pulmonary disorder,

pneumonia, and pulmonary embolism [213, 214]. Since MR-proADM levels have been shown to differ based on New York Heart Association (NYHA) class and severity of HF, it has the potential to help identify those patients who may benefit from more invasive therapy [215].

Adrenomedullin (ADM), a 52-amino-acid peptide, was first discovered from a pheochromocytoma. It is expressed by many endothelial tissues throughout the body including the adrenal medulla, lungs, kidneys, gastrointestinal organs, and heart [216–219]. ADM is secreted as an inactive precursor (pro-ADM) and subsequently cleaved into the active form where it acts as a potent vasodilator through the nitric oxide pathway and increases diuresis and natriuresis [220–222].

Considering emerging biomarkers of hemodynamic stress that are strongly predictive of poor outcomes in patients with heart failure (HF), MR-proADM is the main molecule related to CRS [223]; others include copeptin and midregional proatrial natriuretic peptide [MR-proANP].

5.2. Kidney biomarkers of oxidative stress

Considering renal biomarkers of oxidative stress as part of the pathophysiology, the pool includes oxidized low-density lipoproteins (Ox-LDL), advanced oxidation protein products (AOPP), thiobarbituric acid reactive substances (TBARS), plasma and urinary F2-isoprostanes, malondialdehyde (MDA), protein reduced thiols, total antioxidant status (TAS), protein carbonyls, advanced glycation end products (AGE), rinary 8-hydroxydeoxy guanosine (8-OHdG), 4-hydroxy-nonenal, antioxidant enzyme activities (e.g., superoxide dismutase, glutathione peroxidase, and catalase) [195, 224–229]. It is important to highlight that these biomarkers could indicate the possible correlated diseases, and not strictly renal injuries from CRS. Studies that involve cardiovascular and kidney disease, such as hypertension and CRS, try to correlate oxidative stress to the absence of antioxidant defenses (extrinsic and intrinsic). In general oxidized phospholipids (OxPL) have been associated with cardiovascular disease and new cardiovascular events [230]. OX-LDL, a particle derived from circulating LDL, may have peroxides or their degradation products generated within the LDL molecule or elsewhere in the body. This includes minimally oxidized LDL, but not apoprotein changes, and malondialdehyde (MDA) modified particles with MDA arising from platelets or elsewhere. However, LDL particles with oxidized apo B amino acids without lipid changes have not been described [231]. In kidney diseases, Ox-LDL has been studied as a biomarker to assess end-stage renal failure. Nonetheless, as a CRS biomarker, Ox-LDL needs correlational studies [232].

According to Witko-Sarsat et al. [233], AOPP is a biomarker of phagocyte-derived oxidative stress. The authors point out the role of AOPP in the pathophysiology of chronic renal failure and dialysis-related complications. Considering AOPP production, they describe that myeloperoxidase (MPO) has a significant role in the consequent formation of chlorinated oxidants, contrary to the prior belief of its sole microbicidal action. Undeniably, AOPP seems to mediate inflammation because they can initiate the oxidative burst and the production of cytokines in leucocytes. Therefore, it can be inferred that by the uremia-associated defect in anti-oxidant systems that the AOPP, from the reaction between chlorinated oxidants and plasma proteins, constitute new uremic toxins with proinflammatory effects. Specific plasma proteins are

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critical targets for oxidants that can be evaluated by spectrophotometric assays, which allows AOPP detection in uremic plasma [234], mainly from patients under hemodialysis [235].

F2-isoprostanes are a series of active compounds like prostaglandin F2. They are produced regardless of the route of the COX in the peroxidation of AA. F2-isoprostanes are formed in situ on the membrane phospholipid chains and subsequently released. Their concentrations in the plasma and urine of healthy adults are 10–100 times greater than those of prostanoid formed by way of the cyclooxygenase. They significantly increase oxidative stress. The F2 isoprostanes are potential markers of lipid peroxidation, but their measurement requires sophisticated equipment (mass spectrometer). Recently, Elisa methods have become available [236].

Biomarkers of cell damage due to systemic oxidative stress, such as plasma thiobarbituric acid-reactive substances (TBARS) and 8-epi-isoprostanes, are elevated in patients with hypertension [237, 238] who mainly present kidney injury. Antioxidant capacity and the levels of antioxidant vitamins and enzymes were reduced in patients with hypertension [239, 240] with renal insufficiency.

6. Conclusion

The Acute Decompensated Heart Failure National Registry (ADHERE) database has pointed out that renal dysfunction in patients with heart failure is complex and often multifactorial in origin. Along these lines, CRS is conceived as a moderate or a greater renal dysfunction existing or developing in a patient with decompensated heart failure during treatment [241]. Important works present a common agreement: concurrent kidney and heart failure has a bad prognosis [242–244]. The literature, on the other hand, is not homogeneous in relation to the damages and their mechanisms due to a number of factors, causes, and on the processes that makes CRS reversable in some cases. Since both the RAAS and the SNS are related to the processes leading to inflammation and are tightly involved in production and/or activation of free radicals, this chapter's rationale is that the diagnosis and progression of CRS could be evaluated through oxidative stress. Some CRS pharmacotherapeutics approaches are deficient, although mainly involving the primary condition linking renal dysfunction to heart failure, like in volume-loaded patients with diuretic braking [245]. There is a gap in clinical trials composed of patients with heart failure and with substantial kidney dysfunction, because most patients are recruited from a population with relatively preserved kidney function [246]. Further studies are needed to better define renal function in patients with heart failure or vice-versa. Attention must be taken to drugs that may impair kidney function, and specially evaluated regarding populations selected for clinical trials, who have already had their kidney functions compromised or put at risk. Understanding the involvement of free radicals in the Cardiorenal Syndrome could lead to accurate pharmacological studies and future interventions.

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