Type 1 Cardio-Renal Syndrome

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7.1 Introduction

Co-existence of renal dysfunction is common in patients with heart failure (HF) and often leads to adverse clinical outcomes [1]. The term "cardio-renal" was introduced as early as 1913 by Dr. Thomas Lewis, who described a unique form of paroxysmal dyspnea in the setting of concomitant cardiac and renal dysfunction [2]. The following year, Dr. Alfred Stengel proposed the classification of cardio-renal diseases into three distinct forms: (1) primary valvular or myocardial disease with secondary renal disease; (2) primary arterial or arteriolar disease with secondary renal and myocardial disease; and (3) primary renal disease with secondary myocardial and vascular disease [3].

After a century of medical progress, our contemporary classification scheme for cardio-renal syndrome (CRS) remains largely descriptive of such temporal bi-directional relationships between cardiac and renal dysfunction without specifying precise mechanistic culprit(s) [4]. Nevertheless, there is general agreement that adverse interactions between the kidneys and circulatory components promote increased circulating volume, exacerbate HF symptoms, and accelerate subsequent disease progression [5]. In contrast, contribution of various non-cardiac factors that have been proposed some half a century ago may still be under-recognized [6]. This chapter will review the classical mediators of cardio-renal injury through which acute HF aggravates renal dysfunction leading to Type 1 CRS, and outline the directions for further investigation beyond our current management strategies.

7.2 Definition of Acute (Type 1) Cardio-Renal Syndrome

Clinicians have largely considered acute (or "Type 1") CRS as equivalent to the working definition outlined in a National Institute of Health

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workshop for acute CRS as "an extreme form of cardio-renal dysregulation in which therapy to relieve congestive symptoms of HF is limited by further decline in renal function." [7] There are several key words in this definition: (1) "dysregulation" refers to the dysfunctional cross-talk between the heart and the kidneys to maintain salt and water homeostasis; (2) "congestive symptoms" refers to the volume overloaded state related to HF; and (3) "limited by further decline in renal function" refers to the refractoriness to standard diuretic regimen (sometimes considered as "diuretic resistance"). In simpler terms, the intention to treat congestive HF by aggressive diuresis was deemed inadequate as a result of ineffective renal responses.

It is important to emphasize here that considerations of "abnormal renal function" still relied on indirect biomarkers that estimate glomerular filtration or function (e.g. clearance of creatinine/cystatin C, and leakage of albumin/protein) rather than biomarkers of tubular function (e.g. clearance of urea or toxins, and handling of electrolyte homeostasis). On the other hand, reliable insights into renal hemodynamics remained limited. Therefore, the precise processes and mechanisms in which the kidneys endure injury remain unclear in the setting of acute CRS [8].

7.3 Factors Contributing to the Development of Acute CRS

Contributing factors to the development of acute (Type 1) CRS include hemodynamic disturbance, neurohormonal activation, and inflammation (Fig. 7.1).

Impaired Cardiac Output. In the setting of acute HF, reduced cardiac output can lead to impaired renal blood flow and perfusion, which has long been proposed as the primary driver of renal dysfunction and subsequent injury [9]. Indeed, acute kidney injury (AKI) is more prevalent and severe with impaired cardiac output, being reported more than 70% in cardiogenic shock [10]. Improvement in serum creatinine levels shortly after implantation of left ventricular assist devices also highlights the pathophysiological importance of hemodynamic disruption in CRS [11]. However, this once-prevailing concept of "arterial underfilling" as the single perpetrator of CRS cannot be fully explained by clinical observations, since the majority of patients presented with acute HF also have relatively preserved cardiac output [12–15]. It is likewise important to note that a rise in serum creatinine may not be the primary abnormality to reflect

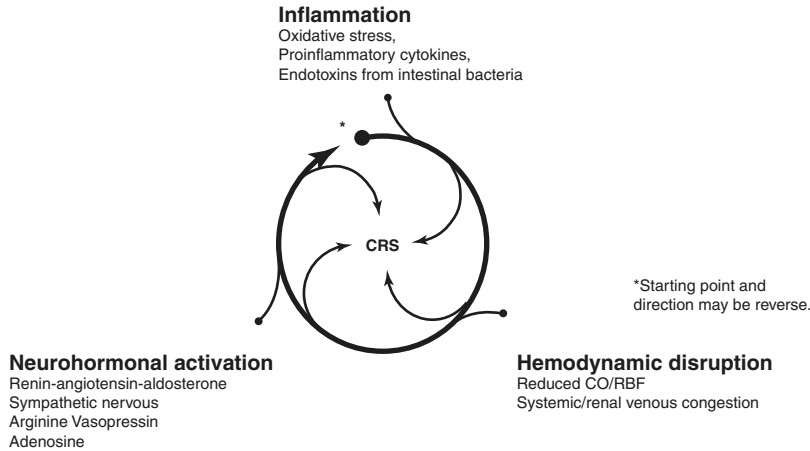

Fig. 7.1 Key Contributors to Cardio-Renal Syndrome. Despite efforts to establish a hierarchy, there seems to be no such hierarchy among cardio-renal connectors. Inflammatory reaction, an activated neurohormonal system and hemodynamic disruption become connected during the subclinical stage of CRS, starting a vicious cycle but staying in a subclinical stage for a period

underlying hemodynamic derangements, as hypochloremia may also be triggered by underlying low cardiac output state [16–18].

Systemic Venous Congestion. Over the past decade, there is growing understanding of an inverse relationship between central venous pressure (CVP), renal blood flow (RBF), and glomerular filtration rate (GFR) in the setting of HF [19]. Like impaired cardiac output, elevated CVP can lead to increased renal interstitial hydrostatic pressure, resulting in a decreased net filtration pressure, and progressive renal dysfunction [20]. This can be exacerbated in the setting of acute decompensated HF, whereby increased CVP on admission as well as insufficient reduction of CVP during hospitalization can be stronger hemodynamic determinants for the development of worsening renal function compared to diminished cardiac index [21]. Recent mechanistic demonstrations with saline loading experiments have further confirmed the impact of increasing "venous impedance" at the level of the kidney on attenuation of diuresis and natriuresis [22, 23]. These observations may imply that beyond impaired renal perfusion in low cardiac output state, the inability to mobilize venous congestion despite aggressive diuresis can also trigger acute (Type 1) CRS.

Raised Intra-Abdominal Pressure. One of the commonly-overlooked contributors of acute CRS is extra-cardiac hemodynamic alteration in the abdominal cavity [24]. Especially in the setting of overt right-sided HF with significant venous congestion or in post-operative/obstructive settings with ileus or organ swelling, abdominal congestion in the form of splanchnic venous and interstitial congestion can manifest via compromised capacitive function of the splanchnic vasculature and deficient abdominal lymphatic flow resulting in interstitial edema [24]. Increased intra-abdominal pressure detectable via bladder manometry, in extreme cases of abdominal congestion, is correlated with renal dysfunction in advanced refractory congestive heart failure [25].

Pre-existing Renal Insufficiency. The most common scenario whereby acute (Type 1) CRS occurs is due to pre-existing renal dysfunction, which may cause worsening pressure and/or volume overload. Furthermore, chronic uremia can induce left ventricular hypertrophy, promote cardiac fibrosis, and induce systemic oxidant stress [26]. Up to one third of patients hospitalized with acute decompensated HF have concomitant AKI (here referred to rise in biomarkers of glomerular filtration accompanying oligouria), and 60% of patients with acute HF who did not have AKI on admission eventually developed AKI during hospitalization [27]. The co-occurrence of AKI in patients with acute HF worsens survival in those patients [28]. While we do not fully understand the mechanisms leading to increased cardiovascular complications among chronic kidney disease (CKD) patients, worsening renal function in patients with HF is primarily caused by reduced renal perfusion pressure following hemodynamic derangement as the primary culprit. However, when renal dysfunctions become clinically noticeable in the setting of HF, over-activation of neurohormonal systems and systemic inflammation occurs concomitantly with progressive deterioration of cardiac function, making it difficult to single out the culprit among the cardio-renal mediators.

Neurohormonal Mediators. The concept of neurohormonal system activation because of circulatory perturbations plays a large part in our expanded understanding of renal physiology and sodium homeostasis [29]. Activated renin-angiotensin system (RAS) and the sympathetic nervous system (SNS) are prototypical cardio-renal mediators that have diverse influences on hemodynamic components such as right atrial/ventricular compliance, venous capacitance, and returning volume of venous blood [30]. Teleologically, over-activated RAS restores renal perfusion pressure by sustaining intraglomerular pressure and promoting volume expansion [31]. However, while angiotensin restores intraglomerular pressure by constricting efferent arterioles, ensuing vasoconstriction of systemic resistance vessels results in increased afterload and detrimental cardiac function [31]. Excessive urinary sodium and chloride loss caused by aggressive diuresis may induce renin release that increases renal sodium avidity, which is a natural response to dehydration [32]. Avid sodium reabsorption

and water retention in the presence of an overactive RAS further aggravates HF and sets up the vicious cycle of CRS [8, 33, 34].

An over-activated RAS can also worsen renal dysfunction through non-hemodynamic mechanism [8]. For example, angiotensin II stimulates production of proinflammatory mediators (e.g. tumor necrosis factor [TNF]-α, interleukin-6, monocyte chemoattractant protein-1, nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB]) and mobilizes inflammatory cells in the glomeruli. Following cell proliferation, fibrosis and apoptosis eventually progress in the heart and kidneys [35]. Of note, mineralocorticoid in concert with angiotensin II stimulates macrophages in the kidney to secrete galectin-3, a HF biomarker in recent spotlight, which in turn induces proliferation of pericytes, deposition of collagen, and eventual renal fibrosis [36].

Although its deleterious effects in renal injury are less elucidated than in HF [31], the over-activated SNS also contributes to the development of renal dysfunction [37]. First, efferent sympathetic nerves are activated by ischemia/reperfusion injury, a common clinical cause of AKI in various clinical settings [38]. Renal ischemia increases glomerular expression of tyrosine hydroxylase, a rate limiting enzyme of noradrenaline production, suggesting morphological alterations of adrenergic nerve terminals in glomeruli of ischemic AKI [39]. The activated SNS facilitates renal fibrogenesis, tubular vasoconstriction, and reduces GFR in manners dependent on endothelial dysfunction and inflammation, acting jointly with elevated angiotensin II and increased oxidative stress [38]. Adrenergic receptors and endothelin receptors are a superfamily of G protein coupled receptors (GPCR). Transverse aortic constriction elevated renal GPCR signaling and endothelin expression in mice, and then led to deterioration of renal function. In addition, pharmacologic inhibition of GPCR alleviated renal dysfunction [40].

Sympathetic nerve denervation can increase basal renal flow, urine flow rate, fractional sodium excretions, and GFR in rats after renal ischemia/reperfusion injury. The denervated rats had less congestion in the medullary portion, lower level of inflammation, and reduced tubular damage than rats with intact sympathetic activity [41, 42]. In mice with transverse aortic constriction, sympathetic renal denervation did not only blunt the increase in norepinephrine level but also blocked reno-cardiac signaling, which was essential for cardiac hypertrophy in response to pressure overload [43]. Recently, a few small-sized human studies reported renal denervation improved cardiac and renal function [44, 45]. Despite skepticism, observations of renal sympathetic over-activity in patients with CRS support continuing innovative investigational strategies for renal sympathetic denervation [31].

Inflammatory Mediators. Ample evidence has supported the inflammatory process as an important pathology of both cardiovascular disease and CKD. In humans, the circulating level of TNF-α was elevated in severe HF with cachexia and was associated with adverse clinical status as well as RAS system activation [46, 47]. When HF with reduced ejection fraction (HFrEF) patients had acute decompensation, biomarkers for inflammatory response such as high sensitivity C-reactive protein, myeloperoxidase, TNF-α, and galectin-3 continued to increase even after clinical improvement, which implied a unique role of inflammation in the pathophysiology of HF exacerbation [48]. In addition, activation of the complement system occurs in HFrEF, where dysregulated alternative pathways of the complement system can worsen the disease severity [49]. Increase in interleukin-6 may also be mechanistically linked with cardio-renal dysregulation [50].

When we induced chronic HF in mice after coronary artery ligation, the peripheral fraction of pro-inflammatory monocytes/macrophages increased with profound splenic remodeling, representative of augmented antigen processing. In particular, splenectomy resulted in cardiac reverse remodeling and attenuated tissue infiltration of inflammatory cells, while adaptive transfer of splenocytes into naïve mice led to resumption of immune-cell mediated injury, which suggested the central role of the mononuclear cell phagocyte network in chronic inflammation and HF progression [51]. In a similar animal model, activated monocytes and macrophages increased in kidney as well as

peripheral blood, mRNA expression of inflammatory cytokines was augmented, and microvascular endothelial permeability and renal tubular cell apoptosis increased through the acute and subclinical phases [52]. Further, depletion of monocytes or macrophages led to alleviation of tubular cell apoptosis and renal fibrosis [52]. Meanwhile, pharmacologic therapy targeting interleukin-1 inhibition [53] or glucocorticoid therapy to promote uricosuria [54] have provided some proof-of-concept demonstrations regarding the inflammatory hypothesis of acute CRS but would require further validation.

Metabolic Contributions. Patients with HF had more permeable intestinal walls than healthy controls, and more pathogenic bacteria were cultured in stool from HF patients. These findings were prominent in patients with severe HF symptoms. Particularly higher serum inflammatory markers in HF patients alluded to bacterial translocation through intestinal walls, which, in turn, is attributable to increased intestinal permeability resulting from intra-abdominal venous congestion [55, 56]. When we incubated renal tubular cells in plasma obtained from CRS septic patients, they had higher levels of apoptosis and caspase-3,-8,-9 expression in plasma with higher endotoxin activity than in plasma with lower endotoxin activity. Plasma inflammatory cytokines were associated with high endotoxin activity and assumed to mediate both extrinsic and intrinsic apoptosis of renal tubular cells, suggesting the presence of detrimental humoral factors in cross-talk between distant organs [57, 58]. Therefore, it is possible that translocation of bacterial endotoxin through intestinal walls worsens renal function in HF patients [59]. Phagocytic systems can generate catecholamine when exposed to bacterial endotoxins, while the disconnection of phagocytes from the autonomic nervous systems leads to reduced inflammatory responses [60]. The autonomic nervous system can influence immunity such as toll-like receptor ligation. During the inflammatory reflex, cytokines locally released from immune cells can transmit signals to the central nervous system through activated vagal afferent nerves [61].

Uremic Toxins. Deterioration of renal function leads to accumulation of protein-bound uremic toxins, such as indoxyl sulfate and p-cresyl sulfate and a tryptophan metabolite produced by gut microbiota, which are excreted by the healthy kidney. Exposure to these uremic toxins can cause, in part, the loss of kidney function [62–64]. Uremic toxins originate mainly from protein metabolism, food intake, and can be produced by gut microbiota. In addition to the rise in production, there is an increase in intestinal permeability in CKD allowing a greater absorption of those uremic toxins. [65] The retention of these substances has been associated with an inflammatory state, progression of CKD, cardiovascular disease, and risk of death in CKD patients [66–68].

There have been reports that oxidative stress can induce cardiac injury, [69] and urinary indoxyl sulfate excretion was reported to have a positive linear relationship to oxidative stress markers in cardiac tissue [70]. Increased levels of indoxyl sulfate were also associated with chronic inflammation, through indoxyl sulfate-associated pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, leading to left ventricular hypertrophy and cardiac fibrosis [71]. Indoxyl sulfate caused cardiac fibrosis and cardiomyocyte hypertrophy in salt-sensitive hypertensive rats, accompanied by increased oxidative stress marker expression, and decreased anti-oxidative protein expression in cardiac tissue [72]. Reduction in serum indoxyl sulfate levels caused decreased myocardial fibrosis in subtotal-nephrectomized rats [73]. Indoxyl sulfate entered cardiac fibroblasts through OAT1/3, and significantly increased collagen synthesis via activating p38, p42/44 MAPK, and NFκB pathways [71, 74]. Elevated levels of indoxyl sulfate were associated with an increased risk of left ventricular diastolic dysfunction in humans [75]. Thus, emerging evidences from clinical and experimental studies reveal that indoxyl sulfate plays a role in the progression of cardiovascular disease in CKD patients. Although other protein-bound uremic toxins possibly also are involved in the pathogenesis of cardiovascular disease, investigation of the cardiovascular effects of the uremic toxins has been limited to a few toxins. Furthermore, a demonstration that treating indoxyl sulfate leads to improved cardiovascular outcomes is lacking.

7.4 Preventing Type 1 CRS: Identifying Sub-Clinical Cardio-Renal Injury

The key to managing acute (Type 1) CRS is to prevent cardio-renal injury by recognizing the underlying substrates at subclinical stages and preventing the development of cardiac and renal failure (Fig. 7.2). This concept, while logical, has not been fully embraced due to the lack of insights into these potential treatable targets.

Biomarkers to Detect Cardio-Renal Injury. The Acute Decompensated Heart Failure National Registry (ADHERE) reported the prevalence of renal insufficiency was about 30% but also likely underestimated [76]. With technological advances, more sensitive and specific novel biomarkers of early organ injuries have been proposed in order to help identify high-risk patients before progression to irreversible stages of CRS [77, 78]. It is therefore postulated that like cardiac troponins for acute coronary syndromes, early detection with AKI biomarker may identify the cohort of patients at higher risk of developing Type 1 CRS and then be triaged to appropriate interventions. Biomarkers of renal tubular damage, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM1), interleukin-18 (IL-18), liver-type fatty acid binding protein (L-FABP), and tissue inhibitor of metalloproteinase 2 plus insulin-like growth factor-binding protein 7 (TIMP2-IGFBP7), have all been investigated for this purpose [79]. However [80], circulating NGAL (a protein of the lipocalin superfamily) was not superior to creatinine for the prediction of worsening renal function (WRF) or adverse in-hospital outcomes [81, 82]. In contrast, few if any acute HF patients who experienced WRF had elevated urinary NGAL levels, and even if levels were high they did not track with poor outcomes despite having pre-existing renal insufficiency [83, 84]. Despite early optimism, few studies have demonstrated the ability of urinary kidney injury biomarkers to provide any prognostic insights or therapeutic directives [84–86].

Weight Loss. Obese individuals, even without frank diabetes mellitus, are at risk of CRS development. Obesity *per se* can induce long-standing glomerular hyperfiltration and obesity-related glomerulopathy, evidenced by focal segmental glomerular sclerosis, foot process effacement,

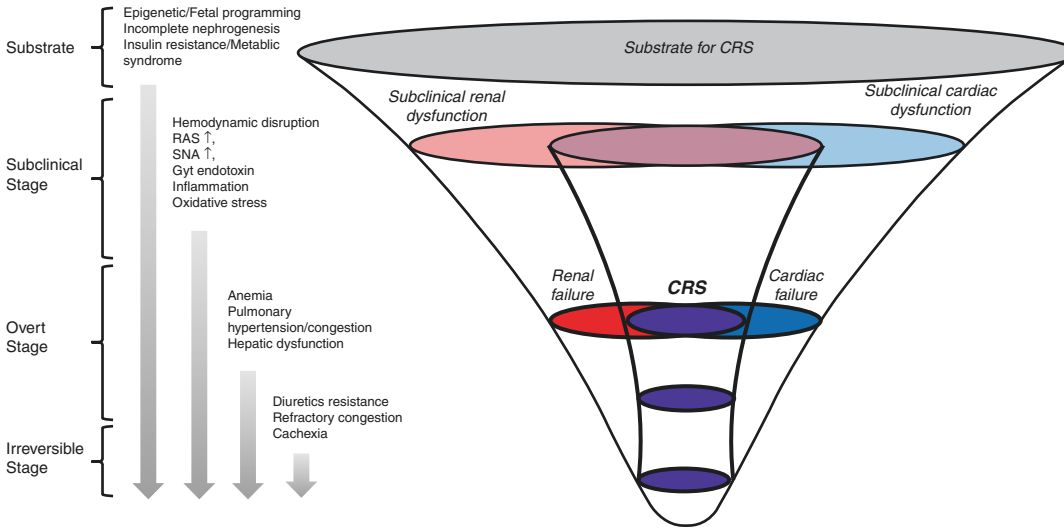

Fig. 7.2 Conceptual Framework of Acute (Type 1) Cardio-Renal Syndrome. Once overt cardio-renal syndrome ensues, it seems very difficult to reverse the natural course of disease. Therefore, early detection of patients at risk of cardio-renal syndrome may be a better therapeutic strategy. At the subclinical period of cardio-renal syndrome, there are substrates for renal dysfunction in, particularly, patients with heart failure. Medical resources may be concentrated on these patients to prevent further deterioration of renal function

and glomerulomegaly [87–90]. In an animal model of HFpEF and insulin resistance, glycosuria/proteinuria and microvascular fibrosis were highly analogous to the earliest change of the human cardio-renal syndrome, suggesting the presence of CRS substrate in humans as well [91]. Indeed, phenomapping of HFpEF subtypes has identified a "natriuretic peptide deficient" subtype that likely promotes fluid retention [92]. Intensive lifestyle intervention reduced the incidence of CKD after long-term follow-up, through reductions in bodyweight, HbA1c, and systolic blood pressure [93–95]. An enhanced metabolic profile via weight reduction in patients with obesity-associated cardio-renal disease draws attention for a novel therapeutic option [96, 97].

7.5 Managing Type 1 CRS

The latest consensus statement in diuretic use highlighted this goal-targeted strategy (Fig. 7.3), with the introduction of assessing urine output or urine sodium excretion following initial dosing of loop diuretics to assess diuretic efficacy [98]. This is based on observations that urine sodium excretion is diminished in acute HF requiring pharmacologic augmentation, and that insufficient natriuresis either due to abnormal drug delivery at the site of action and/or inadequate urine excretion due to renal sodium avidity may contribute to poor diuretic responses and adverse long-term outcomes [99, 100].

Loop Diuretics. Escalation of intravenous (IV) loop diuretic has been the mainstay of decongestion in HF, and often the key adjustment in Type 1 CRS since most patients remain diuretic responsive. The key determination remains whether loop diuretic dosing is insufficient or whether diuretic resistance is inevitable. Effective diuresis with good urine output despite a rise in serum creatinine or "worsening renal function" should not be classified as CRS. In fact, these patients actually have favorable long-term outcomes [101]. The Diuretic Optimal Strategy Evaluation in Acute Heart Failure (DOSE-AHF)

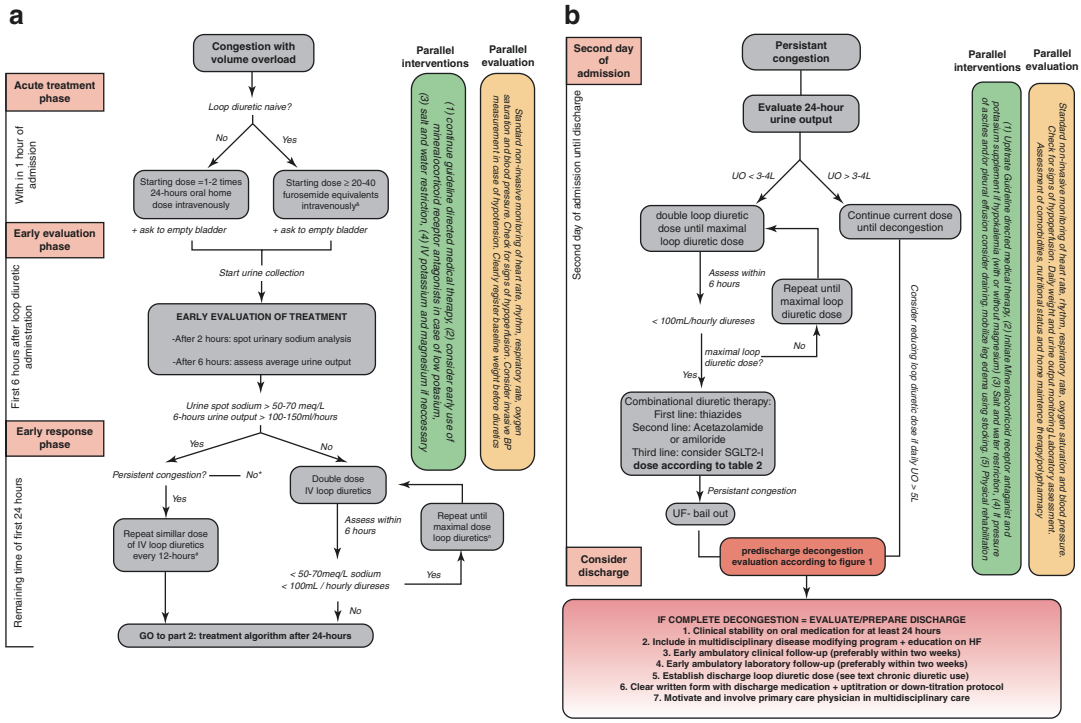

Fig. 7.3 European Society of Cardiology Heart Failure Association Recommendations of the Use of Diuretics in Acute Heart Failure and Cardio-Renal Syndrome. (**a**) Treatment algorithm for the first 24 hours of admission; (**b**) Treatment algorithm of second day of admission until discharge

study attempted to address the question of whether higher-dose or continuous administration is superior than standard-dose or bolus administration [102]. While the overall findings were largely neutral except for a statistically significant subjective assessment of well-being in the high-dose arm, a recent *post-hoc* analysis suggested that when adjusted for total amount of diuretic use, the high-dose strategy may have provided benefits [103].

Part of the challenge has been the inability of the kidneys to excrete loop diuretics to their sites of activity (luminal Na-K-Cl cotransporter at the ascending limb of the Loop of Henle). Indeed, diminished urine sodium per urine furosemide levels in patients with advanced HF receiving IV loop diuretics has been associated with impaired diuresis and natriuresis and poor long-term outcomes [100]. Hence, increasing loop diuretic dosing can be an effective strategy, although doses above the ceiling dose are only moderately effective (despite relatively predictable dose-response curves). Other strategies include increasing frequency of administration (including continuous dosing) or add other types of diuretics for synergistic effects to achieve maximal urinary sodium excretion.

Other Diuretic Drugs. In the stepped pharmacologic uptitration arm of the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) study [104], patients who experienced worsening renal function were treated with a goal-directed escalation of diuretic drugs including continuous loop diuretic infusion and addition of thiazide diuretics (sequential tubular blockade strategy) [105]. In the majority of cases, urine output goals of 3–5 L negative per day can be achieved.

While there was early enthusiasm on mineralocorticoid receptor antagonist to attenuate distal sodium reabsorption, such strategy was deemed not incremental to standard therapy in a prospective trial [106]. An ongoing multicenter study testing the role of acetazolamide to augment proximal sodium excretion by attenuating tubular renin release is ongoing [107, 108].

Inotropic and Vasoactive Drugs. The typical inotropes used in cardiac intensive care units include dobutamine and milrinone (or to a lesser extend oral digoxin loading), and they are effective in restoring hemodynamics in the "cold and wet" patients under hemodynamic guidance. However, prospective data supporting their use is limited [109, 110]. Vasodilators may improve hemodynamic derangements, although overzealous use can lead to hypotension and worsening renal function [111]. In the setting of vasoplegia, norepinephrine (and to a lesser degree dopamine) may be also be used as it has beta adrenergic activity. Less popular now, is the use of dopamine as an inotrope and pressor especially with no added benefit to the renal vasculature as previously thought [112].

Ultrafiltration/Aquapheresis. Ultrafiltration provides mechanical removal of isotonic fluid independent of the kidneys, thus providing effective and consistent salt and volume removal. Although early studies were promising, subsequent randomized controlled trials have more mixed results [104, 113, 114]. Interestingly, ultrafiltration may even exacerbate hyponatremia as the effluent is relatively more hypertonic [115]. This can exacerbate the cycle of renal vascular constriction and neurohormonal activation if the settings are too aggressive. Peritoneal dialysis has also been employed as an alternative treatment strategy [116].

Hypertonic Saline. Considerations of electrolyte depletion leading to renal sodium avidity has implied potential benefits of hypertonic saline (HSS) infusions during aggressive IV diuretics. This was suggested a decade ago in early Italian series, in which low-volume, intermittent, 1.4–4.6% sodium chloride (depending on serum sodium levels) coupled with high-dose loop diuretics can produce effective diuresis and prevent decline in renal function [117–119]. Recent reports using 1.7% salt supplementation (500 mg) with lower doses of IV diuretics also demonstrated improved diuretic efficiencies, especially in those with elevated urinary BUN/creatinine levels [120, 121]. Real-world experience have also supported such a potential strategy in selected patients [122]. However, nephroprotection was not observed in patients with baseline creatinine over >2.2 mg/dL [123]. This was confirmed by

preliminary results from a randomized, double-blind study of 50 patients with acute heart failure and renal insufficiency (creatinine >2 mg/dL, BUN >60 mg/dL) that demonstrated a non-significant increase in diuresis with HSS but also BUN elevation from baseline [124]. Hence, further investigations are warranted.

Mechanical Circulatory Assist Support. With the advent of temporary mechanical support such as the Impella® devices, a bridge-to-decision strategy can be instituted as demonstrated in animal models that improve renal blood flow [125]. After a test period to see if there is myocardial recovery, a durable left ventricular assist device (LVAD) may be considered [126]. Renal recovery following LVAD maybe transient [127], and renal function may deteriorate again after early improvement [11]. However if there is right ventricular dysfunction, orthotopic heart transplantation is the only durable solution. Implantable ventricular assist devices are rarely performed in patients reaching end-stage kidney diseases due to their high mortality rates and are not recommended by clinical guidelines [126, 128].

Temporary Renal Support Device Therapies. Recently, a handful of intriguing hemodynamic support devices have emerged targeting venous congestion and/or renal hemodynamics support. Examples include transcatheter intra-aortic pump [129], transcatheter renal venous decongestion system, innovative fluid/diuretic management systems (RenalGuard) [130]. Other examples of volume removal strategies include implantable pump or device designed to continuously remove excess abdominal fluid or direct sodium removal [131, 132], and catheter-based enhancement of lymphatic drainage [133]. The majority are in early clinical development.

7.6 Conclusions

Acute (Type 1) CRS is associated with an acute cardiogenic disturbance leading to acute worsening of renal function. However this cascade also forms a feedback loop further perpetuating cardiac dysfunction, hormonal dysregulation, and treatment resistance. Once ADHF is recognized, treatment must be initiated quickly to break the cycle but despite medical therapy, short term and long term aftereffects can make treatment a challenge. Ultimately changes in traditional renal biomarkers may not accurately reflect the state of the renal system while new insight into electrolyte metabolism may more accurately predict clinical outcomes.

While increases in serum creatinine have been closely tied to renal function, long term predictors of mortality and rehospitalization have not been closely linked. The response of the kidney in light of an acute cardiac insult should be largely viewed as appropriate and natural in the physiologic setting. However, the clinician should note that breaking the renal cycle will ultimately lead to a decongested patient with a chronic illness rather than an acute hospitalization.

Once developed, CRS becomes a serious medical and economic burden. Although hemodynamic derangement, an over-activated neurohormonal system, and systemic inflammation have been recognized as major players in CRS pathophysiology, there are also other cardio-renal mediators contributing to the development of CRS. The intricate network of these mediators makes their pathophysiologic hierarchy opaque. Investigators may need to divert their attention from overt cardio-renal connector in clinical CRS, to more fundamental substrates during a period of subclinical CRS as a part of an early detection and prevention strategy.

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