Revolutionizing Cardiorenal Syndrome Treatment: From Diuretics to Advanced Devices

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ABSTRACT

Cardiorenal Syndrome (CRS) refers to the complex interaction between the heart and kidneys, particularly when heart failure is present. This disease can have major repercussions for both of these essential organs and involves bidirectional interactions between them. To classify CRS, a number of categorization schemes have been created that consider variables such as the underlying organ malfunction and the duration of the illness. Numerous complicated components, such as hemodynamic variables, neurohormonal systems, inflammation, and more, are involved in the pathogenesis of CRS. These elements may combine to form a harmful cycle that compromises the kidneys' and heart's ability to operate. Because conventional approaches may not be as effective for treating CRS as they could be, biomarkers are being investigated as potential tools. The main goals of CRS treatment are to increase cardiac output and relieve congestion. Although diuretic resistance can be difficult to overcome, diuretics are frequently used to treat fluid overload. To combat this resistance, cutting-edge strategies including peritoneal ultrafiltration techniques and regulated diuresis are being researched. Moreover, vasodilators, inotropic therapy, and neurohormonal modulation contribute to better heart function. Studies on acute decompensated heart failure have demonstrated the potential benefits of natriuretic hormones, such as nesiritide, in lowering heart filling pressure. In summary, Cardiorenal Syndrome presents a complex interplay between the heart and kidneys, requiring multidisciplinary approaches and innovative treatments to address the challenges it poses.

Keywords: cardiorenal syndrome,. Heart kidney interaction, Renal biomarkers, Diuretics, treatment strategies diuretic resistance.

INTRODUCTION

The interaction the heart and kidney during acute and chronic heart failure (HF), which are highly interconnected in illnesses and health. In healthy people, the kidney depending on the perfusion pressure and blood flow supplied by the heart, whose functionality is depending on the kidney's control on the body's water and salt content. Fluid overflow in HF produces mutually destructive and self- between the kidney and the heart, it resulted in the decline of both organs and elevated mortality and morbidity. the word the term "Cardiorenal syndrome" has expanded to include the unhealthy connections between the heart and kidney occurring with various and occasionally cross-reactive illnesses. Although there are a lot of articles have made an effort to summarize the etiology, pathophysiology, prognosis, and therapy for the Cardiorenal syndrome(1).

The association between the heart and kidneys is bidirectional, which means that both organs have similar physiological and pathological characteristics. Therefore, the kidney-regulated homeostasis is dependent on the heart, even as the renal function is increasingly dependent on the blood perfusion function, which is controlled by neurochemical, hemodynamic, and inflammatory mechanisms. simplistic view of CRS is that a relatively normal kidney is dysfunctional because of a diseased heart(2,3).

Background

A well-known pathologic kidney and cardiac disorder is the cardiorenal syndrome (CRS). An organ's severe or acute dysfunction may trigger the severe or chronic dysfunction of an adjacent organ. The medical disease generally manifests as severe or acute dysfunction of one organ after acute or severe dysfunction of the other organ. Heart and kidney disorders frequently coexist, increasing mortality, morbidity, complexity, and treatment costs significantly the relationship between the heart and kidney was examined in 2004 by the Working Group of the National Heart, Lung, and Blood Institute. They determined that the cardiorenal syndrome (CRS) is the outcomeof interactions between the kidneys and other circulatory compartments based on their evaluation(2).

METHODOLOGY

Methodology We deployed the journal repository database review approach. Using the Boolean terms "AND" and "OR, ourliterature search was conducted on PubMed using the keywords 'Cardiorenal syndrome, 'Cardiorenal syndrome types, and 'Cardiorenal syndrome review. Initially, our search yielded a total of 670 articles. To ensure relevance and up-to-date information, we applied inclusion criteria based on the objective of our article's conceptualization plan. Specifically, we focused on articles written in English and focused inhuman subjects. We also limited our selection to articles with free full texts available, excluding preprints. After applying our inclusion and exclusion criteria, we meticulously reviewed and analyzed 25 publications(4).

CLASSIFICATION

Key questions

Three key questions regarding definition and classification were identi-fied by the entire ADQI group, and a subgroup deliberated on these question's, bringing forth recommendations to the group as a whole.

(1) Is there a need for an overall definition of the clinical syndromes de-

rived from cardiac and renal interactions?

(2) What should be the principles of such a definition system?

(3) How should they be defined and classified?(5).

Cardiorenal types	Characteristics	Causes of morbidity
Type 1 (acute cardiorenal)	Acute cardiac impairment leading to acute kidney injury (AKI)	Cardiogenic shock and AKI, acute decompensated heart failure (ADHF) resulting in AKI
Type 2 (chronic cardiorenal)	Chronic cardiac impairment leading to renal impairment	Chronic heart failure
Type 3 (acute renocardiac)	AKI leading to cardiac impairment	Heart failure in the setting of AKI from volume overload, inflammatory surge and accompanying metabolic disturbances
Type 4 (chronic renocardiac)	Chronic kidney disease (CKD) leading to cardiac impairment	Myocardial remodeling and heart failure from CKD-associated cardiomyopathy
Type 5 (secondary cardiorenal)	Systemic condition leading to both cardiac and renal impairment	Diabetes, amyloidosis and sepsis

**Table 1.** classification of cardiorenal syndrome with causes of morbidity

Acute Dialysis Quality Initiative (ADQI) and Ronco et al. developed classification schemes that identified the primary organ malfunction (heart or kidney) and time course (acute or chronic), with an extra subtype for a systemic illness that concurrently affects both organs(6).

Several experts from the fields of internal medicine, cardiology, cardiac surgery, nephrology, and intensive care gathered in Venice in 2008 for a consensus conference sponsored by the Acute Dialysis Quality Initiative (ADQI) to discuss the subject and create a classification of CRS(7).

PATHOPHYSIOLOGY

Cardiorenal syndrome and deteriorating renal function are multifactorial conditions with unclear pathophysiological causes. It has been suggested that there is an overall imbalance in the interactions between the failing heart, the neurohormonal system, and inflammatory reactions. All of which have been suggested to result in a vicious loop that harms the heart and kidneys structurally and functionally. A number of hemodynamic variables, such as (a) arterial filling and renal perfusion, (b) venous congestion, and (c) the presence of elevated intra-abdominal pressure, might contribute to the development of cardiac syndrome and deterioration of renal function during ADHF(8).

There has been a lot of interest in the relationship between the heart and kidneys in CRS, but the molecular mechanisms are still not completely understood. Hemodynamic variables, which were once believed to be the exclusive causes of the CRS, are insufficient to adequately account for the reported clinical effects. In fact, the rate of estimated GFR (eGFR) loss in outpatients with heart failure who do not have severe hemodynamic disturbances is higher than would be predicted from aging alone. Cardiorenal connections are the other main pathophysiological processes that connect the heart and the kidneys. These include activation of the renin-angiotensin-aldosterone system (RAAS), stimulation of the sympathetic nervous system (SNS), inflammation, and dysregulation of the balance between nitric oxide (NO) and reactive oxygen species (ROS; Fig.). There is significant interplay between these cardiorenal connectors, allowing them to potentiate each other and further disrupt cardiac and renal function. Fibrosis, a common result of inflammation and oxidative stress, is also a marker of more severe irreversible heart failure and CKD, which has led some authors to label it as a key driver in the pathophysiology of CRS(6).

Fig 1. pathophysiology of cardiorenal syndrome.
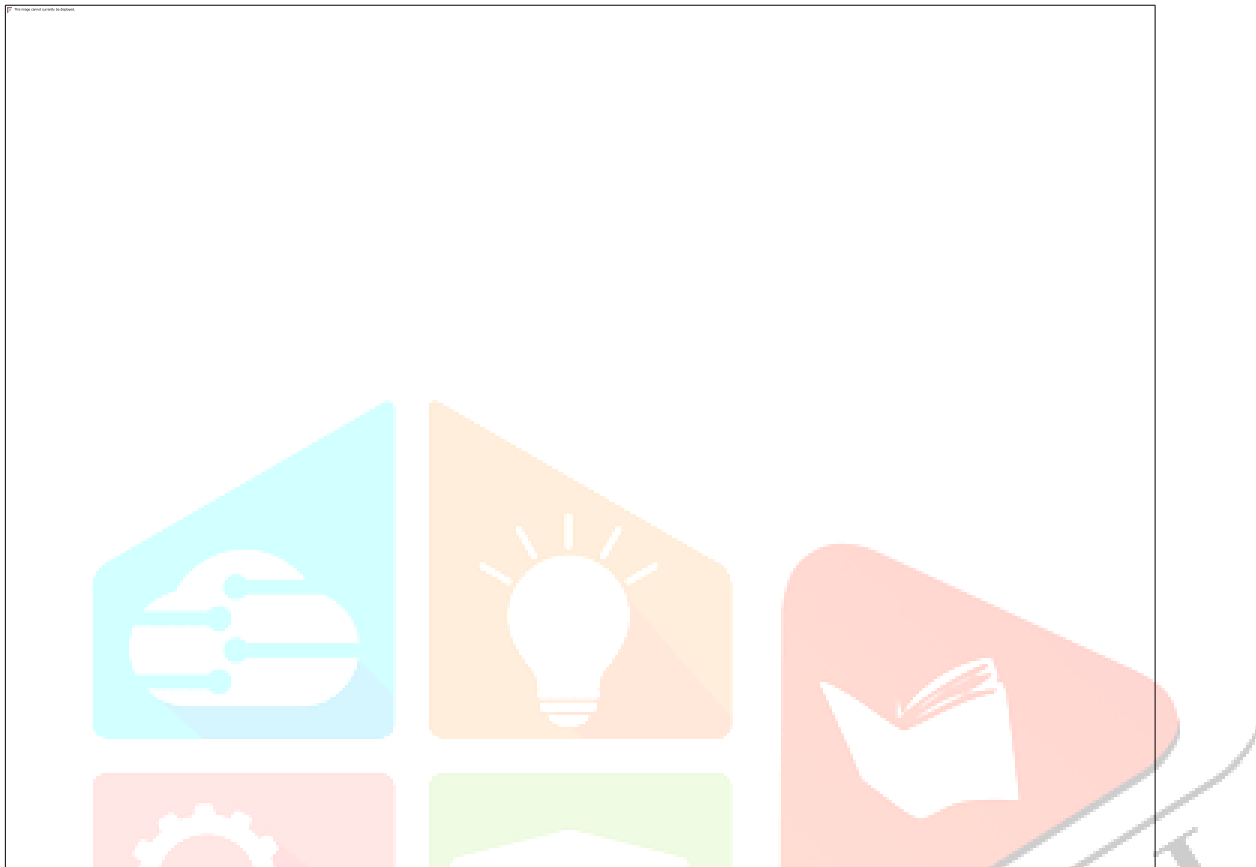
DIAGNOSIS AND BIOMARKERS

Diagnosis

A widely used classification method divides CRS into five categories, with a fifth category characterizing CRS that occurs in the presence of systemic disease, based on the principal organ causing bidirectional failure and the sharpness of decline the clinical practice or research directions have not changed as a result of this classification method, however, and it has a number of notable flaws that limit its usefulness. Primarily, diverse descriptions of cardiac and renal failure are commonplace.

These challenges have led researchers to identify biomarkers that might have utility in the diagnosis of CRS. In the Neutrophil Gelatinase-Associated Lipcalin (NGAL) Evaluation Along With B-type Natriuretic Peptide in Acutely Decompensated Heart Failure (GALLANT)(6).

CRS-1 is diagnosed using clinical and laboratory data, ultrasonography, and other radiological examinations. Creatinine, for instance, is a biomarker with a long history of use in diagnostics. Interleukin 18 (IL-18), cystatin C, liver-type fatty acid-binding protein (L-FABP), serum and urine neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), and other renal damage indicators are emerging biomarkers that open up new possibilities. Clinical practice regularly makes use of markers of myocardial necrosis, such as troponins I (cTnI) and T (cTnT), and indicators of HF, such as N-terminal pro B-type (NT-proBNP) and the active form B-type natriuretic peptide (BNP)(9,10).

Biomarkers

When used in the clinical setting of CRS, biomarkers of cardiac and renal injury may offer useful information by indicating early cardiac or renal injury, the healing process, and long-term consequences.41 They offer a chance to predict CRS, to distinguish different CRS phenotypes, and to act as markers for targeted treatment interventions. Although myocardial damage (troponin) and wall tension (BNP [B-type natriuretic peptide/NT-proBNP [N-terminal pro-BNP]) biomarkers are frequently utilized in clinical practice, biomarkers of AKI are now being included as a new variable in diagnostic algorithms. There is a large time lag of 24 to 48 hours to implement remedial interventions since the criteria of AKI currently in use are tied to changes in creatinine or urine output(4).

Renal Biomarkers in Chronic Kidney and Cardiovascular Diseases

Formulas that estimate glomerular filtration rate (GFR) based on serum creatinine levels are typically used to evaluate renal function. The breakdown of creatine phosphate in skeletal muscle produces serum creatinine. Its production rate is mostly steady, and the kidneys use glomerular filtration and only partially active tubular secretion to remove it from the body(6,11).

Table 2. characteristics of the main renal biomarker's indicative of Cardiorenal and renocardiac syndrome progression

Renal Biomarkers in Cardiovascular Patients with Acute Kidney Injury

Acute kidney injury (AKI) has recently taken the position of acute renal failure in acute situations. It is characterized as a sudden (within hours) decline in kidney function and encompasses both injury (structural damage) and impairment (loss of function). AKI affects about 25% of people hospitalized for CVD, ranging from 15 to 40% in cases of acute coronary syndrome (ACS) to 47% in cases of acute decompensated heart failure. Dialysis is required in 20% of patients with AKI, 1% to 3% of patients with HF or ACS, and roughly 13% of patients with

cardio amino-terminal pro-BNP (NT-proBNP) are helpful for HF patient diagnosis and prognostic classification. It is important to keep in mind that their blood levels, specifically for NT-pro BNP, may be affected by renal function; the more severe the renal dysfunction, the higher the serum levels. Natriuretic peptides continue to be linked to a worse prognosis in individuals with CKD, while the processes behind this association are still not fully understood(12).

Novel biomarkers in the CRS

Prerenal, intrinsic renal, or postrenal AKI should be distinguished from other types of kidney failure, and an ideal biomarker of AKI should be able to pinpoint the primary site of injury (proximal tubule, distal tubule, interstitium, or vasculature). It should also address the

duration of kidney failure (AKI, CKD, or "acute-on-chronic"), the cause (toxins, sepsis, ischemia, or a combination)(4).

The novel biomarkers include

1. Neutrophil gelatinase-associated lipocalin
2. Cystatin C
3. Kidney injury molecule-1
4. IL-18
5. Natriuretic peptides(9).

The emerging biomarkers includes

1 Osteopontin

2 N-acetyl-β-D-glucosaminidase

3 Stromal cell-derived factor-1

4 Exosomes(13).

TREATMENT STRATEGIES

Table.3 major ongoing clinical trials of renal sparing treatment strategies(14).

Drug	Trial acronym	Phase	Sample size
Natriuretic peptides			
Nesiritide	ASCEND-HF	IV	7000
CD-NP	CONDITION-HF	II	380
Vasopressin receptor antagonist			
Tolvaptan	EVEREST	III	3600
Conivaptan	CONVERT-HF	III	105
Lixivaptan	BALANCE	III	650
Adenosine A_1 receptor antagonists			
Rolofylline	PROTECT-1 & -2	III	2000
SLV320	RENO-DEFEND 1	II	500
BG-9928	POSEIDON/TRIDENT	II/III	300/900
Standard treatment			
Loop diuretics	DOSE-AHF	IV	300
Ultrafiltration	CARRESS	IV	200

There is a knowledge vacuum in the management of the CRS despite the fact that many randomized clinical trials have been focused on the therapy of HF and CKD. Its treatment has primarily been focused on CRS type 1, and two main approaches have been developed: (i) approaches to relieve congestion, primarily based on diuretics and ultrafiltration; and (ii) approaches to improve cardiac output, primarily based on neurohormonal modulation, vasodilator, inotropic therapy, and RAAS inhibition in chronic CRS (angiotensin-converting inhibitors, angiotensin receptor blockers, mineralocorticoids antagonists and beta blockers(15).

The idea that venous congestion rather than a lack of forward flow is the main cause of decreasing renal function is currently favored. Initially, it was thought that decreased cardiac output or a lack of forward flow was the main cause of kidney injury. The main approaches of treating cardiorenal syndrome are listed below.

1. Digestive treatments, including diuretics and ultrafiltration

2. Inotropic treatment, vasodilators, and neurohormonal modification

3. Neprilysin/ Renin-Angiotensin Inhibitors, Mineralocorticoid Receptor Antagonists, Beta-Blockers, ACEI/ARB, and Chronic Renal Syndrome.

1. Digestive treatments, including diuretics and ultrafiltration

Diuretics

Since they are essential to treating volume overload, diuretics in general and loop diuretics in particular continue to be the most frequently used therapy in patients with decompensated HF. The only large-scale randomized clinical research that offers high-quality evidence for their use is the Diuretic Optimization Strategies Evaluation (DOSE) experiment, though(4,12). The DOSE trial, which involved 308 patients with decompensated HF, showed that intravenous loop diuretics given as a bolus or continuous therapy produced equal results. Additionally, high-dose loop diuretics (2.5 times maintenance dose) relieved congestion a little bit more quickly than low-dose (equivalent to maintenance dose) loop diuretics, albeit at the expense of a lower GFR. However, individuals with CRS frequently exhibit indications of congestion and so-called diuretic resistance that are resistant to intravenous loop diuretics that are given in an appropriate(16,17).

Diuretics might alleviate symptoms in the short term for patients, but they can also lead to problems like hypertension, elevated intra-abdominal pressure, and renal congestion. Diuretics should have their dosages carefully controlled since large dosages might worsen electrolyte imbalances, reduce fluid volume in circulation, upset neurohormonal balance, and impair renal function.

Although 90% of patients with AHF receive a prescription for a diuretic, evidence-based therapeutic management in HF is still unclear and has no effect in terms of short- or long-term mortality or rehospitalization.. Loop diuretics (furosemide, bumetanide, torsemide and ethacrynic acid) represent the primary class of HF management.

Kidney injury may be predisposed by their effects on renal and systemic hemodynamics, as well as neurohormonal activation. In AHF, declining kidney function is associated with increased mortality and re-hospitalization rates. A post hoc analysis of three randomized clinical trials comparing standard diuretic therapy and a urine volume goal-directed step-wise diuretic algorithm was conducted on 198 patients who developed type 1 CRS. The trials were called DOSE-AHF (Diuretic Optimization Strategies Evaluation in Acute Heart Failure), CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure), and ROSE-AHF (Renal Optimization Strategies Evaluation in Acute Heart Failure).

When compared to normal diuretic medication, a stepwise approach targeting the 24-hour urine volume including furosemide with or without metolazone improved renal function . The results of nesiritide, low-dose dopamine, or placebo. The most common pharmacologic intervention for ADHF patients with volume overload (88%) is the use of loop diuretics. Table 1 is a list of the most often utilized intravenous diuretics for the treatment of ADHF. According to new guidelines from the Heart Failure Society of America, they should be used as the first line of therapy. because they lessen pulmonary congestion and quickly lower the ventricular filling pressure. The benefits of taking loop diuretics when HF patients are admitted with systemic congestion and/or pulmonary edema are widely accepted. This is a typical side effect that improves symptoms and may even enhance kidney function by lowering renal venous pressure(2,18).

Diuretics resistance

Diuretic resistance is defined as the inability to excrete more than 90 mmol of sodium within 72 hours of a 160-mg twice-daily furosemide dose, persistent congestion despite increasing diuretic doses equivalent to ≥80 mg/d furosemide, and sodium excretion as a percentage of filtered load less than 0.2%. The following are measures of the diuretic response: urine sodium-to-urinary furosemide ratio, weight loss per 40 mg of furosemide or similar, and net fluid loss per milligram of loop diuretic.

Diuretic resistance is characterized by a three-fold increase in rehospitalization rates, inadequate symptom alleviation, a higher chance of HF worsening while the patient is still in the hospital, and increased death following discharge. Seventy 71 Of the over 50,000 patients included in the ADHERE (Acute Decompensated Heart Failure National Registry) trial, only 33% lost weight throughout their hospital stay (≤2.27 kg/5 lb), while 16% gained weight. 72 Almost half of hospitalized heart failure patients who receive traditional diuretic therapy are released with residual fluid excess(1,17,18).

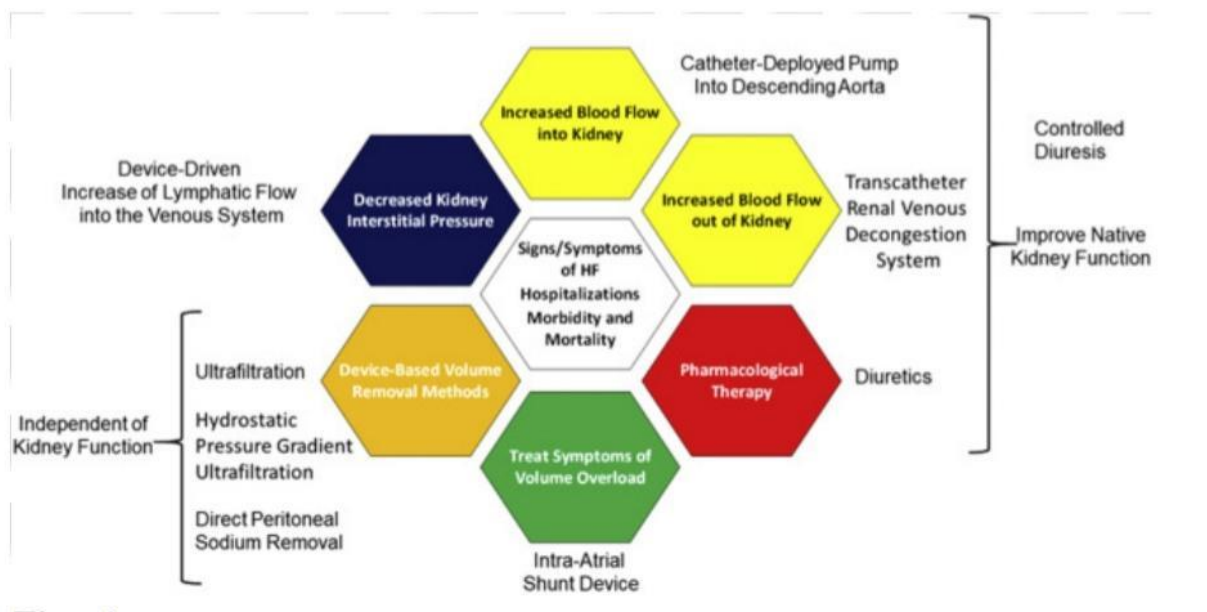**Fig 3.** Mechanism of diuretic resistance
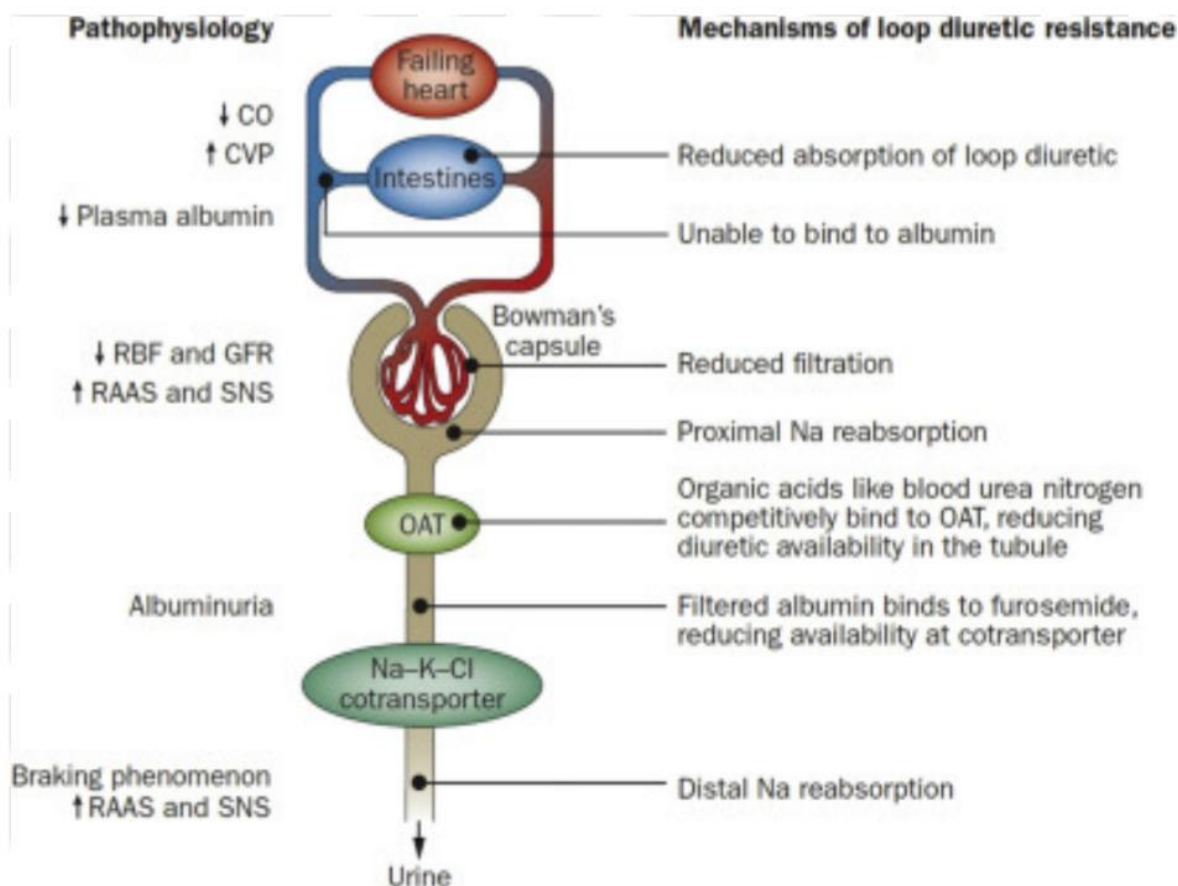
Novel strategies to overcome diuretic resistance

Novel methods to decongest diuretic-resistant HF patients with fluid overload and the cardiorenal Syndrome outlined in Fig 4

Fig 4. Novel strategies to overcome diuretic resistance in HF

Controlled diuresis

The goal of the Reprieve Cardiovascular therapy (Reprieve Cardiovascular, Milford, MA) is to manage venous return in order to avoid intravascular hypovolemia and the ensuing neurohormonal activation. The device substitutes a percentage of the urine volume that the patient produces in response to diuretics, as determined by the physician. Maintaining an appropriate intravascular volume may be possible with the partial, controlled replenishment of volume. Poland is currently doing pilot projects with this technology(1,7).

Peritoneal Ultrafiltration Methods

1.Direct peritoneal sodium removal

Since the sodium concentrations in conventional peritoneal dialysis solutions are practically isotonic to plasma, solute drag with UF—rather than diffusion along a concentration gradient—drives almost all of the salt removal.

2. pressure gradient Device

A permeable absorption chamber is implanted in the peritoneum as part of this innovative procedure.

The fluid is forced into the absorption chamber through the peritoneal membranes by a pump that creates a negative hydrostatic pressure inside the chamber. A percutaneous port receives fluid from the absorption chamber via a microcatheter. Drainage of the stored extracellular fluid into the urinary system will be made possible by ongoing efforts.

3.Decongestive Pumps

With the intention of resting the heart and enhancing RBF, the Aortix device (Procyrion, Houston, TX) is a catheter-deployed pump that is inserted into the descending aorta and disconnects the heart and kidneys. Urine output and hemodynamics improved in patients receiving high-risk percutaneous coronary intervention (PCI) after first-in-man usage.A tiny continuous flow pump is inserted into each renal vein as part of the transcatheter renal venous decongestion device (Magenta Medical, Kadima, Israel) to immediately lower renal venous pressure.Increased diuresis and natriuresis should follow from this better response to diuretics(7,19).

This treatment notion is supported by preclinical data. There is an ongoing multicenter clinical trial in Europe.

The new techniques presented here highlight how fluid management for patients with congestive heart failure has advanced. The emphasis is moving away from diuretics' unexpected removal of hypotonic fluid and toward decongestive techniques that prevent intravascular volume loss and the ensuing renal hypoperfusion. Investigation of novel fluid-management methodsshould focus on assessment of safety, ease of use, candidate selection, reproducibility of effects across HF populations, and costs(8,20).

2.Inotropic treatment, vasodilators, and neurohormonal modification

Patients with poor cardiac output, such as those with acute decompensated HF, should take inotropic medications to Despite being widely utilized to enhance hemodynamics and symptoms in ADHF, short-term inotropic infusion is still controversial. In patients who exhibit severe circulatory collapse, inotropes might be urgently necessary. The use of inotropic medications is not well supported for individuals with ADHF who show signs of diuretic resistance or end-organ hypoperfusion but do not have frank hypotension.

Dobutamine is a synthetic catecholamine that functions primarily as an agonist for the α1-receptor and exhibits some activity for the α2 receptor, which makes it an inotropic vasodilator. When phos-phodiesterase III inhibitors like milrinone are used, the heart and smooth muscle experience increased cyclic adenosine monophosphate levels. Vasodilation and cardiac contractility are boosted as a result. the heart's contractility and keep important organs like the kidneys and heart functioning normally.

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Vasodilators

Vasodilators such as intravenous nitroglycerin or nesiritide (recombinant human B-type atrial natriuretic peptide) have been shown to be much less detrimental to renal function, particularly when used at low doses that do not decrease blood pressure. Vasodilators can rapidly reduce ventricular filling pressures and central venous pressures, and decrease myocardial oxygen consumption. They can also decrease systemic vascular resistance, decrease ventricular workload, increase stroke volume and improve cardiac output under the right circumstances.

Vasodilators that do not lower blood pressure, like intravenous nitroglycerin or nesiritide (recombinant human B-type atrial natriuretic peptide), have been demonstrated to be substantially less harmful to renal function. Vasodilators can quickly lower central venous pressures, ventricular filling pressures, and myocardial oxygen consumption. Under the correct conditions, they can also reduce systemic vascular resistance, lessen ventricular workload, increase stroke volume, and enhance cardiac output(8).

Natriuretic hormones

The synthetic BNP, nesiritide, has been utilized and researched extensively in ADHF patients during the past ten years. The mechanism of action of nesiritide is the activation of guanylyl cyclase-linked natriuretic peptide receptors A and B, which leads to the vasodilation of the arterial and venous systems via cyclic guanosine monophosphate (cGMP). As a result, it lowers heart filling pressure and helps ADHF patients' dyspnea (86). The Vasodilatation in the Management of Acute CHF study (VMAC), the sole nesiritide placebo-controlled trial, demonstrated this. In 15 minutes, nesiritide lowers pulmonary capillary wedge pressure (PCWP), a statistically significant difference from placebo. However, when nesiritide was compared to nitroglycerin (NTG), the impact did not reach statistical significance(18,20).

In every study, a 2-gram/kg bolus was administered, and then an infusion of 0.01-gram/kg/min was carried out. Nesiritide at nonhypotensive doses (0.0025 or 0.005 mg/Kg/min) was found to be safe in a retrospective case-control study. It was also shown to improve renal function when compared to the higher recommended bolus and infusion.

Conclusion and implications

In conclusion, there is a complicated and reciprocal link between the heart and kidneys in both acute and chronic heart failure. The phrase "cardiorenal syndrome" refers to the pathological relationships that result in the degeneration of these essential organs as well as higher rates of morbidity and mortality. Numerous elements, including hemodynamic variables, neurohormonal systems, and inflammatory responses, are involved in the pathophysiology of cardiorenal syndrome. With an emphasis on reducing diuretic resistance and enhancing fluid management, novel biomarkers are being investigated for diagnostic and therapeutic approaches. Numerous therapeutic modalities, including diuretics, inotropic drugs, vasodilators, and natriuretic hormones, are intended to tackle the intricate problems associated with cardiorenal syndrome.

Bibliography

1.   Costanzo MR. The Cardiorenal Syndrome in Heart Failure. Cardiol Clin. 2022;40(2):219–35.

2.   Raina R, Nair N, Chakraborty R, Nemer L, Dasgupta R, Varian K. An Update on the Pathophysiology and Treatment of Cardiorenal Syndrome. Cardiol Res. 2020;11(2):76–88.

3.   Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal Syndrome. J Am Coll Cardiol. 2008;52(19):1527–39.

4.   Helwig NE, Hong S, Hsiao-wecksler ET. No 主観的健康感を中心とした在宅高齢者における 健康関連指標に関する共分散構造分析Title.

5.   House AA, Anand I, Bellomo R, Cruz D, Bobek I, Anker SD, et al. Definition and classification of Cardio-Renal Syndromes: Workgroup statements from the 7th ADQI Consensus Conference. Nephrol Dial Transplant. 2010;25(5):1416–20.

6. Yogasundaram H, Chappell MC, Braam B, Oudit GY. Cardiorenal Syndrome and Heart Failure—Challenges and Opportunities. Can J Cardiol. 2019;35(9):1208–19.

7. Tabucanon T, Tang WHW. Right Heart Failure and Cardiorenal Syndrome. Cardiol Clin. 2020;38(2):185–202.

8. Chan EJ, Dellsperger KC. Cardiorenal syndrome: The clinical cardiologists' perspective. CardioRenal Med. 2011;1(1):13–22.

9. Prastaro M, Nardi E, Paolillo S, Santoro C, Parlati ALM, Gargiulo P, et al. Cardiorenal syndrome: Pathophysiology as a key to the therapeutic approach in an under-diagnosed disease. J Clin Ultrasound. 2022;50(8):1110–24.

10. Sano M. A Role of Sodium-Glucose Co-Transporter 2 in Cardiorenal Anemia Iron Deficiency Syndrome. Int J Mol Sci. 2023;24(6).

11. Goffredo G, Barone R, Di Terlizzi V, Correale M, Brunetti ND, Iacoviello M. Biomarkers in cardiorenal syndrome. J Clin Med. 2021;10(15):1–13.

12. Taub PR, Borden KC, Fard A, Maisel A. Role of biomarkers in the diagnosis and prognosis of acute kidney injury in patients with cardiorenal syndrome. Expert Rev Cardiovasc Ther. 2012;10(5):657–67.

13. Madrigano J. 基因的改变NIH Public Access. Occup Env Med. 2008;23(1):1–7.

14. Tang WHW, Mullens W. Cardiorenal syndrome in decompensated heart failure. Heart. 2010;96(4):255–60.

15. Ronco C. The Cardiorenal Syndrome: Basis and common ground for a multidisciplinary patient-oriented therapy. CardioRenal Med. 2011;1(1):3–4.

16. Méndez AB, Azancot MA, Olivella A, Soler MJ. New aspects in cardiorenal syndrome and HFpEF. Clin Kidney J. 2022;15(10):1807–15.

17. Verbrugge FH, Grieten L, Mullens W. Management of the Cardiorenal Syndrome in Decompensated Heart Failure. Cardiorenal Med. 2014;4(3–4):176–88.

18. Sarraf M, Masoumi A, Schrier RW. Cardiorenal syndrome in acute decompensated heart failure. Clin J Am Soc Nephrol. 2009;4(12):2013–26.

19. Ahmed MS, Wong CF, Pai P. Cardiorenal syndrome - A new classification and current evidence on its management. Clin Nephrol. 2010;74(4):245–57.

20. Uduman J. Epidemiology of Cardiorenal Syndrome. Adv Chronic Kidney Dis [Internet]. 2018;25(5):391–9. Available from: https://doi.org/10.1053/j.ackd.2018.08.009