Cardiorenal Syndrome, Chronic Kidney Disease, Anemia, and Heart Failure

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11.1 Cardiorenal Syndrome

11.1.1 Definition

Cardiorenal syndrome (CRS) was first formally defined in 2004 as the interaction between the renal and circulatory systems with fluid volume. Therapies used in the treatment of acute heart failure to reduce congestion are limited by decreasing renal function [1]. This definition has since evolved as it did not fully encompass the complex bidirectional relationship these two organs share. In 2008, the Acute Dialysis Quality Initiative used a consensus approach to further define CRS which was expanded upon by Ronco et al. into the 5 categories listed in Table 11.1 [2]. This current definition is based on the acuity of presentation and the originating organ of dysfunction wherein acute or chronic dysfunction in one organ causes acute or chronic dysfunction in the other organ as well as possible systemic disorders affecting both organs in Type 11.5 [3].

There is certainly some overlap between these 5 phenotypes which can make accurate identification more difficult, and common comorbidities such as hypertension, vascular disease, diabetes mellitus, and chronic inflammation can further complicate this clinical picture [4]. However, acknowledgment of the pathophysiologic interactions between the heart and kidneys can help promote the delivery of goal-directed therapies, such as the use of diuretics and renin-angiotensin-aldosterone system (RAAS) inhibitors. Modest fluctuations in serum creatinine with these

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Table 11.1 Defining CRS based on the consensus conference of the acute dialysis quality initiative [2, 3]

Category of CRS	Definition
Type 1: Acute cardiorenal syndrome	Heart failure resulting in acute kidney injury
Type 2: Chronic cardiorenal syndrome	Heart failure resulting in chronic kidney disease
Type 3: Acute renal-cardiac syndrome	Acute kidney injury resulting in heart failure
Type 4: Chronic renal-cardiac syndrome	Chronic kidney disease resulting in heart failure
Type 5: Secondary cardiorenal syndrome	Systemic process resulting in both heart failure and kidney disease

therapies do not have the same negative impact on patient outcomes as true acute kidney injury and may not require medication discontinuation as often as once thought (see the section on treatment below).

The exact prevalence of each phenotype of CRS is difficult to estimate since most are treated on an outpatient basis where data is less readily available. CRS Type I is the most studied due to the frequency of hospitalizations in this subgroup. Approximately 40% of patients hospitalized from heart failure also have Type I CRS [4, 5]. At least 30% of all heart failure patients are thought to have moderate to severe renal impairment [6]. One analysis showed acute CRS (Type I and III) carries the highest risk of death [7]. Type IV CRS had better survival than either acute form.

11.1.2 Pathophysiology

There are several pathological mechanisms explaining the development of CRS including hypoperfusion, neurohormonal alterations, hemodynamic changes, and inflammation [4]. Hypoperfusion was the first of these to be explored but may not account for CRS as much as previously thought. In this theory, the reduced pumping function of the heart creates inadequate forward flow leading to prerenal hypoperfusion [4, 6]. The kidneys receive up to 25% of total cardiac output so heart failure can have a profound effect [6]. While this could play a role in some more advanced heart failure cases (patients with a cardiac index less than 1.5), patients with heart failure with preserved ejection fraction (HFpEF) and those with hypertension, not hypotension, have also been noted to have CRS Type I or II indicating low cardiac output is not the sole explanation [8]. Elevated intra-abdominal pressures from fluid retention can also cause renal compression and reduced perfusion leading to decreased GFR which may explain why CRS can be seen in those with and without reduced cardiac output [9, 10].

The relationship of neurohormonal feedback likely plays a larger role in CRS wherein decompensated heart failure leads to elevated renal venous pressures related to increased fluid volume [11], which leads to RAAS activation which causes preglomerular vasoconstriction and further neurohormonal activation. The activation of the

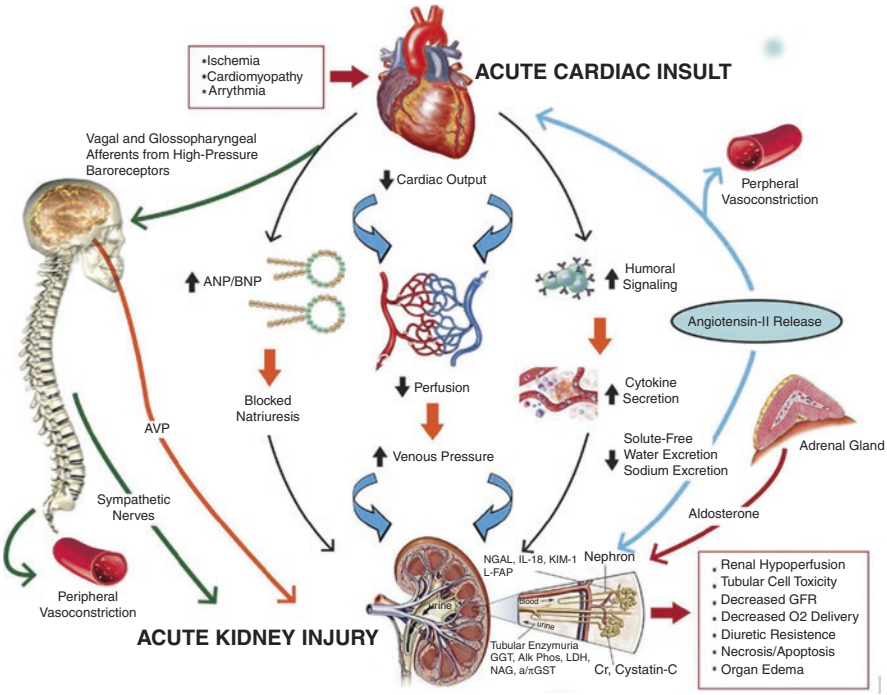

Fig. 11.1 Pathophysiology of neurohumoral and inflammatory pathways involved in cardiorenal syndrome (Reprinted from Seminars in Nephrology 31 (1), Ismail et al., Cardio-renal syndrome type 1: epidemiology, pathophysiology, and treatment, 18-25, 2012 with permission from Elsevier [12]). HAS-BLED bleeding risk score (Reprinted from Chest, 138(5), Pisters R et al., A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation, 1093–1100, 2010, with permission from Elsevier [13])

neurohormonal axis results in increased proximal tubular sodium and water reabsorption resulting in both oliguria and worsening congestion (see Fig. 11.1). This also leads to increased reabsorption of urea leading to a rise in BUN disproportionate to creatinine levels which is further discussed in the biomarker section below [6].

Hemodynamic alterations are associated with CRS as well. Right atrial (RA) pressure is increased with baseline renal dysfunction; however, increased central venous pressure (CVP) has also been associated with transient decreases in glomerular filtration rate (GFR) indicating that increased circulating fluid volume leads to temporarily decreased renal function in those with or without prior renal dysfunction [10, 14].

Persistent RAAS activation is also associated with increased inflammatory markers. This mechanism is associated with Type III and IV CRS wherein increased tumor necrosis factor-alpha, interleukin-1, and interleukin-6, which are elevated in acute kidney injury, can cause cardio-depressant effects such as a reduction in left ventricular ejection fraction (LVEF) [4]. Type IV CRS, also called uremic cardiomyopathy, is

related to fibroblast growth factor-23 (FGF-23) [15]. FGF-23 causes LV hypertrophy leading to reduced capillary density, microvascular ischemia, and heart failure. Figure 11.1 illustrates how the above mechanisms can all work together in creating dual-organ dysfunction while originating from different sources [12].

11.1.3 Differential Diagnosis

Diagnosis and proper classification of CRS require in-depth clinical knowledge as well as a general understanding of both heart failure and renal insufficiency. Obtaining a detailed patient history and review of symptoms is paramount to know if the patient is in heart failure (refer to Chap. 3) and then CRS should be considered based on the testing below. Without thorough patient assessment, CRS can mimic or even simultaneously occur with acute kidney injury (AKI) or chronic kidney disease (CKD), the latter of which will be discussed in a section later in the chapter. This confusion can lead to inadequate medical therapy when basing treatment decisions on lab values alone.

AKI is defined as having a change in serum creatinine of 0.3 mg/dl or higher [16]. Other staging and classifications such as RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) have been created to help further stage severity of AKI based on creatinine and urinary output (UOP) as shown in Table 11.2 [12]. AKI is associated with "an abrupt (within hours) decrease in kidney

Table 11.2 Acute kidney injury classification/staging. (Reprinted from Clinical Biochemist Reviews, 37(2) Makris & Spanou, Acute kidney injury: Definition, pathophysiology, and clinical phenotypes, 85–98, 2016 with permission from the Editor of Clinical Biochemist Reviews [16])

RIFLE criteria for classification/staging AKI			AKIN criteria for classification/staging AKI		
Stage	GFR criteria	Urine output criteria	Stage	Serum creatinine criteria	Urine output criteria
Risk	1.5-fold increase in sCr or >25% decrease in GFR	UO <0.5 mL/kg/h for 6 h	Stage 1	Absolute increase in sCr ≥0.3 mg/dL (≥26.5 μmol/L) or ≥1.5 to 2.0-fold from baseline	UO <0.5 mL/kg/h for 6 h
Injury	2.0-fold increase in sCr or >50% decrease in GFR	UO <0.5 mL/kg/h for 12 h	Stage 2	Increase in sCR >2.0 to 3.0-fold from baseline	UO <0.5 mL/kg/h for 12 h
Failure	3.0-fold increase in sCr or >75% decrease in GFR or sCr >4.0 mg/dL with an acute increase of 0.5 mg/dL	UO <0.3 mL/kg/h for 24 h or anuria for 12 h	Stage 3	Increase in sCr > threefold from baseline or increase of sCr to ≥4.0 mg/dL (≥354 μmol/L) with an acute increase of at least 0.5 mg/dL (44 μmol/L)	UO <0.3 mL/kg/h for 24 h or anuria for 12 h
Loss	Complete loss of kidney function for >4 weeks				
ESKD	End-stage kidney disease for >3 months				

function which encompasses both injury (structural damage) and impairment (loss of function)." These abrupt changes can also occur with CRS which should be considered in patients with heart failure.

11.2 Diagnostic Tools

11.2.1 Biomarkers

Diagnostic testing including cardiac and renal biomarkers and other imaging can help diagnose CRS and distinguish between it and primary renal disease. Cardiac biomarkers commonly used in the assessment of heart failure and CRS include troponin, a measure of cardiac injury, and brain natriuretic peptide (BNP), a measure of wall tension [4]. Troponin elevation is associated with an increased risk of heart failure death in both patients with and without ischemia [17]. It is commonly used in acute/emergency medicine or inpatient evaluation, but troponin can be useful in some outpatient situations as well. Assessment of BNP has a Class 1A recommendation based on current heart failure guidelines for assessment or diagnosis of heart failure. N-terminal pro-B-type natriuretic peptides (NT pro-BNP) are an inactive protein cleaved off BNP and necessary for evaluation of wall tension/heart failure in patients receiving drug therapy with neprilysin inhibitors such as sacubitril-valsartan, because the drug leads to rising BNP levels for several weeks after initiation leading to inconsistent results [18]. NT pro-BNP is not affected by sacubitril and is therefore more reliable for comparison. It is important to note that both BNP and NT pro-BNP are often elevated at baseline in patients with CKD due to primary renal excretion which can further complicate this clinical picture [18]. Cystatin C may also be beneficial in evaluating CRS and can be useful in predicting cardiac mortality; however, this cardiac and renal biomarker is less used in clinical practice currently [4].

Renal biomarkers associated with CRS include serum creatinine, blood urea nitrogen (BUN), and glomerular filtration rate (GFR). Serum creatinine is sensitive and varies vastly with age, gender, muscle mass, medication usage, and hydration [16]. Serum creatinine does not mark true tubular damage; instead, it reflects GFR. The GFR is a more consistent measurement when weight and age are taken into consideration but is less useful with acute fluctuations in renal function. Therefore, creatinine is considered the "imperfect gold standard" for routine monitoring of renal function [16]. Availability of a patient's baseline creatinine is key to interpretation [19]. BUN is a marker of prerenal azotemia and can be disproportionately elevated in CRS and corresponds with increased mortality of heart failure that is independent of creatinine or GFR [4, 6, 13]. Ngal is a biomarker currently used in Europe to help distinguish between CRS and AKI but is not commonly used in the United States as of 2019 [4]. Urinalysis (UA) is also beneficial since a dipstick for blood or protein suggests underlying primary renal disease. Increased urine albuminuria is a known sign of glomerular and tubular damage [20]. Most often, a UA will be unrevealing in type I and II CRS without underlying renal dysfunction with a few rare exceptions [6].

11.2.2 Imaging

Other diagnostic imaging is useful in the diagnosis of CRS. An echocardiogram is a noninvasive and frequently used tool for assessing overall cardiac function and can also provide insightful findings on physiological changes associated with congestion. Dilated inferior vena cava is a good indicator of fluid volume overload [21]. With E' related to mitral inflow velocity, E directly correlates with pulmonary capillary wedge pressure (PCWP) in which an E'/E ratio greater than 15 is associated with a PCWP greater than or equal to 18 [22] also indicating increased volume. Decreased ejection fraction, increased pulmonary artery pressure, and increased right ventricle diameter are all independently associated with an increased incidence of CRS [4]. Global longitudinal strain (GLS) has also been shown useful in predicting mortality in patients with CKD even with preserved EF [23].

Renal Ultrasound (US) is a necessary tool for the evaluation of renal insufficiency and can also lend clues helpful to diagnosing CRS. It can help determine the chronicity of CRS based on renal size, echogenicity, and cortical thickness [24]. Small kidneys are often indicative of underlying renal dysfunction as opposed to CRS alone [6]. One study showed discontinuous renal flow patterns plus increased right atrial pressure are indicative of CRS and had the poorest 1-year prognosis [25]. This renal congestion is also associated with decreased diuretic efficiency [26] which will be discussed more under the treatment section later in this chapter.

Cardiac MRI is considered the gold standard for cardiac structural assessment and evaluation of ventricular function in general. In Type IV CRS, myocardial fibrosis is associated with increased diffuse late gadolinium enhancement which may serve as a warning sign for heart failure outcomes in the patient with CKD [27].

11.3 Treatment

Unfortunately, no specific therapy exists to correct CRS or independently increase GFR; however, correction of the underlying condition has been shown to improve outcomes, i.e., improvement of cardiac function can lead to improvement in GFR in patients with Type I and II CRS, much like improvement in renal function can improve cardiac function in Type III and IV CRS [27]. Therefore, the use of guideline-directed medical therapy for heart failure should be continued in most cases, despite down-trending renal biomarkers, to give the patient the best chance for cardiac recovery and survival (see medication consideration section below).

11.3.1 Diuretics

Management of fluid overload is the primary treatment for mitigating the vicious cycle of CRS. Over 90% of patients with acute heart failure require diuretics [4]. While studies have never been able to prove a true mortality benefit to diuretic use in patients with heart failure via a randomized controlled trial, a Class Ia recommendation endorses the use of loop diuretics for immediate relief of heart failure

symptoms based on expert opinion [17]. Even though a rising creatinine can be associated with loop diuretic use and rising creatinine is also associated with worse clinical outcomes, recent studies such as the ESCAPE trial prove that a rise in creatinine due to heart failure treatment did not result in reduced outcomes so long as it resulted in a resolution of congestion [28, 29]. This is referred to as a functional increase in creatinine. Furthermore, elevated renal biomarkers should not deter diuretic use when clinical congestion is present [28]. Despite the initial rise in creatinine, many patients will return to baseline after decongestion, and some may even improve beyond their baseline due to decreased intra-abdominal pressure and decreased RV dilation as previously discussed in the pathophysiology section.

11.3.2 Diuretic Resistance

Unfortunately, heart failure patients with and without underlying renal dysfunction may struggle with diuretic resistance, defined as a lack of responsiveness to therapy. However, it is generally true that the higher the renal insufficiency, the higher the diuretic dose needed to create a response. This can be caused by several reasons in CRS. First, intestinal absorption of loop diuretics is decreased with abdominal edema [30]. This is true with one of the most commonly used loop diuretics in heart failure, Furosemide. Furosemide absorption varies significantly from one patient to another with average bioavailability of only about 50% [31]. Other oral loop diuretics such as bumetanide and torsemide average closer to 90% absorption which leads to a more predictable response [30]. Other causes of diuretic resistance include decreased diuretic delivery to kidneys due to decreased renal blood flow and increased sodium reabsorption from RAAS activation and/or dietary indiscretion with high sodium intake [4]. Below is a list of helpful tips for increasing diuretic response in patients with resistance (see Table 11.3).

It is important to understand that the diuretic threshold must be broken to elicit a response. This may require a dose increase or temporary use of IV diuretics to

Table 11.3 Tips for overcoming diuretic resistance [21, 30]

• Increase loop diuretic dose by 50–100%
• Change furosemide to bumetanide or torsemide (see Chap. 19 for more information)
• Make sure the patient is on an aldosterone antagonist as part of GDMT
• Advise patient to adhere to a low-sodium diet
• Add a thiazide-like diuretic such as metolazone before loop diuretic dose administration to inhibit sodium reabsorption in the distal tubule (watch for electrolyte abnormalities including hypokalemia)
• Supine position following diuretic administration may be helpful
• Consider heart failure program referral for frequent dose adjustment, lab monitoring, and/or advanced fluid monitoring device implant such as Cardiomems to guide therapy
• Discourage NSAID use as this can counteract diuretic effectiveness
• Consider ER or admission for intravenous diuretic administration
• Remember it is good practice to recheck electrolytes in 1 week following diuretic adjustments

achieve, but diuretic resistance is usually reversible with the correct strategy [21]. Note that increasing the frequency of diuretic dosing is only helpful once an effective dose is identified. For example, if 20 mg of furosemide does not increase UOP, increase it to 40 mg instead of 20 mg twice daily [30].

11.4 Chronic Kidney Disease and Heart Failure

11.4.1 Definitions and Staging of CKD

Underlying chronic kidney disease (CKD) creates a different patient scenario than CRS Type I and II. CKD involves a gradual loss of kidney function and loss of glomerular filtration ability which is graded based on glomerular filtration rate and the presence of disease. The stages of chronic kidney disease are outlined below (Fig. 11.2). Other factors for diagnosis include the presence of albuminuria, urine sedimentation, or structural abnormalities for greater than 3 months [32].

11.4.2 Prevalence with Heart Failure

Heart failure and CKD are commonly found in conjunction with one another. With each stage of CKD, the prevalence of heart failure also increases [32]. An estimated 44% of patients undergoing hemodialysis (HD) have comorbid heart failure. As the stage of CKD progresses, the mortality risk also increases for both patients with HFpEF and HFrEF [32].

11.4.3 Prevention of Heart Failure in a Patient with CKD

Uncontrolled hypertension and diabetes mellitus are both considered risk factors for both CKD and heart failure. House et al. [32] demonstrated that tight blood pressure control, defined as a systolic blood pressure less than 120, in patients with CKD may help prevent new-onset heart failure. In the RENAAL (Reduction of Endpoints

Fig. 11.2 Stages of chronic kidney disease [32]

in Non-insulin dependent diabetes with Angiotensin II Antagonist Losartan) trial, a relative risk reduction (RRR) of 32% was observed in first heart failure hospitalization [33]. Poor glycemic control in CKD was found to be an independent risk factor for the development of heart failure [32]. SGLT2 inhibitors have shown to have a class effect in slowing the progression of CKD and reducing the risk of hospitalization in those with and without prior history of heart failure [34] as seen in the Empa-Reg Outcome trial with a 39% RRR for heart failure hospitalization [35].

11.5 Medication Limitations with CKD and Heart Failure

Although CKD and heart failure frequently coincide, patients with both conditions are less likely to receive GDMT for heart failure due to concerns of hypotension, kidney function, and hyperkalemia [32]. Unfortunately, since most study criteria for commonly used medications have excluded patients with a creatinine of 2.5 or higher, there is limited evidence to support the use or discontinuation of GDMT in this patient population [4]. However, most drug classes show continued benefits up to stage IV CKD. See considerations for each of the four main heart failure therapy classes below.

11.5.1 Beta Blockers

Beta blockers may be the best studied for heart failure GDMT with CKD. At least three clinical trials with a good population of patients with CKD showed a mortality benefit with the use of metoprolol, bisoprolol, and to a smaller extent carvedilol [32]. Atenolol, nadolol, and sotalol are excreted by the kidneys and have not proven to have mortality benefits with heart failure, so these drugs would not be preferred for either patient population. It should be noted that metoprolol is somewhat dialyzable, and consideration may be given to dose timing based on the dialysis schedule.

11.5.2 RAAS-Altering Medications

Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin II Receptor Blockers (ARBs), and Angiotensin Receptor-Neprilysin Inhibitors (ARNIs) are known to be underutilized, under-prescribed, and underdosed in the CKD population [20]. These medications may help slow the development of kidney disease with accompanying proteinuria, but frequently cause an acute rise in creatinine that may lead to dose reduction or even drug discontinuation in patients with CKD. Benefits of using ACE/ARBs in patients with CKD were noted in the CONSENSUS trial which showed a decreased mortality and decreased symptoms of heart failure despite a doubling of creatinine in 11% of subjects [36]. In the majority of these subjects, the creatinine returned to 30% of baseline which is consistent with other trials in the HFrEF population [4]. The benefit of RAAS inhibition did not outweigh the risk,

however, in the HFpEF population with CKD [32]. The only available ARNI, sacubitril/valsartan, has been studied the least in heart failure with CKD, and available data is mixed. In a small sample size, it showed preservation of GFR but also an increase in albuminuria compared to valsartan alone [32].

Close monitoring is recommended with consistent use of ACE/ARB/ARNIs, especially with CKD. A basic metabolic panel should be drawn at baseline and repeated 1–2 weeks later following initiation and titration of dose and then every 3–6 months based on current guidelines [37]. If creatinine increases over 50% of baseline or is over 3.0, GFR is less than 25, or potassium is over 5.5, it is recommended to reduce the dose by 50% and repeat labs in 1 week. Consideration should be given to other causes of worsening renal function including over-diuresis or intrinsic kidney disease. If ACE/ARB/ARNI cannot be tolerated due to worsening renal function, combination therapy with hydralazine and isosorbide dinitrate may be used, although this is more beneficial in African American population as opposed to other ethnicities [38]. Keep in mind that azotemia alone in the setting of diuresis should not lead to a dose decrease or withdrawal of ACE/ARB/ARNI as this can lead to worsening heart failure outcomes [32].

11.5.3 Mineralocorticoid Receptor Antagonists (MRAs)

Mineralocorticoid receptor antagonists, also termed aldosterone antagonists, although known to be generally well tolerated in stages I-III CKD, are another class of heart failure therapy that has not been well studied in CKD stages IV and V [32]. The RALES (Randomized Aldactone Evaluation Study) study set criteria as EF less than 35%, creatinine less than or equal to 2.5, and potassium less than or equal to 5.0 and revealed similar benefits to mortality reduction in groups with GFR less than 60 as GFR greater than 60. However, the population with GFR less than 60 saw a higher incidence of hyperkalemia, reduction of GFR by 30% or more, dose reduction, or drug discontinuation [32, 39]. Continuing studies are underway to evaluate the safety and effectiveness of MRA use in patients undergoing HD [32]. Monitoring of BMP after 1 week and every 3–6 months is the typical practice for stable patients.

11.5.4 Sodium-Glucose Cotransporter 2 (SLGT2) Inhibitors

Sodium-glucose cotransporter 2 (SLGT2) inhibitors, created as glucose-lowering drugs for type II diabetes mellitus, have demonstrated benefits for both HFpEF and HFrEF. These medications have been added to guidelines as a recommended therapy for HFrEF as of 2021 for patients with and without diabetes [17]. Unlike some of the other heart failure therapies mentioned in the sections above, studies have paid particular attention to renal outcomes for patients with CKD and the results are promising. SLGT2 inhibitors are not only safe for all stages of CKD but also slow the progression of CKD [20]. An acute fall in GFR is often noted initially in the first 2 weeks of therapy followed by stabilization with decreased risk that the patient will reach ESRD, indicating a renal protective mechanism is at work.

11.6 Ultrafiltration and Dialysis with Heart Failure

Patients undergoing dialysis for ESRD, both with and without heart failure, are at high risk for frequent fluid and potassium fluctuation. Ultrafiltration is the process of fluid removal during dialysis sessions [40]. The amount of fluid withdrawn is dependent on the rate of filtration, length of sessions, and frequency of sessions. For patients with heart failure, increased frequency of dialysis sessions, such as short daily sessions, has been shown to decrease LV mass and lower the risk of cardiovascular death and hospitalization [32]. Particular benefit has been seen in patients who undergo home hemodialysis which can be both scheduled and as needed/PRN. A 41% decrease in heart failure, cardiomyopathy, fluid overload, and hospitalizations has been seen in this group [32, 41]. Limited data is available to determine the best practice between peritoneal dialysis and in-clinic hemodialysis in this patient population. Studies for using ultrafiltration for fluid removal in non-dialysis heart failure patients have not consistently demonstrated benefit compared to diuretics, nor is it considered to be more renal protective [20].

11.7 Renal Transplant Considerations for Heart Failure

Patients undergoing renal transplant have approximately an 18% chance of developing heart failure in the next 3 years [32]. Heart failure therapy in this population has not been thoroughly studied; however, one trial showed that lisinopril in renal transplant recipients with heart failure decreased LV mass index. Despite limited data available in this unique population, standard GDMT including loop diuretics should not be withheld. For patients with heart failure before renal transplant, outcomes are mixed. There is an increased risk of mortality and graft rejection of the new organ with prior heart failure, but some types of heart failure including uremic cardiomyopathy may significantly improve post-transplant. Patients may also be a candidate for dual-organ (heart and kidney) transplant in those who have end-stage disease of both organs [32, 42].

11.8 Hyperkalemia in CKD and Heart Failure

Hyperkalemia is a frequent complication of CKD and one of the most common reasons for de-escalation or discontinuation of RAAS inhibitors and MRAs as mentioned above which leads to worsening heart failure outcomes. Patiromer [32, 43] and zirconium cyclosilicate [32, 44] have been shown to lower potassium and prevent hyperkalemia when taken daily. Further data is needed to prove whether this will improve GDMT utilization in heart failure, but this may be a strategy to consider for some patients.

11.9 Anemia, Heart Failure, and CKD Considerations

11.9.1 Incidence and Associations

Anemia, heart failure, and CKD are heavily intertwined conditions. The risk of developing anemia increases with both heart failure and CKD. For heart failure, the incidence of anemia goes up with each New York Heart Association (NYHA) functional class, seeing an average of 9% anemia in NYHA Class I and up to 79% in NYHA Class IV [45]. Anemia incidence increases as GFR decreases in CKD [46]. While anemia is only rarely the cause of heart failure directly, it has been shown to worsen outcomes including hospitalizations and mortality. Anemia also increases the risk of developing heart failure in patients with CKD [45].

11.9.2 Pathophysiology of Anemia in Heart Failure

Several mechanisms are suspected to cause anemia with heart failure. First, increased circulating cytokines with heart failure may lead to anemia of inflammation/anemia of chronic disease [45]. Increased plasma volume seen in heart failure may also create dilutional anemia which can be corrected and fluctuates with diuresis. ACE inhibitors have been shown to decrease erythropoiesis in the SOLVD trial which may cause or worsen anemia [47]. CKD and CRS are both known causes of anemia due to erythropoietin production seen with reduced kidney function [45]. Additionally, iron deficiency anemia is found in both the CKD and heart failure populations.

11.9.3 Diagnosis

Common anemia symptoms of dyspnea and fatigue may be mistaken as symptoms of heart failure, which is one of the reasons laboratory screenings are important to detect and diagnose anemia. Complete blood counts with differential, iron studies including serum iron, transferrin, iron saturation, ferritin, creatinine, C-reactive protein, erythrocyte sedimentation rate, serum B12, and folate levels should be drawn at baseline heart failure or CKD diagnosis, and anytime anemia is suspected [45]. Gastrointestinal blood loss should always be ruled out. Identification of the cause of anemia is key to treatment, especially when iron deficiency is suspected. If the cause cannot be identified based on lab results, a hematology referral should be considered.

11.9.4 Iron Replacement

Iron replacement is indicated in anemia with heart failure or CKD when hemoglobin is less than 10 and iron saturation is less than 20%, or ferritin is less than 41 [45, 46]. Ferritin may be sustained in patients with heart failure and can be misleading if

assessed independently of other labs [45]. Several large studies including a meta-analysis in 2019 showed that intravenous (IV) iron replacement decreased heart failure hospitalizations, improved NYHA class and 6-minute walk tests, improved ejection fraction, and lowered BNP and CRP levels in heart failure patients and should be used for saturation less than 17% [45]. Although no randomized controlled trials have compared oral iron supplementation with IV iron replacement, experts recommend the use of IV iron due to better absorption and more efficient correction of iron levels in heart failure patients [45]. Erythropoietin stimulating agents (ESAs) and blood transfusion may be used in severe anemia that does not respond to iron infusion. ESAs are contraindicated in patients with a history of stroke, thromboembolic events, and malignancy [45].

11.10 Conclusion

Cardiorenal syndrome and chronic renal failure in the setting of heart failure, often complicated by anemia, create two different patient profiles with separate considerations for each; however, the overlap is hard not to see. Careful focus on underlying etiology is important to correct management and improve patient outcomes. Primary care providers are key to reducing and identifying risk factors, initiating GDMT, providing patient support, follow up on labs and other testing, and communicating among specialty services. The two case studies below identify two different patients who will likely enter the primary care clinic; will you be able to tell them apart?

Case Study 1: Cardiorenal Syndrome Type II and Diuretic Resistance

Subjective: Ms. Jones is a 68 year-old female with the following past medical history/problem list: Heart failure with reduced ejection fraction, NYHA Class II; status post-ICD implant for primary prevention of sudden cardiac death; dilated, ischemic cardiomyopathy; coronary artery disease, status post-coronary artery bypass grafting >10 years ago; hypertension; diabetes mellitus, type 2.

Family history: Coronary artery disease in her father and paternal grandmother.

Social history: She lives at home with her husband. They have three grown children. Homemaker. Denies alcohol, tobacco, and illicit drug use.

Medications: Carvedilol 3.125 mg BID; Sacubitril/Valsartan 24/26 mg BID; Spironolactone 25 mg daily; Furosemide 80 mg BID; Metformin 1000 mg BID; Aspirin 81 mg daily; Atorvastatin 80 mg QHS.

Allergies: NKDA.

Case Scenario

Chief complaint: The patient called requesting an appointment due to worsening shortness of breath and her "fluid pill not working anymore."

HPI: Ms. Smith returns for episodic visit complaining of increased shortness of breath with mild activity, 11 lb weight gain in 1 week, and lower extremity edema. She has recently returned from a vacation with her grandchildren where she admits she did not watch her sodium intake and ate out almost every day. She states, "I've been taking my furosemide, but it just doesn't seem to be working as well as it used to." She normally limits sodium intake to 2 g daily and fluid intake to 2 l daily and reports taking all medications as prescribed. She admits to bloating, early satiety, 3-pillow orthopnea, and less than expected urinary output. She denies any recent ER visits, hospitalizations, chest pain, or palpitations. No fever, dark or foul-smelling urine, frequency, urgency, frank hematuria, or hesitation.

Objective

Vital signs: BP 102/65; HR 89; oxygen saturation 97% on room air; Temp 98.2°. Weight 172 lbs (last recorded office weight was 161 lbs)

Physical exam: JVD 10 cm. Normal S, S2 without S3 or murmur. Normal work of breathing at rest. Lung sounds decreased in bilateral bases. Abdomen distended but still soft and non-tender. 1 + bilateral lower extremity pitting edema to mid-calves

Labs

Today—Sodium 134; Potassium 4.6; BUN 32; Creatinine 1.8; Pro BNP 3560

2 months ago—Sodium 137; Potassium 3.9; BUN 22; Creatinine 1.2; Pro BNP 540

Diagnostics

The most recent echo 2 months ago showed a stable EF of 35%.

Assessment

Ms. Jones is having a mild acute chronic heart failure exacerbation with NYHA Class III symptoms complicated by an acute decrease in renal function with a rise from baseline creatinine from 1.2 to now 1.8 over the last 2 months. Her pro-BNP is also elevated much higher than baseline. On exam, she appears to have increased abdominal pressure and congestion which is likely causing diuretic resistance to her furosemide and associated lab fluctuations.

Plan

Change furosemide 80 mg BID to bumetanide 4 mg in the morning and 2 mg in the afternoon for the next week starting today. Repeat visit with BMP in 5–7 days. Call in 1–2 days if urinary output does not increase with medication change or if shortness of breath or swelling continues to worsen.

Check weight daily upon waking after emptying the bladder and before eating or drinking. Call for further weight gain of 2 lbs overnight or weight loss greater than 10 lbs in 1 week.

Resume a low sodium diet and reduce fluid intake to 1.5 L/day until symptoms improve.

Return to the clinic for a recheck of symptoms in about 1 week. Would consider the addition of an SGLT2 inhibitor at the next visit for heart failure, diabetes, and renal protective benefits and decrease bumetanide to 2 mg BID (once the goal is reached) with an additional 2 mg PRN for a weight gain of 2 lbs overnight or 5 lbs in 1 week.

Clinical Pearls

- Although this patient is experiencing acute symptoms of both cardiac and renal symptoms, she does not need to be treated as an inpatient or go to ER for IV diuretics unless oral medications do not help or symptoms worsen.
- Changing furosemide to bumetanide should improve diuretic resistance and drug absorption. Increasing the dose temporarily will also be beneficial.
- SGLT2 inhibitor benefits heart failure, diabetes, and renal function.
- Lab monitoring expectations—creatinine will likely rise slightly at the next visit from increased diuretic use, but symptoms and BNP should improve. Renal function will then return to baseline over the next few weeks. Would trend labs every 2 weeks. If creatinine does not return to baseline in the next 1–2 months would consider a nephrology referral.
- Monitor NT pro-BNP while taking sacubitril/valsartan.

Case Study 2: The Complex Interaction of CKD, HF, and Anemia

Subjective: Mr. Greene is a 55 year-old male with a past medical history/problem list: poorly controlled hypertension 20+ years; microscopic hematuria 10 years; nephrolithiasis; depression, obesity

Family history: Hypertension

Social history: Tool and dye maker. Divorced with 2 grown children. Denies current alcohol, tobacco, and illicit drug use. History of 1 ppd smoker for 30 years.

Medications: Lisinopril 20 mg daily, amlodipine 5 mg daily, hydrochlorothiazide 25 mg daily, sertraline 20 mg daily

Allergies: NKDA

Case Scenario

Chief complaint: Increased shortness of breath, swelling in ankles, and a metallic taste in the mouth for 2 months.

HPI: Since his last visit 9 months ago, the patient has noticed shortness of breath with walking short distances, swelling in the ankles, and a metallic taste in the mouth for about 2 months. He has checked his BP at home a couple of times and says it averages 150s/90s. He has also noted weight gain of about 15 lbs, bloating, and poor appetite. He states, "I just feel so tired all the time now." He denies any missed doses of medications, lightheadedness, chest pain, or palpitations. No recent illness or hospitalizations.

Objective

Vital signs: BP 145/100; HR 102; oxygen saturation 96% on room air; Temp 98.0°. Weight 258 lbs

Physical exam: JVP elevated 12 cm; displaced apical beat (mid-axillary line); loud S3; lung fields clear, dull at both bases; liver edge 6 cm below costal margin; No ascites; 2+ Ankle edema

Labs: Serum creatinine 2.8 mg/dl; BUN 30; eGFR 26%; Potassium 4.0; Total CO_2 28; Hemoglobin 10.3; (add diff showing anemia). Total cholesterol 216, LDL 146, triglycerides 362; fasting glucose 122; Albumin-creatinine ratio >300; Urinalysis 3+ protein, 5–10 rbc, No rbc cast–trace granular cast

No prior labs for comparison in the last 12 months.

Assessment: This patient has labs indicative of chronic renal insufficiency and anemia. He also has signs and symptoms of new-onset heart failure.

Plan: The patient needs an echocardiogram to better assess for LV dysfunction and referral to cardiology for management. He also needs a nephrology referral for CKD stage IV based on GFR. Would stop HCTZ and begin furosemide 80 mg BID for better diuresis. Would decrease lisinopril and begin hydralazine 100 mg TID for tighter BP control. Needs iron levels checked and replaced if indicated for anemia. Reduced sodium diet. A renal US for secondary hypertension workup and assessment of intrinsic kidney disease. Avoid nephrotoxins including NSAIDs.

Clinical Pearls

- Diuresis is less effective with low-dose thiazide-like diuretics alone in the setting of CKD; he will need a higher dose loop diuretic to break the threshold and begin diuresis.
- Current guidelines recommend reducing, not discontinuing ACE/ARB, with isolated elevated creatinine reading. Would add hydralazine for blood pressure coverage while further evaluation takes place. Would add isosorbide dinitrate if the echo reveals HFrEF.

- Stabilization including appropriate diagnosis of renal disease, aggressive HTN management, and fluid volume likely to improve cardiac symptoms and quality of life.

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