

Review Article

Cardiac Resynchronization Therapy in the Cardiorenal Syndrome

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The cardiorenal syndrome (CRS) is a complex clinical syndrome in which dysfunction of either the heart or the kidneys affects the functioning of the other organ system. Many therapies used in heart failure have further detrimental effects on renal function. Cardiac resynchronization therapy (CRT) is a relatively new form of device therapy that reduces morbidity and mortality in patients with heart failure. This review will discuss the effects of CRT on renal function in patients with CRS, the impact of baseline renal function on response to CRT, and potential risks associated with CRT in this unique population.

1. Introduction

It has long been recognized that heart failure and renal impairment frequently coexist and that functional decline in one organ system is often associated with a parallel decline in the other. In the past decade, the term “cardiorenal syndrome” (CRS) has been used to describe this complex process. Although initially described as a state in which “therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function,” [1] newer definitions and classification schemes have tried to capture the bidirectional feedback processes and complex pathophysiological interactions which exist between the heart and the kidneys. The CRS is not simply renal dysfunction as a result of a low-flow state induced by depressed cardiac function but rather a complex clinical syndrome in which hemodynamic abnormalities, neurohormonal activation, inflammation and oxidative stress cause dysfunction of both organ systems through symbiotic pathways [2]. In recognition of these complex interactions, Ronco and colleagues recently presented a classification system for CRS (Table 1) [3]. It is well recognized that an individual can simultaneously exhibit the pathophysiological characteristics of multiple types of CRS and that this classification scheme is not meant to discretely categorize patients into subgroups.

As our understanding of the underlying mechanisms of CRS has progressed, so has our recognition of the magnitude of the problem and of its prognostic significance. In ADHERE, a national registry of more than 100 000 nonselected patients admitted to hospital with acute decompensated heart failure, 31% of patients had chronic renal insufficiency, 20% had serum creatinine levels >2.0 mg/dL, and 5% were receiving dialysis [4]. Furthermore, even moderate renal insufficiency is associated with increased mortality in patients with symptomatic or asymptomatic LV dysfunction [5] or heart failure with preserved systolic function [6]; creatinine clearance predicts mortality independent of ejection fraction or functional capacity [7]. In the Studies of Left Ventricular Dysfunction (SOLVD) trials, decline in GFR was independently associated with increased risk of mortality in patients with heart failure, regardless of baseline renal function [8]. In patients admitted to hospital with heart failure, worsening renal function during admission predicts in-hospital mortality, complications, and longer duration of hospitalization [9]. On the other hand, cardiovascular disease including heart failure is common in patients with renal failure, and cardiovascular death is the leading cause of mortality among renal cohorts [10]. The risk of cardiovascular events increases rapidly with declining GFR [10].

TABLE 1: Classification system of cardiorenal syndrome (CRS).

	Description	Examples of inciting events	Examples of consequences
Type 1 CRS	Acute HF leads to AKI	(i) ADHF (ii) Cardiogenic shock (iii) Hypertensive pulmonary edema	(i) AKI (ii) Diuretic resistance
Type 2 CRS	Chronic HF leads to progressive CKD	(i) Chronic systolic HF (ii) Chronic HF with preserved systolic function	(i) Progressive CKD
Type 3 CRS	Acute renal dysfunction leads to acute cardiac dysfunction	(i) AKI (ii) Glomerulonephritis	(i) ADHF (ii) Acute HF (iii) Ischemia (iv) Arrhythmia (v) Decreased CO
Type 4 CRS	CKD leads to chronic cardiac dysfunction and/or increased risk of CV events	(i) CKD	(i) Systolic dysfunction (ii) LVH (iii) Diastolic dysfunction (iv) Coronary calcification (v) Decreased coronary perfusion
Type 5 CRS	Systemic disorder leads to cardiac and renal dysfunction	(i) Sepsis (ii) Vasculitis (iii) Diabetes (iv) Amyloidosis	(i) Acute HF (ii) Chronic HF (iii) AKI (iv) CKD

Adapted from [3]. ADHF: acutely decompensated heart failure; AKI: acute kidney injury; CKD: chronic kidney disease; CO: cardiac output; CV: cardiovascular; HF: heart failure; LVH: left ventricular hypertrophy.

Pharmacologic therapies for heart failure are often limited by adverse effects on renal function. Although angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone antagonists all prolong survival in heart failure patients [11–16], they are relatively contraindicated in patients with unstable renal function and may cause acute declines in glomerular filtration rate (GFR). Furthermore, most trials evaluating the efficacy of these therapies in heart failure excluded patients with evidence of significant renal dysfunction. Similarly, loop diuretics, which have never been demonstrated to improve outcomes in heart failure, are the mainstay of symptomatic treatment for volume overload and are frequently associated with a decline in renal function. Moreover, there is emerging data to suggest an increase in mortality with the use of these agents [17].

Pharmacological therapy centered on neurohormonal blockade remains first-line therapy for the majority of patients with systolic left ventricular dysfunction [18–20]. However, for those with advanced functional symptoms and depressed LV function, despite optimization of evidence-based HF therapies, cardiac resynchronization therapy may provide additional morbidity and mortality benefits.

In up to 30% of patients with heart failure, intraventricular conduction delay produces mechanical dyssynchrony, resulting in inefficient ventricular contraction and negative remodeling. Biventricular pacing may restore synchronous contraction of the interventricular septum and LV free wall with resultant improvement in LV geometry and function. Cardiac resynchronization therapy (CRT)

improves symptoms, functional classification, echo parameters (including left ventricular ejection fraction and end-systolic volume, mitral regurgitation severity, and interventricular mechanical delay) and prolongs survival in patients with intraventricular conduction delay (QRS complex width >120 ms), LVEF \leq 35%, and New York Heart Association (NYHA) class III-IV symptoms [21–24]. As such, each of the major societies' guidelines recommends CRT in this patient population [18–20].

2. Effect of Cardiac Resynchronization Therapy on Renal Function

Our understanding of the impact of CRT on renal function in patients with CRS has been limited by the exclusion of patients with renal failure from many randomized, clinical trials. The MIRACLE trial was a double-blinded, randomized and placebo-controlled trial in which patients with NYHA class III or IV symptoms, QRS duration \geq 130 ms, LVEF \leq 35%, and LV end-diastolic diameter \geq 55 mm underwent implantation of a CRT device and were randomized to device on (treatment group) or device off (control group) [23]. Patients were excluded from the trial if their serum creatinine was >3.0 mg/dL. In a retrospective analysis of the MIRACLE trial [25], Boerrigter and colleagues assessed the effect of CRT on estimated GFR (eGFR) in patients falling into three categories: normal or increased eGFR (\geq 90 mL/min/1.73 m²), mildly reduced eGFR ($60 \leq$ eGFR

< 90 mL/min/1.73 m²), and moderately reduced eGFR (30 ≤ eGFR ≤ 60 mL/min/1.73 m²). CRT significantly improved eGFR compared to control in patients with moderately reduced eGFR, but it had no effect in patients with normal, increased or mildly decreased eGFR. In patients with a baseline eGFR ≤ 60 mL/min/1.73 m², there were fewer patients in the treatment group than in the control group who experienced worsening renal function.

Similar observations have been made in nonrandomized studies. Adelstein and colleagues demonstrated that compared to standard defibrillator (SD) therapy, CRT-defibrillator (CRT-D) implantation was associated with improved renal function, as well as improved survival and improved LV systolic function on echocardiogram, in patients with baseline GFR 30–59 mL/min/1.73 m² [26]. Patients with GFR ≤ 30 mL/min/1.73 m² showed improved renal function but not improved survival after CRT-D implantation, while renal function deteriorated in those with GFR ≥ 60 mL/min/1.73 m². Although the authors did not specifically address the reason for the decline in this latter group, they did hypothesize that preserved renal function may be a surrogate for relatively compensated heart failure. The decline in GFR in this group could reflect the risks associated with device implantation (see below) or simply the natural progression of the cardiorenal syndrome, superimposed on minimal hemodynamic benefit of CRT at the level of the kidney. In another study, patients who were “responders” to CRT (those who demonstrated any improvement in LVEF after CRT implantation) showed mild improvement in GFR, while those who were “nonresponders” showed a decline in renal function [27]. As in other studies, this effect was even more pronounced in patients with baseline eGFR < 60 mL/min. Perhaps as a result of this, prescription of ACEI and ARB therapy increased in “responders”, while it decreased in “nonresponders”. ACEI and ARB therapies have a well-established survival benefit in HF patients, regardless of GFR [28], and the ability to offer them to patients may contribute to the overall benefit of CRT. In a similar study by Fung and colleagues, patients with a 10% reduction in LV end-systolic volume (LVESV) after CRT implantation maintained stable renal function, while those who failed to show improvement in LVESV had a significant decline in GFR [29]. From the limited data available, it appears that CRT-implantation, particularly when associated with improved LV function, is associated with improved renal function in patients with baseline renal impairment.

The proposed mechanisms by which CRT may improve renal function are based on our current understanding of the pathophysiology of renal failure in the broader context of the cardiorenal syndrome. Historically, it was believed that renal failure was a result of renal hypoperfusion, in turn, due to reduced cardiac output and diuretic-induced intravascular volume depletion [30]. More recently, it has been recognized that elevated central venous pressure may play an equally or even more important role in the progression of renal failure among HF patients. Increased right-sided filling pressures ultimately lead to renal congestion, reduced renal perfusion pressure, and direct ischemic injury as a result of increased interstitial pressure in the renal medulla [31, 32]. CRT may

mitigate these processes, in part due to improved cardiac output [24, 33] and increased mean arterial pressure [22, 34]. It also leads to reductions in central venous pressure [34], and therefore, may improve renal perfusion by improving both “forward” and “backward” cardiac failure.

Neurohormonal activation may also play a role in the pathogenesis of the cardiorenal syndrome. Heart failure is clearly associated with activation of the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS) and cardiac natriuretic peptides. Although the specific roles of these messenger pathways at the level of the kidney are still being elucidated, there is indirect evidence to suggest that interruption of both renal sympathetic innervation and of RAAS activation may produce beneficial renal effects [2]. Although catecholamine levels are not reduced with CRT [25], sympathetic nerve activity is diminished [35, 36], suggesting decreased adrenergic tone with CRT. In addition, long-term CRT is associated with reduced RAAS activity and stabilization of NT-proBNP levels in patients who demonstrate reverse LV remodeling but not in those who do not reverse remodel [37]. Taken together, these findings suggest that in addition to the benefits achieved through direct hemodynamic effects, CRT may positively impact renal function by interrupting deleterious neurohormonal pathways that are hypothesized to be culprit in the pathophysiology of heart failure.

3. Effect of Renal Dysfunction on Response to Cardiac Resynchronization Therapy

Baseline renal function may predict response to CRT both in terms of mortality and other clinically important endpoints. Shalaby and colleagues retrospectively studied 330 patients receiving CRT and found that those in the highest tertile of serum creatinine (1.4–3.0 mg/dL) had the highest mortality rate (28.7% versus 14.0% in other tertiles, $P = .008$) as well as the highest rate of the combined endpoint of mortality and heart failure hospitalization (41.6% versus 21.5%, $P = .001$) [38]. When studied as a continuous variable, each 0.1 mg/dL increase in creatinine was associated with an 11% increase in mortality and a 7% increase in the combined endpoint. Several other studies have similarly demonstrated that renal function is an independent predictor of survival [39, 40] and survival-free from heart transplantation or ventricular assist device (VAD) [41, 42] in patients receiving CRT and that the mortality benefit achieved with CRT-D over standard defibrillator therapy may be attenuated or lost at low eGFR [26]. The change in GFR following CRT implantation may also predict long-term outcomes. Fung and colleagues were able to demonstrate that patients whose renal function remained stable at 3 months after CRT implantation had lower all-cause mortality and lower combined mortality and HF hospitalization than those whose renal function declined [29].

Interestingly, in the same study [29], the group of patients who responded to CRT as characterized by LV reverse remodeling had worse renal function at baseline than the group who did not respond. Other investigators have

shown that LV mass may decrease and 6-minute walk distance may increase after CRT implantation in patients with $eGFR < 60 \text{ mL/min/1.73 m}^2$ to a greater extent than in patients with $eGFR \geq 60 \text{ mL/min/1.73 m}^2$ [25]. These findings may reflect the fact that while renal insufficiency is associated with a poor overall prognosis that cannot be completely reversed with current therapies, patients with reduced GFR have the most to gain from reversal of the neurohormonal and hemodynamic disturbances associated with heart failure.

4. Adverse Renal Consequences of Cardiac Resynchronization Therapy: Contrast-Induced Nephropathy

While there are many potential benefits to CRT in patients with the CRS, no procedure is entirely without risks. Implantation of the left ventricular lead typically requires contrast administration in order to locate the ostium of the coronary sinus and to define coronary venous anatomy. Contrast-induced nephropathy (CIN), typically defined as an elevation in serum creatinine of $\geq 25\%$ following intravenous contrast administration, is frequently reported after other procedures such as coronary angiography and is associated with adverse outcomes including mortality [43]. Major risk factors for CIN include preexisting renal dysfunction, diabetes mellitus, congestive heart failure, volume of contrast used, female sex, and mean arterial pressure $< 100 \text{ mmHg}$ [43–45]. In one study, CIN occurred in 10 of 68 patients (14%) undergoing CRT implantation; three of these patients required hemofiltration, and one died [46]. The incidence of CIN was higher (63%) in patients with baseline creatinine $\geq 200 \text{ umol/L}$, and CIN was associated with longer duration of hospital stay (19 versus 4 days, $P < .01$). Epicardial LV lead placement, via an open surgical procedure, has been proposed as an alternative in patients with renal insufficiency [47]. Although this approach is more invasive than catheter-based transvenous lead placement and is associated with longer ICU stay, it avoids the use of intravenous contrast dye and may be equally effective [48].

5. Conclusions

CRS is an important clinical syndrome affecting a large proportion of patients with primary heart failure, primary kidney disease, or both and is associated with a poor prognosis. Many pharmacologic therapies used in the management of heart failure have the potential to worsen renal function, particularly in patients who already have baseline renal insufficiency. Cardiac resynchronization therapy is an additional tool which can be used to manage this complex patient population; CRT may have the added benefit of specifically targeting many of the underlying pathophysiological mechanisms which are felt to be central to the propagation of CRS and data suggest that it may also be an effective means of treating heart failure while improving renal function in this population. CRS patients are at particularly high risk of mortality and other adverse events and they may remain

at higher risk than isolated HF patients when treated with CRT, but the limited amount of available data suggests that they are still able to obtain some benefit from this therapy. More studies of CRT in this specific population, and in the individual subtypes of CRS, as well as the inclusion of CRS patients in large clinical trials, will allow a greater understanding of its impact on this important disease.

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