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Cardiorenal syndrome

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Abstract

Kidney dysfunction in patients with heart failure and cardiovascular disorders in patients with chronic kidney disease are common. A recently proposed consensus definition of cardiorenal syndrome stresses the bidirectional nature of these heart-kidney interactions. The treatment of cardiorenal syndrome is challenging, however, promising new therapeutic options are currently being investigated in recent and ongoing clinical trials.

Introduction and context

The coexistence of heart failure (HF) and renal dysfunction, in which the heart and the kidney fail to compensate for each other's dysfunction, is very common. About one-third of the patients with HF have reduced kidney function that is associated with diuretic resistance and increased mortality [1]. Another cardiorenal connection is observed in patients with chronic kidney disease (CKD), who can have an increased risk of cardiovascular complications and death [2,3]. Until recently, cardiorenal syndrome (CRS) was generally defined as an acute or chronic renal dysfunction resulting from primary changes in cardiac function. A consensus definition of CRS, stressing the bidirectional nature of heart-kidney interactions, has recently been proposed [4] and was endorsed by the Acute Dialysis Quality Initiative group (C Ronco, personal communication). In addition, increasing insights into the pathophysiology of this syndrome have led to promising new therapeutic strategies.

Recent advances

Definition of cardiorenal syndrome

The expanded and refined definition of CRS describes it as a pathological disorder of the heart and the kidney in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ [4]. It includes five subtypes:

1. CRS type I, or acute CRS, describes the acute kidney injury resulting from an abrupt worsening of cardiac function (acute cardiogenic shock or acute decompensation of congestive heart failure, or CHF).

2. CRS type II, or chronic CRS, describes the progressive and permanent kidney disease caused by chronic abnormalities in cardiac function.

3. CRS type III, or acute renocardiac syndrome, describes an abrupt cardiac disorder that results from an abrupt worsening of kidney function, mediated by dysregulation of fluid balance, arrhythmias, or inflammatory mediators.

4. CRS type IV, or chronic renocardiac syndrome, refers to the decreased cardiac function, accelerated atherosclerosis, left ventricular hypertrophy, and remodeling and/or increased risk of cardiovascular events in patients with CKD.

5. CRS type V describes a situation in which a systemic condition (for example, diabetes or sepsis) causes both cardiac and renal dysfunction.

Whether this new classification system will increase our understanding of the pathophysiology or will result in better therapeutic approaches remains to be proven.

Pathophysiology

The overall understanding of the pathophysiology of impaired kidney function in patients with cardiac disease

is limited. Traditionally, impairment of cardiac output and relative under-filling of arterial perfusion have been considered the predominant cause. However, many clinical studies on this condition have not found an association between kidney dysfunction and cardiac output or other hemodynamic parameters, with the exception of right atrial pressure [5,6], which may point to an important role of venous congestion and increased intra-abdominal pressure.

The pathophysiology of CRS is not limited to hemodynamic changes and should be seen as a complex interplay of neurohumoral activation, which is counterproductive and maladaptive and results in a vicious circle with progressive renal dysfunction and worsening HF. The neurohumoral systems involved are the sympathetic nervous system (SNS), the renin angiotensin aldosterone system (RAAS), the endothelin system, and the arginine vasopressin system. Their activation induces inflammation and oxidative stress (imbalances between nitric oxide and reactive oxygen species) and results not only in vasoconstriction and salt and water retention but also in accelerated atherosclerosis, cardiac remodeling and hypertrophy, myocardial and intrarenal fibrosis, and progression of renal disease [7,8]. Treatment of CRS relies mainly on interference with this maladaptive neurohumoral activation.

Treatment

The management of CRS types I and II represents a clinical challenge. Few agents used in the treatment of acutely decompensated HF have been shown to improve clinical outcomes. Many of the current therapies for HF, such as diuretics, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs), may have deleterious effects on kidney function, and aldosterone antagonists are often witheld because of the fear of hyperkalemia [9,10]. In addition, a majority of larger trials on the treatment of HF excluded patients with advanced renal dysfunction.

Diuretics are a vital component of symptomatic management of HF. They improve symptoms of acute decompensated HF but have not been shown to improve long-term morbidity and mortality. Aggressive diuretic therapy promotes neurohumoral activation and may worsen CRS. Diuretic resistance is a frequent and ominous feature of the CRS. Potential therapeutic strategies include the addition of a thiazide diuretic, acetazolamide, or spironolactone, or the use of continuous infusions of loop diuretics [7,11]. The last strategy is under investigation in a large multicenter trial [12]. The combination of hypertonic saline and high doses of loop diuretics produces a reduction of neurohumoral activation, significant increases in diuresis and natriuresis, and reductions in hospitalization time and readmission rates in patients with refractory CHF [13,14]. The effect of hypertonic saline on kidney function in patients with decompensated HF is currently being investigated [15].

An alternative strategy to reduce fluid overload is ultrafiltration. Compared with diuretics, ultrafiltration results in increased sodium removal without an increase of sodium delivery to the distal nephron with activation of the tubuloglomerular feedback (TGF). Theoretically, this will result in less activation of the RAAS and the SNS. The UNLOAD trial compared ultrafiltration with intravenous diuretics in patients with acute decompensated HF. Ultrafiltration induced more weight loss and reduced rehospitalization rates without a difference in terms of worsening renal function [16]. A smaller trial found no difference in fluid balance, glomerular filtration rate (GFR), and renal plasma flow [17]. The role of ultrafiltration in patients with CRS is currently being assessed in a multicenter trial [18]. Other strategies to improve cardiac output and relieve congestion, such as cardiac resynchronization therapy, have also been shown to increase GFR in patients with HF [19].

Interventions that inhibit the activity of the RAAS have been shown to reduce morbidity and mortality in patients with HF and to slow or even halt the progression of CKD, especially diabetic nephropathy [20]. However, ACEIs and ARBs are underused in patients with CRS because of the fear of worsening kidney function [21,22]. In patients with moderate renal dysfunction, they appear to have a survival benefit, despite a transient worsening of kidney function in as much as 30% of the patients. In patients with severe renal dysfunction, the trade-off between efficacy and safety remains unknown, and cautious use with close monitoring of kidney function is advised [23]. In view of the risk of hyperkalemia, the concomitant use of ACEIs or ARBs and aldosterone antagonists is also problematic in patients with CRS. In addition, the two large studies on aldosterone antagonists in HF have excluded patients with severe renal failure, and the effect was absent or less pronounced in those with mild kidney injury [24,25].

Natriuretic peptides induce vasodilation and natriuresis and decrease neurohormonal levels, the latter in contrast to diuretics. In addition, they have anti-fibrotic, anti-hypertrophic, anti-inflammatory, lusitropic, and aldosterone-inhibiting properties. Despite symptom relief in HF, a beneficial effect of nesiritide (a recombinant B-type natriuretic peptide) on mortality [26,27] could not be established. Conflicting results with regard to the effect on kidney function (no effect or worsening) exist

[28-30], but no study in patients with HF showed an improvement. The ongoing phase III Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF) will hopefully provide a definite answer [31]. Urodilatin is an A-type natriuretic peptide that can improve symptoms but did not affect mortality or kidney function in patients with decompensated HF [32].

Newer strategies that target renal function in patients with HF are adenosine receptor antagonists and vasopressin antagonists. Renal TGF is a normal homeostatic mechanism to maintain electrolyte and fluid homeostasis. In the setting of HF, the TGF may become maladaptive and result in diuretic resistance and decreased GFR [7]. The TGF is mediated through the adenosine receptor subtype 1 (A1). Blocking this receptor might enhance diuresis and natriuresis with maintained or increased GFR and reduce loop diuretic requirements, as suggested by phase II protocols in patients with CRS [33-36]. The complexity of adenosine physiology mandates that safety be established. Larger phase III trials with these potential new drugs are ungoing [37].

Blockade of the vasopressin V2 receptor in the collecting duct results in increased free water excretion, which theoretically might correct fluid retention and hyponatremia in HF. Tolvaptan, an oral selective V2 receptor blocker, has indeed been shown to result in symptomatic improvement of patients hospitalized for acute HF, without worsening kidney function. However, mortality or HF readmission was not affected [38-40]. Conivaptan is a dual V1 and V2 receptor blocker that, in addition to inducing aquaresis, may reduce systemic vascular resistance and improve systolic function [41,42].

Implications for clinical practice

Treatment of CRS relies mainly on interference with maladaptive neurohumoral activation but remains very challenging because the traditional treatment of CHF may have deleterious effects on kidney function. Investigational drugs targeting the novel pathophysiologic concepts underlying CRS are promising treatment approaches. Thiazide diuretics, acetazolamide, or spironolactone, the use of continuous infusions of loop diuretics, hypertonic saline, and ultrafiltration have shown promise in overcoming the previous challenges of aggressive diuretic therapy. Cardiac resynchronization therapy has been shown to improve GFR in patients with HF. Although ACEIs and ARBs appear to have some benefit on survival, the trade-off between efficacy and safety remains unknown in patients with CRS and therefore they should be used cautiously and with close monitoring of kidney function. The adenosine receptor subtype 1 (A1) and vasopressin antagonists have shown beneficial effects in improving symptoms for patients with acute HF. Ongoing trials will define their clinical efficacy and safety and will hopefully transform the difficult management of patients with CRS.

Abbreviations

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCEND-HF, Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure trial; CHF, congestive heart failure; CKD, chronic kidney disease; CRS, cardiorenal syndrome; GFR, glomerular filtration rate; HF, heart failure; RAAS, renin angiotensin aldosterone system; SNS, sympathetic nervous system; TGF, tubuloglomerular feedback; UNLOAD, ultrafiltration versus intravenous (IV) diuretics for patients hospitalized for acute decompensated heart failure.

Competing interests

The author declares that she has no competing interests.

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