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Minireview

Advances in pathogenesis and current therapeutic strategies for cardiorenal syndrome

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ABSTRACT

Cardiorenal syndrome (CRS) is characterized as a syndrome involving both the cardiovascular system and kidneys. Due to its complexity and high mortality, it has becoming a significant burden and a universal clinical challenge to society worldwide. The mechanisms underlying CRS are potentially multifactorial, including hemodynamic alterations, neurohormonal activation, inflammation, oxidative stress, iron disorders, anemia, and mineral metabolic derangements. Despite the understanding and awareness of CRS gaining attention, appropriate approaches to manage CRS remain deficient. Loop diuretic and thiazides, inhibition of the renin–angiotensin system, vitamin D receptor activation and dopamine and natriuretic peptides could potentially be helpful to improve the prognosis of CRS. Ultrafiltration might be an alternative therapeutic strategy for the loss of liquid. However, adenosine receptor antagonists do not appear to be superior to furosemide in CRS treatment. novel therapeutic approaches should be explored.

Contents

Introduction

Cardiorenal syndrome (CRS) was first described in 1951, initially indicating the renal injury induced by heart failure (Ledoux, 1951). After that, it has been increasingly recognized and understood as a syndrome. CRS is a frequently occurring condition of heart failure concomitant with renal dysfunction (Ronco et al., 2010). Impairment of one can lead to deterioration of the other, which in turn impacts the function of both. According to previous studies, renal dysfunction is one of the strongest independent risk factors and predictors of mortality in patients with heart failure (Forman et al., 2004; Ronco and Cozzolino, 2012). Frequently, patients with heart failure have decreased glomerular filtration rate (GFR). A potential relationship between cardiovascular disease and renal dysfunction is therefore presumed.

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Even though CRS has been intensively studied over the past decade, there are still significant issues regarding its pathologic processes and therapeutic strategies that need to be addressed. It has been speculated that the salt and water retention combined with neurohormonal activation are important impacts of the pathogenesis in CRS (Blair et al., 2007; Sarraf et al., 2009, 2011). Brammah et al. (2003) indicated that treatment of bilateral renal arterial disease could improve the functions of both the heart and the kidney. Bongartz et al. (2005) raised that organ dysfunction in one system affects the other. In 2008, Ronco et al. (2008) proposed five types of CRS based on the distinct sequence of organ injury and failure as well as the clinical situation. Recently, a series of papers reached a consensus for the definition and classification of CRS, epidemiology and diagnostic criteria, and prevention and therapeutic approaches. According to the etiologic and chronologic interactions between cardiac and renal dysfunctions, CRS is classified into five subtypes. Type 1 CRS is defined as acute renal dysfunction caused by acute heart failure where approximately 25% of patients show a rise in serum creatinine and a reduction of urine output after the first several doses of intravenous diuretics. Altered cardiac and renal hemodynamics are believed to be the most important determinants of CRS type 1. Type 2 CRS is characterized by chronic heart failure that leads to chronic renal dysfunction. Accelerated renal cell apoptosis and replacement fibrosis are considered to be the dominant mechanism. Type 3 CRS is acute heart failure after acute kidney injury from inflammatory, toxic, or ischemic insults. This syndrome is precipitated by salt and water overload, acute uremic myocyte dysfunction, and neurohormonal dysregulation. Type 4 CRS is manifested by the acceleration of the progression of chronic heart failure in the setting of chronic kidney disease. Cardiac myocyte dysfunction and fibrosis are believed to be the predominant pathophysiologic mechanism. Type 5 CRS is also called secondary CRS which is due to systemic diseases. In this case, the predominant pathophysiological disturbance is microcirculatory dysfunction as a result of acutely abnormal immune cell signaling, catecholamine cellular toxicity, and enzymatic activation which result in simultaneous organ injury often extending beyond both the heart and the kidneys.

However, although the pathogenesis contains differences among the five types of CRS, the classification depends on the etiologic and chronologic interactions between cardiac and renal dysfunctions but not pathophysiologic characteristics. It is therefore hard to distinguish pathogenesis for each subtype exactly. Actually, they share several signaling pathways, e.g., hemodynamic alterations, neurohormonal effects, and inflammatory components. In terms of therapy, regardless of the specific type and course of development of the CRS, the eventual outcome is heart failure and renal dysfunction. Generally, CRS is a paradoxical condition to manage for relieving congestive symptoms of heart failure, which is limited by impaired renal function. In this review, we will focus on advances in the pathogenesis and therapeutic issues regarding treatment for CRS.

Pathogenesis in CRS

Although CRS has been intensively studied over the past decade, the pathogenesis of CRS is still incompletely understood. It had been thought that the decreased renal perfusion due to the impaired cardiac output in patients with heart failure was the major pathophysiologic mechanism of CRS. However, many patients with CRS actually did not show a decreased cardiac ejection fraction. Recently, new evidence suggests that cardiac and renal dysfunctions often occur simultaneously since they share causes of diseases and pathogenetic mechanisms. The common risk factors, such as hypertension, diabetes, and atherosclerosis, could explain the high prevalence of coexistent cardiac and renal dysfunction in patients with HF. Additionally, the activation of renin–angiotensin–aldosterone (RAA) and sympathetic nervous systems, as well as ischemia, inflammation, and oxidative stress are considered the important determinants of CRS. In the present review, we therefore highlight some of the key concepts of pathophysiology of the CRS.

Hemodynamic alterations

Among patients with heart failure, especially those with end-stage heart dysfunction, left ventricular ejection fraction is markedly decreased and consequently followed by decreased renal perfusion. Due to decreased renal filtration capacity, the renin–angiotensin–aldosterone system and sympathetic nervous system are activated, aggravating sodium retention, volume expansion, and ventricular remodeling (Damman et al., 2007; McCullough and Ahmad, 2011). Alternatively, cardiac low output causes increased central venous pressure and intra-abdominal pressure. Several studies have shown that central venous pressure is the most important determinant of renal dysfunction and the most important independent predictor of mortality (Damman et al., 2009). Moreover, a close relationship was observed between reductions in intra-abdominal pressure and improved renal function (Mullens et al., 2008). However, the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial did not show any associations between hemodynamics and renal impairment (Nohria et al., 2008). Furthermore, Wencker D. et al. thought that hemodynamic disorders could not fully explain the pathogenesis of acute ACS, which indicated that various mechanisms could be involved (Wencker, 2007).

Neurohormonal activation

Both the renin–angiotensin–aldosterone and sympathetic nervous systems are the key regulatory systems for the maintenance of cardiovascular and renal function. The classical renin–angiotensin–aldosterone system consists of several endocrine factors, principally angiotensin II. In order to maintain homeostatic glomerular filtration, angiotensin II causes glomerular efferent arteriole vasoconstriction during the early stages of heart failure. However, chronic activation of the renin–angiotensin–aldosterone system is associated with stimulation of inflammatory pathways, fibrosis, increased oxidative stress, and endothelial dysfunction, consequently leading to the progression of CRS (Cody et al., 1988; Schrier and Abraham, 1999). Chronic volume overload rats had significantly higher kidney angiotensin II levels, increased levels of AT_{1a} receptors and AGT mRNA (Rafiq et al., 2012). Additionally, it has been shown that angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) have potent protective effects on the heart and kidneys independent of their blood pressure lowering effects (Bock and Gottlieb, 2010). The result shown by Masahito O et al. discovered that aliskiren, a renin inhibitor, could suppress oxidative stress and inflammatory factor elevation effectively and indicated that excessive activation of the renin–angiotensin–aldosterone system plays a pivotal role in inducing renal disorder following ventricular dysfunction (Ogawa et al., 2012). Alternatively, the sympathetic nervous system is markedly activated in patients with heart failure and the activation of the sympathetic nervous system exerts unfavorable effects on renal artery constriction and renin release from glomerular cells. Both chronic renal denervation and olmesartan treatment were able to suppress the increase in the related components of the renin–angiotensin–aldosterone system and sympathetic nervous system (Rafiq et al., 2012). Thus, these two systems have cross talk during the CRS and it lays the fundamental groundwork for developing new targeted therapies for CRS.

Inflammation and oxidative stress

As described above, volume overload and venous congestion cause inflammatory activation during heart failure (Colombo et al., 2012). Recently, there has been increasing evidence regarding the role of the inflammatory response during CRS. Circulating levels of tumor necrosis factor-alpha, C-reactive protein, pentraxin 3, interleukin-1 (IL-1), and IL-6 (Gullestad and Aukrust, 2005; Mann et al., 2004; Anker and Coats,