The role of right-sided heart failure in patients with Cardio-Renal Syndrome

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Abstract

Deteriorated renal function in patients with acute or chronic heart failure represents an important clinical challenge of modern medicine. The term Cardio-Renal Syndrome (CRS) has been brought into use to characterize heart-kidney interaction leading to dysfunction of one another. The pathophysiology of impaired renal function in cardiovascular disease is complex and not precisely understood. Recent investigations suggest that management of patients based on just low-flow theory does not lead to improved outcomes. Relative importance of Right-Sided Heart Failure (RSHF) has not been properly evaluated.

This paper provides a concise overview of definition, classification and pathophysiology of the CRS and its subtypes, particularly types 1 and 2 with special emphasis on the role of RSHF and increased Central Venous Pressure (CVP). The role of RSHF in CRS is difficult to ascertain, as it is frequently combined with left sided heart failure and renal dysfunction can also raise right atrial pressure by causing fluid retention, regardless of concomitant cardiac dysfunction. Proper understanding of CRS subtypes is crucial, as therapies directed towards one organ system may have beneficial or unfavorable effects on the other.

Keywords: Cardio-Renal syndrome, Right-sided heart failure, Central venous pressure, eGFR, Low-flow theory

Introduction

Coexistence of cardiac and kidney diseases is fairly common - the prevalence of moderate to severe renal impairment (defined as a Glomerular Filtration Rate (GFR) less than 60 mL/min per 1.73 m²) is approximately 30 to 60 percent in patients with Heart Failure (HF)1,2,3,4,5. Clinical importance of interactions between heart disease and kidney disease is illustrated by the following observations:

- Mortality is increased in patients with HF who have reduced GFR6;
- Patients with chronic kidney disease have an increased risk of both atherosclerotic cardiovascular disease and heart failure and cardiovascular disease is responsible for up to 50 percent of deaths in patients with renal failure7;
- Acute or chronic systemic disorders can cause both cardiac and renal dysfunctions8.

The term Cardio-Renal Syndrome (CRS) has been brought into use in the last decade. Professor Claudio Ronco et al, has defined five subtypes of CRS, which are distinguishable from each other by the clinical course, pathophysiology, diagnostic approaches and management tactics9. CRS involves both - the acute and the chronic conditions which are characterized by the heart's primary, and primary renal injury:

- **Type 1**: Worsening renal function complicates Acute Decompensated Heart Failure (ADHF) and Acute Coronary Syndrome (ACS). Depending on the population, 27%-40% of patients hospitalized for ADHF develop Acute Kidney Injury (AKI). Consequently, CRS type 1 is often seen in the coronary care and intensive care units11,12,13,14;

- **Type 2**: Chronic abnormalities in myocardial function leading to Chronic Kidney Disease (CKD). The “chronic abnormalities” may include many different heart conditions, such as chronic heart failure, congenital heart disease, atrial fibrillation, constrictive pericarditis and chronic coronary heart disease15;

- **Type 3**: Acute renal failure leading to cardiac dysfunction, such as cardiac ischemic syndromes, congestive heart failure, or arrhythmia16. Type 3 emerges less frequently than CRS type 1, but this may be due to the fact that it has been less thoroughly studied then type10;

- **Type 4**: Primary renal disease leading to cardiac dysfunction, such as ventricular hypertrophy, diastolic dysfunction, increased risk of adverse cardiovascular events17,18,19;

- **Type 5**: Systemic illness leading to simultaneous heart and renal failure. This CRS subtype may cover many acute or chronic conditions in which combined heart and kidney dysfunction is observed (e.g. diabetes mellitus, sepsis, lupus, etc.)20.

When reno-parenchymal disease leads to cardiovascular complications, it’s been recommended to name the latter condition as Reno-Cardiac Syndrome (CRS type 3
and type 4)\textsuperscript{14,21}, CRS type 5 is also called a secondary CRS\textsuperscript{20,22}.

The term - Cardio-Renal Cachexia Syndrome (CRCS) has been suggested when there are complex interrelations that involve transition from CRS to cachexia and from cachexia to CRS\textsuperscript{23}.

**Mechanism of renal impairment**

Pathophysiology of reduction in GFR in patients with HF is complex and includes several major factors: abnormalities in systolic and diastolic myocardial performance can lead to a number of hemodynamic derangements, including reduced stroke volume and cardiac output, arterial underfilling, elevated atrial pressures and venous congestion\textsuperscript{24}. These hemodynamic derangements trigger a variety of compensatory neurohormonal adaptations including activation of Sympathetic Nervous System (SNS), the Renin-Angiotensin-Aldosterone System (RAAS) and a range of adverse cellular processes (including oxidative injury and endothelial dysfunction) leading to apoptosis and renal fibrosis\textsuperscript{15,25,26,27,28,29}.

Novel biomarkers of acute cardiac and renal injury have become accessible for the last several years. These include Cystatin C, NGAL (Neutrophil Gelatinase-Associated Lipocalin), KIM-1 (Kidney Injury Molecule 1), NAG (N-Acetyl-β-D Glucosaminidase), IL-1β (Interleukin-18), L-FABP (Liver-Fatty Acid Binding Protein), Cr (Catactic Iron)\textsuperscript{30}. It is expected, that these biomarkers will facilitate making an earlier diagnosis of CRS, as well as identify the specific type of CRS\textsuperscript{31}. Unfortunately, these tests are not widely available yet.

CKD is common and is associated with increased mortality in HF\textsuperscript{32}. Though, it is not clear whether the effect of CKD on mortality varies by Left Ventricular Ejection Fraction (LVEF). The mechanism of acute cardio-renal syndrome (type 1) is difficult to clarify also because of the complex and multifactorial comorbidities associated with acute heart failure syndrome\textsuperscript{33}. Recent investigations suggest that management of patients with primary cardiac and secondary renal dysfunction based only on the low-flow theory does not lead to improved outcomes\textsuperscript{34,35}. Both animal and human studies have shown that Intra-Abdominal and Central Venous Pressure (CVP) elevation, which also increases the renal venous pressure, lead to reduction of GFR\textsuperscript{36,37,38,39,40}. There is a growing evidence to support the roles for elevated Renal Venous Pressure and Intra-Abdominal Pressure (IAP) in development of progressive renal dysfunction in patients with HF\textsuperscript{39,41,42}. The study by Kevin Damman et al. has shown that CVP is associated with impaired renal function and independently related to all-cause mortality in a broad spectrum of patients with cardiovascular disease\textsuperscript{41}. The study by Heiko Uthofft et al. further supported the concept that CVP is an important hemodynamic factor for impaired renal function, especially in combination with decreased cardiac output\textsuperscript{42}.

The study by Ali Ahmed et al. has shown that CKD-associated mortality was higher in those with diastolic than systolic HF\textsuperscript{43}. Diastolic HF or Heart Failure with Preserved Ejection Fraction (HFPEF) is the most frequent form of HF\textsuperscript{44,45,46} (the incidence of HFPEF is reported to include about 50% of the general heart failure population [47]). Coexistence of renal impairment in heart failure with preserved EF is reasonably common (especially in older females with hypertension and/or diabetes), but may be under-diagnosed\textsuperscript{48}. The Cardio-Renal interactions potentially contributing to HFPEF are complex and include volume overload, due to inadequate renal handling of salt or fluid, renal hypertension, or oxidative stress and inflammatory processes\textsuperscript{49,50}.

The above-mentioned evidence dissuading the role of reduced LVEF as the primary driver of renal impairment has prompted researchers to have a closer look into the role of right ventricle (RV) in the pathogenesis of CRS.

**The role of right ventricle**

Awareness about the role of right ventricle in health and disease traditionally has been lagging behind that of the left ventricle\textsuperscript{51}. Even though, right-sided (or right ventricular) heart failure (RSHF) usually occurs as a result of left-sided failure, RV function may be impaired in pulmonary hypertension (PH), chronic obstructive pulmonary disease (COPD), congenital heart disease (CHD), connective tissue diseases, coronary artery disease and in patients with valvular heart disease. When left ventricular function is normal, the term - Isolated Right Ventricular Failure is used (IRVF)\textsuperscript{52}. Data about prevalence of kidney impairment in those patients is uncertain, as it still remains largely under-diagnosed.

Right ventricular dysfunction may play an important and possibly earlier role in the pathophysiology of impaired renal function\textsuperscript{53}, but assessing RV function remains a challenge. At this time, there is no single commonly accepted and generally applicable index of RV function\textsuperscript{54}. Due to the complex anatomy of right ventricular anatomy, only a few echocardiographic parameters are reliable. Tricuspid Anular Plane Systolic Excursion (TAPSE) is a validated parameter of global right ventricular function\textsuperscript{55}. CVP, which is an estimate of Right Atrial Pressure (RAP), can also help to diagnose RSHF, but it should always be considered in conjunction with other cardiovascular parameters, e.g. LVEF, as the right heart sided pressures should indirectly reflect left sided pressures, and the left sided filling pressure may be an indicator of left ventricular function\textsuperscript{56}.

Frank L. Dini et al. studied relationship between RV dysfunction and CKD in outpatients with chronic systolic HF. The authors found that TAPSE and estimated GFR were significantly correlated\textsuperscript{53}. The findings of the study support the concept that venous congestion from backward cardiac failure might be as important as forward failure in the pathophysiology of renal impairment in HF. Elevated renal venous pressure due to RSHF can decrease GFR by increasing interstitial and tubular hy-
dysostatic pressures within the kidneys and by decreasing renal perfusion pressure and renal blood flow. Hypoxia, as well as local and systemic neurohumoral activation from elevated venous pressure may further compromise kidney function in these patients.  

However, despite the above-mentioned reports, the role of right sided heart failure in CRS is difficult to ascertain, because: (I) it is frequently combined with left sided heart failure with or without reduced ejection fraction; and (II) renal dysfunction can also raise RAP by causing fluid retention, regardless of concomitant cardiac dysfunction.  

Conclusion  
Deteriorated renal function in patients with acute or chronic heart failure represents an important clinical challenge of modern medicine. The pathophysiology of impaired renal function in cardiovascular disease is complex and not precisely understood. Recent investigations suggest that IAP and CVP elevation, which also increases the RVP, lead to reduction of GFR. Relative importance of RSHF has not been properly evaluated.  
Proper understanding of bidirectional pathways by which the heart and kidneys influence each other is necessary to define optimal treatment strategies specific to the subtypes, as therapies directed towards one organ system may have beneficial or unfavorable effects on the other.  
In this review we tried to highlight potential role of RSHF and increased CVP in CRS type 1 and type 2. An evaluation of RSHF is complicated, however, TAPSE and CVP, an estimate of RAP, can help to diagnose RSHF, but they should always be considered in conjunction with other cardiovascular parameters. Despite the recent reports, the role of RSHF in CRS is difficult to ascertain, as it is frequently combined with left sided heart failure and renal dysfunction can also raise RAP by causing fluid retention, regardless of concomitant cardiac dysfunction. Additional high-quality studies in patients with coexisting IRVF and kidney disease are needed for proper understanding the role of RV in CRS.  

Disclosures  
The author has nothing to disclose.  

References  


