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PERIPHERAL VASCULAR DISEASE (CJ COOPER AND R GUPTA, SECTION EDITORS)

Renal Artery Stenosis and Congestive Heart Failure: What Do We Really Know?

Rajesh Gupta[1] · Mubbasher Syed[1] · Nikita Ashcherkin[2] · Katherine Chen[2] · Palavi P. Vaidya[2] · Christopher J. Cooper[2]

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Abstract

Purpose of Review Congestive heart failure (CHF) is a major cause of morbidity, mortality, and health care expenditure. Although the role of renal artery stenosis (RAS) in CHF has been known, there are a number of areas of uncertainty.

Recent Findings The prevalence of RAS in subjects with CHF varies from 15 to 54% depending on the cohort studied and the diagnostic modality used to identify RAS. In subjects with CHF, the presence of RAS is associated with worse renal function and a higher risk for mortality during long-term follow-up.

Summary There are many unanswered questions regarding the role of RAS in subjects with CHF. This review highlights those questions and helps to set the research agenda in this area.

Keywords Renal artery stenosis · Congestive heart failure · Cardiorenal syndromes

Introduction

Congestive heart failure (CHF) and renal artery stenosis (RAS) are major causes of morbidity and mortality in the USA and global populations. CHF accounts for over 1 million hospitalizations per year [1]. RAS is prevalent among subjects with atherosclerotic disease such as coronary artery disease (CAD) or peripheral arterial disease (PAD) [2]. A relationship between RAS and flash pulmonary edema was reported by Pickering et al. in 1988 [3]. Pickering reported a case series of subjects with RAS and recurrent "flash pulmonary edema" and found that bilateral renal artery stenosis was highly prevalent in this group. Since that time, there have been significant investigations into the role of RAS and renal artery angioplasty or stent procedures for the treatment of renovascular hypertension [4, 5•]; however, the role of RAS in CHF has received less attention.

Intercommunication between the kidneys and the heart is critically important in people with CHF, and prior studies have demonstrated that renal function plays a critical role in predicting outcomes in patients with heart failure. Worsening renal function is a powerful predictor of adverse events among subjects with CHF [6]. In fact, impaired renal function is a better predictor of mortality in patients with advanced CHF than left ventricular ejection fraction [7]. However, with regard to RAS and CHF, there are many unanswered questions and much need for further research.

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✉ Rajesh Gupta
rajesh.gupta@utoledo.edu

Mubbasher Syed
mubbasher.syed@utoledo.edu

Nikita Ashcherkin
nikita.ashcherkin@rockets.utoledo.edu

Katherine Chen
katherine.chen@rockets.utoledo.edu

Palavi P. Vaidya
palavi.vaidya@rockets.utoledo.edu

Christopher J. Cooper
christopher.cooper@utoledo.edu

[1] Division of Cardiovascular Medicine, College of Medicine and Life Sciences, University of Toledo, 3000 Arlington Ave, MS# 1118, Toledo, OH 43614, USA

[2] Department of Medicine, College of Medicine and Life Sciences, University of Toledo, Toledo, OH 43614, USA

Multiple studies have demonstrated a high prevalence of RAS in subjects with CHF but the effect of RAS on CHF outcomes has been relatively underexplored. A number of ongoing questions remain unanswered. Is RAS associated with intolerance to ACE-I/ARB/ARNI therapy in subjects with CHF? Is RAS associated with worsening renal function during treatment of acute CHF? Does the presence of RAS predict rehospitalization for acute CHF after an initial CHF hospitalization? What is the role of RAS in cardiorenal syndromes? Can renal artery stenting affect CHF outcomes among subjects with concomitant CHF and RAS? Is RAS equally prevalent among subjects with systolic versus diastolic CHF? The purpose of this review article is to summarize what is known and what is not known about RAS and CHF and highlight areas for future investigation.

Underappreciated Prevalence of Concurrent RAS with CHF

Prior studies demonstrate that the RAS and CHF commonly coexist. MacDowall et al. found that 29/86 (34%) of subjects with CHF had concomitant RAS [8]. A more recent study of 366 subjects with heart failure showed that 112 (31%) had coexistent RAS (defined as > 50% stenosis on MRA). Of these 112 subjects with RAS and CHF, 37% had bilateral RAS [9]. A substudy of the EPOCARES clinical trial, which enrolled subjects with CHF and chronic kidney disease (CKD), found a 56.8% (21/37) prevalence of RAS (defined as > 50% stenosis on MRA). Of those 21 subjects with RAS, 8 (38%) were identified with bilateral RAS [10].

Effect of RAS on CHF Prognosis

There are limited studies addressing the prognosis of subjects with concomitant RAS and CHF. A study by de Silva was one of the first to show that CHF patients with RAS had higher mortality rates than those without RAS, with mortality rates of 29% versus 10%, respectively [11]. This study used magnetic resonance angiography (MRA) and used a definition of > 50% stenosis to identify RAS. Out of the study cohort of 135 subjects with CHF, 54% had RAS with at least one renal artery having > 50% stenosis and 24% had bilateral RAS. Subjects with bilateral RAS also had significant worsening renal function over the 3-year follow-up period. There was a 17% reduction in mean eGFR in subjects with bilateral RAS compared with 1% decline in subjects without RAS and a 3% decline in subjects with unilateral RAS.

Bourantas et al. reported the largest cohort of subjects with CHF assessed for RAS [9]. A total of 366 subjects with CHF were assessed for RAS with MRA. RAS was present in 31% of the study subjects. Interestingly, among subjects with CHF and renal dysfunction (defined as eGFR < 60 mL/min/1.73 m^2), 95/366 (26%) had RAS. In a multivariate model, predictors of RAS in this cohort of CHF subjects included ischemic heart disease, declining renal function, and absence of treatment with ACE-I, ARB, or spironolactone. In the Kaplan–Meier analysis of long-term follow-up, RAS was associated with a higher risk of all-cause mortality (Fig. 1).

Interestingly, a prospective cohort study of 83 subjects with RAS assessed NT-proBNP at baseline and found that baseline NT-proBNP predicted long-term survival [12]. Among the subjects with CKD stages 1–3, elevated NT-proBNP had a HR of 3.63 for death. Among the subjects with CKD stages IV–V, the HR for death among subjects with elevated NT-proBNP was 8.30. Therefore, NT-proBNP may be a sensitive marker for cardiac involvement in subjects with RAS and a powerful prognostic factor among subjects with RAS.

Lastly, the RASHEF study was a retrospective cohort study of subjects hospitalized with CHF who also had renal duplex ultrasound performed [13•]. The presence of RAS was defined by duplex criteria as a renal-to-aortic ratio of ≥ 3.5, a peak renal artery systolic velocity of ≥ 200 cm/s, or a renal artery occlusion on ultrasound. The prevalence of RAS in this study was 15%. Among these subjects with CHF, the presence of RAS was associated with a higher mortality rate. By multivariate analysis, RAS was a significant predictor for all-cause death and cardiovascular death (hazard ratio [HR] = 4.2, 95% confidence interval [CI] 1.5–11.2, $P = 0.005$; and HR = 3.5, 95% CI 1.2–10.1, $P = 0.022$, respectively). In summary, RAS appears to be prevalent among subjects with CHF and is associated with adverse events during long-term follow-up, including all-cause mortality.

Pathophysiology of Concomitant CHF and RAS

The physiology of the heart and kidneys is intricately interwoven and there are multiple signaling pathways by which the two organ systems communicate. These pathways include the sympathetic nervous system, renin-angiotensin-aldosterone (RAAS) system, and the natriuretic peptide system. All of these pathways are involved in CHF pathogenesis and are also affected by RAS.

Renal artery stenosis could have several implications for subjects with CHF. RAS may lead to decreased renal perfusion and GFR. The kidneys attempt to maintain renal perfusion with activation of the RAAS pathway and autoregulation of renal vasculature [14]. In patients with CHF, activation of RAAS has several negative consequences. Activation of renin leads to systemic vasoconstriction through the activation of the sympathetic nervous system (SNS) and via angiotensin II and aldosterone. Additionally, renin action leads to increased fluid retention. This exacerbates congestion in heart

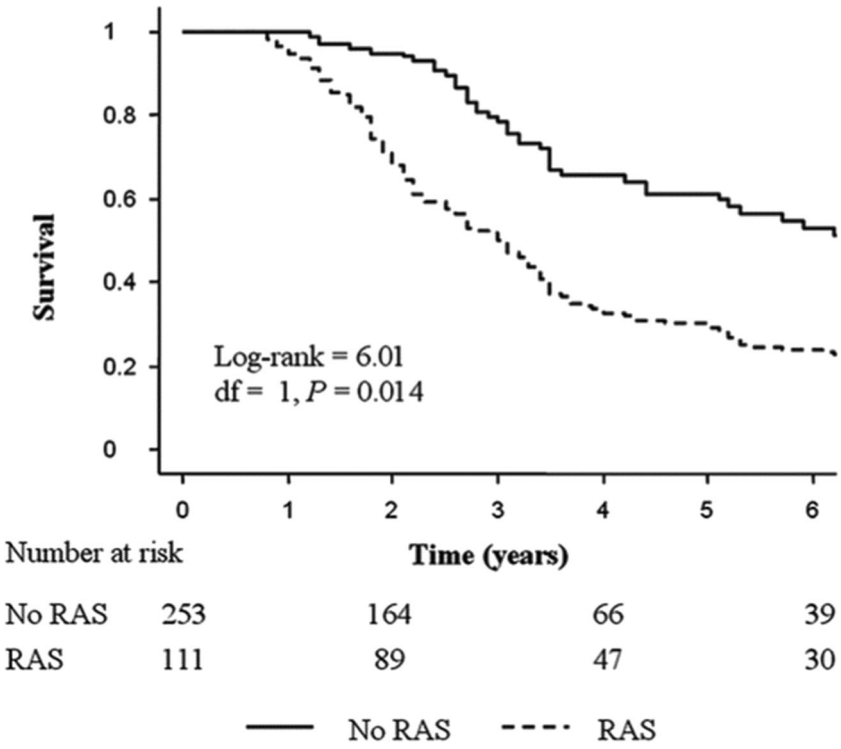

Fig. 1 The Kaplan–Meier plot showing survival for CHF patients with and without renal artery stenosis (RAS). (From Bourantas et al., Copyright © 2012 John Wiley & Sons, Inc. Reprinted with permission) [9]

failure patients. In addition to short-term changes, there are also long-term changes in cardiac remodeling. Prior studies have demonstrated high rates of left ventricular hypertrophy among subjects with RAS [15].

Inhibition of the RAAS activation is typically achieved in CHF patients through the use of ACE-I, ARB, or now with ARNI. However, in patients with renal artery stenosis, this may lead to further decreased renal perfusion and may result in acute kidney injury in some patients with RAS. Intolerance to ACE-I/ARB/ARNI therapy and WRF during acute CHF are common clinical problems for heart failure patients. It is not known if subjects that cannot tolerate ACE-I/ARB/ARNI therapy have a higher prevalence of RAS, although Bourantas et al. did find that the absence of ACE-I, ARB, or spironolactone in their study of CHF subjects was an independent predictor of RAS [9]. In addition, the relation between RAS and worsening renal function during acute exacerbations of CHF is also not well described.

RAS and Acute CHF: the Vulnerable Phase

The susceptibility of ischemic kidney due to RAS may be exacerbated in acute CHF. The ischemic kidney may have altered renal perfusion and may activate adaptive mechanisms to maintain glomerular filtration rate. Subjects with acute CHF can experience an increase in renal venous pressure from baseline levels of approximately 5 mmHg up to 15–20 mmHg or higher in acute CHF. This increase in renal venous pressure can exacerbate worsening renal perfusion and the risk for acute kidney injury (AKI). In subjects with RAS, the ischemic kidney may be dealing with concomitant decreases in arterial perfusion due to the pressure loss in the renal artery. Such subjects may be particularly vulnerable to hemodynamic changes that occur with acute CHF, including both decreased cardiac output and increased renal venous pressure.

Worsening renal function during acute CHF has been classically associated with decreased cardiac output in CHF which leads to hypoperfusion of the kidney. However, more recent research indicates that this may not be the predominant hemodynamic factor leading to decreased renal function in acute CHF. Patients with acute CHF who developed worsening renal function did not have lower cardiac index levels compared with those without worsening renal function [16]. Research studies have suggested that the more predictive hemodynamic variable may be renal venous pressure and that right atrial pressure approximates renal venous pressure. Mullens et al. evaluated 145 people with acute decompensated heart failure for WRF. Elevated central venous pressure in patients with acute CHF was noted at both admission and follow-up. Patients who had a central venous pressure (CVP) of less than 8 mmHg were less likely to develop WRF. Additionally, CVP predicts the risk of WRF across the spectrums of other hemodynamic variables including cardiac index [16]. Another study observing the relationship among venous congestion and renal failure in patients with

CHF found that there was an inverse relationship between the mean right atrial pressure and both renal plasma flow (RPF) and glomerular filtration rate (GFR) [17•]. Clearly, the hemodynamic effects of decompensated CHF on the kidney are complex. The specific hemodynamic effects of decompensated CHF on the ischemic kidney affected by RAS are even more complex and less studied. There is an unmet need for additional studies on the effects of RAS in patients with CHF. While there are many different variables at play, renal perfusion and renal venous pressure seem to have a large influence on predicting cardiorenal outcomes in subjects with CHF.

Review of Treatment Guidelines

Treatment guidelines for RAS patients presenting with hypertension are now well established. The results of the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) randomized controlled trial demonstrated that among hypertensive patients, optimal medical therapy is equivalent to OMT plus renal artery stenting [4]. However, with regard to CHF, the American College of Cardiology and American Heart Association (ACC/AHA) guidelines regarding treatment of RAS patients with CHF recommend that physicians proceed with caution due to the lack of randomized clinical trial data [18]. The ACC/AHA 2005 guidelines state that for CHF patients with hemodynamically significant RAS, the class I treatment is renal percutaneous revascularization. In conclusion, the guidelines caution physicians on implementing revascularization unless RAS is identified as the suggested cause of hemodynamic instability in patients with CHF. The ACC/AHA guidelines emphasize that the current data is based only on a few small prospective case series without large clinical trial data [18].

Small case series of subjects with CHF and RAS undergoing renal artery stenting have reported improved outcomes; however, these studies are limited by small sample size and their observational nature [19, 20]. There are no randomized controlled trial data on the effects of renal artery stenting among subjects with CHF and RAS.

As noted above, the CORAL trial showed that hypertensive RAS patients who underwent stenting, in addition to medical therapy, did not show improvement compared with those who were treated with optimal medical therapy alone [4]. The CORAL study had subjects with known CHF at baseline and others that developed CHF during the study follow-up. Further analysis may provide important insights about the interaction between RAS and CHF. These findings emphasize that additional studies are required to understand the optimal treatment for patients presenting with both RAS and CHF.

Conclusion and Future Directions

There is an unmet need to determine the importance of RAS in contemporary management of CHF. The existing literature is limited in size and scope and thoroughness. Despite Pickering's description greater than 30 years ago, many important questions remain unanswered. Should diagnostic studies for RAS be pursued in subjects with CHF? If so, in which subgroups or which types of patient presentations? Given the frequency of CHF and RAS, these important issues deserve further investigation. Future studies must identify the prevalence of RAS in contemporary cohorts of subjects with HFrEF or HFpEF. The role of RAS in worsening renal function during acute CHF deserves further investigation.

Compliance with Ethical Standards

Conflict of Interest Christopher J. Cooper was the PI for the CORAL study. In addition, Dr. Cooper has a pending patent on Thermomorph.

Rajesh Gupta, Mubbasher Syed, Nikita Ashcherkin, Katherine Chen, and Palavi P. Vaidya declare that they have no conflict of interest.

Human and Animals Rights and Informed Consent All reported studies with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional and national research committee standards, and institutional research guidelines).

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