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Heart failure in subjects with chronic kidney disease: Best management practices

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Abstract

Renal dysfunction is common in patients with heart failure (HF) and can complicate HF therapy. Treating patients with HF and kidney disease is difficult and requires careful assessment, monitoring and balancing of risk between potential benefits of treatment and adverse impact on renal function. In this review, we address the pathophysiological contexts and management options in this adversarial relation between the heart and the kidney, which exists in a substantial proportion of HF patients. Angiotensin converting enzyme inhibitors and β-blockers are associated with similar reductions in mortality in patients with and without renal insufficiency but usually are less often prescribed in patients with renal insufficiency. Careful monitoring of side effects and renal function should be done in all patients with renal insufficiency and prompt measures should be adopted to prevent further complications.

Key words: Kidney disease; Heart failure; Angiotensin; Sympathetic nervous system; Left ventricular hypertrophy

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INTRODUCTION

Heart failure (HF) is the fastest growing cardiovascular diagnosis in the United States. The prevalence of symptomatic HF is approximately 2% in adults with an age greater than 45 years[1]. The annual incidence of HF is nearly 10 cases/1000 in patients ⩾ 65 years and the life time risk of developing HF is estimated to be 20%[2]. Chronic kidney disease (CKD) is present in 10% of the general population and is recognized as one of the major risk factors for cardiovascular disease. Renal function is a dynamic process that may worsen or improve in relatively short periods of time, and is an under-appreciated prognostic factor in HF. Furthermore, renal insufficiency is commonly viewed as a relative contraindication to some proven HF therapies[3]. Renal dysfunction is common in HF patients with studies showing that stage Ⅲ CKD; i.e. an estimated glomerular filtration rate (eGFR) of 60 mL/min per 1.73 m^2 or less, is present in 35%-50% of HF patients[4].

In the last two decades, successful development of a number of therapies such as angiotensin converting

enzyme inhibitors, angiotensin receptor blockers (ARB), β blockers, aldosterone antagonists, implantable cardioverter defibrillators and cardiac resynchronization therapy have all been shown to reduce mortality and morbidity among patients with stable systolic HF in large, prospective randomized trials. However, patients with marked impairment of renal function were generally excluded from these studies.

The prospective outcomes study in heart failure[5] showed that the presence of worsening renal function [defined as an increase in serum creatinine ⩾ 26 μmol/L (0.5 mg/dL) from admission value] in decompensated HF was associated with longer duration of hospital stay (median of 11 d, $P = 0.006$). A sub-analysis of the candesartan in HF: assessment of reduction in morbidity and mortality database[6] revealed that the risk of cardiovascular death or hospitalization for worsening HF was significantly increased in subjects with eGFR less than 60 mL/min per 1.73 m^2, with an adjusted hazard ratio of 1.54 for patients with eGFR of 45-60 mL/min per 1.73 m^2 and 1.86 for those with eGFR < 45 mL/min per 1.73 m^2 ($P < 0.001$).

PATHOPHYSIOLOGIC CHANGES IN CKD AND HF

The relationship between the CKD and HF is an interdependent process, with impaired renal function increasing the risk of HF[7]. The neurohormonal response associated with both heart and renal failure has been proposed as a key link between the two syndromes and has the capability of amplifying both disease processes[8]. On the one hand, activation of the renin-angiotensin-aldosterone system and sympathetic nervous system promotes deleterious myocardial remodeling and accelerated atherosclerosis leading to increased prevalence of HF, coronary artery disease, stroke and peripheral arterial disease. On the other hand, neurohormonal activation induces renal vasoconstriction, intraglomerular hypertension, glomerulonecrosis and tubulointerstitial fibrosis leading to progressive kidney disease. This mutual interaction triggers a vicious circle in which renal insufficiency alters cardiac performance, which in turn leads to further impairment of renal function. For example, a recent study by Damman *et al*[9] showed that renal blood flow and vascular congestion are major determinants of GFR in patients with cardiac dysfunction.

B-TYPE NATRIURETIC PEPTIDE VALUES AND CKD

B-type natriuretic peptide (BNP) is produced by ventricular myocytes, is released in response to muscle stretch and is a useful marker in HF diagnosis and treatment[10]. Normal BNP has a high negative predictive value, effectively excluding HF in both dialysis and non dialysis patients with CKD. Specificity of BNP is lower at all stages of renal impairment.

BNP may be affected by left ventricular hypertrophy (LVH) in patients with chronic renal disease. One study showed that in stable CKD patients, BNP values were elevated only in those with coexistent LVH[11]. The role of BNP values in assessing volume overload in CKD patients is less clear than in patients with normal renal function. High atrial pressures, high aortic pressure and increased ventricular mass are common in CKD patients and have been associated with an increased BNP concentration. Additionally, BNP may be elevated secondarily to decreased renal filtration or decreased clearance by the kidneys. Thus, BNP values may be elevated in patients with renal dysfunction, even in the absence of clinically significant HF[12]. BNP values may still be a useful test for diagnosing HF in the presence of CKD; however, this would require an appropriate upward adjustment of reference ranges.

DIALYSIS PATIENTS AND HF

HF is present in more than one third of dialysis patients[13] with an incidence of 71 per 1000 person-years. For most patients, dialysis is performed 2-3 times per wk, and body water accumulates and fluctuates in between dialysis sessions, which plays a critical role in the development of LVH, which in turn predisposes to CHF[14]. Records from the US renal data system[15] have shown that hemodialysis is an independent risk factor for the development of HF with a 2 years mortality as high as 51%. In addition, a significant percentage of cardiac mortality is due to sudden death which appears to be temporally related to the dialysis procedure. A prospective study of hemodialysis patients identified older age, anemia, hypoalbuminemia, hypertension and systolic dysfunction as risk factors for the development of HF in dialysis patients[16].

MANAGEMENT OF HF IN PATIENTS WITH CKD

The co-existence of CKD and HF has major clinical implications as baseline renal function is a strong determinant of outcome in patients with HF. Moreover, renal function is an important factor in the management of HF as it alters the pharmacokinetics and pharmacodynamics of several cardiovascular medications, necessitating drug dose adjustments. Conversely, certain cardiovascular medications can interfere with renal function and, hence, must be administered with caution in patients with underlying CKD.

Because patients with CKD have been relatively underrepresented in HF clinical trials, evidence based management of patients with concomitant CKD and HF is limited[17]. Therefore, treatment strategies in such patients, including those described in this review, are based mainly on results of observational data from unselected cohorts, or from post-hoc analysis of clinical trials in which patient sub-groups with renal dysfunction were included.

Diuretics

Diuretics have a major clinical role in reducing fluid overload in patients with chronic HF and pulmonary congestion[18]. The selection of the type of diuretic and dosage depend on both the level of glomerular filtration rate and the degree of fluid overload. Loop diuretics should be used as first-line agents in patients with a glomerular filtration rate of less than 30 mL/min per 1.73 m^2, because thiazide diuretics are relatively ineffective in these patients when used alone[19]. A number of strategies can improve loop diuretic responsiveness in chronic HF patients with renal insufficiency[20]. Salt intake should be reduced to no more than 2 g daily. The dosage of the loop diuretic should be progressively increased (to reach appropriate levels of the drug in the tubular site of action) until the effective dose is reached. Intravenous bolus administration is often more effective than an equivalent oral dose, because bypassing the gastrointestinal tract overcomes impaired drug absorption due to gut edema seen in advanced HF. The effective oral or intravenous dose of loop diuretics should be administered as often as needed to maintain the response. If, despite the above measures, diuretic resistance still persists, sequential blockade of sodium reabsorption in the nephron can be instituted by administering a distal-acting diuretic, such as hydrochlorothiazide or metolazone, along with a loop diuretic in a dose determined according to the patient's renal function.

Continuous intravenous infusion of diuretics may be more effective in resistant cases. This process, by maintaining a constant rate of drug excretion, prevents the post-diuretic salt retention associated with sequential doses[21].

Combination diuretic therapy requires close monitoring because it carries a considerable risk of adverse effects including a significant decrease in renal function, hypovolemia, hypokalemia and hyponatremia.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are the cornerstone of HF therapy and improve survival in patients with HF and left ventricular dysfunction. Studies have shown the efficacy of ACE inhibitors in all symptomatic classes of systolic HF patients[22]. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)[23], a trial of ACE inhibitor vs. placebo in patients with severe HF, included the highest proportion of patients with renal insufficiency among published ACE inhibitor trials. The stated enrollment criteria for CONSENSUS excluded patients with a serum creatinine level greater than 300 μmol/L (3.4 mg/dL); however, only 26 of 253 participants had a serum creatinine level greater than 175 μmol/L (2.0 mg/dL) and none had a serum creatinine level greater than 250 μmol/L (2.8 mg/dL). The median serum creatinine level was 123 μmol/L (1.4 mg/dL), and the mean estimated GFR was 45 mL/min per 1.73 m^2, indicating moderate renal insufficiency on average. Participants assigned to the enalapril group of the study had 31% lower mortality at 1 year, and those with baseline serum creatinine levels greater than and less than the median had similar survival benefit[24]. However, the study did not include many patients with severe renal insufficiency (estimated GFR < 30 mL/min per 1.73 m^2); hence the tradeoff between efficacy and safety of ACE inhibitors in these patients remains unknown. Careful use of ACE inhibitors should be attempted in patients with severe renal insufficiency because of the potential to improve survival; however, many patients will not tolerate these agents because of hyperkalemia and worsened renal function.

A meta-analysis of five randomized trials of ACE inhibitor therapy in patients with HF showed that although the proportion of patients who developed renal dysfunction was higher in the ACE inhibitor groups than in the placebo groups, drug discontinuation was required in only a small percentage of patients, and renal function returned to baseline in most patients even without dose adjustment[25]. A retrospective analysis of the studies of left ventricular dysfunction (SOLVD) has shown that the use of ACE inhibitors was associated with a reduced risk of mortality, even at moderately and severely depressed levels of glomerular filtration rate, and did not have an adverse impact on kidney function[26]. Therefore, in patients with chronic HF, mild-to-moderate renal insufficiency should not be viewed as a contraindication to ACE inhibitor therapy, and a mild and nonprogressive worsening of renal function during initiation of therapy should not be considered an indication to discontinue treatment, as the drug may offer the dual benefit of reducing disease progression in both the heart and the kidney[27]. In patients with moderate or severe renal insufficiency, therapy with low doses of ACE inhibitors should be initiated and the dose should be increased gradually with careful monitoring of renal function and serum electrolytes[28]. When the initiation of ACE inhibitor therapy leads to an increase in serum creatinine levels of more than 30% above baseline, several strategies have been suggested[29]. First, ACE inhibitors should be discontinued, and the patients should be evaluated for conditions causing renal hypoperfusion in which the use of ACE inhibitors may result in acute renal failure, such as excessive depletion of circulating volume due to intensive diuretic treatment, concurrent administration of vasoconstrictor agents [most commonly, nonsteroidal anti-inflammatory drugs (NSAIDs)] and severe bilateral renal artery stenosis. Unless renal vascular disease is present, therapy with an ACE inhibitor can be reinstituted after correction of the underlying cause of reduced renal perfusion[30]. The risk of hyperkalemia associated with the use of ACE inhibitors in patients with HF and renal dysfunction is also a source of concern. Several measures may be used to minimize the risk of hyperkalemia in such patients, including discontinuation of drugs known to interfere with renal potassium excretion (e.g. NSAIDs, including cyclooxygenase-2 inhibitors), administration of a low potassium diet, as well as sodium bicarbonate in patients with metabolic acidosis[31]. A potassium level

of ⩾ 5.5 mEq/L should prompt a reduction in the ACE inhibitor dose.

Angiotensin Ⅱ receptor blockers

There is evidence that angiotensin Ⅱ is produced in the myocardium through alternative pathways independent of ACE that involve enzymes such as chymase, which are not blocked by ACE inhibitors[32]. An augmented activity of these local pathways may lead to increased production of angiotensin Ⅱ in patients with HF, and angiotensin Ⅱ is a major adverse influence of cardiac remodeling and dysfunction.

The angiotensin Ⅱ receptor blockers have been compared with ACE inhibitors regarding their effect on survival and renal complications in HF patients. Although the ELITE (Evaluation of Losartan in the Elderly) trial[33] found a mortality benefit in favor of losartan compared with captopril, the larger ELITE-2 trial that followed did not confirm this finding; rather, it found no difference[34]. Unfortunately, patients who experience hyperkalemia or worsened renal function while taking ACE inhibitors are likely to have the same complications with an ARB[35]. Therefore, at present there are two settings in which angiotensin Ⅱ receptor blockers might be used in HF: as an alternative in patients intolerant of ACE inhibitors due to cough, and in combination with ACE inhibitors in patients who remain severely symptomatic on conventional therapy[36].

β-blockers

β-blockers counteract the harmful effects of sympathetic nervous system activation in HF[37]. In addition to its antiarrhythmic properties and protection against sudden death, β blockade may also improve left ventricular remodeling and increase the left ventricular ejection fraction independent of the cause of HF. Therefore, β-blockers are recommended for all patients with stable mild, moderate or severe HF who are on standard treatment including diuretics and ACE inhibitors[38]. The efficacy of β blockers in HF is not influenced by a reduction in glomerular filtration rate. In a retrospective analysis of the Cardiac Insufficiency Bisoprolol Study Ⅱ[39], as well as in several nonrandomized prospective investigations[40,41], the favorable effects of β-blocking therapy on total mortality and rate of hospitalization did not differ in patients with and without moderate or severe renal insufficiency. In the SOLVD study, treatment with β-blockers was associated with a 30% decrease in the risk of worsening renal function, both in the ACE inhibitor and the placebo groups[42]. Because metoprolol and carvedilol are predominantly cleared by the liver, these agents may be safer in patients with renal insufficiency[43].

Spironolactone

High levels of aldosterone have deleterious effects on the heart by promoting the development of cardiac hypertrophy and fibrosis, as well as by contributing to the development of arrhythmias. In patients with HF, aldosterone antagonists counteract these negative effects[44]. In the Randomized Aldactone Evaluation Study (RALES), spironolactone reduced mortality by 30% in patients with severe HF[45]. The RALES investigators excluded patients with a serum creatinine level of 221 μmol/L (2.5 mg/dL) or greater; the median creatinine level in enrolled subjects was 106 μmol/L (1.2 mg/dL). A significant treatment benefit was observed in patients with creatinine levels greater than and less than the median. Only 2% of patients assigned to spironolactone in RALES experienced serious hyperkalemia, and the study did not report an association of renal function with hyperkalemia. Patients in RALES, however, were treated with an average furosemide dose of 80 mg, which may have limited the incidence of hyperkalemia. The proportions of patients in RALES with an estimated GFR less than 30 mL/min per 1.73 m^2 and 30-60 mL/min per 1.73 m^2 have not been published. Thus, spironolactone should not be used in HF patients whose GFR is less than 30 mL/min per 1.73 m^2 and should be used cautiously in patients with an eGFR of 30-60 mL/min per 1.73 m^2, at a dosage no higher than 25 mg/d.

Digoxin

The clearance of digoxin varies linearly with GFR; hence, renal function may affect the safety profile of digoxin[46]. No studies have evaluated whether the effect of digoxin on clinical outcomes is influenced by renal function. The Digitalis Investigation Group (DIG) trial evaluated the efficacy of digoxin in a double blinded placebo controlled manner[47]. An exclusion criterion in the DIG trial was a serum creatinine level greater than 265 μmol/L (3.0 mg/dL), and the median creatinine levels were 115 μmol/L (1.3 mg/dL) in males and 97 μmol/L (1.1 mg/dL) in females. Overall, digoxin did not affect survival but led to a 28% reduction in HF hospitalizations. To be used safely in patients with HF and renal insufficiency, digoxin therapy should be initiated without a loading dose and maintained at a low dose (0.125 mg), perhaps on alternating days and serum digoxin levels should be monitored to maintain a serum concentration in the acceptable range of 0.5-1.0 ng/mL[48], and patients should be monitored carefully for symptoms and signs of digoxin toxicity.

CONCLUSION

CKD is common among patients with HF and is independently associated with an increased morbidity and mortality in this population. Treating patients with HF and kidney disease requires careful balancing of risk to benefit ratio of therapeutic agents. Rather than relying on serum creatinine levels, clinicians should estimate GFR to categorize renal function. The available data indicate that ACE inhibitors offer a survival advantage in patients with HF with mild and moderate renal insufficiency; however, their use in patients with severe renal insufficiency requires caution because of the potential

risk for adverse events. The effect of β-blockers on improving HF survival is less likely to be affected by renal function. Diuretic doses should be adjusted in patients with renal failure with careful monitoring of side effects, including worsening renal function. Aldosterone inhibitors, although associated with improved survival, should be used with great caution in patients, and only in those with mild renal dysfunction.

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