What Physicians Need to Know About Renal Function in Outpatients with Heart Failure

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Key Words

Cardiorenal syndrome · Renal dysfunction · Heart failure · Treatment

Abstract

The majority of outpatients with heart failure (HF) have chronic kidney disease (CKD) as an important comorbidity. Both glomerular filtration rate and abnormal urinary albumin excretion are major predictors of outcome in HF patients. Despite this, patients with renal dysfunction have been systematically excluded from the large randomized HF trials. There is lack of evidence for optimal treatment in these cardiorenal patients and treatment nihilism may account in part for their bad prognosis. Identifying and monitoring the progression of renal disease and making an effort to preserve renal function should be an important task in the management of all patients with HF. In this review, the current understanding of the pathophysiology of renal dysfunction in outpatients with HF will be summarized. Furthermore, important principles of the identification and management of cardiorenal patients will be described in order to make the physician more capable of managing outpatients with HF and renal dysfunction.

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Introduction

Heart failure (HF) is a clinical syndrome in which patients have symptoms or signs of HF and objective evidence of an abnormal structure or function of the heart at rest, usually verified by echocardiographic measurement [1]. The prevalence of HF is between 2 and 3% in the general population and rises sharply in the elderly. In 70- to 80-year-old people the prevalence is estimated to be between 10 and 20%. Coronary heart disease is the most prevalent cause of HF. The overall prevalence of HF is growing as the population is aging and modern treatment modalities have prolonged the survival of patients suffering from coronary disease. Patients with HF experience high morbidity and mortality, and de novo or decompensated HF accounts for a substantial proportion of hospitalized patients.

Renal disease is an underestimated comorbidity in patients with HF. Worsening renal function affects 25% of hospitalized HF patients and is a strong independent predictor of in-hospital as well as 1-year mortality [2, 3]. In outpatients with HF, the majority also have concomitant chronic kidney disease (CKD), and both reduced glomerular filtration rate (GFR) and abnormal urinary albumin

Table 1. Definition and prevalence of CKD in the general population and among HF patients

CKD stage	Description	GFR, ml/min/1.73 m ²	Prevalence in the general population, %	Prevalence in HFREF, %
1	Kidney damage with normal GFR	≥90	3.3	2.8
2	Kidney damage with mild reduced GFR	60–89	3.0	10.6
3	Moderate renal dysfunction	30–59	4.3	45.5
4	Severe renal dysfunction	15–29	0.2	7.8
5	End-stage renal disease	<15	0.2	1.3

Prevalence of CKD in HF is provided for HF patients with reduced ejection fraction (HFREF). Kidney damage is defined as structural kidney disease and/or persistent elevated urinary albumin excretion. Data on the prevalence of CKD in HF patients with preserved ejection fraction are not available, but the GFR distribution is similar [5, 10].

excretion are major predictors of outcome in HF patients [4, 5]. Modern HF treatment recommendations are based on large randomized trials that have largely excluded renal patients. Treatment nihilism due to a lack of evidence and fear of adverse events may contribute to the high morbidity and mortality in cardiorenal patients [6]. In this review the current understanding of the pathophysiology of renal dysfunction in outpatients with HF will be described and important practical principles for the management of patients with HF and renal dysfunction will be highlighted.

Epidemiology of CKD in HF Patients

CKD is defined as the persistent presence of markers of kidney damage and/or reduction in GFR (table 1) [7]. CKD affects more than 10% of the general population and is a strong predictor of all-cause and cardiovascular mortality [8, 9]. In HF patients, renal dysfunction determined by a reduced GFR is far more prevalent than in the general population. About 70% of HF patients with reduced systolic function may be classified as having CKD (table 1) [5, 10]. Furthermore, more than 50% of HF patients have moderate-to-severe renal dysfunction (GFR <60 ml/min) irrespective of systolic function [10]. Both reduced GFR and abnormal urinary albumin excretion are strong independent predictors of all-cause mortality in HF patients [4, 5, 10–13]. Furthermore, worsening renal function during follow-up predicts higher rates of mortality and hospitalization [2, 12]. Hence, to identify, monitor and preserve renal function should be an important priority in the management and follow-up of HF patients.

How to Identify Renal Disease

Healthy kidneys contain about 2 million nephrons. A nephron consists of a glomerulus and an adjacent tubulus. Kidney diseases are largely classified into glomerular or tubulointerstitial diseases depending on the initial site of damage. However, as the nephron is a continuum, normal nephron functioning depends on both a healthy glomerulus and tubulus. Initial damage to either of the structures will affect the function of the entire nephron.

GFR is the parameter used to monitor kidney function, but cannot be directly measured. During ideal conditions, the urinary clearance of a freely filtered substance will reflect the GFR if plasma concentrations are stable and the substance is neither reabsorbed nor secreted in the tubulus. Inulin is a molecule that fulfills these criteria if infused continuously, and inulin clearance is considered the gold standard of GFR measurement. However, inulin clearance is demanding and not useful in clinical practice.

Serum-creatinine has for decades been used as a marker of renal function. Creatinine is produced at a steady rate in skeletal muscle cells and released into the circulation. Creatinine is freely filtered in the glomerulus, and modestly secreted in the tubular system. Because of the tubular secretion, measurement of creatinine clearance will systematically overestimate the GFR. Serum creatinine rises with declining GFR, but the rise will not be linear (fig. 1). Furthermore, the relation to GFR will depend on muscle mass. As HF patients are generally elderly and often have a low muscle mass, GFR could already have been substantially reduced when serum-creatinine levels rise above reference levels (fig. 1). Serum-creatinine is

Fig. 1. Relationship between serum creatinine and GFR. Serum creatinine and GFR are not linearly related and serum creatinine is dependent on both renal function and muscle mass. As a consequence, renal function may be substantially reduced when serum creatinine levels rise above reference levels in HF patients.

therefore an insensitive marker of renal dysfunction in HF patients.

Algorithms for GFR estimation were developed to better classify the severity of renal function. The simplified modification of diet in renal disease (MDRD) formula provided an acceptable estimate of GFR (eGFR) using serum creatinine, age, gender and ethnicity [14]. It was easily available in clinical practice, provided important prognostic information in CKD patients and formed the basis of CKD staging and guidelines [7]. The MDRD formula is still the best validated for GFR estimation in patients with HF [15]. Further elaboration of the formulas has made GFR estimation even more accurate. The newer Chronic Kidney Disease-Epidemiology Collaboration Group (CKD-EPI) formula may lead to higher estimates of renal dysfunction in HF patients and a more accurate categorization of mortality risk [10], but the MDRD formula is still considered a suitable and easily available tool in daily practice.

Besides eGFR, urinary albumin excretion is an important variable to identify and monitor kidney disease. Urinary albumin excretion should be measured with the urinary albumin/creatinine ratio. The ratio may be measured in spot urine, for which a morning sample is preferred. Microalbuminuria is defined as a ratio between 3 and 30 mg/mmol while a ratio above 30 mg/mmol defers albuminuria. Albuminuria or persistent microalbuminuria is consistent with renal disease [16], and is an independent predictor of cardiovascular disease in the general population [9]. In HF patients, abnormal urinary albumin excretion might be an early marker of kidney infection and is a strong predictor of prognosis [13]. Hence, the albumin/creatinine ratio should be regularly measured together with eGFR in HF patients to monitor kidney disease.

Reasons for Reduced Renal Function in HF Patients

To understand how HF contributes to renal dysfunction, one must briefly consider the renal hemodynamics. GFR is the product of the renal blood flow and average filtration fraction in glomeruli. The filtration fraction is the proportion of the renal blood flow that is filtered across the glomerular filtration barrier. In addition to the properties and surface of the glomerular barrier, the filtration fraction is determined by Starling forces, i.e. the difference in hydrostatic and oncotic pressure between the capillaries in the glomeruli and Bowman's space. At normal physiological conditions renal blood flow is about 1.2 liters/min and the filtration fraction is about 10%, giving a GFR of about 100 ml/min in a healthy individual. The kidneys are able to adjust the vascular resistance in response to changes in arterial pressure to maintain renal blood flow and GFR at a constant level as blood pressure fluctuates between 70 and 180 mm Hg (autoregulation).

Various stimuli may modulate the autoregulation of renal blood flow and GFR (fig. 2). Most important are the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). Both the RAAS and SNS are potent vasoconstrictors in the kidneys; angiotensin II constricts the efferent arteriole in particular, while norepinephrine acts primarily on the afferent arteriole (fig. 2).

Neurohormonal activation, including both the RAAS and SNS, is a hallmark of HF and affects the renal blood flow. A 25% reduction in cardiac output will lead to a 50% decrease in renal perfusion [17]. GFR is initially relatively preserved, as autoregulation and efferent vasoconstriction by angiotensin II increase the filtration fraction. However, redirection of blood from the medullary areas

Fig. 2. Renal hemodynamics. The GFR is a product of renal blood flow (RBF) and average filtration fraction (FF) in the glomeruli. Various stimuli may affect the vascular tone in the afferent (aff) or efferent (eff) arteriole. Vasoconstriction is illustrated with converging arrows while vasodilation is illustrated with diverging arrows. The change in GFR is a result of the effect on the renal blood flow and filtration fraction. α_1 blockade = α_1 sympathetic blocking drugs; Ca blockade = calcium-blocking drugs; NSAIDs = nonsteroidal anti-inflammatory drugs.

Fig. 3. How HF contributes to renal dysfunction. Neurohormonal activation and renal hemodynamics counteracts to cause hypoxic and inflammatory tubular injury. Tubular injury may lead to nephron damage and progressive renal dysfunction. Comorbidities, therapeutic interventions, inflammatory and oxidative mediators, among others, will augment the tubular and glomerular changes in a complex vicious crosstalk and add to the progressive renal dysfunction.

of the kidney in states with compromised renal blood flow may cause hypoxic injury of high-metabolic renal tubular cells [18]. Tubular hypoxic injury initiates progressive nephron loss and progressive renal failure. Microalbuminuria in HF patients could reflect early tubular damage

caused by reduced renal blood flow due to impaired reabsorption of filtered albumin in damaged tubular cells [13].

Organ congestion is an important sign of HF, and is closely associated with neurohormonal activation. Both the RAAS and SNS lead to retention of sodium and water.

Increased renal venous pressure could directly affect the Starling forces by lowering the glomerular filtration gradient. In addition, renal congestion may cause tubulointerstitial inflammation that contribute to progressive nephron damage [19].

Hypertension, diabetes mellitus, inflammation, oxidative stress, atherosclerosis, anemia and disturbance of the iron metabolism are all commonly observed in HF patients. All may have important functions in the viscous organ crosstalk and contribute to the high prevalence of renal dysfunction in HF patients [20, 21]. However, neurohormonal activation with resultant reduced renal blood flow and increased renal venous pressure are currently regarded as the main initiators of the cascade leading to loss of nephrons and progressive renal failure in HF patients [18] (fig. 3).

Principles for Management of Patients with HF and Renal Dysfunction

Despite a large proportion of HF patients having renal dysfunction, there is generally a lack of evidence for the optimal treatment for cardiorenal patients. Patients with moderate-to-severe renal dysfunction ($\text{GFR} < 30\text{--}45 \text{ ml/min/1.73 m}^2$) have systematically been excluded from randomized HF trials, probably because of concern that the investigational drug might cause further deterioration of kidney function. Even though substudies of the large randomized HF trials and observational studies generally indicate that patients with moderate renal dysfunction benefit at least as much from the recommended treatment as non-CKD patients [22–24], patients with renal dysfunction are less likely to receive modern HF treatment. Treatment nihilism due to a lack of evidence and fear of adverse events may account in part for the worsened prognosis in cardiorenal patients [6, 25]. The following perspectives and summary of current evidence may help physicians to provide better treatment for cardiorenal patients.

Fragility

HF patients with renal dysfunction are fragile. Minor stimuli may threaten the equilibrium between adequate organ perfusion and organ congestion. Hence, small changes in medication, otherwise harmless intercurrent illness or small changes in body fluid status may cause decompensated heart or renal failure. Patients with estab-

lished CKD are more prone to experiencing acute worsening renal dysfunction or hyperkalemia secondary to medications and diagnostic procedures. The risk increases with the severity of the kidney disease. A common misinterpretation of worsening renal function in an HF patient prompts the withdrawal of RAAS-blocking drugs, which are considered to be contraindicated. Instead, treatment of the intercurrent illness and reestablishment of fluid levels should have aimed to restore equilibrium. An initial reduction of RAAS-blocking medication is often necessary, but retitration to optimal drug doses as soon as the patient is stabilized should be emphasized. A dynamic effort to continuously aim for equilibrium may secure safe treatment and improve prognosis in cardiorenal patients [26]. However, this approach presupposes good patient education, close monitoring and an opportunity for cardiorenal patients to reach their physician in short notice when unexpected incidents occur.

Pharmacokinetics and Target Dose

Many drugs are dependent on renal excretion and doses should be reduced according to the GFR when patients have renal dysfunction. However, renal clearance of drugs is not only dependent on the GFR. Altered tubular reabsorption or secretion is not necessarily reflected by the GFR. Furthermore, renal disease may affect absorption, volume of distribution, binding to proteins and drug affinity through alterations in body composition of water and acid/base balance [27]. Consequently, achieving the target doses provided in guidelines is not always realistic in cardiorenal patients. The optimal dose should be defined as the individually highest tolerable dose for the time being. As the difference in efficacy between intermediate and high doses of HF medication is likely to be small [28] and, given the fragility of cardiorenal patients, it is reasonable to reach the optimal dose by the principle: start low and go slow.

RAAS-Blocking Drugs

Although patients with renal dysfunction have been largely excluded from randomized HF trials, substudies indicate that the relative risk reduction achieved by angiotensin-converting enzyme inhibitors (ACEis)/angiotensin II receptor blockers (ARBs) in HF patients with moderate renal dysfunction is equal compared to patients

with a normal renal function [22, 29]. As the absolute risk is higher, moderate renal dysfunction would actually identify patients with a greater absolute benefit of the treatment [22]. In HF patients with severe renal dysfunction (eGFR <30 ml/min/1.73 m²) there are as yet no conclusive data [29].

ACEis and ARBs are, however, recommended in a wide range of CKD patients. The drugs are considered to be renoprotective beyond their effect on systemic blood pressure [30]. Beneficial hemodynamic effects in the renal circulation combined with antiproteinuric, anti-inflammatory and antifibrotic effects reduce the rate of renal disease progression. Furthermore, they are associated with better survival in CKD patients [31]. Treatment with an ACEi or an ARB is probably beneficial for most HF patients with renal dysfunction, and an effort should be made so that cardiorenal patients tolerate the treatment.

Some patients will not tolerate the treatment as ACEis and ARBs alter the physiological regulation of glomerular hemodynamics (fig. 2). There is a risk of hyperkalemia and worsening renal dysfunction. An initial elevation of serum creatinine by 20% within 2 months from initiation should be expected when starting an ACEi or ARB. Actually, data indicate that the patients experiencing an initial modest increase in creatinine are the ones who may benefit the most from the treatment [32]. Larger increases in creatinine, or decompensation of renal function during treatment, should lead to the suspicion of compromised renal perfusion. Renal artery stenosis or low circulating blood volume due to dehydration or intercurrent disease should be considered. Subsequent correction of renal blood flow might lead to the tolerance of RAAS-blocking drugs.

It is also worth recognizing that ACEis are mainly eliminated by the kidneys. Therefore, the initial and target dose is recommended to be lower in patients with renal dysfunction. ARBs are mainly metabolized in the liver and adjustment of the initial and target dose is not always mandatory.

β-Blocking Drugs

Despite β-blocking drugs being considered neutral concerning renal function, HF trials have systematically excluded patients with severe renal dysfunction. Data from the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) found significant interactions between metoprolol and renal function; the effect of metoprolol was better in patients

with eGFR <45 ml/min/1.73 m² [23]. Although, no definite conclusions can be made for HF patients with severe renal dysfunction, it seems likely that β-blockers also improve outcome in these patients [29].

Although the most widely used β-blocking drugs in HF patients (carvedilol, bisoprolol and metoprolol) are not dependent on renal elimination, one must consider other aspects of pharmacokinetics and dynamics when treating renal patients with β-blocking drugs. As with RAAS-blocking drugs, it is sensible to start low and go slow in cardiorenal patients to avoid adverse events and achieve the individual optimal dose.

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists (MRA) are recommended as add-on therapy to an ACEi or ARB, and as β-blockers in patients with severe systolic HF [1]. MRA have been considered contraindicated in patients with moderate-to-severe renal dysfunction as they may cause life-threatening hyperkalemia and worsening renal failure [33]. Still, there is convincing evidence for a significant treatment benefit of MRA in HF patients with moderate renal dysfunction [24, 29, 34]. A slight decrease in GFR could even be tolerated in patients with advanced HF treated with an MRA, as the beneficial effects may counter the effect of worsened renal function [24]. In patients with severe renal dysfunction there are no convincing data available.

MRA has a potential for both renal and cardiac protection since aldosterone contributes to inflammation and fibrosis in both the heart and the kidneys [35]. However, further research is warranted to determine the role of MRA in HF patients with moderate-to-severe renal dysfunction, and awareness of the potential hazardous adverse effects should motivate close monitoring in every patient treated with these drugs.

Diuretics

Loop diuretics provide efficient symptomatic treatment in HF patients and are considered mandatory in HF treatment, even though they have never been evaluated in large randomized clinical trials. The diuretic response is closely related to renal function, and patients with renal dysfunction need higher doses to achieve adequate decongestion. High diuretic doses are independently associated with an increased risk of mortality in HF patients

[36]. However, others claim that proper decongestion by diuretics is associated with improved prognosis [37]. Recently, the risk associated with high-dose loop diuretics was found to be closely associated with markers of neurohormonal activation [38].

Loop diuretics may also convey diverging results with regard to renal outcomes. Renal decongestion may delay the progression of CKD, but high doses of loop diuretics may activate neurohormonal systems, alter renal perfusion and promote the progression of renal dysfunction.

As no alternatives to proper decongestion without neurohormonal activation are currently available, diuretics are essential in the treatment of HF. Awareness of the potential negative effects of diuretics is important and one should continuously aim for the lowest effective dose. Critical evaluation of diuretic doses may result in improved renal perfusion and a secondary benefit of more patients tolerating RAAS-blocking drugs.

Additional Pharmacological Principles in the Management of Cardiorenal Patients

Ivabradine, digoxin and hydralazine/isosorbide dinitrate are recommended in selected HF patients with reduced ejection fraction. None of these have been thoroughly evaluated in patients with severe renal dysfunction, but significant interactions with renal insufficiency have not been found. Thus, they should be used with care in HF patients with renal disease.

Recently, LCZ696 was found to be superior to enalapril in reducing the risk of death and hospitalization in HF patients [39]. This treatment principle is of particular interest in HF patients with renal dysfunction as inhibition of neprilysin is expected to protect and could even improve kidney function [39, 40]. Further research in cardiorenal patients is warranted, but it is likely that LCZ696 will become a core therapeutic component in HF patients with and without renal dysfunction in the near future [41].

Interventional Cardiology in Cardiorenal Patients

A fear of contrast-induced nephropathy and further deterioration of kidney function may explain why patients with kidney disease are less likely to be treated with interventional angiographic procedures than the general cardiac population [42]. This adds to the pharmacological treatment nihilism in cardiorenal patients and may

partly explain their poor outcome. Contrast-induced nephropathy is indeed a threat [43] and should warrant careful intravenous rehydration prior to the procedure and careful monitoring after the procedure. However, denying patients lifesaving interventional procedures is likely to be a bigger threat to cardiorenal patients than contrast-induced nephropathy.

ICD (implantable cardioverter defibrillator) therapy for the prevention of fatal ventricular arrhythmia, and CRT (cardiac resynchronization therapy) are evolving therapies in selected HF patients, with strong evidence of effects in patients with moderate renal dysfunction, but less clear evidence in patients with severe renal dysfunction [29]. Sudden cardiac death is common in CKD patients and the incidence increases as GFR decreases. In stage 5 CKD patients, sudden cardiac death accounts for more than 50% of cardiovascular causes of mortality [44]. Thus, HF patients with severe renal function should be considered for CRT and ICD treatment if indicated.

Conclusion

CKD is highly prevalent in HF outpatients and an important predictor of mortality and hospitalization. To identify and monitor renal disease and to make an effort to preserve renal function should be of great importance in the management of HF patients.

Neurohormonal activation with resultant reduced renal blood flow and increased renal venous pressure is currently considered the most important causes of renal dysfunction in HF patients. This initiates a complex pathophysiological cascade, including hypoxic and inflammatory injury in the kidneys with progressive renal dysfunction as a consequence.

Treatment nihilism is a major problem in cardiorenal patients. Despite a lack of randomized controlled trials designed for cardiorenal HF patients, it appears that most recommended HF treatments are at least as effective in patients with renal dysfunction as in patients without renal dysfunction. RAAS-blocking drugs are important in both cardiac and renal protection, and an effort should be made for the patients to tolerate an ACEi or ARB. However, cardiorenal patients are fragile; every change in medication, intercurrent illness or interventional procedure may disturb the equilibrium between organ perfusion and organ congestion. These patients are in need of individualized treatment and close monitoring and follow-up to avoid decompensated heart or renal dysfunction.

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