

Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation

Jozine M. ter Maaten¹, Kevin Damman¹, Marianne C. Verhaar², Walter J. Paulus³, Dirk J. Duncker⁴, Caroline Cheng^{2,4}, Loek van Heerebeek³, Hans L. Hillege⁵, Carolyn S.P. Lam⁶, Gerjan Navis⁷, and Adriaan A. Voors^{1*}

¹University of Groningen, Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands; ²University Medical Center Utrecht, Department of Nephrology and Hypertension, Utrecht, The Netherlands; ³Department of Physiology, Cardiology, Pathology, and Surgery, Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, The Netherlands; ⁴Experimental Cardiology, Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; ⁵University of Groningen, Department of Epidemiology, University Medical Center Groningen, Groningen, The Netherlands; ⁶National Heart Centre Singapore and, Duke-National University of Singapore Graduate School Medicine, Singapore; and ⁷University of Groningen, Department of Nephrology, University Medical Center Groningen, Groningen, The Netherlands

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Renal dysfunction in heart failure with preserved ejection fraction (HFpEF) is common and is associated with increased mortality. Impaired renal function is also a risk factor for developing HFpEF. A new paradigm for HFpEF, proposing a sequence of events leading to myocardial remodelling and dysfunction in HFpEF, was recently introduced, involving inflammatory, microvascular, and cardiac components. The kidney might play a key role in this systemic process. Renal impairment causes metabolic and systemic derangements in circulating factors, causing an activated systemic inflammatory state and endothelial dysfunction, which may lead to cardiomyocyte stiffening, hypertrophy, and interstitial fibrosis via cross-talk between the endothelium and cardiomyocyte compartments. Here, we review the role of endothelial dysfunction and inflammation to explain the link between renal dysfunction and HFpEF, which allows for identification of new early risk markers, prognostic factors, and unique targets for intervention.

Keywords Heart failure with preserved ejection fraction • Renal dysfunction • Endothelial dysfunction • Inflammation

Introduction

The co-existence of heart failure and renal impairment in patients presenting with fluid overload is well known. This may be due to the impact of common risk factors (e.g. diabetes mellitus) on both end-organ systems, heart failure causing renal dysfunction (e.g. via renal hypoperfusion), or, conversely, renal failure causing cardiac dysfunction (e.g. via uraemic toxins, increased afterload).^{1–3} Combined heart and kidney failure in patients poses several clinical challenges, including diagnostic difficulties and therapeutic dilemmas, since many proven heart failure medications may cause, or are contraindicated in the presence of, renal failure. The cardiorenal interaction has mainly been studied in heart failure with reduced ejection fraction (HFrEF). However, renal impairment is observed in a great number of patients with heart failure with preserved

ejection fraction (HFpEF) and is associated with an increased risk of mortality.^{4–6} Interestingly, impaired renal function was recently also identified as a risk factor for developing HFpEF.⁷ This review aims to describe the current knowledge, pathophysiology, and future perspectives of the relationship between renal dysfunction and HFpEF. Some of the described mechanisms may not be unique for the relationship between renal dysfunction and HFpEF, and might also apply to HFrEF. Nevertheless, this review will not discuss specific mechanisms related to the relationship between renal dysfunction and HFrEF.

Epidemiology

In large observational cohorts, chronic kidney disease (CKD) [defined as an estimated glomerular filtration rate (eGFR)

*Corresponding author: University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. Tel: +31 50 361 2355, Fax: +31 50 361 8062, Email: a.a.voors@umcg.nl

<60 mL/min/1.73 m²] is observed in 26–49% of patients with HFpEF.^{4,5} This is similar to rates observed in HFrEF patients.⁸ In a contemporary HFpEF population, impairment of renal function, defined as an eGFR <60 mL/min/1.73 m² or albuminuria, was present in 62% of patients; of these, 26% had albuminuria with normal eGFR.⁹ The described prevalence of CKD in different HFpEF cohorts varies greatly (Table 1), possibly due to different inclusion criteria, settings, and cut-off points for HFpEF and CKD. Several studies have investigated the association of impaired renal function and mortality in HFpEF patients. Hillege *et al.* found an association between impaired renal function and increased risk for death, cardiovascular death, and hospitalization for heart failure in HFpEF, similar to rates observed in HFrEF.¹⁰ Multiple other studies have since confirmed these findings; some even suggest a greater prognostic importance of CKD in patients with a preserved EF.¹¹ A meta-analysis, involving >1 million patients with heart failure, found that CKD was associated with an odds ratio (OR) of 3.22 [95% confidence interval (CI) 2.66–3.90] for all-cause mortality in patients with an EF >40%, compared with ORs of 2.00 (95% CI 1.81–2.21) and 2.56 (95% CI 2.24–2.93) for an EF <30% and between 30% and 40%, respectively.¹¹ In the meta-regression analysis performed in this study, a higher EF modified the relationship between renal impairment and clinical outcome in such a way that the association with outcome was significantly stronger in patients with higher EF. Of note, in a hypothesis-free approach using phenotype mapping to identify distinct ‘naturally occurring’ HFpEF categories, Shah *et al.* showed that the phenotype of HFpEF with CKD was distinctly different and associated with the poorest outcome.¹²

Recent studies have focused not only on baseline renal function, which is—most of the time—non-modifiable, but also on worsening of renal function (WRF) over time. Several definitions of WRF have been used, the most common being an increase in creatinine ≥ 0.3 mg/dL; however, recent studies often also include a relative change.¹³ WRF has been associated with increased mortality in the general (acute and chronic) heart failure population, but data on WRF in HFpEF are limited (Table 2). Recently, Voors *et al.* found an overall incidence of 15% of WRF, defined as an increase in creatinine ≥ 0.3 mg/dL and/or >25% at any time point after initiation of LCZ696 or valsartan in HFpEF.¹⁴ In a retrospective analysis of the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial, Damman *et al.* found a similar incidence of WRF, defined as an increase in creatinine ≥ 0.3 mg/dL and a reduction in eGFR $\geq 25\%$, compared with HFrEF patients, and the relationship between WRF and outcomes in HFpEF was also similar to what was previously shown in HFrEF, although different with regard to the association with ARB therapy, which was associated with an increased risk of WRF in HFpEF.¹⁵ Furthermore, in HFpEF patients with a low eGFR, WRF during hospitalization is especially associated with a poor prognosis.¹⁶

Impaired renal function is not only a risk factor in patients with HFpEF, but it is also a risk factor for developing HFpEF.⁷ In PREVEND, a large community-based cohort, including 8592 subjects, during a median follow-up of 11.5 years, 34% of this population was diagnosed with new-onset HFpEF. A poorer renal function, as assessed by cystatin C and albuminuria, was a strong

risk factor for developing HFpEF, but not for HFrEF. Moran *et al.* previously described an association between higher cystatin C levels and both new-onset HFrEF and HFpEF.¹⁷ In a post-hoc analysis from the Framingham Heart Study, it was found that renal function, although slightly lower in patients with new-onset HFpEF compared with new-onset HFrEF, was not associated with HFpEF onset in multivariable analysis.¹⁸ A study investigating predictors of heart failure onset identified the urinary albumin to creatinine ratio as a key risk factor for new-onset heart failure; however, this study included both HFpEF and HFrEF patients.¹⁹ To our knowledge, more studies investigating new-onset HFpEF and renal function are currently lacking.

Based on these data, we can conclude that the association between renal dysfunction and heart failure is at least as strong in HFpEF as in HFrEF.

Pathophysiology of heart failure with preserved ejection fraction

The pathophysiology of HFpEF remains incompletely understood. Recently, several studies have identified a relationship between endothelial dysfunction, chronic low grade systemic inflammation, diastolic dysfunction, and HFpEF.

Endothelium

The endothelium is involved in diverse activities, among which are vasomotor, haemostatic, antioxidant, and inflammatory functions.²⁰ Healthy endothelium has anti-inflammatory properties, whereas dysfunction of the endothelium promotes interaction with circulating inflammatory cells.²¹ Murdoch *et al.* recently showed that activation of endothelial NAD phosphate oxidase-2 enhances cardiac inflammation.²² Additionally, inflammation elicits endothelial dysfunction, as proinflammatory cytokines cause endothelial production of reactive oxygen species (ROS), resulting in endothelial dysfunction.²³

The endothelium also regulates vascular tone, mainly by releasing nitric oxide (NO), in response to various stimuli.²⁴ Together with its paracrine effects, the endothelium therefore has a profound impact on cardiac function.^{25,26} The endothelium is also involved in sodium handling through the endothelial glycocalyx and the glycosaminoglycan network. Sodium is able to bind to the endothelial glycocalyx and is subsequently passed through the endothelial cell into the extracellular matrix.^{27,28} Increased sodium concentration in the endothelial cell—for instance caused by high plasma sodium concentration or increased aldosterone levels—causes stiffening of the endothelial cell, decreased NO levels, and ultimately disruption of the endothelial glycocalyx, resulting in vascular dysfunction.^{29,30} This consequently leads to increased microvascular resistance and extravascular fluid accumulation.

A number of studies have demonstrated a higher prevalence of endothelial dysfunction in HFpEF compared with controls.³¹ An impaired endothelial function was observed in HFpEF and hypertensive patients compared with controls by Borlaug *et al.*, which was in contrast to the available data at the time.³² Shortly

Table 1 Prevalence of chronic kidney disease in different heart failure with preserved ejection fraction populations

Study	Setting	Definition of HFpEF	No. with HFpEF	Definition of renal dysfunction	Incidence of renal dysfunction
Population based					
Ather <i>et al.</i> (2012) ⁴	Across USA, heart failure outpatients	LVEF $\geq 50\%$	2843	eGFR < 60 mL/min/1.73 m ²	49%
Carrasco-Sanchez <i>et al.</i> (2011) ¹¹²	Single centre in Spain, acute heart failure	LVEF $> 45\%$	218	eGFR < 60 mL/min/1.73 m ²	48%
Rusinaru <i>et al.</i> (2011) ¹⁶	Across France, first hospitalization for acute heart failure	LVEF $\geq 45\%$	358	eGFR < 60 mL/min/1.73 m ²	53%
Unger <i>et al.</i> (2016) ¹¹³	Northwestern University cohort, post-hospitalization for acute heart failure	LVEF $> 50\%$	299	eGFR < 60 mL/min/1.73 m ²	48%
Registry					
Lenzen <i>et al.</i> (2004) ¹¹⁴	EuroHeart Failure survey, acute heart failure	LVEF $\geq 40\%$	3148	Serum creatinine ≥ 200 μ mol/L	5%
Yancy <i>et al.</i> (2006) ⁵	ADHERE registry, acute heart failure	LVEF $\geq 40\%$	26 322	Serum creatinine > 2.0 mg/dL	26%
Clinical trial					
Ahmed <i>et al.</i> (2007) ¹¹⁵	DIG trial, chronic heart failure	LVEF $> 45\%$	988	eGFR < 60 mL/min/1.73 m ²	45%
Gori <i>et al.</i> (2014) ⁹	PARAMOUNT study, symptomatic chronic heart failure	LVEF $\geq 45\%$	217	eGFR < 60 mL/min/1.73 m ² Albuminuria > 17 mg/g (men) or > 25 mg/g (women)	46% 39%
Hillege <i>et al.</i> (2006) ¹⁰	CHARM-Preserved, symptomatic chronic heart failure	LVEF $> 40\%$	1087	eGFR < 60 mL/min/1.73 m ²	35%
Massie <i>et al.</i> (2008) ¹¹⁶	I-PRESERVE, symptomatic chronic heart failure	LVEF $\geq 45\%$	4128	eGFR < 60 mL/min/1.73 m ²	30%
Shah <i>et al.</i> (2013) ¹¹⁷	TOPCAT, symptomatic chronic heart failure	LVEF $\geq 45\%$	3445	eGFR < 60 mL/min/1.73 m ²	39%

eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction.

after this, Akiyama *et al.* found significantly more endothelial dysfunction (defined as a reactive hyperaemia index below the median value of 0.49) in patients with HFpEF compared with controls.³³ In addition, endothelial dysfunction had strong prognostic value in these patients with HFpEF. A recent autopsy-based study by Mohammed *et al.* compared HFpEF patients with age-matched controls.³⁴ In this study, HFpEF patients had more hypertrophy, modest myocardial fibrosis, and coronary microvascular rarefaction—an imbalance between vessel destruction and regeneration—assessed by lower microvascular density. Microvascular endothelial dysfunction is associated with microvascular rarefaction, and this finding therefore supports the notion of endothelial dysfunction in HFpEF.³⁵ In addition, systemic capillary rarefaction enforces HFpEF as a systemic disease, driven by endothelial dysfunction and inflammation.³⁶ Many of the cardiovascular risk factors associated with HFpEF, such as diabetes, obesity, dyslipidaemia, smoking, hypertension, and CKD, potentially cause endothelial dysfunction, and microvascular rarefaction.^{37–39} Taken together, HFpEF is strongly associated with endothelial dysfunction.

Inflammation

The association between inflammation and HFpEF has been supported by a number of studies that showed increased levels of inflammatory markers in HFpEF patients.⁴⁰ Kalogeropoulos *et al.* showed that interleukin-6 (IL-6) and tumour necrosis factor- α (TNF- α) were strongly associated with the risk of new-onset HFpEF, which was stronger than the risk of new-onset HFrEF.⁴¹ Other studies revealed higher levels of inflammatory biomarkers such as IL-6, IL-8, monocyte chemoattractant protein-1, pentraxin-3, ST2, and TNF- α receptor 2 in HFpEF patients, compared with patients with either hypertension, dyspnoea of other causes, or HFrEF, or healthy controls.^{42–45} Many co-morbidities in HFpEF, such as obesity, diabetes, hypertension, and CKD, are known to promote chronic low-grade inflammation. Inflammation, through cytokines, causes the endothelium to produce ROS. This, in turn, induces oxidative inactivation of NO, as superoxide anions react with NO and form peroxynitrite, which is supported by the recent finding of high nitrotyrosine expression in HFpEF myocardium.⁴⁶ So, HFpEF is strongly associated with inflammation.

Table 2 Worsening renal function in heart failure with preserved ejection fraction

Reference	Title	Definition of WRF	Main findings
Voors <i>et al.</i> (2015) ¹⁴	Renal effects of the angiotensin receptor neprilysin inhibitor LCZ696 in patients with heart failure and preserved EF	Serum creatinine increase of >0.3 mg/dL and/or >25% after 12 or 36 weeks of treatment	15% of patients developed WRF at any time point. The incidence of WRF was lower in the LCZ696 group (12%) compared with the valsartan group (18%).
Damman <i>et al.</i> (2014) ¹⁵	WRF and outcome in heart failure patients with preserved EF and the impact of ARB treatment	Absolute increase of serum creatinine of ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$), together with a relative increase in serum creatinine of $\geq 25\%$ between baseline and 8 weeks	6.4% of patients developed WRF. The incidence of WRF was more frequent with irbesartan treatment (8% vs. 4%).
Rusinaru <i>et al.</i> (2011) ¹⁶	Renal function and long-term survival after hospital discharge in heart failure with preserved EF	A $\geq 25\%$ decrease in eGFR from admission to discharge	12% of patients developed WRF during hospitalization. WRF was independently predictive of mortality.

eGFR, estimated glomerular filtration rate; WRF, worsening renal function.

A new paradigm

The relationship between inflammation, endothelial function, and HFpEF is intriguing and has led to the proposal of a new paradigm for HFpEF. This paradigm, introduced by Paulus and Tschope, involves a chain of events leading to myocardial remodelling and dysfunction in HFpEF (Figure 1).⁴⁷ In brief, common co-morbidities in HFpEF, such as obesity, hypertension, diabetes mellitus, COPD, and iron deficiency, induce an inflammatory state. This systemic inflammatory state causes the coronary microvascular endothelium to produce ROS, which reduces NO bioavailability and increases peroxynitrite. The consequent reduction in stimulation of cGMP production by soluble guanylate cyclase results in lower protein kinase G (PKG) activity.⁴⁸ Since PKG functions as a constraint on myocardial hypertrophy, lower myocardial PKG activity causes remodelling, impaired relaxation, and myocardial stiffness.⁴⁷ Finally, fibrosis, due to microvascular inflammation (and the consequent influx of inflammatory cells), and cardiomyocyte stiffening together lead to diastolic dysfunction. Furthermore, autocrine and paracrine factors, such as apelin, transforming growth factor- β , and endothelin-1, from the endothelium have an effect on the development of cardiac hypertrophy.⁴⁹

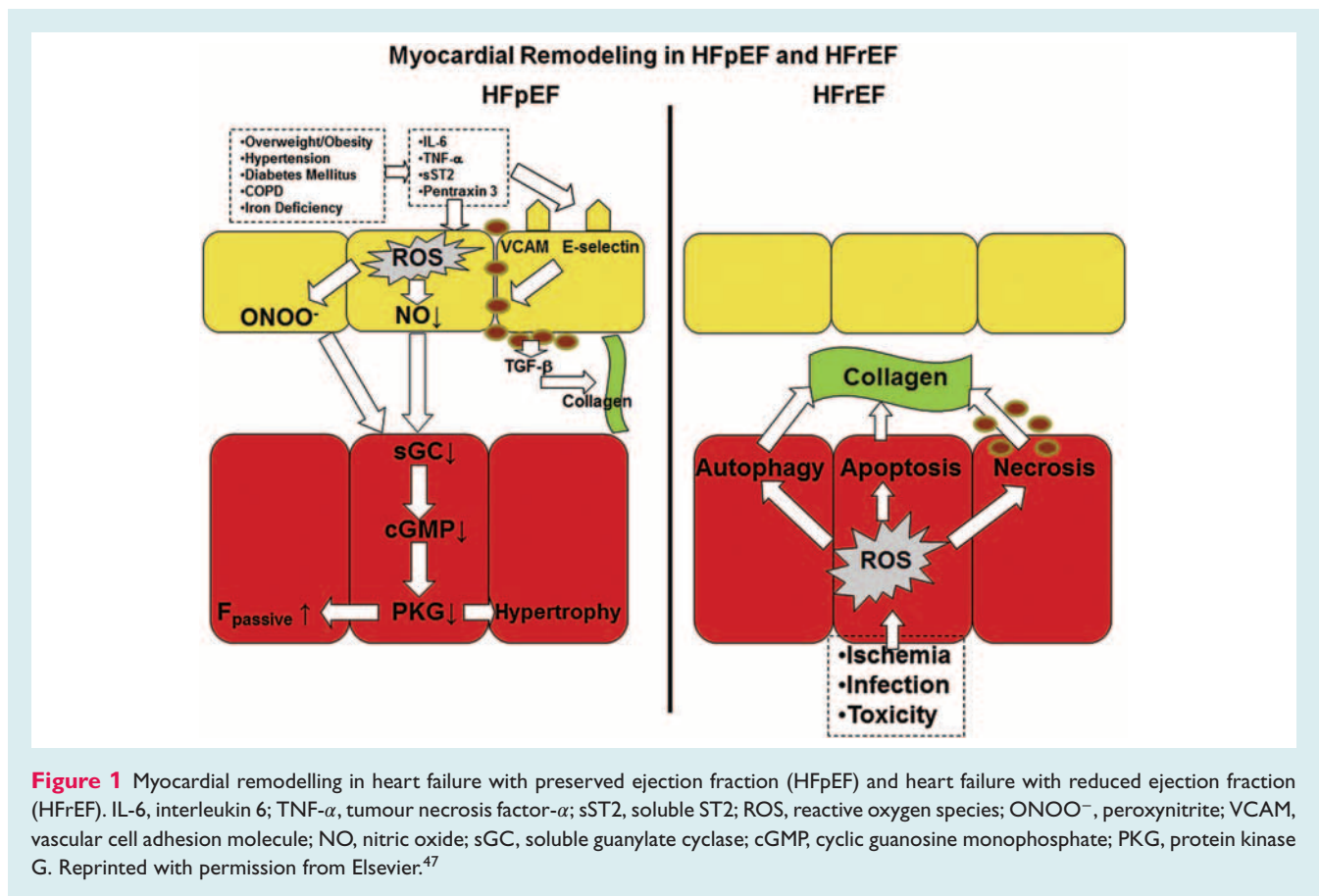
This process is distinctly different from HFrEF, where myocardial remodelling occurs as a consequence of cardiomyocyte death, perturbation in calcium cycling, and contractile dysfunction (Figure 1). The components of the paradigm are all part of an overarching systemic process, of which many are present in CKD.

The renal connection

How heart failure with preserved ejection fraction might cause renal dysfunction

In advanced HFpEF, elevated left- and right-sided filling pressures are the predominant haemodynamic features.⁵⁰ An increased

central venous pressure has been associated with impaired renal function, and is a risk factor for decreased or worsening renal function.^{51–53} This has been observed for patients both with a reduced and with a preserved EF.⁵³ Elevated central venous pressure potentially causes a decreased renal blood flow and renal perfusion pressure, and activates the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system, leading to a reduction in GFR.⁵⁴ Additionally, higher central and renal venous pressure raises intrarenal interstitial pressures, leading to renal interstitial fibrosis and increased tubular pressure, further reducing GFR.¹³ Importantly, high central venous pressure may be even more important than reduced cardiac output, and the association between central venous pressure and reduced GFR was significantly stronger in patients with relatively preserved cardiac output.⁵³ Additionally, right ventricular dysfunction in HFpEF is common and has been shown to be associated with impaired contractility, elevated right ventricular afterload, and lower eGFR, which may be caused by elevated central venous pressure as a consequence of right ventricular failure.⁵⁵ Another key haemodynamic feature of HFpEF is decreased systolic filling, resulting in inadequate stroke volume reserve, and ultimately causing a decreased cardiac output. Furthermore, increasing end-diastolic volume in HFpEF patients requires a remarkable increase in filling pressures. In periods of increased demand, such as exercise, the HFpEF heart is therefore unable to increase cardiac output sufficiently.^{56,57} This is due to a steep diastolic pressure–volume relationship and a steep, almost vertical end-systolic pressure–volume relationship, leading to a fixed stroke volume, and insufficiently increased volumes during exercise.⁵⁸ Consequently HFpEF patients have a greater dependence on preload, and reductions in this, such as by administration of vasodilators, results in a greater drop in stroke volume, and blood pressure reduction, despite high filling pressures.⁵⁹ A fluctuation in preload may therefore dramatically reduce renal blood flow, and ultimately results in renal dysfunction. Other contributors are, among others, chronotropic incompetence, which was



recently associated with decreased eGFR in a HFpEF population, suggesting that autonomic dysfunction may lead to both reduced heart rate reserve and directly or indirectly to impaired kidney function.⁶⁰ Additionally, increased ventricular stiffness and arterial stiffness are commonly coupled in HFpEF patients, resulting in a system in which pressure and load changes are more dramatic, and may therefore negatively affect renal perfusion and function.⁶¹ Decreased cardiac output results in decreased organ perfusion and therefore diminished renal blood flow.^{62,63} Low NO availability in the kidney also reduces renal blood flow.⁶⁴ Renal blood flow is an important factor in determining GFR in patients with heart failure.⁵¹ Under normal circumstances, the kidney is able to maintain GFR by autoregulation of its afferent and efferent arterioles.⁶⁵ However, due to RAAS inhibitors, such as ACE inhibitors, the efferent component of this autoregulatory mechanism is disrupted. Therefore, in line with other patients on RAAS blockade, GFR in patients with heart failure is more directly influenced by the systematic circulatory status and blood pressure than in subjects with an intact autoregulation, although direct evidence in HFpEF is currently lacking. Lower blood pressure can still impact renal function in patients with HFpEF, and probably affects renal function more than in HFrEF. Since cardiac output in patients with HFpEF is largely preload dependent, we may hypothesize that arterial and intracardiac underfilling, lower blood pressure, together with vascular stiffness and impaired ventricular–vascular coupling may reduce

cardiac output and thereby renal blood flow. Finally, episodes of acute kidney injury, for instance caused by therapy for decompensated HFpEF, may ultimately contribute to the development of CKD.

How renal dysfunction might cause heart failure with preserved ejection fraction

Chronic kidney disease is a highly prevalent co-morbidity in HFpEF, and CKD is, similar to HFpEF, associated with endothelial dysfunction and inflammation. Microvascular dysfunction can be caused by CKD, through interaction with co-morbidities such as diabetes mellitus and hypertension, or through renal specific mechanisms. The effects and mechanisms through which factors associated with CKD may cause renal function differ across stages of CKD. In patients with mild CKD or even normal renal function with microalbuminuria, high levels of fibroblast growth factor 23 (FGF23), which is involved in the control of serum phosphate and vitamin D, have been shown to cause endothelial dysfunction by increasing superoxide and decreasing NO bioavailability.^{66,67} Also, vitamin D deficiency has been associated with systemic inflammation, endothelial dysfunction, and LV remodelling.^{68,69} As kidney function deteriorates, abnormalities in the bone–mineral axis accelerate and, in addition to FGF23 and vitamin D, elevated levels of phosphorus and parathyroid hormone have also been

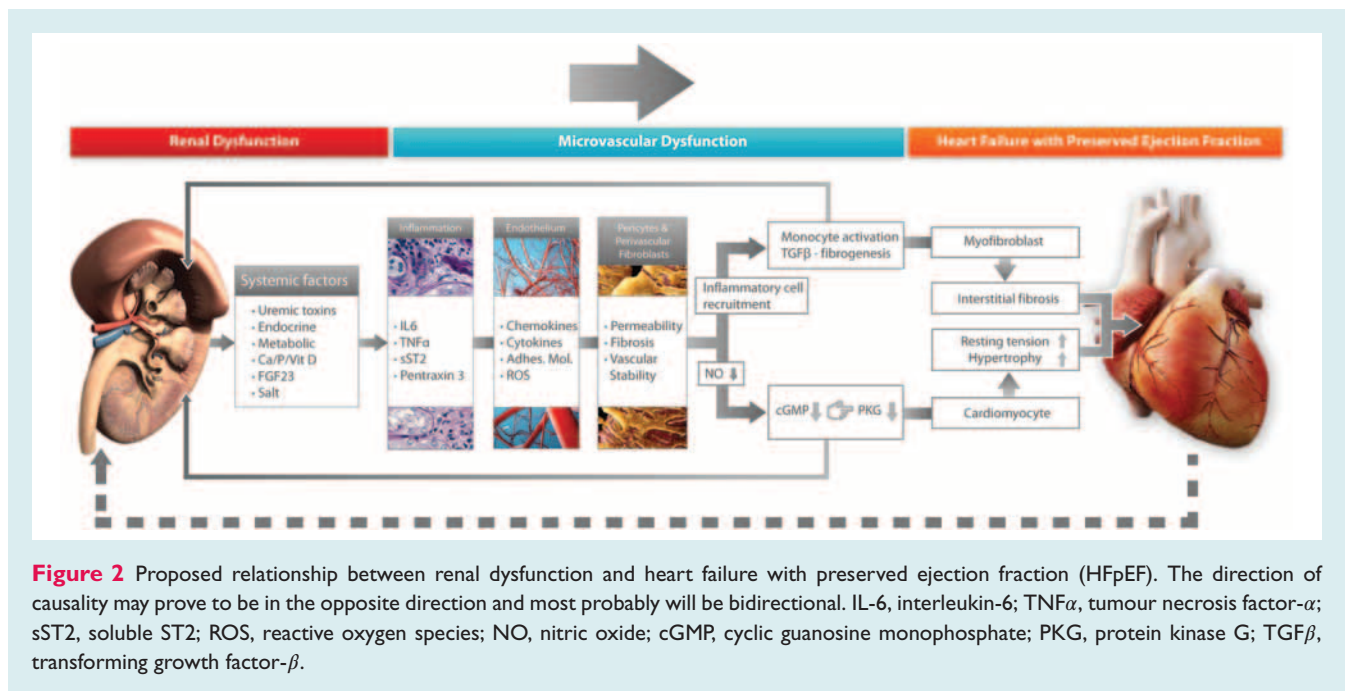
associated with ventricular hypertrophy and fibrosis.⁷⁰ Renal dysfunction may also mediate the development of HFpEF through renally induced erythropoietin deficiency, as this has an effect on endothelial dysfunction, NO availability, and inflammation.⁷¹ Additionally, proteinuria is a sign of endothelial disruption and has been shown to be a risk factor for heart failure.⁷² The effect and role of proteinuria may vary in different stages of CKD. Proteinuria has been associated with elevated levels of inflammatory markers, such as C-reactive protein, and asymmetric dimethylarginine, an inflammatory biomarker that also has the potential to cause endothelial dysfunction through inhibition of NO.^{73,74} Recently, an endothelial nitric oxide synthase (NOS) Glu298Asp single nucleotide polymorphism genotype has been associated with cardiac remodelling in patients with early CKD.⁷⁵ CKD causes sympathetic nervous activation and, as such, may have direct effects on the development of heart failure, as well as indirect effects through its negative effects on endothelial function.^{76,77} Some animal studies have demonstrated that administration of a beta-adrenergic agonist resulted in diastolic dysfunction.⁷⁸ To date, no human studies are available that have studied the association between increased sympathetic nervous system activity and HFpEF onset. There is, however, evidence of increased sympathetic nervous system activity, such as elevated serum noradrenaline levels in patients with HFpEF.⁷⁹

In more severe CKD, impaired renal clearance causes retention of uraemic toxins, and increases in circulating levels of these uraemic toxins are associated with chronic inflammation, through uraemia-associated proinflammatory cytokines and inhibition of endothelial proliferation.⁸⁰ Furthermore, uraemic toxins increase ROS in vascular endothelial cells, and thereby cause oxidative stress.⁸¹ Uraemic toxins have also been shown to cause vascular smooth muscle cell dysfunction.⁸² Not only uraemic toxins, but also urinary sodium retention and altered levels of renal endocrine factors, and serum calcium and phosphate, have all been linked to microvascular dysfunction.^{83,84} Furthermore, a wide range of studies indicate a relationship between CKD and endothelial oxidative stress, impaired NO availability, and reduced endothelial cell survival and regeneration, as well as effects on the immune system, leading to a chronic low-grade inflammatory state that leads to and amplifies microvascular dysfunction.^{71,85,86} Moreover, patients with nephrotic range proteinuria were found to have impaired endothelial function, which is not corrected by administration of L-arginine (a naturally occurring NOS inhibitor), suggesting that other factors also contribute to this.^{87–89} In the Chronic Renal Insufficiency Cohort study, large artery stiffness was an independent predictor of incident heart failure in CKD patients.⁹⁰ Interestingly, the presence of LV hypertrophy increases with declining renal function, and LV mass has been shown to increase in haemodialysis patients with dialysis duration.⁹¹ This might be caused by uraemic toxins, RAAS activation, or pressure overload, or by dialysis itself, as dialysis has been shown to cause regional myocardial stunning, probably due to microvascular dysfunction.⁹² Also, regional LV systolic dysfunction in haemodialysis patients has been associated with a proinflammatory cytokine profile.⁹³ Additionally, in patients on haemodialysis, interaction with the dialysis membrane results in complement activation, which results in microinflammation and may ultimately result in vascular stiffness

and endothelial dysfunction.⁹⁴ Renal failure causes accumulation of advanced glycation end-products (AGEs), due to decreased clearance of AGE degradation products, and increased oxidative stress.^{95,96} AGEs may induce HFpEF by causing fibrosis through cross-linking in the extracellular matrix, by activation of their receptor which has a proinflammatory effect, or by causing a delay in calcium uptake.^{97,98} AGEs also influence endothelial function by reducing NO availability.⁹⁹ Finally, in more severe renal failure, for instance with overt proteinuria, the above-described processes will be more pronounced, and underlying diseases such as hypertension may be sustained by renal dysfunction, hence amplifying their detrimental effects on cardiac function. Some of the above-described processes may also set in motion processes leading to the development of HFpEF, as some underlying mechanisms are overlapping. Taken together, CKD induces abnormalities in inflammation, and endothelial dysfunction, which could all result in HFpEF.

Common mechanisms linking renal dysfunction to heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction might lead to renal dysfunction and vice versa, but a third option is the presence of common denominators causing both HFpEF and CKD. Endothelial dysfunction may cause cardiac dysfunction, as described earlier, however, it may also affect renal function.¹⁰⁰ Endothelial dysfunction and inflammation, for instance caused by diabetes or hypertension, may be present without clinical signs and symptoms of heart failure or renal failure. Therefore, a subtle decline in renal function, microalbuminuria, or LV hypertrophy, may be a sign of common underlying factors causing endothelial dysfunction and ultimately both HFpEF and CKD. An underlying common mechanism might also be systemic and possible renal fibrosis. A marker of (cardiac) fibrosis, galectin-3, has been shown to precede the development of both CKD and incident HFpEF.^{101,102} Infusion of galectin-3 in a rat model of hypertensive HF induces severe LV fibrosis and LV dysfunction.¹⁰³ Similarly, galectin-3 has been linked to the development of renal fibrosis, and inhibition of galectin-3 in rats was found to protect against hypertensive nephropathy, and resulted in reduced proteinuria, improved renal function, and decreased renal damage.^{104,105} In patients with HFpEF, galectin-3 levels were associated with severity of renal dysfunction, however not with cardiac structure, after correction for renal function.¹⁰⁶ The direct effect of galectin-3 on cardiac structure therefore remains unconfirmed; however, hypothetically, a profibrotic pathway, indicated by elevated levels of fibrosis markers such as galectin-3 activity, might also be involved in the relationship between renal dysfunction and HFpEF. In summary, the interaction between HFpEF and the kidney might be bidirectional, or due to common mechanisms underlying both. Additionally, the interaction between underlying factors also changes over time and with different stages of CKD and HFpEF progression, making this a highly complex process. The specific mechanisms driving the interaction between renal function and HFpEF are still poorly understood.



RECONNECT

To address the large knowledge gaps regarding the pathophysiology of the interaction between HFpEF and renal dysfunction, the renal connection to microvascular disease and heart failure with preserved ejection fraction (RECONNECT) consortium was recently formed. The RECONNECT consortium aims to investigate the mechanisms underlying the connection between the systemic consequences of renal dysfunction, coronary microvascular dysfunction, and HFpEF (www.reconnect-umc.eu). The proposed hypothesis of RECONNECT is presented in *Figure 2*; it must be noted that the direction of causality may prove to be in the opposite direction, or bidirectional. Renal impairment causes metabolic and systemic abnormalities in circulating factors, inducing an activated systemic inflammatory state and microvascular dysfunction, which may lead to cardiomyocyte stiffening, hypertrophy, and interstitial fibrosis via cross-talk between the microvascular and cardiomyocyte compartments. The RECONNECT consortium will specifically test the hypothesis that (mild) renal impairment and its systemic consequences adversely impact the coronary microvasculature, modifying the pathophysiology, course, and prognosis of HFpEF. To test our hypothesis, we will conduct a systematic assessment of circulating renal drivers of HFpEF onset, and progression and prognosis, and perform basic fundamental studies to determine the underlying mechanisms and cause–effect relationships, allowing identification of (early) prognostic markers and unique targets for therapeutic intervention within this project. Using well-characterized HFpEF patient cohorts, systemic circulating factors that drive CKD-induced HFpEF onset and progression will be studied. Specific mechanistic pathways will be examined using *ex vivo* bioassays to assess patient material and *in vivo* small and large animals. The most promising therapeutic targets will consequently be tested in newly developed animal models of

CKD-induced HFpEF, and this will hopefully lead to the development of clinical intervention strategies.

Future perspective

A greater understanding of the renal connection in HFpEF may have multiple consequences. First, new early risk markers may be identified. For example, elevated levels of FGF23 in CKD patients might prove to be indicative of new-onset HFpEF. Similarly, markers of (systemic) fibrosis such as elevated levels of galectin-3 might identify patients at risk of either CKD, HFpEF, or both. Second, renal drivers of HFpEF progression are possibly new valuable prognostic factors. Third, new unique targets for intervention can be identified. Endothelial dysfunction might be a potential target for therapy, by activating the cGMP pathway through compounds such as NO donors, guanylyl activators and stimulators, or phosphodiesterase 9A inhibitors. Borlaug *et al.* recently showed that sodium nitrite infusion improves haemodynamics such as cardiac output reserve and stroke volume during exercise in HFpEF patients.¹⁰⁷ Inorganic nitrite may therefore prove to be a beneficial therapy in both HFpEF and CKD as inorganic nitrites improve NO–cGMP signaling. Organic nitrates, on the other hand, have been shown to worsen endothelial function and increase oxidative stress.¹⁰⁸ Treatment of HFpEF patients with organic nitrates showed no beneficial effect on the daily activity level.¹⁰⁹ Of note, the role of syndecan might be of interest, as syndecan is shed in plasma when the endothelial glycocalyx is disrupted.¹¹⁰ Data on other methods to assess endothelial integrity, such as dark field imaging (videomicroscopy), are scarce. In addition, uraemic toxins can be reduced by dietary interventions, or by treatment with the oral sorbent AST-120.¹¹¹ Similarly, calcium/phosphate imbalance can be treated by reducing phosphate intake or using phosphate binders. Finally,

early intervention in renal pathways that are involved in progression of asymptomatic LV impairment may ultimately enable us to prevent the onset or progression of HFpEF.

Conclusions

Renal dysfunction and HFpEF often co-exist and might be bidirectionally causative. In other words, renal dysfunction might cause the onset or progression of HFpEF, and HFpEF might aggravate renal dysfunction. The endothelium and a proinflammatory state have emerged as important mediators in this bidirectional relationship. Renal impairment leads to metabolic and systemic abnormalities in circulating factors, causing an activated systemic inflammatory state and subsequent microvascular dysfunction, which may lead to cardiomyocyte stiffening, hypertrophy, and interstitial fibrosis via cross-talk between the microvascular and cardiomyocyte compartments. Greater insight into the renal connection in HFpEF will allow identification of new early risk markers, prognostic factors, and possibly unique targets for intervention.

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