Heart failure (HF) is very common in the general population, and risk factors for HF, such as coronary artery disease, diabetes, obesity, and hypertension, are frequently present in patients with CKD. Therefore, HF is also an important cause of morbidity and mortality in this population. Diastolic heart failure (DHF), also called HF with preserved ejection fraction, refers to a clinical syndrome in which patients have symptoms and signs of HF, normal or near normal left ventricular (LV) systolic function, and evidence of diastolic dysfunction (e.g., abnormal LV filling and elevated filling pressure). Recent data suggest that HF with normal ejection fraction is even more common in patients than HF with low ejection fraction, including those on hemodialysis. Not surprisingly, DHF is a strong predictor of death in CKD patients. In this article, we review the information available on the mechanisms, clinical presentation, impact, and potential interventions in DHF based on evidence from CKD patients, as well as evidence from the general population potentially applicable to the CKD population.

Heart failure (HF) is very common in the general population, estimated to affect 23 million people worldwide (1). Risk factors for HF, such as coronary artery disease, diabetes, obesity, and hypertension are frequently present in patients with CKD. Not surprisingly, then, HF is also an important cause of morbidity and mortality in this population. The conflicting information on the prevalence of HF in CKD is related to the fact that large differences exist among studies in their definition of the condition and the methods used to establish its presence. In addition, subclinical left ventricular (LV) dysfunction detected in the routine echocardiogram is increasingly being used as an indicator of impending, if not subclinical, HF.

Diastolic heart failure (DHF), also called HF with preserved ejection fraction, refers to a clinical syndrome in which patients have symptoms and signs of HF, normal or near normal LV systolic function, and evidence of diastolic dysfunction (DD; e.g., abnormal LV filling and elevated filling pressure). Recent data suggest that HF with normal ejection fraction is even more common than its presentation with low ejection fraction (1). Indeed, we have recently reported that subclinical DD is also the most common echocardiographic finding in asymptomatic CKD patients on hemodialysis, together with left ventricular hypertrophy (LVH) (2).

The most common conditions associated with DD are aging, hypertension, diabetes mellitus, LVH, coronary disease, and infiltrative cardiomyopathy, all common comorbidities of patients with CKD. Those comorbidities are often associated with the development of myocardial fibrosis and decreased ventricular compliance, physiopathological landmarks of DHF. Among patients with HF, as many as 40–60% have a normal or near normal LV ejection fraction (1,3,4). In such patients, DD is the presumed cause of HF, which can be confirmed by objective measurement (1). Patients with DHF have particular difficulty in tolerating certain kinds of hemodynamic stress including atrial fibrillation (AF), tachycardia, elevation in blood pressure, and acute induction or worsening of DD by ischema. Interestingly, these sources of hemodynamic stress are extremely common in patients with CKD, particularly those on hemodialysis (5).

In the following sections, we review the information available on the mechanisms, clinical presentation, impact, and potential interventions in DHF based on both evidence from the general population potentially applicable to the CKD patients, and therapies that can be particularly applied to CKD patients.

Risk Factors and Mechanisms of DHF in CKD

LVH is the principal myocardial alteration in patients with CKD (6). LVH develops early during the progression of the kidney dysfunction (7), is frequently
accompanied by myocardial fibrosis and DHF, and is an independent risk factor for mortality in this population (8). The structural changes in the uremic myocardium include cardiomyocyte hypertrophy, myocardial fibrosis (due to deposition of type I collagen), and thickening of the intramural arteries and arterioles (9). In concert, these structural changes predispose the heart of patients with CKD to DD, mainly due to the fibrotic changes of the uremic heart in response to a cumulative action of traditional and CKD-related risk factors for DHF.

Interstitial fibrosis is related to changes in collagen myocardial metabolism, which are usually not related to hemodynamic changes, whereas cardiomyocyte hypertrophy and vascular remodeling may be adaptive responses to pressure and volume overload (6). The risk factors involved in LVH and cardiac fibrosis (and consequently DHF) in CKD are divided into three categories: afterload-dependent, preload-dependent, and neither afterload- nor preload-dependent. Preload-related factors involve expansion of intravascular volume, anemia, and high-flow arterio-venous fistulas created for vascular access in hemodialysis patients. The potential myocardial damage generated by these preload factors results in myocardial cell thickening and eccentric LV remodeling. Afterload-related factors include systemic arterial resistance (systolic and diastolic hypertension) and large-vessel compliance (vascular calcification), resulting in myocardial cell thickening and concentric LV remodeling (2).

Preload- and afterload-related factors may operate simultaneously and most likely have synergistic effects. Regardless of the underlying cause, myocardial hypertrophy and myocyte ischemia lead to activation of cellular apoptotic and autophagic signals and activation of pathways causing an increase in production of extracellular matrix, and thus interstitial myocardial cell fibrosis and the functional consequences of DHF (2).

There is now cumulative evidence suggesting that myocardial fibrosis also develops in response to nonhemodynamic factors. This fibrosis occurs not only within the LV but also in the right ventricle and in the interventricular septum. Some of these factors start earlier in the course of CKD, such as hemodynamic overload, oxidative stress, and inflammation; others, such as anemia, hyperphosphatemia hyperparathyroidism, and hypovitaminosis D, play a greater role in more advanced stages of CKD (10,11).

Initially, in response to hypertension, transforming growth factor (TGF)-β and procollagen type I are both increased in patients with LVH, when compared with controls without ventricular alterations (12). Among CKD patients who develop LVH, serum levels of inflammatory biomarkers are significantly higher than those values observed among those without LVH (13). The same relationship has been noted for C-reactive protein and N-terminal pro-B-type natriuretic peptide (14), suggesting a link between LV filling pressure and inflammation.

It is also well known that CKD patients frequently have excessive activation of the renin–angiotensin–aldosterone system (RAS), potentially inducing myocardial fibrosis and hypertrophy. Activation of the intracardiac RAS seems to be critically involved in overload status observed in CKD, but angiotensin II and aldosterone can also be involved in myocardial cell hypertrophy and fibrosis independent of afterload (2). Angiotensin II promotes growth in both fibroblasts and cardiac myocytes, contributing to mycardiopathy of dialysis patients (15), and high aldosterone levels seem to be correlated with LVH independent of hypertension in hemodialysis patients (16).

Anemia also plays a central role in the development of DHF in dialysis patients. The impact of anemia on cardiomyopathy among CKD patients was recently evaluated in a clinical study including serial echocardiograms. In this study, anemia was an independent risk factor for DHF even after adjustment for age, diabetes, and ischemic heart disease (17).

Mineral metabolism disorders, including hyperphosphatemia and elevated parathyroid hormone levels, are common in CKD patients and have been related to cardiovascular mortality in epidemiological studies (18). Exposure of vascular smooth muscle cells to high phosphate concentrations alters its phenotype and induces vascular calcification (19). Indeed, in an animal model of CKD, inducing hyperphosphatemia and a high phosphorus diet were associated with cardiac fibrosis and arterial wall thickening (20). Although there are several mechanisms by which hyperparathyroidism could favor LVH, including direct effects on myocytes and interstitial fibroblasts (21), a permissive role of PTH in interstitial fibrosis has been documented (22).

Finally, hypovitaminosis D is frequently observed in CKD patients (23), is associated with myocardiac hypertrophy (24), and is related to early cardiovascular mortality and sudden cardiac death in dialysis patients (25,26). Although the vitamin D receptor (VDR) is found ubiquitously throughout the body, including in cardiovascular and immune cells, its classical action involves mineral metabolism (27). It has been well established that vitamin D has several biological effects on the heart, including cardiac cell contraction, proliferation, hypertrophy, differentiation, and protein and collagen expression of cardiomyocytes. In addition, vitamin D may play a role in the maintenance of vascular tone and cardiac output (28,29), presenting a potential role of hypovitaminosis D in the development of DHF in CKD.

New approaches to analyze the mechanisms by which DHF develops in CKD V have been emerging in recent years. Much attention has been focused on the novel cellular mediator systems that translate hemodynamic and circulatory alterations to an increase in ventricular mass. Some of these processes can function independently of preload and afterload abnormalities to produce or aggravate LVH. These potential cellular systems involved in DHF include VDR activation, calcineurin/nuclear factor of activated T cells, G-protein-coupled receptor to angiotensin II and endothelin I and the mammalian target of rapamycin (mTOR) pathway (2). Further understanding of these mechanisms is necessary for the development of efficient therapeutic strategies.
Clinical Presentation and Consequences

As described in the previous sections, DD (the pathophysiological substrate for DHF) is a common echocardiographic finding in patients with CKD, and is highly associated with arterial hypertension and LVH (30). Indeed, DD is characterized by alterations in LV relaxation and compliance, often evolving into compensatory elevation of end-diastolic pressure in advanced stages. In a milieu of increased stiffness (secondary to fibrosis), the LV pressure–volume curve shifts to the left, thereby leading to the exacerbation of the effects of blood volume changes on LV filling (31). Hence, a small increase in LV volume could cause pulmonary congestion in patients with adequate fluid control, while volume depletion might elicit a decrease in chamber filling, with hypotension and hemodynamic instability (32).

The potential clinical consequences of this process are an increased risk of hospitalization due to decompensated HF with preserved LV systolic function (33), as well as increased risks of intradialytic hypotension (34) and death (32). In fact, patients with DHF have a very narrow volume (weight) range, presenting with symptoms of fluid overload on the high side, and hypotension on the low side. This may justify, at least in part, the highly common presentation of sudden pulmonary edema and intradialytic hypotension, when even a slight variation in fluid status occurs. Therefore, DHF in patients with CKD should be promptly identified and treated to improve their morbidity and mortality. It is likely that minimizing fluid status shifts will improve outcomes in the patients with DHF, even in its early stages.

Diagnosis: From Gold Standard to Practical Application

Elevation of LV filling pressure is the main physiological finding of DHF and represents a key feature associated with the onset of symptoms (35). LV filling pressures are regulated primarily by filling and passive properties of the LV walls, but may also be affected by alterations in myocardial relaxation and diastolic myocardial tone. Increased afterload can delay myocardial relaxation, particularly when combined with high preload, thereby contributing to filling pressure elevation (36).

According to the European Society of Cardiology, the diagnosis of DHF requires (i) signs or symptoms of HF; (ii) normal or mildly abnormal systolic LV function (ejection fraction > 50%); (iii) and evidence of DD (35). Ideally, gold standard measurement of diastolic function should be invasively obtained with cardiac catheterization. Filling pressure is considered elevated when the mean pulmonary capillary wedge pressure is > 12 mmHg or when the LV end-diastolic pressure is > 16 mmHg (37). However, for practical and ethical reasons, diastolic indices determined by cardiac catheterization cannot be directly applied in the clinical routine.

Therefore, noninvasive Doppler echocardiographic assessment of diastolic function becomes essential in practice, and all efforts should be directed to the achievement of reliable estimates of LV filling pressure. Conventionally, Doppler mitral flow velocities (E, A, and E/A ratio) have been used in clinical practice for the investigation of diastolic function. However, they are strongly load-dependent (38), and may exhibit pseudonormalization of LV filling pattern (mitral flow apparently normal despite the presence of chronic DD) (5). This phenomenon is particularly challenging in patients on HD for whom the relatively high preload before the dialysis session often masks abnormal LV relaxation (39).

Alternative methods have been successfully used to overcome the limitations of Doppler mitral flow velocities, and include assessment of pulmonary venous flow, tissue Doppler of mitral annulus velocity, and left atrium volume index (LAVi). The ratio of early mitral flow velocity (E) to early mitral annulus velocity (e'), called the E/e' ratio, was the most reliable noninvasive predictor of elevated LV filling pressure in a study with renal transplant candidates (40). Likewise, left atrium enlargement, expressed by LAVi, has been recognized as a surrogate marker for chronically augmented LV diastolic pressure in HD subjects (5). In addition, LAVi > 32 ml/m2 was a predictor of mortality in a study with patients on chronic HD, above and beyond clinical data, ejection fraction, E/e’ ratio and LV ventricular mass (5).

As displayed in Table 1, recent guidelines (37) recommend a grading scheme of DD, which integrates information from multiple indices. This approach significantly predicts all-cause mortality in the general (41) and HD population (32).

In patients with DD grade I (impaired relaxation), the mitral E/A ratio is < 0.8, e’ is < 8 cm/second, the E/e’ ratio is < 8 (average septal and lateral), and LAVi can be normal or mildly increased. Nonetheless, it should not be assumed that a decreased mitral E/A ratio in the presence of normal annular tissue Doppler velocity is a manifestation of DD, but rather presents subjacent volume depletion. In general, LV diastolic pressure is not high in patients with DD grade I, with the exception of some cases of long-lasting arterial hypertension or hypertrophic cardiomyopathy.

With further disease progression, LV compliance declines and LV filling pressure begins to increase. Hence, the pattern of DD grade II (pseudonormalization) is observed, with an E/A ratio between 0.8 and 2

| Table 1. Echocardiographic parameters utilized in the classification of diastolic dysfunction (DD) |
|-------------------------------------------------|-----------------|---------------|---------------|
| Normal | DD grade I | DD grade II | DD grade III |
| E/A ratio | 0.8–2 | <0.8 | 0.8–2 | ≥2 |
| e’ (cm/sec) | >8 | <8 | <8 | <8 |
| Average E/e’ | <8 | ≤8 | 9–12 | ≥13 |
| LAVi (ml/m2) | <28 | <34 | ≥24 | >34 |
| Ar – A (ms) | <30 | <30 | ≥30 | ≥30 |

E, early mitral flow velocity; A, atrial mitral flow velocity; e’, early mitral annulus velocity; LAVi, left atrium volume index; Ar – A, time difference between duration of pulmonary venous atrial reversal wave and duration of A wave.
(pseudonormal), $e' < 8$ cm/second, $E/e'$ ratio between 9 and 12, and $LAVi > 34$ ml/m$^2$.

With severe DD grade III (Figure 1), restrictive LV filling arises, with an $E/A$ ratio > 2, a mitral flow duration shorter than Ar pulmonary venous flow duration, $e' < 8$ cm/second, average $E/e'$ ratio > 13 (or septal $E/e' > 15$), and $LAVi > 34$ ml/m$^2$ (often > 40 ml/m$^2$). The later stage predicts the highest LV filling pressure and the worst prognosis, particularly when the restrictive pattern does not revert to impaired relaxation with the appropriate therapy (37). Accurate prediction of LV filling pressure (and therefore prognosis) for a given patient requires the incorporation of all available information, making the integrated approach more consistent than one parameter taken alone.

The presence of LVH is considered sufficient evidence for the diagnosis of DHF when Doppler interrogation yields nonconclusive results (35). Likewise, the onset of AF (which often hinders the interpretation of Doppler data) is also a potential surrogate marker for significant DD (35).

Finally, cardiac magnetic resonance (CMR) may be an interesting noninvasive alternative to the evaluation of DHF in CKD patients (2). CMRI can detect and quantify the presence of intermyocardial fibrosis, as indicated by late gadolinium enhancement (2). This finding has been linked to a predisposition to sudden cardiac death (due to electrical instability) and elevation of LV filling pressures (42) and could indicate the need for a different management strategy. However, CMRI using gadolinium contrast should be avoided in the presence of advanced CKD due to the risk of development of nephrogenic systemic fibrosis (43).

**Treatment**

An increasing number of trials in the CKD population, observational data, and studies in animal models of uremia have strongly influenced the principles of how LVH and DD are managed. The general principles for treatment of DHF can be applied to the CKD population (Table 2), namely control of systolic and diastolic hypertension, control of ventricular rate particularly in patients with AF, control of pulmonary congestion and peripheral edema with diuretics, and coronary revascularization in patients with coronary heart disease when it appears that ischemia is impairing diastolic function (44). Development of strategies to minimize large volume shifts (high-dose loop diuretic use, salt and water restriction, more frequent dialysis, continuous peritoneal dialysis) and identification of the correct dry weight,

**TABLE 2. Strategies for prevention and control of diastolic heart failure in CKD patients**

<table>
<thead>
<tr>
<th>Strategies extrapolated from the general population</th>
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<tbody>
<tr>
<td>Control of systolic and diastolic hypertension</td>
</tr>
<tr>
<td>Control of ventricular rate, particularly in patients with atrial fibrillation</td>
</tr>
<tr>
<td>Reduce fluid overload (salt restriction, diuretics)</td>
</tr>
<tr>
<td>Coronary revascularization in patients with coronary heart disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strategies directed to specific CKD-related factors</th>
</tr>
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<tbody>
<tr>
<td>Maintain hemoglobin levels in the recommended range</td>
</tr>
<tr>
<td>Control hyperphosphatemia, treat hyperparathyroidism (VDR activators, calcimimetics), maintain sufficient 25(OH)D$_3$ levels</td>
</tr>
<tr>
<td>Salt restriction, interdialytic fluid restriction, monitorization of dry weight</td>
</tr>
<tr>
<td>Renin–angiotensin–aldosterone inhibition</td>
</tr>
<tr>
<td>More frequent or longer dialysis sessions; potential benefit of peritoneal dialysis</td>
</tr>
</tbody>
</table>

$^a$Potential therapies based on experimental models, without clinical experience.

VDR, vitamin D receptor.
particularly in hemodialysis patients, are of pivotal importance.

An important caveat is that the patient who has DHF with a small, stiff LV chamber is particularly susceptible to excessive preload reduction, which can sequentially lead to the underfilling of the LV, a drop in cardiac output, and hypotension. In patients with severe LVH due to hypertension or hypertrophic cardiomyopathy, excessive preload reduction can also create subaortic outflow obstruction. For these reasons, the administration of diuretics or venodilators such as nitrates, dihydropyridine calcium channel blockers, and angiotensin converting enzyme (ACE) inhibitors must be done with caution. Restoration and maintenance of sinus rhythm is preferred when AF occurs in patients with DHF. When this cannot be achieved, rate control becomes essential. The lack of direct evidence to support a specific drug regimen to treat DHF in the general population is even more striking in CKD.

The impact of recombinant human erythropoietin on left ventricular mass index (LVMi) was examined in a recent meta-analysis that included 1731 CKD and ESRD patients on dialysis; both low (conventional) target hemoglobin (Hb) levels (≤12 g/dl) and high target values (≥12 g/dl) were examined. Aggregated results suggest that in severe anemia conventional Hb targets are associated with a reduction in LVMi, but that in moderate anemia target Hb above 12 g/dl does not significantly benefit LVMi when compared with conventional targets (45).

Blood pressure control is important and has beneficial effects on LVH in CKD and ESRD patients. Regression of LVH and improvement in diastolic function was observed in hypertensive patients treated with telmisartan (46). The use of candesartan in hemodialysis patients significantly reduced cardiovascular mortality endpoints including congestive HF, severe arrhythmias, and sudden death (47). The observed benefit may be due to regression on myocardial fibrosis. This was demonstrated in a hypertensive population in a clinical study that included endomyocardial biopsies and echocardiographic analysis (48).

Another pharmacological intervention with potential antifibrotic action involves a class of aldosterone block receptors (spironolactone). Studies conducted in CKD patients (49) and in animal models of uremic cardiomyopathy (50) suggested an important antifibrotic effect of spironolactone, resulting in reduction in LV mass and improvement of arterial stiffness that is likely independent of blood pressure control (51). One common problem with these drugs is the development of hyperkalemia, limiting more widespread spironolactone use in CKD patients, particularly those in advanced stages of CKD. In a small non-randomized and non-blinded clinical study in hemodialysis patients, low-dose spironolactone (25 mg, 3 times/week) was not associated with more frequent hyperkalemia during the 8-week follow-up (52).

Activation of VDRs may also play a role in the prevention and treatment of DHF. Dialysis and nondialysis patients receiving vitamin D therapy seem to have a lower frequency of cardiovascular events and improved survival (53), by mechanisms not only related to mineral metabolism control, but also probably related to VDR activation in cardiovascular tissue (29). Several studies in the dialysis population, using activated and nonactivated (nutritional) vitamin D have been conducted with cardiovascular endpoints. In patients with secondary hyperparathyroidism on hemodialysis, intravenous calcitriol caused regression in myocardial hypertrophy (54), as well as improved cardiac systolic and diastolic function (55). Indeed, vitamin D deficiency is highly prevalent among the dialysis and nondialysis population (56,57) and its supplementation with cholecalciferol is associated with a reduction in LVMi and attenuation of systemic inflammation (58).

Other interesting approaches (although primarily based on preliminary experimental observations) to attenuate DHF in CKD patients deserve attention. Torsemide is a loop diuretic with potential myocardial antifibrotic action; unlike furosemide, it may decrease myocardial collagen accumulation (59). In addition, LV mass decreases in renal transplant patients with LVH when converted to a sirolimus-based regimen (60), independently of better blood pressure control. In animal models, this effect appears to involve the mTOR pathway.

Finally, observational studies showed that more frequent or longer hemodialysis sessions are associated with a lower prevalence of LVH (61). More recently, a randomized clinical trial showed that, when compared with patients on conventional dialysis, those on a more frequent treatment schedule had regression of LVH (62). However, there are clear problems with measuring LVMi in dialysis patients. Moreover, regression of LVH as a favorable outcome remains a controversial issue (63).

Summary and Conclusions

DHF represents a common and potentially harmful clinical condition in CKD, particularly in patients on hemodialysis treatment who are more susceptible to shifts in fluid volume. The reasons for this high prevalence are related to the presence of many traditional risk factors, and the synergistic effects of many peculiar factors related directly to CKD and dialysis treatment. The under-recognition of DHF in dialysis patients may be related to the atypical clinical presentation, and to the underuse of simple methods of myocardial function evaluation, such as the echocardiogram. A broader recognition of the condition and the development of clinical trials to test interventions (approaching risk factors both already applied in the general population and those peculiar to CKD) may allow a significant reduction in morbidity and mortality in this patient population.

References


