CHAPTER 117

The Kidney in Diastolic Dysfunction

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OBJECTIVES

This chapter will:

1. Review the pathophysiology of diastolic dysfunction and the complex interaction between the heart and the kidney in the context of cardiorenal syndromes (disorders of the heart and kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other).
2. Explain the role of congestive kidney failure (venous congestion or backward failure) as a critical mechanism of kidney injury in patients with hemodynamic alterations related to diastolic dysfunction and diastolic heart failure.

More than 5 million people in the United States have a diagnosis of heart failure (HF). More than 650,000 new cases are diagnosed annually, with an associated mortality of 50% within 5 years from first diagnosis.[1] Although HF with reduced ejection fraction (EF) has been well studied, HF with preserved EF (EF > 50%), also referred to as diastolic HF (DHF), has been identified only recently as a clinical pathology, despite the fact that it accounts for half of all HF cases and is responsible for the majority of hospital admissions related to HF.[2,3] Recent studies indicate that the incidence of DHF is increasing and that a greater portion of patients hospitalized with HF have a diastolic dysfunction (DD).[4] According to the American College of Cardiology Foundation/American Heart Association task force, DHF may be defined as including the following: (1) clinical signs or symptoms of HF; (2) evidence of preserved or normal left ventricle (LV) EF; and (3) evidence of abnormal LV DD that can be determined by Doppler echocardiography or cardiac catheterization.[2,5] Higher age, obesity, coronary artery disease, diabetes mellitus, atrial fibrillation (AF), and hyperlipidemia have a high prevalence in patients with DHF, whereas hypertension is the most frequent of them with a prevalence of 60% to 89%.[3,6] DD may appear many years before any symptom develops and may represent the first phase of DHF. Therefore it is important to detect DD early and to start treatment as soon as possible after diagnosis. DD and DHF are systemic disorders rather than an isolated cardiac disorder. Distal organ effects, with particular focus on kidney function, are addressed in this chapter.

PATHOPHYSIOLOGY AND HEMODYNAMICS IN DIASTOLIC DYSFUNCTION

The diastolic phase of the cardiac cycle takes over from systolic ejection at aortic valve closure and includes a fall in LV pressure, rapid filling, and atrial contraction. Contraction and relaxation share common molecular processes and are closely interlinked. Diastolic function is an active energy process requiring energy that may be defined roughly as the ability of the LV to receive blood from the left atrium (LA) after the mitral valve has opened.[7] Adenosine triphosphate (ATP) is necessary to release the bridges between the cardiac myofilaments and to restore the cytoplasmic calcium concentration.[8] Perturbations of ATP or calcium levels impair LV relaxation (as seen during myocardial ischemia), leading to DD, the central pathophysiologic feature in patients with DHF. Anatomic alterations of sarcomere muscle tissue resulting from post-translational modifications of titin (a protein that connects the Z-line to the M-line in the sarcomere) are responsible for increased stiffness.[7] Specifically, titin is a sarcomeric protein, which regulates myocardial passive tension, stiffness, and biomechanical stress/stretch, placed from the Z-disk to the M-band. Titin works as a spring responsible for early diastolic recoil and late diastolic resistance to stretching.[9] It has been demonstrated that metabolic and inflammatory diseases may promote posttranslational modifications of titin, resulting in impaired early recoil and reduced LV compliance.[10]

LV hypertrophy, a classic finding in hypertensive patients that frequently is accompanied by myocardial fibrosis, worsens ventricular relaxation, and increases stiffness. Recent studies performed with cardiac resonance imaging have confirmed this by demonstrating that hypertrophic LV is not only thickened but also fibrotic.[11] DD can be found in patients without LV hypertrophy and/or increased fibrocellular stiffness, indicating that diastole is an active process and energetics is at least as important as structural changes. Pharmacologic or molecular changes therefore may have a fast positive or negative effect on diastolic phase of the cardiac cycle.[12] For instance, norepinephrine may have positive lusitropic (promoting relaxation) effects, whereas proinflammatory cytokines (e.g., interleukin-1 [IL-1] and IL-18) may have negative lusitropic effects.[7,13] As a demonstration of the frequency of DD in critically ill

patients, a recent study performed in a general intensive care unit (ICU) showed that approximately half of the patients had LV DD (assessed by tissue Doppler image [TDI]), suggesting that chronic and acute inflammation may impair diastolic function.[14] Most of the negative effects of DD on distal organ (including the kidneys) are directly related to hemodynamic alterations involving the heart chambers, pulmonary circulation, and venous pressure. The abnormal active myocardial relaxation, associated with the (anatomic) passive ventricular stiffness, leads to pathologic ventricular filling that shifts the ventricular pressure-volume loop upward and to the left, increasing LV filling pressure for any given volume. This characteristic (pulmonary capillary wedge pressure > 12 mm Hg or LV end diastolic pressure > 16 mm Hg) is a cornerstone finding in DD because of an increased LV stiffness as opposed to LV filling.[15] Therefore the physiologic trademarks of LV DD are reduced relaxation, loss of restoring forces, reduced diastolic compliance, and elevated LV filling pressure (compensatory mechanism to maintain LV filling and stroke volume). LV pressure during diastole is in equilibrium with LA and pulmonary capillary pressure. Pulmonary hypertension is a common finding in patients with DD because the increase in LA pressure is transmitted in a retrograde fashion to the pulmonary veins in the absence of pulmonary artery disease or mitral stenosis.[15,16] Such hemodynamic changes are reflected clearly to distal organs.

DD is part of a complex clinical picture that includes one or a combination of the following aspects: abnormal ventricular-arterial coupling; systolic dysfunction; pulmonary hypertension; neuroendocrine dysfunction; and multiple comorbidities that frequently act together in the devolvement of complex clinical scenarios. Moreover, diastolic function is affected by several "nonstatic" factors such as circulatory blood volume, preload, and contribution from atrial contraction. Extrinsic factors, mainly pericardial restraint and right ventricle (RV)-LV interaction, also may be involved. With a variable entity, all these factors influence the cardiovascular and respiratory physiology determining different degrees of heart-related organ effects in acute, chronic, or acute-on-chronic clinical pictures. Chronic pressure overload leads to vascular remodeling and functional-anatomic precapillary and postcapillary pulmonary hypertension. Once the pulmonary pressure has increased, the RV afterload increases as well, leading to RV failure.

In patients with heart failure with EF exceeding 50%, it has been shown that 65% have systolic pulmonary pressure greater than 40 mm Hg, and 35% have some degree of RV dysfunction (evaluated by tricuspid annular plane systolic excursion, or TAPSE).[17] Those patients were more likely to be treated with diuretics compared with those with normal RV function, suggesting a type of distal organ-dysfunction relationship to heart disease.[17] In addition, RV dysfunction is known to confer poor outcomes in these patients, including increased hospitalization and higher overall and cardiovascular mortality. It has been demonstrated clearly that RV failure causing systemic venous congestion leads to gut edema, malabsorption, congestive liver disease, cardiorenal syndrome (see later in chapter), and systemic inflammation. Moreover, because of the ventricular interdependence, LV DD, especially when associated with RV failure, may cause a decrease in cardiac output (CO), leading to complex hemodynamic alterations that combine pulmonary artery pressures increase, systemic venous pressure increase, and systemic arterial flow and pressure decrease. In addition, LV contractility is supposed to be normal in DD. However, the contractile velocity in systole measured by tissue Doppler echocardiography is reduced in systolic and diastolic dysfunction. Therefore the systolic phase of the cardiac cycle may be compromised globally or regionally.[18,19] Diastolic function also is impaired in patients with systolic dysfunction, decreasing exercise tolerance and representing one of the determinants of the outcome.[20] As a consequence, patients with DD always should be considered carriers of systodiastolic impairment and vice versa, despite the fact that heart failure with preserved EF or heart failure with reduced EF are used currently to classify these patients.

In light of these mechanisms, it is not surprising that patients with end-stage kidney disease frequently show a pathophysiologic pattern of DD with preserved EF, suggesting a possible bidirectional worsening of heart function by renal disease and renal function by heart failure[20] (see later in this chapter). In addition, it is not surprising that subclinical DD has been reported as the most common echocardiographic finding in asymptomatic hemodialysis patients with LV hypertrophy, because uremic cardiomyopathy includes cardiac hypertrophy, myocardial fibrosis, and thickening of the intramural arteries and arterioles.

FROM HEART TO KIDNEY AND THE CARDIORENAL SYNDROMES

Renal dysfunction and cardiovascular disease are bridled closely around a multifactorial pathophysiology involving decreased renal perfusion, atherosclerosis, inflammation, endothelial dysfunction, and neurohormonal activation. DD often coexists with renal failure and vice versa in acute and chronic clinical conditions. Heart-kidney interaction is a central issue in cardiac (vs. kidneys) and renal (vs. heart) diseases.[21] In fact, renal dysfunction is very common in patients with acute (and chronic) heart failure and is an independent predictor of mortality.[22] It is accepted widely that renal arterial perfusion (antegrade flow) is a foremost determinant of renal dysfunction, but recent studies have identified renal dysfunction as an important predictor in mortality in patients with preserved systolic cardiac function, and many investigations suggest a central relationship between renal dysfunction and venous congestion (backward failure): "congestive kidney failure."[23] In this light, a posthoc propensity score analysis performed on a large trial conducted in the United States and Canada showed that chronic kidney disease–associated mortality was higher in patients with diastolic (371 extra deaths/10,000 person-years; hazard ratio = 1.71; 95% CI = 1.21–2.41; P = .002) than systolic HF (214 extra deaths/10,000 person-years; hazard ratio = 1.19; 95% CI =1.07–1.32; P = .001).[24]

Damman et al. investigated the relationship between increased central venous pressure (CVP), a characteristic hemodynamic condition in patients with DD, obtained during heart catheterization, renal function, and mortality in 2557 patients with cardiovascular diseases.[23] The authors observed that increased CVP was associated with impaired renal function in a broad spectrum of cardiovascular patients and that in a median follow-up time of 10.7 years, in those 741 (29%) patients who died, CVP was an independent predictor of reduced survival (hazard ratio: 1.03 per mm Hg increase, 95% CI: 1.01–1.05, P = .0032) especially when CVP levels exceeded 6 mm Hg. The main finding in Damman et al.'s study was a biphasic relationship between estimated glomerular filtration rate (eGFR) and increasing CVP. Values up to 6 mm Hg were associated with a gradual increase in eGFR; this behavior is explained probably with the positive

effect of increased biventricular preload according to the Frank-Starling low leading to higher systemic flow and increased renal perfusion. Once CVP had exceeded 6 mm Hg, eGFR progressively decreased, suggesting a direct negative effect on renal function. Interestingly, the calculated slope between CVP and impaired eGFR was steeper with relatively preserved cardiac function. Notably, the relationship between CVP and GFR is probably bidirectional: increased CVP may impair GFR, and impaired renal function may initiate salt and water retention, resulting in increased cardiac filling pressures.[25]

Experimental studies performed in the early 2000s have shown that increasing renal venous pressure causes a reduction in glomerular filtration, which was mediated probably by a decreased renal perfusion.[23] Damman et al., in a previous study, demonstrated that in patients with pulmonary hypertension and cardiac failure, increase in CVP was associated strongly with renal impairment.[26] As a confirmation of this relationship, cardiac surgery–associated acute kidney injury (AKI) is one of the most frequent causes of postoperative AKI, affecting up to 30% of patients, because of a number of covariates affecting the renal function in different pathways.[27] Among them, early postoperative CVP above 14 cm H_2O (10.3 mm Hg) was identified as a significant risk factor for development of AKI in a cohort of patients undergoing elective cardiac surgery independently of reduced CO.[28] In support of the direct relationship between DD and kidney dysfunction, a study that compared levosimendan, a calcium sensitizer with positive lusitropic effects, with dobutamine, showed a more pronounced improvement of renal function in the group receiving levosimendan in comparison with those who received dobutamine.[29] Although levosimendan has multiple effects, including inotropic (positive), the specific venodilatation may support a direct pathophysiologic link between CVP and renal impairment.

Although pathophysiology of renal failure in DD with increased CVP is not understood completely, venous congestion (indicated from many authors as increased renal afterload) and increased interstitial pressure may represent central mechanisms. Moreover, the combination of venous congestion with reduced CO, frequently associated with DD, may configure a complex pathophysiologic scenario, involving different types of cardiorenal mechanisms.[21] Consistent data suggest that CVP is an important hemodynamic factor contributing to a worsening in renal function, especially when CO is decreased.[30] Notably, reduced renal blood flow, in the context of acute HF with low-CO, poorly predicts renal failure, suggesting that CO is frequently sufficient to maintain renal perfusion to an adequate level and underlying the central role of venous congestion.[31] Similarly, a worsening in renal function may be attributed, in part, to hypoperfusion of the kidney because of progressive impairment of CO or intravascular volume depletion secondary to diuretic therapy that represents a central therapy in patients with DHF.[30,32,33]

In 145 patients admitted to the hospital for acute decompensated heart failure, Mullens et al. observed that venous congestion, characterized by increased CVP on admission as well as insufficient reduction of CVP during hospitalization, was the strongest hemodynamic determinant for the development of a worsening in renal function.[30] Mullens et al. efficaciously highlighted the central pathophysiologic role of "congestive kidney failure" moving the floodlights from an "antegrade" (from the left heart to the kidney) to a "retrograde" (back from the right heart to the kidney) view. In other words, increased venous pressure may affect independently renal function and structure independently of the maintenance of renal perfusion pressure and flow.[34] However, increase in venous pressure is frequently part of complex systemic pathophysiologic conditions (e.g., acute systolic and systodiastolic dysfunction), in which renal injury derives from multiple causes and strategies aimed to decrease renal vein pressure are of primary importance to improve renal function and limit further worsening.[31,35] A recent study, performed with a large database including elective cardiac surgery patients undergoing coronary artery bypass surgery, was designed specifically to explore the prognostic role, in terms of mortality and renal failure, of 6 hours postoperative CVP.[36] Interestingly, CVP was predictive of mortality and renal failure independently of cardiac index, suggesting that high CVP exposes to the development of renal dysfunction. For renal failure, the risk-adjusted odds ratio (OR) was 5.5 (95% CI, 1.93–15.5; $P = .001$) with every 5-mm Hg rise in CVP for patients with CVP less than 9 mm Hg. For patients with CVP greater than or equal to 9 mm Hg, the risk-adjusted OR was 1.3 (95% CI, 1.01–1.65; $P = .045$).[36]

The direct relationships between heart and kidney have led to the definition of a precise clinical context: the cardiorenal syndromes (CRSs). CRSs include a number of diseases, classified into five subtypes, in which cardiac diseases have negative effects on renal function, leading to complex and mutual relationships between the two.[31] In other words, CRSs are "disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other."[37]

Because *cardiorenal* is a term that indicates a condition in which cardiac dysfunction drives renal dysfunction (the opposite is renocardiac), and because renal congestion is crucial in acute CRSs, kidney consequences of DD can be incorporated in this area. For a specific description of the CRSs, we refer to dedicated reviews[21,37,38] and book chapters. Kidney injury in acute CRS results from the combination of renal venous congestion, decreased renal blood flow (critical in heart failure with reduced systolic function), and activation of inflammatory pathways.[37,38] Any type of decompensated HF may lead to a decrease in renal plasma flow and/or renal perfusion pressure that activate some autoregulation mechanisms aimed at maintaining glomerular filtration (e.g., modulating the vascular tone of the glomerular efferent and afferent arterioles).[39] Although this mechanism tends to maintain GFR, tubuloglomerular feedback, which consists of vasoconstriction of the afferent arterioles in response to a raise of solute concentration at the macula densa of the distal tubule, may impair glomerular filtration. In addition, acute HF is associated with several factors known to impair renal autoregulation: upregulation of the renin-angiotensin-aldosterone system, arterial hypertension, diabetes, atherosclerosis, and angiotensin-converting enzyme inhibitors therapy.[31]

An intriguing pathophysiologic factor that has been postulated to favor renal dysfunction in the presence of DD is the systemic and renal inflammation derived by venous congestion determining endotoxin release from the gut.[31,40] No specific therapy for DD is suggested by current guidelines,[2,41] whereas relief of congestion with loop diuretics remains the primary treatment goal in patients with acute HF and CRS.[2,31,41] In this light, a worsening in renal function could be observed during effective decongestive therapy. In two large, single-center cohort studies of patients who received aggressive fluid depletion and negative fluid balance to treat an acute HF and CRS, worsening in renal function but better mid- and long-term outcomes were observed.[32,33] In a posthoc analysis of the PROTECT (Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function)

trial showed that an increase in hemoglobin (diuretic effect on hemoconcentration) during the first week was associated independently with a favorable outcome, despite a slight decrease in renal function.[42] Additional therapeutic approaches, depending on the clinical context, should be directed toward adequate treatment of hypertension and myocardial ischemia and control of the ventricular rate in patients with AF.[2,41]

In conclusion, LV DD is a combination of complex functional and anatomic alterations that involve the pulmonary circulation, the RV, and the central and peripheral venous circulation. The basic hemodynamic effects of DD, increased LV filling pressures, and increased pulmonary and central venous pressures, cause negative effects on distal organ (including kidneys). These cornerstone hemodynamic features of DD frequently are framed into multifaceted clinical conditions, including pure acute diastolic dysfunction, acute systodiastolic dysfunction, and chronic or acute-on-chronic clinical states. What is critical is to take into serious consideration the pathophysiology of venous congestion in these articulated pictures frequently including variable degrees of kidney dysfunctions.

Key Points

1. Heart failure with preserved ejection fraction (diastolic heart failure) has been identified only recently as a clinical pathology, despite the fact that it accounts for half of all heart failure cases and is responsible for the majority of hospital admissions related to heart failure.
2. Diastolic dysfunction may appear a long time before any symptom develops and may represent the first phase of diastolic heart failure. It is therefore important to detect diastolic dysfunction early because it is a systemic disorder affecting distal organs including the kidney.
3. Most of the negative effects of diastolic dysfunction on distal organ (including the kidneys) are related directly to hemodynamic alterations involving the heart chambers, pulmonary circulation, and venous pressure. Heart-kidney interaction is a central issue in cardiac (vs. kidneys) and renal (vs. heart) diseases.

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A complete reference list can be found online at ExpertConsult.com.

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