INTRODUCTION

In patients with chronic kidney disease (CKD), cardiovascular disease is the most common cause of death. Patients with CKD have a high burden of conventional risk factors that are closely related to accelerated atherosclerosis, left ventricular (LV) hypertrophy, high LV filling pressure, and diastolic dysfunction ***(Fink et al., 2012).***

Chronic Kidney Disease (CKD) is a major public health problem worldwide with increased incidence and prevalence. CKD is risk factor for cardiovascular event and complications increases as CKD progress to end stage renal disease (ESRD) ***(Agodoa et al., 1995).*** Cardiovascular (CV) mortality is 10-20 times more common in ESRD patients on renal replacement therapy as compared to general population. CKD is closely related to LV hypertrophy and fibrosis, which is closely associated with stiff ventricles and abnormalities in ventricular relaxation. Thus, a small increase in preload can result in significantly increased left atrial and pulmonary vein pressures, thereby causing pulmonary edema even with normal LV systolic function ***(Parfrey et al., 1996).***

LVH is the principal myocardial alteration in patients with CKD ***(London et al., 2002).*** LVH develops early during the progression of the kidney dysfunction ***(Levin et al., 1996),*** is frequently accompanied by myocardial fibrosis, and is an independent risk factor for mortality in this population

(Silberberg et al., 1989). 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 lengthening 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 ***(Glassock et al., 2009).*** Consequently, diastolic dysfunction becomes established leading to signs and symptoms of heart failure with preserved ejection fraction (HFpEF).

There is now cumulative evidence suggesting that myocardial fibrosis also develops in response to nonhemodynamic factors, such as anemia, hyperphosphatemia hyperparathyroidism, and hypovitaminosis D ***(Diez et al., 2008; Lopez et al., 2008).*** In chronic renal failure patients, secondary hyperparathyroidism affects cardiac diastolic function by impairing LV passive compliance, by inducing myocardial calcification, and by causing LVH through inducing arterial wall stiffness ***(Rostand et al., 1999).***

According to the European Society of Cardiology, the diagnosis of heart failure with preserved ejection fraction (HFpEF) requires (i) signs or symptoms of HF; (ii) normal or mildly abnormal systolic LV function (ejection fraction >

50%); (iii) and evidence of DD ***(Paulus et al., 2008).*** 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. However, for practical and ethical reasons, diastolic indices determined by cardiac catheterization cannot be directly applied in the clinical routine ***(Nagueh et al., 2009).***

While echocardiography (ECHO) is a conventional method that can measure systolic and diastolic functions of ventricles, most traditional echo parameters of LV diastolic functions are affected by alterations in loading conditions and are therefore called load-dependent ***(Drighil et al., 2008).*** In hemodialysis patients, loading influence is principal for the functional examination of the heart. Certainly, the alterations in volume status cause significant changes in preload and afterload and ultimately effect the LV diastolic function measurements ***(Civilibal et al., 2009; Akkaya et al., 2012; Fijalkowski et al., 2006).***

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 ***(Barberato et al., 2004),*** and may exhibit pseudonormalization of LV filling pattern (mitral flow apparently normal despite the presence of chronic DD) ***(Barberato et al., 2007).*** This phenomenon is particularly challenging in patients on hemodialysis for whom the relatively high preload often masks abnormal LV relaxation. 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) ***(Barberato et al., 2006).***

In this study, we hypothesize that there is a possible interrelationship between LV diastolic dysfunction detected by tissue Doppler imaging and end stage renal disease patients undergoing regular dialysis, correlated with different specific lab values.

Aim of the Work

To evaluate the possible impact of renal replacement therapy in the form of regular dialysis provided to end stage renal disease patients on left ventricular diastolic function by implementing tissue Doppler imaging.

Chapter 1:

HEART FAILURE WITH PRESERVED EJECTION FRACTION AND LV DIASTOLIC DYSFUNCTION

Definition

Heart failure (HF) is a clinical syndrome associated with poor quality of life, substantial health-care resource utilization, and premature mortality, in large part related to high rates of hospitalizations in patients with HF ***(Heidenreich et al., 2013; Ponikowski et al., 2016; Yancy et al., 2013).***

Epidemiology

Heart failure with preserved ejection fraction (HFpEF) is a major global public health issue. Its prevalence is between 1.1% and 5.5%, accounting for a staggering 40%-70% of heart failure cases. Of all patients with heart failure, the proportion of those with HFpEF continues to rise (at about 1% per year). If current trends persist, HFpEF may become the predominant phenotype of heart failure within the next decade ***(Steinberg et al., 2012; Braunwald, 2013).***

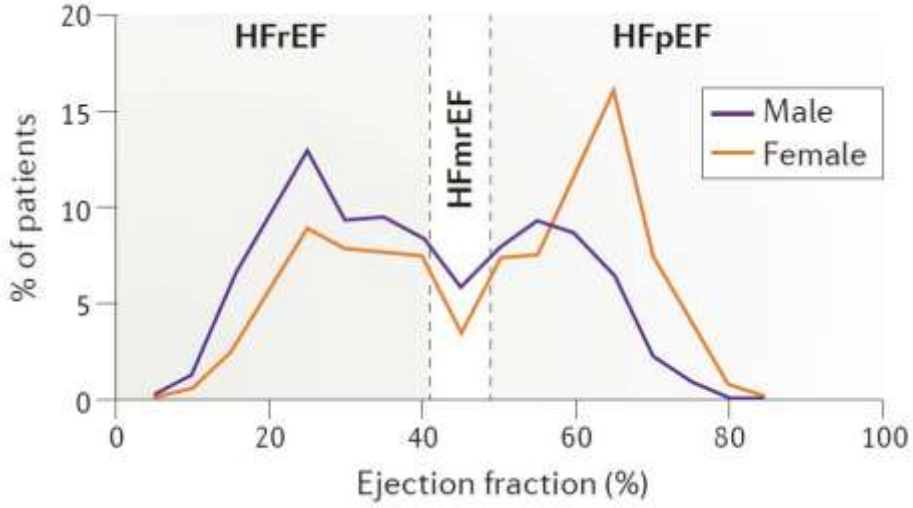

Figure 1: Epidemiology of heart failure

Among 556 HF cases in Olmsted County, LVEF was ≥50% in 55% among whom Doppler evidence of diastolic dysfunction was present in 78% (mild 7%, moderate 63%, and severe 8%). Diastolic assessment was normal in 10% and indeterminate in the remainder ***(Pfeffer et al., 2019).***

Pathophysiology

Among patients with the clinical syndrome of HF, left ventricular (LV) ejection fraction (EF) has emerged as a clinically useful phenotypic marker indicative of unique pathophysiological mechanisms and, most importantly, response to therapies. The EF shows a bimodal distribution among patients with HF and patients are classified as having HF with reduced EF (HFrEF; EF ≤40%) or preserved EF (HFpEF). The EF criteria for defining HFpEF has varied, but

the latest guidelines restrict designation of HFpEF to patients with an EF ≥50%, and assign patients with HF and an EF of 41–49% as having 'borderline' or 'mid‑range' EF ***(Redfield et al., 2016; Dunlay et al., 2012).***

At its core, HFpEF represents severe dysfunction of the diastolic phase of the cardiac cycle that results in elevated ventricular pressures. Impairment of myocardial relaxation and stiffness of the ventricle culminate in reduced left ventricular filling, elevated diastolic pressures, and heart failure symptoms.

Fundamentally, the signs and symptoms of HFpEF are largely related to abnormal hemodynamics, and these are ultimately caused by abnormalities in cardiovascular structure and function.

Many factors contribute to the increases in left ventricular diastolic pressure. In the traditional pathophysiological model, pressure overload leads to concentric left ventricular hypertrophic and fibrotic remodeling and diastolic dysfunction. Ultimately, the left ventricular diastolic dysfunction leads to left atrial hypertension and remodeling, pulmonary venous hypertension, and right ventricular and atrial remodeling and dysfunction ***(Borlaug et al., 2016).***

Among the emerging paradigms is one integrating the underlying metabolic milieu, endothelial inflammation, and

cardiomyocyte function. Following this theory, various proinflammatory conditions provoke microvascular inflammation at the endothelial level. The resultant cytokine storm leads to nitric oxide scavenging with insufficient supply of vasodilator molecules (cyclic guanosine monophosphate content, protein kinase G). Low nitric oxide bioavailability leads to tissue-level oxidative stress, interstitial fibrosis, and cardiomyocyte tension. Stiffness of the myocardium ensues, with the accompanying heart failure symptoms ***(Tschöpe et al., 2014; Paulus et al., 2013).***

In myocardium of patients with HFpEF there is microvascular endothelial activation, presumably related to underlying systemic inflammation, that is demonstrated by upregulation of E-selectin and intercellular adhesion molecule-1 expression levels and uncoupling of endothelial NO synthase associated with reduced myocardial nitrite/nitrate concentration, cGMP content, and PKG activity ***(Franssen et al., 2016).***

Patho- physiologically, diastolic dysfunction is defined by varying combinations of abnormal active relaxation (an energy-requiring process) and passive stiffness related to inherent properties of the myocardium, extracellular matrix, and pericardial restraint. Diastole is an extraordinarily complex process. Active relaxation requires adenosine triphosphate to initiate dissociation and reuptake of calcium from troponin C back into the sarcoplasmic reticulum, resulting in uncoupling of

actin and myosin cross-bridging and return of myofibrils to their pre-contractile length ***(Sharma et al., 2014).***

A recent study of isolated myocardium from patients with HFpEF has revealed that contraction and relaxation are prolonged compared with controls, in tandem with elevated sarcomere calcium levels, even as intracellular sodium and calcium handling protein expression appear unaffected ***(Runte et al., 2017).***

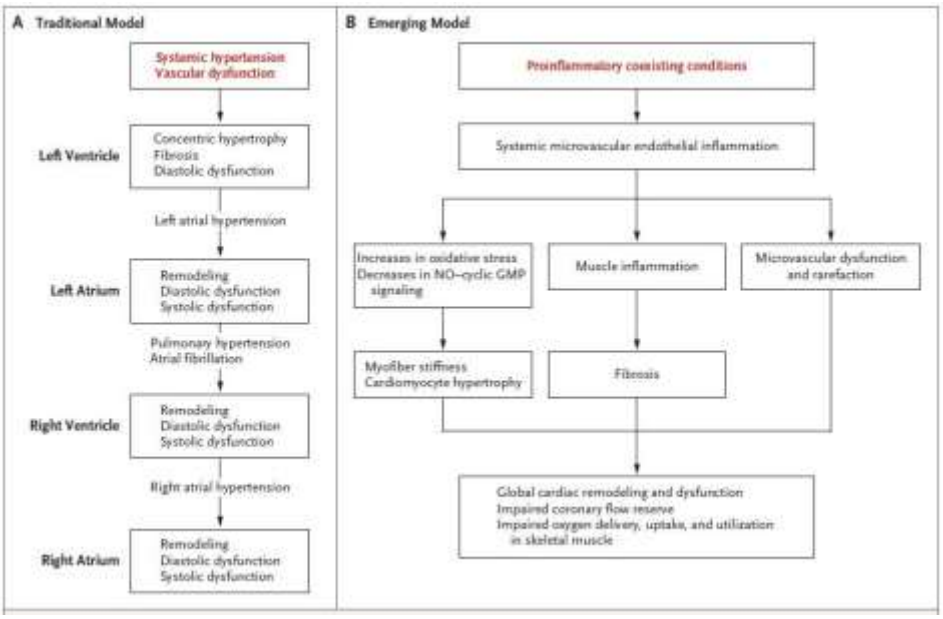

Figure 2: Pathogenesis of HFpEF

Increases in diastolic LV stiffness in HFpEF have also been related to alterations in titin content and phosphorylation as well as fibrillar collagen. Titin, in particular, appears to be a major player since it is a dominant cellular determinant of stiffness that can be dynamically modulated, either by altering

phosphorylation status or protein expression ***(Methawasin et al., 2016).***

Diagnosis

To make a definite diagnosis of HFpEF, the simultaneous presence of the following 3 clinical/ echocardiographic/ hemodynamic abnormalities is required: 1) Evidence of congestive heart failure (typical signs and symptoms, ancillary tests, and response to diuretic treatment); 2) Normal left ventricular systolic function (left ventricular ejection fraction >50%; measured within 3 days of heart failure presentation); and 3) Evidence of left ventricular diastolic dysfunction (impaired left ventricular relaxation/ filling/distensibility) ***(Ponikowski et al., 2016).***

Diagnosis of left ventricular diastolic dysfunction is through invasive hemodynamic measurements (ie, mean pulmonary capillary wedge pressure >12 mm Hg, left ventricular enddiastolic pressure >16 mm Hg, time constant of left ventricular relaxation >48 ms). An alternative way to make the diagnosis is via a tissue Doppler assessment of left ventricular dysfunction. The E/E' value, a ratio of early mitral valve flow velocity to the early diastolic lengthening velocity is typically used. High values (typically >14) reflect heightened left atrial filling pressures and support a diagnosis of HFpEF. Values lower than 8 would make the diagnosis of HFpEF very unlikely. Levels between 8 and 14 are borderline, and a

diagnosis of HFpEF would be made only if natriuretic peptides are elevated (N-terminal pro brain natriuretic peptide [BNP] >220 pg/mL; BNP >200 pg/mL) or with specific tissue Doppler abnormalities suggestive of diastolic dysfunction (ie, left ventricular mass index >122 g/m2 in women; 149 and above in men) ***(Oren et al., 2017).***

Diastolic dysfunction (DD) reflects impaired ability of the myocardium to relax and the left ventricle (LV) to fill appropriately without increasing filling pressures. It may relate to altered LV geometry, myocardial stiffness and fibrosis, molecular mechanisms underlying delayed myocardial relaxation and tone, and disturbed ventricular–arterial coupling ***(Kitzman et al., 2012).***

The majority of patients with diastolic dysfunction exhibit abnormal active myocardial relaxation and passive ventricular stiffness that contribute to abnormal ventricular filling in diastole and shift the normal ventricular pressure-volume curve upward and to the left, thereby resulting in a higher LV filling pressure for any given filling volume. In addition, neurohormonally mediated increases in venous tone and systemic arterial pressure may contribute to shifting blood to the central circulation, and thereby further increase LV filling pressure ***(Komamura et al., 2013).***

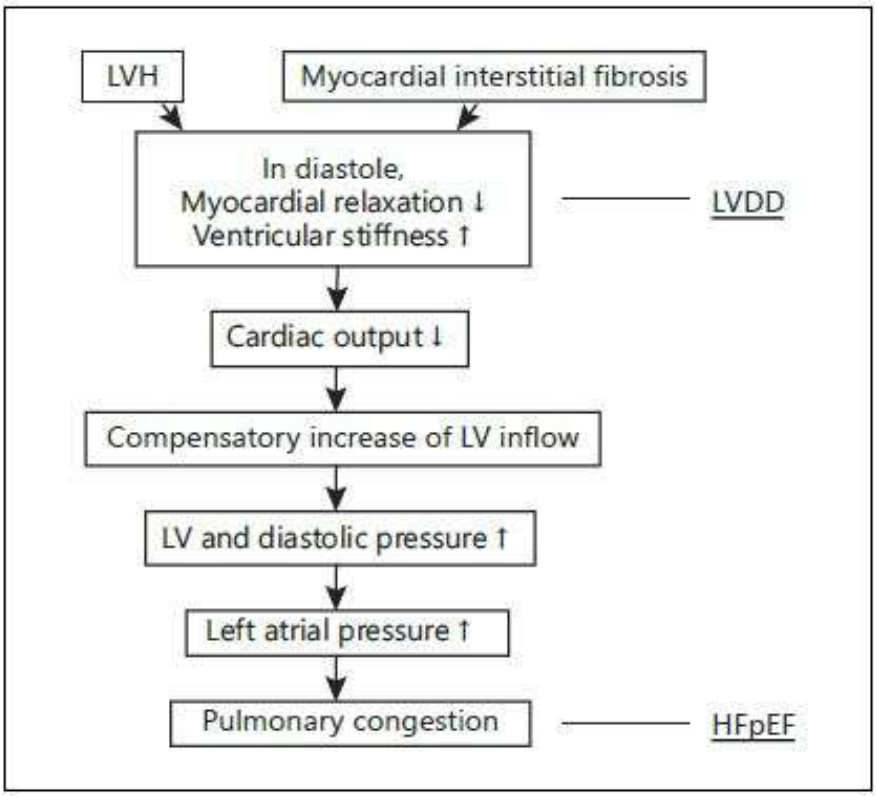

Figure 3: Pathophysiology of LVDD

When LV diastolic function is impaired, cardiac output is reduced, because the LV is not filled enough in diastole due to LV inflow obstruction. By contrast, to compensate for reduced cardiac output, increasing the inflow pressure to the LV and consequently LV end-diastolic pressure becomes necessary, and that in turn increases left atrial pressure. As a result, LV dysfunction tends to cause pulmonary congestion. The end-systolic pressure-volume relationship in diastolic dysfunction is the same as in a normal heart, but the end-diastolic pressure-volume relationship shifts upwards, and LV end-diastolic pressure rises as a result. When an abrupt increase in blood

pressure occurs, since the pressure-volume curve shifts to the upper right without any decrease in Emax (absolute index of contractibility), when an abrupt increase in blood pressure occurs, pulmonary congestion is induced by the significant increase in LV end-diastolic pressure ***(Borlaug et al., 2016).***

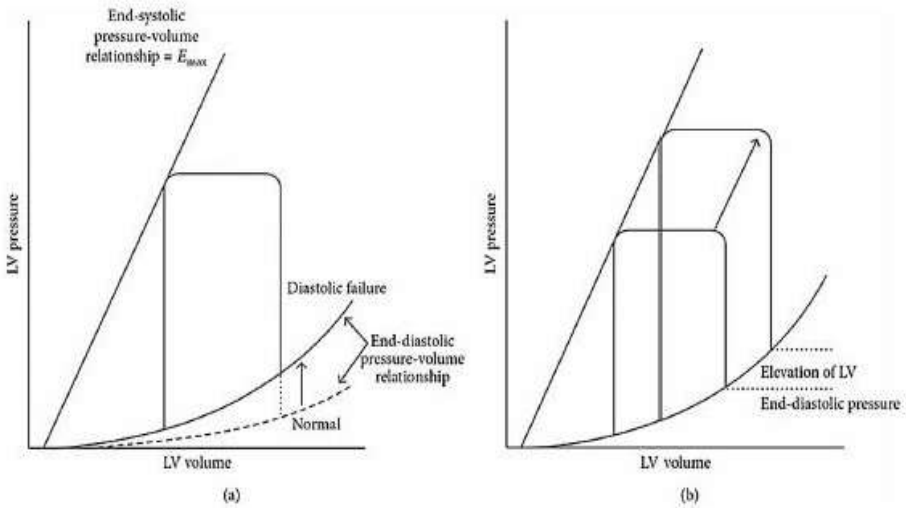

Figure 4: (a) The end-diastolic pressure-volume curve shifts updward in diastolic heart failure, followed by a rise in left ventricular (LV) end-diastolic pressure. (b) When an abrupt increase in blood pressure occurs, the pressure-volume curve shifts to the upper right without any decrease in Emax in patients with diastolic dysfunction.

The most recent ASE document on the evaluation of LV diastolic dysfunction considers LVH with HTN as an indicator of diastolic dysfunction. Left ventricular hypertrophy (LVH) is growth in left ventricular (LV) mass caused by increased cardiomyocyte size. The process is compounded by a complex series of transcriptional, signaling, structural, electrophysiological and functional events that affect all the cardiac cell types. LVH can be a physiological adaptation to strenuous physical