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Advances & Innovations in Heart Failure (AIHF)

A Textbook of Cardiology

Editors-in-Chief

HK Chopra (India) • Navin C Nanda (USA) • Jagat Narula (USA)



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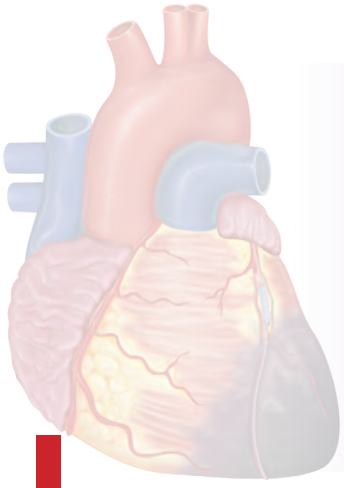
CHAPTER 2



Pathophysiology and Prevention of LV Diastolic Heart Failure

Hanumanth K Reddy, Ravi Komatireddy, Raghuveer Kura, Thirupathi K Reddy

INTRODUCTION

The prevalence of diastolic heart failure is increasing exponentially with rising age of the population, obesity, and inactivity. Left ventricular (LV) diastolic dysfunction and diastolic heart failure with preserved ejection fraction (HFpEF) are usually associated with hypertension, coronary artery disease (CAD), valvular heart disease, hypertrophic and restrictive cardiomyopathies, tachycardia, and atrial fibrillation. Close to 50% of heart failure patients have preserved LV ejection fraction along with diastolic dysfunction.[1] High morbidity and mortality are associated with this condition. Although, left ventricular end-diastolic pressure (LVEDP) has shown to be elevated in these patients on a consistent basis.[2,3] Impaired cardiac reserve, especially during exercise, plays a major role. This is due to a complex interplay of subtle systolic dysfunction (altered strain, twisting, and suction) and impaired diastolic function. Impaired LV diastolic relaxation with stiffness has many causes. Interstitial fibrosis, alteration of structural, architectural, and biochemical properties of actin-myosin complex and reduced SERC-ATPase required for active relaxation. Furthermore, atrioventricular synchrony and coupling, ventricular interaction, ventricular geometry, pericardial restraint as well as ventriculovascular coupling play critical roles in diastolic dysfunction. Although multiple factors are involved, elevated LVEDP and decreased cardiac reserve constitute the clinical substrate for diastolic heart failure. Increased LVEDP causes pulmonary congestion, pulmonary hypertension, and right-sided congestion and dyspnea. Decreased cardiac reserve leads to effort intolerance, fatigue, and dyspnea. Increased heart rate, atrial fibrillation, uncontrolled hypertension, and renal dysfunction may complicate the patient's clinical course. The goals of management include adequate diuresis, control of heart rate and blood pressure, possible cardioversion, and promotion of physical exercise.

PATHOPHYSIOLOGY OF DIASTOLIC HEART FAILURE

Left ventricular diastolic heart failure is multifactorial in origin. A wide variety of risk factors are involved in this type of heart failure. However, all individuals with similar risk factors do not develop diastolic heart failure indicating the fact that some individuals have genetic predisposition to this condition. In fact, there are some reports suggesting genetic predisposition to ventricular stiffness, diastolic dysfunction, and diastolic heart failure.

GENETIC BASIS OF LEFT VENTRICULAR DIASTOLIC HEART FAILURE

Genetic basis for LV diastolic dysfunction (LVDD) has not been well-worked out. Multiple authors have reported a role of micro-ribonucleic acids (miRNAs) in diastolic heart failure. miRNAs work as regulators of gene expression by controlling messenger RNAs (mRNAs). In vitro experiments, either knockdown or overexpression of miRNAs in cultured cardiomyocytes was shown to influence cardiomyocyte hypertrophy.[4] Van Rooij et al. reported that overexpression

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of miRNA-195 in rodent hypertrophic hearts resulted in dilated cardiomyopathy and heart failure.[5] There is continuous flow of new information about the seminal role of miRNAs in the pathophysiology of diastolic heart failure and cardiomyopathies. In the near future, miRNAs are going to be new therapeutic targets in the management of heart failure.

GROSS STRUCTURAL AND SUBCELLULAR SUBSTRATES OF LV DIASTOLIC DYSFUNCTION

Left Ventricular Relaxation

Left ventricular relaxation during diastole is a highly energy dependent process. Any impairment of the energy utilization during diastole is associated with LVDD. This impairment is more evident in late diastole since atrial contribution plays an important role at this stage. Certain individuals have structural predisposition to LVDD based on the type of titin isoform.

Role of Titin in Left Ventricular Diastolic Dysfunction

Titin or elastin is a giant elastic protein noted in human myocardial cells. It is the third most commonly available protein in the human myocardium after myosin and actin. Because of its large size, it is named after the Greek mythological giant *Titan*. Titin molecules link thick filaments to Z-disk and the M-line thus networking sarcomeres and playing an important role in their normal stretching and stretch recovery. It is composed of immunoglobulin and fibronectin like domains. Its kinase domain provides signaling and elasticity properties to the cardiomyocyte. In other words, it works as a molecular spring needed for the normal LV diastolic function. Furthermore, it plays a critical role in myocyte postcontraction recovery and prevention of overstretching of the myocyte. Titin mutations cause dilated cardiomyopathy. Human myocardium has two types of titin isoforms. N2B is the stiffer titin isoform commonly found in patients with LVDD and increased LV stiffness may be attributed to this type of titin (Fig. 1). Borbely et al. showed in heart failure patients that hypophosphorylation of the stiff N2B isoform may contribute to increased myocardial stiffness.[6] N2BA is relatively softer titin isoform and is predominantly present in patients with dilated cardiomyopathy. Alternatively, ventricular relaxation may be related to changes in troponin I protein kinase A (PKA) phosphorylation. This PKA mediated troponin I phosphorylation is energy dependent and leads to reduced myofibrillar calcium sensitivity, increased calcium dissociation from troponin C, and

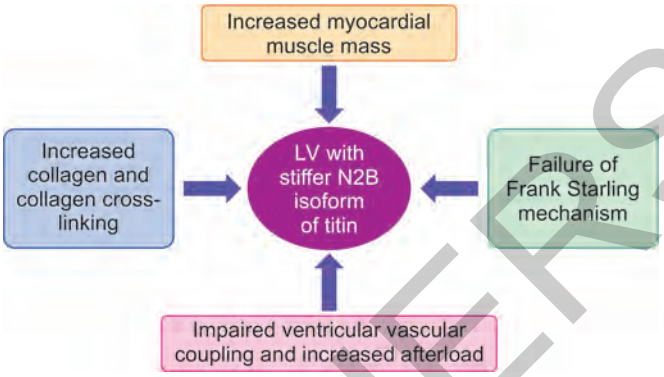

Fig. 1: Interaction of structural and physiological variables in left ventricular diastolic dysfunction (LVDD).

enhanced myocardial relaxation. Decreased reserves of energy at rest mediate impaired LV relaxation at rest and also cause limited contractile reserve (during exercise with decreased phosphocreatine/adenosine triphosphate ratio). The causes of this decrease in resting myocardial energy include aging, insulin resistance, neuroendocrine activation, mitochondrial dysfunction, and impaired substrate metabolism. A phenotype for this pathophysiology is hypertrophic cardiomyopathy where decreased creatine phosphate (PCr)/ATP correlated with fibrous area of the LV myocardium.

Influence of Cellular and Biochemical Homeostasis on Cardiomyocytes and Fibroblasts in LVDD

There is a delicate interplay of cellular and biochemical elements in patients with LVDD. There is an active signal mediated crosstalk among coronary microvascular endothelial cells, cardiomyocytes, and fibroblasts via a myriad of mediators including nitric oxide (NO), cyclic guanosine monophosphate (CGM), and protein kinase G (PKG) (Fig. 2). Normally, these molecules maintain the active relaxed state of the left ventricle and depletion of these elements with inflammation and oxidative stress leads to cardiomyocyte hypertrophy, fibroblast proliferation, and LV stiffness (Figs. 1 and 2).

Hemodynamic Basis and Clinical Presentation

Normal left ventricle has a finite range of elastic properties beyond which LV diastolic pressure rises steeply with an increase in volume. Impaired ventricular elasticity or increased stiffness may be secondary to altered actin-myosin calcium and titin complex associated with genetic abnormality and may be an acquired process related to

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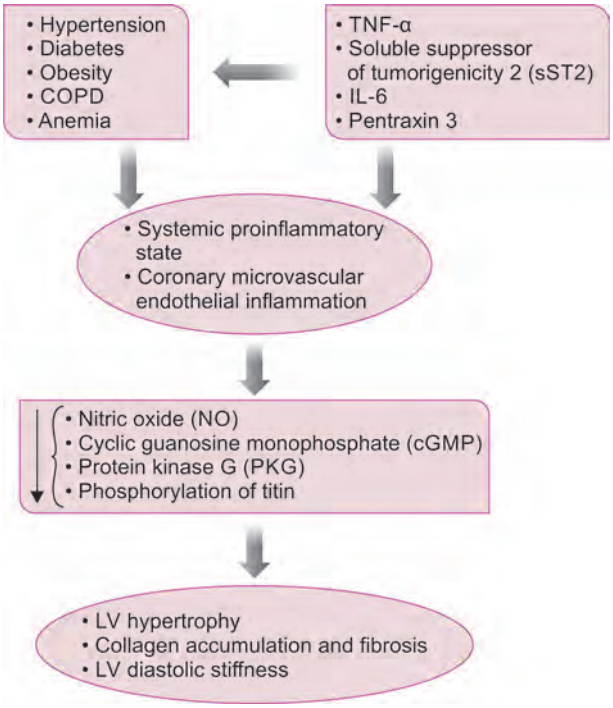

Fig. 2: Proposed mechanisms linking risk factors to LV diastolic dysfunction.
(COPD: chronic obstructive pulmonary disease; IL-6: Interleukin 6; LV: left ventricular; TNF-α: tumor necrosis factor-α)
Source: Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62(4):263-71.

A 52-year man with STEMI with improving LVDD post intervention.

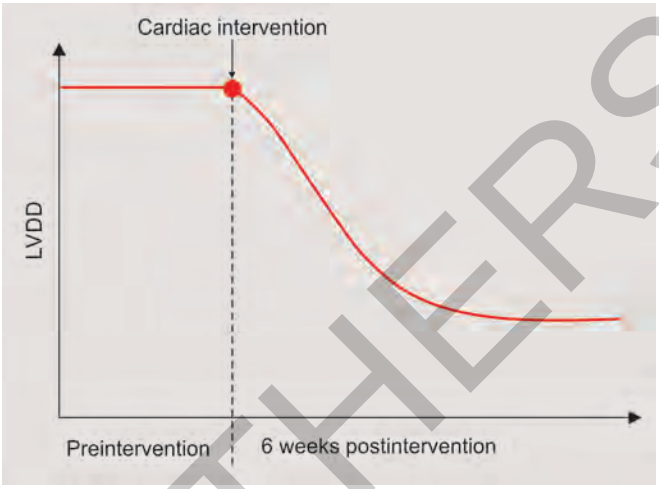

Fig. 3: Impact of ST-elevation myocardial infarction (STEMI) and intervention on left ventricular diastolic dysfunction (LVDD).

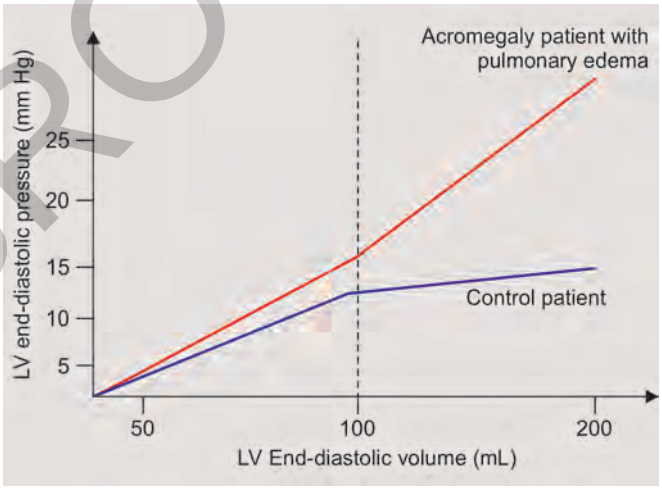

Fig. 4: Interaction between LVDD with severe LVH, pulmonary edema undergoing diuresis in a 57-year-old man with acromegaly.
(LV: left ventricular; LVDD: left ventricular diastolic dysfunction; LVH: left ventricular hypertrophy)

ventricular hypertrophy, dilatation, and scarring. LVDD may be due to dynamic pathophysiological processes such as volume or pressure overload associated with congenital heart disease with shunts, valvular heart disease, obesity/hypoventilation, hypertrophic cardiomyopathy, dilated cardiomyopathy, atrial fibrillation, sleep apnea, anemia, uncontrolled hypertension, and active myocardial ischemia/myocardial infarction (MI) with CAD (Figs. 3 to 10). Dynamic LVDD may be partially or totally normalized with effective management of the causative factors. The time course of LVDD recovery may be short or prolonged based on the severity and duration of the underlying process. In some cases of advanced structural and congenital myocardial abnormalities, LVDD may become severe and irreversible.

Increased Left Ventricular End-diastolic Pressure in Diastolic Heart Failure

The hemodynamic end product of various pathophysiological mechanisms of LVDD is elevated LVEDP which translates into fluid congestion and congestive heart failure (CHF). LVDD is an early partner of LV systolic dysfunction often clinically manifesting as pulmonary edema in situations such as acute MI, papillary muscle rupture, and acute onset of atrial fibrillation with rapid ventricular rate, especially in hypertrophic obstructive cardiomyopathy (HOCM), valvular aortic stenosis, and uncontrolled hypertension patients. With prompt therapy, LVDD mostly improves to a variable degree in these patients (Figs. 3 to 6 and Fig. 10). Chronic LVDD is a slow and an incremental process occurring over a period of decades. Initially subtle in its clinical presentation, LVDD finally manifests itself as LV

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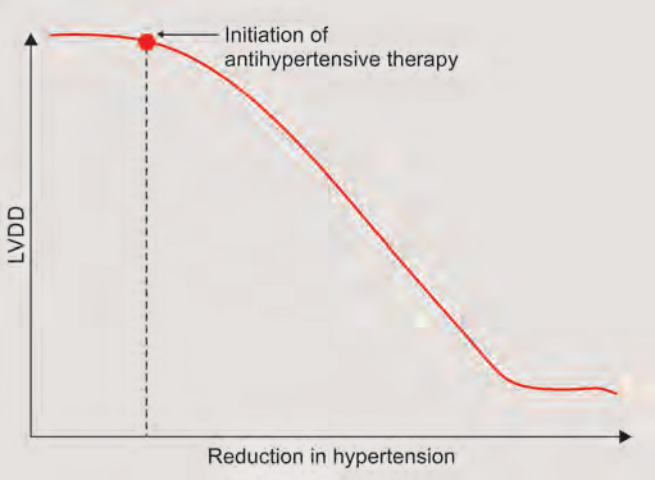

Fig. 5: Left ventricular diastolic dysfunction (LVDD) changes in a 67-year-old man with uncontrolled hypertension, before and after control of hypertension.

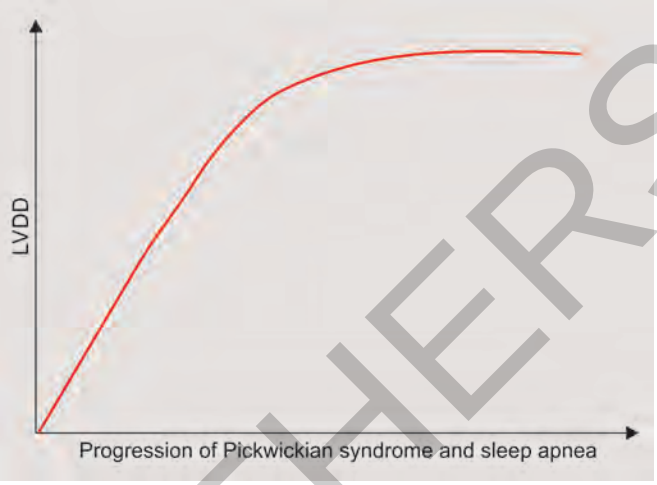

Fig. 7: Left ventricular diastolic dysfunction (LVDD) associated with Pickwickian syndrome and sleep apnea.

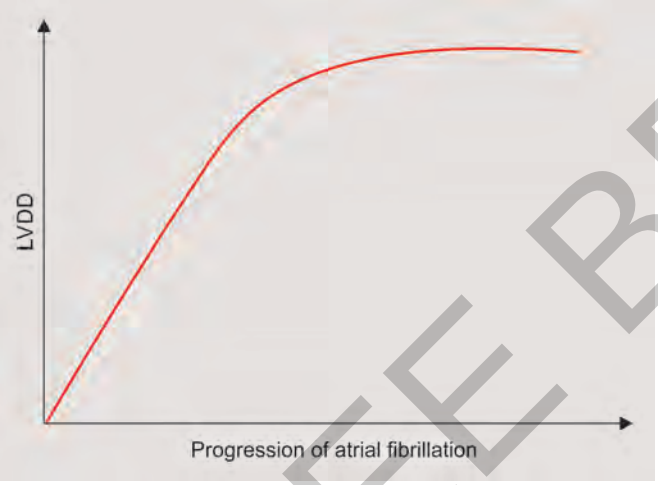

Fig. 6: Left ventricular diastolic dysfunction (LVDD) and atrial fibrillation.

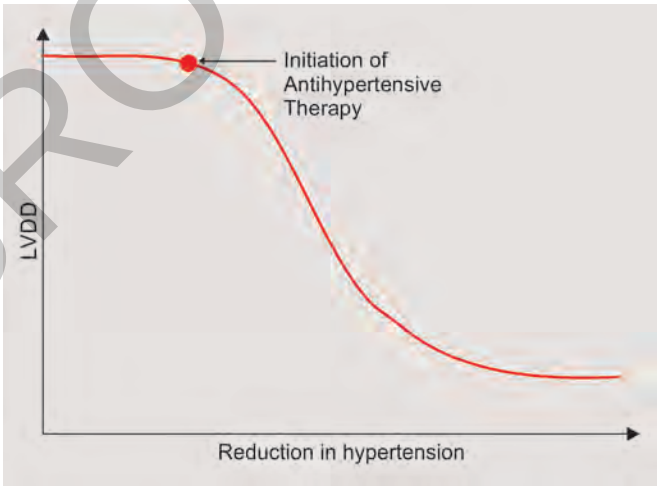

Fig. 8: Left ventricular diastolic dysfunction (LVDD) related to obesity—deconditioning and small vessel disease with hypertensive treatment.

diastolic heart failure often in later stages of life. LVDD becomes an integral part of various clinical conditions as shown in Figures 3 to 10. Chronic elevation in LVEDP is gradually compensated by pulmonary vasculature, both the atria, right ventricle (RV), peripheral veins, lymphatics, and the third space. Structural and electrical remodeling of the atria occurs. Atria are dilated and become dysfunctional, loosing their booster pump function. Cardiac output decreases and the frequently associated atrial fibrillation which makes diastolic heart failure worse. The right-sided compensatory mechanisms with RV dilatation, pulmonary hypertension, and peripheral fluid congestion prevent pulmonary vascular congestion and pulmonary edema thus avoiding a lethal outcome to the patient.

Impaired Cardiac Output and Vasodilator Reserve with Altered Ventricular-arterial Coupling

In patients with diastolic heart failure, increased stiffness is seen both in the left ventricle and the large peripheral arteries.[7] This combined ventricular-vascular stiffness associated with reduced LV diastolic filling leads to decreased cardiac output at rest and during exercise. Furthermore, in these patients, left bundle branch block (LBBB) and atrial fibrillation may cause ventricular-arterial decoupling and further compromise in cardiac output. In fact, peak exercise cardiac output and maximal oxygen uptake ($VOmax_2$) have been reported to be limited in these patients.

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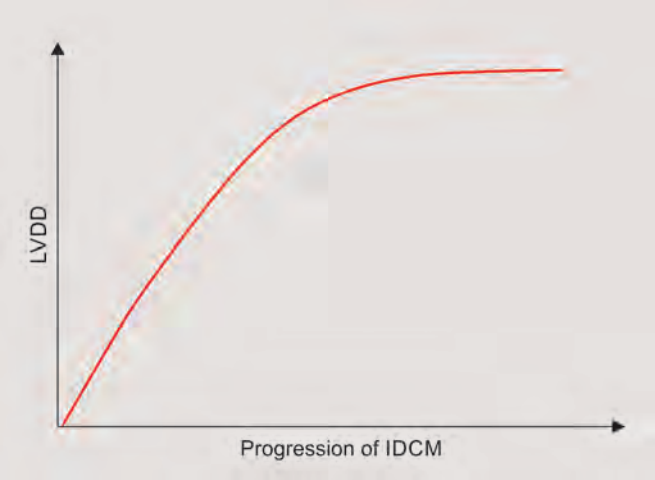

Fig. 9: Left ventricular diastolic dysfunction (LVDD) in patients with idiopathic dilated cardiomyopathy (IDCM).

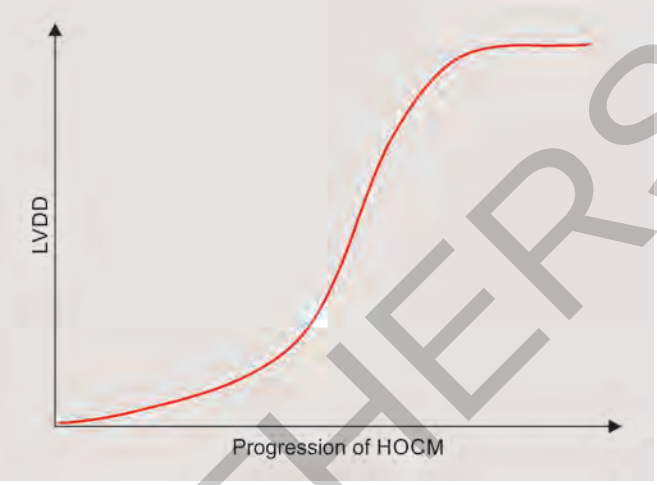

Fig. 10: Left ventricular diastolic dysfunction (LVDD) associated with hypertrophic obstructive cardiomyopathy (HOCM).

Atrial Dysfunction

Left atrial (LA) volume progressively increases leading to LA myopathy and an eventual loss of booster pump function in patients with diastolic heart failure. Furthermore, LA strain decreases, LA stiffness increases, and LA diastolic dysfunction ensues.

Right Ventricle Dysfunction and Pulmonary Hypertension

While the focus has been on the LVDD in diastolic heart failure, the roles of peripheral circulation, vasodilator reserve, atrial and RV dysfunction, and pulmonary hypertension cannot be overestimated. A significant number of diastolic heart failure patients have peripheral circulatory dysfunction, right ventricular dilatation and dysfunction (RVD), pulmonary hypertension, and right heart failure.[8,9] This is an advanced stage of diastolic heart failure and is often irreversible.

Risk Factors for Left Ventricular Diastolic Hear Failure

Diastolic heart failure is more commonly associated with aging, female sex, obesity, metabolic syndrome, hypertension, chronic obstructive pulmonary disease, anemia, and chronic kidney disease.

Primary Prevention

With an alarming rise in childhood and adult obesity and metabolic syndrome, there has been an epidemic of LVDD and diastolic heart failure in the industrialized countries. Outcomes are poor in diastolic heart failure patients and there is no proven and effective therapy. Therefore, the best way to prevent the most common type of LVDD is to prevent metabolic syndrome from childhood. Promotion of the culture of physical activity at home, gymnastic, and sports activities at school and work place should be the fashionable modus operandi of each community. Excessive consumption of calories in the absence of physical activity should be strongly discouraged.

Aerobic Exercise in Patients with LVDD and Diastolic Heart Failure

Aerobic exercise has been shown to prevent and improve diastolic heart failure in patients with LVDD.[10,11] In patients with regular aerobic exercise, it is easier to modify the coexisting risk factors such as obesity, hypertension, and diabetes. Randomized controlled and single center studies as well as meta-analysis of several studies have shown improvement in aerobic capacity and quality of life in diastolic heart failure patients.[12]

Control of Hypertension and Diabetes

Adequate control of blood pressure preferably with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and beta-blockers will prevent and mitigate LVDD and eventual diastolic heart failure. Diuretics are often needed in these patients. Optimal diabetic therapy with sodium-glucose cotransporter-2 (SGLT2) inhibitors has been shown to prevent CHF hospitalizations.

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Secondary Prevention

In patients with diastolic heart failure due to advanced LVDD, optimal medical therapy is unavailable at the present time. In addition to aerobic exercise, drugs including diuretics, ACE inhibitors, ARBs, beta-blockers and vasodilators, aggressive therapies with atrial fibrillation ablation, and biventricular pacing may be needed. However, prognosis in these patients is quite poor.

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