AN OVERVIEW OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

Ahmed Shawky Sherif[1], Montaser Mostafa Alsekely[2], Basem Hammad Mohamed Elawady[3*], Baher Nabil Al dosoky[4]

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Abstract:
Left ventricular diastolic function plays an important role in determining left ventricular filling and stroke volume. Abnormal diastolic function has been recognized in many cardiovascular diseases and is associated with worse outcomes, including total mortality and hospitalizations due to heart failure. Using echocardiography, it is possible to diagnose the presence of diastolic dysfunction and the pathophysiologic mechanisms involved as they affect left ventricular and left atrial structure and function.

Keywords: Left ventricle, Diastolic dysfunction**,** LVDD.

[1*]Cardiology Department, Faculty of Medicine, Zagazig University, Egypt

***Correspondence Author:** Basem Hammad Mohamed Elawady
*E-mail: Basimelawadi@gmail.com

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Introduction:

Left ventricular diastolic dysfunction (LVDD) is a preclinical condition defined as *the inability of LV to fill an adequate end-diastolic volume (preload volume) at an acceptable pressure****(1)***.

HFpEF (heart failure preserved ejection fraction) is a clinical syndrome in which patients have signs and symptoms of HF as the result of high left ventricular (LV) filling pressure despite normal or near normal LV ejection fraction (LVEF; ≥50 percent) ***(2)***

HFpEF shows a rising prevalence in older population (In 2019, more than 8% of people over 65 are estimated to have HFpEF) and is associated with a poor prognosis***(3)***.

a) Risk factors and related Pathological Mechanisms of Left Diastolic Dysfunction:

Patients with LVDD have been mainly older and female, with a high prevalence of cardiovascular diseases (CVD) and other morbid conditions such as obesity, metabolic syndrome, type 2diabetes, salt-sensitive hypertension, atrial fibrillation, chronic obstructive pulmonary disease (COPD), anaemia, and/or renal dysfunction. Each of these pathologies has been linked to LVDD and may lead to LVDD via different pathways***(3)***.

The incidence of LVDD associated to ***HFpEF*** is increasing with *global aging*. LVDD, left atrial remodeling, and cardiac fibrosis along with vascular changes such as endothelial dysfunction, arterial stiffening, and vascular inflammation are all the attributes of the advanced age***(4)***.

The effect of aging on extra cellular matrix (ECM) can be observed at the cellular,extracellular,and tissue levels. Progressive cardiomyocyte hypertrophy,inflammation, and the gradual development of cardiac fibrosis are hallmarks of cardiac aging.In the absence of secondary insult such as hypertension,these changes are subtle and result in slight to moderate impaired diastolic dysfunction. In brief, senescence modifications of the cardiovascular system increase afterload and impair vasodilation, which increases LV wall stress leading to cardiomyocyte hypertrophy***(5)***. Hypertrophied cardiomyocytes have elevated oxygen requirements, and an imbalance in oxygen supply and demand favors reactive oxygen species (ROS) production, which is toxic to cardiomyocytes. Cardiomyocytes release proinflammatory cytokines and chemokines in response to hypoxia, promoting inflammation and recruiting macrophages in the LV. ***(6)***.

Matrix metalloproteinases (MMPs) are abundant in macrophages and have been linked to myocardial ageing and LVDD. Furthermore, ageing promotes amyloid deposit in the LV, which increases myocardial thickening, a condition known as senile amyloidosis. Both macrophages and polymorphonuclear cells express asset (MMPs),zinc -dependent endopeptidases that are involved in a variety of biological functions such as the turnover of extracellular matrix (ECM) components,angiogenesis,and the regulation of inflammation. ***(7)***.

The metabolic syndrome (MetS) that is a clustering of at least three of the following five medical conditions: abdominal obesity, high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (HDL)***(8)***.*Mets* has been linked to LVDD with preserved systolic function. As a result of cardiovascular risk factors clustered in the MetS acting as triggers, inflammatory biomarkers favors pathological changes in the myocardium that lead to relaxation abnormalities***(9)***.

Accelerated oxidative stress (OS) caused myocardial cell hypertrophy and fibrosis in animal models with diet-induced MetS. Endothelial inflammation along with endothelial dysfunction, played an important role in the development of cardiac fibrosis and increased myocardial stiffness in dyslipidemia, high blood pressure, or insulin resistance ***(10)***

Inflammatory biomarkers have a high predictive value for LVDD, with a strong relationship between LVDD and IL-6 levels that is independent of MetS components and NT-proBNP ***(11)***.

The systemic proinflammatory state present in chronic obstructive pulmonary disease COPD patients may contribute to vascular and myocardial abnormalities, increasing the risk of cardiovascular morbidity, particularly during acute exacerbations. LV alterations manifested as LVDD are found in more than 90% of the severe COPD subgroup, regardless of age or the presence of systemic hypertension***(12)***.

Several neurohormonal and mechanistic hypotheses for the inflammatory biomarkers-LVDD continuum have been proposed: (1)Renin-angiotensin-aldosterone system (RAAS) activation, which stimulates the production of proinflammatory cytokines (such as IL-6, IL-8, and TNF-α), directly activating immune cells, and increasing the expression of adhesion molecules such as vascular cell adhesion protein 1, intercellular adhesion molecule 1, selectins, or Monocyte Chemoattractant Protein-1(MCP-1). and (2) increased LV diastolic pressure may

induce cardiac apoptosis and OS, which can then cause regional IF, increasing the production of IL-1, IL-6, and TNF-α***(3)***.

The neurohormonal hypothesis of RAAS activating OS was verified by ***Negi et al.*** in a well-performed clinical study, trying to explain the negative results from RAAS inhibitor therapy in HFpEF patients. The authors found that HFpEF was not associated with RAAS activation or systemic OS ***(13)***.

The activation of mineralocorticoid receptors through aldosterone may be an important factor in the pathogenesis of HFpEF through multiple mechanisms such as cardiac fibrosis or endothelial dysfunction. In this respect, mineralocorticoid receptor agonists (MRA) have been studied in patients with HFpEF or ischemic HFpEF (after myocardial infarction). Although in some of the studies MRA failed to improve mortality in HFpEF, others showed that MRA could improve LVDD and reduce cardiac remodeling having positive impact on the quality of life**(14)**.

Another mechanism proposed in LVDD was myocardial microvascular dysfunction ***(15)***. ***Mohammed et al.*** examined 124 myocardial autopsy specimens from HFpEF patients. The authors discovered that microvascular density and myocardial fibrosis are more common in HFpEF patients and are unrelated to the severity of epicardial coronary stenosis, lending support to the hypothesis of microvascular endothelium inflammation in LVDD pathogenesis ***(16)***.

LVDD was proven to be caused by any mechanism that interferes with actin-myosin cross bridge detachment, intracellular changes extracellular changes in collagen, and infiltration***(17)***

Recent studies on both animal and human models showed that titin isoform shift, ROS, nitric oxide synthetase (NOS) dysfunction that results in decreased nitric oxide (NO), and myosin-binding protein C (MyBP-C) are implicated in LVDD ***(18)***. Increased titin N2B isoform expression and the reduced phosphorylation of titin were linked to elevated cardiomyocyte stiffness in endomyocardial biopsy samples of patients with LVDD***(19)***.

Advanced glycation end products (AGEs) are formed by nonenzymatic glucose interactions with proteins and accumulate in a variety of pathological conditions such as hypertension and diabetes mellitus. Diabetes mellitus patients had AGE accumulation in the myocardium. Some AGE serum concentrations may be predictive of mortality and hospitalization rates in HFpEF patients. As a result, AGE has emerged as a potential therapeutic target***(3)***.

Nitric oxide synthases (NOS) is an important modulator of cardiac nitroso-redox balance and function. Uncoupled NOS in hypertensive mouse models results in decrease in NO that are consistent with increased cytosolic calcium and LVDD. In human studies, G894T polymorphism of the eNOS gene and MetS was related to arterial stiffness and can be a connection pathway between MetS and the increased cardiovascular risk ***(20)***.

Finally, Myosin binding protein C is a thick protein found in striated muscle sarcomeres that is involved in cardiac contraction and relaxation. Experiments revealed that phosphorylation of MyBP-C causes impaired cardiac muscle contraction and, as a result, LVDD ***(21)***.

Further, cMyBP-C decrease LV remodeling in response to pressure overload ***(22)***. The experimental study of ***Jeong et al.*** showed that preventing glutathionylation of MyBP-C using cofactor tetrahydrobiopterin ameliorates diastolic dysfunction through reversing changes of myofilaments ***(23)***. These findings "indicate that cardiac relaxation can be influenced by posttranslational changes in myofilament proteins." MyBP-C demonstrated diagnostic and prognostic properties in patients with HFpEF in clinical studies. According to Tong et al., cMyBP-C is a potential screening biomarker for the presence of severe cardiovascular diseases ***(24)***.

Effects of Inflammation on a Systemic and Myocardial Level

Comorbidities contribute to persistent low-grade inflammation and exert deleterious effects on organ systems beyond the heart: inflammatory cytokines affect skeletal muscle oxygen extraction during exercise, worsen anemia and sarcopenia, promote sodium retention in the kidneys leading to plasma volume expansion, and increase pulmonary pressures during exercise due to pulmonary vasoconstriction, all of which contribute to dyspnea and reduced exercise tolerance in heart failure. On a myocardial level, microvascular endothelial inflammation promotes the expression of adhesion molecules, which attract circulating leukocytes, leading to myofibroblast formation and interstitial collagen deposition. Endothelial inflammation also causes production of reactive oxygen species (ROS) and reduced NO bioavailability; this leads to reduced activity of soluble guanylate cyclase (sGC), cyclic guanosine monophosphate (cGMP), and protein kinase G (PKG), resulting in cardiomyocyte stiffness and hypertrophy.

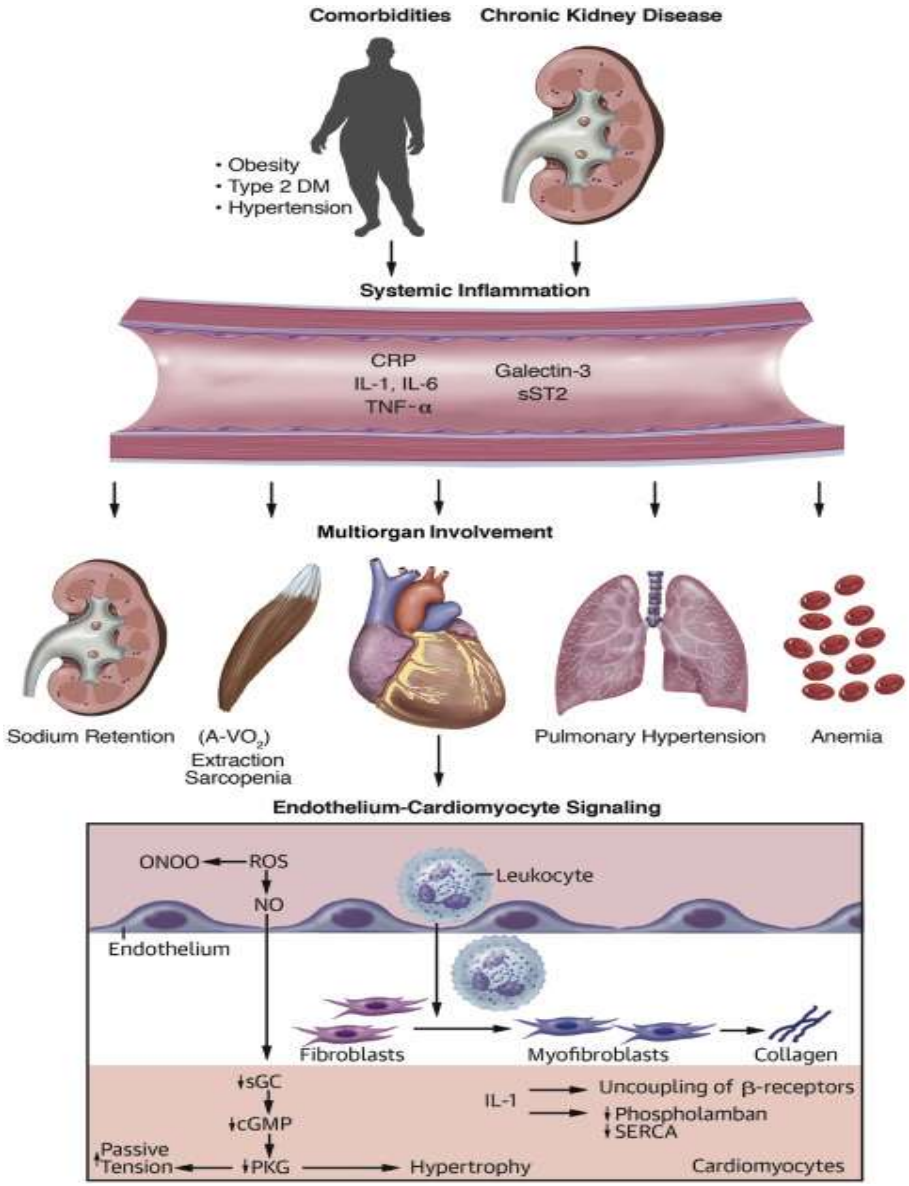

Figure (1): Effects of Inflammation on a Systemic and Myocardial Level (25)

b) Physiology of diastolic filling and compliance

The diastole phase of the cardiac cycle includes the isovolumetric relaxation and filling phases, as well as passive and active components. The LV filling is divided into three phases: rapid filling during early diastole, diastasis, and rapid contraction during the late contraction phase. LVDD can occur as a result of abnormalities at any stage of diastole. As a result, impaired relaxation, high filling pressure, increased LV operating stiffness, mechanical asynchronism, increased peripheral artery stiffness, and atrial contraction loss at higher heart rates are just a few of the underlying mechanisms in LVDD***(26)***

Normal diastolic function allows for adequate heart filling without an increase in diastolic filling pressure, both at rest and during exercise. LV relaxation begins at the end of systole, and LV pressure drops rapidly as the LV expands, resulting in a left atrial (LA)-to-LV pressure gradient when LV diastolic pressure falls below LA pressure (Fig. A).***(27)***.

This causes rapid early diastolic LV filling and accelerates blood out of the LA, with the LA-to-LV pressure gradient considered a measure of LV suction. Following LV filling, the pressure gradient from the LA to the LV apex decreases and then reverses transiently. In diastole, the reversed mitral valve pressure gradient slows and then stops the rapid flow of blood into the LV. The LA and LV pressures equilibrate and mitral flow nearly ceases during the midpoint of diastole (diastasis). Late in diastole, atrial contraction generates a second LA-to-LV pressure gradient, propelling blood back into the LV (Fig. A). As the LA relaxes after atrial systole, its pressure falls below that of the LV, causing the mitral valve to close ***(26)***

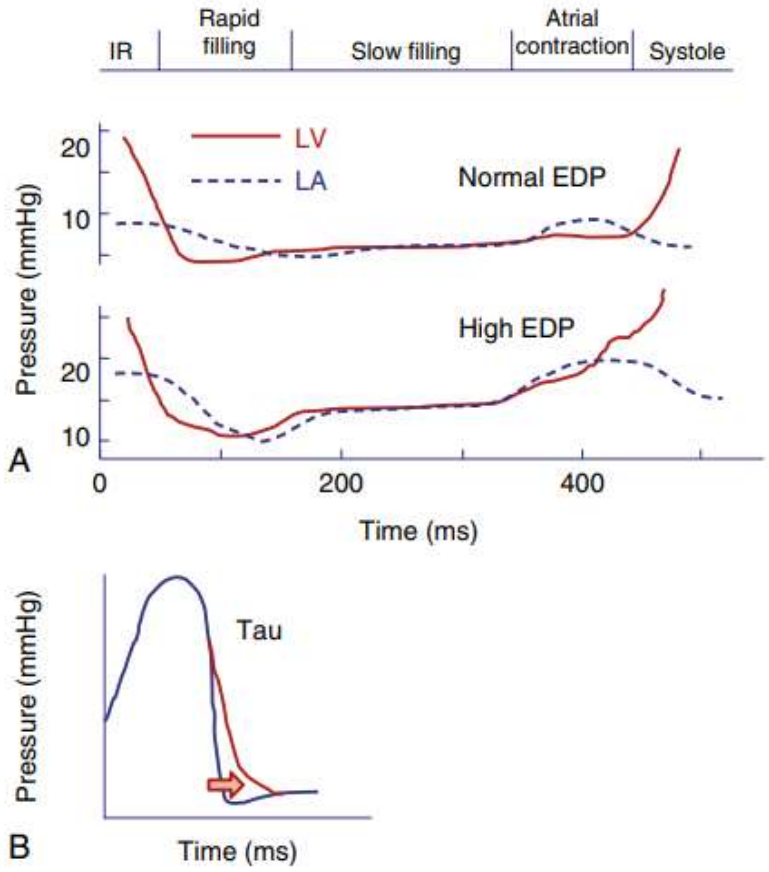

Figure (2): (A) the four phases of diastole are marked in relation to pressure recordings from the left atrium (LA) and left ventricle (LV). The first pressure crossover corresponds to the end of isovolumic relaxation (IR) and mitral valve opening. In the first phase, LA pressure exceeds LV pressure, accelerating mitral flow. Peak early diastolic mitral valve blood flow velocity approximately corresponds to the second crossover. Thereafter LV pressure exceeds LA pressure, decelerating mitral flow. These two phases correspond to rapid filling. This is followed by slow filling, with almost no pressure differences. During atrial contraction, LA pressure again exceeds LV pressure with late diastolic filling from LA contraction.(B) Time constant of isovolumic relaxation (Tau) indicates the rate of LV pressure fall. Tau becomes shorter when LV pressure fall accelerates and longer when LV pressure fall slows. EDP, End-diastolic pressure(26)

Diastolic dysfunction

Usually, early diastole is responsible for the majority of ventricular filling; however, disturbed myocardial relaxation slows the rate of early diastolic LV pressure decline, lengthening the time to reach minimal LV diastolic pressure and emphasizing the importance of atrial contraction for diastolic filling. Despite impaired myocardial relaxation, early diastolic filling becomes more dominant as LA pressure rises. Early filling is caused by increased LA pressure, which pushes blood into the LV rather than negative LV diastolic pressure, which suctions blood from the LA (Fig. A) ***(26)***

As diastolic function deteriorates, LA pressure rises and myocardial relaxation is impaired at rest, as evidenced by an increase in the time constant of isovolumic relaxation (Fig. B). The majority of diastolic LV filling now occurs in early diastole, and LA contraction may not be enough. In this case, LA contraction forces blood back into the pulmonary veins, particularly if pulmonary venous diastolic forward flow has already been completed at the time of atrial contraction***(26)***

Diastolic dysfunction refers to an abnormality in diastolic distensibility, filling, or relaxation of the LV, regardless of whether the EF is normal or abnormal, and whether the patient is symptomatic or asymptomatic. After controlling for known HF risk factors, asymptomatic antecedent LV diastolic dysfunction was linked to incident HF in Framingham Heart Study participants. Thus, diastolic dysfunction refers to abnormal mechanical (diastolic) properties of the ventricle and is found in nearly all HF patients. HFpEF is a clinical syndrome characterized by HF symptoms or signs, preserved LVEF, and diastolic LV dysfunction ***(26)***.

References:

1. **Dunlay SM, Roger VL & Redfield MM (2017)** Epidemiology of heart failure with preserved ejection fraction. Nature Reviews Cardiology.10 (14), 591-602.
2. **Reddy YN & Borlaug BA(2016)** Heart Failure With Preserved Ejection Fraction. Curr Probl Cardiol.4 (41), 145-88.
3. **Mocan M, Mocan Hognogi LD, Anton FP, Chiorescu RM, Goidescu CM, Stoia MA, et al.(2019)** Biomarkers of Inflammation in Left Ventricular Diastolic Dysfunction. Disease Markers.(2019.7583690 ,(
4. **Upadhya B, Pisani B & Kitzman DW(2017)** Evolution of a geriatric syndrome: pathophysiology and treatment of heart failure with preserved ejection fraction. Journal of the American Geriatrics Society.11 (65), 2431-2440.
5. **Meschiari CA, Ero OK, Pan H, Finkel T & Lindsey ML(2017)** The impact of aging on cardiac extracellular matrix. Geroscience.1 (39), 7-18.
6. **Gevaert AB, Shakeri H, Leloup AJ, Van Hove CE, De Meyer GR, Vrints CJ, et al.(20** (17Endothelial senescence contributes to heart failure with preserved ejection fraction in an aging mouse model. Circulation: Heart Failure.6 (10), e003806.
7. **Van Den Berg MP, Mulder BA, Klaassen SH, Maass AH, Van Veldhuisen DJ, Van Der Meer P, et al.(2019)** Heart failure with preserved ejection fraction, atrial fibrillation, and the role of senile amyloidosis. European heart journal.16 (40), 1287-1293.
8. **O'neill S & O'driscoll L(2015)** Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obesity Reviews.1 (16), 1-12.
9. **Wu CK, Yang CY, Lin JW, Hsieh HJ, Chiu FC, Chen JJ, et al.(2012)** The relationship among central obesity, systemic inflammation, and left ventricular diastolic dysfunction as determined by structural equation modeling. Obesity.4 (20), 730-737.
10. **Tuleta I & Frangogiannis NG(2021)** Fibrosis of the diabetic heart: Clinical significance, molecular mechanisms, and therapeutic opportunities. Adv Drug Deliv Rev.(176), 113904.
11. **Mocan M, Anton F, Suciu Ș, Răhăian R, Blaga SN & Fărcaș AD(2017)** Multimarker assessment of diastolic dysfunction in metabolic syndrome patients. Metabolic Syndrome and Related Disorders.10 (15), 507-514.
12. **Balamurugan T. 2019.** Prevalence of Left Ventricular Diastolic Dysfunction in COPD and Its relation with Disease Severity. Madurai Medical College, Madurai.
13. **Negi SI, Jeong E-M, Shukrullah I, Veleder E, Jones DP, Fan T-HM, et al.(2015)** Renin-angiotensin activation and oxidative stress in early heart failure with preserved ejection fraction. BioMed Research International.(2015.(
14. **Jia G, Jia Y & Sowers JR(2017)** Role of mineralocorticoid receptor activation in cardiac diastolic dysfunction. Biochim Biophys Acta Mol Basis Dis.8 (1863), 2012-2018.
15. **Giamouzis G, Schelbert EB & Butler J** 2016, Growing evidence linking microvascular dysfunction with heart failure with preserved ejection fraction. Am Heart Assoc.
16. **Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ & Redfield MM(2015)** Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation.6 (131), 550-559.
17. **Adekunle AO, Adzika GK, Mprah R, Ndzie Noah ML, Adu-Amankwaah J, Rizvi R, et al.(2021)** Predominance of Heart Failure With Preserved Ejection Fraction in Postmenopausal Women: Intra- and Extra-Cardiomyocyte Maladaptive Alterations Scaffolded by Estrogen Deficiency. Frontiers in Cell and Developmental Biology.(9.(
18. **Wan S-H, Vogel MW & Chen HH(2014)** Pre-clinical diastolic dysfunction. Journal of the American College of Cardiology.5 (63), 407-416.
19. **Van Heerebeek L & Paulus W(2016)** Understanding heart failure with preserved ejection fraction: where are we today? Netherlands Heart Journal.4 (24), 227-236.
20. **Cozma A, Taut AS, Orasan O, Procopciuc LM, Farcas AD, Stan A, et al.(2018)** The relationship between eNOS (G894T) gene polymorphism and arterial stiffness in patients with metabolic syndrome. Rev Chim.9 (69), 2351-2356.
21. **Aroor AR, Mandavia CH & Sowers JR(2012)** Insulin resistance and heart failure: molecular mechanisms. Heart failure clinics.4 (8), 609-617.
22. **Rosas PC, Liu Y, Abdalla MI, Thomas CM, Kidwell DT ,Dusio GF, et al.(2015)** Phosphorylation of cardiac Myosin-binding protein-C is a critical mediator of diastolic

function. Circulation: Heart Failure.3 (8), 582-594.

23. **Jeong E-M, Monasky MM, Gu L, Taglieri DM, Patel BG, Liu H, et al.(2013)** Tetrahydrobiopterin improves diastolic dysfunction by reversing changes in myofilament properties. Journal of molecular and cellular cardiology.(56), 44-54.
24. **Tong CW, Dusio GF, Govindan S, Johnson DW, Kidwell DT, Lisa M, et al.(2017)** Usefulness of released cardiac myosin binding protein-C as a predictor of cardiovascular events. The American journal of cardiology.9 (120), 1501-1507.
25. **Murphy SP, Kakkar R, Mccarthy CP & Januzzi JL(2020)** Inflammation in Heart Failure: JACC State-of-the-Art Review. Journal of the American College of Cardiology.11 (75), 1324-1340.
26. **Heerebeek LV & Paulus WJ**. 11 - Alterations in Ventricular Function: Diastolic Heart Failure. In: Felker G M & Mann D L (eds.) Heart Failure: a Companion to Braunwald's Heart Disease (Fourth Edition).2020. Philadelphia: Elsevier.
27. **Shah SJ, Kitzman DW, Borlaug BA, Van Heerebeek L, Zile MR, Kass DA, et al.(2016)** Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation.1 (134), 73-90.