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Research Article

Assessment of Left Ventricle Systolic Function by Strain Imaging in Patients with Heart Failure with Preserved Left Ventricular Ejection Fraction

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Abstract

Background: *Contrary to the popular belief that there is no systolic dysfunction in heart failure with preserved ejection fraction (HFPEF), Global longitudinal strain (GLS) is subnormal in HFPEF. The ability of GLS to predict cardiovascular outcome may be superior to left ventricular ejection fraction (LVEF) as it detects myocardial dysfunction. It will reflect that LVEF has the limited ability to assess the systolic function of ventricles and it will also determine its clinical significance which is poorly understood. LV strain in the long axis uses global longitudinal strain (GLS) calculated as the average from all segments as a global LV function. The positive strain means elongation whereas negative strain is shortening. In 2Dimensional STE, only two directions of strain can be measured at anytime. Normal GLS for most echocardiography system is between-18-25% in healthy individuals. It will reflect that LVEF has the limited ability to assess the systolic function of ventricles and it will also determine its clinical significance which is poorly understood. It is a observational cross sectional study with assessment of left ventricle systolic function by strain imaging in patients with heart failure with preserved left ventricular ejection fraction. LVEF has the limited ability to assess the systolic function of ventricles and it will also determine its clinical significance which is poorly understood.*

AIMS and OBJECTIVES:

Primary Objectives*: Assessment of left ventricle systolic function by Strain imaging in patients with heart failure with preserved ejection fraction*

Secondary objectives:

1. Assessment of distribution of GLS in various strata of LVEF in HFPEF patients i.e, >50%, <55%.

2. There demographic profile and risk factors associated with it.

Method*: Patients were above the age of 18 years with signs of functional/structural causes of heart failure ,symptoms and signs consistent with heart failure preserved ejection fraction of > 50 % by Echocardiography, and /or elevated natriuretic peptides BNP> 35 pg/ml and/or NT-proBNP >125 pg/mL and*

Echocardiography features of HFPEF with at least one additional criteria relevant structural heart disease (LVH and or LAE) as a sign of increase filling pressure and diastolic dysfunction on echocardiography, will be taken into the study. LV function was assessed by Modified Simpson's Biplane method from two standard apical four and two chamber views. The left atrial (LA) volume will be measured by the biplane area length method using apical 4-and 2- camber views at the end systolic frame . The maximal volume of the LA, measured at end-systole from bi-plane and indexed to body surface area [left atrial volume index (LAVI)] is calculated. TR jet velocity was calculated from apical four chamber view by estimation of peak RV systolic pressure from TR velocity and LA volume.

Strain e(t) in the myocardium can be measured by speckle tracking echocardiography (STE). ECG gated cine loops of Apical 4, 3 and 2 chamber was acquired for offline analysis using PHILIPS aCMQ QApp "Automated Cardiac Motion Quantification (aCMQ) with zero click technology". Once desirable tracking was achieved Global Longitudinal Strain was calculated by averaging the strain in all. Cut Off:< -18 considered abnormal.

Result: *In this study there has been increase in abnormal value of GLS was found as age advances though p value is not significant. One fourth of patients has a body mass index ≥30kg/m2. Diabetesmellitus patients were 61.9%, while arterial hypertension were 82.5%.10% HFpEF patients had from chronic obstructive pulmonary disease and 20% of patients had chronic kidney disease. Among patients EF< 55%, 70% had abnormal GLS and EF>55% 58.57% had abnormal GLS, though p value is not significant. Abnormal GLS have significantly lower LVEF.*

Conclusion: *It seems clearly, GLS is an early, reliable and sensitive marker of LV systolic function in HFpEF even in persons with apparently normal LVEF. It can be used as a prognostic marker in follow up of the patient with normal LVEF. It is a very common dreadful and treatable condition, so earlier diagnosis will lead to better outcome. It is very promising method to identify patients with mild systolic dysfunction which is not reflected in EF. In fact it seems to be superior to all other parameters of echocardiography.*

Introduction

Heart Failure is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress[1]. It is a progressive disorder in which signs and symptoms of heart failure (HF) are apparent and it is progressive despite normal ejection fraction.

Definition of HFpEF is symptom and sign (signs may not be present in the early stages of HFpEF and in patients treated with diuretics) of heart failure with left ventricular ejection fraction (LVEF)>=50% classified as "heart failure with preserved ejection fraction" (HFpEF)1 and elevated level of natiuretics polypeptide i.e, BNP 35 pg/ml and/or NT-proBNP 125 pg/mL and atleast one additional criteria:

1. Relevant structural heart disease: Left ventricle hypertrophy and left atrial enlargement (LVH and or LAE) as a sign of increase filling pressure.

2. Diastolic dysfunction on transthoracic imaging.

A number of epidemiological studies conducted since the millennium have shown that around 50 % of heart failure patients have a normal ejection fraction [2,3]. The silent and progressive nature contributes to increase risk of death even with normal ejection fraction. HF symptoms reduce the quality of life, leading to repeated hospital admissions for symptom management although the survival after diagnosis has improved with time, mortality is high 50% over 5 years. HFpEF patients has multiple co-morbidities and prognosis is as ominous as systolic HF.

More than half of HFpEF patients with an LVEF >50% has reduced GLS. Strain rate should provide us opportunity to explore more about HFpEF and its events, so its relationship is explored more. GLS has been found to be an independent predictor of mortality in patients of heart failure not in atrial fibrillation. It was found to be superior to all other parameters of echocardiograhy[4]. Some small studies by Hasselberg et al show GLS has a good correlation with exercise capacity in heart failure patients with both reduced and preserved LV function[5]

Review of Literature

Despite major breakthroughs in the field of cardiology, HF remains a source of significant morbidity and mortality[6]. With the available lines of treatment we have achieved insignificant increases in prolongation of life with some amount of amelioration of symptoms. Acute decompensated heart failure (ADHF) is defined as the acute and gradual progression of heart failure symptoms necessitating hospital care[10, 11, 12,13].

Heart Failure Stage	Description
A	Those at risk for heart failure, but who have not yet developed structural heart changes (diabetics, those with coronary disease without prior infarct)
B	Individuals with structural heart disease (i.e. reduced ejection fraction, left ventricular hypertrophy, chamber enlargement), however no symptoms of heart failure have ever developed
C	Patients who have developed clinical heart failure.
D	Patients with refractory heart failure requiring advanced intervention (biventricular pacemakers, left ventricular assist device, or transplantation)

Table 1: ACC AHA stages of Heart Failure (2005) [17]

In the year 2005, staging of heart failure was introduced by the ACC/AHA (American College of Cardiology, /American Heart Association). The 4 stages of Heart failure are enumerated as A) patients with risk factors B) with structural heart disease alone C) with heart failure symptoms and D) end stage disease[17]. First encounters with these heart failure patients are when they are already in Stage C and above. At this stage the best of therapies available in our armamentarium have only feeble effects on the rate of disease progression so these patients need to be screened, evaluated and treated early. The hallmark of HF is exercise intolerance as evidenced by shortness of breath and dyspnea on exertion. It is a part of the definition of heart failure and is intricately linked to the underlying pathophysiology. The capacity to exercise is often limited in milder forms of heart failure. Here although the cardiac output may be adequate at rest, it becomes overwhelmingly inadequate even with mild exertion. Decreased exercise capacity is well correlated with poor outcomes and increased morbidity and mortality[18, 19].

Patients are more likely to be hospitalized and die from non cardiovascular cause than patient with reduced ejection fraction (EF) reflecting their advanced age, greater burden of comorbidites and systemic inflammation as they have a high prevalence of non-cardiac comorbidities[31].

1. Factors predisposing HFpEF

Risk Factors and Comorbidities (Fig: 1)

A. Aging

B. Female

C. Hypertension

D. Obesity

E. Diabetes Mellitus

F. Chronic Obstructive Pulmonary Disease

G. Chronic Renal Disease

H. Pulmonary hypertension

I. Anaemia

J. Sleep apnoea syndrome

K. Atrial Fibrillation

L. Cardiomyopathy hypertrophic/restrictive/ infiltrative,

M. Coronary Artery Disease

N. Constrictive Pericarditis

O. Valvular heart disease

Pathophysiology

Diastolic properties

Diastole allows ventricle to fill adequately in rest and exercise without abnormal increase in LA pressure. Phases are isovolumic pressure decline and filling. Filling is divided into early rapid filling, diastasis and atrial systole. Early rapid is 70-80% of LV filling, this diminishes with age and various disease states. Early diastole is driven by myocardial relaxation, LV elastic recoil, LV diastolic stiffness, LA pressure, ventricular interaction, pericardial constraint, pulmonary vein, mitral valve orifice area.

Diastasis is when LA-LV pressure are equal it is <5% of diastolic filling, Atrial systole contributes 15-25% of diastole without raising mean LA pressure. In HFpEF relaxation and recoil are abnormal at rest and doesn't enhance during exercise, so filling is maintained by increase LA pressure. During systole potential energy is stored in elastic elements of cardiomyocytes and extracellular matrix. During relaxation potential energy is released as elastic element recoil and return to their original length and orientation, this causes LV pressure to fall rapidly during isovolumic relaxation[15]. This fall in pressure produces diastolic gradient in LA-LV apex, which accelerates blood flow from LA-LV apex diastolic intraventricular pressure gradient pulls blood rapidly, so it is a measure of LV suction. This process gets affected in HFpEF. Extracellular matrix (ECM) consists of fibrillar protein such as collagen types 1 and III, elastin, proteoglycan, basement membrane protein collagen IV, laminin, fibronectin, matrix metalloprotein (MMPs), tissue inhibitors of metalloproteins (TIMP), transforming growth factor b (TGFB), cytokines. This fibrillar collagen is increased in HFpEF75 (Fig: 6).

Aging:

The prevalence of HFpEF increases with age in both sexes[152], it is due to increase comorbidity. LV Diastolic function directly influences some of the pathophysiological mechanisms behind HFpEF. Aging is also linked with an increase in arterial stiffness and a reduction in endothelium-dependent vasodilation[7, 8, 150]. Arterial LV systolic and LV diastolic stiffness increases with aging, there is increase in cardiomyocytes size, apoptosis, decrease in cardiomyocytes number, alter growth factor regulation, focal collagen deposition, blunted beta adrenergic responsiveness, increased transforming growth factor ß signaling reduced expression of elastases leading to interstitial fibrosis, mitochondrial

oxidative stress, genomic instability, excitation contraction coupling, altered calcium handling protein leading to altered calcium handling[154], LV stiffness which increases progressively with age, and this increase is more prominent in women[153].

Female:

Both epidemiological studies and randomized trials consistently showed that most HFpEF patients are women (50–84%)[155]. This sex bias can partly be attributed to the age distribution of the population at risk as women have a higher life expectancy. LV stiffness increases progressively with age, and this increase is more prominent in women.

Obesity, arterial hypertension, and diabetes mellitus are common in HFpEF patients and often coexist[156]. Arterial hypertension increases cardiac structural remodelling and functional changes which increases afterload on the LV, further increasing pro-hypertrophic signalingn in cardiomyocytes. It directly impaires ventricular-vascular coupling[15] and leads to arterial stiffness[161], increases LV systolic and LV diastolic stiffness[17], impaires relaxation. Proinflammatory and profibrotic signal leads to monocyte-macrophage mediated changes in ECM collagen homeostasis and myofilament phosphorylation of cardomyocytes causes increase myocardial fibrosis and titin phosphorylation which increases myocardial stiffness.

Diabetes mellitus:

Diabetes mellitus can contribute to the development of HFpEF through several pathways. It is associated with a systemic inflammatory state and increased oxidative stress, causing microvascular dysfunction and LV hypertrophy[158]. Diabetes accelerates atherosclerosis, leading to myocardial ischemia, progressively impairing renal function, contributing to volume overload. Diabetic heart has myocyte hypertrophy, intramyocardial microangiopathy and ECM fibrosis causing impaired endothelium function, endothelium dependant and independent vasodilatation, impaired LV relaxation, impaired passive LV diastolic stiffness and contractile dysfunction. Microalbuminuria is highly prevalent in HFpEF, being associated with LV remodeling, and is a prognostic marker for further disease development[181, 194, 195, 199, 323]. Elevated circulating and cellular levels of advance glycosylated end prduct (AGEs) have been measured in patients with CKD [192]. It increases with increase collagen accumulation and stiffness due to impaired renal clearance of AGEs together with

their increased formation resulting from oxidative stress. AGE-induces crosslinking of ECM proteins increases myocardial stiffness[160] which is linked to development and progression of both HFpEF and HFrEF[190] and correlated positively with increased diastolic dysfunction in patients with diabetes mellitus type [133]. In the myocardium AGEs impair calcium handling in cardiomyocytes[329] which is mediated by carbonylation of SERCA2a, which impairs its activity[330], as well as by enhancing calcium leakage from the sarcoplasmic reticulum through the ryanodine receptor (RyR2), thereby promoting mitochondrial damage and oxidative stress[159]. Hence, reducing production and enhancing breakdown of AGEs could be a therapeutic option in HFpEF patients [183], particularly in patients with diabetes and CKD[17].

Obesity: Obesity is defined as a BMI ≥30 kg/m2. Patients with HF who have a BMI between 30 and 35 kg/m2 have lower mortality and hospitalization rates than those with a BMI in the normal range[66]. Obesity is a risk factor for HF [141]. The diagnosis of cardiac cachexia independently predicts a worse prognosis [65]. Morbidly obese (BMI 35–45 kg/m2) patients may have worse outcomes compared with patients within the normal weight range and those who are obese. In more advanced obesity weight loss may be considered to manage symptoms and exercise capacity [165]. Arising from a systemic inflammatory state and increased oxidative stress, they have impaired endothelial function [23]. It is a potent inductor of inflammatory signaling as visceral adipose tissue is infiltrated by macrophages, which continuously secrete inflammatory cytokines [63] leading to an increase plasma volume, correlating with LV end-diastolic pressure [119]. It increases metabolic and haemodynamic load on heart. Obesity influences LV geometry substantially more in women than in men- adipose mass is greater in women than men in any weight category and obese women have greater LV mass than obese men.

Chronic Obstructive Pulmonary Disease: Poor lung function is a risk factor for congestive heart failure (CHF), low FEV1 is associated with incident Heart failure (HF) and increases risk of hospitalization due to HF. HFpEF is in 5% of patients with more in older patients and subclinical diastolic dysfunction is there in 75% of COPD. Coronary ischemia with atherosclerosis is associated with diastolic dysfunction (Fig: 1).

Chronic Renal Disease:

Heart failure (HF) and chronic kidney disease (CKD) co-exist, and it is estimated that about 50% of HF patients suffer from CKD characterized by impaired relaxation of the left ventricle (LV) during diastole. These patients have typical co-existence of HFpEF and CKD is partially due to common underlying comorbidities, such as hypertension, dyslipidemia and diabetes (Fig: 1). Multiple processes including cardiomyocyte hypertrophy, interstitial fibrosis, impaired calcium handling, and increased passive cardiomyocyte stiffness contribute to the left ventricular stiffening characteristic for HFpEF. Macrovascular changes accompanying CKD, such as hypertension and arterial stiffening, can contribute to HFpEF (Fig: 2)[137, 136]. Interdependence of the heart and kidneys, similarities between their microvascular networks, and the coexistence of CKD and HF play a role for microvascular dysfunction in development and progression of both diseases ,they are mutually promoting (Fig: 1). HFpEF promotes renal dysfunction by (1) an elevated central venous pressure, which results from pulmonary hypertension and RV dysfunction (2) inability to increase cardiac output following arterial vasodilation because of chronotropic incompetence and fixed LV stroke volume (3) systemic inflammation, endothelial dysfunction, and low NO bioavailability, low erythropoietin and Vitamin D which reduces renal blood flow and sodium excretion [17]

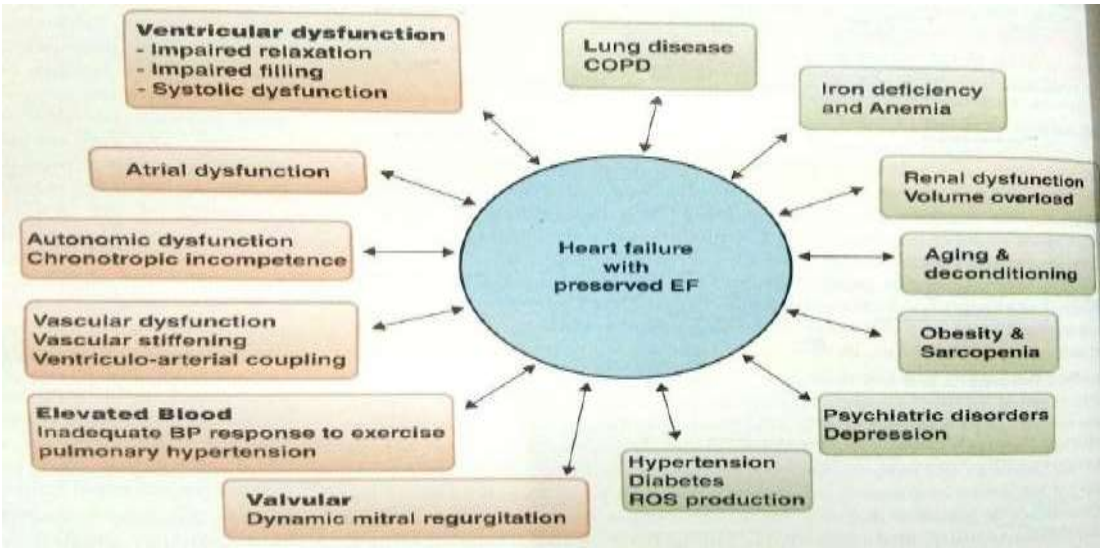

Fig: 1 Pathophysiology of HFpEF: HFpEF presents a heterogenous syndrome characterised by multiple cardiovascular and non cardiovascular comorbidities [100].

renal factors having a direct impact on the heart and/ or coronary microvasculature, these factors include: (1) activation of the renin-angiotensin-aldosterone system (2) anemia, (3) hypercalcemia, hyperphosphatemia and increased levels of fibroblast growth factor 23 (FGF-23)151, (4) uremic toxins.

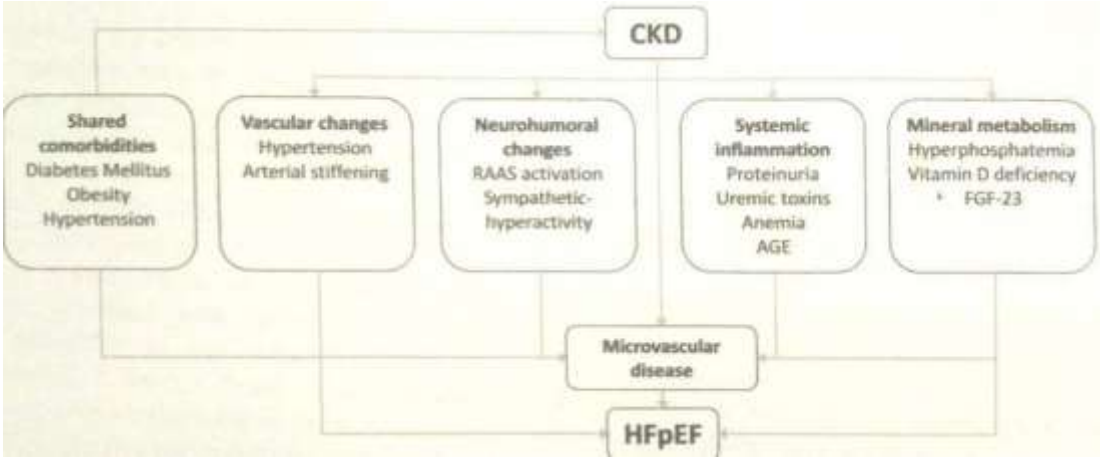

FIG: 2 Schematic overview of the risk factors that can contribute to the development of HFpEF in patients with CKD [17].

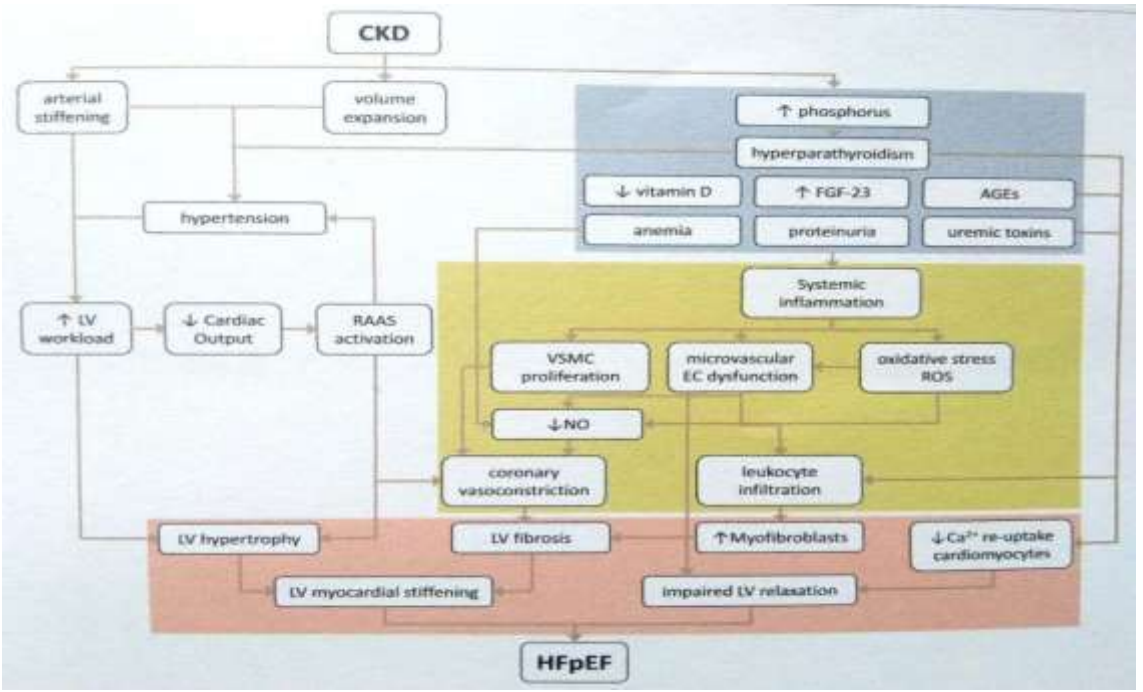

FIG: 3 Proposed schematic overview of the pathological mechanisms that underlie the progression of CKD to HFpEF Blue box depicts renal factors; green box depicts coronary microvascular factors; and red box depicts myocardial changes contributing to HFpEF[17].

CKD can induce coronary microvascular dysfunction and progression of left ventricular hypertrophy and diastolic dysfunction by mechanical effects, neurohumoral activation, systemic inflammation, anemia and changes in metabolism as induced by CKD. Arterial remodeling in CKD patients is characterized by arterial stiffening, increasing pulse pressure, as a consequence of premature aging, and atherosclerosis of the arteries[17].

Myocardial perfusion is also impaired by the vasoconstrictor effects of angiotensin II. During prolonged exercise, vasoconstriction occurs within metabolically less active tissues, mediated by angiotensin II and endothelin-1. Such response is inhibited in metabolically active tissues by NO and prostanoids, resulting in an efficient distribution of blood[147]. In a state of systemic inflammation, locally decreased NO bioavailability in the coronary microvasculature results in disinhibition of angiotensin II-mediated vasoconstriction, resulting in reduced blood delivery to the heart.

Aldosterone has been shown to directly promote myocardial fibrosis, left ventricular hypertrophy, and coronary microvascular dysfunction, acting through endothelial and myocardial mineralocorticoid receptors, independently of angiotensin II[146].

Pulmonary hypertension: HFpEF patients have increase pulmonary artery systolic pressure >40 mmhg due to elevated LV filling resulting increase in pulmonary venous filling pressure, increases reactive pulmonary vasoconstriction which increases pulmonary vascular resistance which is augmented in exercise. In some increase pulmonary venous filling pressure causes pulmonary vascular remodelling causes irreversible pulmonary hypertension.

Anemia and Iron Deficiency: Iron deficiency is the most frequent cause of anemia in HF patients, predict mortality its role in erythropoiesis. Iron is also a key factor in mitochondrial metabolism, crucial for cells with a high energy consumption such as cardiac and skeletal myocytes. In HF, iron deficiency arises from nutritional defects, increased red cell destruction, hepatic congestion, inflammatory bone marrow dysfunction, and chronic kidney disease. Iron deficiency affects functional status exercise capacity, it directly affect microvascular function by inhibiting mitochondrial respiration, cardiomyocyte damage, eventually contributes to progression of HFpEF (Fig: 3), by limiting energy production, impairing energy-dependent Ca2+reuptake during diastole[118] and contributes to oxidative stress.It impairs oxygen-carrying capacity, and the severity of anemia predicts mortality, but

the role of treatment is uncertain[35].

Sleep apnoea syndrome: The pathophysiological interaction between obstructive sleep apnea (OSA) and cardiovascular disease is complex and comprises sympathetic activation, inflammation, oxidative stress, endothelial dysfunction. Both OSA and central sleep apnea (CSA) is present in 60% of heart failure patients with OSA predominant in HFPEF patients. CPAP for obstructive sleep apnea was effective in decreasing the apnea−hypopnea index, improving nocturnal oxygenation, increasing LVEF, lowering norepinephrine levels, and increasing the distance walked in 6 minutes, these benefits were sustained for up to 2 years [228]. Smaller studies suggest that CPAP can improve cardiac function, sympathetic activity, and health related quality of life (HRQOL) in patients with HF and obstructive sleep apnea[226, 229].

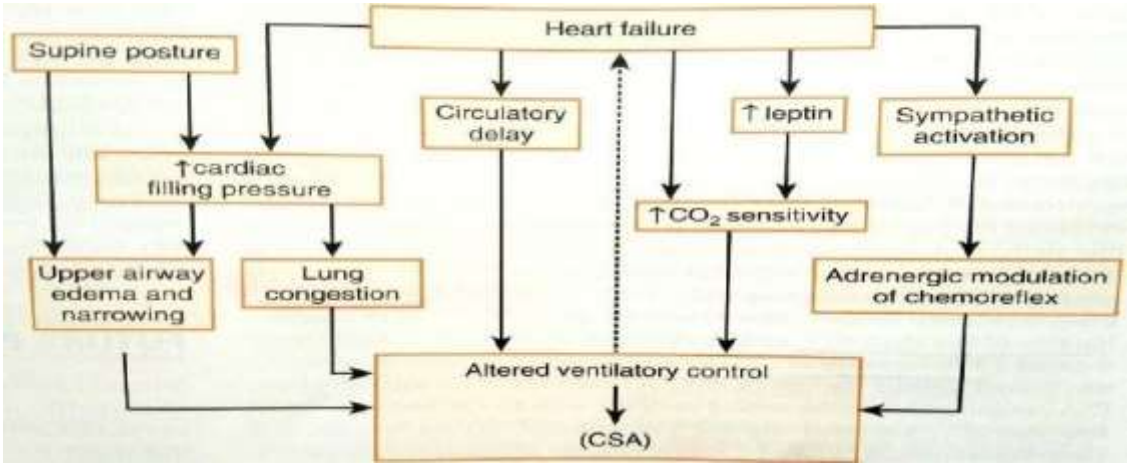

FIG: 4 Schematic outlining possible mechanisms underlying development of CSA and the possible feedback from CSA resulting in exacerbation of heart failure

Sleep disordered breathing (SDB) is a common form of diastolic dysfunction due to chronic pressure overload, impaired coronary flow reserve and inflammation leading to cardiac interstitial fibrosis. LV mass and LV mass volume ratio increases in proportion of severity of SDB. Indices of diastolic dysfunction, increase E/A ratio, reduced mitral deceleration, isovolumetric relaxation are there in SDB. SDB independently predicts new onset heart failure. In patients with heart failure SDB predicts HF exacerbations, and progression, impaired quality of life, increase fatigue, reduced functional status, frequent hospitalization, arrhythmia and death. CPAP treatment reduces BP, improve oxygenation, subendocardial ischemia, the preload, afterload, sympathetic activation, inflammatory and oxidative stress (Fig: 4).

Atrial Fibrillation and Rhythm disturbances: Atrial Fibrillation (AF) is a frequent cause of decompensation in HFPEF, causing loss of atrial contraction and resulting tachycardia. AF causes decompensation in diastolic dysfunction resulting in left atrial enlargement (LAE) and AF. The presence of one increases the likelihood of the other and each can cause the other[48]. As suggested in the 2013 ACC/AHA HF guidelines, AF is managed in patients with HFpEF according to guidelines to improve symptomatic HF[44]. The efficacy of successful restoration and long-term maintenance of sinus rhythm is dependent in part on how long a patient has been in persistent AF and left atrial size. Rate control to prevent rapid AF acutely and/or chronically usually leads to an improvement in symptoms in patients with HF and marked improvement in left ventricular function. Beta-blockers, calcium channel blockers, Digoxin are drugs to be used[17]. Anticoagulation drug use to prevent systemic embolization.

Coronary artery disease: In coronary artery disease (CAD) acute ischaemia contributes to diastolic dysfunction causes change in endothelium vascular function which contributes to HFpEF. CAD is common in patients with HFpEF[36]. In general, contemporary revascularization guidelines should be used in the care of patients with HFpEF and concomitant CAD. It might be reasonable to consider revascularization in patients for whom ischemia appears to contribute to HF symptoms, but whether these interventions improve outcomes is not entirely clear[112, 113].

Genetic Regulation: Cardiomyopathy hypertrophic/restrictive/ infiltrative. Little is known about potential genetic determinants of HFpEF. Some genetic cardiomyopathies do exhibit a phenotype with preserved ejection fraction like hypertrophic cardiomyopathy and hereditary transthyretin amyloidosis. It is difficult to discern genetic determinants of HFpEF from the influence of comorbidities.

Constrictive Pericarditis: The normal pericardium restrains ventricular filling, contributing to the elevation in intracardiac pressures that develop during conditions of increased venous return such as exercise. Patients with HFpEF characteristically develop marked increases in filling pressures with exercise or volume loading owing to diastolic dysfunction[6]. Further study to determine whether pericardial restraint contributes to the pathophysiology of HFpEF, whether surgical approaches to remove pericardial restraint might improve symptoms related to venous congestion[25].

Valvular heart disease: If a catheter-based therapy is being considered it may be particularly beneficial in patients with HF being considered for surgery, transcatheter aortic valve implantation or transcatheter mitral valve intervention.

2. Cardiomyocyte contractile function:

The (giant) elastic sarcomeric protein titin is the dominant regulator of myocardial passive tension, and cardiomyocyte-derived stiffness (Fig: 5). 80% of left ventricular passive stiffness may be explained by titin, especially when sarcomere lengths are still within physiological boundaries, while in overstretched sarcomeres the contribution of the extracellular matrix becomes more dominant[35]. Titin regulates cardiomyocyte stiffness at the transcriptional and post-translational levels. At the transcriptional level, titin shifts from its compliant isoform N2BA toward its stiff isoform N2B have been postulated to contribute to diastolic dysfunction in HFpEF. Post-translational modification of the titin N2B segment by protein kinase A (PKA)- and G (PKG) mediated phosphorylation has been shown to change cardiomyocyte passive tension (fig: 7). In cardiomyocytes, the giant protein titin operates as a bidirectional spring and gives stability to the other myofilaments. Titin determines the sarcomeric viscoelasticity, where as actin and myosin mainly contribute to force generation[32, 33, 34]. Mechanical energy stored in the sarcomeric protein titin during contraction contributes to recoil during relaxation, resting cardiomyocyte tension in diastole is a determinant of contractile force during systole. The relationship between "systolic" and "diastolic" function at the cellular level is expected to be highly interdependent. Titin-dependent stiffness is increased in patients with arterial hypertension and HFpEF, supporting its mechanistic role. Prominent features of myocardial remodeling in heart failure with HFpEF are high cardiomyocyte resting tension (Fpassive) and cardiomyocyte hypertrophy.Titin is able to modulate cardiomyocyte-based F passive by means of isoform switching, phosphorylation and oxidative modifications. Phosphorylation and oxidative modifications occur much faster. For HFpEF, the relative hypophosphorylation of PKG-dependent titin sites, offers potential therapeutic targets. This increases passive stiffness (Fpassive) upon stretch correlates with LV end- diastolic pressures and LV diastolic stiffness caused by changes in both ECM fibrillar collagen and cardiomyocyte titin. They also had increased titin dependent stiffness in association with significant changes in the phosphorylation state of titin, with decreased phosphorylation of a PKA/PKG site in the N2B element and increased phosphorylation of one of the PKC sites in the PEVK element[35]. Sites within the N2B element are

phosphorylated by PKA and PKG, which decreases passive force. Sites within the PEVK element are phosphorylated by PKCα which increases passive force, hyperphosphorylation of the PKC/ calcium /calmodulin-dependent protein kinase II (CaMKII) site in the PEVK segment S4185(S469) of the N2B element is associated with increased myocardial stiffness in HFpEF patients[51].

The current study showed hypophosphorylation of PKG/PKA sites on titin in HFpEF patients, consistent with the reduction in passive tension detected when cardiomyocytes from HFpEF patients are treated with PKA/PKG. The finding that both changes in collagen and titin may play a pivotal role in the development of HFpEF[35].

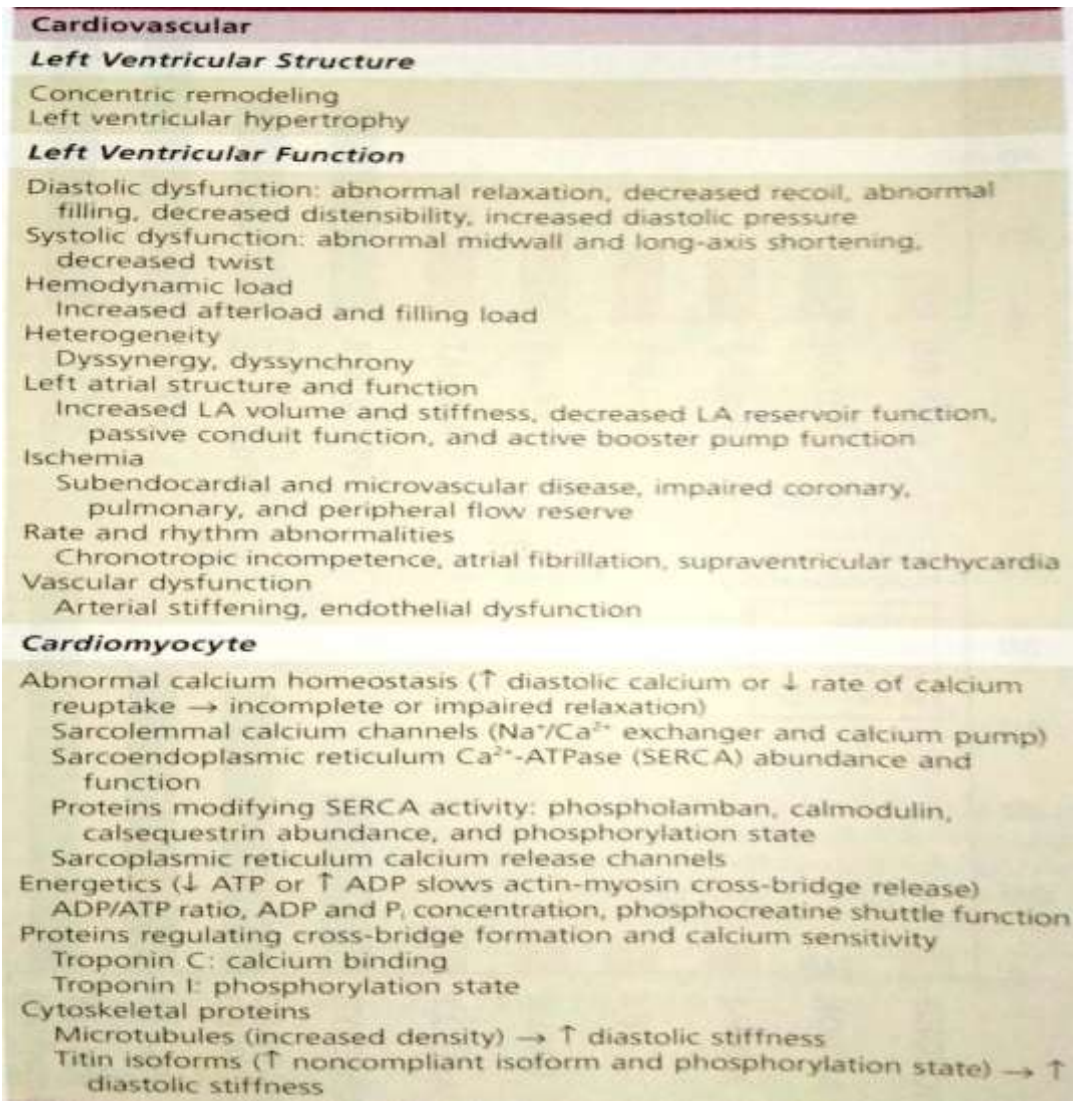

Fig: 5 Mechanism and factors contributing to pathophysiology of Heart Failure with Preserved Ejection Fraction[75]

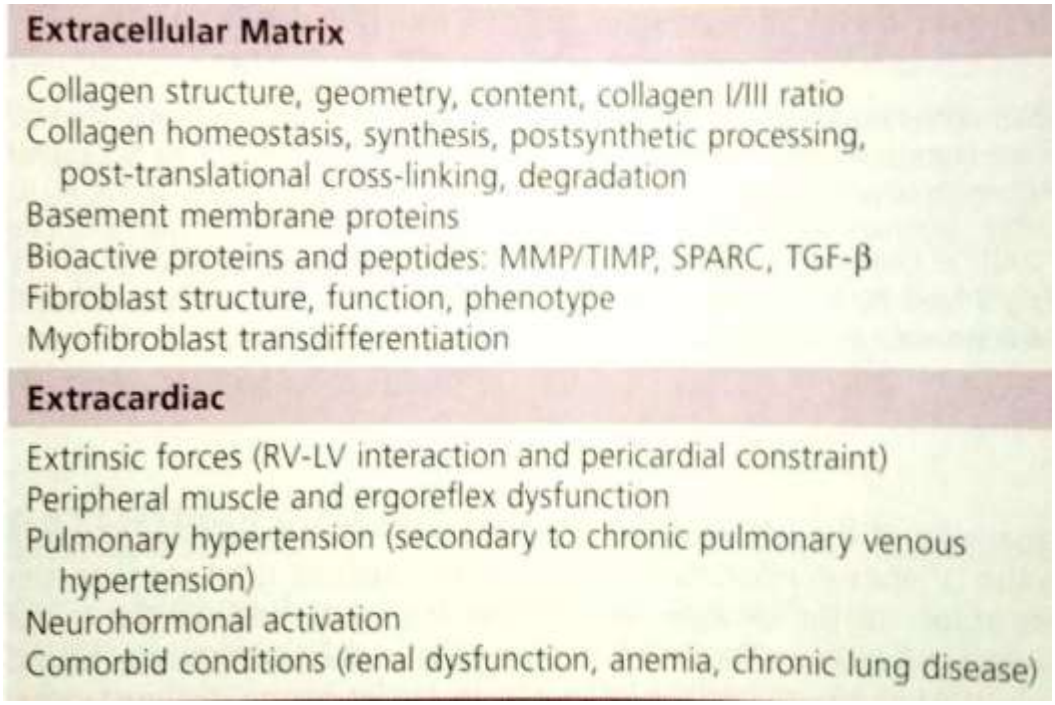

Fig: 6 Mechanism and factors contributing to pathophysiology of Heart Failure with Preserved Ejection Fraction[75]

One of the mechanisms necessary for relaxation to occur is the sarcoplasmic reticulum calcium ATP-ase (SERCA) pump, which removes calcium from the cytosol. Decreased levels or activity of SERCA can decrease the removal of calcium from the cytosol, which impairs relaxation of the ventricles. Several factors can affect the SERCA pump[16] like Ischemia, pathological LVH secondary to hypertension and aortic stenosis. There is a naturally occurring SERCA inhibitory protein called phosphlamban and increased levels of this protein impair relaxation.Diastolic intracellular calcium handling is a major determinant of LV relaxation. Dephosphorylated phospholamban (PLN) is an inhibitor of sarcoplasmic/endoplasmic reticulum Ca(2+)ATPase 2a (SERCA2a), but PKA-catalyzed (or CaMKII) phosphorylation of PLN results in the dissociation of PLN from SERCA2a, thus activating this Ca2+ pump and augmenting SERCA2a activity. In failing hearts, Ca2+ reuptake into the sarcoplasmic reticulum by the SERCA pump is delayed. Cardiomyocyte Ca2+ accumulation in the absence of concomitant enhancement of SERCA activity leads to elevated diastolic Ca2+, Ca 2+ transients with preserved or enhanced amplitude, and slower Ca2+ reuptake kinetics with impaired relaxation and promote remodeling. The inability of SERCA to expeditiously resequester Ca2+ becomes particularly explain the chronotropic intolerance of the myocardium and reduced exercise

capacity of HFpEF patients [11] indicating increased cytosolic Ca2+ load which may contribute to slowed cardiomyocyte relaxation.

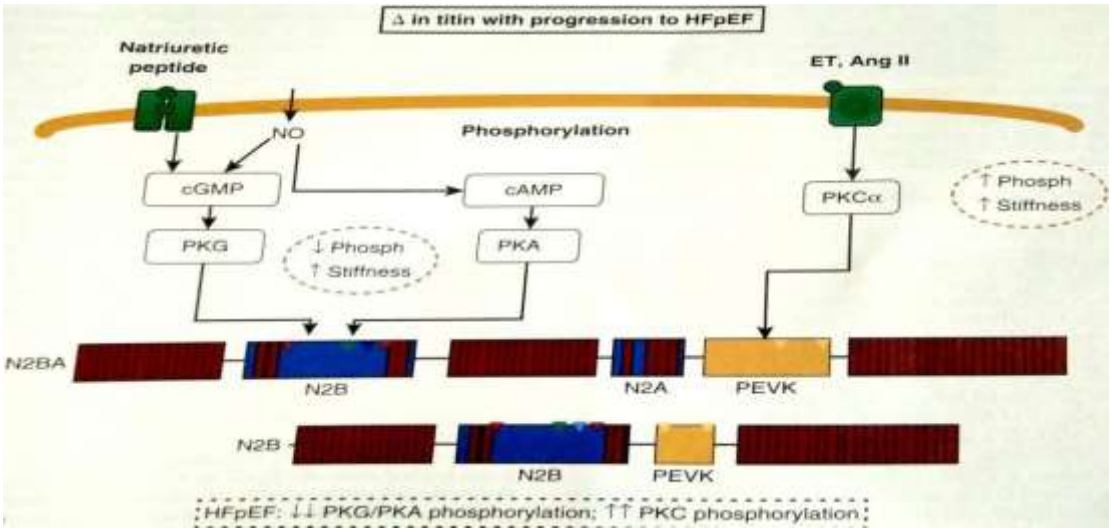

Fig: 7 Cardiomyocyte cAMP and cGMP signalling pathways involved in myofilament regulation and titin-based stiffness.

Generation of cAMP, which stimulates PKA activity. cGMP is generated from activation of sGC by NO. cGMP stimulates PKG activity. Both PKA and PKG induce lusitropic effects, and lower cardiomyocyte stiffness through phosphorylation of the titin N2B segment. Sites within the PEVK element are phosphorylated by PKCα[76].

Trials indicate that combining SERCA2a activation and Na+/K+-ATPase (NKA) inhibition may increase contractility and facilitate active relaxation, improving systolic as well as diastolic heart function, both of which would be beneficial effects in the treatment of chronic HF.

Diastolic dysfunction cannot be observed by echocardiography at rest in one-third of patients with HFpEF as many patients with HFpEF in the early stages did not present an increase in LV filling pressure at rest. These patients usually have normal plasma levels of B natriuretic peptide (BNP), which leads clinicians to make a false diagnosis of no HF. Natriuretic peptides are released and produced in response to increased myocardial wall tension. HFpEF is characterized by hypertrophic hearts with a small LV cavity. Diastolic dysfunction in HFpEF does not appear to impair net LV filling.

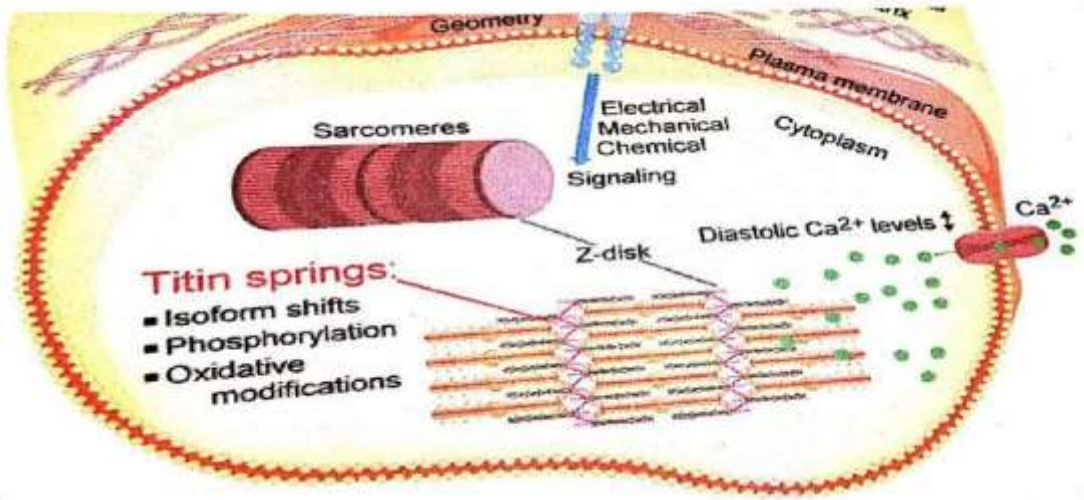

Fig: 8 Collagen and titin as important sources of diastolic passive stiffness in myocardium. Schematic visualizing major determinants of passive stiffness in the heart[35]

Diastolic dysfunction cannot be observed by echocardiography at rest in one-third of patients with HFpEF as many patients with HFpEF in the early stages did not present an increase in LV filling pressure at rest. These patients usually have normal plasma levels of B natriuretic peptide (BNP), which leads clinicians to make a false diagnosis of no HF. Natriuretic peptides are released and produced in response to increased myocardial wall tension. HFpEF is characterized by hypertrophic hearts with a small LV cavity. Diastolic dysfunction in HFpEF does not appear to impair net LV filling, but this level of filling is at the expense of increased LA pressure which can lead to dyspnea, secondary pulmonary hypertension, and atrial remodeling, make patients prone to right ventricular (RV) dysfunction and atrial fibrillation.Abnormalities in patients with HFpEF are related to diastolic dysfunction and may present with impairments in relaxation, increases in chamber stiffness, or both. Increased cardiomyocyte stiffness and cardiomyocyte hypertrophy follows diastolic dysfunction and sets the chain reaction of pathologic maladaptation leading to overt HFpEF. Cardiomyocyte hypertrophy is an almost universal finding in human HFpEF. Comorbidities induce a systemic proinflammatory state with elevated plasma levels of interleukin (IL)-6, tumor necrosis factor (TNF)-a, soluble ST2 (sST2), and pentraxin [3].

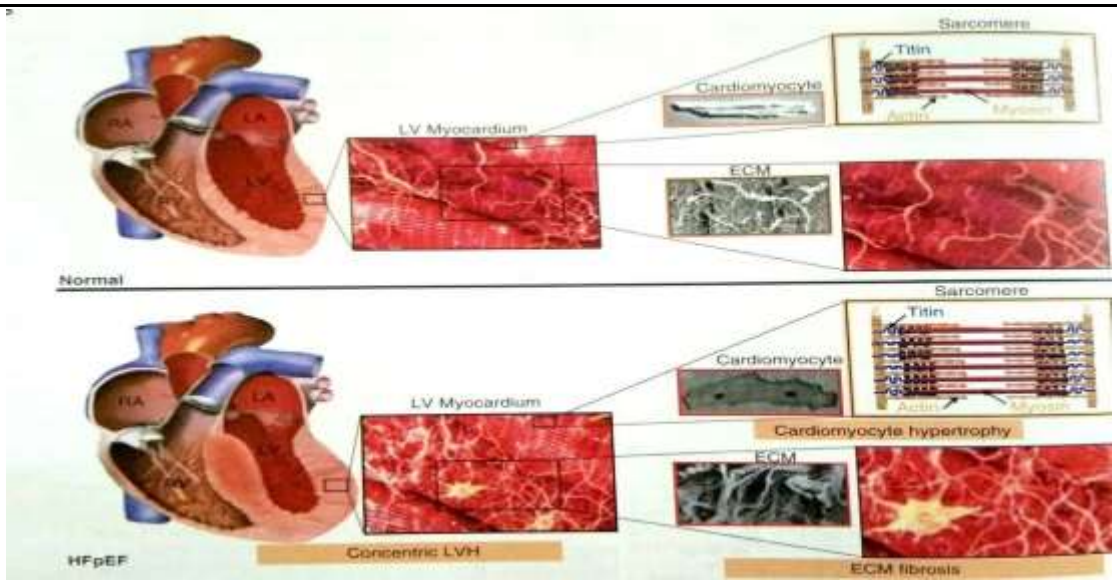

Fig: 9 Ventricular, cellular, extracellular matrix (ECM) and molecular structural changes in patients with HFPEF, there is concentric hypertrophy and remodelling of LV and cardiomyocyte level. LV increases in wall thickness with no change in LV volume, cardiomyocytes increases in diameter but no change in the length is there, there are alterations in titin phosphorylations with increase in the amount of collagen with a corresponding increment in the content, width and number, there is alteration in fibroblast function which causes interstitial fibrosis[51, 82].

Coronary microvascular endothelial cells reactively produce reactive oxygen species (ROS), vascular cell adhesion molecule (VCAM), and E-selectin. Production of ROS leads to formation of peroxynitrite (ONOO) and reduced nitric oxide (NO) bioavailability, both of which lower soluble guanylate cyclase (sGC) activity in adjacent cardiomyocytes.

3. Normal Endothelial Function: The endothelium is the inner most layer of the blood vessels, present from the smallest capillary to the aorta. They are a protective layer between the blood and extravascular tissues, endothelial cells and are dynamic, highly interactive cells that regulate vascular function and homeostasis[161]. The healthy endothelium prevents platelet aggregation and leukocyte adhesion, inhibits smooth muscle proliferation, and regulates vascular tone through release of vasoactive substances. These processes are largely mediated by nitric oxide (NO), the main endothelial effector molecule.

NO has the unique property of being a gaseous signaling molecule, able to diffuse quickly into neighboring cells causing endothelium- dependent vasorelaxation which increases blood flow and the accompanying shear stress. NO activates soluble guanylyl cyclase (sGC) and its second messenger cyclic guanosine monophosphate (cGMP), produces relaxation of the vascular smooth muscles and widening of the blood vessel[161].

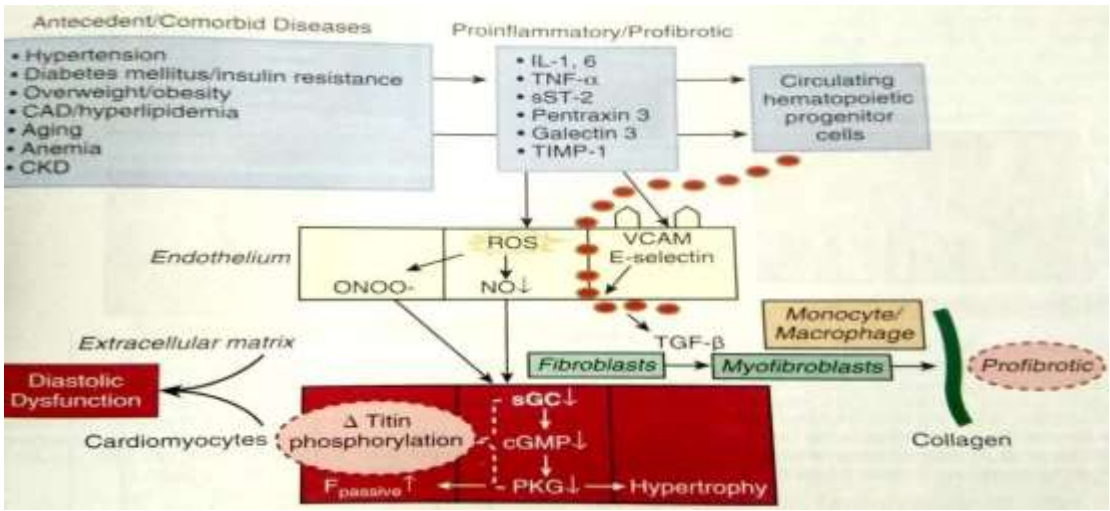

FIG: 10 Pathophysiologic mechanism underlying development of heart failure7.Lower sGC activity decreases cyclic guanosine monophosphate concentration and protein kinase G (PKG) activity. Low PKG activity increases resting tension (Fpassive) of cardiomyocytes because of hypophosphorylation of titin and removes the brake on prohypertrophic stimuli inducing cardiomyocyte hypertrophy. VCAM and E-selectin expression in endothelial cells favors migration into the subendothelium of monocytes. These monocytes release transforming growth factor b (TGF-b). The latter stimulates conversion of fibroblasts to myofibroblasts, which deposit collagen in the interstitial space.

NO-sGC-cGMP pathway: In the setting of cardiovascular risk factors (aging, hypertension, diabetes, obesity, dyslipidemia, and smoking), endothelial homeostasis is disturbed which causes Endothelial Dysfunction[149, 148]. It is considered the first step in the atherosclerotic process and a precursor to overt cardiovascular disease as it sets a vicious circle leads to a vasoconstricting, pro-inflammatory, and pro- thrombotic state. Inflammation and oxidative stress reduces nitric oxide (NO) bioavailability with subsequently less stimulation of soluble guanylate cyclase (sGC), sGC is the only receptor for nitric oxide (cNO), a signaling agent produced by the enzyme nitric oxide synthase (NOS) from the amino acid L-arginine, which catalyses the conversion of guanosine 5'-triphosphate (GTP) to cGMP.

This cascade is an important potential target for future HFpEF therapy. cGMP activates protein kinase G (PKG) in the cardiomyocyte (Fig: 10), Low PKG activity favors hypertrophy development and increases resting tension because of hypophosphorylation of titin. Both stiff cardiomyocytes and interstitial fibrosis contribute to high diastolic left ventricular (LV) stiffness and heart failure development and oxidative stress and contributes to impaired active relaxation and passive stiffness[150].

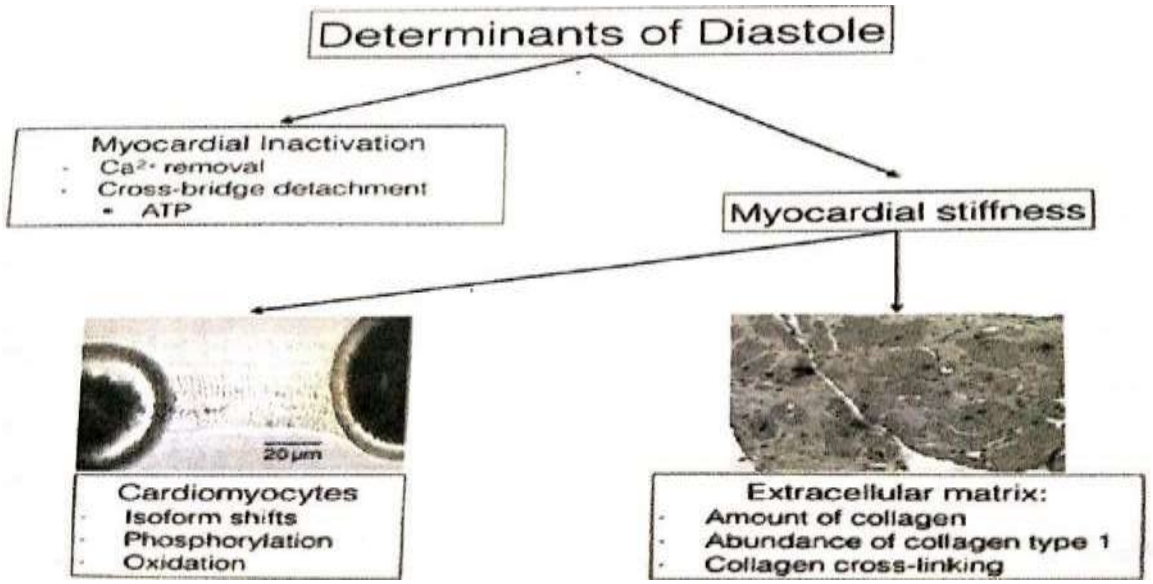

FIG: 11 Determination of diastole. LV can be subdivided into two components: myocardial inactivation and myocardial stiffnes (Fig: 9)[100].

Cardiomyocyte hypertrophy is an almost universal finding in HFpEF. It is additionally induced by molecular pathways, NO-mediated mechanisms, by increased stretch on cardiomyocytes through intrinsic mechanotransduction mechanisms. Cardiac biopsies from HFpEF patients show increased extracellular fibrosis. Extracellular fibrosis is physiologically more important than cardiomyocyte stiffness in HFpEF, as LV end-diastolic pressure is only correlated to collagen-based stiffness, not to titin-based stiffness (Fig: 8). Cardiac fibroblasts play a prominent role in the development of extracellular fibrosis. In HFpEF, fibroblasts are presumed to convert to myofibroblasts because of exposure to transforming growth factor-β as a result of monocyte/macrophage myocardial infiltration16. Circulating inflammatory cytokines induce expression of endothelial adhesion molecules such as vascular cell adhesion molecule and E-selectin (Fig: 10). Secretion of inflammatory mediators

Angiotensin II and aldosterone induces extracellular fibrosis through direct stimulation of collagen secretion by myofibroblasts[107, 106]. The pro-inflammatory state in HFpEF is thought to be systemic as inflammatory endothelial activation is in the coronary circulation but present throughout the vasculature. A reduction in NO bioavailability reduces exercise - induced peripheral vasodilation, reduces vasoreactivity and vascular remodeling in the pulmonary arteries, reduces capillary density in the heart and skeletal muscle, and reduced renal blood flow. There is a higher relative importance of endothelial inflammation compared to endothelial dysfunction, in HFpEF pathophysiology. All these comorbidities can induce a systemic inflammatory state, potent inflammatory cytokines such as IL-6 and tumor necrosis factor alpha (TNF-α) are elevated in HFpEF patients and predict new onset of HFpEF30. PKG activity as an important contributor to myocardial diastolic dysfunction in HFPEF. Lower myocardial PKG activity in HFPEF to correspond with higher cardiomyocyte Fpassive and in vitro administration of PKG acutely lowered the high Fpassive of HFPEF cardiomyocytes (Fig: 11). Prominent features of myocardial remodeling in HFPEF are cardiomyocyte hypertrophy and interstitial fibrosis. It is essential to develop noninvasive biomarkers like CMR for early identification of the alterations in these two components. Clinical limitations of CMR include local expertise, lower availability and higher costs compared with echocardiography, uncertainty about safety in patients with metallic implants (including cardiac devices) and less reliable measurements in patients with tachyarrhythmias. Claustrophobia is an important limitation for CMR. Linear gadolinium based contrast agents are contraindicated in individuals with a glomerular filtration rate (GFR) < 30mL/min/1.73m2, because they may trigger nephrogenic systemic fibrosis (this may be less of a concern with newer cyclic gadolinium-based contrast agents)[108]. Oxidative stress leads to formation of disulfide bridges within the titin molecule, which raises its overall stiffness (Fig: 11) which may significantly contribute towards altered ventricular- vascular coupling. Prognosis is, equally grim as in HFrEF 5-year mortality is around 75%, which is worse than most cancers.

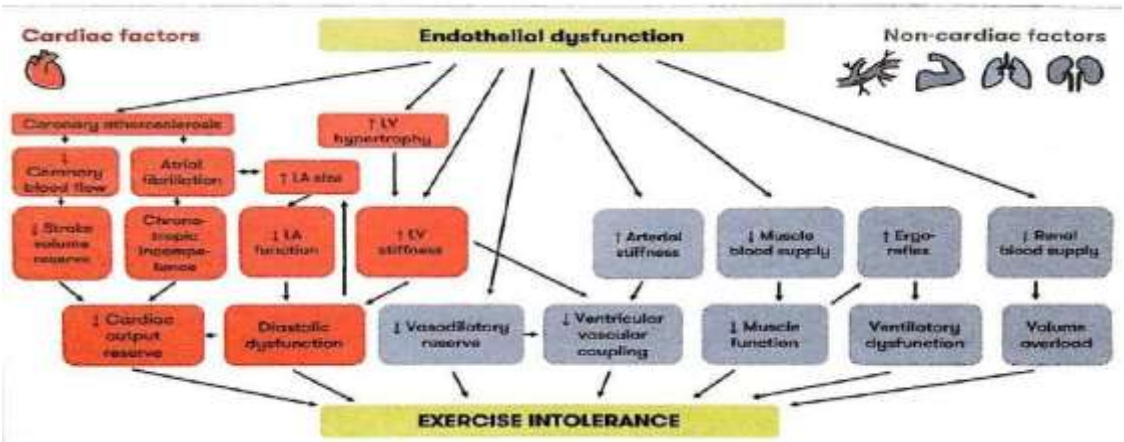

FIG: 12 Cardiac and noncardiac factors linking endothelial dysfunction and exercise intolerance in HFpEF. Besides diastolic dysfunction, which is well known, recent evidence implicates other cardiac (orange) and noncardiac (blue) factors in the development of exercise intolerance in HFpEF. Endothelial dysfunction is an underlying mechanism of many factors associated with exercise intolerance. The "inflammatory microvascular dysfunction" hypothesis puts endothelial dysfunction at the root of LV hypertrophy and LV stiffness. Endothelial dysfunction is also a precursor of atherosclerosis and contributes to many noncardiac factors implicated in exercise intolerance[150].

4 Effects of exercise training: The exercise-induced increase in heart rate in HFpEF is lower than in controls, this is called chronotropic incompetence and can be influenced by the concomitant use of beta blockers. Reduced contractile reserve and chronotropic incompetence combined with reduced cardiac output reserve, which contributes to exercise intolerance in HFpEF. Guidelines currently recommend exercise training as a therapy to improve aerobic capacity and quality of life in HFpEF patients is based on the randomized multicenter Exercise in Diastolic Heart Failure (Ex-DHF) pilot trial and meta-analyses of several single-center trials that showed an improvement in peak VO2 and/or quality of life[29, 39, 38]. How exercise training improves peak VO2 in HFpEF patients remains unclear. Following the Fick principle, i.e., VO2 = cardiac output × arteriovenous O2 difference, improvement in peak VO2 is caused by a cardiac factor (cardiac output), a noncardiac factor (peripheral O2 extraction), or both. In HFrEF patients, both cardiac and noncardiac factors are improved by exercise[40]. In middle-aged sedentary subjects, two years of exercise training was able to improve invasively measured ventricular stiffness.

In HFpEF patients, the Ex-DHF pilot trial indeed showed an improvement in echocardiographic diastolic function with exercise training. The recently completed multicenter Optimizing Exercise Training in Prevention and Treatment of Diastolic Heart Failure (OptimEx) and Ex-DHF 2 trials will soon shed more light on the benefits of exercise training in HFpEF[17]. The main sites for peripheral O2 extraction during exercise are the skeletal muscles. Skeletal muscle abnormalities are an often overlooked but clinically important feature of HFpEF patients as they have abnormal muscle mass, composition, capillary density, and oxidative metabolism have all been described[42]. Exercise improves muscle atrophy associated with HFpEF, although training did not affect muscle strength or fatigability[43]. Muscle atrophy in HF patients leads to enhanced sensitivity of muscle metaboceptors, which drive a feedback system called "ergoreflex"[44]. The ergoreflex promotes hyperventilation, causing premature exercise discontinuation because of dyspnea.

5. Central hemodynamics-Cardiovascular: The capacity of the heart to do aerobic exercise, depends on its ability to augment its output based on the metabolic demands of the body. In this case the metabolic demands are based on the ability of the muscles to extract oxygen from the delivered blood. Thus, maximal oxygen uptake ($\dot{V}$ O2max) = cardiac output × arteriovenous oxygen difference. The increase in cardiac output during maximal upright exercise is typically 4 to 6 fold in healthy subjects. The stroke volume increase is accomplished both by use of the Frank-Starling mechanism to maintain left ventricular (LV) end- diastolic volume and by more complete LV emptying to reduce end-systolic volume. Both enhanced LV contractility and peripheral vasodilation contribute to the more complete LV emptying observed during exercise.

Maximal oxygen uptake (VO2 max)= CO X Arteriovenous (AV) difference

=SV x HR X AV difference

In a normal heart the 4-6 fold augmentation is a result of cardioacceleration increase in the heart rate by 2-4 times and increase in the stroke volume by 20-50% preload reserve of the heart[18]. In a failing heart due to the reduced contractility, diminished beta responsiveness, increases renin angiotensin activity (Fig: 13).

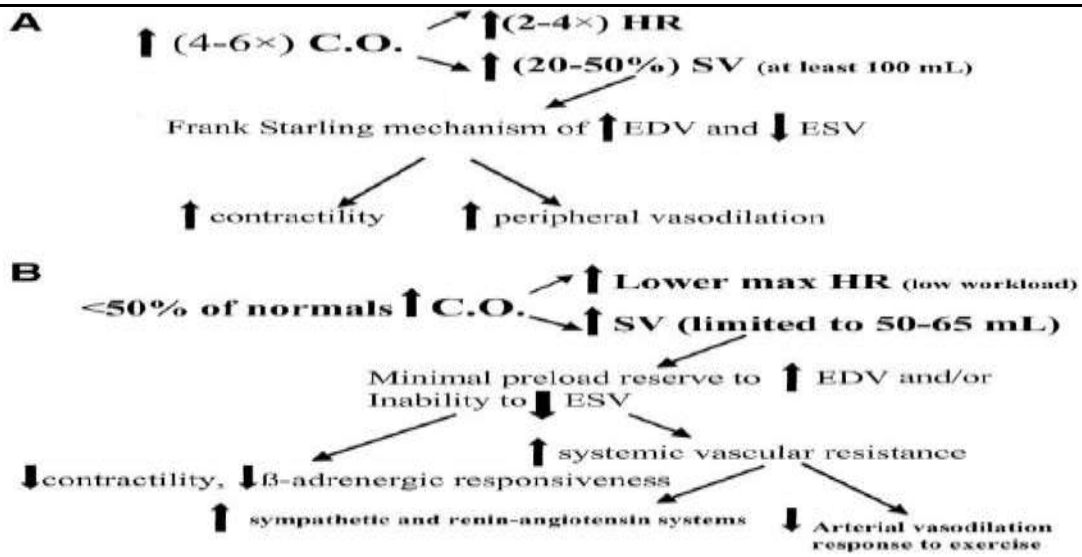

FIG: 13 Mechanisms to augment cardiac output (C.O.) in (A) healthy persons without HF and (B) patients with HF219. V̇ O2max=C.O. (HR×SV) × ΔA−VO2. C.O. indicates cardiac output; HR, heart rate; SV, stroke volume; ΔA−VO2, arteriovenous oxygen difference; EDV, end-diastolic volume; and ESV, end-systolic volume[221].

6. Peripheral factors: Abnormalities in blood flow: Apart from the general hypoperfusion state there is reduced exercise induced vasodilatation due to an overactive sympathetic nervous system, renin angiotensin system and higher than normal levels of endothelin73, 74. Increased vascular sodium content also increases the stiffness of the arteries and prevents vasodilatation45. The "vascular deconditioning" hypothesis suggests that the abnormal vasodilatory capacity is partially related to disuse46. In normal individuals, the degree to which peripheral oxygen extraction i.e., arterio-mixed venous O2 content difference, [C(a-v)O2]) increases in response to exercise is much greater than changes in systolic volume and similar to increases in heart rate. Patients with HFpEF are not able to increase heart rate and systolic volume normally during exercise, which implies a greater reliance on the ability to increase C(a-v) O2 to augment oxygen uptake (VO2)32. Impairment of endothelial dependant peripheral vasodilatation by limiting nutritive skeletal muscle flow during exercise, this could be due to deconditioning largely reversible by training, mediated by improvement in these abnormalities that are peripheral to the heart in the muscle and vasculature. HFpEF causes the rise in end-diastolic pressure is caused by a complex interplay between diastolic dysfunction, subtle systolic dysfunction, atrial and LV stiffness, reduced arterial compliance and prognostic value over clinical

parameters and LVEF. In pathophysiology of diastolic dysfunction many factors contributing are myocardial and vascular stiffening, impaired relaxation and increased passive diastolic stiffness, increased systolic ventricular-vascular stiffening, and cardiac volume overloading peripheral arteries[47]. Peripheral endothelial dysfunction has been reported in HFpEF which impair dynamic flow-mediated dilatation responses during exercise impairing matching of perfusion to regional demand in skeletal muscle microcirculation.

7. Distribution of Cardiac output: Exercise tolerance bears a direct correlation with the amount of oxygen delivered and its local effects in the muscle in extracting increasing amounts of oxygen during times of increased demand(Fig :14). In a healthy heart as much as 85% of the blood flow is diverted to the muscle during episodes of peak exercise. In patients of heart failure there is increased vascular resistance which fails to reduce during exercise[54, 77]. In 75% of the HFpEF patients, peripheral oxygen consumption was impaired due to impaired diffusive oxygen transport and utilization246. Cardiac output needs to be increased to maintain systemic oxygen delivery. A disbalance between myocardial oxygen demand and supply is also present in ischemia with no obstructive coronary artery disease (INOCA), in which myocardial oxygen supply is limited by coronary microvascular dysfunction. INOCA is increasingly being recognized as a risk factor for development of HFpEF[138].

8. Muscle: Within the muscle certain maladaptive changes take place. Skeletal muscle characteristics have major effects on substrate and oxygen utilization during exercise. There is a decrease in Type I oxidative fibres and increase in type 2b glycolytic fibers compared to healthy individuals[81]. Specifically mitochondrial enzymes like citrate synthase, succinic dehydrogenase and enzymes involved in β-oxidation of fatty acids (3-hydroxyl CoA dehydrogenase) have been shown to reduce[83].

Together these changes in skeletal muscle may contribute to abnormal oxygen extraction and substrate delivery and utilization and may further worsen exercise capacity in heart failure patients. Exercise induced LV dilatation, impaired coronary vascular bed dilatation during reactive hyperemia in LV and elevated filling pressure and tachycardia induced reduction in diastolic filling time for coronary arteries.

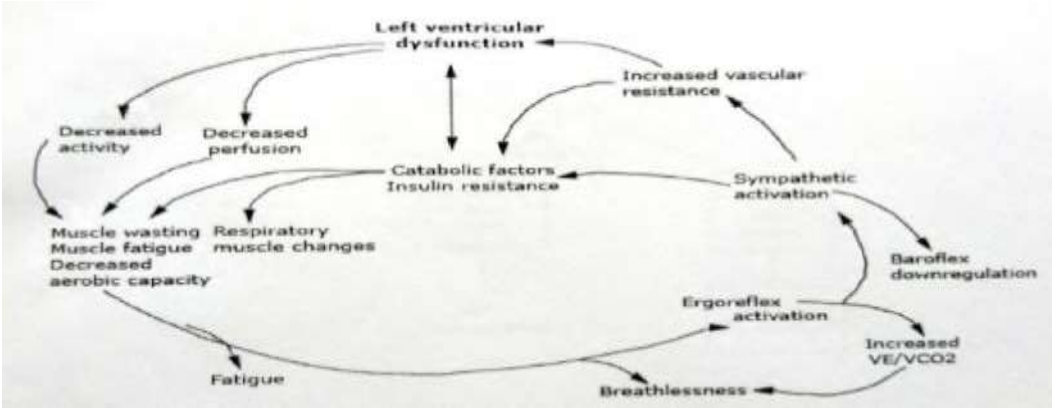

FIG: 14 Skeletal muscle changes in heart failure

Muscle hypothesis in CHF. Skeletal muscle is abnormal in CHF. During exercise, muscle has a limited capacity for aerobic metabolism, resulting in fatigue and ergoreflex activation, which causes an increase in the ventilatory response to exercise and the sensation of dyspnea. Ergoreflex activation causes sympathetic nervous system activation, with a consequent increase in afterload and a decrease in blood flow to the periphery, further exacerbating skeletal muscle abnormalities[79].

9.Ergoreflex activation: Skeletal muscle abnormalities can further contribute to exercise intolerance through overactivation of the autonomic nervous system85. Muscle atrophy in HF patients leads to enhanced sensitivity of muscle metaboceptors, which drive a feedback system called “ergoreflex”[86, 221]. The ergoreflex promotes hyperventilation, causing premature exercise discontinuation because of dyspnea[9] (Fig: 15). Afferent fibers present in the skeletal muscle are sensitive to metabolic changes related to muscular work “ergoreceptors” present in skeletal muscle which aid in circulatory adaptations during early exercise (Fig: 12,14,15)[78,79]. They respond to metabolic acidosis by causing reflex hyperventilation & increase sympathetic outflow which characterize the abnormal hemodynamic, ventilator and autonomic response of heart failure[80]. This results in increased vascular resistance worsening the hypoperfusion. Activation of these reflexes seems to be attenuated by exercise training[50]. Exercise training is able to reduce the overactivation of autonomic reflexes in HFrEF patients[87], but the effect in HFpEF patients has not been tested.

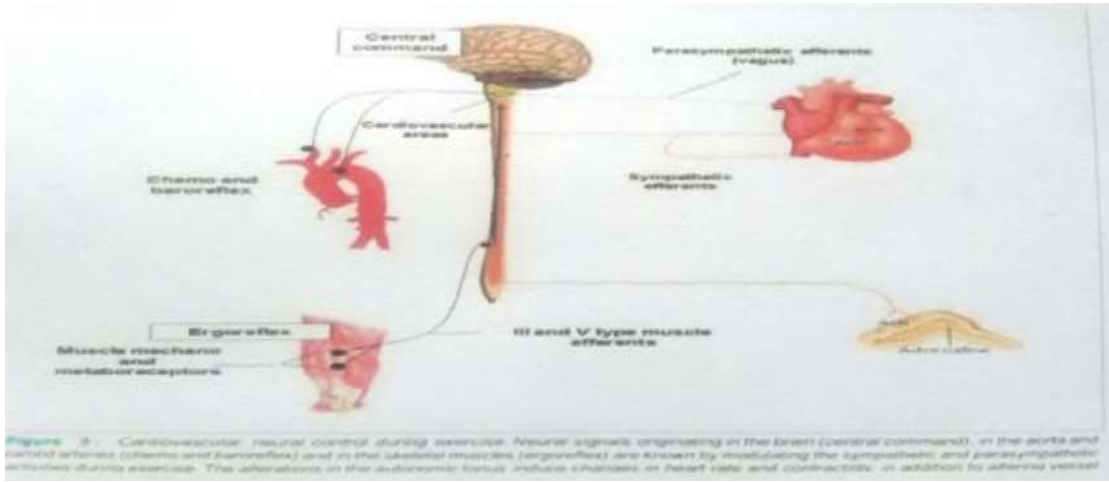

FIG: 15 Ergoreflex cardiovascular neural control during exercise. Neural signals originating in the brain (central command), in the aorta and carotid arteries (chemoreflex and baroreflex) and in the skeletal muscles (ergoreflex) are known by modulating the sympathetic and parasympathetic activity during exercise. The alterations in the autonomic tones induces change contractility.

10. Ventricular-arterial coupling

LV relaxation is also a function of LV afterload (ventricular-arterial coupling). It is an interaction of ventricular stiffness and central arterial stiffness. LV relaxation was more prolonged in hypertensive HFpEF patients related to altered LV- arterial coupling. In the normal heart, cardiac and vascular reserves together maintain an efficient ventricular-arterial coupling during exercise but in HFpEF there is an abnormal ventricular-arterial coupling. With age, stiffness is elevated results in decrease contractile reserve thereby rendering elderly susceptible to HF, blood pressure lability and decreasing exercise tolerance, resulting in poor cardiac efficiency. The arterial elastance and end systolic elastance ratio is reduced and cardiac output increases less in HFpEF patients[88]. The most obvious effect of this mismatch is a lower increase in blood pressure on exertion in HFpEF patients.

11. Chronotropic incompetence broadly defined as the inability of the heart to increase its rate according to increased activity or demand, is common in patients with cardiovascular disease, produces exercise intolerance, which impairs quality-of-life, and is an independent predictor of major adverse cardiovascular events and overall mortality[28]. Chronotropic incompetence is extremely common in

HFpEF, with reported prevalence of 57 to 77%.

The chronotropic reserve is depressed in HFpEF27 even compared with older, age-matched controls and independent of rate-slowing medication use. Similar to HFrEF[28], this is likely related to downstream deficits in b-adrenergic stimulation, because the increase in plasma catecholamines with exercise is identical in HFpEF and healthy controls[29]. Cardiac output is equal to the product of stroke volume and heart rate, and the inability to augment heart rate with exercise, together with the known impairment in stroke volume reserve in HFpEF, significantly limits cardiac output responses to exercise in many patients[30].

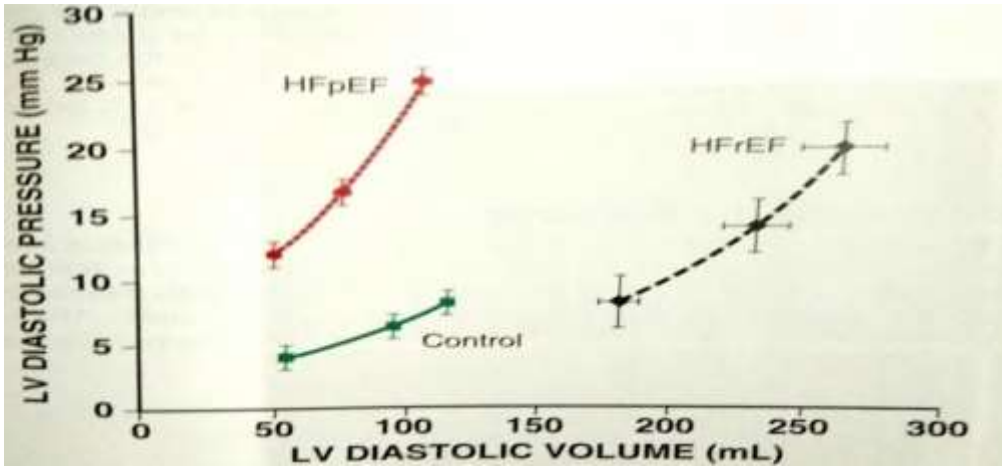

FIG: 16 LV diastolic pressure-volume data from normal controls, patients with diastolic heart failure /HFpEF , and patients with systolic heart failure /HFrEF. In patients with diastolic heart failure, the diastolic pressure volume curve is shifted up and left indicating an increase in passive stiffness of the ventricle as the SV is decreased due to an increase in diastolic stiffness. In contrast, in patients with SHF, the diastolic pressure-volume curve is shifted down to the right and is decreased, indicating a decrease in passive stiffness[345].

There are abnormalities in autonomic balance in HFpEF. In a study, cardio acceleration during the initial phase of exercise, which is driven predominantly by the withdrawal of parasympathetic tone, was blunted in patients with HFpEF[29], although heart rate deficits have been reported only at peak exercise[27]. Heart rate recovery, defined as the reduction in heart rate after cessation of activity, is also frequently abnormal in patients with HFpEF31. This marker is related to autonomic tone, as patients with excessive sympatho excitation and impaired parasympathetic tone have a slower reduction in heart rate after exercise compared with healthy controls. This abnormality in heart rate recovery is

independently associated with adverse outcome.

Role of beta blocker: Cardiac output is the product of heart rate and stroke volume, patients with HFpEF are often dependent on augmentation of heart rate in order to increase cardiac output. Chronotropic incompetence is highly prevalent and associated with exercise disability in HFpEF[20-22]. In the setting of reduced systolic and diastolic reserve, chronotropic reserve may represent the only mechanism to augment cardiac output during exercise, although inadequate ability to enhance relaxation with tachycardia may limit stroke volume responses. β-blockers, especially at high doses may aggravate rather than alleviate exercise intolerance. So careful use of β-blockade is recommended to optimize chronotropic incompetence by stabilizing heart rate and optimizing LV relaxation with regard to heart rate profile under basal and exercise conditions in patients with HFpEF.

Mechanism of action and proposed benefits of beta blocker in HF by decrease myocardial oxygen demand by improving blood pressure control and improving, or prevention of myocardial ischemia, reduced heart rate, leads to increased diastolic filling time, improved myocardial perfusion and controlled ventricular rate[28,48]. Prevention of arrhythmias reduces sudden cardiac death, antihypertensive action, decreased LV hypertrophy, fibrosis, and progression of LV diastolic dysfunction, improves myocardial function, neurohormonal blockade may improve imbalance in autonomic nervous system and decrease effects of maladaptive sympathetic nervous system (SNS) such as cardiac hypertrophy, cardiac fibrosis, apoptosis, arrhythmias [101]. In HF, sustained sympathetic stimulation through elevated catecholamine levels leads to reductions in cardiac beta-1- adrenergic receptor density and function over time, contributing to disease progression[17-20]. Initially thought to be contraindicated in HF, beta-blockers represent a cornerstone of the current medical management of HF based on a well-documented reduction in clinical event rates[21, 22, 48]. These adaptations to the pathophysiology of HF and their resultant effects on autonomic and neurohormonal balance benefits patient in HFrEF with sinus rhythm, beta-blockers leads to reduction in all-cause mortality, and a similar reduction in hospital admissions[15]. Proven survival benefit in HF recommended by the European Society of Cardiology and Heart Failure Association guidelines are bisoprolol, metoprolol, carvedilol and nebivolol[48]. While bisoprolol and metoprolol are highly selective for the beta- 1-adrenergic receptor, carvedilol possesses broader substrate specifities, having alpha-adrenergic and proposed pleiotropic and antioxidant properties[23]. To inhibit the deleterious effect of sympathetic nervous system on HF progression, prevent/ reverse cardiac remodelling and reduce risk of SCD, it is initiated

at low dose and titrated to-2 weeks interval to reduce risk of worsening of symptoms.

Both CKD and HFpEF are accompanied by autonomic dysregulation[78]. Sympathetic hyperactivity has a detrimental effect on both the heart and the kidney and aggravates hypertension and proteinuria. HFpEF patients show attenuated withdrawal of parasympathetic tone and excessive sympathoexcitation during exercise that cause β-adrenergic desensitization, chronotropic incompetence, and may thereby contribute to the limited exercise tolerance of these patients[206]. A critical role for CKD in this process was suggested by Klein et al.[185] showing a clear correlation between CKD, decreased heart rate variability, chronotropic incompetence in HFpEF, and decreased peak VO2.

Registry of HFpEF: In both the ADHERE and the OPTIMIZE-HF Registries, 50% of the patients admitted to the hospital with decompensated HF had normal ejection fractions[11,12]. Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF)[11] designed to evaluate the demographic, pathophysiologic, clinical, treatment and outcome characteristics of patients hospitalized with HF. The ultimate aim of this program is to improve the standard of HF care in the hospital and outpatient settings and increase the use of evidence-based therapeutic strategies to save lives. ADHERE registry showed that with the exception of Angiotensin Receptor Blockers (ARBs) all standard oral HF medications were used significantly less often during patient episodes with HFPEF.

12. MicroRNAs as Biomarkers: MicroRNAs can be secreted in the circulation, packed in exosomes and microparticles, or bound to lipoprotein complexes or RNA-binding proteins. These circulating microRNAs are stable in plasma and thus form attractive biomarkers[89, 90]. Cells release microRNAs in response to stimuli such as ischemia or cell death, and they can be taken up by target cells such as endothelial cells[91]. In HF, microRNAs have been investigated as possible biomarkers to aid in diagnosis, differentiate HFrEF from HFpEF[92, 93]. Several microRNAs are related to aerobic capacity or the response to exercise training[94]. MicroRNAs are released in the circulation after even short-term exercise, and training induces long term changes in microRNA expression[95, 96, 97]. An increasing number of phase I and II clinical trials using microRNA therapy are being started[98]. MicroRNA-based therapies for HFpEF are not yet developed, but some microRNAs have been identified as crucial regulators of pathophysiological processes underlying HFpEF, and are under investigation as therapeutic targets[99].

13 Brain-type Natiuretic Peptide

B- natiuretic peptides (BNP) or its amino-terminal cleavage equivalent (NT-proBNP) is derived from a common 108-amino acid precursor peptide (proBNP108) that is generated by cardiomyocytes by myocardial stretch. Assays for BNP and NT-proBNP have been increasingly used to establish the presence and severity of HF, their values are reasonably correlated, and can be used in patient care. BNP and NTproBNP are useful to support clinical judgment for the diagnosis or exclusion of HF, in the setting of chronic ambulatory HF[217-223] or acute decompensated HF, the value of natriuretic peptide testing is particularly significant when the etiology of dyspnea is unclear. Although lower values of BNP or NT-proBNP excludes the presence of HF and higher values have reasonably high positive predictive value to diagnose HF, clinicians should be aware that elevated plasma levels for both natriuretic peptides have been associated with a wide variety of cardiac and non cardiac causes[268-271] that may weaken their diagnostic utility in HF. Among them Atrial Fibrillation, age and renal failure are the most important factors impeding the interpretation of BNP measurements. BNP levels may be disproportionally low in obese patients. Patients with normal plasma BNP concentrations support but do not exclude the diagnosis of HFPEF especially in presence of obesity[117, 119]. NT-proBNP reference ranges were reported as <125 pg/ml for individuals aged <75 years and <450 pg/mL for individuals aged ≥75 years were considered normal. BNP and NT-proBNP levels improve with treatment of chronic HF [225, 272-274], with lowering of levels over time in general, correlating with improved clinical outcomes[248, 251, 254, 260]. Thus, BNP or NT-proBNP "guided" therapy has been studied against standard care and measurement to determine whether guided therapy renders superior achievement of guideline directed medical therapy (GDMT) in patients with HF. A lower natriuretic peptide goal and/or a substantial reduction in natriuretic peptides during treatment are consistently present in the positive "guided" therapy trials[275].

Galectin 3, an established prognostic marker in HF and a surrogate for fibrosis, was given the importance of fibrotic adverse LV remodeling. It is elevated in acute and chronic HF and identify a high risk phenotype resistant to conventional HF management. soluble ST2 a marker of infammation elevated is associated with phenotype of cardiac decompensation and remodelling in adverse clinical outcome in HF.

14. Diastolic dysfunction tells that there is elevated LV filling pressure resulting in shortness of breath (SOB). It is a marker of poor prognosis. Diastole starts with AV closure ends with MV closure, the process by which heart returns to its relaxed state. Normal Diastole is adequate LV filling without increase LV filling at rest and at exercise. Transmitral Doppler was used to obtain early diastolic (E) and late diastolic

(A) flow velocities recorded by pulse Doppler between the tips of the mitral leaflets. Spectral pulsed-wave tissue Doppler imaging was used to record e′ early diastolic peak velocities at both the septal and lateral mitral annuli from the apical four-chamber view(Fig: 18, 19). The ratio of the peak velocity of mitral inflow during early diastole (E), over the average of e' recorded by pulsed tissue Doppler (fig: 17). These measures were used to calculate E/e′ reflects the mPCWP, average E/e'>=14 at rest has good diagnostic value for high mean pulmonary capillary wedge pressure. It is is elevated filling pressure identified by echocardiography demonstrating aberrant filling patterns and reduced diastolic tissue velocities (TDI) by Mitral septal e'<7cm/sec, Mitral lateral e'<10 cm/sec, average E/e' >=14 at rest, LA maximum volume index 34ml/m2 and peak TR velocity 2.8m/sec2. Supporting the likelihood of diagnosis of HFPEF but E/e' in intermediate range9-14 is less sensitive[134]. The mitral E/ e'index correlates with LV stiffness and fibrosis[129, 130] and is less age- dependent than e'[131]. It also has diagnostic value during exercise[132, 133]. The E/e' index is little influenced by changes in volume7, [135].

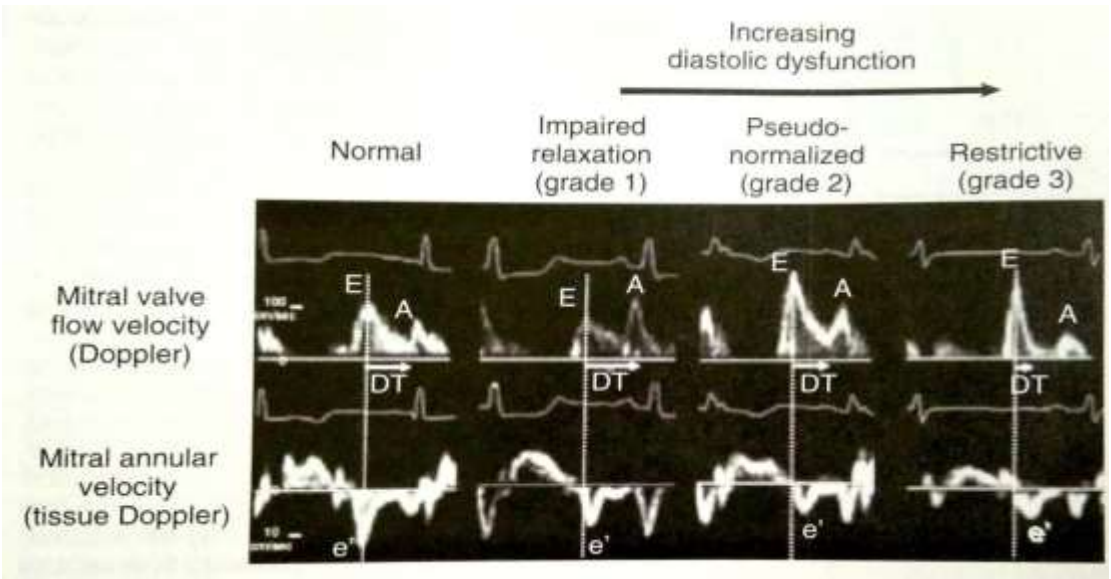

Figure 17: Grading of diastolic dysfunction.

Grade 1 indicates diasolic dysfunction without increase in LA pressure, grade 2 pseudonormalization and grade 3 restrictive filling pattern indicates diastolic dysfunction and increased LA filling pressure[67, 165].

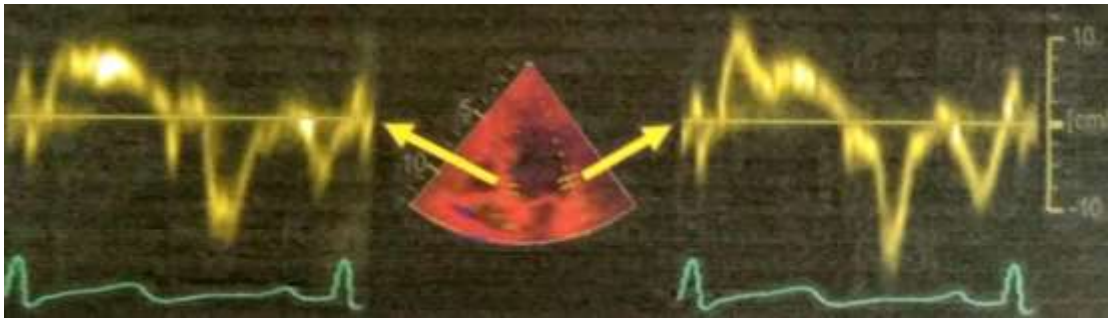

Figure: 18 Normal tissue Doppler spectra obtained from the basal septum (left) and the basal lateral wall (right). Note the different amplitudes and shapes of the curves Voigt267.

According to the European Study Group on Diastolic Heart Failure17, diagnostic criteria for HFPEF were (a) clinical symptoms and signs, (b) normal or mildly reduced LVsystolic function (LVEF >50% and LVEDVI <97 mL/m2), and (c) diastolic dysfunction.

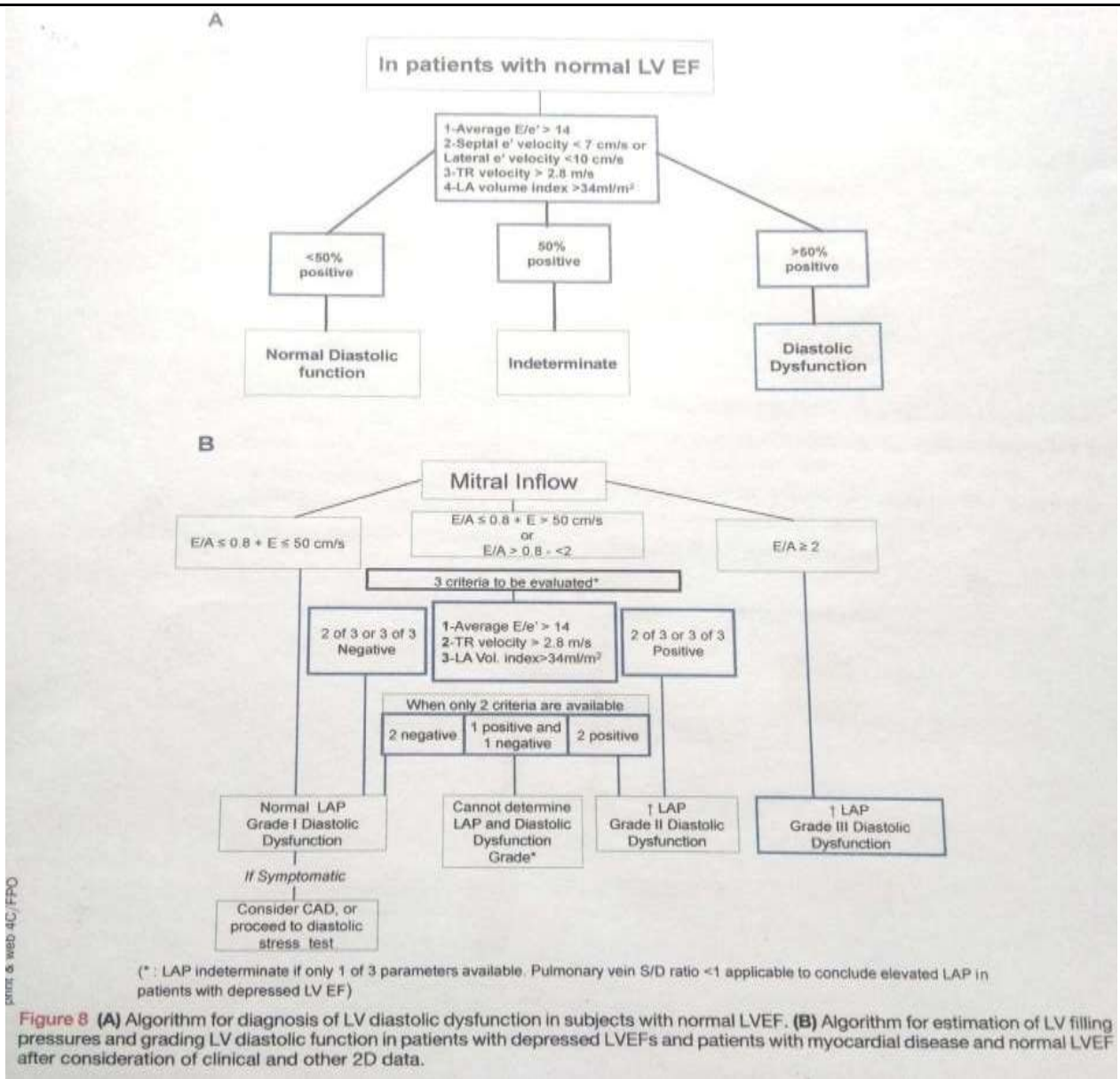

Figure 8 **(A)** Algorithm for diagnosis of LV diastolic dysfunction in subjects with normal LVEF. **(B)** Algorithm for estimation of LV filling pressures and grading LV diastolic function in patients with depressed LVEFs and patients with myocardial disease and normal LVEF after consideration of clinical and other 2D data.

Fig: 19 LV Diastolic dysfunction algorithm134

-Calculating and interpreting the HFA–PEFF score189

Functional testing: If invasive testing demonstrates a high LV filling pressure [left ventricular end-diastolic pressure (LVEDP) >=16mmHg, PCWP >=15mmHg] at rest, the diagnosis may be confirmed or assessment during exercise is recommended, either by non-invasive exercise stress echocardiographyor by invasive haemodynamics. Many have symptoms mainly on exertion that are usually attributed to the increase in LV filling pressures which is needed to maintain adequate filling

and stroke volume[188, 189]. The parameters that have been studied most often, during or immediately after exercise, are the mitral E/e' ratio and the TR peak velocity, which indicate increases in mPCWP and PASP, respectively[139, 140, 142-145,187, 207]. Exercise testing is recommended as a component of the diagnostic work flow in cases of uncertainty, but there is no consensus yet about which stress protocol should be used or which measurements are most important[193].

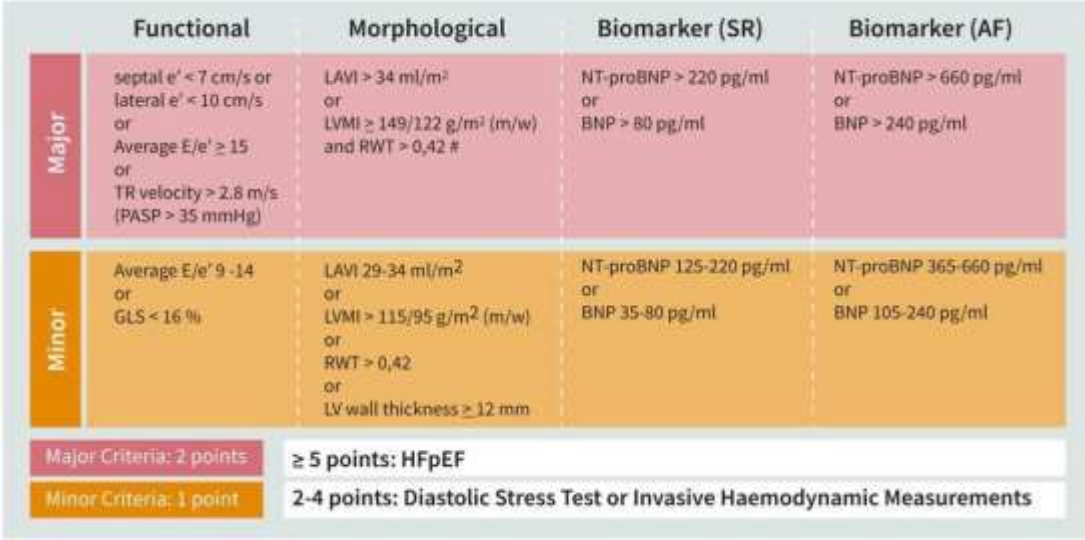

Fig: 20 Echocardiographic and natriuretic peptide heart failure with preserved ejection fraction workup and scoring system (diagnostic workup). The score has functional, morphological, and biomarker domains. Within each domain, a major criterion scores 2 points or a minor criterion 1 point. Each domain can contribute maximally 2 points, if any major criterion from this domain is positive, or 1 point if no major but any minor criterion is positive. Major and minor criteria are not additive in a single domain. Points are added only when they come from different domains. A total score >5 points is considered to be diagnostic of HFpEF, while a score of <1 point is considered to make a diagnosis of HFpEF very unlikely and to mandate investigations for alternative causes. Patients with an intermediate score (2–4 points) need further evaluation[189].

Invasive haemodynamic tests at rest and with exercise: Left ventricular end-diastolic pressure (LVEDP) in the resting supine position is typically obtained by left heart catheterization and bears important diagnostic information in the workup of unexplained dyspnoea (Fig: 22). Invasive demonstration of impaired LV relaxation at rest, measured by elevated LV filling pressures at rest (LVEDP >=16mmHg) confirms definite evidence of HFpEF. A steep increase in PCWP during exercise is a typical haemodynamic response in HFpEF[196, 197], indicating that the dyspnoea on exertion is mainly of

cardiac origin. Patients with peak exercise PCWP >=25mmHg are classified as having HFpEF. A high resting mPCWP and a pathological increase in mPCWP during exercise predict poor outcomes from HFpEF[198, 200, 201].These findings can immediately translate into management strategies, such as anti-ischaemic therapy, improve blood pressure control, removal of bradycardic agents e.g betablockers , and control of exercise induced cardiac arrhythmias.

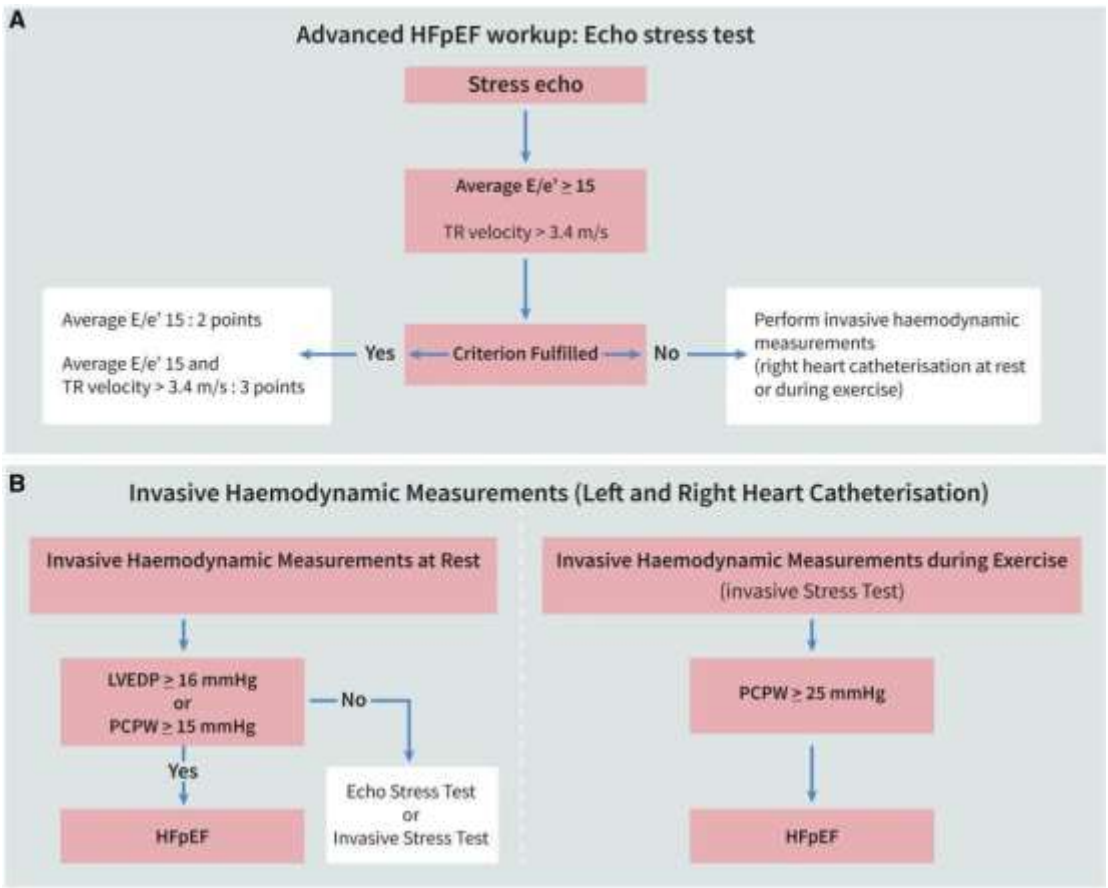

FIG: 21 Functional tests in cases of diagnostic uncertainty. (A, upper panel), shows the diastolic stress test workup with exercise echocardiography. If key haemodynamic abnormalities are identified, a definite heart failure with preserved ejection fraction diagnosis can be made. (B, lower panel) It shows the invasive haemodynamic measurements at rest (left) or during exercise (right) that may complement stress echocardiography and are recommended in cases with remaining diagnostic uncertainty[189].

More sophisticated tools for aetiological workup include CMR which is most accurate for determining LA and LV volumes and mass[256] it detects scar and myocardial ischaemia due to epicardial coronary disease or microvascular dysfunction[257], stress perfusion imaging to reveal diffuse subendocardial defects. Regional and diffuse myocardial oedema (T2-imaging) and infiltration or fibrosis are quantified using late gadolinium enhancement [LGE; for extracellular volume fraction (ECV)] or T1-mapping[258, 259, 177–180]. RV /LV myocardial biopsy, (99m) Tc-DPD scintigraphy to identify cardiac amyloidosis, positron emission tomography (PET)-CT, as well as specific genetic and laboratory tests should be considered in selected cases where a specific aetiology is suspected. Strain imaging is one parameter with which early detection can be done.

Final aetiology: Identification of specific HFpEF aetiologies will advance the field of targeted therapies. Specific heart muscle diseases that may present with the HFpEF phenotype include hypertrophic cardiomyopathies[124,166–168], myocarditis and chronic inflammatory cardiomyopathy [169-176], autoimmune diseases [202, 205], non-infiltrative and infiltrative cardiomyopathies [204, 203], idiopathic or acquired endomyocardial fibrosis[252], storage diseases [203, 252]. Rare causes like toxicity from drugs or heavy metals, radiation, metabolic causes related to hormonal or nutritional disease, should also be considered.The trigger may occur long before the onset of symptoms as radiation-induced HFpEF develops after 10–15 years, even when low mean cardiac radiation doses of 3.3Gy are used[153, 255]. Early detection of covert downfall of LVEF will be useful leading to cange regime or discontinuing the drug. Aetiological workup may include a standard exercise stress test that may identify myocardial ischaemia, an abnormal blood pressure response to exercise, chronotropic incompetence, supra ventricular and ventricular arrhythmias. Molecular phenotyping for a better identification of distinct HFpEF phenotypes is emerging and may also help to develop targeted therapies.

Various risk scores exist but applicability and utility remain uncertain[191].

15. Enlarged Left Atrium (LA) ia a chronic marker of raised LV filling pressure, it is a robust indicator of diastolic dysfunction with elevated left ventricle filling pressure (LVFP) in absence of an athlete, MV Disease. LA volume were additionally indexed to body surface area, upper normal index LA volume is 34ml/m[272].

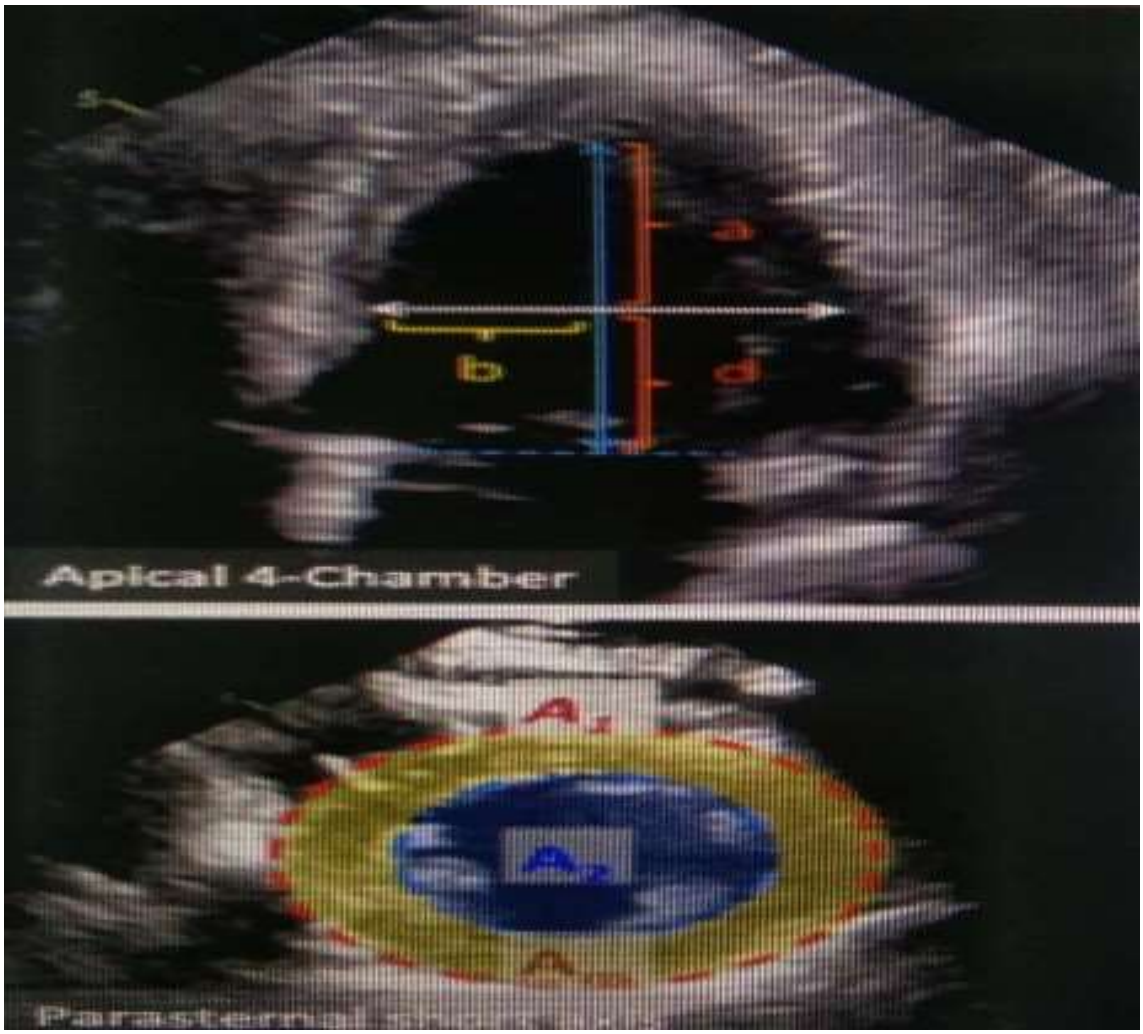

FIG: 22 LV measured from short axis view at the level of papillary muscles and length measured at 4 chamber A1: Total LV area are obtained by tracing the epicardium, A2:LV cavity obtained by tracing the endocardium with the exclusion of papillary muscles. Am the cross sectional area of myocardium A1-A2. a+d=A long axis extending from the widest LV short axis to the LV apex. All measures obtained at end diastole.

The maximal volume of the LA, measured at end-systole from bi-plane or three-dimensional images and indexed to body surface area [left atrial volume index (LAVI)] is an indirect correlate of LV filling pressure[207].

It is more accurate as a marker of chronic LA remodelling than either LA area or diameter[208–210] and it correlates with other echocardiographic indices of LV diastolic function211. A LAVI of 29–33 mL/m2 is considered as a minor criterion since it represents the upper limit in healthy subjects[212, 213]. In patients without AF or heart valve disease, LAVI >34 mL/m2 independently predicts death, heart failure, AF, and ischaemic stroke[162-164].

16.LV mass: Measurements were indexed (I) to BSA where appropriate (Fig: 22). LV hypertrophy (LVH) was defined as LV mass index >95 g/m2 (females) or >115 g/m2 (males) [69, 70, 72].

17.Two Dimensional (2D) Speckle tracking Echocardiography (STE): Strain in echocardiograpy is percentage of thickening of the myocardium or deformation and used to describe local shortening, thickening and lengthening of the myocardium as a measure of regional LV function. Strain in the myocardium can be measured by speckle tracking echocardiograpy (STE) and has a strong relationship to contractility and it tracks speckles (Fig: 24) independent of angle. Basis of measuring strain is tethering and cardiac translation which allows for myocardial deformation in multiple planes. Speckle tracking Echocardiography, the focus of this study is a relatively new, angle independent measure of regional myocardial function (Fig: 23). The speckles which are the basis of this modality off 2D Echocardiography are the result of constructive and destructive interference of ultrasound backscattered from structures smaller than the ultrasound wavelength. Employing this technology random noise is filtered out, while keeping small temporally stable and unique myocardial features called speckles[115, 116]. These kernels of stable speckles (Fig: 24) can be tracked frame by frame simultaneously in multiple planes using patent automatic installed algorithms to provide local displacement information like velocity, strain and strain rate. Myocardial strain and strain rate using tissue doppler imaging (TDI) was introduced in late 1990. GLS is considered to be a marker for LV function which is calculated by using a echo based modalities like tissue Doppler imaging speckle tracking. TDI (Fig: 23a) allows analysis of strain in direction within the imaging plane. Depending on spatial resolution, selective analysis of layers of myocardium is also feasible. Chamber views for offline analysis with in built software. The in built software tracks the speckles and calculates deformation which is angle independent measure of LV function.

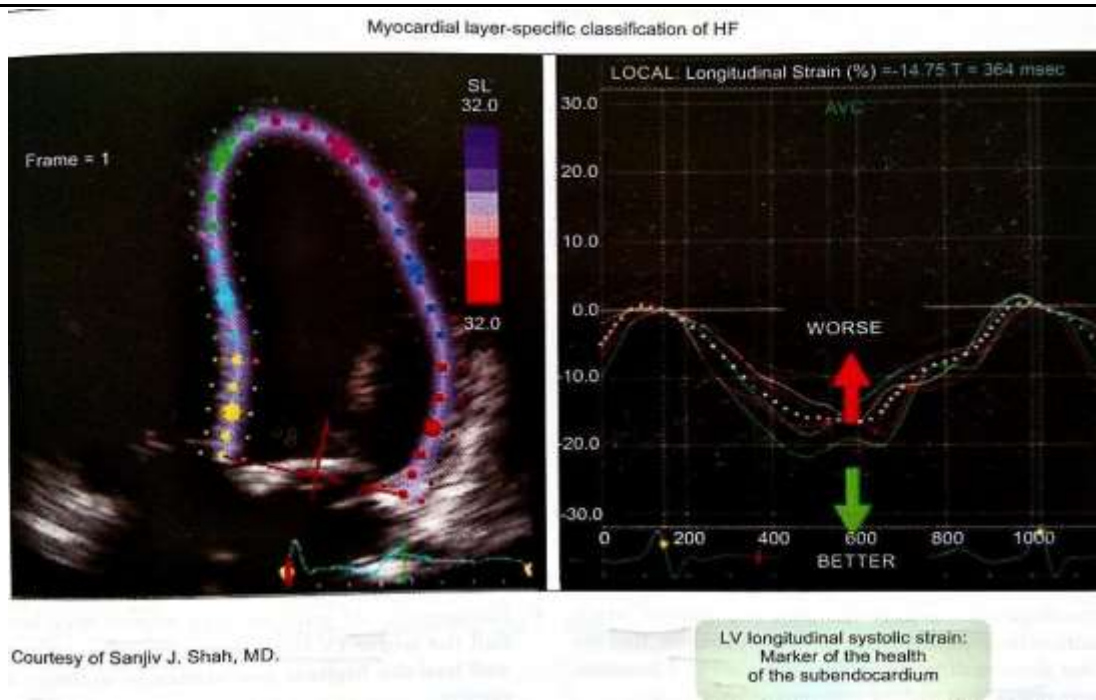

FIG: 23 Phenotyping heart failure with preserved ejection fraction beyond ejection fraction: myocardial layer specific classification of heart failure (a, b).

LV strain in the long axis uses GLS calculated as the average from all segments as a global LV function. The positive strain means elongation whereas negative strain is shortening. In 2 Dimensional STE, only two directions of strain can be measured at anytime. Multidimensional strain and strain rate analysis can be made noninvasively and throws light on the mechanism of heart failure and is a useful clinical tool for long term follow up. For ease of use in these recommendations, normal GLS for most echocardiography system cut-point of -18% in absolute values is taken, so value in between -18-21.5% in healthy individuals[110]. All strain values are dimensionless and are expressed as percentages. STE is a new technique of two-dimensional echo image analysis that allows the study of regional myocardial deformation expressed by a dimensionless parameter, the strain (ε), defined by the Lagrangian formula as the percent change from the original dimension. Strain means "deformation," and it can be calculated as change in length (L - L0) divided by original length (L0): strain (L - L0)/L0 (Fig: 24)[3]. In the situation where the two locations are getting closer, there is myocardial shortening, and when the two locations are moving apart, there is lengthening. Thus, strain is a dimensionless quantity and represents the fractional or percentage change in dimension. Because myocardial deformation or strain is caused by fiber contraction, strain is a measure of myocardial contractile function.

Myocardial strain can be measured accurately by tagged magnetic resonance imaging (MRI). This method provides quantitative data about myocardial deformation in multiple plans, and needs more potential in cardiac research. Unfortunately, tagged MRI is not suited for clinical routine and, owing to limited temporal resolution, does not provide measures of rate of deformation (i.e., strain rate).

Left ventricular peak systolic GLS is not angle-dependent, unlike myocardial velocities recorded by tissue Doppler186. Reduced LV longitudinal systolic strain and LV early diastolic strain rate have both been identified in HFpEF[19, 215, 216]. Impaired GLS predicts HF hospitalization, cardiovascular death, or cardiac arrest[216, 217]. It correlates with invasive measurements of LV stiffness and with NP levels[19, 204, 218]. STE has been validated, TDI[103] and magnetic resonance imaging[114] for strain imaging and also for dyssynchrony assessment.

Global longitudinal strain (GLS) is calculated from the mean of 17 cardiac segments obtained from apical four-chamber, three-chamber and two-chamber views as an average peak strain from the 3 apical projections and the ROI set to cover the entire LV[263]. Here the machine uses the standard grayscale images of the heart obtained in the apical four, three and two chamber views for offline analysis with in built software. The in built software tracks the speckles and calculates deformation which is angle independent measure of LV function.

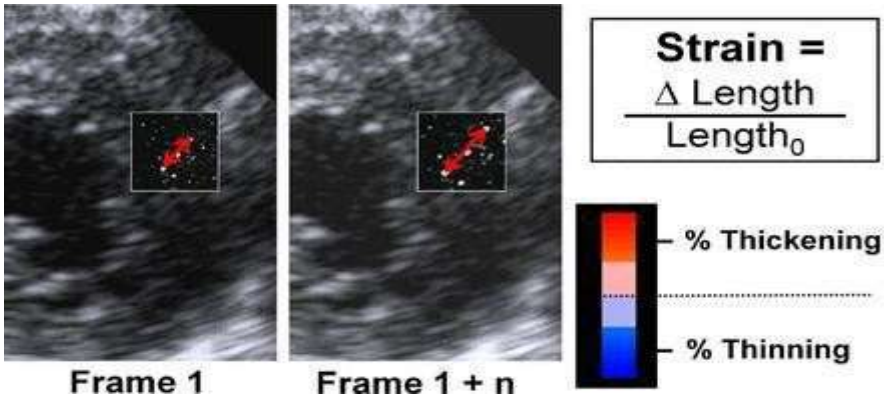

FIG: 24 Showing the basic concept of tracking speckles on gray scale images to produce strain.

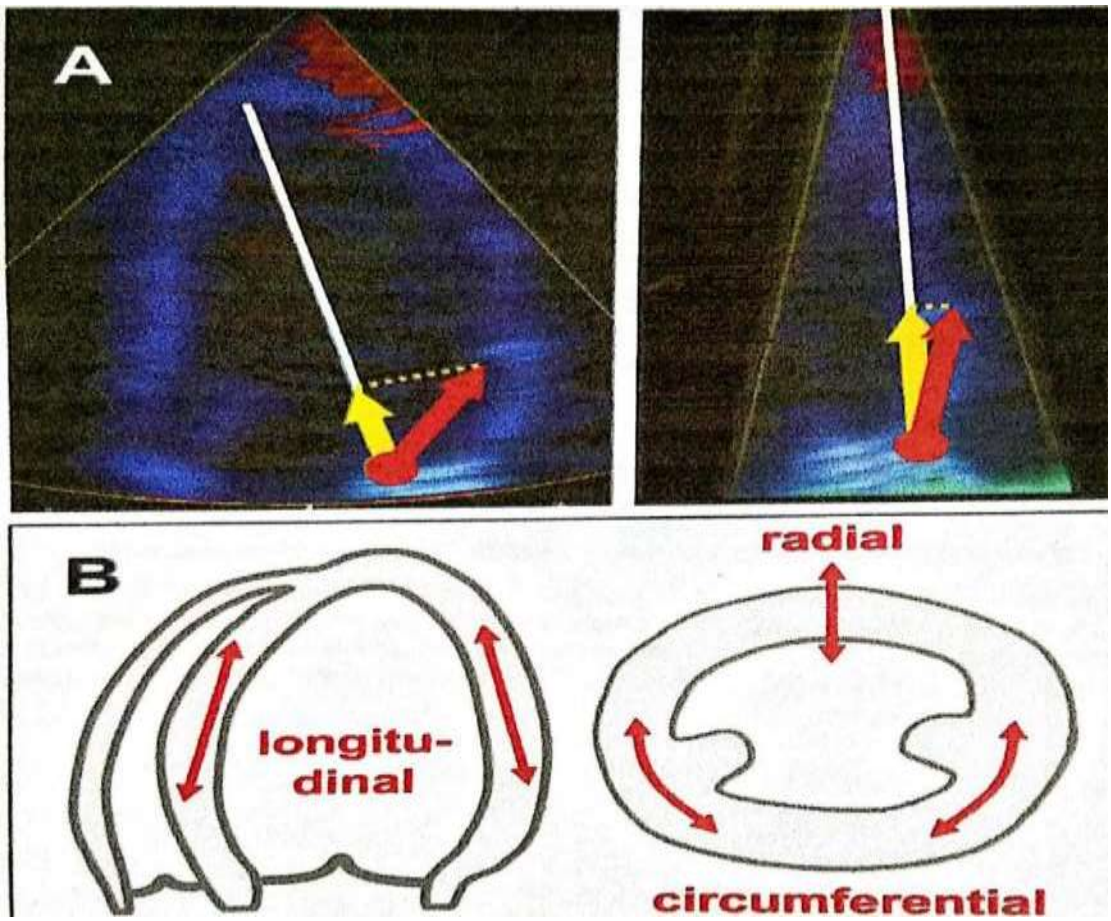

FIG: 25 Doppler techniques measure velocities in one dimension. (A)Alignment of the Doppler beam with the wall is therefore important. (Left) Measured velocities (yellow) are underestimated if the ultrasound beam is not well aligned with the motion to be interrogated (red). (Right)Narrow-sector single-wall acquisition may help minimize this problem. (B) Motion and deformation components that can be interrogated using Doppler techniques. J.U. Voigt [267].

18. Myocardial Fiber geometry

The heart has a very complex geometry and arrangement of myocardial fibers. There are 3 layers of myocardial fibers: i. Subepicardial, ii.Circumferential, iii. Subendocardial.

Fundamentals of LV Torsion: Torsion of the left ventricle (LV) is the wringing motion of the ventricle around its long axis induced by contracting myofibers in the LV wall. It is defined by the difference in rotation between base and apex, the twist. In the normal heart, the base rotates clockwise during systole and the apex rotates counterclockwise, producing a wringing motion.The difference in turning angle between the base and apex is called the "net torsion angle", expressed in degrees[184]. "Torsion" and "twist" are often used interchangeably.

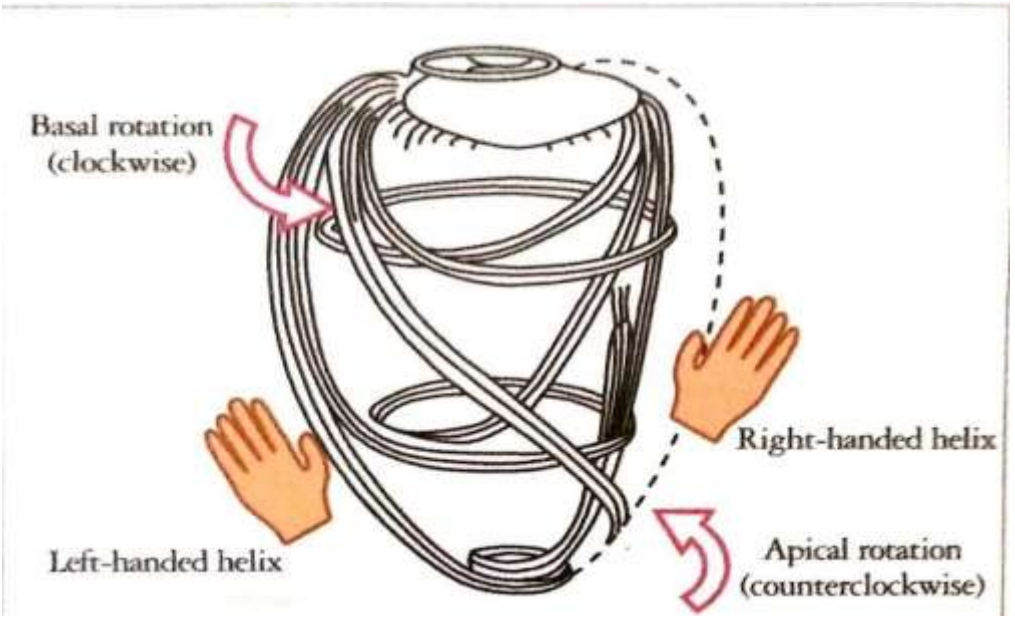

FIG: 26 Myocardial fiber arrangement and its function111

The subendocardial region contributes predominantly to the longitudinal mechanics of the left ventricle, whereas the midwall and the subepicardium contribute predominantly to the rotational motion.The helical nature of the heart muscle determines its wringing motion during the cardiac cycle, with counterclockwise rotation of the apex and clockwise rotation of the base around the LV long axis, when observed from the apical perspective.Twisting and shearing of the subendocardial fibers deform the matrix and result in storage of potential energy. Subsequent recoil of twist, or untwist, which is associated with the release of restoring forces contributes to diastolic suction, which facilitates early LV filling[75].

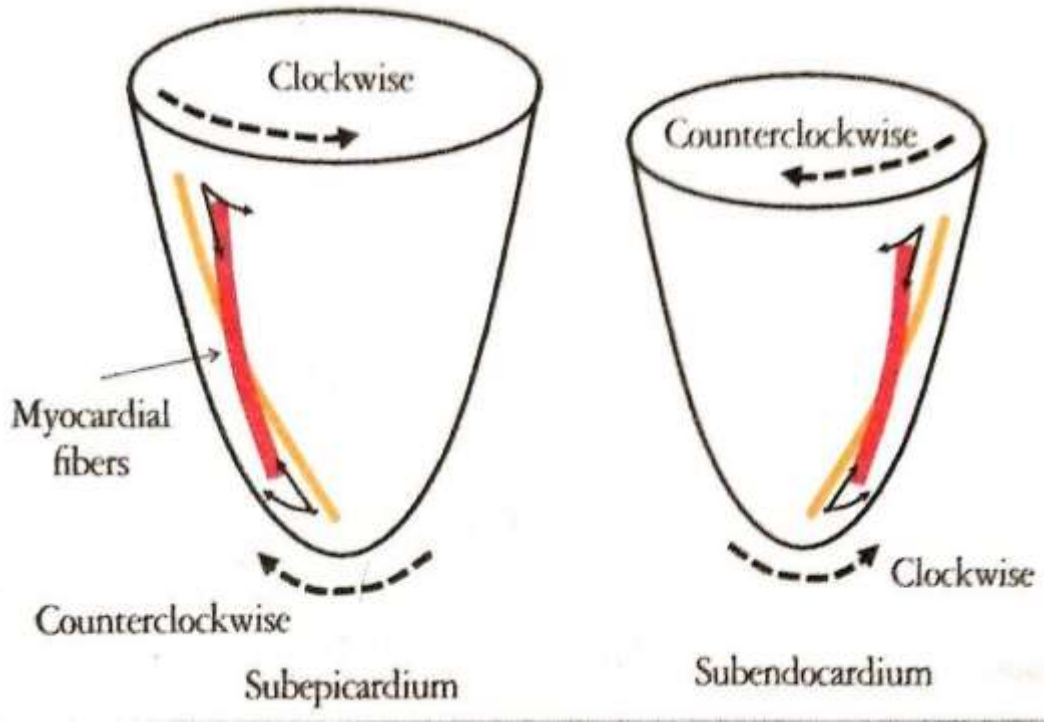

FIG:27 Helical arrangement of Subepicardial (left handed) and Subendocardial fibers (right handed)[111].

In the left ventricle, Myocardial fibers in the subepicardium run in a left-handed direction, and contraction of these fibers will cause the base to rotate in a clockwise direction and the apex to rotate in a counterclockwise direction, fibers in the mid layer run circumferentially, and fibers in the subendocardium run in a right handed direction, and contraction of these fibers will cause the base to rotate in a counterclockwise direction and the apex to rotate in a clockwise direction (Fig: 26, 27, 28). This means that rotations caused by the subepicardium and subendocardium are in opposite directions. The radius of rotation of the subepicardium is greater than that of the subendocardium. The subepicardium consequently provides greater torque than the subendocardium, as a result of which the rotation of the subepicardium is significantly expressed. Both are at an angle of 60 degrees [111]. These myocardial fibers are connected to each other, with a smooth transition from subendcardium to mid layer, and then to subepicardium, about the long-axis. Contraction of these three layers of myocardial fibers causes not only longitudinal, circumferential, and radial movements of the heart, but also contortion of the myocardium.

During contraction, potential elastic energy is stored in the collagen matrix and cytoskeletal proteins (titin); its release (recoil) causes rapid untwisting[124, 184] and contributes to active suction of blood from the atria [261]. Because of its direct relation to fiber orientation, LV torsion is a valuable addition to strain measures such as longitudinal or circumferential shortening or radial thickening. Noninvasive imaging techniques became available to quantify LV torsion. LV torsion is followed by rapid untwisting, which contributes to ventricular filling[262] (Fig: 26). Because LV torsion is directly related to fiber orientation, it might depict subclinical abnormalities in heart function. Thus if the myocardial fibre were to shorten alone the ejection fraction of the heart would be no more than 15-20%. It is because of the added twisting motion around the longitudinal axis that the overall LV function is in the range of 60-70% [75]. The recent introduction of speckle tracking in ultrasound again draws attention to LV torsion. The widespread availability of this tool may lead to a fast introduction of LV torsion as a clinical measure for detection of myocardial dysfunction. Ultrasound speckle tracking was introduced for quantification of LV torsion. LVEF-based HF classification may result inappropriate in providing pathophysiological distinctions. Patients with HFPEF often have subclinical systolic impairment detected by speckle tracking echocardiography as reduction of global longitudinal strain (GLS)[10]

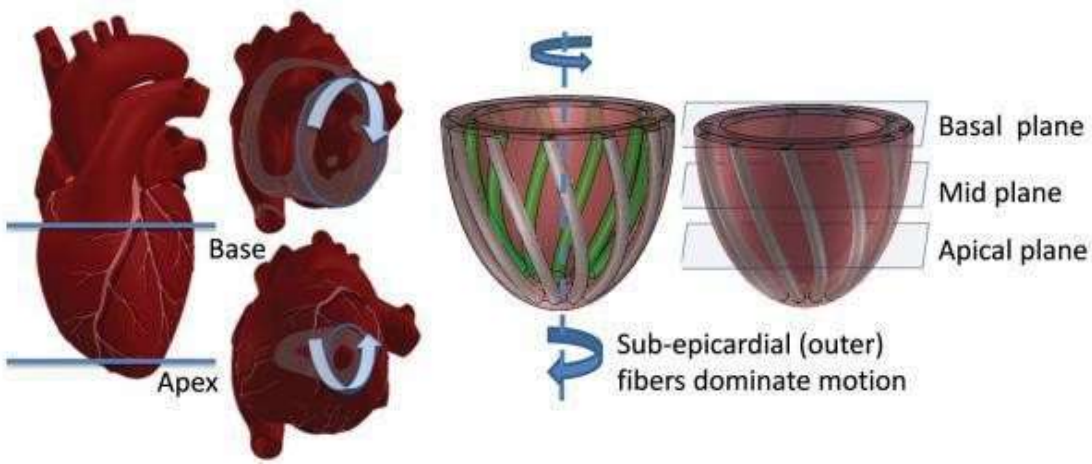

FIG: 28 Cardiac rotation -torsion and twist

Myocardial fiber geometry and its effect on LV function can be assessed to an extent by using strain imaging. Definition wise Strain is myocardial deformation, that is, the fractional change in the length of a myocardial segment. Strain is unit-less and is usually expressed as a percentage. Strain can have positive or negative values, which reflect lengthening or shortening, respectively. Strain rate is rate of change in strain per second.

Despite the complexities of myocardial wall dynamics, some meaningful information has been derived using the simplified linear strain or deformation model by echocardiography and these parameters can be measured both by TDI (Fig: 25) and speckle tracking echocardiography[109].On the other hand, displacement reflects myocardial motion: over a defined period of time, if all parts of a myocardial segment have the same motion, the segment will change position (displacement) but not shape (deformation), whereas when different parts of a segment have different motion, there is overall deformation of the segment. As described for the first time by Heimdal et al, deformation of a tissue occurs over time during the cardiac cycle and the rate of this deformation, the strain rate (SR), is equivalent to the velocity gradient. Myocardial ε can be determined both by TDI and STE. Different from TDI, STE is an angle-independent technique that may allow an accurate assessment of segmental myocardial deformation by grey-scale based imaging analysis frame by frame. Moreover, the lack of angle-dependency is of great advantage because myocardial ε could be tracked in two dimensional echo imaging, along the direction of the wall and not along the ultrasound beam. This means that we can analyze myocardial ε along three spatial axes according to the cardiac muscle physiology. In fact, after electromechanical activation, systolic myocardial deformation occurs in three spatial dimensions: a longitudinal and circumferential shortening and a radial thickening. Thus, longitudinal (Fig: 24) deformations result in a negative ε14. In clinical practice, we track longitudinal ε in a four-chamber view with the ultrasound beam along the major LV axis. When myocardial deformation is graphically represented as time-strain curves, cardiac cycle phases can be recognized as follows: from the original length, during systole, we observe a negative wave that reaches its peak at the aortic valve closure (AVC), which represents the maximal longitudinal myocardial shortening during contraction. In diastole, strain values progressively increase towards the original length. Regarding technical issues, STE needs high quality grey-scale images with an optimal frame rate between 50 and 80 frames/s. TDI pitfalls that can be overcome by the implementation of STE, LV torsion has been recently evaluated[24]. Myocardial strain can be measured accurately by tagged magnetic resonance imaging (MRI). This method provides quantitative data about myocardial deformation in multiple plans, and needs more potential in cardiac research. Unfortunately, tagged MRI is not suited for clinical routine and, owing to limited temporal resolution, does not provide measures of rate of deformation (i.e.,strain rate). CMR with tissue tagging has been used as the gold standard to evaluate LV torsion considering the difference between basal and apical rotation[26]. Echocardiography is an alternative noninvasive method and the recent introduction of STE draws new attention to LV torsion. LVEF providing better

insight into myocardial impairment. GLS can be altered in patients with HFpEF suggesting unrecognized myocardial systolic dysfunction and can be associated with worse clinical outcomes[41, 46, 47].

2D strain can theoretically be applied to both atria and ventricles but the thin walls of the atria and right ventricle may result in poor speckle generation and suboptimal tracking which is why most of its application till date is limited to the left ventricle. It may be considered a general physical principle that the percentage of LV wall deformation measured by true global strain during ejection is directly related to the percentage of blood ejected from within the chamber measured by EF. GLS obtained from apical views was used as an index of cardiac function[111] with an incremental prognostic value over clinical parameters and LVEF[124].

19.3Dimensional echocardiography. Largely remains outside the purview of this study but is worth discussing given its potential advantages. 2D STE is limited by its inherent two dimensional nature where foreshortening of images can result in false interpretation. 3D Echocardiography unlike 2D is able to capture a 3D dataset called a voxel which are tracked frame by frame in all possible directions,thus giving us a more complete and accurate view of myocardial overall and regional function. As a result, 3D STE-based measurements of LV volumes were found to be in close agreement with magnetic resonance-derived reference values, and the levels of 32 agreement were higher than those of 2D STE measurements obtained in the same patients, as reflected by higher correlation coefficients, smaller biases, and tighter limits of agreement[119]. Since the 3D dataset is captured from a single apical transducer position allows for faster and more complete analysis in less time.

Discussion

It is a complex and common disease, with a high and constantly increasing prevalence. Its non-specific nature of symptoms and signs, especially in the elderly population. These patients are at higher risk of death and hospitalizations than similar age and co-morbidity, treatment is still empirical and no therapy has yet shown significant impact on mortality. There is urgent need of increased awareness and clinical research in the field as it is one of the largest unmet clinical needs in cardiology.

DIG trial: Digoxin significantly reduced hospitalizations but had no significant effect on mortality when used to treat patients with systolic heart failure. The DIG ancillary trial, a parallel study to the DIG trial, evaluated the role of digoxin in patients with HF and an LVEF >45%, digoxin had no effect on all-cause or cause-specific mortality, or all-cause or cardiovascular hospitalization[62]. It is not recommended to treat patients with HFpEF except for atrial fibrillation with poorly controlled ventricular rate.

PEP-CHF: The clinical efficacy of an ACE inhibitor in patients with HFpEF was assessed in the PEP-CHF trial in patients 70 years of age had diastolic dysfunction, 79% had a history of hypertension, patients with substantial LV systolic dysfunction or valve disease were excluded. The patients treated with perindopril also had significant improvements in functional class and six-minute walk distance and trend toward reduction in the primary endpoint of combined all cause mortality and unexpected hospitalization for HF, suggesting that it may be of benefit in this patient population[24, 102].

GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto MiocardicodHeart Failure): Inflammation is detectable in many patients with HF, including those with HFpEF, and is associated with worse prognosis. No benefit was seen in the subgroup of patients with preserved EF enrolled in the large, prospective tria[l32], which randomized patients to rosuvastatin or placebo. In an observational study, statin-treated HFpEF patients were less prone to develop atrial fibrillation[47].

Hyperlipidemia is the abnormally elevated levels of any or all lipids or lipoproteins in the blood. Treatment of lipid levels is recommended for the primary and secondary prevention of cardiovascular disease. Statins sould be used in patients with HFpEF who have an indication for statin therapy.

RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure) trial. In the RELAX trial, chronic treatment with sildenafil was used with the rationale that this would inhibit cGMP breakdown and increase its concentrations, leading to higher levels of PKG. Phosphodiesterase-5 inhibitors is not used for the treatment of HFpEF23as Sildenafil appeared to have no beneficial effects in this advanced HFpEF population.

NEAT-HFPEF: The systematic study of anti-inflammatory agents, antioxidants, and agents that enhance NO bioavailability or enhance activity of the cyclic GMP/PKG pathway in HFpEF, trial showed that isosorbide mononitrate, a long working organic nitrate, tended to reduce physical activity

and did not improve quality of life and exercise capacity[264]. Use of organic nitrates to treat HFpEF, evidence of efficacy is lacking and a randomized trial found that use of isosorbide mononitrate tended to reduce activity levels in patients with HFpEF[61].

Inhaled nebulized inorganic nitrate, also did not improve exercise capacity, as recently shown in the INDIE-HFpEF trial[265].

The Vasodilator-Heart Failure Trial I (V-HeFT I) explored the effects of using a combination of antioxidant hydralazine and isosorbide dinitrate in managing heart failure. This showed significant mortality benefit in the treatment of congestive heart failure (CHF), and demonstrated that treating patients with CHF with hydralazine-isosorbide dinitrate significantly reduced mortality when compared with placebo for the initial 3-year period. Chronic use improves outcome in V-HeFT I and A-HeFT trials38 and could be potentially favorable in HFPEF.

SOCRATES PRESERVED trial showed Vericiguat did not change NT-proBNP and LAVI at 12 weeks compared with placebo but was associated with improvements in quality of life in patients with HFpEF. Given the encouraging results on quality of life, the effects of vericiguat in patients with HFpEF warrant further study, with higher doses, longer follow-up and additional endpoints need to be explored[37].

CKD: Hypertension in CKD is thought to be mainly a consequence of volume overload due to increased sodium reabsorption by the kidneys[267]. Increase sodium loading might also contribute to HFpEF development[276]. Empagliflozin, a sodium glucose co-transporter-2 (SGLT2) inhibitor, initially developed as an anti-diabetic drug, resulted in decreased cardiovascular mortality in an initial type 2 diabetes cohort[266]. Three mechanisms have been proposed to contribute to reduced cardiovascular mortality in patients receiving SGLT2-inhibitors / empagliflozin in particular[253], (1) osmotic diuresis and natriuresis lower blood pressure and subsequently reduce left ventricular afterload; (2) empagliflozin may initiates a shift to cardiac ketone body oxidation, increasing mitochondrial respiratory efficiency and reducing ROS production; (3) empagliflozin can lower intracellular Na by inhibition of the cardiac Na/H exchanger (NHE) and induce coronary vasodilation[247] subsequently altering ROS production, which may be ameliorated by SGLT2-inhibitors[253]. SGLT2-inhibitors is both cardio- and reno-protective[247]. The effect of empagliflozin on cardiovascular mortality in HFpEF specifically, regardless of diabetic status, is being investigated in the ongoing EMPEROR-Preserved trial[14].

D-HART trial: This pro-inflammatory state with 14 days of treatment with the recombinant human IL-1 receptor antagonist Anakinra, prolonged treatment in the follow-up did not increase VO2, despite small improvements in exercise duration and quality of life, as well as reductions in CRP [245] and NT-pro-BNP compared to baseline values[240].

FAIR-HFpEF: Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure trial, iron supplementation with IV ferric carboxymaltose is being investigated in both anemic and non-anemic HFpEF patients in the FAIR-HFpEF trial. Iron deficiency was diagnosed when the serum ferritin level was less than 100 μg per liter or was between 100 and 299 μg per liter when the transferrin saturation was less than 20%. Treatment with ferric carboxymaltose for 24 weeks in patients who had chronic heart failure and iron deficiency with or without anemia improved symptoms, functional capacity, and the quality of life[125-128].

CKD patients on erythropoietn (EPO) therapy have shown signs of cardiovascular improvement and reversal of left ventricular hypertrophy[182, 249], suggesting that correction of anemia may prevent progression of HFpEF. In a randomized controlled trial conducted in older adults with HFpEF, EPO supplementation with epoetin alfa did not improve left ventricular geometry or exercise capacity despite increases in hemoglobin levels[250].

In a trial of vitamin D supplementation by cholecalciferol therapy, reductions were observed in the left ventricular mass, CKD is associated with hyperactivation of the renin-angiotensinaldosterone system (RAAS) in response to renal hypoxia resulting in volume overload[242], which may contribute to the development and/or progression of HFpEF. In these patients vitamin D levels were lower and inversely correlated with exercise capacity[244].

Detrimental effect of RAAS activation on HFpEF progression: RAAS activation can increase myocardial workload, by elevating systemic vascular resistance and left ventricular afterload, through vasoconstriction of systemic blood vessels in response to angiotensin II or by causing volume expansion due to increased sodium and water response to increased aldosterone levels[233, 236]. RAAS inhibition is the preferred therapeutic strategy to slow down progression of renal failure and reduce proteinuria in CKD[232]. Despite the fact that most data show RAAS overactivation in HFpEF, clinical trials in HFpEF with drugs acting on the RAAS, have failed to improve all-cause mortality so far[235, 231].

CHARM Preserved: Assessment of Reduction in Mortality and Morbidity potential benefit of angiotensin-receptor blockers (ARB) in patients with heart failure and preserved ejection fraction, candesartan does not significantly reduce the rate of cardiovascular death, but does significantly reduce the rate of hospitalization for heart failure and has a moderate impact in preventing admissions for CHF among patients who have LVEF higher than 40% [57, 58].

I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) trial,the largest trial in the HFpEF population so far, randomly assigned patients to irbesartan or placebo nearly 40% of deaths in HFpEF patients were attributed to noncardiovascular causes[23, 29], Obesity, anemia, diabetes, chronic obstructive pulmonary disease, and renal dysfunction were identified as independent predictors of mortality after multivariable adjustment[24]. AT1-blockade with Irbesartan reduces mortality and improved outcome on cardiovascular endpoints in patients with natriuretic peptides below the median, but not in patients with higher natriuretic peptide levels[237], suggesting that RAAS inhibition may be beneficial in early HFpEF[27].

Unlike HFrEF, in which neurohormonal activation is a central theme that dominates the pathophysiology after the initial myocardial insult. Although Phase 3 trials of spironolactone (TOPCAT) and implantable pulmonary artery hemodynamic sensors (CHAMPION) have demonstrated a reduction in HF hospitalization, several other trials (e.g., CHARM- Preserved [candesartan]], I-PRESERVE [irbesartan] RELAX [sildenafil], and NEAT [isosorbide mononitrate] showed no benefit[343].

Regression of LV hypertension is an important therapeutic goal since diastolic function may improve. Studies with beta-blockers, diuretics, calcium channel blockers demonstrated regression of LV hypertension, though medications targeting the RAAS led to higher rates of LV hypertension reversal. The management of hypertension is a cornerstone of HFpEF management, and careful matching of antihypertensive treatments to patient phenotype holds great promise for improving outcomes in patients with HFpEF[46].

TOPCAT: The 2014 Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) randomized patients with mostly controlled blood pressure to spironolactone or placebo. Patients were included if they had LVEF ≥45%, findings of HF, and either a HF hospitalization

or elevated BNP, there was no difference in the primary composite outcome of CV mortality, aborted cardiac arrest, or HF hospitalization.Spironolactone was associated with a "nominal"reduction in HF hospitalizations. Current ACC/AHA HF guidelines recommend diuretic use for symptom relief in patients with HF volume overload with HFpEF, suggesting that a benefit of spironolactone was associated with a more HFpEF-like phenotype. It improve indices of diastolic function and cardiac structure in HFpEF patients[238]. Shah et al.[53] found that abnormal LV longitudinal strain was a predictor of CV death as well as a composite of HF hospitalizations, CV death or aborted cardiac arrest in chronic HFpEF patients enrolled in the TOPCAT trial with a median follow up of 2.6 years.

PARAMOUNT (Prospective comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blocker on Examination of Heart Failure with Preserved Ejection Fraction) study treatment with LCZ696, a combined angiotensin receptor neprilysin inhibitor that inhibits natriuretic peptide breakdown and enhances cyclic GMP activation, was associated with reductions in circulating N-terminal pro–B-type natriuretic peptide levels in HFpEF over treatment with valsartan alone.

Sacubitrilvalsartan did not result in a significantly lower rate of total hospitalizations for heart failure and death from cardiovascular causes among patients with heart failure and an ejection fraction of 45% or higher. LCZ696's dual mechanism of action thus acts to restore the altered neurohormonal balance in HFpEF52. The favorable effects of LCZ696 seen in patients with HFpEF in the PARAMOUNT trial are encouraging, and further testing of this agent in this patient population is warranted.

PARAGON HF trial: The angiotensin neprilysin inhibitor missed its primary endpoint of reducing total hospitalisation and cardiovascular death in HFpEF patients, but the data suggest there may be benefit in some patient groups of the population with heart failure with mid-range ejection fraction (HFmrEF) and that this disorder have different characteristics and aetiologies. HFmrEF is an emerging HF subtype defined by LVEF 45-49%. Contrary to higher EF phenotypes, HFmrEF appears to benefit from therapies found to be beneficial for HFrEF, like beta blockers. A subgroup analysis identified lower relative risk for the primary outcome among those with LVEF below the median (median LVEF 57%), but not above the median. The observed reduction in the below-median subgroup was similar to that in HFrEF trial, PARADIGM-HF. There were other differences by some subgroups, so it is possible that an ARNI might ultimately prove beneficial for some patients meeting PARAGON-HF's enrollment criteria.This study demonstrated that sacubitril/ valsartan reduces NT-proBNP levels in patients

hospitalized for acutedecompensated heart failure without increased rates of adverse events when compared to enalapril. Taken together, these two trials suggest that HFrEF patients benefit from therapy with an ARNI.The authors concluded that baseline NT-proBNP predicted HF events but did not modify the sacubitril/valsartan treatment effect in patients with HFpEF. PARAGON –HF subgroup trial shows ARNI is effective in patients with HFpEF possibly because of its heterogenus phenotype, but the finding of this study suggests that HF patients with HFmEF and elevated NTpro BNP may benefit from ARNI combination. The drug reduced morbidity and mortality in patients with HFrEF in the PARADIGM-HF trial and it has a class I guideline recommendation for the treatment of HFrEF. Aside from ejection fraction, the entry criteria for PARADIGM-HF and PARAGON-HF were nearly identical, lower end of the normal ejection fraction range should be considered in light of the PARADIGM-HF trial which showed substantial benefit in those with heart failure and ejection fraction below 40%. This findings indicate that the benefit of sacubitril/valsartan observed in PARADIGM-HF could extend to heart failure patients with ejection fraction below the normal range, including those designated HFmrEF. Sacubitril/valsartan reduced NT-proBNP by 19% compared with valsartan, decreases NT-proBNP predicted lower subsequent risk of the primary endpoint of total (first and recurrent) HF hospitalizations and CV death. HF patients with mid-range EF and elevated NT-proBNP may benefit from sacubitril/valsartan combination. Prospective studies are required to confirm these conclusions.

Myocardial extracellular matrix (ECM) homeostasis occur during development of heart failure (HF) in patients with HFrEF and HFpEF. Changes in synthesis, processing, degradation and turnover of proteins such as collagen may result in structural remodeling. These changes can be determined by measuring circulating biomarkers, soluble ST2, collagen I telopeptides (CITPs) and tissue inhibitor of matrix metalloproteinase (TIMP-1).It is in a subanalysis of the PARAGON-HF trial, higher levels of TIMP-1 were associated with risk of the primary endpoint. Treatment with sacubitril/valsartan resulted in favorable changes in some biomarkers (TIMP-1 and sST2). Sacubitril/valsartan may result in beneficial outcomes by reducing fibrosis in HFpEF patients.

PARALLAX study: Sacubitril/Valsartan versus Individualized RAAS Blockade in Patients with HFpEF, indicate sacubitril/valsartan was associated with significant reductions in NT-ProBNP at 12 weeks when compared against individualized medical therapy, but found no significant difference 6-minute walk distance or other secondary end points. A post-hoc analysis of PARALLAX indicated those in the sacubitril/valsartan group had a lower risk of heart failure events.

The SENIORS (Study of effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with HF) trial shows that nebivolol is well tolerated and effective in reducing mortality and morbidity enrolled patients aged greater than 75 years who had either an LVEF less than 35% or a hospitalization for HF, mean 49% patients had preserved LVEF and nebivilol was well tolerated.The SENIORS trial weakly suggests that use of nebivolol in elderly patients with HF with LVEF 35%-40% may decrease mortality and CV hospital admissions[25]. Subsequent analyses suggested nebivolol was of comparable benefit in both HFrEF and HFpEF patients[20].

The mechanism behind β-blockers' therapeutic potential in enhancement diastolic function in HFpEF is to be associated with negative chronotropic and inotropic properties in stabilizing heart rate and optimizing left ventricular (LV) relaxation. The investigators had two primary aims from previous trials on β-blockers. First to demonstrate the safety and efficacy of nebivolol in elderly HF patients, secondly was to demonstrate nebivolol's safety and efficiency across a broad range of LVEF, including the HFpEF population[28]. In the SENIORS trial there was no difference in the primary outcome when patients were stratified according to preserved or reduced LVEF using a cut-off of > 35% to define preserved EF. Subsequent analyses suggested no strong interaction between the therapeutic benefit of nebivolol and LVEF above or below 35%, but this does not entirely allay concerns that there might be no benefit in those with an LVEF greater than 45%. In a separate analysis of patients with an LVEF cut-off greater than 40%, there was no statistical interaction, suggesting that nebivolol was of comparable benefit in HFrEF and HFpEF patients. In the group with LVEF ≤ 35%, nebivolol reduced ESV and improved EF but in LVEF > 35% group this effect was not there in HFpEF. In the separate analysis of patients with an EF cut-off greater than 40%, there was no noted statistical interaction, suggesting that nebivolol was of comparable benefit in reduced EF and preserved EF patients.Most recently, a meta-analysis of RCTs found mortality benefit associated with the use of beta-blockers in patients with LVEF up to 49%, but did not see the same benefit for those with LVEF ≥ 50%. Other meta-analysis and observational studies have mixed results but generally suggest a potential mortality benefit with the use of beta-blockers in patients with LVEF > 40%. Beta-1 selective blocker nebivolol demonstrated a modest reduction in the primary endpoint of all-cause mortality or cardiovascular hospitalization but did not affect mortality alone in an elderly population that included patients with HFpEF.

Swedish HF registry: In patients with HFpEF, use of β-blocker therapy was associated with lower all-cause mortality but not with lower combined all-cause mortality or HF hospitalization. As myocardial ischemia can drive the development of HFpEF, its presence should be detected and treated with anti-ischemic therapies, which still include β-blockers. Patients with evidence of myocardial ischemia could also be considered for revascularization with percutaneous coronary intervention or coronary artery bypass surgery. Current guidelines do not recommend the use of β-blockers solely for HFpEF, unless it is used to optimize treatment of comorbidity, such as controlling ventricular rate in atrial fibrillation or tachyarrhythmia, or hypertension. Since cardiac output is the product of heart rate and stroke volume, patients with HFpEF are often dependent on augmentation of heart rate in order to increase cardiac output[36]. Negative chronotropic medications are recommended in HFpEF to increase the diastolic filling period, but slowing the heart rate in the absent of tachycardia tends to only prolong diastasis, where transmitral flow is minimal or absent. Chronotropic incompetence is highly prevalent and associated with exercise disability in HFpEF. Reduced systolic and diastolic reserve, chronotropic reserve may represent the only mechanism to augment cardiac output during exercise, although there is concern that inadequate ability to enhance relaxation with tachycardia may limit stroke volume responses. β-blockers, especially at high doses may aggravate rather than alleviate exercise intolerance. Slowing elevated heart rate can prolong LV filling time in abnormally stiff LV and also prolong coronary perfusion. Nebivolol possible confer additional effects due to the NO enhancing action of the drug via a signaling pathway starting from the activation of β3-adrenergic receptors and leading to overexpression of inducible NO synthase. Cardiac NO production by nebivolol could participate in the cardiovascular effects of nebivolol treatment in patients affected by hypertension and HF. In this regard Pieske et al (Charité - Berlin, Germany) are planning an additional large multicenter trial with preserved LVEF in order to investigate the effects of β-blockers treatment starting in 2015. Beta-blockers are established drugs in HFrEF, but their role in HFpEF is not established.

Results of the J-DHF trial indicate that carvedilol did not improve survival in patients with HFpEF; however, the study also showed a correlation between carvedilol dose and mortality benefit with greater benefit for higher doses[21, 22, 104]. Trial indicates there may be an association between carvedilol dose and reduction of death or hospitalization for CV cause. No demonstrated benefit of beta-blocker use in patients with LVEF >50%.

Author, year	Population	Primary Outcome	Results	Key Takeaway
Liu, 2014[29]	2 RCTs, 10 observational studies reporting outcomes of mortality and/or hospitalizations for HF with LVEF ≥ 40%	All-cause mortality	9% lower RR for all-cause mortality with beta-blocker use (95% CI 0.87-0.95, p < 0.001); no effect on hospitalization (p = 0.26) or composite mortality and hospitalization (p=0.88)	Beta-blocker treatment in HF with LVEF ≥ 40% is associated with decreased risk of all-cause mortality but not decreased hospitalizations
Bavishi, 2015[30]	17 RCTs, prospective, or retrospective cohort studies comparing beta-blocker to placebo or no beta-blocker reporting outcomes for HF with LVEF ≥ 40%	All-cause mortality	Observational studies: significantly lower all-cause mortality with beta-blockers (RR 0.81, 95% CI 0.72-0.90), I^2 = 71.1% RCTs: no difference (RR 0.94, 95% CI 0.67-1.32], I^2= 0%	Beta-blockers may decrease mortality in non-elderly HFpEF patients, but do not decrease hospitalizations; supported only by observational studies
Fukuta, 2017[31]	11 observational cohort studies, 3 RCTs comparing beta-blockers to standard medical care or placebo in HF with LVEF ≥ 40%	All-cause mortality or HHF	Reduced risk of mortality with beta-blockers (RR=0.79, 95% CI 0.71-0.88); result was driven by observational studies	Suggests a mortality benefit of beta-blockers in patients with HF and LVEF ≥ 40%
Zheng, 2017[32]	25 RCTs comparing drug therapies for 18,101 patients with HF and LVEF ≥ 40%	All-cause mortality	Reduced all-cause mortality with beta-blockers (RR: 0.78, 95% CI 0.65-0.94, p=0.008); reduced CV mortality with beta-blockers (RR: 0.75, 95% CI: 0.60 to 0.94, p = 0.01)	Beta-blockers associated with reduction in all-cause mortality and CV hospitalization in HFpEF

RCT: randomized controlled trial; HF: heart failure; LVEF: left ventricular ejection fraction; RR: relative risk; CI: confidence interval; HHF: hospitalization for heart failure; HFpEF: heart failure with preserved ejection fraction; CV: cardiovascular

Table 2: Studies of Beta-blockers

Randomized and observational studies shows mixed results, but several trials suggest benefit of beta-blockers, mixed results related to hospitalizations, most common benefit was decrease in mortality risk, benefits more commonly observed in elderly patients, single trial found no benefit if LVEF >50%[239]. Meta-analyses results Beta-blockers may decrease mortality risk in HFpEF, mixed results regarding effect on hospitalizations and results mainly for patients with LVEF >40% (Table 2, 3, 4).

Neither the SENIORS trial[29], nor the OPTIMIZE-HF registry[230] showed a beneficial effect of beta adrenoceptor blockade on all-cause mortality or cardiovascular hospitalizations. Beta-adrenoceptor blockade failed to improve LV systolic or diastolic function in patients with LVEF >35%, as measured in the SENIORS echocardiography sub-study[241]. Beta-adrenoceptor blockade was administered on top of existing medication, which often included RAAS inhibitors[241]. In patients with treatment resistant hypertension, renal sympathetic denervation did improve diastolic function and reduce left ventricular hypertrophy, besides reducing blood pressure[302], suggesting that there is indeed an interaction between CKD, sympathetic hyperactivity and diastolic cardiac function[17].

In this single-centre cohort study, it was founded that the majority of patients admitted with acute HFpEF had abnormal LV GLS.Thus, the use of LV GLS to identify a subset of acute HFpEF patients with worse short-term outcomes, independent of diastolic dysfunction, may represent a novel tool to identify high-risk patients with unique cardiac pathophysiology for potential interventions prior to discharge. LV GLS to be an important predictor of clinical outcomes such as mortality or hospitalizations in patients with chronic HFpEF[36, 41–43].

Appendix D: Randomized and Observational Studies

Randomized and observational studies of beta-blockers for HFpEF

Author, year	Design	Population	Primary Outcome	Results	Key Takeaway
Nodari, 2003[33]	Nebivolol compared to atenolol	HFpEF and arterial HTN	Resting and exercise hemo-dynamic parameters	Both agents produced significant decrease in heart rate and blood pressure; increase in VO_2, stroke volume, decrease in cardiac index, MAP with nebivolol	Nebivolol associated with greater hemodynamic benefit compared to atenolol; equal antihypertensive effects
Bergstrom, 2004[34]	Double-blind, multicenter, randomized trial of carvedilol vs. placebo	113 patients with diastolic dysfunction and preserved LVEF	Change in doppler echocardio-gram readings	No effect of carvedilol on primary endpoint	Suggests benefit of carvedilol in patients with diastolic HF and preserved LVEF
Lund, 2014[35]	Propensity score-matched cohort study, treated vs. untreated with beta-blocker therapy	Review of Swedish HF Registry patients with HFpEF	All-cause mortality	1-year survival 80% vs. 79% and 5-year survival 45% vs. 42% for treated vs. untreated patients (HR 0.93; 95% CI 0.86-0.996, p = .04); no decrease in combination all-cause mortality and HHF	Beta-blockers associated with reduced all-cause mortality but not reduced combined all-cause mortality and HHF in HFpEF
Aronow, 1997[36]	Randomized trial evaluating use of propranolol	153 patients age ≥ 62 years with previous Q-wave MI, NYHA class II-III HF, LVEF ≥ 40%, and treatment with diuretics and ACEIs	Total mortality, total mortality + non-fatal MI	Significantly lower mortality (56% vs. 76%) and mortality plus nonfatal MI (59% vs. 82%) in patients receiving propranolol	Propranolol decreases mortality, mortality plus nonfatal MI in patients with HFpEF and prior MI
Nishio, 2008[14]	Rat model of bisoprolol vs. no medication in HFpEF	Diastolic HF model rats	Survival	Improved survival, decreased in expression of myocardial,and decreased LV hypertrophy in high-dose group	Beta-blocker use may decrease remodeling and inflammatory markers
Chan, 2005[37]	Longitudinal, population-based study assessing effects of beta-blockers	Adults age ≥ 65 years with HF prescribed beta-blockers compared to those not receiving beta-blockers	All-cause mortality	Beta-blocker use associated with decreased rate of all-cause mortality (HR 0.74, 95% CI 0.56-0.98); no difference between LVEF ≥ 40% and LVEF < 40% (interaction p = 0.34)	Suggests association of beta-blocker use with decreased all-cause mortality in elderly patients with HF regardless of LVEF
Dobre, 2007[13]	Prospective observational study comparing beta-blocker to no therapy	Patients in The Netherlands with HF and LVEF ≥ 40% discharged from the hospital with or without beta-blocker (metoprolol, carvedilol, bisoprolol, nebivolol)	All-cause death	Significantly lower rate of all-cause death in beta-blocker group; high dose therapy associated with largest benefit	Potential association between beta-blocker use at discharge and decreased mortality in HFpEF; beta-blocker dose affects outcome
Shah, 2008[38]	Review of the effect of statins, ACEIs, and beta-blocker	National sample of Medicare registrants age ≥ 65 years hospitalized with primary HF diagnosis and documented LVEF > 50%	Mortality	Non-significant trend toward decreased mortality (RR 0.93, 95% CI 0.87 to 1.10), significant increase survival at 3 years (RR 0.92%, 95% CI 0.87 to 0.97) in beta-blocker group	Beta-blockers associated with reduced mortality in elderly patients with HFpEF
Hernandez, 2009[39]	Analysis of OPTIMIZE-HF results focused on beta-blocker effects in HFpEF	Patients age ≥ 65 years with HFpEF in OPTIMIZE-HF hospitalized for HF and eligible for Medicare benefits at time of discharge	Time to death or re-admission, first re-admission	Beta-blocker use associated with non-significant decrease in mortality (HR 0.94, 95% CI, 0.84–1.07) and non-significant decrease in readmission (HR 0.98, 95% CI, 0.90–1.06)	In elderly patients with HFpEF, beta-blockers did not significantly improve mortality or rehospitalization rates

Table 3: Studies of Beta-blockers.

Gomez-Soto, 2011[40]	Prospective cohort study of patients started on either bisoprolol or carvedilol	1,085 adults age > 14 years with first-time diagnosis of HF with LVEF ≥ 50% in Spain	Death from any cause, death from CV cause, HHF, visits for any cause	Longer survival (RR 0.37, 95% CI 0.21-0.50), lower CV mortality (RR 0.31, 95% CI 0.18 to 0.45, P < 0.001), lower readmission rate (RR 0.66, CI 95% 0.54 to 0.78, P < 0.001), fewer visits (RR 0.81, 95% CI .75-0.88, p < 0.01) with beta-blockers	Suggests association between beta-blocker use and reduced mortality, readmissions, and visits for patients with HFpEF
Smith, 2010[28]	Prospective cohort study to analyze effects of psychological condition on HF outcomes	Subgroup of patients with HFpEF (13% of total population) and stable CHD	HHF, all-cause mortality	Use of beta-blockers associated with significant decrease in HHF when adjusted for baseline characteristics (HR 0.46, 0.23-0.93; p = 0.03); no significant difference in all-cause mortality	Use of beta-blockers associated with decreased risk of hospitalization for patients with HFpEF and stable CHD
Tehrani, 2009[27]	Observational study of effects of drug therapy in HF	142 patients age > 80 years, LVEF ≥ 50%, and clinical diagnosis of HF	Mortality and rehospitali-zation	Beta-blocker therapy did not significantly affect survival (p=0.89)	No survival benefit with beta-blocker therapy in HF patients age > 80 years and LVEF ≥ 50%
Nevzorov, 2012[41]	Retrospective cohort analysis comparing those receiving beta-blockers within 3 months prior to admission to those who did not	345 adult patients with HFpEF hospitalized for HF	2-year all-cause mortality	Protective effect associated with beta-blocker prescription on 2-year survival (HR 0.69, 95% CI 0.47–0.99, p=0.018)	Use of beta-blockers may increase survival for adults with HFpEF
Patel, 2014[42]	Propensity score matched analysis of the OPTIMIZE-HF study linked to Medicare	Medicare patients age ≥ 65 years from OPTIMIZE-HF with HF and LVEF ≥ 40% receiving new beta-blockers (carvedilol, bisoprolol, metoprolol succinate) at discharge	Composite all-cause mortality or HHF	No decrease in primary outcome with beta-blocker (HR 1.03; 95% CI 0.94–1.13, p=0.569); significant association with HHF (HR 1.17, 95% CI 1.03–1.34, p=0.014); nonsignificant if LVEF > 45% in beta-blocker use	Beta-blocker use not associated with decreased mortality or HHF for elderly patients with HFpEF; decreased risk of HHF if LVEF 40-45%
Farasat, 2009[43]	Observational comparison of men and women with HFpEF receiving beta-blockers or not	66 patients with HFpEF stratified based on beta-blocker or no beta-blocker received at discharge	HHF in 6 months	Beta-blocker use associated with nonsignificant decrease in rehospitalization rate in men (OR 0.25, 95% CI 0.03 to 1.92, p = 0.18) and increased rehospitalization for women (OR 14, 95% CI 3.09 to 63.51, p < 0.001)	Suggests beta-blocker therapy may be associated with increased hospitalization in women but not in men with HFpEF

LVEF: left ventricular ejection fraction; HR: heart rate; HFpEF: heart failure with preserved ejection fraction; HR: hazard ratio; CI: confidence interval; HHF: hospitalization for heart failure; ACEI: angiotensin converting enzyme inhibitor; MI: myocardial infarction; HF: heart failure; RR: relative risk; CV: cardiovascular

Table 4: Studies of Beta-blockers.

There are important differences between acute and chronic HF patients as chronic HF patients therapies target neurohormonal regulation, preventing cardiac remodelling and management of co-morbid diseases. While acute HF therapies target decongestion, maintaining adequate cardiac output, preventing kidney insufficiency and reversing inciting causes of decompensation. These differences in haemodynamic and congestive states between acute and chronic patients may have important unrecognized implications regarding the association of abnormal LV GLS on longer-term outcomes. Another potential explanation is that HFpEF is primarily a disease of the elderly2 and 40–50% of patients with HFpEF die from non-cardiovascular causes[243]. In a population with preserved LVEF, similar echocardiographic measures of diastolic dysfunction and elevated levels of NT-proBNP, LV GLS represents a useful tool to identify myocardial dysfunction independent of diastolic dysfunction that contributes to the complex pathophysiology of acute HFpEF. Among patients hospitalized with acute HFpEF, there is a high prevalence of abnormal LV GLS. We found that LV GLS is associated with worse 30-day but not 1-year post-discharge outcomes. Thus, LV GLS may be a useful tool for identifying a cohort of HFpEF patients with more overt myocardial dysfunction who are at risk for worse outcomes following a hospitalization for HF[234].

Sanjeev Shah identified 3 subcategories of HFPEF which differ in their clinical charactristics, pathophysiology and outcomes[35, 84, 343].

Phenogroup #1 Natriuretic peptide deficiency syndrome: Patient had lowest BNP, were the youngest had least abnormalities in cardiac structure and function, were obese and had best outcome.

Phenogroup #2 Obesity-cardiometabolic phenotype: Patient had higher BNP levels, had worst LV relaxation (lowest e'velocity) and had the highest prevalence of diabetes and obesity.

Phenogroup #3 Right ventricular failure, cardiorenal phenotype: They had highest incidence of ECG abnormalities, right ventricular dysfunction, pulmonary hypertension and renal dysfunction and these patients had the worst outcome.

Shah et al, when applied to large phenotyped (both biological and clinical) datasets in combination with clinical outcomes may help to improve our understanding of how biological phenotypes integrate with clinical phenotypes. Efforts are underway to utilize these concepts to identify novel therapeutic targets, improve the design of future clinical trials, and to develop effective clinical management

algorithms[250].

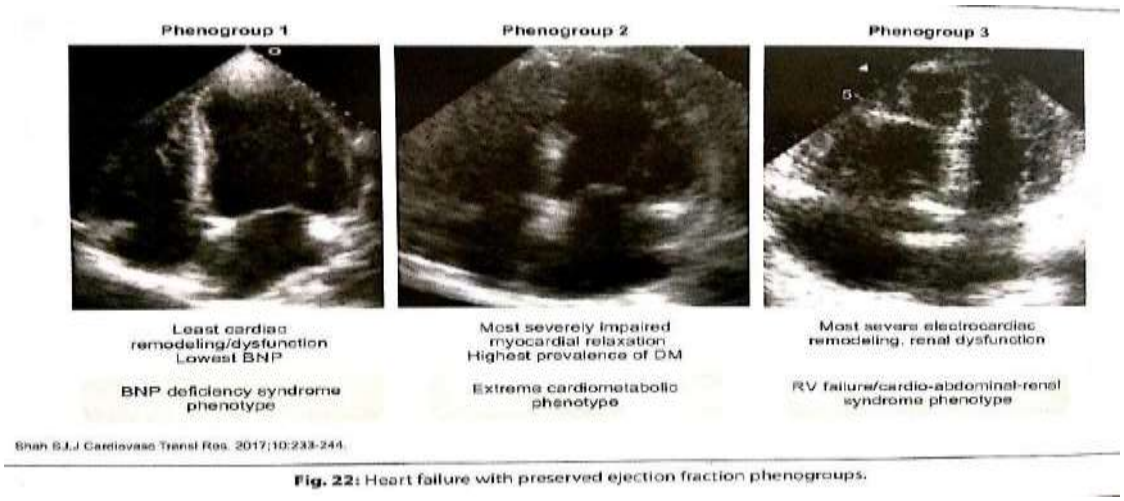

FIG: 29 Heart failure with preserved ejection fraction phenotypes 343.

Treatments are based on various phenomapping (Fig: 29).

HFpEF is likely more complex than a simple amalgamation of comorbidities, although comorbidities do influence ventricular-vascular properties and prognosis, the development of HFpEF may be fueled by alternative, disease-specific mechanisms that are yet to be defined.As it has various phenotypes treatment with guidelines is not proven.

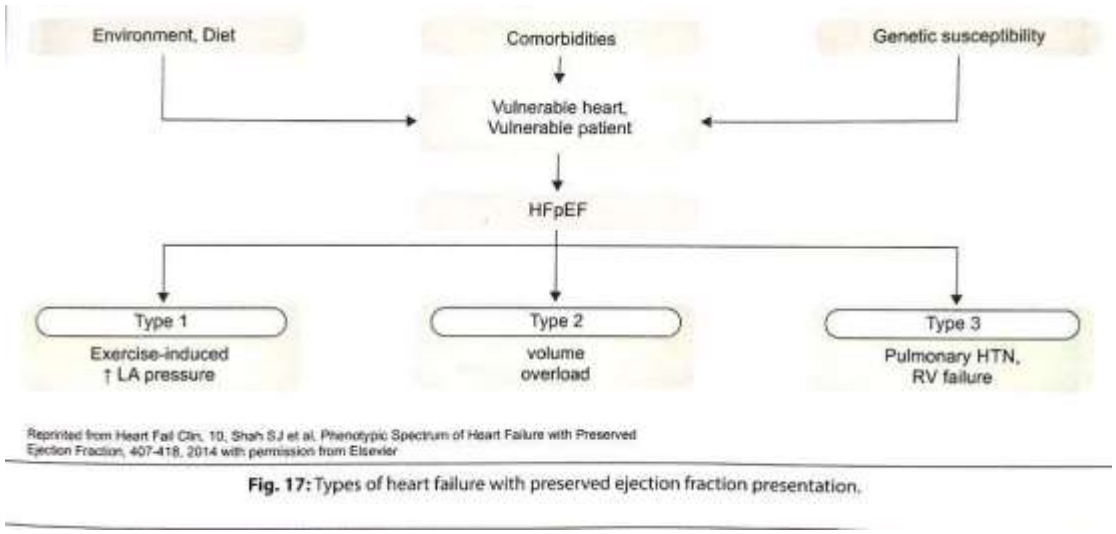

FIG: 30 Types of heart failure with preserved ejection fraction presentation[105].

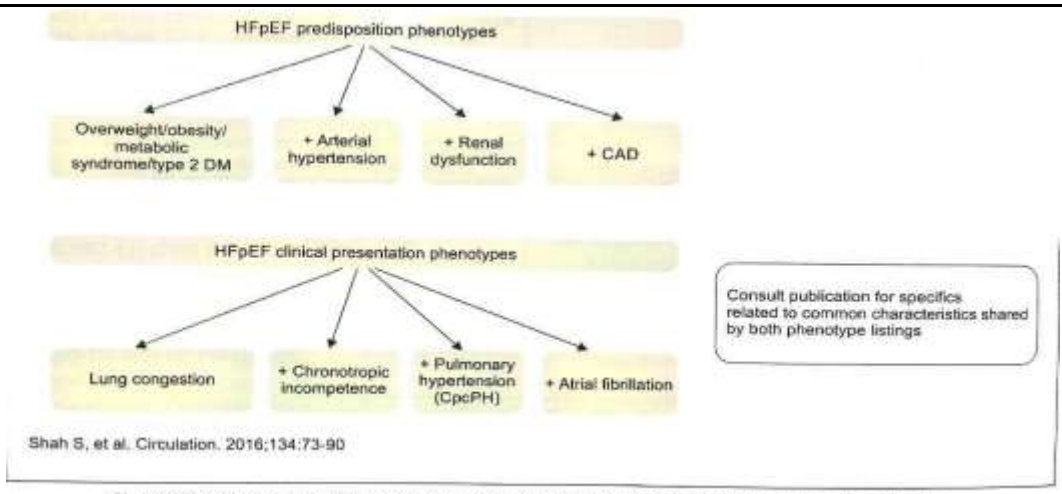

FIG: 31 Phenotypes in heart failure with preserved ejection fraction based on predisposition and presentation[341].

OptimEx and Ex-DHF: The recently completed multicenter Optimizing Exercise Training in Prevention and Treatment of Diastolic Heart Failure (OptimEx)[17] and Ex-DHF 2 trials will soon shed more light on the benefits of exercise training in HFpEF. That will best improve peak oxygen uptake (Peak Vo2) and additionally diastolic function (assessed echocardiographically). The investigators hypothesize that exercise training reverses HFpEF and that intensity of exercise training is more important than duration. Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status[221, 222]. Meta-analyses show that cardiac rehabilitation reduces mortality, improves functional capacity, exercise duration, and HRQOL, and reduces hospitalizations[214]. Other benefits include improved endothelial function, blunted catecholamine spillover, increased peripheral oxygen extraction, and reduced hospital admission[219, 220, 221, 224].

MicroRNAs as a Therapeutic Targets ass active participants in cellular cross talk, microRNAs are also attractive therapeutic targets. Inhibiting a microRNA or mimicking its activity potentially influences dozens of genes, which could lead to larger treatment effects compared to standard drugs[91]. While microRNA-interfering therapy is still in its early developmental stage, several pilot studies have shown promising results in treating cardiovascular disease[98]. Inhibition of proapoptotic microRNA-34 or pro-fibrotic microRNA-21150 improved LV function in mice with HF due to pressure overload[227, 305].

An increasing number of phase I and II clinical trials using microRNA therapy are being started[98]. MicroRNA-based therapies for HFpEF are not yet under development, but some microRNAs have been identified as crucial regulators of pathophysiological processes underlying HFpEF, and are under investigation as therapeutic targets[307].

Efforts are underway to treat heart failure by enhancing myofilament sensitivity to Ca(2+), transfer of the gene for SERCA2a, the protein that pumps calcium into the sarcoplasmic reticulum of the cardiomyocyte, seems promising in a phase 2 trial. Several other abnormal calcium-handling proteins in the failing heart are candidates for gene therapy, many short, non-coding RNAs i.e, microRNAs (miRNAs) block gene expression and protein translation. These molecules are crucial to calcium cycling and ventricular hypertrophy. The actions of miRNAs can be blocked by a new class of drugs, antagomirs, cell therapy, autologous bone marrow derived mononuclear cells, or autogenous mesenchymal cells, which can be administered as cryopreserved off the shelf products, seem to be promising in both preclinical and early clinical heart failure trials and long-term ventricular assistance devices are now used increasingly as a destination therapy in patients with advanced heart failure. In selected patients, left ventricular assistance can lead to myocardial recovery and explantation.

CHAMPION: CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients trial. The beneficial effect of diuretics was suggested study from the CHAMPION trial in which medical treatment decisions driven by the knowledge of pulmonary artery pressure data were associated with a significant reduction in hospitalizations for HF[121, 122]. The majority of medication changes were in diuretic usage, and mean diuretic dose increased significantly more in the pulmonary artery pressure-guided treatment group. These data provide indirect evidence supporting the efficacy of diuretics to reduce morbidity in HFpEF. Lowering of LV filling pressures with diuretics is of paramount importance for HFpEF patients to achieve symptomatic benefit, to reduce pulmonary artery pressures, and to improve right ventricular (RV) loading[157]. Their efficacy relates to a restored pressure-natriuresis relationship in the presence of renal microvascular inflammation64. Administration of diuretics can be guided by the use of implantable hemodynamic monitors that either directly and continuously measure diastolic LV pressures or provide surrogates of pressure[71] and elevations have important prognostic implications[60]. When transition to decompensated HF occurs, diastolic LV pressures progressively increase over weeks. During this time interval, hemodynamic monitoring allows for early uptitration of diuretics, which improves outcome as

demonstrated in the CHAMPION trial. In this study, treatment guided by implantable hemodynamic monitoring significantly decreased cardiovascular death and HF hospitalizations in HFPEF patients[122, 59].

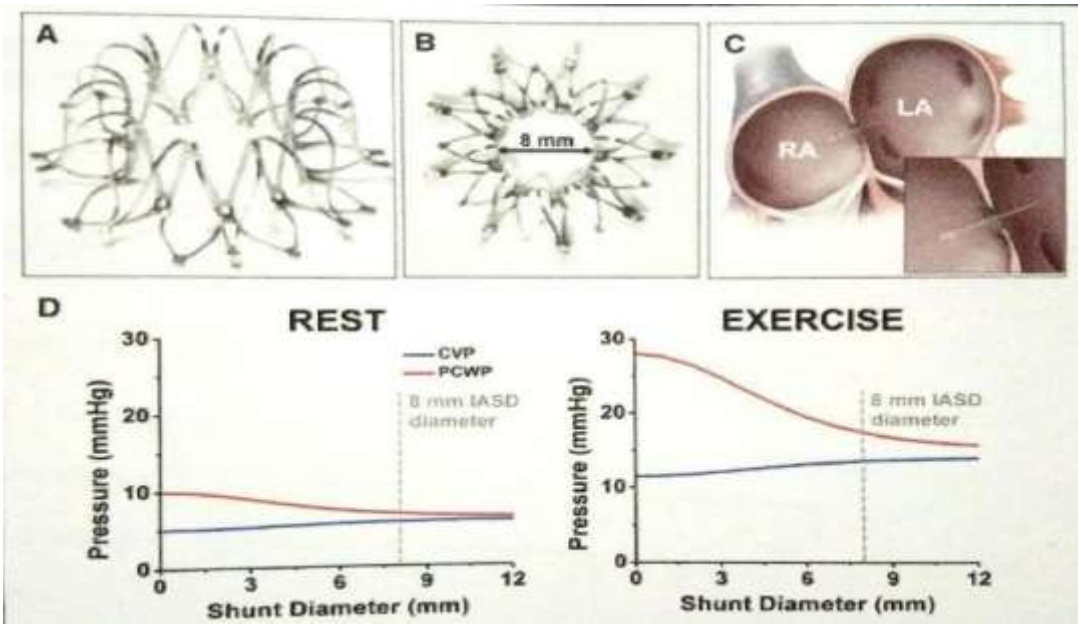

FIG: 32 Interatrial shunt device. A, Corvia Interatrial Shunt Device (IASD) System II. B, En face view of the IASD System II (single size, internal diameter= 8 mm). C, The IASD creates an interatrial shunt that unloads the left atrium by shunting blood from the higher pressure left atrium to the lower pressure right atrium. D, Simulation studies have shown that an 8-mm internal diameter for the shunt device is optimal in maximally reducing left atrial pressure without overloading the right heart (ie, keeping pulmonary-to-systemic flow relatively low at a 1.2–1.3 range)printed from Kaye et al[49] (Fig: 32).

Device therapy: The REDUCE LAP-HF randomized, blinded, sham-controlled trial was designed to test the hypothesis that the implantation of the IASD System II device in the interatrial septum in patients with symptomatic HF and midrange or preserved EF (≥40%).In nonrandomized, open-label studies, a transcatheter interatrial shunt device (IASD, Corvia Medical) was associated with lower pulmonary capillary wedge pressure (PCWP), fewer symptoms, and greater quality of life and exercise capacity in patients with heart failure (HF) and midrange or preserved ejection fraction (EF ≥40%) in the majority, and most of the participants were on a relatively high dose of diuretics and had a prior HF hospitalization or acute care visit within the last 12 months). IASD treatment reduces PCWP during exercise[121].

In patients with HF and EF ≥40%, implantation of an IASD reduced PCWP during exercise to a greater extent than a sham control procedure, demonstrating that in patients with HF with elevated LA pressure during exercise, the creation of an 8-mm interatrial communication unloads the LA. These findings suggest that the IASD could have beneficial effects in patients with HFpEF and HF with midrange EF, setting the stage for a larger scale randomized clinical trial powered to examine the effects of the IASD (Fig: 30)[121] on symptoms, quality of life, exercise capacity, and clinical outcomes. Wireless monitoring of pulmonary artery pressure have been usefull in controlling excessive volume overload in HFpEF patients, to prevent recurrent episodes of acute decompression and progression of multiorgan dysfunction haemodynamic changes prior to an episodes of acute decompensation may vary from patients to patients[123].

Pulmonary artery denervation using radiofrequcny ablation catheter has been reported to improve pulmonary haemodynamicsin patients with PAH.

Potential pitfalls [109, 120].

- Dependancy on image quality and
- Random noise and relatively low temporal and spatial resolution affects its ability to delineate endocardial and epicardial borders.
- Steeper learning curve
- Need more rigorous testing and validation

Potential pitfalls in 2D STE.

- Poor echo window-suboptimal views result in poor tracking
- Suboptimal tracking and endocardial border detection
- Global strain values may be inaccurate if two or more segments have to be discarded because of suboptimal tracking.

- A significant limitation in 2D STE is the difference in vendors, where strain data is stored offline as line (polar) format which cannot be analyzed by other vendors software. Certain vendors allow storage in the raster (Cartesian) Digital Imaging and Communications in Medicine format but there is limited experience in interpreting such images.

Limitation: Poor acoustic windows can limit adequate image acquisition for strain analysis in some patients.

Aim of Study

1. Evaluate whether GLS is superior to LV ejection fraction 2 GLS was higher in patients with HFPEF.

Primary Objectives:

Assessment of left ventricle systolic function by Strain imaging in patients with heart failure with preserved ejection fraction.

Secondary objectives:

1. Assessment of value of GLS in various strata of normal LVEF in HFPEF patients i.e, 50-55%, >55%,

2. There demographic profile and risk factors associated with it.

Materials and Methods

(i) Study population:

Patients presenting with symptoms like breathlessness, ankle swelling and fatigue that may be accompanied by signs e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema, caused by a structural and/or functional cardiac abnormality with LVEF>=50% and atleast one additional criteria relevant structural heart disase (LVH and or LAE) as a sign of increase filling pressure and diastolic dysfunction on echocardigraphy and elevated level of natiuretics polypeptide i.e, BNP> 35 pg/ml and/or NT-proBNP >125 pg/mL was taken into the study.

GLS value in HFPEF is not available in the study area to be used as the average value among the study subjects. expected value among the patients with normal LVEF but with symptoms of heart failure. Thus these two parameters were extrapolated from our internal study findings as the observed sample statistic.

(ii)Study design: This study is single centre observational cross sectional study between HFPEF patient and its relation with Strain rate.

(iii)Sample size Calculation: = zα2p(1-p)/e2 where p is proportion, e is precision here α= 5% hence zα =1.96 p = 1/2 e = 10% n is coming as 97. Hence minimum 97 patients will be included in the study.

(iv) Statistical Methods

Categorical variables are expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate.

Continuous variables are expressed as Mean, Median and Standard Deviation and compared across the groups using Mann-Whitney U test.

Associations between continuous variables are captured using Spearman's Rank

Correlation Coefficient.

The statistical software SPSS version 20 has been used for the analysis.

An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

whether these sample statistics are precise and valid enough to be considered as the population parameters of the said aspects, we conducted a sample size calculation, using these values.

(v) Study intervention: It is an nonintervention study, clinical correlation with Echocardiogram, strain imaging is done.

Inclusion criteria were

- Men and women above the age of 18 years.
- Objective signs of functional/structural causes of heart failure.
- Symptoms and signs consistent with heart failure preserved ejection fraction of >50 % by Echocardiography, Echocardiography features of HFPEF i.e, LA Volume, LA mass, E/E' ratio and /or elevated natriuretic peptides.
- Patients with some cardiovascular (CV) risk factor or disease such as arterial hypertension, diabetes mellitus or history of coronary artery disease (CAD).
- They were on optimal guideline recommended medical therapy.

Exclusion criteria:

- Structural valvular heart disease/pericardial disease.
- On cardiac resynchronization therapy.
- On pacemakers.
- History of unstable angina or myocardial infarction in the last month.
- Atrial fibrillation.

- Poor Echocardiography windows.
- LVEF <50%.

(vii) Study duration:

It should be minimum of 1 year duration. Data collection: November 2018-June2020.

Echocardiographic Assessment:

Each individual patient underwent an exhaustive ECG-gated echocardiographic evaluation of the following parameters which were recorded on a Philips EPIQ 7 Cardiology and Philips Affiniti 70C echocardiography machine in the Department of non-invasive Cardiology in NH-RTIICS.

Pre-echo patient preparation:

1. Ensure patient is comfortable and able to lie down flat or in left lateral decubitus. In patients with excessive chest hair, the hospital barber was requested to shave the chest hair.
2. Ensure proper connection of machine integrated Electrocardiogram (ECG) with each lead connected on the patient as recommended in the Echo machine manual.
3. Lead and gain of the ECG is optimized for calculations of time intervals from the “Utilities” section on the machine.
4. Patients whose image quality is affected by breathing were asked to do breath hold in end expiration during image and cine loop acquisition.
5. Sweep speed set to 50-100 mm/sec for time interval measurements.
6. Cine loop was set to 3 consecutive beat recording.

2D Echo:

- Parasternal long axis view with colour doppler.
- Parasternal Short axis views at the: base, mid-ventricle and apex.
- Apical-4 Chamber, 3 chamber and 2 chamber views with colour doppler.
- LV end diastolic and end systolic volumes were calculated from the apical 4 and 2 chamber views and indexed to body surface area.
- LV ejection fraction was calculated by the biplane Simpson's method.

*The above standard views were obtained during breath hold at end expiration and stored in cineloop from 3 consecutive beats (4 QRS complexes).

M-Mode:

- M-Mode at the level of the mitral leaflets for the left ventricle and again at the level of the aorta and left atrium assuring that the cursor was absolutely perpendicular to the interventricular septum, Posterior wall, the aorta and left atrium. It was obtained in the same sweep to reduce interobserver variability.
- The LV end diastolic diameter was calculated from the M-mode of the parasternal long axis view.

Colour Doppler:

- Colour Doppler was used to look for significant valvular regurgitation.If significant functional mitral regurgitation (MR) was noted, the severity was assessed by Semiquantitative methods like MR Vena Contracta, jet length and jet area.

Doppler:

- Doppler flow velocities were obtained across the mitral valve. Along with that the following parameters were also obtained.

- Mitral inflow patterns were assessed to determine Diastolic function of the left ventricle and tissue Doppler imaging was used to calculate the E/e' ratio.

*Sweep speed was set to 50-100mm/sec for all time interval measurements.

LV Function:

LV function was assessed by Modified Simpson's Biplane method from two standard apical four and two chamber views109.

LV Volume

The above standard views were obtained during breath hold at end expiration and stored in cineloop from 3 consecutive beats (4 QRS complexes). The most commonly used 2D echocardiography methods for left ventricle mass (LVM) estimation are the area-length and truncated ellipsoid methods.14 In both, the area is measured at the midpapillary level in the parasternal short-axis view and at end-diastole (Fig: 21) A limitation of the 2D methods is that they rely on geometrical assumptions that are not applicable when there are major LV distortions or when the LV is foreshortened12.

Moreover, in comparison to the M-mode, the 2D methods require better echocardiography windows to identify endocardial and epicardial borders24.

LA volume

The left atrial (LA) volume will be measured by the biplane area length method using apical 4-and 2-camber views at the end systolic frame preceding mitral valve opening and exclude pulmonary veins (PV) and left atrial appendage (LAA) while tracings. 2D volumetric measurements are based on tracings of the blood tissue interface on apical four and two camber views. LA length is defined as the shortest of the two long axis measured in the apical two and four cambered views, were A1 and A2 are the LA areas. Indexed LA volume is 0.85 X A1 X A 2/shorter length/BSA72. The maximal volume of the LA, measured at end-systole from bi-plane and indexed to body surface area [left atrial volume index (LAVI)].

TR jet velocity was calculated from apical four chamber view by estimation of peak RV systolic pressure from TR velocity and LA volume.

Global Longitudinal Strain by Speckle tracking echocardiography:

- ECG gated cine loops of Apical 4, 3 and 2 chamber was acquired for offline analysis using PHILIPS aCMQ QApp "Automated Cardiac Motion Quantification (aCMQ) with zero click technology".

The key variable under study was GLS (ie, peak systolic LV strain) derived from the myocardial analysis of the LV in longitudinal direction in the apical 4-chamber, 2-chamber and 3-chamber views (i.e,12 LV segments) and Aortic valve closure (AVC) is used for timing of end systole. GLS is defined as the length of change of endocardial borders of the LV from base to apex in each apical view. To determine GLS one needs to image all segments of all three apical views and provide both end diastolic and end systolic frames using 2DSTE at rest. However, measurements may vary among vendors and software versions7. In the echocardiographic examination we aimed for a frame rate 40–80 frames/sec in all images for strain analysis. The region of interest was set to cover the thickness of the myocardium. Appropriate tracking were verified visually and adjusted if necessary. LV GLS were analysed for 17 standardised segments, based on these values a mean value were calculated for each of the three apical projections and then a total LV GLS were calculated as the average of the value from the three apical projections.

- The R to Aortic Valve Closure (AVC) time was calculated by placing a pulse wave doppler across the aortic valve in apical 5 chamber view prior to offline analysis.

- Once the app is initialized it semi-automatically identifies the Region of Interest (ROI) for each view which can be altered as per the echocardiographers need. In certain cases the ROI was generated manually by the echocardiographer by placing 3 sampling points at the medial and lateral mitral annulus and the apex.

- Tracking was considered satisfactory if it covered the entire cardiac myocardium from endocardium to the myo-epicardial border and there was visible motion of speckles. In case of poor speckle tracking the ROI was readjusted and analysis repeated.

- Once desirable tracking was achieved Global Longitudinal Strain was calculated by averaging the strain in all.Cut Off:< -18 considered abnormal.

(vii) Method of measurement of outcome of interest: The outcome variable (primary and secondary) and its measurements must be defined clearly by avoiding all possible biases. The measurement will be done at the time of presentation.

(viii) Data Collection Methods: Data will be collected after doing physical examination, lab value of BNP /NT-proBNP, after doing echocardigrapy and strain imaging.

Table: 5 Observations and Results

Patients with HFpEF	mean and (range)
Age (years) >61 yrs	67.28yrs (35-86). 71.1%
Women	50.5%
Men	49.5%
Arterial hypertension	82.5 %
Diabetes mellitus	61.9%
Obesity (BMI >30kg/m2)	24.7%
History of CAD	38.1%
LV longitudinal systolic strain, -18 to -25 % Normal >-18 Abnormal	-16.51(-23.30 to -6.60) 38.1% 61.9%
LV ejection fraction, %50-70 50-60 >60	57.56% (50-70). 77.3% 22.7%
LV mass index, g/m Females LVMI<122	89.8%

>122 MalesLVMI<149 >= 149.	10.2% 91.7% 8.3%
LA volume index, mL/m²	14-90 (37.65)
<34 ml =>34 ml	18.6% 81.4%
DD grade 2 Grade 3	82.5% 17.5%
TR jet velocity >2.8cms/s	2.63cm/s.(1.8cm/s -3.50cm/s) 34%
Mitral septal-lateral E/e' ratio	14 - 34 (mean 17.56)
NTproBNP>220pg/ml	5399(322 - 26310)pg/ml.
LVEF <55 >=55	Abnormal GLS 70.37% 58.57%

Table 5: Data are expressed as the mean value of each variable from all studies as well as the range of the means from all studies.

In this study among 97 patients with HFPEF 61.86 % had abnormal GLS.

There has been increase in abnormal value of GLS was found as age advances though p value is not significant.

Onefourth of patientshad a body mass index ≥30kg/m2.

Diabetes mellitus patients were 61.9%, while arterial hypertension were 82.5%. 10% HFpEF patients had chronic obstructive pulmonarydisease and 20% of patients had chronic kidneydisease. Among patients LVEF< 55% 70% had abnormal GLS and LVEF>55% 58.57% had abnormal GLS, though p value is not significant. Abnormal GLS have significantly lower LVEF.

	GLS							
	NORMAL			ABNORMAL				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation	p Value	Significance
AGE	68.46	70.00	7.90	66.55	66.50	10.74	0.413	Not Significant
LVEF	59.32	60.00	5.68	56.47	55.50	4.72	0.013	Significant
LEFT ATRIAL MASS INDEX	39.79	37.80	10.22	36.32	35.70	7.51	0.060	Not Significant
Average e/e'	17.66	16.00	3.94	17.50	16.25	3.87	0.778	Not Significant
NATIREITIC PEPTIDE	5630.35	3530.00	5540.87	5256.55	3475.50	5929.03	0.661	Not Significant
TR Jet velocity	2.64	2.80	0.37	2.62	2.70	0.38	0.780	Not Significant

Table 6: Distribution of various factors with normal and abnormal GLS.

		AGE						Total		
		31-40	41-50	51-60	61-70	71-80	81-90		p Value	Significance
GLS	NORMAL	0(0)	0(0)	8 (33.33)	15 (45.45)	11 (36.67)	3 (50)	37 (38.14)	0.667	Not Significant
	ABNORMAL	1 (100)	3 (100)	16 (66.67)	18 (54.55)	19 (63.33)	3 (50)	60 (61.86)		
Total		1 (100)	3 (100)	24 (100)	33 (100)	30 (100)	6 (100)	97 (100)		

Table 7: Association of age with GLS

LVMI	Frequency	Percent
NORMAL	17	17.5
ABNORMAL	80	82.5
Total	97	100.0

Table 8: Left ventricle mass index distribution

		LVEF		Total		
		<55	>=55		p Value	Significance
GLS	NORMAL	8(29.63)	29(41.43)	37(38.14)	0.284	Not Significant
	ABNORMAL	19(70.37)	41(58.57)	60(61.86)		
Total		27(100)	70(100)	97(100)		

Table 9: Association of LVEF <55% and> 55%with GLS

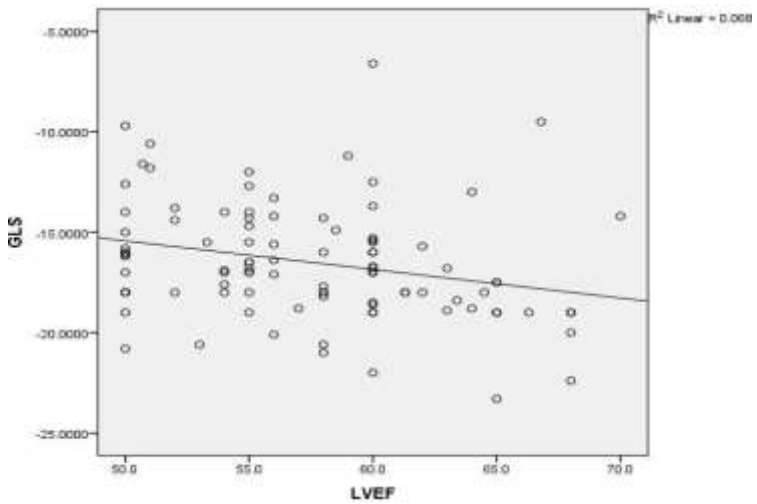

Chart: 1 Scattergrams distribution of LVEF with GLS shows weak negative correlation

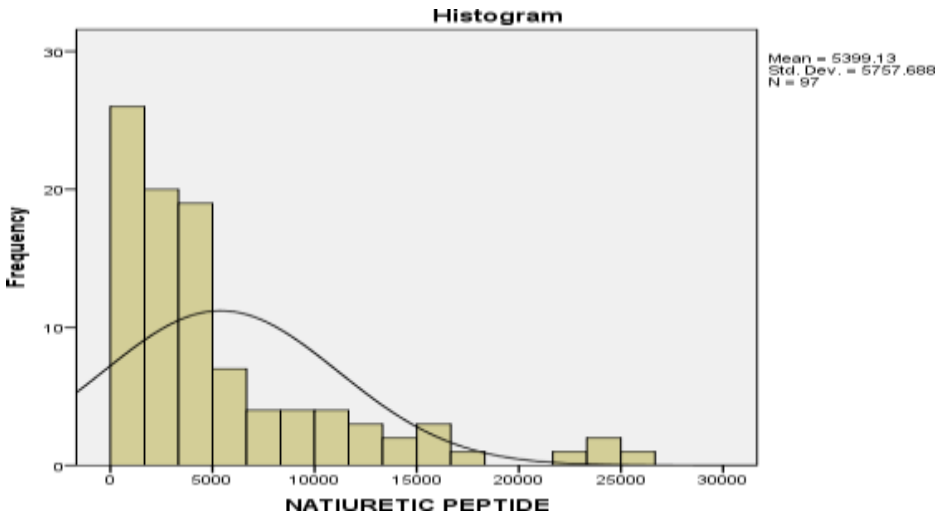

Chart: 2 The Histogram of Natiuretic peptide

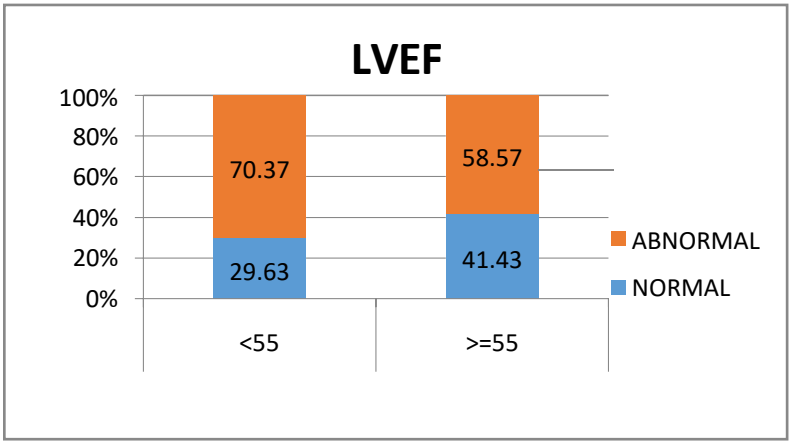

Chart: 3 Bar graph of percentage of patients with LVEF <55% and LVEF >55%.

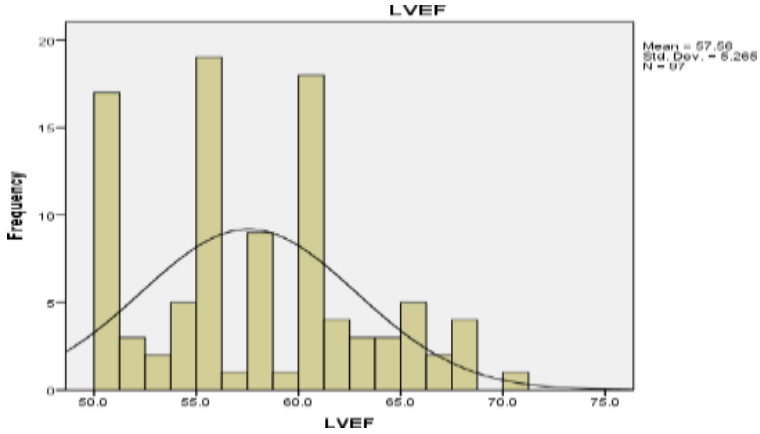

Chart: 4 Histogram of distribution of LVEF

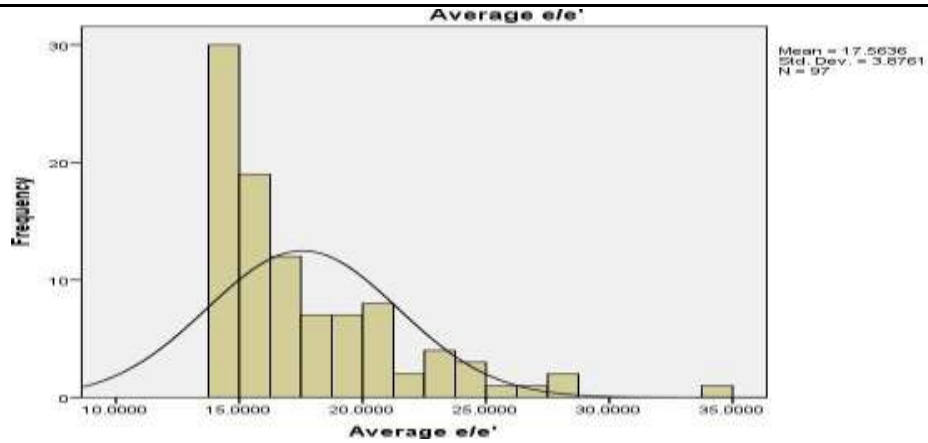

Chart: 5 Histogram of distribution of Average e/e'

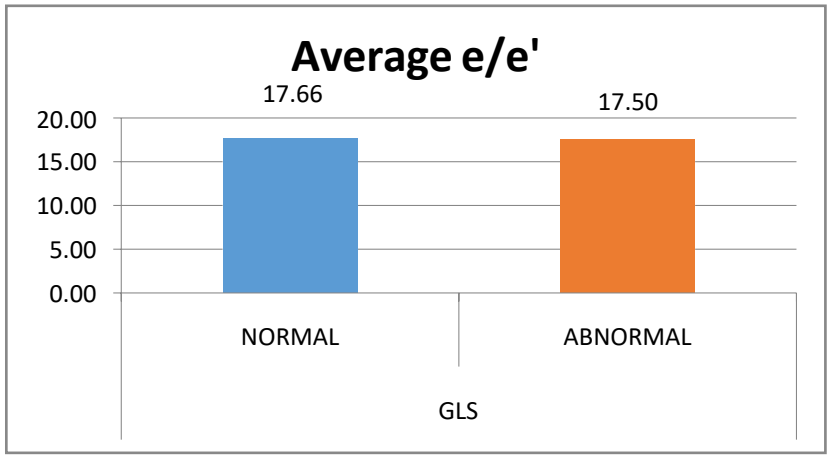

Chart: 6 Bar graph of percentage of average e/e' with normal and abnormal GLS.

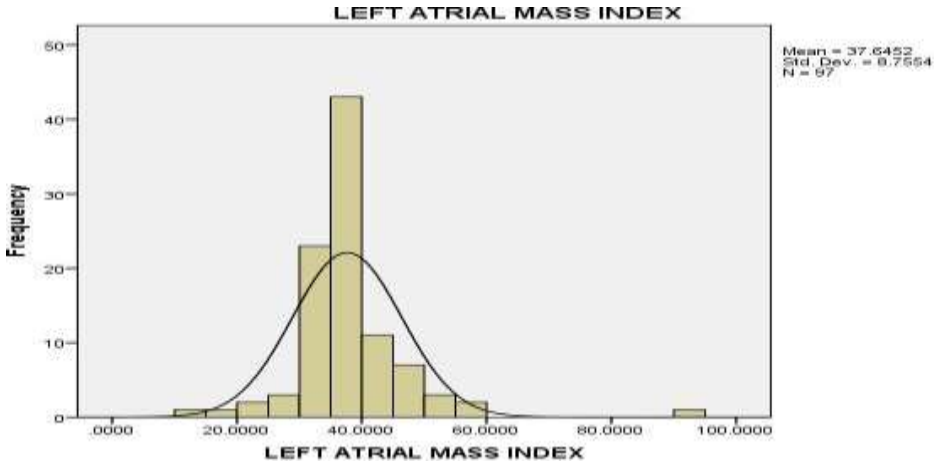

Chart: 7 Histogram of Left Atrial mass Index

	NORMAL			ABNORMAL				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation	p Value	Significance
AGE	68.46	70.00	7.90	66.55	66.50	10.74	0.413	Not Significant
LVEF	59.32	60.00	5.68	56.47	55.50	4.72	0.013	Significant
LEFT ATRIAL MASS INDEX	39.79	37.80	10.22	36.32	35.70	7.51	0.060	Not Significant
Average e/e'	17.66	16.00	3.94	17.50	16.25	3.87	0.778	Not Significant
NATIURE ITIC PEPTIDE	5630.35	3530.00	5540.87	5256.55	3475.50	5929.03	0.661	Not Significant
TR Jet velocity	2.64	2.80	0.37	2.62	2.70	0.38	0.780	Not Significant

Table 10: Distribution of various factors with normal and abnormal GLS

LVEF has significant negative corelation with GLS, p 0.013.

Correlations

			GLS
	AGE	Correlation Coefficient	-0.014
		p Value	0.889
		Correlation Coefficient	-0.291

Spearman's rho	LVEF	p Value	0.004
		p Value	
	LEFT ATRIAL MASS INDEX	Correlation Coefficient	-0.132
		p Value	0.196
	Average e/e'	Correlation Coefficient	0.059
		p Value	0.564
	NATIURETIC PEPTIDE	Correlation Coefficient	-0.005
		p Value	0.964
	TR Jet velocity	Correlation Coefficient	0.056
		p Value	0.589

Table 11: Various variables are compared with GLS.

LVEF has significant negative corelation with GLS Limitation of my study

- Small numbers remain one of the limitations of this study.
- An Echocardiography core lab to analyze images in an unbiased manner

Conclusion

GLS obtained from apical views was used as an index of cardiac function, with an incremental value and should be routinely done as follow up in HF patients as a marker of improvement of therapy. STE analysis seems to provide important information regarding the assessment of myocardial function and abnormal GLS seems to be an ominous marker. Elevated GLS in apparently healthy individuals may represent an aggregate marker of subclinical abnormalities in cardiac structure and function that can develop during the progression from risk factors to heart failure.

With GLS quantification can be done and follow up should be done in all cases of early HEPEF, which seems to be a early marker of prognosis. Gaps in the treatment and investigation options should be explored which can be fulfill by strain rate.

GLS was also found to be abnormal in few patients with LVEF > 55% so should we consider that the GLS value starts getting decline in HF patients even the change in LVEF starts getting evident on Echocardiograpy .

It seems to overcome the subjective and semi-quantitative study of LV function by visual assessment of wall motion and ejection fraction and appears more trustworthy than TDI more trials need to be done with GLS in normal LVEF as a prognostic maker and to identify patients .

It seems clearly, GLS is an early, reliable and sensitive marker of LV systolic function in HFpEF even in persons with apparently normal LVEF. It can be used as a prognostic marker in follow up of the patient with normal LVEF. It is a very common dreadful and treatable condition, so earlier diagnosis will lead to better outcome. It is very promising method to identify patients with mild systolic dysfunction which is not reflected in EF. In fact it seems to be superior to all other parameters of echocardiograpy. It has become obvious in recent years that HFpEF is a complex entity with different pathophysiologic components beyond the myocardial dysfunction itself as multiple factor results in abnormality of GLS so these comorbid conditions should be considered and treated adequately. However this new technique should be used widely in clinical practice in the treatment of primary disease as every risk factor adds to their morbidity The ability to identify myocardial dysfunction as the predominant pathophysiologic mechanism is an essential step in a phenotyping HFpEF because other mechanisms and contributing factors might also lead to heart failure syndrome.

Serial evaluation should be done as a follow up being a numeric value with much less interobserver variation is there.In patients with chronic HFpEF, GLS has been shown to be a potential predictor of HF related hospitalizations and cardiovascular death6, 3–15.

Unmasking LV systolic dysfunction by GLS estimation may be important prognostically and as some early trial-based evidences indicate, such information about subtle systolic dysfunction may help in identifying patients who can potentially benefit from ARNI, MRA and Beta-blocker therapy.This proposition is hypothesis generating and should be followed up by suitably-designed trials in future.

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