Pathophysiology of Heart Failure with Preserved Ejection Fraction

Shantanu P Sengupta

A thesis submitted for the degree of Doctor of Philosophy

Newcastle University

Translational and Clinical Research Institute

United Kingdom

December 2022

Declaration

This thesis is submitted for the degree of Doctor of Philosophy at Newcastle University. I, Shantanu P Sengupta, declare that data and all other information presented in this thesis is the result of my original research. I confirm that work done by others is clearly acknowledged and any published work is clearly attributed and the source stated. I certify that this thesis contains no material that has been submitted for any other academic degree and published material presented was the result of the research carried out during the course of the present doctoral study.

Abstract

Heart failure (HF) is a clinical syndrome causing impaired cardiac performance at rest or during stress. Heart failure with preserved ejection fraction (HFpEF) is a growing health problem associated with high mortality and morbidity. It is a complex multifactorial systemic syndrome with risk factors and mechanisms developing into long term clinical manifestations.

HFpEF accounts for half of all HF patients, and boasts similar re-hospitalization and mortality as HF with reduced ejection fraction (HFrEF). The current knowledge about the pathophysiology of HFpEF is growing with new research methodologies to understand its complexities. Examination of the determinants of cardiovascular performance during exercise in HFpEF may reveal novel pathophysiological mechanisms specific to HFpEF phenotype.

The overall aim of the thesis is to improve the understanding of pathophysiology of HFpEF. This aim was achieved by following objectives: i) provide evidence for use of a novel-technological advance for evaluation of cardiac function at rest and during stress; ii) define differences in cardiac response to pharmacological and physiological stress between HFpEF, HFrEF and controls, iii) define cardiac adaptations to a novel, personalized, home-based physical activity intervention in HFpEF.

The major findings of this thesis suggest: i) bioreactance and two-dimensional transthoracic echocardiography do not show acceptable levels of agreement for estimating cardiac output and cannot be used interchangeably due to disparity in results at rest and after pharmacological stress; ii) HF patients show reduced LV global longitudinal and left atrial reservoir strains, more pronounced in HFrEF than HFpEF at rest and exercise. Left atrial reservoir strain plays an important role responsible for exercise intolerance seen in HFpEF patients; iii) HFpEF and HFpEF patients exhibit different haemodynamic responses to dobutamine stress echocardiography and iv) Active-at-Home-HF intervention is acceptable, safe and feasible in HFpEF patients and helps in increasing daily physical activity levels and improving quality of life.

Dedication

This thesis is dedicated to my parents, Late Dr Pradeep Kumar Sengupta and Late Dr Monika Sengupta.

Acknowledgement

The success and outcome of this thesis were possible by the guidance and support of many people. I am incredibly privileged to have got this all along with the achievement of my work. It required a lot of effort from every individual involved in this project with me and I would like to thank them.

Firstly, I would like to thank my supervisors Drs Djordje Jakovljevic, Guy MacGowan, and Nduka Okwose. Your support and continuous help over the past four and half years have been of immense importance to what I have achieved today. Djordje, you have been a perfectionist. You have been a true mentor to me in the field of research and always helped me in understanding the value of doing good science. Your continuous support and encouragement towards me has helped me immensely through the rough times and also during happy moments of my thesis. You have believed in me and gave me the opportunity to prove myself in carrying out this research independently.

Nduka, thank you for supporting my write up and being a true critic. I thoroughly appreciate your complete involvement in reading my drafts and giving me important suggestions in improving them. I am also thankful to Dr MacGowan for supporting and encouraging me in every step of my research. You have always been available to advise and am thankful to you for taking deep interest in my area of work.

I would like to acknowledge Mr Dhananjay Raje for teaching me the details of statistics. His regular training sessions has helped me in understanding the true value of statistics in the field of research. I am extremely thankful to Dr Kunda, my research assistant and complete staff of Sengupta Hospital and Research Institute, Nagpur, India for being there and providing safe and welcoming environment for our participants. I would also like to thank Dr JC Mohan, who has been a great guide and a mentor to me always. Regular discussions with him has helped me in understanding and updating my knowledge about the advancements in the field of cardiovascular medicine.

Partho, my elder brother has always been a mentor to me in every aspect of life. I would like to thank him for being with me, guiding me and regularly encouraging me to do this research work. I am also grateful to him to teach me the skills to do high value research.

There are also very special people to whom I cannot fail to mention. My lovely wife, Rajasi for supporting me always, my adorable sons, Shubhan and Shahan for encouraging me and loving me always. Without you guys, it simply would have been a difficult task finishing this work. I love and appreciate you.

I would like to mention my mother, whom I lost during the period of my thesis work, but whose encouragement and blessings helped me to complete the uphill task of thesis. I would also like to express my deep gratitude to my late father, who has been a guiding force in my life.

Above all, I thank the Almighty God for all the blessings showered to me.

Table of contents

List of Tables

List of Figures

List of Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin-converting enzyme
ACEI	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
ADHF	Acute decompensated heart failure
AF	Atrial fibrillation
AHF	Acute heart failure
ALT	Alanine aminotransferase
ABPM	Ambulatory based pressure monitoring
ANP	A-type natriuretic peptide
ANS	Autonomic nervous system
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AST	Aspartate aminotransferase
AV	Atrio-ventricular
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
BPM	Beats per minute
BR	Bioreactance
BSA	Body surface area
CABG	Coronary artery bypass graft/grafting

CAD	Coronary artery disease
CCB	Calcium-channel blocker
CI	Cardiac index
CMR	Cardiac magnetic resonance
CO	Cardiac output
CPO	Cardiac power output
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
E/e’	Ratio of early diastolic wave and early wave in tissue doppler
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
GFR	Glomerular filtration rate
HbA1c	Glycated haemoglobin
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFmrEF	HF with mid-range ejection fraction
HFpEF	HF with preserved ejection fraction
HFrEF	HF with reduced ejection fraction
HR	Heart rate
ICD	Implantable cardioverter-defibrillator
IHD	Ischaemic heart disease
IVC	Inferior vena cava
LV	Left ventricular/left ventricle

LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
NICE	National Institute for Health and Care Excellence
NT-proBNP	N-terminal pro-B type natriuretic peptide
NYHA	New York Heart Association
RAAS	Renin Angiotensin aldosterone system
RCT	Randomized controlled trial
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
VF	Ventricular fibrillation
VT	Ventricular tachycardia

List of Publications and Presentations from Thesis

Manuscripts –published

Shantanu P. Sengupta, Kunda Mungulmare, Nduka C. Okwose, Guy A. MacGowan, Djordje G. Jakovljevic. Comparison of cardiac output estimates by echocardiography and bioreactance at rest and peak dobutamine stress test in heart failure patients with preserved ejection fraction. Echocardiography,37:10:2020:1603-1609

Shantanu P. Sengupta, Nduka C. Okwose, Guy A. MacGowan, Djordje G. Jakovljevic. Peak atrio-ventricular mechanics predicts exercise tolerance in heart failure patients. Int J Cardiol,2022 Jul 15;359:84-90

Manuscripts –in preparation

Shantanu P. Sengupta, Nduka C. Okwose, Guy A. MacGowan, Djordje G. Jakovljevic. The effect of a personalized, home-based physical activity intervention on quality of life and cardiac function in heart failure with preserved ejection fraction (to be submitted in January 2023 and is based on chapter 8)

Shantanu P. Sengupta, Nduka C. Okwose, Guy A. MacGowan, Djordje G. Jakovljevic. Cardiac response to pharmacological stress in heart failure reduced and heart failure preserved ejection fraction (to be submitted in February 2023 and is based on chapter 7)

Abstracts presented

Sengupta SP, MacGowan GA, Jakovljevic DG. Haemodynamic differences in response to physiological and pharmacological stress in heart failure with preserved ejection fraction. *European Society of Cardiology Heart Failure scientific session, 25-28 May 2019, Athens, Greece*

Sengupta SP, Mungulmare K, MacGowan GA, Jakovljevic DG. Comparision of cardiac output estimated by bioreactance and echocardiography at rest and peak dobutamine stress test in patients of heart failure with preserved ejection fraction. *American College of Cardiology scientific session, Chicago, 28-30, March 2020*

Sengupta SP, Mohan JC, MacGowan GA, Jakovljevic DG. Peak atrial longitudinal

strain predicts exercise tolerance in heart failure with preserved ejection fraction. *European Society of Cardiology scientific session, Digital, 27-30 August, 2021*

Sengupta SP, Masram S, Sawarkar S, Okwose NC, MacGowan GA, Jakovljevic DG. Haemodynamic effects of a novel, personalized, home-based physical activity intervention for heart failure preserved ejection fraction. *European Society of Cardiology Heart Failure scientific session, Online, 29 June to 1st July, 2021*

Faculty Invitation

Invited as a Faculty to **American Society of Echo (ASE) 2020 Virtual Experience** annual conference on 8-10 August 2020. Topic: **HFpEF in women**

Invited as a Faculty to **Cardiological Society of India,** annual conference on 3-5 December 2021. Topic: **Role of echocardiography in HFpEF**

Invited as a Faculty to **Heart Failure Association of India,** annual conference on 11-13 February 2022. Topic: **Understanding HFpEF phenotypes**

Invited as a Faculty to **Indian College of cardiology,** annual conference on 11-13 November 2022. Topic: **Diastolic stress echo-from basic to advance**

Invited as a Faculty to **Cardiological Society of India,** annual conference on 8-11 December 2022. Topic: **Demonstration of obtaining LV and RV strain values and their clinical significance**

Chapter 1: Introduction to heart failure

Heart failure (HF) is a complex clinical entity wherein the heart is unable to pump enough blood to meet the body's requirement for oxygen. HF causes symptoms of fatigue or dyspnoea at rest and/or exertion thus significantly affecting the quality of life (QOL).(Groenewegen et al., 2020) HF is an important public health issue across the globe and has become an emerging epidemic in last few years.(Groenewegen et al., 2020) The estimated prevalence of HF is around 64 million cases globally (9 per 1000 inhabitants).(Groenewegen et al., 2020) HF causes significant mortality and morbidity despite advancements in treatment and poses a heavy load on the health care system globally.(O'Connor et al., 2012) The precipitating factors of HF vary depending upon age, sex, co-morbidities and environmental factors. The pool of patients with HF is on the rise in developing countries affecting older but also younger age groups. This is because of growing prevalence of obesity, metabolic disorders, hypertension, and coronary artery disease. There have been reports of age dependent differences in risk factors causing HF which may explain differences in clinical phenotypes presented in different age groups.(Virani et al., 2021) These differences may further affect preventive and management strategies of HF.

1.1 Definition, symptoms and signs of heart failure

Heart Failure (HF) represents a clinical entity due to alteration in structural and/or functional parameters in heart resulting in reduced cardiac output and elevated cardiac pressure at rest or during exertion.(Ponikowski et al., 2016b, Yancy et al., 2013, McDonagh et al., 2021) HF is an outcome of a multitude of cardiac diseases. It is characterized by symptoms of breathlessness, and fatigue and signs of raised jugular venous pressure, lung crepitations and pedal oedema.(Ponikowski et al., 2016b)

1.2 Epidemiology and clinical burden

HF is a serious public health issue across the globe associated with increased morbidity and mortality. (Lam et al., 2011) The prevalence of HF is on the rise due to ageing population, better survival in patients having cardiovascular conditions such as acute coronary syndrome, diabetes and hypertension.(Conrad et al., 2018) It is around 1-2% in the general population and 10-15% in those over 70 years of age.(Lam et al., 2011) The major epidemiological data of HF comes from Europe and North America, with emerging data coming from developing countries suggesting that more than half the world's deaths from cardiovascular diseases happen in middle and low income

countries. Few studies have shown that the HF prevalence in Asian subcontinent is comparable with the western world, while in Australia it is around 1-2% based on national survey. (Naik and Narula, 2020) However, there is limited evidence from large epidemiological studies from African countries (Figure 1.1). HF symptoms are seen in 30% of all myocardial infarctions, 16% of men and 18% of women with diabetes and 12% of men and 8% of women with hypertension.(Kaesemeyer, 1994) In developed countries the prevalence of HF is around 1-2% of adult population. Heart failure with preserved ejection fraction (HFpEF) accounts for more than half of all HF patients. The prevalence of HF by echocardiography data in developed countries was around 12% in people more than 65 years of age.(Van Riet et al., 2016)

In UK more than a half million people live with a confirmed diagnosis of HF, i.e. >308,000 men and >250,000 women.(Bhatnagar et al., 2015) Conrad et al. in his work involving around 4 million subjects reported a prevalence of 1.6% from UK Clinical Practice Research Datalink.(Conrad et al., 2019) The recent Heart Disease and Stroke update in 2021 reports that in the US population, 6 million adults above the age of 20 years of age have HF, with prevalence higher in women than men over 80 years of age.(Virani et al., 2021) By 2030, HF prevalence of HF in USA will rise by 46% with an increase in medical treatment cost by 125% to $69.7 billion by 2030.(Benjamin et al., 2017, Mozaffarian et al., 2015, Virani et al., 2021) HF is an important medical cause for admissions in patients above 60 years.(Bui et al., 2013) HF accounts for ~2% of health budgets in developed countries.(Morton et al., 2018) It places a substantial financial burden on healthcare systems. In the UK around 2% of the NHS money is utilized for the treatment of HF patients, of which more than half is needed for HF related indoor admissions.(Cowie, 2017)

Few studies have provided lifetime risks for HF according to age and ethnicity. At 45 years of age, the lifetime HF risk by the age of 90 were 30-46% in white men, 32-39% in white women, 20-29% in black men and 24-46% in black women.(Huffman et al., 2013) But there are few issues regarding understanding the clinical burden of HF. It has been suggested that hospital records may not include all HF patients in data registries as records between primary and secondary care may not be synchronized in all countries.(Du et al., 2018) It is also apparent that HF patients may frequently have been admitted to hospital for non-cardiovascular causes so medical records may indicate HF-related hospitalization.

The global burden of HF is shown in Figure 1.1. The strongest evidence comes from North America and Europe.(Tromp et al., 2019) The prevalence of HF in Asian

countries is similar to Western countries but these should be considered with caution. Australia shows a prevalence of 1-2% based on its national survey, while in China it is about 3.5%.(Sahle et al., 2016, Guo et al., 2016) However, there are no population-based data in African countries.(Tromp et al., 2019)

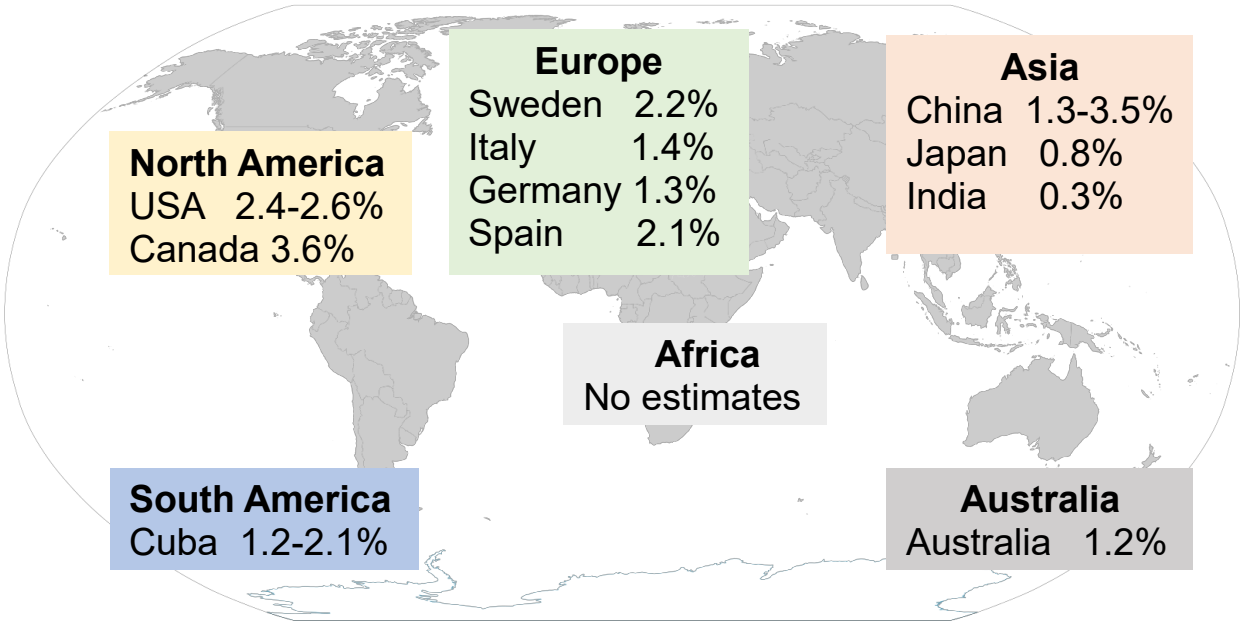

Figure 1.1 Prevalence of heart failure in population-based studies across the globe, in percentage/ region.(Groenewegen et al., 2020)

1.3 Aetiology of heart failure

HF syndrome is a chronic disease with intermittent acute decompensated phase requiring admission. HF patients can have mixed aetiologies and these may vary between developed and developing countries.(Yusuf et al., 2014) Multiple causes co-exist with various co-morbid conditions playing a role in the pathogenesis of the disease process. Presence of more co-morbidities is connected to poor quality of life and more severe HF symptoms. Coronary artery disease is the most common underlying cause of heart failure, followed by chronic hypertension, cardiomyopathies, valve dysfunction, cardiac arrhythmias/conduction problems, pericardial disease, adult congenital heart disease and infection.(Conrad et al., 2018)

Many times, it is difficult to ascertain the main cause of heart failure in presence of co-existing conditions like hypertension, ischaemic heart disease, type II diabetes mellitus, sleep apnoea syndrome, hypothyroidism, atrial fibrillation, etc.(Ponikowski et al., 2016a) It is important to take a proper history in all patients presenting with HF in

the hospital.(Conrad et al., 2018) In all patients of HF, the possibility of CAD should be ruled out by coronary angiography.

The Framingham heart study revealed hypertension as the most important risk factor for HF, with 30% in men and 20% in women.(Andersson et al., 2021) Presence of left ventricular hypertrophy on electrocardiography (ECG) in hypertensive patients increased the risk of developing HF by 15 times. Subsequently, the incidence of coronary heart disease increased and then HF started becoming more common as they started getting diagnosed accounting for 25% during 1950s to around 70% in 1970s.(Bangdiwala et al., 1992) During this time, the relative prevalence of valvular heart disease, mostly rheumatic heart disease declined dramatically. Also, there was a decline in the prevalence of hypertension among both sex. (Collaboration, 2017) This is because of advances in antihypertensive medicines contributing to the decline in hypertension.(Talwar et al., 2000)

In another study,(McDonagh et al., 1997) it was shown that CAD was the most common cause of LV systolic dysfunction in 95% symptomatic individuals and in 70% of asymptomatic individuals. Patients with symptomatic HF most commonly gave a past history of ischaemic heart disease. And valvular heart disease and hypertension are more prevalent in individuals with than those without HF.(McDonagh et al., 1997) Another study reported an undefined cause causing HF in a very high number of cases.(Cowie, 2017)

Presently developed countries show degenerative heart disease as the most common reason for valve involvement, while in developing countries, rheumatic heart disease is the leading cause. HF secondary to valvular heart disease reported worldwide is mostly secondary to rheumatic process. With the use of echocardiography to screen patients in developing countries, the prevalence and incidence has increased ten times.(Marijon et al., 2007)

Another important cause of HF both in developed and developing countries are different types of cardiomyopathies. It is difficult to find the global burden of this due to variations in practice patterns, diagnostic capabilities, and coding structure. Baldasseroni et al described that the most common variant in Italy was dilated cardiomyopathy in 38% of cases, ischaemic heart disease in 35%, 17% hypertensive cardiomyopathy and around 9% from other causes.(Baldasseroni et al., 2002) In developing continents like Africa, it has been suggested that infection, inflammation, and nutritional deficiency are main causes of HF.(Tromp et al., 2019)

1.4 Classification of heart failure

The present HF classification uses clinical symptoms and signs to define the stages of HF. Interestingly, most HF patients are asymptomatic and have functional and structural changes like left ventricular hypertrophy due to thick heart, systolic and/or diastolic problem or valve abnormality. Identifying and managing these presentations without apparent symptoms may halt or delay the progression of HF. ACC/AHA defines four stages of HF (Figure 1.2).(Yancy et al., 2013) Stages A and B are pre-HF stages with no apparent symptoms, while stages C and D are associated with apparent symptoms and signs. The clinical presentation of HF depends upon aetiology, ejection fraction by echo, functional status, time duration and disease severity.(Ponikowski et al., 2016b)

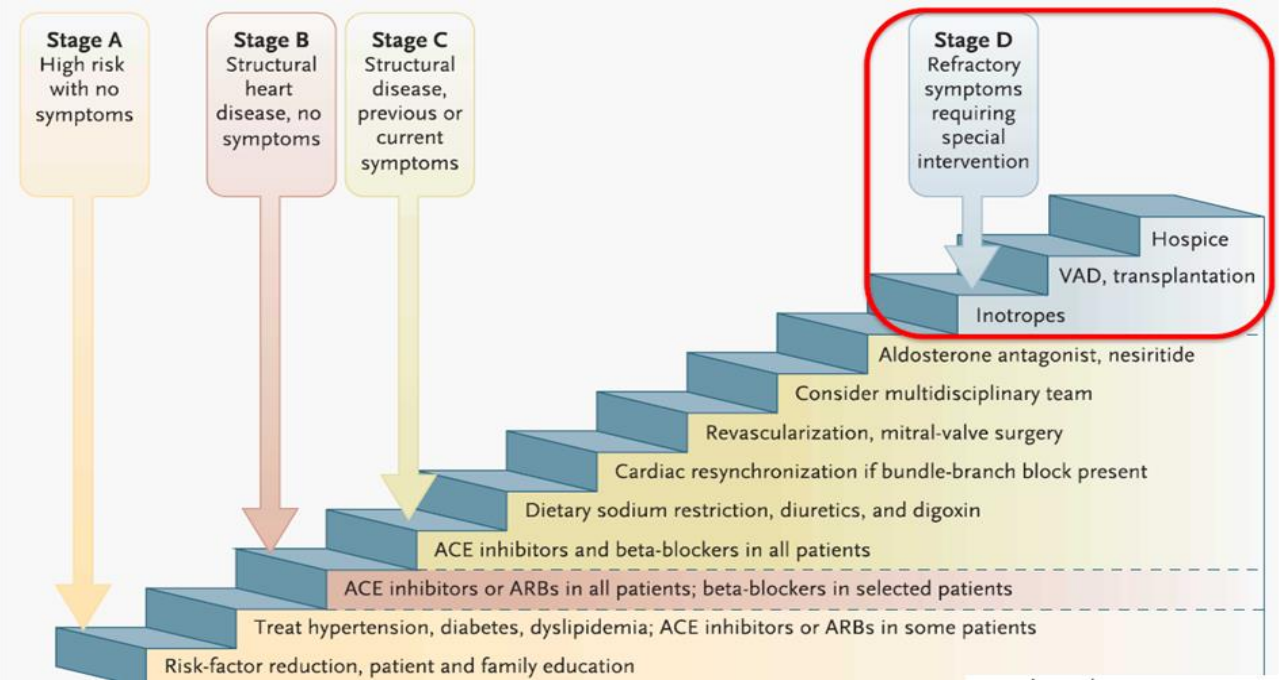

Figure 1.2 American College of Cardiology / American Heart Association classification of heart failure with indication of treatment strategies for each stage.(Brozena and Jessup, 2003)

1.4.1 Functional classification

New York Heart Association (NYHA) functional classification system for HF is based on the severity of patient symptoms and their ability to perform habitual physical activity and is widely used.(Scrutinio et al., 1994, McDonagh et al., 2021) Patients are divided into four categories according to their functional capacity and symptoms (Table 1.1).

Table 1.1 New York Heart Association and Weber classification of heart failure

Class	Patient Symptoms	Peak oxygen consumption / anaerobic threshold (ml/kg/min)
I	No physical activity limitation. Ordinary physical activity does not cause fatigue, palpitation, or dyspnoea (shortness of breath)	>20 / >14
II	Stable at rest. Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, or dyspnea	16-20 / 11-14
III	Marked limitation of physical activity. Stable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea	10-15 /8-11
IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. Unable to do physical activity	<10 / <8

Adopted from Lim et al. (Lim et al., 2018)

1.4.2 Types of heart failure according to left ventricular ejection fraction

In HF clinical guidelines published by the European Society of Cardiology (ESC), left ventricular ejection fraction (LVEF) forms a crucial parameter in diagnosis and management of HF.(Ponikowski et al., 2016b, McDonagh et al., 2021) HF is classified as HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), with the cut-off LVEF of 50% to suggest HFrEF vs HFpEF.

In 2021, ESC guidelines proposed a new entity of HF i.e. heart failure with mildly reduced ejection fraction (HFmrEF) when LVEF is between 40–49%.(Mcdonagh et al., 2021) Patients with HFmrEF present mild systolic dysfunction with various grades of diastolic dysfunction.

Treatment options for HFrEF are evidence-based and highlighted in national and international clinical guidelines. The treatment for HFpEF is evolving with recent reports showing some promising role of SGLT2 inhibitors in this clinical condition. Patients with HFpEF present with LVEF>50%, thick LV wall, bigger left atrial volume, diastolic dysfunction and raised left ventricular filling pressures.(Mullens et al., 2009) Earlier classification used the terms diastolic HF and systolic HF was easier to understand but had limitations.(Ommen et al., 2000) All patients of systolic HF have diastolic dysfunction and all patients of diastolic HF need not have systolic dysfunction but can have subclinical left ventricular dysfunction.(Aizawa et al., 2011) HF is a heterogenous syndrome in which the disease progression is associated with structural

and functional alterations which leads to different phenotypes and clinical presentations. Also, many HF patients have atrial dysfunction along with left ventricular dysfunction or can have isolated atrial dysfunction.(Kim et al., 2020, Frydas et al., 2020)

Hence, terminology i.e. HFrEF and HFpEF are now used instead of systolic and diastolic HF, as per European and American clinical guidelines.(Ponikowski et al., 2016c, Ponikowski et al., 2016b, Bozkurt et al., 2021) Subclinical left ventricular systolic dysfunction defines a clinical condition of a patient presented with no symptoms but with reduced left ventricular global longitudinal strain.(Yancy et al., 2017) These patients carry a greater risk of morbidity and mortality, thus early diagnosis is crucial.

1.4.3 Acute vs chronic heart failure

HF can present as acute or chronic HF based on the temporal course of the disease. Acute heart failure can be further divided into *de novo* acute HF and acute decompensated HF.(Raffaello et al., 2020) Both are associated with increased mortality, morbidity and worsened outcomes, although less severe in *de novo* acute HF than acute decompensated HF. *De novo* acute HF is defined as acutely deteriorated cardiac function without known cardiac etiology, and acute decompensated HF is defined as development of HF which can occur suddenly or gradually in patients having underlying pre-existing cardiac condition.(Joseph et al., 2009) It can be the first presentation of the disease or can be due to clinical deterioration of a patient with chronic stable HF. ASCEND-HF trial showed that HF diagnosed and managed a month prior to hospital admission is associated with relief from breathlessness and also helps reduce post-hospitalization mortality in acute as compared to chronic HF.(Greene et al., 2017)

Conditions like acute coronary syndrome, myocarditis and acute infective endocarditis can lead to acute HF. Acute onset HF can be seen in patients of dilated cardiomyopathy, infective endocarditis, acute onset mitral or aortic regurgitation and acute rheumatic fever.(Greene et al., 2015) Few of these entities respond to therapy but the remaining progress to chronic HF. Acute coronary syndrome (ACS) and infective causes have been found to the two most important precipitating factors to *de novo* acute HF and acute decompensated HF, respectively.(Pranata et al., 2020) Hypertension is more common in *de novo* acute HF and conditions like hypertension,

diabetes, IHD, COPD, AF and a presence of stroke or transient ischaemic attack, are mostly seen in the acute decompensated HF patients.(Pranata et al., 2020)

1.4.4 Other terminology used to differentiate types of heart failure

Other commonly used terminology in clinical practice to differentiate HF includes stable, compensated, and congestive HF.(Kaesemeyer, 1994) These terms are applied to patients depending upon their clinical stage at the time of presentation and examination. The ESC defines compensated/stable HF as “HF patient under treatment and whose signs and symptoms have not altered for at least 1 month”.(Ponikowski et al., 2016b) Congestive HF are patients with acute or chronic HF who have increased volume overload.

1.5 Sex differences in heart failure

HF is one of the main causes of morbidity and mortality in older males and females. The lifetime risk estimated for HF is around 20% and is comparable between males and females.(Cesaroni et al., 2021) However, the biological response to HF precursors are different in both sexes. In response to pressure or volume overload, female hearts develop hypertrophy more often than males, who more often demonstrate eccentric hypertrophy.(Sotomi et al., 2021) After ischemic cardiac insult, adverse cardiac remodelling is more pronounced in males than females. Also, females have lower incidence of HF compared to males at all ages.(Eisenberg et al., 2018) However, the prevalence of HF is similar in both sexes, as HFpEF is found to be more common in women.(Sotomi et al., 2021) Hypertension, diabetes and obesity predispose women to HF more than men.(Eisenberg et al., 2018) By contrast, HFrEF affects more men than women. Inflammation and associated fibrosis are associated with sex-specific role in the pathogenesis of HFpEF. Women with HFpEF are noted to demonstrate a higher life expectancy than men.(Ofstedal et al., 2019)

Cardiovascular Health Study and the Multi-Ethnic Study of Atherosclerosis showed men had almost twice lifetime risk for occurrence of HFrEF than women (11% vs. 6%) while it was similar for HFpEF.(Gottdiener et al., 2000, Bild et al., 2002) Framingham Heart Study showed that frequency of HF was twice in males with diabetes and five times higher in females with diabetes. A large meta-analysis covering more than 45 cohort studies, which included 12 million subjects, revealed the relative risks for HF in patients of diabetes mellitus was higher in women than in men.(Kwak et al., 2021)

Recent reports have shown that women are less included in clinical trials.(Reza et al.,

2020) Women receive lower average dosages of HF drugs, show more side effects and receive less medical therapies for advanced HF like cardiac transplants and ventricular assist devices.(Blumer et al., 2021) Sex does not alter overall mortality outcomes in patients who are hospitalized for decompensated HF, but has been associated with more readmissions in HFpEF and HFrEF patients.(Lopez-Vilella et al., 2021) Thus, it is warranted that a more personalized patient oriented model is advocated in the management of HF patients.

1.6 Pathophysiology of heart failure

HF has traditionally been regarded as a condition where there is an injury to the myocardium which causes the failure of ventricles to eject out adequate blood to meet the demands of the peripheral tissues.(Packer, 1992) HF involves progressive left ventricular remodelling and alteration in haemodynamic, neurohormonal, metabolic, molecular and cellular compensatory mechanisms (Figure 1.2).(Francis, 2001) Death of cardiac myocytes (apoptosis) leads to excessive myocardial stress and eccentric hypertrophy of the remaining myocytes. This causes the ventricle to change shape from elliptical to spherical, followed by fibrosis and progressive left ventricular dilatation resulting in reduced contractile efficacy.(Aizawa et al., 2011) The common causes of cardiac dysfunction and remodelling are ischaemia, myocarditis, cardiomyopathies, valvular heart problem, pericardial diseases, diabetes mellitus, hypothyroidism, and systemic hypertension.(Arrigo et al., 2017) These conditions may directly impact cardiac function via volume - pressure overload.(Gottdiener et al., 2000, Packer, 1992) Evidence-based therapy is available for HFrEF patients, whereas the discovery of optimal treatment for HFpEF is still ongoing. Improved understand of HF pathophysiology is needed particularly in the functional, structural and mechanistic aspects of HFpEF compared with HFrEF. The main hallmark of HFpEF is left ventricle (LV) relaxation abnormality due to alteration in structure and changes in cellular levels of myocardium.(Borlaug and Paulus, 2011) HFpEF patients have associated co-morbidities like diabetes mellitus, hypothyroidism, obesity, systemic hypertension, chronic obstructive pulmonary disease, sleep apnoea syndrome, renal insufficiency, liver disease and cancer.(Francis, 2001) All these co-morbidities are associated by a rise in inflammatory markers like C-reactive protein and IL-6, and endothelial dysfunction. Endothelial cells occupy around 64% of non-cardiomyocytes and endothelial dysfunction is more frequent in HFpEF than HFrEF.(Schwinger, 2021) Most of the comorbidities and risk factors are common for both HFrEF and HFpEF but few

are different between them. There is significant cardiomyocyte loss seen in HFrEF which causes systolic dysfunction. This myocyte loss can be due to myocardial infarction, myocarditis or genetic mutation, or valvular disease.(Borlaug et al., 2006) These results in eccentric remodelling with presence of fibrosis are observed in HFrEF, while HFpEF is characterized by concentric cardiomyocyte hypertrophy. Both HFpEF and HFrEF show different involvement in cardiac titin and calcium levels.(Van Heerebeek et al., 2006) HFmrEF can progress into either HFrEF or HFpEF. It has been observed that CAD is the most commonly associated with HFmrEF like that in HFrEF.(Vedin et al., 2017)

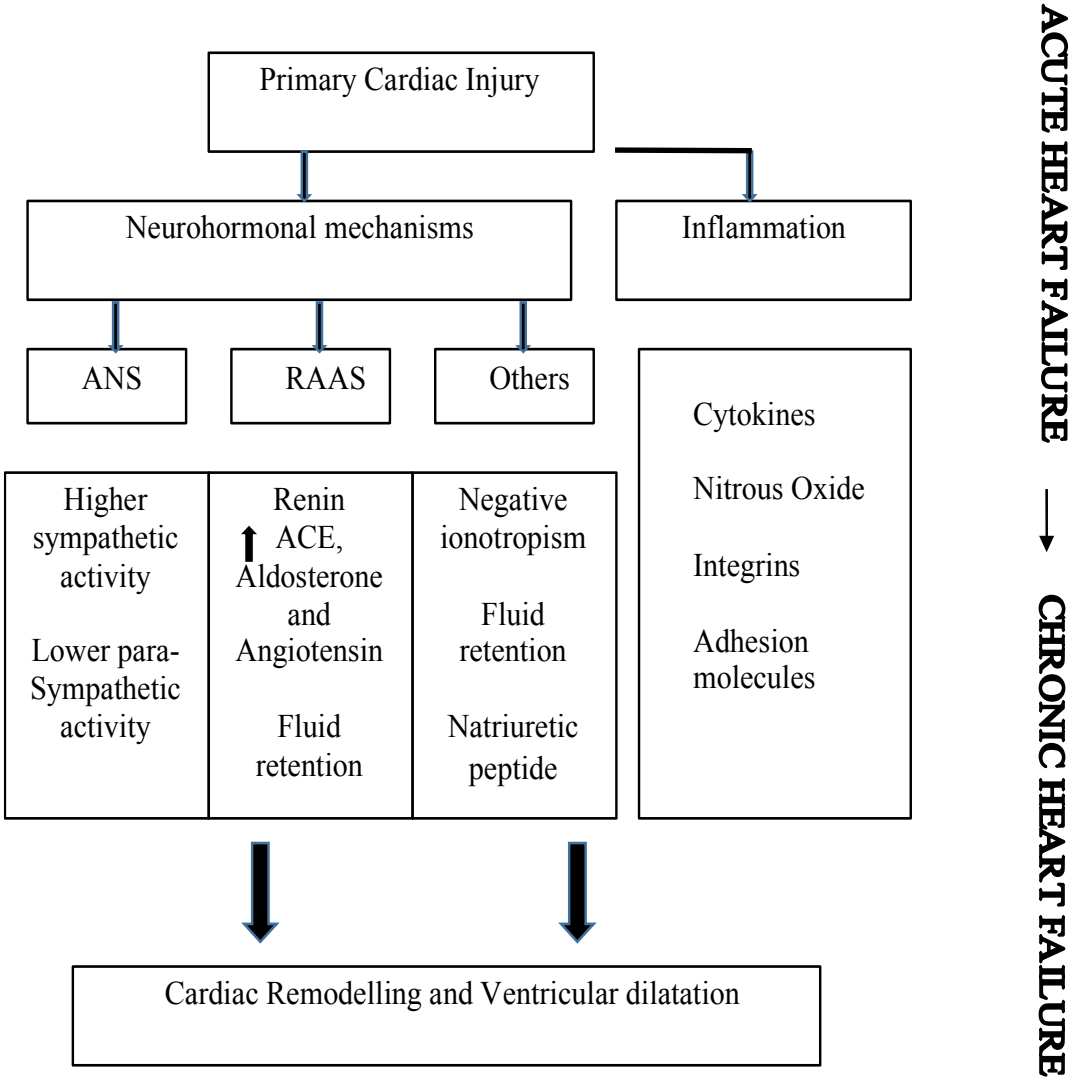

Figure 1.3 Compensatory mechanism in Heart Failure. ANS- autonomic nervous system, RAAS- renin-angiotensin-aldosterone system. Adopted from Francis GS et al.(Francis, 2001)

1.6.1 Haemodynamic and functional alterations

Significant alterations in hemodynamic function occur in HF. These alterations may be caused by altered cardiac energy metabolism.(De Jong and Lopaschuk, 2017) Various factors contribute to altered haemodynamics in HF which contribute to reduced cardiac function and cardiac output both at rest and/or during exertion. These include alteration in LV systolic and diastolic function, LA function, ventricular remodelling, right ventricular (RV) function, ventriculo-arterial coupling and alteration in pulmonary vasculature.(Borlaug and Kass, 2009) Invasive haemodynamic assessment in the catheterization laboratory can be clinically useful in these cases. However, non-invasive methods like echocardiography give similar information like invasive methods.(Borlaug and Kass, 2009) Understanding pathophysiology is very important for the management of patients and also having potential to advance in treatment of HF.

Heart failure causes decreased cardiac output both at rest and after stress and if not treated timely may progress in more advanced disease.(Ponikowski et al., 2016b, Neubauer, 2007) The reduction in cardiac output stimulates sympathetic nervous system and inhibits the parasympathetic tone which maintains tissue perfusion. This stimulates the remaining myocardium to contract and increases peripheral vascular resistance.(Dargie, 1999) Such vasoconstriction increases the afterload and LV filling pressures. The decrease in cardiac output and increase in sympathetic stimulation activates renin secretion by the kidneys and activation of renin-angiotensin-aldosterone system (RAAS). Angiotensin II is a potent vasoconstrictor of the renal and systemic vasculature, it stimulates the secretion of aldosterone and contributes to endothelial dysfunction.(Mcdiarmid et al., 2013) Aldosterone causes retention of water and sodium by kidneys and precipitates pulmonary and peripheral oedema, which are classical symptoms of heart failure.

1.6.2 Structural alterations

Any insult to the myocardium, either acute or chronic and loading conditions (volume or pressure) will trigger cardiac structural and subsequent functional changes.(Kehat and Molkentin, 2010) These changes can be physiological which are transient or pathological like fibrosis. These are seen in cardiomyocytes which may hypertrophy or show apoptosis or necrosis, proliferation of fibroblasts, or affect endothelium and extracellular matrix.(Packer, 1992) These adaptive processes generally involve the entire heart.(Kehat and Molkentin, 2010) Structural changes usually present as

ventricular hypertrophy, increase in chamber size, and disorganization of cardiomyocytes. Subsequently the wall tension rises and subendocardial perfusion decreases which reduces the cardiac function.(Obokata et al., 2018)

1.6.3 Metabolic alterations

The metabolic changes in HF are complex and are not only dependent on the severity and type of heart failure, but also on the co-existence of comorbidities like obesity and diabetes.(Schwinger, 2021) In a normal heart, six kg of adenosine three phosphate (ATP) is utilized daily.(Gibbs, 1978) The major cardiac energy metabolism is fatty acids in normal resting stage and shifts to glucose metabolism in stress conditions like ischemia and pathological hypertrophy .(Li et al., 2021) The energy production pathway depends on the metabolic demand caused by intrinsic (i.e. health vs disease) or extrinsic (i.e. resting state, exercise) factors. Under normal conditions, energy in heart is derived from ATP which is the result of oxidative phosphorylation of fatty acids or glycolysis. With increase in energy demand a substrate shift from phosphorylation to glycolysis occurs.(Gibbs, 1978, Doenst et al., 2013) During remodelling in HF, there is a change in this energy metabolic substrate utilization.(Li et al., 2021) The metabolic remodelling in the failing heart represents a transition from the normal to the ischemic condition and represents a protective compensatory mechanism which is physiological to enhance its working capacity. However, if this status continues for a longer duration, it causes toxic substances to accumulate resulting to the progress to HF. Increased concentration of fatty acids precipitates lipotoxicity, which worsens HF by causing apoptosis and mitochondrial dysregulation and insulin resistance.(Bertero and Maack, 2018)

1.6.4 Molecular and cellular alterations

Heart failure syndrome involves changes at the molecular and cellular level. (Aizawa et al., 2011, De Jong and Lopaschuk, 2017) With the gradual dilatation of ventricles over time there is a decrease in the overlap of sarcomere.(Kehat and Molkentin, 2010) Once the stretch of sarcomere reaches the maximum, there is a decline in the ejected volume of blood reducing stroke volume cardiac output and raising filling pressures.(Kass et al., 2010) The kidneys retain fluid and salt which increases the preload and improves tissue perfusion by activation of the renin-angiotensin pathway.(Felker et al., 2011, Yancy, 2018)

Rise in ventricle volume helps improve the cardiac output and stroke volume, but at

the cost of increase wall stress by the 'law of Laplace' which states that LV wall stress is directly depended to LV radius and pressure.(Fowler, 1971) This stimulates hypertrophy by altering sarcomeres lengthening.(De Jong and Lopaschuk, 2017) Progressive volume overload with loss of active contractile myofibers causes loss of contractile capability, raised oxygen demand in myocardium, ischemia in sub-endocardial region and worsening HF.

Onset of cardiac injury stimulates compensatory mechanisms to maintain stroke volume and cardiac output. In such circumstances adaptions occur in the myocardium, vasculature, neurohormonal system and haemodynamic response.(Packer, 1992) In HFrEF these adaptions are well defined (Packer, 1992, Blair et al., 2020, Dick and Epelman, 2016, Francis, 2001, Lam et al., 2010, Nauta et al., 2020) but their better understanding in HFpEF is warranted.(Francis, 2001)

Inability of ventricle to pump blood during systole causes rise in both LV end-diastolic pressure and volume. This causes a compensatory increase in ventricular contraction of the healthy myocytes based on the Frank-Starling mechanism.(Packer, 1992) The decreased cardiac output causes a reduced blood flow to the aorta which activates baroreceptors to stimulate the sympathetic nervous system activation.(Borovac et al., 2020) This increases the force of contraction of non-injured myocardium to maintain the stroke volume and blood pressure.(Packer, 1992)

The physiological activation of neurohormonal pathway for maintaining cardiac output in turn leads to progression of HF.(McDiarmid et al., 2013) Excessive sympathetic stimulation is associated with cardiomyocyte apoptosis, focal necrosis and hypertrophy.(McDiarmid et al., 2013)

LV secretes natriuretic peptides like B-natriuretic peptide in response to myocardial stretch in order to balance the progressive vasoconstriction and sodium retention caused by activation of RAAS and sympathetic nervous system.(Adams et al., 2005) Natriuretic peptides blunt the baroreceptor reflex and cause cardiac sympathetic inhibition resulting in cardiac unloading, reduction in systemic vascular resistance and subsequently in cardiac output.(Dokainish et al., 2017, Ebert and Cowley, 1988, Kelder et al., 2011) There is also a postulation that alteration in mitochondrial substrates occur including decreased electron transport chain work, stimulation of reactive oxygen species, deranged metabolic substrate uptake and mitochondrial dynamics, and alteration in ion homeostasis cause cardiac dysfunction.(Marin-Garcia, 2003) These mitochondrial dysfunction may be the future target for treatment of heart failure.(Marin-Garcia, 2003, Dick and Epelman, 2016) Also the role of inflammatory cells and

pathways in HF has gained attention.(Dick and Epelman, 2016) HF is also associated with raised cytokines which stimulate inflammation (IL-1β, IL-6, IL-8, TNF-α, NF-κb, etc). But anti-inflammatory drugs have not shown any benefit in HF treatment and so inflammation is considered now as a complication and not a cause of HF.(Marelli-Berg and Aksentijevic, 2019, Chen et al., 2015) Recently, canakinumab, an IL-1β inhibitor has been shown a significant prognostic marker in HFrEF.(Briasoulis et al., 2016) Suppression of inflammatory biomarkers of fibrosis (sST2, galectin-3), have also been associated with better prognosis in HF.(Emdin et al., 2018)

Systemic inflammation can trigger innate immune response which can induce cardiac hypertrophy and fibrosis.(Marelli-Berg and Aksentijevic, 2019) These are due to the release of inflammatory cytokines and transcription factors, which stimulate LV remodelling, hypertrophy and fibrosis. (Frangogiannis, 2012) Microvascular inflammation stimulates secretion of transforming growth factor β (TGF-β) by monocyte-derived macrophages.(Kehat and Molkentin, 2010) This process is pro-fibrotic as myofibroblasts are formed from fibroblasts. Myofibroblasts deposit collagen which in turn may stimulate fibrosis.(Paulus, 2020) The immune-inflammation mechanism has also shown to mediate cardiac extra-cellular matrix remodelling by augmenting ventricular stiffness.(Paulus, 2020, Frangogiannis, 2019) LV stiffness is a hallmark of HFpEF which facilitates diastolic dysfunction. The stiffness is raised because of extracellular deposition of collagen along with reduced elasticity of titin triggered by systematic inflammation, IL-1β and other cytokines.(Paulus, 2020)

1.7 Diagnosis of heart failure

The accurate and timely diagnosis of HF is mandatory for proper management to prevent mortality and morbidity. The following diagram (Figure 1.2) demonstrates algorithm for diagnosing HF.(Leng and Partridge, 2018) A detailed history is needed for the presenting complaints and reasons for any precipitation of symptoms. This should be supported by detailed clinical examination for signs of heart failure. Any history of coronary artery disease requires urgent expert consultation by a cardiologist. ECG, echocardiography and serum natriuretic peptide form cornerstone for the diagnosis of HF and to differentiate between HFrEF, HFmrEF and HFpEF or any other associated cardiac abnormality. Presence of normal ECG is unlikely in HF patients. Blood samples for assessment of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT pro-BNP) are useful in HF diagnosis. BNP levels of less than 35 pg/ml or NT pro-BNP below 125 pg/ml make HF diagnosis unlikely. Along with

this blood samples for complete blood count, renal and liver function tests, blood sugar levels and thyroid profile should always be done. A chest x-ray should be performed for evidence of cardiomegaly, pulmonary congestion and associated pulmonary disease. A detailed echocardiography is needed for look at the LV and RV systolic and diastolic function, valvular function, regional wall motion abnormality and pulmonary hypertension.

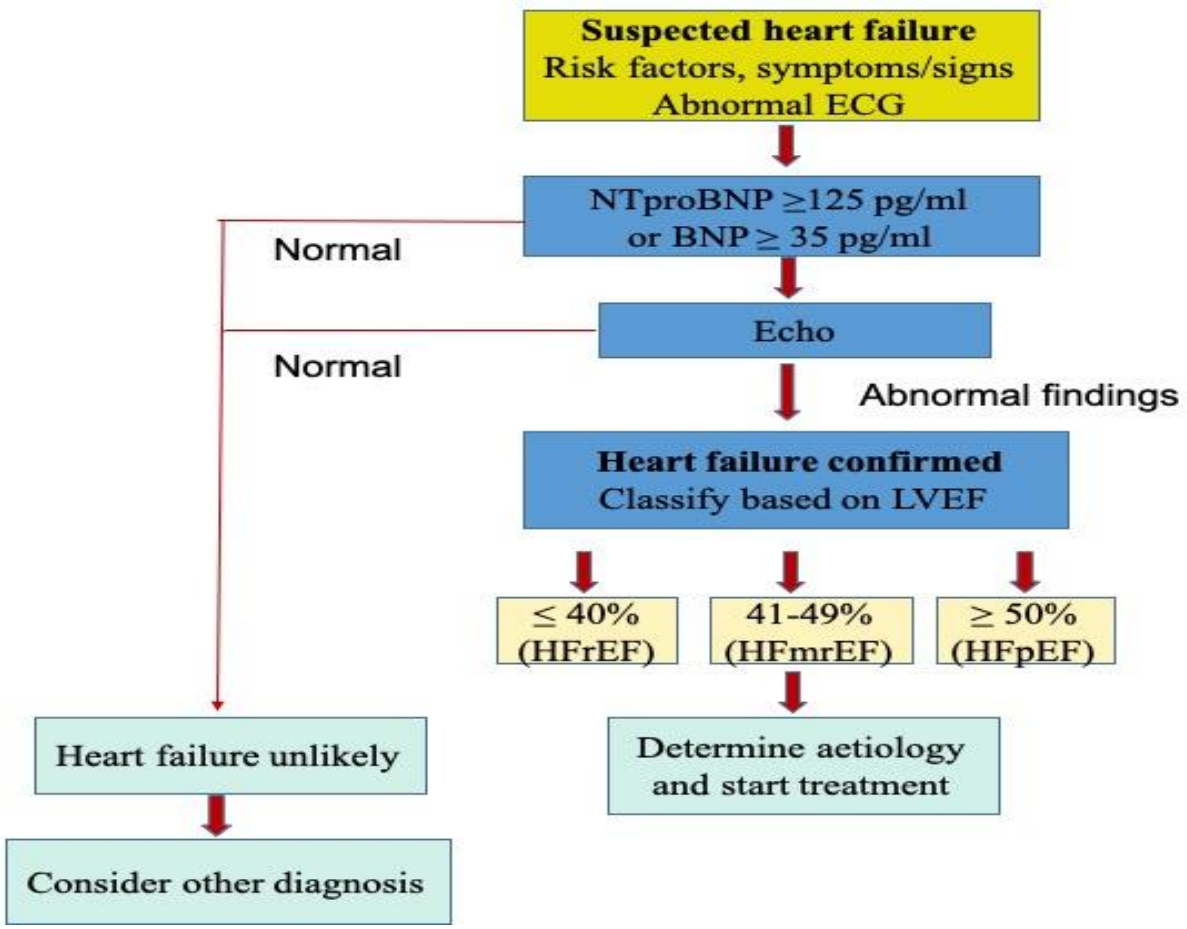

Figure 1.4 Diagnostic algorithm of heart failure clinical pathway (adopted from ESC guidelines 2021). NTproBNP - N-terminal pro b-type natriuretic peptide, BNP - b-type natriuretic peptide, LVEF- left ventricular ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFmrEF- heart failure with mildly reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction

1.8 Management of heart failure

Heart failure management has been evolving with recent evidence showing benefits in treatment of HFrEF with respect to reduction in mortality and hospitalization and betterment in quality of life and functional capacity. However, there has been no ground breaking pharmacologic treatment for HFpEF which impacts the outcome of these patients. HFrEF management involves pharmacological therapy, device therapy and lifestyle management strategies.

1.8.1. Pharmacological therapy

The aims of management of HFrEF patients are to reduce patients symptoms, enhance exercise capacity, improve quality of life (QOL), prevent recurrent admission and decrease mortality.(Yancy et al., 2006, McDonagh et al., 2021) These can be managed by targeting the following:

a. Targeting Renin-Angiotensin System (RAS) with Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin receptor blockers (ARB's)
b. Use of Beta-blockers
c. Volume status optimization with diuretics
d. Use of mineralocorticoid receptor antagonists (MRA's)
e. Angiotensin receptor-neprilysin inhibitors (ARNI)
f. Sodium-glucose cotransporter-2 (SGLT2) inhibitors
g. Ivabradine
h. Digoxin
i. Isosorbide di nitrate with hydralazine

a. Targeting Renin-Angiotensin System (RAS) with ACE Inhibitors (ACEI) and Angiotensin receptor blockers (ARB's)

Initiation of ACEI helps in reduction in symptoms, decrease admission and significantly improves prognosis in HFrEF patients.(Ponikowski et al., 2016b, Arendse et al., 2019) ACE inhibitors are useful in all stages of HF patients (mild, moderate and severe HF) due to any aetiology.(Investigators et al., 1991, Packer, 1992) Meta-analysis of multiple trials with ACEI showed a significant advantage in lowering hospitalization and all-cause mortality in patients of HFrEF.(Garg and Yusuf, 1995) It is recommended that all patients of HFrEF due to any cause should use ACEI.(Ponikowski et al., 2016a)
Use of Angiotensin-receptor blockers (ARBs) can be used if ACEI is not tolerated. They have also been to shown to provide significant haemodynamic, neurohormonal, and clinical advantage in patients with HFrEF.(Cohn et al., 2001, Pfeffer et al., 2015) Trials comparing ARBs with placebo have shown positive effects of ARBs in reducing mortality and hospitalisation in HFrEF patients.(Yusuf et al., 2003) However, ACEI are not superior to ARB and vice-versa in head to head comparison in HFrEF patients.(Tai et al., 2017) There are no specific studies focusing the use of ACEI or ARB in patients with HFmrEF.(McDonagh et al., 2021)

b. Use of Beta-blockers

Beta-blockers in patients of HFrEF significantly decrease cardiovascular mortality, sudden death and hospitalization.(Dargie, 1999, Kulbertus, 1999) Beta-blockers are essential treatment along with other standard medicine in HFrEF management. The various beta-blockers being used are cardio-selective beta-blockers like long acting metoprolol and bisoprolol; and carvedilol, which inhibit alpha-1, beta-1, and beta-2 receptors.(Writing et al., 2021) The present ESC guidelines recommend that beta-blockers should be initiated immediately once the diagnosis of HFrEF is made.(McDonagh et al., 2021) However, these guidelines have not provided any recommendation of usage of beta-blockers according to heart rhythm as studies have not shown any advantage in HFrEF with AF.(McDonagh et al., 2021) Beta-blocker have not been studied exclusively in HFmrEF.(McDonagh et al., 2021) Many patients with HFmrEF will have associated CAD, necessitating initiation of beta-blocker in them.

c. Volume status optimization with diuretics

Diuretics are essential in acute settings in intensive care management of HF. The main aim of diuretic treatment is to optimize the volume status without causing life threatening hypotension or renal insufficiency. Diuretics do not improve morbidity in patients with HF.(Felker et al., 2020) Intravenous diuretics are the choice as first line therapy in HF patients who have high filling pressure and have volume overload.(Ponikowski et al., 2016b) For this purpose, loop diuretics are initially used. The dose should be titrated carefully so it does not cause hypotension or alter renal function. Optimal use helps in improving urine output, dyspnoea and also helps in weight reduction.(Felker et al., 2011)As in all HF patients, diuretics should be used for reducing congestion in patients of HFmrEF also.(McDonagh et al., 2021)

d. Use of Mineralocorticoid receptor antagonists (MRA's)

Use of MRA (spironolactone, eplerenone) along with ACEI/ARBs and b-blockers has helped in reducing cardiovascular mortality by 20-25% in patients taking standard therapy.(Pitt, 2003, Pitt et al., 1999) A meta-analysis involving 1525 patients in 14 trials, n = 1575 showed an improvement of around 3% in LVEF with significant improvement in patient symptomatology after the initiation of MRA's in patients with HFrEF.(Phelan et al., 2012) Spironolactone is a non-selective mineralocorticoid inhibitor and eplerenone is a selective blocker and both are equally effective.(Pitt et al., 2003) However MRAs have not been studied in HFmrEF, but can be used in them.(McDonagh et al., 2021)

e. Angiotensin receptor-neprilysin inhibitors (ARNI)

The PARADIGM-HF trial has been a landmark trial which demonstrated that sacubitril/valsartan was superior to ACEI in HFrEF patients.(McMurray et al., 2014) ARNI can now be used in stable patients with HFrEF who are receiving ACEI and B-blockers, after stopping ACEI for 36 hours. In a meta-analysis, ARNI improves LV size, decreases end diastolic volume and causes reverse LV remodelling compared to ACEI/ARB in HFrEF.(Yan et al., 2021) ARNI also improves quality of life and health status in patients of HFrEF. (Khariton et al., 2019, Moon et al., 2021) ARNI in patients with HFpEF was studied in PARAGON trial.(Solomon et al., 2019) However it did not show any significant effect in reducing rate of hospitalisation due to HF and deaths from cardiovascular disease in HFpEF patients. Combined assessment of PARAGON-HF and PARADIGM-HF trials showed beneficial effect of ARNI in HFmrEF in preventing HF admissions.(Solomon et al., 2020)

f. Sodium-glucose cotransporter-2 (SGLT2) inhibitors

SGLT2 inhibitor is being used as an antidiabetic drug and is able to lower the blood sugar levels and HB1Ac.(Zinman et al., 2015) It also has a weight lowering action and helps in visceral fat loss in diabetic patients. It was unexpectedly shown to provide cardiovascular protective effects in diabetic patients with cardiovascular risk. Previous studies have shown that these agents lower the risk of death or HF hospitalisation in patients with HFrEF who are either diabetic or non-diabetic.(Genuardi and Mather, 2021) The Empagliflozin Cardiovascular Outcome Event Trial in type 2 diabetes mellitus (EMPA-REG OUTCOME) study, was the first large-scale RCT which evaluated the role of empagliflozin on cardiovascular mortality and morbidity in patients with type 2 diabetes with high cardiovascular risk.(Zinman et al., 2015) Pooled meta-analysis data also showed a lower incidence of cardiovascular death or admissions for HF in HFrEF patients taking both SGLT2i and ARNI.(Yan et al., 2021) DAPA-HF trial showed the long term protective effects of dapagliflozin as compared to placebo on mortality and morbidity in patients of HFrEF.(McMurray et al., 2019)

g. Ivabradine

Being a selective inhibitor of pacemaker (I*f)* current in sinoatrial node, Ivabradine helps in reducing heart rate without any effect on blood pressure.(Swedberg et al., 2010) Its use is only for patients in sinus rhythm. Ivabradine has been shown to reduce the endpoint of cardiovascular death in HFrEF patients due to a decrease in HF

hospitalisation.(Swedberg et al., 2010)There is inadequate data on use of this drug in patients of HFmrEF.(McDonagh et al., 2021)

h. Digoxin

Digoxin decreases admissions due to HF but has no advantage in improving longevity in HFrEF patients.(Digitalis Investigation, 1997) Benefits are seen in all spectrum of HFrEF patients despite of any rhythm abnormality and aetiology of HF (ischemic or non-ischemic) along with other medications. However, digoxin use in HFrEF with atrial fibrillation has not been evaluated in randomised control trials. It is also important to check serum digoxin levels as the drug has a small safety profile and levels should be maintained <1.2 ng/ml.(Rathore et al., 2003) Use of digoxin should be done carefully in HF patients who are females, elderly, undernourished and having hypokalemia. In patients of HFmrEF in sinus rhythm, digoxin showed a trend towards lesser hospitalisation, but no change in mortality.(Abdul-Rahim et al., 2018)

i. Isosorbide dinitrate with hydralazine

The use of Isosorbide dinitrate with hydralazine helps in decreasing preload and afterload.(Taylor et al., 2004) Hydralazine has an advantage of preventing nitrate tolerance which helps in avoidance of nitrate free periods. The main advantage of this combination has been shown to benefit African American patients.(Taylor et al., 2004)

1.8.2 Device therapy

Device therapy in HF includes implantable cardiac defibrillator (ICD), cardiac resynchronisation therapy (CRT) and left ventricular assist device (LVAD). The present ESC guidelines recommend ICD for primary prevention in HF patients who have symptoms along with LVEF ≤ 35% despite being for 3 months on optimal medical therapy.(Ponikowski et al., 2016d, McDonagh et al., 2021) ICDs also reduce mortality in patients who have survived from cardiac arrest and also patients who have documented evidence of sustained ventricular arrhythmias. In few clinical conditions like hypertrophic obstructive cardiomyopathy with sudden cardiac death risk, dilated cardiomyopathy, syncope in a patient of cardiac sarcoidosis, or myocardial scarring are indications for ICD regardless of LVEF.(Al-Khatib et al., 2018) Interestingly ICD implantation in patients with recent myocardial infarction with LVEF ≤ 35% did not demonstrate reduction in sudden death or death due to ventricular tachyarrhythmia.(Al-Khatib et al., 2018) Role of CRT therapy is useful in i) HF patients having class III symptoms and LVEF ≤35%, class IV and few class II patients or ii) LBBB of ≥150 ms

with dysynchrony and LVEF ≤ 35% despite optimal medical management who can live for more than 2 years.(Guha et al., 2018, McDonagh et al., 2021) When used properly CRT reduces morbidity and mortality and also improves the QoL.(Naik et al., 2018) HFrEF due to ischaemia show less recovery of LV systolic function due to presence of scar tissue. LVAD is now being used currently for the following situations i) as a bridge to heart transplant for end stage HF patients, ii) as a destination therapy for patients who are unable to go for heart transplantation, iii) as a bridge to decision for those patients who are very morbid during admission and their willingness for heart transplant is unknown and iv) as a bridge to recovery in myocarditis patients who have a possibility of cardiac recovery.(Ponikowski et al., 2016b) There are few devices which are under evaluation like cardiac contractility modulation (CCM) and baroreceptor activation therapy. CCM has been assessed in patients of HFrEF in HYHA class III and IV with LVEF between 25-45% and QRS duration <130 ms. Both CCM and baroreceptor activation have been shown to have marginal improvement in QOL and exercise tolerance.(Abraham et al., 2018, Zile et al., 2020) For HFmrEF, there are no sufficient data of use of ICDs for primary prevention of ventricular arrhythmias.

1.8.3 Lifestyle management strategies

Lifestyle management forms an important non-pharmacological management aspect in the treatment of HF. All patients of HF should be encouraged to have a multidisciplinary HF management program to decrease mortality and risk of HF admissions.(McDonagh et al., 2021) Lifestyle management includes patient education, self-care, nutritional management and rehabilitation by exercise. HF patients who have a disciplined life and undertake self-care show better QOL, lower hospital admissions and reduced mortality.(Jonkman et al., 2016) Heart failure patients can have anxiety on knowing their diagnosis. Relaxation techniques involving meditation and yoga can help patients in improving their quality of life.(Middlekauff et al., 2002, Pullen et al., 2018) It has been said that HF and medication used can affect sexual function which may result in non-compliance of medicines. Use of phosphodiesterase – 5 inhibitors is safe in HF patients but not in combination with nitrates. Patients should be advised regarding discontinuation of alcohol and nicotine containing products. Stopping alcohol can reverse ventricular remodelling with complete normalization of LVEF in individuals taking heavy alcohol .(Aguilar et al., 2004, Salisbury et al., 2005)

1.8.3.1 Nutritional management

Excessive salt intake is one of the precipitating causes of worsening HF.(Bennett et

al., 1998, Yancy, 2018) Restriction of dietary salt helped in reducing the dose of diuretics which help reduce plasma renin activity and improve outcomes.(Tsuyuki et al., 2001) Most of the studies have focused on HFrEF patients and one study evaluated its effect in HFpEF.(Chaudhry et al., 2007) It is advisable to have an intake up to 6 gm of salt daily, and less than 2 gm for patients having hypertension, African Americans and middle-aged people.

Nutritional deficiencies seen in HF patients is termed as cardiac cachexia.(Nishikido et al., 2018) Cachexia due to cardiac reason is accompanied by generation of cytokines and tumor necrotic factor-α which causes long term low cardiac output status. Proper nutritional guidance and recommendations are needed with respect to timing and quantity of food intake to ensure balanced diet. However, anabolic steroids should be avoided. It has been suggested that a multivitamin supplementation with thiamine, should be given to all patients to replenish unknown vitamin deficiencies.(Gorelik et al., 2003)

1.8.3.2 Rehabilitation by exercise

Regular physical activity and exercise training help improve functional capacity of the cardiovascular system, quality of life and reduces hospitalisation in HFrEF patients.(Long et al., 2019, Bjarnason-Wehrens et al., 2020, O'Connor et al., 2009) Also there was a trend of decreasing the mortality by regular exercise training as documented by Cochrane review on exercise training in HF patients.(Taylor et al., 2014b) A Cochrane review has shown that cardiac rehabilitation with low or moderate exercise decreases the risk of hospitalization .(Long et al., 2019) The (CROS-HF) cardiac rehabilitation outcome study in heart failure also showed that cardiac rehabilitation by structured exercise improves functional capacity and quality of life in HF patients.(Bjarnason-Wehrens et al., 2020)High intensity interval training in patients capable of doing it, may improve (VO2) peak oxygen consumption.(Ellingsen et al., 2017) The effect of hospitalisation is best seen in those who do regular exercise and stick to it.(Cooper et al., 2015) No data is however available on HFmrEF. Interestingly, there is no significant difference in change in peak VO2 after 3 months in HFpEF who were given either high-intensity interval or moderate continuous training.(Mueller et al., 2021) In HFmrEF, there are no clinical studies available, but the 2021 guidelines mention that the benefits of exercise which are seen in HFrEF should be applied to HFmrEF patients also.(McDonagh et al., 2021) Chapter 8 will address the effect of physical activity intervention on clinical phenotype and quality of life in HFpEF patients.

Chapter 2: Heart Failure with preserved ejection fraction

2.1 Abstract

Heart failure with preserved ejection fraction (HFpEF) is a clinical condition having similar symptoms and signs as heart failure with reduced ejection fraction (HFrEF). HFpEF patients have left ventricular (LV) ejection fraction >50%, abnormal diastolic function (i.e. alteration in E and A ratio), evidence of raised LV filling pressure and increased level of circulating brain natriuretic peptides. This chapter will focus on the epidemiology, aetiology and updated pathophysiology of this important clinical entity. It will also highlight on diagnostic process along with clinical progress of HFpEF. At the end, all the available treatment modality has been discussed along with the new emerging modalities in pipeline.

HFpEF is seen when the ventricular chamber cannot accommodate normal preload despite normal diastolic pressures necessary to maintain stroke volume. This happens due to decrease in ventricular relaxation and/or a rise in ventricular stiffness.

2.2 Epidemiology and aetiology

HFpEF accounts for 40-70% of heart failure diagnosis. Although around 75% of cases are unrecognized (Van Riet et al., 2016, Yan et al., 2021), the current prevalence of HFpEF is about 1.1-5.5% of the overall population.(Owan and Redfield, 2005) Prevalence is further increased with advancing age and in the female gender.(Ceia et al., 2002) The rates of hospitalisation, duration of admission and quality of life are similar between HFpEF and HFrEF.(Loop et al., 2016)

There are several risk factors that are associated with HFpEF including systemic hypertension (confirmed in 40-70% of all HFpEF patients), type II diabetes mellitus (13-70%), obesity (40-45%), coronary artery disease (30-70%), atrial fibrillation (15-40%), and dyslipidemia (16-77%).(Lee et al., 2009, Bursi et al., 2006, Fonarow et al., 2007, Groenewegen et al., 2020). Earlier studies reported better prognosis in HFpEF compared to HFrEF (Henkel et al., 2008), although these studies have followed up patients upon hospitalisation and from the community. Recent studies show that mortality of HFpEF ranges from 30-60% at 5 years.(Chioncel et al., 2017) HFpEF is further associated with increased hospitalization and impaired quality of life.(Aurigemma et al., 2001). With increased longevity and multiple comorbidities, the prevalence of HFpEF is now rising to epidemic proportions.

There are few studies which have reported mortality outcomes in patients with HFpEF

with a focus on factors associated with mortality risks.(Bhatia et al., 2006) These studies have shown that mortality rates are higher in patients of HFpEF as compared to age and sex matched healthy controls in general population. However, reported mortality rates are different among studies due to the heterogeneity of the condition.(Paulus and Van Ballegoij, 2010, Borlaug and Paulus, 2011) In-hospital mortality is about 3 - 6.5% in patients admitted with an acute episode of heart failure in HFpEF patients.(Fonarow et al., 2007, Tsuchihashi-Makaya et al., 2009) The reported short-term (30-90 days) mortality for HFpEF ranges between 5-9.5%.(Fonarow et al., 2007) while annual mortality rate range from 4-15%.(Yusuf et al., 2003, Cleland et al., 2006, Massie et al., 2008) The longer term (5 years) mortality rates are however higher, ranging between 55-74%.(Henkel et al., 2008) A literature based meta-analysis by Somaratne et al. reported that mortality rates in HFpEF was almost half than that in patients of HFrEF patients.(Somaratne et al., 2009)

2.3 Pathophysiology of heart failure with preserved ejection fraction

Diastolic dysfunction happens due to problems in the heart's mechanical function leading to inability of the left ventricle (LV) to relax properly. Diastole phase of cardiac cycle is longer than the systole phase and during this time, the myocardium relaxes and the chambers fill with blood. The LV sucks the blood from left atrium (LA) in early phase and in next phase the LA contracts to fill the blood into LV. Diastasis is the phase of diastole in between these 2 phases.(Ommen et al., 2000, Mitchell and Wang, 2014) Diastolic dysfunction occurs when there is an alteration in these phases as they get longer, slower, or incomplete. Any alterations in normal diastolic function is dependent on the rate and degree of ventricular pressure decline and filling.(Brutsaert and Sys, 1997) The American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) guidelines grade diastolic dysfunction into four stages.(Nagueh et al., 2016) These are grade 1 diastolic dysfunction, where there is abnormal relaxation of LV, grade 2, characterised by pseudo-normalisation, grade 3, characterised by reversible restrictive pattern and grade 4 is characterised by restrictive pattern which is irreversible despite change in loading conditions.

In HFpEF, the myocardium undergoes structural and cellular changes. These changes are expressed as myocyte hypertrophy, intercellular and interstitial fibrosis, abnormal myocyte relaxation and inflammation.(Schwinger, 2021) Concentric LV remodelling is seen in around 53% of cases of HFpEF patients.(Shah, 2013) This remodelling has been known to mask impairments in myocardial systolic function.(Aurigemma et al.,

1995, Palmieri et al., 2001) Progressive LV concentric remodelling is associated with reduced subendocardial longitudinal deformation assessed by 2D strain imaging despite preserved LVEF.(Kuznetsova et al., 2008)

2.4 Diagnosis of heart failure with preserved ejection fraction

The definite way to diagnose HFpEF needs haemodynamic evaluation at rest and after stress which helps in elevating filling pressure and cardiac output (Figure 2.1). The 2021 ESC guideline focuses on having at least symptoms and signs of HF along with cardiac functional or structural abnormalities.(Ponikowski et al., 2016c) Structural and functional abnormalities that can be measured by echocardiography include LV hypertrophy, LV and right ventricular function, left atrium dilatation, elevation in LV filling pressure and presence of tricuspid regurgitation. Although diastolic dysfunction is a dominant feature, other commonly associated comorbidities like renal dysfunction, increased weight, anaemia, contribute to impairment of cardiovascular reserve and worsening of HFpEF. Several diagnostic algorithm and scores are available for HFpEF diagnosis. The most recent score-based algorithms (H_2FPEF and HFA-PEFF) proposed by the ESC 2020 now represent the standard for diagnosis.(Reddy et al., 2018, Pieske et al., 2019) The 6 variables that form the H_2FPEF score are (1) a body mass index (BMI) of more than 30 kg/m^2(H); (2) use of 2 or more antihypertensive drugs (H); (3) presence of atrial fibrillation (F); (4) pulmonary arterial hypertension defined as pulmonary artery systolic pressure more than 35 mm Hg (P); (5) age >60 years (E); and (6) elevated filling pressures evident from E/e′ >9 (F). HFA-PEFF incorporates pretest assessment (P), diagnostic workup by echo and biomarker (E), advanced workup by functional testing (F1) and aetiological workup for final aetiology (F2).

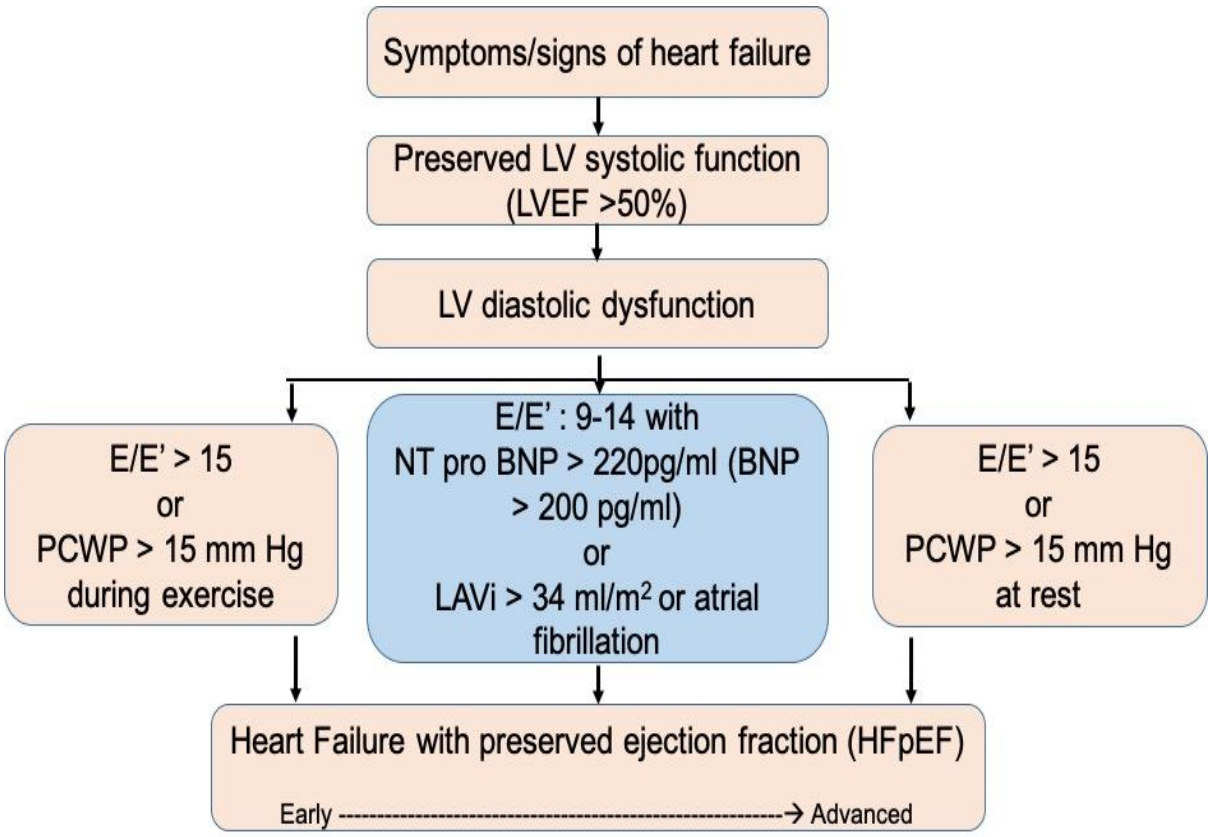

Figure 2.1 Diagnostic pathway for heart failure with preserved ejection fraction (adopted from Huis AE et al. (2016) LVEF- left ventricular ejection fraction, PCWP- pulmonary capillary wedge pressure, NTproBNP - N-terminal pro b-type natriuretic peptide, LAVi- left atrial volume indexed. E/E' – ratio of early mitral inflow velocity to mitral annular early diastolic velocity, BNP- Beta natriuretic peptide

Left ventricular filling pressure reflects pulmonary capillary wedge pressure and can be measured non-invasively via echocardiography by looking at the ratio between early mitral inflow velocity and mitral annular early diastolic velocity, E/e'.(Mullens et al., 2009, Ommen et al., 2000). An E/e' ratio $\leq$ 8, is indicative of normal left ventricular filling pressure.(Mcmurray et al., 2012) while E/e' exceeding 15 indicates raised filling pressure. Higher E/e' ratio is seen in HFpEF patients and helps in differentiating from patients presenting with non-cardiac breathlessness.(Borlaug et al., 2010) When E/e' ratio is intermediate (i.e. >8 to <15), other parameters are needed to aid diagnosis for example, ratio of mitral inflow doppler (ratio of early to late mitral inflow velocity for grading diastolic dysfunction and deceleration time of 0.280 ms), left atrial volume index (LAVi > 34 ml/m^2), LV mass index (females >122g/m^2, males >149g/m^2), or presence of atrial fibrillation.(Lam et al., 2011)

Assessment of left atrial (LA) structure and function has clinical and prognostic significance in cardiovascular patients, especially in HFpEF. It acts as a reservoir receiving blood from pulmonary veins (reservoir function) during atrial filling with mitral

valve closed, letting blood flow passively to the LV at early diastole (conduit function) and as a booster kick during atrial contraction (booster pump function).(Leung et al., 2008) LA function is closely intertwined with LV function during complete cardiac cycle.(Braunwald et al., 1961) During ventricular systole, shortening of longitudinal sub-endocardial myocardial fibre shifts the cardiac base down, helping the filling of atrium from the pulmonary veins, while during diastole, the atrium contributes to ventricular filling by both active and passive mechanism. The LA cavity is in direct continuity to LV diastolic pressure when the mitral valve is open and hence, atrial emptying is affected by LV diastolic properties.(Kono et al., 1992)

LA enlargement occurs in around 50% of stable chronic HF patients.(Hohendanner et al., 2018) The most common echocardiographic parameter used to assess LA structure is left LAVi.(Nagueh et al., 2016) However, LAVi has low sensitivity in detecting LA dysfunction in the presence of LV diastolic dysfunction.(Kim et al., 2020, Kurt et al., 2009) Assessment of LAVi allows calculation of LA emptying fraction and LA expansion index but does not give information about passive (reservoir and conduit) and active (booster) LA function. 2D speckle tracking echocardiography of the left atrium helps in estimating the LA performance by looking at the LA strain. It helps in understanding all 3 periods of LA function (reservoir, conduit and booster) and has been shown to have clinical and prognostic significance in HFpEF patients.(Frydas et al., 2020, Freed et al., 2016) LA strain is similar to a biomarker for the clinical diagnosis and prognosis of cardiovascular disease.(Cameli et al., 2016) Also, LA strain directly correlates with diastolic dysfunction severity.(Morris et al., 2011) However it is load dependent and is affected by LV function. Reduced LA reservoir strain has been reported to be directly correlated with higher cardiovascular event and LA fibrosis.(Freed et al., 2016) Improvement in LA strain which could be prompted by exercise training, weight reduction and intensified risk factor management in HF patients is associated with reverse LA remodelling and decreased mortality.(Hohendanner et al., 2018)

Diagnosis of HFpEF is easier in acutely decompensated patients. In stable patients with dyspnoea, diagnosis of HFpEF is purely based on documentation of elevated LV filling pressure.(Borlaug and Paulus, 2011) In these patients, a stress (exercise) test helps in unraveling the signs and symptoms of HFpEF.(Erdei et al., 2014) Exercising these patients precipitates symptoms and also produces changes in haemodynamics which can be picked up by echocardiography. Interestingly, few stable patients with HFpEF may have normal NTproBNP levels.(Obokata et al., 2017) Obokata et al.

reported that normal NTproBNP values can be seen in around 18% of HFpEF patients. In patients with diastolic dysfunction, there can be limitation of exercise capacity which can be due to anaemia, bronchial asthma, obstructive airway disease, dynamic left ventricular outlet obstruction, coronary artery disease and valvular heart disease.(Okonko et al., 2011)

Invasive haemodynamic stress testing using right heart cardiac catheterisation is the gold standard to make the diagnosis of HFpEF.(Reddy et al., 2018) Various stress protocols can be used including physiological (exercise stress test) on a treadmill test and cycle ergometry or pharmacological stress commonly performed with gradual infusion of an inotropic agent i.e. dobutamine. A normal heart is able to raise flow across the mitral valve with minimal change in LA pressure by decreasing the LV diastolic pressure.(Fletcher et al., 2001, Francis et al., 2001) However, in a failing heart, there is no fall in LV diastolic pressure with peak exercise.(Zile et al., 2013, Bhella et al., 2011) Also a rise in trans-mitral gradient and flow occurs due to elevated LA pressure. Although invasive right heart catheterization is the gold standard to provide haemodynamic data, it is not feasible to perform always. Chattopadhyay et al reported in their small study involving 29 patients that diastolic dysfunction of LV deteriorates by dobutamine stress test in few patients which can explain their symptomatic worsening after exercise.(Chattopadhyay et al., 2010)

2.5 Clinical course of heart failure with preserved ejection fraction

Patients with HFpEF are at high risk of hospitalization due to acute decompensation causing acute heart failure. The Organised Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry reported a rehospitalization rate of around 30% within 60-90 days of first hospitalization.(Fonarow et al., 2007) The most common factors associated with acute precipitation of heart failure resulting in recurrent hospitalization are non-compliance to medication and uncontrolled hypertension.(Joshi et al., 1999) Other important precipitating factors are atrial fibrillation, sepsis, renal dysfunction and lung disease.(Arrigo et al., 2017)These factors precipitate the systemic mechanisms in the presence of risk factors and comorbidities and result in clinical symptoms. These alterations are responsible for all the clinical manifestations of HFpEF (Figure 2.2).

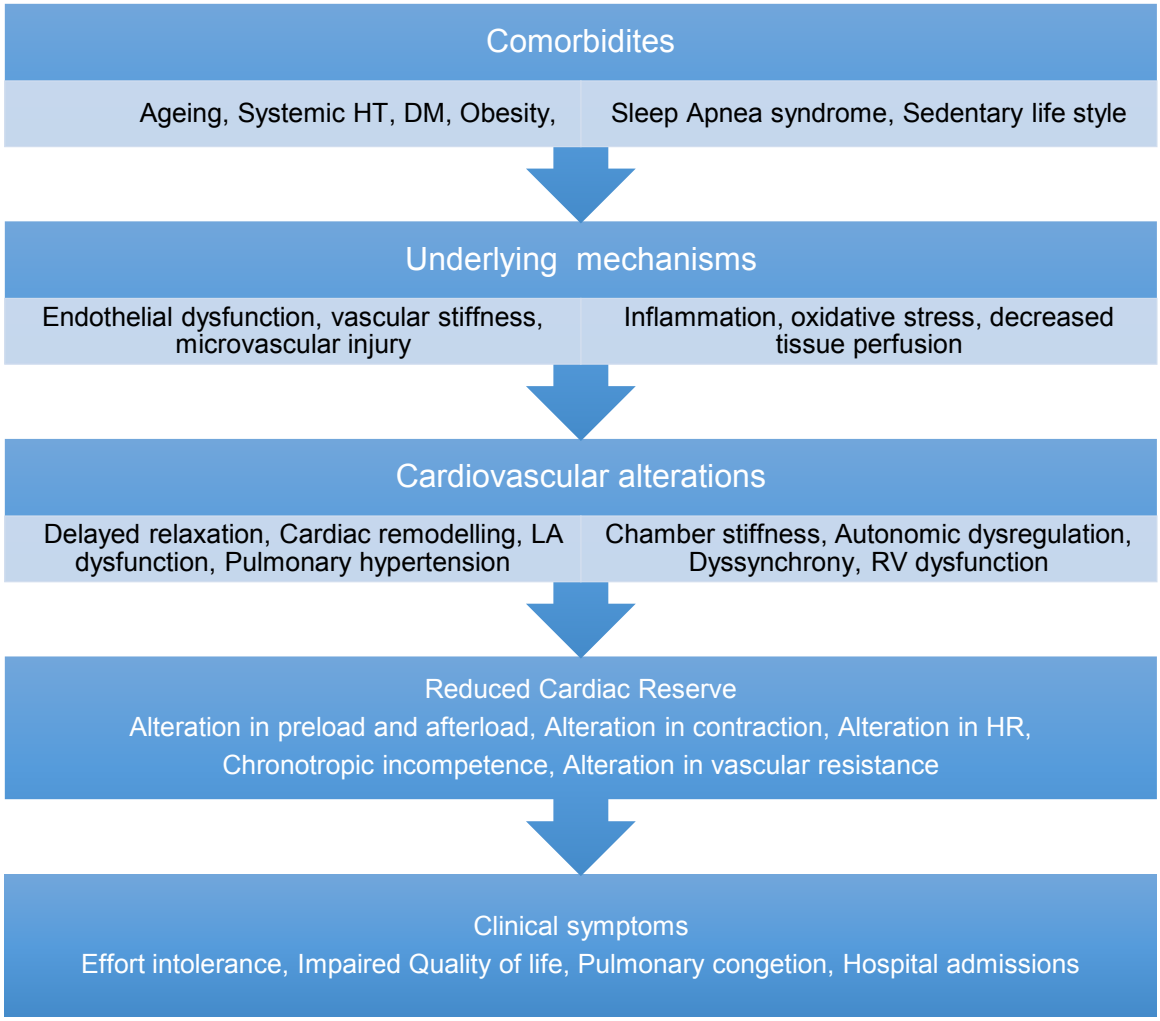

Figure 2.2 Time course of the evolution of Heart Failure with preserved ejection fraction (adapted from Juilliere et al., 2018).(Juilliere et al., 2018) HT – Hypertension, DM- Diabetes mellitus, LA- left atrium, HR- Heart rate.

The cardiac causes of mortality in HFpEF patients are sudden cardiac death, heart muscle pump failure, acute coronary syndrome and stroke.(Henkel et al., 2008, Tribouilloy et al., 2008, Zile et al., 2010, Ahmed et al., 2006) However, survival rate of patients with HFpEF is similar to that of patients with HFrEF.(Bhatia et al., 2006). The predictors of death among patients with HFpEF include older age, hypotension, associated peripheral vascular disease, hyponatremia, a history of cancer, dementia, renal dysfunction, dialysis, anaemia, and tachypnoea.(Bhatia et al., 2006) Interestingly, incidence of cardiovascular mortality is lower, while non-cardiovascular mortality higher in HFpEF compared to HFrEF.(Gerber et al., 2015) Once diagnosed with HFpEF in acute setting, almost two thirds of patients will have LVEF correlating with HFpEF during follow-up. 10-20% of these patients progress to HFmrEF, while in 2-20% patients, the LVEF drops resulting in onset of HFrEF (Figure 2.3).(Tsutsui et

al., 2021) Around 30-40% of HFrEF patients show improvement to feature as HFpEF, while 10-20% of them show features of HFmrEF. 60-80% patients of HFrEF remain as HFrEF over a period of time. In HFmrEF patients one third improve to HFpEF, another one thirds deteriorate to HFrEF while the remaining show features of HFmrEF in long term followup.(Tsutsui et al., 2021)

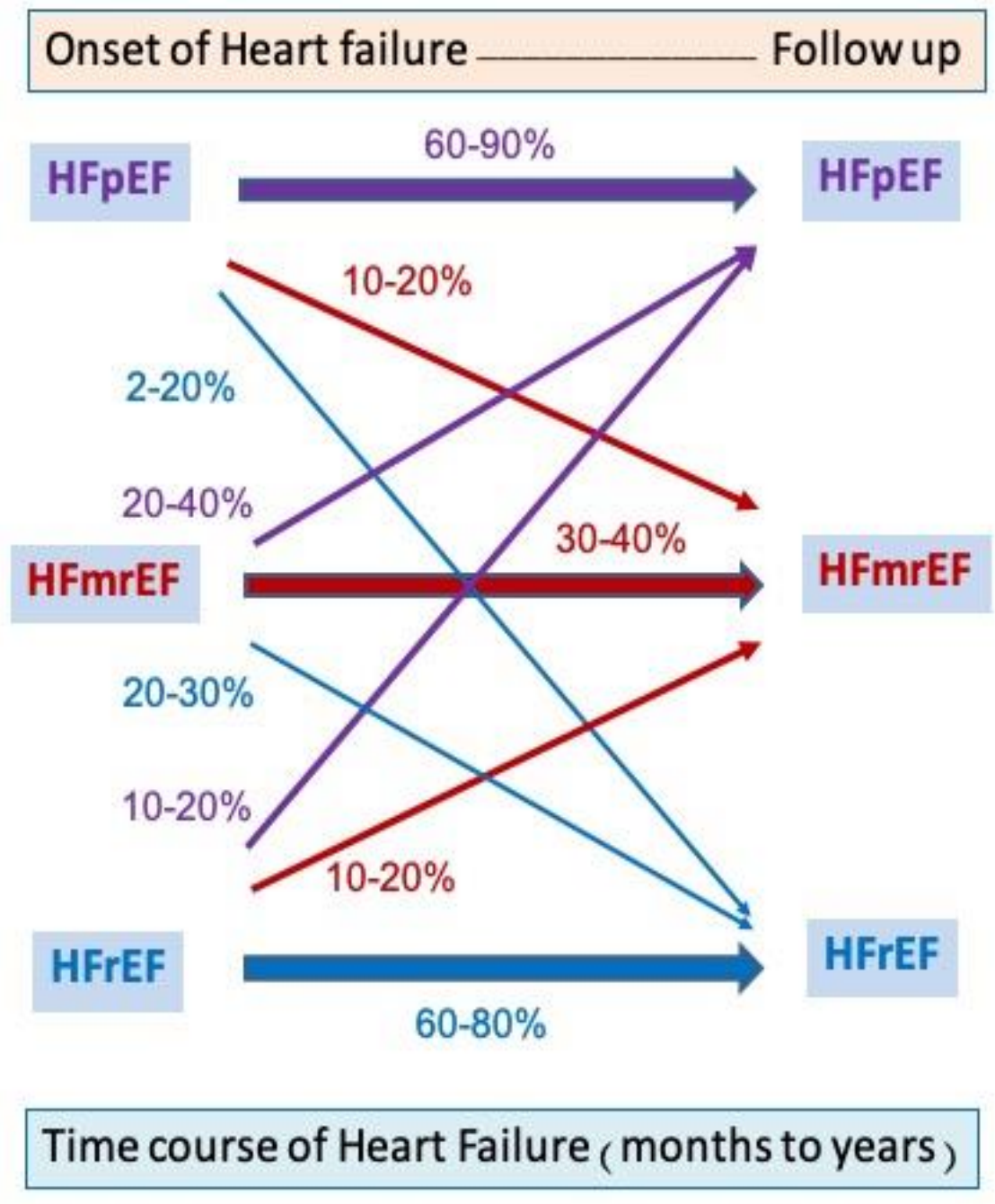

Figure 2.3 Time course of Heart Failure (adapted from Tsutsui et al., 2021).(Tsutsui et al., 2021) HFpEF – heart failure with preserved ejection fraction, HFmrEF- heart failure with mildy reduced ejection fraction, HFrEF- heart failure with reduced ejection fraction.

2.6 Medical management of heart failure with preserved ejection fraction

Management of HFpEF has been challenging to the medical world. But some improvement occurs in few phenotypes of HFpEF. Pharmacological treatment, lifestyle modification comprising nutritional management, weight reduction and exercise are helpful in HFpEF management. Pharmacological treatment revolves around the following principles; fluid management, management of atrial rhythm, control of heart rate, control of hypertension, treatment of comorbidities like anaemia, obesity and device therapy.

2.6.1 Pharmacological treatment

2.6.1.1 Fluid management

Diuretics are helpful in reducing congestion in HFpEF patients. Both loop diuretics and potassium sparing diuretics can be used for the symptomatic treatment of HFpEF patients.(Paulus and Van Ballegoij, 2010, Barsuk et al., 2013) Thiazide diuretics are useful if there is associated hypertension. HFpEF patients are very sensitive to volume changes with volume overloading causing heart failure symptoms and hypovolemia causing prerenal azotemia and hypotension.(Barsuk et al., 2013) Spironolactone was tested in Aldo-DHF study where it significantly reduced LV filling pressure and NTpro-BNP levels in HFpEF patients. It also helped in structural remodelling of LV in these group of patients.(Edelmann et al., 2010) However diuretics have not been reported to improve outcomes in HFpEF patients.(Edelmann et al., 2010). The phase three treatment of HFpEF with an aldosterone antagonist (TOPCAT) did not reduce the cardiovascular death or admissions due to heart failure (Pfeffer et al., 2015) although, a subgroup of patients showed significant decrease in primary endpoint of cardiovascular death and HF hospitalizations.

2.6.1.2 Management of atrial rhythm

Atrial fibrillation (AF) is more prevalent in HFpEF than in HFrEF.(Kotecha et al., 2016) HFpEF patients with AF have poor prognosis, especially when ventricular heart rate is elevated.(Kotecha et al., 2016, Shah et al., 2015) Rhythm control using antiarrhythmic medication helps to improve clinical symptoms. When this is contraindicated or impossible, the focus should be to lower the ventricular rate by beta-blockers or heart rate decreasing drugs like Ivabradine.(McMurray et al., 2012) Kelly et al reported that rhythm control in elderly HFpEF patients over 65 years presenting with AF was associated with lower 1year all-cause mortality.(Kelly et al., 2019) Current guidelines of AF management recommend

initial rate control with anticoagulation followed by rhythm control if symptoms persists.(January et al., 2014)

2.6.1.3 Control of heart rate

Rise in heart rate reduces the duration of diastole. Also a decrease in heart rate may help in symptomatic improvement in patients with HFpEF.(Conraads et al., 2012, Yamamoto et al., 2013) However, studies using beta blockers in HFpEF have not shown any advantage in this regard, moreover, some of these studies have reported an increase in N-terminal –pro hormone brain natriuretic peptide (NT-proBNP).(Scherer et al., 2013, Conraads et al., 2012) Studies using ivabradine which decreases heart rate have shown short term positive effects, but not consistently across all trials.(Kosmala et al., 2013) However, Lam et al. reported that lower heart rate at discharge in HFpEF patients was independently associated with lower risk of all-cause mortality, but not readmission due to heart failure symptoms.(Lam et al., 2017)

2.6.1.4 Control of hypertension

Trials using perindopril in patients with HFpEF has shown reduction in hospitalization due to HF at first year, but the trial did not achieve the primary endpoint.(Cleland et al., 2006) Two big studies have focused on the effect of angiotensin receptor blockade in patients with HFpEF. Irbesartan in patients with HFpEF (I-PRESERVE) trial showed no effect of irbesartan on mortality, HF hospitalisation or quality of life.(Massie et al., 2008) Another trial evaluated candesartan usage in patients of HFpEF (CHARM-Preserved) and showed minimal positive effect of candesartan on hospitalization in HFpEF. However, this study also included HF patients with LVEF < 40%.(Yusuf et al., 2003) Interestingly, use of spironolactone has not shown any added advantage for reduction in mortality and hospitalization.(Pfeffer et al., 2015) Use of angiotensin receptor neprilysin inhibition (sacubitril/valsartan) in patients with HFpEF was studied in PARAGON trial but did not show significant impact in reducing rate of hospitalisation due to HF and deaths from cardiovascular disease.(Solomon et al., 2019)

2.6.1.5 Treatment of comorbidities

The precipitating risk factors and co-morbidities associated with HFpEF should be identified and managed. Presence of iron deficiency anaemia should be assessed by complete blood count, serum ferritin levels and transferrin saturation. At present ongoing studies are looking at the effect of intravenous ferric carboxymaltose in patients with HFpEF with iron deficiency anaemia. Obesity is a major risk factor for

HFpEF and pathophysiological mechanisms in obese differ from non-obese patients presenting with HFpEF.(Packer et al., 2020, Rao et al., 2020) Caloric restriction and structured exercise training protocol have shown significant positive impact on quality of life and functional capacity in HFpEF patients. (Kitzman et al., 2010) HFpEF patients having renal dysfunction have poor long term prognosis. (Shah et al., 2015) Presence of chronic kidney disease and deteriorating renal function are more commonly seen HFpEF than in HFrEF and HFmrEF. Proper treatment of renal dysfunction by nephrologist is warranted by using renal dosages of all anti-heart failure medications.

2.7 Device therapy

To decrease LA pressure, a novel approach of creating an interatrial communication to offload LA is being evaluated.(Kaye and Nanayakkara, 2019) Computer modelling studies have shown that a size of 8 mm interatrial shunt as provided by interatrial shunt device would be helpful in decreasing the exertional rise in LA pressure while creating a small interatrial shunt.(Kaye and Nanayakkara, 2019, Kaye et al., 2019) There are two percutaneously delivered devices currently under investigation. V-wave device and interatrial septal devices (IASD) are being tried in patients with HFpEF in REDUCE LAP-HF TRIAL III and RELIEVE-HF trial.(Al-Sadawi et al., 2020) Initial reports show significant effects on functional capacity and quality of life after device implantation.(Hasenfuss et al., 2016) V-wave device is a tri-leaflet porcine tissue valve on an hourglass shaped nickel-titanium frame. The center of the device is placed under fluoroscopy guidance across fossa ovalis with the ends of the hourglass positioned in right and left atria. There have been no serious side effects of this device after 3 months. The IASD is made of bare metal and has a bigger inter-atrial communication of 8mm. This device also shows great promise for future use with no side effects reported in 3 months follow-up. All patients are being anticoagulated for 3 months post implantation. Early trials have now aimed to decrease chronotropic incompetence and improve dyssnchrony with atrial pacing.(Kass et al., 2010)

2.8 Lifestyle modification

There is evidence to suggest that changes in lifestyle including physical activity, exercise, caloric restriction and optimal nutritional management may slow down disease progression in HFpEF.(McDonagh et al., 2021) Kitzman et al reported in a randomised controlled trial showing significant improvement in cardiorespiratory fitness with regular training in patients with HFpEF.(Kitzman et al., 2010) The following changes are suggested in HFpEF patients: regular physical activity for patients with

sedentary behaviour, cigarette smoking cessation, healthy diet, abstinence from alcohol and periodic vaccination by influenza vaccine. (Mcdonagh et al., 2021) Kitzman et al. investigated the effect of hypocaloric diet in obese HfpEF patients.(Kitzman et al., 2016) They reported that hypocaloric diet when combined with exercise helped in improving exercise capacity, quality of life and also weight loss. A small study has shown positive effects on the use of mono and polyunsaturated fatty acids in HFpEF patients with obesity.(Carbone et al., 2017) Also use of unsaturated fatty acids consumption have shown to be helpful in improving diastolic dysfunction.(Carbone et al., 2017) Dietary sugars have been shown to be inversely proportional to functional capacity in HFpEF patients.(Carbone et al., 2017) A proper exercise prescription should be provided to all HFpEF patients which should include a supervised maximal exercise stress test with controlled ischemia monitoring before patients start exercising.

2.9 Conclusion

This chapter provides a complete overview about HFpEF, which is now a global pandemic. HFpEF has been a multifactorial disease entity gaining a lot of interest in recent past. Understanding the pathophysiology and disease clinical progression will provide new insights to its better clinical management which is the need of the present time. The present work gives new insights about the exercise dynamics in these patients and emphasizes on the role of left atrial dynamics in the pathophysiology of HFpEF at rest and after exercise. It also focuses on the impact of exercise intervention in these group of patients.

Chapter 3: Aims, Objectives and Hypotheses

3.1 Aims

Heart failure with preserved ejection fraction is linked with higher morbidity and mortality with increased risk of hospitalization. It can result in poor quality of life and reduced functional independence. Few recent pharmacological studies have shown improvements in symptoms and reduction in cardiovascular death and hospitalizations in these patients with proper treatment.

Better understanding of pathophysiology and clinical phenotype differences between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) and may facilitate development of more strategies to improve outcomes in patients with HFpEF.

The aim of this thesis is to improve understanding of the pathophysiology of HFpEF.

3.2 Objectives

The above aim will be achieved through the following three objectives:

1. Assess the agreement in haemodynamic measurements obtained by a novel non-invasive technology i.e. bioreactance and echocardiography.
2. Define haemodynamic response to pharmacological (dobutamine) and physiological (treadmill exercise) stress testing in HFpEF and HFrEF patients.
3. Evaluate the acceptability, feasibility, and effectiveness of a novel, home-based physical activity intervention (Active-at-Home-HF) in HFpEF.

3.3 Hypotheses

1. There will be no significant difference between cardiac output estimates obtained by bioreactance and echocardiography methods.
2. Patients with HFpEF will demonstrate significantly lower haemodynamic response to exercise stress testing compared to healthy controls.
3. Patients with HFpEF will demonstrate significantly better haemodynamic response to stress testing compared to HFrEF controls.
4. Active-at-Home-HF physical activity intervention will be acceptable and feasible to patients with HFpEF, and will significantly improve functional capacity and quality of life in these patients.

Chapter 4: Methods and materials

4.1 Methods

This chapter describes main methodology used in the research program on which the present thesis is based. It also gives a description of the equipment and procedures used to generate results contained in the thesis.

4.2 Design

The research program was designed to address main objectives of the thesis. It used a single center, prospective, observational, cross-sectional and longitudinal studies which were conducted from July 2018 to March 2021 at Sengupta Hospital and Research Institute (SHRI), Nagpur, India. Three studies were planned to address the three main objectives of the thesis.

Study 1 - A Prospective observational, direct comparison study to assess the agreement between haemodynamic measurements obtained by bioreactance and transthoracic echocardiography methods.

Study 2 - A Prospective cross-sectional study to evaluate differences in haemodynamic response to pharmacological (dobutamine) and physiological (treadmill exercise) stress testing between patients with heart failure preserved ejection fraction (HFpEF) vs. heart failure with reduced left ventricular ejection fraction (HFrEF).

Study 3 - A Prospective longitudinal pilot study to evaluate acceptability, feasibility, and preliminary effectiveness of a novel, home-based physical activity intervention (Active-at-Home-HF) in HFpEF.

4.3 Recruitment procedures

Patients were included from the Heart Failure Clinic at the above mentioned hospital. Eligible patients were screened during outpatient visits where a written informed consent was obtained. Heart failure patients who were clinically stable for a minimum period of 6 weeks and were on guideline directed medical management were enrolled in the study. Summary of the study participants enrolment is presented in Figure 4.1.

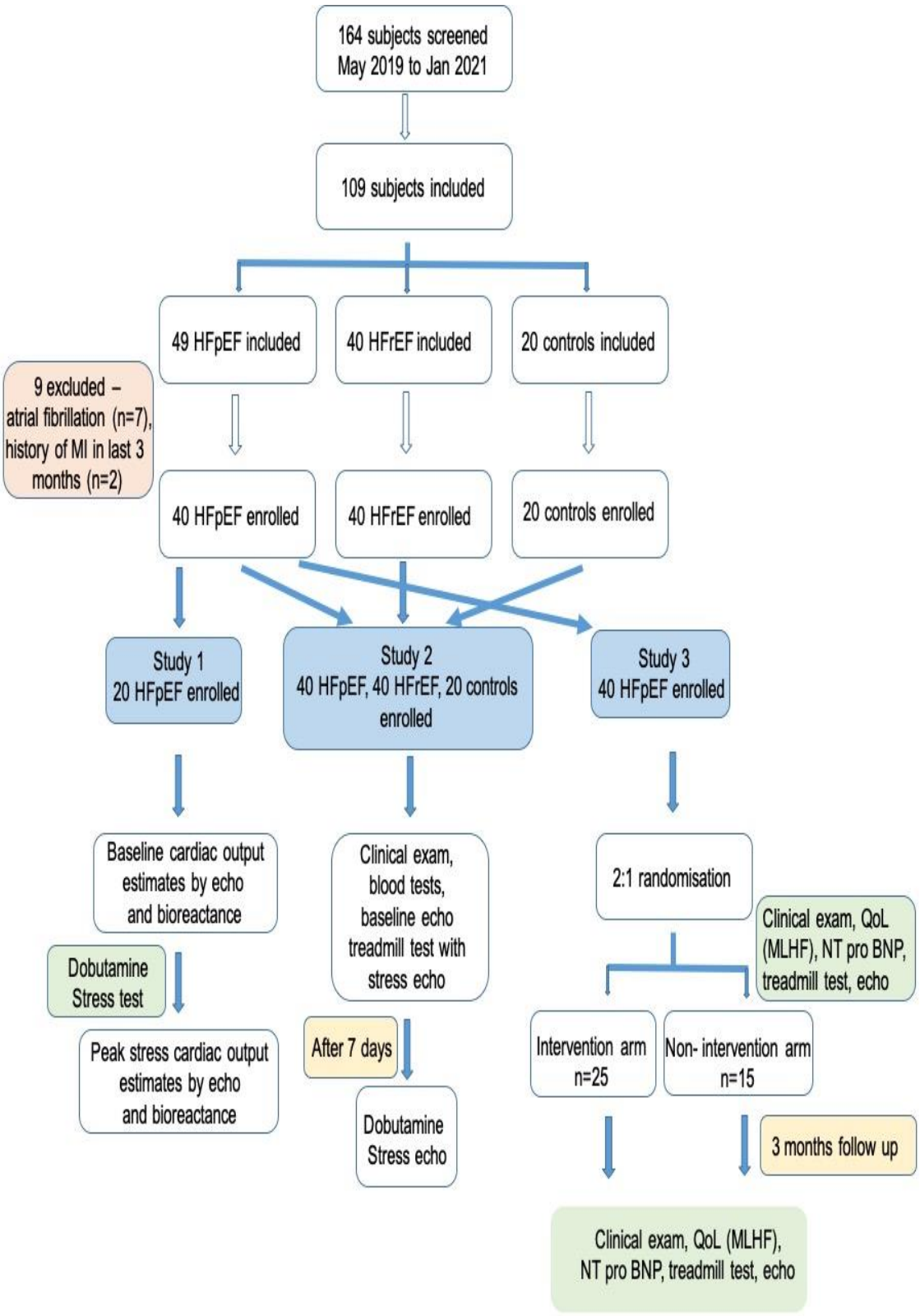

Figure 4.1 Flow diagram of study participants' enrolment for proposed studies. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

4.4 Eligibility criteria

4.4.1 Inclusion criteria

In the proposed studies, only adult patients (>18years of age) with a confirmed diagnosis of either HFpEF or HFrEF were taken. In addition to heart failure patients, a group of healthy age-matched controls was also included into the study to allow comparison of data with those with heart failure. All subjects were able to walk and perform activities of daily living independently. Participants were willing to take part in the research study and provided written informed consent.

4.4.2 Exclusion criteria

The following patients were excluded from the study, patients having problems in their valves, history of atrial or ventricular arrhythmias, implanted left ventricular assist device, recent ischaemic heart disease episode within 12 weeks, primary pulmonary hypertension, malignancy, pregnancy, or unable to give consent.

4.5 Ethical approval

All study essential documents (i.e. research study protocol, consent form, and patient information sheet) and procedures were approved by the local Research Ethics Committee (Sengupta Hospital and Research Institute Ethics Committee; Registration number – ECR/675/Inst/MH2014/RR-20). All procedures were in accordance with the declaration of Helsinki. Consent forms were signed by the participant and by the principal investigator.

4.6 Study visits

Participants were contacted by telephone or talked to in person to provide details about the project and were provided with the information sheet to ensure they understood the type of the study. The eligible participants visited the hospital's research facility for screening and enrollment (visit 1), study procedures and investigations (visit 2) and those with HFpEF who were participating in the intervention (Chapter 8) came for the second (follow-up) visit at 3 months after visit 2. Visit one lasted up to an hour, while visits 2 and 3 lasted between1.5-2.5 hours. The following clinical investigations were performed during the visits.

4.6.1 Consent and screening questionnaires

Participants were allowed to enquire about any queries and requested to provide informed written consent. They were then requested to fill up the Minnesota Living with

Heart Failure, and Physical Activity readiness questionnaires.

4.6.2 Blood sample

Blood samples (10ml) were taken from the antecubital vein and evaluated for haemoglobin, complete lipid profile, glucose, HbA1c, thyroid profile, blood urea, serum creatinine and brain natriuretic peptides (NTproBNP).

4.6.3 Electrocardiography

An electrocardiogram was done by a standard 12-lead electrocardiogram (Maestros, India) in supine position after asking the subject to lie down for 5 minutes.

4.6.4 Transthoracic echocardiography

Echocardiography is a non-invasive method to look at the cardiac structure and function using ultrasound. A detailed echocardiographic examination was done according to the guidelines from American Society of Echocardiography.(Lang et al., 2015) All echocardiography assessments were performed at rest and after treadmill and dobutamine stress testing by a single experienced sonographer from the left lateral position at 50-70 frame rate/seconds, using echo machine (Vivid E95, 2.5 -4.0 MHz transducer, GE Vingmed Ultrasound AS, Norway). The protocol captured three beats for analysis. Measurements taken were for LV septal and posterior wall thickness, left atrial (LA) anterior-posterior dimension and LV internal diameter and obtained from the parasternal long-axis view. LV end-diastolic and end-systolic volumes (LVEDV and LVESV, respectively) and EF was done by biplane Simpson's formula which requires the apical four- and two-chamber views.(Lang et al., 2015) LA volume was calculated by biplane area- length which was then indexed to body surface area. The complete analysis of LV used the 17 segment model. The LV outflow tract measurement was done during systole in the parasternal long axis view.(Lang et al., 2015) Pulse wave doppler at LV outflow tract (LVOT) from apical 5 chamber view gave the time velocity time integral (TVI). Stroke volume was derived from the following:

Stroke volume = 0.785 X $(\text{LVOT diameter})^2$ X LVOT TVI, where LVOT is left ventricular outflow tract (Lang et al., 2015, Orde et al., 2017, Doherty et al., 2017) (Figure 4.2).

Cardiac output and cardiac index were measured by:

Cardiac output (L/min) = Stroke volume (ml/beat) x heart rate (beats/min)

Cardiac index (L/min/m^2) = Cardiac output (L/min) / body surface area (m^2)

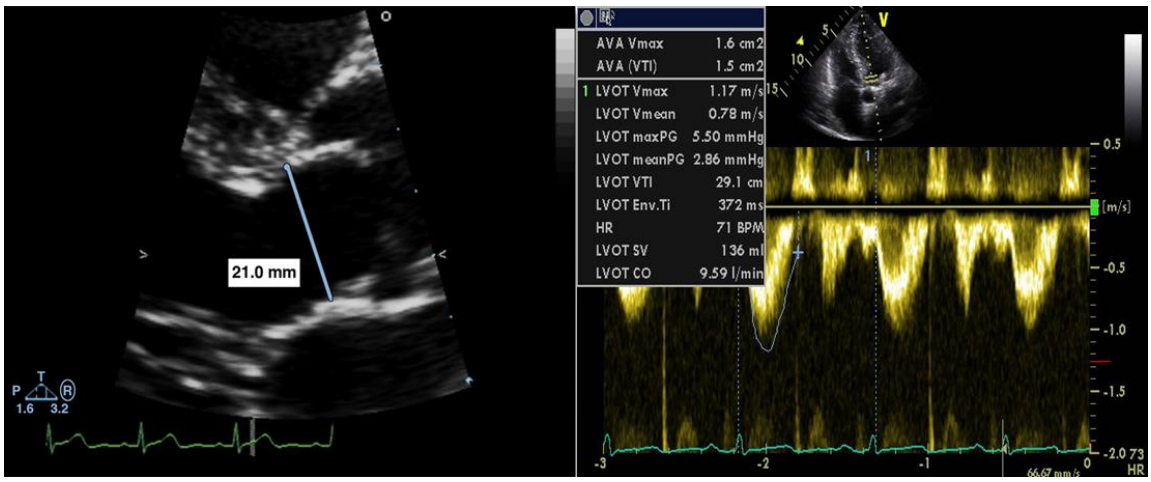

Figure 4.2 Determination of stroke volume by echocardiography.

4.6.5 Bioreactance

The bioreactance machine studied was NICOM, non-invasive cardiac output monitor (Cheetah Medical, Delaware, USA). It uses relative phase of oscillating current shifts which are time-dependent and it passes the thoracic cavity.(Squara et al., 2007) NICOM method takes help of a radiofrequency generator which generates high frequency current passing through the chest (Figure 4.2). The system uses 4 dual surface electrodes which gets attached either anteriorly (i.e. two electrodes placed over the left and right pectoralis major muscle, immediately beneath the midclavicular line and the other two placed on the lower part of the trunk, slightly medial to both left and right anterior iliac spine (Figure 4.3) or posteriorly (i.e. two electrodes placed over the left and right trapezius muscle and the other two placed at the posterior part of lower trunk next to latissimus dorsi muscle. After the signals pass through these electrodes, they are received back for digital process. The system's signal processor establishes the relative phase shift between the input signals relative to the output signals.(Keren et al., 2007) This phase changes are because of rapid changes in blood flow in the aorta.(Squara et al., 2007) Cardiac output (QT) is subsequently calculated by:

$$QT = (C \times VET \times \Delta\Phi / dt_{max}) \times HR$$

where C is a constant of proportionality, and VET determines ventricular ejection time, derived from the bioreactance and electrocardiogram signals, $\Delta\Phi/dt_{max}$ is the relative phase shift of current, and HR is heart rate. The value of C has been optimized in previous work and is related on age, sex and body size of the patient.(Squara et al., 2007)

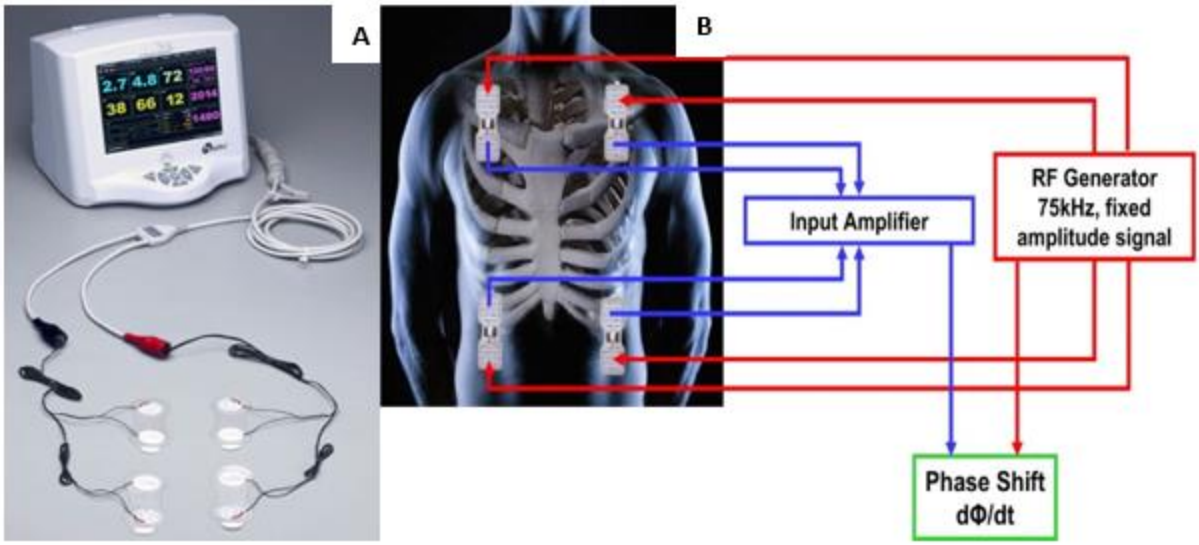

Figure 4.3 Non-invasive cardiac output monitoring system based on bioreactance technology (NICOM, Cheetah Medical, Delaware, USA). Bioreactance device with leads and electrodes (A) Electrodes placement (B). Each electrode contains both electrical current generator and receiver, which also acts as an input amplifier (adopted from Keren et al.(Keren et al., 2007))

4.6.6 Exercise stress testing

Beta-blocker and/or nitrate medication were stopped 24 hours prior testing in all patients. All enrolled participants performed exercise stress test on the treadmill (Schiller Cardiovit, USA) using the modified Bruce protocol. After a rest period of three minutes, the test involved four stages of increasing exercise lasting three minutes each, starting with warm-up at 1.7 mph and 0% grade.(Trabulo et al., 1994) ECG and blood pressure were continuously monitored throughout the test in order to detect any abnormality in heart rhythm and blood pressure response to exercise. Protocols using a constant treadmill speed with small changes of grade, such as the modified Bruce or Naughton protocols provide more data points with less need for gait changes than the simultaneous increases of speed and elevation every 3 minutes during the more commonly used Bruce protocol.{Fletcher et al., 2013) Also it has been suggested that in patients of HF, exercise testing should be performed in a conservative approach for the safety of patients.(Fletcher et al., 2013, Balady et al., 2010) The test was terminated when participants achieved symptoms of exercise intolerance as monitored by Borg's scale level of perceived exertion.(Borg, 1982) An echocardiogram was performed within three minutes post exercise test to evaluate cardiac structure and function.

4.6.7 Dobutamine stress echocardiography

Dobutamine stress echocardiography (DSE) was performed in all subjects (HFpEF, HFrEF and controls) enrolled in the study one week after the exercise stress test. Dobutamine was infused through an intravenous access in the hospital set-up. Subjects were told to be nil by mouth for 4 hours before the study. Beta-blocker and/or nitrates were stopped one day prior to the study. Infusion of dobutamine infusion was done at 3 minute intervals as previously suggested,(Lancellotti et al., 2017) with doses of 5,10,15 and 20 µg/kg/min till highest dose was reached or occurrence of signs and symptoms i.e. chest discomfort, hypertensive response, breathlessness, rhythm abnormalities, ST-T changes, or patient's inability to withstand medication (Figure 4.4).

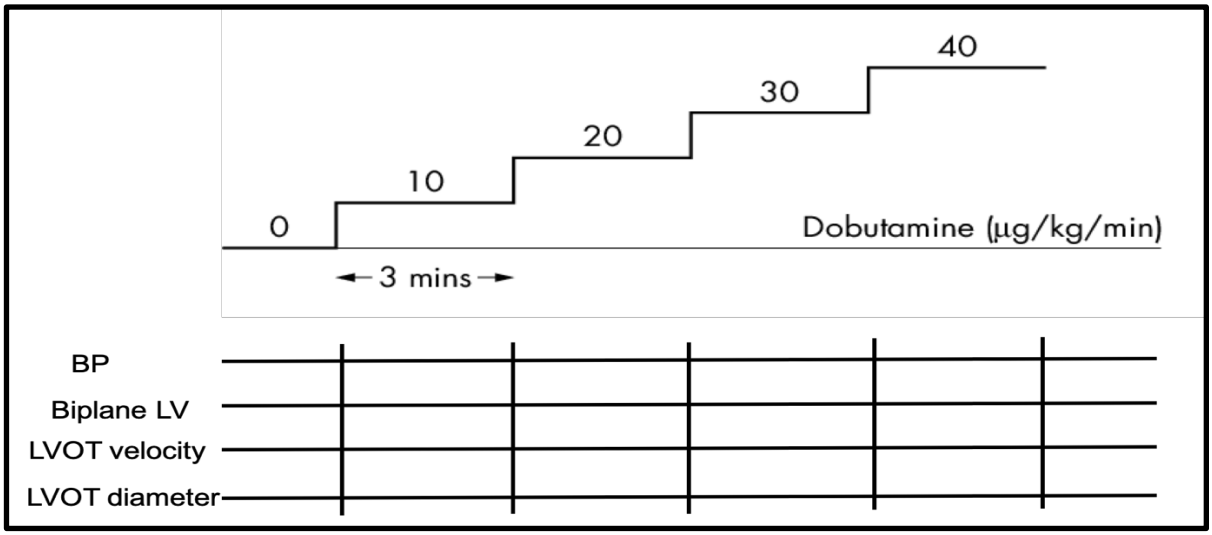

Figure 4.4 The protocol of dobutamine stress echocardiography

All echocardiographic assessments were performed before starting dobutamine infusion and 2-3 minutes after the peak tolerated dose (Figure 4.5).

Figure 4.5 Simultaneous assessment of cardiac output by transthoracic echocardiography and bioreactance method during dobutamine stress testing.

4.7 Physical activity monitoring

After all investigations, participants were provided with a waterproof fitness tracker with pedometer monitor (Muzili Smart fitness band IPX7, China). The pedometer was used to measure daily physical activity (number of steps) over the seven-day period and average daily number of steps was calculated. For those patients taking part in the intervention study, physical activity measurements were repeated after 12 weeks.

4.8 Quality of life

The Minnesota Living with Heart Failure questionnaire is a 21-item disease specific quality of life questionnaire assessing physical, socioeconomic, and psychological impairments in relation to HF.(Rector and Cohn, 1992) Scoring is dependent on how an individual ranked each item on a common scale (0-5) and it was used to assess how much HF had influenced aspects of participants' daily life. Scores range between 0 to 105 points with lower scores indicating less effect of disease and thus a better quality of life.(Bilbao et al., 2016) Change of five points in the quality of life score is considered to be clinically significant.(Riegel et al., 2002)

4.9 Intervention

The aim of the intervention was that study participants raise their overall daily physical activity level by at least 2000 steps from baseline (e.g. walking at low to moderate

intensity for approximately 30 minutes) (Slaght et al., 2017), as detailed in Chapter 7. Patients were told to maintain a logbook updating daily exercise details which was noted weekly over the phone by the research member. The exercise suggestion was updated individually as conditioning took place, with a focus on increasing activity duration more than intensity.

4.10 End of study

At the conclusion of the protocol, each participant was given a report containing their result with explanation. The study was terminated when all participants completed the last research visit within study. The complete work for all the 3 studies was done by me, including measurements and statistical analysis. Research assistant, Dr Kunda along with hospital staff helped me during the complete study process.

4.11 Statistical analysis

All continuous variables were represented as mean and standard deviation. Kolmogorov–Smirnov test was used to define the normality of distributon. Categorical data were represented as percentages and distribution. A p-value less than 0.05 was considered as statistically significant. To understand the significance between haemodynamic measurements obtained by the bioreactance and dobutamine stress echocardiography independent t-test was performed. Pearson's or Spearman's coefficient of correlation was used to look for any relationship between the two methods. Bland–Altman plots were made to understand the mean difference and upper and lower limits of agreements (±2 SD of mean difference) between the two methods. One-way analysis of variance was used to compare each echo parameter across groups and Tukey's post hoc test was done for pair-wise comparison. For the analyses, baseline and peak exercise data was used. The ANOVA test was performed to understand the changes in echo variables between baseline and peak stress state for both treadmill test and dobutamine stress, between HFrEF, HFpEF and controls. To understand for any correlation between exercise time and baseline clinical and echocardiography variables (differences between peak exercise and baseline resting values), Pearson's correlation coefficient was used. A multivariable regression model analysis was run on variables with statistically significant relationship. Intraclass correlation coefficient was done on twenty randomly selected subjects to evaluate intra-observer variability of echo variables. Complete statistics was done on SPSS version 20.0 (IBM Corp.,USA).

Chapter 5. Comparison of cardiac output estimates by echocardiography and bioreactance at rest and peak dobutamine stress test in heart failure patients with preserved ejection fraction

5.1 Abstract

Purpose: The present study assessed the agreement between cardiac output estimated by transthoracic echocardiography and bioreactance methods at rest and during dobutamine stress in heart failure patients with preserved ejection fraction (HFpEF).

Methods: Haemodynamic measurements were assessed in 20 stable HFpEF patients (12 females; aged 61±7 years) by two-dimensional transthoracic echocardiography and bioreactance methods at rest and dobutamine stress echocardiography at incremental dosages of 5,10,15 and 20 μg/kg/min until maximal dose was achieved or patient developed symptoms and sign warranting the test termination.

Results: Resting cardiac output and cardiac index estimated by bioreactance and echocardiography were not significantly different (i.e. 4.15 ± 1.23 vs 4.61 ± 1.09 l/min, p = 0.07 and 2.49 ± 0.61 vs 2.80 ± 0.76 l/min/m^2, p = 0.08 respectively) but not resting heart rate (78 ± 16 vs 78 ± 15, p = 0.93). At peak dobutamine stress, bioreactance reported significantly lower cardiac output, cardiac index and stroke volume compared to echocardiography (i.e. 5.71 ± 1.59 vs 7.06 ± 1.43 l/min, p <0.01, 3.43 ± 0.87 vs 4.27 ± 0.67 l/min/m^2 , p <0.01; and 58.57 ± 21.22 vs 67.77 ± 15.66 ml/beat p = 0.05 respectively). The mean difference (lower and upper limits of agreement) between bioreactance and echocardiography cardiac outputs at rest and peak dobutamine stress was -0.45 (1.71 to -2.62) L/min and -1.35 (0.60 to -3.31) L/min respectively. The mean difference for stroke volume, (with upper and lower limits of agreement) between the two methods at rest and peak dobutamine stress was -5.69 (19.8 to -31.2) ml/beat and -9.2 (9.59 to -27.99) ml/beat respectively.

Conclusion: Based on the mean difference and limits of agreement in haemodynamic variables estimated by bioreactance and echocardiography, it is reasonable to suggest that the two methods should not be used interchangeably.

5.2 Introduction

Evaluation of cardiac output at rest and after stress testing is an important hemodynamic predictor of functional capacity and mortality in patients with heart failure with preserved ejection fraction (HFpEF).(Marik, 2013) The gold standard methods for measurement of cardiac output are the invasive Fick's (Bizouarn et al., 1994), and Swan Ganz pulmonary artery catheterisation thermodilution methods.(Swan et al., 1970) Currently, minimally invasive (e.g. pulse contour, transpulmonary thermodilution, and transoesophageal echocardiography) and non-invasive (e.g. thoracic electrical bioimpedance, electric bioreactance, transthoracic echocardiography) techniques have been developed to monitor haemodynamic function. Non-invasive methods have the advantage of having no risk of infections, arrhythmias, complications related to central line insertion and is also less expensive.(Hodzic et al., 2014) Transthoracic echocardiography and bioreactance technologies are widely used in clinical practice and research. Bioreactance technology is an improvement to bioimpedance technology overcoming limitations seen with bioimpedance such as improved signalling in patients with fluid overload.(Critchley et al., 2000) Transthoracic echocardiography has developed extensively in last decade for assessment of cardiac haemodynamics, and global longitudinal strain for identification of subclinical cardiac dysfunction.(Opdahl et al., 2015, Borlaug et al., 2010) These technologies have been validated and shown to be reliable when compared to the invasive gold standard.(Mercado et al., 2017, Squara et al., 2007) Both the methods are non-invasive, easily accessible and are used in wider medical places where deployment of gold standard methods is not feasible. Their usage comes handy where it is mandatory to assess the haemodynamic response to a physiological or pharmacological stimulus like passive leg raising, response to intravenous fluids or during drug titrations, any kind of surgery or during anaesthesia. However, no study has evaluated the agreement of haemodynamic variables estimated from both technologies. Hence, this study aimed to evaluate the agreement between transthoracic echocardiography and bioreactance methods for estimating haemodynamic variables at rest and at peak stress in HFpEF patients.

5.3 Methods

The present prospective, observational, unicentre, direct comparison study was done for the evaluation of any consensus between the two methods of bioreactance and transthoracic echocardiography for evaluating cardiac output (CO) at rest and at peak

stress. The study was approved by the local Research Ethics Committee at the Sengupta Hospital (Nagpur, India).

5.3.1 Participants

The present study selected and enrolled twenty consecutive clinically stable HFpEF patients (12 females and 8 males) coming to the outpatient department and who were willing to give consent for the study. Heart failure patients who were clinically stable for a minimum period of 6 weeks and were on guideline directed medical management. Patients with significant valve disease, known cardiac arrhythmias, history of ischaemic heart disease or any acute unstable cardiac disease within three months prior, primary pulmonary hypertension and any cancer taking chemotherapy were excluded from the study. Subjects were requested to be nil by mouth for 2 hours before the examination and also avoid strenuous exercise one day before the test. They were also requested to abstain from caffeine or alcohol on the test days. After arriving at the research department of the hospital, the study protocol was discussed with participants and any questions arising were answered after which participants provided written informed consent.

5.3.2 Study assessments

Participants laid in a supine position for 10 minutes and blood pressure was measured twice from the brachial artery of participant's non-dominant arm. Heart rate (HR), stroke volume (SV), CO and cardiac index (CI) were measured by bioreactance (BR) and transthoracic echocardiography (TTE) concurrently at rest and at peak dobutamine infusion stress test.

5.3.2.1 Dobutamine stress echocardiography

Dobutamine stress echocardiography (DSE) test was done according to the protocol earlier described in chapter 4.5.7. (Egstrup et al., 2013) Patients were advised not to take beta-blocker and/or nitrate medication 24 hours before the test. As a safety precaution, patients were told not to take orally four hours before the dobutamine stress test in order to adequately mitigate potential adverse event where patients may need intubation and resuscitation.(Cotrim and Carrageta, 2000) Dobutamine was given intravenously in graded manner of 3 minutes interval, with an increasing dose of 5,10,15 and 20 µg/kg/min till highest dose was reached or sign or symptoms happened like that of chest discomfort, hypertensive response, breathlessness, ST-T changes on ECG, rhythm abnormalities or patients inability to take the medication. Blood pressure

was manually checked at every 3-minute interval. All the necessary echocardiographic views were acquired twice, at the start of the test and at the time of peak tolerated dose.

5.3.2.2 Bioreactance

The BR system used in this study was NICOM, non-invasive cardiac output monitor (Cheetah Medical, Delaware, USA). It uses relative phase of an oscillating current shifts which are time-dependent and it passes the thoracic cavity. This method takes help of a radiofrequency generator which generates high frequency current passing through the chest. The signals come and go the electrodes, get recorded and digitally processed to give information about cardiac output and other haemodynamic details. The details of the bioreactance technology is available in Chapter 4 (4.5.5).

5.3.2.3 Transthoracic echocardiography

Echocardiography is a non-invasive diagnostic method which uses doppler ultrasound for the assessment of cardiac structure and function. The detailed echocardiographic examination was done as per the guidelines of the American Society of Echocardiography.(Lang et al., 2015) All echocardiography assessments were performed at rest and after dobutamine stress testing by a single experienced sonographer from the left lateral position at 50-70 frame rate/seconds, using echo machine (Vivid E95, 2.5-4.0 MHz transducer, GE Vingmed Ultrasound AS, Norway). A total of consecutive three beats were taken for analysis. Measurements taken were for LV septal and posterior wall thickness, left atrial (LA) anterior-posterior dimension and LV internal diameter from the parasternal long axis view. Biplane Simpson's method was used to calculate LVEF which requires assessment of LV end-diastolic and end-systolic volumes (LVEDV and LVESV, respectively).(Lang et al., 2015) LA volume was calculated by biplane area- length which was subsequently indexed to body surface area. For LV analysis, the 17-segment model was done. For LV outflow tract measurement at the time of systole, parasternal long axis view was used.(Lang et al., 2015) Pulsed-wave doppler of the LV outflow tract was measure the best apical view. Further description of the echocardiography is provided in Chapter 4 (4.5.4).

5.3.3 Data analyses

The normality of distribution was defined by Kolmogorov–Smirnov test. Paired t-test was done to understand the differences in haemodynamic measurements obtained by BR and TTE at rest and peak dobutamine stress. Pearson's or Spearman's coefficient

of correlation was used to look for any relationship between the two methods. Bland–Altman plots were made to define the mean difference and upper and lower limits of agreements (± 2SD of mean difference) between the two methods. The statistics was carried out using SPSS software version 20 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± SD unless otherwise stated and statistical significance was indicated if $p<0.05$.

5.4 Results

The patient demographic and clinical characteristics are presented in Table 5.1. In all patients the signals generated from bioreactance was found to be stable and clear both at rest and throughout dobutamine stress test.

Table 5.1 Clinical features and demographics (n=20)

Demographics	Mean ± SD
Age (years)	61±7
Height (cm)	154±7
Weight (Kg)	67±15
Body surface area (m^2)	1.7±0.2
Clinical Characteristics	
NYHA class	1.3±0.5
Left ventricular ejection fraction (%)	54±3
Diabetes mellitus (%)	7 (35)
Hypertension (%)	17 (85)
Ischaemic heart disease (%)	4 (20)
ACEI/ARBs (%)	16 (80)
Beta blocker (%)	6 (30)
Diuretics (%)	7 (35)
Calcium channel blockers (%)	2 (10)

ACE, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blockade; NYHA, New York Heart Association functional class

No difference was seen in baseline HR by BR and 3-lead ECG from TTE. The dobutamine average dose was 18.75±2.22 ug/kg/min for all the subjects. Baseline CO and CI estimated by BR and TTE also did not have any significant difference (Table 5.2).

Table 5.2 Differentiation of echocardiography and bioreactance parameters at rest and peak dobutamine stress test

Parameter	Echocardiography	Bioreactance	P value
Rest			
Heart rate (beats/min)	78 ± 15	78 ± 16	0.93
Cardiac output (L/min)	4.61 ± 1.09	4.15 ± 1.23	0.07
Cardiac index (L/m^2/min)	2.80 ± 0.76	2.49 ± 0.61	0.08
Stroke volume (ml)	59.5 ± 11.9	53.8 ± 13.9	0.06
Systolic Blood pressure (mm Hg)	121 ± 8	118 ± 18	0.29
Diastolic Blood pressure (mm Hg)	77 ± 5	69 ± 10	< 0.01
Peak stress test			
Heart rate (beats/min)	103 ± 15	102 ± 16	0.54
Cardiac output (L/min)	7.06 ± 1.43	5.71 ± 1.59	< 0.01
Cardiac index (L/m^2/min)	4.27 ± 0.67	3.43 ± 0.87	< 0.01
Stroke volume (ml)	67.8 ± 15.7	58.6 ± 21.2	< 0.01
Systolic Blood pressure (mmHg)	137 ± 24	125 ± 42	0.54
Diastolic Blood pressure (mm Hg)	79 ± 9	72 ± 10	< 0.01

There was no significant difference in HR at peak dobutamine stress. BR showed significantly lesser values of SV, CO and CI as that with Doppler echocardiography ($p<0.01$, Table 2). There was a positive relationship between TTE and BR derived CO at rest ($r=0.56$, $p<0.01$) and peak stress ($r= 0.79$, $p < 0.01$; Figure 5.1).

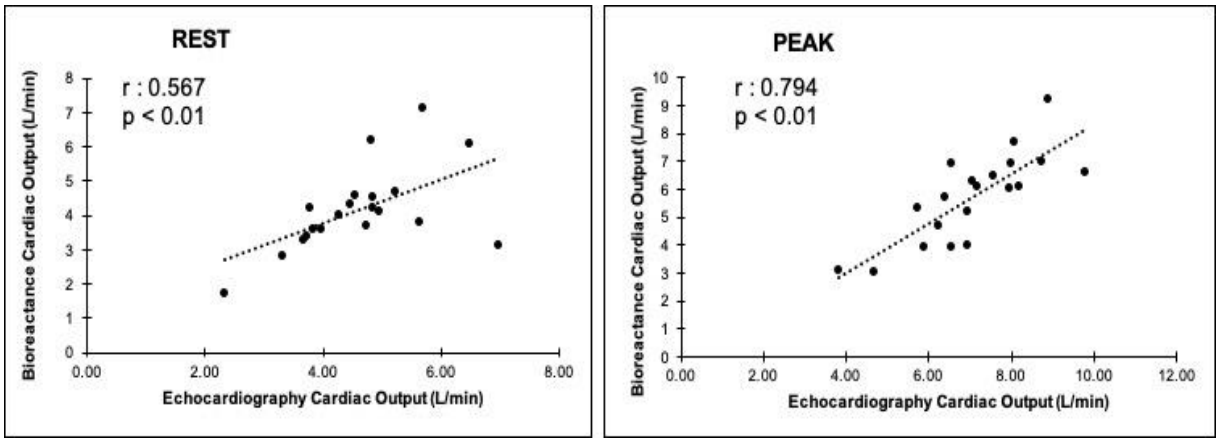

Figure 5.1 Correlation between bioreactance and echocardiography derived cardiac outputs at rest and peak dobutamine stress.

The mean differences (lower and upper limits of agreement) between BR and TTE derived CO at rest and peak dobutamine stress were -0.45 (1.71 to -2.62) L/min and -1.35 (0.60 to -3.31) L/min, and -5.69 (19.8 to -31.2) ml/beat and -9.2 (9.59 to -27.99) ml/beat for SV respectively (Figure 5.2 A-D).

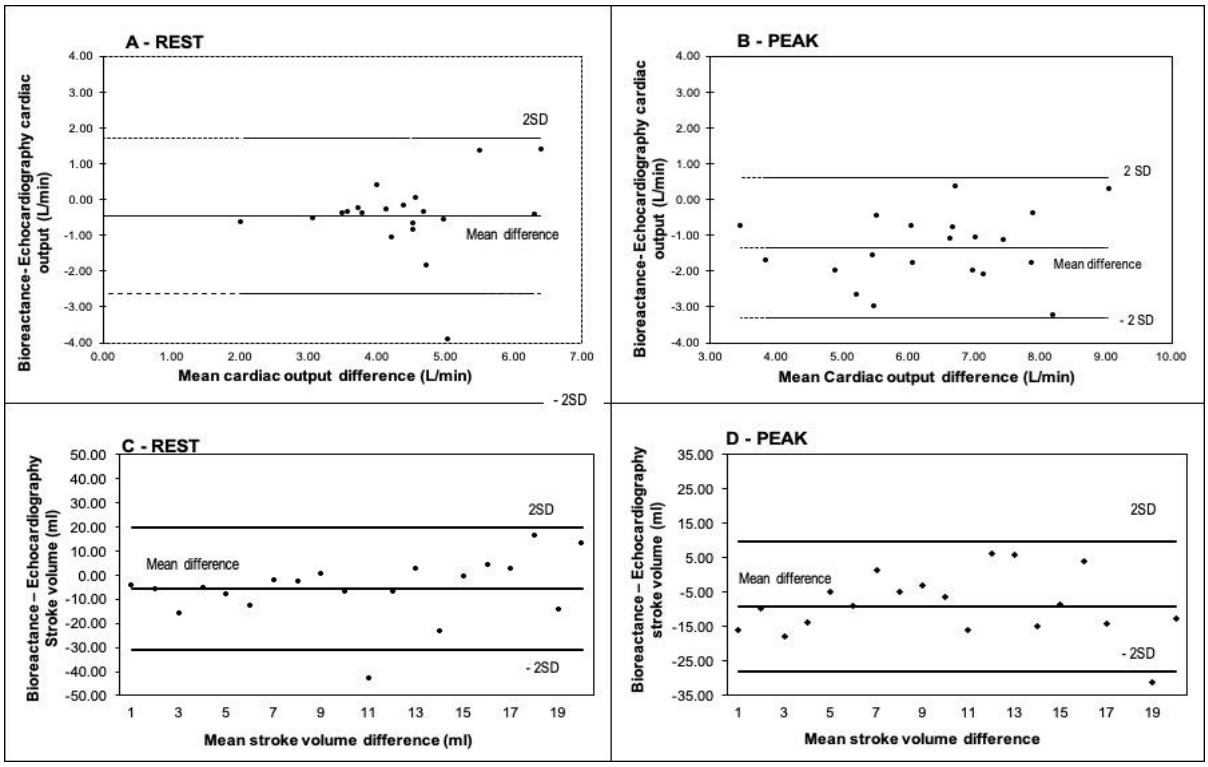

Figure 5.2 Bland-Altman plot featuring agreement between bioreactance and echocardiography derived parameters measured at rest (A), peak dobutamine stress test (B), stroke volume measured at rest (C), and peak dobutamine stress test (D).

5.5 Discussion

The prognostic value of LV ejection fraction at rest and during exercise in HF patients is well established, but much less focus has been given to cardiac output (CO) at rest and during exercise, partly owing to the lack of reliable, reproducible, and non-invasive methods with which to measure it.(Shelton et al., 2010) It has been known that CO measurements at rest are unrepresentative of cardiac reserve in HF patients and hence the need of stress tests in these group of patients. This is the first study to show comparison between two methods which are non-invasive ways to provide CO i.e. TTE and BR at rest and after dobutamine stress test in patients of HFpEF who were clinically stable. The important finding is that there was hardly any difference in values at rest of cardiac output and stroke volumes generated from TTE and BR. At peak dose of dobutamine stress, CO measured by BR was lower as that to derived by TTE. Furthermore, the calculated limits of agreement were not similar and unacceptable,

showing that these techniques cannot be used interchangeably.

Normally, stroke volume is the main determinant of CO in the first part of exercise.(Corrieri et al., 2021) With increasing exercise, the heart rate increases linearly to 85% of maximal exercise capacity after which the heart rate starts to flatten. Then the exercise capacity is mediated by blood flow distribution in the exercise muscles and muscle oxygen extraction. This mechanism gets affected in HF patients. The most recent definition of HF from the European Society of Cardiology suggests that HF results in reduced CO at rest or during stress.(McDonagh et al., 2021) In spite of availability of reliable and non-invasive methods of determining CO at rest and after stress, the guidelines donot incorporate measurement of CO into HF diagnostic pathway. One of the reasons may be that accurate CO determination in not always feasible during exercise.(Warburton et al., 1999) HFpEF patients may show impairment of increase in CO after exercise relative to metabolic requirement.(Abudiab et al., 2013) This may be due to cardiac limitations or non-cardiovascular reasons like patient motivation, limitations due to peripheral causes or fitness issues. HFrEF patients are limited as they have predominant inadequate cardiac reserve, while HFpEF patients are charaterised by normal to sub-optimal CO response but with elevated filling pressure.(Borlaug et al., 2010) HFpEF patients demonstrate a rise in LV preload during exercise, but this occurs at a cost of three fold rise in LV filling pressure which is not seen in normal individuals. Resting CO is lower in HFrEF patients, but make be normal in HFpEF patients.(Shelton et al., 2010) The peak CO is reduced by around 40-50% in HFrEF patients as compared to healthy individuals and is the main determinant of exercise intolerance in them.(McCoy et al., 2017) Peak CO measured noninvasively has been shown to be an independent predictor of outcome in HFrEF patients.(Lang et al., 2009) It has also been suggested that CO and derived variables like cardiac power output at submaximal exercise loads below anaerobic threshold can have prognostic value in HF patients.

The present study showed different CO values response in the two methods used. Differences in CO values between the two methods are likely to be attributed to the different methodology used to derive stroke volume and thus cardiac output, considering that the heart rate was not different. BR uses the concept of electrical stimulation across the thoracic cavity and is affected by fluid accumulation in thorax as seen in HFpEF. TTE uses the principle of Doppler to derive CO from flow across the aortic valve. However, echocardiography requires expert training to acquire optimal images and also to interpret the haemodynamic parameters. BR, on the other hand is

operator-independent and provides continuous haemodynamic measurement.

The use of the technique of BR for the measurement of CO at rest and during exercise has been studied in congestive cardiac failure patients.(Maurer et al., 2009, Myers et al., 2007) In another work, the authors concluded that NICOM technology is not a useful technique for getting CO in unstable acute heart failure patients and patients with cardiogenic shock as that by thermodilution.(Rali et al., 2020) The authors explained that in patients with advanced heart failure, pulmonary and interstitial oedema, signals from bioreactance get affected due to fluid accumulation. This is not the case with TTE which provides better non-invasive assessment of cardiac output. Although BR is thought to be an improvement to the bioimpedance technology which was limited by electric noise, chest wall oedema and pleural effusion.(Critchley et al., 2000) Furthermore, changes in loading conditions which are seen in HF patients tend to impact the intrathoracic impedance affecting the current phase shifts necessary to measure the stroke volume and cardiac output. However, important study has shown that BR has good use in understanding response to fluid in intensive care patients.(Marik et al., 2013) This can hence be applied in conditions like in HFpEF patients where assessment of filling pressure and fluid haemodynamics are key in treatment of patients.

Echocardiography is used globally for calculating cardiac output in critical care setting.(Mercado et al., 2017) The present study used the doppler method of pulse wave across the LVOT for deriving CO. CO calculated from LVOT shows good correlation with that derived from velocities from mitral or pulmonary valves.(Tribouilloy et al., 1991, Dericbourg et al., 1990) For example, in a cohort of 38 patients on invasive ventilator, Mercado et al. mentioned that CO assessed echocardiography correlated well with CO from invasive swan-Ganz technique.(Mercado et al., 2017) Evidence suggests usage of LVOT blood method is better than cardiac outflow derived from ejection fraction in advanced heart failure patients for predicting outcomes.(Tan et al., 2017) However, assessment of cross sectional area of left ventricular outflow tract can be challenging and it should be carefully done in zoom method.(Tan et al., 2017)

Both the methods used in the present study were easy to perform and non-invasive. BR method is patient friendly, providing continuous CO monitoring and can be used everywhere, especially in cardiac critical care where cardiac output assessment is the key in patient management. However, patients with implanted cardiac devices may experience interference with the bioreactance signals thus limiting its effectiveness in this patient group.(Jakovljevic et al., 2012) In addition, the CO derived from BR is

established on the assumption that the area under the flow pulse corresponds to the product of maximum flow and ventricular ejection time. Therefore this method can have lower accuracy in patients with low flow status.(Keren et al., 2007)

There are few limitations in the present study. Firstly, the study did not perform the direct Fick's method, which is the gold standard for measuring cardiac output. However, the Fick's principle is invasive and has inherent risks thus it was not considered appropriate to be used in this comparison study. Moreover, BR and echocardiography have been previously confirmed against the invasive gold standard methods of thermo-dilution and Fick's methods with results showing good levels of agreement for both techniques. Secondly, this was a single centre study with a small sample size potentially limiting generalizability of the main conclusions. The repeatability of data on the bioreactance and echo measurements were not performed in the present study. However, repeatabililty of bioreactance for estimating cardiac output has been previously studied by our group.(Jones et al., 2015)

5.6 Conclusion

TTE and BR give non-identical cardiac output measurements, at rest and during pharmacological stress hence cannot be used interchangeably in patients with HFpEF. These can be due to technological differences between BR and TTE along with changes in preload and afterload parameters, complex haemodynamics and potential alterations in pulmonary vascular reserve observed in HFpEF. However, this should not stop their utility in clinical practice, as its benefits over the gold-standard methods have been well established.

Chapter 6. Cardiac response to pharmacological and physiological stress in heart failure reduced versus heart failure preserved ejection fraction

6.1 Abstract

Purpose: Exercise intolerance is an important symptom of patients with heart failure (HF). This chapter evaluated exercise-related left atrial (LA) and ventricular function in patients with HF preserved ejection fraction (HFpEF) and HF reduced ejection fraction (HFrEF).

Methods: Forty HFpEF (age 59±7 years, 63% females) patients, 40 (age 57±6 years, 38% females) HFrEF patients, and 20 age matched healthy controls (age 56±6 years, 35% females) did resting and exercise stress transthoracic echocardiography by modified Bruce protocol. Speckle tracking echocardiography was used to acquire peak atrial longitudinal strain (PALS) and left ventricular global longitudinal strain (LVGLS).

Results: At rest, HFpEF and HFrEF patients showed significantly lower PALS in comparison with controls (i.e. HFpEF, 23.1±4.7% vs HFrEF, 11.5±1.4% vs controls, 34.0±1.90%, $p<0.01$) and LVGLS (HFpEF, -15.9±2.7% vs HFrEF, -11.51±3.4% vs controls, -20.3±0.90%, $p<0.01$). HFpEF and HFrEF patients had a 28% and 30% reduction in exercise time in comparison with controls (HFpEF, 363±152 vs HFrEF, 352±91 vs controls, 505±42 seconds, $p<0.01$). There was a significant 14% exercise-related increase in E/E' in HFpEF patients (12.6±3.3 vs 14.4±5.1, $p<0.01$) and 17% increase in E/E' in controls (9.4±2.01 vs 11.3±0.24, $p<0.01$) but not in HFrEF. Compared to resting values, PALS declined at peak exercise by 26% in HFpEF (23.1±4.7% vs 18.5±3.5%, $p<0.01$), and 8% in HFrEF (11.5±1.4% vs 10.5±1.5%, $p<0.01$), but there was no change in controls (34±1.9% vs 34.4±1.2%, $p=0.4$). PALS change was associated with exercise time in the cohort ($r=0.36$, $p=0.0002$) and 1% decrease in PALS was associated with a 16-seconds reduction in exercise duration ($p<0.01$). Rest and peak exercise LVGLS were significantly lesser in HFrEF compared to HFpEF and controls (i.e. rest, HFrEF, -11.51±3.4% vs HFpEF, 15.9±2.7% vs controls -20.3±0.90%; and peak, HFrEF, -11.0±2.60% vs HFpEF, -15.5±3.20% vs controls -19.9±0.80%).

Conclusion: Left ventricle and LA strain are lesser in HFrEF than HFpEF at rest and exercise as that to healthy controls. HFpEF patients show marked reduction in LA reservoir function with exercise which appears to contribute to exercise intolerance.

6.2 Introduction

Left atrial (LA) dysfunction and remodeling are key morphological features in heart failure (HF) patients, along with structural and functional alterations in the left ventricle (LV).(Reddy and Borlaug, 2020, Freed et al., 2016) In HFpEF patients, LA dysfunction and dilatation are independent risk factors for the development and progression of HF.(Santos et al., 2014, Santos et al., 2016, Lang et al., 2015, Gan et al., 2018) In HFpEF patients, diastolic dysfunction with raised filling pressures cause LA dilatation and dysfunction.(Solomon and Biering-Sørensen, 2017, Ersbøll et al., 2013) However, LA dilatation and dysfunction may also occur in LA myopathy that develops in presence of LV myopathy, or in isolation.(Patel et al., 2021)

Exertional breathlessness and fatigue are the hallmark of HFpEF and HFrEF.(Schwinger, 2021) Despite similar levels of exercise intolerance across all HF phenotypes, the contribution of LA and LV deformation towards the development of exercise intolerance has been an area of interest in pathophysiology of HFpEF and HFrEF.(Kurt et al., 2009, Westermann et al., 2008, Telles et al., 2019, Von Roeder et al., 2017b, Lundberg et al., 2019b) It is important to know the simultaneous changes in LA and LV mechanical function with exercise stress as they can provide new insights into pathophysiology of HF which can help in better management and provide prognosis. Two-dimensional (2D) speckle tracking echocardiography helps in advanced evaluation of the left ventricular and atrial deformation during exercise.(Lundberg et al., 2019a) The LA and LV coupling along with alteration in LA reservoir and booster pump function may have significance in the pathophysiology of breathlessness and exercise incapacity seen in HF patients.(Schwinger, 2021)

6.2.1 Aims, objective and hypotheses

The present work aimed to define the role of LA function in exercise tolerance in patients with HFpEF and HFrEF. The objective was to compare LA and LV function in patients with HFpEF, HFrEF and age and sex matched controls and to define the relationship between LA and LV function and exercise capacity. Based on prior knowledge, this chapter will test the following hypotheses:

1) Patients with HFpEF and HFrEF will demonstrate significantly reduced peak atrial longitudinal strain (PALS) compared to controls, and

2) There will be a significant relationship between PALS and exercise time in patients with HFpEF and HFrEF.

6.3 Methods

A single centre, prospective cross-sectional study was conducted to evaluate cardiac response to physiological stress in HFrEF and HFpEF in comparison with age-matched controls.

6.3.1 Participants

One hundred and nine stable individuals were first identified for the study of which 49 were HFpEF, 40 HFrEF and 20 age matched controls. Nine HFpEF subjects could not be taken as 7 patients had atrial fibrillation, 2 had recent ischaemic heart disease in last 12 weeks. 40 HFrEF, 40 HFpEF, and 20 age matched controls were then taken in the protocol (Figure 6.1).

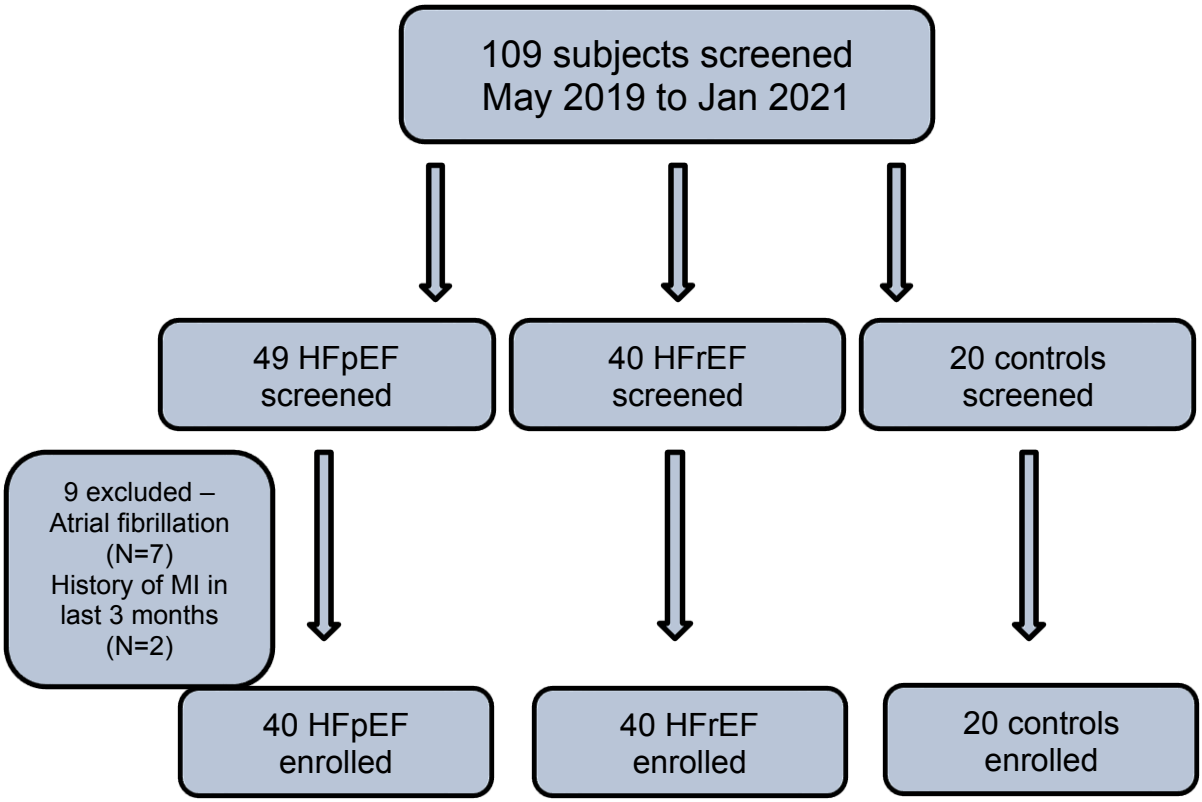

Figure 6.1 Flow chart to demonstrate study participants

Only heart failure patients who were stable were included in the study. The patients had to be clinically stable for atleast one and half months before inclusion and they should be taking optimal medical treatment. HFrEF was defined as patients with LV ejection fraction (LVEF) $\leq$ 40% and symptoms and signs of heart failure and HFpEF, as patients with LVEF > 50% along with symptoms and signs of heart failure with functional and/or structural changes in heart, and elevated N-terminal pro-b-type

natriuretic peptide (NT pro-BNP).(Mcdonagh et al., 2021) Patients with history of recent ischemic heart episode in last 3 months, life-threatening arrhythmias including atrial fibrillation (AF), valvular problem, idiopathic pulmonary arterial hypertension, cardiac implantable electronic device, cancer, pregnancy, or not able to give consent were not taken in the study. AF patients were not taken as LA strain analysis is difficult in patients with AF.(Badano et al., 2018) The different variables included were the demographics and comorbidities, New York Heart Association (NYHA) functional status, treatment history, vital signs, body mass index, and blood information like haemoglobin, kidney function test, and NT pro-BNP. Written informed consent was taken from all participants and the study was approved by the institutional ethics committee. The complete work was executed according to the declaration of Helsinki.

6.3.2 Transthoracic echocardiography

A complete transthoracic echocardiography study was done as per the suggestions of the American Society of Echocardiography (ASE).(Lang et al., 2015) The study was done in the left lateral position using GE Vivid E95 system. The images were recorded taking in three consecutive heart cycles. They were then analyzed offline by a single echo cardiographer who was not knowing about the data. A second echo cardiographer analyzed data from a subset of 20 randomly selected patients. Study was done at end-expiratory breath-hold at 50-80 frames/sec. LV ejection fraction (EF) were calculated by biplane Simpsons method from LV end diastolic and end systolic volumes. Stroke volume and cardiac output measurements were made at LV outflow tract level. The early (E) and late (A) mitral flow velocities were calculated by pulsed wave. LA volume was calculated by area-length method followed by indexing to body surface area to get LA volume index (LAVi). Tricuspid regurgitation peak velocity (TRVmax) was recorded using continuous-wave doppler across tricuspid valve. Tissue doppler velocities (e') were calculated at septal and lateral mitral annulus. The E/e' ratio was derived by averaging septal and lateral tissue velocities. LV mass was calculated by the following formula (Lang et al., 2015):

$$\text{LV mass} = 0.8\{1.04[([\text{LVEDD} + \text{IVSd} + \text{PWd}]^3 - \text{LVEDD}^3)]\} + 0.6$$

where LVEDD, IVSd, and PWd represent LV, interventricular septal, and posterior wall thickness in diastole, respectively, was derived assuming LV dimensions in centimetres. The fraction of LV filling pressure to LV internal diameter in diastole provided the LV stiffness index value.(Westermann et al., 2008)

LV and LA strain was analyzed by 2-D strain imaging. LV global longitudinal strain (LV-GLS) was calculated as the average number of 12 segments obtained from the 3-,4- and 2-chamber apical views. The software traces the LV endocardial border in the end-systolic frame generates myocardial strain curves. It tracks the natural acoustic markers frame by frame over one complete cardiac cycle. This then generates peak-systolic strain curve and values for every myocardial segment. An average of these values provide the main value which is then noted.

LA strain required good LA images acquired from apical 4 and 2 chamber views at 50-80 frames per second. The R-R cycle from ECG is used for tracking. At onset of the QRS complex all longitudinal LA strain values were positive. The LA endocardial border was manually traced to provide a region of interest, which was adjusted to include the full thickness of the LA myocardium. LA then got divided into 6 separate segments by the software and longitudinal strain curves were generated. Subsequently, the average value is then considered. The LA strain components which got defined were LA reservoir strain also called as peak atrial longitudinal strain (PALS) and LA booster strain which is same as peak atrial contraction strain (PACS)(Figure 6.2).(Gan et al., 2018) The fraction of LV filling pressure' to PALS provided the LA stiffness index. Higher values indicate more LA stiffness and correlates with higher grades of diastolic dysfunction.(Kurt et al., 2009)

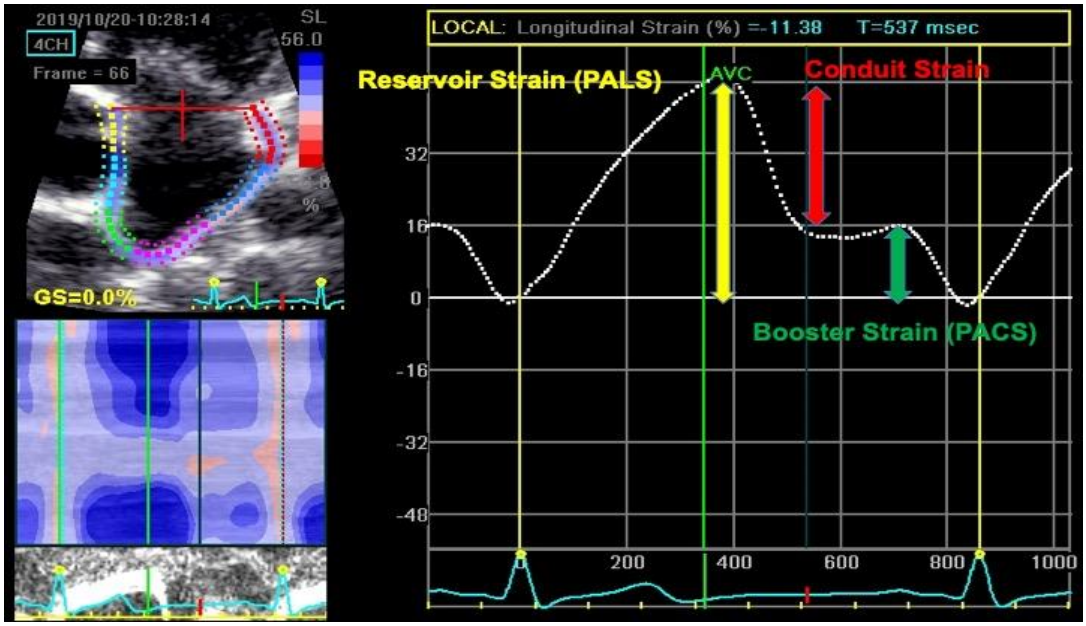

Figure 6.2 Shows measurement of left atrial strain. PALS, peak atrial longitudinal strain; PACS, peak atrial contractile strain

6.3.3 Exercise protocol

The treadmill stress test was symptom limited applying modified Bruce protocol. Limitation of symptom was assessed using the Borg rating of perceived exertion scale.(Borg, 1982) All the vitals and echocardiographic parameters were obtained at baseline and after 2-3 minutes of stoppage of exercise as diastolic parameters remain after completion of exercise.(Ha et al., 2020)(Borg, 1982)(Ha et al., 2020)

6.3.4 Sample size and power calculation

In the absence of any earlier data on PALS and exercise, the sample size could not be estimated apriori. Hence it was calculated posteriori using G-power 3.1 program.(Kang, 2021) A sample of 40 patients was considered in each HFpEF and HFrEF groups, and the change in PALS from baseline to peak were obtained. In HFpEF, the change was -4.58 (SD:4.71), while in HFrEF, the change was -1.04 (SD: 1.92). The data resulted into an effect size of 0.9875. Considering the effect size, the above sample per group and 5% type I error, the resulting power was 95.8%, which was much above the desired 80%.

6.3.5 Data analysis

All data were analyzed at rest and following peak exercise. Continuous variables are presented as mean and standard deviation while categorical variables are expressed as percentages and distribution. One way analysis of variance was used to compare echo parameters across groups and pair-wise comparison was evaluated using Tukey's post hoc test. For understanding correlation between exercise time and clinical and echocardiography parameters (differences between peak exercise and baseline–resting values), Pearson's correlation coefficient was used. Multiple regression analysis was performed with the statistically significant ($p<0.05$) variables and exercise time as dependent variable. B coefficient reflected the effect of independent variable on this dependent variable keeping other variables constant. The independent variables were age, sex, BMI, NTproBNP, change in CO, change in PALS, change in RVSd, change in septal E', MAP and change in LVGLS. The intra and inter-observer variability of echo parameters was assessed by intraclass correlation coefficient. The complete statistics was done by SPSS software version 20.0 (IBM Corp.,USA).

6.4 Results

6.4.1 Demographics

The demographics and clinical characteristics of the participants are presented in Table 6.1.

Table 6.1: Demographic, physical and clinical characteristics

Variable	HFpEF (n=40)	HFrEF (n=40)	Healthy controls (n=20)
Age (years)	59±7	57±6	56±6
Male (%)	15 (37.5)	25 (62.%)	13 (65)
Height (cm)	155±8	161±9	163±7
Weight (Kg)	69.5±14.9	65.7±10.5	62.7±6.2
Body surface area (m^2)	1.68±0.18	1.7±0.21	1.68±0.11
Duration of heart failure (years)	2±1.5	2.6±1.3	-
Coronary artery disease (%)	12 (30)	27 (67.5)	-
Hypertension (%)	36 (90)	23 (57.5)	-
Diabetes Melitus (%)	13 (32.5)	22 (55)	-
Smoker (%)	6 (15)	14 (35)	
B-blocker (%)	12 (30)	35 (87.5)	-
ACEI/ARB (%)	34 (85)	12 (30)	-
ARNI (%)	-	28 (70)	-
Calcium channel blocker (%)	5 (12.5)	4 (10)	-
Haemoglobin (gm%)	11.7±1.7	11.6±1.3	12.9±0.9
Thyroid-stimulating hormone (IU/ml)	2.03±1.27	2.19±0.95	1.81±0.49
NTproBNP (pg/ml)	1291±1404**	2043±1046*	207±78
Serum sodium (meq/l)	138±5	136±5	138±4
Serum potassium (meq/l)	4.09±0.45	3.85±0.5	4.00±0.10
Serum creatinine (mg/dl)	0.95±0.34	1.17±0.23	0.95±0.11
Total Cholesterol (mg/dl)	155±21*	177±26**	171±25
High density lipoprotein (mg/dl)	42.7±7.9	37.1±3.9	38.7±3.7
Low-density lipoprotein (mg/dl)	99.9±27.2*	114±16**	117±13

*p<0.01, HFpEF and HFrEF vs healthy controls; **p<0.01, HFpEF v HFrEF
ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; ARNI, Angiotensin receptor neprilysin inhibitor; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; NTproBNP, N-terminal pro b type natriuretic peptide.

6.4.2 Cardiac structure and function at rest (baseline)

Patients with HFpEF and HFrEF had concentric and eccentric remodelling respectively. In contrast to HFrEF, HFpEF patients had a smaller end diastolic volume

(83±17 mL vs 100±27 mL, p<0.01) and LV mass (115±23 vs 135±19 g, p<0.01). The difference between HR and mean arterial pressure (MAP) was not significant between HF and controls (Table 6.2).

The LV mass index was more in patients of HFpEF and HFrEF as that of controls (p<0.01). The LV end diastolic and end systolic volume were higher at rest in HFrEF as opposed to HFpEF and controls (p<0.01). The E/E' ratio which reflects the filling pressure was higher at rest in both groups as that of controls (p<0.01). At rest, HFpEF patients had higher mean cardiac output than in HFrEF patients (p<0.01). But the systemic vascular resistance (SVR) rest was lesser in HFpEF as opposed to HFrEF (p<0.01). At rest, HFpEF patients had more stroke volume, cardiac power output and LV ejection fraction than HFrEF (p < 0.01) (Table 6.2). Also at rest, HFpEF patients had significantly higher right ventricular systolic parameters than HFrEF (p<0.01).

As compared to controls, LVGLS at rest was lesser in HFpEF and HFrEF. LVGLS was lesser in HFrEF as that to HFpEF (Figure 6.2). Also at rest, the peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS) were significantly lesser in both groups as opposed to controls with the least in HFrEF (Table 6.2).

The E/E' in both the groups were similar. At rest, the mean LA stiffness index was significantly lesser in HFpEF as that to HFrEF (Table 6.2). However, both the groups didn't show any difference in the LV stiffness index.

6.4.3 Cardiac structure and function in response to exercise

There was no statistically significant difference in exercise time between HFpEF and HFrEF, however these were 28% and 30% lesser in HFpEF and HFrEF as opposed to controls (p<0.01, Table 6.2). Similarly after exercise HR, MAP and RV systolic pressure were similar between the two groups. There were no significant changes in LVEF from rest to exercise in any of the groups. The stroke volume increased significantly from test to exercise in HFpEF and controls (p<0.01) but not in HFrEF (p>0.05)

After exercise, no notable change in LVGLS and RV free wall strain were seen in both the groups. HFpEF patients had significant decrease in PALS after exercise which was not evident in HFrEF patients (Figure 6.2).

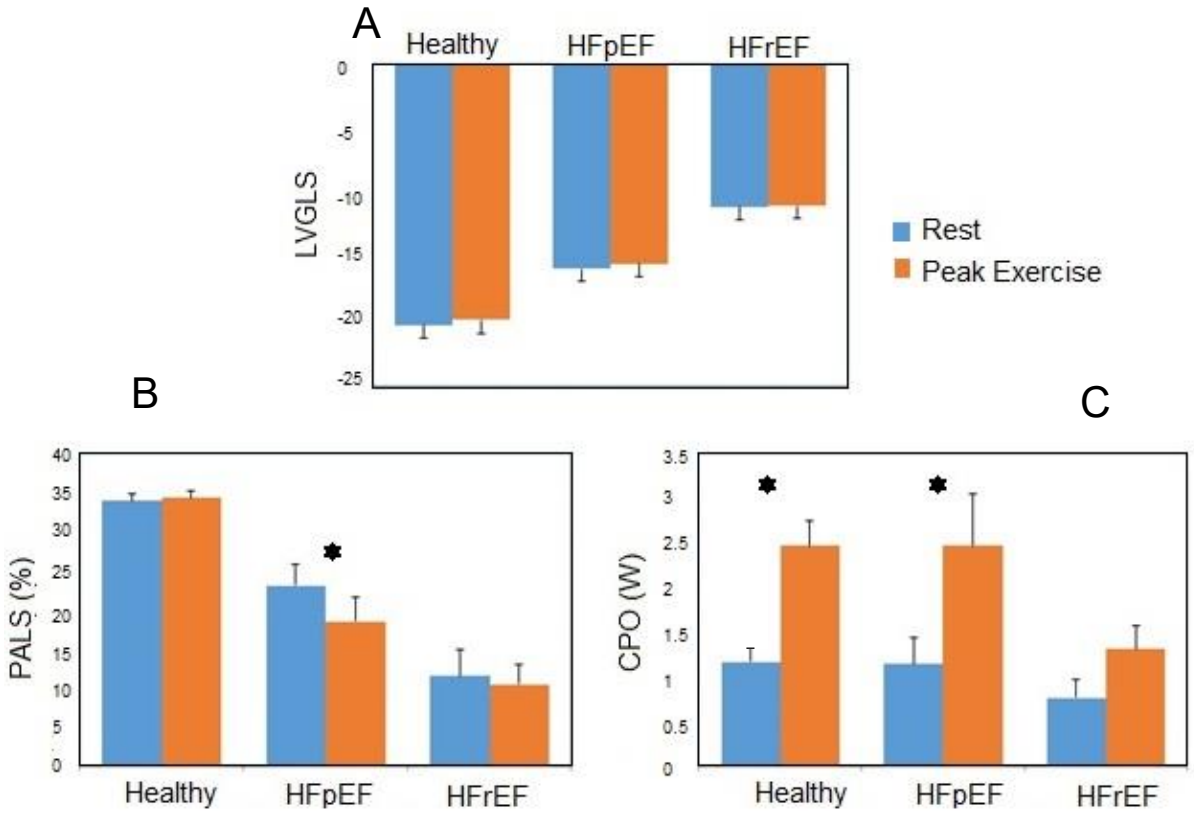

Figure 6.3 Bar diagram showing changes in left ventricular global longitudinal strain (A), peak atrial longitudinal strain (B) and cardiac power output (C) between rest and peak exercise in the cohort (* $p<0.01$).

There were no significant differences in the exercise-induced change in PACS in HFpEF and HFrEF. HFpEF and HFrEF showed a notable rise in LA stiffness index from rest to exercise ($p<0.01$). A notable rise in LV stiffness index after exercise was only observed in HFpEF. Exercise caused a notable 13% rise in LV filling pressure in patients of HFpEF.

Table 6.2: Comprehensive features at baseline and after peak exercise baseline and after peak exercise

Variables	HFpEF (n=40)		HFrEF (n=40)		Controls (n=20)	
	Rest	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*
Functional						
Heart Rate (beats/min)	77±14	116±12*	81±11	114±12*	72±7	116±5*
MAP (mm Hg)	93±6	112±7*	94±6	114±6*	94±5	113±3*
TR (m/sec)	0.13±0.33	1.00±0.23*	0.25±0.44	1.00±0.00*	-	-
PASP (mm Hg)	35.8±2.4	43.7±7.00*	38.4±4.80	49.1±3.70*	-	-
LVOT VTI (cm)	21.6±4.38	24.5±4.35*	14.3±2.63	14.2±3.14	23.5±2.19	26.2±2.41*
Structural						
LV mass (gm)	115±23$^{\$,\&}$	-	134±20$^{\$}$	-	53.4±7.19	-
LV Mass index (g/m^2)	68.8±14.3$^{\$}$	-	78.7±1.00$^{\$}$		31.5±3.70	-
Relative wall thickness	0.43±0.07$^{\$}$	-	0.37±0.05	-	0.32±0.04	-
LVOT (cm)	2.11±0.15	2.11±0.14	2.02±0.06	2.02±0.06	2.02±0.04	2.03±0.06
LVEDV 4C(ml)	83±17	81±17	100±27$^{\$,\&}$	98±25	88±9	85±7*
LVESV 4C(ml)	41±9	40±10	64±17$^{\$,\&}$	64±17	41±3	39±3
Diastolic						
E (m/sec)	0.91±0.24	1.08±0.25*	0.70±0.23	0.81±0.22*	0.79±0.15	0.93±0.10*
A (m/sec)	0.83±0.18	0.92±0.17*	0.68±0.20	0.74±0.20	0.77±0.16	0.85±0.15*
E' septal (m/sec)	0.07±0.02	0.07±0.02	0.05±0.01$^{\$}$	0.05±0.01	0.08±0.01	0.08±0.01
E' lateral (m/sec)	0.08±0.02	0.09±0.02	0.06±0.01	0.07±0.01	0.09±0.01	0.09±0.01
E/E'	12.6±3.3$^{\$}$	14.4±5.1*	13.8±5.85$^{\$}$	13.9±5.47	9.37±2.01	11.3± 0.24*
dTE (msec)	198±41	160±42*	184±42	133±3*	197±21	136±17*
Systolic						
LVEF (%)	54.2±3.11	55.5±3.47	33.9±6.26$^{\$}$	35.6±5.01	60.1±1.36	60.1±1.27
Stroke volume (ml/beat)	75±19	85±16*	46±9$^{\$}$	47±12	75±8	85±11*
Cardiac Power output (W)	1.14±0.30	2.47±0.59*	0.77±0.21$^{\$}$	1.31±0.26*	1.17±0.14	2.47±0.28*
LVGLS (%)	-15.9±2.70$^{\$}$	-15.5±3.20	-11.1±3.40$^{\$,\&}$	-11.0±2.60	-20.3±0.90	-19.9±0.80
TAPSE (cm)	2.18±0.27	2.23±0.37	1.99±0.19$^{\$,\&}$	1.95±0.12	2.07±0.13	2.03±0.20
RV systolic tissue wave (m/sec)	0.13±0.02	0.14±0.03	0.11±0.02	0.11±0.01	0.13±0.02	0.12±0.01
RV free wall strain (%)	-22.6±2.43	-22.5±1.70	-20.0±1.26	-20.0±1.41	-22.2±1.36	-21.9±1.38
PALS (%)	23.1±4.70$^{\$}$	18.5±3.50*	11.5±1.40$^{\$,\&}$	10.5±1.50	34.0±1.90	34.4±1.20
PACS (%)	8.50±1.60$^{\$}$	8.10±2.20	2.60±0.80$^{\$,\&}$	2.50±0.70	9.80±1.80	10.8±1.20*
Haemodynamics						
Cardiac output (L/min)	5.51±1.35	9.93±2.23*	3.70±0.91$^{\$,\&}$	5.18±1.04*	5.38±0.6	9.84±1.04*
SVR (dynes/sec/cm^{-5})	1269±248$^{\$}$	841±167*	1997±463$^{\$,\&}$	1644±291*	1408±185	924±88*
LA stiffness index (mm Hg/ml)	0.57±0.22$^{\$}$	0.83±0.46*	1.19±0.63$^{\$,\&}$	1.37±0.61*	0.27±0.06	0.33±0.04*
LV stiffness index (ml^{-1})	0.16±0.05$^{\$}$	0.18±0.07*	0.14±0.07$^{\$}$	0.15±0.06	0.11±0.02	0.13±0.02*
Ventricular elastance (mm Hg/ml)	3.26±0.74	3.97±0.98*	2.06±0.53$^{\$,\&}$	2.58±0.75*	3.15±0.34	3.89±0.36*
Exercise time (sec)		363±152$^{\$}$		352±91$^{\$}$		505±42

*p < 0.01, rest and exercise, $p<0.01, HFpEF and HFrEF vs control at rest, &p<0.01, HFpEF vs HFrEF at rest

A, late diastolic velocity; dTE, deceleration time; E, Early diastolic velocity; E', early tissue Doppler velocity; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global longitudinal strain; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LVOT, left ventricular outflow tract; LV, left ventricular, MAP- mean arterial pressure; PALS, peak atrial longitudinal strain; PACS, peak atrial contraction strain; PASP, pulmonary artery systolic pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular peak systolic excursion; TR, tricuspid regurgitation; VTI, velocity-time integral.

6.4.4 Determinants of exercise tolerance in heart failure

Regression analysis showed that time of exercise significantly correlated with mean arterial pressure at rest (r=-0.255, R^2=0.065, p=0.01), NTproBNP (r=-0.341, R^2=0.116, p<0.01)), serum creatinine (r=-0.281, R^2=0.079, p<0.01), septal e' velocity (r=0.368, R^2=0.135, p<0.01), baseline PALS (r=0.332, R^2=0.110, p=0.01) and baseline LVGLS (r=-0.358, R^2=0.128, p=0.01) (Table 6.3).

Table 6.3: Relationship between exercise time and selected measures (n=100)

	HFpEF (n=40)			HFrEF (n=40)			Control (n=20)		
Variable	r	R^2	p	r	R^2	p	r	R^2	p
Age (years)	0.011	0.001	0.95	-0.129	0.017	0.43	0.061	0.004	0.8
Sex	0.305	0.093	0.06	0.009	0.0001	0.96	0.315	0.099	0.18
BMI	-0.06	0.004	0.71	-0.034	0.001	0.84	-0.555	0.308	0.01
MAP	0.085	0.007	0.60	-0.124	0.015	0.45	-0.121	0.015	0.61
NT Pro BNP	-0.109	0.012	0.50	0.236	0.056	0.14	0.037	0.001	0.88
Serum creatinine	-0.032	0.001	0.85	0.104	0.011	0.52	-0.161	0.026	0.49
Baseline CO	0.212	0.045	0.19	-0.628	0.394	<0.001	-0.045	0.002	0.85
PALS_ baseline	0.058	0.003	0.72	-0.072	0.005	0.66	-0.038	0.001	0.88
TR_ baseline	-0.049	0.002	0.76	-0.073	0.005	0.66	-	-	-
RVSd_ baseline	0.230	0.053	0.15	-0.399	0.160	0.01	-0.178	0.032	0.45
E' septal_ baseline	0.095	0.009	0.56	-0.005	0.0001	0.98	-0.176	0.031	0.46
LVGLS_ baseline	0.026	0.001	0.87	-0.208	0.043	0.2	-0.398	0.158	0.08

BMI, body mass index; CO, cardiac output; MAP, mean arterial pressure; NTproBNP, N-terminal pro-b-type natriuretic peptide; LVGLS_baseline, left ventricular global longitudinal strain at baseline; PALS_baseline, peak atrial longitudinal strain at baseline; RVSd_baseline, right ventricular size in diastole at baseline; Septal E'_baseline, tissue velocity at septal at baseline; TR_baseline, tricuspid regurgitation velocity at baseline.

Change in PALS from rest to exercise was significantly correlated with exercise time when data from HFpEF and HFrEF were combined (n=100) as shown in Figure 6.3.

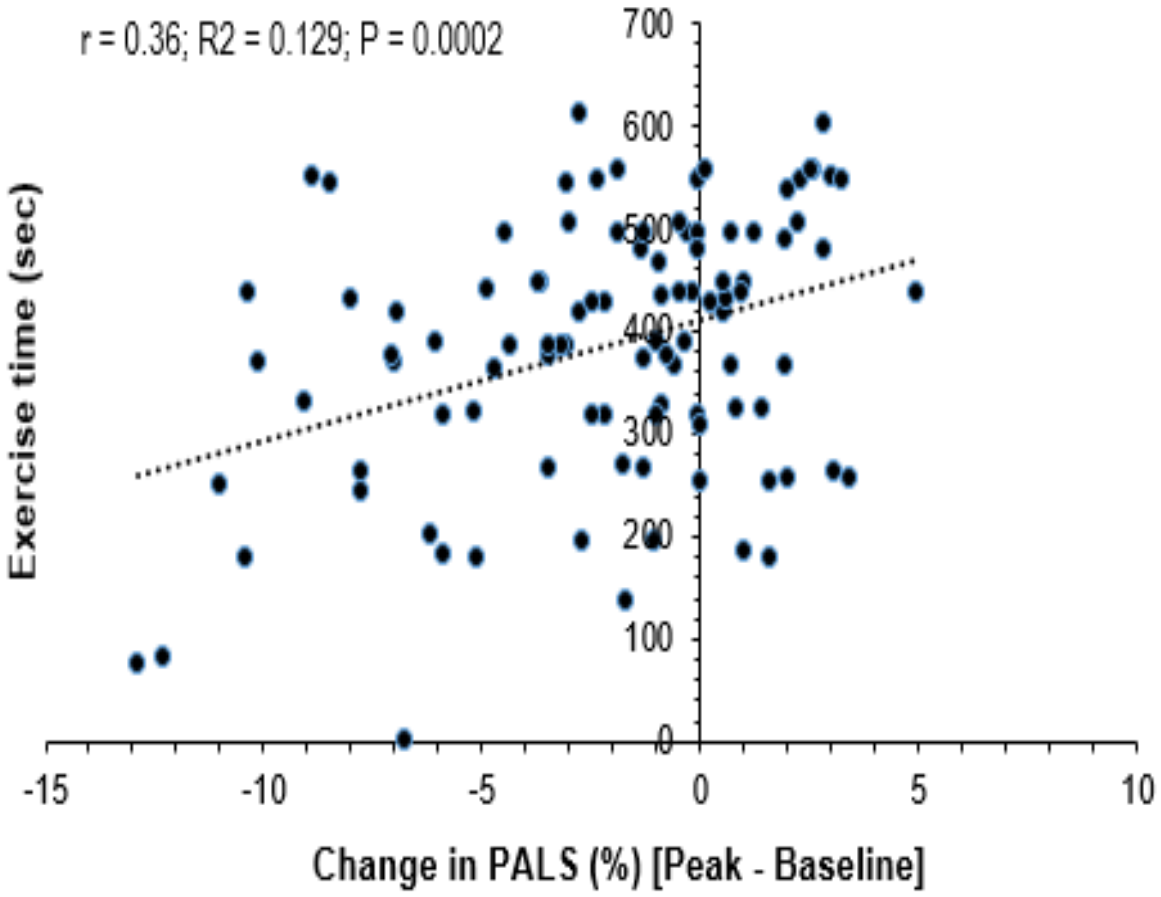

Figure 6.4 Relationship between change (from rest to exercise) in peak atrial longitudinal strain and exercise time (combined data including HFpEF, HFrEF, and controls).

Regression analysis further showed that a reduction of 1% PALS was linked with 16 seconds decrease in exercise time in HFpEF (Table 6.4).

Table 6.4: Multivariable regression analysis to demonstrate predictors of exercise time.

Variable	HFpEF		P-value	HFrEF		P-value	Control		P-value
	B	Std. Error		B	Std. Error		B	Std. Error	
Constant	1529	552	0.01	1235	303	0.00	683	167	0.00
Age (years)	0.31	3.93	0.94	-2.38	2.77	0.39	-0.06	1.26	0.97
Sex	-24.5	49.2	0.62	-1.51	29.6	0.96	23.4	13.2	0.11
BMI	2.13	4.88	0.67	-2.70	4.59	0.56	-0.31	4.41	0.94
NT-ProBNP	-0.02	0.02	0.52	-0.02	0.01	0.23	-0.21	0.11	0.11
CO-change	0.01	0.01	0.42	-0.02	0.02	0.21	0.02	0.01	0.11
PALS- change	15.9	5.43	**0.007**	18.8	9.02	**<0.05**	12.9	3.32	**0.005**
RVSd-change	-587	1003	0.56	-705	961	0.47	597	450	0.22
Septal-E'-change	-2819	1439	0.06	2205	1426	0.13	-2254	1830	0.25
MAP	-12.8	4.49	0.008	-2.93	2.57	0.27	-1.99	1.42	0.2
LVGLS- change	4.62	8.636	0.6	2.07	8.79	0.81	19.9	9.93	0.08
Adjusted R^2		0.25			0.2			0.74	

NTproBNP, N-terminal pro-b-type natriuretic peptide; LVGLS- change, change in left ventricular global longitudinal strain; MAP, mean arterial pressure; PALS-change, change in peak atrial longitudinal strain; RVSd- change, change in right ventricular size in diastole; Septal E'-change, change in tissue velocity at septal.

Figure 6.4 (below) shows a significant positive relationship between PALS and exercise time (p<0.001). In patients of HFpEF, MAP also showed significant relationship with exercise time.

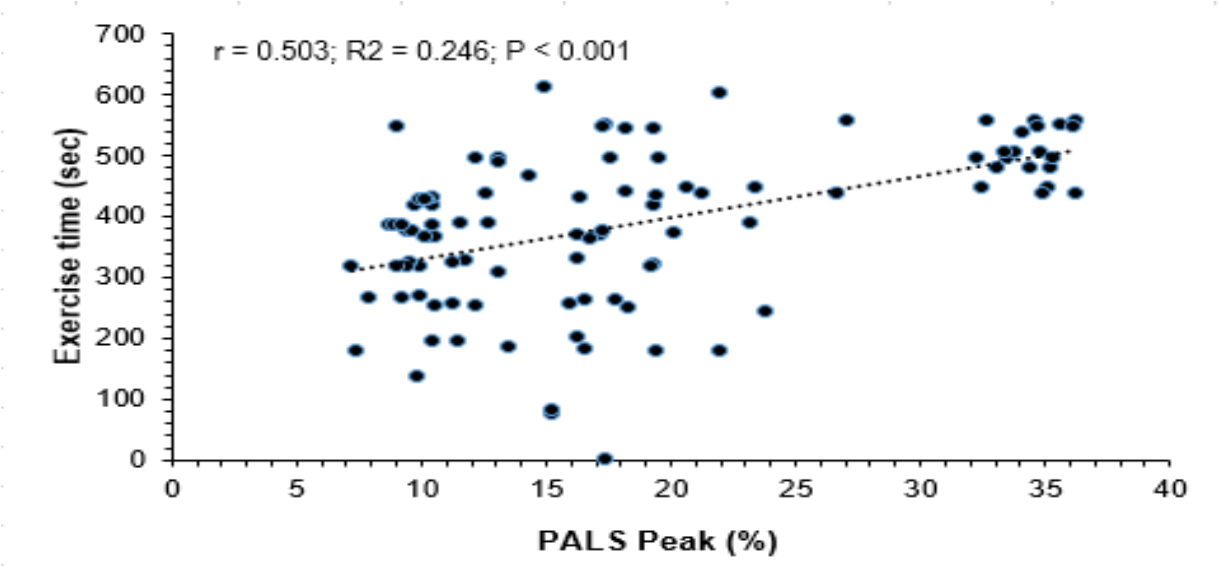

Figure 6.5 Relationship between peak atrial longitudinal strain and exercise time(combined data including HFpEF, HFrEF, and controls).

There was no relationship between E/E', PALS and TRVmax. However, a significant relationship existed between rest and exercise PALS with rest and exercise CO (Figure 6.5).

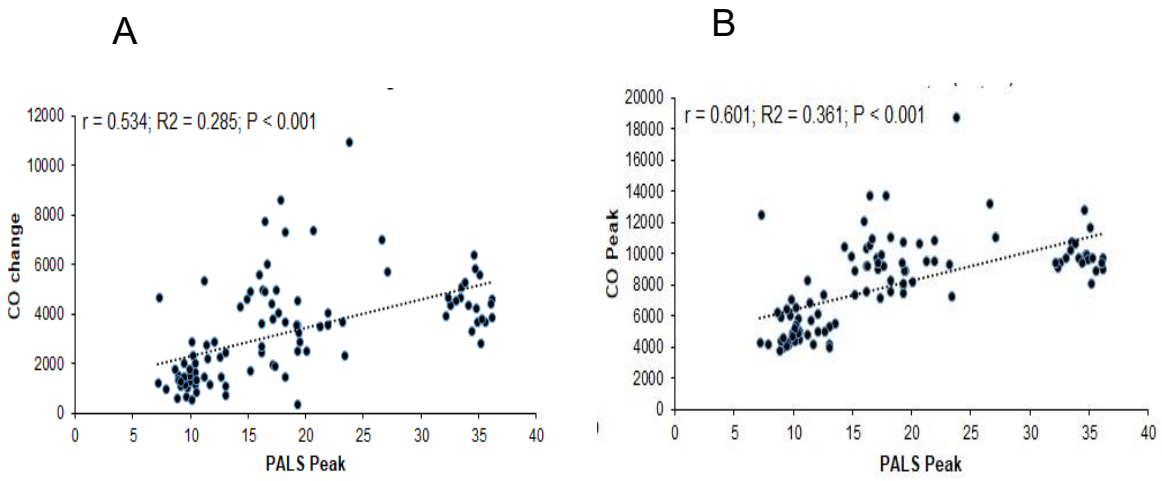

Figure 6.6 Relationship between peak atrial longitudinal strain and change in cardiac output from rest to exercise (A), and peak cardiac output (B)

Intraobserver and interobserver variability for repeated measures of the main variables of interest i.e (E velocity, E' lateral velocity, Left ventricular outflow tract velocity time integral, LVEDV, LVESV, LVEF, LVGLS, PALS and PACS) during rest and after peak

exercise was excellent with an intra-class correlation coefficient of > 0.90.

6.5 Discussion

The prospective observational study compared cardiac structure and function in HFpEF, HFrEF and controls with focus on LA and LV longitudinal strains at baseline and post exercise. The main outcomes of the present study were: 1) both HF groups showed significantly lesser PALS and LVGLS at rest and after exercise as against controls. HFrEF patients had lesser strain values than HFpEF; 2) after exercise, PALS decreased in HFpEF by 26%, with no significant difference seen in other groups; 3) a change in PALS from rest to exercise is an independent predictor of exercise time. This shows that progressive LA remodeling causes a decrease in LA reservoir capacity contributing to exercise incapacity in patients of HFpEF.

Two-dimensional (2D) speckle tracking echocardiography helps in getting the mechanics of both regional and global functions of LV in HF patient.(Smiseth et al., 2016, Blair et al., 2020) Many studies evaluated LV response to exercise in HFpEF patients. Some studies reported diminished, while others no difference at all in measures of LV systolic function in response to exercise.(Bhella et al., 2011, Norman et al., 2011) The present study showed no significant exercise-related changes LV systolic performance as shown by either LVEF or GLS. But, HFpEF patients had a notable increase in stroke volume in response to exercise, as previously reported by Groepenhoff and colleagues.(Groepenhoff et al., 2010) A significant increase in response to exercise in cardiac output and cardiac power output was seen in both HFpEF and HFrEF patients.

LVGLS quantifies LV systolic deformation as the base descends toward the fixed apex and PALS quantifies maximal capacity of LA to expand as a reservoir during the systolic phase of cardiac cycle. Analysis of reservoir function of LA holds key in understanding disease progression in various clinical states including HF. It gets affected by the LV performance and the intrinsic LA compliance.(Aurigemma et al., 1995) Lesser LA reservoir strain is linked to advancement of HFpEF and has prognostic value.(Freed et al., 2016, Santos et al., 2016, Santos et al., 2014) Decreased PALS has also been linked with raised pulmonary arterial wedge pressure as a reason of exercise incapacity in HFpEF.(Lundberg et al., 2019b, Von Roeder et al., 2017b, Telles et al., 2019, Freed and Shah, 2017) In animal study with physiological environment and also in humans with minimal LV diastolic dysfunction, exercise caused a rise in LA reservoir strain, which can be due to rise in LA preload and fast

speed of LV filling.(Nishikawa et al., 1994, Prioli et al., 1998) Limited studies have explored as to how does the LA deform after exercise in different cardiac pathologies. In another study the authors showed that PALS and PACS after exercise were lower in patients of mitral regurgitation.(Sugimoto et al., 2020a) Another work in heart failure patients have shown that LA strains were reduced after exercise and may play a key role in cardiac output response on exercise. This may be due to reduced LV filling and RV to pulmonary artery uncoupling and is associated with a poor cardiopulmonary performance and outcome.(Sugimoto et al., 2020b) However, the LA function and LV function are coupled in a way that during peak LV strains mitral annular decents in systole and this conicides with peak LA expansion and reservoir function. This also explains the LA-LV relationships seen during exercise as the symptoms occur due to modest correlation between LA and LV strain observed in patients of HFpEF.(Solomon and Biering-Sørensen, 2017) This may help in explaining that the interaction between LA reservoir strain and LV function, and hence adverse outcomes may be due to LV dysfunction.(Santos et al., 2016, Ersbøll et al., 2013)

Data from the present study also helps in understanding the mechanism that exercise induced changes in atrial and ventricular deformation hold a key role in pathophysiological alterations in heart function that differentiates HFpEF from HFrEF. Even though LVGLS and PALS are interconnected, multivariate analysis revealed that only change from rest to exercise in PALS is significantly associated with exercise duration after adjustment of various clinical and echocardiographic parameters. This work is also proven by other work which showed the important role of the LA in exercise capacity (Maffeis et al., 2021), although HFpEF has been thought to be a problem where LV and LA mechanical dysfunction is seen. An important sub-analysis of PARAGON-HF trial patients with HFpEF showed a pattern of LV mechanical problem as seen in HFrEF.(Schiattarella et al., 2020) Hence a complete analysis of LA and LV function at rest and after exercise provides incremental value in risk stratification to categorize the subsets of HFpEF patients to provide individualized management strategies.

Chronotropic incompetence has been reported in patients with HFpEF.(Sarma et al., 2020) Whether HFpEF precipitates this, or is due to exercise intolerabiltiy is still a subject of debate. Patients in the present study had no chronotropic incompetence. The cardiac changes after exercise are governed by how the sinoatrial node respondes to neurohumoral stimuli, modulations in autonomic nervous system during various stages of exercise and duration and intensity of exercise done.(Santos et al., 2018) It

has been shown that chronotropic response to exercise represents maximal exercise capacity of an individual.(Al-Najjar et al., 2012)

In the present study, HFpEF and HFrEF showed higher pulmonary artery systolic pressure (PASP) as calculated from TR velocity at rest as that of controls. It got higher after maximum exercise and more so in HFrEF. Deriving PASP from tricuspid regurgitation (TR) acquired by echocardiography accurately correlated with PASP derived from invasive measurements.(Currie et al., 1985, Mcquillan et al., 2001) However, absence of TR jet or poor TR jet signals limits the use of this method in estimating PASP by echo.(Amsallem et al., 2016)

6.6 Limitations

The present study also has some limitations. First, an invasive evaluation of left ventricular and left atrial filling pressures were not performed as was not clinically indicated. Raised NT-ProBNP and altered echocardiography findings accompanied with other signs and symptoms of heart failure helped in the diagnosis of HF. Second, a 3D LV strain analysis was not done which gives simultaneous assessment longitudinal, circumferential, radial, and twist mechanics as it is not validated and is not recommended for routine clinical practice. Assessment of LA strain has its limitations. The normal values provided here might only pertain to the equipment used in the present study but not others. The LA wall is a thin structure and imposes challenges to pure speckle-tracking techniques. An effort of standardization for LA strain assessment by speckle tracking is hence needed from different ultrasound vendors.(Voigt et al., 2015) At present the normal values of LA strain in Indian population is not available and there is a need for a multicentric normative data of LA strain in Indian population. LA strain is load dependent and influenced by LV function. It has been proposed that instead of focusing on reservoir function, a careful look at booster pump function can give important results.(Liao et al., 2017) However this approach has not been widely accepted, but is worthy of consideration in future studies.(Huynh et al., 2015) Lastly, the overall sample size being modest, was powered for evaluating the pathophysiological dissimilarities in two types of HF and not for getting any prognostic information.

6.7 Conclusion

LA and LV mechanics as shown by strains values are lesser in HFrEF than HFpEF at rest and in response to exercise. Patients with HFpEF show more blunting of LA reservoir function after exercise. A discrete form of LA abnormalities seen in HFpEF patients causes a similar amount of effort intolerance seen in HFrEF patients.

Chapter 7. Cardiac response to pharmacological stress in heart failure reduced and heart failure preserved ejection fraction

7.1 Abstract

Purpose: Pharmacological stress test can affect the hemodynamics of heart failure (HF) patients. The aim of the present study was to compare the haemodynamic response to dobutamine stress in heart failure reduced ejection fraction (HFrEF) and heart failure preserved ejection fraction (HFpEF).

Methods: Forty HFpEF and 40 HFrEF patients underwent resting and dobutamine stress echocardiography (DSE). Dobutamine was infused intravenously with increasing dose titration every 3 minutes in dosage of 5,10,15 and 20 μg/kg/min till highest dose was reached or signs and symptoms happened. Echocardiography was performed within two minutes after peak dose.

Results: The duration of DSE was similar in HFrEF and HFpEF (657±70 vs 640±192 sec) respectively. Left ventricular ejection fraction (LVEF) and stroke volume (SV) did not show any notable change from rest to peak dobutamine dose in any of the groups. At peak dobutamine dose, there was a higher ratio of early diastolic velocity to early tissue doppler velocity (E/E') in HFpEF than in HFrEF (14.7±4.55 vs 12.8±4.69, $p<0.01$). The left ventricular global longitudinal strain (LVGLS) significantly increased in HFpEF after dobutamine infusion (-15.9±2.70 vs -13.4±5.85%, $p<0.01$), but not in HFrEF (-11.1±3.40 vs 10.7±1.31%). Both peak atrial longitudinal strain (PALS) and peak atrial contractile strain (PACS) were significantly lower in HFrEF after dobutamine infusion compared to HFpEF (10.7±1.31 vs 18.3±2.20%, $p<0.01$) and (2.53±0.86 vs 6.69±1.26%, $p<0.01$) respectively. HFpEF patients had significant decrease in PALS (23.1±4.70% vs 18.3±2.20%, $p<0.01$) and PACS (8.50±1.60% vs 6.69±1.26%, $p<0.01$) after dobutamine infusion, but not in HFrEF. HFpEF patients showed significant reduction in left atrial (LA) stiffness index (0.57±0.22 vs 0.82±0.27mmHgml^{-1}, $p<0.01$) and in left ventricular (LV) stiffness index (0.16±0.05 vs 0.20±0.06ml^{-1}, $p<0.01$) after dobutamine infusion.

Conclusion: Dobutamine stress accentuates relaxation abnormalities and left ventricular systolic strains more in HFpEF compared to HFrEF, though cardiac output response is greater in HFpEF These differences in haemodynamic response to pharmacological stress in patients with HF may help in improving understanding of complex pathophysiology of HF types.

7.2 Introduction

Heart failure with preserved ejection fraction (HFpEF) is characterized by pathologic hemodynamic alteration including elevated left ventricular end-diastolic filling pressure which may be associated with reduced cardiac output.(Verbrugge et al., 2020) This altered hemodynamics is augmented during physiological or pharmacological stress (Claeys et al., 2022), and is associated with frequent hospital readmissions and higher mortality.(Asrar Ul Haq et al., 2015) A combination of multiple factors (cardiac and extracardiac factors) contribute to altered hemodynamics in HF patients.

The cardiac factors, also termed central factors, include presence of chronotropic incompetence, right ventricular-pulmonary vascular dysfunction, reduced left heart reserve capacity associated with elevated filling pressure, left ventricular (LV) diastolic dysfunction, isolated left atrial myopathy and dynamic valvular involvement. The extracardiac factors, also termed peripheral factors, are related to pleural involvement, impaired peripheral oxygen utilization, reduced skeletal muscle performance, pro-inflammatory state, regional deposition of adipose tissue and peripheral endothelial dysfunction.(Nayor et al., 2020) In the presence of multifactorial abnormalities, stress testing is vital to determine the predominant mechanism responsible for altered hemodynamics.

To understand exercise-based phenotypes of HFpEF, various types of stress modalities have been explored namely treadmill echocardiography, 6-minute walk test, cardiopulmonary exercise testing and invasive exercise hemodynamic assessment.(Bhella et al., 2011, Olsson et al., 2005) Pharmacological stress with the use of dobutamine stress echocardiography (DSE) is an alternative method to exercise stress echocardiography and has been used extensively for the evaluation of ischemia. DSE helps in dynamic evaluation of cardiac function by pharmacological stimulation of heart rate, cardiac output, and myocardial oxygen demand. Recently, few studies have evaluated cardiac mechanics during dobutamine stress echocardiography using speckle tracking imaging in coronary artery disease patients.(Ng et al., 2009, Aggeli et al., 2015) There is hardly any information on the role of DSE in assessment of haemodynamics in HF.

7.2.1 Aims, objective and hypotheses

In the present study, the aim was to assess the cardiac response to pharmacological (dobutamine) stress in HFpEF and HFrEF patients. The objective was to compare

echocardiographic parameters in HFpEF and HFrEF patients in response to pharmacological stress. This chapter will test the following hypothesis:

1) There will be a significant difference in echocardiographic variables between patients with HFpEF and HFrEF in response to pharmacological stress.

7.3 Methods

A prospective, single centre cross-sectional study was conducted to evaluate cardiac response to pharmacological stress in HFrEF and HFpEF.

7.3.1 Participants

One hundred and nine subjects who were clinically stable were at first screened which included 49 patients of HFpEF and 40 of HFrEF. Nine patients with HFpEF were not included as seven had atrial fibrillation and two had episodes of acute coronary event in last three months. Finally 40 HFrEF and 40 HFpEF were finally included in the study. The other details of participants included in the study have been defined in detail in chapter six, section 6.2.1.

7.3.2 Study protocol and measurements

All the eligible patients underwent measurement of cardiac function (haemodynamics, systolic and diastolic function) at rest using transthoracic echocardiography. DSE was performed within two minutes after dobutamine administration. Dobutamine was given through an intravenous line in a hospital setup. Subjects were told to stop beta-blocker and/or nitrate medication a day before the test. Subjects were also told to be nil by mouth 4 hours before the test. Dobutamine was given with increasing dose of 5,10,15 and 20 µg/kg/min every 3 minutes (Lancellotti et al., 2017) with till highest dose was reached or symptoms and sign occurred i.e. chest discomfort, hypertensive response, breathlessness, ST-T changes on ECG, rhythm abnormality or patient's inability to tolerate the drug.

7.3.3 Equipment

Transthoracic echocardiography was performed using a Vivid E95 system (GE Ultrasound, Horten, Norway) equipped with a transducer of 2.5 MHz matrix array. The complete details of imaging have been discussed in chapter 6.2.2.

7.3.4 Data analysis

Data was represented as mean and SD unless otherwise stated. Kolmogorov–Smirnov test was used for normality of distribution. Paired t-test was done to understand differences between rest and peak pharmacological exercise, while independent t-test was done to assess the significance between peak pharmacological tests between two groups, and between delta values at rest and after dobutamine stress. A test was considered statistical significance if $p<0.05$.

7.4 Results

The demographic, physical and clinical characteristics of the cohort has been presented in Table 7.1. The duration of DSE was (657±70 vs 640±192 secs, $p>0.05$) in HFrEF and HFpEF respectively.

Table 7.1: Demographic, physical and clinical characteristics

Variable	HFpEF (n=40)	HFrEF (n=40)
Age (years)	59±7	57±6
Male (%)	15 (37.5)	25 (62)
Height (cm)	155±8	161±9
Weight (Kg)	69.5±14.9	65.7±10.5
Body surface area (m^2)	1.68±0.18	1.7±0.21
Duration of heart failure (years)	2±1.5	2.6±1.3
Coronary artery disease (%)	12 (30)	27 (68)
Hypertension (%)	36 (90)	23 (58)
Diabetes Mellitus (%)	13 (33)	22 (55)
Smoker (%)	6 (15)	14 (35)
B-blocker (%)	12 (30)	35 (88)
ACEI/ARB (%)	34 (85)	12 (30)
ARNI (%)	-	28 (70)
Calcium channel blocker (%)	5 (13)	4 (10)
Haemoglobin (g%)	11.7±1.7	11.6±1.3
Thyroid stimulating hormone (IU/ml)	2.03±1.27	2.19±0.95
NTproBNP (pg/ml)	1291±1404	2043±1046*
Serum sodium (meq/l)	138±5	136±5
Serum potassium (meq/l)	4.09±0.45	3.85±0.5
Serum creatinine (mg/dl)	0.95±0.34	1.17±0.23
Total Cholesterol (mg/dl)	155±21	177±26
Low density lipoprotein (mg/dl)	99.9±27.2	114±16*
High density lipoprotein (mg/dl)	42.7±7.9	37.1±3.9

*$p<0.01$, HFpEF v HFrEF;

ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; ARNI, Angiotensin receptor neprilysin inhibitor; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; NTproBNP, N-terminal pro-b-type natriuretic peptide.

7.4.1 Comparision of cardiac structure and function between baseline and in response to pharmacological stress in HFpEF and HFrEF

Dobutamine induced rise in heart rate (HR), mean arterial pressure (MAP), TR jet and RV systolic pressure were comparable between HFpEF and HFrEF. There were no significant changes in LVEF and stroke volume from rest to peak dobutamine stress in either HFpEF or HFrEF, but cardiac output (CO) and cardiac power output (CPO) increased in both the groups ($p<0.01$). There was no change in early tissue doppler velocity (E') in both HFpEF and HFrEF. Dobutamine infusion caused a notable rise in ratio of early diastolic velocity to early tissue doppler velocity (E/E') in HFpEF but not HFrEF (Table 7.2). Left ventricular global longitudinal strain (LVGLS) significantly deteriorated in HFpEF after dobutamine infusion (-15.9±2.70% vs -13.4±5.85%, $p<0.01$), but not in HFrEF. Atrial mechanics assessment revealed significant reduction in PALS (23.1±4.70% vs 18.3±2.20, $p<0.01$) and PACS (8.50±1.60 vs 6.69±1.26, $p<0.01$) in HFpEF after DSE, but not in HFrEF. HFpEF patients showed significant rise in LA stiffness index (0.57±0.22 vs 0.82±0.27 $mmHgml^{-1}$, $p<0.01$) and in LV stiffness index (0.16±0.05 ml^{-1}vs 0.20±0.06 ml^{-1}, $p<0.01$) after DSE, which HFrEF patients didn't show (Table 7.2).

Table 7.2: Comprehensive features at baseline and after dobutamine stress test

Variables	HFpEF (n=40)			HFrEF (n=40)		
	Rest	*Dobutamine stress*	Delta 1	*Rest*	*Dobutamine Stress*	Delta 2
Functional						
Heart Rate (beats/min)	77±14	109±13.5*	32±20	81±11	113±8.94*	33 ±13
MAP (mm Hg)	93±6	107±16*	14±15	94±6	113±7*	19±8
TR	0.13±0.33	1.03±0.16*	0.9±0.38	0.25±0.44	1±0.23*	0.73 ±0.51
PASP (mm Hg)	35.8±2.4	45.1±5.15*	40.7±12.7	38.4±4.80	48.2±8.31*	37.4±21.6
LVOT VTI (cm)	21.6±4.38	22.9±4.54*	1.34±5.3	14.3±2.63	14.7±3.08$^{\$}$	0.40±2.28
Structural						
LVOT (cm)	2.11±0.15	2.07±0.13	-0.04±0.13	2.02±0.06	2.01±0.05	-0.01±0.04
LVEDV 4C(ml)	83±17	73±13*	-10±19	100±27	93±40*$^{\&}$	-3±11†
LVESV 4C(ml)	41±9	36±7*	-4±10	64±17	61±29$^{\&}$	-1±8
Diastolic						
E (m/sec)	0.91±0.24	0.96±0.26	0.05±0.3	0.70±0.23	0.76±0.24$^{\&}$	0.05±0.17
A (m/sec)	0.83±0.18	0.76±0.37	-0.07±0.42	0.68±0.20	0.71±0.2	0.02±0.18
E' septal (m/sec)	0.07±0.02	0.06±0.01	0.00±0.02	0.05±0.01	0.05±0.01	0.01±0.01†
E' lateral (m/sec)	0.08±0.02	0.07±0.01	-0.01±0.02	0.06±0.01	0.07±0.01	0.01±0.01†
E/E'	12.6±3.3	14.7±4.55*	2.09±5.63	13.8±5.85	12.8±4.69$^{\&}$	-0.69±3.38
dTE (msec)	198±41	162±44.5*	-36.3±53.5	184±42	130±25.3*$^{\&}$	-53.7±37.1
Systolic						
LVEF (%)	54.2±3.11	52.9±3.31	-1.33±4.29	33.9±6.26	35.3±6.07$^{\&}$	0.35±2.82†
Stroke volume (ml/beat)	75±19	78±23	3±20	46±9	46±9$^{\$}$	0.79±7.96
Cardiac power output (W)	1.14±0.30	2.03±0.74*	0.89 ±0.71	0.77±0.21	1.31±0.22*$^{\&}$	0.53±0.19†
LVGLS (%)	-15.9±2.70	-13.4±5.85*	2.47±6.13	-11.1±3.40	-10.7±2.82$^{\&}$	0.46±2.03
TAPSE (cm)	2.18±0.27	2.14±0.18	-0.04±0.33	1.99±0.19	1.94±0.13$^{\&}$	-0.05±0.14
RVS' (m/sec)	0.13±0.02	0.14±0.04	0.02±0.04	0.11±0.02	0.11±0.02	0.00±0.03†
RV free wall strain (%)	-22.6±2.43	-21.8±2.1	0.8±3	-20.0±1.26	-19.9±1.58	0.12±1.40
PALS (%)	23.1±4.70	18.3±2.20*	-4.73±4.54	11.5±1.40	10.7±1.31$^{\&}$	-0.83±2.29†
PACS (%)	8.50±1.60	6.69±1.26*	-1.76±2.14	2.60±0.80	2.53±0.86$^{\&}$	-0.07±0.99†
Hemodynamics						
Cardiac output (L/min)	5.51±1.35	8.51±2.65*	2.99±2.69	3.70±0.91$^{\$,\&}$	5.25±1*$^{\&}$	1.55±0.82†
SVR (dynes/sec/cm^{-5})	1269±248	978±324*	-291± 391	1997±463$^{\$,\&}$	1654±323*$^{\&}$	-353±520
LA stiffness index (mm Hgml^{-1})	0.57±0.22	0.82±0.27*	0.24±0.28	1.19±0.63$^{\$,\&}$	1.20±0.45	0.04±0.47†
LV stiffness index (ml^{-1})	0.16±0.05	0.20±0.06*	0.05±0.07	0.14±0.07$^{\$}$	0.14±0.06$^{\&}$	0.00±0.03†
Exercise time (sec)		657±70			640±192	

*p < 0.01, rest and dobutamine stress test, $^{\&}$p<0.01, HFpEF vs HFrEF after dobutamine stress test, † p<0.05, Delta 1 vs Delta 2.

Delta 1, change between rest and dobutamine stress in HFpEF; Delta 2, change between rest and dobutamine stress in HFrEF. A,late diastolic velocity; dTE, deceleration time; E, Early diastolic velocity; E', early tissue Doppler velocity; EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVOT, left ventricular outflow tract; VTI, velocity time integral; PACS, peak atrial contraction strain; PALS, peak atrial longitudinal strain; PASP, pulmonary artery systolic pressure; RVS', right ventricular systolic tissue wave; SVR, systemic vascular resistance; TAPSE, tricuspid annular peak systolic excursion; TR, tricuspid regurgitation

There was no difference in HR, MAP, TR jet and RVSP after DSE in HFpEF and HFrEF. TAPSE showed significant difference in response to DSE between HFpEF and HFrEF (2.14±0.18 vs 1.94±0.13, p<0.01), however there was no difference in other RV systolic parameters. E/E' and deceleration time were significantly higher in HFpEF than HFrEF after DSE (14.7±4.55 vs 12.8±4.69, p<0.01) and (162±44.5 vs 130±25.3 msec, p<0.01). HFrEF patients showed significant lower values as compared to HFpEF in response to DSE for LVOTVTI (14.7±3.08 vs 22.9±4.54 cm, p<0.01), stroke volume (46±9 vs 78±23 ml/beat, p<0.01), cardiac output (5.25±1 vs 8.51±2.65 L/min, p<0.01), cardiac power output (1.31±0.22 vs 2.03±0.74 W, p<0.01) and LVGLS (-10.7±2.82 vs -13.4±5.85%, p<0.01)(Figure 7.1).

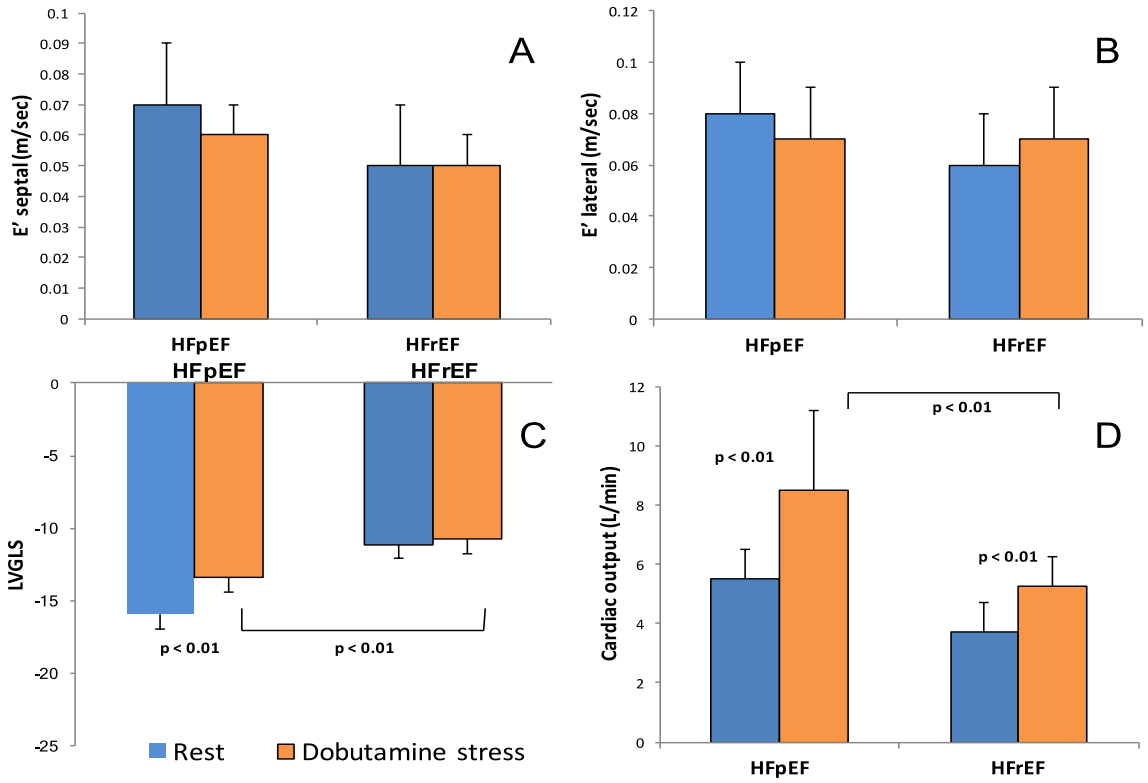

Figure 7.1 Bar diagram showing changes in early (E') tissue doppler velocity at septal mitral annulus (A), at lateral mitral annulus (B), left ventricular global longitudinal strain (C) and cardiac output (D) between rest and dobutamine stress echo in the cohort

However, in response to DSE, HFrEF showed higher systemic vascular resistance (1654±323 vs 978±324 dynes/sec/cm^{-5}, p<0.01), LA stiffness index (1.20±0.45 vs 0.82±0.27 mm Hg/ml, p<0.01) and lesser LV stiffness index (0.14±0.06 vs 0.20±0.06 ml^{-1}, p<0.01) as compared to HFpEF. Both PALS and PACS were significantly lesser in HFrEF after DSE as compared to HFpEF (10.7±1.31 vs 18.3±2.20%, p<0.01) and (2.53±0.86 vs 6.69±1.26%, p<0.01) respectively.

7.4.2 Comparison of change from rest to peak dobutamine dose between HFpEF and HFrEF

Dobutamine stress did not show any difference in delta in HR, MAP and PASP between HFpEFand HFrEF. There was a significant difference in delta between HFpEF and HFrEF in early tissue doppler velocity (E') at both septal (0.00±0.02 vs 0.01±0.01 m/sec, p<0.05) and lateral sections (-0.01±0.02 vs 0.01±0.01 m/sec, p<0.05). HFpEF showed greater delta reduction in LVEDV compared to HFrEF causing a significant difference in delta LVEF (-1.33±4.29 vs 0.35±2.82 %, p<0.05), delta cardiac output (2.99±2.69 vs 1.55±0.82 L/min, p<0.05) and delta cardiac power output (0.89 ±0.71 vs 0.53±0.19 W, p<0.05) between two groups. There was no difference in delta LVGLS. Also the delta change in PALS and PACS was significantly more in HFpEF than in HFrEF(-4.73±4.54 vs -0.83±2.29 %, p<0.05) and (-1.76±2.14 vs -0.07±0.99 %, p<0.05) respectively. The rise in LA and LV stiffness reflecting in delta was higher in patients of HFpEF as that of HFrEF (0.24±0.28 vs 0.04±0.47 mm $Hgml^{-1}$, p<0.05) and (0.05±0.07 vs 0.00±0.03 ml^{-1}, p<0.05) respectively.

7.5 Discussion

This prospective work compared the hemodynamic and echocardiographic parameters in HFpEF and HFrEF patients in response to pharmacological stress. The main findings were: 1) Dobutamine stress induced an increase in heart rate and mean arterial pressure in HFpEF and HFrEF; 2) Rise in E/E' after DSE is significantly more in HFpEF than HFrEF; 3) Dobutamine increases CO and CPO in both HFpEF and HFrEF, but to a lesser degree in HFrEF; 4) At rest, LA and LV stiffness index are more in HFrEF than in HFpEF, but dobutamine stress causes higher rise in LA and LV stiffness index in HFpEF; 5) LV and LA strains are significantly lesser in HFrEF than HFpEF at rest and after dobutamine stress and decrease in LVGLS is more profound in HFpEF after dobutamine stress than HFrEF, Thus dobutamine stress accentuates relaxation abnormalities and left ventricular systolic strains more in HFpEF compared

to HFrEF, though cardiac output response is greater in HFpEF.

DSE is thought to be a good pharmacological alternative to stress echocardiography, with an good safety profile as many HF patients may not be able to walk or cycle due to associated pulmonary, orthopaedic or rheumatological comorbidities.(Kane et al., 2008, Pellikka et al., 2007) The various effects of dobutamine are dose-dependent. Dobutamine has an affinity for cardiac α- and β-receptors. Stimulation of α-adrenergic receptors causes systemic vasoconstriction, increased blood pressure, and more myocardial contractility. β1- adrenergic receptors stimulation, results in an increase in myocardial contractility, atrioventricular conduction, and heart rate. Stimulation of vascular β_2 -receptors causes coronary and peripheral arteriolar vasodilatation. The inotropic effect of dobutamine is mostly seen in lower doses, and the chronotropic effect in high doses.(Ruffolo et al., 1981) In normal physiologic condition, dobutamine increases stroke volume and cardiac output due to its inotropic effects. In low dose heart rate remains unchanged, but increases in higher doses. It is predominantly used for evaluation of viability myocardium in ischemic heart disease.(Aggeli et al., 2015) In the present work, low dose dobutamine was used. Higher dosages were avoided as with tachycardia there is a fusion of E and A waves in mitral inflow pattern, which causes difficulty in measuring their velocities and subsequently in LV filling pressure by E/E' which is needed for understanding diastology.(Egstrup et al., 2013) Also the use of low dose dobutamine helped to assess the contractile behaviour of the myocardium in the absence of rise in heart rate.This work provides insights of the usage of dobutamine stress echo in HF patients for the first time.

The present study demonstrates that in HFpEF patients, dobutamine caused a rise in MAP. Kieu et al.(Kieu et al., 2018) reported similar finding in their retrospective cohort of 413 hypertensive patients. The rise in blood pressure during dobutamine stress is due to more robust arterial vasodilator response and lower peripheral resistance with dobutamine at equivalent cardiac output levels.(Pratali et al., 2001) Dobutamine causes vasodilation and increases cardiac output which in return reduces systemic vascular resistance (SVR).(Egstrup et al., 2013) In the present study, SVR was significantly less in both HFrEF and HFpEF patients by DSE.

In the present study dobutamine caused an increase in E/E' in HFpEF, but an insignificant reduction in HFrEF. Egstrup et al (2013) reported in their study of 14 systolic heart failure patients that DSE causes no change in E/E' in their group of patients.(Egstrup et al., 2013) The reason for this variable effect is unclear but could be result of effects of increased contractility on early diastolic lengthening than on early

mitral inflow velocity.(Egstrup et al., 2013, Kieu et al., 2018, Aggeli et al., 2015)

The echo-derived cardiac power output is proposed to be quantitative indicator of cardiac reserve.(Marmor and Schneeweiss, 1997) DSE is helpful in elucidating the changes in contractile state in patients with dilated cardiomyopathy who can present with HFrEF.(Pratali et al., 2001, Park et al., 2016) DSE increased CO and CPO in both HFpEF and HFrEF. The absolute value of CO and CPO after DSE were lower in HFrEF than HFpEF. This may be explained by the presence of preserved contractile reserve seen in patients of HFpEF.(Bhella et al., 2011, Egstrup et al., 2013) Mechanistically, dobutamine causes beneficial effects of adrenergic signaling in heart failure without causing harmful peripheral vasoconstriction, causing increasing stroke volume, lowering systemic and pulmonary vascular resistance and pulmonary wedge pressure.(Ahmad et al., 2019) The present study showed no change in SV after DSE in both groups. Kieu et al. (2018) reported that DSE is associated with a higher SV in patients who have a hypertensive response. Also this varied response of absolute value of CO and CPO between HFpEF and HFrEF can be explained by the type and extent of fibrosis seen in heart in HFrEF and HFpEF. In HFpEF, myocardial fibrosis is minimal, presents as perivascular and fine interstitial fibrosis due to systemic inflammation and is associated with raised collagen crosslinking.(Shah et al., 2016, Sweeney et al., 2020, Simmonds et al., 2020) whilst HFrEF is characterized by replacement fibrosis which is extensive, chronic, irreversible, associated with scar formation and contributes to organ damage and failure.(De Boer et al., 2019, Simmonds et al., 2020) The systemic and cardiac inflammation have differential role in HFrEF and HFpEF. The inflammatory response precipitating heart failure are of three types namely sterile which is caused by post-ischemia resulting in HFrEF, metabolic, as seen in HFrEF and non-sterile-induced inflammation seen in post-infective resulting in mixed picture.(Simmonds et al., 2020)

The present study demonstrated that LA and LV stiffness index are higher in HFrEF than HFpEF, and dobutamine increases both in HFpEF, but has no effect in HFrEF. In HFpEF patients, raised LV stiffness index is associated with impaired exercise capacity.(Sinning et al., 2011). LA stiffness index has prognostic importance in HFrEF patients and suggests that a stiff LA cannot accommodate raised cavity pressure both at rest and after stress.(Bytyci et al., 2021, Bytyci et al., 2020) Increased LV stiffness index is associated with raised LV end diastolic pressure in patients subjected to physiological handgrip exercise and is accompanied by reduced stroke volume in these patients.(Westermann et al., 2008) LV stiffness is present in both HFrEF and

HFpEF due to alteration in cardiac intracellular calcium (Ca^{2+}) levels and modifications of titin which is one of the main determinants of cardiomyocyte passive tension ($F_{passive}$). In HFrEF, impaired Ca^{2+} release from sarcoplasmic reticulum causes systolic dysfunction and LV stiffness, while in HFpEF there is impaired Ca2+ removal causing increased myocardial Ca^{2+}.(Flesch et al., 1996) Titin is a bi-directional giant spring and dysregulation in titin metabolism causes cardiac functional and structural alterations, which is seen in HF patients.(Simmonds et al., 2020, Nagueh et al., 2004)

Assessment of myocardial strain parameters using stress echocardiography imaging has been limited due to suboptimal speckle tracking quality due to difficulty in tracking the endocardial border at faster heart rates. Advancements in echocardiography has helped in good echocardiography images more suitable for speckle tracking imaging analysis. Few studies have evaluated strain behavior during and after DSE, where they have shown the feasibility of doing strain imaging during DSE in the background of ischaemic heart disease with reduced ejection fraction.(Govind et al., 2009, Aggeli et al., 2015) Leitman et al. recently reported that LVGLS improves after DSE in normal individuals.(Leitman et al., 2022) Another study used 2D speckle tracking during DSE for evaluation of coronary artery disease and reported that value of LVGLS >-16% is useful for identifying significant CAD during recovery phase of DSE.(Park et al., 2016) In the present study, LVGLS deteriorated after DSE in HFpEF, but there was no significant change in HFrEF. This may be because of presence of scared myocardium in patients with HFrEF which don't respond to contractile response to dobutamine. Also DSE was helpful in identifying reduction in PALS and PACS in both HFpEF and HFrEF, which has not been reported earlier in any study.

7.6 Conclusion

Dobutamine stress causes an equal increase in HR, MAP and RV systolic pressure in HFrEF and HFpEF. Dobutamine stress significantly increases filling pressure in HFpEF which is not seen in HFrEF. In HFpEF patients, dobutamine stress augments cardiac output and cardiac power output without affecting the LVEF, but decreases LVGLS, left atrial mechanics and LA and LV stiffness index. Also, DSE with 2D speckle tracking for LV and LA is feasible in both HFpEF and HFrEF patients. This study has shown that there are discrete differences in haemodynamic and echocardiographic parameters between HFpEF and HFrEF in response to pharmacological stress. Further mechanistic research is needed to improve our understanding of complex pathophysiology of HF types.

Chapter 8. The effect of a personalized, home-based physical activity intervention on quality of life and cardiac function in heart failure with preserved ejection fraction

8.1 Abstract

Background: The aim of this study was to assess the acceptability, feasibility, and physiological outcome of a novel, personalized, home-based physical activity intervention in heart failure with preserved ejection fraction (HFpEF) patients.

Methods: Forty HFpEF patients who were clinically stable were taken in present work and randomized in a ratio of 2:1 to an intervention group (60±6 years, n=25, 12 male) or control group (60±7 years, n=15, 4 male). Patients performed supervised exercise stress testing by treadmill, and exercise stress echocardiography was performed on them. They were also assessed for quality of life (Minnesota living with heart failure questionnaire) and N-terminal prohormone of brain natriuretic peptide (NTproBNP) before and after intervention. Subjects in the intervention group took a novel 12-week home-based physical activity intervention (Active-at-Home-HF) which included an escalation of $\geq$2000 steps per day from baseline while those in control group got standard medical management. All patients were monitored weekly using pedometers and telephonically.

Results: In the intervention group, physical activity increased from baseline to 3 weeks (from 4457±653 to 6592±546 steps per day, $p<0.01$), and was maintained over the complete duration. The total time of treadmill test increased in the intervention group (350±122 vs 463±135 secs, $p<0.01$) but not in controls (399±126 vs 358±88 secs $p=0.23$) after 12 weeks. NTproBNP and left ventricular (LV) filling pressure (E/E') decreased in the intervention group (1041±1059 vs 588±378 pg/ml, $p=0.01$, and 12.43±3.6 vs 9.72±1.86, $p<0.01$) respectively as that of controls (1686±1824 vs 1099±463 pg/ml, $p=0.18$, and 12.86±3.17 vs 12.44±2.23, $p=0.11$). There was no alteration in left ventricular ejection fraction, LV longitudinal strain, stroke volume, cardiac output, cardiac power output and right ventricular systolic function in the intervention or control group ($p>0.05$). The intervention group showed a rise in peak atrial longitudinal strain and peak atrial contraction strain (23.33±4.45 vs 25.48±4.39, $p<0.01$ and 8.63±1.21 vs 9.00±0.94, $p<0.01$). There was a reduction by 5 points in Minnesota Living with Heart Failure Quality of Life score after intervention (22.3±4.14 to 16.9±4.27, $p<0.01$). There were no adverse events.

Conclusions: A 12-week personalised home-based physical activity intervention is feasible and helps in improving the exercise tolerance, left ventricular filling pressure, left atrial performance and quality of life in HFpEF patients.

8.2 Introduction

Patients with HFpEF suffer from exercise incapacity because to impaired cardiac, vascular and skeletal muscle function which results in reduced quality of life (QOL).(Fukuta et al., 2016) Cardiac rehabilitation by exercise is advised for people with heart failure.(Mcdonagh et al., 2021) Physical activity forms an important element of cardiac rehabilitation program. Intensity of physical activity is a key component for the improvement of cardiopulmonary function, metabolic control and interventional related outcomes.(Bobenko et al., 2018) In HFpEF patients, exercise training has been shown to be effective in enhancing the aerobic capacity and QOL.(Fukuta et al., 2016, Fukuta et al., 2019)

Active energy expenditure and regular physical activity comprising of walking with step count has been shown to lower all-cause mortality in general adult population.(Saint-Maurice et al., 2020) Higher step count has been associated with lower mortality.(Jefferis et al., 2019) Walking is an independent predictor of clinical outcomes in chronic heart failure patients. (Jehn et al., 2009) The present recommendations for exercise for an individual are 3-5 hours in a week of average intense workout, or 1.5 to 2.5 hours in a week of highly intense aerobic physical exercise, or similar to this.(Piercy et al., 2018) This should be included with muscle strengthening exercises if the person is capable of doing it. For those adults who have chronic debilitating conditions including heart failure, and are not able undertake these recommendations, regular physical task according to their ability is suggested.(Mcdonagh et al., 2021) A patient-centred approach is needed in these group of patients along with behavioural modifications and encouragements. The 2018 Physical Activity Guidelines Advisory Committee noted in their scientific report, that steps form basic unit of locomotion and hence is an easy-to-understand metric of ambulation.(Thompson and Eijsvogels, 2018)

Wearable activity monitors which count steps are easily available, widely used and provide immediate feedback to the user. There is limited information as to how many steps daily are needed for good health (Yates et al., 2014, Bassett et al., 2017) but a

recent meta-analysis has shown that a modest increase in daily step count per day is associated with a lower risk of death.(Jayedi et al., 2022) Interventions using pedometers have shown that increasing step count daily by around 2000 steps helps in better blood pressure control (Richardson et al., 2008), improves insulin sensitivity (Yamanouchi et al., 1995, Yates et al., 2014), and decreases risk of developing cardiovascular events by 10%.(Yates et al., 2014)

The Active-at-Home-HF intervention has been evaluated in patients of congestive heart failure (CHF).(Okwose et al., 2019) It is a home–based physical activity intervention which aims at increasing step numbers daily by 2000 from baseline. The patients are regularly helped with weekly telephone calls to start, increase and continue with their physical activity levels, and encouraged to maintain a log of their weekly step count. This intervention has been shown to be feasible, acceptable and effective in improving quality of life, exercise tolerance and haemodynamic function in CHF patients.(Okwose et al., 2019)

8.2.1 Aims and Hypotheses

The aim of the present work was to assess the acceptability, feasibility, and physiological effects of a novel, home-based physical activity intervention in patients with HFpEF. The study tested the following two hypotheses:

1) Home-based physical activity intervention (Active-at-Home-HF) will be feasible and acceptable to HFpEF patients.
2) Active-at-Home-HF will improve cardiac function, exercise tolerance and quality of life in HFpEF patients.

8.3 Methods

This was a longitudinal, prospective, pilot study. All patients were recruited from cardiology department in SHRI, Nagpur, India. They attended the outpatient department twice (i.e. baseline and after the 12 weeks). The study protocol which was approved by the Institutional Independent Research Ethics committee, was discussed with the patients and their willingness to participate in the study was confirmed with written consent.

8.3.1 Participants

The study included 40 stable HFpEF patients (LVEF> 50%). Stable condition was determined as a patient who is clinically stable for atleast one and half months before

joining the study and taking optimal medical treatment. The subjects were randomized on 2:1 ratio basis into an intervention or control group. They were supposed to do their daily activities independently. Patients with valve disease, rhythm disorders including atrial fibrillation (AF), implanted cardiac device, ischemic heart disease in the last 12 weeks, idiopathic pulmonary arterial hypertension, cancer, pregnancy, or unable to give consent were not taken in the study. The parameters included demographics and comorbidities, New York Heart Association (NYHA) functional status, medicine details, vital signs, body mass index, and blood parameters like haemoglobin, kidney function test, and N-Terminal pro b-type Natriuretic Peptide (NT pro-BNP). The protocol was done according to the declaration of Helsinki.

8.3.2 Study protocol and measurements

Patients had a detailed clinical examination including quality of life using the Minnesota Living with Heart Failure questionnaire, blood sampling for NTproBNP and exercise stress testing using treadmill and stress echocardiography at baseline and after 3 months follow up. A modified Bruce protocol was used for treadmill stress test. Limitation of symptom was assessed using the Borg rating of perceived exertion scale.(Borg, 1982) All the vitals and echocardiographic parameters were obtained at baseline and 2-3 minutes of the exercise cessation as diastolic parameters remain after completion of exercise.(Ha et al., 2020) All essential echocardiographic images were recorded after the exercise on the same device as mentioned earlier (chapter 4, section 4.5.4).

8.3.3 Home- Based Physical Activity Intervention (Active-at-Home-HF)

The intervention (Active-at-Home-HF)(Okwose et al., 2019) was implemented and tested in HFpEF patients to motivate an escalation in their overall day to day physical activity levels by minimum 2000 steps daily from baseline. The control group of patients received standard care. Physical activity (step count) was counted by a pedometer.(Muzili Smart Fitness Pedometer IPX7, China). Patients noted their step counts daily and recorded in the provided diary. The step counts were then informed weekly to a research team coordinator. The home-based physical intervention was different from centre-based programs as it focused on free-living physical exercise, not depending on expensive exercise gadgets, was given telephonically every week and aimed at giving the subjects the information and behavioural skills to augment and regularly do physical activity. After initial enrolment, patients were regularly helped with weekly telephone calls aimed to increase and continue with their physical activity

levels. Difficulties in reaching goal were discussed and solutions were provided. They were motivated to increase their self-confidence to be more physically active. Self-monitoring was encouraged to maintain activity levels, and family and friends were requested to get involved to encourage and support patients in their regular exercise protocol. Daily at the end, the aim was to reach minimum 2000 steps over the average daily steps recorded at baseline according to the pedometer. Physical activity levels were adjusted on an individual basis focusing on duration and number of steps rather than intensity.

8.3.4 Assessment of quality of life

The Minnesota Living with heart failure is a 21-item disease specific questionnaire assessing physical, socioeconomic, and psychological impairment related to HF used to assess quality of life. Score depends on how a person ranks each item on a common scale and it is used to quantify how much HF has influenced aspects of an individual's daily life and how it is affected by therapeutic intervention. Scores range from 0 to 105 points with lower scores indicating less effect from HF symptoms and thus a better quality of life.(Bilbao et al., 2016) Change in the score of 5 is considered to be a clinically relevant change/improvement in a patients quality of life.(Riegel et al., 2002)

8.3.5 Assessment of cardiac function

Assessment of cardiac function was done in all the patients included in both the arms at baseline and after 3 months. It included assessment of stroke volume, cardiac output, systemic vascular resistance, LV filling pressure (E/E'), LV volumes and ejection fraction, LV global longitudinal strain, LA strain and RV function. These measurements were done by standard echocardiographic procedure and the details have been discussed in chapter 6, section 6.2.2.

8.3.6 Assessment of exercise tolerance

All the subjects in the study had to do a symptom limited, supervised treadmill stress test by modified Bruce protocol at baseline. This was again repeated at the end of 12 weeks. Limitation of symptom was assessed by using Borg scale which rates the exertion perceived by the person.(Borg, 1982) The patient's vitals and parameters derived from echocardiography were documented at baseline and 2-3 minutes of the exercise termination as diastolic parameters persists even after completion of exercise.(Ha et al., 2020) The routine echocardiographic parameters were again recorded after exercise as mentioned earlier.

8.3.7 Assessment of blood biomarkers

5 ml blood sample was taken from antecubital vein and assessed for brain natriuretic peptides (NTproBNP) at baseline and after 12 weeks for patients in both intervention arm and non-intervention arm.

8.3.8 Outcomes

The main outcomes were feasibility and acceptability of the intervention in the setting of HFpEF. Secondary outcomes were changes in exercise tolerance, quality of life, cardiac and haemodynamic parameters changes in NTproBNP. Feasibility was defined as readiness of patients to sign up for the intervention and was established by enrolling the targeted number of patients. Acceptability was defined as readiness to join and stick to the intervention and was defined as the percentage of patients who completed the intervention. The intervention was considered acceptable if ≥ 80% of patients completed it. This comprised of weekly adherence by telephone and completion of daily physical activity records. If the adherence was recorded, the intervention was considered successful.

8.3.9 Data analysis

A formal power calculation is not mostly needed for pilot feasibility studies.(Moore et al., 2011) It was important to assess whether this intervention, is acceptable and feasible. In addition pre- and post- comparison was performed for pre-defined clinical outcomes, Paired t-test was used to assess differences between baseline and after 3 months, while independent t-test was used to ascertain the significant difference between the two groups. The relationship between physical activity and clinical outcomes was assessed using Pearson's coefficient of correlation. Statistical significance was defined by $p<0.05$. Complete analyses were carried out using SPSS version 20.0 (SPSS, Chicago, IL, USA).

8.4 Results

8.4.1 Acceptability and Feasibility

Out of 49 HFpEF patients initially screened, 40 patients were willing to take part and were included in the study. Recruitment took place between January 2020 and November 2020. Nine patients were excluded i.e. seven had history of atrial fibrillation and two patients had history of recent myocardial infarction and were not willing to exercise. The demographic and clinical features of the cohort are presented in Table

8.1. No adverse events happened due to participation in the intervention study and all 25 patients in the intervention arm completed the intervention. There were no deaths in the study.

Table 8.1. Patients' demographic and clinical features

Variable	Intervention arm (n=25)	Non-intervention arm (n=15)
Age (years)	60±7	60±7
Male (%)	12 (48)	4 (26.7)
Height (cm)	156±8	153±7
Weight (Kg)	66.8±14.2	75.3±13.7
Body surface area (m^2)	1.66±0.18	1.72±0.17
Coronary artery disease (%)	9 (36)	2 (13.3)
Hypertension (%)	21(84)	14 (93)
Diabetes mellitus (%)	9 (36)	3 (0.2)
B-blocker (%)	2 (08)	9 (60)
ACEI/ARB (%)	23 (92)	13 (86.6)
CCB (%)	4 (16.6)	1 (6.67)

ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CCB, Calcium channel blocker

The target step count goal of 2000 steps from baseline was achieved at week three with average number of steps per day increasing significantly by 2546 (from 4457±653 to 6592±545 steps/day, p=0.03), and was maintained until week 12 (7394±632 steps/day, p<0.01) (Figure 8.1).

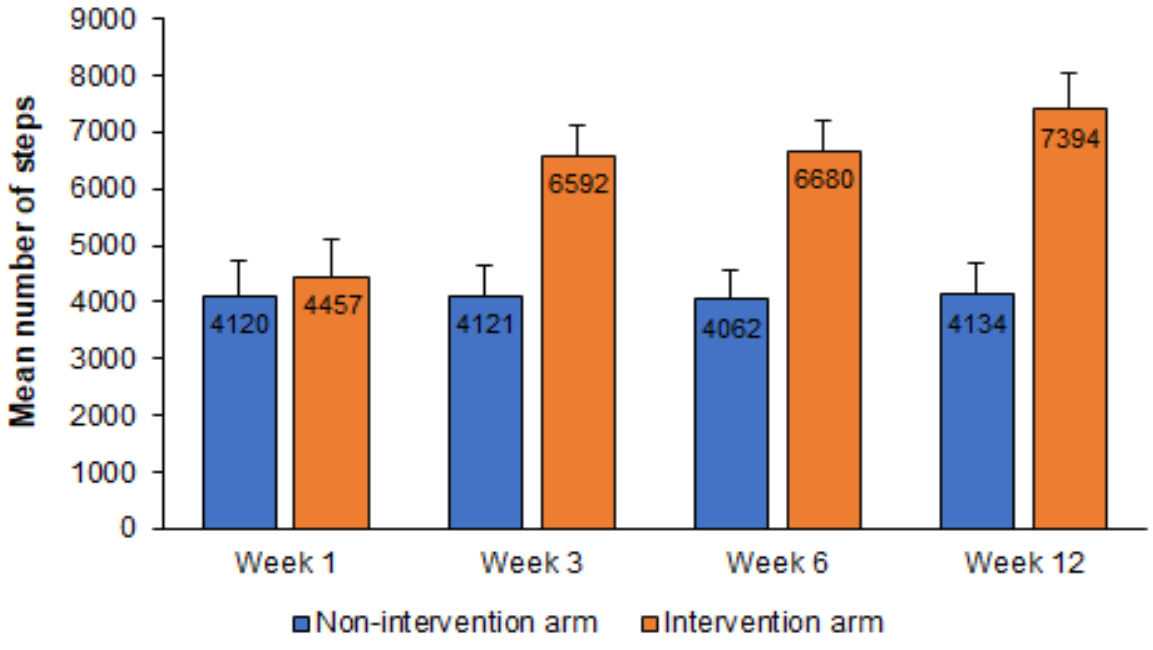

Figure 8.1 Number of steps in both group

The total timing of treadmill test rose in the intervention group (350+122 vs 463+135 secs, p<0.01) but not in controls (399+126 vs 358+88 secs, p=0.23). Resting and peak exercise hemodynamic and echocardiographic variables are presented in Table 8.2. The end of the intervention caused a significant reduction in resting heart rate (78±9 vs. 73±9 beats/min, p<0.01) and mean arterial pressure (93±7 vs. 87±5 mmHg, p<0.01) (Table 8.2).

Table 8.2. Biomarker, haemodynamic, echocardiographic parameters, and quality of life between Intervention and non-intervention arm

Variable	Intervention (n=25)		Non-intervention (n=15)	
	Baseline	After 3 months	Baseline	After 3 months
NT proBNP (pg/ml)	1041±1059	588±378*	1686±1824	1099±463[&]
Heart Rate (beats/min)	78±14	73±9*	78±10	78±9[&]
MAP (mm Hg)	92±5	87±5*	95±7	93±7[&]
SV (ml/beat)	71.3±16.9	76.4±12.9*	81.3±21.2	80.6±14.7
CO (l/min)	5.41±0.98	5.56±0.8	6.21±0.95	6.18±0.86
E/E'	12.43±3.6	9.72±1.86*	12.86±3.17	12.44±2.23[&]
SVR (dynes-sec/cm^5)	1307±215	1195±182*	1122±181	1121±127
LVEDV (ml)	76.8±15.3	75.7±14.9	91.7±17.7	88.4±12.9[&]
LVESV (ml)	38.4±9.2	37.8±8.1	45.1±9.1	43.9±7.9
LVEF (%)	54.2±2.8	54.36±2.7	53.2±2.88	52.2±2.21
LVGLS (%)	-15.9±3.09	-15.9±2.4	-15.5±1.9	-14.8±1.8
TAPSE (mm)	2.11±0.25	2.12±0.17	2.18±0.28	2.12±0.17
RV strain (%)	-22.5±2.6	-22.8±1.8	-22.8±2.2	-21.8±1.4
PALS(%)	23.3±4.5	25.5±4.4*	21.9±4.8	21.8±4.4[&]
PACS(%)	8.6±1.2	9±0.9 *	8.3±2	8.7±1.4
Quality of life	22±4	17±4 *	25±5	22±3[&]

*p<0.01, between baseline and after 3 months; [&]p<0.01, after 3 months post intervention and non-intervention

CO, cardiac output; E/E', ratio of early diastolic flow to early tissue doppler velocity; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; MAP, mean arterial pressure; NT proBNP, N-terminal pro-hormone beta natriuretic peptide; PALS, peak atrial longitudinal strain; PACS, peak atrial contraction strain; RV, right ventricle; SV, stroke volume; SVR, systemic vascular resistance; TAPSE, tricuspid annular peak systolic excursion

The left ventricular end diastolic volume was significantly lower after 3 months in intervention arm as compared to non-intervention arm (75.7±14.9 vs 88.4±12.9 ml, p<0.01). However there was no significant difference in left ventricular (LV) ejection fraction, LV global longitudinal strain and right ventricular systolic parameters after 3 months in both the groups. The peak atrial left longitudinal strain improved significantly in intervention arm after 3 months and was higher than that of non-invention arm (25.5±4.4 vs 21.8±4.4, p<0.01). The quality of life score assessed by Minnesota Living with Heart Failure (MLHF) decreased after intervention by 5 points (22.3±4.14 to 16.9±4.27, p<0.01).

There was a significant difference in NTproBNP following completion of intervention (1041±1059 vs 588±378 pg/ml, p<0.01) from baseline as compared to standard care treatment (1686.2±1824.7 vs 1099.5 pg/ml, p<0.01). Daily steps number correlated positively with post-intervention E/E' (r = 0.52, p<0.01) and peak atrial longitudinal strain (PALS) post-intervention (r = 0.43, p<0.05), but not pre-intervention E/E' (r=0.21, p=0.45) and PALS (r = 0.29, p = 0.3). The significant correlation between average week step count and E/E' and PALS seen post-intervention, although moderate, demonstrates that daily physical activity helps in reducing LV filling pressure and also improves PALS which is seen in active HFpEF and not sedentary patients with HFpEF (Fig. 8.2). This suggests that increasing walking daily improves LV filling pressure and left atrial mechanics in HFpEF patients.

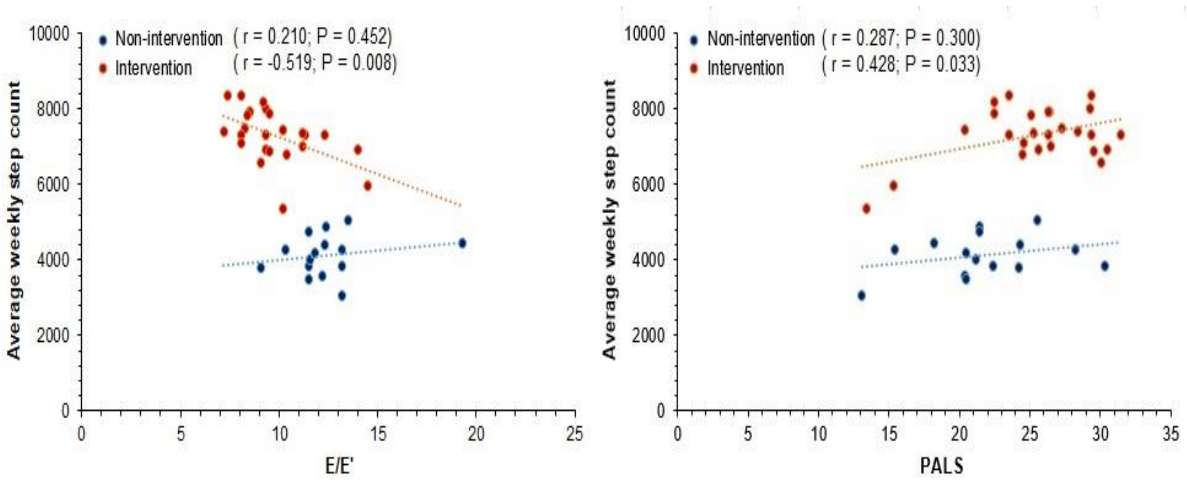

Figure 8.2 Relationship between number of steps and left ventricular filling pressure (E/E') and peak atrial longitudinal strain (PALS) pre and post-intervention

There was no significant relationship between exercise tolerance and number of steps (p=0.74). Also there was no significant relationship between E/E' and QOL (p=0.41), and PALS and QOL (p=0.58).

8.5 Discussion

The present work shows that personalized home-based physical intervention Active-at-Home-HF is feasible and acceptable in patients with HFpEF. Results further indicate that and the intervention helps in adequate alterations in exercise tolerance and haemodynamics. The acceptability and feasibility are confirmed with enrolment and completion rates which were high and these findings are comparable to work by Piotrowicz et al., where in a home-based cardiac rehabilitation which was monitored telephonically had complete adherence as compared to centre-based rehabilitation.(Piotrowicz et al., 2010) Our findings also support recent studies demonstrating the effect of Active-at-Home-HF and other similar interventions in HFrEF.(Okwose et al., 2019, Dalal et al., 2019) Home- based physical intervention have the advantage of being viable, low-cost as compared to centre-based as there is no need for exercise equipment and minimizes the expenditure involved with daily travelling as opposed to center based rehabilitation programmes.(Dalal et al., 2019) It was previously reported that assurance of patients from a clinician towards the safety of home-based physical activity intervention is essential for successful delivery and update of such intervention.(Okwose et al., 2020) High acceptability of the intervention in the present study may also reflect the importance of motivation provided to patients by study research team with regular telephone calls during intervention. Earlier meta-analysis of exercise based cardiac rehabilitation showed significant improvements in clinical outcomes (all-cause and HF-specific mortality, hospitalization, exercise capacity and HRQOL) in exercise as opposed to a control group.(Taylor et al., 2014a) However, most of the studies included in this meta-analysis were hospital- and centre-based and very few focused on home-based cardiac rehabilitation.

The present study had a randomisation of 2:1 into intervention and non-intervention group. If one treatment is expected to be more varying in the outcome than the other, then the statistical power can be increased with unequal sample allocation.(Sverdlov et al., 2019) The treatment with more variation i.e. lower precision, receives more patients than the other treatment group. It is expected that the larger sample size in such groups will reduce the noise in the outcome variables. Accordingly, in this study, we believed that the echo parameters in the intervention group will vary more among patients as compared to the patients in the non-intervention group. Hence, a ratio of 2:1 was opted to allocate patients to intervention and non-intervention groups.

HFpEF patients experience poor QOL and exercise intolerance which is one of the hallmarks of HF.(Fukuta et al., 2019) Exercise training has shown to raise exercise

tolerance and QOL in HFrEF.(Okwose et al., 2019, Dalal et al., 2019) In the present study, HFpEF patients in the intervention arm showed a reduction of 5 points in MLHF questionnaire. Fukuta et al. in a meta-analysis reported that exercise training resulted in improvement of QOL in HFpEF as assessed by MLHF questionnaire without affecting LV systolic and diastolic properties.(Fukuta et al., 2019)

Increasing daily physical activity resulted in decrease LV filling pressure without affecting the LV and RV systolic function. This decrease in LV filling pressure seen after intervention has been shown to be consistent in different intensities of physical exercises used in exercise rehabilitation in HFpEF patients.(Bobenko et al., 2018) Few studies have shown that exercise training improves diastolic dysfunction by reducing E/E' in patients of HFpEF.(Edelmann et al., 2011, Santoso et al., 2019) Exercise training at submaximal levels in HF has no effect on cardiac output and stroke volume.(Belardinelli et al., 1995, Sullivan et al., 1988) The present study also showed that increasing step count by 2000 per day did not have any effect on the stroke volume, cardiac output, LV ejection fraction and LVGLS.

Recent work have shown a link between LA strain measure and reduced exercise capacity in patients of HFpEF.(Leite et al., 2017, Von Roeder et al., 2017a) Impaired PALS has been associated with abnormal exercise hemodynamics in HFpEF.(Telles et al., 2019) However, no studies have previously assessed the effect of exercise training on LA strain in HFpEF patients. This work showed that there was a notable improvement in PALS after 3 months of Active-at-Home-HF intervention which was not observed in non-intervention arm. A recent pilot study involving 25 heart failure with mid-range EF reported improvements in PALS as an acute response to eccentric resistance exercise training.(Caminiti et al., 2022) During exercise PALS function gets augmented as it helps in accelerating LV filling which is needed to maintain an enhanced atrioventricular pressure gradient during the phase of diastole.(Nishikawa et al., 1994, Bhatt et al., 2021) This exercise training when done on a regular daily interval helps in left atrium getting remodeled helping in augmentation of PALS.

8.6 Limitations

There were few limitations in the present study. Firstly, the sample size limits generalizability of results. Of the 49 patients screened, only 40 could be included in the study. Also there was a mismatch of sex between the two groups randomised. This was a pilot work with the intent of proving acceptability and feasibility of the intervention. However, the main motto was not to show the effect of the intervention,

but to evaluate the acceptability and feasibility with a thought that a larger controlled study can help in proving this theme. The design of the pilot study did not demand the application of advanced digital mechanics. Digital mechanics, though provide more benefits of evaluating haemodynamic function such as HR and MAP and may be helpful in further work in improving safety of patients performing daily physical activity. Hence an evaluation of Active-at-Home-HF intervention in HFpEF is needed in large randomised controlled trial to evaluate it clinical effectiveness.

8.7 Conclusion

The present study shows that a 12-week personalised home-based physical activity intervention (Active-at-Home-HF) is feasible, safe and acceptable in patients of HFpEF. It helps in providing clinical and physiological benefits in these patients. It helps in improving exercise tolerance, LV filling pressure, LA performance and quality of life in HFpEF patients.

The current study reinforces the importance of health care professionals in motivating patients of HFpEF. The Active-at-Home-HF programme offers new avenues to HFpEF patients to be physically active at home, who are unable to travel to centres of exercise. These physical activity programs need to be individualized, standardized and made easily available to HFpEF patients to get maximal beneficial outcomes

Chapter 9: General discussion and conclusions

Heart failure (HF) is one of the leading causes of mortality and morbidity worldwide with yearly global cost of treatment and prevention estimated at USD 108 billion.(Savarese and Lund, 2017) The condition is currently considered as an emerging epidemic with the growing burden on western and developing countries.(Roger, 2018) Previously, HF was considered to be a disease of the elderly, but with urbanization, the condition is now seen in people under the age of 50 years.(Lecoeur et al., 2023)(Groenewegen et al., 2020)(Wong et al., 2014) Heart failure with preserved ejection fraction (HFpEF) is a heterogenous clinical condition having a prevalence of 1.1-5.5% in the general population, and associated with high mortality and morbidity.(Teramoto et al., 2022) The current thesis provides new insights into the pathophysiology of HFpEF with a focus on left atrium (LA). It highlights the importance of echocardiography as a robust non-invasive technique used to evaluate the role of the LA in the pathophysiology of heart failure with HFpEF. This thesis improves current knowledge and understanding of the importance of physical activity in HFpEF, i.e., its feasibility, adherence, and physiological benefits.

HFpEF was first described by Robert Luchi, around 4 decades ago.(Luchi et al., 1982) Women have a higher prevalence, poorer quality of life, and greater disease burden compared to men.(Masood and Hamid, 2022) The HFpEF population studied in this research project were younger as reported in earlier studies.(Guha et al., 2018) In the Trivandrum Heart Failure Registry from India, the patients with HF were 10 years younger (mean age 61 years) compared to their western counterparts.(Harikrishnan et al., 2017) In the INTER_CHF study, the mean age among Indians were 56 years.(Dokainish et al., 2016) This shows that the burden of HF is in the younger population in India and explain the the atypical nature of this disease in Indian subcontinent. Our understanding of HFpEF has evolved over last 10-15 years, starting from a primary focus on echocardiographic presence of left ventricular EF$\geq$50% and diastolic dysfunction to association with structural cardiac changes with elevated filling pressure, diastolic alterations, raised biomarkers and poor physical performance. Majority of strategies have focused on research and development of novel technologies that can be used in the monitoring of HF. Advances in the field of translational research are ongoing which are focusing on novel biomarkers, genetic testing, anti-inflammatory treatment, gene therapy, implantable devices and surgical therapy for the management of HF.

Assessment of cardiac output is an important haemodynamic parameter in cardiovascular medicine and the usefulness of non-invasive technologies to monitor cardiac output in routine clinical care of patients with HFpEF can potentially improve outcomes in these patients. Whilst the gold standard invasive thermodilution is still being used to assess cardiac haemodynamics in advance heart failure, non-invasive echocardiography is now standard practice in secondary care and has proven to be a useful tool for measuring cardiac output in intensive care setting.(Mercado et al., 2017). Other non-invasive techniques such as bioreactance (Keren et al., 2007), bioimpedance (Jakovljevic et al., 2014) and pulse contour (Zocalo et al., 2021) have also gained significant research attention.

Echocardiography and bioreactance have been accurately tested against the gold standard thermodilution.(Doherty et al., 2017, Ihlen et al., 1987, Keren et al., 2007) However, Chapter 5 of the present thesis has shown that both technologies cannot be used interchangeably as haemodynamic variables (i.e., cardiac output, stroke volume) derived from two methods show large discrepancies at rest. Both techniques use two different methodologies to derive stroke volume resulting in disparity of results. Bioreactance uses the concept of electrical stimulation across the thoracic cavity and is affected by fluid accumulation in thorax as seen in HFpEF. Echocardiography uses the principle of Doppler to derive cardiac output from flow across the aortic valve. Bioreactance is convenient to use and provides continuous cardiac and haemodynamic monitoring while transthoracic echocardiography requires expertise training and does not provide continuous monitoring of haemodynamic parameters. Notwithstanding, echocardiography gives further information on LV systolic performance indicators like ejection fraction and global longitudinal strain. Hence, a pragmatic approach to ongoing management of patients using these technologies must be followed.

The structure and function of the left atrium (LA) have evolved as important parameters involved in pathophysiology of many cardiac diseases which progress to HF in later stages. LA enlargement is a known marker of LV diastolic dysfunction and is correlated with increased morbidity and mortality.(Frydas et al., 2020) Enlarged LA size is predominantly seen in most HFpEF patients, although around 25-30% of cases will not show enlarged LA at the time of diagnosis. Prior to LA enlargement, remodelling occurs which is marked by alterations at molecular, cellular and tissue level characterized by alteration in cardiomyocyte, fibroblast and non-collagen infiltrative compartments of LA.(Hoit, 2017) Impairment of LA function as assessed by strain

analysis has been observed in HFpEF patients. Strain analysis using speckle tracking imaging helps in direct measurement of LA myocardial deformation and can be evaluated during reservoir, conduit and contractile phases and is relatively independent of geometric assumptions, angle of interrogation and not affected by mitral valve pathology. Also, LA dysfunction is seen in HFpEF patients independent of LA volume enlargement. The speckle tracking imaging can be performed at peak pharmacological and exercise testing to adequately understand HF pathophysiology. Chapters 6 provides new insights about the dynamic changes which occur in LA function in the presence of stress. The LA reservoir function (PALS) has been shown to play a significant part in the progression of diseases like HF and is affected by LV myocardial contractility and innate LA compliance. (Aurigemma et al., 1995) Reduced PALS has been related to progression of HFpEF and has prognostic significance.(Freed et al., 2016) PALS has also been shown to have a positive relationship with raised filling pressure in HF at rest and can estimate disproportional rise in pressure during exercise.(Lundberg et al., 2019a) The present research programme showed that both HFrEF and HFpEF had reduced LVGLS and PALS at rest and after exercise, with lowest strains values exhibited by HFrEF patients. HFpEF patients had a significant decrease in LA reservoir strain with exercise, while no significant change was seen in the HFrEF and control groups. Change in LA strain was also significantly associated with lower exercise time. These findings suggest that lack of LA functional reserve is associated with poor exercise capacity in HFpEF. The use of stress test for understanding and exploring the chamber reserve and haemodynamics represents an emerging frontier in understanding LA mechanics. This shows that the availability of non-invasive tools for assessment of LA mechanics has resulted to an in-depth knowledge of LA structure, thus transcending beyond being just a research tool, but with potential application in clinical practice to improve outcomes for patients.

Besides physiological stress testing, the pathophysiology of HFpEF and HFrEF was assessed using pharmacological (dobutamine) stress in Chapter 7. Dobutamine stress echo (DSE) is a good alternative to exercise stress with an acceptable safety profile and can be useful in HF patients who cannot walk or cycle due to associated pulmonary, orthopaedic or rheumatologic problems.(Pellikka et al., 2007) Moreover, it is easier to acquire echocardiography images using DSE compared to exercise testing. DSE provides pharmacologic inotropic stress and causes more rise in filling pressure in HFpEF, which is absent in HFrEF. Also, it decreases LA and LV strains more in

HFpEF than HFrEF, further highlighting differences in haemodynamic responses between both classes of HF studied. These changes seen are due to myocardial mechanical, energetic and flow reserve alteration with reduced coupling of blood flow to demand and increase in myocardial oxygen demand.(Abouezzeddine et al., 2019) DSE has been regularly used for patients with coronary artery disease, aortic stenosis and mitral regurgitation patients. This study shows that DSE can be used safely in HF patients and provides new insights into the HF pathophysiology.

The primary symptom of HFpEF patients, is exercise intolerance, which can severely undermine quality of life.(Fukuta et al., 2019) HFpEF is now being considered as an exercise deficiency syndrome.(La Gerche et al., 2022) Physical inactivity in patients with HF is associated with increased risk of all-cause death and cardiac death.(Doukky et al., 2016) This association is seen irrespective of LVEF. On the contrary, recent prospective observational studies have shown that regular physical activity and increased cardiorespiratory fitness lower the risk of developing HF.(Santoso et al., 2019) Physical activity is associated with increase in stroke volume, cardiac output, cardiac mass and decrease in clinical events. In Chapter 8, we described the feasibility, effectiveness of personalised physical activity intervention which is home based (Active-at-Home-HF) in HFpEF. Using a single centre study design, data showed that the intervention was easily possible and resulted in improvement in LV filling pressure, LA performance, exercise tolerance and quality of life in HFpEF patients. Functional capacity in patients living with chronic diseases has been a focus of many recent studies. Functional incapacity and sedentary lifestyle correlated with morbidity and has now become very important in patients with HFpEF who have problems related to poor exercise tolerance and breathlessness, forcing them to be dependent on others for activities of daily living. Regular physical activity has proven to be useful in improving exercise tolerance and QOL in HFrEF,(Okwose et al., 2019). In the present research programme, the Active-at-Home-HF intervention was safe and well adhered to, and resulted in a significant improvement in quality of life. It was also associated with the reduction in LV filling pressure and improvement in LA reservoir function. The most common risk involved in physical activity are musculoskeletal injuries like sprained ligaments, strained muscles and overuse injuries. None of the patients in the present study suffered from any adverse event.

9.1 Implications for patients, practice and future research

The present thesis has proven to be timely and important because 1) it provides

evidence that response to different forms of stress is distinctly different between HFpEF and HFrEF suggesting differing pathophysiology, 2) left atrial function contribute to the hemodynamics of HFpEF at rest and during exercise, 3) home-based personalised physical activity intervention can help people with HFpEF to enhance their quality of life, physical and cardiac function. There is a high level of interest in the medical research to identify new prevention, management, and monitoring strategies in HFpEF. Studies contained in this thesis provide evidence for better understanding of the pathophysiology, and the effect of home based physical activity intervention on quality of life and clinical phenotype in HFpEF.

Future research is warranted to investigate molecular and cellular mechanisms underpinning pathophysiological findings in HFpEF. This can further lead to discovery of novel therapeutic targets and interventions. Based on the research conducted as part of this thesis it can be recommended that more attention should be directed towards the assessment of left atrial strain and haemodynamics at rest and in response to stress that can potentially guide management of HFpEF. Integration of home-based physical activity interventions, such as Active-at-Home in patients with HFpEF may improve their quality of life and symptoms.

References

Abdul-Rahim, A. H., Shen, L., Rush, C. J., Jhund, P. S., Lees, K. R., Mcmurray, J. J. V. & Collaborators, V. I.-H. F. 2018. Effect of digoxin in patients with heart failure and mid-range (borderline) left ventricular ejection fraction. *Eur J Heart Fail,* 20**,** 1139-1145.

Abouezzeddine, O. F., Kemp, B. J., Borlaug, B. A., Mullan, B. P., Behfar, A., Pislaru, S. V., Fudim, M., Redfield, M. M. & Chareonthaitawee, P. 2019. Myocardial Energetics in Heart Failure With Preserved Ejection Fraction. *Circ Heart Fail,* 12**,** e006240.

Abraham, W. T., Kuck, K. H., Goldsmith, R. L., Lindenfeld, J., Reddy, V. Y., Carson, P. E., Mann, D. L., Saville, B., Parise, H., Chan, R., Wiegn, P., Hastings, J. L., Kaplan, A. J., Edelmann, F., Luthje, L., Kahwash, R., Tomassoni, G. F., Gutterman, D. D., Stagg, A., Burkhoff, D. & Hasenfuss, G. 2018. A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation. *JACC Heart Fail,* 6**,** 874-883.

Abudiab, M. M., Redfield, M. M., Melenovsky, V., Olson, T. P., Kass, D. A., Johnson, B. D. & Borlaug, B. A. 2013. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail,* 15**,** 776-85.

Adams, K. F., Jr., Fonarow, G. C., Emerman, C. L., Lejemtel, T. H., Costanzo, M. R., Abraham, W. T., Berkowitz, R. L., Galvao, M., Horton, D. P., Committee, A. S. A. & Investigators 2005. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J,* 149**,** 209-16.

Aggeli, C., Lagoudakou, S., Felekos, I., Panagopoulou, V., Kastellanos, S., Toutouzas, K., Roussakis, G. & Tousoulis, D. 2015. Two-dimensional speckle tracking for the assessment of coronary artery disease during dobutamine stress echo: clinical tool or merely research method. *Cardiovasc Ultrasound,* 13**,** 43.

Aguilar, D., Skali, H., Moye, L. A., Lewis, E. F., Gaziano, J. M., Rutherford, J. D., Hartley, L. H., Randall, O. S., Geltman, E. M., Lamas, G. A., Rouleau, J. L., Pfeffer, M. A. & Solomon, S. D. 2004. Alcohol consumption and prognosis in patients with left ventricular systolic dysfunction after a myocardial infarction. *J Am Coll Cardiol,* 43**,** 2015-21.

Ahmad, T., Miller, P. E., Mccullough, M., Desai, N. R., Riello, R., Psotka, M., Bohm, M., Allen, L. A., Teerlink, J. R., Rosano, G. M. C. & Lindenfeld, J. 2019. Why has positive inotropy failed in chronic heart failure? Lessons from prior inotrope trials. *Eur J Heart Fail,* 21**,** 1064-1078.

Ahmed, A., Rich, M. W., Fleg, J. L., Zile, M. R., Young, J. B., Kitzman, D. W., Love, T. E., Aronow, W. S., Adams, K. F., Jr. & Gheorghiade, M. 2006. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation,* 114**,** 397-403.

Aizawa, Y., Sakata, Y., Mano, T., Takeda, Y., Ohtani, T., Tamaki, S., Omori, Y., Tsukamoto, Y., Hirayama, A., Komuro, I. & Yamamoto, K. 2011. Transition from asymptomatic diastolic dysfunction to heart failure with preserved ejection fraction: roles of systolic function and ventricular distensibility. *Circ J,* 75**,** 596-602.

Al-Khatib, S. M., Stevenson, W. G., Ackerman, M. J., Bryant, W. J., Callans, D. J., Curtis, A. B., Deal, B. J., Dickfeld, T., Field, M. E., Fonarow, G. C., Gillis, A. M., Granger, C. B., Hammill, S. C., Hlatky, M. A., Joglar, J. A., Kay, G. N., Matlock, D. D., Myerburg, R. J. & Page, R. L. 2018. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol,* 72**,** e91-e220.

Al-Najjar, Y., Witte, K. K. & Clark, A. L. 2012. Chronotropic incompetence and survival in chronic heart failure. *Int J Cardiol,* 157**,** 48-52.

Al-Sadawi, M., Ortega, R. R., Ariyaratnam, J., Battisha, A., Madoukh, B. & Bukharovich, I. 2020. State of the Art Review of Current Therapies for HFpEF: An Overview of Interatrial Septal Device Therapy in Heart Failure. *Curr Cardiol Rev*.

Amsallem, M., Sternbach, J. M., Adigopula, S., Kobayashi, Y., Vu, T. A., Zamanian, R., Liang, D., Dhillon, G., Schnittger, I., Mcconnell, M. V. & Haddad, F. 2016. Addressing the Controversy of Estimating Pulmonary Arterial Pressure by Echocardiography. *J Am Soc Echocardiogr,* 29**,** 93-102.

Andersson, C., Nayor, M., Tsao, C. W., Levy, D. & Vasan, R. S. 2021. Framingham Heart Study: JACC Focus Seminar, 1/8. *J Am Coll Cardiol,* 77**,** 2680-2692.

Arendse, L. B., Danser, A. H. J., Poglitsch, M., Touyz, R. M., Burnett, J. C., Jr., Llorens-Cortes, C., Ehlers, M. R. & Sturrock, E. D. 2019. Novel Therapeutic Approaches Targeting the Renin-Angiotensin System and Associated Peptides in Hypertension and Heart Failure. *Pharmacol Rev,* 71**,** 539-570.

Arrigo, M., Gayat, E., Parenica, J., Ishihara, S., Zhang, J., Choi, D. J., Park, J. J., Alhabib, K. F., Sato, N., Miro, O., Maggioni, A. P., Zhang, Y., Spinar, J., Cohen-Solal, A., Iwashyna, T. J., Mebazaa, A. & Network, G. 2017. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. *Eur J Heart Fail,* 19**,** 201-208.

Asrar Ul Haq, M., Goh, C. Y., Levinger, I., Wong, C. & Hare, D. L. 2015. Clinical utility of exercise training in heart failure with reduced and preserved ejection fraction. *Clin Med Insights Cardiol,* 9**,** 1-9.

Aurigemma, G. P., Gaasch, W. H., Mclaughlin, M., Mcginn, R., Sweeney, A. & Meyer, T. E. 1995. Reduced left ventricular systolic pump performance and depressed myocardial contractile function in patients > 65 years of age with normal ejection fraction and a high relative wall thickness. *Am J Cardiol,* 76**,** 702-5.

Aurigemma, G. P., Gottdiener, J. S., Shemanski, L., Gardin, J. & Kitzman, D. 2001. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the cardiovascular health study. *J Am Coll Cardiol,* 37**,** 1042-8.

Badano, L. P., Kolias, T. J., Muraru, D., Abraham, T. P., Aurigemma, G., Edvardsen, T., D'hooge, J., Donal, E., Fraser, A. G., Marwick, T., Mertens, L., Popescu, B. A., Sengupta, P. P., Lancellotti, P., Thomas, J. D., Voigt, J. U., Industry, R. & Reviewers: This Document Was Reviewed by Members of The, E. S. D. C. 2018. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging,* 19**,** 591-600.

Balady, G. J., R. Arena, K. Sietsema, J. Myers, L. Coke, G. F. Fletcher, D. Forman, B. Franklin, M. Guazzi, M. Gulati, S. J. Keteyian, C. J. Lavie, R. Macko, D. Mancini, R. V. Milani, C. R. American Heart Association Exercise, C. Prevention Committee of the Council on Clinical, E. Council on, Prevention, D. Council on Peripheral Vascular, C. Interdisciplinary Council on Quality of and R. Outcomes (2010). "Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association." *Circulation* 122(2): 191-225.

Baldasseroni, S., Opasich, C., Gorini, M., Lucci, D., Marchionni, N., Marini, M., Campana, C., Perini, G., Deorsola, A., Masotti, G., Tavazzi, L., Maggioni, A. P. & Italian Network on Congestive Heart Failure, I. 2002. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. *Am Heart J,* 143**,** 398-405.

Bangdiwala, S. I., Weiner, D. H., Bourassa, M. G., Friesinger, G. C., 2nd, Ghali, J. K. & Yusuf, S. 1992. Studies of Left Ventricular Dysfunction (SOLVD) Registry: rationale, design, methods and description of baseline characteristics. *Am J Cardiol,* 70**,** 347-53.

Barsuk, J. H., Gordon, R. A., Cohen, E. R., Cotts, W. G., Malkenson, D., Yancy, C. W. & Williams, M. V. 2013. A diuretic protocol increases volume removal and reduces readmissions among hospitalized patients with acute decompensated heart failure. *Congest Heart Fail,* 19**,** 53-60.

Bassett, D. R., Jr., Toth, L. P., Lamunion, S. R. & Crouter, S. E. 2017. Step Counting: A Review of Measurement Considerations and Health-Related Applications. *Sports Med,* 47**,** 1303-1315.

Belardinelli, R., Georgiou, D., Scocco, V., Barstow, T. J. & Purcaro, A. 1995. Low intensity exercise training in patients with chronic heart failure. *J Am Coll Cardiol,* 26**,** 975-82.

Benjamin, E. J., Blaha, M. J., Chiuve, S. E., Cushman, M., Das, S. R., Deo, R., De Ferranti, S. D., Floyd, J., Fornage, M., Gillespie, C., Isasi, C. R., Jimenez, M. C., Jordan, L. C., Judd, S. E., Lackland, D., Lichtman, J. H., Lisabeth, L., Liu, S., Longenecker, C. T., Mackey, R. H., Matsushita, K., Mozaffarian, D., Mussolino, M. E., Nasir, K., Neumar, R. W., Palaniappan, L., Pandey, D. K., Thiagarajan, R. R., Reeves, M. J., Ritchey, M., Rodriguez, C. J., Roth, G. A., Rosamond, W. D., Sasson, C., Towfighi, A., Tsao, C. W., Turner, M. B., Virani, S. S., Voeks, J. H., Willey, J. Z., Wilkins, J. T., Wu, J. H., Alger, H. M., Wong, S. S., Muntner, P., American Heart Association Statistics, C. & Stroke Statistics, S. 2017. Heart Disease and Stroke

Statistics-2017 Update: A Report From the American Heart Association. *Circulation,* 135**,** e146-e603.

Bennett, S. J., Huster, G. A., Baker, S. L., Milgrom, L. B., Kirchgassner, A., Birt, J. & Pressler, M. L. 1998. Characterization of the precipitants of hospitalization for heart failure decompensation. *Am J Crit Care,* 7**,** 168-74.

Bertero, E. & Maack, C. 2018. Metabolic remodelling in heart failure. *Nat Rev Cardiol,* 15**,** 457-470.

Bhatia, R. S., Tu, J. V., Lee, D. S., Austin, P. C., Fang, J., Haouzi, A., Gong, Y. & Liu, P. P. 2006. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med,* 355**,** 260-9.

Bhatnagar, P., Wickramasinghe, K., Williams, J., Rayner, M. & Townsend, N. 2015. The epidemiology of cardiovascular disease in the UK 2014. *Heart,* 101**,** 1182-9.

Bhatt, A., Flink, L., Lu, D. Y., Fang, Q., Bibby, D. & Schiller, N. B. 2021. Exercise physiology of the left atrium: quantity and timing of contribution to cardiac output. *Am J Physiol Heart Circ Physiol,* 320**,** H575-H583.

Bhella, P. S., Prasad, A., Heinicke, K., Hastings, J. L., Arbab-Zadeh, A., Adams-Huet, B., Pacini, E. L., Shibata, S., Palmer, M. D., Newcomer, B. R. & Levine, B. D. 2011. Abnormal haemodynamic response to exercise in heart failure with preserved ejection fraction. *Eur J Heart Fail,* 13**,** 1296-304.

Bilbao, A., Escobar, A., Garcia-Perez, L., Navarro, G. & Quiros, R. 2016. The Minnesota living with heart failure questionnaire: comparison of different factor structures. *Health Qual Life Outcomes,* 14**,** 23.

Bild, D. E., Bluemke, D. A., Burke, G. L., Detrano, R., Diez Roux, A. V., Folsom, A. R., Greenland, P., Jacob, D. R., Jr., Kronmal, R., Liu, K., Nelson, J. C., O'leary, D., Saad, M. F., Shea, S., Szklo, M. & Tracy, R. P. 2002. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol,* 156**,** 871-81.

Bizouarn, P., Blanloeil, Y. & Pinaud, M. 1994. [Comparison of cardiac output measured continuously by thermodilution and calculated according to Fick's principle]. *Ann Fr Anesth Reanim,* 13**,** 685-9.

Bjarnason-Wehrens, B., Nebel, R., Jensen, K., Hackbusch, M., Grilli, M., Gielen, S., Schwaab, B., Rauch, B., German Society of Cardiovascular, P. & Rehabilitation 2020. Exercise-based cardiac rehabilitation in patients with reduced left ventricular ejection fraction: The Cardiac Rehabilitation Outcome Study in Heart Failure (CROS-HF): A systematic review and meta-analysis. *Eur J Prev Cardiol,* 27**,** 929-952.

Blair, C. A., Brundage, E. A., Thompson, K. L., Stromberg, A., Guglin, M., Biesiadecki, B. J. & Campbell, K. S. 2020. Heart Failure in Humans Reduces Contractile Force in Myocardium From Both Ventricles. *JACC Basic Transl Sci,* 5**,** 786-798.

Blumer, V., Greene, S. J., Wu, A., Butler, J., Ezekowitz, J. A., Lindenfeld, J., Alhanti,

B., Hernandez, A. F., O'connor, C. M. & Mentz, R. J. 2021. Sex Differences in Clinical Course and Patient-Reported Outcomes Among Patients Hospitalized for Heart Failure. *JACC Heart Fail,* 9**,** 336-345.

Bobenko, A., Bartels, I., Munch, M., Trippel, T., Lindhorst, R., Nolte, K., Herrmann-Lingen, C., Halle, M., Duvinage, A., Dungen, H. D., Gelbrich, G., Tschope, C., Hasenfuss, G., Wachter, R., Pieske, B. & Edelmann, F. 2018. Amount or intensity? Potential targets of exercise interventions in patients with heart failure with preserved ejection fraction. *ESC Heart Fail,* 5**,** 53-62.

Borg, G. A. 1982. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc,* 14**,** 377-81.

Borlaug, B. A. & Kass, D. A. 2009. Invasive hemodynamic assessment in heart failure. *Heart Fail Clin,* 5**,** 217-28.

Borlaug, B. A., Melenovsky, V., Russell, S. D., Kessler, K., Pacak, K., Becker, L. C. & Kass, D. A. 2006. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation,* 114**,** 2138-47.

Borlaug, B. A., Nishimura, R. A., Sorajja, P., Lam, C. S. & Redfield, M. M. 2010. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail,* 3**,** 588-95.

Borlaug, B. A. & Paulus, W. J. 2011. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J,* 32**,** 670-9.

Borovac, J. A., D'amario, D., Bozic, J. & Glavas, D. 2020. Sympathetic nervous system activation and heart failure: Current state of evidence and the pathophysiology in the light of novel biomarkers. *World J Cardiol,* 12**,** 373-408.

Bozkurt, B., Hershberger, R. E., Butler, J., Grady, K. L., Heidenreich, P. A., Isler, M. L., Kirklin, J. K. & Weintraub, W. S. 2021. 2021 ACC/AHA Key Data Elements and Definitions for Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Heart Failure). *J Am Coll Cardiol,* 77**,** 2053-2150.

Braunwald, E., Frahm, C. J. & Ross, J., Jr. 1961. Studies on Starling's law of the heart. V. Left ventricular function in man. *J Clin Invest,* 40**,** 1882-90.

Briasoulis, A., Androulakis, E., Christophides, T. & Tousoulis, D. 2016. The role of inflammation and cell death in the pathogenesis, progression and treatment of heart failure. *Heart Fail Rev,* 21**,** 169-76.

Brozena, S. C. & Jessup, M. 2003. The new staging system for heart failure. What every primary care physician should know. *Geriatrics,* 58**,** 31-6; quiz 38.

Brutsaert, D. L. & Sys, S. U. 1997. Diastolic dysfunction in heart failure. *J Card Fail,* 3**,** 225-42.

Bui, A. L., Grau-Sepulveda, M. V., Hernandez, A. F., Peterson, E. D., Yancy, C. W., Bhatt, D. L. & Fonarow, G. C. 2013. Admission heart rate and in-hospital outcomes in patients hospitalized for heart failure in sinus rhythm and in atrial fibrillation. *Am Heart J,* 165**,** 567-574 e6.

Bursi, F., Weston, S. A., Redfield, M. M., Jacobsen, S. J., Pakhomov, S., Nkomo, V. T., Meverden, R. A. & Roger, V. L. 2006. Systolic and diastolic heart failure in the community. *JAMA,* 296**,** 2209-16.

Bytyci, I., D'agostino, A., Bajraktari, G., Lindqvist, P., Dini, F. L. & Henein, M. Y. 2021. Left atrial stiffness predicts cardiac events in patients with heart failure and reduced ejection fraction: The impact of diabetes. *Clin Physiol Funct Imaging,* 41**,** 208-216.

Bytyci, I., Dini, F. L., Bajraktari, A., Pugliese, N. R., D'agostino, A., Bajraktari, G., Lindqvist, P. & Henein, M. Y. 2020. Speckle Tracking-Derived Left Atrial Stiffness Predicts Clinical Outcome in Heart Failure Patients with Reduced to Mid-Range Ejection Fraction. *J Clin Med,* 9.

Cameli, M., Mandoli, G. E., Loiacono, F., Dini, F. L., Henein, M. & Mondillo, S. 2016. Left atrial strain: a new parameter for assessment of left ventricular filling pressure. *Heart Fail Rev,* 21**,** 65-76.

Caminiti, G., Perrone, M. A., Iellamo, F., D'antoni, V., Catena, M., Franchini, A. & Volterrani, M. 2022. Acute Left Atrial Response to Different Eccentric Resistance Exercise Loads in Patients with Heart Failure with Middle Range Ejection Fraction: A Pilot Study. *J Pers Med,* 12.

Carbone, S., Canada, J. M., Buckley, L. F., Trankle, C. R., Billingsley, H. E., Dixon, D. L., Mauro, A. G., Dessie, S., Kadariya, D., Mezzaroma, E., Buzzetti, R., Arena, R., Van Tassell, B. W., Toldo, S. & Abbate, A. 2017. Dietary Fat, Sugar Consumption, and Cardiorespiratory Fitness in Patients With Heart Failure With Preserved Ejection Fraction. *JACC Basic Transl Sci,* 2**,** 513-525.

Ceia, F., Fonseca, C., Mota, T., Morais, H., Matias, F., De Sousa, A., Oliveira, A. & Investigators, E. 2002. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *Eur J Heart Fail,* 4**,** 531-9.

Cesaroni, G., Mureddu, G. F., Agabiti, N., Mayer, F., Stafoggia, M., Forastiere, F., Latini, R., Masson, S., Davoli, M., Boccanelli, A. & Group, P. S. 2021. Sex differences in factors associated with heart failure and diastolic left ventricular dysfunction: a cross-sectional population-based study. *BMC Public Health,* 21**,** 415.

Chattopadhyay, S., Alamgir, M. F., Nikitin, N. P., Rigby, A. S., Clark, A. L. & Cleland, J. G. 2010. Lack of diastolic reserve in patients with heart failure and normal ejection fraction. *Circ Heart Fail,* 3**,** 35-43.

Chaudhry, S. I., Phillips, C. O., Stewart, S. S., Riegel, B., Mattera, J. A., Jerant, A. F. & Krumholz, H. M. 2007. Telemonitoring for patients with chronic heart failure: a systematic review. *J Card Fail,* 13**,** 56-62.

Chen, W. Y., Hong, J., Gannon, J., Kakkar, R. & Lee, R. T. 2015. Myocardial

pressure overload induces systemic inflammation through endothelial cell IL-33. *Proc Natl Acad Sci U S A,* 112**,** 7249-54.

Chioncel, O., Lainscak, M., Seferovic, P. M., Anker, S. D., Crespo-Leiro, M. G., Harjola, V. P., Parissis, J., Laroche, C., Piepoli, M. F., Fonseca, C., Mebazaa, A., Lund, L., Ambrosio, G. A., Coats, A. J., Ferrari, R., Ruschitzka, F., Maggioni, A. P. & Filippatos, G. 2017. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail,* 19**,** 1574-1585.

Claeys, M., Petit, T., La Gerche, A., Herbots, L., Claus, P., De Bosscher, R., Droogne, W., Van Cleemput, J., Voigt, J. U., Delcroix, M., Janssens, S., Willems, R., Verwerft, J. & Claessen, G. 2022. Impaired biventricular contractile reserve in patients with diastolic dysfunction: insights from exercise stress echocardiography. *Eur Heart J Cardiovasc Imaging,* 23**,** 1042-1052.

Cleland, J. G., Tendera, M., Adamus, J., Freemantle, N., Polonski, L., Taylor, J. & Investigators, P.-C. 2006. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J,* 27**,** 2338-45.

Cohn, J. N., Tognoni, G. & Valsartan Heart Failure Trial, I. 2001. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med,* 345**,** 1667-75.

Collaboration, N. C. D. R. F. 2017. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet,* 389**,** 37-55.

Conraads, V. M., Metra, M., Kamp, O., De Keulenaer, G. W., Pieske, B., Zamorano, J., Vardas, P. E., Bohm, M. & Dei Cas, L. 2012. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. *Eur J Heart Fail,* 14**,** 219-25.

Conrad, N., Judge, A., Canoy, D., Tran, J., Pinho-Gomes, A. C., Millett, E. R. C., Salimi-Khorshidi, G., Cleland, J. G., Mcmurray, J. J. V. & Rahimi, K. 2019. Temporal Trends and Patterns in Mortality After Incident Heart Failure: A Longitudinal Analysis of 86000 Individuals. *JAMA Cardiol,* 4**,** 1102-1111.

Conrad, N., Judge, A., Tran, J., Mohseni, H., Hedgecott, D., Crespillo, A. P., Allison, M., Hemingway, H., Cleland, J. G., Mcmurray, J. J. V. & Rahimi, K. 2018. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet,* 391**,** 572-580.

Cooper, L. B., Mentz, R. J., Sun, J. L., Schulte, P. J., Fleg, J. L., Cooper, L. S., Pina, I. L., Leifer, E. S., Kraus, W. E., Whellan, D. J., Keteyian, S. J. & O'connor, C. M. 2015. Psychosocial Factors, Exercise Adherence, and Outcomes in Heart Failure Patients: Insights From Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION). *Circ Heart Fail,* 8**,** 1044-51.

Corrieri, N., A. Del Torto, C. Vignati, R. Maragna, F. De Martino, M. Cellamare, S. Farina, E. Salvioni, A. Bonomi and P. Agostoni (2021). "Cardiac output changes

during exercise in heart failure patients: focus on mid-exercise." *ESC Heart Fail* 8(1): 55-62.

Cotrim, C. & Carrageta, M. 2000. [Stress-exercise echocardiography]. *Rev Port Cardiol,* 19**,** 345-50.

Cowie, M. R. 2017. The heart failure epidemic: a UK perspective. *Echo Res Pract,* 4**,** R15-R20.

Critchley, L. A., Calcroft, R. M., Tan, P. Y., Kew, J. & Critchley, J. A. 2000. The effect of lung injury and excessive lung fluid, on impedance cardiac output measurements, in the critically ill. *Intensive Care Med,* 26**,** 679-85.

Currie, P. J., Seward, J. B., Chan, K. L., Fyfe, D. A., Hagler, D. J., Mair, D. D., Reeder, G. S., Nishimura, R. A. & Tajik, A. J. 1985. Continuous wave Doppler determination of right ventricular pressure: a simultaneous Doppler-catheterization study in 127 patients. *J Am Coll Cardiol,* 6**,** 750-6.

Dalal, H. M., Taylor, R. S., Jolly, K., Davis, R. C., Doherty, P., Miles, J., Van Lingen, R., Warren, F. C., Green, C., Wingham, J., Greaves, C., Sadler, S., Hillsdon, M., Abraham, C., Britten, N., Frost, J., Singh, S., Hayward, C., Eyre, V., Paul, K., Lang, C. C. & Smith, K. 2019. The effects and costs of home-based rehabilitation for heart failure with reduced ejection fraction: The REACH-HF multicentre randomized controlled trial. *Eur J Prev Cardiol,* 26**,** 262-272.

Dargie, H. 1999. Recent clinical data regarding the use of beta blockers in heart failure: focus on CIBIS II. *Heart,* 82 Suppl 4**,** IV2-4.

De Boer, R. A., De Keulenaer, G., Bauersachs, J., Brutsaert, D., Cleland, J. G., Diez, J., Du, X. J., Ford, P., Heinzel, F. R., Lipson, K. E., Mcdonagh, T., Lopez-Andres, N., Lunde, I. G., Lyon, A. R., Pollesello, P., Prasad, S. K., Tocchetti, C. G., Mayr, M., Sluijter, J. P. G., Thum, T., Tschope, C., Zannad, F., Zimmermann, W. H., Ruschitzka, F., Filippatos, G., Lindsey, M. L., Maack, C. & Heymans, S. 2019. Towards better definition, quantification and treatment of fibrosis in heart failure. A scientific roadmap by the Committee of Translational Research of the Heart Failure Association (HFA) of the European Society of Cardiology. *Eur J Heart Fail,* 21**,** 272-285.

De Jong, K. A. & Lopaschuk, G. D. 2017. Complex Energy Metabolic Changes in Heart Failure With Preserved Ejection Fraction and Heart Failure With Reduced Ejection Fraction. *Can J Cardiol,* 33**,** 860-871.

Dericbourg, C., Tribouilloy, C., Kugener, H., Avinee, P., Rey, J. L. & Lesbre, J. P. 1990. [Noninvasive measurement of cardiac output by pulsed Doppler echocardiography. Correlation with thermodilution]. *Arch Mal Coeur Vaiss,* 83**,** 237-44.

Dick, S. A. & Epelman, S. 2016. Chronic Heart Failure and Inflammation: What Do We Really Know? *Circ Res,* 119**,** 159-76.

Digitalis Investigation, G. 1997. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med,* 336**,** 525-33.

Doenst, T., Nguyen, T. D. & Abel, E. D. 2013. Cardiac metabolism in heart failure: implications beyond ATP production. *Circ Res,* 113**,** 709-24.

Doherty, A., El-Khuffash, A., Monteith, C., Mcsweeney, L., Breatnach, C., Kent, E., Tully, E., Malone, F. & Thornton, P. 2017. Comparison of bioreactance and echocardiographic non-invasive cardiac output monitoring and myocardial function assessment in primagravida women. *Br J Anaesth,* 118**,** 527-532.

Dokainish, H., Teo, K., Zhu, J., Roy, A., Alhabib, K. F., Elsayed, A., Palileo-Villaneuva, L., Lopez-Jaramillo, P., Karaye, K., Yusoff, K., Orlandini, A., Sliwa, K., Mondo, C., Lanas, F., Prabhakaran, D., Badr, A., Elmaghawry, M., Damasceno, A., Tibazarwa, K., Belley-Cote, E., Balasubramanian, K., Islam, S., Yacoub, M. H., Huffman, M. D., Harkness, K., Grinvalds, A., Mckelvie, R., Bangdiwala, S. I., Yusuf, S. & Investigators, I.-C. 2017. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. *Lancet Glob Health,* 5**,** e665-e672.

Doukky, R., Mangla, A., Ibrahim, Z., Poulin, M. F., Avery, E., Collado, F. M., Kaplan, J., Richardson, D. & Powell, L. H. 2016. Impact of Physical Inactivity on Mortality in Patients With Heart Failure. *Am J Cardiol,* 117**,** 1135-43.

Du, X., Khamitova, A., Kyhlstedt, M., Sun, S. & Sengoelge, M. 2018. Utilisation of real-world data from heart failure registries in OECD countries - A systematic review. *Int J Cardiol Heart Vasc,* 19**,** 90-97.

Ebert, T. J. & Cowley, A. W., Jr. 1988. Atrial natriuretic factor attenuates carotid baroreflex-mediated cardioacceleration in humans. *Am J Physiol,* 254**,** R590-4.

Edelmann, F., Gelbrich, G., Dungen, H. D., Frohling, S., Wachter, R., Stahrenberg, R., Binder, L., Topper, A., Lashki, D. J., Schwarz, S., Herrmann-Lingen, C., Loffler, M., Hasenfuss, G., Halle, M. & Pieske, B. 2011. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol,* 58**,** 1780-91.

Edelmann, F., Schmidt, A. G., Gelbrich, G., Binder, L., Herrmann-Lingen, C., Halle, M., Hasenfuss, G., Wachter, R. & Pieske, B. 2010. Rationale and design of the 'aldosterone receptor blockade in diastolic heart failure' trial: a double-blind, randomized, placebo-controlled, parallel group study to determine the effects of spironolactone on exercise capacity and diastolic function in patients with symptomatic diastolic heart failure (Aldo-DHF). *Eur J Heart Fail,* 12**,** 874-82.

Egstrup, M., Gustafsson, I., Andersen, M. J., Kistorp, C. N., Schou, M., Tuxen, C. D. & Moller, J. E. 2013. Haemodynamic response during low-dose dobutamine infusion in patients with chronic systolic heart failure: comparison of echocardiographic and invasive measurements. *Eur Heart J Cardiovasc Imaging,* 14**,** 659-67.

Eisenberg, E., Di Palo, K. E. & Pina, I. L. 2018. Sex differences in heart failure. *Clin Cardiol,* 41**,** 211-216.

Ellingsen, O., Halle, M., Conraads, V., Stoylen, A., Dalen, H., Delagardelle, C., Larsen, A. I., Hole, T., Mezzani, A., Van Craenenbroeck, E. M., Videm, V., Beckers,

P., Christle, J. W., Winzer, E., Mangner, N., Woitek, F., Hollriegel, R., Pressler, A., Monk-Hansen, T., Snoer, M., Feiereisen, P., Valborgland, T., Kjekshus, J., Hambrecht, R., Gielen, S., Karlsen, T., Prescott, E., Linke, A. & Group, S. H. F. S. 2017. High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction. *Circulation,* 135**,** 839-849.

Emdin, M., Aimo, A., Vergaro, G., Bayes-Genis, A., Lupon, J., Latini, R., Meessen, J., Anand, I. S., Cohn, J. N., Gravning, J., Gullestad, L., Broch, K., Ueland, T., Nymo, S. H., Brunner-La Rocca, H. P., De Boer, R. A., Gaggin, H. K., Ripoli, A., Passino, C. & Januzzi, J. L., Jr. 2018. sST2 Predicts Outcome in Chronic Heart Failure Beyond NT-proBNP and High-Sensitivity Troponin T. *J Am Coll Cardiol,* 72**,** 2309-2320Erdei, T.,

Smiseth, O. A., Marino, P. & Fraser, A. G. 2014. A systematic review of diastolic stress tests in heart failure with preserved ejection fraction, with proposals from the EU-FP7 MEDIA study group. *Eur J Heart Fail,* 16**,** 1345-61.

Ersbøll, M., Andersen, M. J., Valeur, N., Mogensen, U. M., Waziri, H., Møller, J. E., Hassager, C., Søgaard, P. & Køber, L. 2013. The prognostic value of left atrial peak reservoir strain in acute myocardial infarction is dependent on left ventricular longitudinal function and left atrial size. *Circ Cardiovasc Imaging,* 6**,** 26-33.

Felker, G. M., Ellison, D. H., Mullens, W., Cox, Z. L. & Testani, J. M. 2020. Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review. *J Am Coll Cardiol,* 75**,** 1178-1195.

Felker, G. M., Lee, K. L., Bull, D. A., Redfield, M. M., Stevenson, L. W., Goldsmith, S. R., Lewinter, M. M., Deswal, A., Rouleau, J. L., Ofili, E. O., Anstrom, K. J., Hernandez, A. F., Mcnulty, S. E., Velazquez, E. J., Kfoury, A. G., Chen, H. H., Givertz, M. M., Semigran, M. J., Bart, B. A., Mascette, A. M., Braunwald, E., O'connor, C. M. & Network, N. H. F. C. R. 2011. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med,* 364**,** 797-805.

Flesch, M., Schwinger, R. H., Schiffer, F., Frank, K., Sudkamp, M., Kuhn-Regnier, F., Arnold, G. & Bohm, M. 1996. Evidence for functional relevance of an enhanced expression of the Na(+)-Ca2+ exchanger in failing human myocardium. *Circulation,* 94**,** 992-1002.

Fletcher, G. F., Balady, G. J., Amsterdam, E. A., Chaitman, B., Eckel, R., Fleg, J., Froelicher, V. F., Leon, A. S., Pina, I. L., Rodney, R., Simons-Morton, D. A., Williams, M. A. & Bazzarre, T. 2001. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation,* 104**,** 1694-740.

Fonarow, G. C., Stough, W. G., Abraham, W. T., Albert, N. M., Gheorghiade, M., Greenberg, B. H., O'connor, C. M., Sun, J. L., Yancy, C. W., Young, J. B., Investigators, O.-H. & Hospitals 2007. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol,* 50**,** 768-77.

Fowler, N. O. 1971. Law of Laplace. *N Engl J Med,* 285**,** 1087-8.

Francis, D. P., Davies, L. C. & Coats, A. J. 2001. Diagnostic exercise physiology in

chronic heart failure. *Heart,* 86**,** 17-20.

Francis, G. S. 2001. Pathophysiology of chronic heart failure. *Am J Med,* 110 Suppl 7A**,** 37S-46S.

Frangogiannis, N. G. 2012. Regulation of the inflammatory response in cardiac repair. *Circ Res,* 110**,** 159-73.

Frangogiannis, N. G. 2019. The Extracellular Matrix in Ischemic and Nonischemic Heart Failure. *Circ Res,* 125**,** 117-146.

Freed, B. H., Daruwalla, V., Cheng, J. Y., Aguilar, F. G., Beussink, L., Choi, A., Klein, D. A., Dixon, D., Baldridge, A., Rasmussen-Torvik, L. J., Maganti, K. & Shah, S. J. 2016. Prognostic Utility and Clinical Significance of Cardiac Mechanics in Heart Failure With Preserved Ejection Fraction: Importance of Left Atrial Strain. *Circ Cardiovasc Imaging,* 9.

Freed, B. H. & Shah, S. J. 2017. Stepping Out of the Left Ventricle's Shadow: Time to Focus on the Left Atrium in Heart Failure With Preserved Ejection Fraction. *Circ Cardiovasc Imaging,* 10.

Frydas, A., Morris, D. A., Belyavskiy, E., Radhakrishnan, A. K., Kropf, M., Tadic, M., Roessig, L., Lam, C. S. P., Shah, S. J., Solomon, S. D., Pieske, B. & Pieske-Kraigher, E. 2020. Left atrial strain as sensitive marker of left ventricular diastolic dysfunction in heart failure. *ESC Heart Fail,* 7**,** 1956-1965.

Fukuta, H., Goto, T., Wakami, K., Kamiya, T. & Ohte, N. 2019. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev,* 24**,** 535-547.

Fukuta, H., Goto, T., Wakami, K. & Ohte, N. 2016. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. *Eur J Prev Cardiol,* 23**,** 78-85.

Gan, G. C. H., Ferkh, A., Boyd, A. & Thomas, L. 2018. Left atrial function: evaluation by strain analysis. *Cardiovasc Diagn Ther,* 8**,** 29-46.

Garg, R. & Yusuf, S. 1995. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA,* 273**,** 1450-6.

Genuardi, M. V. & Mather, P. J. 2021. The dawn of the four-drug era? SGLT2 inhibition in heart failure with reduced ejection fraction. *Ther Adv Cardiovasc Dis,* 15**,** 17539447211002678.

Gerber, Y., Weston, S. A., Redfield, M. M., Chamberlain, A. M., Manemann, S. M., Jiang, R., Killian, J. M. & Roger, V. L. 2015. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med,* 175**,** 996-1004.

Gibbs, C. L. 1978. Cardiac energetics. *Physiol Rev,* 58**,** 174-254.

Gorelik, O., Almoznino-Sarafian, D., Feder, I., Wachsman, O., Alon, I., Litvinjuk, V., Roshovsky, M., Modai, D. & Cohen, N. 2003. Dietary intake of various nutrients in older patients with congestive heart failure. *Cardiology,* 99**,** 177-81.

Gottdiener, J. S., Arnold, A. M., Aurigemma, G. P., Polak, J. F., Tracy, R. P., Kitzman, D. W., Gardin, J. M., Rutledge, J. E. & Boineau, R. C. 2000. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol,* 35**,** 1628-37.

Govind, S. C., Gopal, A. S., Netyo, A., Nowak, J., Brodin, L. A., Patrianakos, A., Ramesh, S. S. & Saha, S. 2009. Quantification of low-dose dobutamine stress using speckle tracking echocardiography in coronary artery disease. *Eur J Echocardiogr,* 10**,** 607-12.

Greene, S. J., Fonarow, G. C., Vaduganathan, M., Khan, S. S., Butler, J. & Gheorghiade, M. 2015. The vulnerable phase after hospitalization for heart failure. *Nat Rev Cardiol,* 12**,** 220-9.

Greene, S. J., Hernandez, A. F., Dunning, A., Ambrosy, A. P., Armstrong, P. W., Butler, J., Cerbin, L. P., Coles, A., Ezekowitz, J. A., Metra, M., Starling, R. C., Teerlink, J. R., Voors, A. A., O'connor, C. M. & Mentz, R. J. 2017. Hospitalization for Recently Diagnosed Versus Worsening Chronic Heart Failure: From the ASCEND-HF Trial. *J Am Coll Cardiol,* 69**,** 3029-3039.

Groenewegen, A., Rutten, F. H., Mosterd, A. & Hoes, A. W. 2020. Epidemiology of heart failure. *Eur J Heart Fail,* 22**,** 1342-1356.

Groepenhoff, H., Westerhof, N., Jacobs, W., Boonstra, A., Postmus, P. E. & Vonk-Noordegraaf, A. 2010. Exercise stroke volume and heart rate response differ in right and left heart failure. *Eur J Heart Fail,* 12**,** 716-20.

Guha, S., Harikrishnan, S., Ray, S., Sethi, R., Ramakrishnan, S., Banerjee, S., Bahl, V. K., Goswami, K. C., Banerjee, A. K., Shanmugasundaram, S., Kerkar, P. G., Seth, S., Yadav, R., Kapoor, A., Mahajan, A. U., Mohanan, P. P., Mishra, S., Deb, P. K., Narasimhan, C., Pancholia, A. K., Sinha, A., Pradhan, A., Alagesan, R., Roy, A., Vora, A., Saxena, A., Dasbiswas, A., Srinivas, B. C., Chattopadhyay, B. P., Singh, B. P., Balachandar, J., Balakrishnan, K. R., Pinto, B., Manjunath, C. N., Lanjewar, C. P., Jain, D., Sarma, D., Paul, G. J., Zachariah, G. A., Chopra, H. K., Vijayalakshmi, I. B., Tharakan, J. A., Dalal, J. J., Sawhney, J. P. S., Saha, J., Christopher, J., Talwar, K. K., Chandra, K. S., Venugopal, K., Ganguly, K., Hiremath, M. S., Hot, M., Das, M. K., Bardolui, N., Deshpande, N. V., Yadava, O. P., Bhardwaj, P., Vishwakarma, P., Rajput, R. K., Gupta, R., Somasundaram, S., Routray, S. N., Iyengar, S. S., Sanjay, G., Tewari, S., G, S., Kumar, S., Mookerjee, S., Nair, T., Mishra, T., Samal, U. C., Kaul, U., Chopra, V. K., Narain, V. S., Raj, V. & Lokhandwala, Y. 2018. CSI position statement on management of heart failure in India. *Indian Heart J,* 70 Suppl 1**,** S1-S72.

Guo, L., Guo, X., Chang, Y., Yang, J., Zhang, L., Li, T. & Sun, Y. 2016. Prevalence and Risk Factors of Heart Failure with Preserved Ejection Fraction: A Population-Based Study in Northeast China. *Int J Environ Res Public Health,* 13.

Ha, J. W., Andersen, O. S. & Smiseth, O. A. 2020. Diastolic Stress Test: Invasive and Noninvasive Testing. *JACC Cardiovasc Imaging,* 13**,** 272-282.

Harikrishnan, S., Sanjay, G., Agarwal, A., Kumar, N. P., Kumar, K. K., Bahuleyan, C. G., Vijayaraghavan, G., Viswanathan, S., Sreedharan, M., Biju, R., Rajalekshmi, N., Nair, T., Suresh, K. & Jeemon, P. 2017. One-year mortality outcomes and hospital readmissions of patients admitted with acute heart failure: Data from the Trivandrum Heart Failure Registry in Kerala, India. Am Heart J, 189**,** 193-199.

Hasenfuss, G., Hayward, C., Burkhoff, D., Silvestry, F. E., Mckenzie, S., Gustafsson, F., Malek, F., Van Der Heyden, J., Lang, I., Petrie, M. C., Cleland, J. G., Leon, M., Kaye, D. M. & Investigators, R. L.-H. S. 2016. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. *Lancet,* 387**,** 1298-304.

Henkel, D. M., Redfield, M. M., Weston, S. A., Gerber, Y. & Roger, V. L. 2008. Death in heart failure: a community perspective. *Circ Heart Fail,* 1**,** 91-7.

Hodzic, S., Golic, D., Smajic, J., Sijercic, S., Umihanic, S. & Umihanic, S. 2014. Complications Related to Insertion and Use of Central Venous Catheters (CVC). *Med Arch,* 68**,** 300-3.

Hohendanner, F., Messroghli, D., Bode, D., Blaschke, F., Parwani, A., Boldt, L. H. & Heinzel, F. R. 2018. Atrial remodelling in heart failure: recent developments and relevance for heart failure with preserved ejection fraction. *ESC Heart Fail,* 5**,** 211-221.

Hoit, B. D. 2017. Left Atrial Remodeling: More Than Just Left Atrial Enlargement. *Circ Cardiovasc Imaging,* 10.

Huffman, M. D., Berry, J. D., Ning, H., Dyer, A. R., Garside, D. B., Cai, X., Daviglus, M. L. & Lloyd-Jones, D. M. 2013. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. *J Am Coll Cardiol,* 61**,** 1510-7.

Huynh, Q. L., Kalam, K., Iannaccone, A., Negishi, K., Thomas, L. & Marwick, T. H. 2015. Functional and Anatomic Responses of the Left Atrium to Change in Estimated Left Ventricular Filling Pressure. *J Am Soc Echocardiogr,* 28**,** 1428-1433 e1.

Ihlen, H., Endresen, K., Golf, S. & Nitter-Hauge, S. 1987. Cardiac stroke volume during exercise measured by Doppler echocardiography: comparison with the thermodilution technique and evaluation of reproducibility. *Br Heart J,* 58**,** 455-9. Investigators, S., Yusuf, S., Pitt, B., Davis, C. E., Hood, W. B. & Cohn, J. N. 1991. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med,* 325**,** 293-302.

Jakovljevic, D. G., Moore, S., Hallsworth, K., Fattakhova, G., Thoma, C. & Trenell, M. I. 2012. Comparison of cardiac output determined by bioimpedance and bioreactance methods at rest and during exercise. *J Clin Monit Comput,* 26**,** 63-8.

Jakovljevic, D. G., Trenell, M. I. & Macgowan, G. A. 2014. Bioimpedance and bioreactance methods for monitoring cardiac output. *Best Pract Res Clin*

Anaesthesiol, 28**,** 381-94.

January, C. T., Wann, L. S., Alpert, J. S., Calkins, H., Cigarroa, J. E., Cleveland, J. C., Jr., Conti, J. B., Ellinor, P. T., Ezekowitz, M. D., Field, M. E., Murray, K. T., Sacco, R. L., Stevenson, W. G., Tchou, P. J., Tracy, C. M., Yancy, C. W. & American College of Cardiology/American Heart Association Task Force on Practice, G. 2014. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol,* 64**,** e1-76.

Jayedi, A., Gohari, A. & Shab-Bidar, S. 2022. Daily Step Count and All-Cause Mortality: A Dose-Response Meta-analysis of Prospective Cohort Studies. *Sports Med,* 52**,** 89-99.

Jefferis, B. J., Parsons, T. J., Sartini, C., Ash, S., Lennon, L. T., Papacosta, O., Morris, R. W., Wannamethee, S. G., Lee, I. M. & Whincup, P. H. 2019. Objectively measured physical activity, sedentary behaviour and all-cause mortality in older men: does volume of activity matter more than pattern of accumulation? *Br J Sports Med,* 53**,** 1013-1020.

Jehn, M., Schmidt-Trucksass, A., Schuster, T., Weis, M., Hanssen, H., Halle, M. & Koehler, F. 2009. Daily walking performance as an independent predictor of advanced heart failure: Prediction of exercise capacity in chronic heart failure. *Am Heart J,* 157**,** 292-8.

Jones, T. W., Houghton, D., Cassidy, S., Macgowan, G. A., Trenell, M. I. & Jakovljevic, D. G. 2015. Bioreactance is a reliable method for estimating cardiac output at rest and during exercise. *Br J Anaesth,* 115**,** 386-91.

Jonkman, N. H., Westland, H., Groenwold, R. H., Agren, S., Anguita, M., Blue, L., Bruggink-Andre De La Porte, P. W., Dewalt, D. A., Hebert, P. L., Heisler, M., Jaarsma, T., Kempen, G. I., Leventhal, M. E., Lok, D. J., Martensson, J., Muniz, J., Otsu, H., Peters-Klimm, F., Rich, M. W., Riegel, B., Stromberg, A., Tsuyuki, R. T., Trappenburg, J. C., Schuurmans, M. J. & Hoes, A. W. 2016. What Are Effective Program Characteristics of Self-Management Interventions in Patients With Heart Failure? An Individual Patient Data Meta-analysis. *J Card Fail,* 22**,** 861-871.

Joseph, S. M., Cedars, A. M., Ewald, G. A., Geltman, E. M. & Mann, D. L. 2009. Acute decompensated heart failure: contemporary medical management. *Tex Heart Inst J,* 36**,** 510-20.

Joshi, P. P., Mohanan, C. J., Sengupta, S. P. & Salkar, R. G. 1999. Factors precipitating congestive heart failure--role of patient non-compliance. *J Assoc Physicians India,* 47**,** 294-5.

Juilliere, Y., Venner, C., Filippetti, L., Popovic, B., Huttin, O. & Selton-Suty, C. 2018. Heart failure with preserved ejection fraction: A systemic disease linked to multiple comorbidities, targeting new therapeutic options. *Arch Cardiovasc Dis,* 111**,** 766-781.

Kaesemeyer, W. H. 1994. Survival after congestive heart failure in Framingham Heart Study subjects. *Circulation,* 89**,** 506-7.

Kane, G. C., Hepinstall, M. J., Kidd, G. M., Kuehl, C. A., Murphy, A. T., Nelson, J. M., Schneider, L., Stussy, V. L., Warmsbecker, J. A., Miller, F. A., Jr., Pellikka, P. A. & Mccully, R. B. 2008. Safety of stress echocardiography supervised by registered nurses: results of a 2-year audit of 15,404 patients. *J Am Soc Echocardiogr,* 21**,** 337-41.

Kang, H. 2021. Sample size determination and power analysis using the G*Power software. *J Educ Eval Health Prof,* 18**,** 17.

Kass, D. A., Kitzman, D. W. & Alvarez, G. E. 2010. The restoration of chronotropic competence in heart failure patients with normal ejection fraction (RESET) study: rationale and design. *J Card Fail,* 16**,** 17-24.

Kaye, D. M. & Nanayakkara, S. 2019. Interatrial Shunt Device for Heart Failure With Preserved Ejection Fraction. *Front Cardiovasc Med,* 6**,** 143.

Kaye, D. M., Petrie, M. C., Mckenzie, S., Hasenfubeta, G., Malek, F., Post, M., Doughty, R. N., Trochu, J. N., Gustafsson, F., Lang, I., Kolodziej, A., Westenfeld, R., Penicka, M., Rosenberg, M., Hausleiter, J., Raake, P., Jondeau, G., Bergmann, M. W., Spelman, T., Aytug, H., Ponikowski, P., Hayward, C. & Investigators, R. L.-H. S. 2019. Impact of an interatrial shunt device on survival and heart failure hospitalization in patients with preserved ejection fraction. *ESC Heart Fail,* 6**,** 62-69.

Kehat, I. & Molkentin, J. D. 2010. Molecular pathways underlying cardiac remodeling during pathophysiological stimulation. *Circulation,* 122**,** 2727-35.

Kelder, J. C., Cramer, M. J., Verweij, W. M., Grobbee, D. E. & Hoes, A. W. 2011. Clinical utility of three B-type natriuretic peptide assays for the initial diagnostic assessment of new slow-onset heart failure. *J Card Fail,* 17**,** 729-34.

Kelly, J. P., Devore, A. D., Wu, J., Hammill, B. G., Sharma, A., Cooper, L. B., Felker, G. M., Piccini, J. P., Allen, L. A., Heidenreich, P. A., Peterson, E. D., Yancy, C. W., Fonarow, G. C. & Hernandez, A. F. 2019. Rhythm Control Versus Rate Control in Patients With Atrial Fibrillation and Heart Failure With Preserved Ejection Fraction: Insights From Get With The Guidelines-Heart Failure. *J Am Heart Assoc,* 8**,** e011560.

Keren, H., Burkhoff, D. & Squara, P. 2007. Evaluation of a noninvasive continuous cardiac output monitoring system based on thoracic bioreactance. *Am J Physiol Heart Circ Physiol,* 293**,** H583-9.

Khariton, Y., Fonarow, G. C., Arnold, S. V., Hellkamp, A., Nassif, M. E., Sharma, P. P., Butler, J., Thomas, L., Duffy, C. I., Devore, A. D., Albert, N. M., Patterson, J. H., Williams, F. B., Mccague, K. & Spertus, J. A. 2019. Association Between Sacubitril/Valsartan Initiation and Health Status Outcomes in Heart Failure With Reduced Ejection Fraction. *JACC Heart Fail,* 7**,** 933-941.

Kieu, A., Shaikh, A., Kaeppler, M., Miles, R. J. & Widlansky, M. E. 2018. Patients with hypertensive responses to exercise or dobutamine stress testing differ in resting hypertensive phenotype. *J Am Soc Hypertens,* 12**,** 108-116.

Kim, J., Yum, B., Palumbo, M. C., Sultana, R., Wright, N., Das, M., You, C.,

Moskowitz, C. S., Levine, R. A., Devereux, R. B. & Weinsaft, J. W. 2020. Left Atrial Strain Impairment Precedes Geometric Remodeling as a Marker of Post-Myocardial Infarction Diastolic Dysfunction. *JACC Cardiovasc Imaging,* 13**,** 2099-2113.

Kitzman, D. W., Brubaker, P., Morgan, T., Haykowsky, M., Hundley, G., Kraus, W. E., Eggebeen, J. & Nicklas, B. J. 2016. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. *JAMA,* 315**,** 36-46.

Kitzman, D. W., Brubaker, P. H., Morgan, T. M., Stewart, K. P. & Little, W. C. 2010. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *Circ Heart Fail,* 3**,** 659-67.

Kono, T., Sabbah, H. N., Rosman, H., Alam, M., Stein, P. D. & Goldstein, S. 1992. Left atrial contribution to ventricular filling during the course of evolving heart failure. *Circulation,* 86**,** 1317-22.

Kosmala, W., Holland, D. J., Rojek, A., Wright, L., Przewlocka-Kosmala, M. & Marwick, T. H. 2013. Effect of If-channel inhibition on hemodynamic status and exercise tolerance in heart failure with preserved ejection fraction: a randomized trial. *J Am Coll Cardiol,* 62**,** 1330-8.

Kotecha, D., Lam, C. S., Van Veldhuisen, D. J., Van Gelder, I. C., Voors, A. A. & Rienstra, M. 2016. Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation: Vicious Twins. *J Am Coll Cardiol,* 68**,** 2217-2228.

Kulbertus, H. 1999. [Clinical trial of the month. The CIBIS-II study]. *Rev Med Liege,* 54**,** 128-9.

Kurt, M., Wang, J., Torre-Amione, G. & Nagueh, S. F. 2009. Left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging,* 2**,** 10-5.

Kuznetsova, T., Herbots, L., Richart, T., D'hooge, J., Thijs, L., Fagard, R. H., Herregods, M. C. & Staessen, J. A. 2008. Left ventricular strain and strain rate in a general population. *Eur Heart J,* 29**,** 2014-23.

Kwak, S., Hwang, I. C., Park, J. J., Park, J. H., Park, J. B. & Cho, G. Y. 2021. Sex-specific impact of diabetes mellitus on left ventricular systolic function and prognosis in heart failure. *Sci Rep,* 11**,** 11664.

La Gerche, A., Howden, E. J., Haykowsky, M. J., Lewis, G. D., Levine, B. D. & Kovacic, J. C. 2022. Heart Failure With Preserved Ejection Fraction as an Exercise Deficiency Syndrome: JACC Focus Seminar 2/4. *J Am Coll Cardiol*.

Lam, C. S., Donal, E., Kraigher-Krainer, E. & Vasan, R. S. 2011. Epidemiology and clinical course of heart failure with preserved ejection fraction. *Eur J Heart Fail,* 13**,** 18-28.

Lam, C. S., Grewal, J., Borlaug, B. A., Ommen, S. R., Kane, G. C., Mccully, R. B. & Pellikka, P. A. 2010. Size, shape, and stamina: the impact of left ventricular geometry on exercise capacity. *Hypertension,* 55**,** 1143-9.

Lam, P. H., Dooley, D. J., Deedwania, P., Singh, S. N., Bhatt, D. L., Morgan, C. J., Butler, J., Mohammed, S. F., Wu, W. C., Panjrath, G., Zile, M. R., White, M., Arundel, C., Love, T. E., Blackman, M. R., Allman, R. M., Aronow, W. S., Anker, S. D., Fonarow, G. C. & Ahmed, A. 2017. Heart Rate and Outcomes in Hospitalized Patients With Heart Failure With Preserved Ejection Fraction. *J Am Coll Cardiol,* 70**,** 1861-1871.

Lancellotti, P., Pellikka, P. A., Budts, W., Chaudhry, F. A., Donal, E., Dulgheru, R., Edvardsen, T., Garbi, M., Ha, J. W., Kane, G. C., Kreeger, J., Mertens, L., Pibarot, P., Picano, E., Ryan, T., Tsutsui, J. M. & Varga, A. 2017. The Clinical Use of Stress Echocardiography in Non-Ischaemic Heart Disease: Recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr,* 30**,** 101-138.

Lang, C. C., Karlin, P., Haythe, J., Lim, T. K. & Mancini, D. M. 2009. Peak cardiac power output, measured noninvasively, is a powerful predictor of outcome in chronic heart failure. *Circ Heart Fail,* 2**,** 33-8.

Lang, R. M., Badano, L. P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L., Flachskampf, F. A., Foster, E., Goldstein, S. A., Kuznetsova, T., Lancellotti, P., Muraru, D., Picard, M. H., Rietzschel, E. R., Rudski, L., Spencer, K. T., Tsang, W. & Voigt, J. U. 2015. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging,* 16**,** 233-70.

Lecoeur, E., Domeng, O., Fayol, A., Jannot, A. S. & Hulot, J. S. 2023. Epidemiology of heart failure in young adults: a French nationwide cohort study. *Eur Heart J,* 44**,** 383-392.

Lee, D. S., Gona, P., Vasan, R. S., Larson, M. G., Benjamin, E. J., Wang, T. J., Tu, J. V. & Levy, D. 2009. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. *Circulation,* 119**,** 3070-7.

Leite, L., Mendes, S. L., Baptista, R., Teixeira, R., Oliveira-Santos, M., Ribeiro, N., Coutinho, R., Monteiro, V., Martins, R., Castro, G., Ferreira, M. J. & Pego, M. 2017. Left atrial mechanics strongly predict functional capacity assessed by cardiopulmonary exercise testing in subjects without structural heart disease. *Int J Cardiovasc Imaging,* 33**,** 635-642.

Leitman, M., Balboul, Y., Burgsdorf, O., Tyomkin, V. & Fuchs, S. 2022. Myocardial work index during normal dobutamine stress echocardiography. *Sci Rep,* 12**,** 6813.

Leng, G. & Partridge, G. 2018. Achieving high-quality care: a view from NICE. *Heart,* 104**,** 10-15.

Leung, D. Y., Boyd, A., Ng, A. A., Chi, C. & Thomas, L. 2008. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. *Am Heart J,* 156**,** 1056-64.

Li, Z., Zhao, H. & Wang, J. 2021. Metabolism and Chronic Inflammation: The Links Between Chronic Heart Failure and Comorbidities. *Front Cardiovasc Med,* 8**,** 650278.

Liao, J. N., Chao, T. F., Kuo, J. Y., Sung, K. T., Tsai, J. P., Lo, C. I., Lai, Y. H., Su, C. H., Hung, C. L., Yeh, H. I. & Chen, S. A. 2017. Age, Sex, and Blood Pressure-Related Influences on Reference Values of Left Atrial Deformation and Mechanics From a Large-Scale Asian Population. *Circ Cardiovasc Imaging,* 10.

Lim, F. Y., Yap, J., Gao, F., Teo, L. L., Lam, C. S. P. & Yeo, K. K. 2018. Correlation of the New York Heart Association classification and the cardiopulmonary exercise test: A systematic review. *Int J Cardiol,* 263**,** 88-93.

Long, L., Mordi, I. R., Bridges, C., Sagar, V. A., Davies, E. J., Coats, A. J., Dalal, H., Rees, K., Singh, S. J. & Taylor, R. S. 2019. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev,* 1**,** CD003331.

Loop, M. S., Van Dyke, M. K., Chen, L., Brown, T. M., Durant, R. W., Safford, M. M. & Levitan, E. B. 2016. Comparison of Length of Stay, 30-Day Mortality, and 30-Day Readmission Rates in Medicare Patients With Heart Failure and With Reduced Versus Preserved Ejection Fraction. *Am J Cardiol,* 118**,** 79-85.

Lopez-Vilella, R., Marques-Sule, E., Laymito Quispe, R. D. P., Sanchez-Lazaro, I., Donoso Trenado, V., Martinez Dolz, L. & Almenar Bonet, L. 2021. The Female Sex Confers Different Prognosis in Heart Failure: Same Mortality but More Readmissions. *Front Cardiovasc Med,* 8**,** 618398.

Luchi, R. J., Snow, E., Luchi, J. M., Nelson, C. L. & Pircher, F. J. 1982. Left ventricular function in hospitalized geriatric patients. *J Am Geriatr Soc,* 30**,** 700-5.

Lundberg, A., Johnson, J., Hage, C., Back, M., Merkely, B., Venkateshvaran, A., Lund, L. H., Nagy, A. I. & Manouras, A. 2019a. Left atrial strain improves estimation of filling pressures in heart failure: a simultaneous echocardiographic and invasive haemodynamic study. *Clin Res Cardiol,* 108**,** 703-715.

Lundberg, A., Johnson, J., Hage, C., Bäck, M., Merkely, B., Venkateshvaran, A., Lund, L. H., Nagy, A. I. & Manouras, A. 2019b. Left atrial strain improves estimation of filling pressures in heart failure: a simultaneous echocardiographic and invasive haemodynamic study. *Clinical Research in Cardiology,* 108**,** 703-715.

McCoy, J., Bates, M., Eggett, C., Siervo, M., Cassidy, S., Newman, J., Moore, S. A., Gorman, G., Trenell, M. I., Velicki, L., Seferovic, P. M., Cleland, J. G. F., Macgowan, G. A., Turnbull, D. M. & Jakovljevic, D. G. 2017. Pathophysiology of exercise intolerance in chronic diseases: the role of diminished cardiac performance in mitoch-ondrial and heart failure patients. *Open Heart,* 4**,** e000632.

Maffeis, C., Morris, D. A., Belyavskiy, E., Kropf, M., Radhakrishnan, A. K., Zach, V., Rozados Da Conceicao, C., Trippel, T. D., Pieske-Kraigher, E., Rossi, A., Pieske, B. & Edelmann, F. 2021. Left atrial function and maximal exercise capacity in heart failure with preserved and mid-range ejection fraction. *ESC Heart Fail,* 8**,** 116-128.

Marelli-Berg, F. M. & Aksentijevic, D. 2019. Immunometabolic cross-talk in the inflamed heart. *Cell Stress,* 3**,** 240-266.

Marijon, E., Ou, P., Celermajer, D. S., Ferreira, B., Mocumbi, A. O., Jani, D., Paquet, C., Jacob, S., Sidi, D. & Jouven, X. 2007. Prevalence of rheumatic heart disease detected by echocardiographic screening. *N Engl J Med,* 357**,** 470-6.

Marik, P. E. 2013. Noninvasive cardiac output monitors: a state-of the-art review. *J Cardiothorac Vasc Anesth,* 27**,** 121-34.

Marik, P. E., Levitov, A., Young, A. & Andrews, L. 2013. The use of bioreactance and carotid Doppler to determine volume responsiveness and blood flow redistribution following passive leg raising in hemodynamically unstable patients. *Chest,* 143**,** 364-370.

Marin-Garcia, J. 2003. Mitochondrial dysfunction in heart failure. *J Am Coll Cardiol,* 41**,** 2299; author reply 2299.

Marmor, A. & Schneeweiss, A. 1997. Prognostic value of noninvasively obtained left ventricular contractile reserve in patients with severe heart failure. *J Am Coll Cardiol,* 29**,** 422-8.

Masood, M. S. & Hamid, F. 2022. Sex-Specific Differences in Heart Failure: Pathophysiology, Risk Factors, Management, and Outcomes. *Can J Cardiol*.

Massie, B. M., Carson, P. E., Mcmurray, J. J., Komajda, M., Mckelvie, R., Zile, M. R., Anderson, S., Donovan, M., Iverson, E., Staiger, C., Ptaszynska, A. & Investigators, I. P. 2008. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med,* 359**,** 2456-67.

Maurer, M. M., Burkhoff, D., Maybaum, S., Franco, V., Vittorio, T. J., Williams, P., White, L., Kamalakkannan, G., Myers, J. & Mancini, D. M. 2009. A multicenter study of noninvasive cardiac output by bioreactance during symptom-limited exercise. *J Card Fail,* 15**,** 689-99.

Mcdiarmid, A., Gordon, B., Wrightson, N., Robinson-Smith, N., Pillay, T., Parry, G., Schueler, S. & Macgowan, G. A. 2013. Hemodynamic, echocardiographic, and exercise-related effects of the HeartWare left ventricular assist device in advanced heart failure. *Congest Heart Fail,* 19**,** 11-5.

McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., Bohm, M., Burri, H., Butler, J., Celutkiene, J., Chioncel, O., Cleland, J. G. F., Coats, A. J. S., Crespo-Leiro, M. G., Farmakis, D., Gilard, M., Heymans, S., Hoes, A. W., Jaarsma, T., Jankowska, E. A., Lainscak, M., Lam, C. S. P., Lyon, A. R., Mcmurray, J. J. V., Mebazaa, A., Mindham, R., Muneretto, C., Francesco Piepoli, M., Price, S., Rosano, G. M. C., Ruschitzka, F., Kathrine Skibelund, A. & Group, E. S. C. S. D. 2021. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J,* 42**,** 3599-3726.

McDonagh, T. A., Morrison, C. E., Lawrence, A., Ford, I., Tunstall-Pedoe, H., Mcmurray, J. J. & Dargie, H. J. 1997. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. *Lancet,* 350**,** 829-33.

McMurray, J. J., Adamopoulos, S., Anker, S. D., Auricchio, A., Bohm, M., Dickstein, K., Falk, V., Filippatos, G., Fonseca, C., Gomez-Sanchez, M. A., Jaarsma, T., Kober, L., Lip, G. Y., Maggioni, A. P., Parkhomenko, A., Pieske, B. M., Popescu, B. A., Ronnevik, K., Rutten, F. H., Schwitter, J., Seferovic, P., Stepinska, J., Trindade, P. T., Voors, A. A., Zannad, F., Zeiher, A., Avrupa Kardiyoloji Dernegi Akut Ve Kronik Kalp Yetersizligi Tani Ve Tedavisi Gorev, G., Hazirlanmistir, E. S. C. K. Y. B. I. & Heart Failure, A. 2012. [ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012]. *Turk Kardiyol Dern Ars,* 40 Suppl 3**,** 77-137.

Mcmurray, J. J., Packer, M., Desai, A. S., Gong, J., Lefkowitz, M. P., Rizkala, A. R., Rouleau, J. L., Shi, V. C., Solomon, S. D., Swedberg, K., Zile, M. R., Investigators, P.-H. & Committees 2014. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med,* 371**,** 993-1004.

McMurray, J. J. V., Demets, D. L., Inzucchi, S. E., Kober, L., Kosiborod, M. N., Langkilde, A. M., Martinez, F. A., Bengtsson, O., Ponikowski, P., Sabatine, M. S., Sjostrand, M., Solomon, S. D., Committees, D.-H. & Investigators 2019. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail,* 21**,** 665-675.

Mcquillan, B. M., Picard, M. H., Leavitt, M. & Weyman, A. E. 2001. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation,* 104**,** 2797-802.

Mercado, P., Maizel, J., Beyls, C., Titeca-Beauport, D., Joris, M., Kontar, L., Riviere, A., Bonef, O., Soupison, T., Tribouilloy, C., De Cagny, B. & Slama, M. 2017. Transthoracic echocardiography: an accurate and precise method for estimating cardiac output in the critically ill patient. *Crit Care,* 21**,** 136.

Middlekauff, H. R., Hui, K., Yu, J. L., Hamilton, M. A., Fonarow, G. C., Moriguchi, J., Maclellan, W. R. & Hage, A. 2002. Acupuncture inhibits sympathetic activation during mental stress in advanced heart failure patients. *J Card Fail,* 8**,** 399-406.

Mitchell, J. R. & Wang, J. J. 2014. Expanding application of the Wiggers diagram to teach cardiovascular physiology. *Adv Physiol Educ,* 38**,** 170-5.

Moon, M. G., Hwang, I. C., Choi, W., Cho, G. Y., Yoon, Y. E., Park, J. B., Lee, S. P., Kim, H. K. & Kim, Y. J. 2021. Reverse remodelling by sacubitril/valsartan predicts the prognosis in heart failure with reduced ejection fraction. *ESC Heart Fail,* 8**,** 2058-2069.

Moore, C. G., Carter, R. E., Nietert, P. J. & Stewart, P. W. 2011. Recommendations for planning pilot studies in clinical and translational research. *Clin Transl Sci,* 4**,** 332-7.

Morris, D. A., Gailani, M., Vaz Perez, A., Blaschke, F., Dietz, R., Haverkamp, W. & Ozcelik, C. 2011. Left atrial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. *J Am Soc Echocardiogr,* 24**,** 651-62.

Morton, G., Philip, L., Gilpin, T., Chan, P. E., Guha, K. & Kalra, P. R. 2018. Does specialist review for patients with suspected heart failure predict better outcomes? An observational study on the utility of compliance with NICE guidelines. *BMJ Open,* 8**,**

e021856.

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., De Ferranti, S., Despres, J. P., Fullerton, H. J., Howard, V. J., Huffman, M. D., Judd, S. E., Kissela, B. M., Lackland, D. T., Lichtman, J. H., Lisabeth, L. D., Liu, S., Mackey, R. H., Matchar, D. B., Mcguire, D. K., Mohler, E. R., 3rd, Moy, C. S., Muntner, P., Mussolino, M. E., Nasir, K., Neumar, R. W., Nichol, G., Palaniappan, L., Pandey, D. K., Reeves, M. J., Rodriguez, C. J., Sorlie, P. D., Stein, J., Towfighi, A., Turan, T. N., Virani, S. S., Willey, J. Z., Woo, D., Yeh, R. W., Turner, M. B., American Heart Association Statistics, C. & Stroke Statistics, S. 2015. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation,* 131**,** e29-322.

Mueller, S., Winzer, E. B., Duvinage, A., Gevaert, A. B., Edelmann, F., Haller, B., Pieske-Kraigher, E., Beckers, P., Bobenko, A., Hommel, J., Van De Heyning, C. M., Esefeld, K., Von Korn, P., Christle, J. W., Haykowsky, M. J., Linke, A., Wisloff, U., Adams, V., Pieske, B., Van Craenenbroeck, E. M., Halle, M. & Optimex-Clin Study, G. 2021. Effect of High-Intensity Interval Training, Moderate Continuous Training, or Guideline-Based Physical Activity Advice on Peak Oxygen Consumption in Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. *JAMA,* 325**,** 542-551.

Mullens, W., Borowski, A. G., Curtin, R. J., Thomas, J. D. & Tang, W. H. 2009. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. *Circulation,* 119**,** 62-70.

Myers, J., Gujja, P., Neelagaru, S. & Burkhoff, D. 2007. Cardiac output and cardiopulmonary responses to exercise in heart failure: application of a new bio-reactance device. *J Card Fail,* 13**,** 629-36.

Nagueh, S. F., Shah, G., Wu, Y., Torre-Amione, G., King, N. M., Lahmers, S., Witt, C. C., Becker, K., Labeit, S. & Granzier, H. L. 2004. Altered titin expression, myocardial stiffness, and left ventricular function in patients with dilated cardiomyopathy. *Circulation,* 110**,** 155-62.

Nagueh, S. F., Smiseth, O. A., Appleton, C. P., Byrd, B. F., 3rd, Dokainish, H., Edvardsen, T., Flachskampf, F. A., Gillebert, T. C., Klein, A. L., Lancellotti, P., Marino, P., Oh, J. K., Alexandru Popescu, B., Waggoner, A. D., Houston, T., Oslo, N., Phoenix, A., Nashville, T., Hamilton, O. C., Uppsala, S., Ghent, Liege, B., Cleveland, O., Novara, I., Rochester, M., Bucharest, R. & St. Louis, M. 2016. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging,* 17**,** 1321-1360.

Naik, A., Singh, B., Yadav, R., Pandurangi, U., Kler, T. S., Shankar, B., Radhakrishnan, R., Rajan, V., Bhatia, V., Kaul, U., Varma, J., Dora, S. & Narasimhan, C. 2018. Cardiac resynchronization therapy is associated with improvement in clinical outcomes in Indian heart failure patients: Results of a large, long-term observational study. *Indian Heart J,* 70 Suppl 3**,** S377-S383.

Naik, N. & Narula, J. 2020. Heart failure in low-income and middle-income countries:

failing REPORT card grades. *Lancet Glob Health,* 8**,** e318.

Nauta, J. F., Hummel, Y. M., Tromp, J., Ouwerkerk, W., Van Der Meer, P., Jin, X., Lam, C. S. P., Bax, J. J., Metra, M., Samani, N. J., Ponikowski, P., Dickstein, K., Anker, S. D., Lang, C. C., Ng, L. L., Zannad, F., Filippatos, G. S., Van Veldhuisen, D. J., Van Melle, J. P. & Voors, A. A. 2020. Concentric vs. eccentric remodelling in heart failure with reduced ejection fraction: clinical characteristics, pathophysiology and response to treatment. *Eur J Heart Fail,* 22**,** 1147-1155.

Nayor, M., Houstis, N. E., Namasivayam, M., Rouvina, J., Hardin, C., Shah, R. V., Ho, J. E., Malhotra, R. & Lewis, G. D. 2020. Impaired Exercise Tolerance in Heart Failure With Preserved Ejection Fraction: Quantification of Multiorgan System Reserve Capacity. *JACC Heart Fail,* 8**,** 605-617.

Neubauer, S. 2007. The failing heart--an engine out of fuel. *N Engl J Med,* 356**,** 1140-51.

Ng, A. C., Sitges, M., Pham, P. N., Tran Da, T., Delgado, V., Bertini, M., Nucifora, G., Vidaic, J., Allman, C., Holman, E. R., Bax, J. J. & Leung, D. Y. 2009. Incremental value of 2-dimensional speckle tracking strain imaging to wall motion analysis for detection of coronary artery disease in patients undergoing dobutamine stress echocardiography. *Am Heart J,* 158**,** 836-44.

Nishikawa, Y., Roberts, J. P., Tan, P., Klopfenstein, C. E. & Klopfenstein, H. S. 1994. Effect of dynamic exercise on left atrial function in conscious dogs. *J Physiol,* 481 (Pt 2)**,** 457-68.

Nishikido, T., Oyama, J. I., Nagatomo, D. & Node, K. 2018. A reduction of BMI predicts the risk of rehospitalization and cardiac death in non-obese patients with heart failure. *Int J Cardiol*.

Norman, H. S., Oujiri, J., Larue, S. J., Chapman, C. B., Margulies, K. B. & Sweitzer, N. K. 2011. Decreased cardiac functional reserve in heart failure with preserved systolic function. *J Card Fail,* 17**,** 301-8.

O'connor, C. M., Whellan, D. J., Lee, K. L., Keteyian, S. J., Cooper, L. S., Ellis, S. J., Leifer, E. S., Kraus, W. E., Kitzman, D. W., Blumenthal, J. A., Rendall, D. S., Miller, N. H., Fleg, J. L., Schulman, K. A., Mckelvie, R. S., Zannad, F., Pina, I. L. & Investigators, H.-A. 2009. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA,* 301**,** 1439-50.

O'Connor, C. M., Whellan, D. J., Wojdyla, D., Leifer, E., Clare, R. M., Ellis, S. J.,Fine, L. J., Fleg, J. L., Zannad, F., Keteyian, S. J., Kitzman, D. W., Kraus, W. E., Rendall, D., Pina, I. L., Cooper, L. S., Fiuzat, M. & Lee, K. L. 2012. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. *Circ Heart Fail,* 5**,** 63-71.

Obokata, M., Kane, G. C., Reddy, Y. N., Olson, T. P., Melenovsky, V. & Borlaug, B. A. 2017. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. *Circulation,* 135**,** 825-838.

Obokata, M., Reddy, Y. N. V., Melenovsky, V., Kane, G. C., Olson, T. P., Jarolim, P. & Borlaug, B. A. 2018. Myocardial Injury and Cardiac Reserve in Patients With Heart Failure and Preserved Ejection Fraction. *J Am Coll Cardiol,* 72**,** 29-40.

Ofstedal, M. B., Chiu, C. T., Jagger, C., Saito, Y. & Zimmer, Z. 2019. Religion, Life Expectancy, and Disability-Free Life Expectancy Among Older Women and Men in the United States. *J Gerontol B Psychol Sci Soc Sci,* 74**,** e107-e118.

Okonko, D. O., Mandal, A. K., Missouris, C. G. & Poole-Wilson, P. A. 2011. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. *J Am Coll Cardiol,* 58**,** 1241-51.

Okwose, N. C., Avery, L., O'brien, N., Cassidy, S., Charman, S. J., Bailey, K., Velicki, L., Olivotto, I., Brennan, P., Macgowan, G. A. & Jakovljevic, D. G. 2019. Acceptability, Feasibility and Preliminary Evaluation of a Novel, Personalised, Home-Based Physical Activity Intervention for Chronic Heart Failure (Active-at-Home-HF): a Pilot Study. *Sports Med Open,* 5**,** 45.

Okwose, N. C., O'brien, N., Charman, S., Cassidy, S., Brodie, D., Bailey, K., Macgowan, G. A., Jakovljevic, D. G. & Avery, L. 2020. Overcoming barriers to engagement and adherence to a home-based physical activity intervention for patients with heart failure: a qualitative focus group study. *BMJ Open,* 10**,** e036382.

Olsson, L. G., Swedberg, K., Clark, A. L., Witte, K. K. & Cleland, J. G. 2005. Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review. *Eur Heart J,* 26**,** 778-93.

Ommen, S. R., Nishimura, R. A., Appleton, C. P., Miller, F. A., Oh, J. K., Redfield, M. M. & Tajik, A. J. 2000. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. *Circulation,* 102**,** 1788-94.

Opdahl, A., Helle-Valle, T., Skulstad, H. & Smiseth, O. A. 2015. Strain, strain rate, torsion, and twist: echocardiographic evaluation. *Curr Cardiol Rep,* 17**,** 568.

Orde, S., Slama, M., Hilton, A., Yastrebov, K. & Mclean, A. 2017. Pearls and pitfalls in comprehensive critical care echocardiography. *Crit Care,* 21**,** 279.

Owan, T. E. & Redfield, M. M. 2005. Epidemiology of diastolic heart failure. *Prog Cardiovasc Dis,* 47**,** 320-32.

Packer, M. 1992. Pathophysiology of chronic heart failure. *Lancet,* 340**,** 88-92.

Packer, M., Lam, C. S. P., Lund, L. H., Maurer, M. S. & Borlaug, B. A. 2020. Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: a hypothesis to explain influence of sex on the evolution and potential treatment of the disease. *Eur J Heart Fail,* 22**,** 1551-1567.

Palmieri, V., Wachtell, K., Gerdts, E., Bella, J. N., Papademetriou, V., Tuxen, C., Nieminen, M. S., Dahlof, B., De Simone, G. & Devereux, R. B. 2001. Left ventricular function and hemodynamic features of inappropriate left ventricular hypertrophy in

patients with systemic hypertension: the LIFE study. *Am Heart J,* 141**,** 784-91.

Park, J. H., Woo, J. S., Ju, S., Jung, S. W., Lee, I., Kim, J. B., Kim, S. J., Kim, W., Kim, W. S. & Kim, K. S. 2016. Layer-specific analysis of dobutamine stress echocardiography for the evaluation of coronary artery disease. *Medicine (Baltimore),* 95**,** e4549.

Patel, R. B., Lam, C. S. P., Svedlund, S., Saraste, A., Hage, C., Tan, R. S., Beussink-Nelson, L., Tromp, J., Sanchez, C., Njoroge, J., Swat, S. A., Faxén, U. L., Fermer, M. L., Venkateshvaran, A., Gan, L. M., Lund, L. H. & Shah, S. J. 2021. Disproportionate left atrial myopathy in heart failure with preserved ejection fraction among participants of the PROMIS-HFpEF study. *Sci Rep,* 11**,** 4885.

Paulus, W. J. 2020. Unfolding Discoveries in Heart Failure. *N Engl J Med,* 382**,** 679-682.

Paulus, W. J. & Van Ballegoij, J. J. 2010. Treatment of heart failure with normal ejection fraction: an inconvenient truth! *J Am Coll Cardiol,* 55**,** 526-37.

Pellikka, P. A., Nagueh, S. F., Elhendy, A. A., Kuehl, C. A., Sawada, S. G. & American Society Of, E. 2007. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr,* 20**,** 1021-41.

Pfeffer, M. A., Claggett, B., Assmann, S. F., Boineau, R., Anand, I. S., Clausell, N., Desai, A. S., Diaz, R., Fleg, J. L., Gordeev, I., Heitner, J. F., Lewis, E. F., O'meara, E., Rouleau, J. L., Probstfield, J. L., Shaburishvili, T., Shah, S. J., Solomon, S. D., Sweitzer, N. K., Mckinlay, S. M. & Pitt, B. 2015. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation,* 131**,** 34-42.

Phelan, D., Thavendiranathan, P., Collier, P. & Marwick, T. H. 2012. Aldosterone antagonists improve ejection fraction and functional capacity independently of functional class: a meta-analysis of randomised controlled trials. *Heart,* 98**,** 1693-700.

Piercy, K. L., Troiano, R. P., Ballard, R. M., Carlson, S. A., Fulton, J. E., Galuska, D. A., George, S. M. & Olson, R. D. 2018. The Physical Activity Guidelines for Americans. *JAMA,* 320**,** 2020-2028.

Pieske, B., Tschope, C., De Boer, R. A., Fraser, A. G., Anker, S. D., Donal, E., Edelmann, F., Fu, M., Guazzi, M., Lam, C. S. P., Lancellotti, P., Melenovsky, V., Morris, D. A., Nagel, E., Pieske-Kraigher, E., Ponikowski, P., Solomon, S. D., Vasan, R. S., Rutten, F. H., Voors, A. A., Ruschitzka, F., Paulus, W. J., Seferovic, P. & Filippatos, G. 2019. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J,* 40**,** 3297-3317.

Piotrowicz, E., Baranowski, R., Bilinska, M., Stepnowska, M., Piotrowska, M., Wojcik, A., Korewicki, J., Chojnowska, L., Malek, L. A., Klopotowski, M., Piotrowski, W. & Piotrowicz, R. 2010. A new model of home-based telemonitored cardiac rehabilitation in patients with heart failure: effectiveness, quality of life, and adherence. *Eur J Heart*

Fail, 12**,** 164-71.

Pitt, B. 2003. Aldosterone blockade in patients with systolic left ventricular dysfunction. *Circulation,* 108**,** 1790-4.

Pitt, B., Remme, W., Zannad, F., Neaton, J., Martinez, F., Roniker, B., Bittman, R., Hurley, S., Kleiman, J., Gatlin, M., Eplerenone Post-Acute Myocardial Infarction Heart Failure, E. & Survival Study, I. 2003. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med,* 348**,** 1309-21.

Pitt, B., Zannad, F., Remme, W. J., Cody, R., Castaigne, A., Perez, A., Palensky, J. & Wittes, J. 1999. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med,* 341**,** 709-17.

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G., Coats, A. J., Falk, V., Gonzalez-Juanatey, J. R., Harjola, V. P., Jankowska, E. A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J. T., Pieske, B., Riley, J. P., Rosano, G. M., Ruilope, L. M., Ruschitzka, F., Rutten, F. H. & Van Der Meer, P. 2016a. [2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure]. *Kardiol Pol,* 74**,** 1037-1147.

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G., Coats, A. J., Falk, V., Gonzalez-Juanatey, J. R., Harjola, V. P., Jankowska, E. A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J. T., Pieske, B., Riley, J. P., Rosano, G. M., Ruilope, L. M., Ruschitzka, F., Rutten, F. H., Van Der Meer, P., Authors/Task Force, M. & Document, R. 2016b. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail,* 18**,** 891-975.

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., Falk, V., Gonzalez-Juanatey, J. R., Harjola, V. P., Jankowska, E. A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J. T., Pieske, B., Riley, J. P., Rosano, G. M. C., Ruilope, L. M., Ruschitzka, F., Rutten, F. H. & Van Der Meer, P. 2016c. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. *Rev Esp Cardiol (Engl Ed),* 69**,** 1167.

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., Falk, V., Gonzalez-Juanatey, J. R., Harjola, V. P., Jankowska, E. A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J. T., Pieske, B., Riley, J. P., Rosano, G. M. C., Ruilope, L. M., Ruschitzka, F., Rutten, F. H., Van Der Meer, P. & Group, E. S. C. S. D. 2016d. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J,* 37**,** 2129-2200.

Pranata, R., Tondas, A. E., Yonas, E., Vania, R., Yamin, M., Chandra, A. & Siswanto, B. B. 2020. Differences in clinical characteristics and outcome of de novo heart

failure compared to acutely decompensated chronic heart failure - systematic review and meta-analysis. *Acta Cardiol*, 1-11.

Pratali, L., Picano, E., Otasevic, P., Vigna, C., Palinkas, A., Cortigiani, L., Dodi, C., Bojic, D., Varga, A., Csanady, M. & Landi, P. 2001. Prognostic significance of the dobutamine echocardiography test in idiopathic dilated cardiomyopathy. *Am J Cardiol,* 88, 1374-8.

Prioli, A., Marino, P., Lanzoni, L. & Zardini, P. 1998. Increasing degrees of left ventricular filling impairment modulate left atrial function in humans. *Am J Cardiol,* 82, 756-61.

Pullen, P. R., Seffens, W. S. & Thompson, W. R. 2018. Yoga for Heart Failure: A Review and Future Research. *Int J Yoga,* 11, 91-98.

Raffaello, W. M., Henrina, J., Huang, I., Lim, M. A., Suciadi, L. P., Siswanto, B. B. & Pranata, R. 2020. Clinical Characteristics of De Novo Heart Failure and Acute Decompensated Chronic Heart Failure: Are They Distinctive Phenotypes That Contribute to Different Outcomes? *Card Fail Rev,* 7, e02.

Rali, A. S., Buechler, T., Van Gotten, B., Waters, A., Shah, Z., Haglund, N. & Sauer, A. 2020. Non-Invasive Cardiac Output Monitoring in Cardiogenic Shock: The NICOM Study. *J Card Fail,* 26, 160-165.

Rao, V. N., Fudim, M., Mentz, R. J., Michos, E. D. & Felker, G. M. 2020. Regional adiposity and heart failure with preserved ejection fraction. *Eur J Heart Fail,* 22, 1540-1550.

Rathore, S. S., Curtis, J. P., Wang, Y., Bristow, M. R. & Krumholz, H. M. 2003. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA,* 289, 871-8.

Rector, T. S. & Cohn, J. N. 1992. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. *Am Heart J,* 124, 1017-25.

Reddy, Y. N. V. & Borlaug, B. A. 2020. Left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail,* 22, 486-488.

Reddy, Y. N. V., Carter, R. E., Obokata, M., Redfield, M. M. & Borlaug, B. A. 2018. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. *Circulation,* 138, 861-870.

Reza, N., Tahhan, A. S., Mahmud, N., Defilippis, E. M., Alrohaibani, A., Vaduganathan, M., Greene, S. J., Ho, A. H., Fonarow, G. C., Butler, J., O'connor, C., Fiuzat, M., Vardeny, O., Pina, I. L., Lindenfeld, J. & Jessup, M. 2020. Representation of Women Authors in International Heart Failure Guidelines and Contemporary Clinical Trials. *Circ Heart Fail,* 13, e006605.

Richardson, C. R., Newton, T. L., Abraham, J. J., Sen, A., Jimbo, M. & Swartz, A. M. 2008. A meta-analysis of pedometer-based walking interventions and weight loss.

Ann Fam Med, 6**,** 69-77.

Riegel, B., Moser, D. K., Glaser, D., Carlson, B., Deaton, C., Armola, R., Sethares, K., Shively, M., Evangelista, L. & Albert, N. 2002. The Minnesota Living With Heart Failure Questionnaire: sensitivity to differences and responsiveness to intervention intensity in a clinical population. *Nurs Res,* 51**,** 209-18.

Roger, V. L. 2018. Heart Failure Epidemic: It's Complicated. *Circulation,* 138**,** 25-28.
Ruffolo, R. R., Jr., Spradlin, T. A., Pollock, G. D., Waddell, J. E. & Murphy, P. J. 1981. Alpha and beta adrenergic effects of the stereoisomers of dobutamine. *J Pharmacol Exp Ther,* 219**,** 447-52.

Sahle, B. W., Owen, A. J., Mutowo, M. P., Krum, H. & Reid, C. M. 2016. Prevalence of heart failure in Australia: a systematic review. *BMC Cardiovasc Disord,* 16**,** 32.

Saint-Maurice, P. F., Troiano, R. P., Bassett, D. R., Jr., Graubard, B. I., Carlson, S. A., Shiroma, E. J., Fulton, J. E. & Matthews, C. E. 2020. Association of Daily Step Count and Step Intensity With Mortality Among US Adults. *JAMA,* 323**,** 1151-1160.

Salisbury, A. C., House, J. A., Conard, M. W., Krumholz, H. M. & Spertus, J. A. 2005. Low-to-moderate alcohol intake and health status in heart failure patients. *J Card Fail,* 11**,** 323-8.

Santos, A. B., Kraigher-Krainer, E., Gupta, D. K., Claggett, B., Zile, M. R., Pieske, B., Voors, A. A., Lefkowitz, M., Bransford, T., Shi, V., Packer, M., Mcmurray, J. J., Shah, A. M. & Solomon, S. D. 2014. Impaired left atrial function in heart failure with preserved ejection fraction. *Eur J Heart Fail,* 16**,** 1096-103.

Santos, A. B., Roca, G. Q., Claggett, B., Sweitzer, N. K., Shah, S. J., Anand, I. S., Fang, J. C., Zile, M. R., Pitt, B., Solomon, S. D. & Shah, A. M. 2016. Prognostic Relevance of Left Atrial Dysfunction in Heart Failure With Preserved Ejection Fraction. *Circ Heart Fail,* 9**,** e002763.

Santos, M., West, E., Skali, H., Forman, D. E., Nadruz, W. J. & Shah, A. M. 2018. Resting Heart Rate and Chronotropic Response to Exercise: Prognostic Implications in Heart Failure Across the Left Ventricular Ejection Fraction Spectrum. *J Card Fail,* 24**,** 753-762.

Santoso, A., Purwowiyoto, S. L., Purwowiyoto, B. S. & Soesanto, A. M. 2019. Exercise Training Improved Longitudinal Intrinsic Left Ventricle Function in Heart Failure with Preserved Ejection Fraction. *Int J Angiol,* 28**,** 44-49.

Sarma, S., Stoller, D., Hendrix, J., Howden, E., Lawley, J., Livingston, S., Adams-Huet, B., Holmes, C., Goldstein, D. S. & Levine, B. D. 2020. Mechanisms of Chronotropic Incompetence in Heart Failure With Preserved Ejection Fraction. *Circ Heart Fail,* 13**,** e006331.

Savarese, G. & Lund, L. H. 2017. Global Public Health Burden of Heart Failure. *Card Fail Rev,* 3**,** 7-11.

Scherer, M., Dungen, H. D., Inkrot, S., Tahirovic, E., Lashki, D. J., Apostolovic, S., Edelmann, F., Wachter, R., Loncar, G., Haverkamp, W., Neskovic, A. & Herrmann-

Lingen, C. 2013. Determinants of change in quality of life in the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD). *Eur J Intern Med,* 24**,** 333-8.

Schiattarella, G. G., Tong, D. & Hill, J. A. 2020. Can HFpEF and HFrEF Coexist? *Circulation,* 141**,** 709-711.

Schwinger, R. H. G. 2021. Pathophysiology of heart failure. *Cardiovasc Diagn Ther,* 11**,** 263-276.

Scrutinio, D., Lagioia, R., Ricci, A., Clemente, M., Boni, L. & Rizzon, P. 1994. Prediction of mortality in mild to moderately symptomatic patients with left ventricular dysfunction. The role of the New York Heart Association classification, cardiopulmonary exercise testing, two-dimensional echocardiography and Holter monitoring. *Eur Heart J,* 15**,** 1089-95.

Shah, A. M. 2013. Ventricular remodeling in heart failure with preserved ejection fraction. *Curr Heart Fail Rep,* 10**,** 341-9.

Shah, S. J., Katz, D. H., Selvaraj, S., Burke, M. A., Yancy, C. W., Gheorghiade, M., Bonow, R. O., Huang, C. C. & Deo, R. C. 2015. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation,* 131**,** 269-79.

Shah, S. J., Kitzman, D. W., Borlaug, B. A., Van Heerebeek, L., Zile, M. R., Kass, D. A. & Paulus, W. J. 2016. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. *Circulation,* 134**,** 73-90.

Shelton, R. J., L. Ingle, A. S. Rigby, K. K. Witte, J. G. Cleland and A. L. Clark (2010). "Cardiac output does not limit submaximal exercise capacity in patients with chronic heart failure." Eur J Heart Fail 12(9): 983-989.

Simmonds, S. J., Cuijpers, I., Heymans, S. & Jones, E. a. V. 2020. Cellular and Molecular Differences between HFpEF and HFrEF: A Step Ahead in an Improved Pathological Understanding. *Cells,* 9.

Sinning, D., Kasner, M., Westermann, D., Schulze, K., Schultheiss, H. P. & Tschope, C. 2011. Increased left ventricular stiffness impairs exercise capacity in patients with heart failure symptoms despite normal left ventricular ejection fraction. *Cardiol Res Pract,* 2011**,** 692862.

Slaght, J., Senechal, M., Hrubeniuk, T. J., Mayo, A. & Bouchard, D. R. 2017. Walking Cadence to Exercise at Moderate Intensity for Adults: A Systematic Review. *J Sports Med (Hindawi Publ Corp),* 2017**,** 4641203.

Smiseth, O. A., Torp, H., Opdahl, A., Haugaa, K. H. & Urheim, S. 2016. Myocardial strain imaging: how useful is it in clinical decision making? *Eur Heart J,* 37**,** 1196-207.

Solomon, S. D. & Biering-Sørensen, T. 2017. LA Strain When Ejection Fraction Is Preserved: A New Measure of Diastolic Function? *JACC Cardiovasc Imaging,* 10**,** 744-746.

Solomon, S. D., Mcmurray, J. J. V., Anand, I. S., Ge, J., Lam, C. S. P., Maggioni, A.

P., Martinez, F., Packer, M., Pfeffer, M. A., Pieske, B., Redfield, M. M., Rouleau, J. L., Van Veldhuisen, D. J., Zannad, F., Zile, M. R., Desai, A. S., Claggett, B., Jhund, P. S., Boytsov, S. A., Comin-Colet, J., Cleland, J., Dungen, H. D., Goncalvesova, E., Katova, T., Kerr Saraiva, J. F., Lelonek, M., Merkely, B., Senni, M., Shah, S. J., Zhou, J., Rizkala, A. R., Gong, J., Shi, V. C., Lefkowitz, M. P., Investigators, P.-H. & Committees 2019. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med,* 381**,** 1609-1620.

Solomon, S. D., Vaduganathan, M., B, L. C., Packer, M., Zile, M., Swedberg, K., Rouleau, J., M, A. P., Desai, A., Lund, L. H., Kober, L., Anand, I., Sweitzer, N., Linssen, G., Merkely, B., Luis Arango, J., Vinereanu, D., Chen, C. H., Senni, M., Sibulo, A., Boytsov, S., Shi, V., Rizkala, A., Lefkowitz, M. & Mcmurray, J. J. V. 2020. Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. *Circulation,* 141**,** 352-361.

Somaratne, J. B., Berry, C., Mcmurray, J. J., Poppe, K. K., Doughty, R. N. & Whalley, G. A. 2009. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. *Eur J Heart Fail,* 11**,** 855-62.

Sotomi, Y., Hikoso, S., Nakatani, D., Mizuno, H., Okada, K., Dohi, T., Kitamura, T., Sunaga, A., Kida, H., Oeun, B., Sato, T., Komukai, S., Tamaki, S., Yano, M., Hayashi, T., Nakagawa, A., Nakagawa, Y., Yasumura, Y., Yamada, T., Sakata, Y. & Investigators, P. U.-H. 2021. Sex Differences in Heart Failure With Preserved Ejection Fraction. *J Am Heart Assoc,* 10**,** e018574.

Squara, P., Denjean, D., Estagnasie, P., Brusset, A., Dib, J. C. & Dubois, C. 2007. Noninvasive cardiac output monitoring (NICOM): a clinical validation. *Intensive Care Med,* 33**,** 1191-1194.

Sugimoto, T., Bandera, F., Generati, G., Alfonzetti, E., Barletta, M., Losito, M., Labate, V., Rovida, M., Caracciolo, M., Pappone, C., Ciconte, G. & Guazzi, M. 2020a. Left Atrial Dynamics During Exercise in Mitral Regurgitation of Primary and Secondary Origin: Pathophysiological Insights by Exercise Echocardiography Combined With Gas Exchange Analysis. *JACC Cardiovasc Imaging,* 13**,** 25-40.

Sugimoto, T., Barletta, M., Bandera, F., Generati, G., Alfonzetti, E., Rovida, M., Gnecchi Ruscone, T., Rossi, A., Cicoira, M. & Guazzi, M. 2020b. Central role of left atrial dynamics in limiting exercise cardiac output increase and oxygen uptake in heart failure: insights by cardiopulmonary imaging. *Eur J Heart Fail,* 22**,** 1186-1198.

Sullivan, M. J., Higginbotham, M. B. & Cobb, F. R. 1988. Exercise training in patients with severe left ventricular dysfunction. Hemodynamic and metabolic effects. *Circulation,* 78**,** 506-15.

Sverdlov, O. & Ryeznik, Y. 2019. Implementing unequal randomization in clinicaltrials
with heterogeneous treatment costs. Stat Med, 38**,** 2905-2927.

Swan, H. J., Ganz, W., Forrester, J., Marcus, H., Diamond, G. & Chonette, D. 1970. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *N Engl J Med,* 283**,** 447-51.

Swedberg, K., Komajda, M., Bohm, M., Borer, J. S., Ford, I., Dubost-Brama, A., Lerebours, G., Tavazzi, L. & Investigators, S. 2010. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet,* 376**,** 875-85.

Sweeney, M., Corden, B. & Cook, S. A. 2020. Targeting cardiac fibrosis in heart failure with preserved ejection fraction: mirage or miracle? *EMBO Mol Med,* 12**,** e10865.

Tai, C., Gan, T., Zou, L., Sun, Y., Zhang, Y., Chen, W., Li, J., Zhang, J., Xu, Y., Lu, H. & Xu, D. 2017. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord,* 17**,** 257.

Talwar, S., Siebenhofer, A., Williams, B. & Ng, L. 2000. Influence of hypertension, left ventricular hypertrophy, and left ventricular systolic dysfunction on plasma N terminal proBNP. *Heart,* 83**,** 278-82.

Tan, C., Rubenson, D., Srivastava, A., Mohan, R., Smith, M. R., Billick, K., Bardarian, S. & Thomas Heywood, J. 2017. Left ventricular outflow tract velocity time integral outperforms ejection fraction and Doppler-derived cardiac output for predicting outcomes in a select advanced heart failure cohort. *Cardiovasc Ultrasound,* 15**,** 18.

Taylor, A. L., Ziesche, S., Yancy, C., Carson, P., D'agostino, R., Jr., Ferdinand, K., Taylor, M., Adams, K., Sabolinski, M., Worcel, M., Cohn, J. N. & African-American Heart Failure Trial, I. 2004. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med,* 351**,** 2049-57.

Taylor, R. S., Piepoli, M. F., Smart, N., Coats, A. J., Ellis, S., Dalal, H., O'connor, C. M., Warren, F. C., Whellan, D., Ciani, O. & Extra, M. I. I. C. 2014a. Exercise training for chronic heart failure (ExTraMATCH II): protocol for an individual participant data meta-analysis. *Int J Cardiol,* 174**,** 683-7.

Taylor, R. S., Sagar, V. A., Davies, E. J., Briscoe, S., Coats, A. J., Dalal, H., Lough, F., Rees, K. & Singh, S. 2014b. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev***,** CD003331.

Telles, F., Nanayakkara, S., Evans, S., Patel, H. C., Mariani, J. A., Vizi, D., William, J., Marwick, T. H. & Kaye, D. M. 2019. Impaired left atrial strain predicts abnormal exercise haemodynamics in heart failure with preserved ejection fraction. *Eur J Heart Fail,* 21**,** 495-505.

Teramoto, K., Teng, T. K., Chandramouli, C., Tromp, J., Sakata, Y. & Lam, C. S. 2022. Epidemiology and Clinical Features of Heart Failure with Preserved Ejection Fraction. *Card Fail Rev,* 8**,** e27.

Thompson, P. D. & Eijsvogels, T. M. H. 2018. New Physical Activity Guidelines: A Call to Activity for Clinicians and Patients. *JAMA,* 320**,** 1983-1984.

Trabulo, M., Mendes, M., Mesquita, A. & Seabra-Gomes, R. 1994. [Does the modified Bruce protocol induce physiological stress equal to that of the Bruce protocol?]. *Rev Port Cardiol,* 13**,** 753-60; 735-6.

Tribouilloy, C., Rusinaru, D., Mahjoub, H., Souliere, V., Levy, F., Peltier, M., Slama, M. & Massy, Z. 2008. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. *Eur Heart J,* 29**,** 339-47.

Tribouilloy, C., Slama, M., Shen, W. F., Choquet, D., Delonca, J., Mertl, C., Dufosse, H. & Lesbre, J. P. 1991. Determination of left ventricular inflow by pulsed Doppler echocardiography: influence of mitral orifice area and blood velocity measurements. *Eur Heart J,* 12**,** 39-43.

Tromp, J., Ferreira, J. P., Janwanishstaporn, S., Shah, M., Greenberg, B., Zannad, F. & Lam, C. S. P. 2019. Heart failure around the world. *Eur J Heart Fail,* 21**,** 1187-1196.

Tsuchihashi-Makaya, M., Hamaguchi, S., Kinugawa, S., Yokota, T., Goto, D., Yokoshiki, H., Kato, N., Takeshita, A., Tsutsui, H. & Investigators, J.-C. 2009. Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J,* 73**,** 1893-900.

Tsutsui, H., Ide, T., Ito, H., Kihara, Y., Kinugawa, K., Kinugawa, S., Makaya, M., Murohara, T., Node, K., Saito, Y., Sakata, Y., Shimizu, W., Yamamoto, K., Bando, Y., Iwasaki, Y. K., Kinugasa, Y., Mizote, I., Nakagawa, H., Oishi, S., Okada, A., Tanaka, A., Akasaka, T., Ono, M., Kimura, T., Kosaka, S., Kosuge, M. & Momomura, S. I. 2021. JCS/JHFS 2021 Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure. *J Card Fail*.

Tsuyuki, R. T., Mckelvie, R. S., Arnold, J. M., Avezum, A., Jr., Barretto, A. C., Carvalho, A. C., Isaac, D. L., Kitching, A. D., Piegas, L. S., Teo, K. K. & Yusuf, S. 2001. Acute precipitants of congestive heart failure exacerbations. *Arch Intern Med,* 161**,** 2337-42.

Van Heerebeek, L., Borbely, A., Niessen, H. W., Bronzwaer, J. G., Van Der Velden, J., Stienen, G. J., Linke, W. A., Laarman, G. J. & Paulus, W. J. 2006. Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation,* 113**,** 1966-73.

Van Riet, E. E., Hoes, A. W., Wagenaar, K. P., Limburg, A., Landman, M. A. & Rutten, F. H. 2016. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail,* 18**,** 242-52.

Vedin, O., Lam, C. S. P., Koh, A. S., Benson, L., Teng, T. H. K., Tay, W. T., Braun, O. O., Savarese, G., Dahlstrom, U. & Lund, L. H. 2017. Significance of Ischemic Heart Disease in Patients With Heart Failure and Preserved, Midrange, and Reduced Ejection Fraction: A Nationwide Cohort Study. *Circ Heart Fail,* 10.

Verbrugge, F. H., Guazzi, M., Testani, J. M. & Borlaug, B. A. 2020. Altered Hemodynamics and End-Organ Damage in Heart Failure: Impact on the Lung and Kidney. *Circulation,* 142**,** 998-1012.

Virani, S. S., Alonso, A., Aparicio, H. J., Benjamin, E. J., Bittencourt, M. S., Callaway,

C. W., Carson, A. P., Chamberlain, A. M., Cheng, S., Delling, F. N., Elkind, M. S. V., Evenson, K. R., Ferguson, J. F., Gupta, D. K., Khan, S. S., Kissela, B. M., Knutson, K. L., Lee, C. D., Lewis, T. T., Liu, J., Loop, M. S., Lutsey, P. L., Ma, J., Mackey, J., Martin, S. S., Matchar, D. B., Mussolino, M. E., Navaneethan, S. D., Perak, A. M., Roth, G. A., Samad, Z., Satou, G. M., Schroeder, E. B., Shah, S. H., Shay, C. M., Stokes, A., Vanwagner, L. B., Wang, N. Y., Tsao, C. W., American Heart Association Council On, E., Prevention Statistics, C. & Stroke Statistics, S. 2021. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation,* 143**,** e254-e743.

Voigt, J. U., Pedrizzetti, G., Lysyansky, P., Marwick, T. H., Houle, H., Baumann, R., Pedri, S., Ito, Y., Abe, Y., Metz, S., Song, J. H., Hamilton, J., Sengupta, P. P., Kolias, T. J., D'hooge, J., Aurigemma, G. P., Thomas, J. D. & Badano, L. P. 2015. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *J Am Soc Echocardiogr,* 28**,** 183-93.

Von Roeder, M., Rommel, K. P., Kowallick, J. T., Blazek, S., Besler, C., Fengler, K., Lotz, J., Hasenfuss, G., Lucke, C., Gutberlet, M., Schuler, G., Schuster, A. & Lurz, P. 2017a. Influence of Left Atrial Function on Exercise Capacity and Left Ventricular Function in Patients With Heart Failure and Preserved Ejection Fraction. *Circ Cardiovasc Imaging,* 10.

Von Roeder, M., Rommel, K. P., Kowallick, J. T., Blazek, S., Besler, C., Fengler, K., Lotz, J., Hasenfuß, G., Lücke, C., Gutberlet, M., Schuler, G., Schuster, A. & Lurz, P. 2017b. Influence of Left Atrial Function on Exercise Capacity and Left Ventricular Function in Patients With Heart Failure and Preserved Ejection Fraction. *Circ Cardiovasc Imaging,* 10.

Warburton, D. E., Haykowsky, M. J., Quinney, H. A., Humen, D. P. & Teo, K. K. 1999. Reliability and validity of measures of cardiac output during incremental to maximal aerobic exercise. Part II: Novel techniques and new advances. *Sports Med,* 27**,** 241-60.

Westermann, D., Kasner, M., Steendijk, P., Spillmann, F., Riad, A., Weitmann, K., Hoffmann, W., Poller, W., Pauschinger, M., Schultheiss, H. P. & Tschope, C. 2008. Role of left ventricular stiffness in heart failure with normal ejection fraction. *Circulation,* 117**,** 2051-60.

Writing, C., Maddox, T. M., Januzzi, J. L., Jr., Allen, L. A., Breathett, K., Butler, J., Davis, L. L., Fonarow, G. C., Ibrahim, N. E., Lindenfeld, J., Masoudi, F. A., Motiwala, S. R., Oliveros, E., Patterson, J. H., Walsh, M. N., Wasserman, A., Yancy, C. W. & Youmans, Q. R. 2021. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol,* 77**,** 772-810.

Wong, C. M., Hawkins, N. M., Petrie, M. C., Jhund, P. S., Gardner, R. S., Ariti, C. A., Poppe, K. K., Earle, N., Whalley, G. A., Squire, I. B., Doughty, R. N., Mcmurray, J. J. & Investigators, M. 2014. Heart failure in younger patients: the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). *Eur Heart J,* 35**,** 2714-21.

Yamamoto, K., Origasa, H., Hori, M. & Investigators, J. D. 2013. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). *Eur J Heart Fail,* 15**,** 110-8.

Yamanouchi, K., Shinozaki, T., Chikada, K., Nishikawa, T., Ito, K., Shimizu, S., Ozawa, N., Suzuki, Y., Maeno, H., Kato, K. & Et Al. 1995. Daily walking combined with diet therapy is a useful means for obese NIDDM patients not only to reduce body weight but also to improve insulin sensitivity. *Diabetes Care,* 18**,** 775-8.

Yan, Y., Liu, B., Du, J., Wang, J., Jing, X., Liu, Y., Deng, S., Du, J. & She, Q. 2021. SGLT2i versus ARNI in heart failure with reduced ejection fraction: a systematic review and meta-analysis. *ESC Heart Fail,* 8**,** 2210-2219.

Yancy, C. W. 2018. Sodium Restriction in Heart Failure: Too Much Uncertainty-Do the Trials. *JAMA Intern Med*.

Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Jr., Colvin, M. M., Drazner, M. H., Filippatos, G. S., Fonarow, G. C., Givertz, M. M., Hollenberg, S. M., Lindenfeld, J., Masoudi, F. A., Mcbride, P. E., Peterson, P. N., Stevenson, L. W. & Westlake, C. 2017. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail,* 23**,** 628-651.

Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Jr., Drazner, M. H., Fonarow, G. C., Geraci, S. A., Horwich, T., Januzzi, J. L., Johnson, M. R., Kasper, E. K., Levy, W. C., Masoudi, F. A., Mcbride, P. E., Mcmurray, J. J., Mitchell, J. E., Peterson, P. N., Riegel, B., Sam, F., Stevenson, L. W., Tang, W. H., Tsai, E. J., Wilkoff, B. L., American College of Cardiology, F. & American Heart Association Task Force on Practice, G. 2013. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol,* 62**,** e147-239.

Yancy, C. W., Lopatin, M., Stevenson, L. W., De Marco, T., Fonarow, G. C., Committee, A. S. A. & Investigators 2006. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol,* 47**,** 76-84.

Yates, T., Haffner, S. M., Schulte, P. J., Thomas, L., Huffman, K. M., Bales, C. W., Califf, R. M., Holman, R. R., Mcmurray, J. J., Bethel, M. A., Tuomilehto, J., Davies, M. J. & Kraus, W. E. 2014. Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis. *Lancet,* 383**,** 1059-66.

Yusuf, S., Pfeffer, M. A., Swedberg, K., Granger, C. B., Held, P., Mcmurray, J. J., Michelson, E. L., Olofsson, B., Ostergren, J., Investigators, C. & Committees 2003. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet,* 362**,** 777-81.

Yusuf, S., Rangarajan, S., Teo, K., Islam, S., Li, W., Liu, L., Bo, J., Lou, Q., Lu, F.,

Liu, T., Yu, L., Zhang, S., Mony, P., Swaminathan, S., Mohan, V., Gupta, R., Kumar, R., Vijayakumar, K., Lear, S., Anand, S., Wielgosz, A., Diaz, R., Avezum, A., Lopez-Jaramillo, P., Lanas, F., Yusoff, K., Ismail, N., Iqbal, R., Rahman, O., Rosengren, A., Yusufali, A., Kelishadi, R., Kruger, A., Puoane, T., Szuba, A., Chifamba, J., Oguz, A., Mcqueen, M., Mckee, M., Dagenais, G. & Investigators, P. 2014. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med,* 371**,** 818-27.

Zile, M. R., Gaasch, W. H., Anand, I. S., Haass, M., Little, W. C., Miller, A. B., Lopez-Sendon, J., Teerlink, J. R., White, M., Mcmurray, J. J., Komajda, M., Mckelvie, R., Ptaszynska, A., Hetzel, S. J., Massie, B. M., Carson, P. E. & Investigators, I. P. 2010. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) trial. *Circulation,* 121**,** 1393-405.

Zile, M. R., Kjellstrom, B., Bennett, T., Cho, Y., Baicu, C. F., Aaron, M. F., Abraham, W. T., Bourge, R. C. & Kueffer, F. J. 2013. Effects of exercise on left ventricular systolic and diastolic properties in patients with heart failure and a preserved ejection fraction versus heart failure and a reduced ejection fraction. *Circ Heart Fail,* 6**,** 508-16.

Zile, M. R., Lindenfeld, J., Weaver, F. A., Zannad, F., Galle, E., Rogers, T. & Abraham, W. T. 2020. Baroreflex Activation Therapy in Patients With Heart Failure With Reduced Ejection Fraction. *J Am Coll Cardiol,* 76**,** 1-13.

Zinman, B., Wanner, C., Lachin, J. M., Fitchett, D., Bluhmki, E., Hantel, S., Mattheus, M., Devins, T., Johansen, O. E., Woerle, H. J., Broedl, U. C., Inzucchi, S. E. & Investigators, E.-R. O. 2015. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med,* 373**,** 2117-28.

Zocalo, Y., Garcia-Espinosa, V., Castro, J. M., Zinoveev, A., Marin, M., Chiesa, P., Diaz, A. & Bia, D. 2021. Stroke volume and cardiac output non-invasive monitoring based on brachial oscillometry-derived pulse contour analysis: Explanatory variables and reference intervals throughout life (3-88 years). *Cardiol J,* 28**,** 864-878.

Appendices

Appendix 1 Consent Form

Patient Identification number for this trial:

CONSENT FORM

Title of Project: Pathophysiology of Heart Failure with Preserved Ejection Fraction

Name of researchers: Dr Shantanu P Sengupta, Dr Djordje Jakovljevic, Dr Guy MacGowan, Dr Kunda Mungulmare

Please initial box

1. I confirm that I have read and understand the information sheet dated 30th April 2018 (version 1.0) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I agree to my GP being informed of my participation in the study. ☐
4. I understand that my results will be kept confidential. ☐
5. I understand that my data will be stored securely. ☐
6. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by members of the research team or individuals from Sengupta Hospital and Research Institute and Newcastle upon Tyne Hospital, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
7. I agree to take part in the above study. ☐
8. I agree, that if I am asked I will take part in a focus group discussion with the member of the research team and other participants recruited to the study for the purpose of this research. ☐

Name of patient	Date	Signature
Name of person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

1 copy for patient; 1 copy for researcher; 1 copy for medical records 30th April 2018, Patient consent form Version 1.0

Patient Identification number for this trial:

CONSENT FORM

Title of Project: Physical activity in heart failure with preserved ejection fraction

Name of researchers: Dr Shantanu P Sengupta, Dr Nduka Okwose, Dr Djordje Jakovljevic, Dr Guy MacGowan, Dr Kunda Mungulmare

Please initial box

9. I confirm that I have read and understand the information sheet dated 30th April 2018 (version 1.0) for the above study and have had the opportunity to ask questions. ☐

10. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

11. I agree to my GP being informed of my participation in the study. ☐

12. I understand that my results will be kept confidential. ☐

13. I understand that my data will be stored securely. ☐

14. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by members of the research team or individuals from Sengupta Hospital and Research Institute and Newcastle upon Tyne Hospital, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

15. I agree to take part in the above study. ☐

16. I agree, that if I am asked I will take part in a focus group discussion with the member of the research team and other participants recruited to the study for the purpose of this research. ☐

Name of patient	Date	Signature
Name of person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Appendix 2 Patient Information Sheet

Patient Information Sheet

Pathophysiology of Heart Failure with Preserved Ejection Fraction

You are invited to participate in this research project. Please take time to read the following information carefully. It explains why the research is being done and what it involves. If you have any questions about the information, you are very welcome to ask for further explanation. Thank you for reading this.

- Part 1 tells you about the purpose of this study and what will happen during the study.
- Part 2 gives more detailed information about the conduct of the study.

Discuss with others if you wish and take time to decide regarding your participation.

Part 1

What is the purpose of the research project?

Heart Failure (HF) occurs when the heart's ability to pump blood is reduced. HF can lead to health complications including damage to other organs (e.g. kidneys) and blood vessels. It is a chronic progressive condition that can be treated but not cured. There is no specific treatment for HF which occurs because of relaxation abnormality of the heart (diastolic dysfunction), apart from diuretics. The main aim of this project is to better understand the mechanism of this condition so that better treatment strategies develop and help the generations to come.

Why have I been chosen?

You have been chosen because you have been diagnosed with Heart Failure due to diastolic or systolic dysfunction. You are taking prescribed optimal medication and your condition is clinically stable. The project will involve up to 80 people.

Do I have to take part?

Your participation is purely voluntary and all results will be strictly anonymous. If you decide to take part, you are still free to withdraw at any time without giving reasons and without your medical care being affected. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form.

What will the research project involve?

You will be asked to attend the Clinical Research Facility at Sengupta Hospital and Research Institute, Ravinagar, Nagpur on minimum 4 occasions 0,3,6,12 months as detailed below. During these visits you will have your heart checked.

Visit 1 (Screening): After reading this information sheet and after having had time to make a decision and ask any questions to the researcher, you will be asked to

sign the consent form saying that you would like to take part in this research study. You will be asked to undertake a short physical examination, anthropometric data including height, weight, BMI, waist circumference and blood pressure will be measured, a resting electrocardiogram (ECG), ultra sound of the heart called echocardiography (Echo) and blood sample will be done. Then you will perform either an exercise (treatdmill) test or a medication (Dobutamine) stress test. Echo will be repeated at peak stress. During exercise test you may be wearing a face mask to collect expired gases and measure response of the heart using ECG.
Total visit time: 1 to 1.5 hours

Visit 2,3,4 (Follow-up): The same as visit 1.

Expenses and payments

No expenses for travel are being made.

What do I have to do?

You will continue with your usual treatment(s) during the project. It is very important that you attend all required visits. You will be asked not to drink alcohol or exercise the day before the two visit days. Each of the visits will be in the morning before breakfast and you should not eat from 10pm the prior evening. You can drink water only and take your medication as advised.

What are the side effects of treatment received when taking part?

Exercise and Dobutamine stress tests are performed routinely in clinical practice to help clinical care teams to better understand heart problems and develop appropriate plan in regards to therapy. Normal response to stress tests is that your heart beats faster and your blood pressure raises as in people without heart failure. The following signs and symptoms may also occur including a chest pain, irregular heartbeats, dizziness, nausea, tiredness, and heart attack (rare). For these reasons your visits will be supervised by a doctor at all times.

What you should do if you feel unwell
In case you are feeling unwell during the study you should immediately contact the research team on 9923190925. In case of emergency you should contact the emergency room of the hospital.

Are there any other possible disadvantages of taking part?

There are no anticipated disadvantages to taking part in this study but you will need to attend all of the study visits and complete the physical activity intervention.

What are the possible benefits of taking part?

You will be supported throughout the study by the member of the research team and will be educated regarding heart failure.

What if there is a problem?

If you have any concern or complaint about any aspect of the study this will be dealt with immediately by the study research team members. Contact details for the primary researcher are given at the end of Part 1.

Will my taking part in the project be kept confidential?

All information obtained during the course of the research project will be kept strictly confidential.

What will happen to the results of the research study?

The results of the project will be presented in national and international cardiology and heart failure meetings and will be published in cardiac journals. You will not be identified in any report or publication. You will be welcome to have a copy of the results once they are published.

Who are the contacts for further information?

Further information can be obtained from:

Dr Shantanu P Sengupta
Sengupta Hospital and Research Institute
Ravinagar Square, Nagpur- 440033
India
Phone : 9923190925
Email : senguptasp@gmail.com

Thank you.

Part 2

What if relevant new information becomes available?

If new information is published during the course of a study this can sometimes change how the research should go forward. If this were to happen we would inform you of this revised information and ask you to confirm your consent to participate in the study. For this study it is highly unlikely that this would occur.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time. Any data already obtained from you would still be used if you were to agree to this.

What if there is a problem?

a) Complaints
If you have any concern or complaint about any aspect of this study you should contact the study team directly by phone on 9923190925, or write to them at the address at the end of Part 1 of this document.

b) Harm
In the unlikely event that something does go wrong and you suffer harm due to a member of the team's negligence you should contact the study team directly by phone on 9923190925

c) Detection of abnormal, none heart failure related findings
In the unlikely event of any abnormality being found during the research visits this will be referred to a qualified specialist. This will then be discussed with the lead investigator and they will discuss whether other specialist analysis is required.

Will my taking part in the project be kept confidential?

All information obtained during the course of the research project will be kept strictly confidential. This will be achieved by storing information in password-protected computer files, and appointment information in locked filing systems within the Clinical Research Facility. No individually identifiable information will be stored outside the Centre.

Analysis of the detailed results of the research will be done by the research team members. At this stage no personal information is part of the dataset. Results will be sent to participants, presented at scientific meetings and published in scientific journals without personal identification of any volunteer although thanks to the volunteers will be recorded.

What will happen to blood samples?
Samples will be stored until it is certain that the test results are accurate, and then they will be disposed of. During storage, samples are identified only by a code number, not your name. No other tests will be carried out on the samples.

What will happen to results of the research?

The results will be presented at scientific meetings for discussion by other experts in this field. They will be written up in the form of a scientific paper and this will be intended to be published in a suitable scientific journal. As soon as the results are fully analysed after the end of the entire study you will receive a letter describing what we have found, and what implications it has for people with heart failure. We will also hold an open evening for participants at which we will present the results of the study.

Who is organising and funding the research?

This project is not funded as of now. The design and organisation of the study is the responsibility of Dr Shantanu Sengupta who is internationally recognised expert in this field.

There is no payment to any of the researchers involved in this study. They are employed by Sengupta Hospital and Newcastle University, to teach and to research and have no financial link with the study.

Who has reviewed the study?

The study was reviewed by researchers and clinical care teams based at the Negpur Hospital and Newcastle upon Tyne Hospitals (UK). An Independent Ethics committee of the Sengupta Hospital has reviewed and approved the study protocol.

Appendix 3 Physical Examination Form

Name: _____ Age (years): _____

Body weight (kg): _____ Height (cm) : _____

Pulse rate (/min): _____ , Rhythm : _____

Resting blood pressure (mmHg): _____

Edema feet: Yes/No

Jugular venous pressure :	Yes/No
Auscultation of the lungs *specific attention to uniformity of breath sounds in all areas (absence of rales and wheezes)*	Ok/ Not Ok _____ _____
Auscultation of the heart *specific attention murmurs, gallops, clicks and rubs*	Ok/ Not Ok _____ _____
Evaluation of the abdomen *Bowel sounds, masses, Liver, Spleen enlargement*	Ok/ Not Ok _____ _____
Evaluation of Neurologic function *Power, reflexes*	Ok/ Not Ok _____
Any orthopaedic or medical condition that would limit exercise	Yes/ No _____

Cleared to start exercise test Yes/ No

Completed by _____ Date _____

Physical examination (page 2 on reverse of page 1)

Exercise Stress Testing Exercise Protocol _____

Absolute indicators for terminating the Exercise Stress test:

Drop in blood pressure of >10mm Hg from baseline blood pressure despite an increase in workload, when accompanied by other evidence of ischemia.	Ok/ Not OK _____ _____
Any form of chest pain or shortness of breath	OK / Not OK _____
Ventricular tachycardia / Fibrillation	OK / Not OK _____
ST elevation/ significant ST-T changes	OK / Not OK _____
Fatigue, shortness of breath, wheezing, leg cramps, or patient develops discomfort	OK / Not OK _____ _____
Hypertensive response Systolic blood pressure of > 200 mm Hg and/or diastolic pressure of >100 mm Hg	Yes/ No _____ _____

Competed by: _____ Date _____

Appendix 4

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	**No**			**Very Little**		**Very Much**
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

Appendix 5 Physical Activity Readiness Questionnaire

Physical Activity Readiness Questionnaire

Name: _____ Age (years)_____

1. Has your doctor ever said that you have a heart condition and you should only do physical activity recommended by a doctor? Yes / No
2. Do you ever feel pain in your chest when you do physical activity? Yes / No
3. Do you ever feel faint or have spells of dizziness? Yes / No
4. Do you have a joint problem (also back problem) that goes worse by exercise? Yes / No
5. Have you ever been told that you have high blood pressure? Yes / No
6. Do you have any breathing problems? Yes / No
7. Do you have any problems with liver, thyroid, kidneys or diabetes? Yes / No
8. Are you currently taking any medication? Yes / No if Yes, details _____
9. Are you pregnant, have you had a baby in the last 6 months? Yes / No
10. Has your mother or father had any heart problems? Yes / No
11. Whether you exercise in a week? if Yes, details _____ Yes / No If yes, how many times _____

Signed by : _____ Date: _____

Appendix 6 Telephone Record Sheet / Follow-up OPD record sheet

Patient ID _____ Date _____

Researcher _____

Week of intervention _____ Today's date ____/_____/_____

Time call/meeting started _____

Time call/meeting finished_____ Duration _____

Self-monitoring

Steps each day (record day of week)

Day 1 _____Day 2 _____Day 3 _____Day 4 _____

Day 5 _____Day 6 _____Day 7 _____

Any problems experienced _____

Goal setting

_____

Agreed goal

Look at days of the week (weekday vs. weekend day). Active days?

Ideally, we would like you to achieve 2000 steps more that what you would do normally each day How do you feel about this target? Achievable? Experience any problems? Positive reinforcement (i.e. any increase is positive, but how do you think you could increase further?). Reflect upon baseline. May need to reassess goal, record new goal. Also record in the activity planner the number of steps. Regular encouragement needed.

_____

Signed by : _____ Date: _____

Appendix 7 Telephone Record Sheet (Questions asked by co-ordinator)

Patient ID _____ Date _____

Researcher _____

Week of intervention _____ Today's date ____/_____/_____

Time call/meeting started _____

Time call/meeting finished_____ Duration _____

Self-monitoring

Any problems experienced	Yes / No
Alive	Yes / No
Is the watch and pedometer working properly	Yes / No
Breathlessness	Yes / No
Chest pain	Yes / No
Syncope/ dizziness	Yes / No
Palpitation	Yes / No
Any fall while walking	Yes / No
Any other problem	Yes / No

Specify _____

Signed by : _____ Date: _____

Appendix 8

Activity Planner

Planner start date:

DAY	GOAL Minutes / Steps / Other	ACTIVITY When? Where? Who with? How long for?	ACHIEVED Minutes / Steps / Other
MONDAY			
TUESDAY			
WEDNESDAY			
THURSDAY			
FRIDAY			
SATURDAY			
SUNDAY			

Appendix 9

Sengupta®
Hospital & Research Institute
ETHICS COMMITTEE

Ravinagar Square, Nagpur - 440 033 M.S. ☎: 91-712-2532697, 2536628 Fax : 91-712-2565597
Email : senguptacc@gamil.com

Date – 12 May 2018

To,

Dr. Shantanu Sengupta

Sengupta Hospital & Research Institute

Ravinagar Square,

Nagpur – 440033

Subject :- Ethics Committee Approval

Protocol Title - Pathophysiology of Heart Failure with Preserved Ejection Fraction

Dear Dr. Sengupta,

We have received 09 copies of the following study documents with your submission dated 02May2018 .

The following documents submitted for the referenced study were reviewed & approved by the Ethics Committee members.

S. No	Study Documents
1	Research Protocol V1.0 dated 30th Apr 2018
2	Proposal Questions Sheet
3	Patient Information Sheet
4	Site Specific ICF-Final English Version 1.0 dated 30 Apr 2018

We have reviewed and discussed all the things in the protocol.

We have approved all the documents to the "Pathophysiology of Heart Failure with Preserved Ejection Fraction ."

Sengupta®
Hospital & Research Institute
ETHICS COMMITTEE
Ravinagar Square, Nagpur - 440 033 M.S. ☎: 91-712-2532697, 2536628 Fax : 91-712-2565597
Email : senguptacc@gamil.com

The following members of the Ethics Committee were present during the meeting held on 11 May 2018 at 05:00 PM at Sengupta Hospital & Research Institute Ethics Committee, Ravinagar Square, Nagpur 440033.

During meeting Ethics Committee members decided to give the approval to conduct the above study in its presented form.

Sr. No	Name	Qualification	Affiliation	Role	Gender
1.	Dr. Sanjay Marathe	M.B.B.S, M.D.	Marathe Child Care Hospital, Ramdaspeth, Nagpur	Chairperson	Male
2.	Dr. Prashant Rathi	M.B.B.S, D. Ortho	Sengupta Hospital & Research Institute Ravinagar Square, Nagpur	Member Secretary	Male
3.	Dr. Bhavani Sahay	M.B.B.S, MD (Anaesthesia)	Avanti Heart Institute, Dhantoli, Nagpur	Member Clinician	Female
4.	Dr. Sujata Dudhgaokar	MD(Pharmacology)	Prof. & HOD Dept. Of pharmacology,IGMC College,Nagpur.	Member Basic medical scientist.	Female
5.	Mr. Tejas Deshpande	LLB, LLM	Lawyer & Legal advisor, High Court, Nagpur.	Legal Adviser	Male
6.	Mrs. Shaila Deshpande	MSW	Motion & Narayana Vidyalaya, Nagpur	Social Worker	Female
7.	Mr. Ashish Vinchurkar	XII	Not affiliated with any Institute and patient group	Lay person	Male
8.	Dr. Shashank Bhole	M.B.B.S, MD (Paediatrics)	Chinmay Children & Surgical Hospital, Gokulpeth, Nagpur	Member Clinician	Male
9.	Mr. Shashikant Sahare	M. Pharm	Not affiliated with any Institute and patient group	Member Basic medical scientist	Male

Sengupta®
Hospital & Research Institute
ETHICS COMMITTEE

Ravinagar Square, Nagpur - 440 033 M.S. ☎ : 91-712-2532697, 2536628 Fax : 91-712-2565597
Email : senguptacc@gamil.com

It is also confirmed that neither you nor any of the study team members participated in the voting procedure.

You are expected to report to the Ethics Committee the following :-

- All deviation forms, or changes to the protocol to eliminate immediate hazards to the study subjects.
- Changes that increase the risk to participating subjects and / or those that significantly affect the conduct of the study.
- All serious adverse events.
- New information that may affect adversely the safety of the subjects or the conduct of the study.
- Any changes in the study documents.
- Progress of the study annually.

Please provide a report to the Ethics Committee on completion of the study.

Ethics committee works as per ICH GCP and Local Regulatory Requirement.

Thanking You,

Yours Sincerely,

Research Institute Ethics Committee * Sengupta Hospital & Nagpur

Dr. Sanjay Marathe
Chairman
Sengupta Hospital & Research Institute Ethics Committee
Ravinagar Square, Nagpur- 440033

Sengupta®
Hospital & Research Institute

Ravinagar Square, Nagpur - 440 033 M.S. ☎ : 91-712-2532697, 2536628,02039520396 Fax : 91-712-2565597

To,
The Chairman,
Sengupta Hospital & Research Institute Ethics Committee
Ravinagar Square
Nagpur 440033

Date: 02May2018

Protocol Title: Pathophysiology of Heart Failure with Preserved Ejection Fraction

Subject: Ethics Committee Submission of Study documents for Review & Approval

Dear Sir/Madam,

With reference to the above-mentioned study, kindly find the enclosed 09sets of hard copies of the following documents for your Ethics Committee review and approval

S. No	Study Documents
1	Research Protocol V1.0 dated 30th Apr 2018
2	Proposal Questions Sheet
4	Patient Information Sheet
5	Site Specific ICF-Final EnglishVersion 1.0 dated 30 Apr 2018

Kindly acknowledge the receipt of the above- mentioned documents.

Please let us know should you need further information.

Thanking You,

Dr. Shantanu Sengupta
Sengupta Hospital & Research Institute

Acknowledgement by EC	
Name: DR. PRASHANT B. RATHI	**Date** 02.05.2018
Signature	

Sengupta Hospital & Research Institute Ethics Committee Nagpur