

Aortic Stiffness Across The Heart Failure Continuum

by

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ABSTRACT

Aim: The purpose of this thesis was to examine aortic stiffness across the heart failure (HF) continuum.

Background: Aortic distensibility (AD) decreases with advancing age. In the presence of underlying cardiovascular disease, AD is reduced beyond what which occurs with normal aging. Currently, no study has examined AD in individuals at risk for or with HF.

Methods: 149 subjects were assigned into four different groups: healthy controls (n=37, mean±SD, age: 62±10 ys), at risk of developing HF (n=46, age: 62±11 ys), HFpEF (n=32, age: 69±11 ys), and HFrEF (n=34, age: 65±9 ys). Ascending and descending AD and ventricular vascular coupling (AV) were measured using cardiac magnetic resonance imaging (cMRI).

Results: Descending AD was significantly lower in the at-risk group compared to HFrEF group. No significant difference was found for ascending AD. In addition, HFrEF individuals had significantly impaired ventricular-arterial coupling compared to all other groups.

Conclusion: HFpEF individuals have more marked impairment of arterial compliance, as evidenced by significantly decreased AD compared with controls, with respect to aging. HFrEF individuals had significantly impaired ventricular-arterial coupling, due to impaired systolic function. These findings are clinically important in assessing HF patients and monitoring their arterial stiffness progression. In addition, these findings are important for target therapies that can be beneficial for reversing arterial stiffness in these individuals to improve the outcomes.

DEDICATION

I would like to dedicate this work to my parents, Rajender Kumar and Prem Lata. Thank you for all the support and strength you have given to me and motivate me in my all good and bad days.

I would especially thank my siblings, Lokesh and Dimple, who supported and encouraged me to complete this task with diligence.

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CHAPTER ONE

INTRODUCTION

1.1 INTRODUCTION

Heart failure (HF) is a clinical syndrome whereby the heart is unable to pump sufficient amount of blood to meet the demands of the metabolically active tissues, or does so with increased left ventricular (LV) filling pressures [1]. The hallmark feature of HF is severe exercise intolerance, which can be measured objectively as peak exercise oxygen uptake (peak VO_2) [2]. In Canada, 500,000 individuals are living with HF and 50,000 new cases are diagnosed each year [3]. The average annual mortality rate of HF has an ominous prognosis of 10% per year with a 50% of five-year survival [3].

Population-based studies have shown that more than 50% of HF patients have preserved LV ejection fraction, coined HF with preserved ejection fraction or HFpEF, and the proportion is greatest among elderly, women and those with hypertension [4, 5]. Impaired central aortic stiffness, as measured by decreased aortic distensibility (AD) and associated increased LV afterload accelerate the development of HF [6]. Moreover, impaired ventricular-arterial coupling may result in worsening of HF symptoms [6-11].

In patients with HF with reduced ejection fraction (HFrEF), impaired vascular (endothelial) function is due, in part, to neurohormonal and inflammatory activation [12-15], however, the association of endothelial dysfunction in HFpEF has not been reported [6]. The pathophysiological mechanisms for HFpEF have not been well characterized, and currently there are no proven effective therapies that improve outcomes in this group. One factor that may contribute in pathophysiology of HFpEF is impaired ventricular-arterial coupling, because of the

stiffness of both the systems. However, the relation between aortic compliance and LV dysfunctions has not been well established [16].

1.2 STATEMENT OF THE PROBLEM AND PURPOSE OF THE THESIS

A limitation of the prior investigations was the primary focus on AD in HFpEF or HFrEF patients compared to age-matched healthy individuals, however no study has compared ascending and descending AD across the HF continuum (i.e. healthy subjects, individuals at risk of HF, or with established HFrEF or HFpEF). Moreover, uncertainty regarding ventricular-arterial coupling across the HF continuum has not been studied. Accordingly, the primary purpose of this thesis is to investigate the difference in AD in healthy subjects, individuals at risk for HF, or established HFpEF and HFrEF. A secondary purpose is to compare ventricular-arterial coupling across the HF continuum.

1.3 HYPOTHESES

The primary hypothesis is that ascending and descending AD is significantly reduced in individuals at risk for HF compared to healthy individuals, and reduced in HFrEF compared to all other groups. Secondary hypothesis is that ventricular-arterial coupling is significantly impaired in individuals at risk for HF compared to healthy individuals, and reduced in HFrEF compared to all other groups.

1.4 SIGNIFICANCE OF THIS STUDY

A novel aspect of this study is that it will determine AD and ventricular-arterial coupling across the HF continuum. These findings will determine if abnormalities in vascular and ventricular-arterial coupling are an important aspect in individuals at risk for or with HFpEF.

1.5 DEFINITION OF TERMS

Aortic Distensibility (AD): Ability of an artery to expand during systole, and defined as the relative change in cross-sectional area of an artery (strain) divided by the local pulse pressure. [17]

End Systolic Pressure (ESP): ESP is the left ventricular (LV) pressure at the end of systole, and it is calculated by systolic blood pressure (SBP) into 0.9. [18]

End Systolic Volume (ESV): ESV is the LV volume at the end of systole. [18]

Effective arterial elastance (E_A): A measure of net arterial load which is imposed on the LV, and calculated as ESP divided by stroke volume. [18]

End-systolic elastance (E_{LV}): A measure of left ventricular elasticity, and calculated as ESP divided by ESV. [18]

Ventricular-arterial coupling (E_A/E_{LV}): Interaction between LV and arterial system termed, and calculated as the ratio of E_A and E_{LV} [18]

Pulse pressure (PP): The difference between systolic and diastolic blood pressure.

CHAPTER TWO

REVIEW OF THE LITERATURE

This section reviews the literature related to the pathophysiology of HFpEF and HFrEF and deleterious effect of increased aortic stiffness and underlying mechanisms responsible in healthy aging and individuals at risk of developing HF and in HF patients.

2.1 PATHOPHYSIOLOGY OF HF

HF is a complex clinical syndrome characterized by structural or functional impairment of ventricular filling or ejection that results in an inability to deliver oxygen and nutrients to the metabolically active tissues. [19]. HF phenotypes include concentric hypertrophy (increased LV wall thickness and mass) and preserved EF or eccentric hypertrophy (increased LV cavity size and mass) with markedly reduced EF [19] (Figure: 2.1). In accordance with the Laplace Law, the tension in the LV wall is directly proportional to the pressure and chamber radius and inversely proportional to the wall thickness and the increased LV diastolic cavity size is associated with greater LV diastolic wall stress [20]. In contrast, the increased LV wall thickness reduces LV wall stress in HFpEF patients.

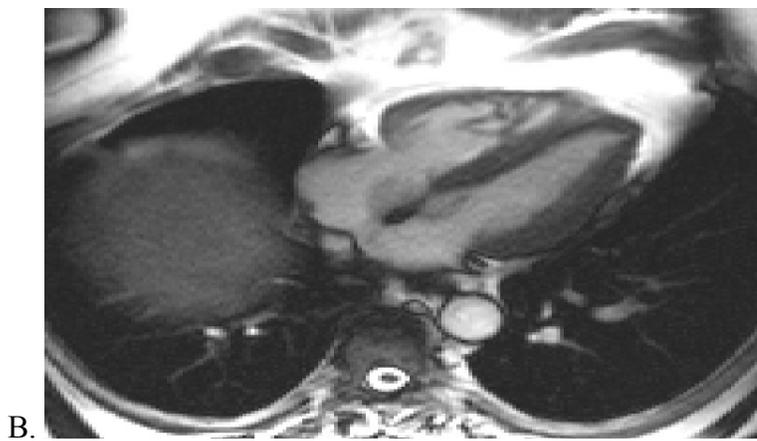
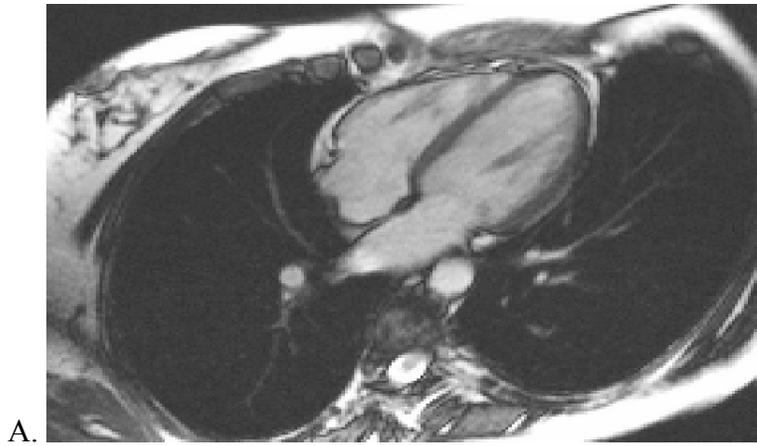


Figure 2.1. Four chamber view of the heart from a normal heart (A), HFpEF (B) and HFrEF (C).

2.2 ASCENDING AND DESCENDING AORTIC MORPHOLOGY

The aorta is composed of the intima (thin inner layer), media (thick middle layer) and adventitia (outer layer). The strongest layer of the aorta is media, which is composed of the elastic component arranged in a spiral manner that affords maximum tensile strength. The elastic property of aorta media withstands the marked increases in pressure without bursting [21]. In contrast to this aortic media, the peripheral arteries contain relatively little smooth muscle and collagen in between the elastic layers. Accordingly, the elastic property of aorta not only gives strength but also distensibility, which provides a vital circulating role [21].

The aorta is divided into thoracic and abdominal components. The thoracic aorta is further divided into ascending aorta and descending aorta. The ascending aorta is 5 cm long, and has two distinct parts, the lower segment (aortic root) and the upper segment [21]. The lower segment of the ascending aorta is aortic root, which starts at the level of aortic valve. The upper segment of ascending aorta joins the aortic arch (left and right coronary arteries and subclavian arteries arise from aortic arch). Distally descending aorta joins aortic arch and the point at which these components join called the aortic isthmus [21].

2.3 AGING AND IMPAIRED ARTERIAL STIFFNESS

Aging is associated with metabolic, structural and functional changes in the large arteries and micro vascular system [22, 23]. Arterial stiffness is an independent risk factor for CV disease [24-26]. Proximal aortic stiffness is the earliest manifestation of vascular aging and leads to structural and functional changes of the aortic wall resulting in increased aortic wall stress. Further, this increased wall stress change leads to the geometric and functional alteration to the aortic arch [17].

It has been shown that with the advancing age the aortic diameter increases and is associated with increased arterial stiffness [27] (Figure 2.2). Redheuil et al demonstrated that alterations in proximal aortic geometry (change in length and width of the aorta) was associated with increased LV mass and remodeling in healthy older (>70 years) individuals [28]. Moreover, increased central pressure was related with decreased AD [28]. From previous studies based on AD, a systematic review was performed and reveals that, in healthy individuals, AD decreases with age, and this decline becomes evident in the fifth decade of life (Table 2.1, Figure 2.3).

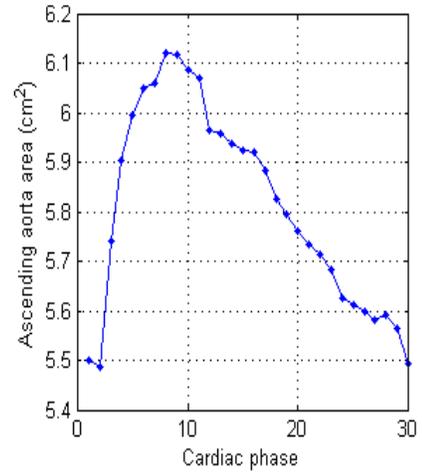
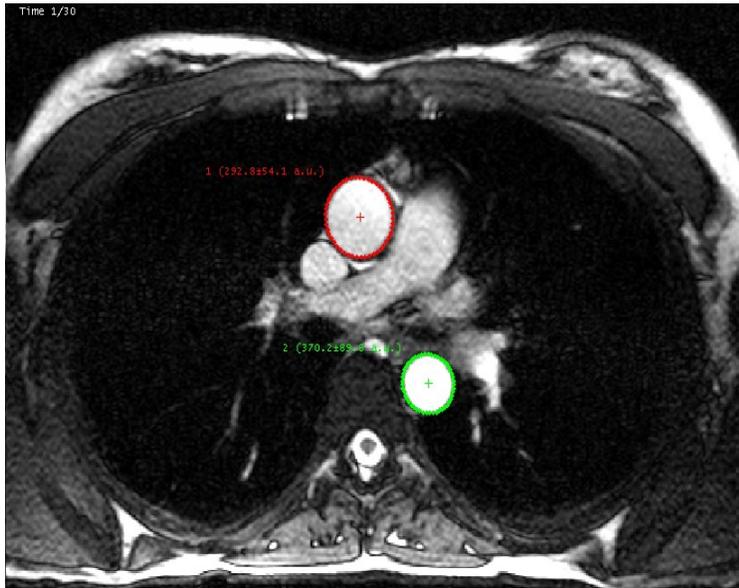
Age-related arterial changes also occur in the aortic media. The aorta is subject to constant pulsatile stress, which over the time affects the elastic component of aortic media fragment and eventually broken down fragments partially replaced by fibrotic non-elastic tissue [29]. These histological changes in the aorta lead to stiffening of the aortic wall and increased mean aortic blood pressure and finally transverse dilatation of the aorta [30].

Aging is also associated with alterations in LV mass that is associated with poor cardiovascular outcomes [29] (Table 2.1). A consequence of arterial-stiffening is that it results in a higher and late systolic load resulting in increased LV remodeling [18]. The interaction between LV and arterial vascular function can be measured as the ratio of effective arterial elastance (E_A) and end systolic elastance ratio E_{LV} (E_A/E_{LV}). E_A is a measure of the net arterial load exerted by the LV whereas E_{LV} is a measure of LV chamber stiffness and contractility[31]. Various studies have documented a gradual increase in E_A with aging [10, 32]. The specific mechanism for increased E_A with age reflects the age-associated changes in the arterial properties [31]. Indeed, Franklin et al demonstrated the arterial stiffening and blood pulsatility alters E_A , which increases with advancing age and thus these changes lead to increase the end systolic pressure required to eject blood thereby increasing arterial load [32]. Alterations in E_A

lead to adaptive changes in the heart by increasing in E_{LV} [11]. Redfield et al. suggested that E_{LV} increases to compensate for the increase in E_A to maintain the E_A/E_{LV} ratio in order to maintain maximal efficiency at rest [10].

An ‘age related’ alteration in vascular function is an important determinant of morbidity and mortality [33, 34]. Recent research suggests that alterations in vascular structural matrix proteins, mitochondrial bioenergetics and cell senescence occur in the third decade of the healthy individuals [27, 35]. Alterations in vascular smooth muscle tone is a key determinant of arterial stiffness, which is associated with stiffening of the large central elastic arteries resulting in increased pulse wave velocity (PWV) with aging [36] (Table 2.1). The reason for decreased AD and increased PWV could be the result of oxidative stress and nitric oxide (smooth muscle relaxant) which modulate vascular smooth muscle cell and arterial stiffness[37]. Sindler et al. reported, short term supplementation of nitrite improved nitric oxide bioavailability and decrease oxidative stress, resulting reverse age-related large elastic artery stiffness[30].

A.



B.

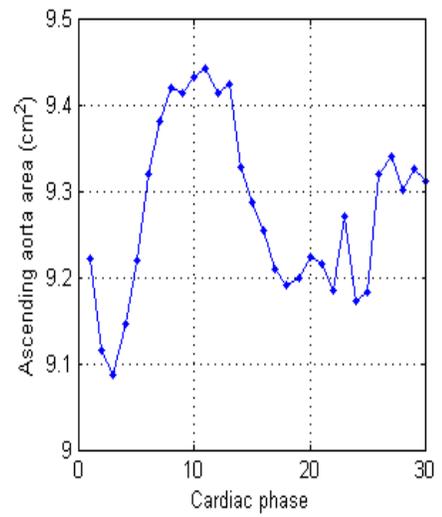
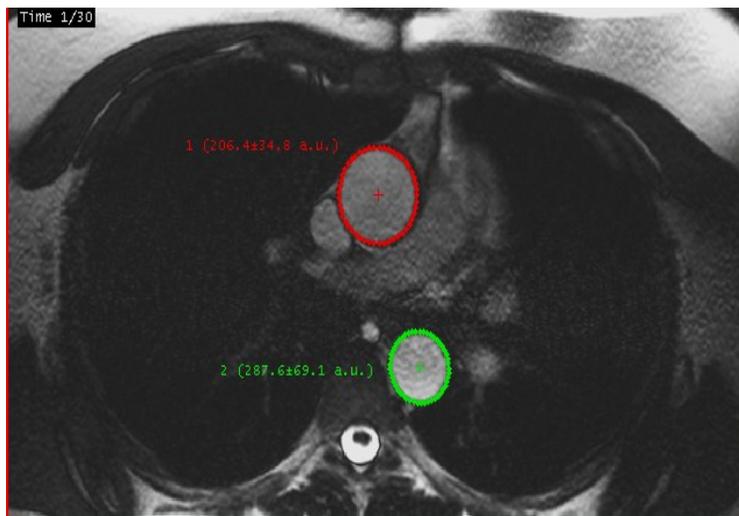


Figure 2.2. Transverse section view of an ascending and descending aorta and change in the area of aorta during the cardiac cycle in a normal aorta (A) and a dilated aorta (B).

Table 2.1: Summary of previous studies which demonstrated aortic distensibility (AD) and, pulse wave velocity (PWV) in healthy populations.

	(20-30years)	(30-40years)	(40-50years)	(50-60years)	(60-70years)
No. of Studies	4	4	8	4	6
Mean Age(years)	24 ± 2	38± 2	46 ± 2	54± 4	67 ±3
Height (cm)	173 ± 5	168 ± 0	168 ± 3	166 ± 0	168 ± 1
Weight (Kg)	73 + 2	68 ± 0	70 ± 6	65 ± 0	77 ± 8
BMI (kg/m ²)	24 ± 1	24 ± 0	26 ± 2	26 ± 2	27 ± 2
SBP (mmHG)	116 ± 4	110 ± 14	119 ± 7	116± 2	127 ±8
DBP (mmHG)	71 ± 2	69 ± 8	72 ± 5	72 ± 3	72 ± 4
PP (mmHG)	50 ± 4	35 ± 0	47 ± 5	43 ± 4	56 ± 8
LVEF (%)	63 ± 0	64 ± 2	67 ± 6	64 ± 1	66 ±3
HR (beats/m)	70 ± 1	–	72 ± 7	74 ± 7	72 ±21
AD (10 ⁻³ mmhg ⁻¹)	4.6± 2	4.5 ± 1	4.4 ± 1	2.8 ± 0	1.7 ± 0
PWV (m/s)	7 ± 1	6 ± 2	8 ± 2	9 ± 0	10 ± 2
Peak Vo ₂ (ml/min/kg)	29 + 2	–	–	–	20 ± 0
LVMI (g/m ²)	66 ± 4	67 ± 5	76 ± 9	93 ± 11	73 ± 7

Data are expressed as mean ± S.D. BMI, body mass index,; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; AD; aortic distensibility; LVMI; left ventricular mass index.

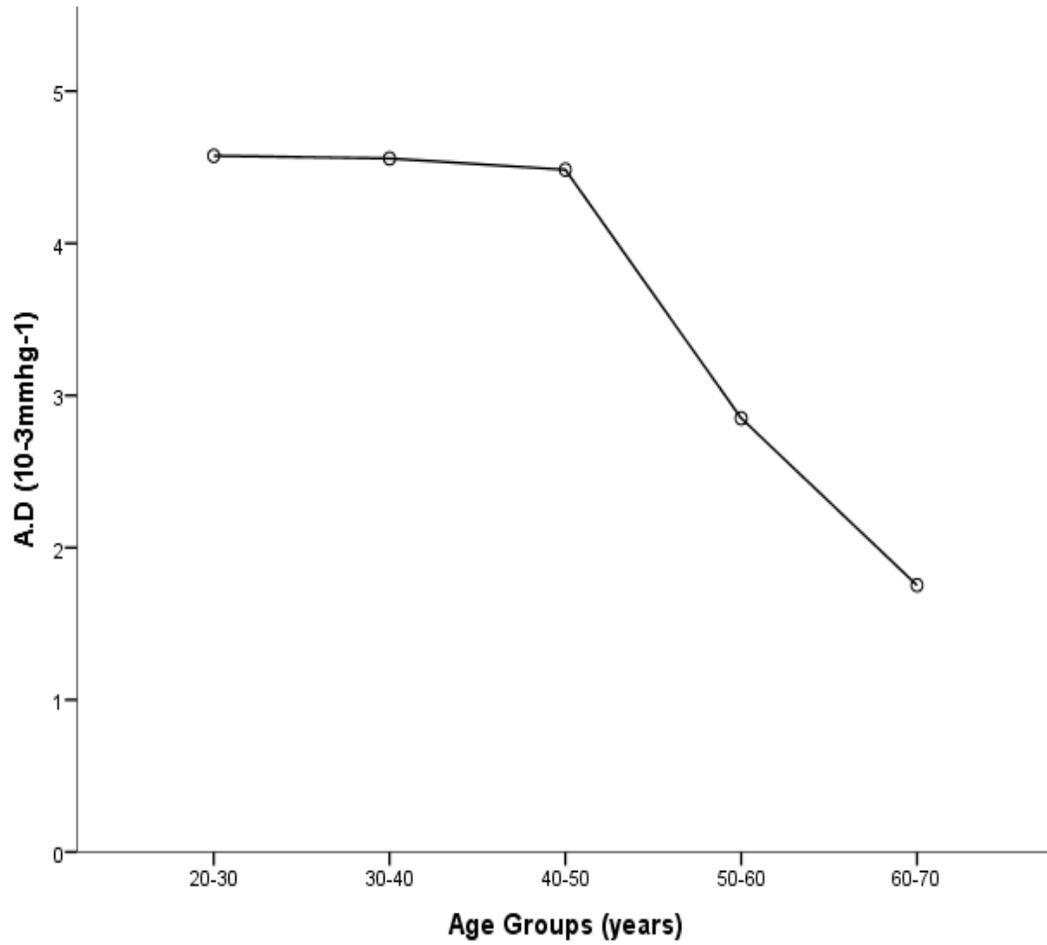


Figure 2.3: Relationship between aortic distensibility and different age groups, in healthy controls.

2.4 AORTIC COMPLIANCE IN INDIVIDUALS AT RISK FOR DEVELOPING HF

Hypertension (HT) is a recognized cardiovascular risk factor characterized by an elevated blood pressure (>140/40 mm/Hg) and affects 30% of the adult population [38]. The elastic properties of major arteries play an important role in maintaining the hemodynamic balance of blood pressure [39-41]. Arterial stiffness is an important factor that causes the hemodynamic alterations that result in increases cardiovascular morbidity and mortality [42]. Epidemiologic studies have shown that increased aortic stiffness is an independent factor of developing atherosclerosis, stroke and cardiovascular mortality in patients with HT [43-45].

In HT patients, as a result of pressure and volume loading various forms of LV remodeling may develop [46, 47]. Kadi et al. reported that LV mass index was significantly increased in HT patients versus age-matched healthy controls [48]. Findings from the Cardiovascular Health Study (CHS) also demonstrated that increased LVM and wall thickness are major risk factors for HF[49]. Raghava et al. found that HT individuals with increased LV mass index also had a greater HF risk [20]. Table 2.2, shows that LV mass index is higher in individuals at risk for developing HF compared to healthy age-matched healthy people. The major pathophysiological mechanism for HT hypertrophy and increased LV mass index are myocyte fibrosis and the accumulation of type I and III collagen in the myocardium. In these patients LV hypertrophy develops in a response to increased pressure load and elevated LV wall stress [50, 51].

In these individuals, endothelial dysfunction is an initial event of vascular disease, which is a critical, potentially reversible stage in the progression of HT and is highly valuable in predicting cardiovascular events [52]. The vascular function properties can be measured by AD

and PWV, which reflects the stiffness of aorta [53]. LV diastolic and systolic function can be influenced by impaired AD and an elevated PWV [54-56]. Many studies have demonstrated that in HT individual's aortic strain and AD are lower, and PWV is higher compared to the age-matched healthy individuals [17, 54, 57] [33]. Table 2.2 (Figure 2.4 and 2.5), reveals that AD is lower compared to healthy aged-matched individuals.

2.5 AORTIC COMPLIANCE IN PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION

Raghava et al. demonstrated that LV hypertrophy was associated with increased HF risk [20]. They suggested after the onset of HF, participants with eccentric hypertrophy are more likely to develop HFrEF, whereas participants presenting concentric hypertrophy were at higher risk for HFpEF [20]. According to the Laplace Law, the LV wall stress is directly proportional to the pressure and chamber radius and inversely proportional to the wall thickness [20]. In the case of dilated LV, a greater amount of tension must be developed in the wall to generate the forward flow compared to the normal ventricle, which is compensated by increased LV wall thickness in proportion to the increased chamber diameter. Similarly in HFrEF, to maintain the Laplace equation, LV wall thickness does not increase in proportion to LV dilatation in eccentric hypertrophy, hence this hypertrophy is likely associated with greater wall stress [20].

The vascular endothelium is responsible for maintaining normal vessels tone, and function hence it regulates the ventricular arterial coupling[58]. Vascular endothelial dysfunction has been well documented, and several mechanisms responsible behind this have been investigated [24, 59-61]. The potential mechanism for endothelial dysfunction in HFrEF is the oxidative stress, which leads to the generation of reactive oxygen species and inactivation of

nitric oxide, which is a potent key factor for maintaining the vascular tone[62]. There are significant evidences that suggest, oxidative stress plays an important role in the development of the pathophysiological process that initiates the arterial dysfunctions in HFpEF [63, 64].

Several other potential mechanisms are also responsible for the impaired endothelial function. First, alteration in the neurohormones in HF individuals. Neurohormonal alteration causes the activation of renin angiotensin system and increases the plasma norepinephrine which may cause the vasoconstriction and sodium retention [65, 66]. Second, excess of angiotensin II on smooth muscles cell of vessels results in structural changes on wall and effects the vasodilation properties of the artery including proliferation of smooth muscle cells. Finally, these vascular changes have been associated with impaired aortic elastic properties [67, 68].

2.6 AORTIC COMPLIANCE IN PATIENTS WITH HEART FAILURE AND PRESERVED EJECTION FRACTION

Increase in ventricular–arterial stiffness is related with aging and HT, and have been correlated in the pathogenesis of HF [17, 69]. In HT individuals increased PWV, and decreased AD in late systole correlated with increased left atrial volume and LV mass, which are associated with impaired myocardial relaxation capacity, which considered as sensitive measure of diastolic dysfunction [69]. However, HFpEF are distinguished on the basis of cardiac structure and function with more pronounced abnormalities of active myocardial relaxation and passive diastolic stiffness, LV mass and left atrial remodeling [70, 71]. HFpEF patients may have a progressive increase in stiffness of the proximal aorta. The changes in central and peripheral conduit vessels occur with the progression from healthy to HT to HFpEF [72].

Mitchell et al. demonstrated that HFpEF patients were associated with elevation of PWV and has long been accepted as a potential marker of arterial compliance and vascular remodeling[36]. In addition to it, PP has been reported greater than HFrEF individuals. Altogether PWV and PP were elevated in this population, compared to healthy aging, HT and HFrEF group, implying that HFpEF is indeed associated with greater impairment of arterial compliance[73].

With severity of disease AD was severely affected in HF individuals. A review of the literature reveals that AD in HF patients is significantly lower than age-matched healthy and hypertensive individuals. Moreover, pulse pressure is increased to a greater extent in HFpEF versus HFrEF, a finding which may indicate that former may have greater impairment in arterial compliance which supports the prior work by Mitchell and associates.

Table 2.2: Summary of previous studies which demonstrated aortic distensibility (AD) and, pulse wave velocity (PWV) in healthy population, at-risk, HFpEF and HFrEF.

	Controls	At-risk	HFpEF	HFrEF
No. of Studies	33	20	12	7
Age (years)	49 ± 15	55 ± 5	68 ± 4	66 ± 6
Gender (m/f)%	55/45	51/49	43/57	71/29
Height (cms)	169 ± 3	166 ± 9	163 ± 2	165 ± 1
Weight (Kg)	73 ± 6	73 ± 9	80 ± 10	71 ± 4
BMI (kg/m ²)	26 ± 2	27 ± 3	31 ± 4	26 ± 1
SBP (mmHG)	120 ± 9	141 ± 11	143 ± 9	128 ± 5
DBP (mmHG)	72 ± 4	85 ± 11	75 ± 6	75 ± 6
PP (mmHG)	49 ± 8	57 ± 9	67 ± 14	52 ± 6
EF (%)	65 ± 3	65 ± 5	64 ± 5	28 ± 6
HR (beats/m)	72 ± 13	71 ± 5	87 ± 31	73 ± 7
AD (10 ⁻³ mmhg ⁻¹)	3.6 ± 1.7	1.9 ± 0.7	0.99 ± 0.31	0.33 ± 0.24
PWV (m/s)	8 ± 2	11 ± 3	12 ± 4	11 ± 3
Peak VO2 (ml/min/kg)	24 ± 5	NR	14 ± 1	11 ± 0.0
LVMI (g/m ²)	78 ± 19	117 ± 26	103 ± 31	124 ± 13

Data are expressed as mean ± S.D. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; AD; aortic distensibility; LVMI; left ventricular mass index.

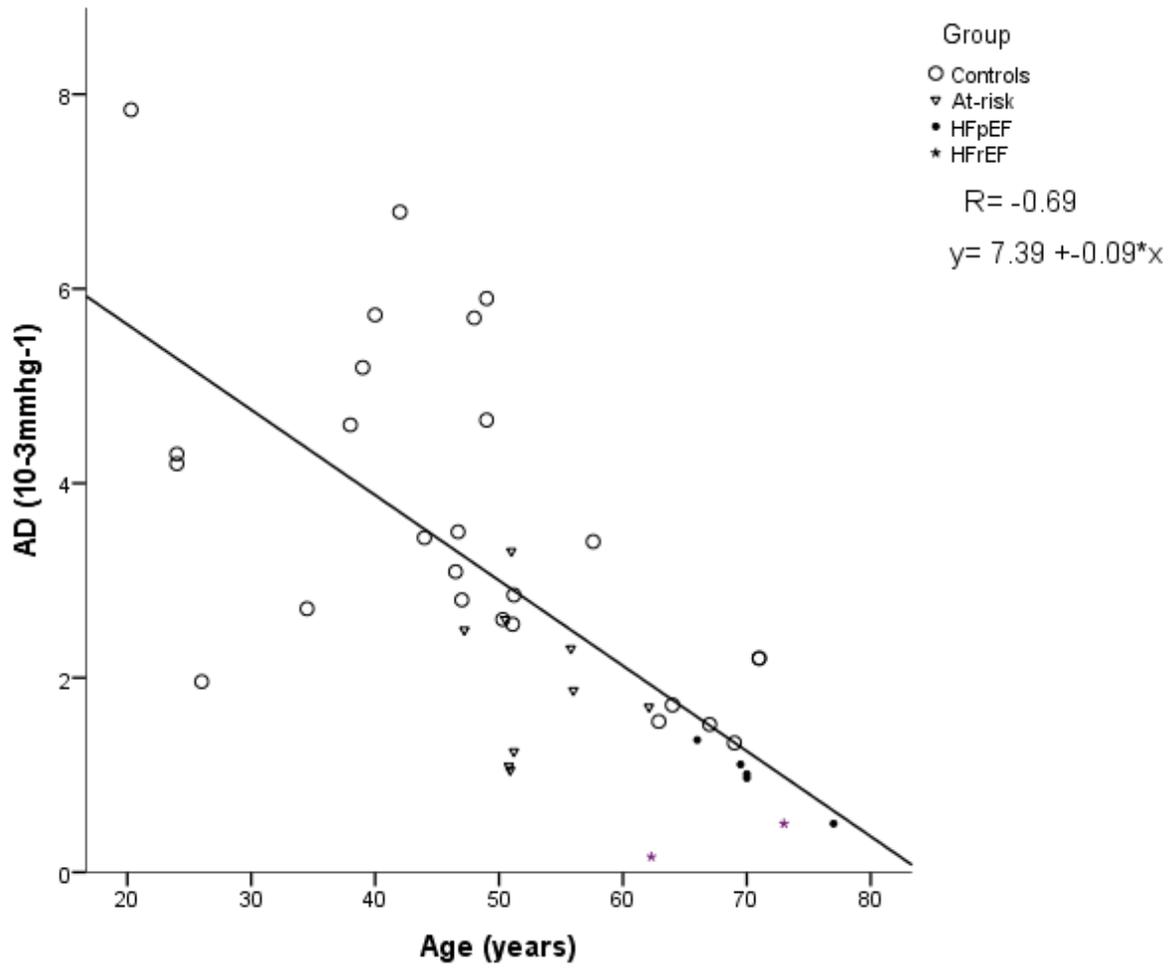


Figure 2.4: Relationship between aortic distensibility and age in healthy controls, at-risk, HFREF and HFpEF subjects.

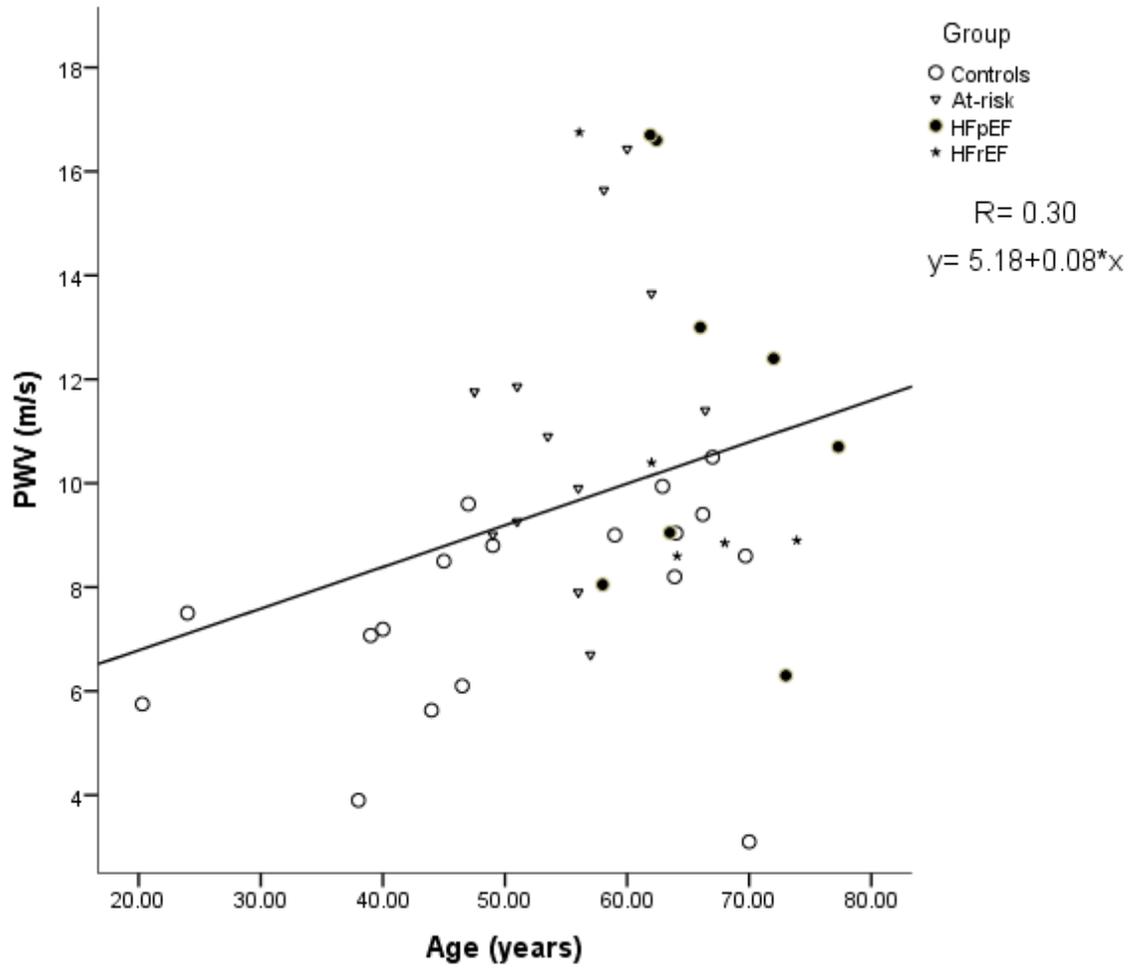


Figure 2.5: Relationship between pulse wave velocity and age in healthy controls, at-risk, HFREF and HFpEF subjects.

2.7 SUMMARY

In summary, in HF patients arterial stiffness is increased with age and progresses with time. Moreover, in individuals with CVD risk factors, increased aortic stiffness and LV afterload, which leads to further ventricular remodeling that, may result in HF. This suggests the arterial vasculature may be an important target of therapy for individuals at risk for or with established HF.

CHAPTER THREE

METHODS

3.1 SUBJECTS

The subjects for the study were recruited from the Alberta Heart Study who were > 18 years of age (Edmonton cohort). The recruitment began in January 2010, and as of March 31, 2014, 649 patients were enrolled [74]. However 149 subjects were selected for this study that had full AD data. All subjects were assigned ‘a priori’ into the following groups:

1. **Healthy Control:** Individuals with no evidence of coronary artery disease, hypertension, diabetes mellitus, no evidence of inflammatory or autoimmune conditions, and not prescribed cardiac medications.
2. **High-risk of developing HF:** These subjects had one or more of the following: hypertension (≥ 3 medications or LVH on ECG or LV mass index greater than gender-matched upper normal limit on an imaging test); diabetes; atrial fibrillation; or obesity (body mass index > 30). These subjects were asymptomatic (no dyspnea or fatigue) and had no known prior HF. Patients with underlying cardiovascular disease included including atrial fibrillation, chronic coronary artery disease (including those with a recent acute coronary syndrome > 2 weeks prior), or chronic obstructive pulmonary disease were also included.
3. **Patients with known HF-PEF:** Patients diagnosed with HF-PEF based on the clinical phenotype of symptoms consistent with HF and an ejection fraction $> 50\%$ were included in this group.
4. **Patients with known HF-REF:** Patients diagnosed with HF based on clinical phenotype

and EF <50% were included in this group.

Control patients were recruited through referrals from patients, clinicians and the broader community via public advertising, media events and other public engagements. All patients signed informed consent, and the study was approved by the Health Research Ethics Board at the University of Alberta. After consent, patients were enrolled and undergone comprehensive clinical, quality of life and imaging assessments. Data was managed on the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease platform.

3.2 EXCLUSION CRITERIA

Study exclusion criteria were: 1) Age <18 years; 2) Known malignancy with expected survival <1 year; 3) Pregnant or recent pregnancy <6 months; Recent event (<2 weeks since Acute Coronary Syndrome, Heart failure or other admissions); 4) Severe mitral or aortic stenosis; 5) Severe pulmonary hypertension (>60mmHg).

3.3 BASELINE ASSESSMENT

All baseline assessments were performed at the Alberta Cardiovascular and Stroke Research Centre (ABACUS) at the Mazankowski Alberta Heart Institute, University of Alberta. Subjects underwent the following imaging assessment using cardiac MRI (cMRI). Blood pressure was taken during the time of cMRI in lying position. (**Appendix A and B**)

3.4 OUTCOME MEASURES

Left ventricular volumes and AD: cMRI assessment of LV volumes and AD was performed using a 1.5-T magnetic resonance scanner. Images were acquired in supine using 12-element phased array coil. Cardiac images were acquired from base to apex, with multislice,

multiphase gradient echo technique which provides a measurement of LV systolic and diastolic volumes and EF. Aortic distensibility was measured by acquiring images at the ascending aorta (**Amax**) and descending aorta (**Amin**). Aortic distensibility was calculated as:

AD = Amax-Amin / (Amin×ΔP), where

Amax and Amin are the difference between ascending and descending aorta luminal area (Amax at the time of full opening and Amin during R wave), and PP is the difference of systolic and diastolic blood pressure, during the cardiac cycle[16] .

Ventricular- arterial coupling (E_A/E_{LV}) - E_A is a measure of net arterial load that is imposed on the LV and it was calculated by the end systolic pressure (ESP) divided by stroke volume (SV) [18]. ESP estimated from the formula ($0.9 \times SBP$) [18]. Where, E_{LV} is a measure of left ventricular contractility and it was calculated as ESP/End systolic volume (ESV) [18]. Thereby, E_A/E_{LV} was calculated as:

$$ESP = 0.9 \times \text{Systolic BP}$$

$$E_A = ESP/SV$$

$$E_{LV} = ESP/ESV$$

$$E_A/E_{LV} = ESV/SV$$

3.5 SAMPLE SIZE CALCULATION

The sample size for this study was calculated based on data from Kitzman et al. who assessed arterial stiffness in HFpEF patients compared with older healthy individuals [75]. Based on these findings, a difference between these groups for AD between groups was $0.36 \times 10^{-3} \text{mmHg}^{-1}$ with a standard deviation of $0.45 \times 10^{-3} \text{mmHg}^{-1}$. Using an alpha level of 0.05, beta of 80%, and a two-tail test, a sample size required for each group was 25 subjects. The sample size

used to compare the at-risk and healthy groups was calculated based on the data from Nar.G et al. [76]. Based on these findings, if the expected between group AD difference of $3.97 \times \text{Cm}^2 \times \text{dyn}^{-1} \times 10^{-6}$ (SD= $2.13 \times \text{Cm}^2 \times \text{dyn}^{-1} \times 10^{-6}$) with an alpha of 0.05 and beta of 80%, using a two tail test, then a sample size required for each group was 5 subjects in each group. **(Appendix D)**

3.6 STATISTICAL ANALYSIS

Statistical analysis was performed by using SPSS 15.0. Data was expressed as mean \pm SD. One-way analysis of variance (ANOVA) was done for mean comparisons of age and BSA between the groups. Gender distribution between the groups was compared using Chi-square statistics. For the primary and secondary outcomes, analysis of covariance (ANCOVA) was used for mean comparisons while adjusting for age, BSA and gender. Post-hoc comparisons were done using a Bonferroni test.

CHAPTER FOUR

RESULTS

4.1 SUBJECTS

One hundred forty nine subjects were recruited from Alberta Heart study (Edmonton cohort) with full AD data (Table 4.1).

4.2 SUBJECT CHARACTERISTICS

The HFpEF subjects were significantly older than healthy controls and at-risk subjects (Table 4.1). No significant difference was found between HF groups for age. A higher percentage of men was found in the HFrEF group (67.6%) compared to healthy controls (29.7%), at-risk group (58.7) and HFpEF group (43.8%). Body mass, BMI and BSA were also significantly higher in the at-risk, HFpEF and HFrEF groups compared to healthy controls. (Table 4.1)

Hypertension was present in 87%, 75%, and 67.6% of the at-risk, HFpEF and HFrEF groups, respectively. While coronary artery disease was present in 14%, 12%, and 6% of the HFrEF, at risk, and HFpEF groups, respectively. Diabetes was present in 28% of the at risk group, 32% of HFrEF and 34% HFpEF subjects. Finally, Table 4.1 shows the medication use of the study subjects.

4.3 HEMODYNAMIC VARIABLES

All hemodynamic variables were adjusted for age, gender and BSA. A significant difference was found between groups for SBP, PP, LVM and LVEF (Table 4.2). Systolic blood pressure was significantly lower in HFrEF (115 ± 20 mmHg) versus healthy controls (126 ± 19

mmHg) and at-risk subjects (128 ± 17 mmHg) groups. Left ventricular mass was significantly increased while LVEF was significantly reduced in HF_rEF subjects compared to all other groups (Table 4.2, Figures 4.1 and 4.2). Heart rate and DBP were not significantly different between groups (Table 4.2)

4.4 ASCENDING AND DESCENDING AORTIC DISTENSIBILITY

Maximal ascending aorta (A_{max}) and minimal ascending aorta (A_{min}) area and ascending AD were not significantly different between groups (Table 4.3, Figure 4.3).

As shown in Figure 4.4, ascending AD was negatively correlated with age ($r = -0.73$, $p < 0.01$). Ascending AD in all groups were negatively correlated with age, however the correlation coefficient was higher in the at-risk group ($r = -0.85$). Moreover, compared to controls, the change in ascending AD with age was significantly lower in the HF_pEF group (Figure 4.5). Finally, in HF patients (HF_pEF + HF_rEF groups), ascending AD was correlated with LVEF ($r = -0.30$, $P < 0.017$) (Figure 4.6).

Maximal descending aorta (D_{max}) and minimal descending aorta (D_{min}) area was not significantly different between groups. Descending AD was significantly higher in HF_rEF compared to at-risk group (Table 4.3, Figure 4.7).

Descending AD was negatively correlated with age ($r = -0.62$, $p < 0.01$, Figure 4.8); however, the correlation coefficient was higher in the at-risk group ($r = -0.78$). Further, compared to controls, the change in descending AD with age was not significantly different in the at-risk, HF_pEF and HF_rEF groups ($P > 0.05$, Figure 4.9). Finally, in HF patients, descending AD is weakly correlated with LVEF ($r = -0.22$, $P < 0.08$) (Figure 4.10).

The coefficient of variation of ascending and descending AD were 8.81% and 7.94% respectively. Similarly the coefficient of variation of maximum and minimum area of ascending aorta during the cardiac cycle were, 0.60% and 0.52% respectively. In addition, coefficient of variation of maximum and minimum area of descending aorta during the cardiac cycle were, 1.83% and 1.71% respectively.

4.5 VENTRICULAR-ARTERIAL COUPLING

Ventricular-arterial coupling across the groups is shown in Table 4.4. End systolic pressure (ESP) was significantly lower in HFrEF (112 ± 17 mmHg) compared to the at-risk group (ESP 122 ± 15 mmHg and [HFrEF] $p < 0.05$). Similarly, E_{LV} was significantly lower in HFrEF group compared to healthy controls, at-risk and HFpEF group (Table 4.4). E_A/E_{LV} ratio was significantly higher in HFrEF group compared to healthy controls, at-risk and HFpEF group (E_A/E_{LV} [healthy controls: 0.60 ± 0.13], [at-risk: 0.64 ± 0.27], [HFpEF: 0.68 ± 0.16] and [HFrEF: 2.39 ± 1.46], $P < 0.05$), (Table 4.4, Figure 4.11 and 4.12). A weak negative correlation was found between E_A/E_{LV} and age, among groups. Compared to controls, the change in E_A/E_{LV} with age was significantly higher in HFrEF group ($p = 0.02$) (Figure 4.12). Finally, arterial elastance (E_A) was not significantly different among groups.

Table 4.1 *Subject Characteristics.*

VARIABLES	CONTROL (n=37)	AT RISK (n= 46)	HFPEF (n=32)	HFREF (n=34)	P-VALUE
Demographics					
Age (years)	62 ± 10	62 ± 11	69 ± 11 ^{*^}	65 ± 9	0.016
Gender [M/F,M%]	11/26 (29.7)	27/19 (58.7)	14/18 (43.8)	23/11 (67.6)	0.007
Height (cm)	167± 8	171 ± 13	169 ± 10	171 ± 9	0.306
Weight (Kg)	69 ± 13	83 ± 17 [*]	88 ± 16 [*]	89 ± 19 [*]	<0.001
BMI (kg/m ²)	25 ± 4	29 ± 5 [*]	31 ± 5 [*]	31 ± 6 [*]	<0.001
BSA (m ²)	1.77 ± 0.18	1.95 ± 0.23 [*]	1.98 ± 0.22 [*]	2.00 ± 0.23 [*]	<0.001
Medical History					
Heart Failure	–	–	32 (100)	34 (100)	
CAD	–	12 (26.1)	6 (18.8)	14 (41.2)	
Hypertension	–	40 (87.0)	24 (75)	23 (67.6)	
Dyslipidemia	2 (5.4)	27 (58.7)	21 (65.6)	24 (70.6)	
Diabetes	–	13 (28.2)	11 (34.4)	11 (32.4)	
Renal insufficiency	–	1 (2.2)	3 (9.4)	5 (14.7)	
COPD	–	3 (6.5)	9 (28.1)	7 (20.6)	
Smoking hx					
Current	2 (5.4)	8 (17.4)	5 (15.6)	4 (11.8)	
Former	1 (2.7)	12 (26.1)	9 (28.1)	20 (58.8)	
Never	33 (89.2)	24 (52.2)	16 (50)	10(29.4)	
PVD	–	–	1 (3.1)	1 (2.9)	
Medication					

Antiarrhythmic	–	1 (2.2)	1 (3.1)	–
ACEI	–	24 (52.2)	18 (56.3)	21(61.8)
ARB	–	14 (30.4)	7 (21.9)	8 (23.5)
ASA	1 (2.7)	10 (21.7)	14 (43.8)	20(58.8)
anticoagulants	–	6 (13)	13 (40.6)	12 (35.3)
BB	1 (2.7)	18 (39.1)	22 (68.7)	31(88.8)
CCB	–	11 (23.9)	12 (37.5)	3(8.8)
Digoxin	–	2 (4.3)	4 (12.5)	1 (2.9)
Diuretic	–	6 (13)	19 (59.4)	24 (70.6)
Spironolactone	–	2 (4.3)	2 (6.3)	13 (38.2)
Thiazide	1 (2.7)	15 (32.6)	1 (3.1)	2 (5.9)
Statin	3 (8.1)	25 (54.3)	18 (56.3)	22 (64.7)
Nitro patch or spray	–	1 (2.2)	3 (9.4)	8 (23.5)
Antiplatelet	–	4 (8.7)	3 (9.4)	1 (2.9)
Diabetes therapy	–	12 (26.1)	9 (28.1)	9 (26.5)

Data are expressed as mean \pm S.D except medical history and medication, where the values are presented as frequency and percentage count. At-risk, patients are at risk of developing heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; n, number of participants; BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary diseases; PVD, peripheral vascular diseases; CAD, coronary artery disease; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers;ASA, acetyl salicylic acid; BB, beta blockers ;CCB, calcium channel blockers; * P-value <0.05 vs. Control; ^ P-value <0.05 vs. At- Risk).

Table 4.2 *Hemodynamic Variables Across the Groups.*

VARIABLES	CONTROL (n=37)	AT RISK (n= 46)	HFPEF (n=32)	HFREF (n=34)	P-VALUE
Hemodynamics					
SBP (mmHG)	126 ± 19	128 ± 17	132 ± 17	115 ± 20 ^{^#}	0.003
DBP (mmHG)	78 ± 8	73 ± 11	73 ± 11	68 ± 12	0.08
PP (mmHG)	54 ± 18	55 ± 13	59 ± 17	47 ± 17 [^]	0.035
HR (beats/min)	69 ± 12	70 ± 12	71 ± 11	70 ± 13	0.90
LVEF (%)	63 ± 5	62 ± 9	60 ± 6	34 ± 11 ^{*^#}	<0.001
LVM (gm)	90 ± 18	116 ± 37	129 ± 30	176 ± 55 ^{*^#}	<0.001

Data are expressed as mean ± S.D. PP, pulse pressure; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; * P-value <0.05 vs. Control; ^P-value <0.05 vs. At- Risk; # P-value <0.05 vs. HFpEF.

Table 4.3 *Ascending and Descending AD Across the Groups.*

Variables	CONTROL (n=37)	AT RISK (n= 46)	HFPEF (n=32)	HFREF (n=37)	P-value
Ascending AD					
A. Max area (mm ²)	8.12 ± 1.75	8.96 ± 2.50	9.83 ± 2.47	9.78 ± 2.52	0.76
A. Min area (mm ²)	7.28 ± 1.80	8.07 ± 2.35	9.00 ± 2.46	8.96 ± 2.31	0.72
(Amax-Amin)/Amin (mm ²)	0.12 ± 0.08	0.11 ± 0.07	0.087 ± 0.054	0.09 ± 0.039	0.83
A. AD (10 ⁻³ × mmHG)	2.83 ± 2.13	2.30 ± 1.75	1.72 ± 1.41	2.40 ± 1.69	0.16
Descending AD					
D. Max area (mm ²)	4.45± 0.91	4.86 ± 1.16	5.22 ± 1.14	5.45 ± 1.01	0.31
D. Min area (mm ²)	3.94± 0.91	4.33 ± 1.12	4.70 ± 1.11	4.86 ± 0.98	0.50
(Dmax-Dmin)/Dmin (mm ²)	0.13 ± 0.06	0.12 ± 0.05	0.11 ± 0.05	0.12 ± 0.055	0.57
D. AD (10 ⁻³ × mmHG ⁻¹)	3.04 ± 2.06	2.57 ± 1.50	2.30 ± 1.55	3.22 ± 2.46 [^]	0.023

Data are expressed as mean ± S.D. A. Max area, ascending aorta maximal area; A. Min area, ascending aortic minimal area; A. AD, ascending aortic distensibility; D. Max area, descending aortic maximal area; D. Min area, descending aortic minimal area; D. AD, descending AD; ANCOVA was used to compare the variables between groups; (^ P-value <0.05 vs. At- Risk).

Table 4.4 *Arterial- Ventricular Coupling Across the Groups.*

VARIABLES	CONTROL (n=34)	AT RISK (n= 40)	HFPEF (n=28)	HFREF (n=30)	P-VALUE
ESP (mmHG)	118.08 ± 14.75	122.08 ± 15.42	118.95 ± 13.2	112.21 ± 17.09 [^]	0.017
E _{LV} (mmHG/ml)	2.62 ± 0.70	2.75 ± 1.26	2.36 ± 0.79 [^]	0.75 ± 0.36 ^{*^#}	<0.001
E _A (mmHG/ml)	1.51 ± 0.36	1.52 ± 0.38	1.54 ± 0.41	1.45 ± 0.49	0.79
E _A /E _{LV}	0.60 ± 0.13	0.64 ± 0.27	0.68 ± 0.16	2.39 ± 1.46 ^{*^#}	<0.001

Data are expressed as mean ± S.D. ESP, end systolic pressure; E_{LV}, left ventricular elastance; E_A, arterial elastance; E_{LV}, left ventricular elastance; E_A/E_{LV}, is the ratio of arterial elastance and left ventricular elastance. ;* p-value <0.05 vs. Control; ^ p-value <0.05 vs. At- Risk; # p-value <0.05 vs. HFpEF.

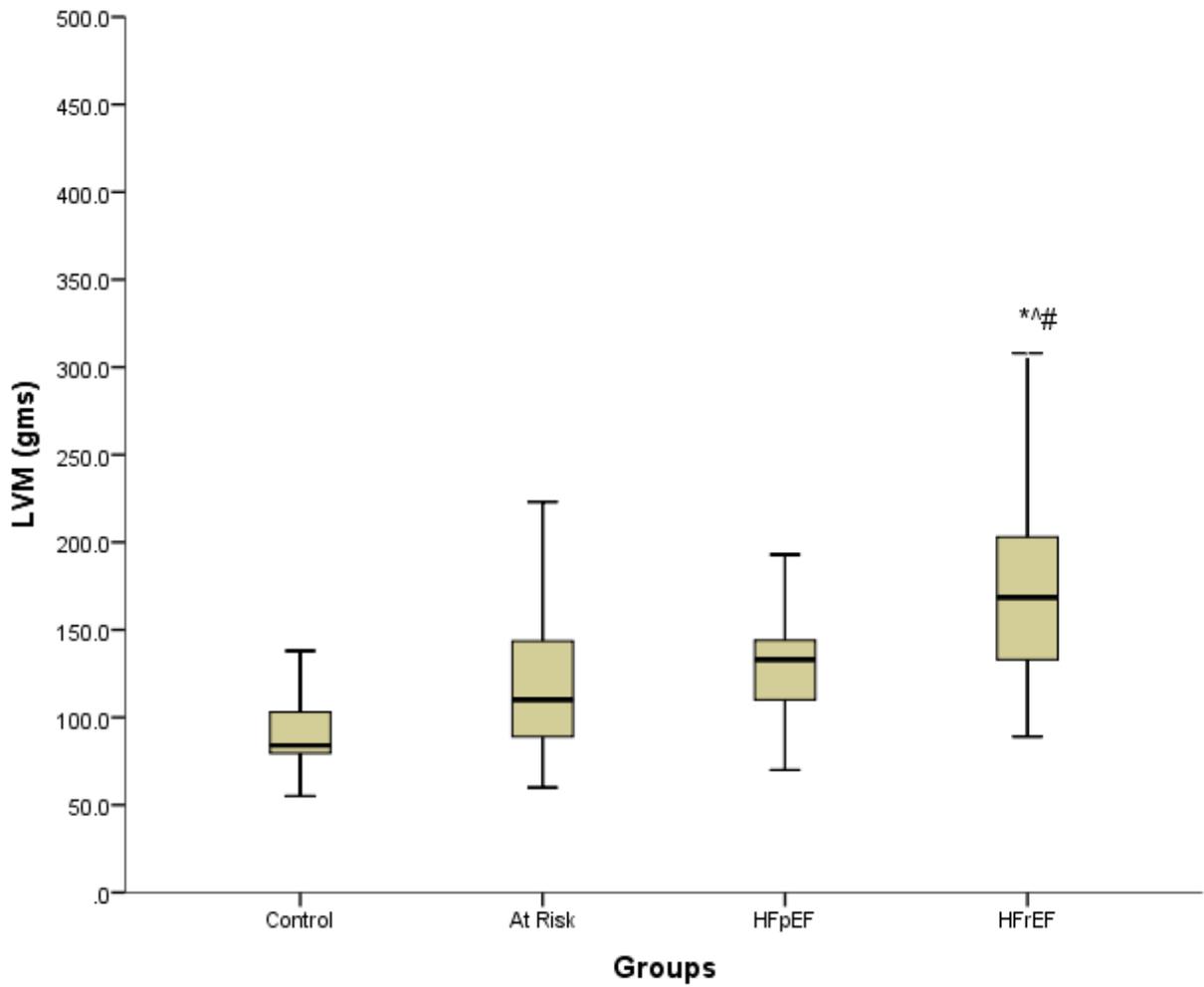


Figure 4.1: Left ventricular mass in healthy individuals, at risk, and HFrEF and HFpEF subjects.

Data adjusted for gender, age and BSA;* P<0.05 vs. control; ^P<0.05 vs. at-risk; #P<0.05vs.

HFpEF.

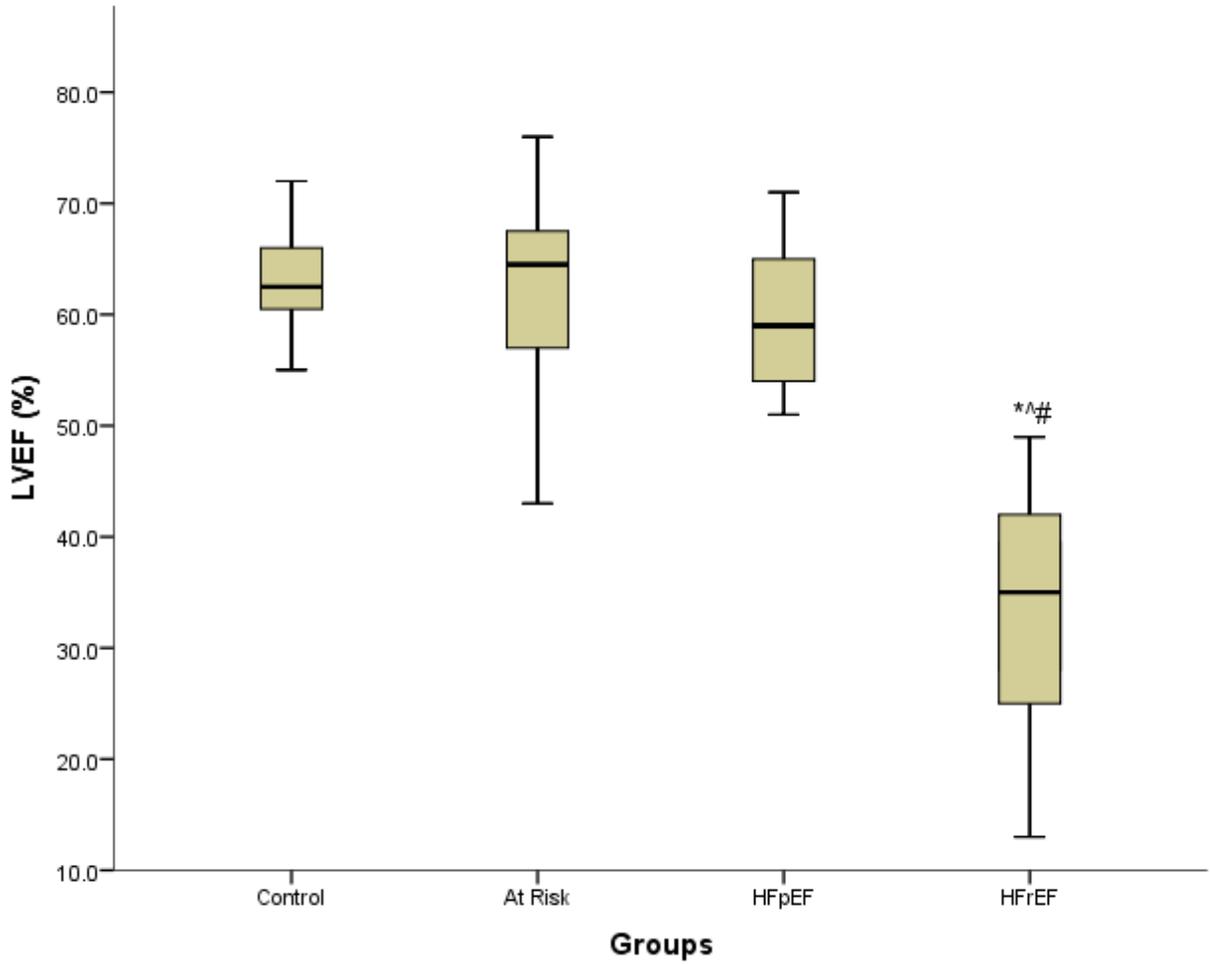


Figure 4.2: Left ventricular ejection fraction in healthy individuals, at risk, and HFrEF and HFpEF subjects; Data adjusted for gender, age and BSA; * P<0.05 vs. control; ^P<0.05 vs. at-risk; #P<0.05vs. HFpEF.

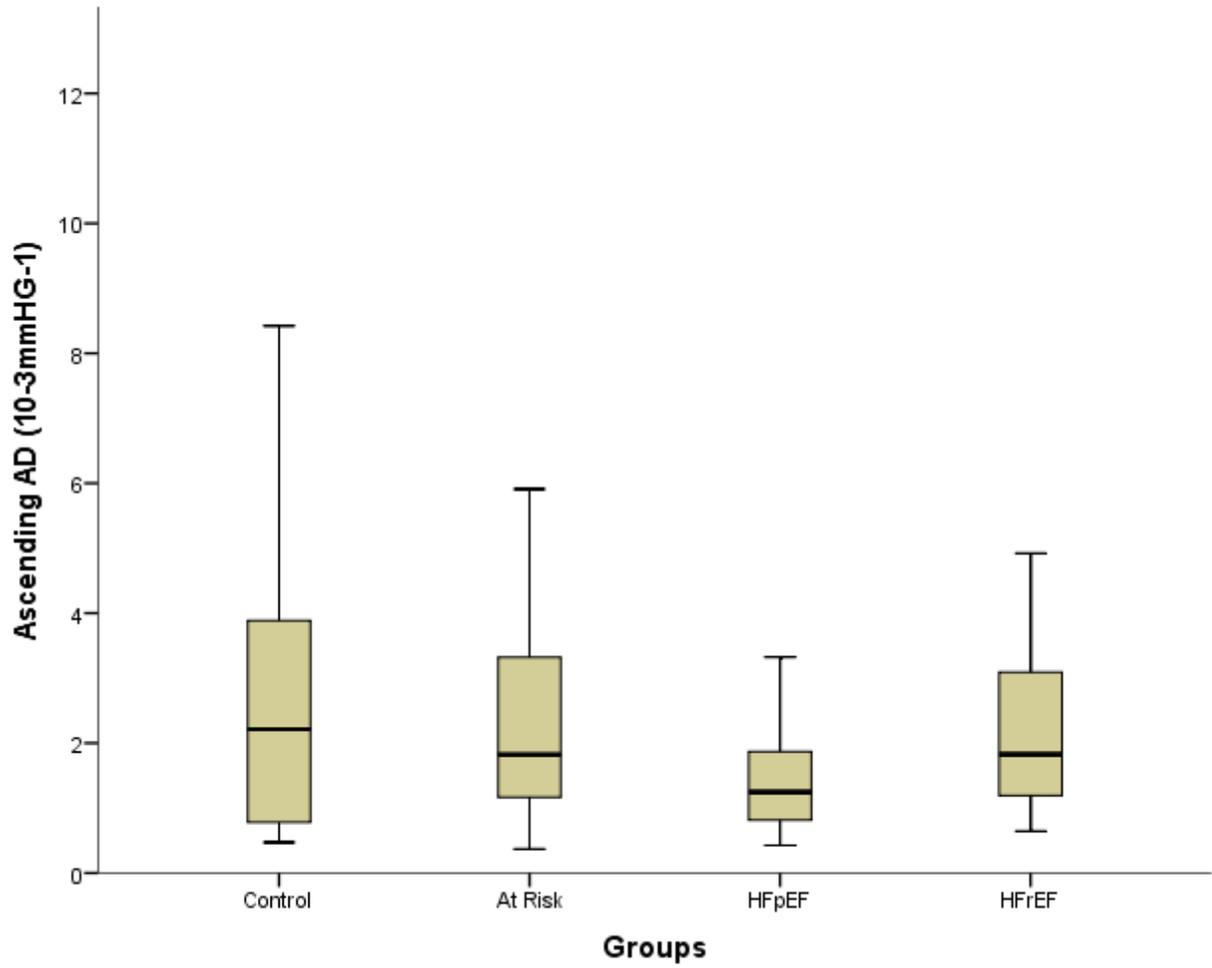


Figure 4.3: Ascending aortic distensibility in healthy individuals, at risk, and HFrfEF and HFpEF subjects.

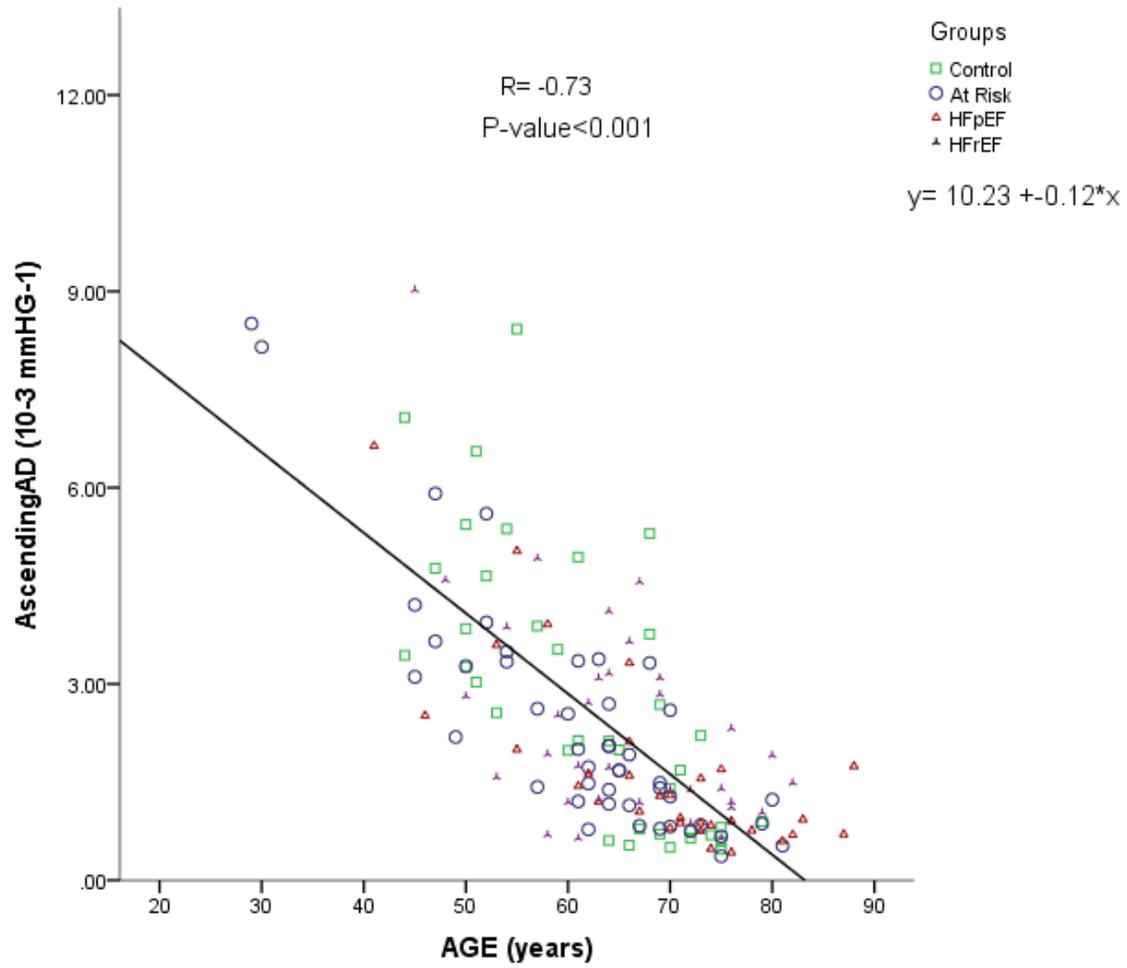


Figure 4.4: Relationship between ascending aorta distensibility and age.

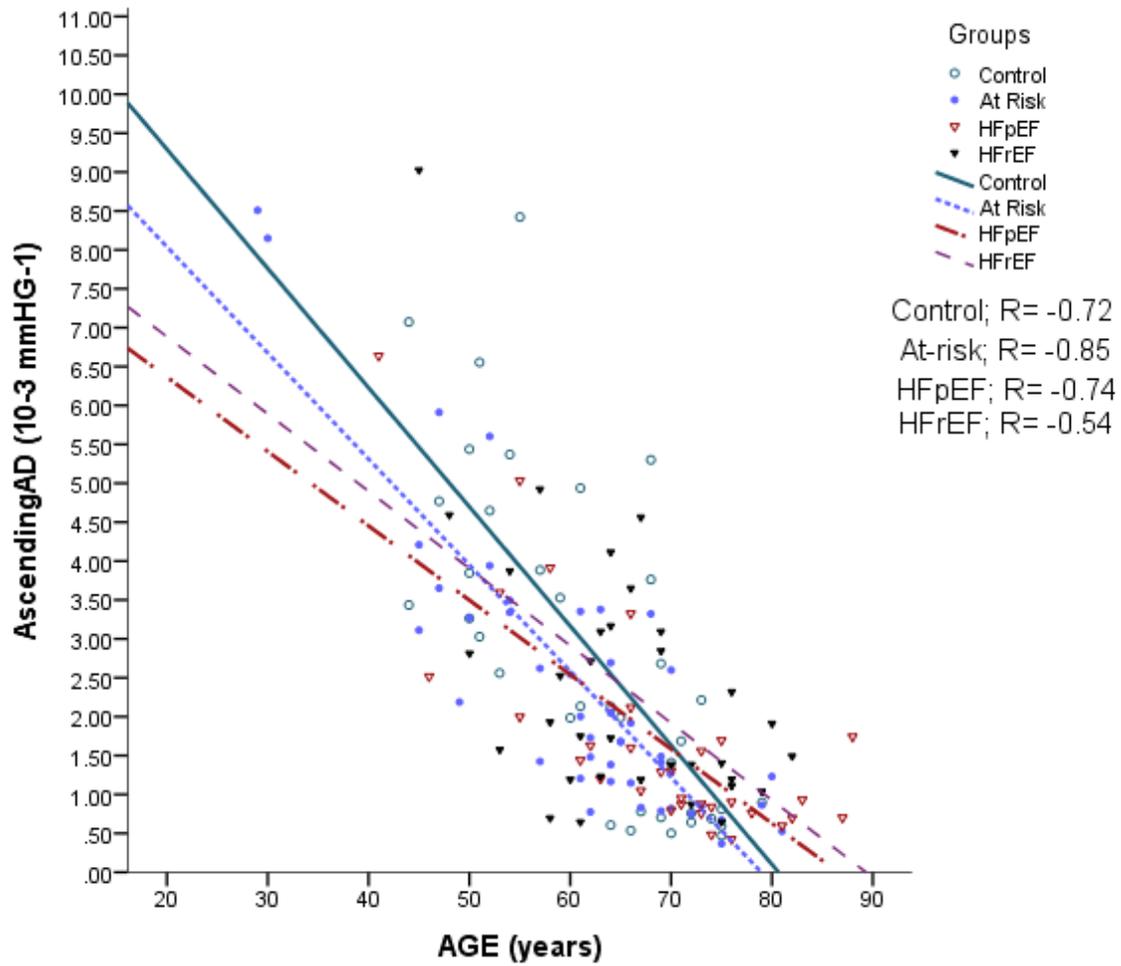


Figure 4.5: Relationship between ascending aortic distensibility and age in healthy controls, at-risk, HFrEF and HFpEF subjects. Control vs. At-risk $p=0.50$; Control vs. HFpEF $p=0.03$, Control vs. HFrEF $p=0.06$.

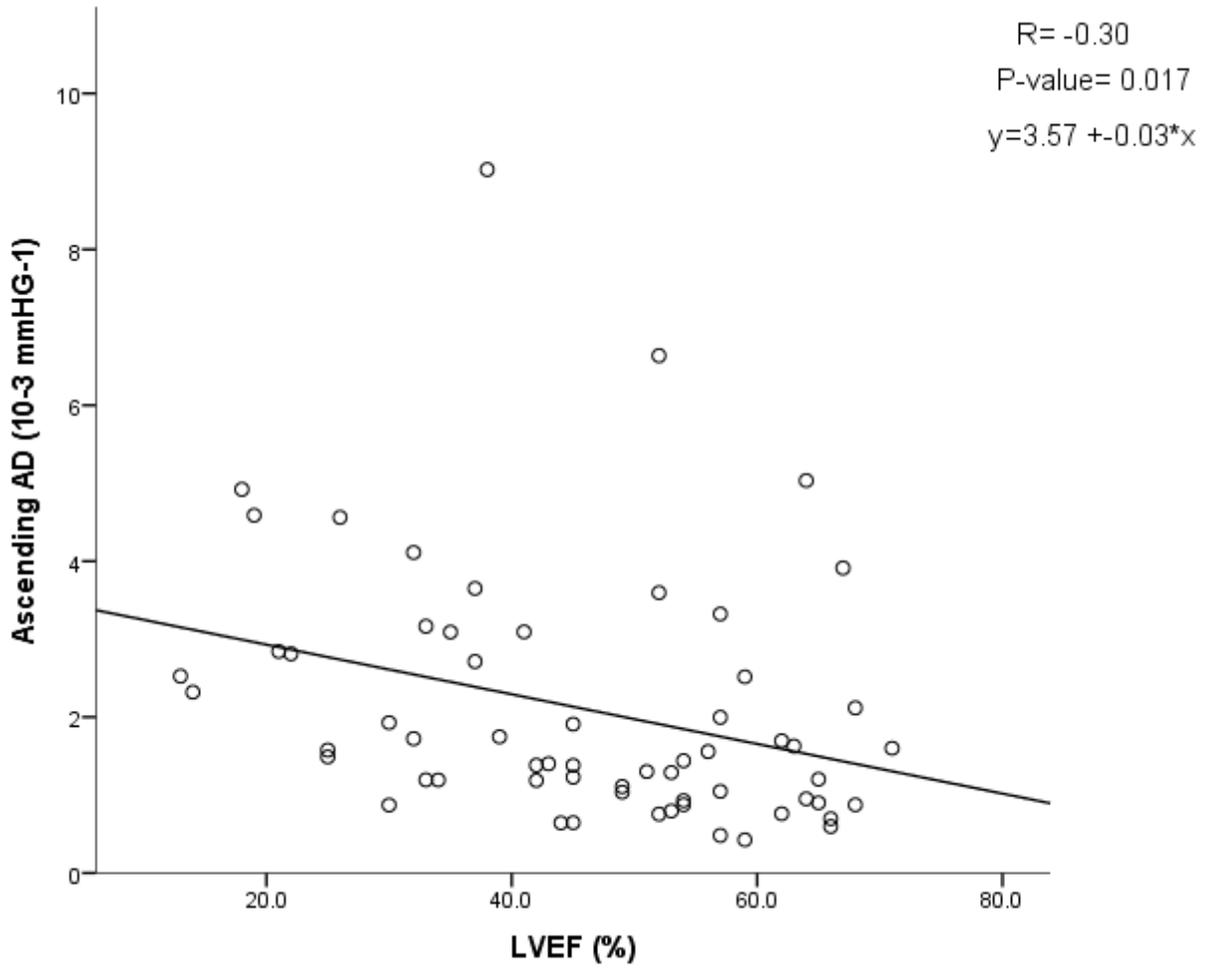


Figure 4.6: Relationship between Ascending aortic distensibility and LVEF in HFpEF and HFrEF groups

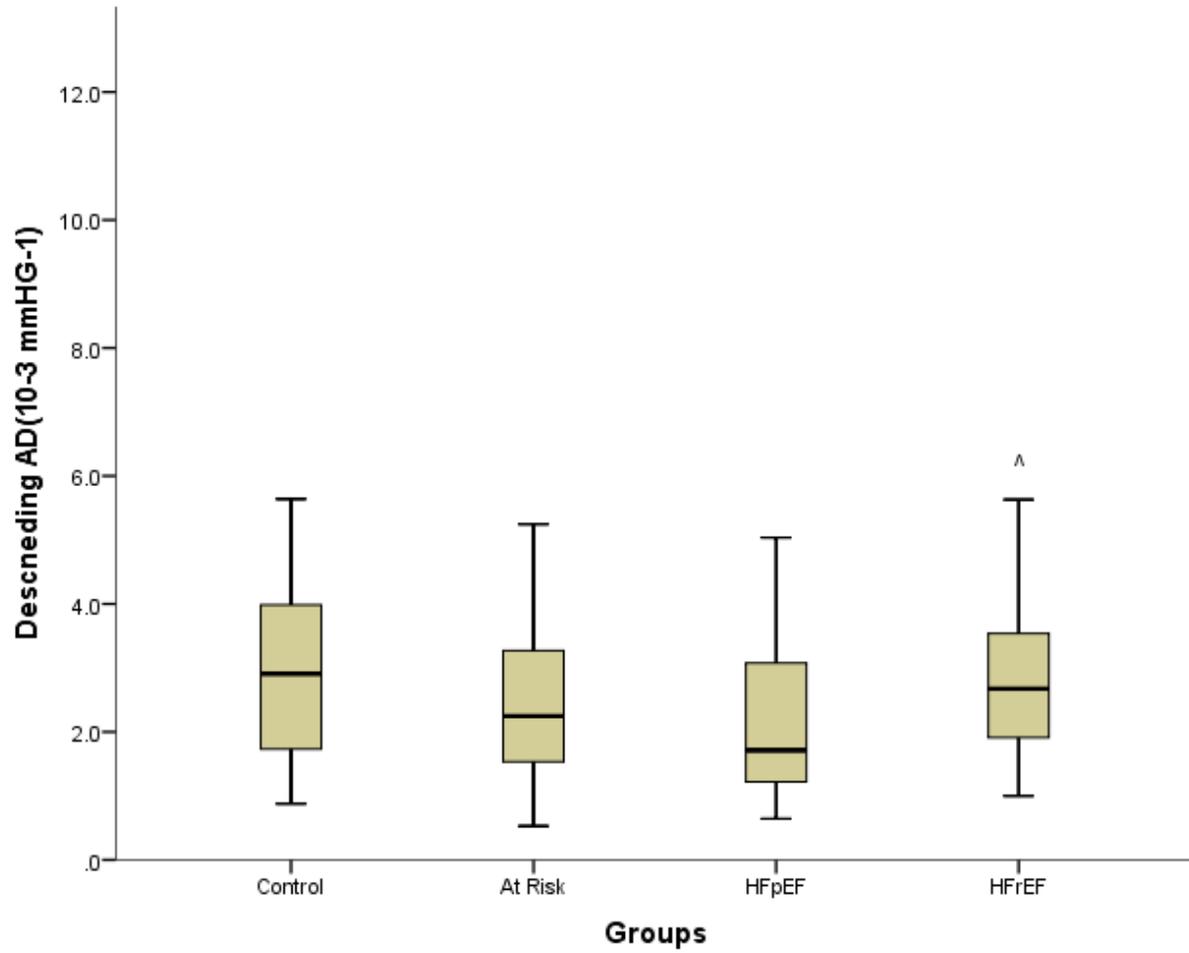


Figure 4.7: Descending aortic distensibility in healthy individuals, at risk, and HFREF and HFpEF subjects. [^]p<0.05 vs. at-risk.

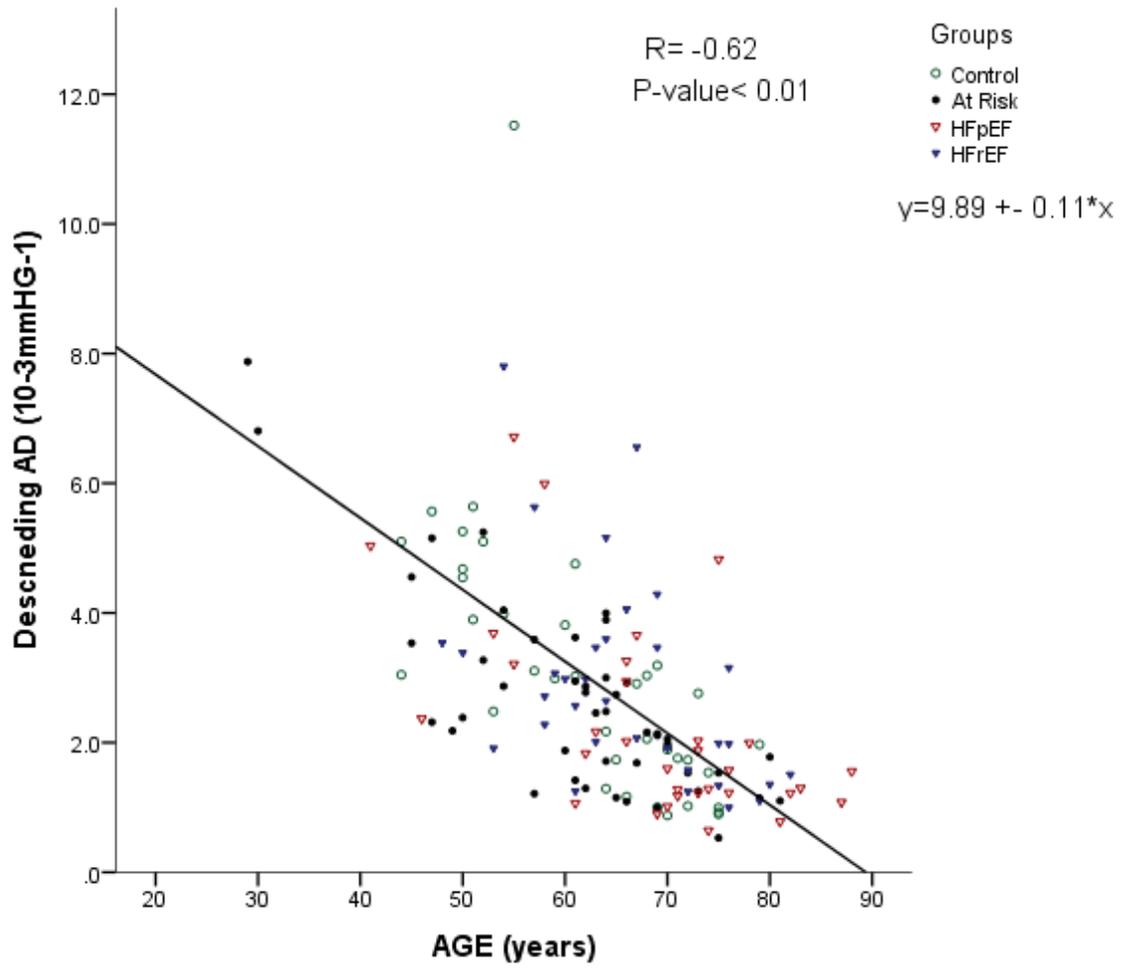


Figure 4.8: Relationship between Descending aortic distensibility and age.

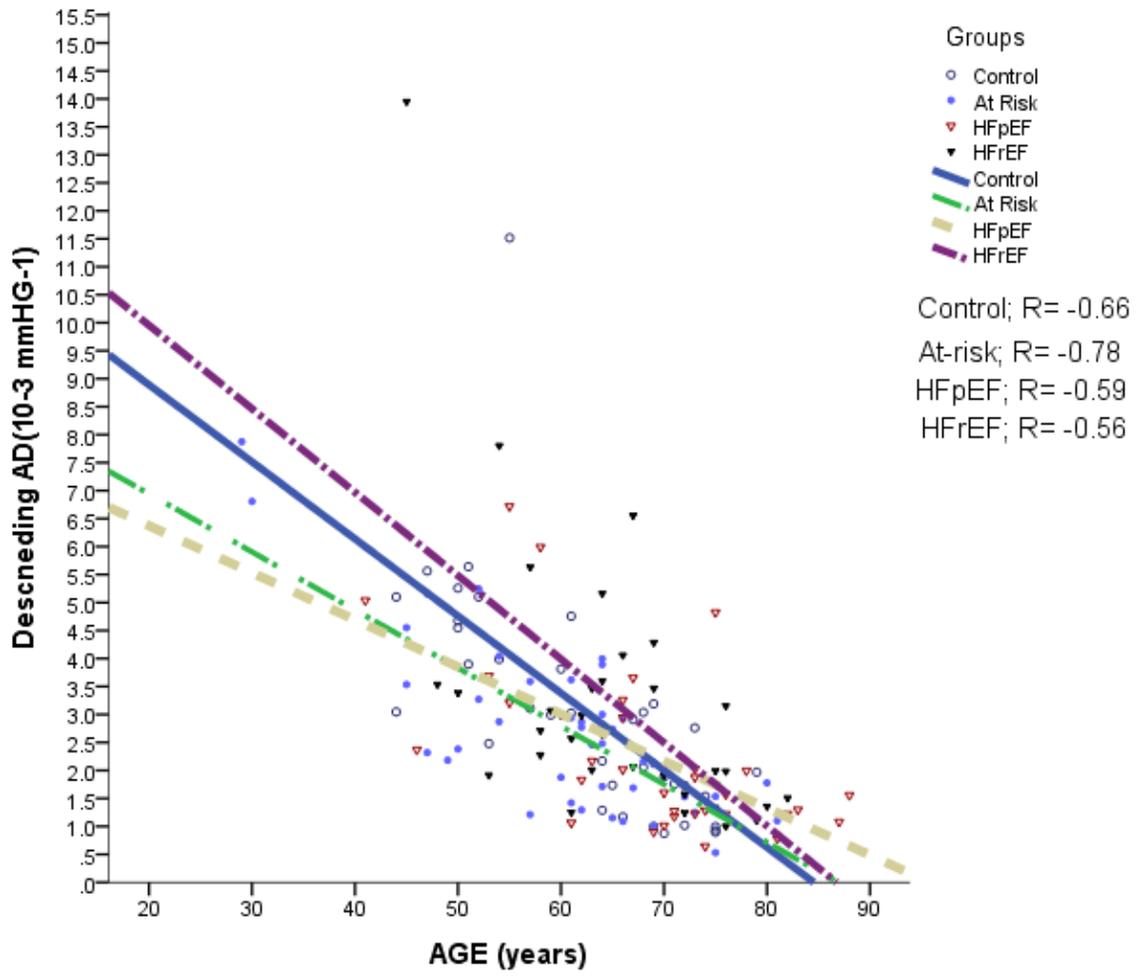


Figure 4.9: Descending aortic distensibility in healthy individuals, at risk, and HFrEF and HFpEF subjects. Control vs. At-risk, $p=0.26$; Control vs. HFpEF, $p=0.11$; Control vs. HFrEF, $p=0.75$.

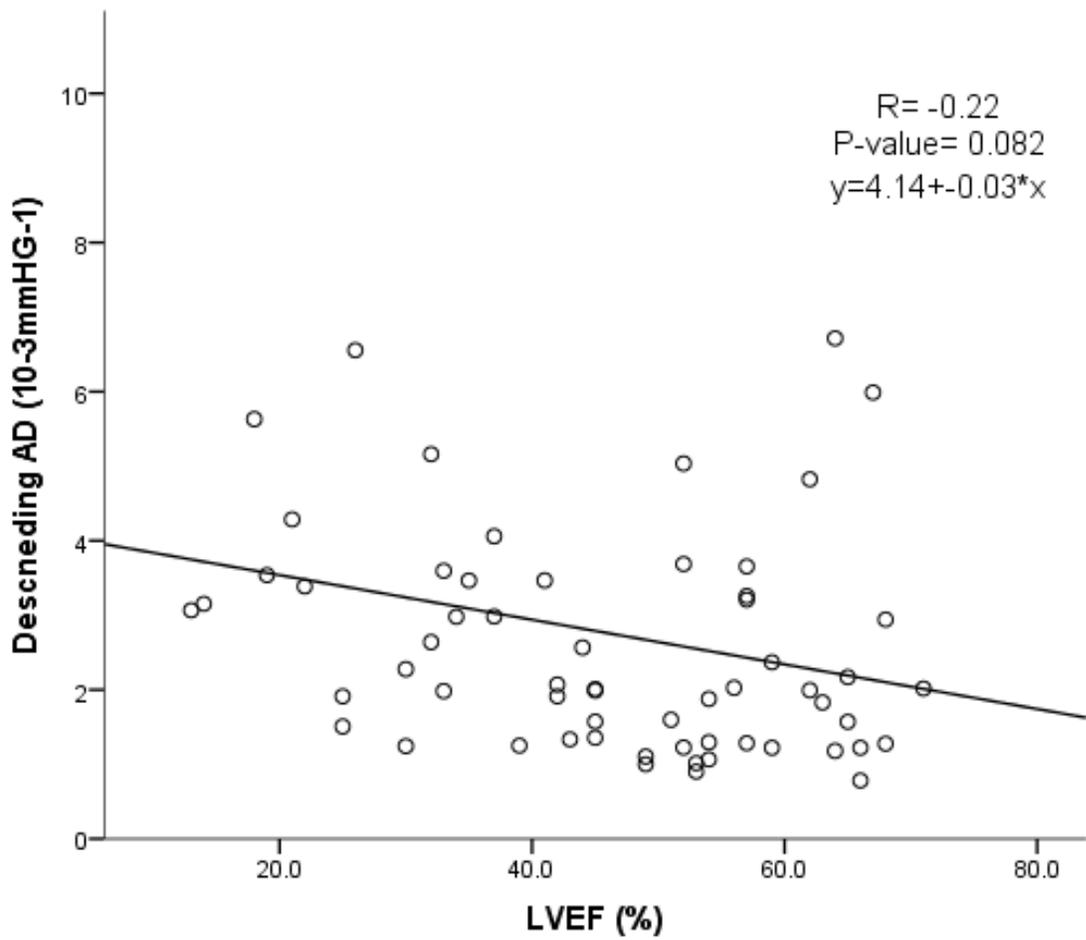


Figure 4.10: Relationship between descending AD and LVEF in HFpEF and HFrEF groups.

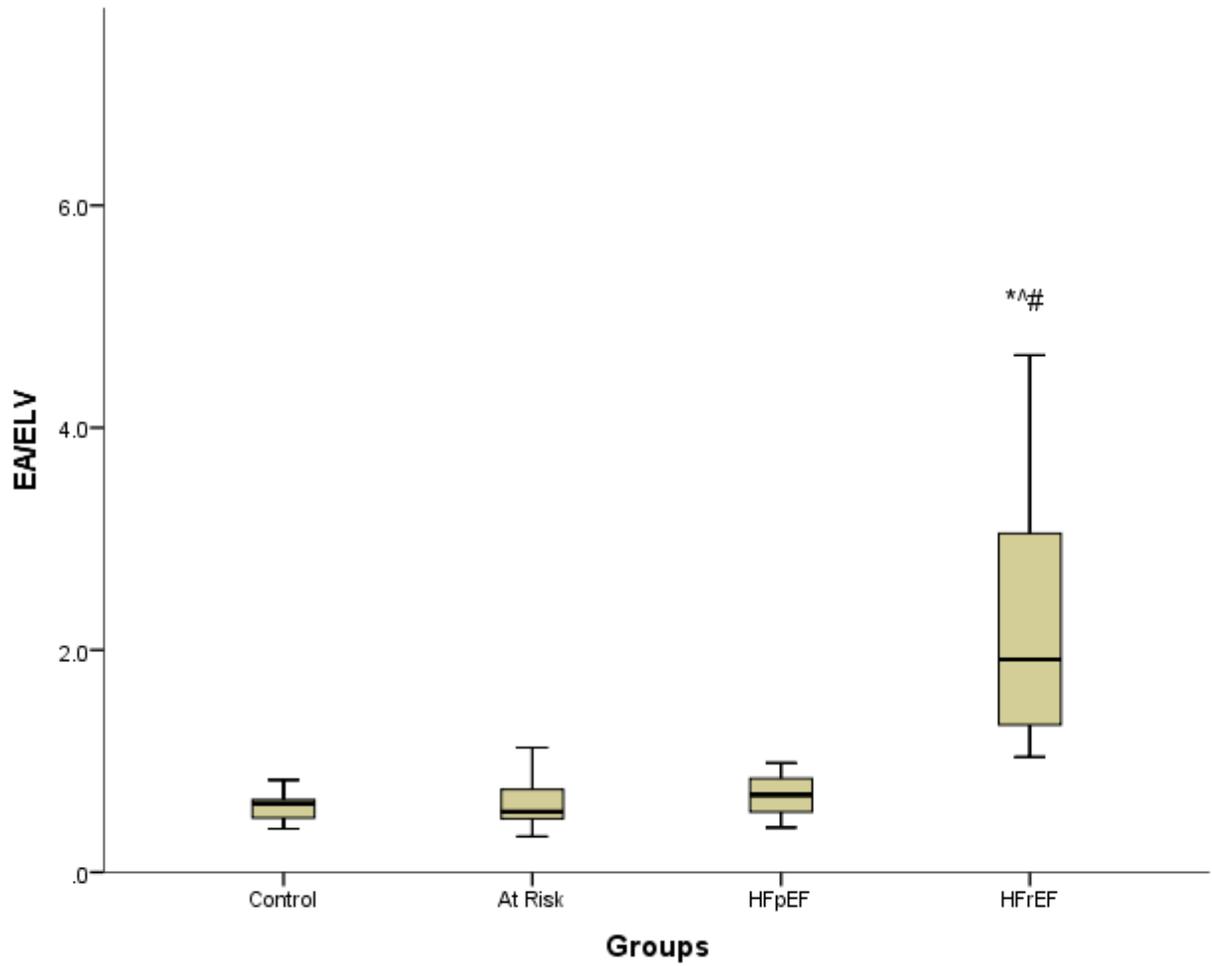


Figure 4.11: Ventricular- arterial coupling in healthy individuals, at risk, and HFrfEF and HFpEF subjects. Data adjusted for age, gender and BSA. * P<0.05 vs. control; ^P<0.05 vs. At-risk; #P<0.05vs. HFpEF.

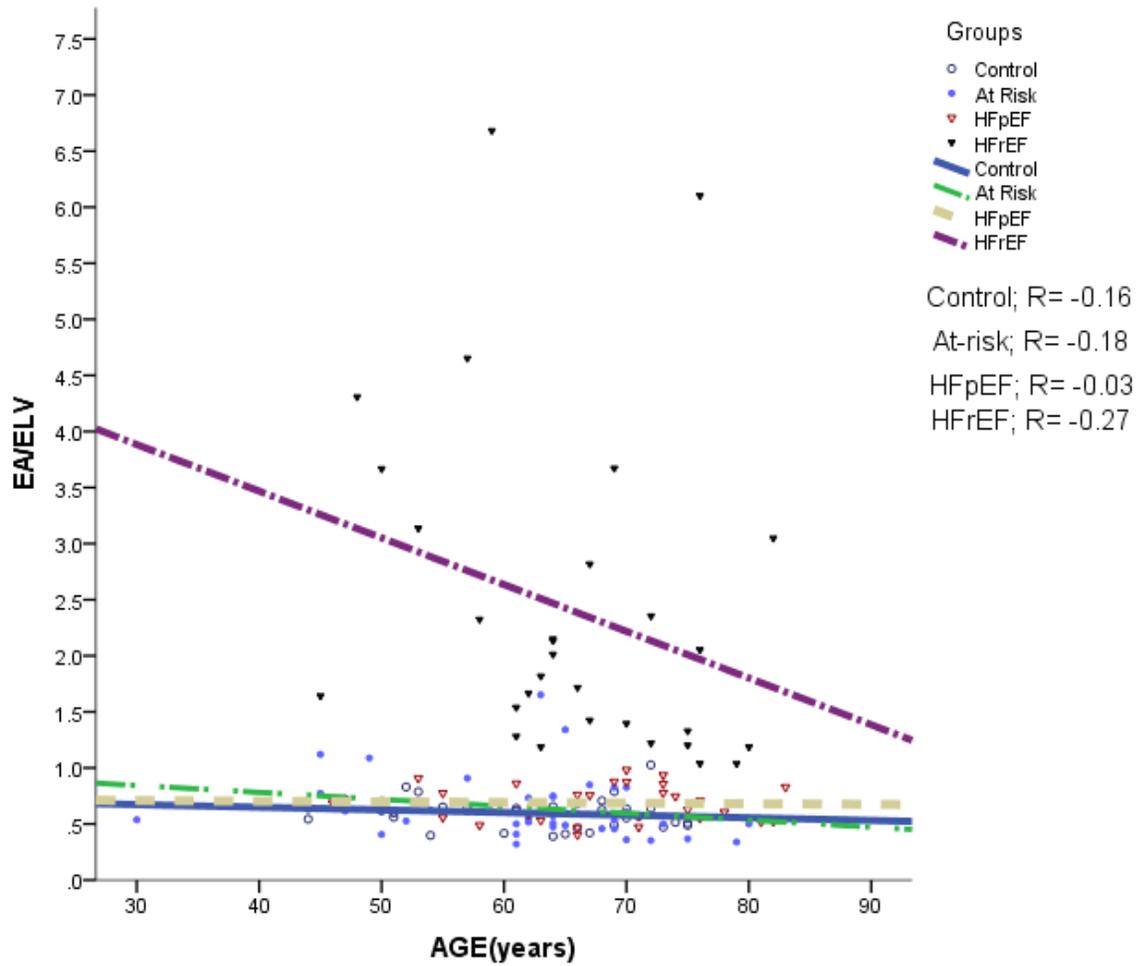


Figure 4.12: Relationship between ventricular- arterial coupling and age in healthy individuals, at risk, and HFrEF and HFpEF subjects. Control vs. at-risk, $p= 0.80$; Control vs. HFpEF, $p= 0.92$; Control vs. HFrEF, $p=0.02$.

CHAPTER FIVE

DISCUSSION

The main finding of this thesis is that descending AD was significantly higher in HFrEF group compared to the at-risk group. Secondly, ventricular- arterial coupling in HFrEF group was significantly impaired compared to all other groups.

ASCENDING AND DESCENDING AD ACROSS THE GROUPS

5.1 Aortic Distensibility in Healthy-Controls

In this present study, ascending and descending AD declined with the age (Table 4.3, Figure 4.4 and 4.8). Kim et al. studied regional aortic stiffness with cMRI in the healthy individuals [77] and reported that AD decreases and, PWV increases with age. In addition, proximal aortic arch and descending thoracic aorta demonstrated the greatest difference in PWV among healthy young and old individuals. They also reported that the PWV was highest among individuals > than 60 years [77]. Rerkpattanapipat et al. reported that AD was significantly lower in healthy older compared to younger healthy individuals. [78]. Redheuil et al. also have shown that ascending AD decreased significantly with advancing age, with a decrease of 5.3% per 10 years [28]. In the same study, the reduction in ascending AD was particularly marked in individuals >50 years of age [28].

Age related changes in aorta may occur due to constant pulsatile stress, resulting the breakdown of fragments of aortic media and partially replaced by non-elastic tissue, and decline in elastic component occurs in 3rd decade [79]. Proximal aorta plays an important role in afterload, which provides the cushion against pulsatile blood flow from the heart. This constant pulsatile stress leads to the breakdown of elastic components, which partially replaced by non-

elastic fibrotic tissue resulting aortic stiffness [79]. These findings support that the stiffness of the aortic wall is the main cause of the left ventricular diastolic dysfunction with advanced aging [77].

Maximum rate of systolic distension (MRSD) is another index of elastic properties of aortic wall, which assess the compliance during the systolic distension provoked by LVEF [80]. The MRSD value decreases with aging, which indicates that the transformation of kinetic to potential energy of systolic ejection gets more slow with aging. Due to impaired elasticity, the imbalance between the uptake and release of energy by the aortic wall might slow the acceleration of aortic wall, increase in wall stress and eventually leading to dilation of the aortic wall [80].

Further, change in the elastic properties of the aorta with aging, can be explained by regional variation in the elastin:collagen ratio [81]. The ratio of elastin:collagen is higher in proximal segment of the aorta compared to the distal segment [82]. It is therefore possible that the detrimental effect of aging which cause the gradual destruction of elastin fibers, would have the greatest impact on ascending and descending AD, because this region contains the higher elastin content [80].

The current study extends prior work by comparing AD with age across the healthy and heart failure continuum (Figure 4.5 and 4.9). The results demonstrate that compared to controls, the change in ascending AD with age was significantly lower in HFpEF patients (Figure 4.5). Balmain et al. reported greater impairment in arterial compliance in HFpEF compared to age-matched healthy controls [83].

Decreased ascending AD with aging in HFpEF may be in part of an expression of the higher prevalence of comorbid conditions such as, obesity, diabetes and renal failure (Table 4.1). All these underlying diseases are associated with accelerated, age-related vascular changes [72]. Endothelial function is known to be severely abnormal in HFpEF individuals, associated with impaired aortic compliance [72]. Conditions like insulin resistance and renal failure increase the oxidative stress and reduce nitric oxide bioavailability. These factors lead to the greater impact on aortic stiffness which might be beyond what occurs with normal aging [72].

In HFpEF, several parameters involve with different degree of impairment including impaired myocardial relaxation and reduced aortic compliances [16]. Ibrahim et al. reported the evidence of both aortic and LV stiffness in HFpEF, which associated with slow early filling, increased arterial filling, increased myocardial stiffness and impaired aortic distensibility [16]. Further, increased PWV and decreased AD in HFpEF was associated with increased LV afterload and myocardial oxygen demand, resulting mismatch between ventricular contraction and arterial pulse wave transmission [84].

5.2 Aortic Distensibility in “At-Risk” Individuals

Aortic stiffness is an important predictor of cardiovascular mortality in individuals at risk of developing HF. Increased arterial stiffness has been associated with various risk factors such as hypertension, atherosclerosis, diabetes mellitus, renal failure and peripheral vascular disease [77]. In present study, ascending and descending AD were not significantly different in the at-risk group versus healthy controls (Table 4.3). In contrast, Kim et al. reported that AD was lowered in hypertensive individuals compared to healthy controls [77].

Further, in current study, the SBP and PP were higher in the at-risk group compared to the HFrEF. However, the previous studies did not compare the deleterious effect of increased systolic and pulse pressure in at-risk group or HFrEF groups. Moreover, patients with HFpEF are more likely to have a history of hypertension compared to HFrEF [83, 85]. In current study, 87% of the at-risk group had hypertension (Table 4.1). Advanced age and hypertension are associated with increased arterial stiffness, due to collagen cross linking, geometric changes, and impaired endothelial and neurohormonal functions [85]. Impaired elasticity of central arteries leads to the generation of wide PP and further elevation of SBP [85]. The maladaptive changes between the LV and the central arteries contributes to ventricular dysfunction, impaired ventricular-arterial coupling and abnormal cardiac mechanics [85].

Arterial stiffness is also associated with arterial wall changes which occur over a long period with advancing age and predisposing factors such as hypertension, atherosclerosis [86]. Gur et al reported that mean aortic strain and AD were significantly lower in hypertensive individuals compared with healthy controls, although impaired elastic properties of aorta independently related with LVM index and relative wall thickness and diastolic functions apart from age [86]. Reduced AD may be responsible for the progression of LV hypertrophy in patients at risk of developing HF. Increased arterial stiffness increases afterload resulting in structural changes of the LV and there by LV diastolic dysfunction [86, 87]. Increased in vascular loading on heart may responsible for the increase LV wall thickness and wall stress. For these reasons, changes in LV geometry by increased aortic stiffness in individuals who are at risk for developing HF may be plausible [33, 86].

5.3 Aortic Distensibility in HFpEF Individuals

In present study ascending and descending AD were not significantly different in HFpEF group compared to healthy controls. A notable finding was that, SBP was significantly higher in the HFpEF compared with HFrEF patients (Table 4.2). In contrast, Hundley et al reported that AD was lower in HFpEF patients compared to age-matched healthy controls after controlling for age and gender [8]. Kitzman et al (2013) demonstrated that carotid AD was severely reduced in HFpEF individuals compared to healthy younger and older individuals, Further, the reduced AD in HFpEF was associated with reduced exercise capacity and increased carotid arterial stiffness beyond what which occurs with normal aging [75]. (Table 5.1)

The abnormal AD develops over many years in older HFpEF patients and is likely due to various mechanisms, including calcification and fibrosis of aorta [88]. Little et al. reported that the glucose cross link breaker alagebrium did not improve AD in HFpEF individuals, a finding which may suggest that these patients may have limited potential for reversibility [88]. Decreased AD contributes to the development of LV dysfunction which is associated with increased PP and LV afterload and impaired LV relaxation [8]. Increased in LV afterload, late systolic augmentation, PP and decrease in diastolic BP can compromise coronary perfusion and may lead to further impairment in myocardial relaxation [89]. Lowered AD is also associated with reduced exercise capacity resulting in a lower cardiac output and skeletal muscle perfusion. For this reason, chronic increases in LV afterload gradually result in in LV hypertrophy by increasing myocyte size and in combination with stiff aorta and LV hypertrophy may severely reduce exercise capacity to a greater extent than the impact from either alone [8].

Table 5.1: Summary of studies that examined AD in HFpEF and HFrEF individuals

	Pairoj et al. ^[78] (HFrEF)	Kitzman et al. ^[90] (HFpEF)	Kitzman et al. ^[75] (HFpEF)	Desai et al. ^[72] (HFpEF)	Kesri et al. ^[57] (HFpEF)	Hundley et al. ^[81] (HFpEF)	Kitzman et al. ^[2] (HFpEF)
Gender (m/f)	(5/3)	(11/60)	(17/52)	(9/7)	(11/12)	(2/8)	(8/23)
Age (yrs)	73 ± 5	69 ± 8	70 ± 7	62 ± 19	66 ± 10	77 ± 2	70 ± 7
SBP (mmHG)	127 ± 21	143 ± 17	191 ± 24	165 ± 27	132 ± 5	146 ± 6	192 ± 27
DBP (mmHG)	79 ± 15	82 ± 8	90 ± 13	65 ± 16	69 ± 3	76 ± 3	91 ± 2
LVEF (%)	22 ± 11	65 ± 7	59 ± 8	69 ± 11	59 ± 2	69 ± 2	56 ± 5
LVM(gm)	248 ± 58	123 ± 20	261 ± 88	–	129 ± 8	124 ± 5	266 ± 94
PP (mmHG)	48 ± 13	–	70 ± 16	111 ± 39	63 ± 3	69 ± 7	102 ± 22
AD (10 ⁻³ mmHG ⁻¹)	0.5 ± 0.4	0.95 ± 0.60	0.97 ± 0.45	1.72 ± 1.2	1.36 ± 0.08	0.5 ± 0.1	0.89 ± 0.35

Data are expressed as mean ± S.D. BMI, body mass index; PP, pulse pressure; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; AD; aortic distensibility; LVM; left ventricular mass.

5.4 Aortic Distensibility in HFrEF Individuals

In current study, descending AD in HFrEF individuals was higher compared to the at-risk individuals (Table 4.4, Figure 4.7). Pulse pressure was also significantly lower in HFrEF compared to the at-risk group, and AD is inversely proportional to PP, resulting higher AD in the HFrEF (Table 4.2 and 4.3). In contrast to these findings, Pairoj et al. reported that AD in HFrEF was significantly lower compared to healthy younger and age-matched older individuals [78]. In contrary to Pairoj et al. findings, our study showed that change in AD is merely an age phenomena, regardless of the disease (Figure 4.5 & 4.9). However, no study compared AD across the HF continuum, therefore it is hard to infer why AD was not significantly different in HFrEF group.

Several potential mechanisms affect aortic function in HFrEF which may result in impaired AD and ventricular-arterial coupling. Neurohormonal changes such as activation of renin angiotensin system and increased in plasma norepinephrine results vasoconstriction and sodium retention in the vascular wall [66]. Angiotensin II has hypertrophic effect on vascular smooth muscle cell resulting in vascular wall structural changes which are associated with vasodilatation properties of the artery and proliferation of smooth muscle cells, resulting change in geometrical structure which leads to the arterial stiffness [67]. Another potential mechanism causing endothelial dysfunction is oxidative stress and production of reactive oxygen species which inactivates nitric oxide, a key factor in the control of vasomotor tone, resulting arterial stiffness [62]. Several other factors are may also be associated with decreased in AD including diabetes mellitus, metabolic protease imbalance and advanced glycation end product accumulation which are also responsible for increase in LV after load, poor A-V coupling, and LV relaxation [57].

The present study extends previous reports by comparing AD and LVEF in HF patients. Indeed, a significant inverse correlation was found between ascending AD and LVEF (Figure 4.6) and suggests that HFpEF patients have greater arterial stiffness than HFrEF.

5.5 Ventricular-arterial coupling

In present study E_A/E_{LV} ratio was significantly higher in HFrEF group compared to all other groups secondary to a reduced E_{LV} (Table 4.4; Figure 4.11 and 4.12). Consistent with our finding, Little and colleagues found that E_{LV} was reduced and E_A was higher in HFREF patients.

The LV and arterial system are efficiently coupled to deliver stroke work when, $E_A = E_{LV}$ or $E_A/E_{LV} = 1$ [91]. HFrEF individuals are characterized by lowered EF and impaired LV contractility [92]. HFrEF individuals have downward and rightward shift of the end systolic pressure volume relationship, which shows reduced E_{LV} and have elevated E_A due to decrease in stroke volume and increased peripheral resistance [92]. Thus, increases in E_A and reduced E_{LV} results in increase in E_A/E_{LV} by threefold in HFrEF. This suboptimal coupling reflects poor cardiovascular performance in HFrEF group [92]. Fox et al. reported, that HFrEF were characterized by reduced LV systolic pressure and SV [93].

In contrast, HFpEF patients have an upward and leftward shift in the end-systolic end pressure volume relationship, which represents decreased ventricular capacitance but normal ventricular elastance [93]. Chantler et al suggested that there is parallel increase in E_A and E_{LV} in HFpEF individuals, hence the coupling ratio remains the same compared to healthy controls [18]. In addition, studies have reported that the E_A/E_{LV} was similar in hypertensive and HFpEF patients with no difference in E_A , E_{LV} and E_A/E_{LV} [6, 26]. We confirm and extend these findings by showing that E_A/E_{LV} was similar between healthy controls, at risk for HF and HFpEF patients,

but was significantly impaired in HFrEF, and may be an important target of therapy for these patients.

CHAPTER SIX

CONCLUSION

6.1 CONCLUSION

Arterial stiffness is an important predictor for the development of HF by increasing the load that the heart has to work to eject blood out of the heart. In addition, aortic stiffness increases markedly with advancing age, further increasing the risk for development of HF.

In this thesis, the primary null hypothesis was rejected since ascending and descending AD were not significantly different between HF_rEF patients compared to all other groups. Importantly, ascending and descending AD were inversely proportional to age regardless of underlying disease. In addition, HF_pEF individuals had greater impairment in arterial compliances, as evidenced by significantly decreased AD compared with controls, with respect to aging. Further, HF_rEF individuals had significantly impaired ventricular-arterial coupling, due to impaired contractile dysfunction or a higher afterload.

Our findings suggest that arterial stiffness and impaired ventricular-arterial coupling may be implicated in the complex pathophysiology of HF continuum. These findings are clinically important in assessing HF patients and monitoring their arterial stiffness progression. In addition to it these findings are important for target therapies that can be beneficial for reversing arterial stiffness in these individuals to improve the outcomes.

6.2 LIMITATIONS

The present study has several limitations. First, to calculate PP a noninvasive brachial cuff blood pressure measurement was incorporated instead of invasive assessment. In addition, at the

time of the cMRI, blood pressure calculation may have varied as a result of anxiety. For these reasons our calculation of ascending and descending AD should be considered an approximation.

Second, most of the patients with HF were taking medication at the time of testing, which could affect the AD measurements, especially in HF individuals. In the present study, the at-risk and HF groups were being treated with several medications which could result in improved arterial compliances, a finding which may have resulting in the non-significance difference in AD among groups. Specifically, in our study the at-risk, HFpEF and HFrEF groups were majorly being treated with ACEI, ARB, BB, CCB, statin, and thiazide (Table 4.1). Studies have shown that calcium antagonist nifedipine, nifedipine, converting enzyme inhibitor captopril improved arterial compliances [94] and administration of thiazide in hypertensive patients improved the left ventricular relaxation [95]. The optimization of hemodynamic is achieved by primarily by reducing preload and afterload [95]. ACEI and ARB known to be improve myocardial relaxation and compliance by decreasing BP and arterial stiffness by decreasing collagen content deposition [95]. Diuretic (thiazide) are effective for reducing LV preload [95]. CALVLOC trial reported that CCB improved SBP which was associated with an increase in E' velocity (early relaxation velocity), which leads to reduction of the E/E' ratio (early filling velocity: early relaxation velocity, resulting improved arterial compliance [96].

Third, the distribution of gender across the groups was different and the sample size was small, thus it cannot reach to the conclusion regarding gender differences in AD. Shim et al. reported that central hemodynamics and LV diastolic functions were significantly different in men and women. Hence it is recommended, that arterial functions should be studied in men and women separately, with larger sample size [89].

6.3 FUTURE RECOMMENDATIONS

Based on the above limitations, the following recommendations should be followed in future studies.

1. Perform an investigation that will examine the difference in AD in HF continuum, by taking PP invasively to measure the accurate AD. In addition, in order to determine the mechanism responsible for the different AD in HF continuum, they should have been withheld from medicine to minimize the chronic effect of medicine on cardiovascular system.
2. Future studies are required to determine if the AD is different among HF continuum with respect to gender and race and BSA.
3. Perform a follow-up study to measure AD across the HF continuum over time.

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APPENDICES

APPENDIX A: INFORMATION LETTER



Heart Failure Etiology and Analysis Research Team (HEART): Understanding and Treating Diastolic Heart Failure Observational

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Background:

Researchers are trying to find new and better ways to treat people with heart failure, especially one type called diastolic heart failure. To do this they need access to good information about the causes, complications and treatments of heart failure. There is little information about patients with diastolic heart failure.

Purpose of the Study:

The purpose of this research study is to collect information on the causes, complications and treatment of heart failure. This study will follow approximately 1000 people from across Alberta who have heart failure, are at risk for heart disease or are otherwise healthy.

Procedure:

This study is observational only. This means that information about your health will be collected but there will be no change in the way you will be treated. There is no experimental treatment (meaning that there is no study drug or change in your treatment). We collect blood and urine samples, pictures of your heart and blood vessels and information on how much energy you use in a day. Blood and urine tests can be used to understand heart disease and help develop future treatments. Some of the blood tests are part of routine care, and some will then be frozen and stored for future research on heart disease so that as scientific discoveries are made, research can be done on the samples we have collected.

If you consent to take part in this study, the following things will be done:

- A member of the study team will collect information about your past and present health by asking you or your family member questions and by reviewing your medical records.

- Blood and urine samples will be collected at the time you have routine blood work or through your IV line. The blood samples will be stored separately from your clinical information, linked through a code number only. In the future, we may ask you for additional blood and urine samples in 6 months and 1 year. Under such circumstances, this signed consent form will be used for another blood draw and urine sample.
- We will arrange for an echocardiogram (an ultrasound of the heart), and a magnetic resonance imaging (MRI) of your heart.
- We will take electrical recordings of your heart with a special electrocardiogram that is timed to your breathing and records for a longer period of time. This is similar to having a regular electrocardiogram and will take less than one hour.
- We will collect Daily Energy Expenditure (DEE) which will be measured using the Sensewear Armband (SWA). The armband uses multi-sensors (such as skin temperature and near-body temperature) to estimate how much energy you use in a day. You will be asked to wear the armband (on your right tricep) continuously for four (4) consecutive days, only removing the device while bathing. If you choose not to wear the armband for the four consecutive days, this will not impact your ability to participate in the other aspects of this study.
- Some participants will also have other tests including exercise tests, or other advanced tests on blood vessels or the heart. A separate consent form will be used for those tests.

The information and blood or urine samples for this study will be stored for up to 30 years, at the University of Alberta. Samples will be analyzed at the University of Alberta and where necessary at other facilities. At all times, your identity will be kept confidential and samples will be identified by a code number only.

You or your family member will be contacted again at 6 months and 1 year. At these times you will be asked questions about your health, any hospitalizations or procedures you may have had since your discharge, and your quality of life. Your medical records will be reviewed for any changes to your health and medical treatment. We will also review your past and future health records for changes in your health status. Each visit will take no more than one hour.

Possible Side Effects:

You may experience some bruising and/or slight soreness at the blood collection site. However, trained medical personnel will perform the blood collection procedures for laboratory tests and will make every effort to minimize any discomfort.

The MRI is painless and involves lying on your back in the MRI machine for about 45 minutes. The MRI has no known harmful effects. While having the MRI, a contrast agent will be injected into a vein in your arm. Up to 3% of people receiving this contrast will experience a temporary feeling of nausea or a cold feeling at the IV site. Other minor reactions include a rash or

headache. Very rarely people will suffer a more serious reaction (about one person in every 400,000), such as: wheezing, shortness of breath or a decrease in blood pressure. If you have a reaction a doctor will treat you immediately. The contrast agent, gadolinium has been approved by Health Canada. In a few patients (< 1/10,000) with poor kidney function, gadolinium has been suspected to cause a new disease, called nephrogenic systemic fibrosis, or nephrogenic fibrosing dermopathy (NSF/NFD). This disease is primarily characterized by changes to the skin, joints, muscles and eyes. This condition occurs exclusively in those with poor kidney function. We will not investigate patients with poor kidney function.

An ultrasound of the heart involves lying on your back and ultrasound pictures are taken. There are no known harmful effects. The electrocardiogram (electrical heart tracing) information is non-invasive and does not carry any risks and has no discomfort associated with it.

Possible Benefits:

There are no guarantees that you will directly benefit from this research; but the results may help others with heart disease in the future.

Confidentiality:

During the study we will be collecting health data about you. Your study records will be identified by a code number only, and not your name. We will do everything we can to make sure that this data is kept private. This project is being conducted in Edmonton and Calgary so some of the information may be shared between the researchers at each place. No data relating to this study that includes your name will be released outside of the study doctor's office or published by the researchers. Sometimes, by law we may have to release your information with your name and so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your health information is kept private.

The study doctor/study staff may need to look at your personal health records held at the study doctor's office, and/or kept by other health care providers that you may have seen in the past (i.e. your family doctor). Any personal health information that we get from these records will be only what is needed for the study.

During research studies it is important that the data we get is accurate. For this reason your health data, including your name, may be looked at by people from the University of Alberta or the Health Research Ethics Board. By signing this consent form you are giving permission to the study doctor/staff to collect, use and disclose information about you from your personal health records as described above.

After the study is done we will still need to securely store your health data that was collected as part of the study. We will keep data stored for 30 years at the University of Alberta. If you withdraw from the study, we will not collect new health information about you, but the medical information that is already collected from you for study purposes, including any samples or data already collected, will need to be kept. You have the right to check your health records and request changes if your personal information is incorrect.

Compensation for Injury:

If you become ill or injured as a result of being in this study, you will receive necessary medical

treatment, at no additional cost to you. By signing this consent form you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

Voluntary Participation:

You do not have to be in this study. You are free to withdraw from this study at any time, and your medical care will not be affected in any way. Your decision will not affect your regular care or the benefits to which you are otherwise entitled.

Study Costs:

No payment will be provided for your participation in this study. You will be reimbursed for any costs you incur if you attend study visits at the hospital (i.e. parking fees).

Contact Information:

Please contact any of the individuals identified below if you have any questions or concerns:

Dr. Justin Ezekowitz 780-407-8719

If you have any concerns about any aspect of this study, or your medical care including your rights as a research subject, in Edmonton you may contact the Research Ethics office 780.492.2615.

APPENDIX B: CONSENT FORM

Title of Project: **Heart Failure Etiology and Analysis Research Team (HEART): Understanding and Treating Diastolic Heart Failure**

Principal Investigator(s):	Phone Number(s):	Research Coordinator	
Dr. Justin Ezekowitz	780-407-8719	Marleen Irwin	780 221 1503
Co-Investigator(s):	Phone Number(s):	Co-Investigator(s):	Phone
Number(s):			
Dr. Alexander Clark	780- 492-8347	Dr. Gavin Oudit	780- 407-8569
Dr. Mark Haykowsky	780- 492-5970	Dr. Ian Paterson	780- 407-1857
Dr. Daniel Kim	780- 407-7206	Dr. Richard Thompson	780- 492-8665
Dr. Finlay McAlister	780- 407-1399	Dr. Harald Becker	780-407-8505
Dr. Leslie Kasza	780-461-6802		

- | | | |
|---|--------------------------|--------------------------|
| | <u>Yes</u> | <u>No</u> |
| Do you understand that you have been asked to be in a research study? | <input type="checkbox"/> | <input type="checkbox"/> |
| Have you read and received a copy of the attached Information Sheet? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you understand the benefits and risks involved in taking part in this research study? | <input type="checkbox"/> | <input type="checkbox"/> |
| Have you had an opportunity to ask questions and discuss this study? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you understand that you are free to withdraw from the study at any time, without having to give a reason and without affecting your future medical care? | <input type="checkbox"/> | <input type="checkbox"/> |
| Has the issue of confidentiality been explained to you? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you understand who will have access to your records, including personally identifiable health information? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you want the investigator(s) to inform your family doctor that you are participating in this research study? If so, give his/her name _____ | <input type="checkbox"/> | <input type="checkbox"/> |

Who explained this study to you? *Marleen E Irwin, Clinical Research Coordinator*
 I agree to take part in this study: YES NO

Signature of Research Participant _____
 (Printed Name) _____ Date: _____

My signature attests that I was present during the informed consent discussion of this research for the above named participant and that the information in the consent form was accurately explained to and apparently understood by the prospective participant or their representative and that the informed consent decision was made freely.
 Signature of Witness _____ Date: _____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate
 Signature of Investigator or Designee _____ Date _____

Marleen E Irwin, CRC for Dr.J.Ezekowitz

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH SUBJECT

APPENDIX C: ETHIC APPROVAL

Re-Approval Form

Date: August 22, 2013

Principal Investigator: [Justin Ezekowitz](#)

Study ID: [Pro00007105](#)

Study Title: AHFMR Interdisciplinary Team Grant on Understanding and Treating Diastolic

Heart Failure: Novel Mechanisms, Diagnostics and Potential Therapeutics

Approval Expiry Date: August 29, 2014

Sponsor/Funding: Prevention of Organ Failure Centre (PROOF)

Agency AHFMR - Alberta Heritage Foundation for Medical Research

The Health Research Ethics Board - Biomedical Panel has reviewed the renewal request and file for this project and found it to be acceptable within the limitations of human experimentation.

The re-approval for the study as presented is valid for another year. It may be extended following completion of the annual renewal request. Beginning 45 days prior to expiration, you will receive notices that the study is about to expire. Once the study has expired you will have to resubmit. Any proposed changes to the study must be submitted to the HREB for approval prior to implementation.

All study-related documents should be retained so as to be available to the HREB on request. They should be kept for the duration of the project and for at least five years following study

completion. In the case of clinical trials approved under Division 5 of the Food and Drug regulations of Health Canada, study records must be retained for 25 years.

Sincerely,

Donald W. Morrish, MD, PhD, FRCPC

Associate Chair, HREB Biomedical

Note: This correspondence includes an electronic signature (validation and approval via an online system).

APPENDIX D: SAMPLE SIZE CALCULATOR

1. Inference for Means: Comparing Two Independent Samples

(To use this page, your browser must recognize JavaScript.)

Choose which calculation you desire, enter the relevant population values for μ_1 (mean of population 1), μ_2 (mean of population 2), and σ (common standard deviation) and, if calculating power, a sample size (assumed the same for each sample). You may also modify α (type I error rate) and the power, if relevant. After making your entries, hit the calculate button at the bottom.

- Calculate Sample Size (for specified Power)
- Calculate Power (for specified Sample Size)

Enter a value for μ_1 :

Enter a value for μ_2 :

Enter a value for σ :

- 1 Sided Test
- 2 Sided Test

Enter a value for α (default is .05):

Enter a value for desired power (default is .80):

The sample size (for each sample separately) is:

Reference: The calculations are the customary ones based on normal distributions. See for example *Hypothesis Testing: Two-Sample Inference - Estimation of Sample Size and Power for Comparing Two Means* in Bernard Rosner's **Fundamentals of Biostatistics**.

Rollin Brant
Email me at: rollin@stat.ubc.ca

2. Inference for Means: Comparing Two Independent Samples

(To use this page, your browser must recognize JavaScript.)

Choose which calculation you desire, enter the relevant population values for μ_1 (mean of population 1), μ_2 (mean of population 2), and σ (common standard deviation) and, if calculating power, a sample size (assumed the same for each sample). You may also modify α (type I error rate) and the power, if relevant. After making your entries, hit the calculate button at the bottom.

- Calculate Sample Size (for specified Power)
- Calculate Power (for specified Sample Size)

Enter a value for μ_1 :

Enter a value for μ_2 :

Enter a value for σ :

- 1 Sided Test
- 2 Sided Test

Enter a value for α (default is .05):

Enter a value for desired power (default is .80):

The sample size (for each sample separately) is:

Reference: The calculations are the customary ones based on normal distributions. See for example *Hypothesis Testing: Two-Sample Inference - Estimation of Sample Size and Power for Comparing Two Means* in Bernard Rosner's **Fundamentals of Biostatistics**.

Rollin Brant

Email me at: rollin@stat.ubc.ca