UNIVERSITY OF CALIFORNIA SAN DIEGO

Similarities and Differences Among Women With Ischemia and No Obstructive Coronary Artery Disease (INOCA) and Women with Heart Failure with Preserved Ejection Fraction (HFpEF) Compared to a Control Group

A Thesis submitted in partial satisfaction of the requirements
for the Master's Degree

in

Public Health

by

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2023

The Thesis of Haider Aldiwani is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California San Diego

2023

DEDICATION

This thesis is dedicated to my wonderful family, including my wonderful wife and my children Taim and Sophia.

EPIGRAPH

If we knew what we were doing, it wouldn't be called research, would it?

Albert Einstein

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme Inhibitors
BNP	B type natriuretic peptide, a hormone secreted by the ventricles when they are under increased pressure and stress, the measure of which helps in the diagnosis of heart failure
CAD	Coronary artery disease
CFT	Coronary function testing, an invasive diagnostic test done by injecting certain vasoactive chemicals such as adenosine directly into the coronary arteries (mainly the left anterior descending artery) to determine their vasoactive function, i.e., dilation, constriction or none
CMD	Coronary microvascular dysfunction, a medical condition that affects small caliber vessels coronary arteries
CMRI	Cardiac magnetic resonance imaging
HFpEF	Heart failure with preserved ejection fraction, a subtype of heart failure more prevalent in women compared to men
INOCA	Ischemia with no obstructive CAD, a condition in which individuals experience symptoms of chest pain or symptoms suggestive of angina or ischemia with no anatomically significant blood flow limiting obstruction of the coronary arteries on imaging
KCCQ	Kansas City Cardiomyopathy Questionnaire, a validated questionnaire to quantify heart failure symptoms
LVEDP	Left ventricular end diastolic pressure, a measure of the left ventricular function to help determine elevated filling pressure and required in the diagnosis of heart failure
MPRI	Myocardial perfusion reserve index, a CMRI measure that determines flow to the myocardium using non-invasive testing (cardiac magnetic resonance)
PCWP	Pulmonary capillary wedge pressure, another measure that helps in the diagnosis of heart failure
SAQ	Seattle Angina Questionnaire, a validated questionnaire to quantify symptoms of angina in men and women

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

This thesis has been the culmination of four years of working with the Barbra Streisand Women's Heart Health Center of the Cedars Sinai Medical Center, their research team, and my mentors Dr. C. Noel Bairey Merz, Dr. Janet Wei, and Dr. Chrisandra Shufelt. It was a team effort to collect all data from the National Institute of Health (NIH) funded Women's Ischemia Syndrome Evaluation Coronary Vascular Disease continuation study. All chapters, in full, are published in Vessel Plus Journal under the title, "Reduced myocardial perfusion is common among subjects with ischemia and no obstructive coronary artery disease and heart failure with preserved ejection fraction: a report from the WISE-CVD continuation study." The thesis author was the first author of this paper.

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ABSTRACT OF THE THESIS

Similarities and Differences Among Women With Ischemia and No Obstructive Coronary Artery Disease (INOCA) and Women with Heart Failure with Preserved Ejection Fraction (HFpEF) Compared to a Control Group

by

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Master of Public Health

University of California San Diego, 2023

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Women with evidence of ischemia and no obstructive coronary artery disease (INOCA) have an increased risk of major adverse cardiac events, including heart failure with preserved ejection fraction (HFpEF), we examined pathophysiological findings present in both INOCA and

HFpEF and compared it to reference control to identify a potential links between INOCA and HFpEF compared to reference controls.

In this study, 56 participants undergone adenosine stress cardiac magnetic resonance imaging (CMRI) in, including 35 women with suspected INOCA, 13 women with HFpEF, and 8 reference control women. Myocardial perfusion imaging was performed at rest and with vasodilator stress with intravenous adenosine. Myocardial perfusion reserve index was obtained and processed using semiquantitative measurement using CVI42 software (Circle Cardiovascular Imaging Inc). Statistical analysis was performed using linear regression models, Fisher's exact tests, ANOVA, or Kruskal-Wallis tests.

Results showed that Age (P = 0.007), Body surface area (0.05) were highest in the HFpEF group. Left ventricular ejection fraction (P = 0.02) was lower among the INOCA and HFpEF groups compared to reference controls. In addition, A graded reduction was noticed in myocardial perfusion reserve index in HFpEF vs. INOCA vs. reference controls (1.5 ± 0.3, 1.8 ± 0.3, 1.9 ± 0.3, P = 0.02), but wasn't statistically significant once adjusted to age. In conclusion, reduced myocardial perfusion reserve appears to be a common pathophysiologic feature in INOCA and HFpEF patients compared to reference control women.

Chapter 1 BACKGROUND

Women with evidence of ischemia and no obstructive coronary artery disease (INOCA) are at increased risk of developing major adverse cardiovascular events, most commonly heart failure with preserved ejection fraction (HFpEF).[1-3] Up to 50% of women with INOCA have coronary microvascular dysfunction (CMD) with impaired myocardial perfusion reserve, most often detected by reduced coronary flow reserve through invasive coronary function testing (CFT) or non-invasive imaging, such as cardiac magnetic resonance imaging (CMRI) or positron emission tomography (PET).[4,5] Previous studies demonstrated that women with CMD often have left ventricular (LV) diastolic dysfunction, adverse ventricular remodeling, elevated inflammatory markers, and myocardial scarring.[6-8] The mechanism(s) linking HFpEF with INOCA require(s) further research.

The objective of this study is to identify similarities and differences between women with HFpEF and women with INOCA compared to a reference control group. To achieve this comparison, we hypothesize that CMD may contribute to adverse ventricular remodeling in INOCA patients and subsequently lead to HFpEF. We will test our hypothesis by evaluating LV remodeling and myocardial perfusion abnormalities in participants with CMD, HFpEF, and reference controls in a cross-sectional observational study. Furthermore, we will examine the differences in baseline characteristics between women and men diagnosed with HFpEF.

For much of the twentieth century, medical professionals thought that the presentation of cardiovascular disease was similar among both men and women, although a majority of studies predominantly used male participants. In the late 1990s, however, a growing consensus emerged among clinicians and healthcare providers that there may be a difference in the presentation of cardiovascular disease between women and men.

The Women Ischemia Syndrome Evaluation (WISE) study was among the earliest studies to recognize this difference in the presentation and pathophysiological process of certain cardiovascular conditions.[9] Initially, the WISE was a National Heart, Lung, and Blood Institute-sponsored, four-center study designed to address ischemic heart disease recognition and diagnosis. The primary objectives of the initial WISE study were: 1) to improve diagnostic testing for ischemic heart disease in women, including symptom evaluation tools, risk assessment algorithms, and noninvasive imaging techniques; 2) to study pathophysiologic mechanisms and prognosis in women with chest pain and abnormal diagnostic testing for myocardial ischemia in the absence of epicardial coronary artery stenoses; and 3) to evaluate the influence of cyclical hormones, menopausal status, and reproductive hormone levels on symptoms and diagnostic testing results.[9]

The WISE study found that coronary artery disease (CAD) in women usually presents with chest pain and other symptoms that can differ from men. Moreover, women were found to have more non-obstructive CAD compared to men, who more often present with obstructive CAD.[1,9] Outcomes of non-obstructive CAD were discussed at the time of the WISE study's initial report, but a ten-year follow-up period was set to evaluate for complications of this condition.

Initially, medical providers did not know the etiology of the symptoms of chest pain suggestive of CAD with radiological findings of non-obstructive CAD, but multiple studies ultimately revealed that cardiovascular disease can manifest not only in large caliber artery diameter, (> 500 μm, epicardial coronary arteries) that can be visualized with imaging, but can also occur in the small caliber arteries, i.e., non-obstructions (<500 μm microvascular coronary arteries).[10] The discovery that diseased small arteries can contribute to symptoms of angina

played a critical role in determining the pathophysiology of non-obstructive CAD. Initially, the condition was known as cardiac syndrome X and then more representatively named coronary microvascular dysfunction (CMD). The symptoms and conditions of CMD were also known as ischemia with no obstructive CAD, which referred to symptoms in the absence of hemodynamically obstructive CAD, INOCA, or microvascular angina.[10] Later, the INOCA label was generalized to include other conditions such as coronary artery spasms.[10]

After the follow-up period of ten years, investigators found that women with non-obstructive CAD were at high risk for non-fatal myocardial infarction, stroke, heart failure with preserved ejection fraction, and death compared to healthy women and women without CAD.[10-12] This discovery was paramount in directing further research to identify how to treat this condition as well as how to decrease or limit its complications.

The National Heart, Lung, and Blood Institute (NHLBI) sponsored a continuation of the WISE study—the WISE coronary vascular dysfunction study—which enrolled women from 2008 to 2015. The study investigated: (1) the utility of cardiac magnetic resonance imaging (CMRI) (non-invasive testing) of abnormalities in left ventricular morphology and function and myocardial perfusion to predict Coronary Function Test (invasive testing)-measured coronary microvascular dysfunction, (2) the value of CMRI abnormalities at a one-year follow-up to predict persistent symptoms of ischemia, and (3) the value of CMRI abnormalities to predict cardiovascular outcomes.[13] The results helped to formalize initial guidelines for the diagnosis and management of women with INOCA.[10] It also helped confirm previous findings from other studies on short-term INOCA outcomes.[10]

According to the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure, Heart Failure is a complex clinical syndrome with symptoms and signs that result from any

structural or functional impairment of ventricular filling or ejection of blood.[14] Heart failure with preserved ejection fraction is a condition that has been defined differently over time as it is very heterogenic but can be simply defined as the impaired filling of the LV with relatively preserved ejection function (EF) ≥50% (normal is ≥55%).[14,15] More recent studies have shown that women primarily develop HFpEF when compared to men.[16] Not only does HFpEF account for a higher proportion of incident HF in women compared to men, but the incidence of HF with reduced ejection fraction appears particularly low in women and has fallen more rapidly over time.[15] Patients with HFpEF have a poor quality of life and frequently require hospitalizations.[17] The survival of patients with HFpEF is also poor, and is associated with high mortality rates.[17] In a major observational study, the five-year survival among patients with HFpEF was reported at 35–40% after hospitalization for HF.[17] While survival in HFrEF has significantly improved over the past decades with the help of HFrEF-specific treatments such as beta blockers and ACEI, the prognosis of patients with HFpEF has not shown any significant change within the same time period despite the use of similar pharmacological agents.[17] The lack of evidence-based treatment options may have contributed to the high mortality and morbidity in HFpEF.[17] The heterogeneity and multiple phenotyping of this syndrome makes targeted treatment and prevention challenging and continues to be a work in progress..

Since previous WISE studies also observed a high prevalence of hospital admissions among women for HFpEF exacerbation, the NHLB sponsored and launched another observational study as a continuation of the WISE study in 2015. This WISE-CVD continuation study or WISE-HFpEF study is still actively recruiting participants (NCT02582021). The main objective of the study is to compare women with INOCA to women with HFpEF. I was involved in recruitment for this study, and the inclusion and exclusion criteria are illustrated in Figure 1 of

the Appendix. Cardiovascular events served as the primary outcome measure, while secondary measures included persistent chest pain symptoms and quality of life outcomes.

The current literature supports the hypothesis that CMD and HFpEF either shares similar cardiovascular physiology, or that one is a catalyst for the other. However, there is significant uncertainty regarding the timeframe and the exact pathophysiological process.

In this project, we compared women with INOCA and women with HFpEF to reference controls. We also examined the symptoms and mechanistically identified cardiovascular processes using non-invasive imaging to help identify the similarities and/or differences among women with HFpEF and women with INOCA compared to the reference control.

Chapter 2 METHODS

Study population:

56 total participants were enrolled, with 35 with suspected INOCA, 13 women with HFpEF, and 8 reference control women.

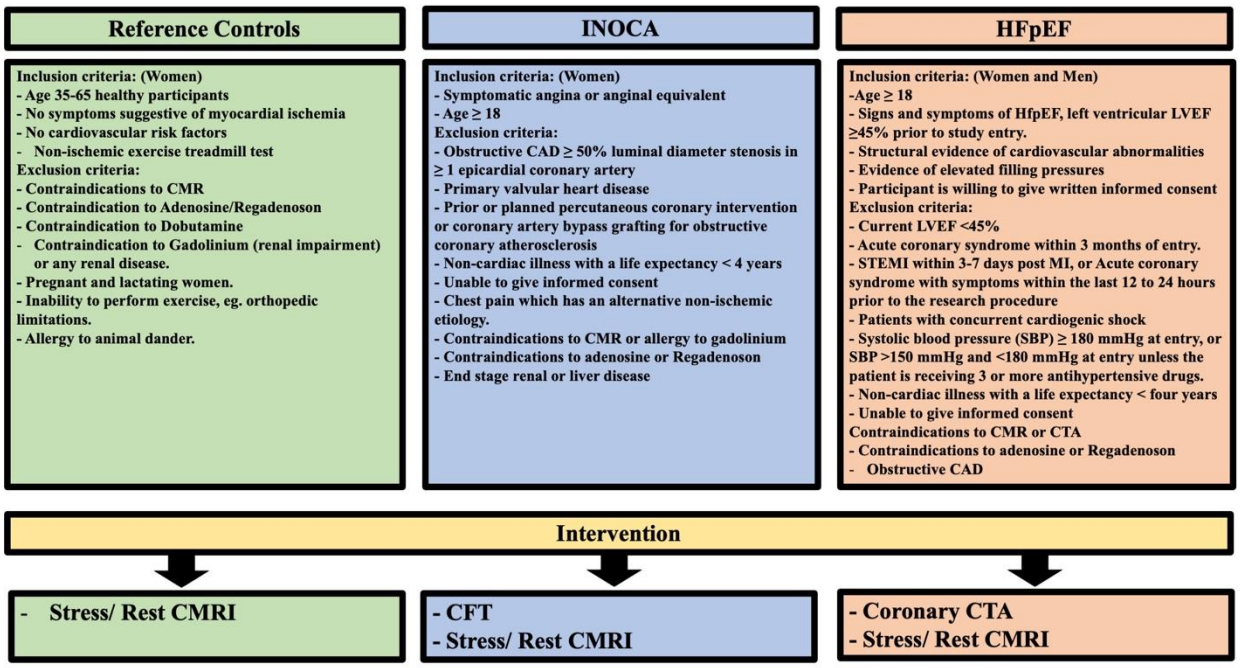

Figure 2.1: Illustration of study participants' selection criteria and the selected intervention for each group. Note: CMRI = Cardiac Magnetic Resonance Imaging; INOCA = Ischemia with no obstructive coronary artery; CAD = Coronary artery disease; HFpEF = Heart failure with preserved ejection fraction; LVEF = Left ventricular ejection fraction; STEMI = ST elevation myocardial infarction; MI = Myocardial infarction; CTA = Computed tomography angiography

The participants from the INOCA and the HFpEF groups were recruited from the Women's Ischemia Syndrome Evaluation – Coronary Vascular Dysfunction (WISE-CVD) Continuation Study, also known as Women's Ischemia Syndrome Evaluation (WISE) – Coronary Microvascular Dysfunction (CMD) and Heart Failure With Preserved Ejection Fraction (HFpEF), which was conducted at Cedars-Sinai Medical Center, Los Angeles, CA

(NCT02582021). Women with suspected INOCA underwent clinically indicated invasive coronary function testing (CFT) to document that there is no obstructive (CAD), and was classified and defined as <50% stenosis. CFT is considered the gold standard invasive test to diagnose CMD in previous publication.[18]

Participants hospitalized for HFpEF were enrolled in this study. All participants met modified criteria for diagnosis of HFpEF, based on the European Society of Cardiology guidelines (2012).[19]

Table 2.1: Study inclusion criteria.

Symptoms of heart failure (e.g., dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and edema)
Left ventricular ejection fraction > 45% prior to study entry
Structural evidence of cardiovascular abnormalities (e.g., evidence of abnormal filling or relaxation, left atrial enlargement or left ventricular hypertrophy documented by echocardiogram)
Evidence of elevated filling pressure pressures (e.g., left ventricular end diastolic pressure (LVEDP) or pulmonary capillary wedge pressure (PCWP) at rest > 15 mmHg, elevated BNP, or use of diuretics)

Table 2.2: Participant exclusion criteria.

LVEF <45%
Acute coronary syndrome (defined by ACC/AHA guidelines, including MI[20]) within three months of entry
Patients who have had an MI or other event within the 6 months prior to entry, unless an echocardiogram measurement performed after the event confirmed a LVEF ≥45%
Primary valvular heart disease (>moderate regurgitation or >mild stenosis)
Primary cardiomyopathies (hypertrophic, infiltrative or restrictive)
Constrictive pericarditis
High-output heart failure and right ventricular myopathies
Patients with concurrent cardiogenic shock requiring inotropic or intra-aortic balloon support or current acute decompensated HF requiring therapy
Alternative reason for dyspnea such as significant pulmonary disease or severe COPD
Hemoglobin less than 10 g/dl
Body mass index (BMI) more than 40 kg/m2
Systolic blood pressure (SBP) ≥ 180 mmHg at entry, or SBP >150 mmHg and <180 mmHg at entry unless the patient is receiving 3 or more antihypertensive drugs
Prior or planned percutaneous coronary intervention or coronary artery bypass grafting
Non-cardiac illness with a life expectancy less than 4 years

Table 2.2, continued: Participant exclusion criteria.

Inability to give informed consent
Contraindication to CMRI
End-stage renal disease
End-stage liver disease

Patients with obstructive CAD were also excluded by noninvasive coronary computed tomography angiography in this group due to the lack of clinically indicated CFT.

The women in the reference control group were recruited from the Cardiac Magnetic Resonance Imaging Normal Reference Control Group Testing study NCT00573339. Reference control women had no symptoms suggestive of cardiovascular ischemia, cardiovascular risk factors, and had to undergo a non-ischemic Bruce protocol exercise treadmill stress test. Consent was obtained from all participants and was approved by the institutional review board of Cedars-Sinai Medical Center.

For the cardiac stress test, all participants received either adenosine (140μg/kg) or regadenoson (n=5) stress-rest perfusion (0.4 mg). CMRI was performed using standardized product sequences (3T Siemens Healthcare, Erlangen, Germany), and a standardized gadolinium bolus of 0.05 mmol/kg injected at 4 ml/s (gadavist gadobutrol injection 1 mmol/ml) during stress and then followed by rest imaging protocols. The initial perfusion images were obtained in 3 LV short-axis slices (basal, mid, and distal LV slice positions) with the following parameters: gradient echo–EPI hybrid sequence, TR per slice 134.8ms, TE 0.94 ms, BW 1240 Hz/pixel, readout flip angle 43°, slice thickness 8 mm, image matrix 155 x 224pixels, in-plane resolution 1.34 x 1.34 x 8mm^2, parallel imaging (GRAPPA) factor 2, imaging three slices every heartbeat. Cardiac morphology and function were assessed using a stack of short axis cine images spanning the entire LV together with a series of long axis images in the horizontal, vertical, and LV outflow tract views. Typical scan parameters included contiguous

8mm/0mm slices, 1.34 x 1.34 x 8mm voxel size, 155mm x 224mm matrix, 25 cardiac phases, 11 segments, 10 heartbeats / slice. Visual assessment of splenic switch-off for evaluation of stress test adequacy was performed for participants who received adenosine.

Data Analysis:

All CMRI data was processed and analyzed using the CVI42 software (Circle Cardiovascular Imaging Inc.). The Myocardial perfusion reserve index (MPRI) was calculated as previously published.[5] The Seattle Angina Questionnaire (SAQ) measured five functional dimensions used to characterize clinical symptoms (higher scores indicate less angina symptoms). The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to characterize heart failure symptoms (higher scores indicate better HF symptoms). Left ventricular mass, end systolic and end diastolic were indexed to the body surface area.

Data Description:

All participants had their demographic information collected, including age and body surface area (BSA). All participants had their CMRI measurements documented, including left ventricular (LV) ejection fraction (EF), end diastolic volume (EVD), LVEDV index, end systolic volume (ESV), LVESV index, LV stroke volume, LV mass, LV mass/volume ratio, LV mass index, MPRI transmural, MPRI epicardial, and MPRI subendocardial. Only women with INOCA had CFT variables documented, including coronary flow reserve (CFR), change in coronary diameter, nitroglycerin response (%), and coronary blood flow % CBF). Cardiovascular risk factors such as hypertension, diabetes, smoking status, dyslipidemia, and family history of CAD were obtained from women with INOCA and women with HFpEF. Medication information,

including beta-blockers, calcium channel blockers, nitrates, aspirin, angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARB)s, and statins, were obtained from women with INOCA and women with HFpEF only. The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to characterize heart failure symptoms for both women with INOCA and women with HFpEF, only documenting physical limitation, quality of life, and symptoms of burden such as dyspnea, self-efficacy, symptoms frequency, social limitation, symptoms stability, and total symptoms score. The Seattle Angina Questionnaire simplified form (SAQ-7), measuring five functional dimensions, used to characterize anginal symptoms among women with INOCA and women with HFpEF [21].

Statistical Analysis:

We predicted that age will be a confounding variable, and age-adjusted p-values were statistically obtained using linear regression models, while non-adjusted p-values were obtained using either Fisher's Exact tests, ANOVA, or Kruskal-Wallis tests using the SAS software. We compared the baseline characteristics and CMRI data among the three groups. Finally, we compared symptoms, cardiovascular risk factors, and medications between the INOCA and the HFpEF groups.

Chapter 3 RESULTS

Baseline characteristics are summarized in Table 3.1. In brief, age and body surface area (BSA) were different among the groups; participants with HFpEF were the oldest and had the highest BSA compared to women with INOCA and reference controls. Participants with INOCA and HFpEF both had common cardiovascular risk factors. Essential hypertension and DM were higher among the HFpEF group compared to the INOCA group (75%,40%, p=0.003, 30.8%,6.5%, p=0.05) while family history of CAD was higher among the INOCA group compared to the HFpEF group (71%,46.2,p=0.04). Both groups had similar use of calcium channel blockers, aspirin, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and statins. INOCA group had lower SAQ scores compared to HFpEF group, referring to more severe angina symptoms. Heart failure symptoms measure using KCCQ questionnaire were reduced among the INOCA and HFpEF groups and there was no statistically significant difference between them across all the domains.

CMRI results are shown in Table 3.1. LV ejection fraction was significantly reduced among the HFpEF and INOCA groups compared to reference controls. There were no statistically significant differences in LV volumes, LV mass, LV mass to volume ratio across the groups. A graded reduction in subendocardial, subepicardial and transmural MPRI was observed among HFpEF, INOCA and reference controls. The epicardial MPRI remained statistically different across the groups after age adjustment. Results for the CFT among the INOCA population are illustrated in Table 3.1.

Table 3.1: Baseline and age-adjusted characteristics and CMRI variables between reference controls, INOCA, and HFpEF

Variable	Reference control (n=8)	INOCA (n=35)	HFpEF (n=13)	P-value	Age-adjusted p-value
Baseline Characteristics					
Age	48 (5)	55 (10)	62 (12)	0.007	-
BSA (m^2)	1.7 (0.1)	1.7 (0.2)	1.8 (0.2)	0.05	0.08
Risk factors					
Hypertension	0	12 (40.0%)	9 (75.0%)	0.003	-
Diabetes Mellitus	0	2 (6.5%)	4 (30.8%)	0.05	-
Former Smoker	0	10 (32.3%)	6 (46.2%)	0.5	-
Current Smoker	0	2 (6.5%)	1 (7.7%)	1	-
Dyslipidemia	1 (12.5%)	2 (8.3%)	1 (10.0%)	1	-
Family history of CAD	2 (25%)	22 (71%)	6 (46.2%)	0.04	-
Medications:					
Beta Blockers	0	6 (22.2%)	8 (80%)	0.002	-
Calcium Channel blockers	0	13 (48.1%)	4 (50%)	1	-
Nitrates	0	12 (48%)	2 (20%)	0.25	-
Aspirin	0	23 (82.1%)	7 (63.6%)	0.24	-
ACEIs	0	10 (35.7%)	2 (20%)	0.45	-
ARBs	0 (0.0%)	1 (3.8%)	0	1	-
Statins	0	19 (67.9%)	6 (54.5%)	0.48	-
SAQ-7 questionnaire	-	52.1 (19.5)	70.2 (30)	0.02	0.09
KCCQ clinical summary	-	70.1 (18.8)	62.9 (22.3)	0.28	0.11
KCCQ overall summary	-	62.7 (22.7)	62.6 (24.1)	0.99	0.49
KCCQ physical limitation	-	73.6 (19.9)	68.5 (27.9)	0.5	0.27
KCCQ quality of life	-	48.9 (29.4)	59.0 (33.1)	0.33	0.7
KCCQ symptom burden	-	63.6 (22.9)	58.3 (27)	0.51	0.25
KCCQ self-efficacy	-	67.9 (29.8)	80.8 (18.1)	0.16	0.26
KCCQ symptom frequency	-	69.4 (20.8)	60.9 (24.6)	0.25	0.07
KCCQ social limitation	-	61.6 (29.9)	66.0 (31.9)	0.68	0.85
KCCQ symptom stability	-	50.8 (24.1)	44.2 (11)	0.35	0.29
KCCQ total symptom score	-	66.5 (21.1)	59.6 (23)	0.34	0.12
CMRI variables					
LV EF (%)	66.6 (4.3)	61.8 (5.5)	62.0 (5)	0.07	0.02

Table 3.1, continued: Baseline and age-adjusted characteristics and CMRI variables between reference controls, INOCA, and HFpEF.

Variable	Reference control (n=8)	INOCA (n=35)	HFpEF (n=13)	P-value	Age-adjusted p-value
LVEDV (ml)	105.7 (10.6)	115.7 (16.7)	113.0 (26.8)	0.4	0.35
LVEDV index (ml/m^2)	63.5 (7.0)	68.5 (8.5)	62.9 (16.8)	0.21	0.24
LVESV (ml)	35.4 (6.1)	44.6 (11.2)	43.7 (15.1)	0.14	0.07
LVESV index (ml/m^2)	21.3 (4.0)	26.3 (5.7)	24.3 (8.7)	0.12	0.07
LV stroke (ml)	70.3 (7.9)	71.1 (9.7)	69.3 (13.6)	0.87	0.84
LV mass (g)	67.8 (7.2)	76 (10.8)	81.9 (23.1)	0.1	0.31
LV mass to volume	0.6 (0.1)	0.7 (0.1)	0.7 (0.2)	0.09	0.4
LV mass index (g/m^2)	40.6 (3.7)	44.9 (4.9)	45.1 (12)	0.28	0.47
MPRI					
MPRI Transmural	1.9 (0.3)	1.8 (0.3)	1.5 (0.3)	0.03	0.13
MPRI Epicardial	2.0 (0.3)	1.9 (0.3)	1.6 (0.3)	0.01	0.03
MPRI Subendocardial	1.7 (0.3)	1.6 (0.3)	1.4 (0.3)	0.11	0.34
CFT variables					
CFR		2.9 ±0.8			
Change in coronary artery diameter (%)		-1 ±15.9			
Nitroglycerin response (%)		22.3 ±32.7			
CBF (%)		48.3 ±56			

BSA = Body mass index, MPRI= Myocardial perfusion reserve index, SAQ= Seattle angina questionnaire, LVESV= Left ventricular end systolic volume, LVEDV= Left ventricular end diastolic volume, CFT= Coronary function test.

Chapter 4 DISCUSSION & CONCLUSION

Our results affirm the hypothesis that reduced myocardial perfusion is a common pathophysiologic feature in INOCA and HFpEF patients compared to reference controls. The data shows a reduction in LVEF and impaired myocardial perfusion reserve in patients with suspected INOCA and patients with HFpEF compared to reference controls. Our data also suggests that it is possible that INOCA and HFpEF share similar pathophysiological mechanism affecting myocardial and possibly worse in HFpef group. Like women with HFpEF, women with INOCA showed significant symptoms related to HF as evidenced by the KCCQ assessment.

As described earlier, women with suspected INOCA are at increased risk of developing major adverse cardiovascular events, most commonly HFpEF[1-3]; but the exact pathophysiological mechanism and factors resulting in HFpEF has not been yet elucidated. Similar to our findings, recent results from the PROMIS-HFpEF trial showed a high prevalence of CMD among HFpEF patients.[22] Emerging data also supports the hypothesis that myocardial ischemia, secondary to CMD, is a key mechanism leading to pathological remodeling in HFpEF and a contributing factor in INOCA patients.[4,12,23] It is also known that CMD has been independently associated with features of HFpEF such as LV diastolic dysfunction and elevated high sensitivity troponin levels a marker for adverse clinical outcomes and recurrent hospitalizations.[4,12] Similar to CMD, other cardiovascular risk factors such as essential hypertension and DM can adversely impact cardiac remodeling.[24] Additionally, previous studies demonstrated that INOCA and HFpEF share similar risk factor including age, obesity, hypertension, and DM.[5,11,25-27] Our current findings expand upon these prior observations by directly comparing LV remodeling parameters and myocardial perfusion in INOCA and HFpEF as compared to reference control participants.

A possible explanation for our findings is that participants in the HFpEF group are older, more obese, have a higher prevalence of DM, relatively more hypertensive, and therefore are at greater risk to have chronic myocardial microvascular ischemia evidenced by reduced perfusion. It is plausible that chronic exposure to myocardial ischemia may be linked to adverse remodeling.

The study was limited by relatively small sample size and, therefore, there was a limitation in adjustment for confounding variables. Our study was also limited by the lack of a longitudinal design and the inability to decide the temporality of our findings. In addition, our findings exclusively focused in women and can't be generalizable to include men.

When taken together, this data supports the hypothesis that CMD and other cardiovascular risk factors may play a pivotal role in both INOCA and failure progression, but temporality could not be established to the previously mentioned limitations. Future studies will need to confirm the exact mechanistic link through longitudinal investigation of women with INOCA.

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