THE RELATIONSHIP BETWEEN CHRONOTROPIC INCOMPETENCE AND EXERCISE RESPONSE IN PATIENTS WITH CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION

by

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of
Doctor of Philosophy
Rehabilitation Science

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The Relationship Between Chronotropic Incompetence and Exercise Response in Patients with Chronic Heart Failure with Reduced Ejection Fraction

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DEDICATION

This dissertation is dedicated to my husband Rich, my daughter Elise, and my son Blake. This journey would not have been possible without their unwavering love and support. Given the unprecedented circumstances under which this dissertation is being submitted, I would also like to dedicate this to all the healthcare workers around the world that are working tirelessly to care for patients fighting COVID-19, especially my sister, who is an ICU nurse. You are all heroes. Sarah, I am so proud of you.

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I would like to thank my family, my friends, my coworkers, and everyone who has supported me through this journey. My husband, Rich, supported me and believed in me when I did not believe in myself. My children, Elise and Blake, encouraged me and always knew when I needed a good laugh. My mom spent hours helping me make data tables; thanks mom! Drs. Keyser, Guccione, Krall, and Keteyian were integral in their roles as experts, mentors, and teachers. Lastly, I would like to thank all the faculty, staff, and my fellow students in the Department of Rehabilitation Science for all their contributions to shaping my doctoral experience. I appreciate all of you!

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LIST OF ABBREVIATIONS AND SYMBOLS

Activities of Daily Living ..... ADL
Age-Predicted Maximal Heart Rate……..…APMHR
Alpha……..……..α
American College of Sports Medicine……...……ACSM
Angiotensin-Converting Enzyme Inhibitor……...…….ACE
Angiotensin II Receptor Blocker……...……ARB
Asterisk……...……*
Beats per minute…….bpm
Biologic Specimen and Data Repository Information Coordinating Center…...BioLINCC
Canadian Cardiovascular Society…….……..CCS
Cardiopulmonary Exercise Test…….……..CPET
Change……...……..Δ
Chronotropic Incompetence……...……CI
Coefficient of determination……...……r^2
Consolidated Standards of Reporting Trials……...……CONSORT
Correlation coefficient…….……r
Cross……..……..†
Equals…….……=
Greater than…….……>
Greater than or Equal to……..≥
Guideline-Directed Medical Therapy……GDMT
Heart Failure ..... HF
Heart Failure - A Controlled Trial to Investigate Outcomes of
Exercise Training……...…...…….…..…HF-ACTION
Heart Failure with Preserved Ejection Fraction…….HFpEF
Heart Failure with Reduced Ejection Fraction..... HFrEF
Heart Rate at Ventilatory Threshold…….……VT HR
Heart Rate…….……HR
Heart Rate Reserve……HRR
Implantable Cardioverter Defibrillator…….……..ICD
Kilograms……...……kg
Left Ventricular Assist Device..... LVAD
Left Ventricular Ejection Fraction……..….LVEF
Left Ventricular Systolic Dysfunction…….LVSD
Less than……..……<
Less than or Equal to……..……≤

Milligrams……mg
Milliliters per beat……..mL/beat
Milliliters per kilogram body mass per minute……...…….mL/kg/min
Milliliters per minute……...…….mL/min
Minutes……...…….min
National Heart, Lung, and Blood Institute……...……..NHLBI
New York Heart Association…….……NYHA
Oxygen consumption…….……VO_2
Oxygen Consumption at Ventilatory Threshold……..……VT VO_2
Oxygen Pulse……...….O_2 pulse
Peak Absolute Oxygen Consumption…… Abs$VO2_{peak}$
Peak Heart Rate……..……HR_{peak}
Peak Oxygen Uptake..... VO_{2peak}
Percent……%
Plus or Minus…….……..±
Probability……p
Rate of Perceived Exertion……...……..RPE
Respiratory Exchange Ratio…….…..RER
Resting Heart Rate……HR_{rest}
Ventilatory Efficiency Slope……...……..VE/VCO_2
Sample Size……..…...……N
Standard Deviation……...……SD
Statistical Package for the Social Sciences……...……SPSS
Stroke Volume ..... SV
The International Business Machines Corporation……IBM
Ventilatory Threshold…….…….……VT
Years……..……..y
6-Minute Walk Test……...6MWT

ABSTRACT

THE RELATIONSHIP BETWEEN CHRONOTROPIC INCOMPETENCE AND EXERCISE RESPONSE IN PATIENTS WITH CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION

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Purpose: The purpose of this study was to (1) characterize the relationship between chronotropic incompetence (CI) and exercise capacity in patients with heart failure (HF) with reduced ejection fraction (HFrEF), and to (2) determine if patients with HFrEF and CI have an attenuated adaptation to exercise training compared to HFrEF patients without CI. **Methods:** This study was a secondary analysis of de-identified, participant-level data from the multicenter, randomized, controlled HF-ACTION clinical trial. Participants with chronic HFrEF (left ventricular ejection fraction ≤35%) on guideline-directed medical therapy (GDMT) that included a beta-adrenergic blocking agent with New York Heart Association (NYHA) class II to IV heart failure symptoms were included. Baseline analyses included all HF-ACTION participants meeting the eligibility criteria for this secondary analysis. Analyses of 3-month exercise training adaptation included participants randomized to the exercise training arm of the HF-

ACTION trial. CI was classified as a failure to achieve at least 80% of heart rate reserve (HRR) on the baseline cardiopulmonary exercise test (CPET), and participants were grouped according to presence or absence of CI at baseline. Pearson correlation and linear regression were used to determine the strength and direction of association of HRR and exercise capacity at baseline. Between CI group differences in baseline characteristics were determined using independent t-tests. Difference in exercise training adaptation after 3-months of exercise training between CI groups was determined using an independent t-test. Pearson correlation and linear regression were used to determine the strength and direction of association of baseline HRR and change in exercise capacity. Potential confounders were added to the linear regression model to determine any substantial effect. The potential confounding effect of adherence to the exercise training intervention on change in VO_{2peak} was examined using correlations and independent t-tests to compare the mean change in VO_{2peak} between adherence quartiles.

Results: 982 of 1,116 participants (88.0%) had CI at baseline. Lower HR_{peak} (118 ± 18 bpm versus 155 ± 13 bpm, $p<0.001$), VO_{2peak} (14.9 ± 4.5 mL/kg/min versus 18.9 ± 5.3 mL/kg/min, $p<0.001$), and HRR (51 ± 16 percent versus 92 ± 10 percent, $p<0.001$) were observed in participants with CI compared to those without CI. Conversely, participants with baseline CI had a higher O_2 pulse (11.8 ± 4.0 mL/beat versus 10.9 ± 3.8 mL/beat, $p=0.015$). HRR was positively correlated with VO_{2peak} at baseline ($r=0.442$; $p<0.001$). Exercise training-induced increases in VO_{2peak} were 0.83 ± 2.35 mL/kg/min and 1.32 ± 2.48 mL/kg/min for the CI and no CI groups, respectively ($p=0.174$). There was a statistically larger increase in O_2 pulse ($p=0.012$) in the no CI group compared to the

group with CI (1.13 ± 1.30 mL/beat versus 0.50 ± 1.66 mL/beat, respectively). HR_{peak} increased in participants with CI (1.4 ± 13.6 bpm; p=0.045) and decreased in participants without CI (-7.4 ± 15.4 bpm; p=0.001). **Conclusion:** CI burden was high in the HFrEF subset. Overall, CI was associated with lower VO_{2peak} and poorer CPET outcomes at baseline. Exercise training appears to be an effective therapeutic strategy to improve exercise capacity in HFrEF patients.

CHAPTER ONE

Introduction

Heart failure (HF) is a chronic, progressive syndrome characterized by an inability of the cardiopulmonary system to effectively pump and extract oxygenated blood commensurate to metabolic demand.[1] Nearly 6 million people in the United States are living with HF and 5-year survival is only 50%. [2,3] Despite a large armamentarium of pharmacologic, device, and surgical therapies, HF continues to represent a significant public health burden and is the only cardiovascular disease with increasing prevalence, incidence, and mortality.[3-5] HF morbidity is also significant, with patients experiencing frequent hospitalizations and poor quality of life.[2,3,6]

A hallmark characteristic of HF is exercise intolerance, which manifests as dyspnea and fatigue at low levels of physical exertion.[1,7] HF patients have difficulty performing simple activities of daily living (ADL) and experience reduced levels of functional independence, resulting in detrimental effects on quality of life. Exercise capacity, operationalized as peak oxygen uptake (VO_{2peak}), is an important prognostic marker in patients with HF and a criterion for both heart transplantation and left ventricular assist device (LVAD) implantation.[8,9] Pharmacologic therapies for the treatment of HF only have modest effects on exercise tolerance,[10,11] making therapeutic strategies for reversing exercise intolerance in HF of critical importance.

Patients with HF, particularly those with reduced ejection fraction (HFrEF), have a significantly lower cardiac output at peak exercise compared to healthy controls and a blunted left ventricular stroke volume (SV) response to exertion. [1,7] This results in a compensatory overreliance on cardio-acceleration which typically becomes maladaptive due to a concurrent impairment in cardiac autonomic control.[1,12,13]

Chronotropic incompetence (CI), defined as an inability to sufficiently increase heart rate (HR) with concomitant increases in exertion, is common in HFrEF, with reported prevalences varying from 20-84%.[14-16] The relationship between CI and exercise capacity in HF remains controversial, with some reports supporting an association and others indicating that CI is merely a consequence of severe HF.[7,14] A study by Jamil et al concluded that CI does not contribute to limited exercise capacity in HF, rather, other cardiorespiratory mechanisms are responsible for exercise intolerance in this population.[17] In an analysis of patients from the Heart Failure - A Controlled Trial to Investigate Outcomes of Exercise Training (HF-ACTION) on beta-adrenergic blocking agent therapy, Dobre et al[18] determined that CI is an independent prognostic marker and is associated with poor clinical outcomes in these patients. However, the interaction of CI and exercise training on exercise capacity in the HF-ACTION patients was not investigated.

Purpose and Hypothesis

The HF-ACTION trial dataset is the largest sample of exercise capacity and exercise training data in HFrEF patients to-date and presents a unique opportunity to explore the role of CI on exercise capacity in HFrEF patients. The purpose of this study

was to (1) characterize the relationship between CI and exercise capacity in HFrEF patients and to (2) determine whether baseline CI is associated with an impaired exercise training response in HFrEF patients. I hypothesize that participants with baseline CI will be less likely to adapt to exercise training. If this hypothesis is correct, after exercise training, participants with baseline CI will have a smaller or no improvement in peak heart rate (HR_{peak}) and VO_{2peak} compared to participants without CI.

Methods

Ethics Approval

The HF-ACTION clinical trial was conducted with ethics committee review and approval at each participating site. All participants signed an institutionally-approved informed consent document prior to participation. The completely de-identified data set was obtained according to standard procedures of the data repository of the National Heart, Lung, and Blood Institute (NHLBI), with no ability for participants to be re-identified. The dataset contains the full data from 2,130 participants who consented to data sharing, which represents 91.4% of participants enrolled in HF-ACTION.

Study Design

This study was a secondary analysis of de-identified, participant-level data from the multicenter, randomized, controlled HF-ACTION clinical trial. Data were obtained from NHLBI's publicly available data repository, the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).

Participants

Detailed eligibility requirements for the HF-ACTION trial have been published previously[19,20] and are listed in Figure 1. Briefly, participants in the HF-ACTION trial were eligible to participate if they had HFrEF with a left ventricular ejection fraction (LVEF) ≤35%, were receiving guideline-directed medical therapy (GDMT) for at least the previous six weeks, and had New York Heart Association (NYHA) class II to IV heart failure symptoms. HF-ACTION randomized 2,331 total participants (1,172 in usual care and 1,159 in exercise training) and median follow-up was 2.5 years.[21]

Inclusion criteria

- LVEF ≤35%
- NYHA class II, III, or IV heart failure for the previous 3 months despite a minimum of 6 weeks of treatment
- Optimal heart failure therapy at stable doses for 6 weeks before enrollment or documented rationale for variation, including intolerance, contraindication, patient preference, and personal physician's judgment
- Sufficient stability, by investigator judgment, to begin and exercise program

Exclusion Criteria

- Age <18 years
- Comorbid disease or behavioral or other limitations that interfere with performing exercise training or prevent the completion of 1 year of exercise training
- Major cardiovascular event or cardiovascular procedure, including implantable cardioverter defibrillator (ICD) use and cardiac resynchronization, within the previous 6 weeks
- Cardiovascular procedure or hospitalization for any reason planned in the future (for ICD or cardiac resynchronization therapy, this is defined as within 6 months)

Figure 1 HF-ACTION Eligibility Criteria

For baseline analyses, all participants were in sinus rhythm with completed baseline cardiopulmonary exercise tests (CPET) that achieved symptom-limited maximal effort, regardless of randomization group. Participants who were not on current beta-adrenergic blocking therapy or who had a pacemaker or bi-ventricular pacemaker were excluded from the analysis. Analyses of exercise training adaptation included only participants randomized to the exercise training arm that completed baseline and 3-month

CPET using the same exercise modality (i.e. treadmill or bike). Detailed diagrams that illustrate the participants included in the secondary analyses (Figures 6 and 7) are in Appendix B.

Exercise Testing

Participants completed a symptom-limited CPET at baseline and 3 months post-randomization. CPET procedures were conducted according to the guidelines of the American College of Sports Medicine (ACSM)[22] using either the modified Naughton treadmill protocol or a stationary cycle ergometer with expired air collected for analysis. The specific characteristics of the exercise testing procedures have been reported previously.[9,19,23]

Participants were instructed to take their beta-adrenergic blocking agent between 3 and 10 hours prior to their scheduled CPET and to take all other medications as usual on the day of their test. Important CPET parameters, including peak oxygen uptake (VO_{2peak}) and respiratory exchange ratio (RER) were measured using expired gas analyses. Ventilatory threshold (VT) was determined using the v-slope method.[24] VO_{2peak} was determined as the highest value achieved within the last 90 seconds of exercise or first 30 seconds of recovery.[9] Heart rate (HR) at peak exercise (HR_{peak}) was classified as the highest HR during the last minute of exercise[18] and resting heart rate (HR_{rest}) was measured after two minutes of seated rest before the CPET.[18] Rating of perceived exertion (RPE) and total exercise duration were also collected. Peak oxygen pulse (O_2 pulse) was calculated from available data using the following formula (Eq. 1):

$$O_2 \text{ pulse} = AbsVO_{2peak}/HR_{peak} \quad \text{Eq. 1}$$

In this equation, $AbsVO2_{peak}$ is peak absolute oxygen uptake (in milliliters per minute) and HR_{peak} is peak HR achieved in the last minute of exercise (in beats per minute).

Characterization of Chronotropic Incompetence

The presence or absence of CI at baseline was determined using the percentage of heart rate reserve (HRR) achieved on the baseline CPET. The HRR method is advantageous because it accounts for HR dynamics rather than a single HR measurement.[15,16] HRR was calculated according to the following formula (Eq. 2):[15,16]

$$HRR = (HR_{peak} - HR_{rest})/(APMHR - HR_{rest}) \times 100 \quad \text{Eq. 2}$$

In this equation, APMHR is the traditional age-predicted maximal heart rate (APMHR) calculated as follows (Eq. 3):[25]

$$APMHR = 220 - age \quad \text{Eq. 3}$$

Presence of CI at baseline was defined as an inability to achieve at least 80% of the HRR, which is a well-accepted definition of CI and has been used previously in the literature as a threshold for determining CI in HF patients.[7,16,26] Therefore, CI status was

dichotomized as presence (<80% HRR achieved) or absence (≥80% HRR achieved) of CI using the baseline CPET.

Exercise Training Adaptation

Exercise training adaptation was characterized in the subset of participants randomized to the exercise training arm in the HF-ACTION trial with baseline and 3-month CPET data. The effect of exercise training on important CPET parameters was determined by calculating the difference between means of baseline CPET parameters and 3-month CPET measurements, with baseline CPET measurements subtracted from 3-month values. Therefore, positive results indicate an increase in the parameter after exercise training and negative results indicate a decrease after exercise training.

Data Analysis

Continuous variables are summarized as means ± SD and categorical and nominal variables are summarized as frequencies and percentages. Histograms were used to determine the distribution for each continuous outcome variable. Data were examined for outliers using box plots, scatter plots, and descriptive characteristics (minimums, maximums, and ranges). Parametric tests were used after checking for normality of continuous outcome variables. All tests were performed using two-tailed hypotheses, with statistical significance set at $p<0.05$. All statistical analyses were performed using IBM Statistics SPSS Subscription for Windows (IBM, 2018).

Baseline Participant Characteristics and CPET Outcomes. Baseline participant characteristics and CPET outcomes were compared between CI groups according to presence or absence using independent t-tests. Levene's test was used to check for

equality of variances. Frequencies of participant characteristics were compared between CI groups using the Chi Square test and Fisher's Exact test, when appropriate.

Association Between Baseline HRR and Baseline Exercise Capacity. In addition to comparing exercise capacity between CI groups, examining the linear association between HRR and VO_{2peak} further characterizes the relationship between the severity of chronotropic incompetence and exercise capacity. Pearson correlations were used to determine the strength and direction of the linear association between the HRR and VO_{2peak} achieved on the baseline CPET. Additionally, VO_{2peak} was regressed on HRR to examine the relationship between these two continuous variables after checking for normality, linearity, and homoscedasticity. Potential confounders, including beta blocker dose using carvedilol equivalents,[18] body mass, and LVEF were individually added to the linear regression model to qualitatively determine whether these variables substantially changed the relationship between HRR and VO_{2peak}.

Exercise Training Adaptation. Exercise training adaptation parameters were compared separately for males and females to examine associations without the confounding of potential sex differences. Mean baseline CPET parameters were compared between CI groups using independent t-tests. Paired t-tests were used to compare mean changes in CPET measures from 3-months to baseline within each CI group. Mean changes in CPET measures from 3-months to baseline were also compared between CI groups using independent t-tests. Additionally, change in VO_{2peak} was regressed on baseline HRR to determine their association. Potential confounders including beta blocker dose using carvedilol equivalents,[18] body mass, baseline VO_{2peak},

age, LVEF, and exercise training adherence were individually added to the linear regression model to qualitatively examine whether there was a substantial change, if any, to the relationship between HRR and change in VO_{2peak}. To further explore the potential confounding effect of exercise training adherence on change in VO_{2peak}, the mean change in VO_{2peak} observed in participants in the first and fourth quartiles of adherence, operationalized as minutes of exercise per week during the 3-month intervention, were compared using independent t-tests. Finally, correlations were used to determine the strength and direction of the linear associations between (1) change in VO_{2peak} and adherence and (2) baseline HRR and adherence.

Results

There were 1,116 total participants included in the baseline analyses and 418 total participants included in the 3-month analyses. Figures 6 and 7 in Appendix B describe the participant sample size based on each eligibility criterion for baseline and 3-month analyses, respectively.

Participant Characteristics

Participant characteristics are displayed in Table 1, using means ± standard deviation (SD). Overall, presence of CI was high, with 982 participants (88.0%) classified as chronotropic incompetent. Age (56 ±13 years in CI group versus 57 ± 13 years in no CI group; p=0.514) and distributions of sex and race were similar between groups. Participants with CI had statistically significantly higher body mass (94.2 ± 24.3 kg versus 89.3 ±23.6 kg; p=0.029) and lower LVEF (26 ± 7 percent versus 27 ± 8

percent; p=0.023), although the difference in LVEF is not clinically meaningful. Participants with CI had more advanced HF based on NYHA functional class (34.4% of CI group with Class III/IV HF versus 19.4% of no CI group; p=0.002), were on a higher dose of their beta-adrenergic blocking agent using carvedilol equivalents (43 ± 28 mg versus 35 ± 29 mg; p=0.002), had a higher frequency of ischemic HF etiology (48.3% of CI group versus 34.3% of no CI group; p=0.003), and were more likely to be a current smoker (21.0% versus 12.7%; p=0.029). These differences in clinical characteristics are both statistically and clinically meaningful and represent more advanced disease in participants with baseline CI.

Table 1 Baseline Demographic and Clinical Characteristics by CI Status

Characteristic	CI (N=982)	No CI (N=134)	p
Age, y	56 ± 13	57 ± 13	0.514
Body mass, kg	94.2 ± 24.3	89.3 ± 23.6	0.029 *
LVEF, %	26 ± 7	27 ± 8	0.023 *
Current smoker, n	206 (21.0)	17 (12.7)	0.029 *
Sex, n			
Males	657 (66.9)	78 (58.2)	0.052
Females	325 (33.1)	56 (41.8)	
Etiology of HF, n			
Ischemic	474 (48.3)	46 (34.3)	0.003 *
Non-ischemic	508 (51.7)	88 (65.7)	
NHYA class, n			
II	644 (65.6)	108 (80.6)	0.002 *
III	332 (33.8)	25 (18.7)	
IV	6 (0.6)	1 (0.7)	
Race, n			
Black	355 (36.2)	54 (40.3)	0.446
White	564 (57.4)	68 (50.7)	
Asian	51 (5.2)	10 (7.5)	
Other	12 (1.2)	2 (1.5)	
CCS angina class, n			
No angina	819 (83.4)	113 (84.3)	0.470
I	85 (8.7)	14 (10.4)	
II	77 (7.8)	7 (5.2)	
Medications			
Beta blocker dose, mg	43 ± 28	35 ± 29	0.002 *
ACE, n	750 (76.4)	107 (79.9)	0.445
ARB, n	221 (22.5)	32 (23.9)	0.742
Loop diuretic, n	746 (76.0)	95 (70.9)	0.201
Aldosterone antagonist, n	421 (42.9)	57 (42.5)	1.000
Digoxin, n	409 (41.6)	51 (38.1)	0.455
Nitrates, n	230 (23.4)	30 (22.4)	0.828

Means are expressed ± SD. All other values are expressed as number (percentage) of participants. P values represent differences between CI and no CI groups, with an asterisk (*) indicating a significant between group difference at the α=0.05 level.

Baseline Exercise Capacity

Approximately 90% of all participants completed the CPET using a treadmill, with no significant difference (p=0.219) in mode of exercise between the CI groups (Table 2). Participants with baseline CI had clinically meaningful and statistically significantly lower HR_{peak} (118 ± 18 bpm versus 155 ± 13 bpm, p<0.001; Figure 2), VO_{2peak} (14.9 ± 4.5 mL/kg/min versus 18.9 ± 5.3 mL/kg/min, p<0.001; Figure 2), exercise duration (9.5 ± 3.9 min versus 12.7 ± 4.5 min, p<0.001; Table 2), and HRR (51 ± 16 percent versus 92 ± 10 percent; Table 2). Conversely, participants with baseline CI had a higher O_2 pulse (11.8 ± 4.0 mL/beat versus 10.9 ± 3.8 mL/beat, p=0.015), which was both statistically and clinically significant (Figure 2). Although there was a statistically significant difference in RER between groups (p<0.001), this difference (1.09 ± 0.11 in CI group versus 1.12 ± 0.09 in no CI group) is not substantially clinically meaningful (Table 2).

Table 2 Baseline Cardiopulmonary Performance Parameters by CI Status

Characteristic	CI (N=982)	No CI (N=134)	p
Exercise mode, n			
Bike	104 (10.6)	9 (6.7)	0.219
Treadmill	873 (88.9)	123 (91.8)	
Resting Blood pressure, mmHg			
Systolic	115 ± 18	116 ± 17	0.347
Diastolic	71 ± 11	72 ± 11	0.171
Cardiopulmonary Exercise Test			
Resting HR, bpm	70 ± 12	74 ± 13	0.002 *
Peak VO_2, mL/min	1398 ± 529	1702 ± 645	<0.001 *
Exercise duration, min	9.5 ± 3.9	12.7 ± 4.5	<0.001 *
RER	1.09 ± 0.11	1.12 ± 0.09	<0.001 *
HRR, %	51 ± 16	92 ± 10	---

Means are expressed ± SD. All other values are expressed as number (percentage) of participants. P values represent differences between CI and no CI groups, with an asterisk (*) indicating a significant between group difference at the α=0.05 level.

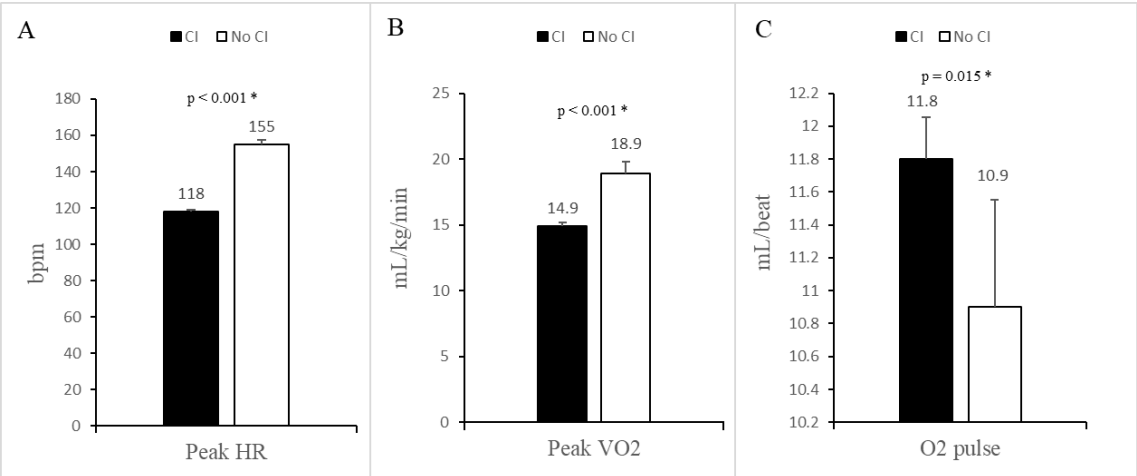

Figure 2 Baseline differences in CPET parameters between CI and no CI groups for (A) HR_{peak}, (B) VO_{2peak}, and (C) O_2 pulse. An asterisk (*) indicates a significant ($p<0.05$) between group difference. Error bars indicate upper bound of the 95% confidence interval.

Association Between Baseline HRR and Baseline Exercise Capacity

In addition to comparing exercise capacity between CI groups, the linear association between HRR and exercise capacity was examined. Baseline HRR was positively correlated with baseline VO_{2peak} ($r=0.442$; $p<0.001$). Figure 3 displays the association of VO_{2peak} regressed on HRR for the total sample (slope=0.11; $r^2=0.195$), males only (slope=0.13; $r^2=0.263$), and females only (slope=0.08; $r^2=0.168$). The association between baseline HRR and baseline VO_{2peak} was larger in magnitude for males than females, with every 1% increase in HRR increasing VO_{2peak} 0.13 mL/kg/min in men and 0.08 mL/kg/min in women, on average (Figure 3). Individually adding clinically-relevant potential confounding variables, including beta-adrenergic blocking agent dose in carvedilol equivalents, body mass, and LVEF to the linear regression model did not substantially change the HRR-VO_{2peak} association.

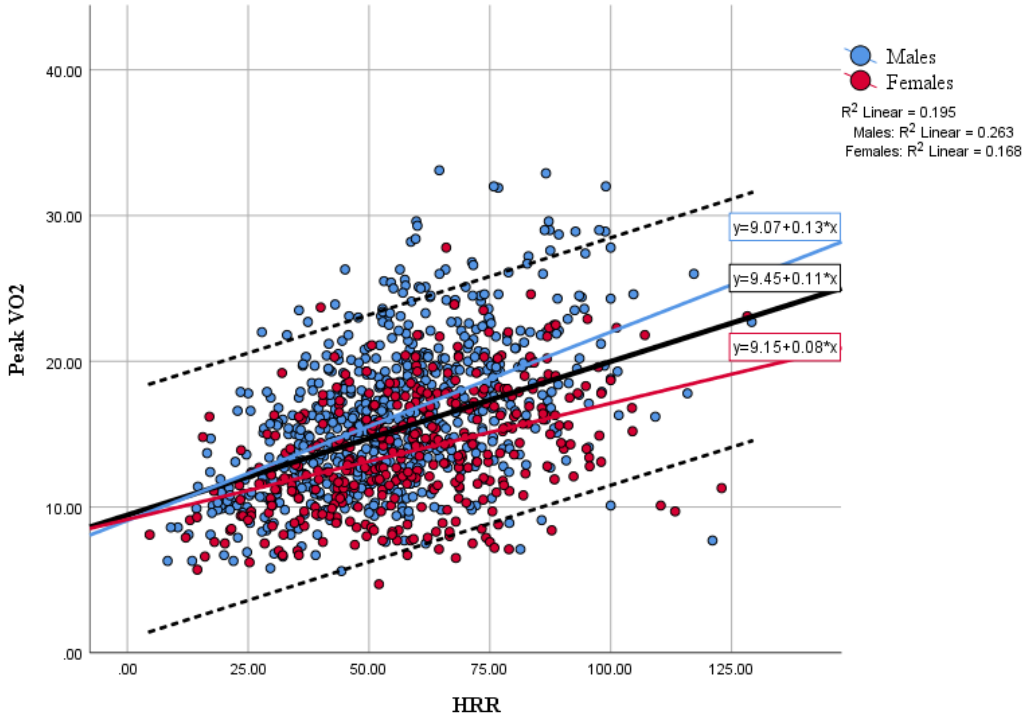

Figure 3 Relationship between baseline HRR and baseline VO_{2peak} for the total sample (black line), males (blue line), and females (red line). Black dotted lines represent the 95% confidence interval for the total sample.

Exercise Training Adaptation

A total of 258 males and 160 females were included in the exercise training analysis. Baseline and change scores are presented separately for males and females in Table 3. Baseline differences in Table 3 represent observations from participants randomized to the exercise training arm. Presence of CI at baseline was high for both males (91.5%) and females (82.5%) randomized to exercise training (Table 3).

Participants with baseline CI had clinically meaningfully and statistically significantly lower HR_{peak} (116 ± 18 bpm versus 153 ± 12 bpm, p<0.001 in males; 121 ± 18 bpm versus 154 ± 15 bpm, p<0.001 in females), VO_{2peak} (15.7 ± 4.4 mL/kg/min versus 20.2 ± 4.3 mL/kg/min, p<0.001 in males; 13.6 ± 4.0 mL/kg/min versus 17.3 ± 4.1 mL/kg/min, p<0.001 in females), exercise duration (10.0 ± 3.8 min versus 12.6 ± 3.7 min, p=0.003 in males; 8.8 ± 3.3 min versus 12.9 ± 4.0 min, p<0.001 in females), and HRR (50 ± 16 percent versus 93 ± 14 percent in males; 53 ± 16 percent versus 93 ± 11 percent in females). Although not statistically significant, O_2 pulse was meaningfully higher in males (12.9 ± 4.1 mL/beat versus 11.8 ± 2.2 mL/beat; p=0.063) and females (9.2 ± 2.5 mL/beat versus 8.3 ± 1.9 mL/beat; p=0.060) with CI at baseline (Table 3). There was no clinical or statistical difference in HR_{rest} between CI groups in women (71 ±12 bpm versus 71 ± 12 bpm; p=0.992), but men with baseline CI had a clinically important and statistically lower HR_{rest} than men without baseline CI (69 ± 12 bpm versus 76 ± 12 bpm; p=0.006).

Table 3 Change in Cardiopulmonary Parameters by CI Status

Characteristic	Baseline			Change from Baseline		
	CI	No CI	p	CI	No CI	p
Males, n	236 (91.5)	22 (8.5)	---	234 (90.7)	24 (9.3)	---
Body mass, kg	95.3 ± 22.5	90.7 ± 19.6	0.369	-0.2 ± 3.5	-0.4 ± 3.0	0.828
Resting HR, bpm	69 ± 12	76 ± 12	0.006 *	-1 ± 9	-8 ± 15	0.031 *
Peak HR, bpm	116 ± 18	153 ± 12	<0.001 *	1 ± 13 †	-10 ± 19 †	0.001 *
Peak VO_2, mL/kg/min	15.7 ± 4.4	20.2 ± 4.3	<0.001 *	1.0 ± 2.4 †	1.2 ± 2.8 †	0.568
Peak VO_2, mL/min	1494 ± 543	1804 ± 399	0.011 *	76 ± 212 †	113 ± 251 †	0.460
Exercise duration, min	10.0 ± 3.8	12.6 ± 3.7	0.003 *	1.7 ± 2.1 †	2.6 ± 3.5 †	0.242
Oxygen pulse, mL/beat	12.9 ± 4.1	11.8 ± 2.2	0.063	0.6 ± 1.8 †	1.4 ± 1.3 †	0.051
RER	1.10 ± 0.11	1.15 ± 0.06	0.005 *	0.00 ± 0.10	-0.01 ± 0.06	0.669
HRR, %	50 ± 16	93 ± 14	---	2 ± 13 †	-12 ± 23 †	0.015 *
Females, n	132 (82.5)	28 (17.5)	---	133 (83.1)	27 (16.9)	---
Body mass, kg	84.4 ± 22.0	75.4 ± 16.6	0.048 *	0.2 ± 3.8	-0.8 ± 3.0	0.206
Resting HR, bpm	71 ±12	71 ± 12	0.992	0 ± 9	2 ± 8	0.139
Peak HR, bpm	121 ± 18	154 ± 15	<0.001 *	3 ± 14 †	-5 ± 11 †	0.006 *
Peak VO_2, mL/kg/min	13.6 ± 4.0	17.3 ± 4.1	<0.001 *	0.8 ± 2.2 †	1.4 ± 2.2 †	0.172
Peak VO_2, mL/min	1109 ± 334	1276 ± 299	0.017 *	72 ± 184 †	92 ± 161 †	0.596
Exercise duration, min	8.8 ± 3.3	12.9 ± 4.0	<0.001 *	1.8 ± 2.3 †	2.0 ± 2.6 †	0.801
Oxygen pulse, mL/beat	9.2 ± 2.5	8.3 ± 1.9	0.060	0.4 ± 1.3 †	0.9 ± 1.3 †	0.037 *
RER	1.06 ± 0.11	1.10 ± 0.10	0.099	0.02 ± 0.10	0.00 ± 0.10	0.328
HRR, %	53 ± 16	93 ± 11	---	3 ± 15 †	-8 ± 15 †	0.001 *

Means are expressed ± SD. All other values are expressed as number (percentage) of participants. P values represent differences between CI and no CI groups for males and females, with an asterisk (*) indicating a significant between group difference at the α=0.05 level. A cross (†) indicates a significant ($p<0.05$) within group difference from the baseline value.

Within Group Exercise Training Adaptation. After 3 months of exercise training, participants in both CI groups had statistically and clinically relevant improvements VO_{2peak}. VO_{2peak} increases were observed in participants with CI (0.83 ± 2.35 mL/kg/min, $p<0.001$; 6.4% increase in men and 5.9% increase in women) and without CI (1.32 ± 2.48 mL/kg/min, $p=0.001$; 5.9% in men and 8.1% in women) at baseline (Figure 4). Increases in O_2 pulse were also observed in both CI groups (0.50 ± 1.66 mL/beat, $p<0.001$ for baseline CI group; 1.13 ± 1.30 mL/beat, $p<0.001$ for no CI at baseline group; Figure 4). Additionally, both CI groups had important changes in HR_{peak} (Figure 4), with an observed increase in participants in the baseline CI group (1.4 ± 13.6 bpm; $p=0.045$) and an observed decrease in the no CI group (-7.4 ± 15.4 bmp; $p=0.001$).

Between Group Exercise Training Adaptation. Figure 4 compares the training effects observed between baseline CI groups after 3 months of exercise training on VO_{2peak}, HR_{peak}, and O_2 pulse. Although there was not a statistically significant difference in VO_{2peak} improvement between CI groups ($p=0.174$), the improvement in the no CI group was 62% greater than in the group with baseline CI (1.32 ± 2.48 mL/kg/min versus 0.83 ± 2.35 mL/kg/min, respectively). Further, there was a statistically significant difference in improvement in O_2 pulse between CI groups ($p=0.012$), with the observed improvement in the no CI group more than double the observed improvement in the group with CI (1.13 ± 1.30 mL/beat versus 0.50 ± 1.66 mL/beat, respectively), which is also clinically important.

There were also important differences in HR responses to exercise training between CI groups, including HR_{rest} and HR_{peak}. There was a clinically important

decrease in HR_{rest} (-8 ± 15 bpm) observed in men without baseline CI, which was not seen in men with CI or in women (Table 3). There was a small increase in HR_{peak} after exercise training in participants with CI (1.4 ± 13.6 bpm; p=0.045), although this change is not clinically meaningful. Conversely, there was a substantial decrease in HR_{peak} observed in the participants without CI, which was both clinically and statistically significant (-7.4 ± 15.4 bpm; p=0.001). Figure 4 displays the disparity in HR_{peak} changes between CI groups (p<0.001) after exercise training.

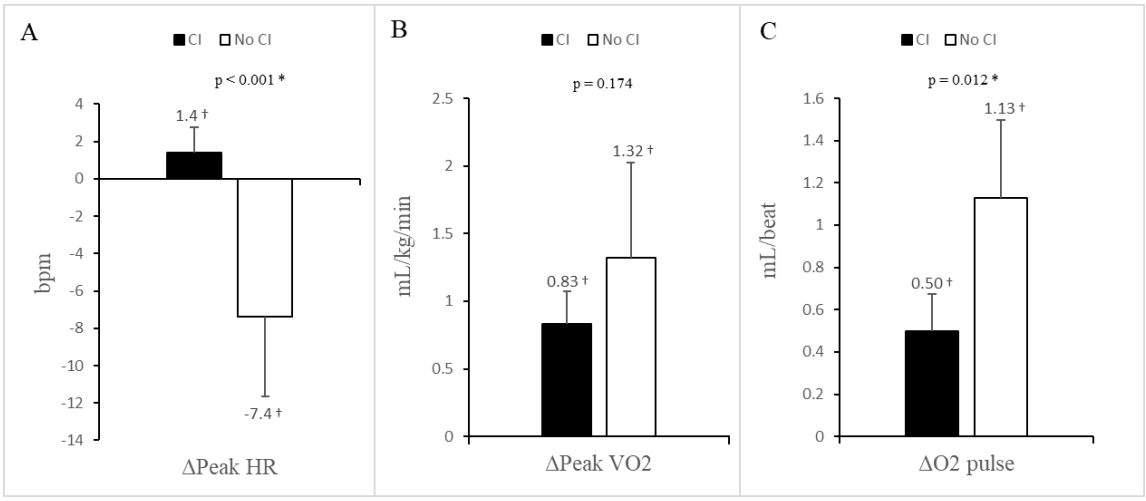

Figure 4 Changes in CPET parameters after 3 months of exercise training between CI and no CI groups for (A) HR_{peak}, (B) VO_{2peak}, and (C) O_2 pulse. An asterisk (*) indicates a significant (p<0.05) between group difference. A cross (†) indicates a significant (p<0.05) within group difference from the baseline value. Error bars indicate upper bound of the 95% confidence interval.

Association Between Baseline HRR and Change in Exercise Capacity. Baseline HRR was not correlated with change in VO_{2peak} ($r=-0.022$; $p=0.659$). Figure 5 displays the association of change in VO_{2peak} regressed on baseline HRR for the total sample, males only, and females only. Individually adding clinically-relevant potential confounding variables, including baseline beta-adrenergic blocking agent dose in carvedilol equivalents, baseline body mass, baseline VO_{2peak}, age, baseline LVEF, adherence to exercise training, and change in body mass to the linear regression model did not qualitatively substantially change the HRR-change in VO_{2peak} association.

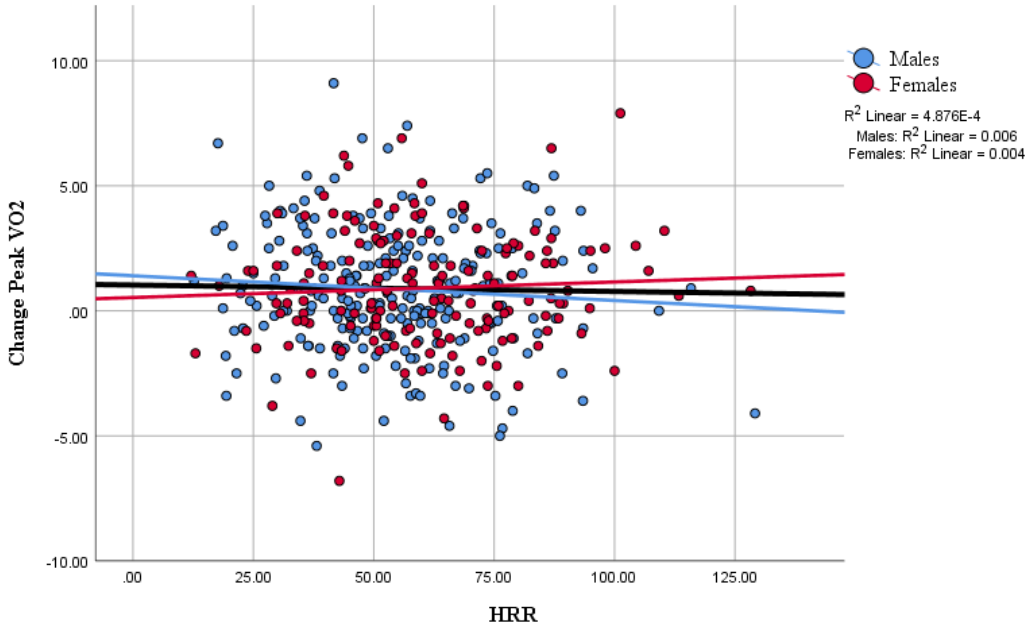

Figure 5 Relationship between baseline HRR and change in VO_{2peak} for the total sample (black line), males (blue line), and females (red line).

Adherence to Exercise Training. There was a positive correlation between change in VO_{2peak} and adherence to the exercise training intervention (r=0.136; p=0.007). To determine how adherence to the exercise training intervention (operationalized as minutes of exercise per week during the 3-month intervention) impacted the observed change in VO_{2peak}, adherence quartiles were compared. Participants in the first quartile of adherence (exercised less than 51.6 minutes per week) had a significantly smaller

increase in VO_{2peak} than participants in the fourth quartile of adherence (exercised more than 119.1 minutes per week), with VO_{2peak} increasing 0.62 ± 2.53 mL/kg/min and 1.45 ± 2.36 mL/kg/min for the first and fourth quartiles, respectively (p=0.019). Additionally, participants with lower baseline HRR tended to have poorer adherence to the exercise training intervention (r=0.125; p=0.012).

Discussion

CI burden was high in this subset of HF-ACTION participants (88%), which is consistent with upper end of the 20-84% prevalence range reported in the literature.[7,14,15,18] Reported CI prevalence in HF populations varies depending on the criteria used to classify CI.[7,14,15,18] The method I chose to calculate HRR and threshold for dichotomizing CI status is advantageous because it accounts for HR dynamics rather than using a single HR measurement, is well-supported in the literature, and is easily calculated and accepted for clinical use.[7,15,16,26] A major limitation of this method, however, is that the traditional method of predicting maximal HR[25] will overestimate HR_{peak} prediction in HF patients on beta-adrenergic blockade therapy.[27] Keteyian et al[27] published an alternative method for calculating predicted maximal HR for HF patients on beta-adrenergic blocking therapy. This method, as well as alternative thresholds for dichotomizing CI, can be explored in future research to further characterize CI in the HF-ACTION cohort.

Exercise Capacity

Exercise capacity in the total sample was poor, with mean baseline VO_{2peak} 14.9 ± 4.5 mL/kg/min for the CI group and 18.9 ± 5.3 mL/kg/min in the group without CI (Figure 2). VO_{2peak} is an important prognostic marker in patients with HF.[8,9,14] The lower VO_{2peak} observed in CI participants suggests that HFrEF patients with CI have poorer clinical status. Participants with CI at baseline also had more advanced HF symptomatology compared to patients without CI and required higher doses of beta-adrenergic blocking therapy (Table 1), which supports the contention that CI is associated with poorer clinical status.

There was a significant correlation between HRR and VO_{2peak} at baseline ($r=0.442$; $p<0.001$), with HRR explaining approximately 20% of the variance in the observed VO_{2peak} for the total sample ($r^2=0.195$; Figure 3). Given the slope of the linear regression model fit to the HRR-VO_{2peak} relationship (slope=0.11; Figure 3), each 10 percentage point change in HRR would result in an approximate 1.1 mL/kg/min change in VO_{2peak}. An increase in VO_{2peak} of this magnitude is clinically significant and has prognostic implications in HF patients.[9,28,29] These data show that CI plays an important role in exercise intolerance in patients with HFrEF, with more severe autonomic dysfunction resulting in poorer exercise capacity. Jamil et al observed a similar association ($r^2=0.179$, slope=0.09) between HRR and VO_{2peak} in 90 patients with severe left ventricular systolic dysfunction (LVSD) but concluded that CI does not limit exercise capacity in chronic HF patients.[17] The size of the cohort in my analysis (1,116 patients

compared to 90 in the Jamil study[17]) likely contributes to the difference in significance found at similar r^2 values.

Although Jamil et al[17] observed smaller HRR-VO_{2peak} associations in patients with LVSD compared to patients with no LVSD, the contribution of CI to limiting exercise capacity is still clinically and prognostically important. In a secondary analysis also from the HF-ACTION cohort, Dobre et al[18] found that patients with a HRR <60% during exercise testing had increased all-cause mortality and all-cause hospitalization, and each 10% decrease in HRR resulted in a 17% increased risk of all-cause mortality and 13% increased risk of cardiovascular mortality or HF hospitalization.[14,15] The mean HRR achieved during baseline CPET was only 51% (Table 2) in the CI group (versus 92% in the no CI group), suggesting that participants with baseline CI in my analysis had significantly higher risk for mortality and hospitalization than participants without CI. This further bolsters the argument that participants with CI have poorer clinical status and prognosis.

Exercise Training Adaptation

Both participants with (0.83 ± 2.35 mL/kg/min) and without (1.32 ± 2.48 mL/kg/min) CI at baseline had significant increases in VO_{2peak} after 3 months of exercise training, which is expected based on previously reported exercise training effects in HFrEF patients.[15,20,30,31] However, in 40 men with HFrEF randomized to exercise training, Keteyian et al[31] reported a mean increase of 2.2 ± 0.5 mL/kg/min after 12 weeks of exercise training. Although the observed improvement in VO_{2peak} was smaller in my analysis, it is still clinically important. In a secondary analysis of the HF-ACTION

cohort, Swank et al[28] found that the modest increases in VO_{2peak} observed in HF-ACTION were associated with improvements in clinical outcomes, and every 6% increase in VO_{2peak} had an accompanying lower risk of all-cause and cardiovascular mortality and all-cause and heart failure-related hospitalization. Similarly, Keteyian et al[9] found that each 1 mL/kg/min decrement in VO_{2peak} in the HF-ACTION cohort increased mortality risk by 16%. This suggests that small improvements in VO_{2peak} can be clinically meaningful. Although the magnitude of improvement in VO_{2peak} did not differ significantly between CI groups in my analysis ($p=0.174$), the exercise-induced training effect was 62% greater in participants without CI. It is possible that this has clinical and prognostic implications in HFrEF patients with CI.

HR responses to exercise training were clinically and statistically different between CI groups ($p<0.001$; Figure 4). The small increase in HR_{peak} observed after exercise training in participants with CI (1.4 ± 13.6 bpm; $p=0.045$) is not clinically meaningful and is contrary to the 10 ± 4 bpm[31] and 9 ± 3 bpm[30] HR_{peak} increases observed in the literature after exercise training in HFrEF.[15] The -7.4 ± 15.4 bpm decrease in HR_{peak} observed in participants without CI (-10 ± 19 bpm in men and -5 ± 11 bpm in women; Table 3) was unexpected, although Keteyian et al[30] reported no change in HR_{peak} after 24 weeks of exercise training in 4 participants with HFrEF without CI at baseline. RER_{peak} measurements in this group reflect sufficient effort on the CPET (Table 3), so this unexpected decrease in HR_{peak} cannot be explained by CPET effort. Men without CI had a higher HR_{rest} at baseline (76 ± 12 bpm versus 69 ± 12 bpm; $p=0.006$) and a clinically important decrease in HR_{rest} (-8 ± 15 bpm) at 3 months, which

was not seen in men with CI or in women (Table 3). It is possible that changes in beta-adrenergic blocking dose during exercise training confounded the HR response in this group.

Based on the Fick principle, VO_2 equals the product of cardiac output and arterial-venous oxygen content difference.[32] This can be extrapolated to VO_{2peak} being equal to the product of HR_{peak} and peak O_2 pulse using parameters derived from CPET.[32] Therefore, the degrees of increase inVO_{2peak} attributed to changes in HR and O_2 pulse were different between CI groups. The VO_{2peak} increase observed in participants with CI was mediated by an interaction of small increases in HR_{peak} and peak O_2 pulse, whereas the VO_{2peak} improvement observed in participants without CI was mediated solely by increasing O_2 pulse, despite a reduction in HR_{peak}. O_2 pulse change was 0.50 ± 1.66 mL/beat in CI participants (an approximate 5% increase), whereas participants without CI had a mean 1.13 ± 1.30 mL/beat change (more than 10% increase) in O_2 pulse. This increase is larger than exercise-induced O_2 pulse changes reported previously in HFrEF patients.[30,31]

Previous literature observed that exercise training can partially reverse CI in stable HFrEF patients.[15,30] In this analysis, improvement in VO_{2peak} was largely attributed to increases in O_2 pulse rather than HR_{peak}. Future research is needed to assess the precise mechanisms of exercise training-induced adaptations in HFrEF patients with CI and potential therapeutic strategies for mitigating the deleterious effects of CI in these patients.

Limitations

Overall adherence to the exercise training intervention was moderate-to-low,[20] with 50% of participants exercising less than 90 minutes per week. Although the data show significant improvements in VO_{2peak} and other important CPET parameters, it is possible that these responses were attenuated due to poor adherence. Increases in VO_{2peak} were significantly greater in participants in the fourth quartile of adherence versus the first quartile, which suggests that there is a dose-response based on volume of exercise. Additionally, since participants with low HRR at baseline tended to have poorer adherence, it is possible that improvements in the CI groups could have been larger with better exercise adherence. This also suggests that reduced exercise capacity at baseline, observed in participants with CI, moderated adherence in these participants.

While there were observed improvements in exercise capacity after exercise training in HFrEF patients, it is not possible to elucidate the mechanisms responsible for these changes. I could not characterize potential cardiac structural or functional changes. I also could not determine if improvements were attributed to changes in sinoatrial node sympathetic responsiveness due to lack of plasma norepinephrine measurements. Similarly, I could not distinguish the mechanisms for changes in O_2 pulse, which can be caused by central factors including increased peak stroke volume or peripheral factors including decreased systemic vascular resistance and increased arteriovenous oxygen difference.

It was not possible to assess the effects of potential changes to pharmacologic regimens and beta-adrenergic blocking agent doses that occurred throughout the 3-month

study interval. It is possible that reductions in HR_{rest} and HR_{peak} observed in some subgroups were due to incremental increases in prescribed beta-adrenergic blocking doses.

I cannot rule out the contribution of a potential learning effect or a greater effort on the CPET to improvements in VO_{2peak}, although these potential confounders were mitigated by performing a practice CPET prior to baseline assessment and including data only for participants who terminated their CPET based on symptom-limited volitional fatigue, which is supported by peak RER and rate of perceived exertion (RPE) data. Additionally, I conducted a sensitivity analysis comparing the change in VO_{2peak} observed in participants with RER≥1.05 and RER<1.05 on CPET and found no significant differences between these groups for participants with and without CI. Therefore, it does not appear that participant effort confounded the CPET measurements in this study.

Although exercise capacity and other CPET parameters are important clinically significant and prognostic markers in HFrEF, I could not evaluate the contribution of peripheral skeletal muscle structural and functional adaptations to the observed improvement in exercise capacity. Peripheral skeletal muscle adaptations provide an alternative mechanistic explanation for improving exercise capacity, independent of central adaptations, and therefore have therapeutic potential in HFrEF patients.

This data is derived from a large, well-represented sample of HFrEF patients and the effects of this exercise training program on clinical outcomes, quality of life, health status, and disease severity have been reported previously.[20,21,23,28,33] However, the

findings cannot be generalized to other types of HF, including heart failure with preserved ejection fraction (HFpEF). Additionally, the potential effects of multiplicity, such as Type I error, should be considered in the context of these findings. I did not perform multiple testing correction for the hypothesis tests in this analysis.

Clinical Implications

Chronotropic incompetence (CI) plays an important role in exercise capacity in HFrEF, and patients with CI may experience more severe exercise intolerance than patients without CI. Evaluating patients for the presence of CI may facilitate interpretation of clinical status, exercise limitations, and prognosis. Additionally, patients with CI can achieve improvements in peak exercise capacity with exercise training, and therefore, CI status should not preclude exercise prescription. Improving exercise tolerance can attenuate the severity of symptoms of dyspnea and fatigue and promote functional independence in HF patients. Exercise training may be a useful therapeutic strategy, in addition to guideline-directed medical therapy (GDMT), in mitigating HF symptoms and enhancing quality of life in HF patients.

APPENDIX A

Dissertation Proposal

Specific Aims

Heart failure (HF) is a chronic, progressive syndrome characterized by an inability of the cardiopulmonary system to effectively pump and extract oxygenated blood commensurate to metabolic demand.[1] Nearly 6 million people in the United States are living with HF and 5-year survival is only 50%. [2] Despite a large armamentarium of pharmacologic, device, and surgical therapies, HF continues to present a significant public health burden as the only cardiovascular disease with increasing prevalence, incidence, and mortality. HF morbidity is also significant, with patients experiencing frequent hospitalizations and poor quality of life.

The hallmark characteristic of HF is exercise intolerance, which manifests as dyspnea and fatigue at low levels of physical exertion. HF patients have difficulty performing simple activities of daily living (ADL) and experience reduced levels of functional independence, resulting in detrimental effects on quality of life. Exercise tolerance, operationalized as peak oxygen uptake (VO_{2peak}), is a validated and important prognostic marker in patients with HF, as well as used as a criterion for both heart transplantation and left ventricular assist device (LVAD) implantation. Although there is a well-known, objective reduction in exercise capacity observed in HF patients,

guideline-directed pharmacologic therapies for the treatment of HF only have modest effects on exercise tolerance. Therefore, novel therapeutic strategies for addressing exercise intolerance in HF are critically important.

The precise mechanisms of exercise intolerance in HF patients have not been fully elucidated. The Fick equation describes the relationship between oxygen delivery and utilization with increasing oxygen demand, such that oxygen consumption is the product of cardiac output and the arterial-venous oxygen content difference.[32] Patients with HF, particularly heart failure with reduced ejection fraction (HFrEF), have a significantly low cardiac output at peak exercise compared to healthy controls and a blunted stroke volume (SV) response to exertion. [7] This results in an overreliance on cardioacceleration for increasing cardiac output to compensate for limitations in SV reserve. This compensation is maladaptive, however, because HFrEF is also characterized by a marked impairment in cardiac autonomic control.[12] Chronotropic incompetence (CI), the inability to sufficiently increase heart rate (HR) with concomitant increases in exertion, is common in HFrEF, with reported prevalence varying from 20-70%.[14] Although there is a clear association between CI and exercise capacity in HF, a causal relationship between CI and exercise intolerance is controversial due to multiple definitions of CI and a lack of clear mechanisms. [15]

Therefore, there is a clear unmet need for elucidating the predictive role of CI on exercise performance in HFrEF patients. Using the dataset from the Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION), the largest

clinical trial of exercise training in HFrEF conducted to-date, the following specific aim is proposed:

> **Determine whether baseline CI is associated with impaired exercise capacity and exercise training response in chronic HFrEF patients in the HF-ACTION trial.**
>
> Hypothesis: Presence of CI will be strongly associated with an impaired response to exercise training, and participants with baseline CI will be less likely to respond to exercise training. If this hypothesis is correct, after exercise training, participants with baseline CI will have a smaller or no improvement in: 1) heart rate reserve (HRR) achieved, 2) peak exercise HR, and 3) $VO2_{peak}$.

The central hypothesis of this proposal is that CI is a significant contributor to exercise intolerance and an independent predictor of exercise training response in HFrEF patients. Elucidating the role of CI on exercise performance in HFrEF is of significant importance, as CI has the potential to be used clinically as a prognostic tool and novel therapeutic target for HF patients. Despite a vast armamentarium of approved therapies, the significant burden of HF persists. Novel therapeutic strategies, if successful, can have profound effects on functional ability, quality of life, and prognosis in HF patients.

Research Plan

Approach

Overview of HF-ACTION**:** The Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) was conducted from April 2003 through February 2007 and randomized 2,331 patients with HFrEF to usual care plus aerobic exercise training or usual care alone.[20] This Phase III, multicenter, randomized controlled clinical trial was conducted at 82 centers across the United States, Canada, and France. The primary outcome was a composite endpoint of all-cause mortality or hospitalization, with various secondary endpoints including all-cause mortality, cardiovascular mortality of cardiovascular hospitalization, and cardiovascular mortality or heart failure hospitalization.[20]

Primary results of the HF-ACTION trial demonstrated that the exercise training program was well-tolerated and safe.[20] There was a non-significant, but clinically relevant reduction in the composite primary outcome and there were modest significant reductions in key secondary outcomes in the exercise training group.[20] Although the exercise training group only had modest improvements in the clinical endpoints of mortality and hospitalization, exercise training significantly improved functional outcomes including 6-minute walk test (6MWT) distance and peak oxygen consumption ($VO2_{peak}$), which were sustained after 12 months of follow-up.[20,28] Additionally, exercise training led to a significant and sustained improvement in self-reported health status, which was observed within the first three months of training and persisted over time.[21]

Although the results of this important trial demonstrate safety and efficacy of exercise training in HFrEF patients, the cardiopulmonary mechanisms that contribute to this improvement in exercise capacity have not been fully elucidated. Further, the potential effects of disease-related physiological derangements, including chronotropic incompetence, have not been explored in this rich sample of HFrEF patients.

Participants: Participants in the HF-ACTION trial were screened for eligibility according to the inclusion and exclusion criteria listed in Table 1, Appendix B.[19] HFrEF patients were eligible for participation in the trial if they were receiving guideline-directed medical therapy (GDMT) for at least the previous six weeks, had a left ventricular ejection fraction (LVEF) equal to or less than 35%, and New York Heart Association (NYHA) class II to IV heart failure symptoms.[20] There were 2,331 total participants randomized into the trial (1,172 in the usual care arm and 1,159 in the exercise training arm). Follow-up time ranged from one to four years, with a median follow-up of 2.5 years.[21]

Cardiopulmonary Exercise Test (CPET): Participants completed a symptom-limited cardiopulmonary exercise test (CPET) prior to randomization and at 3, 12, and 24 months post-randomization according to the guidelines of the American College of Sports Medicine (ACSM).[22] Specific characteristics of the exercise testing procedures have been reported previously.[19,23] Participants underwent the exercise test on either a treadmill or stationery cycle ergometer with expired air collected for analysis of peak oxygen consumption and other important CPET measurements.[23]

Usual Care: Usual care consisted of the same number of follow-up clinic visits and telephone calls as the exercise training arm.[19] Additionally, participants in the usual care arm received educational materials regarding heart failure management and were continuing to receive GDMT as their regular clinical care.

Exercise Training Intervention: The exercise training arm consisted of all aspects of the usual care arm in addition to an individualized, structured exercise training program. Participants completed the first 36 sessions in a supervised setting followed by a home-based program. Participants were also asked to complete a clinic-based training session every 3 months, or after a hospitalization, at the discretion of their physician.[19] Exercise intensity was set at a training heart rate range of 60%-70% of heart rate reserve and was increased over time throughout the exercise program. Cycle ergometer and treadmill modalities were used, and equipment was provided to participants in their homes to facilitate the home-based exercise program. Participants who were unable to monitor heart rate due to arrhythmias or use of beta adrenergic blocking agents used rate of perceived exertion (RPE) for guiding exercise intensity.[19,20]

Secondary Analysis Methodology

Participants: This secondary analysis will be limited to the HF-ACTION participants randomized to the exercise training arm (n=1,159), since it will be examining the effect of baseline CI on response to the exercise training program. Additionally, participants must have completed the baseline CPET, which will be used for determining baseline CI, and the 3- and 12-month follow-up CPETs to be included in this analysis.

Definition of Chronotropic Incompetence: Presence of baseline CI will be defined as an inability to achieve at least 80% of the heart rate reserve (HRR), which is advantageous to other methods because it takes into account HR dynamics rather than a single HR measurement.[15] The 80% HRR threshold has been used previously in the literature and is a well-accepted definition of CI.[7,26] Specifically, the HRR will be calculated as follows[15]:

$$HRR = [(\text{peak HR} - \text{resting HR})/(\text{APMHR} - \text{resting HR}) \times 100]$$

Because age-predicted maximal heart rate (APMHR), calculated as 220-age, has been shown to overestimate predicted maximal HR in patients with HF currently on beta blocker therapy, APMHR will be estimated using the following validated, HF-specific formula for patients on beta blocker therapy[27]:

$$APMHR = [119 + 0.5(\text{resting HR}) - 0.5(\text{age})]$$

Exercise Training Response: Exercise response will be characterized by change from baseline, 3- and 12-month CPET parameters, including: 1) change in HRR achieved (as defined above), 2) change in peak exercise HR, and 3) change in VO_{2peak}.[14,34]

Statistical Analysis: All variables will be presented in mean values ± standard deviation (SD). All analyses will be performed using SPSS for Windows, version 24.0 (SPSS, Chicago, Illinois, USA). Univariate linear regression will be used to determine the association between baseline HRR and changes in CPET parameters for all participants. Differences between groups (patients with and without baseline CI) will be determined using two-tailed, independent t-tests. Multiple regression analysis will be used to

determine whether exercise parameters explain the degree of CI. Potential confounding variables will also be analyzed for significance using linear regression. Anticipated confounders include heart failure severity, adherence to exercise training, and baseline exercise capacity. Statistical significance will be set at $p < 0.05$.

Dissertation Committee Members

Randall Keyser, PhD, FACSM: Dr. Keyser is an Associate Professor in the Department of Rehabilitation Science at GMU. Dr. Keyser will serve as the Dissertation Committee Chair and primary reader. Dr. Keyser's expertise in cardiovascular physiology, particularly the limitations in cardiorespiratory capacity and cardiorespiratory endurance in patients with a variety of chronic diseases, will be an invaluable asset to this research study.

Andrew Guccione, PhD: Dr. Guccione is the Chair of the Department of Rehabilitation Science at GMU. Dr. Guccione will provide feedback on all aspects of this dissertation, including research design and data interpretation. Dr. Guccione's expertise in functional outcomes, gerontology, and rehabilitation science will be vital in the interpretation of findings in this research study.

Steven Keteyian, PhD, FACSM: Dr. Keteyian is the Director of Preventative Cardiology at the Henry Ford Health System and an Adjunct Professor in the Department

of Physiology at Wayne State University. Dr. Keteyian was also an investigator for the HF-ACTION trial and has extensive experience in exercise physiology in heart failure. Dr. Keteyian will serve as a subject matter expert and external reader, leveraging his expertise in heart failure exercise physiology and intimate involvement in the HF-ACTION trial.

Jenna Krall, PhD: Dr. Krall will serve as the primary biostatistician on this project. Dr. Krall will provide feedback and guidance on the analysis of this large, complex dataset and will assist with the statistical analysis plan, performing analyses, and interpretation of findings.

Additional Future Research Questions

1. Aim: Characterize the severity of chronotropic incompetence measured across all participants in the HF-ACTION trial. Describe how this differs using different approaches for measuring and defining chronotropic incompetence.
    a. Question: How severe and prevalent is chronotropic incompetence in this large cohort of HFrEF patients?
    b. Hypothesis: Exploratory.
2. Aim: Determine the effect of exercise training on chronotropic incompetence in HFrEF patients.

a. Question: Does chronotropic incompetence improve in participants randomized to the exercise group compared to participants randomized to usual care only?

b. Hypothesis: Exercise training will reduce the chronotropic incompetence measured during maximal exercise testing compared to participants who did not participate in exercise training.

3. Aim: Define the relationship between baseline CI and baseline exercise capacity in chronic HFrEF patients in the HF-ACTION trial.

   a. Question: Is there an association between CI and exercise capacity in HFrEF patients?

   b. Hypothesis: Baseline CI severity will be associated with baseline VO_{2peak}, with increased CI associated with lower peak VO_2 values.

APPENDIX B

Supplemental Figures

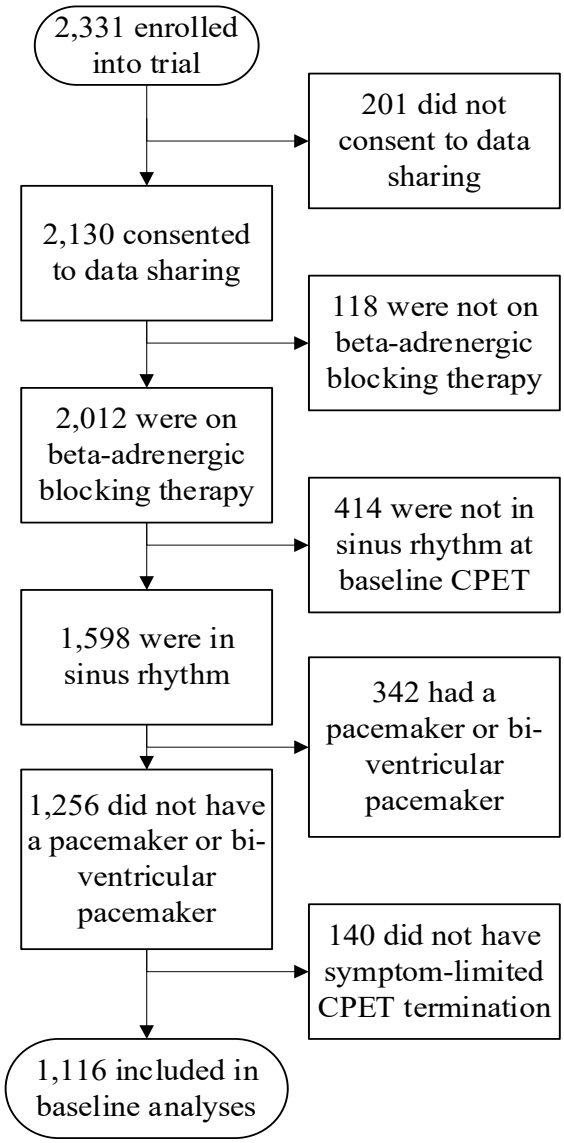

Figure 6 CONSORT flow diagram of participants included in the baseline analyses

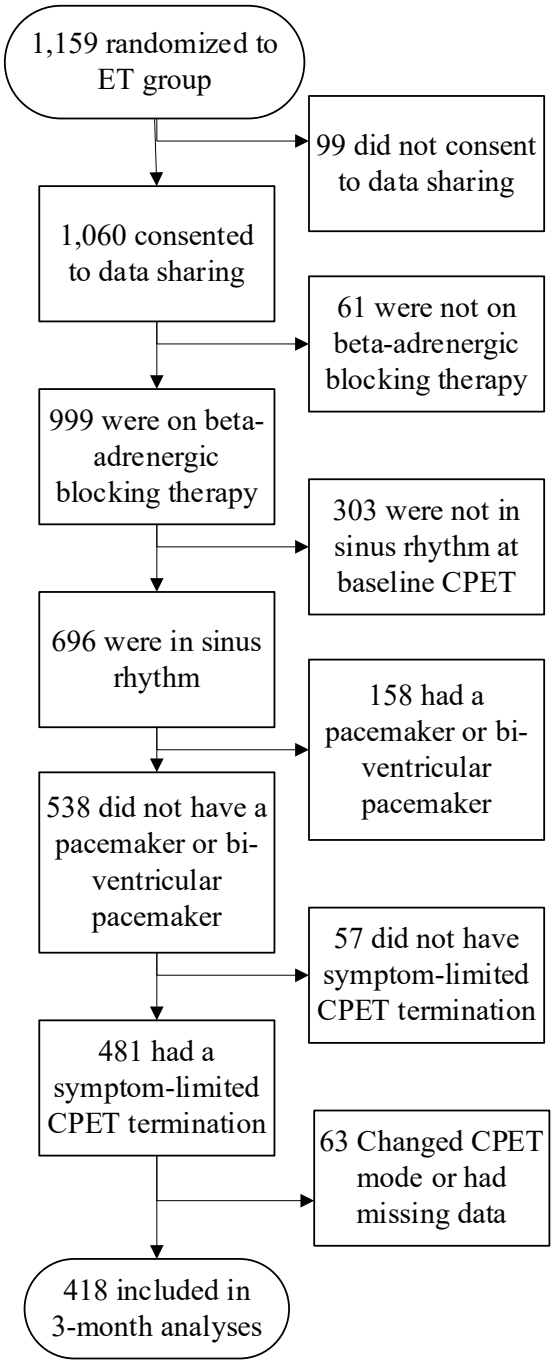

Figure 7 CONSORT flow diagram of participants included in the exercise training adaptation analyses

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BIOGRAPHY

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