Exercise as Therapy for Older Patients with Heart Failure with Preserved Ejection Fraction

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How to Succeed in Aging Research Despite Countless Setbacks: A Journey
Heart Failure with Preserved EF (HFpEF): The Most Common Form of HF in Community-Dwelling Older Persons: The Cardiovascular Health Study

Among older women, >90% of incident HF is HFpEF

Confirmed in Framingham and 4 other NIH-funded population studies

Kitzman et al, Am. J. Cardiol 2001
Aurigemma et al, JACC 2001
Despite the high prevalence and poor prognosis, there are few proven drug treatments for HFpEF!

- >20 negative medication trials
- The most common cardiovascular disorder for which optimal pharmacological treatment is unknown
Older Patients with HFpEF Have Marked Physical Dysfunction

• Severe exertional dyspnea and profound fatigue

• High rates of physical frailty (up to 90%)

• Major contributor to their severely reduced quality of life

• Strong predictor of death, hospitalization, and nursing home placement
Quantifying Exercise Intolerance: Peak Oxygen Consumption (VO\(_2\))

- Non-invasive, standardized, objective measure of exercise capacity.
- Valid and reproducible even in very old HFpEF patients (Scott, Kitzman 2012).

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**Group data**

**Individual data**

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![Line graph showing the correlation between VO\(_2\)max of Test 1 and Test 2 with a correlation coefficient of r = 0.92, p ≤ 0.0004.](image)

![Graph showing VO\(_2\) consumption over time with start of exercise indicated.](image)
Activities of Daily Living as a Percent of Peak VO₂ in Older Patients with HFpEF

Mean age: 63 yr

Kitzman et al, JAMA 2002; Dhakal et al Circulation 2016

Compliments of Mark Haykowsky, PhD
Figure 1: Pathophysiology and Outcomes in HFP EF

Effect of Exercise Training on Exercise Capacity in Older Patients with HFpEF

Kitzman et al, Circulation HF, 2010
Obesity, the Elephant in the Room

- Obesity is the third strongest risk factor for development of HFpEF

- 85% of HFpEF patients are overweight or obese, more than twice the general population

- Obesity promotes inflammation, HTN, insulin resistance, and impairs cardiac, arterial, skeletal muscle, and physical function
SECRET Trial Primary Outcome: Peak VO$_2$ Improved Most with Diet + Exercise

Kitzman et al, JAMA 2016;315:36-46
Dietary Weight Loss in HFpEF Reduced Markers of Inflammation

$r = 0.29$
$p = 0.005$

Kitzman et al, JAMA 2016;315:36-46
Can we extend the benefits of physical exercise to Frail Older Patients Hospitalized with Acute Heart Failure (ADHF)?

- ADHF is the most common hospital discharge diagnosis in older persons
- Poor QOL, frequent rehospitalization, high mortality, loss of independence, and high nursing home admission
- Excluded from prior exercise trials
- Pilot study showed marked impairments in all domains of physical function: balance, mobility, strength, endurance; >90% were frail/pre-frail
- Developed innovative, multi-domain, tailored physical function intervention

Kitzman DW, et al. NEJM July 15 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINIAL ARTICLE

Kitzman DW, et al. NEJM July 15 2021
Physical Rehabilitation for Older Patients Hospitalized for Heart Failure
REHAB-HF Trial Primary Outcome: SPPB at 3-Months

Clinically meaningful change is 0.5 units

Kitzman DW, et al. NEJM 2021
Patients with HFrEF Appeared to Have Much Greater Improvements from the novel REHAB-HF Intervention

Mentz RJ, Kitzman et al. JACC Heart Fail 2021
The difference that applying the right intervention to the right patient at the right time can make:

From being house-bound after her hospital discharge, to paddle-boarding with grandchildren!
Was My Research Career A Carefully Planned, Straight Pathway to Success?

- Many seminal discoveries regarding HFpEF
- Nearly 500 publications: JAMA, Lancet, NEJM
- External funding since first year as faculty
- Many leadership positions and awards
It Was a Journey, Not a Straight, Sure Path!

1. The first grant I applied for as a faculty was not funded, even though I was the only applicant who showed up at the mandatory interview.

2. The mechanistic hypothesis of my first R01 was disproven by the study results.

3. The primary hypothesis of my second R01 was disproven.

4. The primary and mechanistic hypothesis of my third R01 were disproven.

5. The first 12 (!) medication trials I led or helped lead were neutral.
What I Learned Along the Way

1. Never give up on your dream
2. Select an important question, and the answer will be important no matter the results
3. Relentlessly pursue the truth, regardless of where it leads you
4. Reach out to others who can help you learn new techniques
5. Build and foster a multi-disciplinary team
6. Adapt; learn from your ‘mistakes’, they may be your best clue
7. Have fun, enjoy the journey of discovery
17 Essential Ingredients for Success in Medical Research

1. Good training
2. Good environment
3. Important question
4. Preliminary data
5. Good mentors
6. A broad, diverse team
7. Supportive program officer
8. Supportive family
17 Essential Ingredients for Success in Medical Research

9. Affability
10. Writing skills
11. Lots and lots of really hard work and very long hours
12. True passion for the subject matter
13. Fear of failure
14. A lot of curiosity
15. Perseverance
16. A bit of intelligence
17. Some luck
Mentors Who Made a Difference

- Madelynn Roll
  - Taught me to never quit
  - Showed me the devastation of HFpEF
- Barbara Shaver
  - Taught me to follow your dream
- William Edwards
  - Taught me how to write my first journal article
- Michael Higginbotham
  - Taught me how to write my first grant application
- Debra Kitzman
  - Gave me courage and support to start over after a wrong turn
- William Hazzard, Walter Ettinger, William Little
  - Saw something in me that I wasn't sure was there
Key Collaborators Who Made Critical Contributions

- Peter Brubaker
- Barbara Nicklas
- Anthony Molina
- Denise Houston
- Henry Miller
- Lenny Kaminsky
- Steve Kritchevsky
- Steve Keteyian
- Mark Haykowsky
- Gregory Hundley
- Kathryn Stewart
- Ben Nelson
- Russ Newland
- Bharathi Upadhyya
- Alain Bertoni
- Hariom Yadav
- Timothy Morgan
- Haiying Chen
- Mark Espeland
- William Little
- David Herrington
- David Zhao
- Pamela Duncan
- Amy Pastva
- Robert Mentz
- Gordon Reeves
- Chris O’Conner
- David Whellan
- Gordon Reeves
- Shelby Reed
- Many more…
Funding agencies that took a chance on my ideas

National Institute on Aging
National Heart Lung and Blood Institute
American Federation for Aging Research
Hartford Foundation
American Heart Association
Participants

1,526 participants who trusted me and volunteered to partner with me on a quest to discover new knowledge to improve the lives of older persons