

Exercise Tolerance as Endpoint for Heart Failure Trials: Implications for Reimbursement

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Conflict of Interests

Cardiovascular Research Foundation (CRF)- Clinical Trials Center

- Institutional contracts from Abbott Vascular (major) , Edwards Lifesciences (major), Medtronic (major), Impulse Dynamics (major)

Daniel Bensimhon, MD:

- Consultant: sensible medical devices (minor)

Jonathan Myers, PhD:

- Nothing to disclose

Steven J. Keteyian, PhD:

- Technical advisor, Nimble Heart, Inc (minor)
- Member, Board of Directors, American Association of Cardiac and Pulmonary Rehabilitation (minor)
- CPET core laboratory contracts with Heart Metabolics and Actelion (major)
- 6MW core laboratory contract with Covance (major)

Clinton A. Brawner, PhD:

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Ori Ben-Yehuda MD :

- Clinical Trials Center Institutional contracts from Abbott Vascular (major) , Edwards Lifesciences (major), Medtronic (major), Impulse Dynamics (major)

Greg Lewis MD:

- CPET Core Laboratory Contracts with MGH – role of PI (major)
 - NHLBI Heart Failure Network
 - NHLBI Hypertrophic Cardiomyopathy Network
 - NHLBI Cardiac Cell Therapy Research Network
 - Stealth Therapeutics
 - Abbott Vascular

Introduction

- Patients with heart failure (HF) suffer from:
 - Exercise intolerance
 - Overall poor quality of life
 - Frequent hospitalizations for HF exacerbations
- Mortality has been improved by medical therapies and CRT, but is still high
- However, clinical trials testing new therapies aimed at showing improvement in mortality are increasingly difficult due to requirements for a large number of patients and a long duration of follow-up
- Rigorous assessment of exercise tolerance as an endpoint in HF trials is useful because it not only assesses the impact on a primary limitation faced by patients but also correlates with mortality and rates of hospitalizations

Introduction

- Symptomatic heart failure patients uniformly experience exercise intolerance and is a major source of morbidity that is experienced by almost all HF patients daily
- However, modern HF trials that only examine “hard endpoints” such as mortality often result in <10% of the patients experiencing such an endpoint annually and the absolute effect size difference is often on the order of 2% or less.
- Studying endpoints that are important to daily life of all HF patients is relevant as primary endpoints in clinical trials.
- Moreover, exercise measures such as VO₂ outperform subjective measures (NYHA Class, KCCQ etc) in predicting future hard outcomes.

This presentation addresses Question 4:

4. How confident are you that functional assessments [e.g., 6 min walk test (6MWT), VO₂max, ventilatory threshold]:

- a. Are adequate measures which reflect the patient experience;
- b. Should be included as the standalone, meaningful primary health outcomes in research studies;
- c. Should be included as a composite standalone, meaningful primary health outcomes in research studies?

Traditional tests of exercise tolerance in HF clinical trials

- Six minute walk test (6MWT)
 - Indicator of sub-maximal exercise capacity, prognostic (PH, LVSD)
 - Volitional, may be reflective of maximal exercise capacity and source of limitation remains unknown
- Cardiopulmonary Exercise Test (CPET)
 - Gas exchange patterns characteristic of diseases that provide insight into the organ system limiting exercise capacity
 - Peak VO_2
 - Ventilatory anaerobic Threshold
 - VE/VCO_2 slope
- CPET and 6MWT provide different information
 - Choice of which measure of exercise tolerance to use in a clinical trial depends on:
 - anticipated effect of the therapy
 - whether it is a standalone primary endpoint, a component of a composite primary endpoint or a secondary endpoint

Cardiopulmonary Exercise Testing (CPET)

CPET Measures Functional Capacity

- Peak VO_2 is the gold standard indicator of exercise/functional capacity
 - There is significant intrinsic value to patients of increasing exercise capacity, unlike changing circulating biomarkers or echo parameters

The Evolution of CPET: ↑ Feasibility

THEN



Metabolic Cart
Warm-up/Calibration:
60 min

Manual data processing

Focus on peak VO_2

Isolated testing



NOW



Reduced set-up times

Improved software for CPET
pattern visualization

Recognition of submax variables
closely related to pathophys/prognosis,

Integrated testing with imaging/HD

Virtues of CPET/Peak VO_2

- Peak VO_2 is the gold standard measure of cardiopulmonary function
- More precise and reproducible than other measures of physical function
- Peak VO_2 is responsive to therapy (drug, device, exercise training)
- Peak VO_2 and other CPET responses are strongly associated with clinical outcomes

Modest Increase in Peak VO_2 Is Related to Better Clinical Outcomes in Chronic Heart Failure Patients

Results From Heart Failure and a Controlled Trial to Investigate Outcomes of Exercise Training

Ann M. Swank, PhD; John Horton, MS; Jerome L. Fleg, MD; Gregg C. Fonarow, MD;
Steven Keteyian, PhD; Lee Goldberg, MD, MPH; Gene Wolfel, MD; Eileen M. Handberg, PhD;
Dan Bensimhon, MD; Marie-Christine Illiou, PhD; Marianne Vest, MA, RN, CTTS; Greg Ewald, MD;
Gordon Blackburn, PhD; Eric Leifer, PhD; Lawton Cooper, MD; William E. Kraus, MD;
and for the HF-ACTION Investigators

(*Circ Heart Fail.* 2012;5:579-585.)

Every 6% increase in peak VO_2 , adjusted for other significant predictors, was associated with a 5% lower risk of the primary endpoint (time to all-cause mortality or all-cause hospitalization)

Table 3. Trend Tests for Clinical Outcomes Across Tertiles of Peak VO_2 Change

Clinical Outcome	Estimate	χ^2	<i>P</i>
All-cause mortality or all-cause hospitalization	−0.15	13.08	<0.001
Cardiovascular mortality or hospitalization	−0.12	7.35	0.007
Cardiovascular mortality or HF hospitalization	−0.15	5.88	0.061
Mortality	−0.18	4.62	0.032

VO_2 indicates oxygen uptake; HF, heart failure.

When peak VO₂ increases, mortality decreases

Therapy	Change PVO ₂	Effect on Mortality
CRT	<p>Yes-Increased</p> <p>Peak VO₂ increased by 1.1 mL/kg per minute (0.7-1.6) in the CRT group vs 0.1 mL/kg per minute (−0.1 to 0.8) in controls (P= .04) .—NYHA Class III or IV (n=369) ¹</p>	<p>Yes-Decreased mortality</p> <p>Progressive heart failure mortality was 1.7% for cardiac resynchronization patients and 3.5% for controls. Cardiac resynchronization also reduced heart failure hospitalization by 29% ³</p>
Ace-Inhibitors	<p>Yes- Increased</p> <p>Peak VO₂ at baseline, 3 and 6 months were 13.5±0.6, 15.1±1.0, and 15.7±1.1 mL·kg^{−1}·min^{−1} in patients receiving losartan and 14.1±0.6, 14.3±0.9, and 13.6±1.1 mL·kg^{−1}·min^{−1} in patients receiving placebo (P<0.02). ²</p>	<p>Yes- Decreased mortality⁷</p>
β-blocker	No ⁶	Prolong survival ⁶
Ivabradine (Corlanor)	<p>Yes- peak oxygen consumption tended to improve from 13.5 ± 1.3 to 17.9 ± 2.4 mL/kg per minute (P < .0001) ⁴</p>	<p>death rate due to HF dropped significantly (P = 0.014). ⁵</p>
Exercise	Yes- Increased ⁸	Yes- decreased mortality ⁸

References in Appendix

Peak VO_2 :

Clinical trial considerations

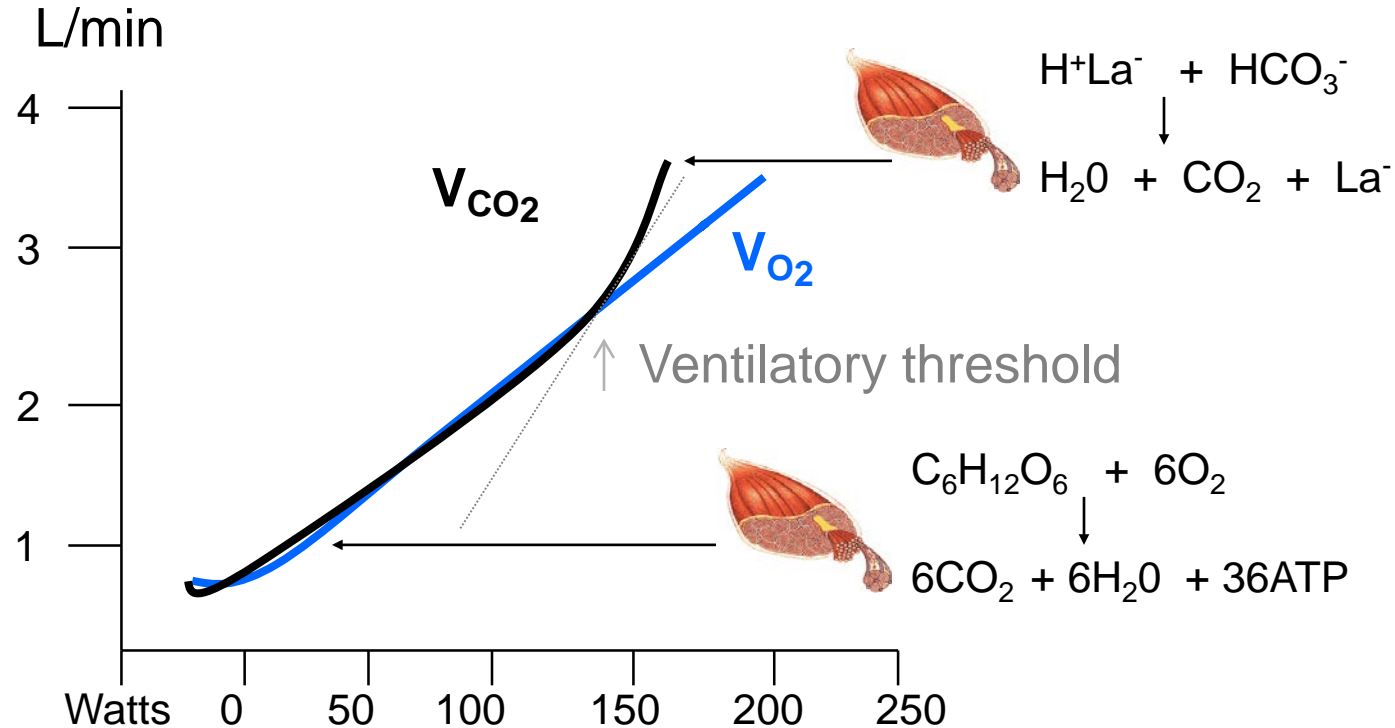
- Requires CPET equipment
- Requires expertise by user
- Is effort-dependent, but can be accounted for
- Requires core lab to:
 - Ensure proper equipment calibration
 - Validate procedures
 - Adjudicate data

Importance of Core Lab

- Modern trials involve multiple technical, clinical, and regulatory demands that necessitate high-quality quantitative information
- Core lab provides expertise/oversight for quality control in multicenter studies
- Serves as a critical intermediary between study sponsor and study sites
- Provides consistency in interpretation and adjudication of CPET data
- Provides blinded, independent analysis of study results

CPET Captures the Amount of Volitional Effort and Variables Beyond Just Peak VO₂ that Relate to Prognosis in HF

$V_{CO_2}/VO_2 > 1.05$ is indicative of maximum effort



Additional Gas Exchange Patterns Easily Discernable
-VE/ V_{CO_2} slope, Exercise oscillatory ventilation

Ventilatory anaerobic threshold (VAT): Theoretically appealing but practical limitations

- In principle, is objective
- Quantification, however, can be highly subjective
- Different methods of determination can yield different values
- Studies have shown significant inter-and intra-reader variability
- Not always discernable; a distinct threshold may not occur in some subjects
- Despite decades of study, physiologic mechanism remains incompletely understood

6 Minute Walk Test (6MW)

6 Minute Walk

- Primary measure is total distance walked
 - Performed in a hallway
 - Patient is permitted to take breaks, but timer continues
- Measure of exercise tolerance
 - Most useful among patients who:
 - have limited exercise tolerance
 - are limited by symptoms (eg, shortness of breath)



6 minute walk: Additional Considerations

Virtues of 6MW:

- Simple, easily administered assessment that can be done at a minimal cost
- Closely reflects activities of daily living (submax, walking)
- High Test-Retest reliability (screening, BL x2, 18wk x2, 43wk x 2) ICC=0.88-0.91¹
- 6MW distance independently predicts HF hospitalization + mortality in moderate HF²
- 6MW distance HF death/hospitalization in advanced HF³
- Moderate correlations with Sx scores, NYHA Class, outperforms both

Therapies that increase 6MW

- Left ventricular assist devices⁴, CRT (4/6 trials)⁵, Iron(2/2 trials)⁶
- Drugs currently approved for Rx of pulmonary arterial hypertension

Limitations

- There is some training effect and clear need for standardization of instructions
- Does not provide information about volitional effort or ex-limiting organ system
- Represents varying degree of maximum effort, performs less well in less sick HF patients

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Conclusions

- Impaired exercise capacity is a cardinal manifestation of heart failure
 - Improvement in exercise capacity is a meaningful endpoint for patients with HF
- Exercise capacity (i.e. peak VO_2 and 6 min walk) is closely related to outcomes across the spectrum of cardiovascular disease, particularly in HF
- Measurements of exercise capacity are safe and increasingly simple to perform
- Exercise-based measurements, done properly with core lab oversight, are highly reproducible and permit ascertainment of clinically meaningful endpoints

Conclusions

Question 4. How confident are you that functional assessments [e.g., 6 min walk test (6MWT), VO₂max, ventilator threshold]:

- a. Are adequate measures which reflect the patient experience:
 - a. Peak VO₂: YES
 - b. VAT: Possibly
 - c. 6MW: YES
- b. Should be included as the standalone, meaningful primary health outcomes in research studies:
 - a. Peak VO₂: YES
 - b. VAT: NO
 - c. 6MW: NO
- c. Should be included as a composite standalone, meaningful primary health outcomes in research studies:
 - a. Peak VO₂: YES
 - b. VAT: NO
 - c. 6MW: YES

APPENDIX

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