CARDIOLOGY GRAND ROUNDS

Presentation: Cardiopulmonary Exercise Testing and Exercise Hemodynamics

Speaker: Michael A. Samara, MD
Advanced HF/Transplant Cardiologist
Minneapolis Heart Institute® at Abbott Northwestern Hospital

Date: Monday, February 16, 2015, 7:00 – 8:00 AM
Location: ANW Education Building, Watson Room

OBJECTIVES
At the completion of this activity, the participants should be able to:
1. Recall the normal cardiopulmonary response to aerobic exercise.
2. Explain the utility of cardiopulmonary exercise testing in patients with cardiovascular disease or undifferentiated dyspnea.
3. Describe the role of invasive exercise hemodynamics in the evaluation in the evaluation of patients with cardiovascular disease.

ACCREDITATION

Physicians: This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Allina Health and Minneapolis Heart Institute Foundation. Allina Health is accredited by the ACCME to provide continuing medical education for physicians. Allina Health designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses: This activity has been designed to meet the Minnesota Board of Nursing continuing education requirements for 1.2 hours of credit. However, the nurse is responsible for determining whether this activity meets the requirements for acceptable continuing education.

Others: Individuals representing other professional disciplines may submit course materials to their respective professional associations for 1.0 hours of continuing education credit.

DISCLOSURE STATEMENTS

Speaker(s): Dr. Samara has declared that he does not have a conflict of interest in making this presentation.
Planning Committee: Dr. Michael Miedema, and Eva Zewdie have declared that they do not have any conflicts of interest associated with the planning of this activity. Dr. Robert Schwartz declared the following relationships - stockholder: Cardiomind, Interface Biologics, Aritech, DSI/Transoma, InstyMeds, Intervale, Medtronic, Osprey Medical, Stout Medical, Tricardia LLC, CoAptus Inc, Augustine Biomedical; scientific advisory board: Abbott Laboratories, Boston Scientific, MEDRAD Inc, Thomas, McNerney & Partners, Cardiomind, Interface Biologics; options: BackBeat Medical, BioHeart, CHF Solutions; speakers bureau: Vital Images; consultant: Edwards LifeSciences.
MHI Grand Rounds
Cardiopulmonary Exercise Testing
Michael A. Samara, MD, FACC
Advanced Heart Failure, Cardiac Transplant & Mechanical Circulatory Support

No Disclosures

Special Thanks To The CVDS Pulmonary Function Lab
Paul Lorenz
Mary Potz
Jason Hyatt
Dr. Randy Burns
CPET remains a relevant and powerful technique for assessing cardiopulmonary disease.

Poorly understood and underutilized in most clinical practices.

Breath-by-breath measures of:
- oxygen consumption (VO$_2$)
- carbon dioxide output (VCO$_2$)
- volume of ventilation (VE)

Outline

I. Normal Cardiopulmonary Response to Exercise
II. Indications for Testing/Testing Protocols
III. Key Variables and their Physiologic Implications
IV. Clinical Applications
V. Invasive Cardiopulmonary Exercise Testing

Wasserman’s Gears: Coupling External and Cellular Respiration

Normal Cardiopulmonary Response to Exercise

Fick Equation

\[ \text{CO} = \frac{\text{VO}_2}{\text{C(a-v)O}_2} \]
\[ \text{VO}_2 = \text{CO} \times \text{C(a-v)O}_2 \]
\[ \text{VO}_2 = \text{SV} \times \text{HR} \times \text{C(a-v)O}_2 \]
Normal Cardiovascular Response to Exercise

VO$_2$ $\uparrow$ 0.33 to 2.55 L/min (7.7x)

Cardiac index $\uparrow$ 3 to 9.7 L/min/m$^2$ (3.3x)

Heart rate $\uparrow$ 73-167 bpm (2.5x)

Stroke volume index $\uparrow$ 41-58 ml/m$^2$ (1.4x)
- $\uparrow$ LVEDP and LVEDVi
- $\downarrow$ LVESVi

Static vs. Dynamic Exercise

Blood Pressure

Heart Rate
Changes in Pressure-Volume Relationship with Exercise

1. ↑ in ESPVR (contractility) - End Systolic Pressure Volume Relationship
2. ↑ in Ea & BP - Effective Arterial Elastance
3. ↑ in Early diastolic relaxation
4. ↑ in EDVi - End diastolic volume index

↑ in Stroke Volume & Stroke Work

Stroke Volume Response to Exercise

- ↑ With ↑ intensity up to 40 to 60% VO2max
- Beyond this SV plateaus
- Trained athletes continue to augment SV
- SV during maximal exercise ≈ double standing SV

Cardiol Clin 1992;10:705-717
(a-v)O₂ Difference

(a-v)O₂ difference (mL O₂/dL blood)
- Resting: ~6 mL O₂/dL
- Max exercise: ~16 to 20 mL O₂/dL
- Venous O₂ from active muscle ~0 mL

Increased Oxygen Extraction Contributes to Widening (a-v)O₂ difference

↑ pH
↑ 2-3 DPG
↑ Temperature
↑ PCO₂ (Bohr effect)
Changes in Autonomic Tone During Exercise

- Vagal control
- Sympathetic control

RBF = Renal Blood Flow
SBF = Splanchnic Blood Flow


Redistribution of Cardiac Output with Exercise

Cardiac Output (L/min)

- Viscera
- Skin
- Skeletal muscle
- Heart
- Brain
Ventilatory Response to Exercise

Tidal Volume (Liters)

Respiratory Rate (bpm)

Minute Ventilation (Liters/min)

Dead Space (mL)

Ventilatory Response to Exercise

Dead Space Ventilation

VD/VT normally falls with exercise.
Lack of decrease or increase suggests intrinsic lung disease.

Normal Ventilation Perfusion Coupling

V/Q matching with exercise is critically dependent on cardiac output keeping pace with increases in minute ventilation.
Summary

1. VO2 = SV x HR x C(a-v)O2
2. Initial increase in CO related to parallel increases in SV and HR.
3. Late increase in CO related to progressive increase in HR.
4. CO increases ~ 5 fold with redistribution to active muscle.
5. Early rise in TV and late rise in RR result in linear increase in VE.
6. Increase in VE is closely mirrored by increase in CO to maintain V/Q matching.

Indications for Testing & Testing Protocol
Cardiopulmonary Exercise Testing

- Airtight mouthpiece
- ECG/HR/BP monitoring
- Processor
  - O₂ and CO₂ Analyzers
  - Must be calibrated prior to each exercise test
- Pneumotachometer
  - Continuous ventilatory volume analysis (VE)
  - Validate before testing
- Ergometer

Contraindications, etc.

- Standard exercise ECG guidelines

Symptom limited CPET is exceptionally safe!

No adverse events: 5,002 (99.84%)
Adverse Events: 8 (0.16%)

- Sustained ventricular tachycardia (6) 0.12%
- ST-elevation myocardial infarction (1) 0.02%
- Other hospital admission (1) 0.02%

Ergometer Selection

<table>
<thead>
<tr>
<th></th>
<th>Cycle ergometer</th>
<th>Treadmill</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VO₂ max</strong></td>
<td>lower</td>
<td>higher</td>
</tr>
<tr>
<td><strong>Leg muscle fatigue</strong></td>
<td>often limits</td>
<td>less often limits</td>
</tr>
<tr>
<td><strong>Work rate quantification</strong></td>
<td>yes</td>
<td>estimation only</td>
</tr>
<tr>
<td><strong>Blood gas collection</strong></td>
<td>easier</td>
<td>more difficult</td>
</tr>
<tr>
<td><strong>Instrumentation noise and artifact</strong></td>
<td>less</td>
<td>more</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>safer</td>
<td>less safe(?)</td>
</tr>
<tr>
<td><strong>Weight bearing in obese</strong></td>
<td>less</td>
<td>more</td>
</tr>
<tr>
<td><strong>More appropriate for</strong></td>
<td>patients</td>
<td>active normals</td>
</tr>
</tbody>
</table>


Protocol Selection

<table>
<thead>
<tr>
<th>Stage (2 min)</th>
<th>Speed (mph)</th>
<th>Grade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>standing</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Modified Naughton

- Protocols with **small stage-to-stage increments** in energy requirement best
- Most critical is tailoring to goal exercise duration of **8-12 min**
  - < 6 min: non-linear relationship between work rate and VO₂
  - >12 min: exercise terminated due to muscle fatigue/orthopedic limitations

ACC/AHA Guidelines: Exercise Testing w/ Ventilatory Gas Analysis

**Class I**
- To evaluate exercise capacity and the response to therapy in patients with heart failure who are being considered for heart transplantation. HF/Transplant/VAD
- To assist in the differentiation between cardiac and pulmonary causes of exercise-induced dyspnea or impaired exercise capacity when the cause is uncertain. Unexplained Dyspnea

**Class IIa**
- To evaluate exercise capacity when indicated for medical reasons when estimated exercise capacity from exercise test time or work rate is unreliable.

**Class IIb**
- To evaluate the response to specific therapeutic interventions when improvement in exercise tolerance is an important goal or end point.
- To determine the intensity of exercise training as part of comprehensive cardiac rehabilitation.

**Class III**
- Routine use to assess exercise capacity.


---

**Indications for Testing**

- Development of the **exercise prescription** in patients with cardiovascular disease or stroke
- Evaluation of **disability** in patients with cardiac or pulmonary disease
- Evaluation of patients with **heart failure**
- Evaluation of patients with **mitochondrial myopathies**
- Evaluation of patients with **unexplained dyspnea.**
- Evaluation of patients with **congenital heart disease**
- Evaluation of patients with cardiac arrhythmias and **pacemakers**
- Evaluation of patients with **pulmonary hypertension**
- Pre-operative evaluation of patients undergoing **pulmonary resection**

## Variables and Their Physiologic Implications

<table>
<thead>
<tr>
<th>Variables</th>
<th>Noninvasive</th>
<th>Invasive (ABGs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Work</strong></td>
<td>WR</td>
<td>lactate</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>$V_{O2}$, $V_{CO2}$, $R$, $AT$</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>HR, ECG, BP, O$_2$ pulse</td>
<td></td>
</tr>
<tr>
<td><strong>Ventilatory</strong></td>
<td>$V_E$, $V_I$, $f$</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary gas exchange</strong></td>
<td>$SpO_2$, $V_E/V_{CO2}$, $V_E/V_{O2}$, $P_{ETO2}$, $P_{ETCO2}$</td>
<td>SaO$_2$, PaO$_2$, P(A-a)O$_2$, $V_E/V_T$</td>
</tr>
<tr>
<td><strong>Acid/base status</strong></td>
<td>pH, PaCO$_2$, HCO$_3^-$</td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Dyspnea, leg fatigue, chest pain</td>
<td></td>
</tr>
</tbody>
</table>
Cardiorespiratory Fitness is a Powerful Predictor of Survival

For each increment of 1 MET (3.5 ml O₂/kg/min)

This relationship frequently overestimates actual VO₂.

Standard Exercise Protocols Overestimate O₂ Consumption

1 MET = 3.5 ml O₂/kg/min

Peak VO₂

- Functional capacity = exercise capacity = exercise tolerance
- Peak VO₂ ≠ max VO₂
- Directly related to cardiac output
- Determined by…
  - Type of exercise
  - Gender
  - Age
  - Activity level
  - Natural endowment
  - Drugs (βb)

If BMI > 30 kg/m²
Indexed to ideal body weight.

**Fitness Classification by Peak VO₂**

### Women

<table>
<thead>
<tr>
<th>Age</th>
<th>Low</th>
<th>Fair</th>
<th>Average</th>
<th>Good</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>&lt;24</td>
<td>24-30</td>
<td>31-37</td>
<td>38-48</td>
<td>&gt;49</td>
</tr>
<tr>
<td>30-39</td>
<td>&lt;20</td>
<td>20-27</td>
<td>28-33</td>
<td>34-44</td>
<td>&gt;45</td>
</tr>
<tr>
<td>40-49</td>
<td>&lt;17</td>
<td>17-23</td>
<td>24-30</td>
<td>31-41</td>
<td>&gt;42</td>
</tr>
<tr>
<td>50-59</td>
<td>&lt;15</td>
<td>15-20</td>
<td>21-27</td>
<td>28-37</td>
<td>&gt;38</td>
</tr>
<tr>
<td>60-69</td>
<td>&lt;13</td>
<td>13-17</td>
<td>18-23</td>
<td>24-34</td>
<td>&gt;35</td>
</tr>
</tbody>
</table>

### Men

<table>
<thead>
<tr>
<th>Age</th>
<th>Low</th>
<th>Fair</th>
<th>Average</th>
<th>Good</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>&lt;25</td>
<td>25-33</td>
<td>34-42</td>
<td>43-52</td>
<td>&gt;53</td>
</tr>
<tr>
<td>30-39</td>
<td>&lt;23</td>
<td>23-30</td>
<td>31-38</td>
<td>39-48</td>
<td>&gt;49</td>
</tr>
<tr>
<td>40-49</td>
<td>&lt;20</td>
<td>20-26</td>
<td>27-35</td>
<td>36-44</td>
<td>&gt;45</td>
</tr>
<tr>
<td>50-59</td>
<td>&lt;18</td>
<td>18-24</td>
<td>25-33</td>
<td>34-42</td>
<td>&gt;43</td>
</tr>
<tr>
<td>60-69</td>
<td>&lt;16</td>
<td>16-22</td>
<td>23-30</td>
<td>31-40</td>
<td>&gt;41</td>
</tr>
</tbody>
</table>


---

**Anaerobic Threshold ≈ Ventilatory Threshold**

Most activities of daily living do not require maximal effort!
AT is an index of submaximal exercise capacity.

Glucose → 2 ATP → 2 NADH

Anaerobic Metabolism → Pyruvate → Aerobic Metabolism

Lactic Acid → Deprotonation → $\text{[H}^+] + \text{[HCO}_3^-] \rightleftharpoons \text{[H}_2\text{O]} + \text{[CO}_2]$ → Citric Acid Cycle + ETC → 34 ATP

Invasive Assessment of the Anaerobic Threshold = Lactate Threshold

Typically occurs at 45-65% of Age and sex predicted max VO₂

Values < 40% suggest cardiovascular impairment

Noninvasive Assessment of Anaerobic Threshold

V-slope method

End-tidal method

Ventilatory equivalents method

Respiratory Exchange Ratio

RER = $\frac{VCO_2}{VO_2}$

- Achievement of APMHR is highly variable
- RER is the most accurate and reliable gauge of effort
- RER $\geq$ 1.1 is generally considered indicative of excellent effort
- RER < 1 suggests submaximal cardiovascular effort or pulmonary limitation
- AT typically seen between RER 0.8-0.99

RER must be similar to compare serial peak VO$_2$ measurements.

Ventilatory Efficiency (VE/VCO$_2$)

- Normal VE/VCO$_2$ = 15
- HEART FAILURE VE/VCO$_2$ = 40
- \(^\uparrow\) minute ventilation (VE)
  - \(^\uparrow\) chemoreceptor output
  - \(^\downarrow\) CO$_2$ delivery (V/Q matching)
  - low cardiac output
  - high PCWP
  - pulmonary vascular dz
Ventilatory Efficiency (VE/VCO₂)

- Reflects poor V/Q matching → ventilation must increase disproportionately to compensate for inadequate perfusion
- Abnormally elevated chemoreceptor and ergoreceptor sensitivity
- < 30 is normal without modification for age or sex
- Values can exceed 60 in severely diseased patients with HF, pHTN, severe COPD
- Correlated with low cardiac output, elevated PCWP, decreased alveolar-capillary membrane conductance, and diminished HR variability

Independent of effort and stress modality.

Powerful independent predictor of prognosis in cardiovascular disease.

Very high test-retest reliability.

Oxygen Pulse (VO₂/HR)

\[ \text{O}_2 \text{ Pulse} = \frac{\text{VO}_2}{\text{HR}} \]

"...the amount of oxygen consumed by the body from the blood of one systolic discharge of the heart."

Fick Equation:
\[ \frac{\text{VO}_2}{\text{HR}} = \text{SV} \times C(\text{a-v})O_2 \]

\[ \text{SV} = \frac{\text{O}_2 \text{ Pulse}}{15} \times 100 \text{ ml} \]

Assuming C(\text{a-v})O₂ is maximal (15 ml/dl) and not anemic

Oxygen Pulse (VO₂/HR)

- VO₂/Work slope = Under normal conditions 10 ml/min/watt
- Shallower slope indicates impaired O₂ delivery or utilization
- Cardiovascular impairment typically results in progressive blunting

VO₂:Workload Relationship

- VO₂/Work slope = Under normal conditions 10 ml/min/watt
- Shallower slope indicates impaired O₂ delivery or utilization
- Cardiovascular impairment typically results in progressive blunting
Dyspnea Index/Breathing Reserve

- **Dyspnea Index**: the proportion of the maximum voluntary ventilation (ventilatory reserve) used during incremental exercise in isotonic patients.
  \[
  \left( \frac{\dot{V}_E \text{ max}}{\text{MVV}} \right)
  \]

- **Breathing Reserve**: \(1 - \text{Dyspnea Index}\)
  \[
  \left(1 - \frac{\dot{V}_E \text{ max}}{\text{MVV}} \right)
  \]

Breathing reserve < 15%  Ventilatory Limit
Dyspnea index > 0.85  To Exercise

---

Breathing Reserve

How much of the maximum voluntary ventilation is left at end of exercise.

- MVV 140 L/min
- Peak Exercise VE 70 L/min
- Breathing Reserve 50%

- MVV 55 L/min
- Peak Exercise VE 55 L/min
- Breathing Reserve 0%

## CPET Parameters with Various Diagnoses

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Deconditioned</th>
<th>Heart Failure</th>
<th>Pulmonary Hypertension</th>
<th>Pulmonary Disease</th>
<th>Mitochondrial Disease</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂</td>
<td>↘</td>
<td>↘</td>
<td>↘</td>
<td>↘</td>
<td>↘</td>
<td>↘</td>
</tr>
<tr>
<td>Anaerobic threshold</td>
<td>↘</td>
<td>↘</td>
<td>normal / ↘</td>
<td>normal</td>
<td>normal / ↘</td>
<td>normal</td>
</tr>
<tr>
<td>VO₂/Work Rate</td>
<td>normal</td>
<td>↘ (&lt;10)</td>
<td>normal</td>
<td>↘</td>
<td>normal / ↘</td>
<td>normal</td>
</tr>
<tr>
<td>O₂ pulse</td>
<td>normal</td>
<td>↘</td>
<td>normal / ↘</td>
<td>normal</td>
<td>normal / ↘</td>
<td>normal</td>
</tr>
<tr>
<td>Breathing Reserve</td>
<td>normal</td>
<td>normal</td>
<td>↑</td>
<td>↓</td>
<td>normal / ↑</td>
<td>normal</td>
</tr>
<tr>
<td>V₆/VCO₂</td>
<td>normal</td>
<td>high</td>
<td>(20-30)</td>
<td>(30-60)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>EOB</td>
<td>none</td>
<td>+/-</td>
<td>↑</td>
<td>none</td>
<td>↑</td>
<td>normal</td>
</tr>
<tr>
<td>PaO₂</td>
<td>normal</td>
<td>normal</td>
<td>variable</td>
<td>↘</td>
<td>normal / ↑</td>
<td>normal</td>
</tr>
<tr>
<td>PetCO₂</td>
<td>normal</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

### Important Emerging Testing Variables
Central Sleep Apnea

Hyperventilation  Circulatory Delay  Cerebrovascular Reactivity

CENTRAL SLEEP APNEA IN HEART FAILURE (HF) PATIENT

J Am Coll Cardiol. 2015;65(1):72-84.
Exercise Oscillatory Breathing in Advanced Heart Failure

Persistence of EOB ≥ 60% of exercise at ≥ 15% of the average resting value

EOB + VE/VCO₂ slope ≥ 36 → Hazard ratio 11.4 for all-cause mortality
(95% CI, 4.9-26.5; P < .001)


Exercise Oscillatory Breathing Predicts Sudden Cardiac Death

VO₂ Kinetics in Exercise and Recovery

Most activities of daily living do not require maximal effort!

VO₂ (L/min)

Exercise Recovery

Baseline

OXYGEN DEFICIT

OXYGEN DEBT

Time (sec)

Phase I          Phase II                     Phase III

On-response:

Exercise RecoveryBaseline

J Am Coll Cardiol 2004;44:2339–48

Delayed on-response:

HF, pHTN, Chronotropic incompetence

Delayed recovery:

HF, pHTN

VO₂(t) = VO₂(b) + A(1 - e^(-t/τ))

Time (sec)

J Am Coll Cardiol 2004;44:2339–48
Peak Circulatory Power

\[
\text{Peak Circulatory Power} = \text{Peak VO}_2 \times \text{Peak Systolic BP}
\]

- Ability to maintain optimal arterial pressure testifies to higher efficiency of the cardiac pump
- Impaired BP response to exercise associated with poor outcome
- Noninvasive approximation of peak Cardiac Power (peak cardiac output \( \times \) peak MAP)

Clinical Applications
Case #1

30 yo F with dTGA s/p atrial switch w/ progressive exercise intolerance and leg fatigue. Subsystemic RV EF 25%.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂</td>
<td>14.1 ml/kg/min (38% predicted)</td>
</tr>
<tr>
<td>Peak SBP</td>
<td>95 mmHg</td>
</tr>
<tr>
<td>Peak Circulatory Power</td>
<td>1350 mmHg*ml O₂/kg/min</td>
</tr>
<tr>
<td>Anaerobic threshold</td>
<td>11.1 ml/kg/min (50% predicted)</td>
</tr>
<tr>
<td>VO₂/Work Rate</td>
<td>depressed</td>
</tr>
<tr>
<td>O₂ pulse</td>
<td>10 ml/beat</td>
</tr>
<tr>
<td>Breathing Reserve</td>
<td>54% normal</td>
</tr>
<tr>
<td>V̇E/V̇CO₂</td>
<td>39</td>
</tr>
</tbody>
</table>

25th percentile for 30-39 F With dTGA s/p atrial switch

Successfully underwent transplantation in 2010

Risk of Developing HF in ACHD

The risk of HF in patients with single ventricle, ToF, TGA (s/p atrial switch) approaches 80% by age 50.

In contrast risk in general population is 12% by age 50.

Exercise Capacity in Asymptomatic Patients with ACHD

Normal Adults

Asymptomatic ≠ Not Impaired
Reduced Exercise Capacity is Uniformly Present

What is normal?
What is acceptable?

CPET in Patients with ACHD

- **Peak VO₂** is an important predictor of death or hospitalization. Index to age/sex/disorder.
- **VE/VCO₂ slope > 38** → 10-fold increased risk of mortality
  - Excessive ventilatory response to exercise across the diagnostic spectrum of ACHD
  - Cyanosis is a strong stimulus for increased VE/VCO₂ irrespective of the presence of pulmonary hypertension
- **Peak circulatory power** (peak VO₂ x peak SBP) < 1476 mmHg*ml O₂/kg/min → 15.4 fold increased 4-year risk of mortality

This finding is pathognominc for …

**Exercise Induced R→L Shunting**

96% Specificity + 90% Sensitivity for PFO in pHTN
Case #2

64yo M with nonischemic cardiomyopathy and chronic systolic heart failure. Slowly dwindling functional status. EF 25%. Working full time.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂</td>
<td>13.6 ml/kg/min (49% predicted)</td>
</tr>
<tr>
<td>Peak SBP</td>
<td>98 mmHg</td>
</tr>
<tr>
<td>Anaerobic threshold</td>
<td>10.3 ml/kg/min (40% predicted)</td>
</tr>
<tr>
<td>VO₂/Work Rate</td>
<td>depressed</td>
</tr>
<tr>
<td>O₂ pulse</td>
<td>12 ml/beat</td>
</tr>
<tr>
<td>Breathing Reserve</td>
<td>63%</td>
</tr>
<tr>
<td>V̇O₂/V̇CO₂</td>
<td>39</td>
</tr>
</tbody>
</table>

Currently UNOS Status 1A

2011 2012 2013 2014 2015

EF 30-35% (n=53)
EF <25% (n=404)
EF <30% (n=447)
EF <40% (n=123)
EF <50% (n=250)

Patients with LVEF < 30% have poor prognosis that is incompletely defined by further reductions in LVEF.

Stevenson et al. Circulation 1996
### Classification of Functional Impairment for Patients with Circulatory Failure

**LONG-TERM VASODILATOR THERAPY WITH TRIMAZOSIN IN CHRONIC CARDIAC FAILURE**


**Abstract**

Patients with cardiac failure have a generalized sympathetic overactivity that may impair cardiac function and exercise tolerance. The ability of long-term α1-antagonist blockade and vasodilator therapy with trimazosin (TMZ) to improve exercise capacity was studied in patients with chronic, stable heart failure of varying severity (functional exercise classes B to D). Exercise performance was monitored by respiratory gas exchange and air flow before and after patients were randomized to placebo (13 patients) or TMZ (10 patients) for six weeks. Twelve of 13 patients given placebo and subsequently TMZ and 10 patients given TMZ were then blinded to treatment for up to 12 weeks. Significant enhanced exercise capacity, increased heart rate, and reduced resting arterial pressure were observed with TMZ treatment in each Class B or C patient and in six of nine Class D patients, and were not observed during treatment with placebo. (N Engl J Med 1980;303:242-250.)

<table>
<thead>
<tr>
<th>Class</th>
<th>Severity</th>
<th>Maximum Oxygen Uptake (mL/kg/min)</th>
<th>Anaerobic Threshold (mL/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>none to mild</td>
<td>&gt; 20</td>
<td>&gt; 14</td>
</tr>
<tr>
<td>B</td>
<td>mild to moderate</td>
<td>16 to 20</td>
<td>11 to 14</td>
</tr>
<tr>
<td>C</td>
<td>moderate to severe</td>
<td>10 to 15</td>
<td>8 to 11</td>
</tr>
<tr>
<td>D</td>
<td>severe</td>
<td>6 to 9</td>
<td>5 to 8</td>
</tr>
</tbody>
</table>


### Hemodynamic Response To Exercise by Weber Class

## Weber and Ventilatory Classification Systems Used in Chronic Heart Failure

<table>
<thead>
<tr>
<th>Class</th>
<th>Severity</th>
<th>Maximum Oxygen Uptake (mL/kg/min)</th>
<th>Anaerobic Threshold (mL/min/kg)</th>
<th>Ventilatory Class</th>
<th>VE/VCO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>none to mild</td>
<td>&gt;20</td>
<td>&gt;14</td>
<td>I</td>
<td>≤ 29.9</td>
</tr>
<tr>
<td>B</td>
<td>mild to moderate</td>
<td>16 to 20</td>
<td>11 to 14</td>
<td>II</td>
<td>30.0-35.9</td>
</tr>
<tr>
<td>C</td>
<td>moderate to severe</td>
<td>10 to 15</td>
<td>8 to 11</td>
<td>III</td>
<td>36.0-44.9</td>
</tr>
<tr>
<td>D</td>
<td>severe</td>
<td>6 to 9</td>
<td>5 to 8</td>
<td>IV</td>
<td>≥ 45.0</td>
</tr>
</tbody>
</table>


## Peak VO₂ and Transplantation

![Graph showing survival rates based on peak VO₂ and transplantation](image_url)

Peak VO₂ and Survival

Survival (%)

VO₂ ≤ 14 listed for OHT
VO₂ ≤ 14 not listed for OHT

Months After Evaluation


ISHLT Listing Criteria for Transplant

Class I
- Maximal Test is defined as RER > 1.05 and achievement of AT on optimal pharmacotherapy (B)
- If beta blocker intolerant, a cutoff for peak VO₂ ≤ 14 ml/kg/min should be used (B)
- If beta blocker tolerant, a cutoff for peak VO₂ ≤ 12 ml/kg/min should be used (B)

Class Ila
- In young patients (< 50 yrs) and women, it is reasonable to consider using alternate standards in addition to peak VO₂ to guide listing including percent predicted VO₂ (<50%) (B)

J Heart Lung Transplant 2006;25:1024-1042
ISHLT Listing Criteria for Transplant

Class IIb

- In the presence of a submaximal test (RER < 1.05), use of Ve/VCO2 slope > 35 may be considered (C)
- In obese patients (BMI > 30 kg/m2), adjusting peak VO2 to lean body mass may be considered. Using a peak VO2 < 19 ml/kg/min can serve as the threshold (B)

Class III

- Listing patients for transplant based solely on the criterion of a peak VO2 measurement should not be performed (C)

No single parameter necessitates transplantation!
**Case #3**

39 yo F with remote tobacco history, AVNRT and LBBB with associated nonischemic cardiomyopathy. With CRT-D LVEF 10→35% but continues to complain of NYHA FC IV symptoms.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂</td>
<td>25 ml/kg/min</td>
<td>(80% predicted)</td>
</tr>
<tr>
<td>Peak MAP</td>
<td>140 mmHg</td>
<td>normal</td>
</tr>
<tr>
<td>Anaerobic threshold</td>
<td>16 ml/kg/min</td>
<td>(52% predicted)</td>
</tr>
<tr>
<td>VO₂/Work Rate</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>O₂ pulse</td>
<td>14 ml/beat</td>
<td>normal</td>
</tr>
<tr>
<td>V̇E/V̇CO₂</td>
<td>29</td>
<td>normal</td>
</tr>
<tr>
<td>Breathing Reserve</td>
<td>6%</td>
<td>↓↓↓</td>
</tr>
</tbody>
</table>

Low risk

PFTs demonstrate moderate COPD

**Case #4**

67 yo M with Hodgkin’s lymphoma s/p cobalt radiation. Progressive exercise intolerance with mild-moderate MS (mean gradient 5 mmHg→10 mmHg with exercise).

No angina or ischemic ECG changes.
Case #5

66yo M with nonischemic cardiomyopathy now with normalized LVEF, persistent AF s/p AVJ ablation, s/p CRT-D. Persistent NYHA FC IIIb symptoms. Normal resting hemodynamics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak $\text{VO}_2$</td>
<td>14.2 ml/kg/min (42% predicted)</td>
<td>Marked Chronotropic Incompetence</td>
</tr>
<tr>
<td>Peak HR</td>
<td>90 bpm</td>
<td>Increased aggressiveness of rate adaptive pacing</td>
</tr>
<tr>
<td>% APMHR</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>Anaerobic threshold</td>
<td>10.7 ml/kg/min (31% predicted)</td>
<td></td>
</tr>
<tr>
<td>$\text{VO}_2$/Work Rate</td>
<td>depressed</td>
<td></td>
</tr>
<tr>
<td>$\text{O}_2$ pulse</td>
<td>15 ml/beat</td>
<td>normal</td>
</tr>
<tr>
<td>$\text{Ve}/\text{VCO}_2$</td>
<td>30</td>
<td>normal</td>
</tr>
<tr>
<td>Breathing Reserve</td>
<td>73.6%</td>
<td>normal</td>
</tr>
</tbody>
</table>

Miscellaneous Applications:
Preoperative Eval for Lung Cancer Surgery

- **Peak $\text{VO}_2 > 15$ ml/kg/min**: no significant increase in morbidity/mortality
- **Peak $\text{VO}_2 < 15$ ml/kg/min**: increased risk of morbidity/mortality
- **Peak $\text{VO}_2 < 10$ ml/kg/min**: 40-50% mortality → non-surgical management

Alberts et al, Crit Care 2007;11:2s.
Invasive CPET
Indirect Fick

\[ \text{CO} = \frac{\text{VO}_2}{\text{C(a-v)O}_2} \]

• \( \text{VO}_2 \) can be influenced by numerous confounders (age, sex, motivation, obesity, deconditioning, localized muscle fatigue).

• Reduced oxygen extraction may be due to anemia, decreased muscle mass, decrease muscle capillary density, myoglobin content, mitochondrial mass, oxidative enzymes.

Noninvasive Assessment of Cardiac Output

\[ \text{VO}_2 = \text{CO} \times \text{C(a-v)O}_2 \]

J Heart Lung Transplant 2006;25:1024-1042
Cardiac Output Response to Exercise is Highly Predictive of Outcomes in AHF

REFERRAL FOR CARDIAC TRANSPLANTATION

INITIAL CARDIOPULMONARY EXERCISE TESTING

VO₂ ≥ 20 ml/min/kg
VO₂ ≤ 20 ml/min/kg

"Excellent" prognosis
No further evaluation for cardiac transplantation.

INVASIVE HEMODYNAMIC EXERCISE TESTING

NORMAL CO RESPONSE TO EXERCISE

VO₂ > 10 ml/min/kg
"Good" prognosis
Need serial cardiopulmonary exercise testing.
Follow up in CHF clinic.
Recruit into exercise rehabilitation program.

ABNORMAL CO RESPONSE TO EXERCISE

VO₂ ≤ 10 ml/min/kg
"Uncertain" prognosis
Suggest initial invasive hemodynamic exercise testing.
Recruit into exercise rehabilitation program.
Consider cardiac transplantation.

VO₂ > 10 ml/min/kg
"Poor" prognosis
Work up for cardiac transplantation.

VO₂ ≤ 10 ml/min/kg
"Very poor" prognosis
Expedite cardiac transplantation.
Consider status 1 waiting list.
New Center Delivers Diagnosis for Unexplained Dyspnea

A 54-year-old woman presented with progressive dyspnea on exertion. Echocardiography and computed tomography of the chest were normal. 6MWD exercise capacity on cardiac catheterization was 12 km.

The patient was started on螺内酯。Within one month, symptoms markedly improved.

**Indications for Testing**

Unexplained dyspnea may be referred to the Unexplained Dyspnea Center for diagnostic evaluation with normal or near-normal pulmonary function tests and imaging.

**Case Study: Identifying Cause of Unexplained Dyspnea**

A 54-year-old woman was evaluated for dyspnea and exercise intolerance. She had a history of congestive heart failure, chronic obstructive pulmonary disease (COPD), and anxiety. Her 6MWD was 12 km, and she had a history of anxiety.

**Functional Performance**

<table>
<thead>
<tr>
<th>Test</th>
<th>Predicted</th>
<th>Actual</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD</td>
<td>12.2 km</td>
<td>11.5 km</td>
<td>95%</td>
</tr>
<tr>
<td>Peak VO2</td>
<td>24.2 mL/kg/min</td>
<td>19.2 mL/kg/min</td>
<td>80%</td>
</tr>
<tr>
<td>Max HR</td>
<td>115 bpm</td>
<td>109 bpm</td>
<td>95%</td>
</tr>
</tbody>
</table>

**Respiratory Data**

<table>
<thead>
<tr>
<th>Test</th>
<th>Predicted</th>
<th>Actual</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute Ventilation</td>
<td>40 L/min</td>
<td>35 L/min</td>
<td>88%</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.70</td>
<td>0.70</td>
<td>100%</td>
</tr>
<tr>
<td>TLC</td>
<td>5.0 L</td>
<td>4.8 L</td>
<td>96%</td>
</tr>
</tbody>
</table>

**Gas Exchange**

<table>
<thead>
<tr>
<th>Test</th>
<th>Predicted</th>
<th>Actual</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>67%</td>
<td>22 mm Hg</td>
<td>21 mm Hg</td>
<td>95%</td>
</tr>
<tr>
<td>67%</td>
<td>21 mm Hg</td>
<td>21 mm Hg</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Advanced Cardiopulmonary Stress Testing**

<table>
<thead>
<tr>
<th>Test</th>
<th>Predicted</th>
<th>Actual</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>R575</td>
<td>64 mm Hg</td>
<td>62 mm Hg</td>
<td>95%</td>
</tr>
<tr>
<td>0.6S</td>
<td>64 mm Hg</td>
<td>62 mm Hg</td>
<td>95%</td>
</tr>
</tbody>
</table>

**Cardiac Catheterization**

<table>
<thead>
<tr>
<th>Test</th>
<th>Predicted</th>
<th>Actual</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>R575</td>
<td>64 mm Hg</td>
<td>62 mm Hg</td>
<td>95%</td>
</tr>
<tr>
<td>0.6S</td>
<td>64 mm Hg</td>
<td>62 mm Hg</td>
<td>95%</td>
</tr>
</tbody>
</table>

**Catheterization**

<table>
<thead>
<tr>
<th>Test</th>
<th>Predicted</th>
<th>Actual</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>55%</td>
<td>55%</td>
<td>100%</td>
</tr>
<tr>
<td>RVET</td>
<td>120 ms</td>
<td>120 ms</td>
<td>100%</td>
</tr>
<tr>
<td>RVSP</td>
<td>35 mm Hg</td>
<td>35 mm Hg</td>
<td>100%</td>
</tr>
</tbody>
</table>
iCPET for Unexplained Dyspnea

**Case #6**


**Exercise Induced pHTN**

Started on tadalafil with modest improvement in symptoms
By Noninvasive CPET
Oxidative Myopathy = Cardiac Limitation
Consider diagnosis when these findings are in absence of other objective evidence of cardiac disease!
Pathognomonic finding is uncoupling of CO and VO2.

OXIDATIVE MYOPATHY

CPET: What to Order

1. CPET
   [CARDIOPULMONARY STRESS TEST 94621]
2. CPET with exercise PFTs
   [+ READ/INTERPRET PFTS 93018]
   • Comorbid lung disease
   • Young, otherwise healthy patient (i.e., exercise induced asthma)
3. CPET with arterial blood gas monitoring
   [ARTERIAL CATHETERIZATION 36620]
   • Need quantification of VD/VT (lung disease)
   • Need quantification of P(A-a)O2 (lung disease)
4. CPET with exercise stress echo
   [STRESS ECHO 208576]
   • Assessing effects of moderate valvular disease
5. CPET with exercise RHC
   [EXERCISE HEMODYNAMICS 93464]
   • Exercise induced pulmonary hypertension
   • Exercise induced diastolic dysfunction
   • Preload failure
   • Mitochondrial/skeletal myopathies

If unsure, just ask…

Workflow
Under Review
Summary

CPET...

1. Evaluation of VE, VO₂, and VCO₂ + standard ETT
2. Can assist in understanding patients with unexplained dyspnea
3. Is a powerful prognostic test in patients with HF, ACHD, pHTN
4. Should be considered in any patient with LVEF < 30% once stable on GDMT
5. iCPET can make conclusively make diagnoses that no other studies can.
Thank you!

Questions?

### CPET Parameters with Various Diagnoses

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Deconditioned</th>
<th>Heart Failure</th>
<th>Pulmonary Hypertension</th>
<th>Pulmonary Disease</th>
<th>Mitochondrial Disease</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO$_2$</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Anaerobic threshold</td>
<td>↓</td>
<td>↓</td>
<td>normal / ↓</td>
<td>normal</td>
<td>↓</td>
<td>normal</td>
</tr>
<tr>
<td>VO$_2$/Work Rate</td>
<td>normal</td>
<td>↓ (&lt;10)</td>
<td>↓</td>
<td>normal</td>
<td>normal / ↓</td>
<td>normal</td>
</tr>
<tr>
<td>O$_2$ pulse</td>
<td>normal</td>
<td>↓</td>
<td>normal / ↓</td>
<td>normal</td>
<td>↓</td>
<td>normal</td>
</tr>
<tr>
<td>Breathing Reserve</td>
<td>normal</td>
<td>normal</td>
<td>↑</td>
<td>↑</td>
<td>normal / ↑</td>
<td>normal</td>
</tr>
<tr>
<td>V$_A$/VCO$_2$</td>
<td>normal</td>
<td>high</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>normal</td>
</tr>
<tr>
<td>EOB</td>
<td>none</td>
<td>+/-</td>
<td>↑</td>
<td>none</td>
<td>↑</td>
<td>normal</td>
</tr>
<tr>
<td>PaO$_2$</td>
<td>normal</td>
<td>normal</td>
<td>variable</td>
<td>↓</td>
<td>↓</td>
<td>normal</td>
</tr>
<tr>
<td>PetCO$_2$</td>
<td>normal</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>