Chapter 111. Clinical Center Cardiopulmonary Exercise Test (CPET) - Invasive

Adapted from the Protocol for Invasive Cardiopulmonary Exercise Test in Clinical Practice; David M. Systrom, M.D.,§ Bradley A. Maron, M.D. §* Used with permission.

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This manual is intended to serve as a training and reference document for persons who perform invasive CPET for the PVDOMICS Study using standardized procedures and techniques. Before performing invasive CPET for the PVDOMICS study, both this chapter on invasive CPET and Chapter 110 on non-invasive CPET should be reviewed.

111.1 Contraindications to Invasive CPET testing

Participants who are excessively anticoagulated or with severe thrombocytopenia are at increased risk. Participants without central venous access are not candidates. Additional common relative contraindications to exercise testing apply to iCPET, including severe/symptomatic aortic stenosis (though the question is usually whether symptoms are related or unrelated to valve disease), decompensated congestive heart failure, unstable coronary syndromes, inability to exercise, severe pulmonary hypertension, unstable arrhythmias or syncope.

The following is a stepwise approach to the application of iCPET testing in clinical practice.

111.2 Participant Counseling

Discuss sequential phases of the iCPET study and obtain consent.

1. Right heart catheterization and radial artery access placement:
   a. In participants for whom the diagnosis of unexplained dyspnea is unresolved despite alternative testing, including non-invasive CPET, right heart catheterization during iCPET is required to evaluate for specific forms of cardiopulmonary disease. Right heart catheterization is safe and, although complication rates vary by center, the risk of death in one large clinical study (n = 7,218) of patients with severe pulmonary hypertension was 0.055% (n = 4); serious adverse events occurred in 1.1% (n = 76), predominately due to bleeding at the site of vascular access. Additional complications include accidental arterial catheterization and transient arrhythmia during passage of the catheter through the right cardiac chambers. To minimize the risk of complication, cardiac catheterization is performed uniformly with the assistance of ultrasound and fluoroscopic guidance at our center.
   b. Radial artery canalization is generally well tolerated; complications are uncommon and include, but are not exclusive to, temporary or permanent vessel occlusion, pseudoaneurysm formation, infection, or, rarely, air embolism. Local pain at the site
of cannulation, however, is common and may persist for days.

2. If the exercise testing is not performed in the catheterization laboratory, the patient is transported with appropriate healthcare provider supervision from the cardiac catheterization laboratory to the iCPET suite with continued cardiac rhythm and pulmonary artery monitoring, the latter to avoid inadvertent and sustained wedging of the catheter.

3. Each vascular access site (i.e., radial, internal jugular) is monitored at each stage.

4. The participant should be familiarized with study devices (e.g., cycle ergometer, pneumotachograph, metabolic cart, waveform screen for pulmonary arterial catheter and radial line, electrocardiography [ECG] leads).

5. Review stages of iCPET Test:
   a. Preparatory phase/set up
   b. Warm up phase
   c. Exercise phase
   d. Recovery phase

111.3 Components of an iCPET

1. Cycle ergometer
   a. An upright cycle ergometer is used for exercise stress where the resistance (i.e., work) is continually and linearly increased until symptomatic exhaustion. A supine or semi-supine cycle ergometer may be used at sites where cycle ergometry is regularly performed supine, but is not preferred.

2. Metabolic cart
   a. Contains gas analyzers and a pneumotachograph for breath-by-breath measurements of expired O₂ and CO₂ and ventilation with calculation of VO₂ and VCO₂. The metabolic cart can also be used to perform spirometry to measure or calculate maximum voluntary ventilation (MVV = 35 × FEV1).

3. Continuous 12-lead electrocardiography to monitor heart rate, rhythm, and signs of ischemia.

4. Peripheral non-invasive oxyhemoglobin saturation level (SpO₂) monitoring

5. Hemodynamic monitoring and vascular access
   a. Continuous measurements of systemic blood pressure through the radial artery catheter; central venous, right atrial, right ventricular, and pulmonary arterial pressures are measured at rest and during exercise via the pulmonary artery catheter. The PCWP is determined by balloon inflation every minute during exercise.

6. Vascular access
   a. Blood samples from radial and pulmonary arterial catheters are also drawn every
minute to measure blood gases and pH. Cardiac output is calculated every minute via the direct Fick method using co-oximeter measured SaO2 and SvO2 and measured VO2. Plasma lactate is also measured, generally via the radial artery.

111.4 Pulmonary Function Testing, and Right Heart and Radial Artery Catheterization

1. Prior to catheterization, spirometry is performed to record Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), FEV1/FVC, and maximum ventilatory volume (MVV, either measured or estimated by FEV1 x 35). In participants for whom neuromuscular disease is a consideration, the MVV should be measured before and after exercise.

2. Exercise flow volume loops and inspiratory capacity measurements may be obtained during exercise in specific participants, such as those where there is suspicion for a vascular ring or with pulmonary disease of unclear severity.

3. Standard sterile technique applies to right heart catheterization and radial artery cannulation, performed in a cardiac catheterization laboratory by an experienced operator.

4. Blood pressure and oxyhemoglobin saturation levels are recorded in each of the following vascular compartments with the participant supine: superior vena cava, right atrium, right ventricle, main pulmonary artery, and cardiac output is measured using the Fick method according to the following formula: Qt = \( \dot{V} \) O2/C(a-\( \overline{V} \))O2, where Qt is cardiac output; \( \dot{V} \) O2, volume of oxygen consumption; C(a-\( \overline{V} \))O2, O2 content of arterial – mixed venous blood.2

5. In the absence of a contraindication to further testing on resting RHC (e.g., severe pulmonary hypertension, decompensated HF), the catheter port is disconnected from the pressure monitoring system and reconnected to a portable pressure transducer and monitor.

6. Calibration: The pulmonary artery and PCWP are recorded under fluoroscopy to ensure proper location of the catheter tip. The participant is then moved to the upright position and the pressure calibrator is opened to ambient air (“zeroed”), calibrated, and leveled to the 4th intercostal space at the mid-axillary line, approximately 5 cm below the angle of Louis or 3 finger breadths below the axilla, which is in the plane of the right atrium in most participants.

7. The monitored participant is then transferred under the supervision of appropriate healthcare provider escort to the iCPET suite.

111.5 Invasive CPET Suite

In addition to the components required for iCPET testing (see above), the iCPET suite should contain a system for pressure measurements and an advanced cardiopulmonary life support (ACLS) emergency cart.
1. Staff required includes the following appropriately trained medical personnel:
   a. An exercise physiologist supervises the metabolic cart and timer, coordinates the timing of blood draws and PCWP measurements, provides encouragement and direction ("coaching") to the participant, anticipates the end of the test based on symptoms and metabolic data, and is positioned to obtain arterial blood gas, pH and lactate samples appropriately (See Section 111.7.3 below).
   b. A second exercise physiologist manages the waveform recorder, records the systemic, pulmonary artery and PCW pressures at the appropriate time intervals (See section 111.7.3 below)
   c. A physician assistant, nurse practitioner, or physician performs the pulmonary artery catheter balloon inflation to obtain wedge pressure tracing at the appropriate time intervals (See section 111.7.3), as well as obtaining mixed venous blood gases and pH from the distal pulmonary artery catheter port at the appropriate time intervals.
   d. A physician is present and supervises the test.

111.6 Determining the Exercise Protocol

1. Pedal resistance increases during the exercise test at a linear rate after a period of freewheel. The rate of increase is determined according to each participant’s prior exercise test performance or self-reported baseline fitness level to aim for a 6-8 minute symptom-limited test as follows:
   a. 10 watts/interval increase for sedentary participants
   b. 15 watts/interval if participants are able to perform light exercise (walking slowly, cooking, washing dishes, or other low aerobic activities of daily living).
   c. 20 watts/interval if participants are able to perform moderate exercise (walking briskly, vacuuming or mopping, using a powered lawn mower, etc.).

2. For the PVDOMICS study, follow the guidelines below to select the appropriate ramp for each participant based on their self-reported abilities. One interval is defined as the time spent at a specific work rate.
   a. If the participant becomes short of breath or fatigued moving between rooms in their house, use a 10 watts/interval ramp.
   b. If the participant is able to walk around their house without difficulty but becomes short of breath or fatigued climbing one (1) flight of stairs, use a 15 watts/interval ramp.
   c. If the participant is able to climb one (1) flight of stairs without difficulty (they do not become short of breath or fatigued in doing so) use a 20 watts/interval ramp.
   d. See Appendix 111.A.2 for suggested script.

3. Participants pedal at a continuous rate of approximately 60 cycles per minute as
resistance increases. The exercise physiologist plays an important role in monitoring the cycling rate. The goal exercise time duration is at least 5 minutes.

### 111.7 Invasive CPET Test

In addition to the information provided below please refer to MOP Chapter 110 (CPET – non-invasive) sections 110.13-110.16 for additional directions for PVDOMICS specific testing.

<table>
<thead>
<tr>
<th>1. Preparation Phase</th>
<th>a. Record demographic and other patient characteristics on a participant report form.</th>
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<tbody>
<tr>
<td></td>
<td>b. Participant is positioned on ergometer with seat height adjusted to comfort, with total or near-total leg extension at nadir of pedal trajectory.</td>
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<td>c. 12-lead ECG system is activated with standard lead positioning. The modified 10-electrode (Mason-Likar) configuration is the preferred method of electrode placement.</td>
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<td>d. With participant on the cycle ergometer, radial and pulmonary artery catheter waveform recorders are connected, zeroed, and leveled according to the methods and landmarks described in Section 111.4.6.</td>
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<td></td>
<td>e. Pulse oximeter is connected to the recording system for continuous SaO2 monitoring. The validity of non-invasive SaO2 assessment is supported by comparing reported HR to the ECG HR and subsequently validated in comparison to radial artery measurements.</td>
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<td></td>
<td>f. The mouthpiece for the pneumotachograph and metabolic cart should be fitted and nose clip placed followed by baseline ventilation and pulmonary gas exchange measurements recorded over a 1-minute period.</td>
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<td>g. Measure baseline ABG (optional), SvO2, and plasma lactate.</td>
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<td></td>
<td>h. Measure baseline systemic and pulmonary arterial pressures, right atrial pressure (central venous pressure), and PCWP.</td>
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<tr>
<td>2. Warm up or ‘Free wheel’ phase</td>
<td>a. Participants will warm up without resistance (aka “free wheel”) for 2 minutes; during this time, re-level all pressure transducers to account for subtle changes in posture that may occur with movement of exercise.</td>
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<td></td>
<td>b. Continuously record ventilation and pulmonary gas exchange measurements.</td>
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<td></td>
<td>c. Repeat systemic and pulmonary arterial pressures, central venous...</td>
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| 3. Exercise Phase | a. Metabolic cart-driven resistance is added to the pedal stroke at the predetermined rate (10 watts/interval, 15 watts/interval or 20 watts/interval).
| | b. Optional: Blood for ABG, VBG, pH, and plasma lactate measurements are drawn at 2-minute intervals (or more frequently if desired).
| | c. PAP and PCWP are measured at 2-minute intervals (or more frequently if desired).
| | d. Central venous (right atrial pressure), systemic arterial, and pulmonary artery pressures are recorded continuously through passive exhalation.
| | e. Peak exercise is defined as the point in time at which the participant is unable to maintain 60 revolutions per minute cycle rate.
| | f. The ABG, VBG, pH, $S\overline{v}O_2$, and plasma lactate are measured at peak exercise.
| | g. The PCWP is measured at peak exercise.
| | h. Coaching is permissible; the goal is achieve at least 5 minutes, though preferably 6-8 minutes, of exercise prior to the completion of the test.
| 4. Recovery Phase | a. The cycle ergometer resistance returns to 0 watts.
| | b. The participant cycles for two minutes at 0 watts, then rests for three additional minutes. Monitoring continues during this time.
| | c. After two minutes of recovery PAP and PCWP are measured.
| | d. After five minutes of recovery PAP and PCWP are measured, and 1 ml of blood may be sampled for ABG, VBG, pH, $S\overline{v}O_2$, and plasma lactate (optional).
| | e. Participant is then transferred, with the appropriate healthcare provider escort, to an area for recovery. Blood pressure and heart rhythm are monitored frequently. PAP and blood lactate levels may be monitored at 30 min and 60 min time points if the catheters are tolerated by the participant. The PA catheter is then removed while the participant is instructed to hum. The catheter insertion site is compressed with direct pressure for at least 5 minutes and occlusive dressing is applied and maintained at the
puncture site for 24 hours. The radial artery catheter is then removed and firm but not occlusive pressure is applied to the insertion site for a minimum of 10 minutes, and a pressure bandage is applied and maintained for 24 hours. The participant should be instructed against lifting for 48 hours and asked to contact the exercise staff in the event of bleed, hematoma, redness, rash, finger pain, and/or cyanosis at either the pulmonary artery or radial artery insertion sites.

111.8 Indications for study cancellation or termination

1. ECG signifying myocardial injury current or potentially lethal arrhythmias
2. Systemic hypotension (e.g., systolic blood pressure < 90 mmHg)
3. Extreme hypertension (e.g., systolic blood pressure > 220 mmHg)
4. Syncope or pre-syncope or lightheadedness
5. Peripheral oxyhemoglobin saturation level <88%
6. Severely elevated PCWP during exercise (> 40 mmHg)

Invasive CPET is an important consideration in the clinical evaluation of patients with unexplained exertional intolerance despite conventional diagnostic testing. By leveraging the simultaneous assessment of full cardiopulmonary hemodynamics and gas exchange performance during exercise, iCPET is well positioned to diagnose exercise-induced pulmonary arterial hypertension, heart failure with preserved left ventricular ejection fraction, and failure to augment right ventricular pressure as occult causes of exertional dyspnea. Our experience is that a multi-disciplinary approach to the application of iCPET in clinical practice that involves pulmonologists, cardiologists, physicians assistants, and exercise physiologists is critical to the completion of a safe and accurate study. With an expanding pool of patients diagnosed with unexplained dyspnea, the implementation of a standardized iCPET protocol is anticipated to enhance the dialogue by which clinicians discuss the pathophysiology of exertional dyspnea and empiric efforts to identify novel treatments for patients afflicted with this condition.

111.9 Referenced Documents

See also:


111.10 Figures & Figure Legends

Figure 1. A diagnostic algorithm for interpreting iCPET results. (A) Assessment of functional capacity is determined by calculating the maximum volume of oxygen consumed per minute ($\dot{V}O_2$), which may be performed during conventional or invasive cardiopulmonary exercise testing (iCPET). (B) A disproportional increase in the minute ventilation relative to maximum ventilatory capacity ($V_{E: MVV}$) indicates a pulmonary mechanical limitation to exercise. Alternatively, early achievement of the anaerobic threshold (AT) suggests disordered oxygen (O$_2$) flux that may be a consequence of (C) decreased cardiac output (i.e., abnormal O$_2$ delivery) and/or (D) impaired O$_2$ extraction by skeletal muscle tissue from arterial blood. This determination, and subsequent analyses presented in the diagnostic algorithm, require iCPET and cannot be performed by conventional exercise stress testing alone. In patients with a central cardiovascular limit to exercise, specific cardiopulmonary hemodynamics profiles observed during exercise are suggestive of (E) exercise-induced PAH, (F) exercise-induced heart failure with preserved ejection fraction (HFpEF) if the left ventricular ejection fraction is normal, or (G) a preload limitation to exercise. COPD, chronic obstructive pulmonary disease; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; $\dot{V}CO_2$, volume of exhaled carbon dioxide; RV, right ventricle; MVV, maximum voluntary ventilation. Figure and legend reproduced with some modifications with permission from Ref. 1.

Figure 2. Modeling of the relationship between cardiac output and mean pulmonary artery pressure. Under physiological conditions, the pulmonary vascular distensibility coefficient approximates 1-2%, which results in a curvilinear relationship between cardiac output and mean pulmonary artery pressure. Adapted with permission from the Protocol for Invasive Cardiopulmonary Exercise Test in Clinical Practice; David M. Systrom, M.D., Bradley A. Maron, M.D.
Figure 1. A diagnostic algorithm for interpreting iCPET results.
Figure 2. Modeling of the relationship between cardiac output and mean pulmonary artery pressure.
111.A.1 Appendix 1 – PVDOMICS Invasive Cycle Ergometer CPET Data Collection Schedule

Data should be captured as indicated below during the last 30 sec of each interval if possible. A direct Fick cardiac output may be calculated based on the data gathered and recorded on this form.

<table>
<thead>
<tr>
<th>Time Elapsed</th>
<th>Work Rate</th>
<th>Target Pedal Rate</th>
<th>Actual Pedal Rate</th>
<th>SpO&lt;sub&gt;2&lt;/sub&gt;</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>Dyspnea (Borg scale)</th>
<th>RPE (Borg scale)</th>
<th>mPAP (mmHg)</th>
<th>PCWP (mmHg)</th>
<th>SvO&lt;sub&gt;2&lt;/sub&gt; (%)</th>
<th>SaO&lt;sub&gt;2&lt;/sub&gt; (%)</th>
<th>VO&lt;sub&gt;2&lt;/sub&gt; (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(min)</td>
<td>(Watts)</td>
<td>(rpm)</td>
<td>(rpm)</td>
<td>(%)</td>
<td>(mmHg)</td>
<td>(mmHg)</td>
<td>(0-10)</td>
<td>(0-10)</td>
<td>(mmHg)</td>
<td>(mmHg)</td>
<td>(%)</td>
<td>(%)</td>
<td>(mL/min)</td>
</tr>
</tbody>
</table>

Pre-Exercise (Resting)

-1 Rest 0

Exercise

<table>
<thead>
<tr>
<th>0</th>
<th>0</th>
<th>60</th>
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</table>

Start ramp

<table>
<thead>
<tr>
<th>2</th>
<th>60</th>
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</thead>
<tbody>
<tr>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
</tr>
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<td>8</td>
<td>60</td>
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<tr>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
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Recovery

<table>
<thead>
<tr>
<th>+1</th>
<th>0</th>
<th>30</th>
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<tbody>
<tr>
<td>+2</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>+3</td>
<td>Rest</td>
<td>0</td>
</tr>
<tr>
<td>+4</td>
<td>Rest</td>
<td>0</td>
</tr>
<tr>
<td>+5</td>
<td>Rest</td>
<td>0</td>
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</table>

Optional measurement
111.A.2 Appendix 2 – Selecting the Appropriate Exercise Protocol

Follow the procedure below in order to select the appropriate exercise protocol for each participant in the PVDOMICS study.

Ask each participant:

1) *Do you become short of breath or fatigued when you walk around your house?*

If the answer to question 1 is “yes” → STOP, select a 10 watts/interval continuous ramp protocol
If the answer to question 1 is “no” → ask question 2

2) *Do you become short of breath or fatigued when you climb 1 flight of stairs?*

If the answer to question 2 is “yes” → select a 15 watts/interval continuous ramp protocol
If the answer to question 2 is “no” → select a 20 watts/interval continuous ramp protocol