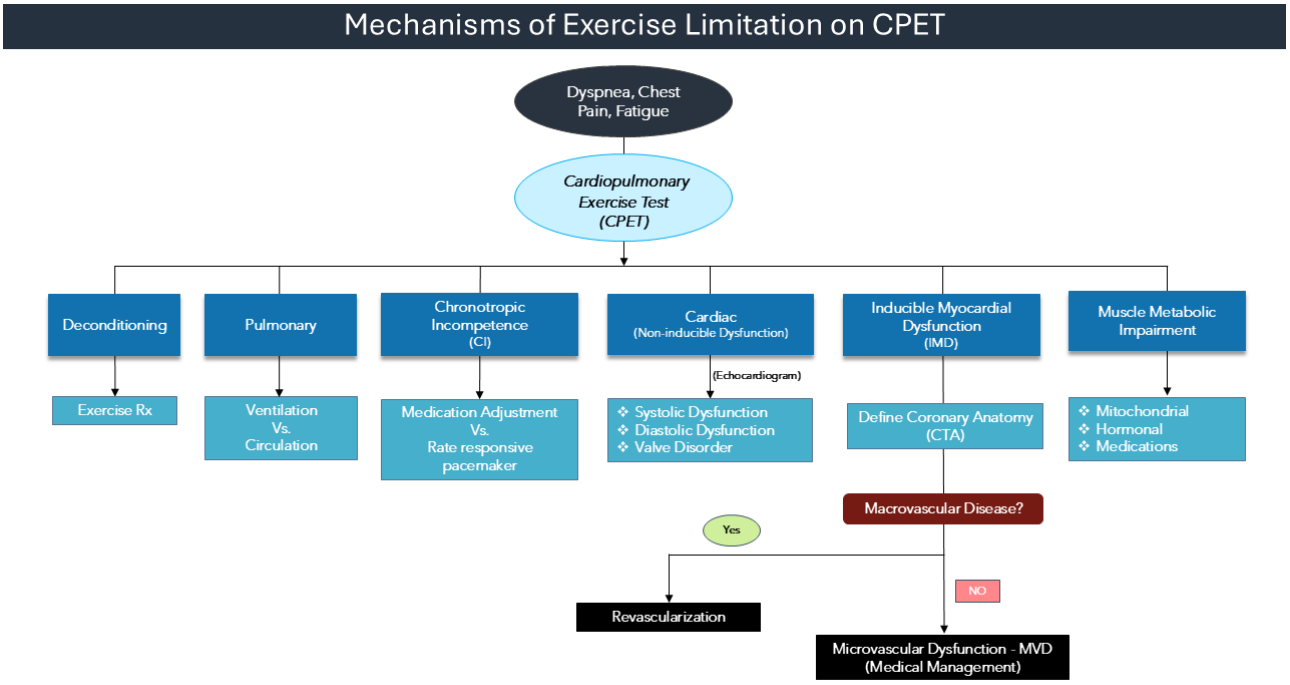
CPET-Insight

Clinician's Guide to Cardiopulmonary Exercise Testing

Criteria for Mechanism of Exercise Limitation

Interpretation of CPET data infers three fundamental questions:

- Did the patient put in a full effort?
- Is the functional/exercise capacity (peak VO_2) normal or reduced?
- What is the mechanism of limitation (symptoms)?



Effort

Effort is determined by the peak respiratory exchange ratio (RER ≥ 1.09) and peak heart rate (HR ≥ 85%). If the equipment was properly calibrated and the patients' breathing patterns are normal, then peak RER is the gold standard for effort determination and achieving a level 1.09 or higher indicates the development of a significant metabolic acidosis and thus maximal CV stress. With improper equipment calibration or erratic breathing, peak RER may not be reliable and in such cases, if peak HR reaches 85% or higher, the test is still considered to be maximal.

The only time a test is considered maximal when both peak RER and peak HR are sub-maximal is when the subject develops dyspnea from a pulmonary limitation. Pulmonary impairment can be due to either ventilation limitation (breathing reserve is less than 10% or 10 L at peak exercise) or to a significant ventilation-perfusion mismatch (impaired pulmonary circulation +/− increased dead space) — abnormally steep VE vs. VCO_2 slope. Tests with low peak RER, low peak HR, normal BR and VE vs. VCO_2 slope represent sub-maximal effort.

Exercise Capacity

Expressed in terms of percentage of predicted peak VO_2. The lower limit of normal for peak VO_2 is 85% predicted (Wasserman Textbook). With good effort, the degree of impairment can be quantified as follows:

- **Mild**: 70–84%
- **Moderate**: 60–69%
- **Moderate to Severe**: 50–59%
- **Severe**: < 49%

A baseline peak VO_2 serves as a reference point for all future studies to track progression/regression of disease as well as response to therapeutic interventions.

Mechanism of Exercise Impairment

From a mechanistic perspective, a CPET study will fall into one of the following seven categories:

1. Normal

Truly normal (optimal) studies are not common and are seen in <10% of the general population as most individuals have some form of CV impairment. Criteria for the normal category are high:

Diagnostic Criteria

- Good Effort: Peak RER ≥ 1.0 and/or Peak HR ≥ 85%
- Normal Peak VO_2 (≥ 85%)
- Normal CV Function:
  - Normal or high peak stroke volume (O_2-pulse) without decrease in slope after the AT (no IT)
  - Normal peak HR without acceleration after the AT (no IT) and with a normal slope (chronotropic index)
  - Normal AT
- Normal Pulmonary Function:
  - Normal breathing pattern and breathing reserve (BR)
  - Normal pulmonary circulation (no V/Q mismatching)

2. Deconditioning

Deconditioning is an overused (wastebasket) term because a clear mechanism for exercise intolerance cannot be readily identified. Relatively few CPET studies fall into this category:

Diagnostic Criteria

- Good effort: Peak RER ≥ 1.09 and/or Peak HR ≥ 85%
- Low normal or mildly reduced Peak VO_2 (~80–85%)
- Normal CV Function:
  - Mildly reduced peak stroke volume (O_2-pulse) without decrease in slope after the AT (no IT)
  - Normal or high peak HR without acceleration after the AT (no IT) and with normal slope (chronotropic index)
  - Mildly reduced or borderline low normal AT
- Normal Pulmonary Function:
  - Normal breathing reserve (BR)
  - Normal pulmonary circulation (no V/Q mismatching)

3. Pulmonary

The number of true pulmonary impairment studies is also relatively low in the general population as the lungs have a large physiological reserve and it takes relatively severe disease to produce symptoms. Shortness of breath from pulmonary impairment falls into three categories:

Dysfunctional Breathing

Can present as hyperventilation and/or erratic breathing patterns during exercise. The diagnostic criteria differ between early and later exercise phases, with specific patterns helping distinguish pathologic hyperventilation from normal physiological responses.

Hyperventilation Syndrome (HVS)

Reflects a state where ventilation (VE) is disproportionately high relative to metabolic demand (VCO_2), leading to hypocapnia. Key indicators:

Diagnostic Criteria

- Elevated VE vs. VCO_2 slope
- Rapid Rise in RER:
  - The RER may exceed 1.0 very early in the test (rest, unloaded cycling, early exercise) because the patient is "blowing off" CO_2 through hyperventilation rather than metabolic production (**Panel 8**).
- High breathing frequency (BF) at rest and lower intensity exercise resulting in increased VE (**Panel 4).**
- Elevated Ventilatory Equivalent (VE/VCO_2) values > 35–40 during light exercise (40–50W). Values remain elevated from the start and fail to decrease during higher intensity workload (**Panel 6**).
- Low End-Tidal CO_2 ($PetCO_2$): Resting values < 30–35 mmHg and persistently low values during first half of exercise reflecting persistent alveolar hyperventilation. (**Panel 9**)
- Typically, low peak VE with high breathing reserve (BR).

Mid to Late Exercise — Findings Highly Specific for HVS

Diagnostic Criteria

- VE/VCO_2 stays elevated (**Panel 6**) and $PetCO_2$ stays low (**Panel 9**) with minimal change.
- Normal subjects show $PETCO_2$ increase of approximately 6 mmHg and VE/VCO_2 decrease of 6–11 units from rest to peak exercise.

Disproportionate Symptoms of Dyspnea

The patient reports severe breathlessness (Borg Scale) that does not match the physiological workload or heart rate. Normal exercise physiology shows VE tightly regulated by $PaCO_2$ at low-to-moderate intensities, with further increases at higher intensities due to lactic acidosis and increased CO_2 production. The flat response of ventilatory parameters throughout exercise distinguishes pathological hyperventilation from normal compensatory hyperventilation during higher intensity exercise.

HVS is a "diagnosis of exclusion." Before confirming HVS on a CPET, clinicians must rule out organic causes of hyperventilation such as pulmonary hypertension, interstitial lung disease, or chronic heart failure, all of which can also cause an elevated VE/VCO_2 slope.

Erratic Breathing

Unpredictable fluctuations in tidal volume (VT) and breathing frequency (BF) may occur at any point during exercise (Panels 4 and 7).

Pulmonary (Ventilation)

Ventilation represents the ability to ventilate air for gas exchange to take place within the lungs. Maximum voluntary ventilation (MVV) is calculated from spirometry prior to exercise and represents the upper ability of ventilation as L/min. Minute ventilation at peak exercise is represented as Peak VE. The difference between MVV and Peak VE at peak exercise represents the Breathing Reserve (BR) and is typically 30–50% in healthy individuals. It represents the unused ventilatory reserve that could have been utilized.

Diagnostic Criteria

- Air hunger at peak exercise
- Inability to develop good metabolic acidosis (Peak RER typically < 1.00) because CV system cannot be fully stressed due to primary pulmonary limitation
- BR < 10% or 10 L/min at peak exercise

Pulmonary (Circulation)

Either impaired pulmonary circulation or increased dead space (alveolar regions that are ventilated but not perfused or vice versa) results in ventilation-perfusion mismatching (V/Q mismatch) during exercise and can cause shortness of breath. The net effect is the inability to exchange and eliminate CO_2 during exercise.

Etiologies

- Thrombo-embolic disease
- Primary Pulmonary Arterial Hypertension (PAH)
- Pulmonary vascular disease (emphysema, interstitial lung disease, etc.)

Diagnostic Criteria

- Significant dyspnea at peak exercise
- Inability to develop good metabolic acidosis (**Peak RER typically < 1.00**) because CV system cannot be fully stressed due to primary pulmonary limitation
- **Elevated VE vs. VCO_2 slope** (typically > 40)
- **Panel 6:** High ventilatory equivalents for O_2 and CO_2 (VE/VO_2 and VE/VCO_2; typically, > 35). The decreasing pattern during exercise typically observed in healthy individuals is blunted with V/Q mismatching.
- **Panel 9:** High resting end-tidal value for O_2 ($PetO_2$ > 110 mmHg) and low resting end-tidal CO_2 ($PetCO_2$ < 30 mmHg). The decrease in $PetO_2$ and increase in $PetCO_2$ patterns up to mid-exercise typically observed in healthy individuals is blunted with V/Q mismatching.
- Desaturation may occur in moderate to severe cases

4. Muscle Metabolic Dysfunction (MMD)

During exercise, the muscles extract and metabolize oxygen to generate the ATP required for fiber contraction. Disorders of substrate utilization result in impaired ability to metabolize oxygen. Whereas cardiovascular disorders limit O_2 delivery to the working muscles, patients with MMD have adequate O_2 supply but are unable to utilize it due to disruptions of the metabolic pathways at the cellular level.

Etiologies

- Mitochondrial Myopathies ranging from mild to severe primary mitochondrial disease
- Medications (e.g., certain antibiotics and chemotherapy)
- Endocrine: most notably profound hypothyroidism or uncontrolled metabolic syndrome
- Glycogen Storage Diseases (GSD): McArdle Disease – deprives mitochondria of pyruvate
- Fatty Acid Oxidation (FAO) Disorders: prevent long-chain fatty acids from entering mitochondria
- Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Diagnostic Criteria

- Good effort (Peak RER > 1.09)
- Low Peak VO_2 (< 80% predicted)
- Reduced Anaerobic Threshold (AT)
- Linear and reduced Peak O_2-pulse (representing impaired peripheral extraction)
- Normal $\Delta VO_2/\Delta WR$ slope
- Linear and blunted HR or BP response

MMD can be accompanied by symptoms of dysautonomia (light-headedness, dizziness, orthostatic intolerance, syncope, palpitations, etc.). Differentiating between primary cardiac disorders and MMD can be challenging. If the resting metabolic rate (RMR) is reduced, then MMD is more likely. Younger patients with MMD should be referred to mitochondrial specialists for further evaluation and treatment which may include muscle biopsy and mitochondrial DNA sequencing; ***Mitoaction.org*** *is a good resource.*

The 2-Day CPET Protocol for ME/CFS

In cases of suspected ME/CFS, a single CPET may not fully capture the pathology. A 2-day CPET (2-dCPET) involves repeating the maximal exercise test exactly 24 hours later to evaluate for Post-Exertional Malaise (PEM). While healthy individuals and those with most heart/lung diseases can replicate or improve their performance on Day 2, ME/CFS patients typically show a significant physiological decline:

Diagnostic Criteria

- Drop in Peak VO_2: Drop in Peak VO_2: A decrease of **> 7% in Peak VO_2** on the second day.
- Drop in AT: A decrease of **> 7% in VO_2 at AT**. This indicates the patient is entering anaerobic metabolism much earlier than on Day 1.
- Lower Peak Work Rate: An inability to reach the same peak workload (watts) despite equal or higher perceived effort.
- Ventilatory Inefficiency: Potential increases in VE/VCO_2 slope on Day 2, suggesting a worsened breathing efficiency.

Clinical Note: while a positive 2-day comparison is helpful for ruling in ME/CFS, a negative test does not necessarily rule it out. Use the data with caution in clinical context.

5. Chronotropic Incompetence (CI)

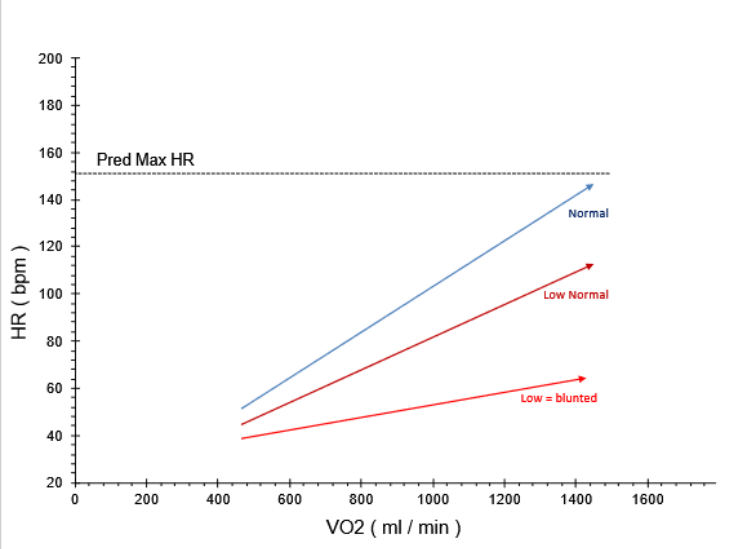
Chronotropic incompetence is defined as the inability to increase HR in proportion to increasing metabolic demand. Since stroke volume (SV) and heart rate (HR) are the two drivers for augmenting cardiac output with increasing workload, exercise capacity (peak VO_2) will be reduced in patients with chronotropic incompetence. This condition is seen as a blunted HR response as a function of increasing VO_2 with reduced peak HR (< 80% of predicted) in panel 3. Patients with chronotropic incompetence fatigue more easily and typically have a lower peak RER (0.95 to 1.05). The prevalence varies from 10–15% in patients referred for CPET.

Etiologies

- Medications (most common)
- Sinus Node Dysfunction
- Advanced Ischemic Heart Disease (IHD)
- Heart Failure
- Atrial Fibrillation
- Hypothyroidism

Diagnostic Criteria

- Low peak HR (< 80%) with peak RER ≥ 0.95
- Blunted chronotropic index (decreased HR-VO_2 slope) in panel 3 — reported as a derived parameter with predicted values
- Linear O_2-pulse (SV) with peak value ≥ 100%
- AT is usually decreased in direct proportion to the severity of CI
- Normal pulmonary function at peak exercise (Breathing Reserve and VE vs. VCO_2 slope)



Panel 3 — HR-VO_2 slope (Chronotropic Index). A blunted slope indicates chronotropic incompetence

High-dose HR-limiting agents or combinations of medications are by far the most common causes of CI. The ideal peak HR for patients on HR-limiting agents is 70–75% predicted to optimize physiological benefits with side effects. Pacemaker assessments will depend on the mechanism of HR triggering. If sensitivity is based on motion, then the HR response on CPET represents native physiology. If sensitivity is based on minute ventilation, then HR response is consistent with actual pacemaker function.

6. Cardiac

Cardiac impairment implies decreased peak cardiac function due to impaired peak stroke volume (SV). Decreased peak SV can be caused by systolic dysfunction, diastolic dysfunction and valve disorders. Patients with cardiac limitation on CPET but with normal ejection fraction and valves on echocardiogram likely have physiologically significant diastolic dysfunction during exertion. Mild to moderate diastolic dysfunction may not reveal resting abnormalities on echocardiogram but impairs SV during exertion because exercise amplifies the underlying pathology. This explains why many patients develop exercise intolerance with normal resting parameters including right-sided cardiac catheterization. Cardiac dysfunction during exercise will also precede changes in biomarkers for diastolic heart failure.

Diagnostic Criteria

- Decreased Peak VO_2 (< 80%)
- Decreased AT
- Decreased peak stroke volume (peak O_2-pulse)
- Linear O_2-pulse response in sub-maximal and maximal exercise
- Elevated resting and/or peak HR
- Steep HR response during exertion (high chronotropic index = HR-VO_2 slope)
- Moderate to Severe Cases (Peak VO_2 < 70%) — Heart Failure
- Decreased $\Delta VO_2/\Delta WR$ slope (< 10 ml/min/Watt) – Heart Failure
- Increased VE vs. VCO_2: mild to moderate V/Q mismatch from pulmonary congestion due to increased left-sided cardiac pressures; > 35 carries a poorer prognosis

In patients with known heart failure or valve disease, serial testing provides an accurate longitudinal tracking mechanism. In serial comparisons, the peak O_2-pulse is the most important parameter to track. Decreasing values indicate progression of disease and increasing values indicate positive response to therapeutic interventions

7. Inducible Myocardial Dysfunction (IMD)

IMD differs from the "Cardiac" impairment classification in that stroke volume (SV) response is normal below a specific work threshold (the Inducible Threshold – IT) with mechanical decompensation starting at and above the IT. IT is a sub-maximal parameter that occurs mid-exercise and typically within 90 seconds of the AT. IT and AT are tightly physiologically interdependent parameters; as the severity of the mechanism driving myocardial dysfunction increases, cardiac function declines proportionally, triggering an earlier onset of AT.

The most common cause of IT is acquired atherosclerotic heart disease, representing > 90% of cases on CPET due to the high prevalence of CV risk factors in the general population. In this scenario, IT is the Ischemic Threshold. Multiple congenital causes of IT exist — including aortic stenosis, HCM, myocardial bridging, anomalous coronary artery anatomy, and mitochondrial cardiomyopathies — and must be considered in younger patients (< 30) without CV risk factors.

Diagnostic Criteria — Trajectory Analysis of Two Parameters (Panel 2)

- **O_2-pulse**: an abrupt change in trajectory at the IT that closely reflects change in SV response in real-time. The trend after IT can:
  - Continue to increase but at a lower slope
  - Completely plateau (more severe)
  - Decrease with increasing work-rate (most severe)
- **HR Response**: an abrupt acceleration at the IT acting as a compensation mechanism for decreasing SV. The **ΔHR-WR Slope** ≥ +15% is abnormal. The **ΔHR-VO_2** trajectory becomes curvilinear past the IT in panel 3; both slopes should be zero or negative in normal subjects.

Severity of IMD

The following parameters change over time in direct proportion to the severity of the underlying condition and serve as prognostic markers:

Prognostic Criteria

- **Peak VO_2**: Can be normal or reduced depending on severity
- **Peak O_2-pulse**: Can be normal or reduced depending on severity
- **Anaerobic Threshold (AT)**: Can be normal or reduced depending on severity
- **VE vs. VCO_2 Slope**: Left-sided cardiac dysfunction can result in pulmonary congestion and worsen V/Q mismatching during exercise. A higher value is consistent with more severe disease.

The first test establishes the baseline for these parameters; they will change in direct proportion to reflect physiological/clinical status. Declining parameters imply increasing global disease burden (worsening prognosis) and improving values imply positive response to therapeutic interventions (improving prognosis).

Concept of Cardiac Work Efficiency

The presence of an IT results in an abrupt loss in cardiac efficiency at that point during exercise. In healthy individuals (particularly athletes), the heart uses stroke volume (SV) as the primary driver to augment cardiac output. The energy (ATP) consumed per cardiac cycle is least when SV is healthy and doing most of the work. If an IT is present, HR response is recruited to compensate for loss in SV and energy consumption per cardiac cycle increases dramatically. HR acceleration also decreases diastolic filling time, further reducing the ability to augment SV. The combination of mechanical dysfunction and reduced filling time results in lower **peak SV (O_2-pulse)** and **Peak VO_2.**

Over time, Peak VO_2 will change in direct proportion to progression of disease as well as response to therapy. Changes of 10% or more from baseline are physiologically and clinically significant. In majority of cases of early to moderate stage atherosclerotic heart disease, the IT is reversible with Zone 2 exercise and aggressive risk factor modification (with or without medications). Reversal of an IT results in higher Peak O_2-pulse or Peak VO_2 or both, signifying improved cardiac function and long-term prognosis.

8. Poor Effort

Poor effort can be due to a variety of reasons including orthopedic, neurological, depression, motivation, and malingering.

Diagnostic Criteria

- Low Peak RER (< 1.05)
- Low Peak HR (< 80% predicted) - when not on HR-limiting agents
- Not attaining the anaerobic threshold (AT)
- Systolic BP does not increase by at least 30 mmHg
- O_2-pulse is linear and still rising at end of exercise (Panel 2)
- HR is linear, rising and not accelerating at the end of exercise (Panel 2)
- No manipulation of breathing patterns (such as hyperventilation)
- Normal pulmonary parameters at peak (normal gas exchange and breathing reserve)

CPET is an excellent tool for disability evaluations. Poor effort can be distinguished from actual decrease in exercise capacity along with its mechanism.

