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Cardiopulmonary Exercise Testing (CPET) & Advanced Diagnostic Testing

An APCCMPD Ambulatory Care Curriculum Teaching Script

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Cardiopulmonary Exercise Testing (CPET) & Advanced Diagnostic Testing

Scenario 1:

You are seeing a 47-year-old man about three months after discharge from an eight-week hospitalization. He was admitted to another hospital for pneumonia that was treated with appropriate antibiotics, complicated by empyema requiring a chest tube. His hospital course was complicated by obstructive shock and respiratory failure due to acute bilateral pulmonary emboli requiring two weeks of mechanical ventilation. Since discharge he has been maintained on a direct oral anticoagulant (DOAC) with excellent compliance.

Now, he reports slow improvement. He finished physical therapy, but his exercise capacity has not returned to his pre-illness baseline. In the past he could exercise for an hour on an elliptical daily, whereas now he can only manage 20-30 minutes due to dyspnea. He has also noted readings down to 85% on his home pulse oximeter at times. He has no chest pain, dizziness, cough, or lower extremity edema. His exam is unremarkable, including normal strength.

PFTs: FEV1 75%pred, FVC 75%pred, FEV1/FVC Ratio 0.77, TLC 76%pred, MIP/MEP WNL, DLCO 81%pred

(FEV1=Forced Expiratory Volume in 1-second; FVC=Forced Vital Capacity; TLC=Total Lung Capacity; MIP=Maximal Inspiratory Pressure; MEP=Maximal Expiratory Pressure; DLCO=Diffusing Capacity of the Lung for Carbon Monoxide; %pred=percent of predicted)

2D Echocardiography showed: Normal left ventricular (LV) size and function, normal left-sided valves. No left ventricular hypertrophy or signs of diastolic dysfunction. Right ventricular (RV) normal size and function, normal inferior vena cava diameter and collapsibility, estimated pulmonary artery systolic pressure (PASP) 25.

A recent chest radiograph revealed mild pleural thickening on the side of his prior empyema but was otherwise normal.

Question 1: In general, what mechanisms of exercise limitation might be considered in a post-ICU patient? Based on the information provided, what could account for exercise limitation in this patient?

Question 2: What do we know generally about the incidence of exercise limitation after an episode of pulmonary embolism? What mechanisms could be implicated?

Question 3: Describe the process of performing a CPET and identify the key data it provides.

Question 4: State the Fick equation and summarize its meaning and utility.

Question 5: What modifiable factors affect the arterial-venous O_2 content difference (AVO2D)? (Hint: consider both the Fick equation and the oxygen content equation.)

Question 6: What is the minute ventilation to carbon dioxide (CO_2) production ratio-also referred to as the ventilatory equivalent for CO_2 (VE/VCO_2)?

Question 7: What CPET parameters suggest a primary cardiac limitation?

Question 8: Which parameters suggest a pulmonary vascular limitation to exercise?

Question 9: CPET was performed for our patient. Values and graphs are listed below in Table 3.

Table 3. Selected CPET variables for our patient

	Patient's Value	Predicted Value	%-Predicted
Peak VO_2	1,857 ml/min	3,172 ml/min	59
Heart rate	144	174	83
Oxygen pulse	13 ml/beat	18 ml/beat	71
Anaerobic threshold (as % of predicted VO_2max)	42%	>44%	-
Peak oxygen saturation	80%	>95%	-
Ventilatory Reserve (VE/MVV)	47%	>30%	-
VE/VCO_2 slope	36	<33	-
Calculated* rest Vd/Vt (Computer's value**)	0.32 (0.29)	<0.4	-
Calculated* peak Vd/Vt (Computer's value**)	0.4 (0.24)	<0.25	-

Peak VO_2 = peak oxygen uptake (mL·kg−1·min−1); HR = heart rate (bpm); O_2 pulse = VO_2/HR (mL/beat); AT = anaerobic threshold (mL·kg−1·min−1 or %pred); % predicted VO_2max = % predicted peak VO_2; SpO_2 = peripheral oxygen saturation (%); Ventilatory reserve (VE/MVV) = VEpeak/MVV; VE/VCO_2 slope = slope of VE vs VCO_2; Rest Vd/Vt and Peak Vd/Vt = physiologic dead-space fraction at rest and peak exercise.

The patient was exercised to 156 watts, which corresponds to approximately 9 METs for a 70kg male.

**Calculated values were obtained using the partial pressure of carbon dioxide in arterial blood ($paCO_2$).*

***Computer generated values were based on transcutaneous CO2 measurement.*

This table was created by Dr. Timothy Scialla and Dr. John J. Popovich for this teaching script.

Scenario 1 (Continued):

The patient undergoes both a ventilation/perfusion (V/Q) scan and CT angiography, which reveal complete occlusion of both lower lobe pulmonary artery branches. He subsequently undergoes resting right heart catheterization, the results of which are:

Resting Right Heart Hemodynamics:
RA 2 mmHg
PA 27/8 (17) mmHg
PCWP 4 mmHg

(RA=right atrial pressure; PA=pulmonary artery pressure; PCWP=pulmonary capillary wedge pressure)

Question 10: Based on this patient's hemodynamics, does he meet criteria for CTEPH?

Scenario 1 (Continued):

The patient is exercised in a near-supine position using an ergometer device to 100 Watts, with a peak HR of 112.

Exercise Right Heart Hemodynamics:
RA 12 mmHg
PA 100/25 (56) mmHg
PCWP 17 mmHg
CO 15 L/min
PVR 2.6 Wood units
TPR 3.7 Wood units
Lactate 0.7 at rest, 1.9 at peak

(RA=right atrial pressure; PA=pulmonary artery pressure; PCWP=pulmonary capillary wedge pressure, CO=cardiac output, PVR=pulmonary vascular resistance; TPR=total pulmonary resistance)

Question 11: Describe the normal hemodynamic response to exercise and contrast it to this patient.

Question 12: You find a six-minute walk test (6MWT) that was not previously commented upon during the patient's initial post-ICU visit. During that test he walked 215m. His resting SaO2 was 96%, which decreased to a nadir of 82% with exercise; his resting heart rate was 78 and at the end of the walk was 155. His Borg dyspnea score was 1 prior to exercise and increased to 6 with exercise. In retrospect, what conclusions about his cardiopulmonary physiology could have been drawn from this information (prior to his completing the full CPET)?

Scenario 2:

A 65-year-old man with heart failure with reduced ejection fraction (HFrEF, LVEF 15%) secondary to ischemic cardiomyopathy is referred for pulmonary function tests and CPET as part of an evaluation for heart transplantation. He is severely limited in terms of his exercise capacity, and his goals are to optimize his heart failure management to allow for a greater quality of life. You are reviewing his pulmonary function tests, six-minute walk test and CPET results, which are shown below and in Table 4 and Figure 2.

Pulmonary Function Tests**:** FEV1 52%pred, FVC 88%pred, FEV1/FVC ratio 0.46, TLC 115%pred, DLCO 69%pred

6MWT: The total distance walked was 180m. His resting oxygen saturation was 94%, which decreased to a nadir of 89% with exercise. His resting heart rate was 78 beats/min, which increased to 160 beats/min at the end of the walk. His Borg dyspnea score was 1 prior to exercise and increased to 5 at the end of the test.

Table 4. Selected CPET Variables for Patient from Scenario 2

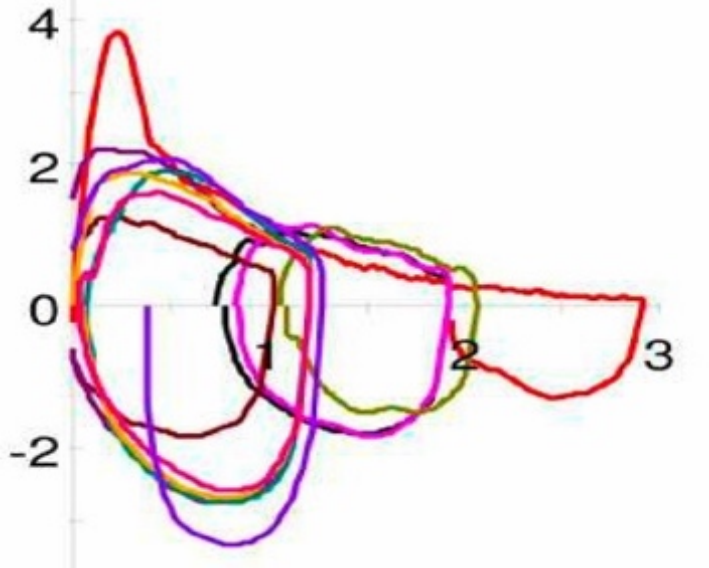
	Patient's Value	Predicted Value	%-Predicted
Peak VO_2	586 ml/min	2282ml/min	26%
Heart rate	72	149	48
Oxygen pulse	8 ml/beat	15 ml/beat	53
Anaerobic threshold (as % of predicted VO2max)	21%	>40%	-
Peak oxygen saturation	97%	>95%	-
Minute ventilation (L)	45.2 (at peak exercise)	56.0 (calculated MVV)	81%
Breathing reserve	19%	>30%	-
Ve/VCO_2 slope	55	<33	-

Peak VO_2 = peak oxygen uptake (mL·kg−1·min−1); HR = heart rate (bpm); O_2 pulse = VO_2/HR (mL/beat); AT = anaerobic threshold (% predicted VO_2max); SpO_2 = oxygen saturation (%); VE = minute ventilation (L/min); BR = breathing reserve (VE/MVV, %); VE/VCO_2 slope = slope of VE vs VCO2 (unitless).

The patient was exercised to 54 watts, which corresponds to 32% predicted.

This table was created by Dr. Timothy Scialla and Dr. John J. Popovich for this teaching script.

Figure 2. Flow-volume Loop



Flow volume loop image courtesy of Dr. Susan Mathai.

Question 12: Would you expect a heart transplant to improve this patient's exercise tolerance?

Cardiopulmonary Exercise Testing (CPET) & Advanced Diagnostic Testing

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Educational Objectives:

1. Summarize the spectrum of exercise limitation after a complicated ICU course
2. Describe how the Fick equation quantifies factors that determine oxygen delivery
3. Describe the physiologic variables measured during cardiopulmonary exercise testing (CPET) and their utility in narrowing the differential diagnosis for exercise limitation
4. Understand the CPET profile of cardiac and pulmonary vascular limitations to exercise
5. Summarize contemporary concepts of invasive exercise hemodynamics
6. Describe features of CPET testing that indicate ventilatory limitation to exercise

Scenario 1:

You are seeing a 47-year-old man about three months after discharge from an eight-week hospitalization. He was admitted to another hospital for pneumonia that was treated with appropriate antibiotics, complicated by empyema requiring a chest tube. His hospital course was complicated by obstructive shock and respiratory failure due to acute bilateral pulmonary emboli requiring two weeks of mechanical ventilation. Since discharge he has been maintained on a direct oral anticoagulant (DOAC) with excellent compliance.

Now, he reports slow improvement. He finished physical therapy, but his exercise capacity has not returned to his pre-illness baseline. In the past he could exercise for an hour on an elliptical daily, whereas now he can only manage 20-30 minutes due to dyspnea. He has also noted readings down to 85% on his home pulse oximeter at times. He has no chest pain, dizziness, cough, or lower extremity edema. His exam is unremarkable, including normal strength. Pulmonary function tests (PFTs) and an echocardiogram obtained prior to his visit showed:

PFTs: FEV1 75%pred, FVC 75%pred, FEV1/FVC Ratio 0.77, TLC 76%pred, MIP/MEP WNL, DLCO 81%pred

(FEV1=Forced Expiratory Volume in 1-second; FVC=Forced Vital Capacity; TLC=Total Lung Capacity; MIP=Maximal Inspiratory Pressure; MEP=Maximal Expiratory Pressure; DLCO=Diffusing Capacity of the Lung for Carbon Monoxide; %pred=percent of predicted)

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A recent chest radiograph revealed mild pleural thickening on the side of his prior empyema but was otherwise normal.

Question 1: In general, what mechanisms of exercise limitation might be considered in a post-ICU patient? Based on the information provided, what could account for exercise limitation in this particular patient?

Specific considerations for this patient with post-ICU-stay exercise limitation include generalized deconditioning after a prolonged hospitalization including sequelae from critical illness myopathy, restrictive lung disease due to a primary lung or pleural injury, residual stress- induced cardiomyopathy, anemia, upper airway pathology (e.g. subglottic stenosis secondary to endotracheal intubation), or chronic thromboembolic disease (CTED).

Question 2: What do we know generally about the incidence of exercise limitation after an episode of pulmonary embolism? What mechanisms could be implicated?

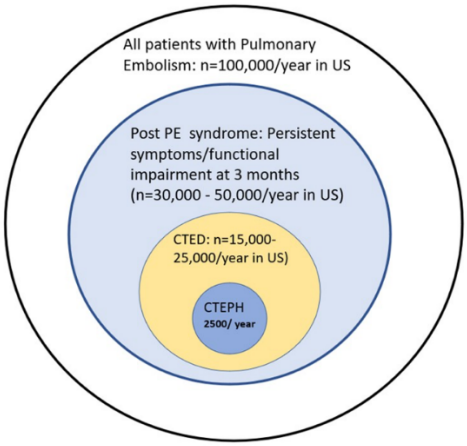
Recent studies report a high prevalence of objective exercise limitation (50-70% at 6-12 months) after acute pulmonary embolism (PE),[1-3] defined by a reduced maximal oxygen uptake (VO_{2max}) on CPET. Chronic Thromboembolic Pulmonary Hypertension (CTEPH) requires demonstration of both persistent pulmonary arterial thrombotic material and *resting* pulmonary hypertension and occurs in up to 4% of patients after acute PE.[4-7] As shown in Figure 1, this is felt to lie on the extreme end of a spectrum of disease. A greater proportion of patients demonstrate various combinations of exercise limitation, right ventricular dysfunction and perfusion abnormalities *without* resting pulmonary hypertension.

The "post-PE syndrome" is broadly defined as the presence of persistent symptoms or functional impairment at three months following an acute PE.

Chronic thromboembolic disease (CTED) defines the subset with ongoing perfusion defects.[8]

Several studies have found persistent perfusion defects on ventilation/perfusion (V/Q) scanning in 25-50% of patients during follow-up after PE,[9,10] with roughly 20% demonstrating persistent RV dysfunction and about 10% reporting moderate to severe dyspnea.[11]

Figure 1. Summary of Post-PE Complications



Adapted from: Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S.[12]

If significant vascular obstruction is present, symptoms and exercise limitation result from

both an impaired cardiac output response and increased physiologic dead space. Recent CPET data suggest that many of these patients are primarily deconditioned. Interestingly, the extent of residual perfusion deficits or RV dysfunction does not necessarily correlate with reduced maximal oxygen uptake (VO_{2max}).[1,2]

Question 3: Describe the process of performing a CPET and identify the key data it provides.

In general, CPET evaluates the relationship between the lungs, heart, and musculoskeletal system, assessing how well (or not) they deliver and utilize oxygen during exercise.

To perform a CPET, a patient exercises on a bicycle ergometer or jogs on a treadmill. They are connected to a mask and a metabolic cart that measure inhaled and exhaled oxygen, carbon dioxide concentrations and total airflow. They are also connected to devices to measure their blood pressure, pulse oximetry, and electrocardiogram (EKG). As an additional option, a right heart catheter or arterial line may be placed for invasive hemodynamic monitoring, though this is far less commonly done.

During the first (resting) phase of a CPET, baseline values of heart rate, blood pressure, resting oxygen uptake (VO_2), resting carbon dioxide production (VCO_2), minute ventilation (VE), and oxygen saturation (SpO_2) are recorded.

Then, incremental exercise is performed. This is achieved by starting the bicycle ergometer or treadmill; every 30 seconds or so the workload is slightly increased, with the goal of achieving maximal exercise capacity within about 10 minutes. During this incremental exercise, all the aforementioned variables are continuously recorded.

Table 1 shows the variables that are most commonly measured or calculated during CPET. Many of these are discussed in greater detail later.

Table 1. Variables Commonly Measured During CPET with Their Units

CPET Variable	Units	What It Measures	Important Values	How It's Used Clinically
VO_2 (oxygen uptake)	mL/min or mL/kg/min	Rate of oxygen consumption	VO_{2max} (peak VO_2) varies with age and fitness; average=20-40 mL/kg/min; normal is >85% predicted	Low values are consistent with reduced exercise capacity, which could still be cardiovascular or pulmonary
VCO_2 (CO_2 output)	mL/min	Rate of carbon dioxide production and clearance	Expect a linear slope until the anaerobic threshold	Helps to identify the anaerobic threshold and used to calculate the respiratory exchange ratio and the minute ventilation to VCO_2 ratio
VE (minute ventilation)	L/min	Total volume of air moved per minute (calculated as tidal volume times respiratory rate)	At rest: 5-10 L/min At VO_{2max}: up to 100 L/min	Low suggests a ventilatory limitation to exercise

VE/VCO_2	N/A (unitless)	Measures ventilatory "efficiency" (how much ventilation is required to clear CO_2)	Slope: <30 normal; 30-34 borderline, >35 abnormal	Abnormal (increased) in heart failure and pulmonary hypertension
RER (Respiratory Exchange Ratio, $=VCO_2/VO_2$)	N/A (unitless)	Primarily used to assess effort	Rest: 0.7-0.9; Maximal Effort: >1.1	<1.0 at peak exercise suggests submaximal effort
AT (Anaerobic Threshold)	mL/kg/min or % of predicted VO_{2max}	VO_2 at onset of anaerobic metabolism (when lactate production > lactate clearance)	Expected at 40-60% of predicted VO_{2max}	Early AT (<40% of predicted VO_{2max}) consistent with cardiac limitation
Oxygen Pulse ($=VO_2/HR$)	mL/beat	Measures oxygen provided by each heart beat; surrogate for stroke volume and oxygen extraction	Should increase linearly; expect 0.2-0.3 mL/kg/beat	Flattening suggests cardiac limitation or chronotropic insufficiency
HR (Heart Rate)	Beats/min	Measures chronotropic response to exercise (i.e., chronotropic competence)	Peak: >85% predicted of max HR for age (220-age)	Blunted response suggests beta blocker use or chronotropic insufficiency
Workload	Watts or METs (METs=metabolic equivalents; 1 MET is the amount of oxygen consumed at rest)	Measures exercise intensity and energy expenditure	Varies by age, sex, and conditioning; light exercise typically requires ~4 METs, vigorous exercise is ~15 METs	Low at peak suggests reduced exercise tolerance
Maximal Voluntary Ventilation	L/min	Maximum amount of air a person can inhale and exhale in one minute, with full effort	Measured by: 1) patient breathing as deeply and rapidly as possible for ~15 seconds or 2) estimated as 35-40×FEV1. Normal is 125-170 L/m in (men) or 80-120 L/min (women)	Quantifies mechanical and neuromuscular limit of ventilation. Low values can suggest obstructive, restrictive, and/or neuromuscular lung disease. Used to calculate ventilatory reserve (next row)
Ventilatory Reserve (VE/MVV)	% or ratio	Percentage of maximum ventilation achieved at peak exercise	VE/MVV<0.8 suggests normal reserve	If high (>0.8), suggests ventilatory limitation

This table and the above adapted from Milani RV, Lavie CJ, Mehra MR, Ventura HO.[1]

Question 4: State the Fick equation and summarize its meaning and utility.

$$VO_2 = CO \text{ x } (CaO_2 - CvO2)$$

- VO2 is the oxygen uptake by the body (mL O_2/min)
- CO is the cardiac output (L/min)
- CaO_2 is the arterial content of oxygen (mL O_2/100 mL blood)
- CvO_2 is the venous content of oxygen (mL O2/100 mL blood)

The Fick equation can be rearranged as follows:

$$CO = \frac{VO_2}{CaO_2 - CvO_2}$$

The cardiac output can be calculated by measuring the arterial and mixed venous oxygen content (from arterial and mixed venous blood gases) and VO_2.

VO_2 can either be directly measured in the exercise physiology lab from inhaled and exhaled oxygen concentrations or estimated from body surface area, age and sex.

CaO_2-CvO_2 is referred to as the arterial-venous O_2 content difference (AVO_2D).

Question 5: What modifiable factors affect the AVO_2D? (Hint: consider both the Fick equation and the oxygen content equation.)

Using the Fick Equation:

$$AVO_2 = CaO_2 - CvO_2 = \frac{VO_2}{CO}$$

Considering the oxygen content equation, which is the sum of the hemoglobin-bound oxygen and dissolved oxygen:

$$CaO_2 = (1.34\ x\ Hb\ xSaO_2) + 0.003\ X\ PaO_2$$

$$CvO_2 = (1.34\ x\ Hb\ x\ SvO_2) + 0.003\ X\ PvO_2$$

$$\text{And } AVO_2 = CaO_2 - CvO_2$$

$$AVO_2 = (1.34 \text{ x Hb x } [SaO_2 - SvO_2]) + 0.003\ x\ [PaO_2 - PvO_2]$$

- 1.34 mL O_2/g is the Hüfner constant (oxygen bound per gram of hemoglobin).
- Hb is hemoglobin concentration in blood (g/dL).
- SaO_2 is arterial oxygen saturation, expressed as a fraction (e.g., 0.97 for 97%).
- SvO_2 is mixed-venous oxygen saturation, expressed as a fraction.
- 0.003 mL O_2·dL−1·mmHg−1 is the solubility coefficient of O_2 in plasma

- PaO_2 is the partial pressure of oxygen in arterial blood (mmHg).
- PvO_2 is the partial pressure of oxygen in mixed-venous blood (mmHg).

Note: the dissolved O_2 term is negligible given the poor solubility and is often omitted in the calculations.

Therefore, *modifiable* factors directly affecting the AVO_2D include:

1. Change in oxygen demand/uptake
2. Change in cardiac output
3. Effective hemoglobin concentration
4. Arterial oxygen saturation

Notice that the lungs are only directly represented in the equation by the SaO_2 component. No other parameter related to lung function (e.g., commonly referenced PFT parameters such as FEV_1) appear here.

Question 6: What is the minute ventilation to carbon dioxide (CO_2) production ratio-also referred to as the ventilatory equivalent for CO_2 (V_E/VCO_2)?

The ventilatory equivalent for CO_2 (V_E/VCO_2) indicates how much ventilation is required to eliminate a given amount of CO_2. In other words, it is a measure of ventilatory efficiency-or the minute ventilation per liter of CO_2 produced.

Some clinical examples of causes of abnormally elevated V_E/VCO_2 ratios are shown in Table 2. A high VE/VCO2 results from:

1. Hyperventilatory states (in which ventilation increases above what is required for a given VCO2, as seen in dysfunctional breathing syndrome and other conditions);
2. Increased dead space fraction (Vd/Vt);
3. Ventilation-perfusion (V/Q) mismatch.

The normal range for V_E/VCO_2 is 25-30 (with some normal variations for age)**.** Small elevations above 30 can be a normal variant, but values of > 34 are considered clinically significant and should prompt additional evaluation.

Table 2. Examples of Mechanisms and Conditions that Cause Elevated V_E/VCO_2 Ratios

Mechanism	Example Conditions
↑ Dead space (Vd/Vt)	Pulmonary hypertension, pulmonary embolism, emphysema
↑ Chemoreceptor drive / hyperventilation	Heart failure, anxiety, early exercise, hyperventilation syndrome (dysfunctional breathing)
↓ Perfusion efficiency	Pulmonary vascular disease

Adapted from Milani RV, Lavie CJ, Mehra MR, Ventura HO.[1]

Question 7: What CPET parameters suggest a primary cardiac limitation?

CPET parameters indicating an abnormal cardiac limitation include:[12]

1. Reduced peak VO_2
2. Early-onset anaerobic threshold (AT)
3. Reduced peak "O_2 pulse" (VO_2/HR) (which reflects reduced maximal stroke volume)
4. Rapid rise in HR relative to VO_2
5. Low reserve between maximum HR achieved and predicted max HR (heart rate reserve)

Question 8: Which parameters suggest a pulmonary vascular limitation to exercise?

Pulmonary vascular limitations to exercise are similar to cardiac limitations in many respects, but there are two important differences.

Elevated Vd/Vt: Patients with pulmonary vascular disease typically have an abnormally elevated dead space fraction (Vd/Vt) during exercise. This produces ventilatory inefficiency and is reflected by an increased V_E/VCO_2. If hyperventilation is excluded, a high V_E/VCO_2 in this setting usually indicates increased dead space ventilation.

The ideal calculation of Vd/Vt uses expired CO_2 and arterial $paCO_2$ via the Bohr equation, but this requires arterial blood sampling. Historically, arterial lines were placed during all CPETs. Now, most laboratories use a less invasive approach for patient comfort-using end tidal CO2 (PetCO2) as a surrogate for paCO2.

End-tidal CO_2 does not reliably track $PaCO_2$ when pulmonary disease or pulmonary vascular abnormalities are present, because V/Q mismatch increases the difference between $paCO_2$ and $PetCO_2$. Consequently, computer estimates of Vd/Vt that rely on $PetCO_2$ are inaccurate in disease: they tend to underestimate abnormal dead space (and may overestimate dead space in healthy subjects). Many labs try to reduce this error by obtaining arterial blood gases before and after exercise, but that still does not provide continuous, minute-to-minute Vd/Vt measurements.

Transcutaneous CO2 can be used when end-tidal values are unreliable. However, PtcCO2 has limitations: it requires sensor calibration and equilibration time, can lag behind rapid changes, is affected by skin perfusion and temperature, and may be less accurate than arterial sampling.

Oxygen desaturation: Unlike most patients with left ventricular heart failure patients, those with pulmonary vascular limitation often develop arterial desaturation during exercise.

Question 9: CPET was performed for our patient. Values and graphs are listed below in Table 3.

Table 3. Selected CPET Variables for Our Patient

	Patient's Value	Predicted Value	%-Predicted
Peak VO_2	1,857 ml/min	3,172 ml/min	59
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Calculated* rest Vd/Vt (Computer's value**)	0.32 (0.29)	<0.4	-
Calculated* peak Vd/Vt (Computer's value**)	0.4 (0.24)	<0.25	-

Peak VO_2 = peak oxygen uptake (mL·kg−1·min−1); HR = heart rate (bpm); O_2 pulse = VO_2/HR (mL/beat); AT = anaerobic threshold (mL·kg−1·min−1 or %pred); % predicted VO_2max = % predicted peak VO_2; SpO_2 = peripheral oxygen saturation (%); Ventilatory reserve (VE/MVV) = VEpeak/MVV; VE/VCO_2 slope = slope of VE vs VCO_2; Rest Vd/Vt and Peak Vd/Vt = physiologic dead-space fraction at rest and peak exercise.

The patient was exercised to 156 watts, which corresponds to approximately 9 METs for a 70kg male.

**Calculated values were obtained using the partial pressure of carbon dioxide in arterial blood ($paCO_2$).*

***Computer generated values were based on transcutaneous CO_2 measurement.*

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Which pattern of exercise limitation is present in this patient?

Our patient's CPET shows all the hallmarks of a pulmonary vascular limitation to exercise, specifically: a low peak VO_2, elevated V_E/VCO_2, elevated Vd/Vt at peak exercise, and arterial desaturation.

Note the discrepancy between the computer reported Vd/Vt (seemingly normal) and the calculated Vd/Vt using transcutaneous CO_2 values (normal at rest, but abnormal at peak exercise).

Scenario 1 (Continued):

The patient undergoes both a ventilation/perfusion (V/Q) scan and CT angiography, which reveal complete occlusion of both lower lobe pulmonary artery branches. He subsequently undergoes resting right heart catheterization, the results of which are:

<u>Resting Right Heart Hemodynamics:</u>
RA 2 mmHg
PA 27/8 (17) mmHg
PCWP 4 mmHg

(RA=right atrial pressure; PA=pulmonary artery pressure; PCWP=pulmonary capillary wedge pressure)

Question 10: Based on this patient's hemodynamics, does he meet criteria for CTEPH?

The resting hemodynamics are normal. As his mean pulmonary artery pressure (mPAP) is less than 20 mmHg, he does not have pulmonary hypertension and thus does not have CTEPH. However, this does not exclude CTED, as his radiology studies clearly show perfusion deficits. Given the remarkable reserve and distensibility of the pulmonary circulation, there may be significant reductions in cross-sectional area of the pulmonary vascular bed that do not cause resting hemodynamic abnormalities. Challenging the cardiopulmonary system with exercise (which is when many patients are symptomatic) can unmask functionally relevant changes.

Scenario 1 (Continued):

The patient is exercised in a near-supine position using an ergometer device to 100 Watts, with a peak HR of 112.

Exercise Right Heart Hemodynamics:
RA 12 mmHg
PA 100/25 (56) mmHg
PCWP 17 mmHg
CO 15 L/min
PVR 2.6 Wood units
TPR 3.7 Wood units
Lactate 0.7 at rest, 1.9 at peak

(RA=right atrial pressure; PA=pulmonary artery pressure; PCWP=pulmonary capillary wedge pressure, CO=cardiac output, PVR=pulmonary vascular resistance; TPR=total pulmonary resistance)

Question 11: Describe the normal hemodynamic response to exercise and contrast it to this patient.

First, understanding exercise right heart catheterization requires differentiating pulmonary vascular resistance (PVR) from total pulmonary resistance (TPR).

$$PVR = \frac{(\mathrm{mPAP} - \mathrm{PCWP})}{\mathrm{CO}}$$

- PVR = pulmonary vascular resistance (Wood units or mmHg/[L/min])
- mPAP = mean pulmonary artery pressure (mmHg)
- PCWP = pulmonary capillary wedge pressure (mmHg)
- CO = cardiac output (L/min)

PVR is primarily a measure of resistance across the pulmonary bed *only* (since it is "normalized" to the PCWP). In other words, it is primarily a measure of precapillary resistance.

$$TPR = \frac{\text{mPAP}}{\text{CO}}$$

TPR is primarily a measure of resistance across the entire pulmonary circuit (including the resistance contributed by the left atrial pressures). It is a cruder measurement that is used when left atrial pressure assessment is not possible. It may not accurately reflect the state of the pulmonary vasculature.

So, if both PVR and TPR are abnormally elevated, that would suggest elevated resistance primarily from pulmonary vascular disease. On the other hand, if TPR is elevated but PVR is normal, that would suggest elevated resistance primarily from left heart disease.

Due to distensibility and recruitability of pulmonary vessels and dynamic changes in left ventricular systolic and diastolic function, the following hemodynamic changes are typically seen in *normal* patients during strenuous exercise:

- A significant increase in CO
- A modest increase in mPAP from baseline but rarely above 30mmHg
- A modest increase in PCWP to 20-25 mmHg
- A substantial decrease in PVR

In contrast to the expected normal changes described above, our patient's exercise hemodynamics are notable for an exaggerated rise in mPAP and an ***increase*** in PVR **and** TPR.

With the publication of a European Respiratory Society (ERS) task force statement in 2017,[13] there is now emerging consensus on the normal pulmonary vascular response to exercise. Historical definitions of exercised-induced PH (eiPH) often used a single mPAP cut-off (e.g., >30 mmHg at peak). However, cumulative appraisal of literature has indicated, perhaps not surprisingly, that the degree of increase in mPAP is correlated with the degree of increase in cardiac output, and thus determining whether a certain pressure response is abnormal should take into account the level of flow achieved.

The mPAP/CO slope (or a single value measured at peak, i.e., the peak TPR) can be used to distinguish normal from abnormal pulmonary vascular responses to exercise.[14] A reasonable upper limit of normal is about 3 Wood units. Younger, healthy individuals typically have lower values. Applied practically, this corresponds to an upper-limit mPAP of 30 mmHg at cardiac output values below 10 L/min.

Our patient's exercise hemodynamics revealed a TPR of 3.7 Wood units, which is above the upper limit of normal, consistent with eiPH.

An abnormal TPR (or mPAP/CO slope) alone does not identify the clinical pathophysiology, as this can be affected by changes in the PCWP and PVR. The rise in PCWP in healthy patients is dependent on the cardiac output, and the upper-limit of normal PCWP is considered to be 20 mmHg in most studies.[15]

Thus, eiPH can be defined as an elevated mPAP or TPR with an exercise PCWP <20.

Question 12: You find a six-minute walk test (6MWT) that was not previously commented upon during the patient's initial post-ICU visit. During that test he walked 215m. His resting SaO_2 was 96%, which decreased to a nadir of 82% with exercise; his resting heart rate was 78 and at the end of the walk was 155. His Borg dyspnea score was 1 prior to exercise and increased to 6 with exercise. In retrospect, what conclusions about his cardiopulmonary physiology could have been drawn from this information (prior to his completing the full CPET)?

We saw previously that this patient had normal spirometry, lung volumes, and diffusing capacity. In addition, his echocardiogram revealed normal RV function and pressure at rest. Reviewing his response to a simple exercise test done in clinic, it is now evident that he has significantly reduced exercise capacity (walking <400m) with significant exertional desaturation. In addition, his peak heart rate exceeded 80% of predicted (his cardiac maximum) at the end of exercise with a subjective dyspnea score that was severe.

The combination of reduced exercise tolerance, exertional desaturation, and attainment of cardiac limits indicates very limited cardiopulmonary reserve with impaired gas exchange despite normal lung volumes. This pattern is most consistent with a pulmonary vascular limitation — and all of this can be inferred from the PFTs and 6MWT.

Scenario 1 Conclusion:

The patient was diagnosed with exercise-induced PH caused by chronic thromboembolic disease (CTED).

Given the functional limitations as documented by CPET and the complete obstruction of blood flow to his bilateral lower lobe pulmonary arteries, he was referred for multidisciplinary discussion in consideration of pulmonary thromboendarterectomy. There is scant evidence to guide this decision, however. In overt CTEPH, a prospective observational study suggested better survival in appropriate candidates who underwent thromboendarterectomy compared to non-operative therapy.[2] He was deemed to be a good candidate and is slated for surgery in the near future.

Scenario 2:

A 65-year-old man with heart failure with reduced ejection fraction (HFrEF, LVEF 15%) secondary to ischemic cardiomyopathy is referred for pulmonary function tests and CPET as part of an evaluation for heart transplantation. He is severely limited in terms of his exercise capacity, and his goals are to optimize his heart failure management to allow for a greater quality of life. You are reviewing his pulmonary function tests, six-minute walk test and CPET results, which are shown in Table 4 and Figure 2.

Pulmonary Function Tests**:** FEV1 52%pred, FVC 88%pred, FEV1/FVC Ratio 0.46, TLC 115%pred, DLCO 69%pred

6MWT: The total distance walked was 180m. His resting oxygen saturation was 94%, which decreased to a nadir of 89% with exercise. His resting heart rate was 78 beats/min, which increased to 160 beats/min at the end of the walk. His Borg dyspnea score was 1 prior to exercise and increased to 5 at the end of the test.

Table 4. Selected CPET Variables for Patient from Scenario 2

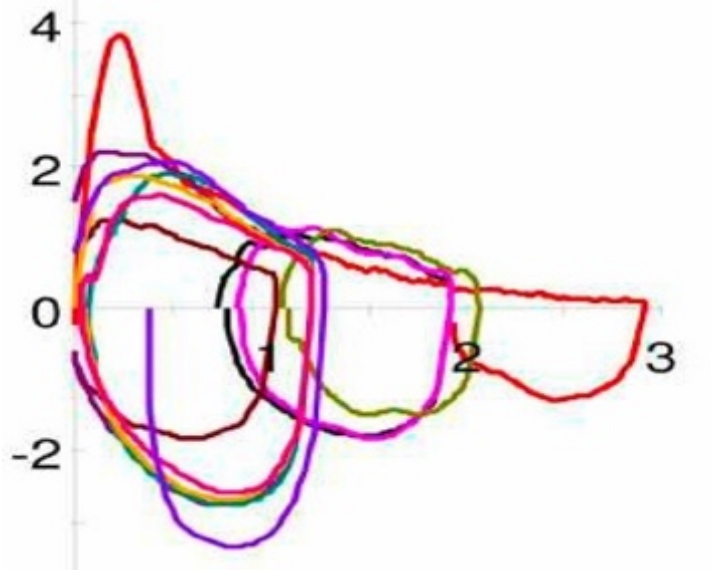
	Patient's Value	Predicted Value	%-Predicted
Peak VO_2	586 ml/min	2282ml/min	26%
Heart rate	72	149	48
Oxygen pulse	8 ml/beat	15 ml/beat	53
Anaerobic threshold (as % of predicted VO_2max)	21%	>40%	-
Peak oxygen saturation	97%	>95%	-
Minute ventilation (L)	45.2 (at peak exercise)	56.0 (calculated MVV)	81%
Breathing reserve	19%	>30%	-
Ve/VCO_2 slope	55	<33	-

Peak VO_2 = peak oxygen uptake (mL·kg−1·min−1); HR = heart rate (bpm); O_2 pulse = VO_2/HR (mL/beat); AT = anaerobic threshold (% predicted VO_2max); SpO_2 = oxygen saturation (%); VE = minute ventilation (L/min); BR = breathing reserve (VE/MVV, %); VE/VCO_2 slope = slope of VE vs VCO_2 (unitless).

The patient was exercised to 54 watts, which corresponds to 32% predicted.

This table was created by Dr. Timothy Scialla and Dr. John J. Popovich for this teaching script.

Figure 2. Flow-volume Loop



Flow volume loop image courtesy of Dr. Susan Mathai.

Question 12: Would you expect a heart transplant to improve this patient's exercise tolerance?

This case illustrates how a CPET can help identify causes of exercise limitation that have been overlooked. Though the patient has CPET features that are consistent with cardiac limitations to exercise, such as the markedly elevated VE/VCO_2 slope and reduced peak VO_2, an additional finding is significant obstructive lung disease.

In terms of exercise measurements, he has minimal breathing reserve. The maximum voluntary ventilation (MVV) is predicted by multiplying the measured FEV_1 by 40 (in this case, FEV_1 = 1.4 corresponds to an estimated MVV of 56 L). His minute ventilation at peak

exercise is > 80% of MVV, suggesting that he approaches his ventilatory ceiling and that he has a ventilatory limitation to additional exercise. Though he has clear clinical history and evidence of cardiovascular disease, he also has previously undiagnosed COPD that needs to be addressed. The CPET findings indicate that it is likely contributing to dyspnea and exercise limitation in addition to his cardiac disease. This will also be an important element in risk stratification and assessment of his candidacy for heart transplantation.

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