Cardiopulmonary Exercise Testing (CPET) & Advanced Diagnostic Testing

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Literature review current through June 2024
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Educational Objectives:

1. Summarize the spectrum of exercise limitation after complicated ICU course
2. Describe the relative contribution of factors responsible for oxygen delivery using the Fick equation
3. Understand the CPET profile of a cardiac and pulmonary vascular limitation to exercise
4. Summarize contemporary concepts of invasive exercise hemodynamics
5. Describe features of CPET testing that would indicate ventilatory limitation to exercise

Scenario 1:
You are seeing a 47-year-old man about 3 months after discharge from an 8-week hospitalization. He was admitted to another hospital for pneumonia that was treated with appropriate antibiotics. His hospitalization was complicated by sudden decompensation due to acute bilateral pulmonary emboli prompting transfer to a higher level of care. Upon transfer, he was in shock and treated with systemic thrombolytics. His hypoxemia and hypotension improved significantly, but his course was complicated by empyema, pneumothorax, and persistent air leak. He slowly improved, was extubated after ~10 days. 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 1 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 and an echo obtained prior to his visit showed:

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

2D Echocardiography: Normal LV size and function, normal left-sided valves. No LVH or signs of diastolic dysfunction. RV normal size and function, IVC collapsing, 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 particular patient?

Specific considerations for this patient with post-ICU-stay exercise limitation include generalized deconditioning after a prolonged hospitalization, restrictive lung disease due to a primary lung or pleural injury, sequelae from critical illness myopathy, residual stress-induced cardiomyopathy, anemia, upper airway pathology, 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 have indicated a high prevalence of objective exercise limitation (50-70% at 6-12 months) after an episode of acute PE,[1-3] as defined by a reduced maximal VO_2 on CPET. Chronic Thromboembolic Pulmonary Hypertension (CTEPH), which requires demonstration of both persistent pulmonary arterial thrombotic material and *resting* pulmonary hypertension, is thought to occur with an incidence of up to 4% post-acute PE.[4-7] This is felt to lie on the extreme end of a spectrum of disease, with a higher proportion of patients demonstrating various combinations of exercise limitation, right ventricular dysfunction, and/or perfusion abnormalities, but without resting pulmonary hypertension. This is referred to as chronic thromboembolic disease (CTED), or sometimes the "post-PE syndrome".[8] Various studies have shown a 25-50% rate of persistent perfusion defects on V/Q scanning during variable follow-up post-PE,[9,10] with an ~20% prevalence of persistent RV dysfunction, and ~10% prevalence of moderate or severe dyspnea.[11]

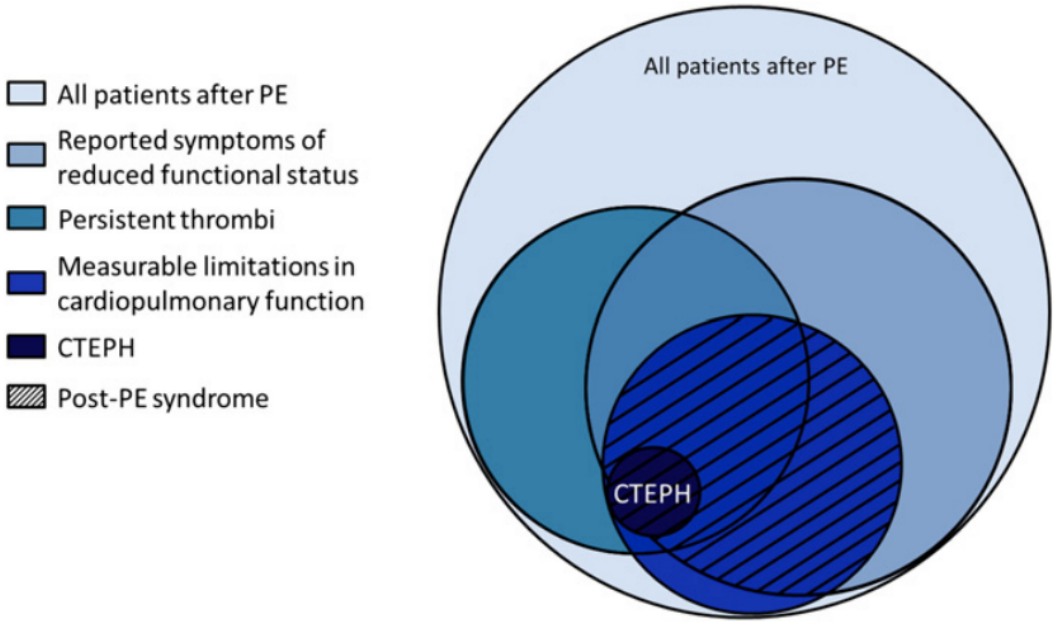


Figure 1. From Klok et al. 2014.

If there is significant vascular obstruction present, both impaired cardiac output response as well as increased dead space contribute to symptoms and limitation. Recent data based on CPET analysis, however, suggest that many of these patients may simply be deconditioned, and, interestingly, the extent of residual perfusion deficits or RV dysfunction do not necessarily correlate well with reduced VO_{2max}.[1,2]

Question 3: State the Fick equation.

VO_2 = CO x (CaO2-CvO2)

Question 4: What pathophysiological processes are "packaged" within in the Arterial-Venous O_2 content difference (AVO2D) term?

VO_2 = CO × (A-V) O_2 content = CO x (CaO2-CvO2)

= CO × $[(SaO_2 - MvO_2) \times Hgb \times 1.34]$
(note: *due to its minimal influence on overall content, we're ignoring dissolved O_2*)

Therefore, the quantity AVO2D captures effects of anemia/hemoglobinopathy, gas exchange function of the lungs, distribution of blood flow to the periphery, and utilization of oxygen by muscles.

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

Question 5: What does the V_E/VCO_2 represent conceptually?

V_E/VCO_2, or "ventilatory equivalents for CO_2," reflects the degree of ventilatory efficiency, or how much minute ventilation is occurring per liter of CO_2 production. (V_E/VO_2 is also a marker of efficiency, but because regulation of minute ventilation is more tightly linked with CO_2, V_E/VCO_2 makes more sense as the best metric for this.)

Mathematically it is proportional to the dead space fraction and inversely proportional to $PaCO_2$. Therefore, an elevated V_E/VCO_2 is due to either elevated dead space or a reduced $PaCO_2$ (hyperventilation). Hyperventilation may be "appropriate" (respiratory compensation in setting of chronic metabolic acidosis, respiratory compensation for severe/early onset of exercise-induced lactic acidosis, or hypoxemia), or "inappropriate" (psychogenic hyperventilation/dysfunctional breathing). Normal range for V_E/VCO_2 is 25-30**.** Slight elevation above 30 can be normal variant in but elevation of > 34 is considered clinically significant**.** (Note, that normal ranges for this value are age-dependent.)

Question 6: What CPET parameters suggest a primary cardiac limitation?

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

- Reduced peak VO_2
- Early-onset anaerobic threshold (AT), reduced $\Delta VO_2/\Delta WR$ (both indirect indicators of adequacy of oxygen delivery/utilization)
- Reduced peak "O_2 pulse" (VO_2/HR) (as a reflection of reduced maximal stroke volume)
- Rapid rise in HR relative to VO_2
- Low reserve between maximum HR achieved and predicted max HR (heart rate reserve)

Question 7: Which parameters suggest a pulmonary vascular limitation to exercise?

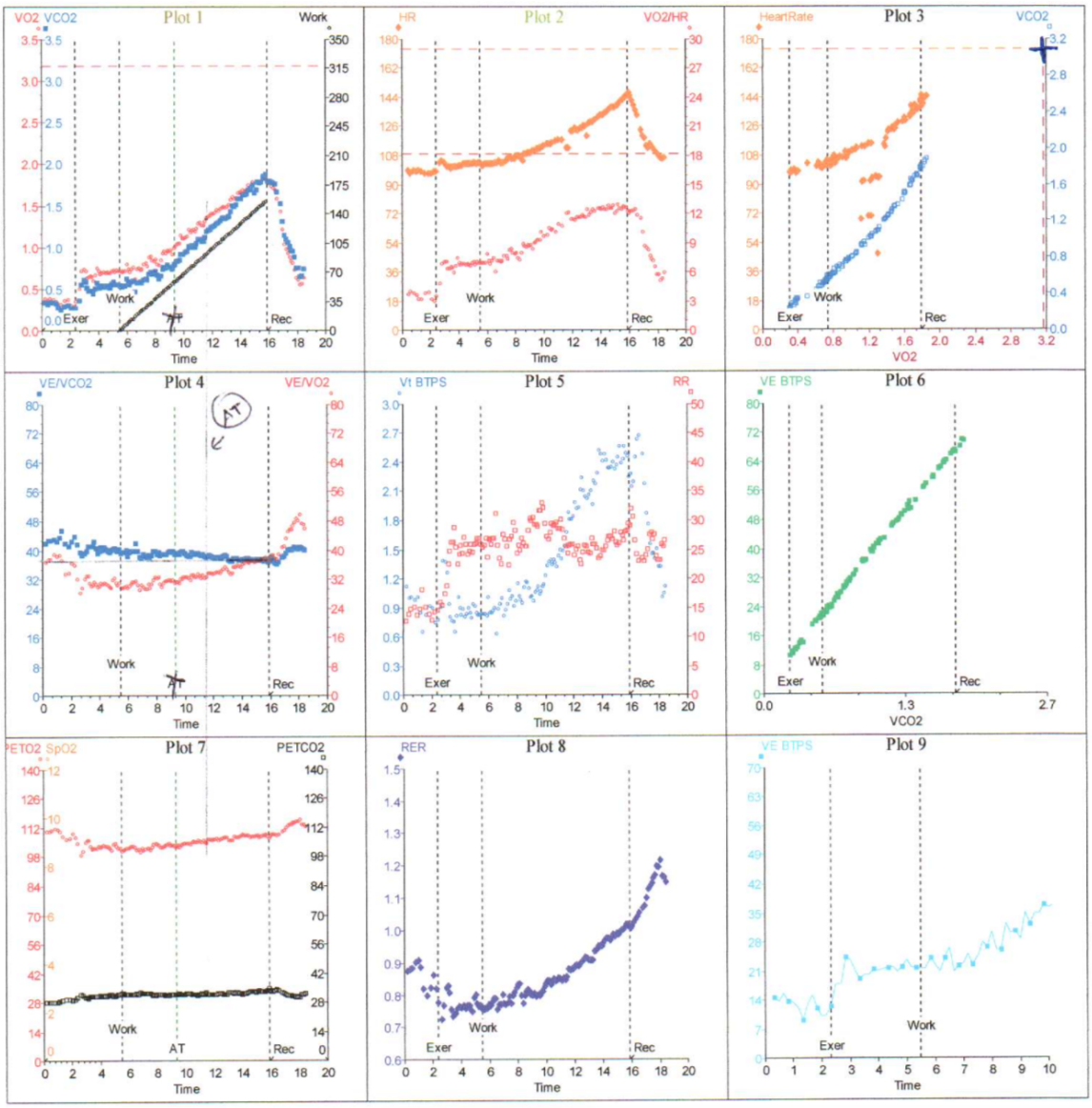
A pulmonary vascular pattern of exercise limitation is like a cardiac limitation; however, a few parameters are notably different in the setting of pulmonary vascular disease. First, patients with pulmonary vascular disease typically exhibit an abnormally elevated Vd/Vt during exercise. This can be manifested as ventilatory inefficiency (notably high V_E/VCO_2). Assuming the patient isn't hyperventilating, a high V_E/VCO_2 is attributed to abnormally elevated Vd/Vt. Vd/Vt can also be calculated using values for expired and arterial CO_2 using the Bohr equation. In addition to elevated Vd/Vt, patients with a pulmonary vascular limitation also frequently experience arterial desaturation during exercise.

Note that the computer-generated estimated of Vd/Vt values based on end-tidal CO_2 measurements are NOT ACCURATE and should be IGNORED, particularly when disease is present. This is because end-tidal values for CO_2 do not correlate with arterial values in disease states (particularly when the pulmonary circulation is affected). As a result, the computer will tend to underestimate abnormal dead space in disease (and overestimate it in health).

Question 8: CPET was performed for our patient. Values and graphs are listed below.

Selected CPET variables (exercised to 156 Watts):

	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%	-
Breathing reserve	47%	>30%	-
End-tidal CO_2 at AT	32		-
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	-



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 including 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 (cont.):
The patient undergoes both V/Q and CTA scanning, which reveal complete occlusion of both lower lobe pulmonary artery branches.

Resting Right Heart Hemodynamics:	
RA	2 mmHg
PA	27/8 (17) mmHg
PCWP	4 mmHg
tCO	6.2 L/min
PVR	2 Wood units

Question 9: Interpret the hemodynamics. Does he have CTEPH?

The resting hemodynamics are normal. Since he does not have pulmonary hypertension as demonstrated by his mPAP <20 mmHg, he doesn't have CTEPH. This, by definition, does not exclude CTED, as his radiology studies clearly show perfusion deficits. Given the remarkable reserve with recruitability and distensibility of the pulmonary circulation, there may be significant reductions in cross-sectional area of the pulmonary vascular bed without resting hemodynamic perturbation. Provoking the system, as with exercise, can unmask functionally relevant changes that are not apparent at rest. And, of course, this is when many patients manifest symptoms.

Scenario 1 (cont.):
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	
tCO	15 L/min	(Predicted peak = ~23 L/min)
PVR	2.6 Wood units	
TPR	3.7 (mPAP/CO)	
Lactate	0.7 at rest, 1.9 at peak	

Question 10: Describe the normal hemodynamic response to exercise and contrast it to this patient.

Due to distensibility and recruitability of pulmonary vessels, as well as dynamic changes in left ventricular function and relaxation characteristics, the following observations can be made regarding hemodynamic changes with exercise:

- During progressive exercise, the following occur in normal individuals:
  - Steady increase in CO, mPAP, and pulmonary capillary wedge pressure (PCWP)
  - **Mild decrease in PVR**
  - **Modest decrease in TPR**

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.

Over the preceding decades, there has been ongoing debate about defining the normal pulmonary vascular responses to exercise. However, there is now some emerging consensus, with publication of a European Respiratory Society (ERS) task force statement in 2017.[13] 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 define normal vs an abnormal pulmonary vascular response to exercise.[14]
    - An upper limit of normal of **3 mmHg/L/min** is reasonable (noting that healthy younger patients likely should have lower values than this)
    - This translates to an upper limit of normal (ULN) of mPAP of 30 at CO <10 L/min

Recall that Ohm's law is used to approximate the relationship between flow, pressure, and resistance in the pulmonary circulation, given by:

$$\text{mPAP} = (\text{CO} \times \text{PVR}) + \text{PCWP}$$
$$\text{TPR (total pulmonary resistance)} = \text{mPAP} / \text{CO}$$

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

However, an abnormal mPAP/CO slope alone does not pinpoint the clinical pathophysiology (you need to tease out whether it is due to rise in PCWP vs increase in PVR).

- The rise in wedge pressure in healthy patients is also dependent on cardiac output.
    - **An absolute peak wedge cutoff of 20 mmHg is used in most studies by reference labs[15]. Thus, eiPH can be defined as an elevated mPAP or TPR with an exercise PCWP <20.**
    - There is some interest in the **wedge/CO relationship**, using an ULN of **2 mmHg/L/min**, but this is not in use clinically.

Scenario 1 Conclusion:
The patient was diagnosed with exercise-induced PH based on chronic thromboembolic disease (CTED).
Given the functional limitations as documented by CPET, with 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.[16] He was deemed to be a good candidate and is slated for surgery in the near future.

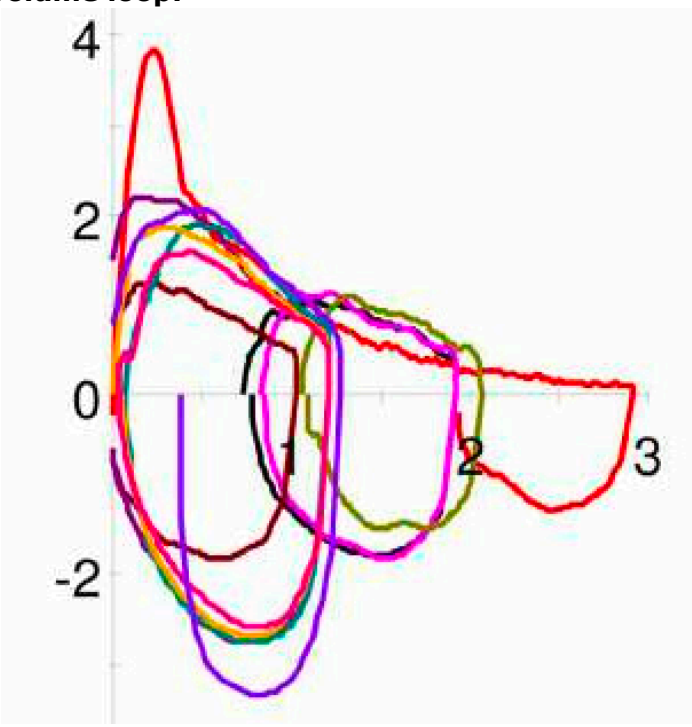
Scenario 2:
A 65 year-old man with heart failure with reduced ejection fraction (HFrEF, LVEF 15%) secondary to ischemic cardiomyopathy is referred for CPET as part of evaluation / consideration for heart transplant. He is severely limited in terms of his exercise capacity, and his goals are to optimize his heart failure management to allow for a greater quality of life.

You are reviewing his CPET results.

Selected CPET variables (patient exercised to 54 Watts, 32% predicted):

	Patient's Value	Predicted Value	%-Predicted
Peak VO_2	586 ml/min	2282 ml/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	-

Flow-volume loop:



Question 11: Will a heart transplant 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/VCO2 slope and reduced peak VO2, an additional finding is significant obstructive lung disease.

Indeed, his flow volume loop from baseline spirometry (red) illustrates a reduced FEV1/FVC ratio (actual ratio was 0.48). Additionally, the tidal volume curves also documented here show that as the patient exercises, he has dynamic hyperinflation such that by later phases of exercise, his residual volume increases--indicated by an end-inspiratory lung volume that is near his tidal volume (brown curve), as well as a shift in his flow volume loop to the left. At this volume, the patient's work of breathing is markedly increased due to trapped air, and he cannot increase his tidal volume any further.

In terms of exercise measurements, he has minimal breathing reserve. The maximum voluntary ventilation (MVV) is predicted by multiplying the measured FEV1 by 40 (in this case, FEV1 = 1.4; multiplied by 40, you get 56 L). In this case, his minute ventilation at peak exercise is > 70% of MVV, suggesting that he approaches his ventilatory ceiling and that he has a ventilatory limitation to additional exercise.[12]

In this patient's case, 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 for heart transplant candidacy.

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