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Evaluation & Management of Post-COVID-19 Patients (Long COVID)

An APCCMPD Ambulatory Care Curriculum Teaching Script

Authors **Susan K. Mathai, MD**
Baylor University Medical Center

Timothy J. Scialla, MD
John J. Popovich, MD
University of Virginia

Editor **Susan K. Mathai, MD**
Baylor University Medical

Associate **Hugo Carmona, MD**
Editors *University of Washington*

Brian Garnet, MD
University of Miami/Jackson Health System

Please find all script contributors listed on the last page.

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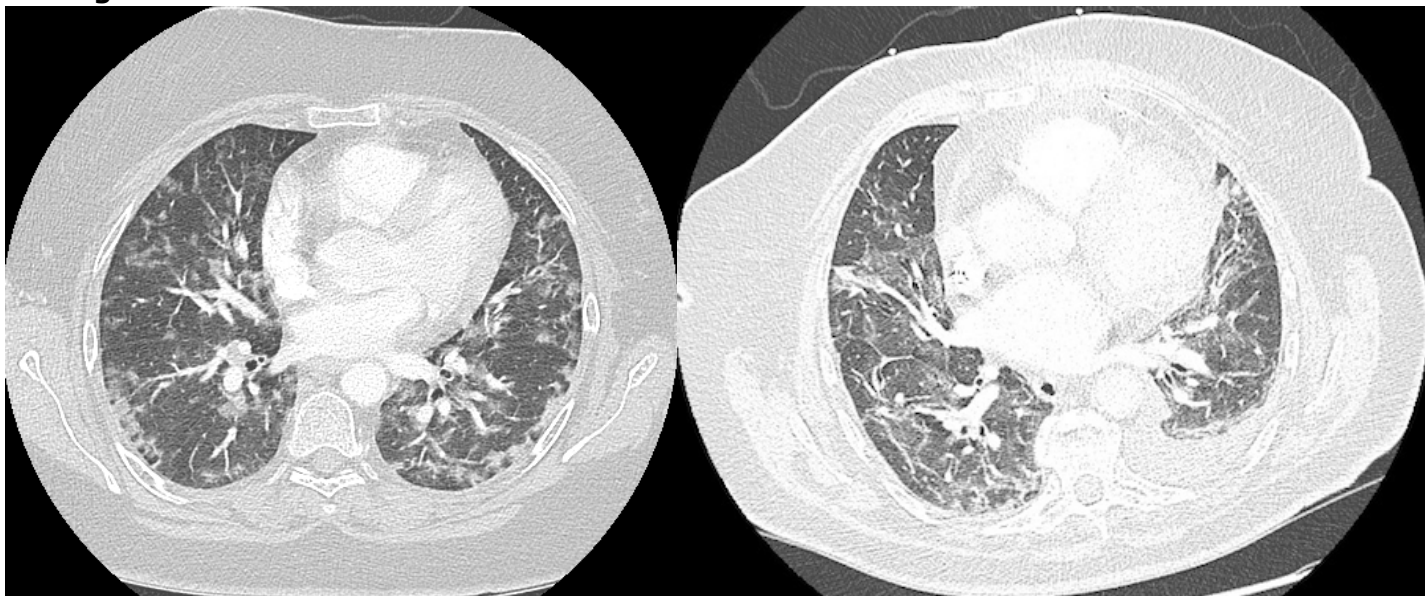
Scenario 1:

Mr. M is a 45-year-old man who has been referred for evaluation for persistent shortness of breath. He was admitted to the intensive care unit for one week about three months prior to this visit for treatment of acute COVID-19 disease. He required high-flow nasal cannula for respiratory support for several days but was not intubated. He was treated with remdesivir and dexamethasone during his hospitalization. He now complains that despite being quite healthy prior to COVID-19 infection, he is weak and very limited by his breathing. He feels that he can barely walk up a flight of stairs. He is bothered by a persistent cough. He also complains of feeling extremely lethargic and describes having "brain fog," with memory difficulties and inability to return to work. He is frustrated by the situation and is feeling quite depressed since being discharged from the hospital. He did not have any prior hospitalizations, and his medical history is significant for obesity, hypertension, and diabetes mellitus for which he is on oral metformin.

Question 1: What is your next step for investigating Mr. M's dyspnea?

Question 2: A CT chest is obtained as below (Figure). How do these findings get incorporated into the evaluation of someone with PACS?

Figure. Mr. M CT Chest



Scenario 1 (Continued):

Mr. M returns to your office after taking prednisone 40 mg daily tapered over subsequent few weeks. He reports that he is subjectively feeling better, though not quite back to his baseline in terms of his breathing. His cough is improved. He asks what other considerations and evaluation might make sense, as he remains short of breath and unable to go back to work. He notes continued depression, which he feels is due to his persistent dyspnea.

Question 3: What other evaluations and considerations are warranted?

Scenario 1 (Continued):

Mr. M notes during his visit that he is not vaccinated yet against COVID-19. He is worried about receiving the vaccine based on things he has read on social media – in fact, he is concerned that getting vaccinated will cause his symptoms to recur. He also does not understand why he should require vaccination since he already had COVID-19 and survived. “I have antibodies, don’t I?”

Question 4: Should this patient be vaccinated against COVID-19? What you can tell him about vaccination based on current data.

Scenario 2:

A 35-year-old female with a past medical history only significant for COVID infection 8 months ago presents to pulmonary clinic with exercise intolerance far below her baseline exercise status before her COVID infection. She has normal pulmonary function testing and a normal echocardiogram. She reports her quality of life as very poor and wants to get back to her baseline exercise status. 6MWT shows she walked 325m. Her resting SpO₂ was 98% and dropped to 97% with exercise; her resting heart rate was 95 and at the end of the walk was 155. Her Borg dyspnea score was 2 prior to exercise and increased to 8 with exercise. Blood pressure was 110/75 at rest and 115/68 at peak exercise. You order a CPET to better elucidate the cause of her dyspnea with exercise—the results of this CPET are shown below in Tables 2 and 3.

Table 2. Measurements Obtained at Rest During CPET for Patient from Scenario 2

Parameter	Value
Heart Rate	90
Respiratory rate	26
PetCO ₂	28
SpO ₂	98%
Arterial Blood Gas	7.48/ 30 / 110 / 22
Vd/Vt (Using PaCO ₂ from ABG)	0.20

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

Table 3. Measurements Obtained During CPET for Patient from Scenario 2 (Patient Exercised to 60 Watts, 70% Predicted):

	Patient's Value	Predicted Value	%-Predicted
Peak VO₂	1200 ml/min	1800 ml/min	72
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Oxygen pulse	9 ml/beat	14 ml/beat	70
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Peak oxygen saturation	97%	>95%	-
Minute ventilation (L)	34 (at peak exercise)	98 (calculated MVV)	34%
RR at Peak	42		
Breathing reserve	66%	>30%	-
Tidal Volume response	Early plateau (800mL)		
Ve/VCO₂	34	<33	-
PetCO₂	26 mmHg		
RER	1.15		
ABG at peak exercise Vd/Vt (pH/PCO₂/PO₂)	7.38/28/120		

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Qualitative Observations:

- Breathing pattern: rapid, shallow, irregular
- Symptoms: dyspnea disproportionate to workload, lightheadedness
- Recovery: prolonged tachypnea, delayed normalization of PetCO₂.

Question 5: How would you interpret this CPET?

Evaluation & Management of Post-COVID-19 Patients (Long COVID)

Pre/Post-Test Questions:

1. Mr. Josephson comes to see you in the office for evaluation after having been discharged from the hospital for COVID-19 infection about 3 months ago. He is having persistent shortness of breath and cough. You review his recent high-resolution CT chest. What is the most common pattern that you might expect to see in a post-COVID patient with persistent respiratory impairment?
 - a. Usual interstitial pneumonia pattern
 - b. Ground glass opacities
 - c. Crazy paving
 - d. Pleural effusions
2. You are seeing a patient in the office with findings suggestive of possible post-COVID organizing pneumonia on their CT scan as well as significant pulmonary impairment with an oxygen requirement. What might be a treatment to consider discussing with them?
 - a. Inhaled Treprostinil
 - b. Sildenafil
 - c. Prednisone
 - d. Nintedanib
3. You are seeing a patient in the office who is hesitant to take the COVID-19 vaccine because he had a mild case of COVID-19 2 months ago, which did not require any medical care. He says that he was told he should wait 9 months before getting vaccinated. What is the most appropriate recommendation and rationale?
 - a. Patients who have recovered from COVID-19 infection are immune from future infection and so have no need to be vaccinated.
 - b. Patients who have had COVID-19 should wait 9 months before getting vaccinated.
 - c. Patients who have survived COVID-19 may have worsened symptoms if they are vaccinated afterward.
 - d. Patients can receive vaccination against COVID-19 at any point, though they should wait until after their acute illness subsides and can consider waiting 3 months since symptom onset.

Evaluation & Management of Post-COVID-19 Patients (Long COVID)

Educational Objectives:

1. Review the initial evaluation of patients presenting with dyspnea after COVID-19 infection
2. Understand common pulmonary findings associated with post-COVID-19 pulmonary impairment
3. Recognize the limitations in evidence-based care and areas of ongoing research in this rapidly evolving field
4. Review the need for a multidisciplinary approach to the evaluation and care of COVID
5. Describe features of CPET testing that are consistent with dysfunctional breathing syndrome in COVID survivors

Scenario 1:

Mr. M is a 45-year-old man who has been referred for evaluation for persistent shortness of breath. He was admitted to the intensive care unit for one week about three months prior to this visit for treatment of acute COVID-19 disease. He required high-flow nasal cannula for respiratory support for several days but was not intubated. He was treated with remdesivir and dexamethasone during his hospitalization. He now complains that despite being quite healthy prior to COVID-19 infection, he is weak and very limited by his breathing. He feels that he can barely walk up a flight of stairs. He is bothered by a persistent cough. He also complains of feeling extremely lethargic and describes having "brain fog," with memory difficulties and inability to return to work. He is frustrated by the situation and is feeling quite depressed since being discharged from the hospital. He did not have any prior hospitalizations, and his medical history is significant for obesity, hypertension, and diabetes mellitus for which he is on oral metformin.

Question 1: What is your next step for investigating Mr. M's dyspnea?

Mr. M is struggling with symptoms consistent with post-acute sequelae of SARS-CoV-2 infection (PASC), otherwise known as post-COVID symptoms or "long COVID." These terms refer to a wide spectrum of symptoms, respiratory and otherwise, that are being observed in survivors of acute COVID-19 infection. By definition, these are symptoms that persist greater than 4 weeks after initial acute infection.¹ Of note, post-acute care symptoms, particularly in ICU survivors, are common.² Acute Respiratory Distress syndrome (ARDS) survivors, in particular, have been known to have respiratory compromise and symptoms that persist long after hospital discharge.³ Whether and why COVID-19 survivors have different post-acute illness symptoms than comparable ARDS/ICU survivors is an area of ongoing study, as many early studies have methodologic limitations that prevent more comprehensive definitions, generalizations, and work-up and treatment algorithms.

The actual prevalence of PASC is challenging to estimate given rapidly changing data. Depending on the study, the frequency can vary from 5-80%, and include both (a) general complications of acute illness and (b) specific post-acute sequelae of SARS-CoV-2 infection.^{1,4,5} Dyspnea has been noted in some studies to be the most common post-COVID symptom reported.¹ There can be many other affected organ systems, however, due to the multi-organ system involvement in the acute phase of illness. These symptoms by some reports are more common in women.⁴

The implications of PASC for the health care system are significant given the high rate of healthcare utilization after acute COVID-19 infection. Readmission rates are high, with approximately 9-20% of patients hospitalized for COVID-19 having a readmission within 2 months of discharge.^{6,7} However, these studies were conducted during the early parts of the pandemic prior to wide-vaccination.

After an acute COVID-19 illness admission, ideally a patient will have short-term outpatient follow-up to include:

- Medication reconciliation
- Physical exam
- Discussion of clinical course and anticipatory guidance
- Include discussion of mental health / wellness (anxiety/depression/PTSD, especially in patients admitted to the ICU).

In some cases, due to limitations in accessing confirmatory tests early in the COVID-19 pandemic, patients may report that they believe that they had COVID-19 but never had a positive test. The illness of COVID-19 is a clinical diagnosis, and so some patients may have had SARS-CoV-2 infection despite never having had a positive nasal PCR test. In current cases where diagnostic testing is lacking, antibody testing can be considered, though it is important to bear in mind that antibody testing can be negative in up to 10-20% of recovered patients.⁴

The Table shows a partial list of the varied post-COVID symptoms, associated diagnoses, and potential work-up that may be considered.

Table 1. Commonly Reported Symptoms Among Post-COVID-19 Patients and Possible Work-up

Symptom	Potential Diagnoses	Work-Up
Fatigue	Hypothyroidism Chronic lung disease Vitamin D or B deficiency Diabetes mellitus Chronic thromboembolic disease	Thyroid function testing (TSH, free T4) Cardiac function testing (TTE) Pulmonary function testing 6-minute walk test Vitamin D levels Vitamin B12 level Hemoglobin A1c
Post-exertional malaise (PEM) or lack of endurance ¹		Cardiac evaluation including stress testing Pulmonary function testing 6 minute walk testing
Brain fog	Cognitive impairment Mood impairment	Montreal Cognitive Assessment (MoCA) Neurocognitive assessment Screening for anxiety, depression, PTSD

¹PEM defined as worsening of symptoms after minor physical or mental exertion, symptoms worse 12-48 hrs after exertion, and can last for days/weeks.

Cough	ILD Upper airway cough syndrome Asthma	Pulmonary function testing Pulmonary stress/exercise testing Chest imaging Echocardiogram
Dyspnea	ILD, reactive airways disease, chronic thromboembolic disease, pulmonary hypertension	MMRC scale, CT scan of the chest, echocardiogram, cardiopulmonary exercise testing, pulmonary function testing
Chest pain	Pulmonary Embolism	Cardiac stress testing CT Pulmonary angiography
Headaches	Migraine	Referral to primary care or neurology
Palpitations/tachycardia	Cardiomyopathy	Echocardiogram Holter monitor
Arthralgias, Myalgias, Paresthesia	Connective tissue diseases	Autoimmune serologies Rheumatologic evaluation
Abdominal pain, diarrhea	Post-infectious irritable bowel syndrome Dyspepsia	Rule out infection
Insomnia/sleep disturbance	Sleep disordered breathing Restless leg syndrome	Polysomnography
Lightheadedness	myocarditis, heart failure, pericarditis, orthostatic intolerance Postural orthostatic tachycardia syndrome (POTS)	Echocardiogram, orthostatic vital signs
Pain	Reactive arthritis Fibromyalgia Connective tissue diseases	Physical exam, when appropriate serologic testing
Rashes	Connective tissue diseases	Serologic evaluation Referral to dermatology
Mood changes	PTSD, Depression, Anxiety	Depression and anxiety screenings
Anosmia / dysgeusia	Persistent loss of senses after viral illness	

TTE - Transthoracic echo; PTSD – Post Traumatic Stress Disorder; ILD - Interstitial Lung Disease; mMRC – modified; CT – computed tomography

Adapted from Nalbandian et al. Respir care 2012;57:764-772 and Hui et al. Thorax 2005;60:401-409

As is evident from this list, the list of symptoms associated with PASC can be extensive. The goal of work-up is to identify organ dysfunction, physical impairments, nutritional deficits, and psychosocial impairments, and then provide targeted therapy as appropriate. This is why many institutions have created “Post-COVID-19” or “Post-ICU” clinics to provide comprehensive care to these patients. ⁸

In this particular patient’s case, there is concern for significant respiratory or cardiac impairment given that he is having respiratory symptoms. Appropriate work-up might include:

- Pulmonary function tests including spirometry, lung volumes, and DLCO to quantify and categorize impairment
- Six-minute walk test
- Chest radiograph
- CT scan of the chest to assess for parenchymal abnormality
- Serologic testing as in the table above
- Consideration of an echocardiogram
- Consideration of bronchoprovocation testing to assess for reactive airways disease

Question 2: A CT chest is obtained as below (Figure). How do these findings get incorporated into the evaluation of someone with PACS?

Figure. Mr. M's CT Chest



Images courtesy of Dr. Susan Mathai.

The CT above demonstrates areas of ground glass opacities suggestive of organizing pneumonia. Early studies of COVID-19 survivors indicated that about half had abnormalities on their high resolution CT scans of the chest (HRCT), usually ground glass abnormalities (see Figure) ⁹ though moderate to severe cases are noted to have fibrotic changes such as reticulation and traction bronchiectasis in up to 65% of survivors. ¹⁰

Evidence-based guidance on the treatment of these patients remains an evolving area of study. However, there is some evidence that for patients with organizing pneumonia pattern of post-COVID injury (as indicated by histopathologic diagnosis or compatible clinical and radiologic findings), treatment with corticosteroids can be helpful.¹¹ In a small observational study, patients with organizing pneumonia findings on HRCT (>15% involvement) and pulmonary impairment were offered 0.5 mg/kg prednisolone with a rapid tapering over 3 weeks.¹¹ All treated patients reported improvement in subjective symptoms, and CT scans showed improvement, as well, though the observational nature of the study and its lack of a placebo arm leave the role of steroids uncertain. Additionally, a separate study indicated that low dose steroids may be as effective as higher dose courses, which may be particularly important for patients who experience significant side effects with steroid therapy and/or have comorbid illnesses affected by it.¹² Overall, the data to support use of corticosteroids in these patients is weak.

Question 3: What other evaluation and treatments are indicated in this case?

Post-COVID-19 studies from China indicated that at 6 months after acute illness, 6-minute-walk (6MWT) distances were lower than normal in COVID-19 survivors, similar to what had been observed in SARS-CoV-1 and MERS virus survivors.^{1,3} Reduction in diffusing capacity of carbon monoxide (DLCO) is the most common pulmonary function testing abnormality noted in patients post-COVID-19 with respiratory symptoms and is related to the severity of their original illness.^{13,14} This is similar to what has been noted in other post-ARDS patient cohorts.¹

Pulmonary rehabilitation programs and physical therapy are critical components to patient recovery.¹ Though rare, in a minority of patients with severe and prolonged acute illness, there have been cases of lung transplantation.¹⁵ There have been studies investigating whether antifibrotics are helpful in these patients; to date, these have been negative.¹⁶

For a patient such as Mr. M, given ground glass opacities throughout his lung fields and his subjective significant respiratory limitation, it would be reasonable to discuss treatment with oral corticosteroids with close monitoring of response to therapy and acknowledgment of potential complications, especially with his comorbid conditions (diabetes and obesity).

Scenario 1 (Continued):

Mr. M returns to your office after taking prednisone 40 mg daily tapered over subsequent few weeks. He reports that he is subjectively feeling better, though not quite back to his baseline in terms of his breathing. His cough is improved. He asks what other considerations and evaluation might make sense, as he remains short of breath and unable to go back to work. He notes continued depression, which he feels is due to his persistent dyspnea.

Question 3: What other evaluations and considerations are warranted?

Thromboembolic disease: While early in the pandemic, there was a practice of extending DVT chemoprophylaxis to the outpatient setting, no conclusive evidence exists around prolonged chemoprophylaxis or anticoagulation in the outpatient setting. Evaluation for venothromboembolism should include history and physical exam, with appropriate testing if

warranted. For any patients who had confirmed thromboembolic disease during their acute illness, the current recommendation is to use direct oral anticoagulants (DOACs) or low molecular weight heparin (LMWH) for anticoagulation for at least 3 months, with further duration to be a topic of shared decision-making. ¹

Cardiovascular complications: Patients who suffered from cardiovascular complications during their acute illness may be at higher risk of longer-term post-COVID cardiac complications, and so echocardiography and Holter monitor evaluation should be considered on a case-by-case basis. ¹ Additionally, competitive athletes should consider avoiding extreme sports or aerobic activity for 3-6 months after COVID-19 infection due to concern for ongoing damage, though this is based on relatively weak evidence. ¹⁷

Underlying illnesses: It is important to review the patient's medical history thoroughly – not only their COVID-19 illness course, but also to understand other conditions that may have pre-dated their COVID-19 infection and may be worsened afterward, including common pulmonary and non-pulmonary (e.g. cardiac, renal, endocrine) disorders. Some underlying disorders (such as asymptomatic or minimally symptomatic ILD) may have been unmasked by the COVID infection, so review of pre-COVID imaging (if available) is critical. ⁴

Social support and mental health: Social history is critical– assess social support and resources, as well as risk factors for mental health disease and substance use disorders. Hospitalization and critical illness, along with PASC, may lead to mental health, cognitive, and physical impairments which can be isolating, in addition to disruptive to daily routines, employments, and self-care. Addressing mental health needs directly with pharmacotherapy and counseling, including treatment of substance use, if present, can be instrumental in a patient's recovery. Post-ICU PTSD is well described in other forms of ICU-survivorship, and has also been reported in COVID survivors. ¹

Depending on his level of impairment and symptoms, it would be reasonable to obtain an EKG and echocardiogram, consider stress testing given his CAD risk factors, and screen for depression/anxiety/PTSD, with appropriate referrals for mental health support.

It should also be stressed to him that so-called “objective testing” may not reveal a clear etiology for the symptoms that the patient is experiencing. This is not meant to minimize the impact of such symptoms, but only to clarify that we cannot clearly link symptoms to abnormal testing in all cases. It would be important to acknowledge that the medical community is still learning about how best to evaluate and treat patients with post-COVID-19 symptoms—and that our approaches may evolve as scientific knowledge does.

Scenario 1 (Continued):

Mr. M notes during his visit that he is not vaccinated yet against COVID-19. He is worried about receiving the vaccine based on things he has read on social media – in fact, he is concerned that getting vaccinated will cause his symptoms to recur. He also does not understand why he should require vaccination since he already had COVID-19 and survived. “I have antibodies, don’t I?”

Question 4: Should this patient be vaccinated against COVID-19? What you can tell him about vaccination based on current data.

COVID-19 vaccination should be offered to all eligible patients, regardless of whether they have had prior infection.⁴ There is no evidence of worsening symptoms of PASC after vaccination.¹⁸ It is also important for patients to make sure to remain up to date on yearly influenza vaccination and appropriately scheduled pneumococcal vaccines.⁴

It is important to share with the patient that at this time, it is not known how long immunity after infection lasts for COVID-19 survivors, and so up-to-date immunization for all patients is important. This applies to all respiratory viruses for which we have approved vaccines. Vaccination provides a “boost” in immunity for those who have already had the infection.¹⁹ Since the initial approval of vaccination for COVID-19, studies have shown that additional or booster doses of the vaccine may be necessary for patients, especially those who are elderly and/or immunosuppressed. Expert opinion on the timing and frequency of booster doses continues to evolve.²⁰

Scenario 2:

A 35-year-old woman with a past medical history only significant for COVID infection 8 months ago presents to pulmonary clinic with exercise intolerance far below her baseline exercise status before her COVID infection. She has normal pulmonary function testing and a normal echocardiogram. She reports her quality of life as very poor and wants to get back to her baseline exercise status. 6MWT shows she walked 325m. Her resting SpO₂ was 98% and dropped to 97% with exercise; her resting heart rate was 95 and at the end of the walk was 155. Her Borg dyspnea score was 2 prior to exercise and increased to 8 with exercise. Blood pressure was 110/75 at rest and 115/68 at peak exercise. You order a CPET to better elucidate the cause of her dyspnea with exercise—the results of this CPET are shown below in Tables 2 and 3.

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Qualitative Observations:

- Breathing pattern: rapid, shallow, irregular
- Symptoms: dyspnea disproportionate to workload, lightheadedness
- Recovery: prolonged tachypnea, delayed normalization of PetCO₂.

Question 5: How would you interpret this CPET?

This is a challenging study and it highlights the challenges in ordering CPET studies on patients with Long COVID symptoms. Such patients can develop substantial dyspnea with activity for myriad reasons including muscular deconditioning, low preload states from orthostasis, and dysfunctional breathing. In most cases, there is more than one driver it can be quite challenging to tease out the dominant culprit.

First, use the simple exercise test to assist you in developing a pretest differential. The 6MWT shows a mild reduction in exercise capacity with the patient reaching cardiac maximums without desaturation and significant breathlessness. The blood pressure response to exercise is not consistent with her heart rate elevation and shortness of breath. The aforementioned differential remains in place.

A step wise approach to reading a CPET study is important considering the wealth of variables and data presented to the interpreter.

The first question to ask is whether the patient has performed a maximal physiologic stress. In this case, the patient reached 98% of her predicted maximum heart rate so it is a maximal effort. Next, we look at her peak VO₂ which reaches only 72% of predicted making this an abnormal study. The anaerobic threshold can be used next to see if a circulatory impairment predominates. In this case, the subject reaches AT at 55% of predicted maximal VO₂, which is normal. The breathing reserve is next reviewed to see if there is an obvious ventilatory impairment. In this case there is a substantial breathing reserve present (66%). In most circumstances this points to deconditioning as the primary culprit. Looking at the O₂ pulse at this point can help gain an idea of the patient's stroke volume response to exercise. The values in this case do point to a component of deconditioning.

The ventilatory equivalents for carbon dioxide are abnormal in this patient with a higher value than expected at peak exercise. This suggests inefficient ventilation. The V_d/V_T increased with exercise which is also consistent with this. At this point the interpreter, when faced with a mixed process, must look deeper into the variables for additional findings. In this case, the resting respiratory alkalosis and qualitative observations about shallow irregular breathing pattern suggest dysfunctional breathing.

The respiratory rate and tidal volumes at peak exercise further suggest dysfunctional breathing with hyperventilation. With normal pulmonary function, the expectation is a steady rise in tidal volume to 1.5 to 2.0 L at peak exercise with higher respiratory rates late in exercise with increased metabolic demands. In our patient, the respiratory rate starts high and increases early in exercise with an early plateau in tidal volume.

Final Interpretation: Reduced exercise capacity with findings of dysfunctional breathing/hyperventilation syndrome with a component of deconditioning.

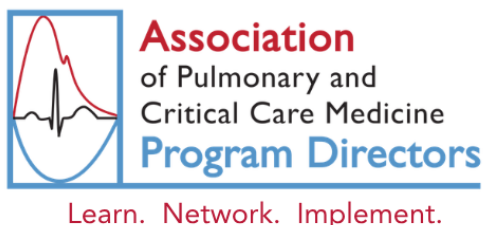
(Case interpretation from Mancini DM, Brunjes DL, Lala A, Trivieri MG, Contreras JP, Natelson BH. Use of Cardiopulmonary Stress Testing for Patients with Unexplained Dyspnea Post-Coronavirus Disease. JACC Heart Fail. 2021 Dec;9(12):927-937.²¹)

Pre/Post-Test Questions:

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Authors

Susan K. Mathai, MD

*Program Director, Pulmonary and Critical Care Medicine Fellowship
Baylor University Medical Center at Dallas
Clinical Associate Professor of Medical Education
Texas A&M School of Medicine*

Timothy J. Scialla, MD

*Associate Professor, Fellowship Program Director
University of Virginia*

John J. Popovich, MD

*Fellow Physician
University of Virginia*

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