Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/video-demo-cardiopulmonary-exercise-testing-in-pulmonary-arterial-hypertension-part-2/16332/

Released: 10/31/2023
Valid until: 10/31/2024
Time needed to complete: 4h 16m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Video Demo: Cardiopulmonary Exercise Testing in Pulmonary Arterial Hypertension - Part 2

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Cooper:
So let's go into another video here. Now we need to turn attention to the software of the metabolic measurement system and choose our program. We will select a UCLA ramp protocol with 3 minutes of unloaded pedaling. This protocol will give us a four-panel graphical display, showing the important physiological couplings during the test. And the key variables are shown on the right-hand side and at the bottom of the screen.

Let's give some additional thought to the selection of the work rate increment that would be appropriate to give an approximately 10-minute test in our subject. Let's consider a graphical representation of oxygen uptake on the Y axis and time on the X axis. At rest, our subject will have an oxygen uptake of about 0.25 liters per minute. We'll have a 3-minute period of unloaded pedaling, during which time we might expect the oxygen uptake to approximately double to 0.5 liters per minute. The subject had a predicted maximum oxygen uptake of 3.18 liters per minute, let's anticipate that he's physically fit and up that to 3.50 liters per minute. If we want a 10-minute ramp test, the oxygen uptake is going to have to increase from 0.5 at unloaded pedaling to 3.5, an increase of 3000 mils per minute. We know that there is a 10-mil per minute increase in oxygen uptake for every watt increase in work rate, and therefore, this would imply we need a 300-watt ramp in order to achieve the subject's maximum oxygen uptake. Since this is optimally a 10-minute test, we need to increment the work rate by 30 watts per minute. Here, we see the software allowing us to select our work rate increment for the chosen protocol for this subject.

Now we take a look at the electrocardiogram to make sure this is giving a good signal. We examine this during the test for evidence of myocardial ischemia or rhythm abnormalities that would be unduly concerning. We use this screen to look at resting data and to make sure that the heart rate is coupled with the metabolic measurement system, and the oxygen uptake and carbon dioxide output are reasonable values for resting data in unsteady state.

At this point, the subject is going to be told to start pedaling and informed that this will be very easy for the first 3 minutes. Thereafter, the workgroup will gradually increment. He is to continue as long as possible, and signal when he can no longer maintain cadence at 60 turns per minute. Take a note of the resting values, with R value of 0.82. We will now follow oxygen uptake and carbon dioxide as they gradually increase for unloaded peddling. A quick check of the electrocardiogram. Note at the bottom of the screen, the end-tidal partial pressures of oxygen and carbon dioxide accurately reflect the composition of alveolar gas. We have just begun the ramp phase of the exercise test, and you can note that the work rate is beginning to increment. From this point on, we should see steady increases in oxygen uptake and carbon dioxide output, and we'll watch what effect this has on the respiratory exchange ratio.

Note that ventilation has increased now greater than 24 liters per minute, with increased breathing frequency and tidal volume. Another quick check on the electrocardiogram. You can see that oxygen uptake and carbon dioxide have increased in proportion to each other

as shown in the upper right-hand plot. Heart rate has hardly changed at this point. Ventilation is increasing with a linear relationship to carbon dioxide output.

Here's a plot where we can see tidal inspiratory and expiratory flows from breath to breath, and on the left, a plot of exhaled carbon dioxide versus oxygen uptake. The X intercept of this linear relationship is the inspired oxygen concentration. We have just reached a work rate of 100 watts, and it is important to note the oxygen uptake about 1.5 liters per minute is approximately 1 liter per minute greater than that value obtained for unloaded pedaling.

This confirms that we are seeing an increase in oxygen uptake of approximately 10 mils per minute for every watt increase in work rate, this confirms we have a good test.

Note that the respiratory exchange ratio is gradually increasing, and at this point it is almost 1.0. If we look at the plot of carbon dioxide output versus oxygen uptake in the upper right-hand panel, we can now discern that there is an inflection point so that the carbon dioxide output is now increasing more steeply than oxygen uptake. This indicates that there is additional carbon dioxide coming from bicarbonate buffering of lactic acid.

If we examine the plot of oxygen uptake versus work rate and carbon dioxide versus work rate in the upper left panel, we can see that at the beginning of the test, carbon dioxide output values were consistently less than those for oxygen uptake. But now they have risen to equal or even exceed the values for oxygen uptake. Again, this is a sure indication of anaerobiosis. Note the linearity of the plot of heart rate versus oxygen uptake on the bottom right-hand panel.

The relationship between ventilation and carbon dioxide output in the bottom left panel also shows linearity, although we will carefully examine this for the appearance of an upward inflection.

At this point, we offer the subject encouragement and check that he is feeling okay. Oxygen uptake values over 3 liters per minute have now been recorded.

We're going to turn on audio so we can listen to the subject’s breathing.

Note that there is now an upward deflection seeing the bottom left-hand plot, indicating an uncoupling of ventilation and carbon dioxide output.

The test has ended, we have frozen the screen for further detailed analysis. We will now look at the data together.

So we could just have a quick look at these plots which you just saw derived in an actual subject, and then Alex and I will go through a series of slides which show you how we sort of break down this four-panel display and obtain all the key variables. But the inflection that we saw here in the VCO2/VO2 relationship, you heard me say that this reflects additional carbon dioxide output coming from bicarbonate buffering of lactic acid. So that's a lactate threshold. And it's somewhere here.

Now, the inflection on this plot of ventilation versus CO2 output, because we were all going to be interested in this slope, but the lactate threshold occurred somewhere down here, when there was still linear coupling between ventilation and CO2 output. So in spite of the fact that more CO2 was coming from bicarbonate buffering of lactic acid, ventilation still remain tightly coupled to CO2 output. But at this point, that relationship was uncoupled. And this is when we've exhausted the bicarbonate buffering capacity of the blood, unbuffered hydrogen ion in the blood stimulates the carotid body, this drives that ventilation independently of CO2 output, and we see a second inflection point. So the first slope here is all to do with ventilatory control through the central chemoreceptor controlling minute ventilation, or specifically alveolar ventilation in relation to CO2 output. This inflection point here reflects the addition of carotid body stimulation, but further drives that ventilation.

Dr. Sherman:
And I think that's a really important point for you to take home is that when you're thinking about the minute ventilation to carbon dioxide output, or VE/VCO2 slope, that we're not considering that part on the right-hand side of the graph, that no longer represents just the alveolar ventilation, or the ventilatory efficiency or inefficiency that you can often see in pulmonary arterial hypertension, that you should really only be looking at sort of the slope of the left portion there, or some people will even just look at the value at the metabolic threshold.

So, you know, this is, you know, there are several ways of looking at CPET data. And at UCLA, we, you know, we're working on, you know, putting together sort of a more simplified approach to look at the data, really just focusing on 10 key variables. And just the four plots that we've been looking at. You know, this is to help quickly understand and quantify the degree of exercise impairment and attempt to, you know, in a more simple way, understand what the underlying etiology is, whether it is a cardiac limitation, ventilatory limitation, or if you do have a suggestion of pulmonary vascular disease, limiting exercise.

Dr. Cooper:
So those 10 key variables are really four maximal values, maximum work rate, maximum oxygen uptake, maximum heart rate, and maximum ventilation. Four important slopes, that is the relationship between oxygen uptake and work rate which we can call metabolic efficiency, the lower slope of the relationship between CO2 output and oxygen uptake, which represents aerobic muscle metabolism, so we can call that muscle respiratory coercion. It's close to 1, reflecting the fact that for typical laboratory-based cardiopulmonary exercise tests, we use glucose as the metabolic substrate. The third slope is the so-called chronotropic index, that's the relationship between heart rate and oxygen uptake. They are coupled mathematically by the Fick equation, and so we expect a linear relationship. And the fourth slope is the one you'll all be interested in, the ventilatory efficiency slope. But as Alex points out, it's important to consider that below that second threshold when carotid body stimulation uncouples, the relationship between ventilation CO2 output. And then finally there were the two thresholds that we illustrated on the previous slide.

So let's take a look at this first upper left-hand plot, and we can show you the key features here.

Dr. Sherman:
Yeah, so you have here on the Y axis on the left, the VO2 or the oxygen uptake. This is how you're going to quantify the aerobic capacity of the patient. This is what's used in determining if somebody has, quote unquote, normal or abnormal exercise capacity. On the Y axis on the right, you have the carbon dioxide output, which allows you to identify those thresholds. And then along the X axis, you have the increase in work rate over the course of the study. So this plot allows you to see whether or not the person's getting to their predicted maximum work rate, whether or not they had a good quality study or if they had any abnormalities in their metabolic efficiency. As we mentioned, the slope of the VO2 to work rate relationship should be approximately 10.

And then if it is abnormal, you know, what was the reason for this? Was there any evidence of impaired oxygen delivery? Perhaps a decrease in the slope partway through the study, which could potentially indicate the onset of cardiac ischemia or some sort of arrhythmia? Or perhaps they had significant mechanical inefficiency because they weren't, you know, using the bike properly, it wasn't set up properly, or they're using you know, a lot more of their body? Unlike peloton, they should not be standing up near the end of the study, in order to, you know, get to the end.

Dr. Cooper:
Well, we can use the same graph to, as Alex just said, to quantitate maximum oxygen uptake, and we can determine whether that is normal increased or decreased by comparison with the reference value. But we can also, based on the actual body weight of the patient, we can determine what we call their functional capacity, that is taking the maximum oxygen uptake in mils per kilogram per minute. And this is, you know, how a person can utilize that aerobic capacity in activities of daily living. There's a very useful compendium of physical activities that assigns a MET or oxygen uptake level for every imaginable human activity. And you can literally look at this chart. It's published by Ainsworth. And you can see for the functional capacity that you measured in your patient, what they would be capable of doing, and what they would predictably be unable to do. And we can use functional impairment classes based on the New York Heart Association. Anything greater than 25 mils per kilogram per minute is considered no functional impairment. And then we have degrees of mild, moderate, severe, or very severe functional impairment.

But bear in mind a couple of things, as people get older and their achievable maximum oxygen uptake falls, it may fall to a point that it crosses that 25 mils per kilogram per minute threshold, and a person develops functional impairment purely because of age. And that makes sense. We know that happens in real life.

The other situation to think about is obesity. If people are overweight, they're calculated VO2 max in mils per kilogram per minute is less, and they may fall into a category of functional impairment simply because they are overweight.

This same graph also enables us, at a glance, to see that the carbon dioxide output started to increase more steeply at some point, well before these lines crossed, and the R value was 1. But the fact that the CO2 output exceeds the oxygen uptake at the end of the test is a sure sign that there was anaerobiosis and lactate accumulation.

Dr. Sherman:
And I'll just add that, you know, I think one of the reasons that that is of particular importance is that when you have a patient doing a cardiopulmonary exercise test, and you're trying to identify their limitation to exercise, really, the data from this test is most useful in what we call a maximal study. So you need the patient to put forth enough effort so that you're able to identify, at maximum effort, what organ system is the one that is no longer able to keep up, where everything else is able to continue going on, what is the limitation there?

So, looking at the next plot, so this is looking at the carbon dioxide output to oxygen uptake relationship, or the V slope. You can see here on the left side, you have this linear relationship between the production of carbon dioxide and the uptake of oxygen. This represents, you know, predominantly aerobic metabolism where you're using up 1 mole of – or I guess you're producing a mole of CO2

for every mole of oxygen that you're taking up. And then you know, at a certain point, now you're producing more carbon dioxide than you are taking up oxygen, and that additional carbon dioxide is coming from lactic acid production, which is now playing a larger proportion in energy production than it was previously in order to pick up with demand.

And, you know, having an early metabolic threshold is a common finding in pulmonary arterial hypertension, for a variety of reasons, just like, you know, anybody deconditioning can certainly cause earlier reliance on anaerobic metabolism. Early cardiovascular disease can be a cause of these low normal metabolic thresholds. And then if you have a clearly early onset of anaerobic metabolism and reliance on that, it's often associated with either cardiovascular disease, which you'll see as a result of pulmonary arterial hypertension, or from muscular disease.

Dr. Cooper:
We're sometimes asked how do we tell the difference between deconditioning and early cardiovascular vascular disease, and in fact, they're one and the same thing really. The difference being that if we can safely provide a patient with an exercise training prescription, then the impairment that is due to deconditioning is potentially reversible. But the impairment that is due to cardiovascular disease is likely not. So I consider, you know, cardiovascular impairment has these two components, the reversible part, which is due to deconditioning, and the other part that is due to the disease process itself.

Now, going to the bottom left-hand plot, this is the plot of ventilation versus carbon dioxide output. There's some very important features of this. So we'll spend a few moments thinking about those. The lower slope is that ventilatory efficiency slope. Also on this plot, we can examine the maximum ventilation and see if it approaches the ventilator capacity that was either measured by an MVV maneuver, or predicted from FEV1. And now that inflection point indicates that there was sufficient effort and motivation on the part of the subject, that they developed sufficient lactic acidosis to overwhelm the bicarbonate buffering capacity, and experienced carotid body stimulation of ventilation.

Dr. Sherman:
So if there's one portion of the CPET data that you should be looking at in patients with pulmonary arterial hypertension or in patients where you're evaluating for pulmonary arterial hypertension, it is this graph. Because the slope of the minute ventilation to carbon dioxide production, or the VE/VCO2 slope, that changes based on one of two things, either it's going to be elevated if you have a reduction in the arterial carbon dioxide setpoint, or perhaps in the case of PAH, you have an increase in the fraction of deadspace. In other words, you are having less efficient release of carbon dioxide, requiring more movement of air to get rid of the same amount of carbon dioxide, which occurs in PAH.

Dr. Cooper:
It's a really important point that the slope is valuable. And there are two key determinants, as Alex has just said. And it's a matter of figuring out which is responsible. Of course, if we have an arterial blood gas, we'll know whether the setpoint for arterial PCO2 was normal or abnormal through this phase of the study. And if we have an arterial blood gas and a PaCO2, of course, we can calculate VD/VT. So that would be a level 2 CPET essentially.

Now, we can also throw in some additional plots, although we tend not to include these in our reports, our clinical reports, because we don't want to sort of overwhelm the referring physicians with too much data. But we can plot ventilatory equivalents, end-tidal gas partial pressures, breathing frequency, tidal volume, and the respiratory exchange ratio. These plots give us additional information on breathing pattern which is sometimes dysfunctional. And also the two right-hand plots the with the red box, offer a mechanism to verify the detection of the metabolic threshold.

Dr. Sherman:
And in the final plot here, you can see the heart rate on the Y axis compared to the oxygen uptake. And this allows you to see whether or not there's a cardiovascular limitation to exercise. So is the patient getting to their maximum predicted heart rate? And how much of that heart rate is being used as you go up in your oxygen uptake. And so, there are different - so the slope of this line is the chronotropic index. This is also highly related to another parameter; you may be familiar with the oxygen pulse, which is sort of the inverse of this, but it allows you to see whether or not, at somebody's peak exercise, whether or not they were limited by their heart rate, and at what VO2 did that occur at.

Dr. Cooper:
Now, just like the ventilatory efficiency slope, the chronotropic index is determined by two important variables. And these are cardiac stroke volume, a central variable, and arterial venous oxygen content difference, which can be thought of as the ability of the peripheral muscle to extract oxygen from the circulating blood. So you get a steeper chronotropic index if you have any disease that reduces cardiac stroke volume, and that might include pulmonary arterial hypertension. You have a steeper slope if you have muscular diseases, myopathies, or even deconditioning. That reduces the muscle's ability to extract oxygen from the circulating blood. And the

linearity again of this relationship is tight because it's mathematically determined by the Fick equation. And we can see, you know, various situations where there might be a bit an abrupt change in the slope of the chronotropic index that is due to the development of a tachydysrhythmia or myocardial ischemia with ventricular wall motion abnormalities and falls in stroke volume. We can see the effects of medications, we can see the effects of pacemaker malfunction. And so again, these are very valuable key variables.

Dr. Sherman:
So, you may not always have the information presented in that format. You know, the common way that CPET data is also presented is in the nine-plot panel. And there are quite a few different variables that can be found in patients with a pulmonary vascular limitation on cardiopulmonary exercise testing. And I'll just sort of run you through a few of them. Most of them we've actually already spoken about, but just presented in a different manner.

So these patients will often have aerobic limitation or a reduced peak oxygen uptake. They may or may not have a reduced metabolic efficiency, which would be represented by a reduced oxygen uptake to work rate slope. They may have an early reliance on anaerobic metabolism, which is shown by an early metabolic threshold. They may have an early plateau and low peak oxygen pulse, which would represent a stroke volume limitation, which in PAH is often due to limitations from the right ventricular stroke volume, leading to reductions in the overall stroke volume. You can have a high chronotropic index, which is another representation of the same information or similar. They will often have the high VE/VCO2 slope, which can also be displayed as a high nadir of the ventilator equivalence of CO2. If you have access to arterial blood gases, they'll often have arterial hypoxemia with a high A-a gradient. So as we mentioned before, they'll have a high deadspace fraction. And if you're looking at end-tidal CO2, they will often have a low end-tidal CO2 at the metabolic threshold, which can also represent their ventilatory inefficiency. And then importantly, they will not have a mechanical limitation, which could be an alternative explanation for their exercise limitation.

So CPET can be particularly useful in diagnosis of pulmonary vascular disease. You have sort of the classic, I guess, flow diagrams that walk you through the data allowing you to look at that. Some other groups have taken this information and actually applied different cutoffs looking at it to produce fairly useful algorithms to diagnose pulmonary vascular disease noninvasively. So this particular one looks at patients who have a low peak VO2, early metabolic threshold, a normal breathing reserve, and that high VE/VCO2, either slope or, in this case, value AT, anaerobic threshold, which they use 34 or greater than 33, which resulted in 88% specificity and 85% accuracy.

Also CPET has been used in looking at treatment response in pulmonary arterial hypertension. The GOODEYE trial actually looked at newly diagnosed patients with PAH and used CPET data to guide their therapy to determine whether they should actually have an increase from oral therapy up to parenteral therapy. You can see here, they started off with an ERA and then added PDE5 inhibitor, and then depending on their CPET parameters, determined whether they should have the addition of parenteral therapy. And the group that had their therapy guided by CPET, actually did have improvements in their brain natriuretic peptide, their peak VO2, and their pulmonary vascular resistance.

Finally, CPET is also particularly valuable in prognosis. There's been, you know, a lot of discussion around how do we determine prognosis in patients, especially in those who are termed intermediate risk? And this study was looking at patients who were deemed to have intermediate risk PAH and actually dichotomized them by peak VO2 and the stroke volume index, and they were actually able to separate out even patients who were all deemed to have intermediate risk PAH into patients who either were at high risk or low risk of having further progression of their disease.

Dr. Cooper:
So just to summarize, we hope that you enjoyed the video of the cardiopulmonary exercise test as a reasonable substitute for an actual live demonstration, but I think the key points were displayed. And then we went through various aspects of the data, the energetic response, the aerobic response, and identifying anaerobic metabolism, looking at the cardiovascular response, is there cardiovascular impairment, is the cardiovascular response pattern in terms of chronotropic index normal or abnormal. And finally, the ventilatory response; was that ventilatory limitation? And was the ventilator response pattern normal in terms of that ventilatory efficiency slope?

So I think with that, Alex and I will conclude.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, LLC. and is part of our MinuteCE curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.