[MUSIC PLAYING]

MICHAEL G. RISBANO: This is still a relatively new topic. There's been a lot of research out about this, but I think it's a growing field.

Overview of what we're going to be talking about during this next hour or so-- we're going to talk about defining post-acute sequelae of COVID-19. We're going to review a little bit of the epidemiology and symptoms. We're going to talk briefly-- one slide, a single slide-- on the pathophysiology. And then also, briefly, talk about, how do we evaluate these patients?

And then we're going to go into phenotype, and there's going to be, probably, some 30 slides of phenotype. I don't know if someone needs to be muted.

And then we're going to talk very briefly about management because there's not a lot of data out there on management. So throughout this talk, I'm going to be mentioning long COVID, maybe PASC-- different names for this disease state, but they all mean the same thing.

So this was an editorial that was written in the*New England Journal* in 2021 that talked about long COVID as, potentially, our next national health disaster. I don't know if that's hyperbole, but we're certainly seeing it in clinic, and we're seeing the echoes of the aftermath of people being infected with COVID, whether they've been in the ICU, or they were managed at home.

And one of the hard things about this disease state is that there's no objective tests or biomarkers. So there's no way that we could take a test, take blood work, do a specific study and say, hey, you have long COVID. So that makes it a little bit harder.

But, really, according to the CDC, long COVID is a range of symptoms that can last weeks or months that can happen to virtually anyone who's had COVID. Again, you could be majorly ill or minorly ill, and then you can wind up with some degree of symptoms downstream.

And part of what makes this disease state a little bit complicated, as well, is that multiple-- symptoms may affect multiple organ systems. It can occur in diverse patterns, and then there's this waxing, and waning, and worsening of symptoms that can occur after physical or mental activity. And that winds up being troublesome to a lot of patients because some days they feel good, then the next day, they may feel awful.

Typical timeline of patients who have post-acute COVID-- you get your initial infection where you get infected. There's a spike in the amount of viral replication that occurs, and that can occur anywhere from point of infection to at least three, four weeks beyond. Beyond three, four weeks, you really don't get active viral replication.

But at that point, you sort of pass over the acute effects of, COVID or acute COVID-19, and then you start getting into post-acute COVID-19. So after four weeks, people can have subacute, or ongoing, COVID. And, beyond that, 12 weeks or so, people can have chronic or post-COVID-19 syndrome, which is-- this is the portion that we're going to be focusing on for this talk.

I think it's helpful to categorize, what are the potential complications after having COVID? And I think there's three ways to think about this. Because when we see these patients in clinic, or maybe when you guys see these patients in clinic, you may have to think about, what's wrong with this patient who recently had COVID? How should we manage them?

And I think this may be a helpful framework. So initial infection-- patients can have direct cellular damage due to COVID-19. So examples of this may be that patients get pneumonia, then they have some degree of lung damage that results in fibrotic lung disease. And I just saw a patient like this earlier this week in clinic who was admitted-- hospitalized-- for about two weeks or so, sent home, was on a ton of oxygen, came back for another two weeks, and now has fibrotic lung disease.

His lung disease has gotten a little bit better, but he's still on oxygen and still having trouble getting around and shortness of breath. So this is direct damage to the lung. The same thing may occur with people who have pulmonary emboli. We know that this is a common complication, or fairly common complication, of having acute COVID-19 where people may get pulmonary emboli. Or there may be some other-- and organ damage that occurs-- let's say, the kidneys.

And then there's other things that can occur. Patients who get hospitalized for a prolonged period of time-- that can result in post-ICU care syndrome. So these are things that would happen to someone who got hospitalized for a prolonged period of time, let's say, due to a gram-negative sepsis, or they have the flu and they wound up in the ICU. They can get weak. They get myopathy. There could be cognitive brain dysfunction.

This is different than what's happening with direct cellular damage. This is someone who just happens to be hospitalized for a prolonged period of time, and there could be significant amounts of deconditioning, as well. Now, what we're going to be discussing here, for the most part, are symptoms that occur after recovery from acute illness. Again, you could be treated at home, or you could be treated in the hospital.

And this is really what post-acute COVID is, what long-haul COVID is, and it really relies on this interplay of inflammation and autoimmunity. There was recently a WHO definition that was put out in post-COVID-19 condition. This is people who may have confirmed or probable SARS-CoV-2 infection.

Now, the probable sometimes may not sit well with people. But early on in 2020, there weren't a lot of tests going around where people could test say, hey, I have COVID. They just had symptoms consistent with COVID, and it seems like they most likely had COVID. So they would fall into that category.

The other are people, nowadays, who are doing more testing at home. We have widely available tests. They may have swabbed themselves, tested positive. And some of these don't get reported, and these tests go right in the garbage, and they never take a picture or document that they had it. So we don't really know if patient has had COVID or not. Or some people just aren't testing at all.

So that's population that we're looking at. And these are people who have greater than three months from onset of their initial acute infection and lasts about two months in duration, not explained by an alternate diagnosis. And that's important. A lot of patients who come in to see us in clinic, we really have to look and rule out other etiologies of their exercise intolerance, shortness of breath, whatever they're coming in with.

We can't assume that it's just all post-COVID because they had COVID a year and a half ago. But I think we need to look and do our due diligence and see, why are they coming in with these complaints? Also, the complaints are usually going to be new. They've never had them before.

They didn't have shortness of breath. It's brand new. Or shortness of breath that they developed during acute COVID and persisted. And, again, these symptoms can fluctuate or relapse.

So just a little information about the types of symptoms that people will come in with. There was this study that came out by Davis in 2021 that was an international, longitudinal, online study that followed people for approximately seven months and the impact of their symptoms. And they were asked questions, probably about monthly or so.

And this was, again, an online survey. So they weren't seen by physicians. They weren't vetted. But they just got online, and these surveys were given out to COVID-19 support groups.

So they got a large number of individuals in the study-- about 3,700 individuals. And, again, those who were suspected-- they didn't have a confirmed test-- about 2,700. And the confirmed was about 1,000.

Out of that population, 78%, 79% were female. 85% were white, and then 80% fell into the age of 30 to 60 years. The most symptoms that these patients typically had were fatigue, post-exertional malaise-- meaning that you went and did something and then, afterwards, you got tired or fatigued. So I usually say, you pay the price for doing something-- or brain fog. Those are the top three.

But there's also the sense that there's a lot of neurologic issues, musculoskeletal issues, shortness of breath, some pulmonary issues, and then even some cardiac issues where there's palpitations and tachycardia. And we see the gamut of a lot of this when patients come to see us in clinic.

Now, how do these symptoms evolve over time? Now, these patients were asked questionnaires over the course of seven months. And patients who had severe or very severe-- in the orange and in the red-- they tended to get better over time. But, interestingly, patients who had moderate, mild, and very mild symptoms, they tended to get worse over time, which is interesting.

I don't know exactly why this happens. I don't know if this is some degree of anxiety that may be contributing to this, or it's the disease process itself. But some people tended to get worse over time.

And those who got better, those who recovered within 90 days, they tended to get better, and their symptoms went away. Patients who don't get better than 90 days-- within that three-month period-- they tend to have persistent symptoms and last. Now, at least 85%, 86% of patients who were in the study had some degree of relapse. So at some point during this questionnaire process they had either symptoms that were triggered by exercise, mental or physical activity, or stress.

Interestingly-- and we've seen this in clinic-- here, 1,700 respondents, or 45%, had a reduced work schedule. They couldn't go back to work the same way that they did prior to having these groups of symptoms. And then 839, or 22%, of patients who were questioned here were not working at the time of their survey due to illness.

So there's a significant burden to this illness that occurs and will impact the job market, will impact people returning to work. And if you think about the number of infections that are out there, there's a proportion of these people that may be impaired. And it's something to watch out for.

So if you look at the COVID-19 infections, this was last updated the last time I gave the talk sometime in April. I didn't update the numbers because they're probably not that much different. But in the United States, about 80 million, almost 81 million, probably, now, patients who have had-- people who have had COVID-19 infection.

Pennsylvania-- 2.8 million, Allegheny County-- 265,000, 266,000, and Lycoming County-- about 28,000. If you think that approximately 10% to 30% of people who've had COVID-19 infections will go on to develop long COVID, those are pretty significant numbers.

So if you say the upper limit of this being-- let me see. The upper limit being 24 million, it's quite a large number. Same thing with Pennsylvania-- 840,000. Allegheny County-- 79,000. Lycoming County-- about 8,000.

And even if you look at the lower limit what could be expected, about 10%, still, there's 8 million people in the United States who are impaired. 280,000 in Pennsylvania. Allegheny-- 200-- sorry-- 26,000, and Lycoming, about almost 3,000. The average age of people who develop long COVID are somewhere in their 40s. So this definitely impacts the job market, people returning to work even now.

So pathophysiology-- this is the one slide that I mentioned that I was going to talk about. I think it's helpful to set up what we're looking for when patients come in to see us in clinic. So there's the acute infection. So this is the host cell. This is the virus, the SARS-CoV-2 virus that gets brought into the cell by the ACE2 receptor.

So there's definitely some direct cytotoxic effect, like we mentioned, that can happen in the lungs. There's a dysregulation that can occur in the renin-angiotensin system. This mediates some tissue injury, remodeling, inflammation, vasoconstriction, vascular permeability. Then this could go on to affect endothelial cells and cause some thromboinflammation.

And when I first got interested in post-acute COVID, there was some word going around in 2020 in some early paper saying that there is probably some degree of pulmonary vascular disease that may be associated or patients who have had pulmonary embolism. So then you think, OK, could these people develop chronic pulmonary emboli?

So early on in 2020, probably in the spring, I wrote a grant trying to look at what happens to people who may develop long-term consequences of having had COVID. Of course, it didn't get funded.

And then I went around, running around to different meetings saying, hey, send me these patients if they've had COVID-- thinking there'd only probably be a handful of them-- sending them to me just to study and see what could be physiologically wrong with these patients. And that turned out to be quite an undertaking.

So, finally, there can be some immune response related to COVID-19, as well, that there's some degree of hyperactive immunity and then cytokine release, and then this may develop into some autoimmunity, as well. So you often wonder, what are the risk factors for developing post-acute COVID? There's a little bit of data out there. I think we're going to need a little bit more time to determine what the risk factors are.

But there is a group of people led by Sue and colleagues who looked at about 309 patients aged 18 to 89. Most were hospitalized, and a small amount were outpatients.

And what they did was they did this multi-omics longitudinal investigation where they looked at people's blood-- so they took patients genomes. They looked at metabolomics, as well-- the study of patients metabolism. And they drew blood at three different time points, one of the time-- and they also sent questionnaires out, as well, to correlate with this.

The first time point was when they were initially diagnosed, so that's why there are so many hospitalized patients. So they came into the hospital. They got diagnosed. They got blood work then if they enrolled in the study.

Time 2 was about one to two weeks after the initial infection, still in the acute phase. They sent out questionnaires. They got blood work. And then, finally, time 3 was about two to three months post-onset of COVID-19.

So what they looked at was, there was four factors that they found that they thought were associated with post-acute COVID or long COVID. One was pre-existing diabetes-- so type 2 diabetes. The other is high levels of SARS-CoV-2 RNA levels at time point 1.

So if you really had a lot of circulating RNA, if you were really infected by COVID-19, you tended to have longer-lasting effects. And we sort of thought that maybe this is the case-- that how sick people got in the hospital, maybe they just had a really high viral load. So this may translate to long-term effects, as well.

Also, what they noticed was that there are some reactivation in the Epstein-Barr viremia at time point 1. So this may have stirred up, or stirred the pot, in terms of patients' inflammation and may have reactivated a prior mononucleosis. And then, finally, there's some antibodies that popped up later on at time point 3.

And what was interesting with these autoantibodies is that they're mature. They're not brand new. So they're able to determine that these were possibly preexisting things that somehow got stirred up after having infection.

Now, the issue I have with this study is a couple of things-- is the timing in which that they did the study. So time point 3 is within two to three months. So technically it's not past. It's not, technically, long COVID. Really long COVID is defined as what happens after three months. But this gives us a little bit of insight.

And these patients weren't actually vetted. They were just given questionnaires, and they said, OK, do you have these type of symptoms? And they reported the symptoms. So really not sure to what degree these patients fall into the category of having long COVID. But this provides a little bit of insight into what we're dealing with downstream.

So our workup of post-acute COVID is pretty multifaceted. We'll get patients who come into clinic. And there's a few of us pulmonary providers-- I have one physician assistant, as well-- who's been seeing the bulk of these patients.

And they get referred after they have a COVID-19 test. We actually prefer that they would have a positive COVID-19 test, but we won't turn anyone away who self-reports or says, hey, I had COVID. We'll still see them in clinic.

We also get some referrals for people who've had a reaction to the COVID vaccine. That's not for us, so, usually, we'll refer those patients over to allergy immunology. This is really for people who have had post-acute COVID. And we're not a clinic who just fills out disability paperwork, either, so i they're just coming in for that, that's really not our role. We'll punt that back to primary care physicians.

So, really, what this is just an evaluation of symptoms related to having COVID-19. And what we typically will do is what you normally would do in any clinic. We'll do a history, a physical examination. We'll figure out why they're coming in.

And, really, since we're the pulmonary clinic, we focus quite a bit-- or at least I do-- on exercise capacity, exercise limitation. Is there any issues with post-exertional malaise, fatigue, tachycardia-- anything that limits them getting around. And that's, preferentially, what I've been looking at.

And we'll do a standard workup, so pulmonary function tests, echocardiogram, six-minute walk, NT-proBNP, and then we'll send off some blood work. Initially, we would send this off on almost everyone who walked in through the door. But I think someone who comes in with a loss of sense of smell and no cardiopulmonary issues is probably not worth getting all of this data on them if they're really not exercise-limited or loss of exercise capacity. So we'll selectively order some of these tests.

Now, if someone comes in and they have what sounds like pulmonary hypertension-- or they sound like they have chronic-- or pulmonary embolism, we'll send a D-dimer. And if that's positive, we'll send them for a CAT scan. Or if there's a concern that there is, maybe, chronic PE, then we send them for a VQ scan, which is something that we typically do with patients in the pulmonary hypertension world. VQ scans are better at picking out chronic pulmonary embolism.

Now, if someone comes in with tachycardia, dizziness, brain fog, fatigue, we may do just a quick screening for POTS-- Postural Orthostatic Tachycardia Syndrome where we'll just have them stand up for five minutes or so and see if their heart rate goes up. There's additional testing that we could do for that.

Now, if patients come in and they say, look, I've had persistent fevers or other issues, we may send them out to another physician. Now, we're not the clinic that handles everything. We're the depot to initially receive some of these patients and then send them out to our physician collaborators or collaborators for post-COVID. Because we think that this should really be a multidisciplinary clinic, so we'll send patients out for other things.

So if there's any cardiac issues, cardiac ischemia, worry about cardiomyopathy, we'll send those patients to cardiology. Certainly, neurocognitive testing we'll send out for. Psychiatry or social work, we'll send that out, as well.

All patients get asked if they want to take part in research, and we will enroll them into our research program. But we also have-- if anything turns up where the studies are unrevealing or their symptoms are disproportionate to resting studies-- meaning that if they have problems with exercise capacity or shortness of breath, we'll send them for additional testing, such as invasive cardiopulmonary exercise tests.

And then from there, we'll send them off for dysautonomia testing depending on what we find, cardiac MRI, again, VQ scan. And a lot of these patients wind up going to cardiac or pulmonary rehab or physical therapy. But, again, one of the important things that we do is we need to rule out other disease states. Because, sometimes, people can have two things at once.

So I'm going to spend a lot of time talking about phenotyping, probably the rest of the lecture, in post-acute COVID, so long COVID. So this is my professional disclaimer that when we want to talk about phenotyping or describing who these patients are, we're talking about a specific type of complaint and specific population.

So I am a pulmonologist. I'm the Director of the Invasive Cardiopulmonary Exercise Testing Program. I'm a pulmonary hypertension doctor, and I'm interested in cardiopulmonary and exercise physiology. I'm not a neurologist or psychiatrist. So a lot of the neuro and psych issues, we're not going to really address in terms of how we're going to phenotype these patients. We're going to be really focused on the cardiovascular and pulmonary issues.

So, again, PASC is a constellation of symptoms that persist three months after acute infection. And it can affect different organs-- cardiovascular, pulmonary, neurologic, psychologic, constitutional. And, really, if you look at what the NIH wrote about PASC is that it's a population that may represent a heterogeneous group of patients experiencing symptoms related to different biological mechanisms representing different subphenotypes of PASC.

So, essentially, what that means is, everyone's going to wind up being different. Is there a way that we could categorize these people in order to understand potentially similar biologic mechanisms that's driving symptoms? And if we could identify those biologic mechanisms, then we could figure out a way to treat them.

And phenotyping, in case people don't understand phenotype, it's a sum of an organism's observable characteristics that are influenced by genotype, epigenetic modifications, environmental and lifestyle factors. So, essentially, what that means is it's who you are and what's external to you that modifies what you look like or how your health is behaving.

So we're going to talk a little bit-- or a lot-- about physiologic studies in post-acute COVID patients. So just a little intro on what cardiopulmonary exercise testing is, this is something that's familiar to cardiologists. It's familiar to pulmonologists.

However, we often-- people who don't do this every day-- learned it during medical school and then subsequently forgot it as soon as they took the test. So this, we'll talk about very-- sort give an introduction. So cardiopulmonary exercise testing is a noninvasive measure of resting and exercise measurements of metabolic rates to identify organ systems that are limiting exercise capacity.

So, essentially, what we do is we put someone on a treadmill or a bicycle, which is what we use, and we could measure a number of parameters. We can measure breathing parameters, heart rate, blood pressure-- all different things that consist of people's exercise physiology and identify where the limitation may be. And I got into this field primarily through pulmonary hypertension, pulmonary vascular disease where we were doing a lot of tests on patients at rest.

However, patients would come in and say, hey, I get short of breath when I do something. Yet we do a resting echo. We do pulmonary function tests that are at rest. We do CAT scans that are at rest. But, yet, everyone comes in and says, we're short of breath when I do-- I'm short of breath when I do something.

That didn't really jibe well for me. So, really, I think a great way to identify what patients symptoms are with exercise is, you make them exercise. And we could find a number of limitations. And there's limitations to how-- what we could use this test for. But we could identify cardiac limitation, pulmonary limitation, ventilatory limitation, pulmonary vascular limitation. We could identify deconditioning or poor effort.

And, really, what identifies whether someone has a decent or poor exercise capacity is this thing called the VO2 at peak exercise. The VO2 at peak exercise is someone's oxygen consumption. Normal number for that is somewhere between 80% to 84%-- so the higher the better.

So if you consume more oxygen, we could measure what you're breathing in. We can measure what you're breathing out that mouthpiece, and we could identify what the difference is. And we could see what it is at rest and then peak exercise. From that information, we could tell whether you do a good job during the exercise test or you have normal exercise capacity.

In some prior CPET studies in post-acute COVID that have occurred-- I initially had these in great detail, and then I realized, that probably wasn't what everyone needed. The bottom line of these initial studies performed 90 days after infection-- these were in Italy, Norway, and France-- was that they identified, primarily, deconditioning as the main source of exercise limitation.

Again, this was in cardiopulmonary exercise tests. Although they did notice that there was a ventilatory limitation that was identified, there was a number of patients who had some residual lung disease on CAT scan-- about 57% to 63%. But there is really no lung limitation that really said that their lungs are the issue.

They did note a large proportion of these patients had an exaggerated ventilatory response, meaning that they huffed and puffed. They really breathed fast and heavy-- deep volumes and fast respiratory rate. And we'll go into that a little bit later.

The other thing that these groups noticed, or at least the group from Italy noticed, was that the severity of disease did not impact COVID-19 survivors-- exercise capacity in COVID-19 survivors. So what that meant was that people who were limited, who had mild disease, were similar to people who were hospitalized in the ICU and had severe disease.

So, really, anything goes for having COVID. So you can be managed at home. You can be managed in the ICU, and there may be equal rates of long-term effects.

A recent French study called the COVulnerability study, where they looked at 105 patients. They performed CPET. They looked at skeletal muscle mass evaluated by imaging-- muscle imaging-- not biopsy. They noticed that 35% of patients had reduced exercise capacity.

And of those patients who had a reduced exercise capacity, almost 40% had sarcopenia, which more or less means that they've had either deconditioning or loss of muscle mass. So there's something driving this, again, could be related to deconditioning-- sorry about the email-- could be related to deconditioning or could be related to just loss of muscle mass. Sorry.

Next-- so a couple of caveats to the cardiopulmonary exercise testing is, one, we don't know what patient's premorbid or baseline values are. We know that a lot of these patients said, I was completely normal weeks ago, months ago, but, now, I get short of breath when I do something. We also don't understand that if someone would have had-- because we don't have the data.

So let's say, months ago, prior to having COVID, if we would have done one of these CPET studies that they had a VO2 peak of 104%, which is very normal. And they dropped down to 84% which, again, is above the lower limit of normal. Does that mean anything?

So if you have this 20-point drop but yet your study is still normal, but you're coming in with exercise problems, does that mean anything? Well, again, we don't have these premorbid values. And then if someone has a normal VO2 peak and they're symptomatic, what does that mean? We don't know.

And I don't know if we're going to be able to answer some of these questions because this is missing data. But additional questions that we can have out of this is, what's the physiology beyond three-month duration of having had COVID? So what does it look like someone who's had post-COVID for 12 months? Is that going to be different than these initial European studies?

And then is there any testing beyond CPET alone? Is there any physiologic testing that we could do? Well, that's a setup. Of course it is. There is invasive cardiopulmonary exercise test. And this is a picture from my lab.

This is super Dave. He's one of our exercise physiologists. And this is one of our CPET studies. These are the blood gas tubes. We draw some blood gases. I'll show you.

So what's invasive cardiopulmonary exercise tests? Essentially, what we do is we do a breath-by-breath analysis. We have that mouthpiece, just like regular CPET. We put in a right heart catheter. We'll measure number of different pulmonary artery, pulmonary vascular parameters.

There's a ton of numbers that we can generate, as well as calculate. We measure pressures at the right atrium, the right ventricle, the pulmonary artery all simultaneously. And we measure cardiac output, as well.

We have the radial artery line that gets put in the non-dominant hand, and then we make patients exercise. And these catheters give us a number of different information-- a lot of information. We'll measure pressures. We'll measure blood gases.

We can measure cardiac output through what we call the true Fick equation. So it's not an estimate. We actually measure it. And we can get resting hemodynamics, and then we'll do exercise values and then get peak exercise hemodynamics, as well.

So it's a test that lasts about an hour and a half. We do it at Shady Side. We used to do at Presby. Now, we've moved to Shady Side, and it's been going well.

So this is-- I don't know if the video is going to work. This is what one of the studies looks like. It may slow down and then stop. When I talk about this, people are like, oh, it sounds barbaric. You're putting catheters in people, and you're going to make them ride a bike.

There we go. It's kind of glitchy. But it's not a big deal. I mean, I've put in thousands of right heart catheters. It's not a big issue. The radial artery line sometimes can be a little tricky to get, but I've gotten that down to a science. It's not really difficult to do much of this study.

But as you can tell, the room has not burst into flames. The patient is not on fire. It's not the end of the world to have to do one of these studies. And people tolerate them pretty well.

And, usually, I'll ask them what was the worst part of the study? And they'll complain, the bike seat was bad. I couldn't-- the mouthpiece was annoying me. I didn't like it. It made my jaw tired.

Or they had to lay on the cath lab table for half an hour or so, 40 minutes, and that hurt their back. Or the lidocaine hurt when you were numbing me up. So if I get that sort of feedback, then I know this isn't the worst test in the world.

But we'll do these studies for clinical purposes. We'll do it for research purposes. And we get a number of diagnoses. We can measure, again, cardiac issues, whether someone has exercise pulmonary hypertension. We can see if they have regular pulmonary hypertension.

We can see if there's exercise pulmonary hypertension where we wedge the pulmonary artery catheter and the wedge pressure goes up. We can identify something called preload insufficiency, which we'll talk about shortly, decrease peripheral oxygen extraction, which we'll talk about, ventilatory limitation, deconditioning, poor effort. Those are the main clusters of things that we'll identify.

This is a couple of pictures that showed up-- magically-- in the*Pittsburgh Post Gazette* when we did a study on one of our patients who had symptoms of long COVID. Turned out he had heart failure, but he gave his consent for all of this. We got a nice write up in the newspaper.

So there is a group that beat us to the publication on doing invasive CPET in patients who have had post-COVID. It's a group out of Boston combined with Yale. I know these guys. They published about 10 patients who had long COVID, and they compared them to 10, extremely fit, normal, symptomatic controls.

And they compared the groups, and they found that there was no difference between these two selected populations in terms of age. Most were females. And they studied their COVID patients, post-COVID patients, 11 months after initial infection. Most of these patients were outpatient.

These patients had a reduced VO2 max. They had reduced exercise capacity compared to a very, very, very fit population. There was no difference in their cardiac output, meaning, heart squeeze was normal between the two. There's no lung limitation, no ventilatory limitation, and there was no evidence of pulmonary hypertension.

So, as I mentioned, I initially got into this because I thought there would be some pulmonary hypertension. They didn't note any pulmonary hypertension in their population. But what they did note was something called the systemic extraction ratio, which is a measure of how oxygen is consumed in the periphery was different between these two populations.

So what does that mean? So when we do these CPET studies, we can measure what your oxygen content is at the level of the radial artery. So we do that by measuring your saturation off the blood gas. We know what your hemoglobin is, and then we do an equation to identify that. And normal is about 20.

The level of the pulmonary artery catheter-- we measure what the venous blood is the same way. And that's usually about 6, 7. But if it comes back where it's too high or elevated, that means that blood is going out normally-- normal oxygen content-- but is returning with too high oxygen content.

What that means is that there's probably something the periphery that's causing a decreased extraction, so you're not extracting oxygen the way you should. And this SER cannulation looks at the ratio of what your oxygen extraction is. And if it's less than 80%, it's abnormal. So in this case, this example is 57%, which is low.

So you say, OK, blood is going out fine but coming out too high-oxygenated. There's a problem with the skeletal muscle. There's a problem with something going on with how you're extracting. And for pulmonologists, most things-- our normals are 80% because we only want to remember one number.

So who cares? Well, if you look at the VO2 max, like I mentioned-- what the exercise capacity is, that's our number. This is the Fick equation, so this is how we can measure cardiac output. But this CavO2 how much oxygen is extracted-- is a key component of this equation.

So if the VO2 is low, it may be that the CavO2 is low. Then you say, OK, why would the CavO2 be low? There's a number of different reasons, and it boils down to three primary reasons.

One is there could be a dysfunction in the skeletal muscle at the level of the mitochondrion. Now, that's usually not something that's inborn-- well, at least in this case, in post-COVID, it's not something that's inborn. But maybe it's something that's acquired. Maybe there's some degree of mitochondrial poisoning that occurs after having had COVID. We don't have any great evidence of that yet.

There can be hyperventilation, and we know that most patients who've had COVID have a robust hyperventilatory response. So this causes a left shift of the oxyhemoglobin dissociation curve. So some of this may just be hyperventilation mediated.

Or it's possible that there may be some limb muscle microcirculatory dysregulation, meaning, are the blood vessels in the legs abnormal that you can't get oxygen to where it needs to go? Is there a diffusion problem? That's certainly possible. I mean, any one of these three can be possible in post-COVID.

So this leads me to my data that's all unpublished. We're currently refining the manuscript. I'm hoping to send this out soon to probably get rejected and then sent to another journal. But we'll see. So the title of this-- at least I think it's going to be-- "Invasive Cardiopulmonary Exercise Testing Defines Distinct Physiologic-- should be Endotypes or Phenotypes-- in Post-Acute COVID."

So what we did was we took a whole bunch of patients who came to me for invasive cardiopulmonary exercise tests who had persistent symptoms-- so shortness of breath, exercise intolerance. We had about 39 patients that we performed invasive CPET on. Seven had to be excluded. Two had submaximal studies, so we can't really use that.

One patient refused the study. The second she came into the cath lab, we had her lay down. We didn't even do anything. She sat bolt upright, looked around, and said, I'm not doing this, and then left.

We had two patients who got referred prior to COVID-19 infection. So they were on the list to have invasive CPET for other medical issues, then they got COVID. I didn't think that that was kosher to include those two patients.

And then we had one patient who had incomplete data. Happened to have an air leak with her CPET mouthpiece during the study. So we can't use that. That got tossed. She did a really great study, too, but that got tossed. And then we had one patient with preexisting heart failure. So those people got excluded.

Now, out of the 32 remaining subjects, we had 10 who were completely normal. Now, these, mind you, are patients who came in with some degree of dyspnea-- that's shortness of breath-- but, yet, they had a normal study. I'm going to posit that even though they had normal study, they may not be entirely normal. I'll show you some information.

There's also 22 patients who had to reduce VO2 peak-- less than 80% VO2. And we broke them down and phenotyped them. And this is different than what the Singh study had provided where they just said, hey, these are post-COVID, and these are normal, so let's compare the two and see what happens. But, here, we actually broke them down and said, who are these people?

Primarily, I've always thought that this was going to be a heterogeneous population. It seems like the NIH and even the WHO think that this is a heterogeneous population. And, lo and behold, it's heterogeneous. So we found six patients who have something called preload insufficiency that I'll describe on the next slide.

Four patients had this preload insufficiency but also this decreased peripheral oxygen extraction that I just talked about. Four patients had decreased peripheral oxygen extraction alone. One patient had chronic pulmonary thromboembolic disease, so meaning, they didn't have exercise pulmonary hypertension. They had an acute clot. Turned out on a VQ scan to be chronic, months down the road, and had some gas exchange abnormalities.

I thought we were going to find more than that. And some of my friends who do chronic PE work have said they've seen a lot of people post-PE. So far, we've only seen one. And a good number of these patients have had VQ scans after and really didn't show anything.

Two patients had exercise pulmonary hypertension. I won't go into the details on how to define that, but when people exercise, they go from normal pressures at rest to high pressures at the level of the pulmonary artery-- high resistance. And that's called exercise pulmonary hypertension. Four people had deconditioning, and one person, for a number of different reasons, couldn't do the exercise portion with the heart catheter in place because she would get vasovagal, so we didn't do that.

So what's this preload insufficiency? The definition of this-- again, it's the Systrom group out of Brigham and Women's who initially defined this years ago-- where patients had some exercise limitation. They had a low VO2 max. They had a low right atrial pressure. They had a low cardiac output and normal left ventricular function.

Different reasons that this can happen in which, also, interestingly, can happen in post-COVID, as well, where there's some degree of dysautonomia, adrenal insufficiency-- patients who have had COVID have been exposed to steroids-- volume depletion, POTS, medications, pre-existing illness, and then something called ME/CFS. And there's been this overlap between PASC and ME/CFS.

So this is the myalgic encephalomyelitis chronic fatigue syndrome. So there's an estimate that maybe somewhere between 10% to 12% of all COVID patients could develop this ME/CFS. And cardinal symptoms for this are post-exertional malaise.

So when patients come in and say, ah, I do something, I get really tired and fatigued after I do it. I went out and mowed the lawn, and then I paid for it for the next two days. Maybe that's what this is post-COVID. And there's an association with preload insufficiency and ME/CFS, so this is interesting.

Now, and sort of a related topic, looking at patients who have COVID and tend to huff and puff. Now, this has been described in the European literature, even that Singh paper, David Systrom paper that I highlighted with the 10 patients also noted that there's an increased incidence of patients you tend to have this hyperventilatory, exaggerated hyperventilatory response.

Now, they fall into this category up here in this box here where we look at what we call VEVCO2. Now, cardiologist, pulmonologists will know this. This is a measure of something that we look at called ventilatory efficiency.

And what that means is-- the VE-- how fast or how deep you're breathing and how you're handling your carbon dioxide. Now, if you tend to have a high VEVCO2, or two which is defined as a level that's greater than 31-- normal is 21 to 31-- you are not breathing efficiently. So you're really huffing and puffing to handle your carbon dioxide.

Additionally, hypocapnia-- so PACO2 that's lower than 35, fall into this category, you can have increased chemosensitivity. Now, the opposite of this-- straight and up-- is dead space. So these are people who have chronic blood clots, pulmonary vascular disease.

But we identified a population that had this increased chemosensitivity. And what's different from the Systrom/Singh article is that we have groups of people who fall into specific diagnostic categories. So one is, there's one out of two people who had exercise PH, who had chemo sensitivity.

There are, I believe, four patients who had preload insufficiency, plus one who had a combined preload insufficient and decreased oxygen extraction who fell into this high chemosensitivity population. One patient out of the decreased O2 extraction fell into this chemosensitivity. I believe one deconditioning and one out of one CTED patients.

But, also, what was interesting, there was 6 out of the 10 normal patients had increased chemosensitivity, which is odd. You think, well, they're normal. They should behave normally. But these are people who tend to huff and puff.

So you go, OK, what's chemosensitivity? Chemosensitivity is the ability of the brain to actually detect carbon dioxide levels and then alter your level of breathing to regulate these carbon dioxide levels in the blood. So it's possible-- again, not a neurologist, but somehow we come back to this-- that there may be something going on with how COVID affects the brain that may reset their carbon dioxide levels and make people breathe differently.

It turns out that with this VEVCO2, this ventilatory inefficiency-- these people have fallen to this box-- they tend to feel more short-- or they tend to have shortness of breath. This correlates with more shortness of breath.

So a couple of other things that can cause high levels of breathing. So there's chemosensitivity, certainly. But there's lung problems that can cause it. So if there's a mechanical issue, some lung issue-- COPD, emphysema-- people may tend to huff and puff more. This is this minute ventilation-- so how fast how deep you're breathing. We didn't really note that.

But there is some degree of deconditioning. There's metabolic demand. There's deconditioning, skeletal muscle dysfunction, which manifests as early anaerobic threshold. That can contribute to people huffing and puffing when they breathe.

The other thing that we note is is that if there's metabolic acidosis. So what I did was I split patients up according to people who have high chemosensitivity and normal chemosensitivity. And we saw that patients who had more metabolic acidosis were in the high chemosensitivity group compared to the normal chemosensitivity. So maybe these people are academic for some reason or another.

It's not a lactic acidosis because there wasn't a difference during exercise. Patients who had high chemosensitivity tended to have lower-- relatively lower-- hemoglobin levels. They weren't anemic, but they were lower compared to people who had normal chemosensitivity, so maybe that's driving some degree of their will to breathe faster.

We also see that there could be other reasons, such as baroreceptors triggering some higher levels of breathing. And this may be a little hard to see, but, here, there are patients-- we looked at the change in right atrial pressure. So people who had low right atrial pressure, that preload phenotype, correlated with how fast people breathed or how much people's minute ventilation changed during exercise.

And there was a statistically significant correlation-- inverse correlation. So what that means is that the lower your pressures are, the higher your minute ventilation was. And then, finally, the other thing that we saw, too, was the change in right atrial pressure directly correlated with PACO2, or carbon dioxide levels in the blood.

And what that means is is that the lower your right atrial pressures are, the lower your carbon dioxide levels were-- or changed. And then, finally-- and no one has shown this before-- there may be some degree of ventilation perfusion inequity. And if we compare the increased chemosensitivity to normal chemosensitivity, there may be more VQ inequity in the increased chemo sensitivity population.

So final slide-- I'll give us a little bit of time for questions-- or final two slides. Treatment-- there's no specific treatments for PASC. There's nothing-- there may be some groups out there out in California that will tell you, hey, your IL-6 is high, or your MMC, or whatever-- CCR5 is elevated. You should take this type of drug, or you should take this antiviral drug that will help clear the virus from the system.

I'm not entirely clear that that's the way to go because what we find in blood doesn't always necessarily correlate with symptoms. They haven't published any studies to show this, so I'm not clear. There's other things-- people who come in with neuro and psychiatric phenotypes that we can send them for cognitive behavioral therapy. We could send people for smell therapy. We've sent people for ENT evaluation for that, as well.

But, really, what I think is worth looking at is saying, hey, there is a physiologic phenotype that we could identify. If we could diagnose you with this physiologic phenotype and you have a low oxygen consumption, low exercise capacity, what can we do to modify that? What can we do to treat that? Now, if someone comes in and they have exercise pulmonary hypertension, we can always start some pulmonary vasodilators.

I have paper that's been done years ago that showed that people's hemodynamics improve if we put you on something like Sildenafil, Tadalafil, Ambrisentan. So we know that pulmonary vasodilators will make you better. Does this apply to everyone? No, because if we gave this pulmonary vasodilator someone had preload insufficiency, that's not going to treat their underlying issue and may actually make them worse.

So someone who has preload insufficiency, you could try a number of different things-- volume, salt, exercise. Everyone's going to get exercise therapy, anyway, because there could always be an underlying component of deconditioning. But there's been a recent paper out by the Systrom group who noted that Mestinon, which served as a venoconstrictor, may actually improve right atrial pressure, oxygen consumption, cardiac output.

Now, patients who have decreased peripheral O2 extraction phenotype-- really, not a lot to treat or to manage, here, that I know of. Usually, we'll send these patients for exercise training. Deconditioning-- again, exercise training. Patients who have chronic PE-- that's a whole other story.

Obviously, they would get anticoagulation. They could do balloon pulmonary angioplasty, which we do at Presby. Or you get sent for surgery if you have chronic PE that's hemodynamically significant.

And then for increased chemosensitivity, maybe exercise training-- treat the underlying driver of this. And then patients who may have a relative anemia, or relatively low hemoglobin, it may be worth treating them with iron. Do I have any data for that? No. But if you identify that there's a low hemoglobin level in this population, then a little bit of iron may not hurt.

Conclusions-- PASC is heterogeneous. Pathophysiology is likely to be multifactorial. We have some signals that there are some deconditioning, preload insufficiency, exercise, PH, reduced peripheral oxygen extraction. And increased chemosensitivity-- this high VEVCO2, may drive some patients sense of dyspnea.

Finally, I'd like to thank people who have helped me out with this post-COVID recovery clinic-- Division Chief Alison Morris, Danny Dunlap, Corinne, Carl, Karla, who have been seeing a lot of these patients throughout the past couple of years. And then members of the invasive or advanced cardiopulmonary exercise testing program, my two exercise physiologists, Rob and super Dave, my nurse Chris, and one of the study coordinators, Yasmin.

Whoops, back-up slides. That's it. Thank you.