CDC's 20th ME/CFS Stakeholder Engagement and Communication (SEC) Call

December 6, 2022

3:00 p.m. ET

Christine Pearson: Good afternoon, everyone. Welcome to today's ME/CFS Stakeholder Engagement and Communications call, which we call S-E-C or "SEC." My name is Christine Pearson, and I'm the Associate Director for Communications in the division where the ME/CFS program is located within CDC.

As you may know, we host these S-E-C calls twice a year, as part of our regular outreach and communications activities to provide information for people with ME/CFS as well as their loved ones, clinicians, and anyone else interested in the disease.

Our goals during these calls are to provide updates on the work of CDC's ME/CFS Program and for you to hear from external experts in the field. Today, we'll hear program updates from Dr. Elizabeth Unger, the branch chief of CDC's Chronic Viral Diseases Branch, and from a new member of our ME/CFS team, Dr. Jennifer Cope. Then, we'll turn it over to our guest speaker from Brigham and Women's Hospital and Harvard Medical School, Dr. David Systrom.

After Dr. Systrom's presentation, we'll have a Q&A session. During today's Q&A, you will have the opportunity to ask questions through the webinar platform or by phone if that's how you joined today. We'll provide more information on that when we get to the Q&A session. Before we start, I'd like to remind everyone the call is open to the public, so please consider that before sharing personal information. We're also recording this call. Please disconnect now if you have any concerns about recording. We will post the transcript and video as soon as possible after the call is complete. Now we'll turn it over to Dr. Unger to start the program.

I did want to mention one last thing, which is if you would like to access the closed captioning or to read along with the text of the program update, the links for both of those are posted in the chat box.

Now, welcome, Dr. Unger.

Dr. Elizabeth Unger: Thank you, Christine, for that introduction. And welcome everybody to the 20th SEC call. I would like to begin with a celebration and recognition of the hours and years of work of many ME/CFS patient organizations and advocates that led to the update of the ICD-10-CM codes on October 1, 2022, to include a specific code for myalgic encephalomyelitis/chronic fatigue syndrome. Code G93.32 applies to "myalgic encephalomyelitis/chronic fatigue syndrome," "chronic fatigue syndrome," and "myalgic encephalomyelitis." The update also directs coders to add the code U09.9 for post-COVID conditions, when appropriate, thus making it clearer when ME/CFS occurs following SARS-CoV-2 infection.

The code enables clear documentation of ME/CFS in the medical records. The new release also modifies the description of the tabular listing code G93.3 to encompass both viral and non-viral causes. Even though there is a new code, it can't be used if providers don't know how to accurately diagnose. To make sure they can, we continue to focus our efforts on educational activities.

And so now I'll turn to provide updates on some of these activities. As of October 2022, we have partnered with Medscape to produce six online courses and one print supplement on ME/CFS. Through the online courses, we have reached over 110,000 learners, 45,170 test takers, and issued about 36,285 certificates. The spotlight online course titled, "A Fresh Look at ME/CFS: Diagnosis and Management of a Multi-symptom Illness," and our webpage content is being promoted by WebMD, the National Association of School Nurses (NASN), and the Association of American Medical Colleges (AAMC) through their member listservs and network. To promote the course to a wider audience, we worked with the Medscape team to publish a print supplement titled, "Update on the Clinical Evaluation and Care of Patients with ME/CFS" in the July issue of Medscape's partner journals: Family Practice News, Rheumatology News, and Internal Medicine News. We will renew the accreditation for the spotlight course for another year in December and have just issued a new contract to Medscape for a new spotlight course expected to launch January 2024.

As we shared during our last call, we partnered with WebMD to assess knowledge, attitudes, and beliefs about ME/CFS among the general public. The results were featured in a new article

and accompanying video posted on the WebMD website in May 2022. The video includes interviews with a former nurse who is living with ME/CFS and with Dr. Valerie Montgomery-Rice, the Dean of the Morehouse School of Medicine, and highlights the challenges of getting care for ME/CFS, especially for women of color. The article and video webpage on WebMD.com has attracted over 12,000 unique visitors. A shorter video was also posted on Medscape.org. The links to the video and the article and can be found on CDC's ME/CFS website. WebMD has been promoting the article and video through their Facebook ad, and those posts have a click-through rate of more than 10 percent. This far exceeds WebMD's social media benchmark of 2 percent click-through rate, which shows us there is public interest in learning more about ME/CFS. We also presented this work at the 2022 conference of the International Association for CFS and ME, known as IACFS/ME.

We continue to partner with the National Association of School Nurses to not only collect information about ME/CFS in schoolchildren but also to educate school nurses about ME/CFS. The training curricula include three courses, a toolkit, and a manual to educate school nurses on the symptoms of ME/CFS and how to identify and refer students for diagnosis. To date, there have been about 22,000 school health professionals who completed the training. As part of the educational modules, our Medical Officer Dr. Nanda Issa, also recorded a webinar highlighting the similarities between ME/CFS and post-COVID conditions. School nurses anticipated the need to track and identify post-infectious symptoms in students as they returned to school after the summer break. They believe that the school-based active surveillance process for absenteeism and ME/CFS will be instrumental to track symptoms among students.

An overview of the School-Based Active Surveillance project can be found on our website under the section called "CDC's ME/CFS Program." In brief, the first phase was completed in September 2021. We shared some preliminary work at the 2022 IACFS/ME conference and the manuscript was recently accepted for publication in the Journal of School Nursing. The title of the paper is "Chronic Absenteeism and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Nurse-Led Approach to Establish the School-Based Active Surveillance Process." The next phase of this project expands the work to more than 24 states over the next two years.

We continue to add to our publications based on findings from our multi-site clinical assessment of ME/CFS, or MCAM, study, which was closed in 2020. In previous calls, we mentioned two manuscripts in review by journals. The first, titled "Assessing Sleep and Pain among Adults with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Psychometric Evaluation of the PROMIS® Sleep and Pain Short Forms" has been published in the journal Quality of Life Research. The second manuscript, titled "Natural Killer Cytotoxicity in ME/CFS: A Sub-study of the Multi-site Clinical Assessment," is still in review. Other manuscripts in progress include one describing cognitive dysfunction in people with ME/CFS, one describing the burden of multiple medical conditions in people with ME/CFS, and one describing the differences among individuals with ME/CFS in different MCAM clinical sites. We expect to have at least three of these manuscripts published next year.

Next, we'll turn to a discussion about our work and plans regarding Post-COVID Conditions, often called Long COVID. As you know, the similarities between ME/CFS and Long COVID offer a unique opportunity to study and gain a better understanding of chronic conditions that begin after infection. We are leveraging interest and study of Long COVID to raise awareness of ME/CFS and related conditions among members of the healthcare community. Through our work on post-COVID conditions, we have successfully recruited several new experts to our branch. And now I'd like to introduce one of our new members, Dr. Jennifer Cope. Dr. Cope is board certified in infectious diseases and a 2011 graduate of CDC's Epidemic Intelligence Service program. In 2013, she completed CDC's Preventive Medicine Residency and earned a Master of Public Health degree. She is a captain in the US Public Health Service and joined our branch after spending more than a decade working at CDC on waterborne diseases. She began working on post-COVD conditions in December 2020 as part of CDC's COVID-19 emergency response and will continue that work, in combination with ME/CFS, now within our branch. Dr. Cope will finish our CDC updates and introduce our guest speaker, Dr. David Systrom. Dr. Cope.

Dr. Jennifer Cope: Thank you for the introduction, Dr. Unger. I am very pleased to have the opportunity to talk with you today. Since joining the branch in March, I have become thoroughly involved in the work examining the link between ME/CFS and Long COVID.

Last month, I was interviewed by Medscape about what providers should know about both ME/CFS and Long COVID, how to diagnose and manage these conditions, and ongoing areas of research. In the article, I provided an update to clinical audiences on the new ICD-10 code we mentioned earlier that will aid in the diagnosis of ME/CFS. The article is available on the Medscape website, titled “ME/CFS and Long COVID: Q&A with the CDC's Dr. Jennifer Cope.”

Last September, we posted our 9th story in the Voice of the Patient web series, offering the first-hand account of a nurse who was diagnosed with ME/CFS following COVID illness. Over the past four years, these Voice of the Patient stories have had hundreds of thousands of views. They are also promoted through channels like the National Association of School Nurses Weekly Digest and one of CDC’s Twitter accounts.

In early Fall, our Branch entered into a cooperative agreement with the CDC Foundation to bring together patient advocacy groups and community-based organizations working to raise awareness and help people with Long COVID, ME/CFS and similar infection-related long-term illnesses. The Infection-Initiated Chronic Conditions Understanding and Engagement, or ICUE Project, aims to develop collaborations, tools, and strategies to address the concerns and challenges of people living with Long COVID, ME/CFS and similar conditions. The kickoff meeting with patient advocacy groups and community-based organizations will be held in January 2023.

Our work to empower primary care providers to manage the health of patients with complex post-infectious illness like Long COVID and ME/CFS continues through the Long COVID and Fatiguing Illness Recovery Program, or LC&FIRP. This program is a collaboration with the Family Health Centers of San Diego, the ECHO Institute at the University of New Mexico, the University of Washington Post-COVID Rehabilitation and Recovery Clinic, and the Western Regional Public Health Training Centers at the University of Colorado. The monthly ECHO webinar series from this program offers didactic presentations by subject matter experts in Long COVID, on topics such as the History of ME/CFS and Disability and Post-COVID Conditions. The webinar series includes an expert panel with patients who have lived with these conditions and caregivers of those who have ME/CFS or Long COVID. This year, we have held 11 monthly webinar sessions

averaging over 400 attendees per session. The next monthly webinar will be this week on December 8. We encourage patients with ME/CFS or Long COVID to participate. Information on upcoming webinars can be found online by searching LC&FIRP, F-I-R-P, and the ECHO Project, spelled E-C-H-O. Additional information on CDC's studies of post-COVID conditions can be found on CDC's post-COVID conditions webpages.

If you have suggestions for speakers or ideas for other topics for the upcoming SEC calls, please e-mail us at mecfssec@cdc.gov. This address can also be used if you'd like to be added to our e-mail notifications about upcoming calls. And finally, just a note that the transcript of this program update presented by me and Dr. Unger can be found on our website.

Now, I would like to introduce our guest speaker, Dr. David Systrom. Dr. Systrom is a member of the pulmonary and critical care staff at Brigham and Women's Hospital and an Assistant Professor of Medicine at Harvard Medical School. In early 2022, Dr. Systrom became co-director of the newly named Ronald G. Tompkins Harvard ME/CFS Collaboration at the Harvard Affiliated Hospitals. He received his medical degree from the Geisel School of Medicine at Dartmouth, completed his residency in Internal Medicine at the Emory University School of Medicine, and a fellowship in internal medicine at Massachusetts General Hospital. Dr. Systrom is the principal investigator of an ongoing $8 million study of limb skeletal muscle mitochondrial dysfunction in ME/CFS and just completed the first randomized clinical trial of pyridostigmine for treatment of ME/CFS. His presentation today is titled, "Neurovascular Dysregulation Underlies Exercise Intolerance in ME/CFS." Welcome, Dr. Systrom.

Dr. David Systrom: Well, thank you Dr. Cope very much for the kind introduction. And Dr. Unger for the invitation to speak to the CDC, and your audience. Congratulations to both of you for the phenomenal work that you have done at the ME/CFS area and emerging work in Long COVID.

So, what I hope to do over the next 45 minutes is give you perhaps an unusual perspective from the eyes of a lung doctor. And along the way I'm going to tell you how a lung doctor found himself with a little bit of serendipity getting into this business of exercise intolerance in both

ME and Long COVID. A little bit on Long COVID toward the end here. I have no disclosures except that I am a lung doctor.

I would like to call out a special place back in the day and the irony is not lost on me, but the name of this place, the Harvard Fatigue Lab, and the fact that many years later we have come round and begun studying fatigue again. It was a unique place set up by the Dean of the Harvard Business School and the Dean of the Medical School and Dr. Henderson, one of the premier physiologists of his day of the famous Henderson-Hasselbalch Equation. And they studied human exercise, they absolutely got right many of the basic tenets of exercise physiology. They measured cardiac output and breathing and ventilatory control in athletes and nonathletes, and it was a phenomenal place that put many of the basic concepts of exercise physiology on the human on the map.

The following definitions will not be lost on this audience, and I think we can have conversations about exact definitions. I will give you a basic framework of how we attack ME/CFS and Long COVID symptomatically and then take a deep dive into the physiology.

So, we borrow from the Institute of Medicine's old definition now the National Academy of Medicine, where they require three major criteria to have a diagnosis, a clinical diagnosis of ME/CFS. And those were intractable fatigue for more than six months and the unique symptom post-exertional malaise, which serves to differentiate ME/CFS and to a degree Long COVID from many other diseases of the heart, lungs, and related disorders that cause fatigue. Where the patient will overdo one occasion usually physically but sometimes intellectually and emotionally and then pay the price and feel like they have the flu a day or two later. Non-refreshing sleep is the third major criterion, and then one should have at least one of the two minor criteria: brain fog or cognitive issues and orthostatic intolerance, largely lightheadedness and perhaps palpitations.

Long COVID is a much more nebulous definition, but what I would like to point out is that there is some major overlap even with the clinical definition of fatigue and post-exertional malaise. There may be a bit more dyspnea I'm going to come back to that in Long COVID than in—

Christine Pearson: Dr. Systrom, I am so sorry. I am so sorry to interrupt, but we are not seeing your slides. And I just realized that. I am sorry.

Dr. David Systrom: All right.

Christine Pearson: You might want to try to click and see if that will help.

Dr. David Systrom: All right. Let me go back. I am sorry.

Christine Pearson: Apologies to all those on the call.

Dr. David Systrom: No, no worries. Okay, how about now?

Christine Pearson: Yes, I think you just need to make it full screen. There you go.

Dr. David Systrom: All right. There we go. Well, that was an important one. Thanks for that. Let me just clean things up here, and I will flash back just for a second to the previous slides.

So, little picture of the Harvard Fatigue Lab, which you heard about but didn't see. The criteria that I mentioned for ME/CFS clinical criteria. And then we were just beginning to talk about Long COVID. So again, I would point out that there is some overlap symptomatically with ME/CFS and Long COVID. And we will focus a bit on that, and we will focus later in this talk on the notion of shortness of breath during exercise, especially in Long COVID.

This comes from the CDC, a little shout out, a recent bulletin which really frames how prevalent Long COVID is. Nearly 20% of Americans who, at least adults, who have had acute COVID still have symptoms that persist afterwards.

Little bit on the prevalence. Here is the overall prevalence in the US. There is an age predilection shown here, like ME/CFS there is a female predilection that is poorly understood. It is the subject of our studies and others. There are racial and ethnic disparities shown here, which most of you are probably aware of. And then one I like to tell the youngsters who are thinking about vaccinations: you may have mild disease or even asymptomatic disease and still develop Long COVID.

This is a little bit of a table of contents about some of the exercise pathophysiology I would like to cover. I'm going to talk to you pretty extensively about systemic vascular dysregulation, these are some of the findings we have come up with over the last five or six years using a special test called the invasive cardiopulmonary exercise test. More on that in a second.

We have attempted to link the vascular dysregulation to a neurologic problem, as the title of this talk implies, and in particular small fiber autonomic neuropathy. I will explain more about that. I'm going to touch down briefly on how activation of the inflammasome including that by acute exercise may be relevant to ME/CFS and perhaps Long COVID. I will touch down a little bit of the notion of skeletal muscle mitochondrial dysfunction in ME/CFS. I will then turn to shortness of breath and ventilatory control and just a little bit on treatment at the end of the talk.

So, this is our… the basement of the Brigham and Women's Hospital, where we do invasive cardiopulmonary exercise testing about 15 times per week. This test was developed originally to detect early heart failure in both pulmonary vascular disease, but over the past five or six years we found the data that emerge from it phenomenally useful and taken a deep dive into the pathophysiology of ME and more recently Long COVID. I'll just point out a couple of things in this gentleman who agreed to be filmed. He's peddling away; we do incremental exercise up to maximum—it's only about a five or a six minute test—most patients do not realize a crash of any kind afterwards with ME, important to note. Here is the noninvasive portion of the test. There's a pneumotachograph in his mouth, and there's a line coming out of the pneumotachograph which measures expired gases, pulmonary gas exchange. And then what makes the test special are two catheters that were placed in our cardiac Cath Lab before the test. One is a radial artery catheter in this gentleman's left wrist, and the other is a pulmonary artery catheter placed in his right internal jugular vein and whose tip resides in the pulmonary artery. So, I'll show you the sort of data that we get from this.

This is a sort of a simplified version of our exercise invasive exercise test algorithm and the diagnosis that we can make. I'm not sure if you see this, but I've got something in the way here. Anyway. Up at the top is the VO2 peak. This is the maximum oxygen uptake, the end of an

incremental cycling bout. It gets us an index of how impaired the patient is, an overall index. It reflects really all the internal machinery, respiratory function, cardiovascular function, autonomic nervous system function, as you'll see and crudely speaking, when individuals' VO2 peaks are above eighty percent of predicted, we'll deem them normal. I will caution you folks who are doing non-invasive testing and rely in part on this number that many of our patients with ME/CFS and Long COVID end up in a pretty well preserved VO2 peak range. So do not write them off, please, as not having anything wrong with them if you see a VO2 peak of, for instance, eighty percent of predicted.

A couple of other things I'll mention just along the way they're probably more relevant to Long COVID than to ME/CFS. We have the ability noninvasively to rule out a pulmonary mechanical limit. This is the notion that the lungs' ability to move air is limiting. This would be relevant to somebody, perhaps with a history of ARDS [Acute respiratory distress syndrome] and Long COVID, who survived the ICU stay, get off of a ventilator and had fibrotic lung disease. These are not the types of patients that I'm going to be talking about here today.

Another one that can happen more often with Long COVID than with ME/CFS is that we might have some evidence of left heart disease, cardiomyopathy associated with COVID. We can determine if that is at play here with this testing by measuring the cardiac output at peak exercise by the Fick Principle and then determining whether there is backwards elevation of pressures, the pulmonary capillary wedge pressure, is elevated and that would be a hallmark of left heart disease.

Very uncommonly with Long COVID survivors of serious disease, there may be pulmonary hypertension we can rule that out as well. Again, I'm not going to be talking about lung limits or central cardiac limits, but I will be focusing on two other things here because they have emerged as totally relevant to ME/CFS and Long COVID.

One we'll call preload failure. This is where the VO2 peak is depressed in part by the cardiac output at peak exercise being depressed but not due to the left heart or right heart disease but rather due to failure to prime the pump. So, this is the inability to move blood volume out of the lower extremities and the abdomen up to the right heart. And we measured at peak

exercise by pressures and when those pressures are low, we call this preload failure. Much more on this to come.

Then the other class of abnormalities are really on the arterial side. Peripheral limitations and they include mitochondrial problems in the muscle, and they include what we call left-to-right shunting. This is ineffectual blood flow that's sent out the aorta but doesn't get to the exorcising muscle as it should, with a mitochondrion would have an opportunity to take up oxygen and use it. Both of these disorders, they can coexist, and we'll see that in a bit, are reflected in our testing by impaired systemic oxygen extraction. Namely the inability to depress the mixed venous oxygen saturation or content we normalize that for the hemoglobin. So when there is an inability to depress the mixed venous oxygen content, we may have one or both of these entities at play.

I got into this business five or six years ago, when Will Oldham, who helped us out as our first author, and other collaborators investigated unexplained exertional shortness of breath or dyspnea but additionally it turned out exertional fatigue with the invasive cardiopulmonary exercise testing, we increasingly recognized over time that there were certain individuals who came to us complaining of exercise intolerance who were not explained by any disorder of the lungs or of the heart per se. The heart checked out fine, the lungs checked out fine, something else was going on.

So, we systematically took a look at this about six years ago. And the way we did that was we analyzed the invasive cardiopulmonary exercise test at the Brigham database at that point in time had about 600 patients. We ruled out everything else under the sun; so, this included some of the things I just mentioned: pulmonary hypertension, right heart failure, left heart failure, and pulmonary mechanical limits. So, no disorder of the heart or the lung yet the patient is complaining of symptoms with exercise. And we identified a cohort of nearly 50 patients who had an impaired VO2 peak. So, their aerobic capacity was diminished but it was not due to our classic disorders of the heart or the lung. We compared them to 28 normal individuals. These are symptomatic normals who came to our lab complaining of exercise intolerance, but we couldn't find anything wrong with them.

And interestingly what differentiated these patients from the normal controls, was identifiable only at peak exercise, not at rest, and was identified only invasively, not noninvasively, by the pulmonary artery catheter. And what was relevant was that the filling pressures of both sides of the heart here, the right atrial pressure and here a surrogate for the left atrial pressure, the pulmonary capillary wedge pressure, was lower in the patients with impaired VO2 peaks. So it was inadequate preload that defined these patients and was responsible for their depressed VO2 peak and their depressed cardiac output peak.

And shown over here is a regression attempting to illustrate that where filling pressures moving right to left are abnormally low, on both sides of the heart. And what results is a lower VO2 peak and a lower cardiac output peak. So, we call this preload failure, and in these early days, we increasingly recognized that many of these patients met clinical criteria, and I outlined earlier, for ME/CFS.

So, this is where they landed with our algorithm. Their peak exercise VO2 is depressed. Their cardiac output was slightly depressed and the reason for it was not left or right heart disease but was failure to prime the pump, so called preload failure. So, my interim summary here would be that vascular dysregulation in this case on the venous side, namely preload failure, contributes to exertional intolerance in ME/CFS.

We took a deeper dive into this last summer, almost 2 summers ago now, with Phillip Joseph, the lead author on this particular study. And we were attempting to further refine our look at the vascular phenotypes in ME/CFS. And additionally, because we were becoming increasingly aware that many of these patients carried a skin biopsy diagnosis of small fiber neuropathy. We wanted to look at the interaction between autonomic small fiber neuropathy and the vascular dysregulation that we were identifying with the invasive exercise test.

So, we took a similar approach to the Oldham paper, where we had about three times the number of invasive CPETs. We again ruled out everything else under the sun. We focused on the preload failure patients with low right atrial pressures, and additionally those with skin biopsies. And the first question was okay how many of these folks with exertional complaints,

preload failure, and happen to get a skin biopsy had a clinical diagnosis of ME/CFS. And the answer is here in the red. It was a majority of patients had classic clinical criteria for ME/CFS.

And the next question was how many of these patients had a skin biopsy diagnosis of either definite or probable small fiber neuropathy defined by the neurite density in the epidermis with a single biopsy above the lateral malleolus, the ankle. And here was the answer; it was about 45% of patients either with definite or probable small fiber neuropathy who had preload failure and ME/CFS. This is a frighteningly similar prevalence to that previously described in the literature, and very closely related disorders including fibromyalgia and postural orthostatic tachycardia syndrome, POTS.

Our deeper dive into the vascular phenotypes is shown here. We were very much aware that in POTS with an upright tilt table test there have been previously described a low-flow group, low cardiac output, and high-flow group, very interesting hypotheses about why that might be in POTS. So we did an analysis where we determined tertiles of cardiac output versus VO2 slopes, during instrumental cycling exercise with the invasive CPAP. And by definition defined a low-flow group, a normal-flow group and here is a normal comparator over here. The normal slope during exercise in a human is about 5 to 6 mL of cardiac output to mL of VO2. And then at the other end of the spectrum in red, and I am going to focus on the red, is a high-flow group.

All these patients with these vascular subtypes, had mildly depressed VO2 peaks as a percent predicted, the difference however is that the folks with high flow had more pulmonary blood flow. So, step back for a second and remind ourselves that we're measuring the cardiac output by the Fick Principle, which is the VO2 measured at the mouth, and the difference between arterial and mixed venous O2 content in the denominator that gives us a cardiac output but it's pulmonary blood flow. So, what we determined was that there is a high pulmonary blood flow group here on the red. And they were further defined by impaired systemic O2 extraction. And this is the inability to depress the mixed venous oxygen content and saturation at peak exercise; so, they have a lot of pulmonary blood flow and not enough extraction of oxygen in the periphery by the exercising muscle mitochondrion. All of them had preload failure that was by study design.

So, this interesting group high flow, high pulmonary blood flow, and low extraction reminded us of cardiac septal defects in particular atrial septal defects, where there was left-to-right shunting. So, one hypothesis that emerged from this paper last summer is that a subset of patients with ME/CFS suffered in addition to the preload failure from left-to-right shunting in the periphery.

So, this is where they land in our algorithm, mildly depressed VO2 peaks, a subset of them with low cardiac outputs and predominantly preload failure but an additional subset with both of these things, impaired systemic O2 extraction and the preload failure.

We attempted to marry neurologic or neuron anatomy in the skin to the physiology during incremental invasive exercise testing, and we were woefully disappointed here. So you can see at first glance we have four scatter grams here. When we attempted to regress the skin biopsy neurite density, abnormal is down at this end toward zero, with classic exercise parameters including the VO2 peak as a percent predicted, the cardiac output, the extraction of oxygen, and then the right atrial pressures. And my takeaway from this is that the neurite density tells us just about the anatomy and it's not the same as physiology. There are small fibers that remain, and they are likely very dysfunctional. This type of biopsy that we did at first pass was epidermal and probably not capturing the autonomic small fibers that innervate sweat glands. More on that in a little bit to come.

Wanted to leave you with this notion of left-to-right shunting. I'll give you a little anecdote from the clinic. I ask patients regularly with ME/CFS and more recently Long COVID, if you're in the hot shower, do you notice you get dizzy? And do you notice that your lower extremities turn red or even purple? And there is a phenomenally high prevalence of yes answer.

And this may be some of what's going on, this is a hypothesis. And I'm borrowing a little bit from this beautiful diagram from Frank Rice from Albany, who's investigated fibromyalgia with hypothenar biopsies, so that's the palm of the hand. That enables him to capture both the epidermis that we got with our biopsies previously over at Mass General and the vascular bundles underlying in the dermis. So, what he is determined is that, in normal individuals and patients afflicted with fibromyalgia, we have got arteries coming into the skin, we have got

veins draining the skin, we have got potential shunts between the two. And those shunts interestingly are enveloped by small fibers. Remember the small fibers that remain in ME/CFS and small fiber neuropathy are dysfunctional, they are overactive, they cause pain. And interestingly they also secrete a vasodilator which is called calcitonin gene-related peptide. So one can envision that, when dysfunctional, the remaining small fibers may vasodilate and open up these shunts in the skin. And perhaps this is one of the reasons for migraine headaches in the head, but also peripheral left-to-right shunting in that shower phenomenon I gave you a second ago.

So interim summary here is that, in ME/CFS we've got vascular dysregulation. We've got pretty high prevalence, approaching 50 percent, of small fiber neuropathy done by an epidermal skin biopsy. All right. I'm going to digress here a little bit with a bit of a dive into inflammation. So, I think most on this call are aware of the fact that many times in ME/CFS and Long COVID we have relatively nonspecific markers of both autoimmunity, often low-titer ANAs and friends markers of inflammation that are sort of nonspecific things like the sed rate are high and the CRP are high.

So, autoimmunity and inflammation. So, I went to a meeting in 2019, immediately pre-COVID, that was dedicated to these issues in ME/CFS, and I met a very interesting group from intramural NIH who were studying this pathway, TRAIL, it's TNF-related apoptosis-inducing ligand. So, for those of you who aren't familiar with this one it's a ubiquitous cytokine that's secreted by multiple cells in the body. It's provoked by a lot of things that precipitate crashes in ME/CFS and Long COVID, viruses for instance. And when it's secreted, it does some interesting things. So over here is apoptosis, and I won't get out on a limb here. This is a bit of out of my wheelhouse. But what's a little closer is that TRAIL, when it interacts with some of its receptors, activates NF-kB and the inflammasome. Now what's also interesting is that there is a dummy receptor shown over here that tamps down this entire process, but neurons both central nervous system and peripheral nerves lack the dummy receptor. So in theory they are more exquisitely susceptible to this pathway and this inflammatory response that may end up being neurotoxic.

So, the NIH group helped us out with the following study. We looked at acute exercise and the bump in plasma TRAIL during our invasive CPET and focused on patients with small fiber neuropathy, asking a larger question. Could inflammation be responsible for the small fiber neuropathy? And we had a hint. This is not published, it's not significant, it's trendy, that patients with bona fide small fiber neuropathy by skin biopsy had more of a TRAIL bump during acute exercise than those who did not have small fiber neuropathy.

And then we did a network analysis of inflammatory cytokines. There's a forty-panel multiplex that measures the who's who of the inflammasome. And what we found in the bold blue here were tight connections amongst inflammatory cytokines in ME that was disproportionate compared to normal controls. This, too, we're continuing to work on, but the notion and the hypothesis here is that acute exercise elicits more inflammation in ME/CFS and that might be the harbinger or the beginning of post-exertional malaise. So, another interim summary is that acute exercise activates the inflammasome in ME/CFS disproportionately compared to normal controls.

All right. Little bit of another digression, and this was with the help of Katie Melamed, who's now a pulmonary attending at UCLA but a former Brigham resident who helped us out with this study. Another similar approach where we took the invasive CPET database and analyzed it, looking for evidence of poor systemic oxygen extraction and focusing on those folks. And in fact, we found a cohort of patients whose exercise intolerance and depressed VO2 peak could only be explained by poor systemic O2 extraction.

And this is where they land with an elevated mixed venous oxygen saturation and content at peak exercise compared to normal controls. This raised the specter yes of left-to-right shunting which would do that but additionally reminded us that mitochondrial disease does exactly that during exercise.

And this we borrowed from the UT Southwestern group, who did incremental cycling exercise in patients with muscle biopsy proven mitochondrial disease and where they quantified during the muscle biopsy the degree of mutations. So more severely affected patients out here, and here's something we're used to by now during this talk, that's the impairment of systemic

oxygen extraction, meaning inappropriately narrow difference between arterial and mixed venous oxygen content. Abnormal being low. So patients with more severe mitochondrial disease in the muscle have more impaired systemic oxygen extraction. And this goes back to Dr.—sorry.

A brief diversion here. Immediately pre-COVID, we began to investigate this phenomenon in our patients who had done an invasive cardiopulmonary exercise test, had poor systemic oxygen extraction shown here, impaired by VO2 peak, shown here. And we organized a muscle biopsy study where fresh gastrocnemius muscle was sent to Baylor for interrogation of the respiratory chain. It emphasized that in this business, in ME/CFS in adults anyway, and we think in Long COVID as well, in general mitochondrial disease is not determined by genetics, but it's functional, it's acquired, perhaps related to autoimmunity and inflammation.

But what we found that was pretty ubiquitous in 10 of 11 patients was the citrate synthase defect or deficiency, which is thought to be a global marker of mitochondrial dysfunction. So that was enough to get a drug company in Japan that Dr. Cope alluded to earlier to fund this study, which actually has just been ended, and we are beginning to analyze. Six-week study of a PPARdelta modifier that favorably affects fat metabolism in the muscle in ME/CFS versus placebo. We're asking the question: is mitochondrial disease relevant to ME/CFS and symptoms and exercise intolerance by our invasive CPET and additionally looking at a promising drug versus placebo. So more on that to come.

So, I raised the hypothesis the question of whether some of the impaired systemic oxygen extraction that we see with an invasive CPET is actually due, perhaps due to left-to-right shunting, but additionally due to intrinsic limb skeletal muscle mitochondrial dysfunction. More on that to come. Important to note that the treatments for dysautonomia and left-to-right shunting and mitochondrial disease, on the other hand, are entirely different.

So, a little bit on dyspnea, and this will be more recent work published in *Chest* last summer with our colleagues at Yale, where we did a small study admittedly 10 patients with Long COVID and 10 normal controls with invasive CPET and asked what does Long COVID look like? And I

think you heard this in the introductory remarks, in our world anyway, in the exercise world, it looks remarkably like ME/CFS.

So a little bit on that. This will look familiar to you by now. Here are our controls with their peak exercise VO2 expressed as a percent predicted, their peak cardiac output as a percent predicted, their measure of extraction of oxygen peripherally, and right atrial pressure shown here at peak exercise. So, what differentiated Long COVID from normal controls was a mildly depressed VO2 peak as a percent predicted. But interestingly, their pulmonary blood flow measured by the Fick Principle did not differentiate them. It was high, and what did differentiate them was severely impaired systemic oxygen extraction, whose differential diagnosis was the one I just gave you, mitochondrial disease and/or left-to-right shunting in the periphery. They additionally had a hint of preload failure. I think this was a Type II error. Just numbers did not give us this distinction, but every Long COVID patient I had met who's done this test since this study has had preload failure. So this is where these patients with Long COVID land. It's the combination of preload failure and impaired systemic oxygen extraction, with one or both of these entities at play.

A little bit on dyspnea and breathlessness, which may be slightly more prevalent in Long COVID than ME. But I know that in certain subsets of ME/CFS, shortness of breath with exertion is part of the syndrome. The important distinction between normals and ME, in the Singh study I've just begun to show you, was that there they have ventilatory inefficiency. So, this is a noninvasive number it means the unit cost of minute ventilation required to excrete a unit of CO2 during exercise is excessive.

And physiologically there are two reasons for a high VE/VCO2 slope, meaning ventilatory inefficiency. One is hyperventilation when the individual regulates PaCO2, arterial PaCO2 too low, lower than required for the usual lactic acidemia of exercise. The other is true inefficient breathing where the physiologic dead space to tidal volume ratio was too high. So, this would be intrinsic lung disease. This is something else, respiratory drive and related disorders.

And what we found was it's all hyperventilation and Long COVID. So, the pHs at peak exercise are too high, the PCO2s are too low when compared to normals, and when we looked at the

dead space and its pattern of change from rest to peak exercise is perfectly normal in the Long COVID patients. So, hyperventilation seems to be a theme in Long COVID, and I will give you anecdotally, not published, in certain subsets of patients with ME/CFS. And there is associated shortness of breath.

A little bit more on hyperventilation. This is from tilt table testing. And this comes from the lab of our close collaborator and neurologist, Peter Novak at Brigham Faulkner, where he measures of course heart rate during upright tilt table test and end tidal CO2 as a surrogate for hyperventilation. And we published this paper last year. We looked at normal controls for the tilt table test, patients with old-fashioned POTS with a lot of overlap with ME/CFS and those with PASC, post-acute sequelae of COVID-19, a-k-a Long COVID. Turns out of course POTS has the most exaggerated heart rate response, but in terms of the ventilatory control and dyspnea, it was interesting to us that Long COVID and ME/CFS share hypocapnia during the upright tilt table test when compared to controls.

And then if we look at cerebral blood flow, and what Peter Novak does is transcranial Doppler of the middle cerebral artery where he's able to measure decrement and cerebral blood flow associated with hypocapnia during the upright tilt table test. What he found was that both POTS and PASC had a similar reduction in brain blood flow. And you can begin to hypothesize this might be relevant to things like orthostatic lightheadedness of course and perhaps even to brain fog in the upright position cognitive issues. What differentiated POTS from PASC, however, was that when he corrected the cerebral blood flow decrement during upright tilt table test for the end tidal CO2 decrement, there was a correction for POTS, meaning all of the POTS decrement and cerebral blood flow was accounted for by hypocapnia and the increase in resistors in their tone in the head. But not in PASC. This suggests something that is emerging as a hypothesis in several places across the country and the world. That there's an intrinsic vasculopathy at play in Long COVID, which might be different from ME/CFS.

Others have begun to recognize—this is the Cleveland Clinic—that shortness of breath is a feature actually of these low ventricular preload states, meaning preload failure, shared both by ME/CFS and by Long COVID. And this statement was made last summer by one of our

thoracic society groups. And the Europeans have jumped onboard as well, recognizing that hyperventilation is part of the dyspnea problem in Long COVID.

I'm going to leave you with, before I turn to treatment, a little bit of commonalities. I'm part of the RECOVER task force charged with demonstrating this among ME/CFS and Long COVID, but the pathophysiology that underlies exertional intolerance. So, our patients are largely, come to us, defined by preload failure, but most of them—87 percent—meet clinical criteria for ME/CFS when they have preload failure. And then the important point is here that, if you add all of these parts of the Venn diagram, that about two thirds of them have POTS by an upright tilt table test in the Novak Lab. And if you do two skin biopsies, including a thigh biopsy that gets sweat glands, you will determine that about two thirds of the patients with preload failure, and mostly with ME/CFS, have a small fiber autonomic neuropathy, innervation of the sweat glands is abnormal. So unpublished data but suggestive. So interim summary here is that dyspnea and shortness of breath with exercise are highly prevalent in both ME/CFS and Long COVID. And there's a lot of overlap with the hyperventilation during upright tilt table and POTS.

Finally, I'm going to give you a bit of the study Dr. Cope alluded to. This was a placebo-controlled, randomized study that we finished last summer, in ME/CFS. Basically, patients came to us with ME/CFS and exertional complaints. They underwent the clinical invasive cardiopulmonary exercise test. When we identified preload failure, which is most of them, I just showed you that, they were randomized to receive placebo or a single dose of 60 mg of Pyridostigmine, or Mestinon. We borrowed that dose and this experimental design from Vanderbilt, who did something very similar a decade ago with upright tilt table testing in POTS and showed that Mestinon mitigated the heart rate response during upright tilt table test in that disease. So, 45 minutes after they ingested placebo or Mestinon, they were asked to pedal again with the existing lines in place.

And what we found was a small effect size but statistical concordance and therefore significance. When patients got Mestinon and pedaled for a second time, their VO2 peak went up. If they got placebo, their VO2 peak went down 45 minutes later. And we hypothesize

maybe this is the beginning of PEM, or post-exertional malaise, identified with this type of testing.

And the reason the VO2 peak went up or down was what we expected a priori, which is that the peak exercise cardiac output went up after Mestinon and in turn related to better filling pressures, at least on the right side, the right atrial pressures. Whereas patients who got placebo actually worsened both of these things. Perhaps that's the acute inflammation and neurovascular dysregulation.

This is a little cartoon that shows you how pyridostigmine, an FDA-approved drug for not ME/CFS but for myasthenia gravis, is thought to work. In myasthenia gravis, it works at the end plate, the motor neuron, and the muscle. We think in ME/CFS it may work at this cholinergic step in the sympathetic ganglion and promoting adrenergic outflow, which is a secondary step. And then improved vascular tone, perhaps both on the venous side, measured by the right atrial pressure, and on the arterial side, measured by less left-to-right shunting.

Just a couple other shout-outs to some repurposed drugs. Of course, the RECOVER project at NHLBI is getting into this business of repurposed drugs for Long COVID. And we've been using these drugs for ME/CFS with some success. Mestinon I just mentioned. Florinef and Midodrine are old-fashioned POTS drugs. We use an increasingly low dose of Naltrexone in both diseases, which is thought to be anti-inflammatory. And in severe cases, who don't come around with these drugs, we will consider in the right setting that would be a skin biopsy proven small fiber neuropathy and evidence of autoimmunity IVIg, or perhaps even better, the subcutaneous variety Hizentra, which are thought to interrupt the autoimmune pathogenesis of these diseases.

So, this is what I wanted to leave you with. We think that, with our invasive cardiopulmonary exercise testing, we've been able to demonstrate that vascular dysregulation, in particular preload failure but additionally on arterial side left-to-right shunting, is ubiquitous in ME/CFS and also in Long COVID. That associated with these vascular problems on the systemic side is small fiber autonomic neuropathy. One potential reason for all of this might be the inflammasome is activated by lots of things but including acute exercise. There is a tantalizing

hypothesis that there is a subset of patients with intrinsic mitochondrial dysfunction in the muscle. I wanted to call out dyspnea and hyperventilation in both ME but especially Long COVID. And then leave you with the thought that repurposed drugs, especially POTS drugs, but those that address autoimmunity might be useful here.

Some thanks to a bunch of people. The late Ron Tompkins, who organized the MGB/Harvard ME Consortium, and related investigators. We meet every other week. The Brigham team, including our cardiovascular team shown up here. Our Yale contingent, and then a whole bunch of youngsters who have helped me accomplish all that we've done in this business, especially these folks who are active currently. So many thanks to them. And I think I will end there and show you two new additions to my family and ask if there are any questions here. But thank you very much.

Christine Pearson: Thank you very much for your presentation, Dr. Systrom. You can go ahead and stop sharing. So, we're now going to move on to the Q&A portion of the call. There are a number of ways you can ask questions. If you're joining us via Zoom and want to ask a question by voice, you can click on the raise hand function. You can also type in the Q&A box. We have quite a number of calls already. If you have joined only by phone, you can enter *9 on your phone to join the question queue and then we will announce you when it gets to your turn. So, we will try answer to answer as many questions as possible. And so, we'll go from there. First question we have is for Dr. Systrom. Can you give an update on the Astellas trial, please?

Dr. David Systrom: Yeah, the drug company decided to do an interim look. We had planned on 40 patients. We have accomplished 32 patients. But they did an interim look that took a little while, and they looked at two outcomes. One was a questionnaire, and the other was a VO2 peak, of course placebo versus drug—their drug. And determined based on looking at two outcomes in 21 patients that they were going to terminate the study. There was no safety issue involved. It was—and we don't have the full reason for—stopping the study. Having said that, they have agreed, and we are in the process of doing a breaking the code and analyzing the data—and all of the data—which will include replicate muscle biopsies and all of the relevant physiologic variables during the invasive CPET.

So of course there, I think their major priority in making that decision was whether there was a signal with this PPARdelta modifier of improvement or not. There was no safety signal involved, as I said. So anyway, more to come. We're analyzing the data. We've got 32 out of the 40 patients, and we will analyze all of the data and publish it.

Christine Pearson: Thank you. Okay, so most of the questions are for you, so we're just going to keep on that track. So, Dr. Systrom, are you aware of connections or similarities between ME/CFS and myasthenia gravis? Specifically, is there evidence of binocular diplopia or ptosis. And apologies in advance because I am a communicator, not a medical person.

Dr. David Systrom: Sure. No, so diplopia is seeing double and then related extraocular movement disorders. So, there is some overlap, not very frequent, with the autoimmune panel that we get both in ME and Long COVID. And occasionally, we will see some of the autoantibodies directed against the acetylcholine receptor, and there's a small panel of those. Most of the time we think they're nonspecific markers. But sometimes it's tantalizing to believe that maybe, especially given the Mestinon study I just gave you and those results, that some of them might be the underpinnings of the actual disease.

So, there is a neuronal variety of the acetylcholine receptor antibody. It's a ganglionic receptor blocker. So, when that's positive, and we're given a drug that we think works at exactly that same place, it's sort of tantalizing to hypothesize that myasthenia of the sympathetic ganglion could be responsible for some of the preload failure and perhaps the systemic left-to-right shunting.

Christine Pearson: All right, thank you. So next question. Could EECP, Enhanced External Counter Pulsation, be a potential treatment for ME/CFS for the vascular issues?

Dr. David Systrom: Yes, it's a great question. So, like many things in this business, I'm going to give a special shout-out to our patients because they make me aware of all these things. And that's true of the EECP, recently. And so, for those of you who don't know the technique—and full disclosure we have not yet used it, but we're considering a clinical trial—it is a sort of an augmentation. It's almost, for those of you in the cardiovascular business, an intra-aortic

balloon pump but noninvasive and related to sort of cuff compression of the veins that is tuned into the cardiac cycle. So, it facilitates venous return.

And somewhat interestingly, it's been used in a variety of disorders but not systematically to my knowledge in big studies in ME or Long COVID. But it's tantalizing because I think it has the promise of mechanically favorably influencing preload, which is as I've tried to tell you, I think ubiquitous in these diseases.

The other interesting thing about it is that it appears that, if one does a series of interventions—and I think there's a variety of them but—for a finite period of time that the beneficial effects on vascular tone actually persist after termination of the mechanical device. So something good happens and they persist in terms of vascular tone after using the device. And to my knowledge, it's safe and an occasional allergic reaction on the skin but really attractive. So I've heard about this from some of my patients and we're thinking about a clinical trial.

Christine Pearson: Thank you. So, the next question is: how will your research translate to treatment and/or a cure?

Dr. David Systrom: Yes, so we are—. I approach the research in maybe two different ways. One is we have the invasive CPET, which we think is sort of a gold standard for the exercise variables that we want to measure. And additionally, it's an incredible experimental set up in that we can measure everything omic, at least bloodborne, in two compartments, the radial artery and the pulmonary artery. And we can measure those omics be it proteomics, metabalomics, transcriptomics, even coagulomics, and others. We can measure them at rest, we can measure them at peak exercise, and then one hour after exercise, while the lines are still in place.

And, so what I envision is that places like ours with the capability of invasive CPET—and it's not for everybody I freely admit and it's not scalable for huge studies—can put on the map proofs of concept, perhaps related to the question. Not only the observational studies that describe the pathophysiology of the disease and improving biomarker identification of subtypes of the disease, but additionally we can use the invasive CPET to test as we did with Mestinon, repurposed drugs, and to see if they work and how they work at least acutely.

Having said all of that what I envision is moving forward into clinical trials of repurposed drugs—because we don't want to wait eight years for all the new ones—and doing less invasive testing. And in fact we are moving in that direction, where we use exercise as the perturbation because I think that gives, that enhances the signal of the abnormalities. Antecubital blood draws instead of radial artery and pulmonary artery blood draws. And then a simplified exercise test. And we're fans clinically anyway of a simple test called the SHAPE study, which is a three-minute step test that can be done anywhere, in a clinic. Doesn't require much training. Simple, one person can do it. We use it as part of the vital signs at the Brigham in the dyspnea clinic.

So, but what I could envision is larger, really phase III, studies of drugs using that approach. So I hope it's a combination of what we're doing with the invasive CPET and then more scalable, less invasive studies that'll lead us to not only better understand the pathophysiology but best treatment.

Christine Pearson: Thank you. Now we have a couple questions about the small fiber neuropathy that you mentioned. So, would small fiber neuropathy be something like having what feels like raw spots on the skin for no reason?

Dr. David Systrom: Yes, there's a variety—I'm not a dermatologist, full disclosure—but there's a variety of skin abnormalities that go with small fiber neuropathy. And I think that diagram of Frank Rice serves us well. There are erythematous skin rashes that come and go. Lot of overlap with mast cell activation syndrome. And there are, yes, other soft of poorly defined abnormalities of the skin. There were the color changes I mentioned in the hot shower. Red feet, burning soles of the feet—all go with it. So there's a whole slew of skin changes. I am even aware that, with small fiber neuropathy and presumably because one loses the nutritive layer of the epidermis, that fingerprints can disappear. So beware of that as you're going through TSA are clear. That small fiber neuropathy can cause a lot of skin changes.

Christine Pearson: And are you able to determine if autonomic fibers are affected?

Dr. David Systrom: Right, so I think our best shot at that there are some research techniques that are probably beyond the lung doc's pay grade here. But there I think the best scalable and clinically useful look is what I described with the Peter Novak form of skin biopsy. And this is

also being done now over at Mass General, at least in Boston. You do dual skin biopsies. One is the one that I described initially in the Phillip Joseph paper. That's the epidermal skin biopsy above the lateral malleolus.

But additionally, and I think this is where the money lies, a skin biopsy done in the thigh that captures sweat glands. The nerve fibers innervating the sweat glands are the autonomic fibers. So, if they're deficient in number, and then if one can demonstrate functional abnormalities using things like the QSART test and electrical impedance that reflects sweat gland function, I think you can put together a much better picture of the autonomic fiber disarray that I think underlies a lot of this.

Christine Pearson: Thank you. So, we also had a number of questions about whether or not you have researched or are looking into the effects of environmental toxins and particularly toxic mold.

Dr. David Systrom: Yes, very much aware there's a whole field out there. I really defer to the environmental folks, and we have some of them here at the Brigham to address that one. But clinically I would just say, absolutely I am aware that many patients date the onset of their symptoms or worsening subsequent symptoms to environmental issues including toxic mold. So, it's out there, but I don't claim to be an expert on that one.

Christine Pearson: Okay, so the next one is: might controlling CO2 in a room at 400 ppm, versus 800, help with ME/CFS due to hyperventilation and high pH?

Dr. David Systrom: Yes, yes. So great question. So, we think that—. I'll preface it by saying we think that hypocapnia that results of course from hyperventilation is not as benign as you might think. So, I showed you the data about cerebrovascular blood flow abnormalities decrease related to hypocapnia. So, there's all of that going on in the head with exercise and with the upright position. So potentially read all forms of orthostatic intolerance and perhaps even fatigue and PEM.

Additionally, the hyperventilation—and this was part of the Melamed paper, but I didn't do a deep dive into it—impairs oxygen delivery to the exercising muscle by virtue of a left shift of the Oxyhemoglobin Dissociation Curve.

So normally in the muscle capillary, we get lactic acidemia. And we also get CO2 coming both from Krebs and from the buffering of lactic acid. All those things serve to normally shift the Oxyhemoglobin Dissociation Curve down to the right. And in English what we mean is that there's more offloading of the oxygen in the muscle capillary under acid conditions. And hypercarbic conditions with hyperventilation, all of that normal unloading of the oxygen is adversely affected. So, hyperventilation is not good for the brain and it's probably not good for the exercising muscle, especially at peak.

So how to mitigate that it is actually a subject of a study that we're proposing to do with medications. More on that to come. We think that what might be relevant is the muscle chemoreflex, the muscle metaboreflex, which may have excessive gain out in the setting of small fiber neuropathy and drives ventilation during exercise.

So, the prospect of adding CO2 to a room or with conditioned air is interesting. I do know that that's been done in other states. Panic attacks and things like that, where hyperventilation has some overlap with panic attacks. And what it actually does is increases ventilation, the ventilatory, the levels of ventilation that result are greater. So I don't know this because we haven't done it, but I would predict potentially that that might not be a very practical way to address it, the hypocapnia, and that it actually might exacerbate the sensation of dyspnea. So that would be my conjecture.

Christine Pearson: Okay. So, the next question is: are there any NO-level measures on ME/CFS preload failure?

Dr. David Systrom: Not to my knowledge. So, I presume this would be exhaled NO, and I think it's a brilliant suggestion that the vasoconstrictor, vasodilator yin-yang of course involves nitric oxide in the systemic blood vessels. And the notion that NO-mediated vasodilation could play a role in some of the things we observed is absolutely spot on. We've not yet studied that.

Christine Pearson: All right. So I'm trying—sorry everybody. There are so many questions. Thank you, everyone. So again for Dr. Systrom: what's the role for functional autoantibodies against GPCRs, especially beta(2)AR and preload failure?

Dr. David Systrom: Yes, I'm aware of some of the data coming out of Germany in that area but also about neurology presenta—neurology national meeting presentation—this past summer that suggested that, as opposed to some of the initial reports, that these autoantibodies might not be as prevalent or disproportionally prevalent in dysautonomia related to ME/CFS as previously suggested. So I would put it firmly in a controversial area.

Christine Pearson: All right, thank you. So what are your thoughts on defects in the citric acid cycle in terms of mitochondrial dysfunction?

Dr. David Systrom: Sure, so it sounds right. I think most of the, with the exception of things like McArdle's disease, the hallmark of mitochondrial dysfunction is a slowing down or an impairment of Krebs cycle. Our data I think—and I think more to come from especially metabolomics—but our data suggest that the action may be more in the respiratory chain so a little downstream of Krebs. With some of the cytochromes disproportionately affected and leading to impaired oxygen use and therefore ATP production. I think I would leave it at that.

Christine Pearson: All right, great. Thank you so much. I know we had tons of questions for you. I really appreciate you taking all the questions and giving the answers. We did have one for Dr. Unger, which I wanted to fit in here, which is: when will CDC start counting people with ME/CFS via epi surveillance? With the new ICD-10 code, we need to create a strategic plan to figure out how we can do this.

Dr. Elizabeth Unger: Yes, that's a great question, and we do look forward to ways to incorporate the new ICD-10 code into our medical record searches. We do know that medical record coding is very inaccurate at this point. NCHS told us it takes about a couple of years for new codes to be fully adopted and used in a systematic way. So, we're going to continue to support the educational initiatives that will support use of proper coding. But as you're aware we have some other ways that we're looking at ME/CFS in the US population, and they include questions that we've added to the National Health Interview Survey and the BRFSS.

Christine Pearson: Great, thank you so much. All right, everyone. Well, that will conclude our call for today. Thanks everyone for joining us. As I mentioned, we will be posting the information—the transcript and the video—on our website as soon as we possibly can. Thanks so much, and have a great day.

Dr. David Systrom: Thank you all.