

Transcript

Melissa McPheeters

Welcome today to our webinar. I'm Melissa McPheeters. I'm a senior scientist at RTI International, and we are the RECOVER Administrative Coordinating Center. One of the things that we get to do as the ACC is to put on these webinars. And so, we're so excited to do another one today. So, welcome to the RECOVER Research Review or R3 Seminar.

The goal of our webinar series is really to catalyze a shared understanding of the research of the scientific stakeholder community within the RECOVER consortium. It's important that we note that this seminar series is focused on scientific research. It's not intended to provide any clinical guidance. I want to start by thanking all of you who registered and submitted questions in advance. If you have questions during the seminar, please submit them, as Shane said, using the Q and A feature in Zoom. We'll be keeping an eye on those, and after the presentation will answer as many as we can about today's topic. Some of the questions may also appear in Q and A that we'll be posting on our website.

We very much want to get to everyone's questions, but we do get a lot of questions during the webinars. We will be collecting them, and we'll be working hard when we go to post the video of this webinar on our website, the Q and A will be right there with it. There are also lots of other materials on the website, which is RECOVERcovid.org. So, you should feel free to go there to see if there may be additional answers for some of your questions on our FAQs that we continue to add to. There are also questions about other scientific topics there and about future webinars.

As I said, this is part of a series, and there are lots of other interesting topics coming up. We hope you'll join us for more of these. Today's speakers will be providing an overview of dysautonomia and diagnostic approaches. And then, describe what is known about dysautonomia and POTS, as well as what the research is showing us about treatment strategies. I think it's a very important and timely topic, and we're so lucky to have such great speakers with us today. So, let me tell you a little bit about them.

Dr. Mitchell Miglis is a fellowship-trained autonomic and sleep disorder specialist at Stanford University. He treats a wide variety of neurological diseases, and has a special interest in autonomic disorders, sleep disorders, and the interaction between these conditions. His current research interests include mechanisms and treatment of postural tachycardia syndrome and long COVID and PASC.

Professor Lauren Stiles is an attorney and a research assistant professor of neurology at the Stony Brook University Renaissance School of Medicine. She's also president of the Dysautonomia International, which she founded in 2012 after her own experience with the condition. She's gonna share some really interesting information today about symptoms and really looking forward to that.

Dr. Peter Novak is the director of the Autonomic Laboratory at Brigham and Women's Hospital. He's a board certified neurologist and a board certified autonomic specialist. He has special interest in autoimmune, small fiber and autonomic neuropathies associated with MCAS, hereditary tryptasemia, COVID 19 and Lyme disease, postural tachycardia syndrome, POTS, and multiple system atrophy, lots there. He's gonna talk to us about findings in recent studies of dysautonomia and PASC in particular.

Dr. Tae Hwan Chung is an assistant professor of physical medicine and rehabilitation and neurology at Johns Hopkins. His main areas of clinical interests are myositis and POTS dysautonomia. He founded the Johns Hopkins POTS Clinic, which is a multidisciplinary program with physiatrists, nurse practitioners and physical therapists. He also established Johns Hopkins Autonomic Laboratory. He'll be talking to us today a little more about what we're learning about treatment in the research today.

And finally, we're lucky to have a great discussant with us today. He's gonna help tie this all together. Dr. Satish Raj is the section chief of the Adult Cardiac Arrhythmia Group at the University of Calgary in Alberta. His primary research interests relate to understanding and better treating postural tachycardia syndrome, vasovagal syncope, orthostatic hypertension, and initial orthostatic hypertension, and now long COVID. So without further ado, I'd like to hand this over to our fantastic speakers. So Shane, if you could tee up our first person, Dr. Miglis, that would be terrific.

Mitchell Miglis

Great. Well, thank you. Thank you to the NIH for allowing us to present on this very important topic. Next slide, please. So, I'm gonna start with an overview of what dysautonomia is and just the autonomic nervous system in general, and try to do this in 10 minutes. So, the autonomic system is an incredibly complex component of the nervous system that maintains homeostasis or equilibrium in the body. And, we generally divide the autonomic system into three components, the sympathetic, which regulates fight or flight responses. And, it generally does this through the release of epinephrine and norepinephrine, and the parasympathetic system, which regulates rest and relaxation, and generally accomplishes this through the release of acetylcholine.

As we can see here, the autonomic system innervates almost every organ in the body. And, when we're evaluating patients with autonomic disorders, we try to localize sort of which organs are involved. Common organs that we see involved in our patients, and this applies to those with PASC, include the heart, blood vessels, gastrointestinal system, general urinary functions, sweating and pupillary functions. And then, as neurologists, we sometimes like to localize where the disorder is. Is it coming from the brain or the spinal cord or central, or is it more in the peripheral nervous system and the peripheral nerves? We don't have all the evidence yet, but it does seem that COVID likes to involve the peripheral system, preferentially. Next slide, please.

So, what is dysautonomia? So, this is a term that we're hearing a lot these days. So, it's an umbrella term that encompasses not only autonomic disorders, but autonomic symptoms. So, it's not a specific diagnosis. It's sort

of a catchall descriptive term. Some conditions that are more specific that we do diagnose include postural tachycardia syndrome or otherwise called postural orthostatic tachycardia syndrome or POTS, orthostatic hypotension, recurrent and early mediated syncope, autonomic neuropathies, very common causes include diabetes and very rarely familial dysautonomia. Next slide.

So, common disorders that we see and treat in our clinics are what we call disorders of orthostatic intolerance. And, we'll define this term in the next slide. And these include orthostatic hypotension or OH, POTS and syncope. So, one key distinguishing feature here that I wanna draw everyone's attention to, you know there's a difference between OH and POTS. So, OH, is a sustained drop in blood pressure of at least 20 points systolic or 10 points diastolic within three minutes of being upright. Patients may or may not have symptoms associated with this. POTS is defined as a sustained increase in heart rate of at least 30 beats per minute, within 10 minutes of being upright in the absence of OH. So, we cannot diagnose POTS if there was an abnormal drop in blood pressure. If that's the case, then the heart rate increase is most likely compensatory.

Most patients with POTS have a heart rate increase of greater than 120 beats per minute. In individuals that are in age of 12 to 19, in teenagers, the heart rate increase has to reach at least 40 beats per minute. And, there has to be associated symptoms of orthostatic intolerance. There's a chronic duration here defined in the consensus statement of at least six months. This is evolving. But, the point is POTS is thought to be chronic. Neurally mediated syncope is not necessarily a disorder by itself. It's a reflex that can happen to normal stimuli under stress, but if it is recurrent, which it can be in COVID, then we tend to define this as a disorder. Next slide.

So, orthostatic intolerance, this is a descriptive term that includes a lot of different symptoms, including the common symptoms of lightheadedness and dizziness, but also more non-specific symptoms like fatigue, nausea, shortness of breath. We query all our patients about this symptom. And, when we're evaluating patients with autonomic disorders, we're trying to really get at, are these symptoms brought out or are they worse with standing? Are they relieved with recumbency, because most autonomic disorders are. Next slide.

And, Lauren's gonna describe the symptoms in more detail, but I thought I'd include this. There's a, a reference here on the bottom of a review that we described a lot of these symptoms in, but this is when we were calling long COVID post-acute COVID syndrome. But, some of the symptoms that we see commonly in patients with long COVID or PASC are orthostatic intolerance, tachycardia, temperature regulation issues, sometimes labile blood pressures, or new onset hypertension, and a lot of GI symptoms. A lot of these symptoms are commonly seen in autonomic disorders. Next slide.

So, how do we evaluate these patients in the autonomic lab? How do we perform testing? And, this is not readily available. This is only available in a few select academic centers, but I thought I'd just give an overview of what we can do to help localize these symptoms objectively. So again, we're dividing the evaluation into sympathetic functions and parasympathetic. It's important to note that the testing we do really evaluates cardiovascular reflexes. We don't do gastrointestinal testing. We rely on our GI colleagues for that. We rely on our

urology colleagues for urologic testing. So, aside from sweating, which is a sympathetic function, most all these other tests are evaluating cardiovascular reflexes. Next slide.

And so, this is what we'll see on a tilt table test in a patient with POTS. This is actually from our case report of the first patient that you know was published with post-COVID POTS. And, what we can see here is blood pressure on the top. We measured blood pressure with a continuous beat to beat monitor here on the finger, so we can detect any sudden changes. We also like to correlate that with a manual blood pressure on the arm. And, you can see here in the middle, the heart rate increases dramatically by 60 beats per minute. There's no drop in blood pressure. In fact, the blood pressure goes up, which we commonly see in these disorders of sympathetic hyperactivity. And so, the patient has symptoms with this tilt response. We're able to diagnose POTS. Next slide. On contrast, this is what we'd see in orthostatic hypotension. I'm not showing you the heart rate here, but the blood pressure drops on tilt up pretty significantly. The patient's symptomatic. The patient sits down blood pressure increases again. If there was a dramatic increase in heart rate, we would not be able to diagnose POTS here, because of this abnormal drop in blood pressure. Next slide.

And, this is what we see in a patient with neurally-mediated syncope. We see a fairly stable blood pressure for several minutes during the tilt, and then a very precipitous drop in blood pressure and heart rate resulting in loss of consciousness. Next slide.

But, we don't need autonomic testing to diagnose some of these disorders, including POTS or orthostatic hypotension. This can be done in the office. This can be even be done at home by the patient. We give a lot of our patients home orthostatic logs to track this at home. And, we're advocating that this should be included in evaluation of patients with PASC and suspected autonomic dysfunction. We should be doing orthostatic blood pressure and heart rate checks with at least a five minute rest period supine. And then, we'll have the patient stand for at least five minutes and check the blood pressure and heart rate every minute. We like to do an active stand test, and not a NASA lean test because it does produce more of a physiological stress. Next slide.

And then, just to finish up very briefly showing you some of the other tests we do in the lab. The Valsalva Maneuver measures very similar functions that the tilt measures. It's measuring the baroreflex. And, what we like to see is that we have a blood pressure, nice blood pressure increase when the patient is blowing into the tube on this, we call phase two. A patient with autonomic failure will not increase their blood pressure in that phase two with this stress. And, what we'll see in POTS is actually the opposite. We'll see very dramatic increases in blood pressure, which also suggests that sympathetic hyper activation. Next slide.

And then, the very simple test we do of parasympathetic cardio vagal function is just deep breathing. And, we'll measure the change in heart rate with deep breathing. On inspiration, we should see an increase in heart rate and on expiration, a decrease in heart rate. And so, we simply calculate the difference on this heart rate change with deep breathing. If we see something where there's a, for instance, an autonomic neuropathy where there's diffuse damage to the autonomic system, we'll see a significant reduction in this heart rate variability. Next slide.

And, then very final slide here. These are more specialized tests of sweating that we can do. Common test is called a QSART where we'll infuse acetylcholine into this capsule, this vacuum sealed capsule on the extremities. And, that will stimulate sweating, which is again, a sympathetic function. And, we'll see this nice sweat response here if the patient has normal sweat function. So these, this function is regulated by the small fiber, the small autonomic unmyelinated fibers in the skin. We're seeing a potentially significant prevalence of small fiber neuropathy with COVID. And, in this case, the sweat function would be reduced. We can look at this even more specifically with a skin biopsy, which is a relatively noninvasive punch biopsy, where we can take a few millimeters of the skin and then stain this with axonal pan axonal markers, and just count the epidermal nerve fibers. And, this is a little bit more of a specific test, and more readily available for diagnosis of small fiber function. And, with that, I'll hand it over to Lauren to discuss common symptoms in PASC.

Lauren Stiles

So, I wanna talk a little bit about symptoms, but also why it's so important that we understand autonomic dysfunction that's happening in long COVID as we study it and also as we offer clinical care to these patients. So, a little background. The idea that a virus or any infectious agent can cause dysautonomia is not new. The prior coronaviruses have also caused a post-viral syndrome in about half of patients with a lot of symptoms that were similar to, suggestive of autonomic dysfunction and lots of other infectious agents can cause this. It is definitely not a complete list. Also wanted to highlight that it's not just POTS. Postviral autonomic dysfunction can present in lots of different ways causing different autonomic disorders, but it seems that POTS is probably the most common presentation that's appearing in COVID, although we do need further research to really clarify that. And, I think, Dr. Novak is gonna share some of that with us later.

I just wanna talk about a little bit, two slides on like, what is POTS? 'Cause, I think a lot of clinicians are not really familiar with it. We don't have a lot of great training on autonomic disorders when people go through medical school, even if they're in, you know, electrophysiology or neurology fellowships. So, it's, POTS is defined by excessive orthostatic tachycardia on tilt. And, its, you know, primary symptom manifestation is orthostatic intolerance, but really the entire autonomic nervous system can be impaired in these patients, and they can have a wide range of symptoms. It's not just tachycardia. It is the most common diagnosis seen in autonomic clinics before COVID. Again, these numbers are before COVID. We had an estimate of one to 3 million Americans having POTS. I think that number, I would not be surprised if it has doubled as a result of COVID or even more, but we're gonna need good epidemiology data to let us know that. POTS is about 90% female before COVID. Peak age of onset at age 14, but I don't want anyone to think it's a pediatric only condition, because half of patients develop it in adulthood.

I actually developed POTS triggered by a snowboarding concussion and probably worsened by having an autoimmune disease Sjogren's Syndrome 10 years ago. I was 31 years old. So, 50% of POTS patients have a

postviral onset, but we have other triggers like bacterial infections, concussions, pregnancy, car accidents, surgeries. And, the thing that all of these have in common is that there's something that could stimulate your immune system and, you know, irritate your autonomic nervous system. And, you know, many people will bounce back from these problems without a problem, but there's just a subset of people who kind of evolve into this chronic autonomic disorder. And, I'm hoping that RECOVER Research is gonna help us understand what that process is, what those risk factors are and how we can help people kind of get their autonomic nervous system back to functioning more normally.

So, here's a symptom survey that I did with Dr. Raj, who is our moderator today. We surveyed, this is about 4,000 POTS patients. This is pre-COVID. And, these patients, if you looked at the symptom list and the percentages of patients that reported the symptoms, it looks very similar to long COVID studies that are reporting on all the different symptoms in long COVID patients. So, there's really a lot of overlap. And, a lot of the symptoms we're seeing in long COVID, you know, could potentially be driven by autonomic nervous system problems. So POTS patients universally have lightheadedness and tachycardia is sort of part of the diagnostic criteria. I think that another really important thing to focus on is that 94% of POTS patients report headaches. 40% have migraine. Difficulty concentrating and memory problems are pretty much universal in POTS patients. And, we actually have other studies showing it's not just in the upright position that this happens, that POTS patients actually have cognitive deficits in the supine and upright position. It's worse when they're standing up, but it's also present when they're laying down. They also have signs and symptoms of small fiber neuropathy like numbness, tingling, and burning. And, we have clinical research studies from multiple centers showing that about half or a little bit more than half of POTS patients have autonomic and sensory, small fiber neuropathies. They have profound fatigue and exercise intolerance.

This woman who has lent me a photo of her legs, we call this kind of for fun, you know, purple POTS legs, but the more scientific name for it is dependent acrocyanosis and it happens just after a minute or two of standing in about half of POTS patients. They also have a delayed capillary refill if you sort of press on their shin or their foot. And so, this is sort of, you know, a complex process. It's oversimplifying it to call it just blood pooling, but conceptually there's, you know, there's a problem with their hemodynamics. POTS comes with quality of life, similar to endstage renal failure.

That's a study out of Vanderbilt that Dr. Raj was part of. Disability similar to COPD and congestive heart failure. That's a study out of Mayo Clinic. And it's weird, you know, these are younger people that have sort of quality of life and disability that's just usually what you think of in sort of older people who look a lot sicker. So, I think one of the challenges POTS patients have is that they are generally younger looking people and people assume that there can't be anything wrong with you. You look fine is sort of a common thing that these patients hear. So please, you know, don't say that to your patients. Take their symptoms seriously. Also important to note, while they do have signs of sympathetic activation like tachycardia and tremulousness and whatnot, they have

psych profiles similar to the national norm from a couple of different studies. So, don't misinterpret their autonomic symptoms as, oh, that must just be anxiety.

So quickly, the study that Mitch and I did is a similar survey looking at autonomic symptoms in long COVID patients. And, we found that 67% of long COVID patients have moderate to severe dysautonomia which we assessed using a patient self report form, COMPASS-31, and importantly, the autonomic severity and the presence of autonomic dysfunction didn't differ between the hospitalized and non-hospitalized patients. So, acute viral severity is not really predicting the autonomic problem. So, the most common symptoms were very similar to the symptoms you see listed in the prior slides on POTS, fatigue, cognitive impairment, headache, shortness of breath, body aches, palpitations, lightheadedness, and tachycardia. And, other PASC surveys have found this too. I'm not gonna get into this in detail, but if anyone wants, you can get a copy of COMPASS-31 and the scoring algorithm from this open access article in Mayo Clinic proceedings. And, it's a good review of systems if you're working with PASC patients to try to understand if they have an autonomic problem, even if you don't have a full autonomic lab at your disposal.

So, we have, you know, good research showing that autonomic dysfunction drives a lot of these postviral syndrome symptoms. Something we don't really talk about is the role of the autonomic nervous system in driving immune dysregulation and our coagulation pathways. So, I have two slides on this, just wanna sort of plant the seed and get the idea out there in the research world as new research is happening. So, if you haven't heard of the cholinergic anti-inflammatory reflex, I urge you to look it up on PubMed. There's a lot of really fascinating research happening in this space. And, almost any discipline, no matter what field you come from, there's some relevance to your field in learning about this. This is basically how the autonomic nervous system through primarily through the vagus nerve regulates inflammation and the predisposition towards autoimmunity in the body.

So, once you understand the cholinergic anti-inflammatory reflex is this neural reflex that regulates inflammation. It kind of makes sense that people with autonomic dysregulation might end up with immune dysregulation. And so, there's this great new research happening showing vagus nerve stimulation can provide some benefit in a wide range of autoimmune conditions, things like IBS. We have four studies and POTS so far with good preliminary data, and there are some trials happening in long COVID, and we're hearing some anecdotes and, you know, kind of small case reports on this. So, I think this is a space to pay attention to. It's actually very accessible and affordable if it can actually be done with a modified Tens unit. So, I think it's something to look into if you are working with long COVID patients.

And then, last slide on a substantive thing I have is so there's a lot of talk in the long COVID community about hyper-coagulation and micro-clots, not only in acute COVID, but also in long COVID. And, I don't have, that's not my area of expertise, but I do know that the sympathetic nervous system, which we are finding is sort of over-activated in a lot of long COVID patients, sympathetic activation, even in healthy people increases hyper-coagulation. So, you know, it increases coagulation, and that's part of normal physiology. I have this silly little

cartoon, you know, I'm sure everyone remembers, you know, if you're being chased by a lion, and you get scratched, you don't wanna bleed out. So, it's probably a good time for your coagulation to kick in. And unfortunately, when you have a virus, you're not being chased by a lion, but your body sort of is in that fight or flight state for a prolonged amount of time in a lot of the long COVID patients. Related to this, we have one study showing kids with POTS before COVID. Kids with POTS have an 11-fold increase of DVTs compared to other children using chest ports within the whole Children's National Health System. So, I think that's a hint that this is going on in other people with chronic activation syndromes, not just necessarily in long COVID.

So, I hope that future research in RECOVER and other long COVID studies will really dig into the coagulation pathology and how this may or may not relate to the autonomic function. So, my last slide, I just have some links that might be helpful to clinicians, as well as patients. Dysautonomia International is offering, we don't have the NIH's money, but we're offering some research funding through the long COVID research fund. And, we also have an autonomic disorders video library with over a hundred lectures from the top experts on autonomic disorders. So, thank you very much.

Peter Novak

Thank you. My name is Peter Novak. In next few minutes, I will talk about post-acute sequela of COVID in the context of cardiovascular and autonomic abnormalities. So, initial study did show that PASC affects about 50% of survivors of COVID infection. More recent study did show 30%. Clearly, prospective studies are needed to clarify the true prevalence of the PASC. Neurological symptoms vary across patients and can be disabling irrespective of severity of initial infection. Typical neurological symptoms are fatigue, brain fog, headache, sleep difficulties, cognitive and emotional problems, dizziness, muscle weakness, myalgias, hyposmia, sensory motor deficit, and of course, dysautonomia. Neurological symptoms can reflect involvement of neurosystems or can be linked to underlying organ dysfunction due to COVID. For example, affecting respiratory, renal, psychiatric, endocrine, hematologic, autoimmune systems.

According to WHO and NIH, neurological symptoms are core aspects of long COVID. As of yesterday, there were almost 81 million of COVID cases in US. Assuming 30% of COVID prevalence, which is kind of a conservative estimate, the total number of PASC is about 24 millions. As to be expected, the highest prevalence is in California and Texas. And in Massachusetts, we have about a half million. And, the true incidence of PASC is still unclear. This is nice, a retrospective study from England, looking on the 273,000 COVID survivors. And, they show incidence of 50% in combining any signs at six months. The most common was anxiety and depression, full but abnormal breathing. Autonomic symptoms are very common. One survey did show that the most common symptoms were attributed actually to autonomic dysfunction. The Long COVID Advocacy Project noted that 34% of patients with past patients had new diagnosis of autonomic dysfunction. And, this is a lower end study, which showed that in 2,300 PASC patients, 67% of PASC patients had dysautonomia which was moderate to severe based on the

COMPASS survey for autonomic dysfunction. Exact incidence of dysautonomia, and its clinical significance is still not clear, because a lack of objective autonomic testing studies. So, this surveys prompted us to design a study to evaluate dysautonomia and related problems in PASC using objective test. We used the comprehensive evaluations that I will explain in next few minutes.

So, this was a retrospective study that included nine PASC patients that completed comprehensive autonomic testing with skin biopsies. All had mild COVID disease. All were treated as a home observation, and there was too a delta variant, and those are one of the initial patients. And typical presentation was fever, cough, dyspnea, headache, loss of smell, and no one was vaccinated. And, PASC patients were age and sex-matched with 10 women with postural tachycardia syndrome and 15 healthy controls.

Patients were evaluated using Brigham Protocol, which consist of standard or standardized autonomic function tests, which are combined with cerebrovascular and respiratory assessments and skin biopsies. They are using to continue transcranial Doppler for measurement of cerebral blood flow in the middle cerebral artery during the tilt test. Standard autonomic cardiovascular tests, which were described by Mitchell a few minutes ago, measures cardio vagal for sympathetic system, and sympathetic audiologic system. We are using also pseudomotor test for postganglionic measurement and skin biopsies for evaluation of small fibers. We're looking for both sensory and pseudomotor fibers. We also evaluate several inflammatory and autoimmune markers for assessment of low grade inflammation. So, results show that PASC is associated with multisystem involvement affecting cerebral vascular, including cerebral vascular dysregulation with persistent cerebral arterial vasal constriction. It was also evidence of small fiber neuropathy and related widespread dysautonomia. Also, we find respiratory dysregulation and evidence of chronic inflammation.

Few words about small fiber neuropathy. We find this type of neuropathy in 89% of PASC patients and 60% of POTS patients. There were no small fiber neuropathy controls. Most common type of neuropathy was mixed affecting sensory and autonomic fiber simultaneously. Slide on the left side shows typical example of the healthy control with number of the epidermal fibers marked on this red arrows. And, the right side is a PASC subject with reduced number of the fibers, which is consistent with a small fiber neuropathy. Our finding was actually confirmed by our colleagues from MGH, Anne Oaklander and her team that found also evidence of small fiber neuropathy in 65% of PASC patients. Also, these patients were treated with steroids and IVIg, and about half of the treated patients improved.

So, it was concluded that the results of this study support hypothesis that some of the long COVID symptoms are results of small fiber neuropathy and also positive response to immunotherapy with IVIg on steroids strengthen the link between small fiber neuropathy and this immunity in PASC. There's another report described painful paresthesia and numbness associated with small fiber neuropathy in PASC. This came from Mount Sinai Hospital. Most of patients improved on symptomatic therapy. Cerebrovascular dysregulation is one of the major findings of our study. Abnormal cerebral blood flow was detected in 100% of the PASC patients. So, in everybody.

Orthostatic cerebral blood flow velocity declined in average, 20% in PASC patients, which is similar to the POTS patients.

So, this is a group statistic from the tilt test, showing supine and orthostatic response in the cerebral blood flow. The orthostatic cerebral blood flow decline in both PASC and POTS in spite that no one had orthostatic hypotension, meaning that decline is due to cerebral vascular dysregulation. And again, the decline was about 20% in both the POTS and the PASC patients, which is clinically significant since that decline is associated with signs of cerebral hypo perfusion in POTS patients. And, this slide shows somebody of the tilt test showing orthostatic tachycardia in the POTS, reduced cerebral blood flow velocity in POTS and PASC. And, this particular pattern of the respiratory dysregulation associated with hypocapnia, which I will mention a few minutes. Dysautonomia was also frequent in PASC. In our group, objective evidence of dysautonomia detected in everybody in both PASC and POTS patients when we combined abnormalities in different, simple autonomic systems.

For example, so the motor dysfunction was detected in 67 of our PASC patients, parasympathetic in 40% and sympathetic adrenergic in 100%, which kind of similar in terms of the frequency than in the POTS. And, no one had dysautonomia in controls. We just completed another retrospective study with expanded number of the patients, which is in the submission that confirmed widespread dysautonomia in PASC. In this cohort, autonomic failure was slightly worse in POTS compared to PASC. Again, orthostatic hypertension was not present in anybody. Mayo Clinic also evaluated dysautonomia in PASC patients, and they find out pseudomotor dysfunction in 36, cardio vagal in 27, and cardiovascular adrenergic 7%.

So, this is kind of similar than our finding. And interestingly, it's also very similar than in we found most common was orthostatic symptoms, most common complaint were orthostatic symptoms without evidence of tachycardia in 41%. It was concluded that dysautonomia was frequent, but mild. But, the most common finding is orthostatic intolerance was without any objective finding. We think these patients, they had decreased the cerebral blood flow as in our case.

And, this is another study that Blitshteyn and Whitelaw published as a retrospective chart study. And, they look on the patients referred to autonomic clinic for new onset of dysautonomia. They evaluated 20 patients, and the most common diagnosis was POTS in 75%. Although the diagnosis were not made by autonomic testing, but by standing test. But, dysautonomia was quite disabling. 60% of patients were unable to work. But, another study found POTS only in two percent out of the 85 patients prefer probably (indistinct) plays a role. Autonomic system controls all organ, as you heard before in lectures, therefore widespread dysautonomia is found in the PASC patients can affect multiple organs causing variety of complaints.

We also find respiratory dysregulation, which was common as well. Supine and orthostatic hypocapnia was present in the PASC patients while orthostatic hypercapnia only was in the POTS, which is typical finding for the POTS. So, this is the end tidal of CO₂. PASC patient data or the decreased end tidal CO₂, even supine slightly, which persisted throughout the field, while in the POTS patient, normal supine in the end tidal CO₂, which declined

during the upright position. Carbon dioxide has a profound effect on the cerebral blood flow hypoxemia is causing cerebral basal constriction and reduction of cerebral blood flow. Hypoxemia is cause of the reduced cerebral blood flow in POTS since adjustment, when you are adjusting the effect of the blood flow due to a hypoxemia, it will correct the blood flow in the POTS patient, but not in the PASC. It implies that in PASC reduced blood flow is due to cerebral autoregulatory failure associated with stiffness of the cerebral arterials. Inflammation was also checked with our cohort.

And, inflammatory dysregulation was also found in majority of the patients. Elevated inflammatory markers were found in the 67% of the PASC and 70% of POTS patient, which is very similar. These findings are considered with low grade inflammation. In the summary, PASC is associated with multiple system dysfunction. It can be argued that we have a low number of the patients, but all our findings were replicated by other studies. Cerebrovascular dysfunction results in cerebral orthostatic hypoperfusion due to persistent cerebral arteriolar vasoconstriction. And, it may cause orthostatic intolerance, fatigue, brain fog. Dysautonomia may contribute to orthostatic intolerance, fatigue, dyspnea, and temperature dysregulations, GI and urinary problems. Small fiber neuropathy may cause pain and other sensory disturbances. Respiratory dysregulation may causing with hypoxemia may cause dyspnea, increased fatigue via alkalosis and maybe tissue ischemia. And low grade inflammation probably affecting the small vessels can be a pathological substrate of PASC.

We think that virus, some are triggers of dysregulation of autoimmune system be subsequent release of probably inflammatory cytokines that can lead to low grade inflammation. Few words about the therapy are therapy is mostly supportive, symptoms oriented. There's a limited evidence about effectiveness of pharmacological approaches. There are multiple ongoing clinical trials using off-label medications or new medication, exploring role of supplements, vitamins, probiotics, antioxidants steroids, IVIG and other immunomodulators. And, based on suggested pathophysiological mechanisms of PASC, this picture is taken from Dr. Umesh from Infection Journal. Based on his current knowledge, PASC mechanisms are very complex and interrelated, multiple mechanisms in parallel. And, the main mechanisms can be divided by three major categories. Those are direct cellular tissue injury caused by cytotoxicity. Second, immune activation and inflammation probably through antigen growth reactivity or via injured cells damage. And third, the effect of physiological response or maladaptive response with hormonal changes and abnormal intracellular signaling pathways.

It is postulated that combination of these three mechanisms are responsible for the respective clinical symptoms. And these slides are, there are several potential therapeutic neuroimmune targets. The list is not complete and only show some examples. The therapy can focus on particular metabolite or protein, for example, an interleukin six blocking or using antibody against certain antibodies. For example, recently described antibodies against several types of the GPCR receptors. Those antibodies found in the PASC patients, they might activate those receptors causing for example, autonomic dysregulation. They can probably, they can, for example, activate genetic receptors. Or potential target, therapy can target more widespread or more generalized pathways.

For example, to moderate (indistinct) receptors or modulate B or C, T cells, or moderate coagulation cascades. There are multiple clinical trials that hopefully will give us some answers soon. There was also interesting study in Nature recently showing several genomic loci that are associated to be either predisposed to COVID or to severity of the COVID disease. And, there are a number of clinical trials, and as September 21 there were registered 201 clinical trials. About half of them were observational, less than half interventional. And interestingly, most of the trials originated in academia. And this was my last slide. Thank you.

Tae Chung

My name is Tae Chung. I'm from Johns Hopkins. I'm a neuromuscular specialist by fellowship training, but in my residency in physical medicine rehabilitation. So, I have a privilege of working with other rehab therapists, which I think is very important for the treatment of this condition. So, for this 20 minutes, that's assigned to me, I'll focus on some treatment strategies for dysnomia in PASC patients. Next slide, please.

So, before I talk about the treatment, I briefly touch on kind of a little bit of a framework for diagnosis, how I approach to this condition. So, when I say PASC, at this point, it's very loosely defined. It really, you know, includes everything that can arise and causing long lasting symptoms after COVID infection that includes, you know, pulmonary fibrosis or post-ICU syndrome, cardiomyositis, and pulmonary embolism, and everything. Obviously, I've been focused on POTS and dysautonomia, which I believe a lot of people here believe to be one of the probably most significant and largest problem in PASC patients that's also very debilitating. Next slide, please. And, in the previous talks, you know, Dr. Miglis, Professor Stiles and Dr. Novak really beautifully pointed out that first, you know, although at this point, a lot of PASC symptoms are discussed as filling some mysterious conditions. A lot of people in the field have actually recognizes symptoms pretty well. The clinical phenotypes are very typical for, in many cases, clinical diagnosis of POTS that includes, you know, difficulty breathing, especially after some short activities or exercise, severe debilitating fatigue, brain fog, sleep problems, and, you know, lightheadedness and so on. So, I'm not gonna go over the symptoms, this actually a table, I got it from CDC Government that listed all the symptoms of PASC. And, you recognize by now that these symptoms are very typical for, again, clinical diagnosis of POTS. Next slide, please.

So what is POTS? So, how do we explain all the kind of multi-systemic symptoms? Again, just before I get to the treatment part, I see those symptoms as primarily vasomotor symptoms, Can you kind of move over slides, please. It's an animation. So if you can just keep going. So, basically they have a lot of post-exercise malaise and flares because basically their blood flow is not really getting to muscles when they exercise. They have a brain fog with this concentration and Dr. Novak, just beautifully illustrated in his slides that, you know, there's a severe reduction or just about 20% reduction in blood flow to cerebral blood flow whenever there have been brain fog. And also, they have a chronic fatigue, orthostatic intolerance.

Now, you know, these symptoms by default, they check our brain, heart. I work at the very large post-COVID clinic collaboration at Johns Hopkins. And, in the beginning of COVID pandemic, they've actually done pretty much all the tests for heart, whenever they have a heart palpitation and so on, they actually check heart MRI, cardiac MRI, for pretty much all the post-COVID patients. They get the MRI of the brain. We did everything, and rarely we find any primary heart infection or inflammation or brain, you know, disease in the imaging studies or other things. So, you know, it looks like it's, you know, each organs are probably likely normal. It's more vasal or blood flow kind of problem that's affecting these multiple organs. And, you know, but that's probably likely coming from autonomic nerve denervation that's regulating the blood flow. Can you go over the next slide, please?

So, I call this pump failure symptoms, and just, can you please move on? Yeah. At the same time, maybe it's a compensatory mechanism or maybe this abnormal barrier reflex function. Can you move? Yeah. There's also, paradoxically, increased sympathetic activation. And, can you go on? And causing, oh, go back to slide, too. So, causing all these sympathetic central, sympathetic symptoms that causes anxiety, palpitation insomnia. They wake up in the middle of the night all the time. They have a slow GI motility that may pre dispose nausea, vomiting, or constipation down there, and hyperhidrosis. So, next slide.

Basically, when I approach like, you know, therapeutically approaches POTS, I kind of see two different clusters of symptoms, which is one vasomotor dysfunction denervation symptoms. Basically, it's a blood flow pump failure symptoms, which explains fatigue, brain fog, exercise intolerance, migraine, and other things. On the other hand, there's a kind of more central sympathetic activation that causes anxiety, palpitation, you know, insomnia and GI problem and so on. And, I think this is very important kind of diagram, because their symptoms are very diverse, but it comes down to vasomotor symptoms and sympathetic symptoms. These are very paradoxical, because you have those symptoms that's coming from too much excessive adrenaline or sympathetic, you know, activation, and also at the same time, peripheral sympathetic denervation.

So, like for example, there has a lot of therapy implication, for example, in generally in POTS field, it's been well known that, you know, beta blockers are very important to reduce palpitation and calms them down and helps with a lot of patients. But, at the same time, especially with the higher dose, it can worsen some of the fatigue and orthostatic symptoms and vice versa. So, I think it's really important for clinicians to really understand this paradoxical nature. And, in my experience, these symptoms can be very diverse and dynamic.

So, for example, for same patient, certain dose of beta blocker may work beautifully for maybe a few months. And then, you know, afterwards it may actually work the other way too. So, I think it's essential to understand the paradoxical nature of this symptoms. And, also closely monitor their symptoms and make sure we are kind of very flexible in terms of using our medications. And, for these reasons I try to avoid polypharmacy, 'cause, if they're getting like five or six medications, there's no way to know what's helping and what's not. So, keeping that in mind. Well first, next slide, please. You know, I think from a neuromuscular standpoint, I think the localization to me with some indirect evidence, I think this is more like sympathetic ganglionitis. It's a post

infectious. There are symptom onset is very acute and probably a text inflames some different sympathetic ganglia, chain ganglia, and then causing both vasomotor symptoms, and, you know, pseudomotor symptoms and other things too. Now, next slide, please.

Then, how do we approach this problem? I think, well, generally there are probably two approaches there, and I'm gonna talk about, you know, potential antiinflammatory, immunomodulatory, you know, approach a little later on, but, you know, for symptomatically, they have these vasomotor symptoms, and excessive sympathetic symptoms, how do you approach to that? So, I try to approach it a little differently for the different kinds of problems. So, for example, for vasomotor symptoms, pump failure symptoms, we try to do very aggressive volume expansion. Whereas, for sympathetic overcompensation, we try to do use some medication or some meditation techniques to bring down their, you know, kind of adrenaline and anxiety level. Next slide, please.

So, volume expansion for audience here, I don't have to really explain too much. We're trying to expand the volume and, you know, increase blood volume to, you know, help with the vasomotor symptoms. And, the effect of volume expansion. Well, the reason that I think those, you know, like for example, for insomnia and other things are connected to this whole POTs symptoms is that, oftentimes if you do really aggressive volume expansion, other symptoms get better too. Not only their fatigue level gets better, brain fog gets better. Oftentimes, they sleep better and anxiety level goes down as well. So, I think couple of things to keep in mind is the volume expansion is really easy in the concept, but actually to do is not that easy. They have to drink a lot of excessive amount of water and a high level sodium as well. And, oftentimes it takes a lot of time for patients to modify their lifestyle to achieve this.

Oftentimes, I do IV saline hydration, and just acute volume expansion with IV saline bolus. And, you'll see that a lot of these patients, immediately, some of their symptoms improve. Well, the problem is that IV saline infusion is really not for long-term solution. You know, each time, because even if you get one liter bolus or two liter bolus, it doesn't stay in your body for long time. I try to do this, limit this IV hydration to bridge some physical therapy. I'm gonna mention a little bit later in the next slide about the exercise intolerance, but sometimes whenever they try to do physical exercise, if they cannot tolerate it, I just try to bridge them with the IV solution, you know, for a short period of time for a few weeks, or for a few months. Of course, on top of, you know, oral hydration and salt intake, we use various medications such as midodrine or fludrocortisone to optimize volume expansion. I try not to use those medication until I make sure that they are really actually modifying their lifestyle and diets and drink a lot of water, 'cause without it, usually it doesn't help a lot.

Now, I see physical exercise as a part of volume expansion treatment, and my rationale for physical exercise. Why does it works? I think it's some for long term cardiovascular training, it increases our blood volume. It's possibly because they increase their hematocrit. They made more red blood cells, or in part because of skeletal muscle pump, that's returning more blood back to the heart and lung. So either way, it's really, it works really well. As I said, we have a multidisciplinary clinic. I work closely with our physical therapists, and over long term, once

they can achieve physical exercise, certain level, they actually feel much better. They actually feel better with their fatigue and brain fog and other things. Now, next slide.

However, there are a couple of issues that we really need to address. First of all, it's a gradual cardiovascular training. It takes a long time. I think for both clinicians and patients, they really have to understand it takes a long time. Oftentimes, more than several months a year. So, the key is really not to give up in the middle. It's not something that they do just better after a few weeks of exercise. And also, they have a lot of limitation in exercise in the beginning. So, next slide please. So, this is kind of the, just move all the animation please. So, this is kind of theoretical graph for exercise in POTS patient. Now, the black line is whenever the normal patients, normal people do the exercise.

Now, the X axis is time. The Y axis is heart rate? Go back to the previous slide, please. Yeah. So, normal people, when you start exercising, your heart rate goes off, and then when you stop the training, it goes down, cools down right away like that. POTS patients is kind of red graph. It's called theoretical graph that we see all the time. In the beginning, they kind of increase nicely as they match to, you know, increasing metabolic requirements from their (indistinct). But, at some point they shoot up, and they cannot tolerate after at some point. And, this, well just call this point on the return. And, that point can be only five or three minutes into a stationary bike. And, these patients can be, you know, very young 20 and 30 kind of patients. And, the thing is that before that point, people really have a hard time tolerating the exercise. And, the idea of this gradual training program is to really push this point further to the right side over time. Next slide, please.

So, we use another medications to bring down sympathetic symptoms. I, again, for the reason that I mentioned, I try to do more non-pharmacological stuff with such as meditation and mindfulness. They can be very effective. Next slide, please. And also, again, with education for a lot of different things, it's very important, like avoiding dehydration, certain things like caffeine can actually dehydrate people, avoiding infection can avoid flares. So, they need a lot of education piece to change it. A lot of people have MCAS activation syndrome. And, because of that, we, you know, they need to go over certain different dietary kind of regimen to avoid possible triggers. Next slide.

And, a lot of people have kind of hard time ambulating because of orthostatic tolerance. We use certain, you know, devices for them to be able to get around better. For POTS patients, something like, you know, Rollator can be helpful with a sitting function, 'cause sometimes they can faint or they can sit down. Next slide.

Of course, we use physical measures such as compression stocking and binders. We make sure that it's thigh high and abdomen binders are very important. Next slide. So, for it's says animation. So please go through that. So, so basically the basis immune therapist is that it's post infectious. So the, I think that the idea is that whenever the, you know, we make, whatever the antibody we make to fight against COVID-19, maybe one of them or a few of them is over-reactive, and they kind of recognize our autonomic ganglia, potentially. We don't know

exactly what target organism at this point, but potentially the auto-reactive antibodies inflaming our own body and causing post-COVID POTS, causing sympathetic vasomotor fibers. So, next slide, please.

So, the idea, and it's possible that the target can be, can move this animation as well. It can be kind of interfering at the synapse, or it can be axonal. It can be neuronal attack at the sympathetic fibers. Next slide, please. So, can you keep moving? Yep. So, the idea for the immune therapy is to bring down potentially auto reactive, auto antibodies. There are actually few available for the treatment immuno-modulating treatment that includes a high dose IVIG. We know that this kind of brings down auto IVIGs in the body. So, you know, it kind of probably precipitates neutralized, autoreactive IVIGs.

FcRn receptor antagonist is a newer kinds of medication. We'll be doing clinical trials on post-COVID POTS patients using this medication. Basically, this medication also brings down auto IVIGs in the body. So, it's a bit, we don't have to know which target, you know, which, you know, target organs are for these old reactive antibodies. And, it just brings on all the IVIGs in the body. So, we are hoping that all the inter-mediated POTS from post-COVID, I think is gonna work. Now, I know some people have used rituxan or high dose steroids before. I'm a little bit kind of hesitant to use Rituxan on this kind of patient for many reasons, but I know somebody ask questions about potential HDS, TSHDS, FGFR three antibodies. Those are IgM mediated auto antibodies. So, we don't know if auto antibody for PASC are IG mediated or IgM mediated. So, potentially there's a role for things like Rituximab, but although these are, to me, it's a little too strong immunosuppression. And, you know, based on potential risk can benefit, I'm still not a 100% convinced about using this, but, we'll need some more research to, you know, find out what the autoreactive antibodies are at this point. Next slide, please.

Okay. Well, I'm gonna skip this mass activation syndrome for the interest of time. And, this is actually my last slide. Thank you very much for your attention.

Satish Raj

So, I think I believe I'm up next. Welcome to you all. My name is Satish Raj, and I have no slides. Basically, I think I've been asked to give sort of a couple of minute overview of some of the stuff we've heard and seen and try and put this in the context. And, what I'm hoping to do is actually leave a little more time than perhaps we had planned for some of the questions that have been entered into the Q and A.

I think one of the key messages from all of our speakers that should come through is that this is complicated. And, it's complicated for different reasons. There are lots of things you could argue are complicated, but I think one of the challenges, there are many challenges, right? I mean, and these challenges are all things that we've seen in the POTS world, and in the autonomic dysfunction world before COVID, and it's not been made easier.

One is, at least until recently, there was no real administrative data to determine, you know, how common these diagnoses are, assuming that people can make the diagnosis, the physicians can make the

diagnosis. I think that's changed for the PASC or long COVID. It actually still true for POTS, although that will change at some point. So, it's tough to get a handle on how much there is. The other challenge when discussing the different pathophysiologic mechanisms is that not everyone has all of these, right?

These are things that are, have been seen in some patients with POTS in the older literature and in the long COVID cohorts. And, that's important to understand, that, you know, I think, you know, certainly my source of medical knowledge, Twitter, you know, often people seem to sort of look at one treatment and assume it's a treatment for all. And, if one person got better with a treatment, that's great, right? Because, this actually can be debilitating, you know, out of all proportions to individuals. But, it's important not to jump from that anecdote of one and say, "Well, this is everyone should be on X or Y or Z," because the truth is we don't understand what's causing it in the different subgroups of people. I think in the POTS world, I suspect that, you know, my colleagues on this session would agree that there is not a thing that causes POTS.

There are different things that end up with a similar phenotype. And, I think PASC or long COVID is that, but even more so, because the presentations are even more varied than we see in POTS overall. So, I think, you know, while, you know, we all want answers, you know, I think we really need to take these initial steps. Quite frankly, what are really small studies so far, because this is all still relatively new to us. And, we need to actually start trying to figure out who those subgroups are and then do studies of therapies.

And, I applaud, you know, in several of the talks today, my co-invest, not co-investigators, my co-presenters have highlighted some of the studies or areas for study that are coming up. And, I wanna emphasize that that is needed. It's not adequate to say, "Hey, you know, three people said, this is the problem. And so, everyone should go on therapy X or therapy Y." I mean, I think we've learned in the POTS world, it's not that simple. And certainly, we have to sort of step back and not give up. I think, you know, I think this has brought a lot of, it long COVID the presentation overlapping with POTS has brought a lot of attention to this, much needed attention. And, that could be used to help springboard us to hopefully what's a better future as we start to understand it, because I think a lot of the solutions are gonna be common.

In the beginning, it's going to be using treatments that we've used traditionally for POTS and other related autonomic disorders in long COVID patients that look like that. But over time, we may actually be able to use the attention brought to it by the long COVID patients to help the larger group of patients that have suffered with POTS and other, you know, related disorders for decades. And that's, you know, maybe the good that can come of all this otherwise not so good stuff.

With that, actually, I'd like to sort of, you know, poke my panelists a little bit to press further on some of the stuff they brought up. And, I was particularly intrigued by one of the slides that Dr. Novak showed. And, in fairness, Safuan from Stanford was also intrigued. And so, I will ask on his behalf. You indicated that the, the end tidal CO₂ in, you know, POTS patients and the PASC patients are low on standing, but when not standing, when supine, the PASC patients had a low end tidal CO₂ while the POTS patients did not. Any thoughts on why,

what this means in terms of underlying pathophysiology? And, if that's the explanation for the cerebral blood flow velocity changes that you also showed?

Peter Novak

Well, we don't know exact mechanism, but respiratory dysregulation is very common in the PASC. Actually, when I, this was one of the, actually the most common complaint in the UK study in post-COVID patient. So, for some reason, the virus has propensity to affect the pulmonary respiratory system. We, in our patients, most of them, they do indeed have like a very thorough pulmonary evaluation. So, normal CT scans. There was no any evidence of any organ damage. So, it is probably something to do with the regulation. We don't know. It could be, for example, metabolic derangement. It could be damage of the small fibers, which are sensors in the lungs. So, the brain's being fooled that it has not enough, not oxygen, but brain is reacting to CO2 level.

So, it is might overcompensation, but short answer is we don't know, but it's very common. Dyspnea is extremely common in PASC patients.

Mitchell Miglis

Satish, I'll just, I can add into that. You know, there is literature in the MECFS world already describing that baseline supine hypocapnia in patients with chronic fatigue syndrome. So, there is some precedent for that.

Satish Raj

Any thoughts on why?

Mitchell Miglis

I don't think, I, I think metabolic derangement and inflammation, you know, some theories there, but yeah, like Dr. Novak mentioned, no one's really elucidated those mechanisms.

Peter Novak

Okay. Also orthostatic hypocapnia is long known for years and there are two probably likely explanations. Julian Stewart described thoracic hypovolemia. So, it is sub to do with thorax or chest perfusion. And, secondary is because in general, POTS patient tend to be hypovolemic. So, it might be different perfusion, upper and lower portion of the lungs. So, they have selective mismatch in sensing the CO2 levels, which might cause drive the brain with to be hypocapnic.

Satish Raj

Great. And before I hand the reins back to Dr. McPheeters, I did wanna address one other question that I saw and it had to do with anxiety and long COVID. And, the question related to the, you know, the presence of sympathetic symptoms of sympathetic nervous system activation, and whether that could lead to anxiety in the setting of at times, very high heart rates and this touches on, I think something that professor styles sort of alluded to, and that is that there's no reason why a long COVID patient or a POTS patient can't have an anxiety disorder. The reality is that a good percentage of the North American population does, right, but we haven't found that it's higher. And, there very much is an issue where the somatic symptoms of anxiety are tachycardia and palpitation and lightheadedness, and the things that are actually part of the hemodynamic presentation that we see.

And, certainly it's not to say that all anxiety in POTS patients can be controlled by heart rate control, but if someone's heart rate's very fast, and that's actually either associated temporally with the anxiety every time or worse, that's the reason someone diagnosed anxiety. Before, you know, pulling out the Prozac, you know, it may be worth trying to lower the heart rate a little bit and see. I've cured a lot of anxiety with beta blockers. It really, they are wonder drugs when used appropriately as Dr. Chung pointed out.

Lauren Stiles

Yeah, Can I add to that, Dr. Raj? I just wanna say, I think that it's normal for patients who have new symptoms that are poorly understood and they can't find a doctor to help them. It's really normal for that to be a scary experience, and for patients to express a fear of their symptoms. But, I don't think you should interpret that as this is all caused by an anxiety disorder.

I was, I could tell you, I was terrified of my symptoms, 'cause nobody was telling me why it was happening or how to get rid of it for about two years. Hopefully, long COVID patients are gonna get diagnosed faster with the increasing awareness, but taking the time to explain to your patient why they might be having tachycardia and palpitations and assuring them that it's not fatal might really help a lot in their quality of life and not sort of worrying about their symptoms. You know, patient education is a big part of managing dysautonomia.

Satish Raj

Dr. McPheeters, over to you.

Melissa McPheeters

Thank you, Dr. Raj. What fantastic presentations. We have so many questions. So, we're not gonna be able to get through all of them, but we'll get, we'll get through a few of them. And, as I said before, we'll get answers to questions posted on our website as soon as we can.

I wanted to, well, Dr. Raj took the question that I was gonna ask first, but I wanted to bring us back to one other question related to the research. And, Dr. Miglis and Professor Stiles. I think you both sort of touched on some of these issues in some of your responses to questions that came in through the Q and A, but how hard it is to study all of these conditions given the lack of data that's existing in the HRS, for example, in our administrative data systems, and what we need to do better in terms of how we study dysautonomia and all these related conditions.

So, I'm gonna pitch it to the two of you, and ask you to come up with the one thing that you think we really need to do better now to get a handle on what is clearly very complex and common? Professor Stiles, I'll start with you since you came right off mute.

Lauren Stile

Sure. So, I think that the simplest thing, you know, I recognize that not every RECOVER site, and not every long COVID clinic has a substantial autonomic expertise. That's, and it's not their fault. They just, most doctors aren't trained on this.

I think the simplest thing we can do is have all of the sites doing 10 minute orthostatic vitals the right way, 'cause you could definitely mess that up, doing it the right way and screening all of their PASC patients for this, not only for research purposes, but to also make sure that we are accurately diagnosing these patients, which affects the EHR research down the road, right. And, to make sure that they're gonna get proper intervention and treatment if they are suffering from it.

While we don't know the whole mystery of long COVID. We do know effective treatments for orthostatic disorders. Mitch. I'm sure. I mean there's a lot more I could say, but I, I don't wanna occlude the whole call.

Mitchell Miglis

Yeah, no, I agree completely. I think we're advocating at a minimum for at least five and preferably 10 minute orthostatic stand tests for all RECOVER patients and a COMPASS-31. These are very low-cost tools that'll really help us understand the true prevalence of these conditions.

Lauren Stiles

Yeah. We've also advocated for in a sub-cohort doing a full autonomic testing at like the autonomic labs that these doctors run. Not every site's gonna have that, but that's the more detailed testing that really is necessary. Like B2B blood pressure monitoring and stuff. You're not gonna get that from bedside orthostatic vitals. So, I hope that that can be done in a sub-cohort of the overall study population.

Melissa McPheeters

Great. Thank you. This is very complex to study.

Peter Novak

I like to add that this is a big problem, because again, those surveys they're validated, but they are still nonspecific, and they are not really designed to replace diagnosis. So, the still the best is to do established autonomic testing, to get a detailed profile of dysautonomia. And also, if judgment of the effect of intervention, it is usually not a yes to no answer. So, if you want to detect some mild progression or regression, then autonomic testing is, cannot replace it.

Melissa McPheeters

Take us in a slightly different direction, now with a couple of questions that have come up multiple times in our Q and A. So, clearly they're on people's minds. And, one of them is for patients with existing diagnoses, pre-COVID of various dysautonomic conditions. Are we seeing anything about what COVID does in those patients in terms of post COVID, whether symptoms worsen or improve? What direction? Are we seeing anything in the literature right now or in the research? I'll point that Dr. Novak.

Peter Novak

There are a couple of, like, I think anecdotal studies that show worsening of underlying small fiber neuropathies. We actually publish one case study. The worsening of the autonomic failure in general. We did not publish, but we have probably like 10, 11 patients. We, for other reasons, we have three in post COVID autonomic tests. And, most of them had autonomic neuropathies or small fiber neuropathies biggest at the autonomic end. Most of them, actually, it got worse. So, most commonly, it can cause worsening of the underlying autonomic problems.

Lauren Stiles

I just wanna add to that in the survey based study that Dr. Miglis and I did, we saw an over representation of people who had preexisting dysautonomias, and we did not recruit through the Dysautonomia International support groups. We were going to long COVID groups. So, I think that it's not surprising, because we have known prior to COVID that when people with dysautonomias get a viral infection or other kind of immune stimuli, a subset of them will kind of worsen. And, I guess it remains to be seen like how long does that flare last? Is it permanent? Is it for three to six months?

You know, I think that needs more research. We actually don't have good longitudinal research in POTS and other conditions to know that, but hopefully some of that comes out of RECOVER, at least in tracking long COVID POTS patients over time.

Melissa McPheeters

Sure. Dr. Raj, you came off mute. I think you have something say.

Satish Raj

Well, I was gonna say, I, you know, I don't have any patients who've come to me to tell me that COVID has done wonders for their POTS symptoms, right, I mean, I have zero. We have some the other way, and some that sort of, you know, recovered back to baseline. So, you know, if the question was, is there, you know, a therapeutic hope that COVID will be helpful, I think the answer is no. I think we deal with the fallout.

Melissa McPheeters

Absolutely. Another question that came up in multiple times in the Q and A was whether or not there was any sort of hormonal influence on these various conditions? And, I just saw you nod Professor Stiles. And, so I think you might have something to say, or Dr. Novak, Dr. Chung, do you have any thoughts about that?

Peter Novak

Can you say it again, please, your question? I don't understand.

Melissa McPheeters

The question was asked several times in the Q and A as to whether or not there was a hormonal influence on symptoms? Either on symptoms, but then also a question was asked as to whether or not hormones could be considered in treatment as well.

Peter Novak

Well, I very limited experience with maybe someone else can answer, but I have only so a few patients, they did have accompany adrenal insufficiency, for example. So, they also had concomitant hormone treatment or replacement, but I'm not sure it is how common it is.

Tae Chung

Yeah. In the beginning, I think a lot of POTS patients with the fatigue to our endocrinology colleagues and with the potential journal. Sometimes some people say adrenal fatigue, and our colleagues all think this is not really scientific term. And, you know, they believe it's not really primarily endocrinological problem. Professor Stiles and Raj may have more.

Lauren Stiles

I was actually gonna say, Satish is the only one on this call. Who's actually done a sort of, you know, gynecological related study in POTS. But just, I almost think that's a question that is so obvious. It's so funny that we actually don't have good hormone research. POTS, pre-COVID was 90% female. Of course, there's a role of sex hormones, but no one's bothered to study it so far. And, in long COVID, I think it's also female predominant. And, I don't think this is surprising, because most patients are probably gonna have some post viral, autoimmune immune mechanism. And, the vast majority of people who have autoimmune diseases are also women. So, there is a role for sex hormones, and sort of tolerance to self, you know.

And, anecdotally we have a couple of case reports on adolescent POTS patients who were transgendered, who transitioned from female to male using sex hormone testosterone, and their POTS symptoms improved. So, I'm not telling women with POTS to go out and get on testosterone, 'cause, you know, there's all kinds of reasons you might not wanna do that, but there absolutely needs to be more research on sex hormones and on whether that can lead to treatment options as well. But, I think Dr. Raj has, you know, he has actual studies he's done on this.

Satish Raj

So, the two things I'd say is that, so hormones obviously can mean lots of things, but in terms of sort of cyclical variability in young women, we did a study that was actually very simple, a long time ago at Vanderbilt where we got patients with POTS and actually healthy volunteers. And, those that know, a Vanderbilt study means, you know, Vanderbilt grad students largely. But, basically we got people to rate relative lightheadedness at four different phases of their menstrual cycle.

And, the interesting thing was the pattern was identical, right? So, in around menstruation, and second worst was just before women were more lightheaded than at other phases of their cycle. And, this was amplified in the POTS patients, right, who had more lightheadedness as part of their disorder. But, if you just shifted the pattern down, the cyclical pattern was the same, right? So, whatever's going on, there's something in the background, and then, you know, other things contribute to lightheadedness, it may amp it up or down.

And so, it's not uncommon for POTS patients that we have to sometimes go on longer term birth controls where they, you know, keep their hormonal levels sort of higher and have breakthrough bleeds say every three or four months instead of every month, not because it makes everything better, but it decreases the number of worse times if you will. Right? So, it's a management strategy.

Separate from that, hormones could refer to blood volume regulating hormones, and we've certainly done some work that lots of the majority of POTS patients when we were looking at this aggressively at Vanderbilt, I'd say 70 plus percent actually had a low blood volume when you objectively measure it. And, in one of our early studies, we found that the renin angiotensin aldosterone system seemed to act a little funny in some of those folks. And again, that's not everyone. That's, you know, in the cohort that we saw, where aldosterone responses were blunted. And interestingly, this ties back to exercise, you know, where one of the things that exercise does and I forget who, but one of the speakers alluded to this is that it actually both acutely, and then chronically there's a slightly separate effect. It actually increases the responsiveness of aldosterone release to renin activity. Right? So you actually, one of the things exercise does is it actually increases your blood volume aside from other exercise-y things, right? So, it does actually alter your hormonal pattern in terms of blood volume regulation. So that there are lots of different things.

The challenge with all of these are, you know, how to make them actionable. Right? So, even in the patients with blunted aldosterone, it's very sensitive to things like sodium intake and volume status. And so, most of these patients weren't out of the normal range, right. But, when you look at a group compared to sort of a similar group, that's matched, there may be something there.

Melissa McPheeters

Dr. Chung, did you have anything you wanted to add to that?

Tae Chung

Oh, no. Not for now.

Melissa McPheeters

OK, great. And, I'm getting the message that we need to wrap up really quickly, which is terrible, because what an amazing set of presentations this was, and what an incredible conversation. So, we do have just a couple of minutes.

So, I'm gonna just put our speakers on the spot and ask them to share with us the one thing, in one sentence, that they'd like folks to take away from this? And, it might be something that you answered in the Q and

A that you feel like other people might want to hear, because there was so much going on. Dr. Novak, we'll start with you.

Peter Novak

Well, from my perspective, we are extremely eager to go to the root cause of the PASC. It is probably the most studied virus ever. And, as I show potential that multiple potential targets, so we are hoping we will get some answers. And we are looking forward, not only because of that, but also we can extrapolate principles of the treatment and also some other condition like POTS in general, or post viral syndromes, chronic fatigue syndromes.

Melissa McPheeters

Okay. Thank you. Dr. Miglis, we're running down the clock.

Mitchell Miglis

So, autonomic dysfunction is common in PASC. We know that, and it may not be related to the severity of the infection, which is another important point.

Melissa McPheeters

So, Professor Stiles.

Lauren Stiles

We need clinicians and researchers to really take the initiative to learn how to screen for and treat autonomic dysfunction in long COVID and in all the preexisting patients who are out there who are not getting good care.

Melissa McPheeters

And Dr. Chung.

Tae Chung

Yeah, my last comment is answer to your first question about what's the most single important thing about the research I think is biomarker study, the discovering biomarker, which I think is very kind of relative low hanging fruit at this point, because actionable. If you find auto antibodies it's actionable. We can use immune drugs. So, that's what I like to emphasize for research.

Melissa McPheeters

Great, Dr. Raj, one sentence.

Satish Raj

Two.

Melissa McPheeters

Okay.

Satish Raj

So, I think, you know, the goal of finding underlying cause and the holy water to fix it is laudable. I'm getting old. And, I like to think I wasn't so cynical in my youth, but you know, the truth is that I think it's a mistake to avoid treating the symptoms, at least in the short term. You know, while Dr. Novak and Dr. Chung find the cure, I think the danger is that a lot of physicians say, "Well, this is too complicated. I don't know about this," And they won't treat what can be treated. And, a lot of the symptoms will respond to treatments within their expertise and their specialty that are organ based. And, I think the patients need that now, while these other things go on for the big picture.

Melissa McPheeters

Great. Thank you. Yes. So we just want to thank everyone for joining us today. We really appreciate you registering, sending in questions, engaging in the Q and A. We will be getting this ready to post on our web, just as fast as we can. Recovercovid.org is that website. Also on that website is information on upcoming webinars. These are the topics that are currently laid out. More to come as this program grows. So, really we do hope that you join us and continue to check back for more information as more is learned.

Thanks again to our amazing speakers. You are absolutely outstanding today. Thank you. We will see you all at the next webinar.

Webinar Slides

To request a copy of the R3 Webinar slides, please email RECOVER_ACC@rti.org.

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