CDC's 24th ME/CFS Stakeholder Engagement and Communication (SEC) Call
December 4, 2024, CDC ME/CFS

Christine Pearson: Good afternoon, everyone, and welcome to today's ME/CFS stakeholder engagement and communications call, which we abbreviate as S-E-C or SEC. My name is Christine Pearson, and I am Associate Director for Communications, in the division where the ME/CFS program is located within CDC.

As you may know we host these SEC calls twice a year as part of our regular outreach and communication activities to provide information for people with ME/CFS as well as their loved ones, clinicians, and anyone else who may be 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 for CDC's Chronic Viral Diseases Branch and then will turn the call over to our guest speaker Dr. Satish Raj from the University of Calgary in Canada. After the presentations we'll have a Q&A session.

During today's Q&A session you can ask questions through the webinar platform or by phone if that is how you joined today. Before we start, I would like to remind everyone that this call is open to the public so please consider that before sharing any personal information. We are also recording this call. Please disconnect now if you have concerns about the recording.

We will post a transcript and video as soon as possible after the call is complete. If you would like to access the closed captioning or to read along the text of the program update, the links of both are going to be in the chat box. Now we'll turn it over to Dr. Unger to start the program review. Welcome, Dr. Unger.

Dr. Unger: Thank you very much, Christine for that introduction, and welcome everyone to CDC's 24th SEC call. I would like to start the call by letting you know of a couple staff changes within the Chronic Viral Diseases Branch. First, we were said to say farewell to Dr. Jeanne Bertolli who retired from CDC November 30th. We're extremely grateful for her strategic planning and dedication to the ME/CFS program and our branch. At the same time, I would like to welcome Dr. Joanna Regan as our new medical officer and team lead working on ME/CFS. Joanna is trained as a pediatrician and also has a master's in public health. She came to work at CDC in 2009 in the Rickettsial Zoonoses Branch as a medical officer. Her past work at CDC has included investigations on an outbreak of Rocky Mountain spotted fever, and on Ebola, and

Middle East respiratory syndrome. She has worked with health departments and travelled to more than 20 countries for CDC. We are excited to have Joanna as part CDC's ME/CFS program.

Our program is continuing outreach and educational activities for healthcare professionals and the general public. As mentioned in our last SEC call, during planning for international ME/CFS awareness activities with MEAction Georgia we arranged for an educational session with nursing students in conjunction with the Emory School of Nursing. We planned this in recognition of the important role nurses play in the care of people with ME/CFS. The session occurred on September 18 in the Emory School of Nursing building. The event was titled "ME/CFS Voice of the Patient: A Panel Presentation with MEAction Georgia." The session included a brief overview of ME/CFS diagnosis and epidemiology followed by presentations from a patient with ME/CFS and two family members of people with ME/CFS who shared their personal experience in living with this illness. Each panelist used photos and stories that showed how living with ME/CFS has impacted their daily lives as well as those of their family and friends. To recognize the patients stories are so much more meaningful and understandable to students than impersonal clinical description of the illness provided in textbooks. We're grateful to members of MEAction Georgia for their support in the panelists' willingness to spend their time and energy to provide this memorable educational experience for students. We also appreciate the Emory University School of Nursing for hosting this event.

Over the past year, we have been working with the NIH-funded ME/CFS Data Coordinating Center at Research Triangle Institute to make a baseline data and biospecimens from the adult cohort of the multi-site clinical assessment of ME/CFS study (the study name is abbreviated as MCAM) available to the research community to test their ideas about ME/CFS without the need to collect additional materials. This should allow studies to be completed more rapidly and with less cost. We are thrilled to announce that an extensive collection of more than 70 datasets and biospecimens from MCAM are now accessible through websites mapMECFS and searchMECFS, respectively. Applications for data use biospecimens are approved through data use agreements.

In addition to making MCAM data available more broadly through websites I just mentioned, our group also continues to publish information from the MCAM study. Since our last call in May we published "Chronic Overlapping Pain Conditions in People with ME/CFS: A Sample from the Multisite Assessment of ME/CFS Study" and "Cognitive Assessment in ME/CFS: A Cognitive Substudy of Multi-site Clinical Assessment of ME/CFS." Briefly we report in these two

publications that more than 75% of people with ME/CFS had at least one of the following chronic overlapping pain conditions: chronic low back pain, chronic migraines or headaches, fibromyalgia, interstitial cystitis or irritable bowel syndrome, or temporal mandibular disorder. The people with ME/CFS who had these pain conditions had significantly poorer quality of life compared to those who did not. In the cognitive study, we found processing speed was significantly slower for people with ME/CFS when compared to healthy controls. We also found that the challenges associated with the clinic visit that includes cognitive testing worsened processing speed to the same extent as exercise testing.

Now I would like to switch to telling you a little bit about other projects our ME/CFS group is working on. We moved into the third yearly contract with the national association of school nurses, or NASN as it is abbreviated. As a reminder, CDC and NASN work together to collect information about ME/CFS among school children with chronic school absences. To do this, NASN trained school nurses to recognize ME/CFS symptoms and to help children and their families find appropriate medical resources to evaluate whether the children might have ME/CFS. Through the partnership with NASN, we have reached more than 40,000 school nurses with educational material designed to increase awareness and understanding of ME/CFS. Of these, 11,000 school nurses completed the educational activity nursing continuing professional development courses on ME/CFS during the past year. Additionally, we have tracked absences for over 15,000 students, identifying that approximately 3% were due to ME/CFS related symptoms. In October we began the next phase and aim to expand our data collection efforts across eight more states. This step will allow us to contribute even more significantly to the body of knowledge regarding ME/CFS among school-age populations, and hopefully guide the development of school accommodation interventions to help students experiencing health related academic challenges.

In October, we wrapped up our partnership project, Infection Associated Chronic Conditions Understanding and Engagement, also known as ICUE. The last webinar of the ICUE project “Uniting Voices Amplifying Impact” was held on Friday, October 11th and attracted 144 participants. Our branch funded the CDC Foundation to implement the ICUE project in December of 2022 and aim to bring together patient advocacy groups and community-based organizations focused on raising awareness and helping people living with infection associated chronic conditions to identify common objectives and opportunities to collaborate. The CDC Foundation’s lead partner organizations, SolveME, the Covid Long-Hauler Advocacy Project, and the Patient Led Research Collaborative hosted the final webinar, with logistical assistance

from the group Commonality Incorporated. At the webinar, speakers discussed the findings from the project and about how interested organizations and individuals can contribute to, and benefit from working together to increase awareness of infection associated chronic conditions, support patients, and inform research.

During previous SEC calls we've mentioned our collaboration with the Emerging Infections Program in California and Kaiser Permanente Northern California. This is the Stop ME/CFS Project, standing for "Surveillance To Optimize Protocols for Early Identification and Subgrouping of ME/CFS." Recently the STOP ME/CFS investigators have been exploring the relationship between COVID-19 and ME/CFS. They surveyed over 9,825 patients in Kaiser Permanente of Northern California health plan about their symptoms and their COVID-19 history, casting a wide net to find people who may have symptoms that fit the definition of ME/CFS but have not been diagnosed. In September, findings from this work were published in the PLOS one Journal. Overall, the researchers estimated 1.67% or about 45,892 of the 2.7 million adult members of the Kaiser plan in Northern California had an ME/CFS like syndrome during the period, which was July to October 2022. Of those, 14% developed the illness after COVID-19. The patients whose ME/CFS-like syndrome began after COVID-19 were more likely to have been unvaccinated against COVID-19 and to have had COVID-19 before June 2021. We can't yet say how much COVID added to the overall incidence of ME/CFS. Part of the next stages of our study we expect to learn more about the interplay of these conditions.

We are also continuing our work to educate primary care providers about Long Covid, ME/CFS and other post-acute infection syndromes through the Long Covid and Fatiguing Illness Recovery program. This project is a collaboration with one of the largest federally qualified health centers, the Family Health Center of San Diego, along with the ECHO Institute at the University of New Mexico, and the Schools of Medicine at the University of Washington and University of Colorado. In this third year of the program our collaborators have continued to host monthly webinars for continuing medical education credit. From the program's inception, the webinars have included presentations and discussion by both medical and lived experience experts meaning either a patient or patient caregiver. In the past six months, webinars covered recent research findings and other topics such as a diagnosis of post-exertional malaise and Long Covid patient navigation. Beginning November 7th, the program expanded the opportunity to enroll in monthly case consultation and mentoring to the ECHO online platform to primary care clinicians nationwide. On November 14th, the program's 10th online short course for

continuing medical education credit called “Long COVID in Children and Adolescents” was posted.

Finally, in early November we published a paper in BMC Infectious Diseases resulting from the COVID Relief project, our collaboration with the University of Washington. The paper describes quality of life impairments and subjective cognitive decline associated with Long COVID two or more years after the patient's initial SARS-CoV-2 infection. Clinically significant cognitive complaints, fatigue, and pain were present even in those who reported they had recovered Long Covid. These findings are important to document because of the implications for people's participation in work, education, and social activities.

Before I turn the call over to our guest speaker, I’d like to remind you that if you have suggestions for speakers or ideas for other topics for upcoming SEC calls, please email us at MECFSSEC@cdc.gov. This address can also be used if you’d like to be added to our email notifications about upcoming calls. And finally, just a note that the transcript of the entire SEC call will be posted on the website as soon as we can.

Now I'd like to introduce our guest speaker Dr. Satish Raj. Dr. Raj is a heart rhythm cardiologist. He completed his internal medicine and cardiology training at Queens University and then further trained in cardiac electric physiology at the University of Calgary. He then spent 12 years working at the Vanderbilt autonomic dysfunction center in Nashville, Tennessee. He is currently a Professor of Cardiac Science at the Libin Cardiovascular Institute and the University of Calgary's Cumming School of Medicine and founder of the Calgary Autonomic Investigation and Management clinic. His primary research interests relate to understanding and better treating postural [orthostatic] tachycardia syndrome (POTS), vasovagal syndrome and orthostatic hypotension. He's conducting studies into the role of autoantibodies and inflammation in POTS and understanding the brain fog. He is also looking at repurposing drugs in novel ways to treat vasovagal syndrome and orthostatic hypotension. Welcome, and thank you very much Dr. Raj.

Dr. Satish Raj: Thank you, I will share in a moment my slides. Let me get these slides down before I can pull the other ones up though. Perfect, let me just pull up my slides here. With luck you should be able to see slides now. Thank you all for attending the call. As was mentioned my focus research and a lot of my outpatient clinic focus deals with POTS or postural orthostatic tachycardia syndrome and I will try and do is go over a fairly quick outline of what we think we know about it and some approaches to treatment, although these are like other disorders so limited. My disclosures are listed here. None have much to do with the things I’m going to be

talking about. I do have peer reviewed research funding from different foundations dealing with POTS as well as the Heart and Stroke Foundation of Canada. I will say that the consulting disclosures here related to POTS would not have been here five years ago. The point of that is in the last several years, and we can get into why if there is interest in that, there has been increasing, and increasing new, industry interest in trying to understand POTS and really get at the mechanism and with that comes the potential for new treatment. Hopefully if I were giving this talk 10 years from now, we will have new treatments that may come out of some of these efforts.

Let me start by saying I think originally I was asked to talk about dysautonomia and I veered towards POTS, but I think the key point that I'd like to make is that dysautonomia isn't a diagnosis. One could argue that what we're saying is that there's something wrong or dysfunction in the autonomic nervous system and assuming that we all accept that that is true, it's still a collection of diagnoses, not one.

One way to think about it is from a cardiac perspective. Certainly, my clinics are theoretically part of a Heart Institute, and it is probably true that people, everyone, that comes in as a patient to the Heart Institute could be labeled as having heart disease. Within heart disease are very different areas. I've listed a handful here. I'm an arrhythmia doctor, a heart rhythm doctor by training, but there is valvular heart disease, coronary artery disease or heart attacks, the most probably famous bit of what we handle as adults, there's congenital heart disease. Kids are born with tubing that did not quite connect properly, and each of these have very different prognosis. In fact, within each of these there are very different disorders with very different prognoses. And within each of these there are different treatments. While it is technically probably correct to diagnose everyone here with heart disease, it is useless. The overall point of dysautonomia is not whether it is true or not it is as much as possible we can hone in and give a more specific diagnosis that might help us in terms of our efforts to at least start with treatment. Treatment in many disorders has a trial-and-error element but by basically saying there this specific sub disorder and patients with this usually respond to XYZ, that can help us get started and learn from the other patients. In the dysautonomia world I point out that POTS is what we are going to be talking about but vasovagal syncope was mentioned in the introduction, but then there are the autonomic failures these typically a different demographic, typically older patients where there is nerve damage and the presentations often include orthostatic hypotension often the absence of heart rate going up.

Dina Garrett: Dr. Raj, sorry to interrupt you very quickly. We are not seeing all of your slides can you stop sharing and reshare?

Dr. Satish Raj: I could. This is just the title slide, is that better? Or are you seeing…

Dina Garrett: Yes, you're good to go, thank you so much. Apologies for that interruption.

Dr. Satish Raj: No worries. What I'll start with is "what is it?" right. The term is thrown around but there are criteria, for the most part we use definitions that were largely developed about 30 years ago, or just over 30 years ago out of Mayo Clinic. The key to postural tachycardia syndrome/postural orthostatic tachycardia syndrome is an excessive increase of heart rate. And I want to be clear, orthostatic tachycardia, an increase in heart rate is not abnormal. That is actually physiologic. We all have it or should have it. But there are patients that they found in the initial description whose heart rate went up more than they thought was normal and based on normative healthy control data from tilt studies at the time they set that threshold at 30 bpm. Now one of challenges is that not only is orthostatic tachycardia physiological, but it changes with age. In younger people and kids, it can go up a lot, normally. As we get older it goes up less, normally. One of the things they were finding is there were lot of teenagers that had excessive orthostatic tachycardia even though they were perfectly well. They went and redid a study in the kids and redefined the criteria for children aged 12 to 19 as greater than 40 beats a minute. Now even that is not perfect because a heart rate increases of say 32 beats per minute in a 20-year-old is much less impressive than a heart rate increase of 32 beats per minute in a 50-year-old because that would normally be expected to go down with aging. But nonetheless, it is what we have for simplicity. And importantly, this has to occur in the absence of orthostatic hypotension. It is not the patients with POTS can never have drops in blood pressure but if the only time they have excessive orthostatic tachycardia is in response to a significant drop in blood pressure, then that is called a reflux tachycardia it is part of orthostatic hypertension. That has been recognized for well over 100 years, and so it is not that is not important, but it is not POTS. Now, what I described as physiology I've talked about heart rate, and I've talked about blood pressure that is postural orthostatic tachycardia that is POT. The key in POTS is the "S", it is a clinical syndrome. That means that these patients have symptoms that fit a typical pattern. The typical pattern is that some of the dominant symptoms are worse when they're upright and get better when they lie down. There is a strong positional component to it. Everything I've described right now actually occurs to many of us if we get a bad viral infection. I live in Canada, we are good for a bad cold once or twice a winter here. I would argue that those of you that are not unwell already if you actually, at the time you have a cold and you're feeling unwell if you

actually were to measure your orthostatic vitals you may find you meet these criteria. If you were to pay attention to your symptoms, you may have a lot of the symptoms, and we'll get into some of those are when you are acutely unwell. The difference is most people when they get a cold get better quickly -- within a few days. These patients don't. This is a chronic illness; they are left with residual symptoms that are often very severe. We used to define chronic as at least six months, more recently I think it has been dropped to three months. Truth is, it probably doesn't make too much difference. I don't think that most people that are unwell at three months suddenly get better in six months. Usually, if they're going to recover occurs earlier. And finally, this should be in the absence of another obvious cause or reason for orthostatic tachycardia so we need people off of drugs like stimulants or with other diseases like Addison's disease for example is known to cause severe hypovolemia and reflex orthostatic tachycardia.

I've broken down some of the common symptoms we see in POTS patients here, into those that I could blame on the heart and those I would have more trouble blaming on the heart. This is obviously a cardiology centric view of the world. Not surprisingly in a disorder with tachycardia in its name, patients describe a rapid heartbeat or palpitation, chest discomfort or pains, shortness of breath, and lightheadedness when they're up, typically. But almost as commonly patients describe mental clouding or brain fog, headaches very common, nausea, tremulousness or shakiness, and everything here in black and the tops of both columns are worse, or typically worse, with upright posture, upright position, and better lying down. But not all of the symptoms are like that either. Patients routinely are exercise intolerant. I put that under a cardiac symptom although it could be non-cardiac as well. Almost all the patients are fatigued chronically and we'll get into some overlap with ME/CFS afterwards but even if they do not meet ME/CFS criteria, fatigue is ubiquitous and many of the patients have disturbed sleep. Not all the positions, not all the symptoms are upright, but a lot of the symptoms have to be the dominant symptoms have to be worse upright to make this diagnosis.

I show you here a tilt table test of a healthy control subject on the left and a POTS patient on the right, there are three channels, the top one is heart rate, blood pressure in the middle and then tilt angle just shows you when the table was up and when it came down. There are a couple of things I want you to get from this slide. The first is if you look at the heart rate in the healthy control subject, top left, the heart rate goes up when they are upright. This just reinforces the point that I made earlier that orthostatic tachycardia is physiologic and not pathologic. The second is if you look at the blood pressure traces and compare that POTS trace on the right to the healthy control subject trace on the left, you can certainly look at it and argue that the tracing

from the POTS patient looks different than from the healthy control subject. It looks like I do when I wake up in the morning in desperate need of a haircut. It is spiky your hair is all over the place. It is disorganized and quite frankly that may actually be important. We are doing work into trying to understand the message -- the signals telling us, I believe it is a form of the body's attempted sort of hemodynamic correction to try and prevent hypotension, but nonetheless you couldn't look at the average blood pressure and argue that the POTS patients have a lower average blood pressure. It's not fundamentally a hypotensive disorder. Finally, if you look at the heart rate trace in the top right in the POTS patient it goes up like the control subject, but it goes up more aggressively and it keeps going up. This patient actually, was part of a protocol where we were trying to do 30-minute tilts, and she did not last 30 minutes. We stopped early because she told us to and when she told us to stop, her heart rate was almost at 180 beats per minute. The truth is that is not our average, that is a more extreme end of the variant, but certainly not the only one and not the highest that I've seen. Now importantly I've said, this is unique physiology, but physiology is not sufficient. You need symptoms as well. And during one of the early studies I did at Vanderbilt we actually were rating symptoms and getting patients to rate their symptoms actually during that study where the tilt traces came from. What you see here for the healthy controls shown in black is that they were fundamentally asymptomatic until they weren't. Occasionally someone would have a symptom, you'd report a few symptoms and then they'd faint and they'd drop out and it would get better. In contrast the POTS patient shown here in red were symptomatic almost immediately and they continued to be symptomatic and get worse throughout the 30-minute tilt. The interesting thing is that more of the POTS patients survived or made it through the full 30-minute tilt than did the healthy control subjects, because the healthy control subjects got symptomatic and they fainted. The POTS patients kept telling me they are going to faint, and they would say that early and tell me for 30 minutes. And the important point from this is that POTS is not fundamentally a fainting disorder. POTS is, at its core, is a feeling faint disorder. Patients are very lightheaded they feel like they would faint or they're on the verge of fainting, and some do. A minority of POTS patients do actually have full-blown faint that is often due to vasovagal syncope. But more of our healthy control subjects had vasovagal syncope during the tilt.

One of the challenges that we had is that we've done a lot of work at Vanderbilt and Mayo published stuff and these tertiary care centers and we thought we knew what we thought we knew. But one of the concerns was whether the patients that were coming to us often from out-of-state, often needing reasonable insurance in the U.S., whether that was really representative of the broader POTS population. And so in conjunction with our partners at Dysautonomia

International we actually created a patient survey. Largely it was run through Vanderbilt ethics, so it's an ethics approved survey. Largely distributed through the Dysautonomia International social media platforms and there have been several papers that came out of it.

There is a follow-up survey that is just launching right now. But from the original paper that was published now five years ago, what we found just in terms of rough demographics is that the POTS patients what we thought they look like from the studies that we had at Mayo, Vanderbilt and other centers was pretty close. Overwhelmingly female, over 90% of the respondents were female. Over 90% of the respondents were Caucasian or white. The truth is there are some biases built in. The survey was only in English and so certainly a language bias could affect the racial mix that we had in response, but certainly it was more democratic approach than having to be able to come to one of the centers, but we see similar findings. When looking at the age of onset of symptoms in the people who filled out the survey the most common age, or the mode, was 14 years of age. But, it was not all one distribution, you can see there was a long tail into adulthood. Just a little under half of the patients developed symptoms after the age of 18. And this probably reflects heterogeneity in the different causes of POTS, the different ways of getting to POTS we will touch on that in a bit. In the survey we had a laundry list of symptoms patients could endorse or not. The first few are the ones you would expect for a disorder with tachycardia in its name: lightheadedness, tachycardia, pre-syncope, but the next few, almost as common were headache, difficulty concentrating, nausea, memory problems.

Things that, again, I have trouble blaming directly on the heart. So, the point here is that POTS isn't actually a cardiovascular disorder, it is a multisystem disorder with certainly a prominent cardiovascular presentation or features. A high percentage of the patients actually had other medical conditions. We asked about different potential comorbidities and co-diagnoses. Migraine headaches were seen in 40%, irritable bowel syndrome 30%, Ehlers-Danlos syndrome in 25%. Interestingly vasovagal syncope, again only in 13%. Again, a minority of patients have this reflex making disorder. Autoimmune diseases were seen in about 16% of the group. We have individual autoimmune disorders here if you add them all up it was about 16% as well. Mast cell activation disorder about 10%.

We asked about education, if the onset of a disease peaks at age 14, this is a critical age for many kids. in terms of schooling, sort of entering high school, trying to map out not just the next few years of their lives, but the next few years determine the course of their adult life in many cases, the next several decades of their life. The impacts were scary. They were significant. Almost 90% of patients report missing some school, 30% were being home-schooled and again

we made the assumption this was for health reasons and not other reasons. Twenty-five percent had to drop out of school, at least for some time. Almost 40% either delayed college or didn't go or weren't able to complete university. Right so, huge impacts not only for the year or two around the time we are asking the question, but the downstream impacts were significant.

When we were at Vanderbilt, we wanted to look at the quality of life in POTS patients and this work was done in conjunction with Kanika Bagai who is a sleep neurologist at Vanderbilt. These are not our data. We use the SF-36, this a very generic quality of life, health related quality of life tool. It is not specific to POTS at all, but the beauty of this tool is that it has been studied in just about every disorder. We went to the literature and pulled out the data for patients with chronic back pain in green and patients with end-stage renal disease on hemodialysis in purple, these are disorders generally viewed as having a pretty poor quality of life, and then we just want to superimpose our data so the red data, in red here, are for POTS patients we studied. Quality of life in the two different subscales of the SF-36 were comparable to patients on dialysis.

Right now this does not speak to why, it doesn't speak to whether it is right or wrong, quality of life is self-reported but for whatever reason or reasons the patients have a very poor quality of life. Often patients will be dismissed as having a psychiatric illness and so this was formally assessed -- it was actually work led by my wife before she did her psychiatry residency. She was a research fellow in psychiatry at Vanderbilt. The question when people are asking if POTS is a psychiatric disorder -- the question they're really asking is are POTS patients crazy. And so they did an exhaustive study with long questionnaires mapping to what was then the DSM-4-TR, which was the diagnostic bible. I think we're probably a couple of versions beyond that now. But the short version of the answer is that yes there were some patients that met criteria for depression disorders and anxiety disorders but wasn't actually any higher than the US general population. It is probably not fair to say that because of the disorder that these patients have more mental illness.

Now, they looked at different psychometrics tools. This is anxiety sensitivity index looks at anxiety and this is actually an important lesson that may apply to other studies when interpreting them. If you looked at the data for the POTS patients, and they had their normative controls; the POTS patients had more anxiety. They were in actually in the mild anxious, mildly anxious range of the ASI. My wife took great pleasure in pointing out I would not have qualified as normal. These patients were screened, they had psychiatric screening tools, and so these were the uber-normals. And I think the lesson here is we have to be careful in interpreting other studies

because they do not always tell you that but depending on how they select their controls, they may be selecting people that are better than the general population to compare to. And so, in fact, when we went back and looked at the population data, so published US general population data on the far right, you can see the anxiety sensitivity index score if anything it looks like it is a little bit higher. The truth is that is probably isn't significantly different, it is in the same range, but we just have to be careful when we interpret these data compared to controls, and we do not understand what the controls or the normals are. One thing that came out of the study as a positive interesting finding was around inattention. This was using the Conners ADHD Rating Scale adult ADHD rating scale, obviously an ADHD score, you can see compared to the uber psychiatrically normal folks the POTS patients had a higher score. It is true that they also had higher scores against the background or general US population. Not as bad as the patients, they did not score as poorly or as high as the patients with diagnosed ADHD, but they clearly had inattention problems. This got us thinking because patients would that they have memory problems, and we assumed it was all memory problems, but this raised the issue that part of the issue might be not just memory, but it might be the processing of the memory because of the inattention.

Now it turns out it is a little more complicated. Memory is not just one thing, there are different aspects of memory and there are some memory problems when we've done more detailed neuropsychiatric testing, but this actually got us started. So, that leads to the question of why? Why do patients have POTS? My mentor at Vanderbilt who has unfortunately passed away now, was David Robertson, he was a really a great physiologic thinker. He would argue that a diagnosis of POTS is like a diagnosis of fever. It is objectively, there are criteria, it can be objectively true. There can even be treatments that target that. Those of you who have young kids, I was marveling when my daughter, my first child, was a baby and she developed a fever and all of the sudden this child that is usually running around, you know, lay like a ragdoll on the sofa. Gave her some Tylenol and her fever came down from 103 to 100. She was still febrile, or 101, still febrile but not as much so, and all of the sudden she was running around again. Tylenol is a wonder drug in those circumstances. But the diagnosis of fever does not tell you why. There are different reasons that she could've had the fever. It could have been viral illness or bacterial illness, cancer in some cases, there are lots of things that can cause a fever. POTS is a little bit like that. We can objectively diagnose POTS based on the criteria we have; we even have some treatments for POTS, and we'll go over some of that, but there are a lot of ways of getting to that. The challenge is figuring out what these are in the individuals. In most patients we can't necessarily figure it out, but it is worth keeping that in mind the end goal is to get there.

The real challenge in studying POTS is illustrated in this old parable of the blind man and the elephant. There are different research groups that all bring their own skills and their own background and knowledge to trying to understand POTS. Each one focuses on what they know. This story many of you are familiar with it. It's a story that crosses over different groups in the Indian subcontinent. This is the Hindu version, but every group has a similar version. And like many things Indian a Brit came and took credit for it, Jeffery Saxe, or John Saxe, sorry. The story goes like this, it was six men of Hindustan to learning much inclined, who went to see the elephant though all of them blind, that each by observation might satisfy his mind. They conclude that the elephant is like a wall, a snake, a spear, a tree, a fan or a rope depending upon where they touch. That is the challenge with POTS research. Those of us, each of us have different interests, and depending on what you are assessing, pick up different things. The challenge is trying to put that all together.

In terms of the relationship between ME/CFS and POTS, it probably isn't separate. Luis Okamoto who's still at Vanderbilt on faculty there did a study when he was junior faculty, when he was a fellow where he actually took patients that were coming to our research unit, and we had an inpatient research unit where we did a lot of our more detailed studies. And we tried to match them up against CDC criteria at the time, and in fairness the do evolve. At the time we found out that of the 47 POTS patients in this cohort, about 2/3 actually met ME/CFS criteria and about 1/3 didn't. Every time people look at it the numbers may change a little, but there is certainly overlap between these disorders. Both of these, both each of POTS and ME/CFS, I think are a cluster of different underlying physiologies that get you there. I think ME/CFS is a bigger basket, if you will, so that that is why I made a bigger on the Venn diagram, but there's overlapping concerns certainly.

In terms of the treatment approaches that we use for POTS, the foundation certainly in my clinic is non-pharmacological treatments, and then we add drugs as needed. Just to be clear, that does not mean everyone has to fail non-pharmacological treatment to get drugs, there are some patients based on the severity of their symptoms and their wishes, we will sometimes embark on both simultaneously. But it is not usually an either or, right. The foundation of non-pharmacological stuff we use regardless. I'm going to touch on three things. Diet, I wrote salt, but salt and water, compression garments, and exercise as the non-pharmacological foundation. Historically we have told people, patients with tachycardia disorders, to eat more salt and drink more water. I think that is fairly ubiquitous advice. Until fairly recently there was actually very little data that this worked. And so one of my last studies at Vanderbilt that was NIH funded was

to do a dietary salt study we actually brought patients and control subjects who were all female into our research unit for two one week stays, seven-day states. It was about a month apart because we wanted to make it around the same phase of the menstrual cycle. What we did for the first six days was just fed them. During one of the phases they were on a very low sodium diet, on the other phase they were on a very high sodium diet. And then once they reached a steady state, which is why we wanted to wait, we then did our analyses, and we looked at formally looked, we looked at blood volume. The argument for salt was always that we would retain the fluid and augment the blood volume was the underlying first step. And so we looked to see if it happened, and it did. You can see the low salt group plots shown in red had a plasma volume, the liquid part of blood is plasma deficit, and we are able to correct it with a high sodium diet or high salt diet, well it's high sodium. The healthy controls also increased their plasma but did not have a deficit to begin with but they did augment it with a high sodium diet. Red cell volume the other big physical part of blood, the red cells, didn't change. Now, in fairness if we had run the study for a month or several months, I suspect that that would've changed as well, but in a week it didn't change. So blood volume increased. Then you know, what drives the heart rate in many patients is an increase in sympathetic nervous system tone. Plasma norepinephrine levels are biochemical a marker of that, it is an imperfect marker but a marker nonetheless. The theory is always that increased blood volume will decrease this sort of surge or, conversely, a low blood volume will cause increased sympathetic tone as a reflex, and we can reverse that. We did show that patients went from really really hyperadrenergic, really high levels of upright plasma norepinephrine to a less really high, but still high. Healthy control subjects started high normal went down a little bit. One of the important things to look at when focusing on the POTS data here is that these patients were hyperadrenergic so sometimes people say, I do not have I'm hyperadrenergic my pressures are sometimes high, does the salt still apply to me. The point is on average this would still seem to fit into the category and improve in terms of decreasing sympathetic tone. Finally, we looked at the upright, the lying, and upright heart rate and orthostatic vitals. And you can see when patients are lying down on the left really not much difference. Even with the high sodium diet maybe the heart rate dropped a few beats per minute, but not a ton. If you focus on the right-hand side there are two panels the first looking at the standing heart rate, or the upright heart rate and the second looking at the delta, so the standing minus the supine. You can see from the POTS patient data in red there was a significant decrease in the standing heart rate and the delta heart rate. In the control subjects it decreased a little, but less so and not significantly so. The short version is, this did what we thought it would do. High sodium diets do work. Importantly, the results show that there

is a strong trend towards improvement in symptoms using the Vanderbilt orthostatic symptoms score. It is physiologically what we thought it would do to improve symptoms.

This is how I actually do it in clinic. Obviously, I don't have a medical kitchen in my clinic that I can use like we did during the study. I will get patients to target drinking a minimum of 3 liters of water a day, and that pretty much means having a dedicated water bottle they carry with them all the time. Three liters is a lot, but it is absolutely doable. Between the heart rhythm society statement and the Canadian cardiovascular society statement, there are different recommendations for the amount of extra salt that is recommended, but basically its about 10 grams. The problem is that I can't sit and count 10 grams. I can't tell patients how to do that I don't know how to do that. Just adding up stuff on the labels, so I don't bother. What I've figured out is that this is a horseshoes and hand grenade thing. We want to get close, we don't have to be perfect. And so a teaspoon of salt is about 5 grams. So the target dose is about an extra two teaspoons. You could take it all at once, but that is sort of a tough way to go, and so our approach has been to encourage patients to spoon it out in the morning and put it into a ziplock bag or a similar container, and then later in the day when adding salt to their food or drink or whatever they're going to do, instead of shaking it in from whatever source they have handy is to add it from the bag. That way it's not a perfectly quantified, but a semi quantified approach to how much salt they're getting in. The vast majority of my patients like the taste of salt in food, they find it is best tolerated by adding to food, and quite frankly that is the cheapest way of getting it in as well. There are some patients that don't. There are some patients that don't like the taste of salt in food, and they won't eat the food if you add all that salt and they have to find a different way. Some of my younger patients add 1/3 of a teaspoon to shot glasses and do saltwater shots. Now that can cause nausea on an empty stomach, so you want to do that not on an empty stomach. Some patients will add it to hot water and lemon juice and drink it. Some will add it to their water bottles. A liter water bottle, if they have a 750(ml)-water bottle they need to have 4 of those per day and add half a teaspoon to each one. The truth is that each patient needs to find what works for them because it's not that I need them to do this once, this is an ongoing approach. It needs to be sustainable. They need to find something that works for them. I don't tend to use salt tablets very often; I only use it if the dietary approach isn't tolerated. The regular salt tablets like the one-gram tablets I find tend to cause more nausea than the table salt. It's not too expensive, but it is not brilliantly tolerated. There are tablets that are better tolerated, so one is a brand called Vitassium by a company called Saltstick. They are coated they get absorbed a little later in the gut, most patients tolerate it from a GI point of view. But if that is your only source of salt 10 grams of salt means four and a half grams of sodium that is

18 tablets a day. You run through them, and so it can get quite expensive if that is your only approach and so some people will do a hybrid approach.

Coming back to the summary data, low salt diet, lower blood volume, high sympathetic tone, high norepinephrine levels on standing, and high heart rate, an increase in dietary salt intake we increase blood volume, this is actually not entirely correct, we don't actually lower the norepinephrine, but it doesn't go up as much, so lower compared to the low salt diet, and the heart rate goes up when you stand up still, that is physiologic, but does not go up as much.

The next approach that we advocate strongly is compression garments, and this is based on a study done by a former PhD student of mine, she just graduated earlier this year named Kate Bourne. What she did was using a segmental compression suit it was made of neoprene Velcro in the lab, did a study where we used different compression configurations and did 10-minute tilts. In one morning, patients actually had multiple ten-minute tilts, and you can see with full compression the heart rate went up and then basically plateaued while, whereas, without compression or none the heart rate would keep going up on tilt. It clearly lowered the heart rate when upright. The reason for the fluid shifts, the reason we do this, is when we stand up fluid shifts from our chest where heart is to below our chest where our heart isn't. And, that fluid does not come back to the heart. You can see that here in this nice illustration from André Diedrich and Italo Biaggioni from Vanderbilt published several years ago using biological impedance. In this case, increased impedance means less fluid. Decreased impedance is more fluid because fluid is a good conductor of electricity, and you can see when we tilt someone up fluid shifts away from the upper torso or thorax right away and it shifts lower. The other thing to see here is where shifts. It doesn't, most of the, very little shifts to the calves. A little bit does. A little more shift to the thighs. The vast majority sits in the lower abdomen and pelvis. That is where the money is in terms of compression. And so, Kate didn't actually look at just two groups, she looked at four configurations. The full and none that we showed earlier, but then an abdominal upper thigh compression, so a bicycle short compression shown here in green, and the calf compression shown here in red. And what she found is that there was a dose-dependent improvement in symptoms where the full compression and abdominal compression was almost as good as full compression, the leg compression almost as useless as no compression and that the compression decreases the increase in heart rate in a does dependent way and that correlated very tightly with symptom improvement. That was published a few years ago.

The challenge is that the garment we used was made of neoprene and Velcro and no one in their right mind would wear that voluntarily outside of the study. And so Kate then did a study

looking at commercial garments. Patients, garments patients had in their home for this, that they purchased, and we sent them monitors and instructions to evaluate them at home. The study involved doing orthostatic vitals four times in a day, in a study day, in the morning before they put the garments on, and then 30 minutes after. We asked them to keep the garments on for at least three to six hours during the day and then do the same thing in reverse. Do vitals before taking it off and then after, to see if the effect was sustained. What Kate found was that in the morning, shown in the top here, was that the heart rate decreased by using the garment the patients had a home, their commercially purchased garments; you can see “A” shows the absolute heart rate on the left and on the right top you can see the delta heart rates. In fact, it lowered the heart rate increase to below this magical 30 beat per minute threshold. In the afternoons we did it in reverse. You can see when the garment was on, we were well below threshold, and when the garment came off it increased. If you actually, I don’t know that we present the data this way, if you actually were to compare them on effect in the morning and evening, morning and afternoon, it is about the same. But, without the garment the heart rate is higher in the morning than in afternoon and that reflects something else which is that there is a diurnal variability in standing heart rate, where it’s higher early in the morning and decreases by midmorning and to late morning and into the afternoon. This paper, [the slide] says it’s in press, that is now incorrect actually, just in the last week actually it is now available online and published in JACC ([Journal of the American College of Cardiology]) electrophysiology. With compression we are able to squish more blood backup into the thorax where the heart is, the chest and that increases the stroke volume the amount of blood the heart is able to pump with every beat and lowers the heart rate. So, how to do this? I used to prescribe compression tights, so high waisted tights, but the challenge is that they are hot, tight, itchy, ugly and patients didn’t love them. And so I’ve gone more to a commercial approach. I actually tell people to go to a sporting goods store and purchase high-end athletic wear, triathlon tights, for example. The high-end garments have a rating, that should say 15, I apologize, not 5 to 18 but 15-18 millimeters of mercury, just under 20. Now, pros and cons, right, its not as tight, so some people actually need the tighter prescription grading. But the flipside is that because they’re not as tight they’re more comfortable, they’re definitely more fashionable. And I find patients are more likely to wear these. The best tights the patients don’t wear are useless.

The third non-pharmacological treatment is exercise in POTS. A study that came out of Dallas about 15 years ago now where they measured a whole bunch of things in a before and after study design, between, before, and after three-to-six-month exercise interventions mainly focused on aerobic reconditioning, And they measured improved fitness levels, okay, improved

blood volume, I used to study that, that is of interest, improved cardiac remodeling. What I mean there is that they actually increased the size of the heart. They increased the stroke volume. They improved those cardiovascular parameters. It decreased the elevated sympathetic nerve activity. They put a needle in the nerve and measured it directly. All things I'm interested in, but most patients don't care about. It also decreased the orthostatic tachycardia. Some patients care about this because they can measure this at home. It decreased the amount that their heart rate went out. Everyone who completed the protocol, and in fairness not the same as everyone that started it, but everyone that completed the protocol reported an improvement in quality of life. Some a lot and some a little, right. I don't want to make this sound like it is a cure. It is a treatment. But it is one of our treatments. In clinic I do not have the exercise physiologist that they have in the study and the supervision, but the principles of it are the focus is aerobic training. They wanted regular activity at least four time per week and there are different approaches. Most of the approaches people use for exercise and POTS are modified versions of the Dallas protocol or the Levine protocol. Our approach in Calgary has been to encourage patients to get 30-minute sessions fairly quickly. We'll talk about that in a moment. That has to be individualized, in fact people are in charge of how they can progress themselves. The most important thing that they did in the study that is clever and important in terms of starting is that they forbid upright exercises. We had a patient who gets really tachycardic and feels unwell just standing and then asking the patient to go on a treadmill for 30 minutes is not realistic and it is counterproductive. Because the heart rates are wasted on gravity, and you're not going to get the training effect. In the study they actually encourage the use of rowing machines. If that cannot be done under certain circumstances or that is not an option, recumbent cycles will work, swimming is also an option. But I will say that the study done in Dallas every other person probably has a pool there, in Calgary we call outdoor pools "ice rinks". There are some indoor swimming pools but not enough. Most of my patients realistically use the rowing machine or recumbent cycle. We can talk about how we do that afterwards. One of the important things is that early on when patients would start to do this they come back and say "it was not working for me." I had to go back to Qi Fu and ask what I was doing wrong. What she said is, "we reported who got better, we didn't say when." It can often take up to six weeks before patients start to notice improvement with this. It was longer than I would give it if not knowing to wait that long.

So I'll finish with a few words on some drug treatments, propranolol an old school short-acting centrally-acting beta blocker works. It lowers the standing heart rate, it lowered the orthostatic tachycardia, it improved symptoms. We'd have patients coming up to us all the time in our research unit at Vanderbilt s saying, "I don't tolerate beta-blockers," and we'd say okay, and then

we'd study a bunch of drugs including propranolol, and propranolol would typically win. By win I mean they would have the best heart rate reduction and the best symptom improvement. And so we were trying to figure out why and it was Bonnie Black, our research nurse that said we typically use a low-dose of drugs we are using low-dose propranolol, maybe it's a dose thing. In fact when we used fuller dose beta-blockade with higher dose propranolol, symptoms got worse again. The key to using beta-blockers is to use a little bit, low doses. The key is to take the edge off the heart rate increase, not to normalize the heart rate. If you normalize the heart rate patients will often feel worse.

More recently a couple years ago Pam Taub from UCSD in San Diego published a placebo-controlled trial of Ivabradine showing that it lowered the heart rate and improved symptoms in some patients. We do not at this point know which is better. We are doing in Calgary a comparative effects study of propranolol, Ivabradine, and a placebo in a crossover design so hopefully we'll have a lot of data in the next year or two. I'm not going to talk about the other drugs, I'm happy to answer any questions about them. I do want to mention norepinephrine transport inhibitors. So this is actually a mechanistic class of drugs most commonly received them in SNRI as opposed to SSRI drugs. These are fairly common in the anti-anxiety antidepressant space but also, it is also common in some drugs used for fibromyalgia and related conditions. The "N" stands for a norepinephrine transport inhibitor this is a clearance transport of the sympathetic nervous system, and if you block it, you actually increase sympathetic tone. So when we gave Atomoxetine which is the purest norepinephrine transport inhibitor on the North American market, what we found is that the heart rate actually increased on then seated, the orthostatic tachycardia increased, and the symptoms worsened, this is the only drug we tested where we saw this. So, in fairness, not everyone got worse about 2/3 did and 1/3 didn't. This is a class of drugs I tend to worry about in our POTS patients, and we try to get them off of it if possible.

I will finish just with these take-home messages. That POTS is a chronic disorder associated with significant disability. It is not one disease it is a syndrome and there are probably multiple pathophysiologies that can affect different people and that may be why what treatment works for one person doesn't necessarily work for another. The treatment principals involve foundation of exercise, volume expansion, heart rate control, right, directly, the propranolol and Ivabradine. And then the final point is that these are chronic illnesses, I don't cure people with POTS, these are things that patients learn to manage and live with and hopefully function better than before we saw them. Part of that is learning to live with the chronic illness and that it is a bit of a

journey. From a physician point of view I think we have to actually bring that up and get permission for the patients to figure out what works for them. And It is not a one-size-fits-all there are different answers that work for different patients. We need to make it clear this is not "is it in my head or in my body," the answer is both they both need to be treated. So with that I'll stop and I'm happy to answer questions.

Dr. Unger: Thank you, Dr. Raj, so much, there's been a lot of questions that Christine will get to, I did want to ask you. We have discussed the challenges of patients that have the overlap between POTS and ME/CFS and those that have post exertional malaise and the difficulties of managing the two and how you modify exercise in those situations?

Dr. Satish Raj: I'd say the following, post exertional malaise wasn't explicit. They didn't do two-day CPETs (cardiopulmonary exercise tests) in that Dallas study. It is one of the few things they didn't do. It definitely exists, it exists in our POTS patients with or without a co-diagnosis of ME/CFS. Even without that, it definitely exists in terms of the history. What people are able to do, I'll say that's the first thing. The second thing is the exercise they are able to do to begin with and what will qualify as exercise varies. People have different abilities and functions coming in. For some people it is a matter of sort of getting them up and being able to sort of veer into it. In our patient population with the tachycardia group, I cannot really speak to those with ME/CFS without tachycardia and perhaps that is a different group, different response that needs to be looked at separately. In the tachycardia group there is no doubt that some patients with post exertional malaise improve over time with the exercise, but it does take time. It is not a fast thing, and it has to be, the exercise has to be more gradual in the beginning as part of that. And then the patients, I do not sit there and tell them on day two you have to do this, on day three you have to do this, I give them the principles and they listen to their bodies and figure out what can be done.

Christine Pearson: So sorry everyone, still working on the technical piece here. I just wanted to mention, we are obviously going into the Q&A now, we have many many questions, probably more than I've seen on one of these calls in quite a long time, we will do our best to get to as many as possible and we will combine some that are about the same thing. One question that we did get and I just wanted to go ahead and ask it, Dr. Raj, so we can be explicit here, is whether or not you guys did screen for ME/CFS and either exclude those patients or include them and how that worked if so?

Dr. Satish Raj: Screened for them in what?

Dr. Unger: The study that was published, that was when the question came up. You listed a bunch of comorbidities, but not ME/CFS as one.

Dr. Satish Raj: I can see what the number was. We screen for nothing. Honestly, this was like anyone could have clicked on this and filled out the survey. Most of the patients, do I know a few of the patients, I suspect a few of my patients filled out the survey. Just to give you some perspective we've had now about 10,000 patients touch this. There probably was CFS in there it's what patients report whether they report the ME/CFS or not is on them but there is no screening, what we did say is we want patients with a physician diagnosis of POTS to complete it. If they did not have that they were not supposed to complete it. Having said that we asked the question again in the survey, "do you have a physician diagnosis of POTS. And as it turns out about 8% actually didn't. In the analysis we excluded them afterwards. There were some ME/CFS, that is one of the things we did ask about, but we certainly did not screen out patients.

Christine Pearson: Thank you so much. Sort of on a related note, I think it is not the same. there was a question about orthostatic intolerance. As you know that can be part of a ME/CFS diagnosis criteria. The question is how that relates to the work you are discussing here and how it or if it is something that was addressed or considered.

Dr. Satish Raj: Orthostatic intolerance simply put, symptoms that are worse upright than not. That can be due to different causes. We see it in patients who drop their blood pressure we see, the orthostatic hypotension group I alluded to, we see it in patients with orthostatic tachycardia and we see it in some patients without excessive orthostatic tachycardia. Even that falls into different subgroups of just missing the 40-beat target and you can question whether 30 beats is the right target then. But there are also patients with orthostatic intolerance who's heart rates may go up five beats upon standing. It is a hodgepodge. In our studies when we say POTS we mean that they met the hear rate criteria. It may have been useful, I alluded to a Canadian Cardiovascular Society statement a position statement that came out a few years ago that I was a chair of and we actually in that put up a little cartesian plane showing that, you know, for diagnosis of POTS you need both lots of orthostatic intolerance symptoms on the X axis and lots of heart rate or orthostatic tachycardia on the Y axis and you need both for diagnosis of POTS. One challenge was if they did not meet criteria physicians were telling patients you do not have POTS. That was correct and they may have just been meaning you do not meet criteria. But what a lot of patients were hearing is there is nothing wrong with you, and that wasn't necessarily correct, right, the patients were there having something going on. And so one of the things we did in that statement was actually create a nomenclature of orthostatic

intolerance around POTS. We came up with a term that is probably not a great term, if you come up with a better one that's great, but for patients that didn't meet the heart rate criteria but had a lot of orthostatic intolerance symptoms, and we called it postural symptoms without tachycardia or PSWT. It doesn't roll off of the tongue so if you come up with something that rolls off the tongue that might be better. But the point is we wanted to have a way of basically recognizing that there's something going on, it is not POTS. Even that might be a few somethings that we need to define better afterwards.

Christine Pearson: Thank you. So the next question is: Does POTS have more sympathetic or less parasympathetic activity or a combination? Any changes on systemic inflammation or brain inflammation, and any relation with SFN and alpha- synuclein, and are POTS post-covid different than other conditions? Apologies if I mangled any of the technical terms I'm a communicator by trade.

Dr. Satish Raj: So I don't know if you've seen the movie Back to School by Rodney Dangerfield, I'm aging myself when I speak to lab students they don't understand any of my movie references. He was an adult learner that went back to college and had an oral exam with a teacher that hated him. The teacher came up and said "I have one question for you", and he got all excited, "with 21 parts". And this question reminded me of that. I might need you to break down the questions for me again, because they have answers, but there are a lot of them.

Christine Pearson: Sure, Is POTS more sympathetic or less parasympathetic? I think they might mean sympathetic or parasympathetic, not less necessarily, or a combination?

Dr. Satish Raj: It is heterogeneous. I do not like subtyping there are certainly some patients that have a very ramped up sympathetic nervous system. The issues around parasympathetic tone, which are all indirectly measured, certainly all the POTS data is indirectly measured, the truth is there are different subgroups and its all over the place. And so there is not a clean answer for that. Even for the sympathetic parts, the group at Vanderbilt more recently, I wasn't involved in this study it was after I left, took a group of patients and did muscle nerve recordings for sympathetic tone where you could quantify it and actually describe different groups of patients with POTS and try describe different features. And they answer is there is not a clean answer to that. It can be either or both. Part 2?

Christine Pearson: I think the second part was if there were changes on systemic inflammation or on brain inflammation?

Dr. Satish Raj: Systemic inflammation may have been in the same study, I'm not sure now, that reported earlier about the overlap of POTS and CFS, but we looked at CRP and IL-6 and certainly there were elevated levels of interleukin-6 or IL-6 overall in the group. There's been a lot of interest in autoimmunity related to inflammation. There certainly is a subgroup of patients that seem allergic to lots of things. We've often labeled them as having a mast cell activation syndrome, whether or not it is related to mast cells I think is debatable but there is no doubt there is a strong immunologic component. We've done some work on autoantibodies; it's been a bit tougher to hone done exactly what. But as I mentioned there is a group of patients, a significant minority that have autoimmune diseases and the demographics of POTS overlaps with a lot of autoimmune diseases. Sort of young females, females of childbearing age. I think the inflammation thing is being looked at certainly in the long covid POTS group. Presumably the POTS is either triggered by something about the virus, autoimmune response, or inflammation, right those are the big possibilities and there is some work and some interest in trying to target inflammation in long covid POTS to see if that helps. As for brain inflammation I do not know if there is great data. We are actually the early end of a study trying to understand brain fog that involves doing MRIs of the head, research MRIs of the head. One of markers we're looking at is actually iron deposition as a marker of information, so I will get back to you, but I cannot answer that question yet.

Christine Pearson: Thanks, so, there was one question, and I can't find it in the long list right now, basically it was asking, saying, some people cannot tolerate salt well. And basically, how do you then deal with that if that is one things that is recommended but they perhaps can't do an increase in salt?

Dr. Satish Raj: It is a challenge. Ultimately there are various things that can be done or not done. It's a matter of seeing if there is a way to do it. When you cannot tolerate salt there's different reasons. Sometimes it's nausea, sometimes it's you don't like the taste of the food, right. You add the salt to the food you just don't like the taste. I had a patient I saw yesterday in clinic where that was the taste. If it is a taste issue, then that is where salt tablets maybe better because you still taste a little but you don't taste as much of the salt because taste is a function of surface area. Some people the tolerability has to do with nausea, the salt actually induces more nausea. That is where sometimes, most time actually, a preparation that is coated and absorbed beyond the stomach, like the vitassium, may be a better approach than just adding salt to food. For the vast majority salt to food works. If these other things don't work, is a matter

of finding a way around it and ultimately if it cannot be done it cannot be done but the vast majority of patients are able to find a way to try and do that.

Christine Pearson: So the next one is, can you speak to differential diagnoses or co-occurring issues such as CSF leaks or venus jugular compression or how peripheral neuropathy is a factor for patients with dysautonomia.

Dr. Satish Raj: There are things that can certainly coexist with POTS and maybe trigger some of it. There are some patients, so CFS leaks can certainly occur if someone sticks a needle in your back and nicks the dural space the classic would be a woman during labor that gets an epidural, but the needle actually goes beyond epidural space into the dura, and you get a leak out, and it can present with severe headaches when standing, so positional headaches. And again, our POTS patients do not tolerate standing and 90% of them get headaches, but this is usually a very sharp headache. If it is due to acute injury like that where someone has put a needle in it can be usually fairly well treated with a blood patch. You sort of put another needle in inject a bit of blood it moves around and when it clots it seals up the hole. Patients can get it spontaneously though, especially patients with Ehlers-Danlos syndrome, where collagen may not be robust as we would like, and they can get spontaneous leaks those are harder to treat. But certainly worth trying with blood patches and other approaches, and these patients can present also tachycardia, orthostatic tachycardia.– Jugular vein compression I do not know as much about, but certainly there are some patients with pelvic vein congestion, so sometimes caused by something like May-Thurner which is an iliac vein compression that can lead to collaterals lots of other small veins, varicose veins forming in the pelvis that when you stand up allows more blood to pool there. In theory if you can find pelvic vein congestion, show us using a dye test a venogram, and you can find the source. If most of those come from one source, then interventional radiologists can sometimes go in and embolize it they can sort of close off the source and that may help with pelvic pain which is one of the presentation and might help with orthostatic tachycardia as well. Although in my experience tachycardia does not always respond. There was a third thing in there, but small fiber neuropathy. So small fiber neuropathy is problematic. Certainly, it exists in our patients they will complain of it the treatment is largely symptomatic. There are some people who are investigating the issues as to whether small fiber neuropathy is related to inflammation and autoimmunity and whether targeting immune treatments will help that, right now, that is still very investigational. There is not specific how we got from here to there. I can a theory as to how lower limb neuropathy can predispose a

diagnosis of POTS, but would do about it right now is often treat symptomatically, that may change in the future.

Christine Pearson: I think we have time for one more, and I apologize if this does not make sense, I do not have a medical degree. Basically, the question was, if you can comment on vagus nerve neuropathy and if there is a connection to diabetes, like a higher risk if someone is diabetic. And then also, as it relates to if there are treatment recommendations in that case.

Dr. Satish Raj: I'm not sure I can comment on, I thought the question, when you started, was going in a slightly different direction, which I'll touch on, but I'm not sure I can comment on vagus nerve. By vagus nerve neuropathy I wonder if they meant blunted cardio vagal tone. You can measure that with heart rate excursion, response to things like deep breathing, that is pretty much vagus mediated. I will say in the vast majority not all, but the case majority of our POTS patient, it is normal. That actually is not usually affected. It certainly is affecting diabetes. That's actually when people talk about cardiac autonomic neuropathy in diabetes, that's usually some version of that measurement is what they're talking about. Can diabetic patients get POTS? Absolutely. The very first description of the term Postural Orthostatic Tachycardia Syndrome was actually in a case report in a diabetic patient. It wasn't, it was actually before the Mayo report that came up with criteria that we use now but it was originally a diabetic patient. Having said that, do I see it a lot? Diabetes is very uncommon in the patients that I see with POTS. It is not the common cause, but it certainly could, the bigger concern in diabetes over time is that you can get a more aggressive autonomic failure and present with orthostatic hypotension. And not just the tachycardia you could certainty through a phase with orthostatic tachycardia. What I thought the question was going to be about was vagal nerve stimulation when you started the vagal nerve thing. I did not actually get into a lot of that but there's been a lot of interest in last few years in vagal nerve stimulation it, not so much in the sort of acute heart rate lowering effects, but by providing low a little bit of stimulation for a little bit of time on daily basis that it may actually decrease inflammation. So there is an anti-inflammatory, vagus mediated anti-inflammatory pathway involving the spleen, for example and it may modulate that. Professor Tracy has done a lot of work on that in animals and in other conditions in humans. Earlier this year there was a paper that came out in JACC EP, which is a small single center trial in Oklahoma looking at vagal nerve stimulation in POTS. Small numbers but it showed for two months of vagal stimulation for I think an hour a day lowered the heart rate. It was a small study it did not address symptoms properly and mechanisms and so I know Doctor Stavrakis, the PI on that study has put in a grant to NIH to actually look at this in a multicenter study and we are

involved in that grant application. This might be a new nonpharmacological treatment for POTS in a few years but right now there is promise, there is smoke, but haven't seen the fire yet.

Christine Pearson: Thank you so much. Now that I am done with questions, I can turn my video back on. Hi everyone, I wanted to thank you again Doctor Raj for joining us today. Thank you to all of our callers for joining us. On behalf of the entire program, we wish you the best in the coming months and look forward to our next call. This will conclude our call today. We will work to get materials on our website as soon as possible. Have a good rest of the day. Thanks, bye.