# Responses to Participants' Questions

This document provides responses* to questions raised by webinar participants related to the following presentations:

- **Presentation 1:** ***Pathobiology and Spectrum of COVID Myocarditis and Cardiac Injury in Adults***
  **Aloke Finn, MD**
- **Presentation 2:** ***Clinical Spectrum of COVID Myocarditis in Children***
  **Jennifer Su, MD**
- **Presentation 3:** ***Intermediate and Long-term Cardiac Outcomes in Children and Adults with COVID-19***
  **Matt Oster, MD, MPH**

* Responses may have been edited for clarity.

## All Presenters: Questions and Responses

### Q1. *How do we determine if there are microthrombi in living patients?*

**Responses:**

**Dr. Finn**: Myocarditis is typically a clinical diagnosis. We rarely have tissue samples for diagnosis. Because we can't detect microthrombi clinically, we don't have any known modalities or tests that definitively can diagnose microthrombi. Consequently, we don't know how many of these cases that we're reporting as myocarditis or other cardiac injury are actually microthrombi induced. At this current time, I don't think we have a good way to get that data. And that's a big problem because it speaks to the pathogenesis of the disease. We didn't find any evidence of myocarditis in any of the cases we've examined so far, so I think it's a much rarer entity that what is reported in the literature.

**Dr. Oster:** There was a study of BIG 10 athletes who had COVID, and about 2% of them had inflammation visible on an MRI. However, it is unclear what this means, because these were asymptomatic people. Also, it is unclear how the rate of inflammation compares to prior infections (e.g., the flu), since we don't have previous MRI data. Getting to the mechanisms, these are differences between the myocarditis after COVID vs. after MSID (Multi-System Inflammatory Disease) vs. after different vaccines. So, there are different pathways, and we need to learn more about exactly what they are, so we can better understand how these symptoms are happening and how we can treat and prevent them.

**Dr. Su:** I want to highlight that, outside of myocarditis, in cardiology in general, we often see if an ECG or cardiac MRI is normal, there are subclinical elements that manifest later in life. We see this in cases of dilated cardiomyopathy, sometimes in myocarditis, and sometimes in anthracycline or other toxicity-related cardiomyopathies. People may actually have normal heart functioning and testing during pediatrics, but we know now that they are at increased risk with multiple factors during adulthood for developing heart failure later in life, earlier than their cohort.

## Q2. What is the connection between PEM (post exertion malaise) and cardio lung involvement in covid PASC? Can the panel comment on potential causes of post-exertional fatigue and malaise in PASC in the absence of objective findings on routine work-up, including ECG, echo, cardiac MRI, PFTs (pulmonary function tests), etc.? Has CPET (cardiopulmonary exercise testing) been performed in this context and, if so, have you seen impaired oxygen consumption? Any speculation on the possible role of occult mitochondrial pathology and/or oxidative stress?

**Responses:**

**Dr. Finn:** I've personally seen that, after acute COVID-19 infection, fatigue is very common, some of that persists for a long time. It's unclear what that is caused by, but I do think that cardio-pulmonary exercise testing will begin to give us some idea if there's objective evidence of some sort of issue with the cardio-pulmonary system in terms of the ability to exercise. There is a mandated test in the RECOVER clinical cohort, so I think we'll begin to learn something about it.

**Dr. Lala-Trindade**: Speaking from our Mt. Sinai experience, we published a study just a few months ago of 41 patients with a mean of 9 months after infection. All of these patients had normal echos, normal CTs, normal PFTs, normal ejection fraction, and so forth. But interestingly enough, 80% still had changes that represented circulatory impairment or some cardio-pulmonary impairment and so I think we're just scratching the surface at this point. I think having a lot of the CPET data will uncover a wealth of information. The unexplained dyspnea after COVID-19 is a very frequent symptom that we don't fully understand the mechanism behind.

**Dr. Oster:** I'd echo that. It's important to learn more about people who are having long term fatigue. It is a real thing, and it certainly affects their exercise capacity as well. I will mention that we did a recent study in our Multisystem inflammatory syndrome in children (MIS-C) patients. We were having a number of those who had poor functions come back for exercise tests 3 months afterwards. They all did great! That might be unique to MIS-C, but I was very surprised at how well they did. Again, these are people who tend to recover and feel better after a few months. People who have lingering symptoms are in a different bucket and could benefit from further evaluation.

### Q3. So far there is a lot of discussion of myocarditis and direct effects on the heart. Are you finding any evidence of effects on the vascular system without discernible effects on the heart according to current testing protocols like echos? For example, that might cause blood flow issues or the heart to beat harder (not faster)? In Long COVID patients specifically, that were not hospitalized.

**Responses:**

**Dr. Finn:** The heart and the brain are closely linked. The heart rate is often controlled by the balance between the sympathetic and parasympathetic nervous system. COVID-19 can be found in the brain in some situations, so I sometimes wonder if there is some relationship between autonomic nervous system balance and having COVID-19 and whether there is something the virus does to throw off that balance. That is just speculation.

**Dr. Oster:** I would echo that. You can have sinus tachycardia or sinus bradycardia; it can be all over the place. We have talked a lot about myocarditis, but apart from MIS-C, in my clinic, I've seen more children with nuance at POTS than myocarditis. That's certainly an autonomic phenomenon. It's not new, it's been around for a while, but COVID-19 is a new trigger for it. So yes, COVID-19 can have vascular long-term effects that we're just on the cusp of starting to appreciate better.

**Dr. Finn:** One of the things RECOVER will do is get the brains of dying people who had a history of COVID-19 to see if there are any abnormalities. We'll also try to do a study at viral persistence to see if there is evidence of viral reservoirs. There is a hypothesis that some tissues serve as reservoirs for the virus and those are maintained long-term. Whether or not that really exists in Long COVID cases is hard to know but can be answered by autopsies.

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