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Understanding Preload Deficiency in SLE: A New Look at Fatigue and Exercise Intolerance

# Mr. Quigley:

Welcome to *Living Rheum* on ReachMD. I'm Ryan Quigley, and joining me to discuss the role of preload deficiency in fatigue among patients with systemic lupus erythematosus, or SLE, are Drs. Luigi Adamo and Andrea Fava. Their research on this topic was published in *The Lancet* in September 2025.

Dr. Adamo is an Associate Professor of Medicine and the Director of Cardiac Immunology at Johns Hopkins Medicine in Baltimore. Dr. Adamo, thank you so much for being here.

# Dr. Adamo:

Thank you, Ryan, for inviting me.

# Mr. Quigley:

And Dr. Fava is an Assistant Professor of Medicine in the Division of Rheumatology and Director of Lupus Translational Research, also at Johns Hopkins Medicine. Dr. Fava, it's great having you here with us as well.

# Dr. Fava:

Thank you. It's my pleasure.

# Mr. Quigley:

So to start us off, Dr. Adamo, what initially motivated you to explore fatigue and exercise intolerance in patients with SLE?

# Dr. Adamo:

So I was hired at Johns Hopkins as Director for Cardiac Immunology to start a basic translational research program in how the immune system interacts with the cardiovascular system and to take care of patients where alterations of the immune system affect the cardiovascular system. And so, as part of this, I overlap with cardio-rheumatology. We don't use this term much at Hopkins because we decided to look at it a little bit more broadly, but still, a lot of the patients that I see in clinic are patients with rheumatologic diseases who have some cardiovascular complaint.

And actually, Andrea Fava, who's one of the colleagues at Hopkins and our friend, started sharing with me these patients with lupus in which lupus was controlled, but they continued to have fatigue. So really it was a clinical journey in which these patients came to my clinic, and I was asked by my colleague, "I am controlling their lupus, but they're still short of breath. They still have exercise intolerance. What do you think is going on?"

# Mr. Quigley:

And now turning to you, Dr. Fava, can you walk us through some of the methodology behind this work?

# Dr. Fava:

So the methodology is quite simple. It's a case series of 10 patients we've seen in our clinic, and then we report these patients that have not just fatigue, but mostly inability to exercise. They have inability to tolerate heat. What's particular about their inability to exercise is that they seem to have more endurance when exercising lying flat as compared to standing up, and they tend to have lupus that is well controlled. This inability to exercise comes up when they try to exert themselves, and they tend to have a higher heart rate at baseline.

And in a few of them, Dr. Adamo was able to obtain an exercise right heart catheterization to monitor the change in the pressures in the heart upon exercise, and these patients could not mount an adequate preload. Now, preload is a word that, if you're not cardiologists,





you may have forgotten since medical school. But when during exercise, our cardiovascular system has to pick up the pace and increase the cardiac output. And one way to do so is by increasing the amount of venous return and eventually increasing the pressure in the right part of the heart so the system can catch up with the output. And these patients were unable to do so.

And so we're trying to understand why this happens, but that also is a rationale for how we are currently treating these patients.

# Mr. Quigley:

Now, Dr. Adamo, as I understand it, you found low or undetectable NT-proBNP levels across the cohort. What might that tell us about this biomarker's role in identifying preload deficiency?

#### Dr. Adamo

So NT-proBNP is a marker that is used in clinical medicine to identify an increase in filling pressures in the heart. The idea is that if the heart is stretched because there is too much fluid, then NT-proBNP goes up.

So in my practice outside of cardiac immunology, I'm also a heart failure specialist. When a patient comes with exercise intolerance, if the NT-proBNP is high, that is a diagnostic of heart failure. The sensitivity and specificity is north of 95 percent in the general population. So the fact that the NT-proBNP was not only low but undetectable was one of the things that tipped us toward the problem with filling pressures of the heart.

So I think in a practical scenario, when I see the next patient of Dr. Fava's, we rule out heart failure, structural alterations of the heart, and functional alterations of the heart per se. And having an NT-proBNP that is undetectable has a negative predictive value close to 99 percent for structural abnormalities of the heart that are associated with heart failure.

It's not necessarily abnormal to have an undetectable BNP, so I don't think it's something that is just because a patient has an undetectable BNP, it means that they have preload deficiency. But in the right clinical scenario, I think it rules out a lot of other possible diagnoses and makes this one a lot more likely—something that is worth investigating further.

#### Mr. Quigley:

Thank you for that. For those just joining us, you're listening to *Living Rheum* on ReachMD. I'm Ryan Quigley, and I'm speaking with Drs. Luigi Adamo and Andrea Fava about new findings on preload deficiency and fatigue among patients with SLE.

So, Dr. Fava, turning back to you now, once you confirmed preload deficiency, what interventions did you find most effective in alleviating symptoms?

# Dr. Fava:

Because most of these patients tended to have low blood pressure—soft blood pressure—at the beginning, with this physiology, we suggested to increase their fluid intake. So we recommended to go toward one gallon of fluid a day and with caution to also increase salt intake—similar to what we do in patients who have POTS, which is postural orthostatic tachycardia syndrome.

Now, for several of these patients, given that one of the components of their symptomatology during exercise was the fast heart rate, Dr. Adamo also recommended ivabradine, which tends to reduce the pickup of the heart rate upon exercise. And that had, in a few of the patients, a dramatic improvement. Now, I don't think we can say that these interventions have fixed the issue for all of our patients, and that speaks to the fact that we really need to better understand what is the root cause of the situation. But I would also like for Dr. Adamo to comment on this since, from the cardiac perspective, he has seen this in more depth.

# Dr. Adamo:

Yeah. I think going back to pleural deficiency, these patients are basically functionally dehydrated. So if we take an athlete—an 18-year-old kid who does cross country and you don't allow him to drink for two days and then you tell him, "Go do your race," he's going to have exercise intolerance. And so these patients, even though they drink and they try to keep to have a normal diet and then not stay in the heat, they are functionally dehydrated. When they will try to work out, the right atrial pressure cannot increase as if they didn't have fluid to bring back to the heart, so it made sense to increase the fluid intake. And for some patients it was a gallon. For some patients it was three.

And then if you just drink and you don't eat salt, the fluid is not going to stick around in your body, so we recommend an increasing salt intake up to five grams of sodium per day. But for some patients, it's really hard, so we started recommending Gatorade, Propel water, or Liquid IV.

And the most common drug that we use to control the heart rate are beta blockers, but beta blockers can also lower the blood pressure and can dilate the veins. That is the opposite of what we want to do. So after we tried it once on one patient, we went to ivabradine, which is a drug that also in cardiology is not used very frequently but is actually very selective for the heart rate, and it has no effect on





blood pressure and is typically very well tolerated.

Importantly, for the lupus patients, ivabradine can prolong QT on the EKG. And also, hydroxychloroquine, if frequently prescribed in lupus patient, can prolong QT, so it's very important to get an EKG at baseline after initiating ivabradine. But we're prescribing now about 15 times, and we never had to lower the dose or stop it. But that proper medical care would be started with EKG monitoring.

## Mr. Quigley:

Now, Dr. Adamo, how could these findings reshape how we approach chronic fatigue in patients with SLE, especially when the disease appears inactive?

#### Dr. Adamo:

Andrea and I hope that our experience might enrich the experience of other providers. And in the same way that we were able to help this handful of patients, other providers around the world might be able to help other patients. So I think that there is something to learn from our clinical journey. When a patient comes with lupus and they have a controlled disease and they still have more than fatigue exercise intolerance, I think this should be in our differential.

So we tested the exercise tolerance of our patients with a cardiopulmonary exercise stress test. That is a quantitative way to measure what is their ability to exercise. And these patients had reduced exercise tolerance. It was quantifiable. It wasn't just fatigue, which is not lethal—but it wasn't just a feeling. They could not exercise as much as other people. And then the structure in normal heart—we did cardiac CT, echocardiogram with strain, and cardiac MRI—they didn't have arrhythmias, and their pulmonary function tests were fairly normal. Nothing to justify that.

So I hope that now when practitioners find this, the answer will not just be "We don't know," but it will be "Maybe you have preload deficiency." We hope to be able to study this and really bring forward the knowledge for everyone. But I think even just this little experience that we did rigorously, hopefully, can be beneficial for the practitioners around the world.

#### Mr. Quigley:

So final question here—and, Dr. Fava, this is for you—if we look ahead for a moment, what are the next steps in researching preload deficiency in SLE?

# Dr. Fava:

I think that we do not really know what's causing it. We have many hypotheses, but we don't even know exactly which is the component of the human body that is driving this condition. We have initially thought that this could be part of dysautonomia, which has been described in lupus and can be part of lupus. But when we tested for it—provided that our tests are not perfect—the test did not meet the threshold to call this dysautonomia. So is this because there is an autoantibody, because lupus is an autoimmune disease, and then it tends to make autoimmune reactions against many parts of the body? Maybe it's immune mediated. Maybe it's something different.

So we don't really know, and so I think that the first step is to get a sense of how frequent this is outside of Johns Hopkins—and how prevalent it is—and better understand the risk factors and eventually what is causing this. Because if this is immune, maybe we could target it with an immune-mediated treatment or immune-targeting treatment. If it's not immune and it's part of damage or other features of lupus, then that can help us in devising the best treatment strategy for these patients.

And ultimately, the treatments that we are using are based out of our experience and creativity in trying to address this problem, but there may be a better way to do this. And so we want to find what the best approach to improve the lives of our patients.

# Mr. Quigley:

With those insights in mind, I want to thank my guests, Drs. Luigi Adamo and Andrea Fava, for joining me to discuss their recent findings on preload deficiency in patients with SLE. Dr. Adamo, it was great having you on the program today.

# Dr. Adamo

Thank you very much for hosting. It was my pleasure.

# Mr. Quigley:

And, Dr. Fava, it was a pleasure speaking with you as well.

# Dr. Fava:

Thank you very much.

# Mr. Quigley:

For ReachMD, I'm Ryan Quigley. To access this and other episodes in our series, visit *Living Rheum* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.



