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A Look at What COVID-19 Does to the Lungs

Dr. Wilner:
Coming to you from ReachMD, this is *COVID-19: On the Frontlines*. I'm Dr. Andrew Wilner, and joining me to discuss his research published in the *New England Journal of Medicine* on COVID-19 is Dr. William Li, President of the Angiogenesis Foundation.

Dr. Li, welcome to the program.

Dr. Li:
Well, thank you very much. It's a pleasure to be on.

Dr. Wilner:
To start us off, Dr. Li, can you tell us about your medical background and how you came to establish the Angiogenesis Foundation?

Dr. Li:
Well, I'm an internal medicine doc. And I'm also a research scientist, a vascular biologist specifically, and that means that I study blood vessels, and angiogenesis is the process the body uses blood vessels to grow. And 25 years ago I had the inspiration and a bit of a vision to start a not-for-profit organization that could look at common denominators of health and disease focused on how blood vessels help our organs to remain healthy on one hand and how out-of-control blood vessel growth can lead to diseases, and that's what we've done over the last 25 years is to help focus a variety of research scientists, industry, government agencies, patients, and advocacy groups to focus in on what diseases share in common and what can do from medicines to diet to lifestyle to be able to actually get our blood vessels back in control.

This field of angiogenesis now is well-recognized to be one in which the microcirculation is not only important for growing through angiogenesis to heal wounds, like after surgery or trauma, but to actually help the heart develop new collateral channels, the brain to remain well-perfused.

How clinicians need to be aware of it is a new dimension of blood vessels that has been discovered in COVID-19, which is that the virus that causes a respiratory infection, the SARS-CoV-2, has now been discovered to infect our vascular cells, our circulation, and cause a whole host of problems that we're beginning to see outside of the lungs in COVID-19 disease.

Dr. Wilner:
Okay, well that's a great lead into your study. Tell us about what you published in the *New England Journal of Medicine*. What was your goal? And then how did you design the study?

Dr. Li:
Like many people that felt blindsided by COVID-19, I became interested in understanding what was happening in the disease, particularly because in the clinic, in the emergency rooms, in the ICUs, what was happening is that the physicians and nurses were really struggling to, No. 1, diagnose a disease, No. 2, support patients as they got sicker up until the point of respiratory collapse, requiring intubation and ventilatory support, and then really not knowing who was going to live and who was going to die. This wound up becoming a real enigma, I think, to everyone concerned, and it's still an enigma.

We also began seeing beyond respiratory compromise these odd phenomenon-like strokes, blood clots in the lung and the brain, in the limbs, and also peripheral organs like kidneys being damaged, but also, even the COVID toe, this bright red, beefy, warm, inflamed toe, and this constellation of the disease of COVID-19 really made me wonder what could possibly connect all of these disparate organs from lung to toe, to brain to heart. And, of course, being in my wheelhouse of our blood vessels was the circulation. So, with an

international group of pathologists and ultrastructural vascular biologists, we actually got autopsy tissue from people who died of COVID-19 and dove into the lungs just to kind of look at what's going on, and what we found was indeed the respiratory virus was causing acute respiratory distress syndrome, with massive inflammation, pneumonia-like findings, but also, we found that the SARS-CoV-2 virus was also making a beeline in the lungs for the vascular endothelial cells, the cells lining our blood vessels. We have the first pictures of this virus entering the vascular cells, filling them up like a gumball machine and damaging the vascular lining from the inside out, and what that meant was that we observed for the first time the damaged endothelial lining was leading to blood clots all over the lung in large geographical planes, helping us understand what was contributing to this respiratory collapse, which was not just pneumonia and blockage of airflow but also blockage of the actual circulation that's required for gas to oxygen exchange, and then helping us understand how the same type of phenomenon might actually be happening in other organs of the body, which is really what's going on right now.

Dr. Wilner:
Well, I have read that article, and the pictures, the pictographs, the electron microscope photos really are very impressive. Just to reiterate, you can get the flu from a virus and be on respiratory support and die. In your study you compared the lungs of COVID-19 to the lungs of patients who died of the flu. Were they different?

Dr. Li:
We wanted to find out what was unique about COVID-19 going on in the lungs, because clearly, although there were many similarities to flu, like H1N1, or even the SARS-1 virus, we felt like there was something distinct. Not only was this virus more infective and more deadly in some ways because of all these other phenomenon, we wanted to actually compare the H1N1, the flu, versus the COVID-19 lungs, and what we found were a couple things. No. 1, while they were both causing ARDS, the picture was different. The H1N1 ARDS were heavy, really inflamed lungs with a lot of puss in them. The COVID-19 didn't have as much puss, they were not quite as fluid-filled, but they were equally inflamed. When we actually took a look at the blood clots, there were many, many more blood clots in the COVID-19 lung compared to the regular flu, the H1N1. And when we actually looked at the blood vessels around the COVID versus H1N1, it turned out we saw something rather unique and unusual in the COVID-19 lungs. The blood vessels were undergoing a form of reactive blood vessel growth, reactive angiogenesis, in which single blood vessels would try to divide into two. This is actually normally what happens when you have a wound and the blood vessels are immediately trying to create some bypass, but that happens in minutes. It doesn't actually happen for a long time. What we found was that this was happening at an order of magnitude greater in COVID-19 compared to the flu. And what was even more remarkable was that the longer the patient was in the hospital, the sicker they got, the more of this sort of reactive angiogenesis called intussusceptive angiogenesis was actually occurring.

And then when we actually dove down into the genes—because we looked at the genetic expression as well— COVID-19 genes were indeed having a cytokine-like reaction but very different and distinct from the H1N1, so this is a very different type of disease. It's not just generic pneumonia occurring causing respiratory distress and failure. There is something very distinct going on with this particular virus and the diseases that it's causing in the lung and in the blood vessels.

Dr. Wilner:
For those just tuning in, you're listening to *COVID-19: On the Frontlines* on ReachMD. I'm Dr. Andrew Wilner, and today I'm speaking with Dr. William Li about the results of his study comparing healthy lungs versus those infected with COVID-19.

So, Dr. Li, let's continue delving into your study's results. Do they help us understand the complications of COVID-19, such as pulmonary embolism or stroke?

Dr. Li:
Well, our findings I think take us one step forward into this type of understanding. This disease is still very much of an enigma because the coronavirus has really only been known to research, medical science, for about 5 months or so. What we do know is that this pulmonary embolism, stroke, and also thromboembolic disease of the extremities that we see, the DVTs that we're actually seeing, are all blood clots that are actually forming, as we've always known in medicine, due to damaged endothelium, and so, while we do see, obviously, embolism and stroke and DVTs in sepsis, what we're beginning to see now is that this is a disease that has a capability where the virus can infect the endothelium and damage the lining from inside the cells, from the intracellular perspective. And it's not like sepsis where you're producing endotoxin and having all kinds of platelet aggregation and cumulative damage to the vascular lining from within the lumen of the blood vessel. This is actually from the intracellular side of damage.

Dr. Wilner:
Well, now that we have this definite but albeit preliminary information, does it help guide our treatment approach?

Dr. Li:
Well, a few weeks back, published in the *Journal of the American College of Cardiology*, a study was done looking at the role of

anticoagulation in patients who were hospitalized with COVID-19, and it was actually reported that patients who were on anticoagulation of any sort for any reason actually had less severe disease and had better outcomes in terms of being able to leave the hospital, so better survival, less severe illness and being able to be discharged from the hospital, all very important markers attached to anticoagulation. With our study this actually makes sense. Beyond supporting the respiratory system and staying hydrated, this is actually a viral infection that affects the circulation and can set up for blood clots, so being on anticoagulation is something that's now being considered for patients as a means to protect them from blood clots. Now, obviously there are many patients who come to the hospital already on blood thinners if they have had a valve replacement or some other reason, a history of stroke, and so I think that those are important parts of intake and important parts of a risk assessment going forward.

What's really interesting that it raises is this possibility of, post-discharge, how long should patients continue to be on anticoagulation if they weren't on it to begin with? In other words, should there be long-term anticoagulation up to a point to help patients protect themselves from getting blood clots going downstream? In the early days of COVID-19, some of the early patient experiences were people would get flu-like symptoms, maybe get pretty ill, they would actually recover, sometimes being discharged from the hospital, and they'd be at home and then suddenly have a secondary decline, and that secondary decline may well be accounted for by having the virus still in the vascular lining and causing secondary blood clots. This is now a question that remains to be answered.

Dr. Wilner:
Well, I think this is a great example of how understanding the pathophysiology leads to a logical and rational decision regarding treatment, and the good news is that we're well versed with anticoagulation with different doses and different drugs. This isn't something we have to invent to fight the virus, but it's something that we already have on hand and know how to use that may help decrease some of the viral complications. Would you agree?

Dr. Li:
Absolutely. Every time we can peel back the layer of this enigma and gain knowledge, knowledge gives us power, and I think this is where we are now a few months into the pandemic is that from a largely unknown disease based on a virus to actually understanding how the virus impacts the body. We're beginning to really hack into what's actually happening in the pathophysiology of this condition and trying to figure out how we can ameliorate that. Now, this is still a far way from having a vaccine or an effective treatment, but this is actually a very, very important part to moving things forward.

Dr. Wilner:
Dr. Li, you've done some great work here on COVID-19, but as we come to the end of today's program, I'm curious to know what the next steps are for you. Do you have plans to conduct any further research on this pandemic?

Dr. Li:
Yes, I'm looking at things in a couple different ways. No. 1, I'm trying to understand timing of disease, to what point from infection do we start to see symptoms and what distinguishes somebody who is symptomatic from asymptomatic, and obviously, the role of testing in that. Secondly, I'm very interested in further diving into whether or not blood vessels help explain some of the other unusual findings, like the loss of sense and smell and taste, because obviously the circulation around the olfactory bulb and around some of the taste buds are something that also depends on vascular health. It's also interesting to try to figure out are there other inflammatory consequences with this cytokine storm that tell us a little bit more about the downstream effects. Beyond the lung, beyond blood vessels, we're clearly seeing other impacts potentially in the organs and well. Finally, what's going to happen long-term? Even when our body clears the virus, is there residual vascular damage that's going to need to be repaired? That is a really, really important question to be answered, and I think both laboratory studies and clinical studies are going to play a role in helping us get a hold of the long-term recovery from this disease.

Dr. Wilner:
Well, I, for one, hope to have the chance to speak with you again, Dr. Li, once you get some new research results. But for now, I want to thank you for joining me to discuss this fascinating paper and for helping us better understand how this infectious disease impacts our lungs. Dr. Li, it was great having you on the program.

Dr. Li:
Always a pleasure to speak with you, Dr. Wilner.

Dr. Wilner:
I'm Dr. Andrew Wilner. To add your perspective on the fight against the global pandemic, visit us at ReachMD.com and become Part of the Knowledge. Thanks for listening.