Photo by Sharona Jacobs

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Solving the mystery of long COVID

Why is imaging of the pulmonary vasculature so crucial for our understanding of the short- and long-term consequences of COVID-19? Prof. William W. Li explains the need for novel parameters, such as BVX, to tackle long COVID. "This novel parameter is a turnkey for drug developers."

"Angiogenesis and vascular imaging form a very pressing issue because of the pandemic we are emerging from," said William Li, who has 25 years of experience in vascular imaging and its application for clinical decision making. He is president, medical director, and co-founder of the Angiogenesis Foundation. Its mission is to improve global health by advancing angiogenesis-based medicine, diet, and lifestyle.

ANGIOGENESIS AND TUMOR GROWTH

Li explained the importance of angiogenesis by describing its role in tumor growth. Microscopic tumors lack their own blood supply, limiting their growth and ability to spread. Some tumors gain the ability to switch on and produce angiogenetic growth factors: 'pro-fertilizers'. These factors can bind to receptors in nearby, pre-existing blood vessels, and activate vascular endothelial cells. In turn, these cells will perform a repertoire of behaviors, including sprouting, penetration of the tumor, and delivery of oxygen and nutrients, allowing the tumor to enter its vicious cycle of growth and metastasis.

But angiogenesis is also the key to health – it is the most important process in wound healing and maintaining tissue viability. The human body contains no fewer than 60,000 miles of vessels. Capillary beds are unique and specific to tissues and organs, with shape following function. For a long time, capturing this microcirculation in a dynamic way has been "one of the big conundrums we faced for imaging," said Li. He argued that angiogenesis imaging is of key importance for drug development. "It impacts the entire clinical pathway: from preclinical evaluation, clinical trial design, and regulatory evaluation, to oncology practitioner education, reimbursement related to chronic treatment, and managing patient expectations."

WILLIAM W. LI

William W. Li, MD, is an internationally renowned physician, scientist, and author of the New York Times bestseller "Eat to Beat Disease: The New Science of How Your Body Can Heal Itself." His groundbreaking work has led to the development of more than 30 new medical treatments and impacts care for more than 70 diseases including cancer, diabetes, blindness, heart disease and obesity. His TED Talk, "Can We Eat to Starve Cancer?" has garnered more than 11 million views. Dr. Li has appeared on *Good Morning America, CNN, CNBC, Rachael Ray, Live with Kelly & Ryan* and the *Dr. Oz Show*, and he has been featured in *USA Today, Time Magazine, The Atlantic* and *O Magazine*. He is president and medical director of the Angiogenesis Foundation and is leading research into COVID-19.

CONSEQUENCES IN THE LUNGS

COVID-19 is "a highly diabolical disease," confirmed Li. "We still lack a good understanding of what is going on." Many extra-respiratory signs are very untypical for a respiratory virus, such as brain hemorrhage, kidney failure, encephalomyelitis, and 'COVID toes': red, swollen toes due to impaired microcirculation.

However, the possible impact on the lungs is the most profound. A study under the co-authorship of Li examined the associated morphologic and molecular changes in the peripheral lungs of patients who died from COVID-19 [1]. By affecting the vascular endothelium inside the lungs, the virus changed gene expression, altered cell shape, altered vascular function at a microcirculatory level, and caused reactive angiogenesis very similar to wound healing. The microthrombi in the capillaries are an unexpected phenomenon in that perspective. "It is very rare that the small capillaries are impaired. The body is designed to use them as emergency bypasses."

Samples of patients who died of COVID-19 show destroyed lung tissue architecture. "The virus takes the lung vessels apart," said Li. "Capillaries are splitting in a desperate attempt to bypass themselves, and patients develop an auto-immune vasculitis. There is continuous injury but not much sprouting, resulting in a chronic wound. This is a critical feature."

POSSIBLE LONG-TERM ORGAN DAMAGE

Li made a clear case that, on top of everything else, COVID-19 is a vascular disease. [2] This makes the disease systemic, causing short- as well as long-term damage – possibly even in children. Some 30% to 70% of people recovering from COVID-19 develop long-term symptoms, such as muscular weakness. This is sometimes referred to as 'post-acute sequelae of COVID' (PASC), 'long-term COVID', or simply 'long COVID'.

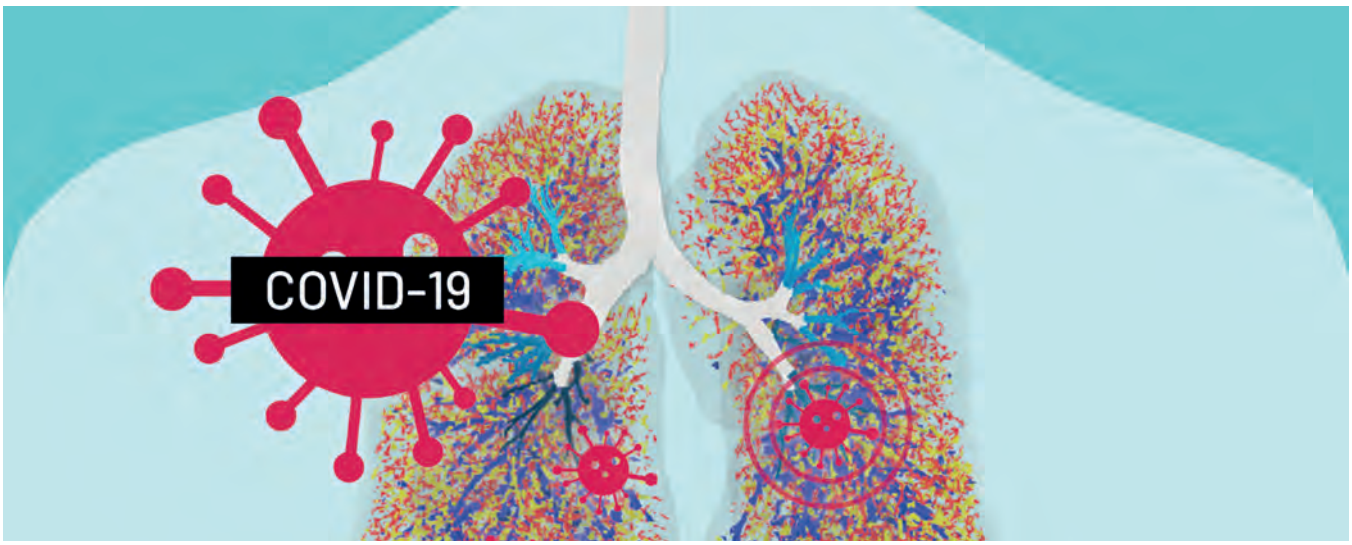
Long COVID is a very real syndrome that may even occur in people who have had COVID-19 but were never hospitalized. Possible symptoms include memory problems, a racing heart, lack of strength, hot flushes, stomach pain, and obstipation as well as diarrhea. Over 100 patient-reported symptoms have been sampled. About 30% of all people who have had COVID-19 worldwide may develop long COVID, which is a conservative estimate according to Li.

That is why Li calls long COVID a second pandemic, emerging from the first. "It is a tragedy in the making. We do not know yet how to prevent it, how to treat it, and how to rehab from it." But this also presents an opportunity, he added: for medical imaging, for drug development, for medical devices. 'It is time to focus on potential long-term organ damage from COVID-19' is the title of an article in the Washington Post (September 14, 2020) that Li co-authored. "We need to orchestrate biotech, biopharmaceutical, medical devices, patient advocacy, imaging devices, the NIH, and the private sector, to look at long-term organ damage from COVID-19."

FUNCTIONAL LUNG IMAGING: BVX

In the summer of 2020, Li began to work with FLUIDDA because of "a need to telescope from our understanding of acute COVID-19 to seeing what goes on in the blood vessels" in chronic COVID-19. After examining COVID-19 at the ultrastructural level, he also wanted to understand better what happens on a functional level, especially in patients with long COVID. "They continue to have intermittent respiratory problems, though their X-ray and CT scans look normal."

Li was thrilled to speak with FLUIDDA about the use of their recently developed BVX parameter, part of FLUIDDA's Functional Respiratory Imaging (FRI) repertoire. The BVX (Blood Volume) parameter measures blood vessel volumes of the pulmonary vascular bed. It is in use for triage and predicting adverse outcomes in patients with COVID-19 disease seeking acute medical care. In the words of Li, "BVX analysis is used to examine lung CT scans and make 3D reconstructions of the vasculature, identifying small (red), medium (yellow), and larger (blue) vessels.



These images can be rotated three-dimensionally and allow for calculating distances and density, and comparing tissue from healthy people and acute COVID-19 patients."

The results reflect what is seen in autopsy samples: severely damaged microcirculation. "We analyzed these CT scans with BVX and carried out 3D reconstructions," Li said. "We looked at the small, medium, and larger vessels and compared them to CT scans of normal lungs, of which FLUIDDA has accumulated a massive database." Li pointed out that the middle picture (long COVID) does not look as bad as acute COVID (on the right), but still does not look as good as a healthy lung (left). This confirms and visualizes residual damage in long COVID.

But how 'bad' exactly is this lung? It is possible to do a quantitative estimation as part of the BVX analysis, revealing that the microvascular structure of the lung shown in the middle is only 48% of normal. This quantitative estimation is a starting point for the pulmonologist as well as the patient: from here they can work on recovery as best as possible through pulmonary rehab, pharmaceuticals, etc.

Li is convinced that FRI of the pulmonary vasculature is "absolutely crucial" for the future, as it can assist in the following:

- diagnosis of long COVID;
- defining its pathology/pathophysiology;
- quantitative, qualitative and functional assessment, to be correlated with pulmonary function testing;
- establishing entry criteria for clinical trials of drugs to help restore the microcirculation;
- establishing theragnostic markers/biomarkers for treatment response;
- yielding information not captured by regular CT/MRI/PET scanning;
- guiding the physician and patient in clinical care.

TRANSLATIONAL SCIENCE: THE BIGGER PICTURE

The translational process seems somewhat underdeveloped compared to other parts of medical science: bridging vertical silos of expertise, tying the micro- and macrolevel together, to better understand diseases as well as develop proper therapeutics. It touches on Li's work at the Angiogenesis Foundation, which he described as an independent multidisciplinary third party, a convener of expertise. "Without all those different skill sets coming to the table, which my organization has successfully been doing for the past 25 years, you're stuck," Li said. "You can go an inch wide and a mile deep; but then you lose the forest for the trees. You must resurface to see how other experts can benefit from the bigger picture."

The Foundation bridges silos, bringing expertise together, Li emphasized. "You can marry these with 'enabling technologies', of which FLUIDDA's BVX is one. It is a turnkey for drug developers interested in understanding how to tackle long COVID, microvascular disease, IPF, or any other microvascular disease." The key, Li stressed, is to have the biggest possible toolbox, to solve a problem as a team. COVID-19 touches on so many organs and medical disciplines that cooperation is imperative.

VACCINE-RELATED HOT TOPICS

Prof. Li identified some urgent questions related to COVID-19 vaccines. Does vaccination prevent you from developing long COVID? Why does a large proportion (about 41%) of patients with long COVID report relief of symptoms after receiving their first or second vaccination? "Why would a vaccine clear up underlying residual disease? That is still a mystery," Li said. "Unless there are hidden reservoirs of virus, like we see in Lyme disease, that are not detectable with a nose swipe or even serology testing."

Li broadly outlined a trial that could be done to gain insight into the impact of vaccination on long COVID: Establish baseline pulmonary function in a large population of COVID long-haulers with respiratory problems, then see if their respiratory symptoms improve after they receive a vaccine; find if there is a qualitative or quantitative change in their microcirculation which can be tied to pulmonary function test results. "How do we measure improvement? That is where BVX comes in. We may learn from the results to develop a therapeutic."

Li is highly aware of the consequences of the pandemic, not the least in the long run. He is ready to make the best of it. "We are standing at the beginning of a long road of opportunities," he said. "What matters is not how good you are now, it's how good you are going to be."

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