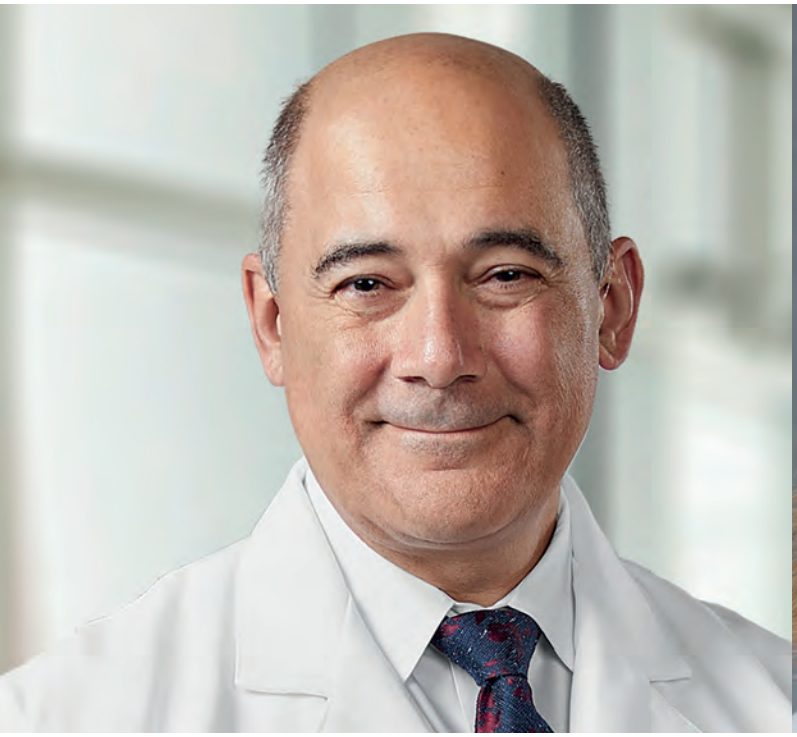

FRI is the missing link for pulmonary vascular disease

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> **Lung biopsies can be risky, and FRI might be the first virtual imaging biopsy.**
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> MARDI GOMBERG-MAITLAND, MD

Novel imaging technologies to identify and monitor patients with pulmonary vascular disease (PVD) are needed. Clinical researchers and cardiologists, Dr. Raymond L Benza of The Ohio State University and Dr. Mardi Gomberg-Maitland of George Washington University, share their expertise on PVD, highlighting their collaborations with Fluidda. Functional Respiratory Imaging (FRI) creates an image of the minute details of lung vasculature, which can serve as a surrogate readout of what's happening in the hearts of patients with PVD. In the context of PVD, FRI may be a useful tool throughout the patient journey – for early identification of disease, as a diagnostic instrument, and as a monitoring tool during treatment. Taken together, FRI has the potential to be a true imaging technique to monitor disease-modification for PVD.

As a clinical researcher in the field of PVD, Dr. Raymond Benza's major interest lies in developing risk stratification tools to predict pulmonary hypertension (PH). Benza says, "In my vascular biology lab, along with genomic studies, we employ machine learning and artificial intelligence to develop tools to limit clinical worsening of the disease."

A fellow researcher and collaborator, Dr. Mardi Gomberg adds, "I am particularly interested in drug development. What intrigues me about PVD is that it is a cardio-pulmonary disease and – being cardiologists – we offer a unique perspective."

LUNG IMAGING FOR PVD

Pulmonary hypertension, a type of PVD, is characterized by high blood pressure in the vessels of the lung which stresses the heart and leads inevitably to heart failure. Imaging plays an important role in the screening and monitoring of PH to evaluate the structural changes of the heart and lungs over time, but current routine clinical protocols still have their shortcomings. In the case of PVD, researchers have an unmet need when it comes to imaging the veins in addition to the arterioles; previous imaging technologies haven't had high enough resolution to monitor the veins of the pulmonary vasculature. Benza states, "In the past, we only had indirect tools, such as invasive hemodynamic monitoring. But now with FRI, we can create images of the lung vasculature affected by the disease."

Gomberg adds, "We initially asked, in the patients with PH, how do we evaluate the veins early enough and potentially target the PVD? Now, FRI helps us to image not only the arterioles but also the venules of the lungs."

Now, employing the uniqueness of FRI, Benza and Gomberg are designing a clinical trial that treats patients with Group 2 PH. Benza explains, "In the most prevalent form of PH, the prior lack of imaging technology to visualize the veins affected the therapeutic interventions. If a drug is designed to target lung arteries but not the veins, it could result in pulmonary edema – the Achilles heel in treating patients with Group 2 PH." Gomberg explains the role of FRI in the trial: "We are incorporating FRI – with a probable intention to use it as an endpoint to understand the precise effects in the lung vasculature. Establishing this system would help future therapeutic interventions."

FROM CLINICAL TRIALS TO CLINICAL PRACTICE

When discussing the potential of FRI in clinical practice, Benza states, "FRI is applicable to clinical practice. Dr. Gomberg and I are both developing risk prediction tools, but those are restricted to final phases of disease manifestations. FRI functions at a step ahead: you could actually see in advance what you are remodeling and predict the treatment route." He adds, "It could be periodically applied throughout the course of a patient's clinical journey to see whether a treatment alteration is needed."

Gomberg reflects on the utility of FRI, "It supplements existing tools like CT scans, which are often done as a part of routine clinical protocol, making FRI more accessible." She adds, "In PVD, although MRI is a useful tool both for heart and lungs, it is not available in every center. CT scanners are widely available, which highlights how FRI could be even more important." Some centers may have repositories of historical patient data, including CT scans. "We can go back in time and use old CT scans and apply FRI for retrospective investigations as well."

Benza reconfirms the need for FRI, "We couldn't image the lungs due to the incapability of current technologies, except for the diffusing capacity of the lungs for carbon monoxide (DLCO). But now we can image the lungs as well as the heart, and this could help identify the secondary effects of PVD and other diseases." Gomberg concurs, "Lung biopsies can be risky, and this might be the first virtual imaging biopsy using FRI." she adds, "The more researchers would understand the technique and see how it can help, the more it may become the standard of care."

APPLICABILITY OF FRI IN A POST-COVID-19 WORLD

The COVID-19 pandemic brought new challenges, not only for researchers in pulmonary medicine, but also for healthcare systems and management. Benza discusses the changes in organizing clinical trials: "COVID-19 impacted clinical trial management, particularly earlier in the pandemic. However, the pandemic is showing us, we have the potential to run clinical trials distantly. We never tried that before, but it worked. Using technologies that can remotely help assess patients without going to a crowded hospital is appreciated by most patients. Technologies can certainly alter the ways that trials are designed in the future and reduce expenses."

Gomberg explains her clinical experience from the recent past: "We could not conduct some tests (e.g., ventilation/perfusion scans) due to the chances of higher COVID-19 exposure. Comparably, CT scans are much faster, and once FRI is widely available, we can assess everything that the older testing methods could not do during the pandemic. During the pandemic, we saw many patients with PVD and varied risk status. To meet this problem, FRI could help detect individuals with or without pulmonary pneumonia – to screen the risk level." Both Gomberg and Benza are interested in research on long-hauler COVID and the associated attrition of the pulmonary vasculature, which causes long-term breathlessness and fatigue. Several preliminary studies suggest that this attrition could be measured by FRI. To this end, research on the topic is ongoing.

Other diseases could also benefit from a widespread adaptation of FRI. Benza explains, "Nearly 60% of patients with scleroderma could develop Group 1 PAH. With FRI, we could detect the effects in their blood vessels." Benza suggests further that patients with heritable PH experience changes in their lungs before symptoms develop, and that imaging changes to the blood vessels would be highly beneficial. HIV is another example – people living with HIV have a five-fold higher risk of developing PH than the general population. Using screening tools like FRI, PH could be detected in at-risk patients earlier in the course of the disease.

POTENTIAL CHALLENGES FOR FRI IMPLEMENTATION

As with any new technology, there are challenges to acceptance and use, including competing technologies. Benza discusses his experience with a Xenon-based MRI imaging technique, "It involves cardiac MRI, which is far less practical than the CT scans. Not to forget, CT scans have their own negative implications in terms of radiation (1 CT scan = ~ 50 X-rays). But FRI uses a minor amount of radiation compared to a standard CT scan."

Gomberg raises another significant challenge: reimbursement of imaging techniques from payers. "In the USA, refund of imaging techniques could be challenging and works on a case-to-case basis. Radiologists are particularly concerned about new technologies from an operational standpoint."

THE FUTURE OF FRI

"The USA FDA is looking for disease-modifying outcomes in clinical studies, and FRI could be one of the first technologies that can actually be described as a disease-modifying endpoint," explains Benza. In his view, FRI may serve as a tripartite tool: for early diagnosis and screening of at-risk individuals, to track disease progression and manage patient expectations, and to stratify patients into different treatment groups based on their disease state. Benza explains, "Using FRI, we could track the effects of treatments, and learn which would be effective to stabilize patients in an early stage without needing a transplant." Gomberg supports Benza and concludes, "We are also excited about FRI because of its capacity not only in Group 1 but also in Groups 2 and 3 PH. Imaging the small vasculature is going to make a big difference."