FRI advances the patient care journey in pulmonary hypertension

Innovative technologies are necessary to improve diagnosis and treatments in patients with pulmonary hypertension (PH). As a non-invasive tool that gives detailed information about the smallest blood vessels of the lungs, Functional Respiratory Imaging (FRI) could become a pivotal tool to evaluate novel disease-modifying therapies in clinical trials and to improve early diagnosis of this disease. Dr. Roham Zamanian, Associate Professor of Medicine at Stanford University School of Medicine and the director of the Adult Pulmonary Hypertension Service at the Vera Moulton Wall Center for Pulmonary Vascular Disease, explains how his current collaborations with the Fluidda team have convinced him that FRI could revolutionize the way that PH is diagnosed and treated.

PH is a chronic and progressive disease associated with high blood pressure in the vessels of the lungs which causes symptoms like shortness of breath and fatigue. Currently, there is no cure for PH and the standard of care consists of vasodilators, which relieve symptoms but cannot halt disease progression.

Zamanian explains why the current strategies for patient care are not satisfactory, "PH is not only a vasoconstrictive disease, which is what vasodilators treat, but an angio-proliferative disease in which a certain lineage of cells present cancer-like proliferation and create vascular occlusion and vessel dropouts, which in time cause severe damage to the lung vasculature. We need new therapies that can have a more lasting impact by addressing the underlying mechanisms of the disease and the vascular changes that occur in PH."

ROHAM ZAMANIAN

Roham Zamanian, MD, is associate professor of medicine (pulmonary and critical care medicine) at Stanford Hospital and Clinics. Dr. Roham Zamanian specializes in the treatment of pulmonary hypertension, right heart failure, and pulmonary embolism. He has more than 19 years of sub-specialty experience in pulmonary vascular diseases. Zamanian is considered one of the leading national experts in clinical trials and drug development for pulmonary hypertension.

THE SEARCH FOR DISEASE MODIFYING THERAPIES IN PULMONARY HYPERTENSION

Researchers have studied the damage to the vasculature that occurs in PH by looking at the explanted lungs of patients who have received a transplant to save their lives. "The pathology of these end stage organs was very advanced with vascular occlusion and lesions," explains Zamanian. "This shows that while vasodilators cause physiologic improvement there is no reverse remodeling and the disease keeps progressing even when the patient gets treatment. We currently have approximately 14 advanced therapies that can improve vascular constriction, but these cannot prevent the damage to the lungs, and most only offer temporary relief."

Over the past five years, there has been an increasing interest in making new therapies that can have long lasting effects available to PH patients. "Unlike vasodilators, these therapies would be disease modifying. This means that they could effectively slow disease progression and even revert lung damage over time," explains Zamanian. "Some of the genetic and molecular mechanisms responsible for the damage in the vasculature of the lungs of PH patients have been identified. So, we have a starting point to develop therapies that can address the angio-proliferative aspect and prevent lung damage, but we need a technology that will allow us to evaluate whether a drug is indeed disease modifying, and I think this is where FRI may play a relevant role."

FRI AS A TOOL TO ASSESS DISEASE MODIFYING THERAPIES FOR PH

The damage to the pulmonary vasculature of PH patients starts in the smaller blood vessels of the lungs. To evaluate the potential of an experimental therapy in a clinical trial, researchers require a technology that can accurately assess subtle changes in these vessels over time. Currently, it is possible to measure how a therapy alters general processes like blood flow patterns or ventricular function, but these approaches cannot reach the level of detail required for new PH therapies. It is also possible to examine changes in the small vasculature through lung biopsies, but this approach is invasive and poorly tolerated by patients who may already be quite sick. FRI allows clinicians to study changes in blood vessels with a diameter of one millimeter or more and relies on CT scans, which are non-invasive procedures, making it an ideal tool to assess new PH therapies in clinical trials.

"If FRI has the capacity to accurately define small vascular changes – and I think it has a high potential to do so – it could become the first surrogate marker of distal vascular changes in pulmonary arterial hypertension. This would be extremely important for the field," explains Zamanian. "FRI by itself will not be enough, but in combination with the right drug acting on the right mechanism and the right clinical trial design, it could be the technology that helps us convince ourselves and the regulatory agencies that an experimental therapy is indeed disease modifying."

IMPROVING PH DIAGNOSIS AND MANAGEMENT

PH is a rapidly progressing disease and even small increases in pulmonary artery pressure have a substantial impact on long term morbidity and mortality, so ensuring early diagnosis is as important as developing new disease modifying therapies. Currently, clinicians rely on invasive pressure measurements in the pulmonary artery to diagnose PH. The threshold for high pulmonary artery pressure was recently decreased from 25 mm Hg to 20 mm Hg to improve the chances of early diagnosis. However, it would be ideal to have a non-invasive approach, such as FRI, to detect early disease.

"We need to gather more data and answer some questions before we can implement FRI for early diagnosis of PH," says Zamanian. "For example, what exactly is normal and abnormal, what are meaningful clinically incremental changes over a period of time, and what is a normal BV5% [1]. In the future, these parameters could become adequate markers for early disease."

FRI could also play a role in evaluating disease progression and overall patient state once PH has been diagnosed. Follow up currently relies on the results of several exams such as CT scans, MRIs, and exercise tests. According to Zamanian, combining these approaches and taking advantages of new technologies could give a better picture of the state of a patient, informing the clinical course of action. "I would like to see if FRI could be combined with what we consider provocative maneuvers for the diagnosis of earlier disease. In our lab, we perform re-catheterization with exercise plus incremental resistances. Currently, it is plausible to obtain adequate CT images of a person at different exercise stages and identify

> **FRI could become the first surrogate marker of distal vascular changes in pulmonary arterial hypertension.**

the overall vascular conditions for each exercise state. If we can use FRI data to determine what early PH looks like under these conditions, that would be a tool for patient follow up. There is already research showing that you can do these kind of exercise challenges with cardiac MRI. I think it is possible to put together a similar protocol using CT and FRI."

GATHERING THE MISSING DATA

The Fluidda team has a strong interest in establishing academic collaborations to better understand pulmonary vascular disease and help generate the data that would allow FRI to become a relevant tool in clinical trials and in clinical practice. "The culture of the Fluidda team is one of discovery and advancement," says Zamanian. "As an academic, it was easy to connect with them and have a conversation about what can be done, what are the hurdles, and what is the missing information that needs to be generated by research. This is not very common in collaborations between academia and industry."

In collaboration with the Fluidda team, Zamanian and other researchers are studying a large cohort of patients with PH and well-established phenotypes. CT scans are assessed using FRI to understand how changes in BV5 relate to clinical changes and responses to medication. These data could help predict clinical outcomes and guide patient management in the future. In a second collaboration, researchers use a combination of FRI and molecular imaging data to characterize hidden phenotypes of PH and refine molecular clusters that were previously identified as relevant for long term outcomes.

Zamanian is also collaborating with Fluidda in a clinical trial that is assessing the impact of a novel therapeutic for COVID-19 in non-hospitalized patients with mild symptoms. They are using FRI to evaluate the impact of the disease on the patients' vasculature, and to determine whether treatment with the investigational drug alters this process.

THE FUTURE OF FRI

FRI is reaching the tipping point where it could stop being just a research tool and enter the clinical space. "Once we establish the normal and abnormal thresholds and clinically meaningful incremental differences that FRI can show us, the clinical applicability of this technology will become increasingly apparent," says Zamanian. "I can think of scenarios where clinicians could use FRI to evaluate if a therapy is making substantial progress in curing the patients, not only in the context of PH, but also pulmonary embolism and other vascular diseases of the lung."

"As soon as enough data come through, I do think that the medical community will embrace FRI and incorporate it into their routine procedures," concludes Zamanian. "A typical PH workup already includes a CT scan so it's not unreasonable to think that along with that CT scan one would request an FRI analysis of the vasculature."

REFERENCES

1. BV5% is the percentage of blood volume in vessels with a cross-sectional area between 1.25 and 5 mm^2 relative to the total pulmonary blood volume