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Functional Respiratory Imaging can predict the course of COVID-19

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Functional Respiratory Imaging (FRI) quantifies and visualizes the distribution of blood vessels in the lungs in great detail. This simple model, which combines the results of the imaging with the patient's age, can accurately predict the risk of dying and the necessity for ventilation. Experts in the field of pulmonary diseases and radiology shared their thoughts on this model and its implications for healthcare and research.

Clinical research evaluating inhalation medication has traditional-Research conducted on autopsies has revealed that inflammation of the endothelium and microangiopathy occur commonly in the blood vessels of the lungs of people who died as a result of a SARS-CoV-2 infection. This observation led to the hypothesis that visible changes in the perfusion of the lungs on a CT scan could be a biomarker for a poor prognosis with COVID-19. Important changes in perfusion were visible in the blood vessels with a cross-sectional surface area of 1.25 to 5 mm^2.

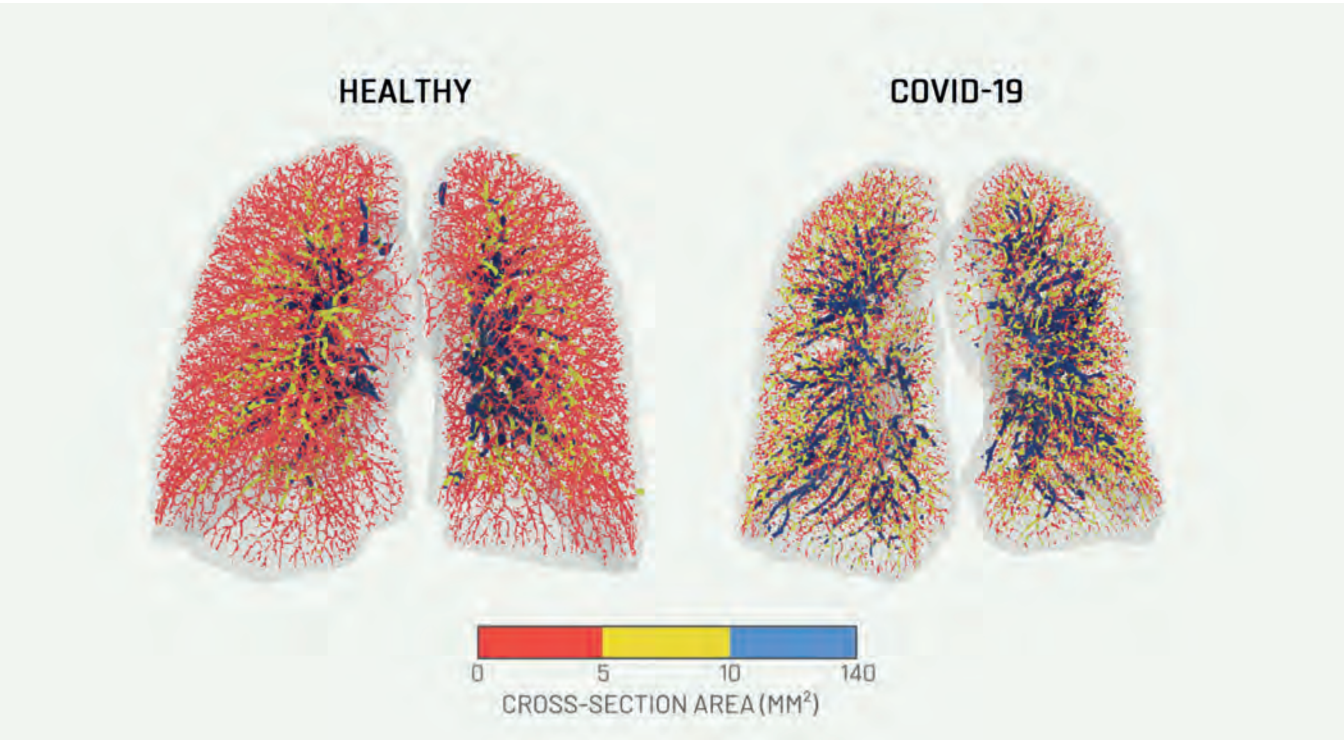
VASCULAR SYSTEM

A group of American researchers tested this hypothesis during a retrospective study using high-resolution CT images.[1] During a webinar about the results of their research, the first author Mike Morris, radiologist at the Banner University Medical Center in Phoenix, USA, presented a 3D-reconstruction of the pulmonary blood vessels of two COVID-19 patients (Figure 1).[2] Both patients had been admitted to the A&E Department of a hospital. For one patient, the anatomical distribution of blood vessels of varying size was relatively normal. For the other patient, the small, peripheral vessels with a cross-sectional surface area between 1.25 and 5 mm^2 had largely disappeared. Morris stated, "The question is now, can we use the data from these images to predict the outcome of a COVID-19 infection? The short answer is: yes, we can."

The digital technique that the researchers used for the analysis of HR-CT scans of the lungs is Functional Respiratory Imaging (FRI), an imaging technique that visualizes and quantifies in 3D all relevant structures in the lungs such as the airways, blood vessels, and lung volume. The technology essentially uses standard CT scanners that were taken over time to quantify these lung structures and assess the regional disease-related changes.

The researchers analyzed CT scans of patients from 10 hospitals in Arizona and Colorado: 313 with COVID-19 and 195 without this disease who sought emergency medical care.[1] Using FRI, the researchers quantified the blood volume of the lung and looked at how the blood was distributed across vessels with different cross-sectional areas. The volume of blood in blood vessels with a cross-sectional surface area of 1.25 to 5 mm^2 (labelled as BV5) was quantified and analyzed. The lower the BV5 value, the lower the blood volume in vessels of that size range.

Figure 1. Volume-rendered images of chest CT scans from two different patients with COVID-19, with color-coded segmentation of the pulmonary vascular cross-sectional area. (a) Patient with BV5% of 21%; (b) Patient with BV5% of 55%. Red color denotes blood volume in vessels between 1.25-5 mm^2, yellow color is vessels between 5-10 mm^2, and blue color is vessels >10 mm^2.



	COVID-19 Positive		COVID-19 Negative	
Mortality	OR (95% CI)	p-value	OR (95% CI)	p-value
BV5% continuous	0.87 (0.79, 0.96)	<0.01	1.02 (0.94, 1.10)	0.61
BV5% categorical <25%	5.58 (1.54, 2.01)	<0.01	0.50 (0.08, 3.24)	0.46
Intubation	OR (95% CI)	p-value	OR (95% CI)	p-value
BV5% continuous	0.89 (0.84, 0.95)	<0.01	1.00 (0.91, 1.10)	0.96
BV5% categorical < 25%	3.20 (1.55, 6.63)	<0.01	3.31 (0.59, 18.5)	0.17
Mortality or intubation	OR (95% CI)	p-value	OR (95% CI)	p-value
BV5% continuous	0.90 (0.84, 0.96)	<0.01	0.99 (0.93, 1.05)	0.69
BV5% categorical <25%	2.54 (1.15, 5.60)	<0.01	2.05 (0.62, 6.73)	0.24
Length of stay	exp (Beta (95% CI)	p-value	exp (Beta (95% CI)	p-value
BV5% continuous	0.98 (0.96, 1.00)	0.075	0.97 (0.96, 0.98)	<0.01
Intubation days	exp (Beta (95% CI)	p-value	exp (Beta (95% CI)	p-value
BV5% continuous	0.99 (0.93, 1.06)	0.83	1.02 (0.95, 1.09)	0.51

Table 1. Multivariate regression analysis of outcomes relative to BV5% as a continuous and categorical variable in patients with and without COVID-19 infection. Percentage of blood volume in vessels between 1.25 and 5 mm^2 relative to the total pulmonary blood volume (BV5%).

This study revealed that BV5 was significantly reduced in COVID-19 subjects compared to healthy individuals, and it was found to be related to the severity of COVID-19 infection. If less than 25% of the blood could be found in those smaller and more peripheral blood vessels (BV5 < 25%), then the odds ratio for dying was 5.58. The odds ratio for requiring ventilation was 3.20, and for the combination of dying and ventilation was 2.54 (Table 1).

MODEL

Based on these data, the researchers developed a predictive model that took into account age and the BV5 value. "The BV5 only has predictive value if the CT scan is done within 24 hours after presentation at the A&E Department," added Morris. "After that time, the predictive value is no longer statistically significant. We think this is due to multiple variables present during the time of admission that affect the outcome." The model apparently could not predict the outcome for the 195 patients who sought emergency care for reasons other than a COVID-19 infection.

Morris illustrated how useful the BV5 is in clinical practice. "We prepared a very simple graph with the patient's age on one axis and the BV5 value on the other. You could read the risk of a poor outcome from it. For example, someone aged 70 years old with a BV5 of 25% had a 70% risk of dying or ventilation. The important question is now whether we can favorably influence the disease outcome with this clinical model. We know that vascular inflammation and thrombosis can produce a severe course of a COVID-19 infection. A low BV5 is possibly a reason to start anti-coagulation therapy sooner."

HYPOXIA

Marilyn Glassberg was involved in the study as a pulmonologist at the Banner University Medical Center. She reflected on the origin of the study. "In March 2020 we were surprised by the people with silent hypoxia. We did not understand what we were seeing, nor how we could help the patients. The findings made during the first autopsy studies revealed clots in the blood vessels of the lungs, among other organs, which suggested that COVID-19 was associated with problems in the pulmonary vasculature. But we lacked a good diagnostic and prognostic technique. The clinical tools available then could not help us."

Glassberg knew about FRI from her research into idiopathic pulmonary fibrosis. "On Twitter I saw an image of the pulmonary vasculature, created on the basis of HR-CT scans analyzed with FRI. I subsequently contacted Mike Morris to see if FRI could help us to diagnose COVID-19." The results of the collaboration between Glassberg, Morris and their colleagues led to the clinical decision model based on BV5 and age.

RELEVANCE

Ben Lavon, Chief Scientific Officer at FLUIDDA, asked Morris about how useful FRI would be in clinical practice and in scientific research, now and in the future. Lavon commented first, "Radiologists translate an image into an objective judgment. This demands years of experience and training to be able to interpret CT images and assign meaning to phenomena that you see on a CT image, like ground glass opacity."

"In general, radiology has reached a plateau in terms of the information that we can obtain from the visual evaluation of scans," answered Morris. "We know, though, that there is much more diagnostic and potentially prognostic information contained in the scans. The question is, how can we harvest that information in a way that fits well into our current clinical workflow. The information must also be clinically relevant. There are too many models, prepared e.g. by machine learning, that are statistically very significant but not clinically relevant."

RAPID RESULTS

About the BV5 study, he said, "The power of our study is that we have developed a simple, clinically relevant model based on BV5 and age that helps with making clinical decisions. I think that FRI represents an advance that has the potential to provide clinically relevant results for other disease processes as well." Glassberg added, "We were looking for a biomarker to help diagnose COVID-19 and found that this one was valuable for the diagnosis and prognosis. I think therefore that FRI will also be valuable for other diseases that involve changes in the vascular system."

Glassberg, talking about the time taken for an FRI analysis, "A fast diagnostic and prognostic tool is required with COVID-19, because the patients' condition can deteriorate rapidly. The algorithm supporting FRI is fast, I do not have to wait a week as I do for the analysis of a biopsy because the pathologist has to carry out a range of stains before giving me an answer."

AGREEMENT

Evaluating HR-CT scans of the lung is difficult, and not every radiologist is experienced in this, argued Lavon. "Most radiologists working in peripheral hospitals have not followed the same specialized training of a cardiothoracic radiologist. Can tools like FRI simplify the interpretation of lung scans and thus lead to better management of lung problems?"

> **Imaging can contribute to prompt clinical decision-making, so we can prevent the necessity for oxygen therapy.**

"Peripherally working radiologists are not the problem," replied Morris. "Studies into the agreement in the interpretation of CT scans by cardiothoracic radiologists with an expert status show significant differences. I myself am participating in a study with five experienced radiologists evaluating lung CT scans of COVID-19 patients. The agreement between our analyses is not great. Thus, considering the qualitative analysis of CT images, this is not always good enough. A quantitative analysis, like FRI, can level the playing field between radiologists and lead to a comparable output, regardless of the place where the radiologist works."

SCIENTIFIC RESEARCH

The uniform and quantitative data that FRI provides can also simplify clinical scientific research according to the panel members. Jan de Backer, CEO of FLUIDDA, stated, "With FRI we can learn to understand the disease itself and the success of an intervention with a single technique." Glassberg added, "I expect that the inclusion period for clinical trials will be shorter because FRI can clarify quickly whether a patient meets the inclusion criteria. Currently, several radiologists evaluate one scan. If their conclusions differ, the patient is not eligible for the trial, even if appears later that they did meet the criteria and thus could have participated."

Research will have to provide an answer soon about the long-term effects of COVID-19. A substantial proportion of the COVID-19 patients are expected to retain long-term symptoms by developing a form of lung fibrosis. This occurs not only in people who survive severe episodes of COVID-19 disease. Some people retain chronic lung damage after a mild variant of COVID-19. De Backer said, "I wonder whether we can use FRI to ascertain early who will develop fibrosis and who will require oxygen therapy." Morris added, "Most of our attention is focused on people with a severe form of COVID-19 infection because we want to keep them alive. This group forms just the tip of the iceberg. The large group that develops complications of the disease in the long term will have an enormous impact on the healthcare sector. I hope that imaging can contribute to prompt clinical decision-making, so we can prevent the necessity for oxygen therapy."

CONCLUSION

Functional respiratory imaging has the potential to standardize and quantify the analysis of CT images of the lung at a level that not every radiologist can achieve. For COVID-19, FRI is proving to be useful as part of a simple clinical decision model. Research into and the treatment of other pulmonary diseases may have high expectations of this new technique.