Functional respiratory imaging (FRI): An alternative to pulmonary function tests (PFTs)

The author suggests that FRI could be a useful tool in assessing the parameter defined as "lung health."

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In the field of respiratory medicine, the majority of lung diseases are chronic and, for the time being, incurable. Patients with asthma and chronic obstructive pulmonary disease (COPD) often need to rely on medication to keep their diseases under control and maintain an acceptable quality of life. The situation may be more dire for patients diagnosed with interstitial lung disease, such as idiopathic pulmonary fibrosis (IPF), where therapeutic options and life expectancy for patients can be very limited.

Many of the discussions at pulmonary conferences revolve around the regional expression of these diseases, specifically the role of the small airway disease manifestations and their links with patient-reported outcome parameters and exacerbations.

Limitations of conventional pulmonary function tests

At present, virtually all disease phenotyping and development of disease management guidelines have been based on conventional lung function tests, such as the forced expiratory volume in one second (FEV_1) or forced vital capacity (FVC). However, such tests do not yield regional information, for instance, indicating where in the lung a disease is most prevalent or revealing from where measured exhaled air is coming. Consequently, they fail to express the heterogeneity of disease in individual patients. For example, two patients with the same FEV_1 can have very different expressions of the same disease (e.g., emphysema vs. bronchitis) or can even have very different lung diseases (e.g., asthma vs. COPD) as shown in Figure 1.

It has been observed that the correlation between conventional lung function measures and the patient's perception of wellbeing or even mortality is weak at best.[1,2] In a recent letter Fluidda received from the United States Food and Drug Administration (US FDA)[2] in support of our biomarker development for IPF, the agency stated that "Forced Vital Capacity (FVC) was used as the primary endpoint for two recent drug approvals; however FVC has not been validated as a surrogate for likelihood of death or other clinically meaningful efficacy variables in IPF. Sensitive biomarkers measuring disease stage and biological response to treatment would facilitate clinical development decisions and accelerate drug development."

"Lung health" and FRI

In our view, development of the sensitive biomarkers that the FDA alluded to requires a paradigm shift from merely assessing "lung function" towards assessing "lung health," which we define as the current state of a patient's regional lung structure and function relative to a matched healthy subject.

Over the last ten years, Fluidda has developed a novel technology called "functional respiratory imaging (FRI)." This method is a combination of high-resolution, low-dose computerized tomography (CT) scans and computational fluid dynamics (CFD), which yields regional information related to lung structure and function. FRI can provide insights about ways lung diseases affect crucial parts of the respiratory system, such as lung and lobe volumes, airway volumes and resistance, and blood vessel density. FRI has been applied in many lung diseases including asthma, COPD, IPF, cystic fibrosis, bronchiolitis obliterans syndrome and pulmonary hypertension. We believe that FRI, once fully validated, could be an appropriate tool to assess overall lung health.

FRI, lung health and patients with asthma and COPD

It has long been believed that a key difference between patients with asthma and those with COPD was a history of smoking. It was assumed that noxious particles from cigarette smoke were the main contributor to decline in lung function for patients with COPD and that may still

Figure 1

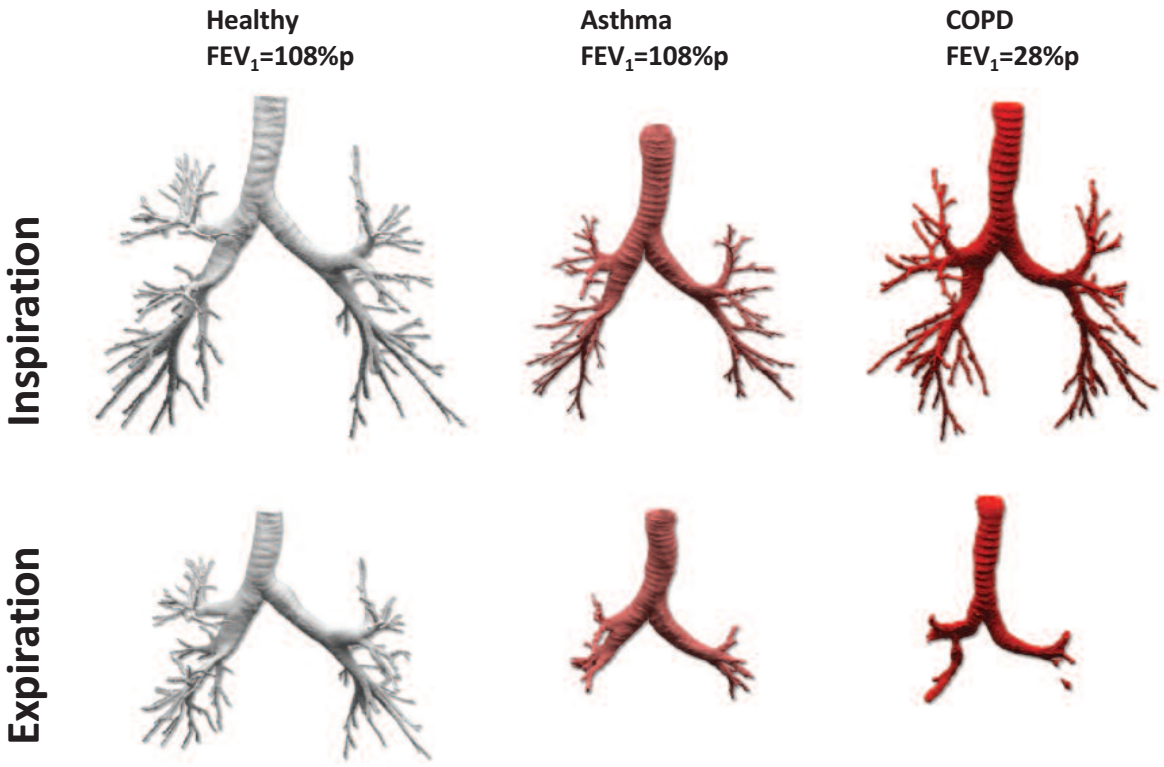

Figure 1. Airway volumes at inspiration (total lung capacity, TLC) and expiration (functional residual capacity, FRC) for a healthy subject (FEV_1 = 108% predicted), a "mild asthmatic patient" (FEV_1 = 108% predicted) and a COPD patient (FEV_1 = 28% predicted). Although the FEV_1 is identical for the healthy and asthmatic patients, their airway dynamics, and consequently their lung health, are very different. The change in airway volume in the healthy subject (grey geometries on the left) is limited between inspiration and expiration. The asthmatic patient (pink geometries in the middle), however, already shows a large degree of airway closure on expiration (airways disappear in the image), a pattern that can also be observed in severe COPD patients (red geometries on the right). In this example, FEV_1 would classify a patient as mildly asthmatic yet the patient's central and distal airway dynamics seem to be more akin to those of a COPD patient.

be true. However, in an age when smoking has been banned in many public places, other causes of COPD, such as pollution, have become more apparent.

Another difference between asthma and COPD patients is the reversibility of FEV_1. Generally, patients with asthma may be more likely to exhibit reversibility of FEV_1 (i.e., improvement) than those with COPD. However, due to the inherent characteristics of the diseases or suboptimal treatment, one may not be able to use inhalation medication or disease definitions to determine whether a patient's FEV_1 is reversible.

A term that has become more popular in recent years is the "asthma COPD overlap syndrome" or ACOS. While the definition of this phenomenon is unclear, it at least hints at the need for better descriptions of the obstructive diseases. The concept of lung health and the subsequent use of FRI may facilitate this discussion.

Earlier we mentioned the limitations of FEV_1 in providing information regarding regional or subtle changes in lung structure and function. Nonetheless, a novel technology such as FRI will initially still have to be compared to the gold standard endpoint, which is in this case FEV_1. Fluidda's studies typically look at strong FEV_1 responders with a signal above the measurement error and correlate the observed regional FRI changes (e.g., lobar hyperinflation, lobar airway volumes and resistances) with the FEV_1 changes. This approach reveals the mechanisms behind the FEV_1 response, which can subsequently be used to assess the potential presence of these mechanisms in a patient group with more modest FEV_1, thereby facilitating more efficient phenotyping.

These principals were applied in a recent study[3,4] that demonstrated a subset of COPD patients showed improvements in FEV_1 by more than 150 ml when treated with roflumilast, a systemic phosphodiesterase-4 (PDE4) inhibitor, in addition to a triple combination inhalation treatment (ICS/LABA/LAMA). Based on the observed changes in FRI parameters, it appeared that the systemic drug reached areas in the lung that are chronically undertreated by the triple inhalation therapy. The drug subsequently reduced the regional (lobar) hyperinflation and caused a redistribution of airflow, altering the deposition patterns of the concomitant inhalation medication, leading to the significant improvement in FEV_1 and exercise tolerance observed. In other words, the lung health of this subset of patients was improved by providing a combination of systemic and inhalation therapies.

Figure 2

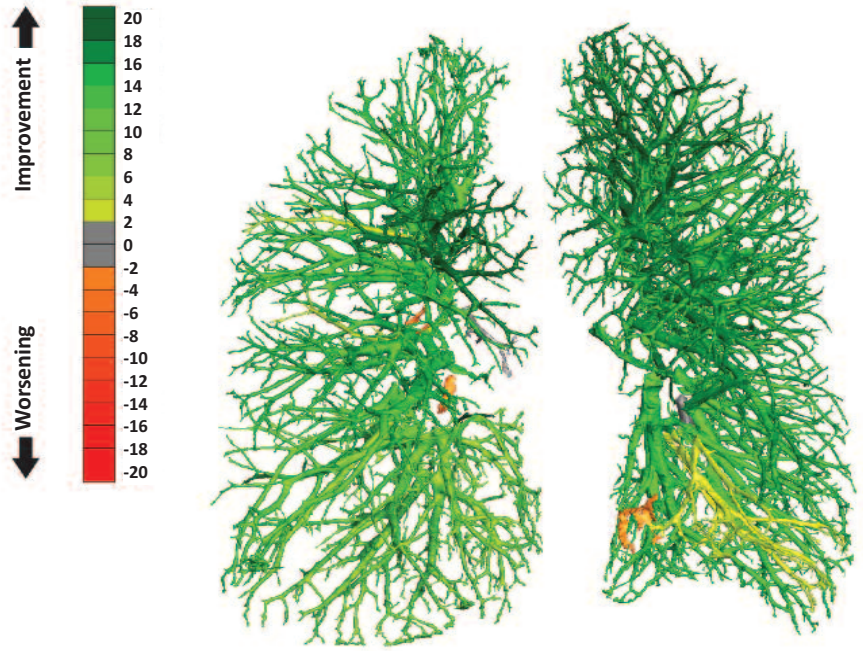

Figure 2. Changes in blood vessel volume determined using functional respiratory imaging (FRI) in a COPD patient with pulmonary hypertension after the administration of pulsed inhaled nitric oxide (iNO). Green areas indicate an increase in blood vessel volume, i.e., vasodilation, which induces a reduction in pulmonary pressures. This demonstrates the ability of FRI to provide relevant information in a significantly less invasive way compared to catheterization, thereby greatly reducing burden on the patient.

Over the years, more attention has been given to patients' quality of life, measured via patient-reported outcome parameters (PRO). Yet these PRO are often confounded by comorbidities and psychological elements. From a respiratory point of view, different parameters probably play an important role. Not only lung volume parameters such as hyperinflation, or airway characteristics such as airway resistance, determine the patient's perception of their condition; the regional vasculature and the associated ventilation/perfusion ratio likely also impact patients' quality of life. For example, patients suffering from pulmonary hypertension (elevated blood pressure in the pulmonary vessels) may benefit from the administration of vasodilators that lower blood pressure and enhance oxygen transport.

In another recent study, Fluidda explored the potential of FRI to assess the effect of pulsed inhaled nitric oxide (iNO) on blood vessel caliber.[5] It was observed that iNO increased FRI-derived blood vessel volume to significantly more than the natural variability level of the blood vessel volume (Figure 2). This not only demonstrated the mode of action of the drug itself but also showed that FRI can be a sensitive tool for detection of relevant changes. Regional vasodilation correlated well with regional ventilation, thereby improving the ventilation/perfusion (V/Q) ratio while limiting the risk for shunting. Following treatment, patients also reported an improvement in perceived wellbeing.

FRI, lung health and patients with IPF

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease characterized by progressive loss of the ability of the lungs to absorb oxygen due to scarring (fibrosis). As a result, patients with IPF can experience shortness of breath and cough and have difficulty participating in everyday physical activities. The cause is unknown and there is no known cure. The median survival time from diagnosis is two to five years and the five-year survival rate is approximately 20 to 40 percent. IPF typically occurs in people over the age of 45 and tends to affect slightly more men than women.

Forced vital capacity (FVC) was used as the primary endpoint for efficacy evaluation of the two drugs approved in the US for IPF.[6] FVC is a functional measurement of the lungs as a whole and does not capture local information about deterioration and potential compensation by healthier areas of the lung. In addition, FVC depends on a forced maneuver to be performed by the patient, which can further increase the potential for variability of the measurement. During their development processes, the FDA voiced concerns about the applicability of this measurement given, among other aspects, that the clinically meaningful effect size is unclear.[2]

In a range of studies,[7-11] it was observed that IPF is expressed in terms of FRI parameters by smaller lungs and lobe volumes but larger airway radii (Figure 3). It seems that while fibrosis reduces the lobe volume, the airway volumes are

Figure 3

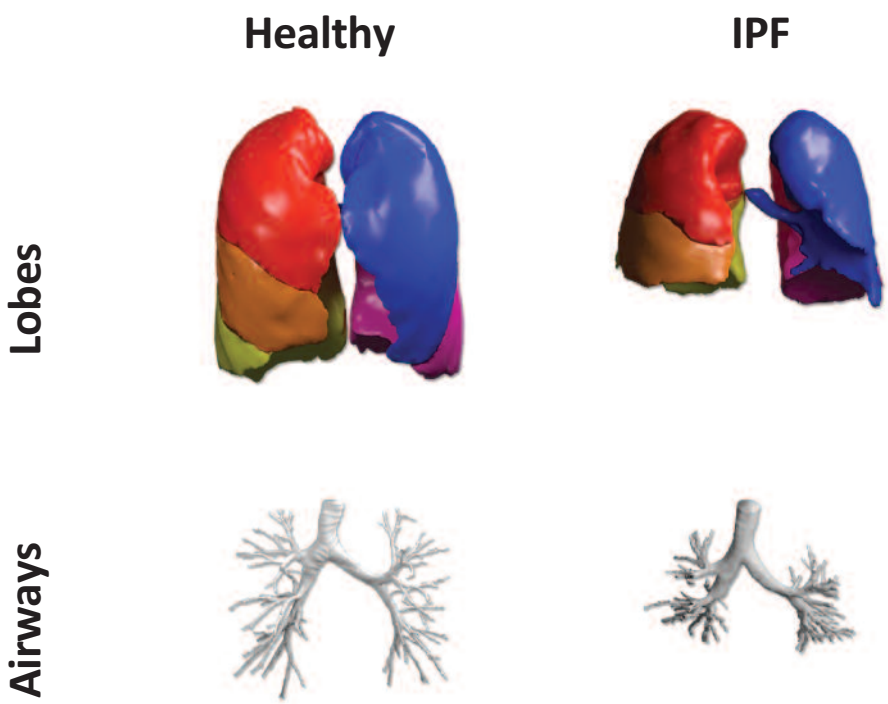

Figure 3. Lung lobes and airways of an IPF patient (right) and a matched healthy volunteer (left). In comparison to the healthy subject, the IPF patient has smaller lobe volumes (shown in color) but larger airway radii (shown in black and white).

relatively larger compared to a matched healthy volunteer. The latter can be explained by the fact that the increased stiffening of the small airways and alveoli associated with disease progression in IPF patients results in a redistribution of the intrapulmonary pressure at total lung capacity (TLC) during breath-hold, leading to a relative expansion of the central and distal airways despite a reduction in lung and lobe volume. Early manifestation of IPF is mainly observed in the lower lobes, with the upper lobes increasingly affected as the disease progresses.

These findings emphasize the importance of regional information and the need for better diagnostics to reflect disease heterogeneity. The capability of FRI to accurately capture and quantify these regional lung characteristics may offer key potential in development of biomarkers and diagnostics.

Changes in lung structure will always precede changes in lung function. Sensitive tools that measure changes in lung structure therefore, conceptually, can offer opportunities to become adequate biomarkers for disease progression or detect the effect of interventions, compared to measurements of lung function alone.

Views from the FDA

In a recent guidance for industry on the development of drugs for COPD,[12] the US FDA stated "The primary efficacy endpoint can be a sensitive radiological assessment of lung structure with supportive evidence that the regenerated lung tissue is functional and that the treatment provides clinically meaningful benefit to patients." In addition, in a letter of support issued to Fluidda,[1] the FDA stated "We encourage exploration of the use of the listed FRI biomarkers measured via HDCT scans and quantitative imaging technology in clinical trials to evaluate disease stage and progression, biological response to therapeutic intervention, provide quantifiable predictions about drug performance, and contribute to clinical development decisions."

Lung health assessments in clinical practice

Functional respiratory imaging is increasingly demonstrating its value in clinical trials as a sensitive biomarker to assess changes in lung health.[13] Yet we believe that for FRI to reach its full potential, the technology must become available in routine clinical practice. If respiratory physicians can assess the lung health of their patients with FRI and use the information to select an appropriate treatment, which was itself studied using the same FRI endpoints in clinical trials, this could represent a significant step forward in the evolution towards personalized medicine.

Recently, Fluidda launched the Broncholab platform,[14] which enables physicians to upload CT scans to our servers and receive FRI parameters calculated for a patient. Broncholab has initially focused on difficult-to-

treat patients who have severe and costly indications such as lung transplantation, idiopathic pulmonary fibrosis and severe COPD, but eventually the technology should become available for all relevant lung diseases.

Challenges in assessing lung health

One of the advantages of the conventional lung function tests, yet at the same time is their greatest limitation, is reduction of the heterogeneity of the lung to a single number. The patient's physiology determines which areas in the lung (for example, the peripheral airways, central airways or healthy areas) drive the endpoint measured using lung function tests such as FEV_1. Subsequently, that single number can be easily used in univariate regression or in t-tests.

In contrast, image-based measures to describe and quantify lung regions yield a combination of regional parameters indicative of changes in lung disease[14] or may even be potentially predictive for future adverse events.[15-19] The challenge will be to convert the multitude of regional information offered by FRI to a composite endpoint that can be easily interpreted relative to clinically meaningful thresholds. Then a robust framework based on multi-regression analysis needs to be developed.

If this understanding of lung disease heterogeneity can be achieved, we are convinced it will materially improve the lives of many patients.

References

1. Jones P, Health status measurement in chronic obstructive pulmonary disease. Thorax. 2001;56:880-887.

2. Food and Drug Administration (FDA). Biomarker Letter of Support to Fluidda (author). June 6, 2016. (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM506218.pdf).

3. Vos W, Hajian B, De Backer J, Van Holsbeke C, Vinchurkar S, Claes R, et al. Functional respiratory imaging to assess the interaction between systemic roflumilast and inhaled ICS/LABA/LAMA. International Journal of Chronic Obstructive Pulmonary Disease. 2016;Feb;263-271.

4. De Backer W, Vos W, Van Holsbeke C, Vinchurkar S, Claes R, Hufkens A, et al. The effect of roflumilast in addition to LABA/LAMA/ICS treatment in COPD patients. European Respiratory Journal ; 2014Aug;44(2):527-529.

5. Hajian B, de Backer J, Vos W, van Holsbeke C, Ferreira F, Quinn D, et al. Pulmonary vascular effects of pulsed inhaled nitric oxide in COPD patients with pulmonary hypertension. International Journal of Chronic Obstructive Pulmonary Disease. 2016;Jul;11:1533-1141.

6. Rogliani P, Calzetta L, Cavalli F, Matera MG, Cazzola M., Pirfenidone, nintedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis. Pulmonary Pharmacology and Therapeutics. 2016;Jul 29; Accepted for publication.

7. Vos W, Van Holsbeke C, Ferreira F, De Backer J, Goldin JG, Porter S, et al. Functional respiratory imaging (FRI) in IPF: Regional information matters. American Journal of Respiratory and Critical Care Medicine. 2016;193:A4988.

8. Vos W, Van Holsbeke C, Ferreira F, Nuyttens L, O'Riordan TG, De Backer J, et al. Comparison of IPF disease pathology to healthy subjects using functional respiratory imaging. American Journal of Respiratory and Critical Care Medicine. 2015;191:A4377.

9. Ferreira F, Verplancke V, Vos W, Van Holsbeke C, De Backer J, De Backer W, et al. Progressive TLC loss after unilateral lung transplantation in IPF: Functional respiratory imaging differentiates between transplanted and native lung. European Respiratory Journal. 2015;46 (Suppl 59):PA3750.

10. De Backer J, Vos W, Van Holsbeke C, Ferreira F, Nuyttens L, Trehu B, et al. Assessment of IPF disease pathology using functional respiratory imaging. American Journal of Respiratory and Critical Care Medicine. 2015;191:A1568.

11. De Backer J, Vos W, Smaldone G, Skaria S, Condos R. Disease progression in IPF assessed using pulmonary function tests and functional respiratory imaging (FRI)—A pilot study. American Journal of Respiratory and Critical Care Medicine. 2014;189:A2383.

12. Food and Drug Administration (FDA). Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment Guidance for Industry Draft Guidance May, 2016. (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071575.pdf).

13. Hajian B, De Backer J, Vos W, Van Holsbeke C, Clukers J, De Backer W. Functional respiratory imaging (FRI) for optimizing therapy development and patient care. Expert Review of Respiratory Medicine. 2016;Feb 1;10(2):193-206.

14. Broncholab, an online platform tool for Functional Respiratory Imaging (FRI) in the clinical practice: www.broncholab.com.

15. Vos W, Van Holsbeke C, Van Geffen W, Kerstjens H, Pistolesi M, Usmani O, et al. Lower lobe air trapping is linked to exacerbation recovery rate. American Journal of Respiratory and Critical Care Medicine. 2016;193:A5214.

16. Vos W, Van Holsbeke C, Van Geffen W, Kerstjens H, Pistolesi M, Usmani O, et al. Changes in FEV_1 after recovery from COPD exacerbation are driven by heterogeneous regional changes in airway caliber and hyperinflation. European Respiratory Journal. 2015;46 (Suppl 59):PA2271.

17. Vos W, Van Holsbeke C, Van Geffen W, Kerstjens H, Pistolesi M, Usmani O, et al. Changes in functional respiratory imaging (FRI) endpoints correlate with

changes in patient reported outcomes (PRO) after recovering from acute COPD exacerbation. European Respiratory Journal. 2015;46(Suppl 59):OA2948.

18. Van Holsbeke C, Vos W, Van Geffen W, Kerstjens H, Pistolesi M, Usmani O, et al. Improvement in FEV_1 after acute COPD exacerbations are driven more by changes in hyperinflation than changes in proximal airway volume. European Respiratory Journal. 2015;46(Suppl 59):PA4612.

19. Van Geffen W, Vos W, Van Holsbeke C, De Backer J, Cahn A, Usmani O, et al. COPD exacerbation recovery quantified by functional respiratory imaging. American Journal of Respiratory and Critical Care Medicine. 2015;191:A2270.

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