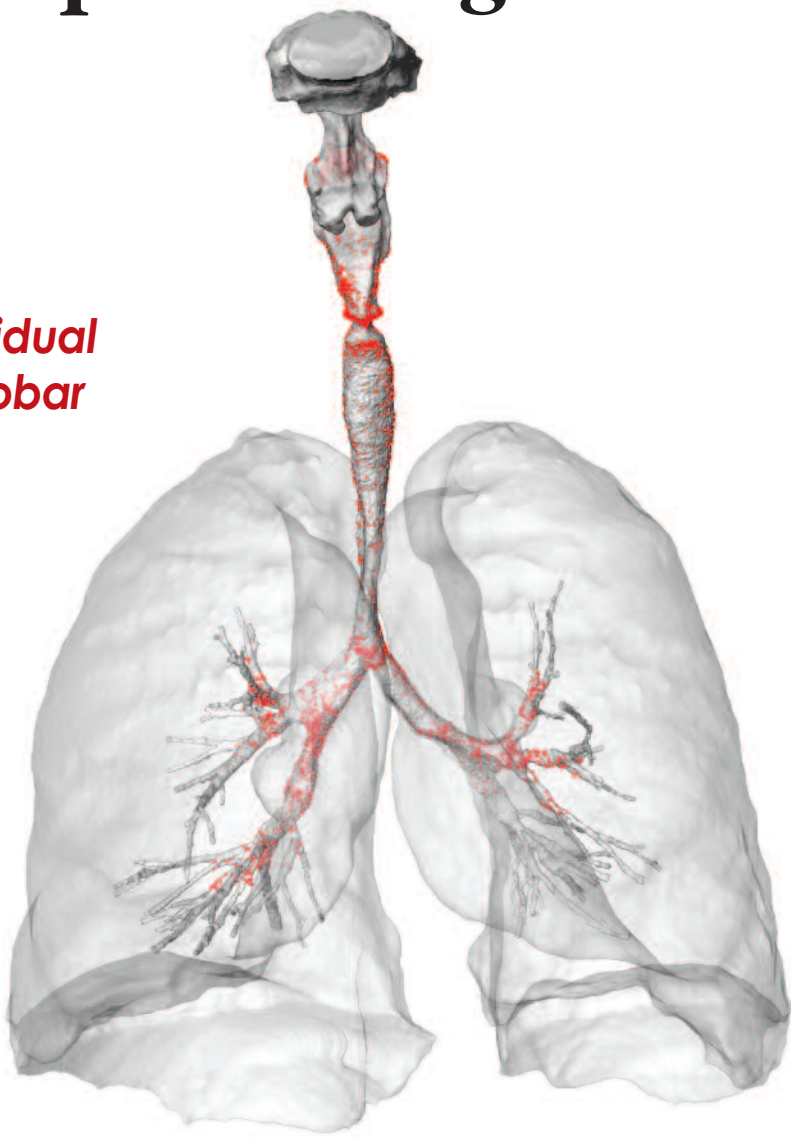
Functional respiratory imaging (FRI): Enhancing biomarker sensitivity to expedite drug development



FRI allows a quantitative assessment of the imaged airway volume of an individual airway at the aggregate lobar and lung level.

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Introduction

It has become increasingly difficult and costly to bring efficacious pharmaceutical products to market. This is especially true in the field of respiratory medicine. The inherent "black box" approach of the current gold standard diagnostic tools, in particular the forced expiratory volume in one second (FEV_1), lacks the sensitivity to assess local characteristics of the respiratory system. Virtually all conventional pulmonary function tests rely on the patient's effort, introducing another source of variability. This raises the need to perform large studies in a high number of patients and clinical centers over a long period of time. With more than a billion dollars per developed product,[1] the development costs could be considered excessive, which results in only a limited number of companies taking on the challenge of attempting to develop therapies for lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), etc. Companies with more limited resources often decide to invest in therapeutic areas with higher returns on the invested capital. This presents a real risk for lung disease patients who are relying on the pharmaceutical and biotech industry to bring new and better products to market. Although an increasing number of researchers advocate the use of novel outcome parameters, limited progress has been made.

Medical imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) have the capabilities to "open the black box" and provide regional assessments of airway function. A growing number of papers discuss the use of imaging in research trials. Work by Martonen, et al provided important insights into the general aerosol deposition

characteristics,[2,3] often in generalized or idealized airway geometries. Also, Longest, et al used advanced tools to understand aerosol deposition behavior.[4-6] The COPDgene cohort has yielded interesting results on the airway and blood vessel structure in relation to smoking,[7] exacerbations[8] and healthy lungs[9] using CT scans. Despite increasing evidence of the added value of imaging, the overall usage of imaging tools in clinical trials is low, with a number of exceptions such as lung volume reduction interventions. This could be partially attributed to the fact that often a reader (radiologist or pulmonologist) interprets the data, introducing subjectivity in the process. This increases the level of variability over the clinical centers and over time when performing longitudinal trials. Over the last seven years, a proprietary quantitative image analyses approach called functional respiratory imaging (FRI) has been developed (FluidDA NV, Belguim), that combines methods from aerospace engineering with medical imaging.

Functional respiratory imaging (FRI)

The method comprises reconstructing low-dose CT images into patient-specific, three-dimensional computer models, allowing a quantitative assessment of the imaged airway volume (iVaw) of an individual airway at the aggregate lobar and lung level. The patient-specific geometry is captured up to the level of the smaller airways with a diameter of 1-2 mm. This region contributes most to the overall resistance of the respiratory system and therefore plays a vital role in the manifestation of airway diseases.

Typically, lung diseases also manifest themselves in the peripheral airways. FRI takes the compliance and resistance of the peripheral airways into account by including the patient-specific internal airflow distribution in the workflow. The latter is determined by assessing lobar expansion from expiration to inspiration.[10] The method relies on images, which can be obtained from virtually all modern CT scanners that could acquire images with a reconstructed slice increment of 0.3 mm. This allows FRI, in a later stage, to be implemented across a broad range of hospitals.

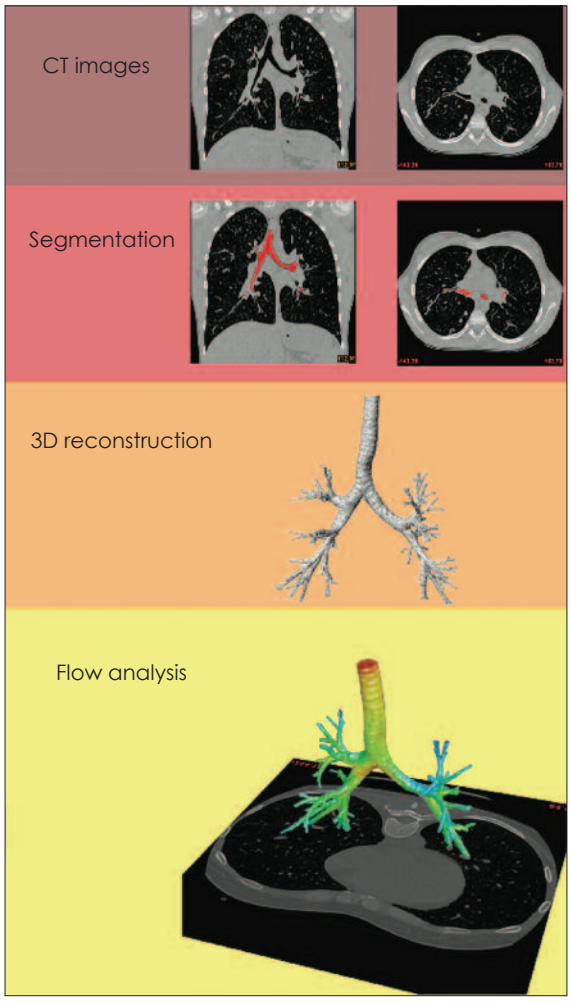
The CT scans for FRI are taken using a dose reduction protocol, such that repetitive scans can be obtained without increasing the dose the patient receives compared to a standard CT exam. A typical low dose scan has a radiation dose in the order of 1-2 mSv, while a standard CT thorax dose is around 10-12 mSv. Phantom scanning showed that the FRI method is highly repeatable in a longitudinal sense when using the same equipment in a clinical center. The average difference was below 0.5% when looking at the segmented volumes of the phantom tubes (representing the airways). It is known that the variability between scanners and centers can be larger. In tests of FRI, this variability was around 1%. This emphasizes the need for further standardization and calibration of scanners when trying to assess cross-sectional data.

As will be discussed below, virtually all clinical trials of FRI assess intra-patient, longitudinal changes. Therefore, the developers are confident that the observed changes are induced by the therapy or the instability of the patient (for instance, after the administration of placebo) and not by variability of the FRI method. In addition, whenever cross-sectional studies are performed, the same equipment is used for all subjects.

The three-dimensional airway morphology obtained from the CT images via segmentation is subsequently used to simulate the respiratory flow to determine local airway resistance (iRaw) using computational fluid dynamics (CFD) (Figure 1). In addi-

Figure 1

Functional respiratory imaging (FRI) workflow[15]



tion to simulating the flow, it also becomes possible to assess the patient-specific effective lung dose by simulating deposition behavior, taking into account aspects such as particle size, inhalation profile and lung geometry/function. The hypothesis is that using image-based outcome parameters or imaging biomarkers, the mode of action and efficacy of inhalation medication can be assessed with higher sensitivity. Furthermore, the insight into individualized aerosol deposition characteristics may help to explain the difference in treatment effect between patients. All the image processing described above is done "off site." The patient is effectively only needed for acquiring the CT scans, which makes FRI a minimally-invasive method for the patient with minor disruption in the day-to-day clinical hospital practice, which is often already over-utilized.

FRI in clinical trials

The challenges of developing and validating a method with the ability to detect small but significant changes in regional airway morphology with an enhanced sensitivity compared to existing clinical response measurements is often difficult. For that reason, FLuidDA decided to perform, and is still performing, multiple clinical trials in several lung diseases (asthma, COPD, idiopathic pulmonary fibrosis (IPF), CF and alpha1 antitrypsin deficiency) using a number of interventions (bronchodilators, inhaled corticosteroids, PDE4 inhibitors and mechanical ventilation) to obtain information from different angles that, when assessed in a comprehensive fashion, provides solid evidence of the value of the novel method. Below, a brief overview of the published clinical studies is given, focusing on both the validity and clinical relevance of FRI. The full papers, including all details of the studies, have been referenced.

To validate the method, a trial using single-photon emission computed tomography (SPECT CT) in asthmatic patients has demonstrated that the margin of error is below 2% when compared to the state-of-the-art method to assess lobar ventilation and tracer deposition.[10]

Another trial using gamma scintigraphy and FRI demonstrated the importance of patient-specific features, such as upper airway morphology, as they have a significant impact in the effective lung dose and therefore, the treatment efficacy.[11]

A crossover trial in COPD patients demonstrated the stark differences of the effect of a short acting muscarinic agonist compared to a short acting beta-2 agonist, in terms of responders and non-responders.[12] It was found that even in a small population, some patients responded highly to one product, either ipratropium bromide or salbutamol, while at the same time there was little or virtually no observable effect when using the other drug (Figure 2). The changes, observed using FEV_1, were almost always within the measurement error of the test, greatly complicating the interpretation of the data.

In a recent, placebo-controlled, crossover study using a budesonide/formoterol combination, FRI could demonstrate the bronchodilating effect mainly resulting from formoterol inhalation in severe COPD patients.[13] When using the combination product, the patients remained stable, while after the administration of the placebo, the occurrence of bronchoconstriction was observed using FRI. This demonstrates the tendency of severe-lung-disease patients to become unstable when the medication is withdrawn for a longer period of time, in this case 16 hours in total. Again, the FEV_1 ($p > 0.05$) was not able to describe these changes due to the inherent black box approach. A sample size calculation revealed that, in order to obtain sufficient power using FEV_1, a total of 91 patients were required, while only 16 patients were needed when using FRI (Figure 3). This reduction demonstrates the potential of more sensitive outcome parameters or biomarkers which could significantly lower the time to market and reduce the associated development costs for the drug in question.

A very recent study, currently in press at "Respiration," demonstrated how FRI can be used to assess the effect of transferring asthma patients from the standard fine particle treatment (MMAD ~ 3-4 μm) to an extrafine particle treatment (MMAD ~ 1-2 μm).[14] It was demonstrated that smaller particles reached different areas in the lung and thereby created a long-term anti-inflammatory effect at a pre-bronchodilation state. Again, the power calculation showed an impressive reduction in the required number of patients. When using FEV_1, a total of 359 patients was needed compared to only 25 patients when using the imaging biomarkers (Figure 3). Furthermore, changes in FRI parameters correlated with patient reported outcomes (PRO), demonstrating that the changes observed in the images are clinically relevant.

Following an initial successful pilot study,[15] current ongoing studies are investigating fine particles in a COPD population, the mode of action of exacerbations, the effect of PDE4 inhibitors and mechanical ventilation.

Future implications of FRI

It is not uncommon these days for potentially-promising drugs to only receive conditional regulatory approval or approval on a reduced label.

Figure 2

FRI to assess the difference between a short acting muscarinic agonist (top) and short acting bronchodilating agonist (bottom) in one COPD patient[12]

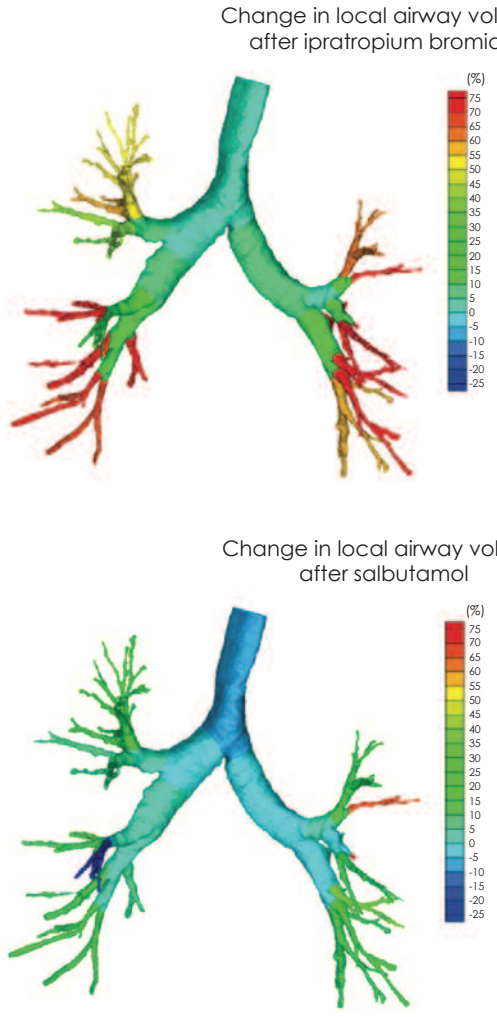
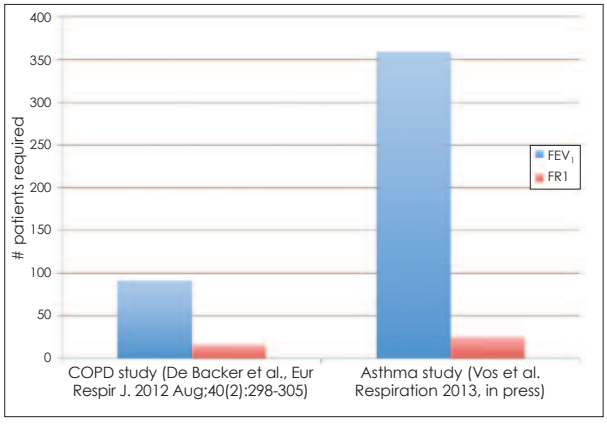


Figure 3

Required sample size for clinical trials using FEV_1 and FRI[13,14]



Often, this is caused by inconclusive results on the general study population, requiring additional sub-analysis or post-registration trials. In many cases, there are subgroups of responders (patients who would benefit greatly from the drug) who are "lost in the average." The significant reduction in the number of patients and the additional regional information that FRI provides effectively make it possible to use early clinical trials as a design tool rather than a mere analysis tool. Fewer patients in fewer centers reduce the overall overhead and heterogeneity costs of the clinical trial, thereby offsetting the additional cost incurred for the image analyses. A myriad of information about the efficiency of the intervention becomes available through FRI, allowing tailoring of the formulation and the device to optimize the treatment. Furthermore, it can shift the development risk from the very expensive phase III trials to phase II trials, facilitating the crucial go/no go decision.

Another challenge that can be tackled using FRI is the bio-equivalence question, often raised when generic drugs attempt to enter the market without a large clinical trial program. FRI can be used to assess the effective lung deposition of both the generic drug and the brand name counterpart, based on the formulation characteristics obtained via *in vitro* measurements such as the Andersen Cascade Impactor or laser diffraction. In addition, the *in vivo* effect (bronchodilation or anti-inflammation) can be assessed in relatively small clinical trials in a short period of time using a crossover design. This way, the deposition, and therefore the device characteristics, can be linked to therapeutic effect and thereby determine whether the two products induce similar effects.

FRI and the role of personalized medicine

The topic of personalized medicine has been on the agenda for quite a while. However, it remains difficult to link specific treatments to individual patients based on the current diagnostic tools. With FRI and the high level of detailed information it provides, scientists and clinicians can consider developing real-patient target therapies, from improved phenotyping to individualizing therapy via companion diagnostics.

Critics and cynics will argue that personalized medicine will "never happen," as the market will never be big enough to justify the developments. However, one could argue that, in respiratory medicine, there is little choice. The era of blockbusters seems to be over and there are no one-size-fits-all therapies on the (short-term) horizon. Regulatory

and reimbursement agencies will increasingly demand superiority over the standard of care to justify the additional expenditure in times of austerity. Apart from very novel breakthrough therapies that would have a strong (average) signal using FEV_1, the only way to demonstrate the added value of a new therapy seems to be selecting the appropriate patient for the right therapy, the patient who was previously lost in the average.

In times where information is freely available and patient advocate groups are stronger than ever, patients will rightfully demand better therapies and better care. Unless we, as a field, succeed in meeting these challenges, there will be an incentive for drug developers to invest in other therapeutic areas with a higher return on investment. This would be detrimental for the millions of patients suffering from lung diseases and for society in general.

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