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**Title page**

**Title:** Functional Respiratory Imaging as a tool to personalize respiratory treatment in subjects with unilateral diaphragmatic paralysis.

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data, Analysis of data, Data interpretation, Manuscript preparation, Review of manuscript, Preparing figures and tables), JDB (Literature search, Data interpretation, Review of manuscript), SV (Processing of data, Analysis of data, Review of manuscript), MG (Data collection, Analysis of data, Review of manuscript), PV (Data interpretation, Review of manuscript), PP (Data collection, Analysis of data, Data interpretation, Review of manuscript, Case-managing physician), PVS (Literature search, Data collection, Analysis of data, Data interpretation, Manuscript preparation, Review of manuscript, Case-managing physician), WDB (Data collection, Analysis of data, Data interpretation, Manuscript preparation, Review of manuscript, Case-managing physician)

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## Abstract

In two subjects with a unilateral diaphragmatic paralysis and complaints of dyspnea, a completely different treatment approach was chosen despite similar anatomical and physiological abnormalities. These decisions were supported by the results generated by Functional Respiratory Imaging (FRI). FRI was able to generate functional information with respect to lobar ventilation and local drug deposition. In one subject, it was found that some lobes were poorly ventilated and drug deposition simulation showed that some regions were undertreated. This subject underwent a diaphragm plication to restore the ventilation. In the other subject, it was found that all lobes were still ventilated. A conservative approach with regular follow-up was chosen to wait for spontaneous recovery of the diaphragmatic function. Both subjects improved subjectively and objectively. These cases demonstrate how novel medical imaging techniques such as FRI can be used to personalize respiratory treatment in subjects with unilateral diaphragmatic paralysis.



## Key words (MeSH terms)

Diaphragmatic paralysis, Thoracic Surgery, Pulmonary Ventilation, Respiratory Drug Administration, Computer-Assisted Decision Making, Personalized Medicine

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## Introduction

In the last decade, personalised medicine has received special attention for its potential of individually tailored treatment, based on genetic or other information on an individual's health status. Following a statement of the European Society of Radiology, medical imaging plays a critical role in all aspects of personalised medicine[1].

New medical imaging techniques are capable of combining medical images with the quantification of certain biological processes in organs in order to detect diseases at the earliest possible time, to personalize diagnosis and to individualize medical or surgical treatment. Functional Respiratory Imaging (FRI) is a clinically validated computational workflow where functional data are added to respiratory anatomical images[2]. Starting from low dose high resolution computed tomography (HRCT) scans, three-dimensional models of airways and lung models are extracted. When performing this extraction on HRCT scans that are taken during breath hold at two (spirometry controlled) distinct lung levels, functional respiratory capacity (FRC) and total lung capacity (TLC), it is now possible to assess the geometry changes of the airways and lung lobes over the breathing cycle. These data are then used as boundary conditions for computational fluid dynamics simulations from which functional information like the behaviour of flow and deposition of inhalation medication can be calculated. A detailed description of the FRI methodology can be found in De Backer et al[2]. One of the design features of FRI is that local analyses can be performed while pulmonary function tests (PFT) are based on a black box approach where the information of the whole respiratory system is incorporated into single numbers. This results in an increased sensitivity of FRI as compared to PFT[3,4].

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In this case report the clinical value of FRI to personalize and deliver the most optimal treatment is demonstrated in two subjects with an idiopathic unilateral paralysis of the diaphragm. The FRI workflow is an additional post-processing step based on paired HRCT scans that are taken as a part of routine clinical practice for these types of patients.

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## Case report

### Study subject 1

A 57-year-old male subject (102kg, 175cm) with a known unilateral diaphragmatic paralysis since 1.5 years was referred to the hospital with recent complaints of increasing dyspnea and orthopnea. Medical history revealed a condition of asthma. On clinical examination diminished vesicular breath sounds at the right lung base were present. The previous practitioner prescribed the subject four doses of salmeterol 25µg - fluticason 250µg (Seritide, GlaxoSmithKline) and fluticason 250µg (Flixotide, GlaxoSmithKline) per day to control asthma exacerbation. PFT showed a highly reduced lung function (see Table 1) with both restrictive and obstructive elements. HRCT confirmed unilateral paralysis of the right diaphragm in combination with hypoventilation-induced atelectasis in the right middle (RML) and right lower lobe (RLL).

To investigate how much ventilation was still distributed to the RML and RLL, FRI was performed. The HRCT scans were loaded into the Mimics 15.0 (Materialise, Leuven, Belgium) software suite. This validated package (Food and Drug Administration, K073468; Conformité Européenne certificate, BE 05/1191.CE.01) was used to generate three-dimensional representations of the airways and lobes. The lobar expansion from FRC to TLC was considered as a measure for the lobar ventilation as this represents the internal airflow distribution (IAD) as defined in Equation 1.

### Equation 1: Internal airflow distribution

$$IAD_{lobe}\ [\%] = 100\ (V_{TLC\_lobe} - V_{FRC\_lobe}) / (V_{TLC\_lungs} - V_{FRC\_lungs})$$

In this equation, $IAD_{lobe}$ is the internal airflow distribution to a specific lobe, $V_{TLC\_lobe}$ is the volume of that lobe at TLC, $V_{FRC\_lobe}$ is the volume of that lobe at FRC, $V_{TLC\_lungs}$ is the total volume of all the lobes at TLC and $V_{FRC\_lungs}$ is the total volume of all the lobes at FRC. Moreover, computational fluid dynamics calculations were performed using Fluent 14.0.0 (Ansys Inc, Lebanon, NH, USA) and provided measures of local deposition of inhalation medication[2]. In this way, it was possible to assess to which zones the drug was delivered.

FRI analysis showed a poor ventilation of the RLL and no ventilation of the RML (Figure 1). In addition, very low levels of drug deposition were found in these lobes (Figure 2) when performing particle simulations using the compound data of Tarsin and Stein et al[5,6]. The poor drug deposition results found by FRI explain why a combination of several inhalation compounds were needed to treat the asthma, as these zones were probably pharmacological undertreated. Furthermore, a long-term non-ventilatory status of the RML could set the stage for repeated episodes of infection accounting for a vicious cycle of recurring bouts of inflammation that may result in a non-functional lobe[7].

In recent review Groth and Andrade[8] concluded that diaphragm plication seems a promising surgical technique to improve ventilation in subjects with diaphragm paralysis. Therefore, a diaphragm plication was performed to place the paralyzed diaphragm in a position of maximum inspiration to relieve compression on the lung parenchyma and to allow its re-expansion.

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Six weeks postoperatively, dyspnea was subjectively better. This was confirmed by an improvement in PFT (Table 1) and FRI, where the RML and RLL were much better ventilated than preoperatively (Figure 1). FRI also showed an improved drug deposition in these regions (Figure 2). It can be observed that the amount of active compound reaching RML and RLL increased from 38.2µg (using salmeterol - fluticason) to 117.1µg (using only salmeterol). This was clinically confirmed as the subject's asthma was kept stable using only four doses salmeterol 25µg - fluticason 250µg per day and as the obstructive components of the PFT improved despite the reduced medication.

**Study subject 2**

A 57-year-old male subject (92kg, 181cm) with a known unilateral diaphragmatic paralysis since eleven months presented at follow-up with recent complaints of increasing dyspnea and orthopnea. Clinical examination showed diminished vesicular breath sounds at the left lung base. The subject did not use any inhalation medication. PFT showed a significantly reduced lung function (Table 1) of restrictive nature. HRCT confirmed the unilateral paralysis of the left diaphragm and associated atelectasis of the left lower lobe was observed.

Subject 2 underwent the same FRI analysis as subject 1. This showed that all lobar regions were ventilated (Figure 1). Taken into account these FRI results, the physician considered a further conservative approach with regular follow-up since spontaneous recovery of the diaphragmatic function has been reported[9]. After 6 months, the breathlessness was completely resolved and total lung capacity was

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significantly improved (Table 1). No new FRI analysis was performed as the physician found this unnecessary from a clinical point of view.

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## Discussion

Unilateral diaphragmatic paralysis is characterized by the loss of muscle contractility with progressive muscular atrophy that leads to an elevated position of the affected diaphragm. Treatment depends mainly on the cause of the paralysis, anatomical and physiological impairment (e.g. atelectasis) and the severity of symptoms. A conservative approach, with or without pharmacotherapy, may be considered since spontaneous recovery of the diaphragm can occur when clinical symptoms are minimal or tolerable and physiological impairment is absent[9]. In those subjects with anatomical and physiological impairment with persisting symptoms despite optimal therapy, surgical correction is indicated. Plication of the diaphragm in a series of 13 subjects with an unilateral impairment showed improvement in symptoms, lung function and quality of life that was maintained during 4-7 years[10]. Despite the promising results on both short-term and long-term outcomes, precise selection of suitable subjects is necessary[10,11].

This case report demonstrates the potential of FRI as a new functional imaging technique in respiratory medicine to choose the right treatment plan in subjects with an idiopathic unilateral diaphragmatic paralysis. In both subjects, radiological examination revealed the appearance of atelectasis in the lower lobes. Atelectasis is commonly seen in combination with compression of the lung parenchyma, which affects compliance, therefore diminishing the regional ventilation of certain parts of the lung. Traditional clinical techniques are however not able to quantify these effects.

Although both subjects had the same anatomical and physiological abnormalities on HRCT, FRI showed a clear difference in regional ventilation. In our first case there

was no lobar expansion of RML and a minor expansion of RLL. However all lobar regions in study subject two were ventilated. In other words, FRI was able to identify functional differences in these two subjects with apparently the same clinical and radiological findings.

Secondly, FRI was able to calculate local deposition of inhalation medication. In subject one, FRI showed that inhalation therapy was not reaching all zones. As a result, the proposed pharmacotherapy was probably inefficient in treating the obstructive symptoms.

Based on the clinical and radiological results, both subjects could be scheduled for surgery since they presented with anatomical and physiological abnormalities and still experienced symptoms despite optimal treatment. On the one hand, FRI analysis in subject two revealed that there was still regional ventilation in the left lower lobe even though atelectasis was present. Therefore a conservative approach with regular follow-up was chosen and spontaneous recovery of the diaphragm occurred after 6 months. On the other hand, taking into account the FRI results of subject one, we could conclude that surgery in subject one was the correct decision. Finally, this report demonstrates also that FRI was able to quantify the regional functional redistribution of airflow to the right lung after the diaphragm plication, and this even without major clinical changes in classical lung function tests.

In conclusion, this case report demonstrates the clinical value of FRI as a tool to personalize medical treatment. In the future, this new functional imaging technique

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may result in a more precise diagnosis and treatment in a rapidly growing number of respiratory patients.

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## Tables

### Table 1: Pulmonary function tests subject 1 & 2

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## Figures

**Figure 1: The internal airflow distribution of the right upper lobe (red), right middle lobe (yellow), right lower lobe (orange), left upper lobe (blue) and left lower lobe (magenta) of subject 1 & 2. FRC: functional residual capacity, TLC: total lung capacity**

**Figure 2: A visualisation of drug deposition simulations of subject 1. The green dots are the locations where the particles deposit. It is shown how much salmeterol and fluticason deposits in the right upper lobe (red), right middle lobe (yellow), right lower lobe (orange), left upper lobe (blue) and left lower lobe (magenta) in the pre- and post-operative situation.**

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**Table 1: Pulmonary function tests subject 1 & 2**

| | Subject 1 | | Subject 2 | |
|---|---|---|---|---|
| Parameter * | Initial visit | Postoperative | Initial visit | After 6 months |
| VC [% predicted] | 52 | 61 | 75 | 86 |
| FEV1 [% predicted] | 48 | 57 | 71 | 82 |
| Tiffeneau index [%] | 70 | 71 | 94 | 94 |
| RV [% predicted] | 113 | 96 | 69 | 95 |
| FRC [% predicted] | 77 | 77 | 67 | 94 |
| TLC [% predicted] | 71 | 71 | 71 | 87 |
| $R_{aw}$ [kPa.s/l] | 0.670 | 0.419 | 0.330 | 0.209 |
| $sR_{aw}$ [kPa.s] | 2.029 | 1.310 | 0.969 | 0.810 |

*: VC: vital capacity; FEV1: forced expiratory volume in 1 second; Tiffeneau index: FEV1/VC; RV: residual volume; FRC: functional residual capacity, TLC: total lung capacity; $R_{aw}$: airway resistance; $sR_{aw}$: specific airway resistance

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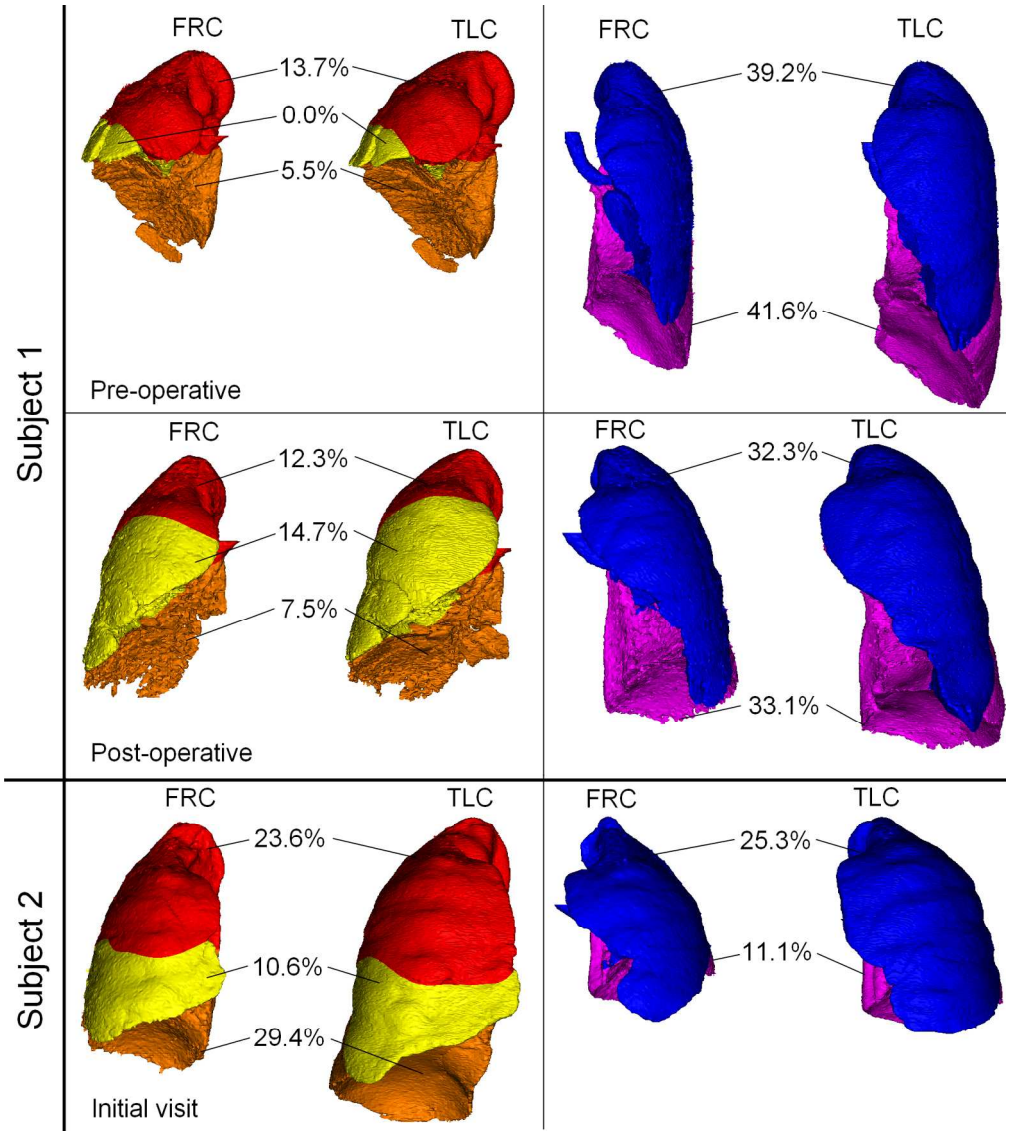


Figure 1: The internal airflow lobar distribution of the right upper lobe (red), right middle lobe (yellow), right lower lobe (orange), left upper lobe (blue) and left lower lobe (magenta) of subject 1 & 2. FRC: functional residual capacity, TLC: total lung capacity

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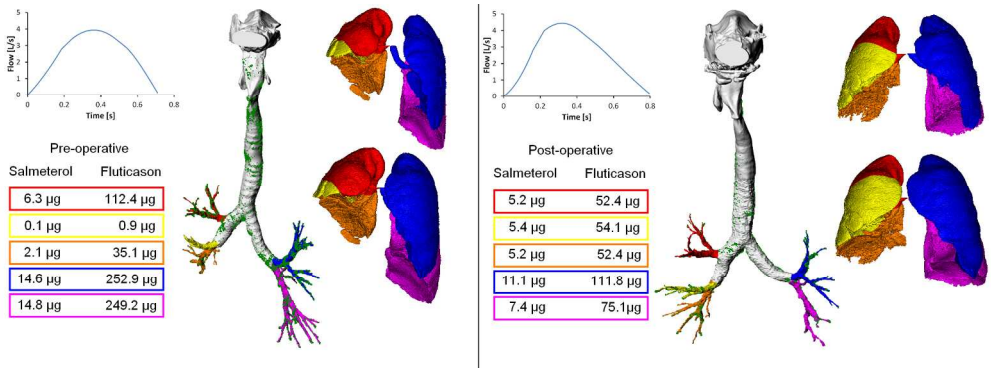


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