ANALYSIS OF PULMONARY FIBROSIS IN MRI, USING AN ELASTIC REGISTRATION TECHNIQUE IN A MODEL OF FIBROSIS: Scleroderma

ORAL DEFENSE

Charlotte MARTIN
Supervisor: Pr. MP REVEL

8th of September 2017

M2 Bio Medical Imaging
Subtract: Imaging from molecular to human
2016-2017
1. BACKGROUND - Scleroderma

- Scleroderma also known as systemic sclerosis (SSc) is a multisystemic connective tissue disease
- There is 70 to 100% of pulmonary involvement, which is the first cause of death
- Infiltrative lung disease (ILD) in scleroderma progresses from non fibrotic ILD towards fibrotic ILD
- HRCT and pulmonary function testing are the two mains examinations to evaluate pulmonary involvement
1. BACKGROUND — Scleroderma evaluation

- **HRCT**:  
  - Has high spatial and contrast resolution  
  - Provides radiation exposure and no functional information

No ILD       ILD without fibrosis       ILD with Fibrosis
1. BACKGROUND — Scleroderma evaluation

- Pulmonary Function Testing:
  - Is the Gold Standard for pulmonary evaluation
  - Is not very sensitive to small changes in pulmonary function
  - The two main parameters of pulmonary fibrosis evaluation are:
    - Forced vital capacity (FVC)
    - Corrected free diffusion of CO (DLCOc)
1. BACKGROUND - Lung MRI

- MRI of lung parenchyma is not currently used in clinical practice, due to:
  - **Lack of signal** (low H+ proton density and short T2* relaxation time)
  - **Important artifacts** (heterogeneity of the local magnetic field and respiratory movements)

- New MR sequences named UTE (ultra-short time of echo) have been developed (1):
  - TE < 0.5 msec
  - It allows **minimizing the T2* signal decay** and obtaining images from the lung parenchyma with sufficient signal intensity

OBJECTIVES

To evaluate the feasibility of an elastic registration method based on MR images for the detection of pulmonary fibrosis in patients with scleroderma.
2. MATERIEL AND METHODS - Population

- We evaluated scleroderma patients referred for cardiac MR as part of their routine follow-up

- Patients were classified in 3 groups:
  - No pulmonary involvement (SSc-no-ILD)
  - Infiltrative lung disease without fibrosis (SSC-ILD)
  - Infiltrative lung disease with pulmonary fibrosis (SSc-fibrosis)

- We also evaluated a cohort of healthy volunteers
2. MATERIEL AND METHODS — MR examination

- Two UTE sequences named **spiral VIBE** (volumetric Interpolated Breath-hold Examination) were performed, one at the end of **full inspiration** and another after **full expiration** on a 3T-unit.
- 3D sequences, acquired on the coronal plane.
- Voxel size 2.14 x 2.14 x 2.5 mm.
- Echo time: 0.05 ms.

![Inspiration and Expiration Images](image-url)
2. MATERIEL AND METHODS — MR segmentation

- We created lung masks for inspiratory and expiratory volumes
2. MATERIEL AND METHODS — Elastic registration

- We used an elastic registration algorithm (1)
- We chose to make the registration from inspiratory to expiratory images
  - Because inspiratory images contain more information
- Registration was helped by the pre-processing masks

The first step was to evaluate the validity of the elastic registration algorithm.

11 anatomic landmarks were manually placed by one observer on inspiratory images.

Then, the same landmarks were placed on expiratory images by:
- the same observer (manually)
- another independent observer (manually)
- the algorithm (registered)
2. MATERIEL AND METHODS – Evaluation of elastic registration

- Mean distances between points were compared:
  - Distance A: Observer 1 - Observer 2
  - Distance B: Observer 1 - Registered
  - Distance C: Observer 2 - Registered

- Variance test:
  - No significant difference
  - $p = 0.49$
Elastic registration produces **deformation maps** from which the Jacobian determinant of each voxel is obtained.

Jacobian determinant is the **quantitative** value of the **deformation matrix** of each voxel.

**DEFORMATION**

Source image = V0

V0 = V1
Jacobian determinant = 1
Elastic registration produces deformation maps from which the Jacobian determinant of each voxel is obtained.

Jacobian determinant is the quantitative value of the deformation matrix of each voxel.

**2. MATERIEL AND METHODS — Deformation analysis**

- **Deformation analysis**
  - Background
  - Material and methods
  - Results
  - Discussion
  - Conclusion

- Source image = V0
- **DEFORMATION**
- Deformed images
- \[ V_0 = V_1 \]
  - Jacobian determinant = 1
- \[ V_0 > V_1 \]
  - Jacobian determinant [0;1]
2. MATERIEL AND METHODS — Deformation analysis

- Elastic registration produces **deformation maps** from which the Jacobian determinant of each voxel is obtained.
- Jacobian determinant is the **quantitative** value of the **deformation matrix** of each voxel

![Deformation diagrams]

Source image = V0

- $V_0 < V_1$
  - Jacobian determinant $> 1$
- $V_0 = V_1$
  - Jacobian determinant $= 1$
- $V_0 > V_1$
  - Jacobian determinant $[0;1]$
- $V_0 < V_1$
  - Jacobian determinant $> 1$
2. MATERIEL AND METHODS — Deformation analysis

- Post-processing steps of Jacobian determinant maps:

  - **Step 1**: Normalization of the Jacobian determinants of each patient using the ratio between its expiratory and inspiratory volumes, to **minimize the effect of the quality of inspiration/expiration**
2. MATERIAL AND METHODS – Deformation analysis

- Post-processing steps of Jacobian determinant maps:

  - **Step 1:** Normalization of the Jacobian determinants of each patient using the ratio between its expiratory and inspiratory volumes
  
  - **Step 2:** Mapping to a common template (expiratory mask for a healthy volunteer) through elastic registration of the binary masks of the lung
2. MATERIEL AND METHODS — Deformation analysis

- Post-processing steps of Jacobian determinant maps:
  - **Step 1:** Normalization of the Jacobian determinants of each patient using the ratio between its expiratory and inspiratory volumes.
  - **Step 2:** Mapping to a common template (expiratory mask for a healthy volunteer) through elastic registration of the binary masks of the lung.
  - **Step 3:** For each patient, calculation of the mean of the Jacobian determinant along each axis (x; y; z).
2. MATERIEL AND METHODS — Deformation analysis

- Post-processing steps of Jacobian determinant maps:
  - **Step 1:** Normalization of the Jacobian determinants of each patient using the ratio between its expiratory and inspiratory volumes
  - **Step 2:** Mapping to a common template (expiratory mask for a healthy volunteer) through elastic registration of the binary masks of the lung
  - Step 3: For each patient, calculation of the mean of the Jacobian determinant along each axis (x; y; z)
  - **Step 4:** For each group of patients
    - Calculation of the mean of the Jacobian determinant for each voxel and representation with 3D color maps
    - Calculation of the mean of the Jacobian determinant along each axis.
2. MATERIEL AND METHODS – Quantitative analysis

- We isolated lung regions with the most important positive values of the Jacobian determinant logarithm (= areas with the most important positive deformation), using a **threshold of 0.15**: 
  - In the healthy volunteers group
  - And for each patient

- We calculated similarity index, Dice coefficient, between the healthy volunteers group and each patient
3. RESULTS - Population

- 33 subjects were included:
  - 11 healthy volunteers
  - 22 patients
- 1 patient was excluded of the analysis because of poor quality of examination due to a misunderstanding of breathing instructions, so 32 subjects were evaluated

<table>
<thead>
<tr>
<th></th>
<th>Total N = 32</th>
<th>Healthy Volunteers N = 11</th>
<th>SSc-no-ILD N = 9</th>
<th>SSc-ILD N = 5</th>
<th>SSc-Fibrosis N = 7</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19 (59%)</td>
<td>2 (18%)</td>
<td>7 (78%)</td>
<td>5 (100%)</td>
<td>5 (71%)</td>
<td>0,005</td>
</tr>
<tr>
<td>Male</td>
<td>13 (41%)</td>
<td>9 (82%)</td>
<td>2 (22%)</td>
<td>0 (0%)</td>
<td>2 (29%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>45,6 (19,5)</td>
<td>29,1 (9,3)</td>
<td>59 (17,5)</td>
<td>43,6 (14,7)</td>
<td>60 (16,3)</td>
<td>0,001</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0,79</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>21,9 (2,5)</td>
<td>21,8 (1,6)</td>
<td>22,6 (2,3)</td>
<td>21,1 (3,9)</td>
<td>21,8 (2,9)</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>7 (21%)</td>
<td>3 (27%)</td>
<td>4 (44%)</td>
<td>0 (0%)</td>
<td>3 (42%)</td>
<td>0,042</td>
</tr>
<tr>
<td></td>
<td>N = 21</td>
<td>N = 9</td>
<td>N = 5</td>
<td>N = 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>2,76 (1,47)</td>
<td>3,2 (1,16)</td>
<td>2,83 (0,24)</td>
<td>1,94 (0,86)</td>
<td></td>
<td>0,012</td>
</tr>
<tr>
<td>DLCO</td>
<td>60 (20)</td>
<td>67 (14)</td>
<td>66 (27)</td>
<td>38 (6)</td>
<td></td>
<td>0,001</td>
</tr>
</tbody>
</table>
3. RESULTS – Qualitative analysis

- Maps of the mean value logarithm of Jacobian determinant for each group of patients show:
  - **Differences** in the repartition of the Jacobian determinant in each group
  - In healthy volunteers, the most important stretching (red color) in the **posterior part of lung bases**
  - In the corresponding areas, the lungs of **SSc-fibrosis patients show only few changes**, with Jacobian determinant near to 0 (green color)
3. RESULTS – Quantitative analysis

- A whole cohort analysis was performed with:
  - Disease+: SSc-fibrosis + SSc-ILD
  - Disease-: SSc-no-ILD + Healthy Volunteers

![ROC curve / AUC= 0.802](image)

- Dice coefficient: Best cut-off: 0.44

<table>
<thead>
<tr>
<th></th>
<th>Disease +</th>
<th>Disease -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Test -</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>20</td>
</tr>
</tbody>
</table>

Se = 91%  Sp = 75%
3. RESULTS – Quantitative analysis

- A sub-group analysis was also performed:
  - Disease+: SSc-fibrosis
  - Disease-: Healthy volunteers

![ROC curve / AUC=0.929](image)

<table>
<thead>
<tr>
<th></th>
<th>Disease +</th>
<th>Disease -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Test -</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Se = 86%</td>
<td>Sp = 100%</td>
<td></td>
</tr>
</tbody>
</table>

**Dice coefficient**

**Best cut-off : 0.44**
3. RESULTS – Correlation with PFT

- DLCOc could not be evaluated for 2 patients due to severity of disease
- Analysis was performed:
  - FVC: n=21
  - DLCOc: n=19

\[ R = 0.12; p = 0.6 \]

\[ R = 0.16; p = 0.5 \]
4. DISCUSSION

TO SUMMARIZE OUR FINDINGS

- Feasibility of an elastic registration algorithm applied on MR inspiratory and expiratory sequences
- Visual differences in Jacobian maps between subjects with and without ILD
- Distinction between healthy and fibrotic subject with acceptable sensitivity and perfect specificity
- No correlation between PFT and our method of evaluation of fibrosis
4. DISCUSSION

OUR LIMITATIONS

- Small size of the cohort
- No evaluation of repeatability
- Subjective choice of threshold for Dice coefficient
4. DISCUSSION

OUR PERSPECTIVES

- Evaluation on a larger cohort
- Quantitative analysis of Jacobian determinant repartition analysis with no subjective threshold:
  - Principal component analysis of the whole volume
  - Comparison of joint entropy
- Application to other types of fibrosis
First study to assess ILD using an elastic registration between inspiratory and expiratory lung MR images

Lung deformation pattern was different between healthy subjects and scleroderma patients with pulmonary fibrosis

This functional approach of lung deformation based on elastic registration allows diagnosis of pulmonary fibrosis with an acceptable sensitivity and a perfect specificity, and no radiation exposure
Thank you for your attention


