Thoracic configuration in patients ageing with cystic fibrosis: A retrospective single-blinded cohort study

Niklas Sinderholm Sposato a,*, Rauni Rossi Norrlund b,c, Marita Gilljam d, Kristofer Bjerså e, Louise Lannefors a,f, Monika Fagevik Olsen a,e,f

a Department of Health and Rehabilitation, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
b Department of Radiology, Sahlgrenska University Hospital, Gothenburg, Sweden
c Department of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
d Department of Respiratory Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
e Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
f Department of Physical Therapy and Occupational Therapy, Sahlgrenska University Hospital, Gothenburg, Sweden

ABSTRACT

Background: In patients with cystic fibrosis (CF), thoracic morphology and its role in respiratory function is conditioned by anthropometric factors, as well as by pathological changes. While the lungs are continuously monitored, examinations of potential thoracic cage adaptations to the disease are rare. Hence, the aim of this study was to investigate thoracic configuration, and its correlation to spirometry measures over time.

Methods: In total, 344 high-resolution computed tomography (HRCT) examinations from 90 patients were assessed and analysed. Those results were subsequently related to spirometry measurements performed within the same period.

Results: The cohort displayed no homogenous change in thoracic configuration over time, and correlation between thoracic area and spirometry variables could not be supported statistically.

Conclusions: Although the current study included a larger cohort of patients with CF compared to previous studies on thoracic morphology, no patient group-specific changes in thoracic configuration were revealed. Furthermore, no correlations between structural findings and functional respiratory measurements were found.

1. Introduction

In all individuals, thoracic morphology is conditioned by anthropometric factors as well as by respiratory mechanics (De Troyer and Boriek, 2011; Epstein and Ligas, 2012; Holcombe et al., 2017; Ratnovsky et al., 2008; Sverzellati et al., 2013). In addition, particular changes to the thoracic configuration have been shown to be a consequence of both anthropometric factors, as well as by pathological changes. While the lungs are continuously monitored, examinations of potential thoracic cage adaptations to the disease are rare. Hence, the aim of this study was to investigate thoracic configuration, and its correlation to spirometry measures over time.

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* Corresponding author.
E-mail address: niklas.sinderholm.sposato@gu.se (N. Sinderholm Sposato).

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Troyer, 1992), and the thoracic changes that have previously been shown following lung diseases (Laurin et al., 2012; Lim et al., 2018; Sverzellati et al., 2013), the aim of this study was to investigate thoracic configuration over time by measuring intra-thoracic distances on high-resolution computed tomography (HRCT) images from patients with CF, and to study correlations between these observations and spirometry measures.

2. Methods

2.1. Study design and data collection

This study was performed as a retrospective longitudinal single-blind cohort study and included HRCT images taken during yearly follow-up of patients with CF enrolled at the adult CF centre at Sahlgrenska University Hospital (Gothenburg, Sweden). This centre routinely performs yearly CXR, and HRCT every third year. When indicated, HRCT examinations are performed at more frequent intervals. Inclusion criteria were patients >20 years old with two or more HRCT images. CT images taken within a time frame of one year or following lung transplantation were excluded from the study. Images from an initial total of 110 patients, taken between 2001 and 2020 were included. Following inclusion and exclusion evaluation, 90 patients with a total of 344 HRCT examinations were assessed and analysed. Imager extraction and de-identification was performed by the study’s thoracic senior radiologist (RRN), who also coded each included patient and labelled all images by year. Measurements were subsequently performed, blinded by the first author (NSS). HRCT examinations were performed with one of the following systems: Light Speed Pro16, Light Speed VCT, Discovery CT750HD, Optima CT660 (GE Healthcare, Milwaukee, WI, USA) and Somatom Definition (Siemens Medical Solutions, Forchheim, Germany). A constant tube voltage of 120 kV, a dose-modulated tube current in the range 35–110 mA and a rotation time of 0.5 s were used in the inspiratory helical scan. Transverse images with a slice thickness of 1.25–1.5 mm and 10 mm interspace. All examinations were performed without an intravenous contrast medium. Functional spirometry data was extracted from the Swedish cystic fibrosis patient registry, and demographical values (year of birth and sex) were retrieved from patient records. This study was approved by the Swedish Ethical Review Authority (case number 2019–02628).

2.2. Measures

In order to examine anatomical changes in the thorax as a whole over time, a study protocol was constructed. Three different distances in mm, at three different thoracic levels (Incisura Jugularis, Angulus Sterni, and Processus Xiphoideus) were chosen and measured on axial CT images (Fig. 1). Distances at each level included a transverse distance (TVD), and two antero-posterior distances, i.e., right (APD), and left (AP) hemi-thorax. All measurements were conducted on images at maximum inspiration. Measurements for all included images were conducted by the first author. To test for inter-rater reliability, a senior radiologist measured a random sample of 20 images. A Bland-Altman plot was produced and the interclass correlation coefficient was determined, showing a high level of inter-rater agreement (ICC = 0.99).

2.3. Data analysis

All measures were coded, sorted, and analysed using Microsoft® Excel, version 16.48. For descriptive data, mean and standard deviation (SD), median and range (min-max) were calculated on both actual values as well as calculated differences. Statistical analysis was performed with IBM SPSS® version 28.

The primary variable was calculated as the mean value of the left and right antero-posterior distances multiplied by the transverse distance, resulting in a thoracic area. This measure was then used to calculate the difference between two consecutive measurements, and then divided by the number of years between the two occasions, thus, determining the mean difference of the thoracic area per one year, at each thoracic level. Additionally, five-year age intervals were constructed to better overview changes over time. Correlation analysis was performed using the Spearman’s Rho (rₛ) for thoracic area and three spirometry variables: total lung capacity (TLC), forced expiratory volume in one second (FEV1), and forced vital capacity (FVC). Differences between sexes concerning change in thoracic area were analysed using a Mann-Whitney U test with post hoc correction by Bonferroni. However, only age interval groups 20–24, 24–45, 46–50 were analysed due to the low number of patients in the higher age interval groups (Fig. 2).

3. Results

In total, 344 HRCT images from 90 patients with CF over the age of 20, were extracted. The patients (54% male and 46% female) were born between 1950 and 1995 and were on average 34.8 (SD 9.8; 24–70 years of age) years old at the time of HRCT imaging. The mean number of years was 8.8 years (SD 4.7) and the median time was 9.0 (1–18) years between the first and the last HRCT.

The mean age at the first HRCT was 26.8 (SD 8.4) and the median age was 23 (20–55). Concerning lung function, the mean FEV1 (percent predicted) value at the first measurement was 76.1 (SD 23) median 77.7 (25.5–126.1), and at the last measurement, the mean FEV1 (percent predicted) value was 66.8 (SD 24.9) median 65.5 (19.1–113.7).

Within each age interval, there was a spread where no clear trend could be detected, either regarding change in thoracic area or regarding the specific measured distances. In addition, in the higher age intervals, >50 y, the number of patients was low (Figs. 3 and 4). Further statistical analysis was omitted due to skewed distribution of participants and measures between age intervals.
A comparison of change in thoracic area between sexes within each age interval group (n = 89) found minor, yet significant differences within the 20–24 y (p < 0.001) and 30–34 y (p = 0.004) intervals, at the Proc. Xiphoideus level. The difference was shown as a greater increase in thoracic area among men compared to women.

Furthermore, the change per year at each age interval for spirometry variables was calculated and used to investigate potential correlation between the thoracic area at each thoracic level and each spirometry variable. No statistically significant correlation was found (TLC (litres): Incisura Jugularis $r_S = 0.12$, p = 0.293, Angulus Sterni $r_S = 0.09$, p = 0.454, Processus Xiphoideus $r_S = 0.01$, p = 0.962; FEV1 (percent predicted): Incisura Jugularis $r_S = -0.07$, p = 0.500, Angulus Sterni $r_S < 0.01$, p = 0.992, Processus Xiphoideus $r_S = -0.13$, p = 0.220; FVC (percent predicted): Incisura Jugularis $r_S = -0.10$, p = 0.350, Angulus Sterni $r_S = -0.11$, p = 0.316, Processus Xiphoideus $r_S = -0.06$, p = 0.589).

4. Discussion

To the best of our knowledge, this is the first report on in-group thoracic configuration associated with aging in patients with CF. Furthermore, studies investigating thoracic morphology in adjacent fields based on HRCT images are currently sparse. The current study revealed no significant changes in thoracic distances over time in patients > 20 years of age with CF. In addition, no distinct patient group-specific patterns of structural change to the thoracic cage were observed. Therefore, correlation of the results from this study to thoracic...
morphology presented in previous work (Bellemare et al., 2001; Laurin et al., 2012; Lim et al., 2018; Sverzellati et al., 2013) is limited. Similarly, the study showed no correlation between changes in thoracic configuration over time and ongoing spirometry measures, which for patients with CF are associated with a progressive functional decline.

Lung hyperinflation is a known negative consequence in respiratory diseases such as chronic obstructive pulmonary disease (COPD), emphysema, and CF (Bellemare et al., 2001; Laurin et al., 2012; Lim et al., 2018; Sverzellati et al., 2013). In terms of respiratory mechanics, hyperinflation progressively leads to changes in rib angulation, and flattening of the diaphragm, which in turn impede proper musculoskeletal respiratory action (Aliverti et al., 2007; De Troyer and Boriek, 2011; Ratnovsky et al., 2008). These negative effects primarily affect the expiratory phase. Maintaining adequate expiratory function is challenging for patients with CF. Yet the present study revealed only minor, heterogenic changes in thoracic distances over time. Therefore, a potential decrease in expiratory capacity cannot at this time be attributed to thoracic configuration in these patients. In contrast, studies comparing thoracic changes to lung function in patients with COPD and emphysema, demonstrated altered thoracic dimensions (Lim et al., 2018; Sverzellati et al., 2013). A possible explanation for these differences between patient groups may be age, rather than an exclusive correlation to disease. Although life expectancy for patients with CF has increased considerably over the last three decades (i.e., at present close to 50 years), they are still very young as compared to patients with COPD and emphysema. In addition to the age parameter, the lack of correlation between thoracic structural changes and lung function could also be related to a relatively high level of physical activity within this patient group. Even though types- and levels of physical activity were not investigated in this study, the importance of an active lifestyle has continuously been stressed as part of the CF physiotherapy regimen in Sweden (Dennersten et al., 2009). Thus, it is conceivable that structural changes in the thoracic cage that could be correlated to impaired lung function only appear later in life and in more severe presentations of the disease, which would hinder the ability to engage in physical activity also for patients with CF. On the other hand, functional musculoskeletal symptoms, such as stiffness and pain, could still present at earlier ages. However, this was not the focus of the current study.

Previous studies have shown variations of thoracic adaptation between men and women with CF when compared to healthy controls (Bellemare et al., 2001; Laurin et al., 2012). These differences were greater in women and mainly presented as thoracic adaptation to pulmonary hyperinflation. By contrast, patients included in the study at hand presented with almost indistinguishable morphological patterns between sexes. This difference in results between the current and previous studies may be of value, but for now there is little to justify any specific hypothesis, and a discussion on causality regarding these results would therefore be too speculative.

As in previous studies on thoracic configuration related to other respiratory diseases (Kuo et al., 2014; Laurin et al., 2012; Lim et al., 2018; Sverzellati et al., 2013; Zorzo et al., 2020), HRCT images also provided a reliable basis for the purpose of investigating thoracic adaptation over time in patients with CF. All HRCT examinations included in this study were performed in a standardised manner that demonstrated high inter-rater reliability, and all distances were subsequently measured by one investigator, thus providing a uniform basis for the collected data. However, the number of HRCT images differed in the yearly follow-up examinations, which affected the ability to ensure that the measurements were performed at precisely the correct thoracic level. Furthermore, the main objective of this study was to investigate thoracic configuration in patients ageing with CF. Given this musculoskeletal approach, data from a relatively large number of patients could be collected, thereby providing a broad overview of the cohort. However, this approach also entailed that potentially important individual circumstances, e.g., severity of the disease, were not separately investigated. Also, although this study involved a large number of images, the
data was limited for patients in the higher age intervals. It would therefore be interesting to test this study model with an even larger population, to enable further analyses. However, such an approach is likely to necessitate a multi-centre collaboration.

5. Conclusions

The present study did not show any specific thoracic configuration or morphological pattern in patients ageing with CF. Furthermore, no differences were found between sexes, and no correlation was found between thoracic configuration and the progressive decline in lung function in this cohort. Further studies are needed to better understand the intricate relationship between the musculoskeletal and visceral components of respiration in patients with CF. Such studies may take on a more individualised approach and may include breathing patterns and the patients’ experience of pain or stiffness related to their thoracic cage.

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