Cystic Fibrosis in Adults: Short-Term and Long-Term Reproducibility of the Brody Score for Lung Morphology in Low-Dose MDCT Scans

Cystische Fibrose (CF) bei Erwachsenen: Kurz- und Langzeit-Reproduzierbarkeit des Brody-Scores bei Niedrig-Dosis-MDCT-Aufnahmen

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Zusammenfassung


Material und Methoden: Die Niedrig-Dosis-Multidetektor-CT-Aufnahmen (Schichtdicke 1,5 und 3 mm, 120 kV, mAs/Schicht 10 – 15, effektive Dosis 0,5 mSv, CDTi 1,0 Gy/Patient) von 15 Patienten (8 weiblich, 7 männlich, Altersspanne 18 – 50 Jahre, durchschnittliches Alter 33 Jahre) wurden von 3 unabhängigen Radiologen (1 – 20 Jahre Berufserfahrung) zweimal ausgewertet (Zeitintervall zwischen den Aussagen, 1 – 84 Monate).

Ergebnisse: Die durchschnittliche Inter-Betrachter-Reproduzierbarkeit des Brody-Score betrug +/- 7% (2 – 30%). Die Intra-Betrachter-Reproduzierbarkeit betrug +/- 6% (3 – 12%) (KZI, 4% – 0 – 12%, LZI, 12%, 1 – 36%). Für die Subscores betrug die Inter-Betrachter-Reproduzierbarkeit durchschnittlich +/- 25% (15 – 41%), die Intra-Betrachter-Reproduzierbarkeit +/- 23% (12 – 46%).

Schlussfolgerung: Der Brody-Score zeigt die hohe Inter-Betrachter-Reproduzierbarkeit bei LDCTs erwachsener CF-Patienten sowie eine gute Intra-Betrachter-Reproduzierbarkeit im KZI und LZI, welche jedoch im LZI sinkt. Im Vergleich zum Gesamtscore zeigen die Subscores durchschnittlich eine geringere Inter- und Intra-Betrachter-Reproduzierbarkeit.

Abstract

Purpose: The semi-quantitative Brody score measures the severity of cystic fibrosis (CF)-related lung disease. We investigated the short-term (28 – 60 days) and long-term (2 – 7 years) intra- and inter-observer reproducibility of the Brody score in low-dose multidetector row computed tomography examinations performed in inspiration (LDCTs) of adult CF patients.

Materials and Methods: Composite Brody scores and respective underlying bronchiectasis, mucus plugging, peribronchial thickening, parenchymal opacity, and hyperinflation subscores were evaluated twice (time interval, 1 – 84 months) by each of 3 independent radiologists (1 – 20 years of professional diagnostic radiology experience) in LDCTs (4 – 64 rows, 120 kVp, 10 – 15 mAs/slice, CTDIw approx. 1.0 mGy, effective dose approx. 0.5 mSv) of 15 adult patients with CF-related lung disease (8 female, 7 male, age, 18 – 50 years, mean, 33 years).

Results: The average reproducibility of the Brody score was within +/- 7% (range, 2 – 30%) between radiologists, and +/- 6% (3 – 12%) within radiologists (short-term, 28 – 60 days, 4%, 0 – 12%, long-term, 2 – 7 years, 12%, 1 – 36%). For the different subscores, the reproducibility was within +/- 25% (15 – 41%) between radiologists and +/- 23% (12 – 46%) within radiologists.

Conclusion: The Brody score shows high average inter-observer reproducibility in LDCTs of adult CF patients. The Brody score also demonstrates high average intra-observer reproducibility if subsequent assessments are made within 28 – 61 days. With time intervals of 2 – 7 years between subsequent evaluations, however, intra-observer reproducibility decreases. Respective subscores each demonstrate lower intra- and inter-observer reproducibility than does the composite Brody score.
Introduction

Cystic fibrosis (CF) is the most frequent life-shortening autosomal recessive disease among the Caucasian population in Europe, with an incidence about 1 in 2,500 live births and a carrier frequency of about 4 – 5% [1 – 3]. Mutations in a single large gene on chromosome 7 cause dysfunction of cAMP-dependent chloride channels in exocrine tissues, particularly in the lung and pancreas [3, 4]. Due to improved health care, life expectancy among CF patients has continuously increased, from about 25 years in 1985 to 37 years in 2008 [5].

There is no generally accepted gold standard for imaging CF-related lung disease in adult patients. However, some clinical institutions have established follow-up examinations at regular intervals that include computed tomography (CT) imaging [6]. In our institution, adult CF patients over the age of 18 years are regularly assessed by means of lung function tests once every 6 months and by low-dose-CT of the chest (LDCT) for lung morphology once every four years. Computed tomography (CT) has become the gold standard for imaging CF-related lung disease, with lung morphology appearing to be complementary to lung function tests (LFTs) in at least 50% of CF patients. Chest radiographs and LFTs alone fail to recognize structural lung alterations caused by CF [7]. MRI has not been widely applied to evaluate normal or mildly damaged lung structure in CF patients. Despite radiation exposure, the risk of CT-induced mortality is likely to be minimal in CF patients when compared to the benefit of a more accurate diagnosis [7]. The ACE systems of modern CT scanners significantly reduce dose exposure [8, 9]. Also, low-dose multidetector row CT of the lung (LDCT) shows high morphologic accuracy in non-malignant lung disease [10].

Different high-resolution (HR) CT-based scoring systems, with a range of morphologic parameters and different weighting of results, have been designed to support the evaluation of structural lung damage in CF patients. For some scoring systems, HRCT findings have been correlated with LFTs [11, 12]. A modification of the Bhalla score for structural lung alteration in CF has previously been applied in an adult population [2]. Brody and co-workers have developed a scoring system for HRCT scans obtained in both inspiration and expiration in children suffering from CF [13], which demonstrates both high reproducibility and accuracy [12, 14]. Since many CF patients live through adulthood, it appears necessary for optimal radiological patient management to extend CT scoring systems for children with CF to include adults with CF-associated lung disease [15] who underwent LDCT in inspiration.

Since the reproducibility of scoring results in the repetitive evaluation of the same chest CT images is a key feature of clinical reliability of any particular CT scoring system, we conducted an intra- and inter-observer reproducibility study of the Brody scoring system in a selected set of LDCTs of the chest performed in adult CF patients. We determined the short-term reproducibility (28 – 60 days) of the Brody score among second-year radiology residents, to understand how firmly its different features would be integrated in new clinical knowledge. We also assessed the long-term (at least two years) reproducibility of the Brody score in an attending radiologist with 10 years of post-fellowship chest radiology experience, since time intervals between follow-up CT scans of the chest in CF patients are often in the range of several years [2, 6]. It has previously been established that the short-term reproducibility of the Brody score is high among experienced chest radiologists [12, 14].

We hypothesized that the intra-observer reproducibility of the Brody score and its different subscores in adult patients with CF who undergo LDCT of the chest in inspiration would be within +/- 10% of the average score, both with a short time interval of 28 – 60 days for second-year radiology residents and with a long time interval of at least 2 years for an attending radiologist. Similarly, we hypothesized that the inter-observer reproducibility of the Brody score and its different subscores in adult patients with CF who undergo LDCT of the chest in inspiration would be within +/- 10% of the average score between second-year radiology residents and an attending radiologist.

Materials and Methods

Patients

This retrospective analysis was based on LDCT examinations of the chest performed between February 2006 and October 2010, in 15 consecutive adult CF patients (male, n = 7, female n = 8, age range, 18 – 50 years, average, 33 years), each of whom had only had one LDCT examination at our institution. The clinical indication for LDCT was to assess the current lung morphology status. Institutional policy for adult CF patients over the age of 18 years includes the assessment of lung morphology status by means of LDCT once every four years. Additional MDCT scans are acquired when there is clinical suspicion or evidence of aggravation of CF-related lung disease.

Ethical Issues

Institutional ethics committee approval was obtained for the retrospective analysis of data previously obtained for individual clinical treatment of CF patients. Data included in this study were evaluated and presented in accordance with the World Medical Association (WMA) Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects, as last amended by the 59th WMA General Assembly, Seoul, Korea, October 2008.

LDCT Protocol

LDCT of the chest was invariably performed in inspiration, at a tube charge of 120 KVP, with the lowest technically achievable tube current that would still generate images of diagnostic value and left no option of further dose reduction by means of dose modulation programs. Through January 2007, examinations were conducted on a 4-row MDCT scanner (Mx 8000, Philips Medical Systems, Hamburg,

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Germany) at tube current, 35 mA, collimation, 4x1 mm, rotation time, 0.5 s, pitch, 1.75, effective slice thickness, 1.3 mm, effective tube-current-time product per slice (CTTP), 10 mAs, weighted CT dose index (CTDIw), 1.0 mGy, reconstruction algorithms “C” and “D”. For an adult female patient of average weight and height, the protocol results in a mean effective dose of 0.5 mSv [7]. From February 2007, a 64-row MDCT scanner (Brilliance-CT64, Philips Medical Systems, Hamburg, Germany) was applied, at tube current, 35 mA, pitch 1.173, collimation, 64x0.5 mm, rotation time, 0.5 s, CTTP, 15 mAs, reconstruction algorithms “C” and “YA”, effective slice thickness, 0.625 mm, CTDIw, 1.0 mGy. After reformattting images in the sagittal, coronal, and axial planes (slice thickness 3 mm), and images with 1.0 – 1.5 mm slice thickness in at least one plane, from primary LDCT reconstructions with a slice thickness of 1.0 to 1.3 mm and 50% slice overlap, the images were filed in an electronic picture archiving and communication system (Syngo PACS, Siemens Medical Solutions, Erlangen, Germany).

LDCT Evaluation
Axial and coronal images (slice thickness 3 mm and 1.5 mm) were obtained from the PACS and analyzed side-by-side on two 1k-PACS monitors, with one image per display, at window width and window level settings of 1,600 HU and -600 HU (lung window), respectively. Sagittal images were only evaluated to match findings when this was not possible on coronal or axial images alone.

Independent of each other, three radiologists (R1, R2, R3) with different clinical work experience each evaluated all LDCT examinations twice, according to the scoring system previously introduced by Brody and co-workers for children with CF [13]. R1 was an attending radiologist with 10 years of post-fellowship clinical chest radiology experience. R2 and R3 were second-year radiology residents, with 17 and 12 months of post-graduate clinical work experience, respectively, who were on a 6-month CT training rotation with approximately 50% of the case load involving chest CT assessments.

The “Brody score” is a weighted composite (total) score for CF-related changes in lung morphology that describes and quantifies the respective presence, location, and extent of bronchiectasis, mucus plugging, peribronchial thickening, parenchymal opacity, and hyperinflation in the periphery and in the center of the upper, lower and middle right and left lung lobes, respectively. The lingual segment constitutes the left middle lobe equivalent. The Brody score ranges between 0 and 207.00 points, at increments of 0.25 points, and increases with the severity of the CF-related changes in lung morphology [13]. The Brody score was originally developed to assess lung morphology in incremental HRCT scans obtained in both inspiration and expiration in 6- to 10-year-old children [13]. We analyzed LDCT scans of adult CF patients obtained in inspiration, only, for parenchymal opacity and hyperinflation.

Statistical Analysis
Average values of the six individual scoring results (two each for R1-R3) of the Brody score and its five different subscores [13] were plotted along the x-axis of modified Bland-Altman Mann plots [16], and respective deviations of individual scoring results from the average were plotted along the y-axis. Both the absolute deviations (in Brody scoring points) and the relative deviations (in percent of the mean) were recorded.

Results
The respective median time intervals and ranges between the first and second LDCT readings were 4.7 years (2.0 – 7.0) for R1, 42 days (32 – 60) for R2, and 37 days (28 – 47) for R3.

Brody Score (Total Score)
Among the 15 patients, the average Brody scores between the three independent readers ranged from 20.0 to 132.7 points (median, 58.4 points, mean, 68.0 points, possible range, 0 – 207.0 points). The individual Brody scores ranged from 10.0 – 146.5 points (median, 63.0 points, mean, 70.7 points) for R1, 25.0 – 133.5 points (median, 57.9 points, mean, 66.4 points) for R2, and 22.0 – 134.5 points (median, 59.9 points, mean, 66.9 points) for R3.

The average deviation of all individual Brody scores from the mean value of all readers was 4.9 points (7%), with a range of 1.5 – 10.3 points (2 – 30%). The mean deviation of Brody scores from individual respective average values was 8.7 points (12%, range, 0.5 – 26.0 points, 1 – 36%) for R1, 3.1 points (5%, range, 0 – 6.3 points, 0 – 12% for R2, and 2.2 points (3%, range, 0 – 7.0 points, 0 – 9%) for R3. Findings implied an average intra-individual reproducibility of Brody scoring results within about 7% of the individual mean score, with greater deviations in the long-term re-assessment by the most experienced reader. There was no evidence of skewing of the average deviation toward lower or higher average values of the Brody score (Fig. 1a – 3).

Bronchiectasis Subscore
The average deviation of individual bronchiectasis subscores (possible range, 0 – 72.0 points) from the mean value of all readers was 4.2 points (16%), with a range of 1.2 – 11.7 (8 – 43%). The mean deviation of bronchiectasis subscores from individual respective average values was 7.9 points (25%, range, 0.5 – 17.0 points, 2 – 67%) for R1, 3.7 points (16%, range, 0.5 – 21.0 points, 1 – 57%) for R2, and 1.2 points (5%, range, 0 – 4.0 points, 0 – 20%) for R3, implying an average intra-individual reproducibility of bronchiectasis subscore results within about 15% of the individual mean score, with greater deviations for long-term re-assessment by the attending radiologist (Fig. 1b, 3).

Mucus Plugging Subscore
The average deviation of all individual mucus plugging subscores (possible range, 0 – 36.0 points) from the mean value of all readers was 1.9 points (19%), with a range of 0.3 – 4.2 points (2 – 133%). The mean deviation of mucus plugging subscores from individual respective average values was 2.1 points (18%, range, 0 – 6.0 points, 0 – 67%) for R1, 1.4 points (16%, range, 0 – 5.0 points, 0 – 67%) for R2, and 1.1 points (11%, range, 0 – 6.0 points, 0 – 100%) for R3, implying an average intra-individual reproducibility of mucus plugging subscore results within about 12% of the individual mean score, with similar deviations for short-term and long-term re-assessment (Fig. 1c, 3).

Peribronchial Thickening Subscore
The average deviation of all individual peribronchial thickening subscores (possible range, 0 – 54.0 points) from the mean value of all readers was 2.7 points (15%), with a range of 0.3 – 7.0 points (3 – 38%). The mean deviation of peribronchial thickening subscores from individual respective average values was 4.7 points (22%, range, 0 – 12.0 points, 0 – 67%) for R1, 2.4 points (14%, range, 0 – 10.3 points, 0 – 36%) for R2, and 0.67 points (4%, range,
0–2.8 points, 0–13 %) for R3, implying an average intra-individual reproducibility of mucus plugging subscore results within about 13 % of the individual mean score, with greater deviations for long-term re-assessment by the attending radiologist (Fig. 1d, 3).

**Parenchymal Opacity Subscore**

The average deviation of all individual parenchymal opacity subscores (possible range, 0–54.0 points) from the mean value of all readers was 1.8 points (41 %), with a range of 0–5.2 points (0–111 %). The mean deviation of parenchymal opacity subscores from individual respective average values was 2.6 points (86 %, range, 0–13.0 points, 0–200 %) for R1, 1.5 points (35 %, range, 0–5.0 points, 0–200 %) for R2, and 0.9 points (17 %, range, 0–7.0 points, 0–93 %) for R3, implying an average intra-individual reproducibility of parenchymal opacity subscore results within about 46 % of the individual mean score, with similar deviations for short-term and long-term re-assessment (Fig. 1e).

**Fig. 1** Intra- and inter-observer reproducibility of the Brody score and its five different subscores between three independent readers in 15 patients with CF-related lung disease of different severity. a Brody score (possible range, 0–207.00 points, average observed range, 20.00–132.67 points), b bronchiectasis subscore (possible range, 0–72.00 points, average observed range, 10.17–56.63 points), c mucus plugging subscore (possible range, 0–36.00 points, average observed range, 0.50–15.83 points), d peribronchial thickening subscore (possible range, 0–54.00 points, average observed range, 4.67–36.38 points), e parenchymal opacity subscore (possible range, 0–54.00 points, average observed range, 0–13.67 points), f hyperinflation subscore (possible range, 0–54.00 points, average observed range, 4.17–20.08 points).
**Hyperinflation Subscore**

The average deviation of all individual hyperinflation subscores (possible range, 0 – 27.0 points) from the mean value of all readers was 3.1 points (37 %), with a range of 0.9 – 7.4 points (4 – 71 %). The mean deviation of hyperinflation subscores from individual respective average values was 2.7 points (62 %, range, 0 – 8.0 points, 0 – 200 %) for R1, 1.2 points (11 %, range, 0 – 5.5 points, 0 to 71 %) for R2, and 1.4 points (14 %, range, 0 – 10.5 points, 0 – 67 %) for R3, implying an average intra-individual reproducibility of hyperinflation score results within about 29 % of the individual mean score (Fig. 1f), with greater deviations for long-term re-assessment by the attending radiologist (Fig. 1f).

**Discussion**

In a retrospective analysis, we applied the Brody score to assess lung morphology in adult CF patients, based on LDCT scans of the lung performed in inspiration, and tested for the reproducibility of scoring results. The Brody score is a weighted composite...
score that was developed to describe and quantify lung morphol-
ogy in children suffering from CF based on incremental HRCT
scans of the lung obtained in both inspiration and expiration. The Brody score sums up its five different subscores for bronchiectasis, mucus plugging, peribronchial thickening, par-
enchymal opacity, and hyperinflation [13]. Reproducibility was
tested among two second-year radiology residents, with short-
term intervals of 28 – 60 days between subsequent assessments
of the same LDCT, and an attending radiologist with 10 years
of post-fellowship clinical chest radiology experience who re-as-
essed all LDCT scans in this study after long-term intervals of 2 –
7 years.

The respective mean, median, and range values for the Brody
score were similar between readers. The range covered both
very minor and severe lung involvement with CF-related disease,
leaving out only the most severe part of the possible range. The
findings imply that, overall, the different radiological features
underlying the Brody scoring system are easy to understand, re-
cognize, and weigh in their respective severity even with rela-
tively little chest radiology experience. These findings expand
previous experience which was largely based on expert readings
of chest images of CF patients [12 – 14, 17].

For the Brody score as the weighted composite score sum of its
different subscores, the study hypothesis of inter- and intra-obs-
server deviations of 10% or less from the respective averages
was met by the average of our findings, and, particularly, by the
second-year radiologists who re-assessed LDCTs within 28 – 60
days. The latter finding corroborates previous reports of high
short-term reproducibility of different HRCT scoring systems for
CF patients of different ages among expert readers [12 – 14, 17].

The findings appear to expand previous knowledge to include a
more general perception of the Brody score as a tool that repro-
ducibly assesses lung morphology changes not only among pe-
diatric patients in the hand of expert readers [12 – 14], but also
among adult CF patients in the hands of radiology residents, as
in this study. However, high reproducibility only seems to hold
for short-term re-assessments. In fact, our finding of decreased
reproducibility of Brody scoring results in the hands of an experi-
enced chest radiologist after time intervals of 2 – 7 years, when
compared with short-term reproducibility among radiology resi-
dents, implies that either memory effects play a role in the short-
term reproduction of scoring results or visual perception may
drive change over time. From a clinical point of view, it appears to be
better to review the previous chest CT along with the current
one and perhaps newly apply the Brody scoring system to both
than to score only the current scan and rely on the old Brody
scoring results of the previous one.

For the individual subscores, the study hypothesis of an inter-
and intra-observer deviation of 10% or less from the respective
averages was not met. Rather, individual sub-scoring results de-
viated by as much as 200 percent from the average. This finding
was more pronounced among subscores with smaller score point
ranges, i.e., mucus plugging and hyperinflation, and among sub-
cores that appear to be more difficult to assess by visual means,
i.e. parenchymal opacity and hyperinflation. Among the former,
the lower point range increases both the susceptibility to small
changes and the relative impact of deviations between subse-
quent assessments. Among the latter, visual impressions of lung
parenchymal density and its distribution could be a source of un-
certainty. When two neighboring areas of lung parenchyma
show with different densities, the first could be hyperinflated
while the second is normal, or the first could be normal while
the second demonstrates ground glass opacity of some origin.

Possible solutions would include the addition of an expiratory
CT scan of the chest to more easily recognize areas of hyperinfla-
tion by their relative lack of volume change when compared with
normal lung, or the addition of CT density measurements in areas
of uncertainty. While the former would expose the patient to
additional radiation, potentially at uncertain gain in the indi-
vidual case, the latter would require lists of CT density value
ranges that would be accepted as normal, too high, or too low
for CF patients.

Limitations of our retrospective reproducibility study include
the lack of experienced readers reassessing CT examinations after a
short time interval, the restriction of experience at long time in-
tervals to one experienced reader only, and the relatively low
number of patients included. Since previous studies were based
on the short-term reproducibility of CT scoring results in CF pa-
tients among experienced readers, it did not appear to add cru-
cial knowledge to the field to obtain those results in addition.

Among readers with brief postgraduate medical experience, it
would not have been possible by design to perform a reproduc-
ibility study with intervals of several years between individual
readings. Therefore, long-term reproducibility results could only
have been obtained for readers with more extensive post-gradu-
ate chest radiology experience. In our department, such long-
term experience with radiological examinations in CF patients
was restricted to only one attending radiologist.

In conclusion, the Brody score, as a weighted composite score
that describes and quantifies the respective presence, location,
and extent of CF-related changes in lung morphology as detected
by means of CT, appears to be reproducible within about 10% of
an average value between different radiologists, both with a
short time interval of 28 to 60 days, and with a long time interval
of 2 to 7 years. However, its individual subscores for bronchiecta-
sis, mucus plugging, peribronchial thickening, parenchymal opa-
city, and hyperinflation are less reproducible, with values ex-
ceeding 10%. Overall, the long-term reproducibility was not as
good as the short-term reproducibility. For clinical practice, it ap-
ppears advisable to review both the previous chest CT and the
associated Brody score along with the new chest CT and new
Brody score and perhaps newly apply the Brody scoring system
to both.

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