Altered Relaxation Times in Magnetic Resonance Imaging Indicate Bronchopulmonary Dysplasia

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Abstract

We developed a Magnetic Resonance Imaging (MRI) protocol using T1- and T2-mapping sequences to characterize lung structural changes in preterm infants with Bronchopulmonary Dysplasia (BPD). We prospectively enrolled 61 infants to perform 3-Tesla MRI of the lung in quiet sleep. Statistical analysis was performed using logistic Group Lasso regression and simple logistic regression. Increased lung T2- and decreased lung T1 relaxation times indicated BPD yielding an AUC of 0.80. Results were confirmed in an independent study cohort (AUC 0.75) and mirrored by lung function testing, indicating the high potential for MRI in future BPD diagnostics.

Introduction

Bronchopulmonary Dysplasia (BPD), notable for its significant long-term sequelae, affects up to 50 % of VLBW infants worldwide. Clinically defined by the need for oxygen supplementation or ventilator support at term, specific diagnostic tools for the assessment of structural pulmonary changes are missing. Our aim was to identify and validate reliable imaging markers indicating BPD with high sensitivity using T2 and T1 mapping strategies in a newly developed Magnetic Resonance Imaging (MRI) protocol.

Methods

Study population. 61 very preterm infants with a gestational age (GA) ≤32 weeks (Table S1) were prospectively included in the study upon informed parental consent (exploration cohort n=40, Perinatal Centre LMU Munich, EC #195-07; confirmation cohort n=21, Perinatal Centre UKGM Giessen**,** EC #135/12). BPD (mild, moderate, severe) was diagnosed at 36 weeks GA [1].

MRI protocol & analysis. Lung MRI was performed at 36 weeks GA in spontaneously breathing infants (fiO_2=0.21) using a 3-Tesla whole-body scanner. The protocol included pulse sequences for assessment of morphology, volume, and quantitative relaxation parameters: i) ECG-triggered T2-weighted single-shot fast-spin-echo (ssFSE) sequences in 3 orthogonal orientations (echo time TE: 57 ms; repetition time TR: 2 RR intervals), ii) single-slice ssFSE T2-mapping (TR 2000 ms, 4 TEs 26-92 ms) and T1-mapping (TR/TE 3000 ms/26 ms, 6 inversion times TI (slice-selective): 25-2600 ms and no inversion) acquiring 8 averages (total acquisition time ≈5 minutes).

For T2-/T1-mapping analysis, manual segmentation into 4 lung quadrants was performed (Osirix MD). T2 and T1 relaxation times were calculated by non-linear exponential signal fitting for 4 lung quadrants separately and the total lung.

ILFT. Standardized ILFT (tidal breathing analysis, passive respiratory mechanics, functional residual capacity (FRC_p)) was performed at 36 weeks GA according to the guidelines of the American Thoracic and European Respiratory Society in spontaneously breathing infants (fiO_2=0.21) under light sedation (chloral hydrate, 30-40 mg/kg; orally).

Statistics. Missing values were imputed by sampling from a normal distribution (sample mean, standard deviation) and accounting for the covariance structure of the highly correlated MRI variables. To model binary disease outcomes, BPD was dichotomized (no vs. mild/moderate/severe BPD; no/mild vs. moderate/severe BPD). A Grouped Lasso Logistic model was used to estimate the impact of different variables on the outcome BPD; independent variables included GA, gender, weight, steroids, early onset infection and imaging data.

The Grouped Lasso Logistic model was repeated using lung function and imaging data as independent variables. Quality of the models was assessed by leave-one-out cross validation for unbiased validation avoiding overoptimistic AUC for model validation. Confirmation of the results was obtained using logistic regression (no vs. mild/moderate/severe BPD) under consideration of the confounders GA, gender, steroids and early infection. Model validation was realized in an independent study cohort calculating ROC and AUC by comparing predicted results with true output. Methods are detailed in the online supplement (S1-S4).

Results

Quantification of structural changes in the BPD lung by MRI relaxation times

By regularized linear modelling, we identified quantitative MRI parameters associated with the diagnosis of BPD in premature infants near term. With significant clustering of regional values, total lung values are presented (Figure S9).

Increased lung T2 and decreased lung T1 relaxation times are associated with an overall increased risk for BPD (mild, moderate and severe BPD vs. no BPD, T2: β=0.037 (OR 1.038); T1: β=-0.0001 (OR 1)) as well as an increased risk for higher disease grades (moderate and severe BPD vs. no or mild BPD, T2: β= 0.007 (OR 1.007); T1: β=-0.003 (OR 0.997)) (Table 1, Figure 1). Leave-one-out cross-validation yielded an AUC of 0.8 [0.65;0.95] (mild, moderate, severe BPD vs. no BPD) and an AUC of 0.68 [0.49;0.86] (moderate/severe BPD vs. no/mild BPD) (Figure 1), respectively. The variable GA showed significant impact on the study results.

We confirmed the findings using logistic regression showing a significant, positive association of T2 relaxation times with BPD (mild, moderate and severe BPD vs. no BPD, β=0.137 OR 1.147; p=0.044)). The regression models including GA, gender,

steroids, early infection and T2 and T1 relaxation times as covariables revealed an AUC of 0.85 [0.71;0.98] (mild, moderate and severe BPD vs. no BPD) and an AUC of 0.59 [0.32;0.85] (moderate/severe BPD vs. no/mild BPD), respectively.

A logistic imaging model confirmed the results in an *independent study cohort* (AUC 0.75 [0.44;1] (mild, moderate and severe BPD vs. no BPD); AUC 0.61 [0.33;0.88] (moderate/severe BPD vs. no/mild BPD) (Figure 1). Furthermore, replacement of the primary outcome BPD in the logistic regression analysis by the count variables 'days of oxygen' or 'days of mechanical ventilation (MV)' (birth to discharge) confirmed the results obtained by the grouped Lasso Logistic model (Figures S1 and S2).

Structural abnormalities correlate with functional and long-term effects

The Grouped Lasso model selected the variables FRC_p (β=0.003; CI [0;0.15]), compliance (C_{rs}/kg) (β=-0.09; CI [-1.85;0]) and tidal volume (VT/kg) (β=-0.05; CI [-0.71;0]) together with T1 (β=-0.002; CI [-0.04;0]) and T2 relaxation times (β=0.002; CI [-0.13;0.12]) as predictors for the outcome variable BPD. In addition, infants with the need for home monitoring showed significantly higher T2 relaxation times when compared to preterms discharged without a device (p=0.04). *Detailed results are provided in the online supplement (Figures S5 and S8).*

Discussion

By the use of a comprehensive MRI protocol in non-sedated, spontaneously breathing infants we identified quantitative imaging markers with high sensitivity for BPD at term-equivalent age. Namely, increased T2- and decreased T1-relaxation times were revealed to indicate BPD and to identify higher disease grades by Lasso-Model, confirmed by logistic regression analysis.

Functional data obtained by ILFT and confirmation of the findings using count variables [2], i.e. ('days of oxygen', days of MV' underlined the validity of the results.

Transverse (T2) and longitudinal (T1) relaxation times are two of the most widely used tissue parameters for image contrast in MRI, their quantification allowing for objective MRI analysis [3]. Higher lung T2 relaxation times in in preterm infants with BPD may indicate increased interstitial remodelling, i.e. fibrosis, potentially associated with pulmonary inflammation and interstitial edema, recently described for adult lung-disease patients [4-6]. Shortened T1 relaxation times potentially indicate emphysematous changes or relative changes in pulmonary perfusion [7, 8]. The blood concentration of dissolved molecular oxygen can also influence pulmonary T1 relaxation times with oxygen acting as a (weak) paramagnetic contrast agent. The imaging findings thereby reflect characteristic histologic changes described for BPD [9], in line with the follow-up data indicating decreased pulmonary stability in infants with abnormal imaging findings as indicated by the need for home monitoring.

In summary, the use of an advanced, quantifiable mapping technique strongly supports the value of MRI lung imaging in preterm infants with BPD, significantly adding to recent findings obtained by a small-footprint 1.5-T scanner using commercially available sequences in neonates after birth [10]. The use of a newly developed protocol in a larger number of patients as well as a confirmation cohort underscore the importance of our findings, next to the application of complex statistical modelling that allowed us to account for disease complexity and the multitude of confounders with significant correlation.

Our results hint at possible mechanisms of BPD pathology (and pathogenesis) and provide a step towards improved imaging-based phenotyping in BPD with increased diagnostic accuracy, proven to be critical for personalized treatment strategies and

disease monitoring. Future studies will need to join forces between different perinatal centres in order to allow for the identification of disease subtypes and long-term outcome while increasing patient numbers when studying this unique patient cohort with high-end imaging techniques.

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Conception and design: AH, BEW, HE

Acquiring data: KF, OD, HE, CH, AWF

Analysis and interpretation: AH, KF, HB, SS, OD, AP, LN, BEW

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Table 1: Coefficients Logistic Group Lasso model

Variable	mild, moderate and severe BPD vs. no BPD	moderate/severe BPD vs. no/mild BPD
Intercept	15.183	5.590
Gestational age	-0.649 (0.522)	-0.139 (0.870)
Gender (female) (Reference: male)	0 (1)	0.592 (1.808)
Birth weight	0 (1)	-0.001 (1)
ANCS (Reference: no)	0 (1)	0.137 (1.146)
Early onset infection (Reference: no)	0.080 (1.083)	0 (1)
T2 (total)	0.037 (1.038)	0.007 (1.007)
T2 (upper right quadrant)	0 (1)	0 (1)
T2 (lower right quadrant)	0 (1)	0 (1)
T2 (upper left quadrant)	0 (1)	0 (1)
T2 (lower left quadrant)	0 (1)	0 (1)
T1 (total)	-0.0001 (1)	-0.003 (0.997)
T1 (upper right quadrant)	0 (1)	-0.002 (0.998)
T1 (lower right quadrant)	0 (1)	-0.001 (0.999)
T1 (upper left quadrant)	0 (1)	0.004 (1.004)
T1 (lower left quadrant)	0 (1)	-0.002 (0.998)

Table 1: Coefficients and odds ratios obtained from the logistic Group Lasso model with alpha optimization for clinical and MRI variables best explaining the disease outcome. BPD is graded according to Jobe et al and dichotomized (mild, moderate and severe BPD vs. no BPD; moderate/severe BPD vs. no/mild BPD). ANCS=antenatal corticosteroids, RDS=respiratory distress syndrome. Total and regional values are indicated for T1 and T2 relaxation times, i.e. upper right, lower right, upper left and lower left lung quadrant.

Legends and captions Figure 1

Increased T1 and decreased T2 relaxation times in the preterm lung significantly associated with BPD.

Figure 1: Leave-one-out cross validation for the logistic imaging model with an area under the ROC of 0.8 [0.65;0.95] (mild, moderate and severe BPD vs. no BPD **(A)**) and an area under the ROC of 0.68 [0.49;0.86] (moderate/severe BPD vs. no/mild BPD **(B)**). Confirmation of the cross validation by the logistic imaging model for BPD in an independent study cohort with an area under the ROC of 0.75 [0.44;1] (mild, moderate and severe BPD vs. no BPD **(C)**) and an area under the ROC of 0.61 [0.33;0.99] (moderate/severe BPD vs. no/mild BPD **(D)**). **(E)** Representative T1-weighted MR images (i, ii) without inversion pulse (TI = ∞) and inversion times (TI) between 25 and 2600 ms. Calculated T1 maps of two subjects with BPD 0 (iii) and BPD 3 (iv). T1 relaxation time is decreased in severe BPD. **(F)** Representative T2-weighted MR images (i,ii) with echo times (TE) between 26 and 92 ms and calculated T2 maps in BPD 0 (iii) and BPD 3 (iv). T2 relaxation time is increased in severe BPD.