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Fetal Lung Apparent Diffusion Coefficient (ADC) Measurement Using Diffusion-Weighted MRI at 3T: Correlation with Gestational Age

Onur Afacan^{1,2}, Ali Gholipour^{1,2}, Robert V. Mulkern^{1,2}, Carol Barnewolt^{1,2,3}, Judy Estroff^{1,2,3}, Susan Connolly^{1,2,3}, Richard B. Parad^{3,4}, Sigrid Bairdain^{2,5}, and Simon K. Warfield^{1,2}

¹Department of Radiology, Boston Children's Hospital, Boston, Massachusetts, USA

²Harvard Medical School, Boston, Massachusetts, USA

³Advanced Fetal Care Center, Boston Children's Hospital, Boston, Massachusetts, USA

⁴Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

⁵Department of Surgery, Boston Children's Hospital, Boston, Massachusetts, USA

Abstract

Purpose—To evaluate the feasibility of using diffusion-weighted magnetic resonance imaging (DW-MRI) to assess the fetal lung Apparent Diffusion Coefficient (ADC) at 3T.

Materials and Methods—71 pregnant women (32 second trimester, 39 third trimester) were scanned with a twice-refocused Echo-planar diffusion-weighted imaging sequence with 6 different b-values in 3 orthogonal diffusion orientations at 3T. After each scan, a Region-of-Interest (ROI) mask was drawn to select a region in the fetal lung and an automated robust maximum likelihood estimation algorithm was used to compute the ADC parameter. The amount of motion in each scan was visually rated.

Results—When scans with unacceptable levels of motion were eliminated, the lung ADC values showed a strong association with gestational age ($p < 0.01$), increasing dramatically between 16 and 27 weeks and then achieving a plateau around 27 weeks.

Conclusions—We show that in order to get reliable estimates of ADC values of fetal lungs, a multi b-value acquisition, where motion is either corrected or considered, can be performed.

Keywords

Fetal MRI; Diffusion MRI; motion artifacts; Fetal lung

Introduction

Normal fetal lung parenchyma passes through the embryonic and pseudoglandular stages through week 16 of gestation, the canalicular phase starting at 16 weeks, the saccular stage starting at 24 weeks and the alveolar stage starting at 36 weeks gestation (1). Maldevelopment of the fetal lung parenchyma may lead to life threatening physiologic dysfunction due to pulmonary hypoplasia and pulmonary hypertension (2,3). The ability to accurately assess structural lung maturation prior to delivery might be valuable as newborns with inadequate *in utero* lung development are at risk for respiratory failure or death after birth (4). Currently available non-invasive imaging modalities for fetal lung parenchymal assessment include volumetry by ultrasonography (US) (5) and magnetic resonance imaging (MRI) (6,7). Diffusion measurements can provide additional information in these studies as a potential biomarker for lung development and gestational age appropriate maturity (8).

Assessing fetal lung maturation using diffusion-weighted MRI was first suggested by Moore et al. (8) in 1999. These authors reported that ADC values derived from a set of diffusion-weighted MRI images with different diffusion weightings was highly correlated with gestational age and this information could be used to assess fetal lung parenchymal maturation. However, they also showed that ADC increase with gestational age did not correlate with surfactant levels which increase between 24 weeks gestation and term. That trial was carried out with a 0.5T scanner. Subsequently, there have been some inconsistent reports considering whether ADC can be reliably measured *in utero* and whether it can be used as a biomarker for fetal lung parenchymal maturation. Balassy et al. (9) found no significant correlation between gestational age and ADC when ADC was measured using a 2 b-value diffusion acquisition (b=0 and b=1000) on a 1.5T scanner. Cannie et al. (10) showed that ADC calculated from low b-values (b=0, 100, 250) showed a high correlation with gestational age, whereas ADC calculated from high b-values (b=500, 750, 1000) showed an inverse correlation with gestational age. In a similar study, Manganero et al. (11) showed high correlation between gestational age and ADC when 3 b-values were acquired (b=0, 250, 750). Thus a consensus has yet to be achieved in the literature on the appropriate acquisition protocol to be used for reliable ADC estimation for fetal lungs.

Diffusion-weighted MRI of the fetus is challenging. The first and foremost challenge with any fetal MRI scan is intermittent motion of the fetus that adds to the maternal respiratory and abdominal motion and disrupts the spatial encoding and correspondence required for the analysis. This is especially critical in diffusion MRI, as this non-invasive method that measures the variability of the mobility of water molecules is intrinsically highly susceptible to motion. For structural brain imaging of fetuses, a promising approach is to acquire a stack of fast 2D spin echo slice images in multiple orientations and then combine them using super-resolution MRI reconstruction techniques as described by Gholipour et al. (12). This also has been recently applied to T2-weighted images of the fetal chest (13).

A second challenge with diffusion-weighted MRI of the fetal lungs is the weak signal available from the small fetal lungs, especially at earlier gestational ages and at lower magnetic fields. This reduces the signal-to-noise ratio, raising the need for imaging at lower spatial resolutions to boost signal, which is undesirable. With fetal MRI increasingly

performed on 3T scanners (14, 15) using multi-channel body coils, there are gains in the signal-to-noise ratio. However, this results in an increased risk for the third challenge, which are increased artifacts at higher magnetic fields. Although signal level increases with field strength, MRI artifacts, such as main magnetic field inhomogeneity (B0) and RF field inhomogeneity (B1), also increase with field strength (14,15). These artifacts are especially critical in fetal MRI as the fields of view (FOV) tend to be larger than those used in many other studies.

Considering these challenges, the aims of this study were threefold: 1) to determine the sequence parameters and evaluation methods to obtain reliable diffusion measurements to help apply the use of diffusion-weighted MRI of fetal lungs in clinical practice; 2) to establish the normal range of fetal lung diffusion values measured at 3T MRI in fetuses with increasing gestational age; and 3) to determine whether diffusion-weighted MRI of fetal lungs can be used to assess fetal lung development *in-utero*.

Materials and Methods

Study group

Between January 2013 and September 2015, a total of 71 pregnant women (32 second trimester, 39 third trimester) were imaged at our hospital with an MRI protocol that consisted of an additional diffusion-weighted MRI scan of the fetal lungs. Subjects were selected from volunteers with no incidental findings (N=26) and clinical patients (N=45) with clinical presentations and imaging findings showing no lung abnormalities, i.e lung cyst, small lungs, abnormal lung signal. Our study was carried out under a protocol approved by the Institutional Review Board which specifically included recruiting subjects to undergo research imaging with DWI, and the comparison of research imaging to imaging data acquired clinically. Subjects with incidental findings related to lung malformations and cases with known lung abnormalities were excluded. Median gestational age of the fetuses was 26.1 weeks, with a range from 18 to 37.3 weeks. The patients were not sedated, and no contrast agent was administered during the examinations. No maternal breath-holding or triggering was applied during the acquisitions.

MRI acquisition

All scanning was performed on a Siemens 3T Skyra scanner equipped with an 18-channel body matrix coil. Each patient was first scanned with the clinical standard fetal MRI protocol. Multiple acquisitions in 3 orthogonal planes (axial, coronal, sagittal) with respect to the fetal brain and body were performed using T2-weighted half-Fourier acquisition single shot turbo spin echo (HASTE) sequences. Sequence parameters for these acquisitions were: TE=100ms, TR=1.6sec, FOV=256mm, 1mm in plane resolution with 2–3mm slice thickness. Depending on the quality of the HASTE images of the body, a balanced steady state free precession (TRUE-FISP) sequence was also acquired in 3 planes to help clarify the non-neurologic fetal anatomy. This process was repeated until satisfactory images of the brain and body were acquired for each case. After these acquisitions, a multi-slice single shot Echo Planar Imaging (EPI) sequence was used to acquire diffusion-weighted scans of the lungs. In-plane resolution was 2.5mm × 2.5mm for each study, and slice thickness was

set at 3mm. Echo time (TE) was 60ms, whereas repetition time (TR) ranged from 2s to 4.4s depending on the number of slices required to cover the lungs. Each patient was scanned with 6 different b-values (0, 50, 100, 200, 400, 600 sec/mm²) in multiple planes (axial, coronal). For each b-value, 3 orthogonal diffusion directions were acquired. Total scan time for additional lung images was between 32 seconds to 75 seconds, depending on the number of slices.

Post processing

After the image acquisition, cases were analyzed visually. Six cases were eliminated from the study due to severe image artifacts due to B0 and/or B1 inhomogeneities. Most of the B0 artifacts were result of magnetic susceptibility differences between maternal intestinal gas and tissue.

Scans from the remaining 65 subjects were then graded for severity of motion artifacts using a scale of 3, where 3 represented cases with no motion artifacts, 2 denoted minor motion artifacts and 1 represented severe motion artifacts. This analysis was done in the time domain to identify motion occurring between each volume. For each slice, location of the lungs was visually checked for each diffusion-weighted image and graded according to how much motion occurred between that b-value image and b=0 image. If the motion was smaller than 1 voxel, the dataset was labelled with a grade 3; less than 3 voxels was labelled with a motion grade 2; and motion larger than 3 voxels was labelled grade 1. For each case, a region of interest (ROI) was manually drawn in the right lung (Figure 2), and apparent diffusion coefficient (ADC) value was calculated using a robust maximum likelihood based curve fitting procedure (16,17). This approach was shown to produce reliable diffusion parameter maps by leveraging spatial information from neighbouring voxels. Motion analysis and ROI placement was done by an experienced research fellow with 4 years experience in fetal MRI (OA) trained and supervised by pediatric radiologists (JAE, CEB, SAC) with more than 10 years of experience in fetal MRI. In cases with more than one set of motion-free diffusion scans, the coronal plane was selected for ROI placement.

Data analysis

For each case fetal gestational age and motion grade were noted and plotted against the calculated ADC. For each case, the diffusion-weighted scan with the best motion grade was used.

After the ADC vs. gestational age data was plotted, an exponential saturation model described in Equation 1 was fitted to the data. ADC_{sat} defines the saturation ADC value and alpha is the exponential decay parameter.

$$ADC = ADC_{sat}(1 - e^{-\alpha(\text{age})}) \quad (\text{Equation 1})$$

Statistical analysis

After the exponential saturation model was fitted to the data, first, we calculated the coefficient of determination of the fit between the ADC and age for different amounts of motion. This value shows how well the data is described by the model described by equation 1. As part of this analysis we also calculated the 95% confidence intervals for each fit. Second, we used paired t-test to evaluate whether ADC shows a statistical significant correlation with gestational age, with a null hypothesis that ADC does not change with gestational age.

Results

Figure 1 shows sample diffusion-weighted images with different motion grades. Images on the top row are from a study with motion grade 3; whereas images in the middle row are from a study with motion grade 2. The bottom row shows a case with severe motion, grade 1. The left column shows $b=0$ images and the right column shows $b=200$ images. Figure 2 shows a sample ROI placement and a sample ADC map from a case with no motion.

Table 1 summarizes the relationship of different motion grades in our study. Out of 65 cases, 39 had at least one scan with motion grade 3.

Figure 3 shows ADC parameter plotted against gestational age, color-coded by motion grade. The red curve shows the exponential saturation model fitted to the data with motion grade 3. Dotted red curves shows the 95 percent confidence intervals for the fit. When the saturation exponential curve was fitted only to the data with no motion artifacts (motion grade grade 3), ADC_{sat} was found to be $2.6 \times 10^{-3} \text{ mm}^2/\text{s}$ and α was 0.21. R-squared (R^2) value of the fit was 0.71. When data with minor motion (motion grade 2) was added, R^2 dropped to 0.232, and when all data was used R^2 dropped to 0.102.

The ADC values between fetuses with a gestational age less than 24 weeks and fetuses with a gestational age greater than 24 weeks were significantly different ($P < 0.001$). Fetuses with a gestational age less than 24 weeks had a mean ADC of $1.89 \times 10^{-3} \text{ mm}^2/\text{s}$, with a standard deviation of $0.29 \times 10^{-3} \text{ mm}^2/\text{s}$, whereas fetuses with a gestational age greater than 24 weeks had a mean ADC of $2.46 \times 10^{-3} \text{ mm}^2/\text{s}$, with a standard deviation of $0.23 \times 10^{-3} \text{ mm}^2/\text{s}$.

Figure 4 shows sample signal decay curves with differing amount of motion. The data shows an exponential decay when there is no motion, and when there is a significant amount of motion, the decay is no longer exponential and the fitted ADC value is no longer meaningful.

Discussion

Our results show that when motion was systematically analyzed and the data with limited motion artifacts were analyzed, the ADC parameter was positively associated with gestational age. According to our results, ADC increases with gestational age, most rapidly in the canalicular phase of lung development, between 16 and 24 weeks of gestation. As reported in the literature (1), as the canalicular period progresses, interstitial tissue decreases and capillary growth increases, which may explain the increase in ADC in this period.

This result was obtained from analyzing 39 of 65 cases with no other artifacts, which indicates a success rate of 60 percent. This result shows that it is important to consider motion when analyzing such datasets. Any method that corrects for motion artifacts in fetal diffusion MRI studies may potentially be valuable in transitioning this method into more robust clinical practice. The success rate might also be increased with multiple repetitions of the study, but this would increase the length and cost of the scan and reduce patient comfort/tolerance.

Our results show that it is not possible to calculate ADC parameters reliably using only 2 b-values. This is especially true for experiments using $b=0$ and a $b=600$. When ADC was calculated from 2 b-values only ($b=0$ and $b=600$), R-squared value of the fit was 0.21. When only two b-values are used, calculated ADC does not show a significant dependence on gestational age ($P=0.16$), compared to when all b-values were used ($P<0.01$). This is most likely due to the reduced accuracy of the method when only 2 b-values are used. In our study with a 3T scanner and the given voxel resolution, $b=600$ images were very close to the noise level, which limits this combination as a possible acquisition strategy. Multiple b-values also improve the goodness of fit, but increase the susceptibility of the scan to motion because of the increased total scan time.

Moore et al. (8) speculated that an increase in pulmonary vasculature might be the reason for an increase in ADC. A more complex diffusion model that considers the effect of perfusion, such as an intra-voxel incoherent motion model, might be useful in determining whether it is the perfusion (pseudo diffusion) or diffusion component that is responsible for this increase. Future work involves the development of new methods to improve imaging in the presence of motion and low signal, which were the most important barriers limiting the analysis of diffusion and perfusion at this stage. One possible solution is repeating the scan until fetus stops moving, which might increase the success rate but increases the overall scan time. Faster acquisitions, like simultaneous multi slice methods, might reduce the effect of motion and allow for repeating scans within the same total acquisition time, leading to a higher success rate than the 60% attained in this study. There are technical challenges in the application of these techniques in fetal diffusion-weighted MRI which will be explored in future work.

Currently, imaging biomarkers are needed to gauge level of concern regarding pulmonary maladaptation that may lead to the clinical consequences of pulmonary hypoplasia and pulmonary hypertension that might be associated with inadequate gas exchange, perfusion or predisposition to airleak. Such markers may be independent of lung immaturity (18). For example, a baby with chronic oligohydramnios and small lung volumes, at term might have adequate surfactant levels, but because of alveolar and vascular maldevelopment be unable to adequately ventilate/oxygenate (19). Whether markers from diffusion-weighted MRI of the lungs can be used to help predict such cases in the clinical setting will be investigated in future work.

This study had some limitations. The motion assessments and ROI placements were done by a single observer; therefore inter-observer variability was not assessed. Our results show that a two b-value acquisition is not producing similar results as the multi b-value acquisition,

however, it should be noted that a two b-value acquisition is faster and would be less susceptible to fetal/maternal motion if acquired as a separate scan. Another limitation of the study was the non-uniform frequency distribution of gestational age of the sampled population at the time of the scans. Due to the scan time frames of the fetuses and challenges in the recruitment and scheduling for volunteers, it was not easy to obtain a perfect distribution of gestational age among subjects.

This work presents the first *in vivo* measurements of diffusion in the fetal lungs with a 3T scanner. We found a strong association between ADC and gestational age in fetuses with normal lung development. Our results show that when motion is considered and controlled as a confounder and multiple b-values are acquired and used in a maximum likelihood analysis, diffusion-weighted MRI can offer a promising technique to help evaluate the structural development of fetal lungs, and can potentially lead to a biomarker for predicting the functionality of the fetal lungs in congenital lung abnormalities such as congenital diaphragmatic hernia (CDH) or congenital pulmonary airway malformation (CPAM), or in the setting of early and prolonged oligohydramnios. Measurement of ADC in cases with these lung abnormalities will be investigated in future work.

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Figure 1.
Sample images from the cohort. B=0 images are on the left and B=200 images are on the right. Top row (a) shows images labelled as “no visible motion artifacts”, middle row (b) shows an example of “minor motion” and bottom row (c) shows a case with severe motion.

Figure 2. Sample ADC map on a subject with no motion artifacts (left). ROI was drawn on the right lung. B=0 (middle) and B=600 (right) images are also shown as reference.

Figure 3.

ADC plotted against gestational age for all subjects. Dots (•) show the cases where no motion artifacts were observed. Pluses (+) show the cases with minor motion artifacts in the diffusion direction and crosses (x) show cases with severe motion artifacts. The fitted curve shows an exponential saturation curve fitted to the “no motion” data. ADC increases until 24 weeks of gestational age and then starts to saturate after 26 weeks. Dotted red lines show the 95% confidence intervals.

Figure 4.

Sample decay curves with different amounts of motion. When the fetus stays relatively still, decay curves tend to show an exponential decay, whereas with severe motion ADC values calculated from an exponential do not represent real decay values.

Summary of the cohort analyzed in this study. Of 71 fetuses, 39 were scanned without any artifacts. The motion grades were also evaluated in 2 gestational age (GA) groups. The percentage of no motion studies was much lower for younger fetuses. (6 out of 16).

Table 1

	No motion	Minor Motion	Severe motion	Other artifacts	Total
GA<22W	6	4	5	1	16
GA>22W	33	12	5	5	55
All GA	39	16	10	6	71