Phase-Resolved Functional Lung (PREFUL) MRI of Ventilation and Perfusion in Premature Infants

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Introduction

Challenges of lung MRI

Imaging the lung via MRI has proven challenging in the past due to several caveats. The bulk magnetization signal obtained in MRI is related to: $M_0 \sim PD\ \gamma^2\ B_0/T$ where PD represents the proton density of ^1H in the voxel, γ the gyromagnetic ratio, and B_0 the strength of the main magnetic field. Assuming that most soft tissues of interest (brain, muscle, etc.) have a density of 1.05 g/cm^3–1.1 g/cm^3, the average proton density of lung parenchyma is < 0.2 g/cm^3 during inspiration. This is a factor of 5 times lower, which directly reduces the signal-to-noise ratio of the lungs compared to other soft tissues, keeping all other factors the same [1]. The respiratory motion of the lungs requires rapid acquisition schemes, which were not always clinically available. During inspiration, the air we breathe contains only ~ 0.000055% ^1H, which eliminates any MRI signal in the alveoli and causes a reduction in signal intensity. Magnetic susceptibility also plays a role in image quality, as the bulk susceptibility difference between air in the lungs and parenchymal tissue is $\Delta X_0 \sim 8$ ppm. In this regard, imaging the lung at 1.5T reduces the artifact between the air–tissue interface that would occur at 3T. This, combined with the extremely short T2* of lung parenchyma (1.41 ms ± 0.41 ms at 1.5T), requires imaging with the lowest echo time (TE) possible (ideally < 1.0 ms) in order to achieve the maximum MRI signal before decay [2]. All of these factors must be taken into account when designing a lung imaging protocol for MRI.

Imaging of the neonatal lung

Clinical scanners now offer options which address some of the issues mentioned above, using advanced MRI pulse sequences and techniques to achieve excellent structural lung imaging in children[1] and adults in the clinic. However, additional challenges come with imaging neonates[1] either in the neonatal intensive care unit (NICU) or in a standard imaging suite. At our institution, we have imaged both premature and term infants in both the hospital imaging environment and on the 1.5T MAGNETOM Amira MRI scanner which is uniquely sited within our NICU [3, 4]. In this article, we will describe our clinical experience with neonatal lung imaging and the associated challenges, such as small patient size, patient motion, lack of breath hold, and reduction of auditory noise to protect the infant.

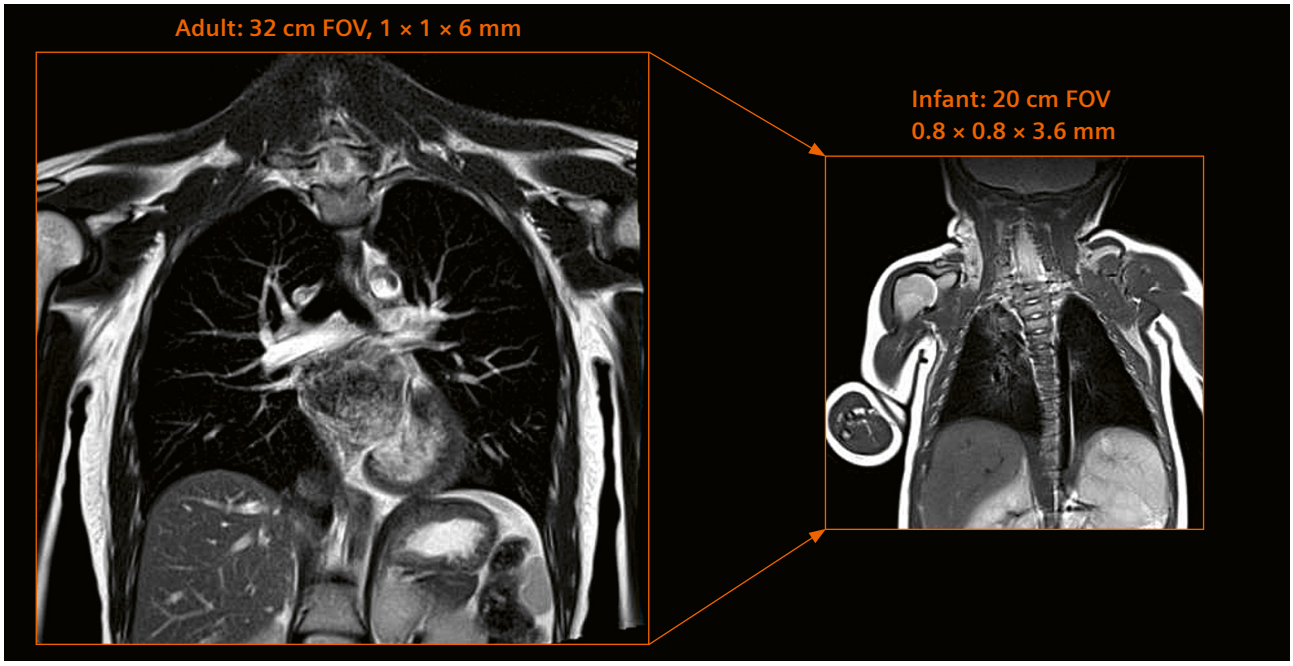
Patient size / neonatal-specific MRI receive coils

The size difference between adult and infant lungs (Fig. 1) requires a set of MRI coils that are optimized to receive signal from such a small volume. Several options are available, including the NORAS 16-channel VARIETY flex coil (NORAS MRI products, Höchberg, Germany), which provides a single 8-channel coil anterior and one 8 channel coil posterior on the infant. This coil provides optimal signal-to-noise in the infant lungs and includes a cylindrical foam insert to allow the infant to lie comfortably during the scan.

Patient motion

Since these infants are scanned without sedation using a feed-and-swaddle technique, patient motion in neonatal lung imaging periodically becomes an issue. However,

[1]*Siemens Healthineers disclaimer: MR scanning has not been established as safe for imaging fetuses and infants less than two years of age. The responsible physician must evaluate the benefits of the MR examination compared to those of other imaging procedures. This disclaimer does not represent the opinion of the authors.*



1 The raw size difference between the lungs of a healthy adult and those of a premature infant at term are shown with the same coronal T2 BLADE pulse sequence on the 1.5T MAGNETOM Amira MRI scanner.

during the phase-resolved functional lung (PREFUL) imaging sequence, which acquires 6.4 frames/s, one can immediately see whether the motion is severe enough to stop the scan. This is possible by enabling the in-line real-time display on the MRI scanner. Periodically, the infant will awaken and move significantly in-plane or even roll out of the single coronal plane of imaging. The scan can be immediately stopped, as they are only ~ 1 minute in length, and repeated later in the study once the infant has returned to a more relaxed state as shown by the patient monitoring unit. Moreover, in post-processing, images prone to through-plane motion may be retrospectively removed from the stack prior to analysis.

Noise reduction techniques for neonatal imaging

Limiting auditory noise to protect the infants' hearing is of prime importance. At our institution, we use multiple levels of hearing protection to reduce the scanner noise for neonates as much as possible. The first step is to insert half of a standard foam earplug into each ear. Another option is to use Mack's soft moldable silicone earplugs (McKeon Products, Inc., Warren, MI, USA), which can also be cut in half and fit to the infant ear. Earplugs in general can reduce the noise in the MRI by between 20 and 30 decibels (dB) and are always the first line of defense (Fig. 2A). The second layer of ear protection for the infants are the MiniMuff neonatal noise guards (Natus Medical, San Carlos, CA, USA) (Fig. 2B). These MRI-safe disposable

2 **(2A)** Mack's silicone putty earplugs, **(2B)** MRI MiniMuffs disposable neonatal noise guards, **(2C)** Ima·X noise-canceling MRI headphones.

noise guards have a gentle hydrogel adhesive to provide a secure fit and reduce sound levels by an additional 7 dB. The last layer of ear protection focuses on headphones that will not slip off the infant. We purchased the world's first noise canceling infant MRI headphones (Fig. 2C) (Ima·X, Luxembourg), which reduce the noise by an average of 22 dB and up to 30 dB @ 1kHz. Prior to purchasing these headphones, our in-house technique was to remove the center bar between an MRI-compatible set of adult headphones and to secure each side with Coban adhesive wrap (3M, Maplewood, MN, USA) to prevent sliding. Note that the earplugs, MiniMuffs, and headphones can be placed while the infant is feeding in the mother's room, before they are brought to the MRI scanner. This means that once the infant falls asleep after feeding, they do not have to be disturbed again to apply the ear protection.

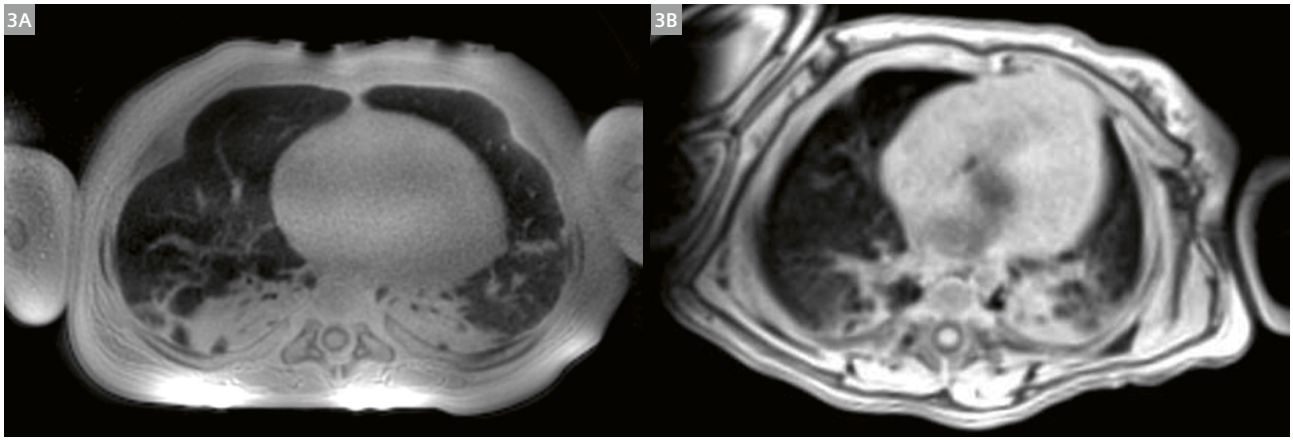
Structural imaging of the neonatal lung

Imaging of the neonatal lung can be divided into two main categories: 1) anatomical or structural imaging, and 2) functional imaging. Typical standard-of-care structural imaging of the neonatal lung relies on chest X-rays (CXR), which are routinely ordered in neonates and were first reported in the literature in 1967 [5]. One main advantage of CXR in the NICU and hospital setting is accessibility. The radiographs can be performed using a portable X-ray unit which can be brought directly into the mother's room. Current diagnostic studies typically limit the dose to between 24 µG and 32 µG, and are associated with a very low risk of induced malignancy [6, 7]. However, CXRs provide only single-plane 2D images and have decreased sensitivity in detecting milder disorders of the lung. Many neonates in our NICU are also required to have multiple CXR exposures during their stay. Although this is generally considered safe, it does add to the cumulative radiation dose received in this vulnerable population early in life.

The modality without ionizing radiation that shows the most promise for structural imaging of the neonatal lung is MRI. The incorporation of 3D ultra-short echo-time (UTE) or even zero echo-time (ZTE) imaging has provided "CT-like" imaging of the lung using product MRI sequences available on Siemens Healthineers scanners [8]. These sequences compensate for the fast T2* decay time of lung parenchyma by acquiring echo times in the tens of µs. Specifically, Siemens Healthineers provide several pulse sequences for use in clinical lung imaging. These include a 3D stack-of-spirals VIBE UTE along with the pointwise encoding time reduction with radial acquisition (PETRA) [9]. Our group has incorporated the 3D PETRA sequence in the NICU for structural lung imaging (Fig. 3A). One advantage of the PETRA sequence in the neonate population is that it is completely silent and tends not to disturb the infant during scanning. We also acquire the free-breathing stack-of-stars radial VIBE (StarVIBE) product sequence in both axial and coronal planes to study the airway, lung parenchyma, and lung volume (Fig. 3B).

Functional imaging of the neonatal lung

While structural MRI of the lungs has gained ground in clinical use, assessment of lung function, especially in this vulnerable population, is lacking. The feasibility of acquiring quantitative ventilation and perfusion data in the newborn period without sedation or contrast administration is novel. This information is especially important in the NICU as the most common complication of preterm birth is bronchopulmonary dysplasia (BPD), also known as chronic lung disease of prematurity (CLDP). Premature infants represent approximately 10% of all births in



3 **(3A)** PETRA MR image from an infant born at 24 weeks 4/7 days with grade 3 BPD demonstrating bilateral bibasilar atelectasis. Acquired resolution was 0.78 mm isotropic showing an image reconstructed to 0.78 × 0.78 1.56 mm. **(3B)** A StarVIBE sequence from another infant with grade 2 BPD at 0.9 × 0.9 × 2.0 mm resolution.

developed countries and are associated with a mortality rate of up to 10% for very premature infants born at fewer than 29 weeks' gestation [13]. BPD is the major respiratory complication of premature birth, affecting 10,000 to 15,000 infants in the U.S. annually, and up to 50% of infants born < 1kg [10, 11]. This disease was first described more than 50 years ago, and was initially characterized by inflammation and fibrosis secondary to administration of oxygen and mechanical ventilation in moderately premature infants (~ 34 weeks' gestation) [5, 12].

Current means of non-invasively detecting BPD in premature infants in the NICU rely on the surrogate measure of whether respiratory ventilator support is required for more than three consecutive days (either invasive or non-invasive ventilation to maintain arterial oxygen saturation above 90%) [13]. Techniques such as lung spirometry and pulmonary function testing, which can be done in children and adults, cannot be performed in infants without the risk of sedation and intubation. Also, this technique is not available in most neonatal units, and lacks sensitivity to detect early lung disease [14, 15]. Currently, there is no other means of acquiring this information in this population; our group's work using phase-resolved functional lung (PREFUL) MRI technique[2] in premature infants meets this need.

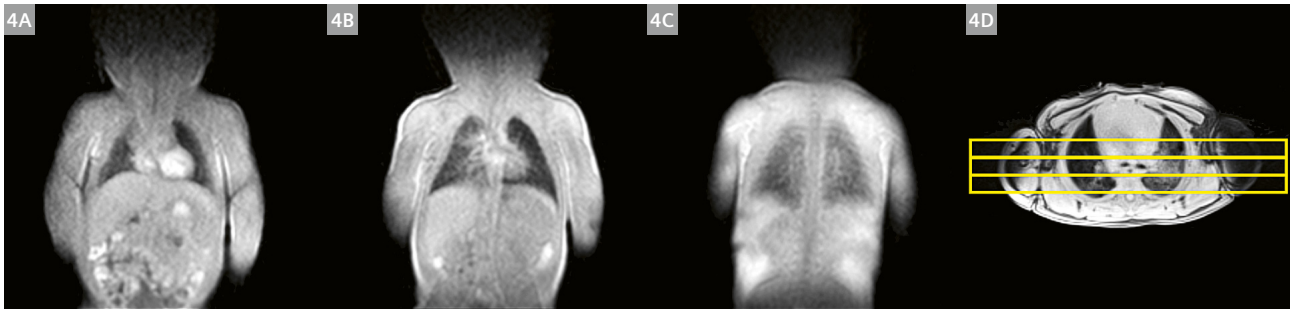
In addition, there are no means in the clinic to identify the BPD phenotypes of airway, lung parenchyma, and perfusion in each infant. Clinical care only assesses the degree of respiratory support or oxygen that each infant needs and for what time period, without knowledge of the underlying cause of the disease. However, specific treatment would differ knowing that the large airways/tracheal area was decreased in comparison with an infant having pulmonary hypertension and perfusion abnormalities. Our group is the first to use the PREFUL MRI technique in premature infants to quantify perfusion defect % (QDP), ventilation defect % (VDP), V/Q defect, non-defect match %, and quantitative pulmonary perfusion values [mL/min/100mL]. Another group has also used PREFUL MRI in normal-term infants and toddlers with and without sedation in a pilot study [16].

PREFUL MR lung imaging technique

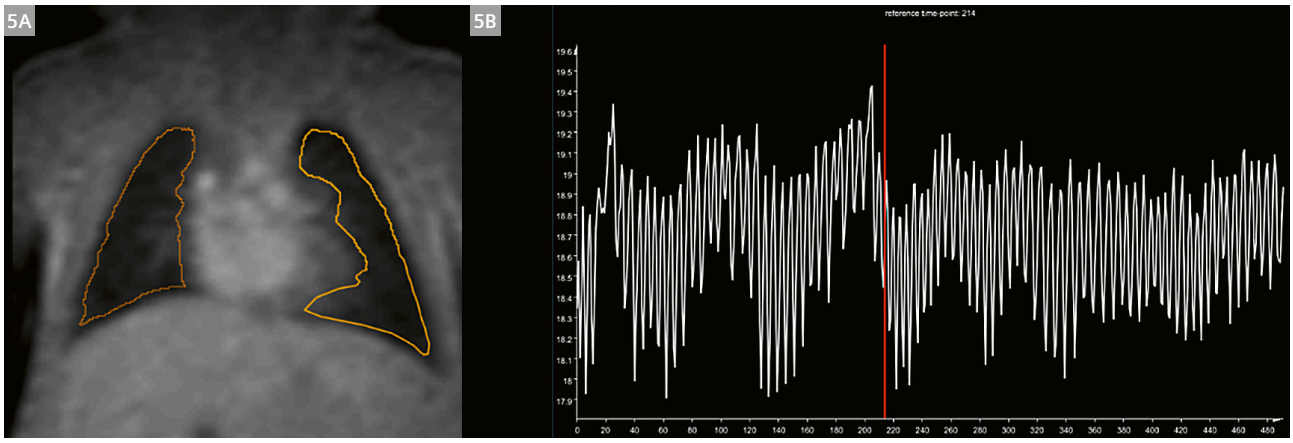
Phase-resolved functional lung (PREFUL) imaging is a method to evaluate dynamic MR data acquired in free breathing without any need for contrast agent administration [17]. Three coronal slices are placed at the level of the tracheal bifurcation, one slice anterior, and one posterior to this slice using a 2D spoiled gradient echo (TFL) sequence with a 1.57 ms TR, 0.99 ms TE, 5° FA, 10 mm slice thickness, 30 cm FOV and a 128 × 102 matrix reconstructed to 256 × 256 resulting in an in-plane resolution of 1.2 × 1.2 mm^2. A total of 512 images were acquired continuously (80 s) with a temporal resolution of 6.4 frames/s during free breathing. No respiratory or cardiac gating was done (Fig. 4).

A custom MATLAB based implementation of PREFUL (courtesy of Hannover Medical School) was utilized, first transforming the acquired image time series to a fixed lung volume with a group-oriented registration approach [18]. This enables the analysis of the signal time course in each voxel, which is mainly influenced by two variables: First, by proton density, which will change during inspiration and expiration. Second, by the time-of-flight effect, which describes the inflow of spins with a higher magnetization into the imaging plane. While the first effect is directly connected to ventilation, the second is related to perfusion. Since both signal changes occur at different frequencies (cardiac frequency vs. respiration frequency), they can be separated with an adequate filtering approach (Fig. 5). A low-pass filter is applied to evaluate the ventilation, and a high-pass filter is used for perfusion. Further, an image-guided, edge-preserving filter can be applied to increase the signal-to-noise ratio while preserving fine structural details [19]. Note that similar functionality is available in Siemens Healthineers' MR Lung research

[2]The research application is currently under development and is not for sale in the U.S. and in other countries. Its future availability cannot be ensured.



4 The three coronal slices are centered at the level of the tracheal bifurcation in the infant. Note that optimal signal intensity should be visibly centered on the lungs from the anterior and posterior flex coils on the infant. This should be confirmed in the localizer image at the beginning of the exam.



5 **(5A)** A single-slice PREFUL image of a neonate showing automated artificial intelligence (AI) segmentation of the lungs. Manual editing of the contours was performed to include minor regions at the periphery of the lung (MRLung 2.0, Siemens Healthineers, Erlangen, Germany). **(5B)** Inspiration and expiration cycles of the free-breathing acquisition are shown on the right with a temporal resolution of 200 ms/frame.

application.The Hannover group, which invented the processing algorithm, is also available for consultation at the company BioVisioneers GmbH in Germany (biovisioneers.com; info@biovisioneers.com).

In the next step, the respiratory and cardiac phase are estimated for each image with a sine-model. The sorting of the images allows one to interpolate a complete cardiac and respiratory cycle. This 3D ventilation (V) and perfusion (Q) information (2 spatial dimensions + 1 temporal dimension) can be further processed to calculate a series of V/Q parameters, including regional ventilation, quantified perfusion, and flow-volume correlation metric [20–22]. By applying thresholds, binary parameters can be derived and combined to V/Q maps, which can provide the percentage of lung volume affected by ventilation and perfusion defects, and the respective match and mismatch ratios. The thresholds for V/Q maps were determined by correlating with independent validation methods such as hyperpolarized ^{129}Xe MRI, dynamic contrast-enhanced (DCE) MRI, and SPECT.

Validation has been performed for the PREFUL MRI sequence by the Hannover group. The repeatability of the parameters was recently demonstrated in healthy subjects and in chronic obstructive pulmonary disease (COPD) patients [23]. Furthermore, comparisons with gold-standard and more established techniques were carried out. Specifically, PREFUL was validated with fluorinated and hyperpolarized xenon MRI (direct ventilation measurement), DCE MRI (perfusion measurement with contrast agent application), and standard single-photon emission computed tomography (SPECT) [24–28]. Recently, dynamic PREFUL parameters showed treatment response in COPD in the CLAIM trial: indacaterol/glycopyrronium (IND/GLY) improved the regional ventilation dynamics, perfusion, and V/Q match [29, 30]. Additionally, the dynamic parameter was able to predict survival using only a baseline scan [31].

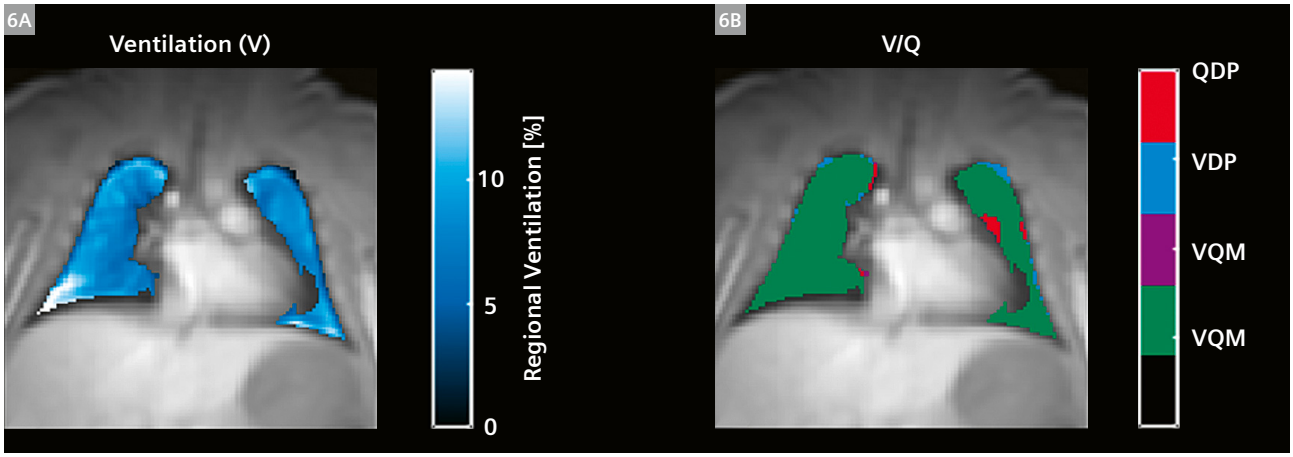
PREFUL MRI results

The following parameters were calculated: perfusion defect % (QDP), ventilation defect % (VDP), V/Q defect and non-defect match %, and pulmonary perfusion [mL/min/100mL] [22, 28]. Defects < 30% are considered normal or mild (grade 1) for both ventilation and perfusion. Defects between 30% and 60% are categorized as moderate grade 2 BPD, and defects > 60% as severe grade 3 BPD. Figure 6 shows ventilation and perfusion maps from a normal infant. Figure 7 displays V/Q defects in an infant with grade 2 BPD, showing the mismatch between ventilation and perfusion.

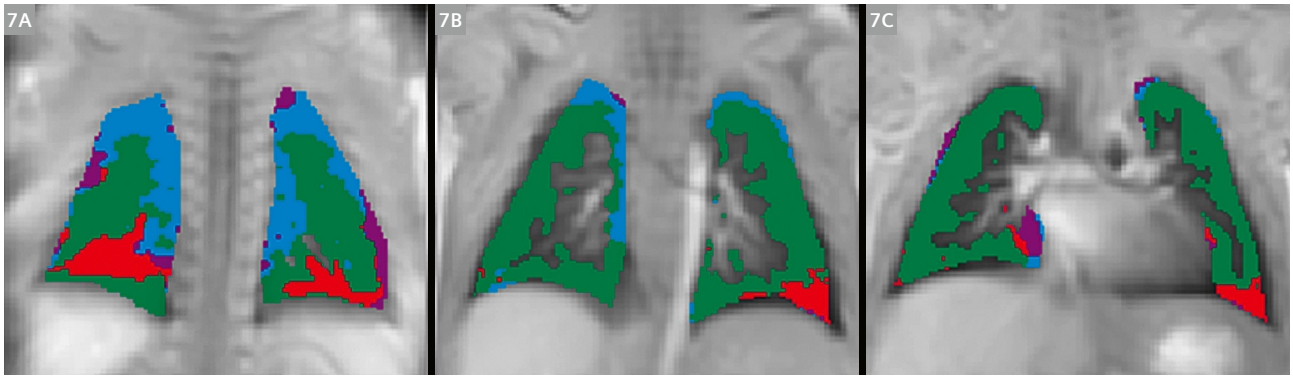
The PREFUL MRI is used to evaluate lung ventilation and perfusion defects and to obtain quantitative estimates of pulmonary perfusion in units of mL/min/100mL. Of clinical interest is the ability to define a perfusion defect % and compare with the ventilation defect %. This allows independent assessment of these two components of BPD phenotypes in the same patient with the same scan.

Conclusion

PREFUL MRI is a non-invasive technique performed under free breathing without the need for sedation or exogenous contrast agents. It has the potential to identify localized defects in ventilation and perfusion in premature infants. There are currently no means to non-invasively quantify respiratory function in premature infants. PREFUL can be implemented with default MRI pulse sequences. Therefore, once a post-processing pipeline is implemented, the method can be applied in a multi-center or cooperative setting as an outsourced analysis pipeline without high technological prerequisites, and can be applied to studies in premature infants with BPD. Non-invasive functional lung imaging in infants can be done safely and routinely with the proper setup and staff.



6 **(6A)** Ventilation and **(6B)** ventilation/perfusion(V/Q) defect maps are shown in a normal infant at term. Notice the homogeneity in the **(6A)** ventilation map shown in blue. **(6B)** V/Q defect map shows minimal ventilation defect percentage in blue and minimal perfusion defect percentage in red. Green = VQM non-defect; purple = VQM defect; VQM = ventilation/perfusion match



7 Functional lung. A perfusion map acquired using PREFUL MRI is displayed from an infant with grade 2 BPD. A 19% total ventilation defect percentage (VDP%) and a 13.3% total perfusion defect percentage (QDP%) is shown averaged across the three slices. Red = QDP% exclusive; blue = VDP% exclusive; green = VQM non-defect, purple = VQM defect; VQM = ventilation/perfusion match

Acknowledgments

The authors would like to acknowledge the assistance of the pediatric and NICU nursing staff at NYP, who played an invaluable role in the success of this study. Funding for this work is provided under NHLBI R01HL167003-01A1. Research reported in this publication was supported by the National Heart, Lung and Blood Institute of the National Institutes of Health under award R01HL167003.

Statements and declarations

None of the authors have a competing financial interest in this study. Robert Grimm is employed by Siemens Healthineers, which manufactures the MRI scanner and provides the research analysis software. Filip Klimeš, Andreas Voskrebenzev, and Jens Vogel-Claussen are shareholders of BioVisioneers GmbH, a company which has interest in pulmonary MRI methods.

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