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Retrospective respiratory self-gating and removal of bulk motion in pulmonary UTE MRI of neonates and adults

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Abstract

PURPOSE—To implement pulmonary 3D radial ultrashort echo-time (UTE) MRI in non-sedated, free-breathing neonates and adults with retrospective motion-tracking of respiratory and intermittent bulk motion, to obtain diagnostic-quality, respiratory-gated images.

METHODS—Pulmonary 3D radial UTE MRI was performed at 1.5T during free-breathing in neonates and adult volunteers for validation. Motion-tracking waveforms were obtained from the time-course of each free induction decay's initial point (i.e. k-space center), allowing for respiratory-gated image reconstructions that excluded data acquired during bulk motion. Tidal volumes were calculated from end-expiration and end-inspiration images. Respiratory rates were calculated from the Fourier transform of the motion-tracking waveform during quiet-breathing, with comparison to physiologic prediction in neonates and validation with spirometry in adults.

RESULTS—High-quality respiratory-gated anatomic images were obtained at inspiration and expiration, with less respiratory blurring at the expense of signal-to-noise for narrower gating windows. Inspiration-expiration volume differences agreed with physiologic predictions (neonates; Bland-Altman bias = 6.2 mL) and spirometric values (adults; bias = 0.11 L). MRI-measured respiratory rates compared well with observed rates (biases = -0.5 and 0.2 breaths/min for neonates and adults, respectively).

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CONCLUSIONS—3D radial pulmonary UTE MRI allows for retrospective respiratory self-gating and removal of intermittent bulk motion in free-breathing, non-sedated neonates and adults.

Keywords

neonatal; self-gating; retrospective motion-tracking; lung MRI; ultrashort echo time; 3D radial

INTRODUCTION

Magnetic resonance imaging (MRI) is promising as a technique for longitudinal evaluation of pulmonary diseases and function. However, structural lung MRI is challenging and currently plays a limited role in clinical diagnosis of respiratory pathologies, with a major challenge arising from the low proton density of the lung parenchyma (~20% of muscle density) (1). In addition, magnetic susceptibility gradients at air-tissue interfaces within the lung parenchyma result in a short T_2 (~0.5–3 ms at typical field strengths (1–5)), which requires rapid data sampling after spin excitation and maximizing k-space coverage while minimizing acquisition time. The long pulmonary T_1 (6,7) requires small flip angles (FAs) or long imaging times, and image quality is further degraded by respiratory and cardiac motion. As a result of these challenges, advancements in pulmonary MRI have historically been difficult. However, there is increasing recognition that x-ray computed tomography (CT), the current gold standard for clinical lung imaging, can expose patients to sufficiently high doses of ionizing radiation to increase cancer risk, particularly for longitudinal studies and in pediatric populations (8,9,10); with a mean lung dose of ~10 mGy per chest CT for patients under 5 years old, one radiation-induced solid cancer is projected to result from every ~360 and every ~1200 chest CT scans for girls and boys, respectively, in this age group (9). Moreover, effective evaluation of pulmonary disease using MRI has benefited from the recent, widespread development of ultrashort echo time (UTE) techniques that use a variety of radial k-space sampling schemes. These techniques (11–15) not only provide increased signal-to-noise (SNR) in the lung parenchymal tissue by minimizing the echo time (TE), but also are more robust against respiratory and cardiac motion as compared to Cartesian acquisition schemes (16). These developments open the door to new possibilities for quantitative structural evaluation of lung disease using MRI (6,14,17,18).

MRI is particularly appropriate for assessment of pulmonary development and pathology in pediatric and neonatal populations, especially for longitudinal studies, in which cumulative x-ray exposure during repeated CT exams becomes non-trivial. While pulmonary morbidities are present in over 60% of our Neonatal Intensive Care Unit (NICU) patients at Cincinnati Children's Hospital Medical Center (CCHMC), these morbidities (commonly bronchopulmonary dysplasia, BPD, and congenital diaphragmatic hernia, CDH) and their time-course are poorly defined and understood. The current standard of care for these infants includes chest x-rays for longitudinal monitoring and management guidance during acute changes. In more severe cases, CT scans are used to further define underlying pathology. There are few strong prognostic indicators of later outcomes, particularly for BPD infants, with inadequate clinical ability to reliably predict which infants will require long-term ventilation, which will be discharged with oxygen requirement, and which will be discharged with no further respiratory support. As clinical care and survival rates of

extremely premature infants continue to improve, we will likely see an even greater need for understanding the development of BPD in particular. The potential for MRI to predict later respiratory prognosis is promising; we believe that this presents an opportunity for longitudinal imaging to begin to define the time-course of neonatal pulmonary disease. Indeed, preliminary quantification of lung disease arising from premature birth has been recently demonstrated in the neonate using conventional Cartesian sequences, despite respiratory and bulk motion artifacts (19); this work can be further refined via UTE MRI. However, neonatal pulmonary MRI faces unique challenges of its own. In particular, the small size of neonatal lungs (on the order of 100 mL, about 2% of the volume of the adult lung) requires higher spatial resolutions and gradient strengths to resolve the smaller anatomical structures.

In general, MRI is susceptible to artifacts from both gross bulk and physiologic (i.e. respiratory and cardiac) motion, with pulmonary MRI in particular suffering from respiratory motion artifacts. When scanning with conventional sequences that last only a few seconds, most adults and some cooperative children are able to remain still and also perform a sustained breath-hold, which mostly mitigates both bulk and respiratory motion artifacts. On the contrary, neonates are unable to perform breath-holds and will not predictably remain motionless for a scan of any duration. Neonatal cardiac imaging has seen some success using “the feed-and-swaddle” method without sedation or anesthesia (20). However, these scans typically last only a few minutes, whereas the duration of typical UTE scans exceeds 10 min, during which unpredictable intervals of bulk motion can also occur. The technique of retrospective motion-tracking and respiratory gating, as described in this work, will obviate the currently common practice of administering sedation and/or anesthesia during neonatal imaging. While the benefits of this motion-tracking are clear for infant imaging, we also envision benefit for any non-compliant adult patient population and for adult UTE imaging more generally, where application of this technique for a typical ~10–15 min scan of quiet breathing will reduce the rate and severity of motion artifacts in any population.

Historically there has been little success with neonatal external respiratory detection equipment (i.e. respiratory bellows) or with cardiac-like respiratory navigator windows, due to the neonate’s rapid respiratory rate (~1 Hz) and small displacement of the diaphragm and chest wall during free-breathing (approximately a few mm) (21). For these rapid and small respiratory excursions, image-navigator and respiratory bellows methods generally lack time-efficiency and/or sensitivity (22). Several gating techniques have recently been developed to minimize respiratory and/or cardiac motion during MR imaging, with varying drawbacks. Some studies have attempted to use the inherent tracking property of the k-space center via 2D or 3D radial acquisition schemes (23–28). Others have sampled the k-space center separately from the data required for imaging via navigator echoes (29), which increases overall scan time, or use Cartesian acquisition schemes (30), which are susceptible to bulk-motion artifacts. Prospective gating allows for reconstruction of cine images (31,32), but acquires data only at a specific phase of the respiratory cycle and prevents a true steady state from being established.

Separate from the reduction of motion artifacts, effective respiratory gating for lung imaging has the potential to provide several important quantitative functional measurements. While

adult pulmonary function tests (PFTs) routinely identify volumes at various stages of inflation, infant PFTs (iPFTs) are technically challenging, pose significant risks, and require sedation or anesthesia. Thus, iPFTs are typically only performed at large research institutions and are rarely if ever performed within the NICU. Lung segmentation from end-phase (i.e. end-expiration and end-inspiration) respiratory-gated images can provide functional measurements of tidal volumes in neonates and adults and has the potential to assess regional ventilation (33,34).

In this work, we use 3D pulmonary radial UTE MRI (13,35) to produce diagnostic-quality respiratory-gated images in free-breathing neonates without requiring sedation. A retrospective motion-tracking technique allows for rejection of motion-corrupt data and then respiratory-gating of remaining data, with subsequent reconstruction of gated images. This method yields quantitative pulmonary function assessments of tidal volume and respiratory rates during scanning. Technique validation was performed with six healthy adult subjects, and physiologic comparisons of predicted tidal volumes were performed for neonatal subjects. These results demonstrate strong potential for retrospective respiratory-gating and removal of bulk motion in any population, but particularly in neonatal and young pediatric patients, for whom there is a great need for reliable, non-ionizing lung imaging and pulmonary disease quantification.

METHODS

Study Subjects

For the method validation component of this study, six healthy adult volunteer subjects (23–32 years old) were enrolled with Institutional Review Board (IRB) approval and written consent (Table 1). MRI was performed in 16 neonatal patients recruited from the NICU at CCHMC with IRB approval and written parental consent. This neonatal population consisted of 6 control patients (defined as NICU patients with putatively normal pulmonary function), 5 BPD patients, and 5 CDH patients (Table 1). These diseased populations were chosen because they represent the most common pulmonary morbidities seen in our NICU, with clear potential to benefit from further definition of disease via MRI. Neonates were fed, swaddled, and equipped with standard ear protection before placement on the MRI bed. Patients were imaged during quiet-breathing (i.e. room air) with the exception of Subjects BPD 4, CDH 1, and CDH 2, who were mechanically ventilated (via methods that allow spontaneous breathing). No intravenous contrast agent or sedation was administered as part of this protocol. In five cases (Subjects Control 1, BPD 4, CDH 1, CDH 3, and CDH 4), the research MRI scan was performed directly following a clinically-indicated MRI scan that included administration of sedation (Midazolam, 1–2 doses of 0.05–0.5 mg/kg). In one case (Subject CDH 2), the patient was on a clinically-indicated continuous sedation drip throughout the research scan (Midazolam, 0.2 mg/kg/h). The patients' heart rates and SpO₂ levels were monitored by clinical staff throughout each exam.

Spirometry

Two standard adult PFTs were performed to measure tidal volumes for all adult validation subjects using a KoKo portable spirometer (nSpire, Longmont, CO). In both tests, adult

subjects were free-breathing and supine, to match their position during imaging. The first test was performed immediately following imaging, with the subjects recumbent on the MR table (after removal from the magnet room). It was originally thought that this immediate measurement would most closely replicate the breathing conditions during imaging. However, this method potentially affected tidal breathing by rapidly moving subjects from the MR scanner to a crowded control room. Thus, a second test was performed several weeks after imaging to more closely replicate the restful breathing conditions during imaging, with the subjects recumbent on a patient bed and resting quietly for ~5 min prior to measurement. Three spirometry measurements of tidal volume were acquired and averaged per test, and one measurement of respiratory rate was acquired (estimated from number of breaths observed over approximately 60 s; Subject Adult 3 was observed for 120 s due to this subject's low respiratory rate).

Respiratory rates of all neonatal patients were recorded by clinical staff four times at bedside (2 measurements at 0–3 hr pre-MRI, 2 measurements at 0–4 hr post-MRI; ~60 s of measurement). Ventilator settings for respiratory rates were recorded for the three ventilated neonates (Table 1). Clinical measures of neonatal tidal volumes were unavailable, since iPFTs were not performed as part of this study nor as part of the NICU patients' clinical care.

MR Imaging Systems

All adult validation imaging experiments were performed on a conventional adult-sized GE Signa HDx 1.5T MRI system using a standard 8-channel cardiac coil. All neonatal imaging experiments were performed on a unique, small-footprint, neonatal 1.5T MRI system (originally an orthopedic scanner from ONI Medical Systems, Wilmington, MA; currently GE Healthcare, Waukesha, WI) sited within the CCHMC NICU (36–38). The scanner has a 21.8-cm bore size, which in this work is reduced to 18 cm with the insertion of a quadrature body coil, accommodating neonates up to ~4.5 kg. Both systems operate with GE HDx software and are software-limited to a maximum gradient amplitude of 33 mT/m and slew rate of 120 mT/m/s.

Image Acquisition

A 3D radial UTE spoiled gradient echo (SPGR) acquisition sequence was developed based on a previous technique (13) and uses a 3D radial pseudo-randomized sampling scheme with variable density readout trajectories (35). This UTE acquisition allows imaging of pulmonary structural pathologies at high isotropic spatial resolution while mitigating signal loss in the lung parenchyma due to short T_2^* . The repeated sampling of the k-space center mitigates motion artifacts (especially cardiac) (12,13,30) and allows for tracking of bulk and respiratory motion, as described further in this work. UTE scan parameters differ slightly between clinical adult and NICU MRI systems due to differences in subject and coil sizes. Adult UTE parameters were: TE = 120 μ s; repetition time (TR) = 3.9 ms; FA = 5°; field of view (FOV) = 40 cm; number of radial projections = ~200,000; 3D isotropic resolution = 0.78 mm; and scan time = ~13 min. Typical neonatal UTE parameters were: TE = 200 μ s; TR = 4.4–5.2 ms; FA = 5 or 10°; FOV = 18 cm; number of radial projections = ~108,000–200,000 (during early scan parameter optimization, a few patient scans acquired ~36,000–

76,000 projections); 3D isotropic resolution = 0.70–0.86 mm; and scan time = ~9–16 min. The number of acquired projections was sometimes reduced due to scan time limitations; scans with a slightly reduced number of projections demonstrated slightly lower SNR in parenchymal tissue. As well, TR values varied during optimization of read-out pulse shapes, and resolution varied slightly due to optimization of matrix size. Diagnostic image quality was maintained over all variation of scanning parameters.

As a reference for comparison to the UTE images, 3D fast gradient-recalled echo (FGRE) images were acquired in the axial plane on all adult and neonatal subjects. Adult FGRE parameters were: TE = 1.5 ms; TR = 4.2 ms; FA = 4°; FOV = 40 cm; matrix = 512 x 512; in-plane resolution = 0.78 x 0.78 mm²; slice thickness = 3.5 mm; number of partitions = 80; number of averages = 4; and scan time = ~7 min. Typical neonatal FGRE parameters were: TE = 1.9 ms; TR = 7.7 ms; FA = 4°; FOV = 18–20 cm; matrix = 256; in-plane resolution = 0.70 x 0.70 - 0.78 x 0.78 mm²; slice thickness = 3 mm; number of partitions = 25–32; number of averages = 5; and scan time = ~5 min. Neonatal FGRE parameters were varied slightly as needed for full chest coverage of each patient.

One adult (Subject Adult 2) was instructed to perform a specified sequence of quiescence and bulk motion during a second set of UTE and FGRE scans (~100 s of quiescence at Position 1, ~100 s of quiescence at Position 2, and bulk motion for the remainder of the scan) to mimic typical neonatal activity (i.e. bulk shift of chest and moving limbs). Due to scanner scheduling restrictions, the motion-corrupt UTE scan acquired half as many projections (~100,000) as the quiescent scan, and the motion-corrupt FGRE acquired half as many averages (two).

Image Reconstruction

For each subject's scan, a respiratory waveform was generated from the time-course of either the phase or magnitude of the initial point of each projection's free induction decay (FID). This initial point represents the k-space center, the phase and magnitude of which are modulated by respiratory motion (39). The choice between using phase or magnitude was based on which waveform had higher peak-to-peak respiratory signal to noise ratio during quiescence. The raw waveform was processed in MATLAB (Mathworks, Natick, MA) via smoothing using an 800-ms Savitzky-Golay sliding-window average filter (2nd degree polynomial), which is a very commonly-used digital smoothing filter in signal processing (40). Filter width was chosen to be slightly shorter than the typical neonatal respiratory period (~1 s) to suppress higher frequency components unrelated to respiration (e.g. cardiac, ~0.4 s period) while avoiding the need for higher-order models of respiratory modulations within the window.

Periods of intermittent bulk motion were identified in MATLAB using estimated breath-wise respiratory periods determined from automatically-identified local minima and maxima, which are heavily corrupted by bulk motion. Projections acquired in regions with estimated respiratory periods greater than 4 times the interquartile range above the median were excluded from image reconstruction.

All remaining projections acquired during quiescent periods were binned to specified acceptance windows (i.e. a percentage of time spent near end-expiration and end-inspiration) by applying a custom 16-s adaptive sliding-window algorithm to the smoothed respiratory waveform in MATLAB. At each window position, data points within the window are binned into quantiles according to amplitude values, resulting in each point receiving multiple bin assignments within the sliding window interval. Each data point's final bin assignment is calculated from the mean of all bin assignments for that point. By examining a local 16-s interval of the modulated respiratory waveform, the algorithm accounts for any variation in respiratory rate during data binning. In this work, 25% and 50% acceptance windows were explored, yielding 4 and 2 bins associated with different respiratory phases, respectively. 50% acceptance windows were chosen initially for preliminary demonstration of image gating via this technique, and 25% acceptance windows were later used to increase the amount of gating while still maintaining sufficient image quality and SNR. Retrospectively-gated images were reconstructed for each bin, with end-expiration and end-inspiration images being of particular interest for calculation of lung tidal volume. Clinical evaluations of image quality were determined by clinical radiologists.

MRI-based Functional Assessments

Whole-lung segmentations were generated semi-automatically from end-expiration and end-inspiration images (25%-gated and 50%-gated) using Amira (FEI Visualization Sciences Group). Images from both acceptance window sizes were analyzed for adults and neonates to demonstrate the increase in measured tidal volumes when using narrower gating windows. Major vessels were consistently excluded from segmented parenchymal regions based on visual identification. MRI-determined tidal volumes were calculated from the difference between end-expiration and end-inspiration volumes. For neonatal comparison, physiologically-predicted tidal volumes were calculated from literature-based scaling values based on mass (4–6 mL/kg (41)). For adult comparison, spirometry was performed as described above.

The Fourier transform of the quiescent respiratory waveform provides a spectrum of physiologic frequency components, with the respiratory rate being of particular interest. Subjects' respiratory rates during quiescence were estimated via calculation of the approximate center-of-mass of the main low-frequency peak in order to appropriately weight the subjects' slightly varying respiratory rate during scanning.

For quantitative image assessment, lung parenchymal SNR calculated from the ratio of the signal from a region of interest (ROI) in the parenchyma without major vasculature to the standard deviation of a noise ROI. Identical ROIs were used for SNR comparisons between ungated images and images reconstructed with different gating acceptance windows.

Statistical Analysis

Bland-Altman analysis was performed for validation of MRI-measured respiratory rate measurements compared to bedside-observed respiratory rates (for adults and neonates). This analysis was also performed for 25%-gated MRI-measured tidal volumes compared to

physiologically-predicted tidal volumes (neonates) and spirometry-based tidal volumes (adults).

RESULTS

Removal of bulk motion via k-space center

Periods of quiescent breathing and of bulk motion events were evident in motion-tracking waveforms (Subject CDH 4's phase waveform shown in Figure 1A). Both the phase and magnitude of the signal are clearly modulated by the respiratory cycle during quiescent breathing (phase shown in Figure 1B) and disrupted by bulk motion events (Figure 1A). On average, the peak-to-peak respiratory signal to noise ratio during quiescence was 3.6 ± 1.6 and 2.9 ± 1.8 for phase and magnitude waveforms, respectively. The peak-to-peak phase signal varied widely for the neonatal subjects (range ~ 0.005 – 0.8 rad, mean 0.15 ± 0.21 rad) but was more consistent for the adult validation subjects (range ~ 0.03 – 0.06 rad, mean 0.04 ± 0.02 rad).

Images acquired during intentional bulk motion events (i.e. chest and arm displacements) for Subject Adult 2's second set of scans are shown in Figure 2B. The motion-tracking phase waveform clearly matches the specified pattern of quiescence and bulk motion events (plot in Figure 2B). When all of the data collected during the motion-corrupt scan were used for reconstruction (Figure 2B plot – black line), only undesirable blurring was introduced into the UTE images, whereas the corresponding FGRE images were severely degraded (Figure 2B – images). When UTE images were reconstructed excluding data acquired during the period of sustained bulk motion (Figure 2C plot – grey line) but including quiescent data from Positions 1 and 2 (Figure 2C plot – black line), images demonstrate lower parenchymal SNR but appreciably less blurring, as well as a 'doubling' effect for specific anatomical features that shifted between the two positions (Figure 2C images, green arrows; anterior lung wall and anterior chest tissue). Finally, UTE images were reconstructed with a reduced subset of raw data acquired from only Position 1 (Figure 2D plot – black line); these images (shown in Figure 2D) demonstrate further decreased parenchymal SNR but a clear increase in structural detail as compared to UTE images reconstructed with motion-corrupt data.

Retrospective respiratory self-gating via k-space center

The bin assignments for data acquired during normal tidal breathing are shown for 25% acceptance windows in Figure 1B. Note that the modulation of the smoothed waveform compares well with the expected modulation of the raw waveform at the independently measured frequency of respiration (Table 3). Example reconstructions demonstrate the utility of the self-gating technique (Subjects Adult 4 in Figure 3 and Control 6 in Figure 4) with improvement most apparent at the lung-diaphragm boundary. Ungated images (Figure 3A and 4A) were reconstructed with all acquired projections and thus have higher k-space oversampling and higher parenchymal SNR (for example, ungated SNR = 21.5 for a mid-slice right lung ROI in Figure 4A). However, since these images are reconstructed from data acquired during free-breathing, they are blurred by respiratory motion, particularly at the lung-diaphragm boundary. Images retrospectively gated with 50% acceptance windows (Figures 3 and 4, middle rows) demonstrate an improvement in spatial resolution of

anatomical features, at the cost of a small decrease in parenchymal SNR ($\text{SNR} = \sim 14.5$ in Figure 4B, a factor of $\sim \sqrt{2}$ relative to the ungated SNR). Likewise, images retrospectively gated with 25% acceptance windows (Figures 3 and 4, bottom rows) exhibit an additional reduction in parenchymal SNR ($\text{SNR} = \sim 10.1$ for Figure 4D, a factor of $\sim \sqrt{4}$ relative to the ungated SNR) but depict a narrower window of respiration with less respiratory blurring.

More finely-resolved structure is evident for several anatomical features in the gated images of Figures 3 (Subject Adult 4) and 4 (Subject Control 6), particularly for the 25% binning scheme: the major pulmonary vessels, the diaphragm, and (for Subject Control 6) the inferior vena cava (Figure 4 – magenta arrows). Signal intensity profiles extracted from UTE images along the superior-inferior (S-I) direction (Figure 5) show the quantitative transition from lung to diaphragm tissue for ungated, 50%-gated, and 25%-gated images, with a larger transition slope indicating decreased image blurring for smaller acceptance windows. Ungated, 50%-gated, and 25%-gated slope values for Adult 4 are 0.032 mm^{-1} , 0.041 mm^{-1} , and 0.058 mm^{-1} , respectively; slope values for Control 6 are 0.072 mm^{-1} , 0.079 mm^{-1} , and 0.094 mm^{-1} , respectively.

Functional measurements from self-gated UTE imaging

Tidal volumes—Adult tidal volumes from the first and second spirometric measurements compared well with MRI-based tidal volumes from 25%-gated images ($P = 0.071$ and 0.040 , respectively). Bland-Altman biases were 0.14 L and 0.09 L for the first and second spirometric tests, respectively (mean spirometric results shown in Figure 6A). MRI-measured tidal volumes, with comparisons to spirometry (adults) and physiological predictions (neonates) are detailed in Table 2.

Neonatal MRI-measured tidal volumes were in general smaller than physiologically-predicted tidal volumes (41); these MRI-based tidal volumes were on average $8.6 \pm 3.2 \text{ mL}$ and $4.6 \pm 1.7 \text{ mL}$ for 25% and 50% acceptance windows, respectively. For all neonates' 25%-gated and 50%-gated tidal volumes, Bland-Altman biases were $6.2 \pm 3.5 \text{ mL}$ and $10.3 \pm 2.4 \text{ mL}$ (difference range $0.4\text{--}10.1 \text{ mL}$ and $6.9\text{--}15.2 \text{ mL}$), respectively. Specifically, MRI-measured tidal volumes were within the physiologically-predicted range for four neonatal patients (Subjects Control 1, BPD 2, BPD 5, and CDH 1) and below the physiologically-predicted range for the remaining twelve neonatal patients.

Respiratory rates—An example frequency spectrum, calculated from the respiratory phase waveform during a 100-s period of quiescent breathing, depicts the respiratory frequency peak during this interval of time (spectra from raw and smoothed waveforms of Subject Control 2 shown in Figure 1C). MRI-calculated and bedside-observed respiratory rates compared well (detailed in Table 3), with $P = 0.006$ and 0.184 and Bland-Altman biases = $0.2 \text{ breaths/min (bpm)}$ and -0.5 bpm for adults (Figure 6B) and neonates, respectively; see Discussion for details on neonatal correlations. The mean MRI-calculated respiratory rate was $16.3 \pm 5.7 \text{ breaths per minute (bpm)}$ (mean $\pm$ standard deviation (SD)) and $50.0 \pm 10.8 \text{ bpm}$, compared with the observed respiratory rate of $16.2 \pm 6.6 \text{ bpm}$ and $50.5 \pm 7.5 \text{ bpm}$, for adults and neonates, respectively. While some neonatal patients' bedside-observed respiratory rates (4 measurements taken a few hours apart) were very

consistent (9 of 16 patients with SD/Mean = 15%), others' rates were widely variable (7 of 16 patients with 15% < SD/Mean = 36%). Furthermore, the ventilator rate setting for the three ventilated neonates (Subjects BPD 4, CDH 1, and CDH 2) compare well with their MRI-calculated respiratory rates (within 15%, 32%, and 2%, respectively). Notably, bedside-observed respiratory rates can be significantly different from ventilator settings due to spontaneous breathing (true in two mechanically-ventilated neonates, Subjects BPD 4 and CDH 1).

DISCUSSION AND CONCLUSIONS

To our knowledge, this work represents the first application of the k-space center to track and discard motion-corrupt MR data and the first FID-based respiratory-gating of neonatal pulmonary MR images to be reported. These results demonstrate the feasibility for retrospectively reconstructing respiratory-gated MR images of free-breathing, non-sedated neonates at multiple lung inflation volumes.

Motion-tracking via k-space center

The combination of 3D radial trajectories and the retrospective tracking of bulk and respiratory motion used here shows robustness to unpredictable and intermittent intervals of bulk motion. The flexibility to retrospectively select valid data in exchange for SNR highlights a strong advantage of radial UTE, particularly if a patient is non-cooperative or if the scan must be stopped early due to patient condition or discomfort. Due to the UTE sequence's motion-tracking capability, it is not necessary for the patient to remain motionless throughout the entire scan in order to obtain diagnostic quality images. The safety risks associated with sedation or general anesthesia in children are uncertain (42). Moreover, atelectasis appears within 5 min of anesthesia induction (43). Thus the UTE method provides a significant advantage over the need for sedation or general anesthesia during CT and conventional MRI in order to maintain the requisite quiescence in neonates and young children (44).

As mentioned, previous work describes the use of the k-space center acquired using various radial trajectories as a respiratory-gating signal. Tibiletti et al. (27) processed the self-gating waveform via application of a Butterworth bandpass filter with the passband set to a window of 0.1 Hz around the frequency of the respiratory waveform's local maxima. This filtering method assumes that subjects maintain a constant breathing rate (± 0.05 Hz, ± 3 bpm) over the course of several minutes, notably without any pauses in breathing (i.e. lower frequency components) or changes in the depth of respiration (which will broaden peaks). This is unrealistic for neonates and young children, who as individuals have widely varying respiratory rates (Table 3) and breathing patterns. In particular, neonatal lung imaging is restricted by fast respiration (~ 1 Hz) and small diaphragm displacement (on the order of 1 mm; Figure 5B shows full diaphragm displacement of ~ 3 –4 mm). Thus any proposed neonatal respiratory gating scheme must be efficient and accurate. Pencil navigators typically utilize 5-mm acceptance windows ($\sim 10\%$ of the anterior-posterior neonatal lung dimension), while low-resolution image navigators do not provide adequate temporal resolution for rapid respiratory rates.

The processing method used in the present work is effective, particularly in subjects whose respiratory rates may vary within a single scan. Unlike some previous self-gating work (30,45), the gating scheme employed in this work requires no additional data beyond that needed to produce ungated images and maintains a high temporal resolution equal to the scan TR (~5 ms) before and after filtering. Furthermore, a true steady state is maintained, and data acquisition efficiency is not compromised, since it does not require the insertion of occasional navigator echoes or self-gating lines during acquisition. The algorithms for motion-discarding, respiratory-binning, and image reconstruction have a total run-time of 5 min, making it feasible for future use in a clinical workflow.

Functional measurements from self-gated imaging

Tidal volumes—MRI-measured tidal volumes likely underestimate the true tidal volumes due to the non-zero size of the acceptance windows of end-phase respiration. This is evidenced by the fact that both the adult (Figure 6A) and neonatal MRI-measured tidal volumes were slightly smaller than the spirometrically-measured and reference values (and we expect slightly lower values in babies with CDH). Even with gating, images demonstrate slightly blurred anatomical structures, particularly at the diaphragm for this analysis. In this case, blurring at the lung-diaphragm boundary makes accurate segmentation of the lung challenging. This effect is more noticeable in the 50%-gated images than in the 25%-gated images (Figures 3 and 4), and correspondingly the tidal volumes from 50%-gated images are lower (and less accurate) than those from 25%-gated images. Ideally, further narrowing of the acceptance windows would yield more structurally-resolved images of end-phase respiration, thus improving segmentation accuracy and generating more accurate MRI-based tidal volume measurements. However, smaller window sizes provide fewer projections for the reconstruction of each retrospectively-gated image, resulting in degraded image quality via either decreased SNR or pixel resolution.

There was one outlier data point for adult tidal volumes: the spirometrically-measured tidal volume of subject Adult 2 was larger than the MRI-measured volume. This may be reflective of environmental differences affecting tidal volumes during scanning and post-scan testing (applicable to all subjects). Our spirometric equipment was not MRI-compatible and could not be used during the scan itself. Differences between MRI-measured and physiologically-predicted neonatal tidal volumes may be due to a number of factors, including disease state, sleep, or anxiousness during the scan. Indeed, infants born premature and/or with pulmonary disease may have tidal volumes that vary widely from this predicted physiological scaling.

Although neonatal pulmonary MRI is not currently common, it is an emerging modality, and UTE MRI is becoming accessible on all MR platforms. Since tidal volume cannot easily be measured in neonates by any other means, these MRI-determined tidal volumes may represent the safest and most accurate measurements available, particularly in diseased and at-risk patients.

Respiratory rates—Notably, MRI-measured and bedside-observed respiratory rates correlated well for adults ($P = 0.006$) but not for neonates ($P = 0.184$), with narrow adult and wide neonatal Bland-Altman 95% limits of agreement (± 5 bpm and ± 21 bpm, respectively).

It is important to emphasize that MRI-measured respiratory rates are calculated from a weighted average of a neonate's quiescent breathing rate during several minutes of scanning, while the observed rates are the average of four 1-min 'snapshot' clinical measurements at different time-points. Thus the MRI-measured value may be a more accurate and representative measure of a subject's respiratory rate during the scan. Notably, two mechanically-ventilated neonates had bedside measurements (obtained while mechanically-ventilated) that do not match well with ventilator settings (Subjects BPD 4 and CDH 1), but we note that the supported ventilation allows spontaneous breathing, making consistent respiratory-rate measurements challenging.

Parenchymal signal as a function of inflation level—While not assessed in this work, quantification of parenchymal density as a function of lung volume using images reconstructed at multiple lung inflation volumes may provide an assessment of regional ventilation during both early normal development and the progression of disease (34). Similar techniques for parenchymal tissue quantification using CT already exist (34,46,47), but an MRI-based method has the potential to provide such images and measurements in neonatal or other non-cooperative populations without the use of ionizing radiation or sedation.

Conclusions

The present work demonstrates an effective and novel technique for retrospective tracking of bulk and respiratory-related motion using radially-acquired 3D UTE MRI, providing diagnostic-quality lung images at different stages of respiration, with validation in an adult cohort. This method is particularly useful for structural pulmonary MRI in non-cooperative patient populations, such as neonates or young children, since it does not require ionizing radiation, sedation, or anesthesia and can accommodate the high respiratory rates and small yet non-negligible amounts of chest wall and diaphragmatic motion presented by the neonate. The practical utility of this method is also demonstrated through its role in quantifying tidal volume. Although additional work is needed to improve accuracy, the potential for clinical assessment of lung volume changes relevant to pulmonary disease and development early in life is high.

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GLOSSARY

APRV	airway pressure release ventilation
BPD	bronchopulmonary dysplasia
bpm	breaths per minute
CCHMC	Cincinnati Children's Hospital Medical Center
CDH	congenital diaphragmatic hernia

FA	flip angle
FGRE	fast gradient recalled echo
FD	free induction decay
FOV	field of view
iPFT	infant pulmonary function test
IRB	Institutional Review Board
NICU	Neonatal Intensive Care Unit
PFT	pulmonary function test
ROI	region of interest
S-I	superior-inferior
SIMV PC/PS	synchronized intermittent mandatory ventilation, pressure controlled/pressure support
SNR	signal-to-noise ratio
T₁	longitudinal relaxation time
T₂*	effective transverse relaxation time
TE	echo time
TR	pulse repetition time
UTE	ultrashort echo time

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Figure 1.

A) The entire phase component of the motion-tracking time-course for a neonatal UTE scan (Subject CDH 4) demonstrates periods of quiescent breathing used in image reconstruction (colored, 25%-gated data; red, end-expiration; yellow, near end-expiration; green, near end-inspiration; light blue, end-inspiration) and periods of discarded bulk motion (black). B) The raw phase time-course (solid grey) and the smoothed phase time-course (solid colored) match well, as shown during a representative 5-s interval of quiescent breathing. The peak-to-peak phase signal to noise ratio was ~ 3.3 for this patient. C) The frequency spectrum (raw data, grey; smoothed data, purple) of a ~ 100 -s interval of quiescent breathing, highlighted by a large respiratory peak (~ 1.1 Hz, ~ 66 bpm; peak width ~ 0.8 – 1.2 Hz, 48–72 bpm).

Figure 2.

Ungated FGRE and UTE images in an adult validation subject (Adult 2) during (A) quiescent breathing and (B–D) bulk motion between quiescent Positions 1 and 2 followed by constant bulk motion for the remainder of the scan. Plots of the phase time-course of each UTE FID's initial point are shown for A–D; each time-course clearly reflects the sequence of positioning and motion performed by Subject Adult 2. UTE images in C and D are reconstructed using raw data acquired during select intervals of the scan (black data in plots). Note that in C (images reconstructed from data acquired in Positions 1 and 2), a 'doubling' effect is demonstrated for specific anatomy that shifted between the two positions (green arrows; anterior lung wall and anterior chest tissue), and that in D, parenchymal signal has been further exchanged for improved spatial resolution of anatomy. Note that approximately half of the duration of A is shown in the plot at the right.

Figure 3.

3D radial UTE pulmonary MR images (coronal plane reformats) of an adult subject (Adult 4), with 3D isotropic resolution of $\sim 0.8 \times 0.8 \times 0.8$ mm³. Ungated images (A) use all k-space projections (here, $\sim 200,000$ projections). Images gated with 50% acceptance windows (B, end-expiration; C, end-inspiration; $\sim 100k$ projections each) separately depict inspiratory and expiratory phases of the respiratory cycle. Similarly, images gated with 25% acceptance windows (D, end-expiration; E, end-inspiration; $\sim 50k$ projections each) depict end-phases of respiration with more narrow windows and less apparent respiratory-blurring artifact, particularly around the heart and vasculature and at the lung-diaphragm transition. See Figure 5A for adult signal intensity profiles of the lung-diaphragm transition (with corresponding S/I regions shown here in colored boxes).

Figure 4.

3D radial UTE pulmonary MR images (coronal plane reformats) of a neonatal patient (Subject Control 6), with 3D isotropic resolution of $\sim 0.7 \times 0.7 \times 0.7$ mm³. As with the adult images in Figure 3, ungated images (A) use all quiescent k-space projections (here, ~ 190 k projections). Images gated with 50% acceptance windows (B, end-expiration; C, end-inspiration; ~ 95 k projections each) separately depict inspiratory and expiratory phases of the respiratory cycle. Similarly, images gated with 25% acceptance windows (D, end-expiration; E, end-inspiration; ~ 48 k projections each) depict end-phases of respiration but with more narrow windows and less apparent respiratory-blurring artifact. Note that the inferior vena cava (magenta arrows) is more finely-resolved with a 25% acceptance window (D, E). See Figure 5B for neonatal signal intensity profiles of the lung-diaphragm transition (with corresponding S/I region shown here in colored boxes).

Figure 5.

Signal intensity profiles extracted from adult (A, Adult 4) and neonatal (B, Control 6) UTE images along the lung-diaphragm transition. The relevant adult and neonatal S-I regions are shown with corresponding colored boxes in Figures 3 and 4, respectively (ungated: solid green; 50% and 25% end-expiration: solid and dashed blue, respectively; 50% and 25% end-inspiration: solid and dashed red, respectively). The profiles shown here are averaged from the signal of 50 and 20 pixels in the right-left direction for Subjects Adult 4 and Control 6, respectively. The ungated profiles clearly demonstrate a blurred transition (i.e. smaller slope) across ~20 mm and ~7 mm for Adult 4 and Control 6, respectively. In contrast, the reduction in respiratory-blurring artifact is evident in the gated profiles, with sharpness at the lung-diaphragm boundary particularly improved (i.e. larger slope at the transition) when using the 25%-gating scheme. Ungated, 50%-gated, and 25%-gated slope values for Adult 4 are 0.032 mm^{-1} , 0.041 mm^{-1} , and 0.058 mm^{-1} , respectively; slope values for Control 6 are 0.072 mm^{-1} , 0.079 mm^{-1} , and 0.094 mm^{-1} , respectively.

Figure 6.

Bland-Altman plots for validation of pulmonary function measurements from adult UTE MRI. Shown are comparisons of tidal volumes acquired by 25%-gated image segmentation to tidal volumes acquired by spirometry (A, bias = 0.11 L), and comparisons of MRI-based respiratory rates to observed respiratory rates (B, bias = 0.2 breaths/min).

Table 1

Subjects' demographic information.

Subject	Sex	Age at MRI (adults, yr; neonates, wk (PMA ^a))	Mass at MRI (kg)	Respiratory Support at MRI: Method, approx. ventilator rate (bpm)
Adult 1	M	23	68	—
Adult 2	F	29	77	—
Adult 3	M	32	95	—
Adult 4	M	28	82	—
Adult 5	F	23	74	—
Adult 6	M	27	70	—
Control 1	M	36	2.7	None
Control 2	F	40	3.2	None
Control 3	F	38	2.5	None
Control 4	F	41	2.6	None
Control 5	F	38	2.5	None
Control 6	M	33	2.2	None
BPD 1	M	38	3.0	None
BPD 2	F	37	2.3	None
BPD 3	M	40	3.7	None
BPD 4	M	39	3.5	SIMV PC/PS ^b , 40
BPD 5	M	43	3.1	None
CDH 1	M	39	3.0	SIMV PC/PS ^b , 25
CDH 2	M	43	3.0	APRV ^c , 46
CDH 3	M	43	3.7	None
CDH 4	M	41	2.9	None
CDH 5	M	42	3.7	None

^aPost-menstrual age, defined as gestational age plus chronological age since birth.^bSynchronized intermittent mandatory ventilation, pressure controlled/pressure support^cAirway pressure release ventilation.

Table 2

Subjects' functional measurements of tidal volumes.

Subject	Tidal Volume (mL)		
	Spirometry-based ^a : Mean $\pm$ SD	MRI-measured (50% bins):	MRI-measured (25% bins):
Adult 1	460 $\pm$ 20 530 $\pm$ 60	230	400
Adult 2	890 $\pm$ 40 750 $\pm$ 90	230	380
Adult 3	1070 $\pm$ 120 950 $\pm$ 180	780	1170
Adult 4	600 $\pm$ 110 470 $\pm$ 50	240	370
Adult 5	390 $\pm$ 90 360 $\pm$ 40	230	340
Adult 6	440 $\pm$ 80 460 $\pm$ 60	200	340
	Physiologically-predicted^b:	MRI-measured (50% bins):	MRI-measured (25% bins):
Control 1	10.8–16.2	6.3	12.5
Control 2	12.8–19.2	4.4	8.3
Control 3	10.0–15.0	1.4	5.1
Control 4	10.6–15.8	6.1	8.6
Control 5	10.0–15.0	5.1	5.4
Control 6	8.8–13.2	3.9	5.5
BPD 1	12.0–18.0	3.9	5.1
BPD 2	9.2–13.8	2.6	9.5
BPD 3	14.8–22.2	5.5	9.8
BPD 4	14.0–21.0	2.3	8.9
BPD 5	12.4–18.7	5.2	14.7
CDH 1	12.8–19.2	6.3	14.6
CDH 2	12.0–18.0	3.1	7.9
CDH 3	14.8–22.2	6.8	8.7
CDH 4	11.6–17.4	3.3	4.4
CDH 5	14.6–22.0	7.3	9.3

^aTwo spirometry tests were performed, with three measurements per test.^bPhysiologically-predicted neonatal tidal volumes are calculated with the scaling factor 4–6 mL/kg (41).

Table 3

Subjects' functional measurements of respiratory rates.

Subject	Respiratory Rate (bpm)	
	Observed at bedside ^a : Mean $\pm$ SD (range)	Calculated from MR-waveform:
Adult 1	13	14
Adult 2	12	16
Adult 3	8	7
Adult 4	16	17
Adult 5	25	24
Adult 6	23	20
Control 1	50 $\pm$ 5 (44–55)	44
Control 2	40 $\pm$ 10 (25–46)	33
Control 3	55 $\pm$ 4 (49–59)	65
Control 4	49 $\pm$ 11 (39–63)	46
Control 5	42 $\pm$ 2 (40–44)	62
Control 6	48 $\pm$ 7 (40–57)	62
BPD 1	55 $\pm$ 12 (40–69)	53
BPD 2	42 $\pm$ 15 (33–64)	53
BPD 3	56 $\pm$ 8 (45–62)	51
BPD 4	50 $\pm$ 11 (40–62)	46
BPD 5	45 $\pm$ 10 (36–59)	36
CDH 1	59 $\pm$ 8 (52–70)	33
CDH 2	45 $\pm$ 1 (43–45)	45
CDH 3	66 $\pm$ 4 (61–70)	65
CDH 4	61 $\pm$ 15 (42–74)	59
CDH 5	45 $\pm$ 3 (41–48)	47

^aFour and one observations were made for neonates and adults, respectively.