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Accelerated Fractional Ventilation Imaging with Hyperpolarized Gas MRI

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Abstract

PURPOSE—To investigate the utility of accelerated imaging to enhance multi-breath fractional ventilation (r) measurement accuracy using HP gas MRI. Undersampling shortens the breath-hold time, thereby reducing the O₂-induced signal decay and allows subjects to maintain a more physiologically relevant breathing pattern. Additionally it may improve r estimation accuracy by reducing RF destruction of HP gas.

METHODS—Image acceleration was achieved by using an 8-channel phased array coil. Undersampled image acquisition was simulated in a series of ventilation images and images were reconstructed for various matrix sizes (48–128) using GRAPPA. Parallel accelerated r imaging was also performed on five mechanically ventilated pigs.

RESULTS—Optimal acceleration factor was fairly invariable (2.0–2.2 $\times$) over the range of simulated resolutions. Estimation accuracy progressively improved with higher resolutions (39–51% error reduction). *In vivo* r values were not significantly different between the two methods: 0.27 ± 0.09 , 0.35 ± 0.06 , 0.40 ± 0.04 (standard) versus 0.23 ± 0.05 , 0.34 ± 0.03 , 0.37 ± 0.02 (accelerated); for anterior, medial and posterior slices, respectively, whereas the corresponding vertical r gradients were significant ($P < 0.001$): 0.021 ± 0.007 (standard) versus 0.019 ± 0.005 (accelerated) [cm⁻¹].

CONCLUSION—Quadruple phased array coil simulations resulted in an optimal acceleration factor of $\sim 2\times$ independent of imaging resolution. Results advocate undersampled image acceleration to improve accuracy of fractional ventilation measurement with HP gas MRI.

Keywords

Pulmonary ventilation; Quantitative lung imaging; Fractional ventilation; Hyperpolarized gas MRI; Mechanical ventilation; Parallel MRI; GRAPPA; Accelerated ventilation imaging

INTRODUCTION

Fractional ventilation (r) is defined as the ratio of inspired to end-inspiratory gas volume and is directly related to specific ventilation (SV) according to $r = SV/(1+SV)$ (1). Specific ventilation – the ratio of inspired to residual gas volume – is arguably the most established quantitative measure of regional respiratory gas distribution (1,2) and has been used to investigate regional lung function (3). Imaging of regional lung ventilation therefore plays a significant role in studying the physiological basis of respiratory gas distribution and its

alteration as a function of disease, posture and exercise (4–10). The majority of the effort on ventilation imaging using Hyperpolarized (HP) gas MRI has been based on single-breath scans to detect and evaluate gross ventilation defects (11,12). Ventilation distribution in human lungs is known to be non-uniform (9,13,14). Ventilation heterogeneity is even larger in presence of airflow obstruction due to air entering the affected regions by means of collateral ventilation from the adjacent normally ventilated lung (15). These effects can lead to a respiratory gas distribution pattern that may not be observable over the time course of a single breath. This is why all SV imaging techniques developed so far, including xenon-enhanced computed tomography (16–18) and oxygen-enhanced MRI (19), as well as traditional pulmonary assessment tools such as the multi-breath N₂ washout maneuver (20), rely on multiple breath maneuvers to attain a reliable ventilation measurement.

A multi-breath HP gas fractional ventilation imaging technique was introduced and implemented in rodents a decade ago (21). A key technical improvement which consisted of acquiring a series of ventilation images in a consecutive fashion (22), as opposed to the original cascade approach (21), recently enabled single-pass, multi-slice *r* imaging in large species – Yorkshire pigs – with comparable respiratory rate and lung volume to humans (23). The present work investigates the utility of accelerated HP gas MRI in fractional ventilation imaging. Acceleration through undersampling can potentially improve the accuracy of *r* measurement in three distinct ways. First, large mammalian species breathe over a respiratory time scale of a few seconds (4–8 s/cycle at rest) – an order of magnitude slower than rodents. The slower breathing rate means that oxygen-induced signal decay of HP gas in airways (*in vivo* $T_1 \sim 18$ s (24)), would no longer be negligible. Accelerated image acquisition shortens the breath-hold time necessary to acquire the images, thereby reducing the associated O₂-induced signal decay. This advantage becomes especially more pronounced when lengthier acquisitions are necessary to acquire higher resolution or 3D images. Second, faster image acquisition allows subjects to maintain a respiratory rate closer to normal breathing, which in addition to providing a more physiologically relevant ventilation measurement, may assist in identifying ventilation defects otherwise masked by a slower breathing rate and longer breath-holds. Third, and most importantly, the inherent undersampling of accelerated MRI techniques present an opportunity in a more efficient utilization of the finite polarization of HP gases. The smaller number of RF pulses necessary to acquire and reconstruct images reduces the associated irrecoverable polarization loss. This property is critical for accurate measurement of fractional ventilation which depends on HP gas signal buildup in the airways over the course of several breaths (22). Acceleration through undersampling in this context presents another unique advantage that is not accessible in a conventional setting. The finite irrecoverable magnetization of HP nuclei eliminates the traditional constraint on SNR as a function of the number of excitations (25), and provides some freedom on how it can be budgeted over a series of pulses in order to maximize the overall SNR and image fidelity.

METHODS

Fractional ventilation imaging

Theoretical basis of fractional ventilation imaging has been described previously (22). Briefly *r* is measured using a series of *N* consecutive HP gas breaths (with time interval Δt) with images acquired during short end-inspiratory breath-holds. The magnetization of gas in three ventilatory compartments are referred to as M_A (acinar airways), M_S (ventilator static dead space), and M (HP gas source), related to each other as follows:

$$M_A(j) = r \cdot M_S(j-1) + (1-r) \cdot M_A(j-1) \cdot \exp [N_{PE} \ln(\cos \alpha) - \tau \cdot P_A O_2 / \xi], \quad M_A(0) = 0 \quad [1]$$

with two independent variables r and M . V_T is the tidal volume and V_S represents the static dead space (22). For large species where $V_T > V_S$, we have $M_S(j) = M$ for all breaths except for the very first breath where the magnetization of inspired gas is diluted with the dead space volume according to $M_S(0) = [1 - (V_T/V_S)^{-1}]M$. Of the two exponential decay terms in Eq. [1], flip angle is estimated by acquiring n consecutive images after correcting for T_1 effect during an end-inspiratory breath-hold (26), for a given number of RF pulses, N_{PE} (PE: phase encoding). The polarization in acinar airways decays according to alveolar partial pressure of oxygen (P_{AO_2}) nominally assumed stationary at 140 mbar. The oxygen-induced relaxation time constant for ^3He is given by λ/PO_2 , with $\lambda \approx 2.6 \text{ bar}\cdot\text{s}$ under physiological conditions (27).

r estimation model sensitivity and optimization simulations

Given a constant P_{AO_2} level, measurement of α and r is a coupled estimation problem susceptible to uncertainty in model parameters and noise. Model sensitivity analysis was therefore carried out simultaneously for both variables with respect to noise and N_{PE} . Normally distributed noise (28), with zero mean and a proper variance, was randomly added to all images to yield the desired SNR value in the reference ventilation image in the series. Each noise level was simulated at least 50 times. The standard deviation of successful trials corrected for sample size was recorded as the relative estimation error for r . If at any given trial the estimation failed to converge, a value was randomly selected in the range of $\alpha_{\text{nominal}} \pm 2^\circ$, and r was computed accordingly. Optimal α value was determined based on minimum r error as a function of N_{PE} . Since the resulting signal intensity varies as a function of N_{PE} and α , the comparisons were normalized by the resulting SNR in each case. This was achieved by assigning an arbitrary SNR value to a nominal set of model parameters (α , r and N_{PE}), deriving the corresponding noise variance in the reference image, and adding the same noise intensity to all other cases. The second image in the ventilation sequence was used as the reference for all simulations.

GRAPPA image reconstruction simulations

In order to quantitatively assess the effect of image undersampling and spatial resolution on r estimation accuracy, a series of simulations were performed using Generalized Auto-calibrating Partially Parallel Acquisition (GRAPPA) parallel image reconstruction algorithm. Details of GRAPPA acquisition and image reconstruction are extensively described in published literature (29). Two key parameters of GRAPPA parallel acceleration scheme are: auto-calibration lines, ACL (number of PE lines acquired from the central region of the k -space) and acceleration ratio, AR (undersampling ratio outside the ACL region; i.e. only one every AR phase encoding lines is acquired). The effective acceleration factor is given by the ratio of reconstruction matrix size along PE direction, N_y , to the number of RF pulses, $N_{PE} = \text{ACL} + (N_y - \text{ACL})/\text{AR}$. A representative 2D image of the middle slice of a pig lung was used as the reference equilibrium HP ^3He magnetization, $M(x,y)$. The corresponding $r(x,y)$ map – derived experimentally from the same pig – was used as the matching reference fractional ventilation map. A uniform distribution of $\alpha = 5^\circ$ and $P_{AO_2} = 140 \text{ mbar}$ was assumed throughout. A series of $N = 7$ ventilation images and $n = 4$ flip angle images were generated based on the fractional ventilation signal buildup model, Eq. [1], using previously reported parameters in pigs (23). Accelerated ventilation imaging was simulated over $\text{ACL} = 8\text{--}32$ and $\text{AR} = 2\text{--}5$, and for a matrix size ranging from 48×48 through 128×128 . The range of these parameters were selected to be comparable to animal studies described in the next section. Cartesian k -space sampling was used to simulate the MR signal according to:

$$S_c(k_x, k_y) = \sum_{x=1}^{N_{PE}} \sum_{y=1}^{N_{PE}} M_A(x, y) \cdot B_c(x, y) \cdot \sin \alpha \cdot \cos^{k_x-1} \alpha \cdot \exp[-(k_x-1)TR \cdot P_A O_2 / \xi] \cdot \exp[j2\pi(k_x + k_y)/N_{PE}], \quad [2]$$

where $B_c(x, y)$ represents the sensitivity profile for c -th coil. Parallel sampling on simulated images was performed using a 1×4 phased array coil model. Each coil element was considered a rectangular surface coil with a sinusoidal sensitivity profile (25), with a similar geometry to that of our experimental setup. Complex random noise was added to the k -space signal to obtain the desired SNR value. Final images were generated by summing the signal magnitude of four channels, which were then fit to Eq. [1] to yield ρ and r maps.

Animal studies

In order to demonstrate feasibility of accelerated fractional ventilation imaging with HP gas MRI in large species and to compare the results with and without undersampling, a series of experiments were conducted on five healthy Yorkshire pigs. The details of the *in vivo* imaging protocol is described previously (23). Parallel imaging was performed on an 8-channel phased array chest coil (Stark Contrast, Erlangen, Germany). This coil consisted of a rigid Helmholtz transmit coil and two sets of 1×4 receive arrays; one mounted in a rigid enclosure at the bottom and the other within a flexible jacket placed on top. Each coil element was a rectangular surface coil. Image acceleration was achieved using standard GRAPPA with ACL = 16 and AR = 4, resulting in an effective acceleration factor of 2 (24 versus 48 PE lines). Ventilation images were acquired during a ~ 1.5 -s end-inspiratory breath-hold following each HP ^3He breath ($N = 7$) with a 500-ms pre-acquisition time delay. Breath-hold was shortened to 1 s for accelerated imaging. As described in (23), the concentration of the administered HP gas was controlled with a ventilator at $^3\text{He}:\text{N}_2:\text{O}_2 \approx 2:2:1$ using 500 mL of ^3He in order to maintain $P_A\text{O}_2$ at around 140 mbar throughout the imaging session. Each set of r imaging sequence was completed in 1.5–2.0 min. Flip angle map was measured by acquiring $n = 5$ consecutive images with no inter-scan time delay and imaging parameters identical to the ventilation scans while holding the last HP ^3He breath for approximately 5 s. The effective ρ used for imaging the lungs of all five animals was in the range of $3.6 \pm 0.2^\circ$.

Data analysis

Data analysis was performed in MATLAB environment (Mathworks, Natick, MA) on a voxel-by-voxel basis. Flip angle maps were smoothed using a 3×3 moving average filter within each slice. The sequence of images and the derived ρ map were fit to Eq. [1], yielding M and r as free parameters for each voxel. Voxels with $r > 0.9$ (conductive airways) were excluded from the analysis. The intrasubject comparison of r measurements in pig lungs using both methods was performed through a voxel-by-voxel linear regression analysis.

GRAPPA simulation results of the pig lung were evaluated in two different ways: (i) the RMS difference between the estimated and reference r maps, $r_{\text{err}} = \|r - r_{\text{ref}}\|_2$, where $\|\cdot\|_2$ denotes the 2-norm; and (ii) the correlation coefficient R for the voxel-by-voxel linear regression between the two maps. RMS r error was normalized with respect to the minimum error observed in the entire process, $\|r_{\text{err}}\|_2 / \|r\|_{2, \text{min}}$. Since in theory any given acceleration factor can be achieved using more than one combination of ACL and AR, the pair of parameters with the largest ACL value was used as the basis for comparison. Both error quantities were plotted as a function of the effective acceleration factor and fit to a bi-exponential function to derive the optimal acceleration coefficient to minimize the error quantity.

Statistical analysis of *in vivo* fractional ventilation data in pigs was performed using a mixed linear regression model with the backward elimination procedure based on likelihood ratio tests. Tested fixed effects included a slice term to account for gravity-dependent gradients in regional ventilation and an acceleration term to account for possible differences between the two acquisition methods. These terms were allowed to interact. The random effects included an animal term to account for variation between pigs, a residual term accounting for standard errors associated with the regression process, and a slice term accounting for variation in the gravitational ventilation gradient. The random slope term was nested in the animal term. Experimental-wide alpha error was set at 0.05.

RESULTS

GRAPPA-reconstructed ventilation simulations

The variation of RMS error and correlation coefficient of r maps for a representative matrix size (64×64) is plotted in Figure 1 as a function of α over the full range ACL and AR parameters, where the effective acceleration factor is given by N_y/N_{PE} . Error bars represent the standard deviation of each computed parameter over approximately 50 iterations. Both $\|r\|_2/\|r\|_{2,\min}$ and R reach a local optimal point as a function of α . Based on the RMS error, the relative r estimation accuracy improves with increased acceleration, compared to the baseline ($N_{PE} = 64$ in this case). The error, however, reaches a global minimum (around $N_{PE} \approx 31$, corresponding to an effective acceleration factor of $\sim 2.1\times$ in this case), beyond which the trend reverses. A similar behavior is observed in the correlation coefficient of r maps, where a global maximum is reached around $\sim 2.2\times$. Figure 2 summarizes the variation of r error as a function of acceleration factor for all simulated matrix sizes; 48, 64, 96, and 128 respectively. The optimal acceleration factor was fairly independent of imaging resolution: 2.0 ± 0.1 (based on $\|r\|_2$) and 2.2 ± 0.1 (based on R). The improvement in estimation accuracy, however, was progressively larger for higher resolutions: 39, 42, 49, 51% (based on $\|r\|_2$) corresponding to the four matrix sizes as above.

Accelerated fractional ventilation imaging in pigs

Summary of r measurements in five pigs are shown in Table 1 for each of the non-dependent, middle, and dependent slices. Middle slice r maps for the five animals are shown in Figure 3. Both standard and accelerated r maps are depicted along with the corresponding voxel-by-voxel correlation graphs. The two sets of measurements correlated well ($R = 0.83$ – 0.89). Pig #5 was an exception ($R = 0.69$), primarily due to the much lower than average SNR (12 vs. 50) in the accelerated r measurement caused by a technical problem with the second batch of HP ^3He gas. Additionally, an unplanned animal care event made it necessary to reposition this pig inside the MRI scanner between the two measurements, which further contributed to misregistration of the two r maps.

The r distribution was qualitatively identical between each pair of measurement across the five pigs. Regression results are shown in Table 2. Only significant covariates are included in the table. The acceleration term was not significant suggesting there is no bias between the two measurements: $r = 0.27 \pm 0.09$, 0.35 ± 0.06 , 0.40 ± 0.04 versus 0.23 ± 0.05 , 0.34 ± 0.03 , 0.37 ± 0.02 corresponding to nondependent, intermediate and dependent slices, respectively. The intrasubject standard deviation of r by accelerated method was approximately half of that of the standard technique. Conductive airways ($r > 0.9$) – which were excluded from the analysis – contributed to approximately 5.7 ± 0.7 [%] and 4.7 ± 1.6 [%] of all voxels in the standard and accelerated methods respectively.

Compared to the constant term in the mixed linear model (0.188 , $SE = 0.024$, $P < 0.001$), the slice term showed a moderate but significant gravity-dependent gradient in fractional

ventilation (0.073 , $SE = 0.008$, $P < 0.001$); vertical ventilation gradients in supine pig lungs were $r/z = 0.021 \pm 0.007$ versus 0.019 ± 0.005 [cm^{-1}] for the standard and accelerated technique respectively. A small but statistically significant slice-to-acceleration cross term was observed (-0.007 , $SE = 0.001$, $P < 0.001$) suggesting that there was a slight difference between the way accelerated and standard methods measured the gravity-dependent slope. This effect however is an order of magnitude smaller than the slice (gravity) term and therefore presents little practical significance. Given that the two acquisitions were performed at different times during the imaging session, it is not unlikely that the observed difference largely stems from the variation in the physiological state of the sedated and ventilated animal between the two runs..

DISCUSSION

Model sensitivity and optimality of undersampled ventilation imaging

Undersampling cannot indefinitely improve r measurement accuracy. It is expected that a limit exists beyond which the information loss due to undersampling artifacts outweighs the gain in reducing RF pulse effect and image acquisition time. In regards to GRAPPA acceleration, the normalized RMS error $\|r\|_2 / \|r\|_{2,\min}$ not only reflects the effect of the number of RF pulses and noise, but also incorporates the inaccuracy introduced by image reconstruction artifacts as a result of excessive undersampling. As shown in Figure 2, the RMS error declined rapidly with increasing acceleration ratio towards a local minimum (around $\sim 2.0\times$, fairly independent of imaging resolution) and then increased with higher acceleration. A similar behavior was observed based on the maximum correlation coefficient reaching around $\sim 2.2\times$ acceleration. We note that the optimal acceleration coefficient may substantially change as a function of the number of receive coils or the undersampling and reconstruction algorithms. The simulation results presented here are therefore by no means extensive and only provide a general guideline to investigate the undersampling effects and to interpret the experimental results.

Ventilation measurements in pigs

In order to retain fairness in comparing the results of accelerated fractional ventilation imaging in pigs to fully sampled results, acquisition parameters were kept almost entirely unchanged between the two measurements, except for the acceleration coefficient ($2\times$) and the breath-hold length (1.0 vs. 1.5 s). The utilized flip angle for animal studies ($\sim 3.6^\circ$) was selected rather conservatively prior to extensive investigation of optimality conditions for accelerated imaging. Based on the RMS error values derived from GRAPPA simulations, it is expected that the r measurement accuracy in pigs would improve by approximately 10% (standard) and 15% (accelerated), if $\alpha = 5.7^\circ$ and 6.3° were used, respectively.

In the absence of ground truth for direct validation of r measurements, a few observations were made to support better relative accuracy of the accelerated measurements. As discussed earlier, no statistically significant slice-wise difference was observed between the two sets of r measurements. However the group standard deviation of accelerated r measurements was approximately half of that of the standard method. Normalized by group mean values, the coefficient of variation of r for nondependent, intermediate, and dependent slices were 35%, 18%, and 10% (standard) compared to 20%, 9%, and 4% (accelerated), respectively. The smaller intersubject coefficient of variation suggests a smaller disparity of measurements among the five animals using the accelerated method.

Even though fractional ventilation has not been measured with other imaging modalities, it is directly comparable to SV. Postural ventilation gradient is generally independent of V_T and has been extensively reported in SV studies. An early study by Kaneto *et al.* reported

measurements of SV with ^{133}Xe scintigraphy in three supine human subjects (10), corresponding to a gravitational ventilation gradient of $r/z = 0.022 \pm 0.003 \text{ [cm}^{-1}\text{]}$. These values agree well with our results: $r/z = 0.021 \pm 0.007$ versus $0.019 \pm 0.005 \text{ [cm}^{-1}\text{]}$, for standard and accelerated techniques, respectively. Sá *et al.* measured SV in eight consciously breathing human subjects using O_2 -enhanced MRI (19), reporting $r/z = 0.028 \pm 0.012 \text{ [cm}^{-1}\text{]}$ in supine position. Similar to our study, they also reported statistically significant different SV values between the nondependent, intermediate, and dependent lung regions.

According to GRAPPA simulation results, accelerated r measurements are expected to be equally or more accurate than their standard counterparts under similar SNR conditions (e.g. in pigs #1 and #4). Apart from the inherently better utilization of magnetization, the observed differences between standard and accelerated r measurements are also likely a function of the breathing pattern (e.g. breath-hold time). A slower acquisition results in a longer breath-hold time, which in turn affects the mixing of inspiratory and residual gas compartments. This effect also means that images are captured at a different time point in the respiratory cycle. Both effects can potentially change the apparent fractional ventilation value measured from signal buildup in the airways.

Conclusion

This work suggests that when possible, an acceleration method would be more beneficial for multi-breath ventilation imaging as compared to full k -space sampling. The limited scope analysis described in this work using the quadruple phased array coil configuration led into an optimal acceleration factor of $\sim 2\times$ across a relatively wide range of imaging resolutions. Independent from its temporal characteristics, undersampled image acquisition can improve the accuracy of r measurements, mainly due to enhancing the ventilation signal build-up by suppressing the RF-induced depolarization of HP gas. The results obtained in Yorkshire pigs demonstrated the feasibility of this imaging technique in large species. This experimental setup can serve as a stepping-stone towards implementation in human subjects, while providing a platform to address the technical challenges associated with long breathing time scales and to optimize acquisition parameters.

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Figure 1.

Accuracy of r estimation in a 64×64 2D image set of pig lungs reconstructed with GRAPPA parallel acceleration using a 4-channel phased array coil. The simulations cover the range of $ACL = 8-32$, and $AR = 2-5$; The RMS error of the estimated r map is normalized by the minimum global error. The variation of $\|r\|_2$ (left panel) and correlation coefficient between the estimated and reference r maps (right panel) versus a is fit to a second order function to assist in estimating the global minimum error associated to each undersampling scheme (ACL, AR) and the corresponding effective acceleration factor. Error bars represent the standard deviation of $\|r\|_2$ and R error over ~ 50 iterations. All lines are fit to the simulated data points. Any (ACL, AR) pair is shown by a combination of the corresponding symbol and line type.

Figure 2.

Variation of r RMS error and correlation coefficient as a function of effective acceleration factor, for four different matrix sizes, $MS = 48, 64, 96$ and 128 . Each data point corresponds to the minimum error achieved with the respective optimal α , as determined by the analysis demonstrated in Figure 1. Error bars represent the standard deviation of $\|r\|_2$ and R over ~ 50 iterations. The lines are bi-exponential fits to the simulated data points and are only added for visual enhancement and to objectively estimate the extrema.

Figure 3.

Fractional ventilation maps for the intermediate slice in lungs of five healthy Yorkshire pigs. Results are shown for both standard and accelerated measurement techniques along with the linear regression analysis. r maps are overlaid on top of the corresponding ^1H images of the thorax acquired at the same tidal volume.

Table 1
Summary of ventilation parameters and fractional ventilation measurement results in pigs.

<i>r</i> , Standard Acquisition						
Pig No.	Nondependent Slice #1	Intermediate Slice #2	Dependent Slice #3	Overall <i>r</i>	Overall (°)	Gradient [cm ⁻¹]
1	0.27 ± 0.15	0.38 ± 0.16	0.40 ± 0.15	0.36 ± 0.17	3.7 ± 0.5	0.018
2	0.15 ± 0.13	0.29 ± 0.16	0.38 ± 0.14	0.30 ± 0.17	3.5 ± 0.5	0.032
3	0.35 ± 0.14	0.40 ± 0.12	0.45 ± 0.13	0.41 ± 0.13	3.3 ± 0.3	0.014
4	0.17 ± 0.13	0.26 ± 0.17	0.34 ± 0.15	0.27 ± 0.17	3.6 ± 0.5	0.024
5	0.32 ± 0.15	0.39 ± 0.18	0.43 ± 0.15	0.38 ± 0.17	3.7 ± 0.5	0.015
	0.25 ± 0.09	0.34 ± 0.06	0.40 ± 0.04	0.34 ± 0.06	3.6 ± 0.2	0.021 ± 0.007

<i>r</i> , Accelerated Acquisition						
Pig No.	Nondependent Slice #1	Intermediate Slice #2	Dependent Slice #3	Overall <i>r</i>	Overall (°)	Gradient [cm ⁻¹]
1	0.29 ± 0.16	0.38 ± 0.18	0.38 ± 0.16	0.36 ± 0.17	3.8 ± 0.9	0.013
2	0.17 ± 0.15	0.30 ± 0.17	0.35 ± 0.15	0.29 ± 0.17	3.7 ± 0.6	0.025
3	0.25 ± 0.16	0.35 ± 0.17	0.38 ± 0.16	0.33 ± 0.17	3.4 ± 0.4	0.018
4	0.21 ± 0.13	0.31 ± 0.15	0.37 ± 0.15	0.31 ± 0.16	3.5 ± 0.4	0.022
5	0.26 ± 0.13	0.34 ± 0.16	0.38 ± 0.18	0.33 ± 0.17	3.6 ± 0.7	0.017
	0.23 ± 0.05	0.34 ± 0.03	0.37 ± 0.02	0.32 ± 0.03	3.6 ± 0.2	0.019 ± 0.005

Table 2

Mixed linear regression model analysis results with fixed factor coefficient statistics, along with estimated standard deviations of random terms.

Fixed Factors				
Coefficient	Estimate	Standard Error	P-value	95% Confidence Interval
Constant	0.188	0.024	< 0.001	(0.123, 0.252)
Slice	0.073	0.008	< 0.001	(0.057, 0.088)
Slice * Acceleration	-0.007	0.001	< 0.001	-(0.009, 0.005)

Random Factors			
Parameter	Estimate	SE	95% Confidence Interval
SD Slice	0.017	0.006	(0.009, 0.032)
SD Constant	0.073	0.023	(0.039, 0.136)
SD Residual	0.157	0.001	(0.156, 0.159)