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FULL PAPER

Quantification of gas exchange-related upward motion of the liver during prolonged breathholding—potential reduction of motion artifacts in abdominal MRI

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Objective: To test the hypothesis that there is a measurable upward motion of the diaphragm during prolonged breath-holds that could have a detrimental effect on image quality in liver MRI and to identify factor that potentially influence the magnitude of this motion.

Methods: 15 healthy volunteers underwent MRI examination using prolonged breath-holds in the maximum inspiratory position and a moderate inspiratory position. Coronal T_1 weighted three-dimensional gradient echo sequences of the entire thorax were acquired every 6s during breath-holding allowing the calculation of total lung volume and the measurement of the absolute position of the dome of the liver. The potential impact of subject's gender, body mass index, and total lung capacity on the change in lung volume/diaphragmatic motion was assessed using random coefficient regression.

Results: All volunteers demonstrated a slow reduction of the total lung volume during prolonged breath-holding

up to 123 ml. There was a measurable associated upward shift of the diaphragm, measuring up to 5.6 mm after 24 s. There was a positive correlation with female gender ($p = 0.037$) and total lung volume ($p = 0.005$) and a negative association with BMI ($p = 0.012$) for the maximum inspiratory position only.

Conclusion: There is a measureable reduction of lung volumes with consecutive upward shift of the diaphragm during prolonged breath-holding which likely contributes to motion artifacts in liver MRI.

Advances in knowledge: There is a measureable gas exchange-related reduction of lung volumes with consecutive upward shift of the diaphragm during prolonged breath-holding which likely contributes to motion artifacts in liver MRI. Correcting for this predictable upward shift has potential to improve image quality. The magnitude of this effect does not seem to be related to gender, BMI or total lung capacity if a moderate inspiratory position is used.

INTRODUCTION

MRI examinations of the upper abdominal organs are performed in large numbers and are considered essential for the evaluation of a wide variety of clinical problems.^{1–3}

The quality and therefore diagnostic value of in particular hepatic and pancreatic MRI is substantially negatively affected by image degradation through motion artifacts, mostly secondary to cardiac and respiratory motion. Several strategies have been employed to remedy motion artifacts including breathing navigators. However, a significant number of imaging sequences, in particular the dynamic post-contrast T_1 weighted sequences still rely on suspended respiration to eliminate breathing artifacts and optimize image quality.

During a study to investigate the effectiveness of targeted breathing to improve navigator efficiency in coronary MR angiography using a biofeedback approach,⁴ an upward motion of the diaphragm during prolonged breath-holding was noticed. In order to maintain a stable craniocaudal position of the diaphragm, subjects had to repeatedly take in small amounts of air (data not reported). The most likely explanation for this finding is a gas-exchange-related reduction in lung volume^{5–8} during suspended respiration. A more recent study⁹ could show that there is an upward motion of the diaphragm during breath-holding, however the majority of this effect was attributed to relaxation of the diaphragm after glottis closure.

Due to the significant advances in MRI hardware technology and sequence development over the recent years

increasingly smaller structures are being visualized and characterized within the upper abdomen. Given common slice thicknesses of 2–3 mm in breath-hold post-contrast T_1 weighted gradient echo imaging, a diaphragmatic motion of only 5 mm during a breath-hold would represent a bulk motion of about two slices, and blurring in addition to that related to the existing voluntary or involuntary patient motion would invariably occur. If the magnitude of this diaphragmatic upward motion would either be the same in all patients or could be predicted based on patient-specific parameters, correction algorithms could be developed. Reducing this bulk motion could be expected to have positive effects on image quality.

The purpose of this study is to test the hypothesis that there is a diaphragmatic upward motion during prolonged breath-holding and to identify factors that potentially have an impact on the magnitude of this effect, as this would allow prediction and possibly correction of this bulk motion.

METHODS AND MATERIALS

Before the initiation of this investigation, a waiver of informed consent was obtained by the Institutional Review Board. The study was carried out in compliance with the Health Insurance Portability and Accountability Act.

MR imaging

MR imaging data were acquired on a 1.5 T research scanner (Magnetom Avanto, Siemens Healthcare, Malvern, PA, USA) with body phase-array receiver coil. Ultrafast coronal T_1 weighted three-dimensional (3D) spoiled gradient echo sequences of the entire thorax was performed without respiratory triggering. Imaging parameter: repetition time 2.29 ms, echo time 1.1 ms, slice thickness 4 mm, flip angle of 10° , in plane resolution 3.9×1.3 mm (right-left $\times$ craniocaudal), field of view 500 mm, right-left phase-encoding direction.

Acquisition protocol

The study protocol consisted of a total of six breath-holds per individual, three of which in maximum inspiration and the other three in a moderate inspiratory position attempting to simulate breath-holding as used in clinical routine. Before the exam, subjects were instructed to either take a “absolutely maximum breath and hold it as long as possible” or to take a “comfortable moderately deep breath that can be held for 30 s”. During each breath-hold 15 vol data sets of the entire thorax were acquired every 6 s without gap covering a total of 90 s. Maximum inspiratory and moderate inspiratory efforts were alternated with at least 90 s between breath-holds to allow for adequate recovery.

Image analysis (lung volume)

To calculate lung volumes for the right and left pulmonary lobe the acquired 3D data sets were used to create a single-subject template constituting an average shape and intensity estimate of the series.¹⁰ This template-building approach has been used in a variety of studies involving different animal¹¹ and human anatomies including lungs¹² and is publicly available in the open-source Advanced Normalizations Tools repository. An initial template is estimated by voxelwise averaging the 3D images

Figure 1. Illustration of different positions of the diaphragm. A 29-year-old volunteer, coronal T_1 weighted gradient echo MR images demonstrating the differing positions of the diaphragm in maximum and moderate inspiratory positions (in this case about 1.6 cm).

comprising all time points. This initial template is then iteratively refined by performing pairwise, diffeomorphic image registration¹³ between each time point and the current estimate of the template. In this study, template estimation stabilized after four iterations for each subject.

A labeled segmentation lung mask denoting the left and right lungs were then generated in the template space using an automated joint label fusion approach.¹⁴ This lung mask was then propagated back to each time point image using the transforms generated from the single-subject template construction.¹¹ Lung mask physical volumes at each time point were then quantified by summing the number of voxels in the mask multiplied by the voxel resolution. For each breath-hold (total of six: two different breath-hold positions and three repetitions each), the total long capacity was calculated for all time points, until blurring of the data sets indicated that the subject was no longer holding its breath. Relative volume change in mL were calculated for each breath-hold and documented in an Excel spreadsheet (Microsoft Corp, Redmond, WA). Averages with standard deviations for the three repetitions per breath-hold position were calculated.

Image analysis (diaphragmatic shift)

Imaging analysis was performed on our PACS system (Carestream Health, Rochester, NY) by one radiologist with 4 years of post-fellowship experience in MR imaging. For each individual breath-hold the absolute craniocaudal location of the dome of the right hemidiaphragm was identified on the coronal slice showing the hepatic venous confluence (Figure 1) for time point 0. For all following time points within the same breath-hold, the relative shift of the diaphragmatic dome in mm was determined on the same slice location and documented in a spreadsheet. The reader was blinded to subject number and individual breath-hold position. Averages with standard deviations for the three repetitions per breath-hold position were calculated.

Statistical analysis

Demographic categorical data were summarized by frequencies and percentages and continuous scaled demographic data were

summarized by the mean and range of the distribution. The linear relationship between the reduction in lung volume (mL) and intrabreath-hold time was examined under moderate and under maximum inspiration by way of random coefficient regression (RCR). RCR was also used to examine the linear and non-linear components of the relationships between diaphragmatic shift and intrabreath-hold time under moderate and under maximum inspiration. Subject-specific factors such as gender, body mass index (BMI) and total lung capacity as measured during the beginning of each individual's maximum breath-hold and average over the three maximum thresholds, were also examined with respect to their influence in the aforementioned relationships by way of multivariate RCR. Note that RCR is a mixed model analytical technique for analyzing longitudinal relationships in which the repeated measures of the dependent variable from the same observation unit are non-independent. RCR has the advantage over traditional fixed effects repeated measure regression in that the RCR model specification includes subject specific random effects (e.g. subject-specific random intercept effects and subject-specific random slope effects) that allow *subject-specific* time profile predictions to be derived from the RCR model in addition to the predictions for study population *marginal* (i.e. average) time profile. With regard to RCR hypothesis testing, all hypothesis tests for testing for a non-zero regression coefficient were examined at the 0.05 significance level. The RCR analyses were conducted by way of the MIXED procedure of SAS v. 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Subjects

15 healthy volunteers (11 male, 4 female) were enrolled in the study. Average age was 32.8 years with a range of 23–51 years. Average weight was 75.6 kg (range 47.2–108.9 kg) and average height was 176 cm (range 165–192 cm). Average total lung capacities were 5.55 L (range 3.24–7.64 L). None of the volunteers had a history of lung or heart disease; all were non-smokers.

Lung volume

The average volume losses during the moderate/maximum breath-hold were: 34/26 mL (6 s), 68/38 mL (12 s), 95/51 mL (18 s), 122/67 mL (24 s), 151/82 mL (30 s) and 200/98 mL (36 s) (Table 1 and Figure 2). The subject-specific time profiles for reduction in lung volume are shown for the moderate and maximum breath-hold positions in Figure 2A. The RCR marginal linear slope parameter estimates of the moderate and maximum breath-hold positions were 0.0049 l/s [95% CI (0.0035, 0.0062), $p < 0.001$] and 0.0025 l/s [95% CI (0.0019, 0.0030), $p < 0.001$], respectively. For both breath-hold positions, the RCR analysis for examining the influence of gender, BMI and total lung capacity on the time course of reduction in lung volume did not demonstrate any statistically significant associations (p -values 0.781, 0.758 and 0.479 respectively for the moderate breath-hold position and p -values 0.823, 0.536 and 0.664 respectively for the maximum breath-hold position) (Table 2).

Diaphragmatic shift

The average diaphragmatic shifts for the moderate/maximum breath-hold were: 1.9/1.9 mm (6 s), 3.4/3.0 mm (12 s), 4.6/3.7 mm

Table 1. Diaphragmatic upward shift and lung volume loss ($n = 15$)

Inspiratory position	Time point											
	6 s		12 s		18 s		24 s		30 s		36 s	
	Shift (mm)	Vol (mL)	Shift (mm)	Vol (mL)	Shift (mm)	Vol (mL)	Shift (mm)	Vol (mL)	Shift (mm)	Vol (mL)	Shift (mm)	Vol (mL)
Maximum breath-hold	1.9	25.5	3	37.5	3.7	51.3	4.3	67	5	82.4	5.4	98.1
Maximum	4.5	73.3	5.5	103.3	6.7	113.3	8.8	133.3	9.4	150	10	170
Minimum	0.1	-33.3	0.1	-20	1.2	-16.6	1.9	10	2.4	16.6	2.8	30
Standard deviation	1.28	31.7	1.77	38.7	1.87	39.5	1.82	37.5	1.75	39.7	1.87	44.1
Moderate breath-hold	1.9	34	3.4	68.1	4.6	94.8	5.8	122.4	6.5	151.2	7	199.5
Maximum	3.8	123.3	4.8	140	6.1	193.3	7.3	240	8.9	293.3	8.1	340
Minimum	0.4	-120	1	-20	1.3	-6.6	2.5	6.6	3.2	25	5.4	110
Standard deviation	0.9	52.1	1.13	40.9	1.5	55.3	1.47	67.5	1.5	75.6	1.06	77.2

Average upward shift of the diaphragm and lung volume loss at different time points during prolonged breath-holding using maximum and moderate inspiratory positions. Maximum, minimum and standard deviations are listed. Three breath-holds per individual were averaged.

Figure 2. Observed subject-specific pulmonary volume time profiles (A) and liver shift time profiles (B) on moderate and maximum inspiratory breath-hold positions. The dotted lines represent the individual subjects and the solid lines represent the average across all subjects.

(18s), 5.8/4.3 mm (24s), 6.5/5.0 mm (30s) and 7.0/5.4 mm (36s) (Table 1 and Figure 2). The subject-specific time profiles for diaphragmatic shift (mm) are shown for the moderate and maximum breath-hold positions in Figure 2B. The RCR marginal linear slope parameter estimates of the moderate and maximum breath-hold positions were 0.0326 m/s [95% CI (0.0224, 0.0428), $p < 0.001$] and 0.0183 m/s [95% CI (0.0130, 0.0235), $p < 0.001$], respectively, and the RCR marginal quadratic parameter estimates of the model and maximum threshold positions were -0.004 m/s^2 [95% CI (-0.0007 , -0.001), $p = 0.016$] and -0.0001 m/s^2 [95% CI (-0.0003 , 0.000), $p = 0.016$], respectively. For moderate breath-hold positions, the RCR analysis for examining the influence of gender, BMI and total lung capacity on the time course for diaphragmatic shift (mm) did not demonstrate any statistically significant associations (p -values 0.918, 0.075 and 0.742 respectively). However, for the maximum breath-hold

position there was a positive correlation with female gender ($p = 0.037$) and total lung capacity ($p = 0.005$) and a negative association with BMI ($p = 0.012$) (Table 2).

DISCUSSION

Our data show not only that there is a consistent upward motion of the diaphragm during prolonged breath-holding, but also that this motion is accompanied and likely causally related to a simultaneous decrease in total lung volume. This decrease in intrapulmonary gas volume during prolonged breath-holding has been explained by the fact that the partial pressure gradient between the alveoli and the capillary blood remains high for oxygen because of continuing peripheral oxygen consumption but progressively decreases for carbon dioxide, which cannot escape the alveoli. The persistently high extraction of oxygen from the alveoli in light of a stagnant CO_2 transport lead to

Table 2. Correlation of lung volume reduction with gender, BMI and total lung capacity ($n = 15$)

A. DIAPHRAGMATIC SHIFT			
	Degrees of freedom	F-statistic	p-value
Moderate inspiration:			
Gender	8.4	0.01	0.918
BMI	10.7	3.88	0.075
Total lung capacity	7.5	0.12	0.742
Maximum inspiration:			
Gender	11.2	5.63	0.037*
BMI	11.5	8.85	0.012*
Total lung capacity	11.0	12.60	0.005*
Table 2B			
B. LUNG VOLUME			
	Degrees of freedom	F-statistic	p-value
Moderate inspiration:			
Gender	10.9	0.08	0.781
BMI	11.0	0.10	0.758
Total lung capacity	10.9	0.54	0.479
Maximum inspiration:			
Gender	11.0	0.05	0.823
BMI	11.0	0.41	0.536
Total lung capacity	11.0	0.20	0.664

BMI, body mass index.

Random coefficient regression summary for a model that includes: gender, BMI, and total lung capacity as predictors of diaphragmatic shift (A) and reduction in lung volume (B) with moderate and maximum inspiratory breath-hold positions. Regarding the diaphragmatic shift on moderate inspiration and the pulmonary volume reduction on both moderate and maximum inspiration neither of the examined factors demonstrated any statistically significant correlation with the magnitude of diaphragmatic shift and lung volume reduction respectively. However regarding the diaphragmatic shift on maximum inspiration the female gender ($p = 0.037$) and total lung capacity ($p = 0.005$) were positively associated with the magnitude of the diaphragmatic shift ($p = 0.037$), while a higher BMI was negatively associated with the magnitude of the diaphragmatic shift ($p = 0.012$).

overall reduction in the number of intra-alveolar gas particles and therefore volume.^{5,7,8} According to our data, the average volume loss can be as high as 200 ml after 36 s for the moderate breath-hold position. However, given that breath-holds used for clinical imaging are rarely longer than 20 s, the highest volume loss that would typically be encountered during clinical imaging is 95 ml after 18 s.

The general phenomenon of upward motion of the diaphragm during breath-holding has been shown⁹ using navigator echo sequences. In this study, average motion in 10 volunteers was 0.15 mm/s, which would result in 1.8 mm after 12 s and 2.7 mm after 18 s. Our data show comparable however slightly higher average shifts of 3.0 mm after 12 s and 3.7 mm after 18 s for the maximum breath-hold position. The moderate breath-hold position, which is felt to be more relevant because it is most commonly used in clinical imaging, resulted in slightly higher shifts of 3.4 and 4.6 mm after 12 and 18 s respectively. With a typical in-plane resolution of 1.5 mm and a 2 mm slice thickness used for the post-contrast T_1 weighted gradient echo sequences on modern scanners, this bulk motion would be in the order of

up to three pixels or two-and-a-half slices during a 18 s breath-hold and can therefore be expected to introduce substantial blurring into the reconstructed images.

Our methodology used a volumetric approach compared to a two-dimensional navigator echo in the paper by Holland *et al.*⁹ Our study is therefore not only able to confirm the vertical motion of the diaphragm but also connect this motion to a progressive reduction in lung volume. We are therefore postulating that a volume reduction due to continuing asymmetric O2 extraction is a better explanation for the vertical diaphragmatic motion than diaphragmatic relaxation following glottis closure.⁹

All 15 individuals demonstrated the described diaphragmatic upward shift for both breath-hold positions (Table 1, Figure 2). Our data suggest that the effect of lung volume reduction during prolonged breath-holding is more pronounced when a moderate breath-hold position is used than at maximum inspiration. This interesting observation is not sufficiently explained by the mechanism proposed by several previous publications^{5,7,8} as outlined above. One possible explanation is a decrease in venous return

caused by the increased intrathoracic pressure associated with maximum inspiratory effort breath-holding. This in turn would lead to a reduction in pulmonary and systemic perfusion (Frank-Starling mechanism) and slower gas exchange mitigating the phenomenon of asymmetric O₂ extraction detailed above. Given that the moderate breath-hold position is most commonly used in clinical routine, this observation further supports the idea that correcting for this component of motion might have a perceivable impact on image quality.

Our data further suggest that the magnitude of the observed change in lung volume and diaphragmatic shift in moderate breath-hold position does not seem to depend upon the subject's BMI, total lung capacity or gender. The magnitude of the diaphragmatic shift in the maximum breath-hold position, however, did show a positive correlation with female gender and total lung capacity as well as a negative correlation with BMI. This is difficult to explain, however, given that most clinical exams are not performed at maximum inspiration, a "one size fits all" approach in correcting for this effect may still be feasible.

Our study has limitations. We limited the study population to healthy volunteers, which might not adequately represent the real world clinical scenario, where many patients with systemic disease are limited in their breathholding abilities. Also, the observed effect of volume reduction and diaphragmatic upward shift might be more or less pronounced in patients with pulmonary disease. Further work will be necessary to evaluate this effect

in different patient populations. In contrast to previous studies⁹ using navigator echos with very high temporal resolution for the localization of the diaphragm, our temporal resolution of 6 s was relatively low. However, we were able to quantify total lung volumes in addition to the diaphragmatic shift, which allowed us further insight into the underlying mechanism of true volume reduction versus a simple "rearrangement" of the diaphragmatic position as suggested in the reference paper. Our sample size of 15 was relatively small and not gender balanced, likely decreasing the sensitivity for potential gender related differences in the observed effect. Finally, our study design was only able to observe the diaphragmatic shift in a single craniocaudal dimension. Given the anatomy of diaphragm and liver the upward motion is, however, likely a complex 3D process which would substantially complicate attempt of correction through change of imaging parameters or post-processing strategies.

In conclusion, there is a measurable reduction of lung volumes with resulting upward shift of the diaphragm and upper abdominal organs during prolonged breath-hold. Correcting the upward shift has substantial potential to improve image quality especially when very small lesions are targeted with improved MRI technology. The magnitude of this effect does not seem to be related to BMI, total lung capacity or gender. It seems reasonable to hypothesize that a prospective algorithm incorporated into the acquisition sequence could be able to correct for at least part of this motion and thereby improve image quality, although further work will be necessary to prove the validity of this assumption.

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