Published in final edited form as:

Magn Reson Med. 2013 December ; 70(6): . doi:10.1002/mrm.24608.

Novel Retrospective, Respiratory-Gating Method Enables 3D, High Resolution, Dynamic Imaging of the Upper Airway during Tidal Breathing

M.E. Wagshul^{1,2,*}, S. Sin³, M.L. Lipton^{1,4,5}, K. Shifteh⁵, and R. Arens³

¹Department of Radiology, Gruss MRRC, Albert Einstein College of Medicine, Bronx, NY 10461, USA

²Department of Physiology and Biophysics, Albert Einstein College of Medicine, Bronx, NY 10461, USA

³Department of Pediatrics, Division of Respiratory and Sleep Medicine, The Children's Hospital at Montefiore, Bronx, NY 10467, USA

⁴Departments of Psychiatry, Behavioral Sciences and Neuroscience, Albert Einstein College of Medicine, Bronx, NY 10461, USA

⁵Department of Radiology, Division of Neuroradiology, Montefiore Medical Center, Bronx, NY 10467, USA

Abstract

Purpose—To develop a retrospective, respiratory-gated technique for measuring dynamic changes in the upper airway over the respiratory cycle, with the ultimate goal of constructing anatomically and functionally accurate upper airway models in obstructive sleep apnea (OSA) patients.

Methods—3D cine, retrospective respiratory-gated, gradient echo imaging was performed in six adolescents being evaluated for polycystic ovary syndrome, a disorder with a high OSA prevalence. A novel retrospective gating scheme, synchronized to flow from a nasal cannula, limited image acquisition to pre-defined physiological ranges. Images were evaluated with respect to contrast, airway signal leakage, and demonstration of dynamic airway area changes.

Results—Two patients were diagnosed with obstructive sleep apnea. Scan efficiency ranged from 48–88%. Soft tissue-to-airway contrast-to-noise ratio varied from 6.1–9.6. Airway signal leakage varied between 10–17% of soft tissue signal. Motion artifacts were absent in all image sets. Automated segmentation allowed calculation of airway area changes over the respiratory cycle. In one severe apnea patient, the technique allowed demonstration of asynchronous airway expansion and contraction above and below a severe constriction.

Conclusions—Retrospective, respiratory gated imaging of the upper airway has been demonstrated, utilizing a gating algorithm to ensure acquisition over specified ranges of respiratory rate and tidal volume.

Keywords

Dynamic imaging; retrospective gating; sleep apnea; tidal volume; upper airway

---

*Correspondence: Dr. Mark E. Wagshul, 1300 Morris Park Avenue, Gruss MRRC 208, Bronx, NY 10461 USA, Telephone: (718) 430-4011, Fax: (718) 430-3399, mark.wagshul@einstein.yu.edu.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a growing public health problem affecting children and adolescents (1), and is linked to the rapidly rising prevalence of pediatric obesity (2). It affects as many as 1–4% of children (3), with an odds ratio of 4.5 in obese children (2). Transient upper airway obstruction during sleep leads to cardiovascular and cognitive morbidity in children with OSAS (4). Adenotonsillectomy and weight loss may reduce the clinical manifestations of OSAS in some cases, but their effectiveness remains unclear and the identification of patients likely to benefit continues to be a challenge (4).

Recent studies have identified several important anatomical and physiological factors which contribute to the development and progression of airway constriction in children with OSAS (5–10). It is clear from these studies that a comprehensive understanding of the underlying pathophysiology of the disorder will require precise temporal and anatomic characterization of upper airway obstruction. A number of investigators, including our group, have developed techniques for quantifying changes in upper airway anatomy over the respiratory cycle (11–15). Previous studies utilizing prospectively-gated, single-shot, fast imaging techniques suffer from various technical limitations. For example, CT-based techniques require radiation exposure (11,16), optical coherence tomography is limited to studies of the airway lumen itself with no information on the surrounding soft tissues (17–18), and MRI techniques tend to be signal-starved, requiring the use of non-isotropic voxel dimensions, and often provide limited anatomical coverage (13,15,19–22) unsuited to comprehensive airway modeling. In addition, most techniques have used prospective gating for respiratory synchronization, thus not allowing for rejection of respiratory events outside the range of the airway dynamics being studied.

Here, we describe a novel method for retrospective, respiratory-gated MRI with high, isotropic spatial resolution of the entire upper airway. The technique follows the general methodology of retrospective gating used in cardiac imaging, in which arrhythmia detection is used to reject invalid cycles whose length lie outside a pre-determined acceptable range. For respiratory gating, we utilized the flow waveform from a nasal cannula to retrospectively reject cycles during which the tidal volume was outside a pre-determined acceptable range for normal tidal breathing. While only providing pseudo-real time imaging of upper airway motion, the retrospective rejection technique allows careful selection of a predefined range of respiratory parameters, potentially allowing exploration of respiratory dynamics during different types of breathing, such as during an apneic event.

We show feasibility of the technique for producing high quality, dynamic imaging of the upper airway across the respiratory cycle in six young female subjects being evaluated for polycystic ovary syndrome (PCOS). PCOS is a disorder affecting girls and women of reproductive age and is associated with irregular or lack of menstruation, polycystic ovaries, clinical signs of hyperandrogenism, obesity and cardiometabolic abnormalities (23). Research has shown a high prevalence of OSAS in this disorder (24–27).

METHODS

Subjects

Subjects were recruited from a pool of patients being evaluated at Montefiore Medical Center for PCOS, and were all females between 14–18 years old. Following overnight polysomnography, subjects underwent an awake, upper airway MRI without sedation. The study was approved by the Institutional Review Board at the Albert Einstein College of Medicine, and informed consent was obtained from each subject (or subject's parent for minors; subject assent was obtained from minors), prior to enrollment in the study.

Gating System

Qualitative breathing airflow waveforms were collected from a nasal cannula coupled to a pressure transducer (TSD-160B, Biopac Systems, Inc, Goleta, CA). The Biopac signal was digitized with a National Instruments data acquisition board (DAQCard-6036E coupled to a SCB-68 board) and displayed on a custom graphical user interface written for Labview (National Instruments, Austin, TX). The cannula signal was initially zeroed for each subject to the no-flow condition. A gating signal was generated at the upward-going zero crossing at end expiration, and fed into the scanner external trigger input. Because a nasal cannula was used, calibrated tidal flow-volume information was not available. However, based on 2–3 minutes of flow data from the patient, mean and normal variation of relative tidal volume was calculated and used to limit MRI data acquisition to within the normal range of tidal breathing. While an exact algorithm was not used, the limits were generally set from 50–200% of the mean relative tidal volume. Subjects were instructed to breathe through their nose and keep their mouth closed during the duration of the scan.

MRI retrospective gating systems are typically designed to accept or reject input waveforms based on timing information, *i.e.* periods that are unusually short or long. This type of rejection system is optimized for cardiac imaging, where the beat-to-beat variation in heart rate is usually small, and large changes in rate are indicative of an arrhythmia which should be rejected from image acquisition. In contrast, in respiratory physiology the tidal volume is an equally important parameter which can potentially alter respiratory dynamics. A shallow breath, a very deep inspiration or breathing during a swallow will have very different respiratory dynamics compared to normal tidal breathing.

Thus, it was necessary to transform the standard arrhythmia rejection software on the scanner into an abnormal-tidal-breath rejection system. This was accomplished by measuring relative tidal volume in real-time within the Labview software, and producing gating signals based on the calculated relative inspiratory tidal volume for each breath; a flowchart of this rejection scheme can be found in Figure 1. As noted above, a gating trigger was generated at end expiration for each breath, independent of relative tidal volume. At end inspiration (*i.e.*, the downward-going zero crossing), relative tidal volume was calculated and compared to the acceptable relative tidal volume range. If the relative tidal volume was within range, this constituted a valid breath, nothing further was generated during the cycle and the scanner regarded this as an “accepted” respiratory cycle. If the calculated relative tidal volume was out of range, however, an additional gating signal was generated at end inspiration and again every 500 ms for the remainder of the expiratory period. Thus, the scanner receives two consecutive gating pulses separated by the inspiratory period alone; the scanner’s timing-based rejection algorithm judges the entire cycle as a rejected respiratory period and re-acquires the data until a valid respiration is detected. The additional gating pulses every 500 ms during expiration ensure that the expiratory portion of this invalid cycle is not judged as a valid respiratory period on its own. Because rejection was still ultimately based on timing information, an abnormally deep, and long, inspiratory period could still be judged as a valid respiratory period. However, the lower acceptance bound for arrhythmia rejection could usually be set high enough to prevent this from happening.

MRI Acquisition

All MRI images were collected on a 3T Philip Achieva scanner (Philips Medical Systems, Best, The Netherlands). The patient was positioned in the RF coil (described below) with padding on both sides of the head to prevent motion during the scans. A 3D, T1-weighted, inversion-prepared gradient echo sequence, acquired in the sagittal plane and reconstructed in the axial and coronal planes, was used for planning of the 3D dynamic study. The dynamic study used a 3D, retrospectively-gated, turbo gradient echo sequence with the

following parameters: TE/TR = 3.3/6.9 ms, flip angle 8°, FOV 24 (FH) × 18 (AP) cm, matrix 220 × 164, bandwidth 209 Hz/pixel. Thirty-six 1.1 mm thick sagittal slices were acquired (with 30% oversampling in the slice encode direction), a SENSE acceleration factor of 2.0 in the primary phase encode direction (AP), and 42 phase encode lines were collected per frame, resulting in a total of 91 valid breaths required for image reconstruction. The 18 cm FOV in the anterior-posterior direction was chosen to minimize scan time, but would normally result in a SENSE-related artifact in the center of the FOV. SENSE-based fold-over suppression (28) was used to minimize these effects utilizing a SENSE fold-over factor of 2.0. Ten respiratory phases were reconstructed across the respiratory cycle, independent of individual subject respiratory rate. Minimum scan time, assuming a respiratory period of 3 seconds, was approximately 4.5 minutes.

Our new, 3D retrospective technique was compared qualitatively to 2D, prospectively-gated, single shot imaging, which has been used previously for real-time imaging of airway motion (10,14,29). Two dimensional, axial images used a balanced steady-state free precession sequence with the following parameters: TE/TR = 2.57/5.14 ms, flip angle 35°, FOV 18×14 cm, matrix 164 × 128, slice thickness 3 mm/slice gap 0.3 mm, bandwidth 362 Hz/pixel, SENSE factor 2.0 and temporal resolution of 345 ms/frame. Eleven to fourteen frames were collected following the initial gating pulse at end expiration to cover at least one full respiratory cycle. Total scan time for 50 slices, assuming a respiratory period of 3 seconds, was 5 minutes.

Optimal coverage of the upper airway with adequate spatial and temporal resolution, and specifically for the study of OSAS involving a typically obese patient population, places constraints on the RF coil arrangement. The standard 16-channel neurovascular coil (NV) available on most MRI systems should be the best option with respect to airway coverage and SNR, but has two significant limitations: 1) the larger, obese patients being studied either do not fit into the coil or are extremely uncomfortable, and 2) accurate quantification of airway dynamics ideally requires collection of the entire flow-volume using a mask and pneumotachometer, which would not fit inside of the full NV coil for any patient. While a mask and pneumotach was not used for the current work, future work requiring quantitative flow information will utilize this option. To overcome these limitations, we utilized the lower portion of the NV coil, coupled with a 2-element flexible surface coil pair (16.5 × 14 cm diameter) to recover signal loss from the removal of the anterior NV elements. One element of the flex-coil pair was placed over the face and the second over the neck. Typical SNR loss was 10–20% relative to the full NV coil in the tissues surrounding the upper airway.

Image quality and scan performance evaluation

Performance of the dynamic sequence was based on the following measures: 1) temporal efficiency of the sequence, calculated as the minimum scan time (based on the patient's mean respiratory rate) divided by actual scan time, 2) presence of artifacts in the images and their proximity to the airway and surrounding tissue, 3) contrast-to-noise ratio (CNR), with contrast calculated as the signal difference between the airway and surrounding tissue, with the surrounding tissue signal taken as the mean of signal within three regions-of-interest, in adenoid, soft palate and esophageal wall (CNR will determine the ease with which the airway can be reliably segmented from the surrounding tissue, a requirement for reliable airway size measurements; airway SD was calculated within the same three ROI's listed in item 4, and assumes a Rayleigh noise distribution), 4) mean airway signal and temporal coefficient of variance of signal within the airway, (both measures taken as an indication of gating quality, because poor gating will produce motion artifact and spurious signal within the airway), measured within three airway ROI's (in velopharynx, oropharynx and trachea) and measured relative to mean tissue signal for comparison across all subjects, 5) timing

consistency of the “accepted” respiratory flow pattern over the 91 breaths required for image acquisition, reported as the standard deviation of the position of peak inspiration and expiration flows.

Demonstration of dynamic imaging

The quality of the dynamic images was evaluated according to the ability to extract airway cross sectional area changes over the respiratory cycle from axial reconstructed images, as follows: Histogram analysis of a 20×20 pixel region centered on the airway was used to identify a cutoff threshold for airway signal intensity; in most cases, identified as a low-intensity-value peak in the histogram. Based on this threshold, the airway region was automatically segmented and airway area was measured in mm^2 as the total number of pixels below the threshold times the pixel area. Waveforms of airway cross-sectional area over time were also evaluated qualitatively for demonstration of periodic changes in airway size over the respiratory cycle and consistency of temporal variation from slice to slice along the length of the airway.

A distinct advantage of the retrospective gating technique is the ability to collect the entire 3D volume under conditions representing the same respiratory dynamics, as opposed to single slice techniques where each slice is collected over a different cycle with potentially different respiratory dynamics. To demonstrate this strength, airway area changes over the cycle were extracted on a slice-by-slice basis over the entire upper airway and evaluated in terms of *timing* of the area changes. Mean waveforms of airway cross-sectional area over time were first compared qualitatively at the mid-velopharynx and mid-oropharynx levels. A quantitative measure of the timing of airway motion was extracted from the phase of the fundamental harmonic of the Fourier transform of the airway size change waveform.

Three-dimensional surface renderings of the airway were constructed with Amira 4.1 (Visage Imaging Inc., San Diego, CA) from MR image stacks at each phase of tidal breathing. The upper airway was segmented by the identification of voxels in selected slices using a single threshold value taken from top of the velopharynx to the upper tip of the epiglottis.

RESULTS

Patients – clinical assessments

Patient demographics and clinical assessment data are summarized in Table 1. Only two of the patients had a confirmed PCOS diagnosis (Cntrl4 and OSA2). Overnight polysomnography confirmed sleep apnea as moderate in one patient (apnea-hypopnea index, AHI, of 8.1, the number of apnic/hypopneic events per hour), and severe in one patient (AHI 36.9), labeled subjects OSA1 and OSA2, respectively. All other subjects had normal values (AHI ranging from 0 to 4.6) and were considered controls for the purposes in this study.

Image quality and scan performance evaluation

The NV-flex coil combination worked well, with all patients being comfortable in the coil setup, the coil providing excellent signal recovery in the anterior regions, with signal levels similar to those obtained with the full NV coil. The dynamic 3D sequence completed successfully in all patients. Image quality measures are summarized in Table 2. Overall, scan times varied considerably depending on respiratory rate and scan efficiency, ranging from 3.3 to 10.1 minutes (mean 7.0 min). SENSE-related artifacts were detected in 3 patients but were only severe in one of these. However, even in these cases, the artifacts were only notable within the brain and did not affect image quality in the vicinity of the upper airway in any case.

Figure 2 shows examples illustrating the typical airway-to-soft tissue contrast achieved with the dynamic sequence, with a comparison to the 2D technique illustrating the improvement in airway-tissue contrast, along with the obvious isotropic resolution advantage of the 3D technique allowing high quality display along multiple orientations. Although not seen in this example, the 2D technique occasionally suffered from SSFP-related banding artifacts which often intersected the airway and were difficult to avoid because of the expected susceptibility difference between the airway and surrounding tissue. For the 3D technique, CNR varied from subject-to-subject, although this was likely due to an effect on coil performance in the larger patients; CNR was negatively correlated with both patient weight and BMI ($p < 0.05$). Nonetheless, automated airway segmentation was successful even in the cases with lowest CNR, allowing slice-by-slice calculation of airway dynamics (see insets). Mean airway signal and its temporal coefficient of variation were low in all cases. Mean airway signal was correlated with both BMI and with the flow consistency measure (variation in peak inspiration across all acquisitions, discussed below), indicating contributions to airway noise from coil and gating performance.

Because retrospective gating relies on the collection of k-space across multiple respiratory cycles, an important consideration is the reproducibility of the respiratory pattern over time. In fact, the consistency varied from subject to subject (see Table 2). Three different cases, representing the different types of variation seen, are illustrated in Figure 3. All waveforms have been scaled in time and amplitude to illustrate changes in flow *pattern* only. In some subjects, flow waveforms were very consistent across all acquisitions, as seen with the very tight distribution of the plots in Fig. 3a. In others, there was considerable variability, with both peak inspiration and peak expiration varying in time from shot-to-shot, as seen in Fig. 3b. As discussed above, there were occasional, erroneous acquisitions with the entire cycle being acquired during inspiration only; one such acquisition can be seen in Fig 3b. Data from three patients contained one such error each. In one extreme case, where the rejection timing window was set too large, ten such erroneous acquisitions were encountered, as illustrated in Fig. 3c. There was an association between the peak inspiration timing variability and either image CNR ($p = 0.04$) or mean airway signal ($p = 0.02$).

Demonstration of dynamic information

Figure 4 demonstrates the image quality obtained over the respiratory cycle with the dynamic sequence, showing both one patient with near-perfect gating performance and another with suboptimal gating performance (OSA2, improper setting of the rate rejection window, as discussed above). The suboptimal gating is presumed to lead to the signal leakage into the airway seen. Nonetheless, the CNR of 6.1 was still adequate for automated segmentation of the airway from the surrounding soft tissue and calculation of airway size over the respiratory cycle (figure inset). Although the images were acquired in the sagittal plane, allowing full coverage of the upper airway, the isotropic resolution of the 3D technique allows these high-quality reconstructions across the respiratory cycle for accurate calculations of airway size irrespective of local airway orientation.

Calculations of airway area changes over the cycle are shown in three non-OSA subjects (Figure 5), revealing inter-subject variation in the relative timing of size changes along the airway. However, in all cases airway motion was roughly synchronous along the entire length of the upper airway. Irrespective of sleep apnea symptoms (*i.e.*, absent in these subjects), these dynamic changes may be a sensitive gauge of respiratory physiology and dynamics. In contrast to these cases, patient OSA2 with severe sleep apnea ($AHI = 36.9$) had a significant narrowing of the airway in the lower velopharynx with a complete phase reversal of the airway area motion from above to below the airway constriction (*i.e.*, asynchronous motion of the airway above vs. below). These, likely pathologic, dynamics are

demonstrated in Figures 6 and 7, and can best be appreciated from the cine movie available in the online supplement.

3D reconstructions yielded closed, contiguous surface-rendered maps of the upper airway in all cases (see Figure 8).

Discussion

We have demonstrated a novel method for dynamic upper airway imaging. Retrospective, respiratory-gated MR imaging was controlled based on flow through a nasal cannula, in order to generate dynamic, 3D, isotropic resolution images of the entire upper airway over the respiratory cycle. The technique can be used to collect images during normal tidal breathing, limiting acquisition to a specific, pre-determined range of respiratory rate and relative tidal volume, depicting changes in airway size with 300 ms temporal resolution at ~ 1 mm isotropic spatial resolution. The isotropic resolution facilitates multi-planar reconstruction and airway size determinations based on optimal oblique cross-sectional slice orientation, even at the abrupt 90-degree bend of the nasopharyngeal airway.

Historically, retrospective MRI gating techniques were developed for cardiac imaging (30), and have not been applied to imaging of respiratory-related airway motion. In cardiac imaging, heart rate and stroke volume variations are assumed to have minor impact on retrospectively-gated cine MRI image quality. For airway imaging, in contrast, respiratory rate and tidal volume vary considerably, potentially invalidating the basic assumptions of retrospective gating. In this study, we assumed that respiratory rate variations do not impact airway dynamics, using very conservative rate rejection windows. Tidal volume, however, may play an important role in respiratory dynamics; we therefore developed a technique to retrospectively reject acquisitions outside of a pre-determined relative tidal volume range. For this initial study, relative tidal volume acceptance ranges were deliberately broad to ensure reasonable scan times. Nonetheless, dynamic images in all cases had no evidence of motion-related artifacts. Future study will investigate narrower acceptance ranges for improving image quality. Our rejection scheme will allow for future studies exploring the effect of tidal volume on airway dynamics (*e.g.*, limiting acquisition to high vs. low tidal volume ranges), potentially offering valuable insight into the ongoing question of the relationship between airway stiffness and parenchymal tethering (31–32), which can be affected by tidal volume and airway resistance.

The retrospective gating technique used in this study differs from those used in prior airway dynamics studies which almost exclusively utilized rapid, single slice scanning, with each slice gated on a different breath (10–13,33–34). In comparison to the technique developed here, these prior studies suffer from three potential drawbacks: 1) the acquisition is inherently prospective, so that no information about the respiratory pattern is available until after image acquisition, 2) breath-to-breath variations in airway dynamics allow for the possibility that different slices in the image dataset will record changes in the airway relating to different airway dynamics, and 3) single slice techniques are inherently lower in signal-to-noise compared to true 3D volume technique and thus are limited in their ability to acquire images with high isotropic resolution which can later be reconstructed in an orientation optimal for airway segmentation. The retrospectively gated, 3D technique described here overcomes these issues by: 1) collecting real-time respiratory rate and relative tidal volume information to ensure that image acquisition occurs over breaths with a similar respiratory pattern, 2) using a 3D acquisition, so that all slices in the dataset relate to the identical collection of respiratory dynamics, and 3) collecting high isotropic resolution images allowing multi-planar reconstruction tailored to the local airway geometry, a particularly important issue in the nasopharyngeal region.

This first demonstration of the technique was in a group of patients being evaluated for polycystic ovary syndrome, a condition with a significant prevalence of obesity and concomitant obstructive sleep apnea. Obstructive sleep apnea syndrome was confirmed by polysomnography in two subjects. The MRI technique was sensitive enough to detect airway area changes as small as 2 mm^2 over the cycle. In the patient with severe sleep apnea, the technique proved extremely useful; we demonstrated a unique and likely pathologically-based asynchrony in the motion of different parts of the airway. While the airway motion below the constriction follows the expected pattern for a passive airway (*i.e.*, motion dictated by the flow-related pressure changes), the reverse pattern above the constriction would seem to indicate active airway motion, possible evidence of neuromotor activation of the surrounding tissue. Although it is possible that this particular patient drifted into sleep during the scan leading to this unique motion pattern, we should note that all patients were carefully instructed to remain awake for the duration of the scan. In addition, given the high AHI for this patient, apnic-like respiratory periods would have been likely had she fallen asleep and none were recorded during the scan. This particular case highlights a specific advantage of the retrospective approach noted above; because the entire airway is imaged using the same set of tidal breaths, quantitative comparison of both amplitude and timing characteristics of airway motion at multiple levels within the image volume is possible.

Our technique, as demonstrated here, is an ideal method for obtaining isotropic, high spatial and temporal resolution dynamic images of the upper airway during normal tidal breathing. However, the interesting dynamics in this population occurs either preceding or during an apnea. Because of the flexibility of our novel gating approach, we believe that it would be possible to adapt our methodology for studying apneas as well. Considering that each apnic event is preceded by an inspiratory period, gating with the flow waveform may still be feasible in these cases. Alternatively, a respiratory bellows could be substituted for the nasal cannula to measure respiratory effort, as described previously (10). In either case, additional temporal bounds would confine accepted cycles to the long apnic periods. Of course, because of the infrequent occurrence of apnic events, additional acceleration techniques such as keyhole or kt-BLAST (35) need to be explored to allow for 3D reconstruction within a reasonable scan time.

A prior study of airway caliber changes over the respiratory cycle reported a consistent pattern across both control subjects and patients, with maximum airway size occurring at early-to mid-expiration and little change in size during inspiration (11). In fact, this might be expected in a purely passive airway where caliber is determined by airway pressure – positive pressure during expiration should expand the airway, while the negative pressure generated during inspiration should cause airway collapse. Our results, in contrast, show significant variability in this pattern, although peak airway size generally occurred toward the beginning of expiration (see Figure 5). However, a recent series of studies using MR tagging to track tissue motion clearly shows anterior motion of the genioglossus during inspiration, *i.e.* motion which would tend to increase airway caliber, as well as subject-to-subject variability in the direction of the tissue motion in the more superior portions of the upper airway (21–22). These results are in concert with earlier studies of electromyographic activity of the genioglossus during inspiration (36–37). Thus, in addition to the expected passive pressure response of the airway, there are clearly neuromuscular activation-related changes in airway caliber affecting airway dynamics, which can vary over the length of the airway and from subject-to-subject.

A few limitations of the study should be addressed. Our RF coil used the lower half of the standard neurovascular coil coupled with a 2-element flex coil pair over the face and neck, to ensure that all patient could fit into the same coil setup. Our finding of a negative correlation between image quality and patient weight is unfortunate because it indicates that

in larger patients, those most likely to have OSAS, this more open coil configuration is suboptimal. The flex coil elements are much larger than the individual NV elements and in fact comparable in size to the patient's head, so that their noise performance will be most affected by patient head size (38). Given that the added flex coil over the face is the one which most effects image upper airway CNR, the lower CNR in larger patients is therefore not surprising; further work will be needed to investigate alternate coil options less sensitive to patient size.

While our analysis focused on airway segmentation, one of the primary applications for airway imaging in OSAS is for visualization of surrounding soft tissue motion for CFD and fluid structure interaction (FSI) simulations to understand airway-soft tissue interactions and their effect on obstruction dynamics (10,39–42). For this first demonstration, sagittal slices covered a limited region of the surrounding soft tissues. However, we still need to determine the degree of motion of the lateral tissues not covered, and adequate models might be constructed from the available dynamic information coupled with static images of the remaining anatomy. In addition, higher acceleration factors along two dimensions of the 3D volume could be used to increase anatomical coverage without loss of temporal resolution.

Finally, the strategy for limiting data acquisition to pre-determined ranges for relative tidal volume worked well in most cases, but was subject to occasional erroneous gating in some of the subjects. This was due to the fact that our tidal volume rejection scheme relied on the timing based rejection algorithm of the native scanner software and could erroneously accept an abnormally long inspiration as a full respiratory cycle. Nonetheless, these erroneously gated events were rare; dynamic image quality was not significantly affected even in the one case with a few occurrences. Future implementations of the sequence will utilize an improved rejection algorithm to recognize such erroneous gating in real-time and reacquire the data.

In conclusion, we have demonstrated a technique for 3D, isotropic resolution, retrospectively gated, cine imaging of the upper airway based on both respiratory rate and relative tidal volume acceptance criteria, which limits image acquisition to a desired range of tidal breathing. The contrast between the airway and the surrounding soft tissue allows for automated, slice-by-slice airway segmentation and depiction of very small changes in airway cross sectional area over the respiratory cycle. The proposed technique will permit construction of high-resolution 3D dynamic models of the upper airway and surrounding tissues, which can facilitate improved understanding of the mechanical and functional mechanisms leading to airway obstruction and apneic events. Moreover, this methodology, coupled with sophisticated CFD and FSI models, may allow better insight into the above mechanisms and may better predict treatment outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant Support: NIH, HD-053693 and HL-105212

The authors would like to thank Joseph McDonough, MS, and Jayaram Udupa, PhD, of the University of Pennsylvania, and David Wootton, PhD, of the Cooper Union for the Advancement of Science and Art for reviewing and commenting on the manuscript. We thank Philips Medical Systems for research support of the project.

References

1. Farber JM. Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2002; 110(6):1255–1257. author reply 1255–1257. [PubMed: 12456928]
2. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. *Am J Respir Crit Care Med*. 1999; 159(5 Pt 1):1527–1532. [PubMed: 10228121]
3. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. *Proc Am Thorac Soc*. 2008; 5(2):242–252. [PubMed: 18250218]
4. Gozal D, Kheirandish-Gozal L. The multiple challenges of obstructive sleep apnea in children: morbidity and treatment. *Curr Opin Pediatr*. 2008; 20(6):654–658. [PubMed: 19005334]
5. Arens R, Marcus CL. Pathophysiology of upper airway obstruction: a developmental perspective. *Sleep*. 2004; 27(5):997–1019. [PubMed: 15453561]
6. Arens R, McDonough JM, Costantino AT, Mahboubi S, Tayag-Kier CE, Maislin G, Schwab RJ, Pack AI. Magnetic resonance imaging of the upper airway structure of children with obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 2001; 164(4):698–703. [PubMed: 11520739]
7. Arens R, Sin S, Nandalike K, Rieder J, Khan UI, Freeman K, Wylie-Rosett J, Lipton ML, Wootton DM, McDonough JM, Shifteh K. Upper airway structure and body fat composition in obese children with obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 2011; 183(6):782–787. [PubMed: 20935105]
8. Marcus CL, Fernandes Do Prado LB, Lutz J, Katz ES, Black CA, Galster P, Carson KA. Developmental changes in upper airway dynamics. *J Appl Physiol*. 2004; 97(1):98–108. [PubMed: 14990559]
9. Marcus CL, McColley SA, Carroll JL, Loughlin GM, Smith PL, Schwartz AR. Upper airway collapsibility in children with obstructive sleep apnea syndrome. *J Appl Physiol*. 1994; 77(2):918–924. [PubMed: 8002548]
10. Persak SC, Sin S, McDonough JM, Arens R, Wootton DM. Noninvasive estimation of pharyngeal airway resistance and compliance in children based on volume-gated dynamic MRI and computational fluid dynamics. *J Appl Physiol*. 2011; 111(6):1819–1827. [PubMed: 21852407]
11. Schwab RJ, Geftter WB, Hoffman EA, Gupta KB, Pack AI. Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep disordered breathing. *Am Rev Respir Dis*. 1993; 148(5):1385–1400. [PubMed: 8239180]
12. Schwab RJ, Geftter WB, Pack AI, Hoffman EA. Dynamic imaging of the upper airway during respiration in normal subjects. *J Appl Physiol*. 1993; 74(4):1504–1514. [PubMed: 8514663]
13. Arens R, Sin S, McDonough JM, Palmer JM, Dominguez T, Meyer H, Wootton DM, Pack AI. Changes in upper airway size during tidal breathing in children with obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 2005; 171(11):1298–1304. [PubMed: 15750038]
14. Donnelly LF. Obstructive sleep apnea in pediatric patients: evaluation with cine MR sleep studies. *Radiology*. 2005; 236(3):768–778. [PubMed: 16014437]
15. Ikeda K, Ogura M, Oshima T, Suzuki H, Higano S, Takahashi S, Kurosawa H, Hida W, Matsuoka H, Takasaka T. Quantitative assessment of the pharyngeal airway by dynamic magnetic resonance imaging in obstructive sleep apnea syndrome. *Ann Otol Rhinol Laryngol*. 2001; 110(2):183–189. [PubMed: 11219527]
16. Schwab RJ. Properties of tissues surrounding the upper airway. *Sleep*. 1996; 19(10 Suppl):S170–174. [PubMed: 9085502]
17. McLaughlin RA, Armstrong JJ, Becker S, Walsh JH, Jain A, Hillman DR, Eastwood PR, Sampson DD. Respiratory gating of anatomical optical coherence tomography images of the human airway. *Opt Express*. 2009; 17(8):6568–6577. [PubMed: 19365482]
18. Armstrong JJ, Leigh MS, Sampson DD, Walsh JH, Hillman DR, Eastwood PR. Quantitative upper airway imaging with anatomic optical coherence tomography. *Am J Respir Crit Care Med*. 2006; 173(2):226–233. [PubMed: 16239620]

19. Abbott MB, Dardzinski BJ, Donnelly LF. Using volume segmentation of cine MR data to evaluate dynamic motion of the airway in pediatric patients. *AJR Am J Roentgenol.* 2003; 181(3):857–859. [PubMed: 12933494]
20. Donnelly LF, Casper KA, Chen B, Koch BL. Defining normal upper airway motion in asymptomatic children during sleep by means of cine MR techniques. *Radiology.* 2002; 223(1): 176–180. [PubMed: 11930064]
21. Cheng S, Butler JE, Gandevia SC, Bilston LE. Movement of the human upper airway during inspiration with and without inspiratory resistive loading. *J Appl Physiol.* 2011; 110(1):69–75. [PubMed: 20966195]
22. Cheng S, Butler JE, Gandevia SC, Bilston LE. Movement of the tongue during normal breathing in awake healthy humans. *J Physiol.* 2008; 586(Pt 17):4283–4294. [PubMed: 18635645]
23. Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med.* 2005; 352(12):1223–1236. [PubMed: 15788499]
24. Fogel RB, Malhotra A, Pillar G, Pittman SD, Dunaif A, White DP. Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2001; 86(3):1175–1180. [PubMed: 11238505]
25. Nandalike K, Strauss T, Agarwal C, Coupey SM, Sin S, Rajpathak S, Cohen HW, Arens R. Screening for sleep-disordered breathing and excessive daytime sleepiness in adolescent girls with polycystic ovarian syndrome. *J Pediatr.* 2011; 159(4):591–596. [PubMed: 21645911]
26. Tasali E, Van Cauter E, Hoffman L, Ehrmann DA. Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2008; 93(10):3878–3884. [PubMed: 18647805]
27. Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. *J Clin Endocrinol Metab.* 2001; 86(2):517–520. [PubMed: 11158002]
28. Winkelmann R, Bornert P, Nehrke K, Dossel O. Efficient foldover suppression using SENSE. *MAGMA.* 2005; 18(2):63–68. [PubMed: 15599667]
29. Donnelly LF. Magnetic resonance sleep studies in the evaluation of children with obstructive sleep apnea. *Semin Ultrasound CT MR.* 2010; 31(2):107–115. [PubMed: 20304320]
30. Lenz GW, Haacke EM, White RD. Retrospective cardiac gating: a review of technical aspects and future directions. *Magn Reson Imaging.* 1989; 7(5):445–455. [PubMed: 2607896]
31. Khan MA, Ellis R, Inman MD, Bates JH, Sanderson MJ, Janssen LJ. Influence of airway wall stiffness and parenchymal tethering on the dynamics of bronchoconstriction. *Am J Physiol Lung Cell Mol Physiol.* 2010; 299(1):L98–L108. [PubMed: 20435686]
32. Bates JH, Lauzon AM. Parenchymal tethering, airway wall stiffness, and the dynamics of bronchoconstriction. *J Appl Physiol.* 2007; 102(5):1912–1920. [PubMed: 17204575]
33. Barrera JE. Sleep magnetic resonance imaging: dynamic characteristics of the airway during sleep in obstructive sleep apnea syndrome. *Laryngoscope.* 2011; 121(6):1327–1335. [PubMed: 21557247]
34. Barrera JE, Holbrook AB, Santos J, Popelka GR. Sleep MRI: novel technique to identify airway obstruction in obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2009; 140(3):423–425. [PubMed: 19248956]
35. Tsao J, Kozerke S. MRI temporal acceleration techniques. *J Magn Reson Imaging.* 2012; 36(3): 543–560. [PubMed: 22903655]
36. Katz ES, Marcus CL, White DP. Influence of airway pressure on genioglossus activity during sleep in normal children. *Am J Respir Crit Care Med.* 2006; 173(8):902–909. [PubMed: 16439714]
37. Katz ES, White DP. Genioglossus activity during sleep in normal control subjects and children with obstructive sleep apnea. *Am J Respir Crit Care Med.* 2004; 170(5):553–560. [PubMed: 15172891]
38. Wang ZJ. Improving SNR of RF coils using composite coil elements. *NMR Biomed.* 2009; 22(9): 952–959. [PubMed: 19582771]
39. Mylavarapu G, Murugappan S, Mihaescu M, Kalra M, Khosla S, Gutmark E. Validation of computational fluid dynamics methodology used for human upper airway flow simulations. *J Biomech.* 2009; 42(10):1553–1559. [PubMed: 19501360]

40. Vos W, De Backer J, Devolder A, Vanderveken O, Verhulst S, Salgado R, Germonpre P, Partoens B, Wuyts F, Parizel P, De Backer W. Correlation between severity of sleep apnea and upper airway morphology based on advanced anatomical and functional imaging. *J Biomech.* 2007; 40(10):2207–2213. [PubMed: 17178125]
41. Xu C, Sin S, McDonough JM, Udupa JK, Guez A, Arens R, Wootton DM. Computational fluid dynamics modeling of the upper airway of children with obstructive sleep apnea syndrome in steady flow. *J Biomech.* 2006; 39(11):2043–2054. [PubMed: 16098533]
42. Sung SJ, Jeong SJ, Yu YS, Hwang CJ, Pae EK. Customized three-dimensional computational fluid dynamics simulation of the upper airway of obstructive sleep apnea. *Angle Orthod.* 2006; 76(5): 791–799. [PubMed: 17029512]

Figure 1.

Relative tidal volume rejection scheme for retrospective gating. Flow is sensed through a nasal cannula coupled to a Biopac pressure sensor. The flow signal is fed into a data acquisition board which generates gating trigger pulses at each upward-going zero crossing of the flow signal (*i.e.*, end expiration). The program calculates the relative tidal volume for each inspiratory period (positive flow) and compares it to a reference tidal volume acquired earlier. The current tidal breath is then accepted if it is within a pre-determined range of the reference tidal volume (solid gray lines), and rejects it otherwise. In the case of rejected tidal breaths, an additional gating pulse is generated at the downward-going zero crossing (*i.e.*, end inspiration), as well additional pulses every 500 ms, dashed black lines). The gating pulses are then sent to the MRI scanner. By strategically setting the temporal rejection window on the MRI scanner, the short inspiratory-only period from each rejection will be judged as outside the scanner's "arrhythmia" rejection window; the data from this period are rejected and reacquired in the next valid period.

Figure 2.

Dynamic image quality. Both original sagittal acquisition images (A&C) as well as axial reconstructions (B&D) are shown for two patients, representing the extremes of airway contrast-to-noise from the subjects studied. Even in case of lower CNR (A&B), there was adequate soft tissue-to-airway contrast to allow automated segmentation of the airway and calculation of airway size waveforms from a single 1.1 mm thick slice over the respiratory cycle (insets). In comparison, the original axial image from the 2D scan (F) and the sagittal reconstruction (E) show inferior image quality, resulting in noisy performance of the automated airway segmentation and airway area waveform (inset) as well as the obvious disadvantage of a non-isotropic acquisition not permitting subsequent high quality reconstruction in an arbitrary image plane.

Figure 3.

Consistency of the respiratory flow pattern over the imaging acquisition. In each plot, the flow waveforms from the individual 91 acquisitions which were needed for the dynamic imaging are shown (black) as well as the mean flow waveform (grey). Each waveform has been scaled to a standard period (*i.e.*, respiratory period) and amplitude (*i.e.*, relative tidal volume) so that only differences in the flow pattern are highlighted. Three examples are shown with the three general patterns seen for the six subjects in the study, in which flow was either a) very tightly distributed about the mean flow pattern, b) had marked variation in the position of peak inspiration or peak expiration (most cases with variation were due to shifting of peak expiration), and c) contaminated with erroneous acquisitions in which a full cycle was collected over inspiration only (shown is the most extreme case, most subjects showed at most 1–2 such acquisitions). Upward-pointing arrows indicate end expiration and downward-pointing arrows indicate end inspiration.

Figure 4. Dynamic images over the respiratory cycle, starting at end expiration in the two OSA patients. One example shows only subtle changes in airway shape and size (mostly at the lateral edges) and very little contamination in the airway signal (OSA1, upper frames), while the other shows dramatic dynamic changes in airway size over the respiratory cycle and some airway contamination (OSA2, lower frames). While subject OSA2 had the largest variations in size over time as well as the largest airway contamination, this was also one of the largest patients studied, and the association between CNR and patient weight likely accounts for some of this contamination.

Figure 5.

Airway size changes over the cycle in three control subjects. In order to plot changes in the velopharynx and oropharynx (which may have very different mean size due to the widening of the airway in the oropharynx) on the same scale, mean airway size has been subtracted out. While the same general pattern is seen in all three examples, namely increasing size during inspiration and decreasing size during expiration, the exact timing of the size changes relative to gating signal (i.e. flow in the nasal cannula), as well as the relative timing of the size changes in the two regions, does not appear to have a consistent pattern. In one patient (Cntrl1, 5a), the proximal expansion of the airway occurs first, followed by distal expansion, in another (Cntrl3, 5b) the expansion of the airway occurs first distally followed by proximal expansion, while in the third (Cntrl2, 5c) the airway expansion at both levels occur synchronously. Upward-pointing arrows indicate end expiration and downward-pointing arrows indicate end inspiration.

Figure 6.

Airway size changes over the cycle in one patient with severe sleep apnea (OSA2). As in Figure 5, mean airway size has been subtracted from each waveform in order to allow plotting of all waveforms on the same scale. The waveforms calculated from individual axial slices are shown for airway position just superior to the constriction (a), 3 mm below the constriction (b) and 11 mm below that (c, just above the epiglottis). The airway above and below the constriction are moving exactly out of phase, expanding above when it is constricting below and vice versa. The constriction is at the lower edge of soft palate, as can be appreciated in Figure 2a. Upward-pointing arrows indicate end expiration and downward-pointing arrows indicate end inspiration.

Figure 7.

Timing of the airway size change over the length of the upper airway (from same patient depicted in Figure 6, OSA3), expressed as the Fourier phase shift in radians. The effect of the constriction on airway dynamics can be clearly seen in this graph, showing the phase shift at the site of the constriction (arrow), where the minimum size of the airway narrows to 6 mm².

Figure 8.

Three-dimensional surface renderings of the airway in one subject (Cntrl2). Except for certain portions of the nasopharynx where other low intensity structures were occasionally difficult to distinguish for the airway, the 3D retrospective-gating and contiguous nature of the sequence enable high quality reconstruction of the outer surface of the airway in all cases. A cine movie of all 10 frames of the dynamic image is available in the online supplement.

Table 1

Subject demographics, polysomnography results and respiratory parameters

	OSA1	OSA2	Cntrl1	Cntrl2	Cntrl3	Cntrl4
Age, yr	15	15	18	14	18	17
BMI, kg/m ²	34.1	41.5	36.6	46	24.8	30.9
AHI, events/hr	8.1	36.9	0	4.6	0.9	0
Snoring	moderate	severe	moderate	mild	mild	moderate
Resp. rate, min ⁻¹	19.3	19.9	23.7	30.8	15.3	17.6
Rate, min/max	15/25	15/39	16/30	25/40	12/20	12/30
rTV, min/max	44/154	49/225	46/195	32/173	45/195	25/214

AHI (apnea-hypopnea index) is a commonly used index for assessing severity of OSA, and is measured as the total number of apneic (cessation of respiration for > 8 sec) or hypopneic (O₂ sat drop of > 4%) events per hour. rTV (relative tidal volume) was measured from the flow waveform collected the nasal cannula, and thus was only a relative measure of net tidal volume, quoted as a percentage of the mean relative tidal volume over the scan. The large range for this variable indicate the amount of variability in relative tidal volume in these patients, which can be further limited through the gating rejection algorithm but obviously will impact scan efficiency and total scan time.

Table 2

Image quality measures

	OSA1	OSA2	Cntrl1	Cntrl2	Cntrl3	Cntrl4
Scan efficiency	88.35	65.47	47.64	90.10	58.71	65.00
SENSE artifacts	no	faint	no	faint	no	yes
CNR	7.71	6.10	9.14	6.42	9.32	9.56
Mean airway signal	15.1	17.8	12.1	16.1	12.3	13.6
Temporal COV	16.29	14.31	14.95	17.85	15.65	12.31
Flow consistency	4.8/6.3	12.6/7.2	2.7/4.2	9.6/5.7	5.3/7.1	5.6/5.8

All measures except for CNR are quoted as percentages. Scan efficiency indicates the length of time for collecting the image compared to the theoretical minimum scan time given the patient's respiratory rate, and was reduced from 100% due to scan rejections based on respiratory rate or relative tidal volume being outside of a pre-determined acceptance window. CNR, airway signal and temporal coefficient of variance (COV) were all measured within three airway ROI's (see definition in Methods). Flow consistency is the standard deviation of the timing of peak inspiration and peak expiration, quoted as a percentage of the average length of the respiratory cycle.