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Investigation of Hyperpolarized ^3He MRI Utility in Examining Human Airway Diameter Behavior in Asthma through Comparison with High-Resolution Computed Tomography

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Abstract

Rationale and Objectives—Application of a previously developed model-based algorithm on hyperpolarized (HP) ^3He MR dynamic projection images of phantoms was extended to investigate the utility of HP ^3He MRI in quantifying airway caliber change associated with asthma.

Materials and Methods—Airways of seven volunteers were imaged and measured using HP ^3He MRI and multidetector-row computed tomography (MDCT) before and after a methacholine (MCh) challenge. MDCT data was obtained at functional residual capacity (FRC) and one liter above FRC (FRC+1L).

Results—Comparison of the resultant data showed that HP ^3He MRI did not match MDCT in measuring the ratios of airway calibers before and after the MCh challenge in 37%–43% of the airways from the first six generations at the two lung volumes tested. However, MDCT did lead to the observation that 49%–69% of these airways displayed bronchodilation following MCh challenge.

Conclusion—The current implementation of HP ^3He MRI did not match the MCh-induced post-challenge to pre-challenge airway caliber ratios as measured with MDCT. Elevated parenchymal tethering due to bronchoconstriction-induced hyperinflation was proposed as a possible explanation for this airway dilation.

Keywords

Hyperpolarized ^3He MRI; asthma; HRCT; airways

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Introduction

High-resolution computed tomography (HRCT) has been the imaging modality of choice for assessing airways in asthma studies [1–5]. Numerous algorithms have been developed to process the acquired MDCT data [3,6–12]. Sophisticated software has been successfully developed for the visualization and 3D rendering of the airway tree [9,11–12]. However, multidetector-row computed tomography's (MDCT) employment of ionizing radiation makes it undesirable in the event that repeated imaging is necessary to follow the progress of disease.

Hyperpolarized (HP) ^3He MRI has been used to visualize ventilation distribution in both animals [13–15] and humans [16–18] during breathhold of HP ^3He . HP ^3He MRI has also been used to visualize the airways by acquiring the MR images as the gas travels down the respiratory airway tree of both animals [19–22] and humans [22–25]. HP ^3He MRI was able to observe correlations between ventilation dropouts and airways with low MR signal in broncho-challenged human subjects. Whether or not HP ^3He MRI could be an effective tool in evaluating airway constriction/dilation in asthmatics has become a subject of interest [26].

This study seeks to examine the utility of HP ^3He MRI and the model-based algorithm [27–28] to quantify human respiratory airway response to bronchial challenge, by comparing airway cross-sectional changes as measured from 2D ^3He MRI and 3D MDCT data. Instead of grouping imaged airways by size and confined to particular locations [29–32], this study tracked individual central airway calibers. HP ^3He MRI could be established as a viable alternative for quantitatively assessing bronchial response if it could be demonstrated that it measures airway diameter changes comparable to those derived from MDCT data. A successful trial would justify the advancement of HP ^3He MRI to clinical assessment of bronchial response, and enable the future evaluation of airways in asthma without risking unnecessary radiation exposure.

Methods

Subject Enrollment

The research protocol in this study was approved by the Partners Healthcare Institutional Review Board. Informed consent was obtained from all recruited subjects. Data were obtained from five asthmatic (3 male, 2 female) and two healthy (0 male, 2 female) subjects, ranging in age from 23–60.

A primary test for pulmonary function is the forced expiratory volume in one second (FEV_1) measured using spirometry. Asthmatics sought for this study were those with mild-to-moderate asthma, defined as diagnosed asthmatics having $\text{FEV}_1 \geq 60\%$ predicted without inhaled or oral steroids, asthma symptoms < 7 times a week requiring β_2 agonist use, and well-controlled on a low dose regimen of inhaled corticosteroids (168–504 μg Beclomethasone or 88–264 μg Fluticasone, or equivalent) [33]. Asthmatic subjects were diagnosed based on the dose of methacholine (MCh) at which they achieved a 20% drop in FEV_1 (PC_{20}) [34].

MRI Hardware and Imaging

MR imaging was carried out on a General Electric Signa LX 1.5T MRI scanner. For HP ^3He MRI, a heterodyne system was appended to the MRI system to enable imaging at the ^3He Larmor frequency. Signal was collected using a flexible quadrature wrap-around lung coil (Clinical MR Solutions, Brookfield, WI) tuned to the ^3He frequency.

^3He was hyperpolarized via collision spin exchange with optically-pumped rubidium [35] using a ^3He polarizer built in-house, achieving polarizations between 10–20%. For each scan, one liter of approximately 33% HP ^3He - 67% N_2 mixture was administered for the subject to

inhale. Each scan began immediately upon initiation of the inhalation. Subjects were instructed to try to inhale the one liter of gas within a 5–8 second period of time. The scans employed a Fast Gradient Echo pulse sequence acquiring coronal projection images with the following parameters: 46 cm FOV, 0.75 PhaseFOV, 128×256 matrix, 13°–14° flip angle, 1.048/3.404 ms TE/TR, 62.5 kHz bandwidth, minimum delay after acquisition as permitted by the scanner software (50 ms), 35 phases/location, and sequential phase acquisition order (resulting in 35 consecutive projection images acquired). Each scan took a total of 11 seconds. Zero-padded to 256×256 pixels, the images has resolutions of 1.8 mm.

CT Hardware and Imaging

The lung was scanned using a 64-slice MDCT scanner (Siemens Sensation 64) during breath hold at two lung volumes: functional residual capacity (FRC), and one liter above FRC (FRC + 1L). Scanner settings were: pitch 1.25, slice thickness 1.3 mm, slice increment 0.65 mm, 120 kV, 100 mAs. Each scan took no more than three seconds. The combined radiation dose from two chest CT scans was no more than 0.28 rem.

Protocol

Each subject came on two different days, and was imaged on each day using a different modality. On the day of the scans, subjects were asked to withhold caffeine consumption from the beginning of the day. Asthmatic subjects must have not used any fast-acting β_2 -agonist inhalers for at least eight hours, and long-acting β_2 -agonist inhalers for at least 48 hours.

Baseline FEV₁ values were first obtained through spirometry. The subject was then given the baseline scan, followed by an aerosol MCh challenge [34]. The MCh concentrations administered were, in mg/ml: 0 (diluent), 0.078, 0.156, 0.3125, 0.625, 1.25, 2.5, 5.0, 10.0, and 25.0. Every other MCh concentration in the challenge could be skipped until 10.0 mg/ml for healthy subjects, or until the concentration one order of magnitude below the asthmatic subject's known PC₂₀ dose. The MCh challenge ended upon causing a 20% drop in FEV₁ or the 25.0 mg/ml dose. A table of the maximum concentration administered to each subject using this protocol is presented in Table 1. After the maximum dose of MCh was administered, subjects were asked to refrain from deep breaths to maximize the probability of developing a bronchoconstriction response [36–37]. The MCh challenge took 29±6.5 minutes.

The subject then went through the second scan. All subjects must have returned to at least 90% of their baseline FEV₁ prior to being released from the experiment session. In the event this recovery did not occur spontaneously after all data acquisition, albuterol was used to aid this process.

Image Post-Processing

From the MDCT images, airways were measured using the airway visualization and 3D airway measurement software package Pulmonary Workstation (VIDA Diagnostics, Inc., Iowa City, IA 52242) [11–12]. This measurement methodology identifies the centerline of the 3D airway tree. The centerline defined branch points, which in turn defined the airway segments. The middle two-thirds of the airway segments were assessed by calculating oblique sections determined to be perpendicular to the segment centerline. Airway luminal edges were then determined to subvoxel resolution based upon a method that takes into consideration the measured point spread function of the scanner and reconstruction method employed [38].

An image was selected from the dynamic projection MR images based on airway visibility. In this image, diameters were measured from features judged to be clear and isolated airways that corresponded to airways measured in the MDCT data sets. The basis for qualifying an airway to be clear and isolated involved zooming in on the airway of interest, and determining that

the pixel intensity profiles followed a simple rise and fall pattern across sections along its length. For each airway, the start and end positions of the processed sections were prescribed to be distant enough from airway bifurcations, such that according to user judgment, the local rates of area change should be negligible. One airway section refers to a single cross-section as can be distinguished by HP ^3He MRI. Diameters of the chosen airway sections were measured using a model-based least squares fit approach [27]. Airways were labeled based on their bifurcation sequence on the HP ^3He MR images starting from the trachea. For example: LRR indicates that from the trachea, first follow the left main bronchus; follow the right airway at the next bifurcation, and the right airway again at the subsequent bifurcation.

All the diameter values from evaluating individual airway sections along the length of an airway were output from the MR images, enabling the computation of means and 95% confidence intervals for the airways. However, only the average values for airway segments' major and minor diameters were available from the CT data processing. Thus, using the airway cross-section geometry data from both imaging modalities, the degree of bronchoconstriction or dilation for each airway was evaluated by computing the ratios of the mean airway diameters after MCh challenge (postMCh) to the corresponding values before bronchoprovocation (preMCh). Because the MDCT data involved both major and minor diameters, the geometric means of these two numbers were used in computing the postMCh-to-preMCh diameter ratios. Only airways visible through both imaging modalities at least prior to MCh challenge were included in this analysis.

The postMCh-to-preMCh airway diameter observed using the two imaging modalities were plotted in two scatter plot. Both plots employed the same MRI-based results, but different CT-based results due to the two lung volumes. Two linear fits and evaluation of correlation were attempted for each scatter plot: no constraint was imposed on the first fit, while the second fit was required to pass through $(x,y)=(1,1)$.

Results

The HP ^3He MR images were acquired throughout the lung expansion from FRC to FRC+1L, while the MDCT images were acquired at the two lung volume end points. Due to its poorer resolution and non-recoverable signal source in this application, MRI was the limiting factor in identifying the airways for evaluation.

Figure 1 and Figure 2 show representative HP ^3He MR projection images and MDCT 3D rendering, respectively. We again point out that as the MR images were dynamically acquired during the inhalation process, their exact lung volumes between the FRC and FRC+1L end points could not be definitively known. It can be seen from Figure 1 that the SNR of the airways taper off very quickly with increasingly airway generation. The reduced SNR in increasingly distal airways raises the level of uncertainty for the measured diameters of those conduits. Some of the physical factors contributing to each airway's SNR include: initial ^3He gas polarization, rate of polarization consumption from RF pulse, rate of subject inhalation, and airway size. Because the testing of this protocol on airway phantoms [28] involved a mechanical syringe whose rate of gas introduction could be more stably controlled, as well as the phantom's consistent geometry, the subjective perception is that human airways are more difficult to identify than phantom airways. The SNR in the trachea and main bronchi from each subject's HP ^3He MR image before and after bronchial challenge is provided in Table 2 in the hopes of enabling the reader to estimate expected SNR in subsequent airways. Signal in the airways should scale linearly with the cross-sectional area of the airway and inversely with the number of pulses that has been applied to the local gas bolus.

Figure 3 shows the postMCh-to-preMCh diameter ratio with the MDCT data evaluated at FRC for the airways in the first three airway generations across the seven subjects, while Figure 4 shows the same for MDCT at FRC+1L. Appearance in the upper-right or lower-left quadrants indicates that the two imaging modalities qualitatively agree on whether the airways constricted or dilated. Breaking down into individual airway generations, agreement was found in 57% of the tracheas, 64% of the main bronchi, and 52% of the second-generation airways at FRC. Similarly, at FRC+1L, agreement was found in 57% of the tracheas, 71% of the main bronchi, and 57% of the second-generation airways. Overall, MDCT and MRI observed the same qualitative airway cross-sectional change in 47 (37%) out of the 127 airways observable in both imaging modalities at FRC, and 55 (43%) out of the 127 airways, at FRC+1L.

An unexpected observation was that through MDCT, a vast majority of the major airways dilated following the MCh challenge, as evidenced by the position of their data points being in the upper half of the plots in Figure 3 and Figure 4. This involved six out of the seven tracheas (86%), 13 out of the 14 first generation airways (83%), and 16 out of the 21 second generation airways (76%) at FRC. As for FRC+1L, this was observed in six out of the seven tracheas (86%), all of the first generation airways (100%), and 19 out of the 21 second generation airways (90%) at FRC+1L. As detailed in Table 3, of all the airways within the first six airway generations visible in both imaging modalities preMCh, a total of 49% were observed to dilate post-challenge at FRC, and 69% observed to dilate postMCh at FRC+1L. Due to greater difficulty in identifying airways in HP ^3He MRI, MRI was the limiting factor in finding airways visible in both imaging modalities. As airways constrict, the number of airways visible following MCh challenge reduces in both MDCT and MRI, and may vary between these two modalities. The unconstrained linear fit of the MDCT postMCh-to-preMCh diameter ratios at the two lung volumes with the MRI-based ratios returned correlation coefficients of -0.12 and -0.23 , for FRC and FRC+1L, respectively. The linear fit with the constraint that the line must pass through (1,1) yielded no correlation coefficient.

Discussion

The development of the model-based diameter measurement algorithm [27] had presented an opportunity for quantifying airway narrowing in asthmatics without ionizing radiation exposure associated. Previously, the same measurements for an anthropomorphic airway tree phantom [28] had four out of 14 airways that satisfied the defined criteria for diameter measurement concordance. Similarly, comparison of the limited data from HP ^3He MRI and MDCT for the seven human subjects of this study shows that HP ^3He MRI, in its current implementation (dynamic projection imaging protocol and/or the diameter measurement algorithm) did not produce measurements that match the airway caliber change determined with MDCT. Irrespective of whether the FRC or FRC+1L lung volume was used, examination of postMCh-to-preMCh diameter ratios revealed that agreement between HP ^3He MRI and MDCT on whether airways constricted or dilated did not exceed 75% in any individual airway generation. Furthermore, no meaningful correlation could be found between the airway caliber changes as observed using the two imaging modalities.

It must first be recognized, and emphasized, that fundamental differences in the approaches by which the airway cross-section is quantified with HP ^3He MRI and MDCT prevent a rigorous back-to-back comparison of the airway diameter measurements. HP ^3He MRI estimates cross-sectional diameters from 2D projection pixel intensity profiles on the assumption that all airway sections are circular, while the Pulmonary Workstation can manipulate 3D MDCT data to explicitly measure major and minor diameters in airway sections normal to the flow path. Because different geometric resolutions make it difficult to identify which airway sections in the HP ^3He MR images correspond to which airway sections in the MDCT data, section-by-section comparison of airway geometry could not be achieved. These issues and others

pertaining to the measurement of airway diameters using HP ^3He MRI have been previously discussed [28]. In light of the difference in the physical parameters being measured from the two imaging modalities, utilization of the geometric mean diameter acquired through MDCT should be limited to its original intended purpose: to provide a single-parameter proxy for evaluating luminal area constriction or dilation, rather than compare against MRI for evaluating concordance.

An obstacle to the assessment of the HP ^3He MRI modality for quantifying airway narrowing by comparison with MDCT was the difficulty in identifying corresponding airways between the 2D MR projection images and the 3D MDCT data sets. While the airways compared in this study were limited to those that could be identified with certainty on both imaging modalities, the presence of airways on either modality whose counterparts could not be determined has serious implications, especially if the airway is absent or indeterminate in the HP ^3He MR image. Tracking airways in HP ^3He MRI is particularly challenging as even unconstricted airways may not emit ^3He MR signal if all its downstream flow paths to the distal alveoli have been obstructed. The law of continuity in fluid mechanics prevents HP ^3He from even arriving at such airways. This implies that HP ^3He MRI may not depict all unconstricted airways, let alone accurately, so as to generate meaningful data for comparison with MDCT.

Measurement Accuracy

Despite the prevailing school of thought that peripheral airways have a significant role in the pathophysiology of asthma [39–40], the exact contributions of both central and distal airways remains unclear [41]. Though MDCT resolution may approach 0.25 mm, diameter measurement accuracy starts becoming a concern once airway luminal areas decrease to approximately 12 mm², or about 3–4 mm in diameter [7]. MDCT imaging, when applied to small airways less than 1–2 mm in diameter, is limited to inferring air trapping and scarring from the resultant density images [42]. These suggest that the lower bound of MDCT utility in directly measuring human airways is located somewhere between the seventh and ninth generation airways and assessments of airway behavior beyond would have to be indirect.

During the development of the model-based algorithm [27], results from processing images of hollow plastic tubes indicate that on average, the technique has a minimum error of approximately a quarter of a pixel. Assuming the airways are perfectly circular, with pixel dimensions of 1.8 mm, this translates to roughly 0.45 mm. However, the accuracy the model-based approach depends on how well the assumption that airway cross-sections are circular is satisfied. While measurement of the plastic tubes suggested that HP ^3He MRI is promising for measuring conduits of circular cross-section, results from anthropomorphic lung phantom experiments [28] foreshadowed that the lack of circular airway sections may be the key obstacle in using this tool to accurately measure individual diameters. Even in the absence of individual measurement concordances, if airways conserve their cross-sectional shapes in constriction or dilation, then the measurement errors would be bias errors, allowing the quantification of airway caliber change to move forward. In retrospect, however, comparison of major diameter-to-minor diameter ratios of the airways from the MDCT data reveals that the cross-sectional shapes of the airways have not been preserved.

It is expected that the HP ^3He MRI airway diameter measurement results will be sensitive to the SNR of the individual airways. The SNR issue is a complex and multi-faceted one. Individual airway SNR's depend on the polarization of the gas, the unsteady rate at which the subject inhales the gas, and the flip angle imparted by the continuous train of RF pulses. There are two sides to how the inhalation rate and flip angles affect the SNR: for larger airways, these two components decide how much signal is extracted; for smaller airways, these two components also decide how much signal survives to alveolar regions and obscure the airway

signal. Exactly how does diameter measurement errors increase with reduced airway SNR has not been quantified.

Potential Experimental Sources of Difference between MRI and MDCT Measurements

It is possible that the lack of agreement between the HP ^3He MRI- and MDCT- measured airway caliber changes was due to the airways responding differently on the two different days of experiment. Ventilation defects have been observed to differ in static ventilation images obtained from MCh challenges three weeks apart [43], suggesting variation in the airway response on the separate occasions. Fifteen months passed after the acquisition of MR images from HEAL2 before her MDCT images were obtained; for HEAL3, it was six months. On the other hand, the elapsed time between the acquisition of MR and MDCT images for the asthmatics ranged from two to 10.5 months.

A significant potential contributor to the diameter measurement differences may be that the airways were imaged via MDCT during a static breath hold while MRI imaging occurred throughout the inhalation of HP ^3He . An improved understanding of the issues related to dynamic airway HP ^3He MRI, including fluid mechanics (turbulence, velocity profiles, mixing, secondary flows), magnetic field inhomogeneity, motion artifacts, and signal dynamics associated with molecular scale interaction between polarized gas and airway surface, may lead to more rigorous ^3He MRI airway section pixel intensity profile processing algorithms. Once again, it was hoped that consistent protocol implementation would produce only bias errors, which cancel out when changes between airway states were evaluated.

We know of no instances where researchers were successful acquiring airway tree data using HP ^3He MRI at breathhold. It cannot be known a priori how much ^3He gas to give a subject such that the occupied volume of the ^3He mixture is limited to the airways only. Our own attempts at using such as approach consistently resulted in airway images with poor SNR even at the trachea. Our attempts at acquiring dynamic multislice airway images for the sake of comparing 3D MRI data to 3D CT data have also been stalled by several problems. The sequential acquisition of coronal images allowed ^3He gas in neighboring coronal slices to escape RF pulses and remain relatively highly polarized upon reaching the distal airways, effectively raising the “noise level” around airways. This prevented the algorithm from having a clean pixel intensity profile to evaluate, or worse, obscures airways of interest thereby hindering their identification in several coronal slice images. Slice thicknesses in the neighborhood of 13 mm is necessary to achieve sufficient SNR for static ventilation scans, but the same slice thickness for a dynamic multislice scan was unsatisfactory: voxels for constructing a 3D rendering of the airway tree were not isometric, having aspect ratios of 7.3, and the continuous RF pulsing resulted in lower surviving polarization and SNR at the smaller airways. The sequential image acquisition also resulted in individual slices being acquired at slightly different lung volumes, leading to minute discontinuities between airways across neighboring slices.

An approach that can circumvent the problems that prevent dynamic multislice imaging of the airway tree from producing a useful 3D rendering is the imaging of the airway tree by dynamic projection reconstruction. Projection images of the lungs can be taken in rapid succession, at different angles perpendicular to the superior-inferior axis of the subject. Individual axial slices can then be reconstructed by applying the Radon transform analysis. This approach consumes polarization more uniformly, preventing boluses of gas that still have significant polarization to reach the periphery, and circumvents the issue of high voxel aspect ratio. However, any implementation will be a trade-off between the angular resolution of the successive projection images, and the scan time which is constrained by how long the subject could sustain an inhalation. Because the images will still be acquired as the subject is inhaling the ^3He gas, motion artifacts affecting the present data will continue to affect those results. Our projection

reconstruction efforts were carried out by selecting scan parameters that best satisfy our functional requirements using a Fast Gradient Echo pulse sequence that was available on the GE Signa system. We achieved up to five generations of airway visibility, but airways were visible no more than one bifurcation away from the main airway tree structure. A devoted pulse sequence could streamline the acquisition algorithm to circumvent the inefficiencies of a clinical pulse sequence that was designed to accommodate a variety of scan configurations. This would result in higher spatial/angular resolution within the inhalation time frame, and such studies are being pursued [44–45].

Pathophysiological Implications

As shown in Figure 3 and Figure 4, and Table 3, the MDCT measurements indicate that most of the airways in the first six generations for which data were available dilated after the MCh challenge. Methacholine is a bronchoconstrictive agent, and should act to narrow the airways, rather than further opening them. The first mechanism that comes to mind that might explain this counter-intuitive observation is that shunting in the central airways may be occurring as a result of constriction in the peripheral airways. During the process of inhalation, the lungs exert a transpulmonary pressure to create a negative pressure difference between the pleural space and the alveoli and airways, to enable the inspiration of air. Prior to the MCh challenge, most (or all) of the airways were open, enabling one liter to be inhaled from FRC with minimal effort and relatively uniformly distributed to the alveolar units across the lung. However, with the administration of the MCh challenge, the pressure difference needed to inhale the one liter from FRC became larger than that required by an unobstructed lung, demanding a greater effort to sustain the alveolar and peripheral airway expansion necessary for pulling in the same air volume with less participating units. The higher net pressure of the air in the central airways relative to the pleural space and obstructed lung periphery remained insufficient to overcome the established constriction. Instead, it extended the local airway apparatus until the structural recoil balanced the transpulmonary pressure. As a result of this stretching, the central airways dilated.

The plausibility of this hypothesis was easily assessed by examining the postMCh-to-preMCh airway diameter ratios at FRC, where parenchymal tethering should play a much smaller role propping up the airway lumen than at FRC+1L. It was found that even at FRC, although a handful of extra airways from the first three generations displayed bronchoconstriction following the MCh challenge, the vast majority maintained a bronchodilatory response.

Two previous human studies using HRCT suggest the observation of bronchodilation in some of the measured airways. Following MCh challenge, Brown et al. [30] reported airway reductions with standard error values sufficient to suggest that for airways >7 mm at baseline, dilation instead of constriction after bronchoprovocation occurred in slightly less than half of the airways in healthy subjects, and slightly less than 16% of the airways in asthmatic subjects. Likewise, Bland-Altman plots put forth by King et al. [29] show 18.5% of measured healthy airways and 20.8% of measured asthmatic airways dilated following MCh challenge. Both studies include data from airways smaller than what we can measure using HP ³He MRI. Although the fraction of airways that bronchodilated following MCh challenge in these studies is much less than what we found, their presence is consistent with the possibility of obtaining such a counter-intuitive observation postMCh.

The only study to date found tracking individual airway diameters from baseline to after MCh administration is one involving mongrel dogs, in which ten airways spanning the first through the fourth generation airways were imaged using CT in each animal [46]. Methacholine challenge was administered to the dogs via intravenous injection, a decision made based on prior studies which found that aerosol administration of MCh induced constriction in both the airways and the parenchyma, while the response of injection-infused MCh was limited to the

airways [47–48]. Whether tensile tethering of airway structures due to parenchymal constriction arising from methacholine delivered via the aerosol route, or due to hyperinflation of a bronchoconstricted lung, could account for the difference in airway behavior following MCh challenge between this study by Han et al. and our study remains to be resolved.

Conclusion

HP ^3He MRI and MDCT data on airway diameters were obtained from seven human volunteers before and after MCh challenge. Airway caliber changed as captured using these two imaging modalities currently do not match. For HP ^3He MRI to be used in future clinical airway evaluation, additional work would be required in understanding the various physical and perhaps physiological processes that take place as the HP ^3He gas flows down the airway tree, to better characterize the airway section pixel intensity profiles imaged. An interesting result is that both imaging modalities show that a significant number of central airways dilated postMCh. However, comparing the measurements acquired using HP ^3He MRI against the current gold standard MDCT did not result in consistent trends in a large fraction of the airway diameter changes, i.e. some airways constricted in ^3He MR images but dilated in MDCT images. Nevertheless, the observation with MDCT-imaged airway data showing bronchodilation following a MCh challenge was unexpected. How airways could behave this way is unknown, and while we could offer speculations as to the reason behind such a response, these experiments were not designed to address the mechanism underlying this phenomenon.

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Figure 1.
HP ^3He dynamic projection MR images from subject ASTH21 a) baseline, b) after MCh challenge

Figure 2.
3D rendering of airway tree using HRCT from subject ASTH21 at FRC+1L a) baseline b) after MCh challenge

Figure 3.

Ratio of postMCh-to-preMCh airway caliber as measured using HP ^3He MRI and MDCT for first 3 airways generations of all subjects with MDCT data at FRC

Figure 4.

Ratio of postMCh-to-preMCh airway caliber as measured using HP ^3He MRI and MDCT for first 3 airways generations of all subjects with MDCT data at FRC+1L

Table 1

Maximum methacholine dose administered to each subject during imaging experiments

Subject	MCh dose [mg/ml]	
	HP 3He MRI	MDCT
HEAL3	25.0	25.0
HEAL4	25.0	25.0
ASTH1	10.0	5.0
ASTH 8	0.3125	0.156
ASTH 13	0.3125	5.0
ASTH 16	5.0	25.0
ASTH 21	25.0	25.0

Table 2SNR in the trachea and main bronchi from selected HP ^3He MR image before and after bronchial challenge

Subject	Tracheal SNR		Main Bronchi SNR [*]	
	preMCh	postMCh	preMCh	postMCh
HEAL3	67.7	89.7	70.9	71.9
HEAL4	120.8	108.1	75.1	62.4
ASTH1	133.4	97.1	79.7	38.5
ASTH 8	114.3	113.7	72.3	39.7
ASTH 13	98.4	92.2	75.4	67.8
ASTH 16	86.9	59.5	51.5	36.9
ASTH 21	107.8	94.7	90.7	63.8

* averaged from left main bronchus and right main bronchus

Table 3
Number of airways visible and their response as observed through the MDCT

Airway Generation	Airways visible with both imaging modalities*	CT measurements available both at preMCh and postMCh**		CT measurements indicate airway dilation due to bronchial challenge**	
		FRC	FRC+1L	FRC	FRC+1L
Trachea	7	7	7	6	6
1st	14	14	14	13	14
2nd	21	21	21	16	19
3rd	43	34	42	17	27
4th	26	16	20	7	13
5th	16	5	14	3	9
sum	127	97	118	62	88

* There are more airways visible with MDCT than with HP ³He MRI. The numbers reported here pertain to the airways visible with both imaging modalities before MCh challenge.

** The airways included in this counting are limited to those visible with both imaging modalities at baseline, as reported in the second column; not all airways visible in MDCT are amenable to measurement via MDCT.