ERJ Express. Published on April 18, 2013 as doi: 10.1183/09031936.00104512

TITLE: Spirometer controlled cine-magnetic resonance imaging to diagnose tracheobronchomalacia in pediatric patients

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Keywords: bronchoscopy, cine-MRI, CT, pediatrics, spirometer-controlled, tracheobronchomalacia.

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Abstract

Background

Tracheobronchomalacia (TBM) is defined as an excessive collapse of the intrathoracic trachea. Bronchoscopy is the gold standard to diagnose TBM, but bronchoscopy has major disadvantages, such as general anesthesia. Cine-CT is a non-invasive alternative to diagnose TBM, but its use in children is restricted by ionizing radiation. Our aim was to evaluate the feasibility of spirometer-controlled cine-MRI as alternative to cine-CT in a retrospective study.

Material and Methods

12 children (mean 12 years, range 7-17), suspected to have TBM, underwent cine-MRI. Static scans were acquired at end-inspiration and expiration covering the thorax using a 3D SPGR sequence. 3D-Dynamic-scans were performed covering only the central airways. TBM was defined as a decrease of the trachea or bronchi diameter greater than 50% at end-expiration in the static and dynamic scans.

Results

The success rate of the cine-MRI protocol was 92%. Cine-MRI was compared with bronchoscopy or chest-CT in 7 subjects. TBM was diagnosed by cine-MRI in 7 out of 12 children (58%) and was confirmed by bronchoscopy or CT. In 4 patients, cine-MRI demonstrated tracheal narrowing that was not present in the static scans.

Conclusions

Spirometer-controlled cine–MRI is a promising technique to assess TBM in children and has the potential to replace bronchoscopy**.** (197 words)

Introduction

Tracheobronchomalacia (TBM) is defined as an excessive collapse of the intrathoracic part of the trachea and/or main bronchi during expiration[1]. When TBM is suspected, a diagnostic bronchoscopy, which is the current gold standard, is used to confirm the diagnosis[1,2]. In pediatric populations, bronchoscopy has the disadvantage that it is invasive and requires general anesthesia, while the child maintains spontaneous breathing [1]. In addition, relevant daily life breathing maneuvers, such as forced expiration and coughing, cannot be routinely performed during the procedure[3-4]. Bronchoscopy using conscious sedation, which preserves spontaneous ventilation for the evaluation of TBM, is used in adults. [4]. However, in children this technique is in general not feasible due to lack of cooperation[4]. Finally, bronchoscopy does not provide exact measurements of airway dimensions as imaging techniques can supply[3,4,5].

For these reasons, as alternative to bronchoscopy, cine-computed tomography (cine-CT) has been used to assess TBM[6]. An advantage of this technique is that the collapsibility of trachea and main stem bronchi can be evaluated during static and dynamic conditions[7,8,9]. However cine-CT to detect TBM exposes the patient to ionizing radiation[1], which is a more significant problem for children than adults because they are more susceptible to the harmful effects of ionizing radiation[10-14]. Cine-Magnetic Resonance Imaging (Cine-MRI) might be an attractive, radiation-free alternative to cine-CT to diagnose TBM [15-19]. Recent improvements in MR technology (ultrafast imaging) allow dynamic evaluations of the central airway dimensions (cine-MRI)[15]. Ideally, breathing maneuvers during cine-MRI should be standardized using cine-MRI spirometry. A MRI compatible spirometer was recently developed and tested[20]. To our knowledge, spirometer controlled cine-MRI has not been applied before in TBM assessment[16, 18].

We have previously demonstrated feasibility of the spirometer-controlled cine-MRI protocol in healthy adult volunteers [21]. The aim of this study was to retrospectively evaluate the diagnostic feasibility of this protocol in a group of children, who needed a chest MRI for various indications and in whom the treating clinician requested assessment of TBM to be included in the evaluation. In this paper we describe our methodology and the results of a retrospective image analysis of static and dynamic changes in central airway dimensions in 12 patients.

(354 words)

Material and Methods

MRI

The cine-MRI protocol for the diagnosis of TBM was developed in 10 healthy adult volunteers (mean age 31 years, range 30-33 year) for which approval was obtained from our institutional ethics committee[21]. Scanning was performed using a 1.5T Signa Hdxt MRI (General Electric Healthcare, Milwaukee, WI, USA) using the whole body coil for radio-frequency (RF) excitation and an 8-channels torso coil for signal reception. The protocol consisted of static and dynamic acquisitions. Three-dimensional (3D) "static" images at TLC and RV were acquired by two 13-second breath-holds covering the complete thoracic region at end-inspiration and end-expiration using a 3D rf-spoiled gradient echo sequence (SPGR) with TR/TE=1.4/0.6ms, flip angle 2°, sagittal volume acquisition with a true isotropic 3.0 x 3.0 x 3.0 mm^3 voxels. 3D cine-MRI acquisitions were acquired with the same imaging parameters and voxel resolution but only covering the trachea and main stem bronchi (12 cm sagitally). This was used to measure their dimensions and to monitor in pseudo-real time the airway dimensions to detect dynamic TBM during forced expiration and cough. The temporal resolution of 400 ms per volume was achieved using the Temporally Resolved Imaging of Contrast Kinetics -TRICKS- scan platform with accelerated imaging options[22]. 48 volumes were collected in 19 seconds. Overall acquisition time per patient including localizers, adjustments, breathing instructions and executing all scans was around 15 minutes (range 9-20 minutes).

Bronchoscopy

Bronchoscopies in 6 out of the 11 patients were carried out by a pediatric pulmonologist as part of diagnostic workup in routine patient care, using a flexible bronchoscope with external

diameter 3.5 mm or 5.5 mm (Olympus; Tokyo, Japan) during general anesthesia while maintaining spontaneous breathing. Airway malacia was diagnosed by visual inspection of airway shape and dynamics during spontaneous breathing without positive end-expiratory pressure, and during spontaneous coughing in case this occurred. Malacia was defined as collapse of at least 50% of the airway lumen, during the expiration phase while spontaneous breathing or while the patient was coughing [2].

Breathing instructions

Pediatric patients, who needed a chest MRI for various clinical indications and in whom the treating clinician requested assessment of TBM based on their clinical presentation, were scheduled for a spirometer controlled cine-MRI. Half an hour before the MRI all children did a routine upright spirometry coached by a lung function technician. Next, the required breathing maneuvers were repeated in supine position on a stretcher using a MRI-compatible spirometer (custom made Masterscope, CareFusion, Houten, The Netherlands). The purpose of the training were: 1) to monitor and standardize breathing maneuvers by using spirometer volume data during the MRI; 2) to reduce anxiety related to MRI investigations; and 3) to increase the number of successful MRI investigations. For the static MRI acquisitions, children were trained to obtain a maximal breath hold time of 15 seconds at ≥95% of the inspired vital capacity (VC) and at ≥ 90% of the expired VC. For the dynamic cine-MRI sequences, patients were asked to perform 2 expiration maneuvers, both starting at ≥95% of the inspired VC. The first dynamic maneuver was a full forced expiration, which was done as follows. From tidal breathing, patients were asked: 1) to take a deep breath to reach ≥95% of inspired VC; 2) to hold his/her breath for few seconds; 3) to perform a forced expiration to reach ≥90% of the expired VC; 4) to hold his/her breath for a few seconds and 5) to breathe quietly i.e. tidal volume breathing. The second

dynamic maneuver was a full expiration maneuver while the patient produced a series of repeated coughs starting at ≥95% of inspired VC up to ≥90% of the expired VC

After the training session, the patient was transferred to the MRI scanner. Breathing instructions during the MRI were given by the same lung function technician that performed the training, using the MR compatible built-in patient audio system. During the MRI investigation, the lung technician sitting next to the MRI-technician monitored the inspired and expired volumes and dynamic flows on the computer screen of the MRI-compatible spirometer setup (Fig.1). Based on the spirometer data, the lung function technician instructed the MRI-technician on when to start or stop the scans in case of patient error.

Image analysis

The first post-processing step for the lung and central airway images was performed on the scanner console and consisted of equalizing the inhomogeneity/signal attenuation of the receiver array coil by using a surface coil correction intensity algorithm (SCIC) and adaptive filtering to enhance the signal-to-noise ratio (SNR). Image quality criteria were defined for both static and dynamic scans. Static scans were repeated if blurring of structures and ghosting were observed. Dynamic scans were repeated when excessive blurring and ghosting of the chest wall was observed. The latter was indicative of a lack of temporal resolution or due to a suboptimal breath-hold, as shown on the spirometer screen.

The image data were then transferred to an Advantage windows workstation, or onto the Advantage Windows Server (General Electric Healthcare, Milwaukee, WI, USA) to perform cine multi-planar reformats (MPR) from the 3D cine-MRI data collected. The MRIs were jointly

evaluated by two radiologists (PC, MHL) and a standard report was written. For the retrospective analysis, all images were assessed by a radiologist (PC) blinded to all clinical data using manual tracing as described below.

The manual assessment started by analyzing both the end-inspiration and end-expiration static volumes in the 4D MPR platform. Reformats were performed to measure the diameters of the trachea and main stem bronchi using a window and magnification setting (zoom factor 3.0). Windowing was performed by setting the window level at one half the maximum signal recorded around the trachea with a window width of 0. First, the narrowest section of the trachea in expiration was determined using a 2D caliper to measure the anterior-posterior (AP) diameter in a view perpendicular to the trachea midline (Fig 2). To compare the degree of narrowing, a similar section angled according to the main tracheal axis, was reformatted using the surrounding anatomical structures as spatial reference and the distance to the carina. Next, the dynamic acquisitions (both forced expiration and coughing) were evaluated in cine-mode on the 4D reconstruction platform both in longitudinal and perpendicular views of the trachea to determine which one of the 48 volumes showed the greatest tracheal collapse (Fig.3). Having selected the "most collapsed" volume, the same distance measurements were performed as described for the breath-hold acquisitions.

TBM was defined as a reduction in airway AP diameter of the trachea of > 50% between static end-inspiration and end-expiration scans or between end-inspiration and dynamic scans as routinely used in the bronchoscopy assessment of TBM[17]. This definition was used to compare the diagnosis of TBM using cine-MRI with the subjective diagnosis made by the physician for those patients in whom a bronchoscopy was performed.

Comparison between MRI and bronchoscopy or CT

In 6 subjects bronchoscopy reports were available which were compared to 3D cine-MRI. Since in bronchoscopy TBM is diagnosed by visual assessment and not by exact measurements of airway dimensions, bronchoscopy reports were used to verify the 3D cine-MRI findings. In one subject, only a spirometer controlled CT was available for confirmation of the diagnosis of TBM. For this patient, Chest CT images were compared to cine-MRI findings.

(1205 words)

Results

Our retrospective analysis included 12 pediatric patients (Table I), who all had a cine-MRI made for various clinical diagnostic reasons. Informed consent was obtained from the parents of the patient for anonymous analysis of the data and registered in the electronic patient record. Approval for this retrospective study was obtained from the institutional review board.

The success rate of the MRI protocol was 92 %, only one participant was not able to successfully complete all required breathing maneuvers because of fear induced by the noise in the MRI scanner. Images were of diagnostic quality for analysis in all subjects, except for the patient mentioned above. Airway dimensions measured by the manual assessment are displayed in table 1. TBM was diagnosed in 7 children (58%): patient B, C, D, F, L, M and N (See Table 1). In patients B and C, TBM was visible on the static and dynamic MR images, whereas in patients D, F, L, M and N, TBM was visible only in the dynamic MR acquisitions. Patient B and N had severe TBM that involved the trachea at the level of the carina and the left main bronchus. In patient B, who declined bronchoscopy, a follow up chest-CT scan confirmed the diagnosis of TBM. Patient C had TBM 1 cm above the carina, confirmed by bronchoscopy (Fig.3). Patient D had complete collapse of the left main bronchus during forced expiration, which was defined as "isolated distal narrowing" by bronchoscopy. Patient F had a severe TBM just above the carina clearly visible during forced expiration, which was confirmed by bronchoscopy evaluation (Fig. 4-5). Patient L and M had TBM about 1.5 cm above the carina bifurcation. Patients H and I had negative results for TBM both on MRI and bronchoscopy assessments. Patients A, E, and G resulted negative for TBM to cine-MRI assessment and no further diagnostic procedures was felt necessary by the treating physician Patients L and M resulted positive for TBM by cine-MRI assessment, further assessment by bronchoscopy was proposed by the treating physician but

declined by the parents. Hence, for all 7 patients with available bronchoscopy/CT, cine-MRI was in concordance with bronchoscopy/CT for the presence or absence of TBM. For 4 patients this could not be evaluated.

(372 WORDS)

Table I. Evaluation of the Pediatric Airway.

Patient	Age	Sex	Clinical diagnosis and indication MRI	Cine-MRI	Bronchoscopy	CT	Ins (mm)	Exp (mm)	%Δ	Ins (mm)	Exp (mm)	%Δ	Notes on the point of maximal collapse
							Static			Dynamic			
A	11	M	Recurrent upper airway infections and atypical cough	No TBM	NA	NA	11.3	9.7	14.15	18	12.1	32.77	--------
B	15	F	Cystic fibrosis, routine bi-annual examination	TBM	NA	TBM	13	4.2	67.7	13	4	69.23	Static, TM and LBM (ØΔ= 52.88% (10.4 vs. 4.9 mm)
C	7	M	Tracheo-oesophageal fistula, recurrent lower airway infections	TBM	TBM	NA	11.5	6.2	46.08	11.3	4.2	62.83	TM, :dynamic and complete collapse above carina
D	13	M	Atrial Sept Defect Type II, recurrently lower airway infections	BM	BM	NA	12.1	10.5	13.22	10.5	8.1	22.85	LBM, dynamic and complete collapse of left Bronchus
E	14	F	Chronic cough	No TBM	NA	NA	12.5	9.5	24	12.5	8.4	32.8	--------
F	17	M	Lower respiratory tract infections, Laryngomalacia	TBM	TBM	NA	13.3	8.4	36.84	11.3	4.2	62.83	TM above carina
G	11	F	Chronic cough	Incomplete	NA	NA	15.3	13.4	12.41	15.4	10.1	34.41	--------
H	9	M	CCAML, and recurrent infection	No TBM	Mild laryngomalacia	NA	12.2	7.8	36.06	11.9	7.1	40.33	--------
I	15	M	Therapy resistant asthma	No TBM	Normal anatomy	NA	12.9	8.3	35.65	12.9	7.5	41.86	--------
L	16	M	Premature, therapy resistant asthma	TBM	NA	NA	17.2	11.8	31.39	17	5.6	67.05	--------

M	13	M	Atypical Asthma	TBM	NA	NA	13.5	8.8	34.81	13.3	6	54.88	--------
N	11	F	Cardiomyopathy and Frequent upper and lower airway infections	TBM	TBM	NA	11.8	9	23.72	11.8	5.1	56.77	Dynamic, (T and LMB)

TBM=Tracheobronchomalacia, BM= bronchomalacia; TM=tracheomalacia; LBM= left bronchomalacia; B=bronchoscopy; CCAML = Congenital Cystic Adenomatoid malformation of the lung; CT=computed tomography; NA not available; T=trachea LMB=Left Main Bronchus; INS=inspiration; EXP=expiration, %Δ=caliber reduction expressed as a % of inspiratory cross sectional area.

Discussion

Our retrospective study shows that Spirometer-Controlled 3D Cine-MRI is a promising technique in children for the static and dynamic evaluation of central airway dimensions and could potentially replace bronchoscopy for the evaluation of TBM.

Cine-MRI versus Bronchoscopy

The most important advantage of 3D cine-MRI was that airway dimensions could be studied during standardized static and dynamic breathing maneuvers, such as forced expiration and cough. The use of a MRI compatible spirometer allowed us to monitor in and expiratory flows and volume during the MRI acquisitions [20]. By acquiring simultaneous functional and morphological data, the severity of the TBM can be established in a standardized fashion.

To evaluate airway dimensions using bronchoscopy in a child, general anesthesia is mostly needed. The challenge for the anesthesiologist is control the level of anesthesia in such a way that the child continues to breathe spontaneously. In case anesthesia is not deep enough the patient begins to move and often coughs, this is a situation, which the anesthesiologist in general tries to avoid. In case anesthesia is too deep or when muscle relaxation is used, spontaneous breathing stops and positive-pressure ventilation is needed which can obscure TBM due to the positive trans pulmonary pressure. Conscious sedation, which allows controlled breathing maneuvers during flexible bronchoscopy can be attempted. However, in children, this technique is not used routinely since it is highly dependent on cooperation, which is considered challenging for most children. [4]. Hence, cine-MRI in children of eight years and older is an attractive alternative for bronchoscopy to study airway dimensions using standardized breathing maneuvers.

The second advantage of cine–MRI was that it allowed us to obtain objective airway dimensions using post-processing image analysis tools. This is complicated to do with bronchoscopy and therefore, not routinely done[5]. Despite developments in bronchoscopy optics, the image remains essentially two-dimensional and distorted[5]. Hence, the diagnosis of malacia using bronchoscopy is mostly subjective and not very reproducible[5]. Importantly MRI has multiplanar imaging capabilities, so 3D data sets can be reconstructed providing measurements in every possible plane and cross-section[16,18].

The third advantage of 3D cine-MRI is that the procedure is less invasive relative to bronchoscopy, since it does not require general anesthesia and anesthesia related risks can be avoided. Bronchoscopy under general anesthesia introduces a small risk of complications, such as respiratory depression, oxygen desaturation, apnea, bradycardia, epistaxis, airway bleeding, excessive cough, transient laryngospasm, procedure induced atelectasis, pneumothorax and in rare cases, even fatalities [3-4].

Cine-MRI versus cine-CT

The most important advantage of cine–MRI compared with cine- CT was that it did not expose the children to ionizing, which is a greater risk for children than adults[10-14]. Since cine-MRI does not require ionizing radiation, all required breathing maneuvers can be tested without concerns for radiation exposure. In addition, the procedure can be repeated when not executed correctly. In our group of patients, we had to repeat at least one acquisition per examination in 50% of tested children. Hence, this could be done without adding risks for the child.

Feasibility of spirometer controlled cine-MRI

Cine-MRI also has a number of limitations, the most important of which is the need for optimal cooperation by the patient. This is a clear challenge, especially in young children. Most children are able to do spirometry from age 6 years and older, however, having a child enter the bore of the MRI covered by a body-coil, with a spirometer in their mouth (Fig. 1c), followed by the requested breathing maneuvers, requires careful preparation and coaching. In general we consider our spirometer-controlled cine-MRI feasible for children 8 years and older. In our small series, we only had one child, who was 11 years old, that could not complete the intended maneuvers.

The second limitation of our cine MRI protocol was the low spatial resolution. Clearly, the resolution of the MRI images is inferior to that of CT[9]. In our MRI protocol we obtained an isotropic voxel of 3.0 mm^3, which is inferior to the submillimetric voxels that can be achieved with CT[9]. However, this resolution was sufficient to detect the reduction of the airway lumen of the large airways, whit diameters ranging from 1 to 2 cm in children 6 to 18 years[24]. For smaller airways and dynamic images a higher spatial resolution will be needed. We expect that by using parallel imaging, a dedicated torso coil and a higher field strength, spatial and temporal resolution can be further improved in the near future.

Further validation

A major limitation of our retrospective study is that we evaluated a small selected group of patients. However, the main aim of our study was to test the feasibility of the method for later use on a larger scale with a more heterogeneous group of patients [25] Therefore, further validation of cine-MRI as a diagnostic method for TBM is required using a prospective study.

We aim to do this comparing the diagnostic performance of bronchoscopy to Spirometer-Controlled 3D Cine-MRI.

Conclusions

This retrospective study showed that spirometer-controlled 3D cine-MRI is a promising method to assess static and dynamic changes of central airway dimensions when TBM is suspected. Cine-MRI may be a more sensitive, faster and safer alternative for the diagnosis of static and dynamic TBM in cooperative children than bronchoscopy or cine-CT. Further prospective validation studies are required comparing the sensitivity and specificity of cine-MRI versus bronchoscopy and/or CT to diagnose TBM.

(891 words)

TOTAL WORDS COUNT 2264

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Figure 1

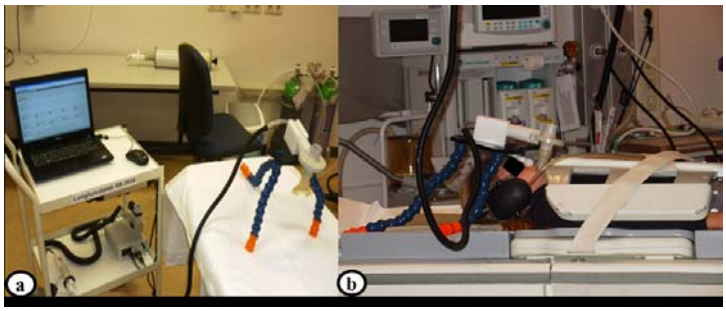

Figure 2

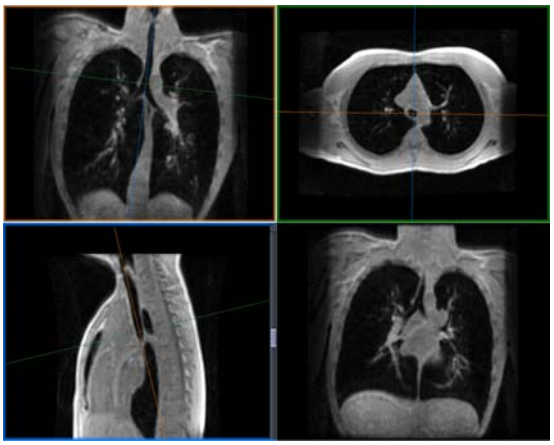

Figure 3

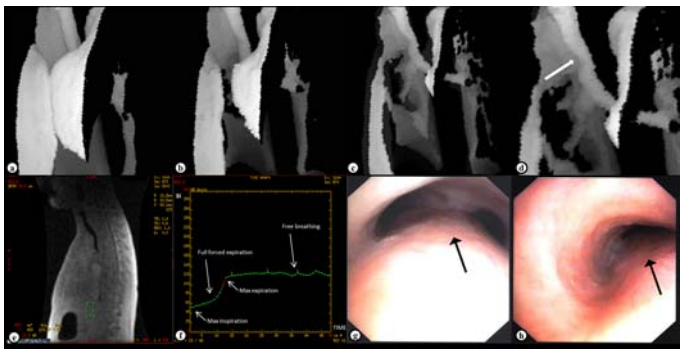

Figure 4

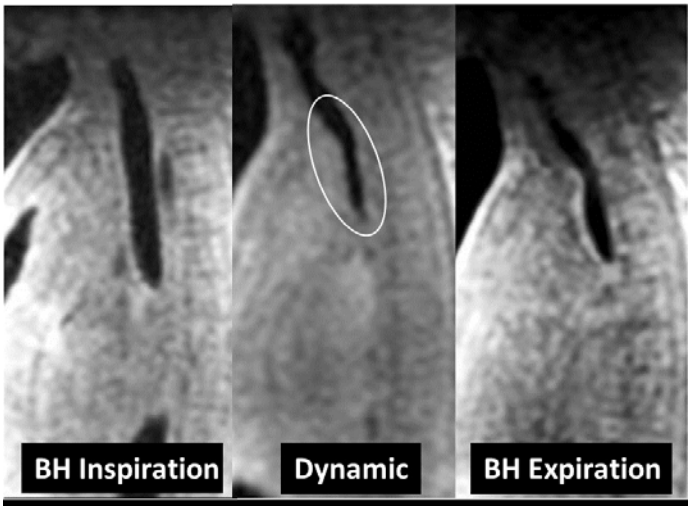

Figure 5