Evaluation of bronchial wall thickness in asthma using magnetic resonance imaging

Ilyes Benlala [1,2,3], Gaël Dournes [1,2,3], Pierre-Olivier Girodet[1,2,3], Thomas Benkert[4], François Laurent[1,2,3] and Patrick Berger [1,2,3]

[1]Centre de Recherche Cardio-thoracique de Bordeaux, Universite de Bordeaux, Bordeaux, France. [2]CHU Bordeaux, Service de Radiologie et d'Imagerie Diagnostique et Interventionnelle, CIC-P 1401, Service d'Exploration Fonctionnelle Respiratoire, Bordeaux, France. [3]INSERM, Centre de Recherche Cardio-thoracique de Bordeaux (U1045), Centre d'Investigation Clinique (CIC-P 1401), Bordeaux, France. [4]MR Application Predevelopment, Siemens Healthcare GmbH, Erlangen, Germany.

Corresponding author: Patrick Berger (patrick.berger@u-bordeaux.fr)

Shareable abstract (@ERSpublications)
Magnetic resonance imaging of the lung using sequences with ultrashort echo times is a radiation-free alternative to computed tomography to assess bronchial thickness in asthma, and will help improve the management of severe asthma https://bit.ly/3fGLE4B

Cite this article as: Benlala I, Dournes G, Girodet P-O, *et al*. Evaluation of bronchial wall thickness in asthma using magnetic resonance imaging. *Eur Respir J* 2022; 59: 2100329 [DOI: 10.1183/13993003.00329-2021].

This article has supplementary material available from erj.ersjournals.com

Received: 3 Feb 2021
Accepted: 20 May 2021

Abstract

Background Bronchial thickening is a pathological feature of asthma that has been evaluated using computed tomography (CT), an ionising radiation technique. Magnetic resonance imaging (MRI) with ultrashort echo time (UTE) pulse sequences could be an alternative to CT.

Aims The primary aim of this study was to measure bronchial dimensions using MRI-UTE in asthmatic patients by evaluating the accuracy and agreement with CT, by comparing severe and non-severe asthma and by correlating with pulmonary function tests.

Methods We assessed the bronchial dimensions of wall area (WA), lumen area (LA), normalised wall area (WA%) and wall thickness (WT) by MRI-UTE and CT in 15 patients with non-severe asthma and 15 age- and sex-matched patients with severe asthma (NCT03089346). Accuracy and agreement between MRI and CT was evaluated using paired t-tests and Bland–Altman analysis. Reproducibility was assessed using the intra-class correlation coefficient and Bland–Altman analysis. Non-severe and severe asthmatic parameters were compared using t-tests, Mann–Whitney tests or Fisher's exact tests. Correlations were assessed by Pearson or Spearman coefficients.

Results LA, WA% and WT were not significantly different when measured by MRI-UTE and CT, with good correlation and concordance. Inter- and intra-observer reproducibility was moderate to good. WA% and WT were both higher in patients with severe asthma compared to non-severe asthma. WA, WA% and WT were all negatively correlated with forced expiratory volume in 1 s.

Conclusions We have demonstrated that MRI-UTE is an accurate and reliable radiation-free method to assess bronchial wall dimensions in asthma, with enough spatial resolution to differentiate severe from non-severe asthma.

Introduction

Asthma remains a frequent chronic airway disease worldwide [1], causing a high burden to patients and healthcare systems and presenting a need for better management and, ultimately, prevention and cure [2]. Asthma is a heterogeneous disease, characterised by various patterns of bronchial inflammation and remodelling [3] that are related to multiple pathophysiological processes. Improved measurement of these pathophysiological processes is needed to enable better phenotyping of this disease, and to go beyond the highly limited measurements that are currently used: spirometry and symptoms [2].

Both bronchial inflammation and remodelling increase bronchial wall thickness, which is the main morphological characteristic of stable asthma, and which can be assessed using *post mortem* specimens

[4, 5] as well as in a noninvasive fashion. Indeed, proximal bronchial wall dimensions have been extensively assessed in asthma using computed tomography (CT) [6–12]. From a methodological point of view, wall thickness and/or area was initially evaluated manually in grossly vertical bronchi such as the apical bronchi of the upper lobes [9]. Semi-automated methods were then developed, first in two dimensions [13] and then in three [14]. Using these various methods, bronchial wall thickness assessed by CT has been repeatedly shown to be a reliable parameter for assessing asthma severity [6–12]. Moreover, bronchial wall dimensions assessed by CT have been associated with immunohistological markers of bronchial inflammation and remodelling [11, 12] and with airflow obstruction assessed by lung function testing [6–9]. In addition, these measurements have been used as secondary end-points in clinical trials and longitudinal studies in severe asthma [15, 16]. However, the risk of developing cancers with cumulated X-ray exposure has been shown to be non-negligible, at least with standard dose CT [17–19]. Therefore, a non-ionising modality is needed as an alternative to CT, especially in clinical trials that require repeated examinations to test new therapeutics in asthma.

Magnetic resonance imaging (MRI) of the lung could be considered as a free-ionising radiation alternative to CT, although the low signal acquired from lung structures using conventional proton MRI has limited its use in asthma [20]. Indeed, for years, airway measurements in asthma have never been reported using lung MRI because it was technically impossible to get the airway signal. However, recent developments in lung MRI with the use of ultrashort echo time (UTE) pulse sequences have improved spatial resolution and image quality, leading to isotropic millimetric voxels with structural information close to that of CT [21]. Such MRI-UTE has been successfully validated in cystic fibrosis and chronic obstructive pulmonary disease (COPD) compared to CT [22–24]. To the best of our knowledge, however, the use of MRI in asthma has been limited to functional MRI using either hyperpolarised gas or proton MRI [25–27]. Most of the time, this functional MRI requires expensive contrast agents, *e.g.* hyperpolarised helium or xenon, with short half-lives, limiting its use to the measurement of ventilation heterogeneity and clinical research in a very small number of expert centres [20]. Thus, the primary objective of the present study was to measure proximal bronchial wall dimensions using MRI-UTE without any contrast agent in asthmatic patients by evaluating the accuracy and agreement with CT. Secondary objectives were 1) to determine the reproducibility of MRI-UTE bronchial measurements, 2) to compare bronchial wall dimensions in patients with non-severe and severe asthma and 3) to assess their correlations with lung function. We also compared bronchial wall dimensions in patients with chronic obstructive and intermittent obstructive asthma.

Materials and methods

A complete description of all methods used in this study is provided in the supplementary material.

Subjects

Asthmatic patients aged >18 years were eligible for enrolment if they satisfied all inclusion and exclusion criteria (supplementary methods). Patients were categorised as having either non-severe or severe asthma according to the American Thoracic Society/European Respiratory Society task force guidelines [28].

Study design

This prospective single-centre study was performed between May 2017 and June 2018. The local ethics committee approved the study and all participants were required to give written informed consent (ClinicalTrials.gov number: NCT03089346). The study was funded by Novartis SAS, France, and sponsored by the University Hospital of Bordeaux.

15 patients with severe asthma were sex- and age-matched with 15 patients with non-severe asthma. All participants underwent a chest CT scan and MRI-UTE on the same day, with pulmonary function testing (PFT) within a maximum interval of 30 days.

MRI and CT examinations

Three-dimensional (3D) lung MRI-UTE was performed with a 1.5 Tesla system (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany) using a prototypical 3D-gradient echo Spiral VIBE sequence with a voxel size of 1 mm^3. Respiratory synchronisation at end normal expiration was allowed by an automated navigator-triggered prospective synchronisation [23].

Unenhanced chest CT images were acquired with a 64-slice multidetector CT scanner (Somatom Definition; Siemens Healthcare) at end normal expiration and with a voxel size of 0.625 mm^3. Images were reconstructed using standard (B30f) and sharp (B70f) algorithms.

Bronchial measurements

Segmentations of bronchial wall area (WA) and lumen area (LA) using CT and MRI-UTE were performed manually in random order and blinded from other participant data using commercial software (Myrian, Montpellier, France) (figure 1 and supplementary figure E1) [29]. A set of four bronchial paths was analysed at the third generation, starting from RB1 (right upper lobe), RB10 (right lower lobe), LB1 (left upper lobe) to LB10 (left lower lobe). Measurements made over these four bronchial paths were averaged to get a single mean value per patient and per imaging method for each bronchial parameter.

The percentage of bronchial wall area (WA%) was calculated as WA%=(WA/WA+LA)×100. The plain wall thickness (WT) was calculated as previously described [16].

Lung signal intensity was assessed automatically using MRI-UTE, as described previously [24]. The skewness of the lung signal intensity distribution curve was also determined automatically [24].

Assessment of reproducibility

Bronchial measurements performed by IB and GD using MRI-UTE were analysed to assess inter-observer reproducibility. The junior reader (IB, 5 years of thoracic imaging experience) repeated MRI bronchial measurements 2 months later, in random order and blinded to previous measurements, to prevent recall bias and assess intra-observer reproducibility.

Statistical analyses

Comparisons of quantitative and categorical variables were performed using t-tests or Mann–Whitney tests and Fisher's exact tests, respectively. Accuracy and agreement of bronchial measurements assessed by MRI-UTE in comparison to CT was evaluated by paired t-tests and Bland–Altman analysis. Univariate correlations were evaluated using Pearson or Spearman tests. Reproducibility was assessed using intra-class correlation coefficients (ICC) with 95% confidence intervals and Bland–Altman analysis. A p-value <0.05 was considered statistically significant.

Results

Study population

In total, 30 participants were prospectively enrolled, including 15 with non-severe asthma and 15 with severe asthma. Patient characteristics, including maintenance treatment, are presented in table 1. Because

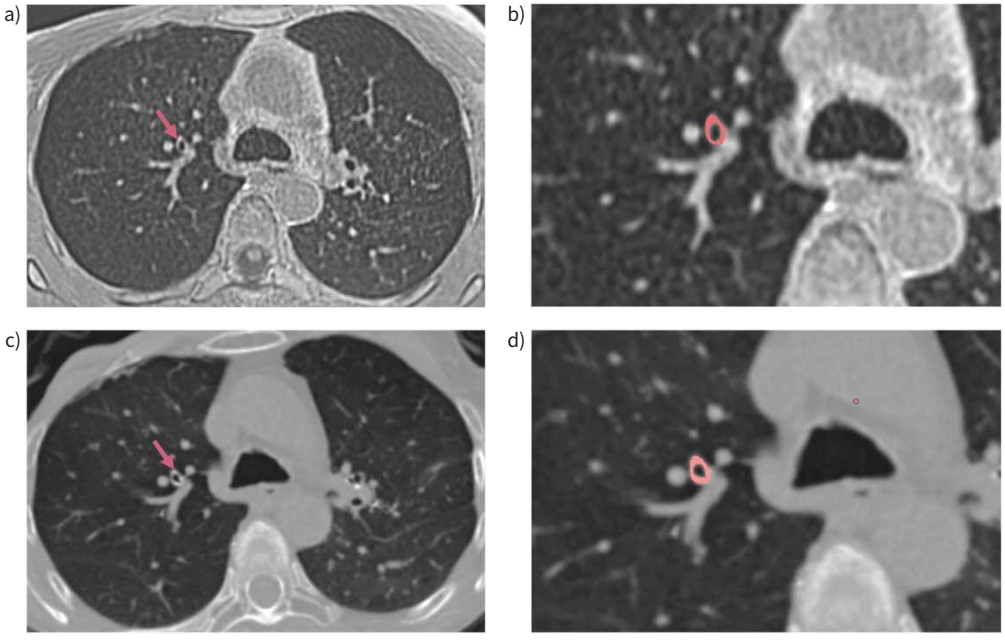

FIGURE 1 Representative lung images from a 59-year-old patient with severe asthma. Visualisation of wall area measurements of RB1 (right upper lobe) (red arrow) using magnetic resonance imaging with ultrashort echo time pulse sequence (a, b) or computed tomography (c, d).

TABLE 1 Patients' characteristics

	Non-severe asthma	Severe asthma	p-value
Subjects	15	15	
Age (years)	50±15	51±16	0.89
Sex ratio (M/F)	1/14	1/14	1.00
BMI (kg·m^{-2})	24 (22–32)	26 (21–32)	0.78
Tobacco			
Never-smoker	12	11	1.00
Former smoker	3	4	1.00
Pack years (no)	0 (0–0.7)	0 (0–0)	0.71
Questionnaire			
ACQ	0.7±0.9	2.3±1.5	<0.01
AQLQ	6.2±0.7	4.1±1.1	<0.01
Asthma duration (years)	31±15	21±14	0.07
Number of exacerbations in the previous 12 months	0 (0–0)	3 (2–5)	<0.01
PFT			
FEV_1 % pred	101±18	80±26	0.01
FVC % pred	108±15	94±21	0.06
$FEF_{25–75\%}$ % pred	83±34	51±36	0.01
PEF (L·min^{-1})	418±106	314±116	0.01
F_{ENO} (ppb)	20 (12–31)	21 (15–24)	0.87
Blood eos (cells·µL^{-1})	120 (80–230)	140 (70–340)	0.58
Treatment			
ICS (µg·day^{-1})	716±844	2166±1128	<0.01
OCS (yes/no)	0/15	2/13	0.48
LABA (yes/no)	7/8	15/0	0.01
LAMA (yes/no)	0/15	8/7	<0.01
LTRA (yes/no)	1/14	9/6	<0.01
Biologic[#] (yes/no)	0/15	5/10	0.09

Data are presented as mean±SD or median (95% CI) for continuous variables and n for categorical variables. BMI: body mass index; ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; PFT: pulmonary function tests; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC; PEF: peak expiratory flow; F_{ENO}: exhaled nitric oxide fraction; eos: eosinophil count; ICS: inhaled corticosteroids; OCS: continuous oral corticosteroids; LABA: long-acting β-agonists; LAMA: long-acting muscarinic antagonists; LTRA: leukotriene receptor antagonists. [#]: four patients were on omalizumab and one patient on mepolizumab.

patients from both groups were age- and sex-matched, the two groups were similar in terms of age and sex ratio, but also in terms of body mass index (BMI), tobacco consumption and asthma duration (table 1). None of the patients was a current smoker. The mean Asthma Control Questionnaire score and number of exacerbations were higher in patients with severe asthma. The mean Asthma Quality of Life Questionnaire score, forced expiratory volume in 1 s (FEV_1) and peak expiratory flow (PEF) were significantly lower in patients with severe asthma (table 1). Exhaled nitric oxide fraction (F_{ENO}) and blood eosinophil counts were similar between patients with non-severe and severe asthma.

Concordance of bronchial wall measurements between CT and MRI

After log-transformation, bronchial measurements assessed by MRI-UTE were not significantly different from those assessed by CT except for WA (p=0.047, paired t-test) (supplementary table E1). Good correlations and good concordance were found between MRI-UTE and CT for the assessment of bronchial dimensions (r⩾0.78; p<0.001; ICC⩾0.77, 95% CI 0.64–0.93) (figure 2). Using Bland–Altman analysis, we found that the mean difference of log-transformed bronchial measurements ranged from 0 to 0.03, with SD of bias between 0.02 and 0.11 (figure 2). Error measurement assessed using the within-subject SD was low (0.05 mm^2, 0.08 mm^2, 1.04% and 1.07 mm, for WA, LA, WA% and WT, respectively). The within-subject differences between MRI and CT bronchial measurements did not correlate with the mean values (supplementary table E1).

Reproducibility of the bronchial wall measurements using MRI-UTE

Intra-observer reproducibility of all bronchial measurements was good (*i.e.* ICC⩾0.76) (supplementary table E2). Similarly, inter-observers' reproducibility was moderate to good (*i.e.* ICC⩾0.69) (supplementary

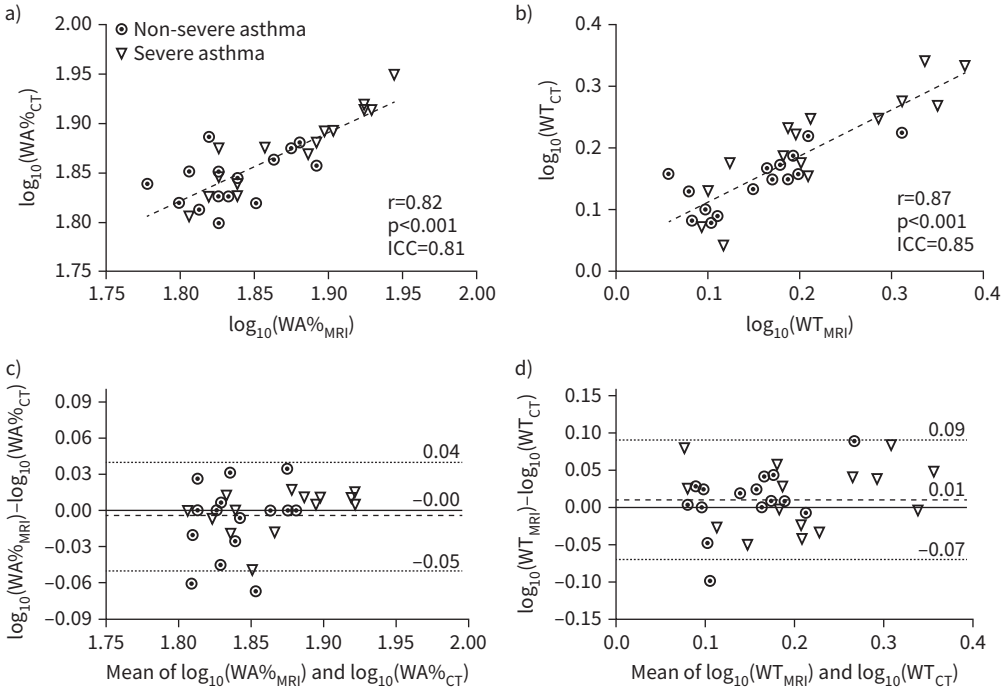

FIGURE 2 Validation of bronchial wall measurements using magnetic resonance imaging (MRI) with ultrashort echo time (UTE) sequencing *versus* computed tomography (CT). a, b) Pearson correlations (r) and intra-class concordance (ICC) of the log-transformed bronchial measurements between MRI-UTE and CT. c, d) Bland–Altman analysis of log-transformed bronchial measurements between MRI-UTE and CT. Horizontal dashed line indicates the mean. Dotted lines represent ±1.96SD. Values as given. WA: bronchial wall area; WA%: (WA/WA+LA)×100; WT: wall thickness.

table E2). For both intra- and inter-observers' reproducibility, the mean differences at Bland–Altman analysis were around 0 (supplementary table E2).

Comparison of bronchial wall measurements between asthma subgroups

We first compared all bronchial parameters between the two pre-specified asthma populations (supplementary table E3). Both WA% (figure 3a) and WT (figure 3b) were significantly higher in severe asthma than in non-severe asthma using either MRI-UTE or CT (supplementary table E3). LA was not different between the two groups using either MRI-UTE or CT (supplementary table E3). WA was increased in severe asthma compared to non-severe asthma but only when measured by CT (supplementary table E3, figure 3c). The skewness of the lung signal intensity was significantly higher in severe asthma than in non-severe asthma (figure 3d). Both the mean and the median lung signal intensities were unchanged in these two groups (supplementary table E3).

We also performed two additional analyses. When comparing patients with type 2-high (n=20) *versus* type 2-low (n=10) asthma, we did not find any significant difference in any bronchial parameters assessed by MRI-UTE (supplementary table E4). We showed that both WA% and WT, assessed by MRI-UTE, were significantly higher in chronic obstructive asthma than in intermittent obstructive asthma (supplementary table E5). LA assessed by MRI-UTE was significantly lower in chronic obstructive asthma than in intermittent obstructive asthma (supplementary table E5). Similar results were obtained when bronchial parameters were assessed by CT (supplementary table E5). The skewness of the lung signal intensity was significantly higher in chronic obstructive asthma than in intermittent obstructive asthma (supplementary table E5). It should be noted that baseline characteristics (*i.e.* age, sex and tobacco status) were not different between patients with chronic obstructive asthma and intermittent obstructive asthma (supplementary table E6).

Correlations of bronchial wall measurements with PFT

When considering the whole asthma population (n=30), bronchial wall measurements assessed by MRI-UTE, including WA, WA% (figure 4a, b) and WT (figure 4c, d) were all significantly correlated with

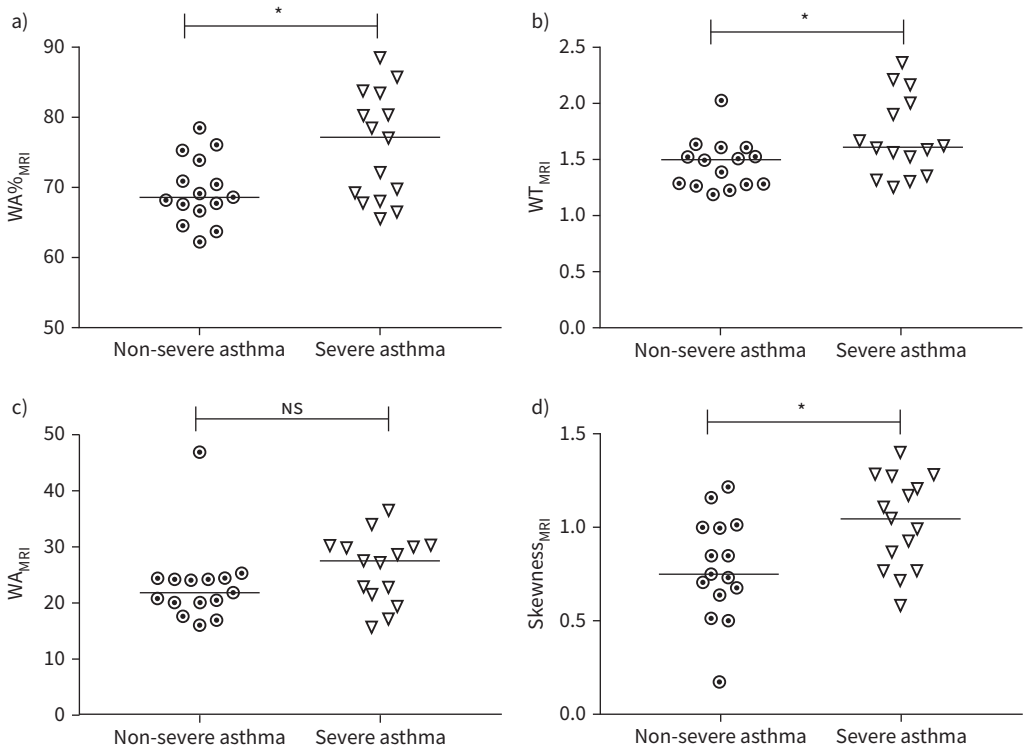

FIGURE 3 Comparison of magnetic resonance imaging (MRI) with ultrashort echo time sequencing bronchial measurements between non-severe and severe asthma. Data are a) individual normalised bronchial wall area (WA%), b) wall thickness (WT), c) wall area (WA) and d) the skewness of the MR signal from 15 patients with non-severe and 15 patients with severe asthma. Bars represent the median. WA%: (WA/WA+LA)×100. *: p<0.05.

FEV_1, forced vital capacity (FVC) and forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) (supplementary table E7). Because correlation coefficients were all negative, the higher the WA% or WT, the lower the lung function (figure 4). Similar results were obtained using CT for WA% and WT (supplementary table E7). WA% assessed by MRI-UTE was also correlated with PEF (supplementary table E7). The skewness of the lung signal intensity was significantly and negatively correlated with FEV_1, FEV_1/FVC and $FEF_{25–75\%}$ (supplementary table E7). None of the bronchial parameters assessed by either MRI-UTE or CT was correlated with F_{ENO} or eosinophil count (supplementary table E7).

In patients with non-severe asthma (n=15), only WA% and the skewness of the lung signal intensity assessed by MRI-UTE remained correlated with FEV_1 and $FEF_{25–75\%}$ (supplementary table E7). In patients with severe asthma (n=15), WA, WA% and WT assessed by MRI-UTE were all correlated with FEV_1 and FVC (supplementary table E7). Using CT, both WA% and WT were correlated with FEV_1 in severe asthma, whereas only WA% was correlated with FVC. The skewness of the lung signal intensity assessed by MRI-UTE was not correlated with any lung function parameters in patients with severe asthma.

Discussion

Taken together, we have demonstrated that bronchial dimensions can be accurately measured in asthmatic patients using MRI-UTE as compared to CT. Moreover, MRI-UTE was able to demonstrate that bronchial wall thickness was increased in patients with severe compared to non-severe asthma, and was significantly and negatively correlated with PFT data, including FEV_1.

In order to validate MRI-UTE as a new tool for measuring bronchial wall dimensions, we used CT as the standard method of reference. Indeed, a wide range of studies have identified and validated the interest in measuring various bronchial wall parameters using CT, including WA, WA% and WT [9, 10, 12, 16, 30]. In the present study, we showed a good agreement with minimal error measurements of bronchial dimensions between MRI-UTE and CT. Except for WA, no other parameters (LA, WA% and WT) were significantly different between MRI-UTE and CT. However, WA is an absolute measurement that is

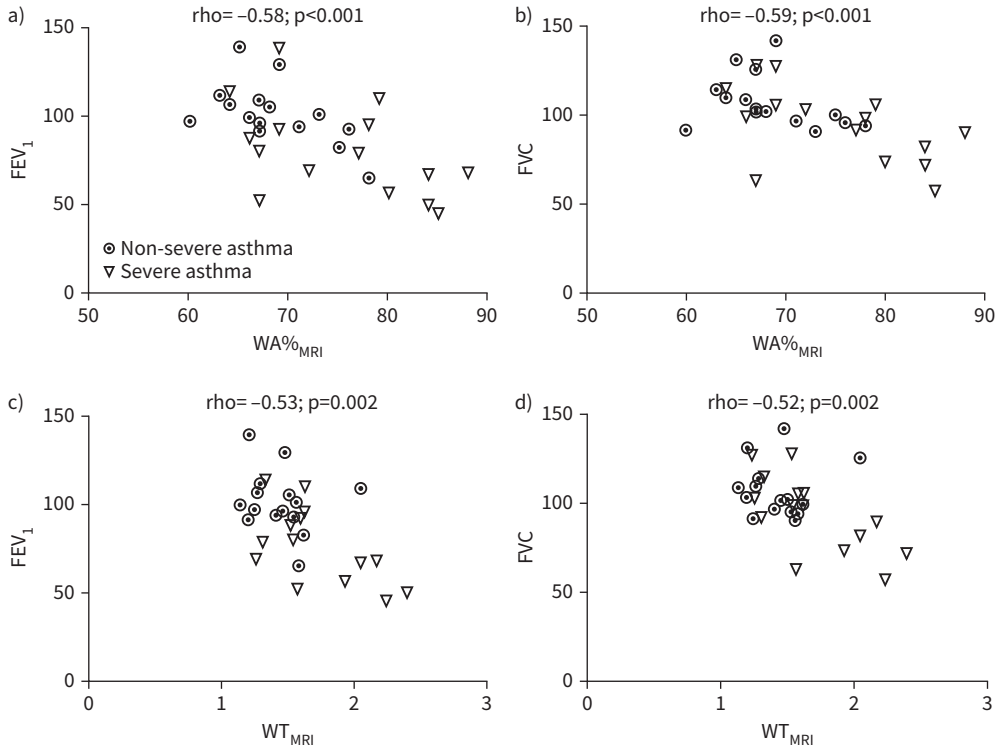

FIGURE 4 Correlations between magnetic resonance imaging (MRI) with ultrashort echo time sequencing bronchial measurements and pulmonary function tests. Individual data of normalised bronchial wall area (WA%) (a, b) or wall thickness (WT) (c, d) are plotted against forced expiratory volume in 1 s (FEV_1) (a, c) or forced vital capacity (FVC) (b, d). Rho are Spearman correlation coefficients. WA%: (WA/WA+LA)×100.

usually normalised by the lumen area [12]. Although spatial resolution of lung MRI has been improved using MRI-UTE, it still remains lower compared to that of CT, which may lead to an overestimation due to partial volume artefacts. Intra-observer reproducibility was good (ICC≥0.76), and inter-observer reproducibility was moderate to good (ICC≥0.69), thus validating MRI-UTE as a non-ionising alternative to CT. The inter-observer reproducibility referred to a systematic comparison between two readers with different levels of expertise (5 and 10 years of thoracic imaging experiences).

MRI-UTE of the lung has recently emerged as an alternative to CT in describing structural changes of the lung in various lung diseases [21–23]. In addition, we recently demonstrated that MRI-UTE was able to quantify emphysema in COPD [24] and volumetric signal intensity related to cystic fibrosis severity [31]. However, to the best of our knowledge, this study is the first to quantify bronchial wall dimensions in asthma or in any other lung disease using MRI-UTE. MRI with hyperpolarised gas has been used to quantify the functional consequences of mucus plugs leading to ventilation heterogeneity in severe asthma [26]. Neither inhaled nor injected contrast agent was used in the present study. Thus, this MRI-UTE methodology could easily be used in all 1.5 T MRI set-ups.

We paid particular attention to prospectively recruiting fully characterised asthmatic patients. We designed the study to age- and sex-match patients with severe asthma to patients with non-severe asthma. Therefore, these two groups were fully comparable in terms of age, sex, BMI and tobacco consumption, but were significantly different in terms of asthma questionnaires, lung function and some asthma medications. Although patients with severe asthma represent only 3–5% of the asthmatic population, they are prone to severe exacerbations with hospitalisations and to being treated by biological medications, both of which lead to increased asthma management costs in the healthcare system [28]. In the present study, the median rate of exacerbations was high (*i.e.* three per year) in patients with severe asthma, and 27% of these patients were on biological medication.

Here, we have demonstrated that the bronchial wall, as assessed by quantitative MRI-UTE, was significantly thicker in severe asthma than in non-severe asthma. Similar results have been previously

demonstrated using quantitative CT, although not age- or sex-matched [9, 11, 12], thus confirming the accuracy and validity of bronchial wall measurements by MRI-UTE. Although bronchial measurements were significantly different in chronic obstructive asthma compared to intermittent obstructive asthma, results have to be considered carefully. To further support the validity of quantitative MRI-UTE, bronchial wall measurements were significantly and negatively correlated with PFT data, including FEV_1, as previously demonstrated with CT [9, 11, 12]. Thus, MRI-UTE provides bronchial morphological information close to that obtained by CT but has the advantage of being a radiation-free modality [32].

Moreover, MRI-UTE allows lung signal intensity to be assessed, as described previously in COPD [24]. In this previous study, we described an automated method that allowed the lungs to be isolated from the rest of the thoracic structures, including pulmonary vessels, and the distribution curve of normalised signal intensities to be built [24]. Using this automated method, we demonstrated that the skewness of the lung signal intensity, which describes the histogram asymmetry and shift, was significantly higher (*i.e.* towards the lowest signal intensities) in severe asthma than in non-severe asthma, suggesting increased air trapping in severe asthma. Whereas the presence of emphysema in asthma remains debated [33–35], we can assume that such increased air trapping reflects a more pronounced obstruction of the distal airways.

In asthma, bronchial wall thickening can be related to either bronchial inflammation or remodelling [3]. We previously demonstrated that quantitative CT was unable to differentiate whether increased bronchial wall thickness in asthma was related to bronchial inflammation or remodelling [12]. Using histological and immunohistochemical analyses, Benayoun *et al*. [3] showed that higher numbers of fibroblasts, larger mucous glands and bronchial smooth muscle areas distinguished patients with severe persistent asthma from patients with milder disease. In the present study, we did not perform histological analysis. Because the F_{ENO} level was low in our two asthma populations and there was no correlation between bronchial wall measurements assessed by MRI-UTE and F_{ENO}, one could suggest that bronchial dimensions assessed by MRI-UTE are more related to bronchial remodelling than to bronchial inflammation. Further studies, combining MRI with histology, are required to confirm this hypothesis. However, MRI T2-weighted images have been used to detect lung inflammatory processes such as lung consolidation, bronchial wall oedema and mucus plugins in cystic fibrosis [36]. These inflammatory changes can be evaluated quantitatively over time, as very recently demonstrated by our team in cystic fibrosis [37]. A co-registration of UTE and T2-weighted MRI images would be worth exploring to provide a comprehensive evaluation of both bronchial remodelling and inflammation in asthma, by combining both morphological and functional information.

Our knowledge of asthma remains poor, notably because of a lack of tools to assess the disease's longitudinal progression. Thus, safe radiation-free imaging at high resolution is desirable and, to the best of our knowledge, has not previously been reported. It opens the possibility of a radiation-free longitudinal study design that could be extended to young populations.

The present study has several limitations. First, this was a single-centre study with a small number of participants. Nevertheless, this was a pilot feasibility study, and our results are in line with previously published CT bronchial wall measurement results in asthma. Second, bronchial LA and WA were manually delineated on CT and MRI-UTE images. However, similarly to early studies of bronchial measurements on CT [9, 29], reproducibility was moderate to good. We recently assessed the feasibility of automated airways segmentation using a specific UTE sequence (*i.e.* pointwise encoding time reduction with radial acquisition (PETRA)) [38]. However, further developments are ongoing to generalise the technique to other UTE sequences. Third, we did not correlate MRI-UTE bronchial measurements with histological analysis, as mentioned above. However, in our study, CT was the standard reference, a modality that has extensively been correlated with pathological findings [11, 12]. Fourth, the spatial resolution of MRI remains lower than that of CT. However, the MRI spatial resolution was enough to differentiate severe from non-severe asthma and the smallest measured bronchus had a luminal diameter of only 2.25 mm. Fifth, multivendor MRI-UTE assessment of bronchial dimensions in a large multicentre longitudinal study would be worth evaluating.

In conclusion, we demonstrated that MRI-UTE is an accurate and reliable radiation-free method to assess bronchial wall dimensions in asthma, with enough spatial resolution to differentiate severe from non-severe asthma.

Acknowledgements: The authors thank the study participants, Rkia Achkir and the whole staff of the radiology department at the University Hospital of Bordeaux, and Isabelle Goasdoue, Benedicte Bestieu, Virginie Niel and

Marine Servat from the Clinical Investigation Center for technical assistance. The authors thank Solenn Toupin for technical support and for providing the prototypical MR sequence. The study was achieved within the context of Laboratory of Excellence TRAIL ANR-10-LABX-57.

Conflict of interest: I. Benlala has a patent “Method for generating a biomarker system” (PCT/EP2020/065380) pending. G. Dournes has a patent “Method for geometrical characterisation of the airways of the lung by MRI” (EP number 17726309.2) issued and a patent “Method for generating a biomarker system” (PCT/EP2020/065380) pending. P-O. Girodet reports grants, personal fees and non-financial support from AstraZeneca, and personal fees and non-financial support from GSK, Novartis and Sanofi, outside the submitted work; and has a patent “New compositions and methods of treating and/or preventing COPD” (EP number 3050574, PCT/EP2016/051771) issued and a patent “New compositions and methods of treating COVID-19 disease” (EP number 20173595.8) pending. T. Benkert is an employee of Siemens Healthcare GmbH. F. Laurent reports personal fees and non-financial support from Chiesi, Boehringer, AstraZeneca, Bayer, Gilead and GSK, outside the submitted work; and has a patent “Method for geometrical characterisation of the airways of the lung by MRI” (EP number 17726309.2) issued and a patent “Method for generating a biomarker system” (PCT/EP2020/065380) pending. P. Berger reports grants from Novartis SAS, France, during the conduct of the study; grants, personal fees and non-financial support from AstraZeneca, GSK, Novartis, Chiesi and Boehringer, and personal fees and non-financial support from Menarini and Sanofi, outside the submitted work; and has a patent “New compositions and methods of treating and/or preventing COPD” (EP number 3050574, PCT/EP2016/051771) issued, a patent “Method for geometrical characterisation of the airways of the lung by MRI” (EP number 17726309.2) issued, a patent “Method for generating a biomarker system” (PCT/EP2020/065380) pending and a patent “New compositions and methods of treating COVID-19 disease” (EP number 20173595.8) pending.

Support statement: This study was funded by Novartis SAS, France, and sponsored by the University Hospital Center of Bordeaux (“Centre Hospitalier Universitaire - CHU - de Bordeaux”). The pharmaceutical company had no role in the design and conduct of the study. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2016. www.ginasthma.org. Date last accessed: November 15, 2016. Date last updated: April 2021.
2 King GG, Farrow CE, Chapman DG. Dismantling the pathophysiology of asthma using imaging. *Eur Respir Rev* 2019; 28: 180111.
3 Benayoun L, Druilhe A, Dombret M-C, *et al.* Airway structural alterations selectively associated with severe asthma. *Am J Respir Crit Care Med* 2003; 167: 1360–1368.
4 Carroll N, Elliot J, Morton A, *et al.* The structure of large and small airways in nonfatal and fatal asthma. *Am Rev Respir Dis* 1993; 147: 405–410.
5 Kay AB. Pathology of mild, severe, and fatal asthma. *Am J Respir Crit Care Med* 1996; 154: S66–S69.
6 Kasahara K, Shiba K, Ozawa T, *et al.* Correlation between the bronchial subepithelial layer and whole airway wall thickness in patients with asthma. *Thorax* 2002; 57: 242–246.
7 Little S, Sproule M, Cowan M, *et al.* High resolution computed tomographic assessment of airway wall thickness in chronic asthma: reproducibility and relationship with lung function and severity. *Thorax* 2002; 57: 247–253.
8 Matsumoto H, Niimi A, Takemura M, *et al.* Relationship of airway wall thickening to an imbalance between matrix metalloproteinase-9 and its inhibitor in asthma. *Thorax* 2005; 60: 277–281.
9 Niimi A, Matsumoto H, Amitani R, *et al.* Airway wall thickness in asthma assessed by computed tomography. Relation to clinical indices. *Am J Respir Crit Care Med* 2000; 162: 1518–1523.
10 Niimi A, Matsumoto H, Takemura M, *et al.* Relationship of airway wall thickness to airway sensitivity and airway reactivity in asthma. *Am J Respir Crit Care Med* 2003; 168: 983–988.
11 Aysola RS, Hoffman EA, Gierada D, *et al.* Airway remodeling measured by multidetector CT is increased in severe asthma and correlates with pathology. *Chest* 2008; 134: 1183–1191.
12 Montaudon M, Lederlin M, Reich S, *et al.* Bronchial measurements in patients with asthma: comparison of quantitative thin-section CT findings with those in healthy subjects and correlation with pathologic findings. *Radiology* 2009; 253: 844–853.
13 Berger P, Perot V, Desbarats P, *et al.* Airway wall thickness in cigarette smokers: quantitative thin-section CT assessment. *Radiology* 2005; 235: 1055–1064.
14 Montaudon M, Berger P, de Dietrich G, *et al.* Assessment of airways with three-dimensional quantitative thin-section CT: *in vitro* and *in vivo* validation. *Radiology* 2007; 242: 563–572.
15 Haldar P, Brightling CE, Hargadon B, *et al.* Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360: 973–984.

16 Girodet P-O, Dournes G, Thumerel M, *et al.* Calcium channel blocker reduces airway remodeling in severe asthma. A proof-of-concept study. *Am J Respir Crit Care Med* 2015; 191: 876–883.
17 Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med* 2007; 357: 2277–2284.
18 Brenner DJ, Hall EJ. Cancer risks from CT scans: now we have data, what next? *Radiology* 2012; 265: 330–331.
19 Pearce MS, Salotti JA, Little MP, *et al.* Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* 2012; 380: 499–505.
20 Hatabu H, Ohno Y, Gefter WB, *et al.* Expanding applications of pulmonary MRI in the clinical evaluation of lung disorders: Fleischner Society position paper. *Radiology* 2020; 297: 286–301.
21 Dournes G, Grodzki D, Macey J, *et al.* Quiet submillimeter MR imaging of the lung is feasible with a PETRA sequence at 1.5T. *Radiology* 2015; 276: 258–265.
22 Dournes G, Menut F, Macey J, *et al.* Lung morphology assessment of cystic fibrosis using MRI with ultra-short echo time at submillimeter spatial resolution. *Eur Radiol* 2016; 26: 3811–3820.
23 Dournes G, Yazbek J, Benhassen W, *et al.* 3D ultrashort echo time MRI of the lung using stack-of-spirals and spherical k-space coverages: evaluation in healthy volunteers and parenchymal diseases. *J Magn Reson Imaging* 2018; 48: 1489–1497.
24 Benlala I, Berger P, Girodet p-O, *et al.* Automated volumetric quantification of emphysema severity by using ultrashort echo time MRI: validation in participants with chronic obstructive pulmonary disease. *Radiology* 2019; 292: 216–225.
25 Svenningsen S, Guo F, Kirby M, *et al.* Pulmonary functional magnetic resonance imaging: asthma temporal-spatial maps. *Acad Radiol* 2014; 21: 1402–1410.
26 Svenningsen S, Haider E, Boylan C, *et al.* CT and functional MRI to evaluate airway mucus in severe asthma. *Chest* 2019; 155: 1178–1189.
27 Sheikh K, Guo F, Capaldi DPI, *et al.* Canadian Respiratory Research Network. Ultrashort echo time MRI biomarkers of asthma. *J Magn Reson Imaging* 2017; 45: 1204–1215.
28 Chung KF, Wenzel SE, Brozek JL, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343–373.
29 Lederlin M, Laurent F, Dromer C, *et al.* Mean bronchial wall attenuation value in chronic obstructive pulmonary disease: comparison with standard bronchial parameters and correlation with function. *AJR Am J Roentgenol* 2012; 198: 800–808.
30 Dournes G, Laurent F, Coste F, *et al.* Computed tomographic measurement of airway remodeling and emphysema in advanced chronic obstructive pulmonary disease. Correlation with pulmonary hypertension. *Am J Respir Crit Care Med* 2015; 191: 63–70.
31 Benlala I, Point S, Leung C, *et al.* Volumetric quantification of lung MR signal intensities using ultrashort TE as an automated score in cystic fibrosis. *Eur Radiol* 2020; 30: 5479–5488.
32 Leuraud K, Richardson DB, Cardis E, *et al.* Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. *Lancet Haematol* 2015; 2: e276–e281.
33 Kondoh Y, Taniguchi H, Yokoyama S, *et al.* Emphysematous change in chronic asthma in relation to cigarette smoking. Assessment by computed tomography. *Chest* 1990; 97: 845–849.
34 Haraguchi M, Shimura S, Shirato K. Morphologic aspects of airways of patients with pulmonary emphysema followed by bronchial asthma-like attack. *Am J Respir Crit Care Med* 1996; 153: 638–643.
35 Gelb AF, Zamel N. Unsuspected pseudophysiologic emphysema in chronic persistent asthma. *Am J Respir Crit Care Med* 2000; 162: 1778–1782.
36 Renz DM, Scholz O, Böttcher J, *et al.* Comparison between magnetic resonance imaging and computed tomography of the lung in patients with cystic fibrosis with regard to clinical, laboratory, and pulmonary functional parameters. *Invest Radiol* 2015; 50: 733–742.
37 Benlala I, Hocke F, Macey J, *et al.* Quantification of MRI T2-weighted high signal volume in cystic fibrosis: a pilot study. *Radiology* 2020; 294: 186–196.
38 Baldacci F, Laurent F, Berger P, *et al.* 3D human airway segmentation from high resolution MR imaging. Proceedings from the 11th International Conference on Machine Vision (ICMV 2018) Abstract 110410Y. Available from: https://www.spiedigitallibrary.org/conference-proceedings-of-spie/11041/110410Y/3D-human-airway-segmentation-from-high-hesolution-MR-imaging/10.1117/12.2522948.short?SSO=1