SUPPLEMENTAL MATERIAL AND METHODS

Evaluation of bronchial wall thickness in asthma using magnetic resonance imaging

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Supplemental Methods

Subjects

Subjects aged more than 18 years were eligible for enrolment if they had a clinical diagnosis of asthma including characteristic symptoms (*i.e.*, wheezing and breathlessness) (E1), as well as bronchial hyperresponsiveness confirmed either by a significant improvement by >12% and 200 ml in the forced expiratory volume in 1 s (FEV1) 10 min after the inhalation of 400 μg of salbutamol, or a provocative concentration of methacholine required to lower the FEV1 by 20% (PC20) of <4 mg/ml according to the American Thoracic Society criteria (E2). Patients were categorized as either non-severe or severe asthma according to ATS/ERS task force (E3).

Inclusion criteria

- Male or female aged more than 18 years
- Patients with diagnosis of asthma according to 2016 "Global Strategy for Asthma Management and Prevention (GINA)" definition (E1)
- Pulmonary Function Testings (PFTs) should be available within a maximum of 30 days before inclusion
- With a written informed consent

Exclusion Criteria:

- Recent asthma exacerbation (less than 4 weeks from the study inclusion)
- Subject without any social security or health insurance
- Prisoner

- Protected adult
- History of chronic obstructive pulmonary disease, lung fibrosis, pulmonary hypertension, lung cancer or cystic fibrosis
- Pregnancy or breastfeeding woman
- MRI contraindications: Magnetically activated implanted devices (cardiac pacemakers, insulin pumps, neurostimulators, cochlear implants), metal inside the eye or the brain (aneurysm clip, ocular foreign body), cardiac valvular prosthesis (Starr-Edwards pre-6000), subject with claustrophobia, waist line circumference over 200 cm.

All subjects provided written informed consent to participate to the study, after the nature of the procedure had been fully explained.

Study design

This prospective single-center pilot study was performed between May 2017 and June 2018. The study protocol was approved by the local research ethics committee ("CPP Sud-Ouest et Outre Mer III") and the French National Agency for Medicines and Health Products Safety. The study has been registered under the N° NCT03089346 at ClinicalTrials.gov (*i.e.*, "AsthMagRI" study).

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Since it was a pilot study, the minimum number of participants was not calculated, and the number of 30 participants was set arbitrary. Fifteen severe asthmatic patients were sex- and age-matched with 15 non-severe asthmatic patients. All patients had to undergo a chest three-dimensional lung magnetic resonance imaging (MRI) and a computed tomography (CT) scan on the same day with pulmonary function testing (PFT) within a maximum interval of 30 days (including the forced expiratory volume in 1 second (FEV1); forced volume capacity (FVC); forced expiratory flow at 25%-75% of FVC (FEF25-75); fractional exhaled nitric oxide (FeNO)).

We also performed 2 additional analyses by subgrouping patients in:

(i) Type 2-High asthma (defined by blood eosinophil count ≥ 150 /µl and/or FeNO ≥ 20 ppb) vs Type 2-low asthma (defined by blood eosinophil count < 150 /µl and FeNO < 20 ppb);

(ii) Chronic obstructive asthma (defined by FEV1 < 80% predicted) vs intermittent obstructive asthma (defined by FEV1 ≥ 80% predicted)

All clinical data (including age, sex, body mass index (BMI), tobacco smoking, Asthma Control Questionnaire (ACQ); Asthma Quality of Life Questionnaire (AQLQ); number of asthma exacerbations during the previous year, peak expiratory flow (PEF) and asthma treatments) and blood eosinophil count were collected at the inclusion visit in the clinical investigation center (CIC 1401) from the University hospital of Bordeaux (CHU).

MRI Examinations

Three-dimensional lung MRI with ultrashort echo time (UTE) pulse sequence was performed using a 1.5 Tesla system (MAGNETOM AVANTO; Siemens Healthcare, Erlangen, Germany) using 3D-gradient echo Spiral Vibe sequence with the following parameters: repetition time msec/echo time msec, 4.3/0.05; flip angle, 5°; and voxel size, 1 mm^3. Respiratory synchronization at end normal expiration was allowed by an automated navigator-triggered prospective synchronization (E4). The acquisition time was about 10 minutes. MRI datasets of images were anonymized and analyzed in random order.

Computed tomography

CT protocol

Unenhanced chest CT images were performed with a 64-slice multidetector CT scanner (Somatom Definition; Siemens Healthcare, Erlangen, Germany) without contrast medium administration by using the following parameters: 110-kV tube voltage, 50-mAs tube current and 0.75-mm collimation. Data were acquired in the supine position. Patients were instructed, before and during the procedure, to hold their breath at end normal expiration (functional residual capacity). CT datasets were reconstructed with an isotropic voxel size of 0.625 mm^3, images were reconstructed using standard (B30f) and sharp (B70f) algorithms, 320x320-mm field-of-view, and 512x512 matrix. CT doses ranged from 120 to 150 mGy.cm. The scanner was calibrated regularly with air and a water phantom to allow reliable measurements. CT datasets of images were anonymized and analyzed in random order independently of MRI analyses.

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 (E5) (Myrian®software, Montpellier, France) (Figure 1 and E1). An arbitrary set of four bronchial paths were analyzed 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) value was calculated from WA and LA as follows:

$WT = \sqrt{[(WA+LA)/\pi]} - \sqrt{(LA/\pi)}$ (expressed in mm)

Quantitative analysis of the lung MRI signal

First, lung volume was segmented from the rest of the thoracic structures using an in-house written software in MATLAB (The Math Works, Inc., and Natick, Massachusetts USA). An iterative automatic segmentation algorithm was used based on splitting the image histogram into two classes (background/foreground) (E6). A threshold value was computed as the average of the two sample means. This process was repeated until the threshold value did not change anymore and considered as the optimal threshold to create the lung mask. Finally, both the mean lung signal intensity

and the skewness of MRI signal intensity histogram, which depicted the asymmetry and shift of the lung MRI signal, were calculated, as described previously (E7).

Assessment of reproducibility

Bronchial measurements performed by IB and GD using MRI-UTE were analyzed to assess inter-observers' reproducibility. The junior reader (IB) 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

Statistical analyses were performed using NCSS software (NCSS 2001, Kaysville, UT, USA). Normality was assessed using the Shapiro-Wilk test. Log transformations were performed with data that did not follow a normal distribution.

For quantitative variables, comparisons were performed using Student's t-tests or Mann-Whitney tests according to variables normality. Comparisons of categorical variables were performed using the Fisher's Exact tests.

Accuracy of MRI bronchial measurements in comparison to CT bronchial measurements was evaluated with paired t-tests. The agreement was assessed using Bland-Altman analysis. Univariate correlations were evaluated using the Pearson test for normally distributed variables and the Spearman test for not normally distributed variables.

Reproducibility was assessed using intraclass correlation coefficients (ICCs) with 95% confidence interval (CI) and Bland-Altman analysis (E8). ICC values were

classified from poor (<0.50), moderate (>0.50 and ≤0.75), good (>0.75 and ≤0.90), to excellent (>0.90) (E9). A p-value<0.05 was considered statistically significant.

References

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Supplemental Tables:

Table E1. Comparison of bronchial measurements between CT and MRI

	log_{10} (WA)	log_{10} (LA)	log_{10} (WA%)	log_{10} (WT)
Paired t-test (p-value)	0.047	0.11	0.33	0.14
Pearson correlation	0.78 (<0.01)	0.79 (<0.01)	0.82 (<0.01)	0.87 (<0.01)
Mean difference (BA)*	0.03 ± 0.07	0.03 ± 0.11	-0.00 ± 0.02	0.01 ± 0.04
ICC	0.77 [0.56-0.88]	0.78 [0.59-0.89]	0.81 [0.72-0.93]	0.85 [0.64-0.90]
Sw	1.13	1.2	1.04	1.07
Spearman rank correlation&	0.03 (0.85)	0.13 (0.48)	0.31 (0.09)	0.16 (0.38)

*Data are mean difference ± SD of log-transformed bronchial measurements between MRI and CT. Data in parentheses are p-values. &Data are correlation coefficients between mean MR measurements and the within-subject difference between MRI and CT measurements.

Abbreviations: BA=Bland-Altman analysis; ICC=intraclass correlation coefficient; SW=error measurement between log-transformed MRI and CT bronchial measurements; WA=bronchial wall area; LA=lumen area; WA%=ratio WA/WA+LA*100; WT=wall thickness.

Table E2. Reproducibility of MR bronchial measurements

	log_{10} (WA)	log_{10} (LA)	log_{10} (WA%)	log_{10} (WT)
Intra-observer				
ICC*	0.76 [0.56;0.88]	0.84 [0.69;0.92]	0.80 [0.63;0.90]	0.82 [0.65;0.91]
Mean difference (BA)[&]	-0.01 [-0.17;0.15]	0.09 [-0.10;0.28]	-0.03[-0.08;0.03]	-0.03 [-0.13;0.07]
Inter-observer				
ICC*	0.69 [0.45;0.84]	0.81 [0.64;0.90]	0.77 [0.58;0.88]	0.74 [0.52;0.86]
Mean difference (BA)[&]	-0.10 [-0.34;0.13]	0.00 [-0.23;0.24]	-0.03 [-0.10;0.04]	0.08 [-0.23;0.07]

*Data are intra and inter-observers intra-class correlation coefficients with 95% CI of the log-transformed bronchial measurements. [&]Data are intra and inter-observers mean differences with 95% limits of log-transformed bronchial measurements' agreements.

Abbreviations: BA=Bland-Altman analysis; ICC=intraclass correlation coefficient; WA=bronchial wall area; LA=lumen area; WA%=ratio WA/WA+LA*100; WT=wall thickness.

Table E3. Comparison of bronchial measurements between severe and non-severe asthma

		Non-severe		Severe		p-value
N		15		15		
MRI						
	WA_{MR}	22.5	(19.9-23.7)	27.7	(21.2-31.1)	0.07
	LA_{MR}	8.3	(7.5-12.6)	7.1	(6.1-11.6)	0.11
	$WA\%_{MR}$	67	(65-73)	77	(67-84)	0.02
	WT_{MR}	1.4	(1.2-1.5)	1.6	(1.3-2.1)	0.02
	Skewness	0.75	(0.65-0.99)	1.04	(0.79-1.25)	0.02
	Mean	202	(189-245)	208	(164-241)	0.68
	Median	186	(168-232)	189	(150-217)	0.78
CT						
	WA_{CT}	21.1	(17.8-22.9)	27.1	(18.4-28.3)	0.03
	LA_{CT}	9.1	(6.8-9.5)	7	(5.6-11.9)	0.37
	$WA\%_{CT}$	70	(66-73)	75	(69-82)	0.02
	WT_{CT}	1.4	(1.2-1.5)	1.6	(1.4-1.9)	0.02

Data are median with (95% confidence interval)

Abbreviations: WA=bronchial wall area in mm^2; LA=lumen area in mm^2; WA% =ratio WA/WA+LA*100; WT=wall thickness in mm.

Table E4. Comparison of bronchial measurements between Type2-Low and Type2-High asthma

		Type2-Low		Type2-High		p-value
N		20		10		
MRI						
	WA_{MR}	23.0	(18.9-33.7)	23.3	(20.8-27.5)	0.72
	LA_{MR}	7.7	(7.2-14.2)	8.1	(6.6-11.5)	0.45
	$WA\%_{MR}$	67	(65-77)	70	(67-77)	0.67
	WT_{MR}	1.5	(1.3-1.9)	1.5	(1.3-1.6)	0.75
	Skewness	0.88	(0.67-1.13)	0.89	(0.75-1.15)	0.62
	Mean	191	(124-233)	213	(198-246)	0.12
	Median	173	(108-209)	194	(173-234)	0.13
CT						
	WA_{CT}	26.2	(19.4-30.1)	21.7	(18.4-26.7)	0.11
	LA_{CT}	9.5	(7.4-15.0)	7.3	(5.7-9.0)	0.02
	$WA\%_{CT}$	68	(64-77)	73	(69-75)	0.20
	WT_{CT}	1.5	(1.3-1.7)	1.5	(1.3-1.6)	0.44

Data are median with (95% confidence interval)

Abbreviations: WA=bronchial wall area in mm^2; LA=lumen area in mm^2; WA% =ratio WA/WA+LA*100; WT=wall thickness in mm.

Table E5. Comparison of bronchial measurements between chronic obstructive and intermittent obstructive asthma

		intermittent obstructive		chronic obstructive		p-value
N		21		9		
MRI						
	WA_{MR}	22.7	(20.3-24.4)	30.1	(20.1-33.4)	0.05
	LA_{MR}	9.6	(7.4-11.5)	6.6	(4.7-8.1)	0.01
	$WA\%_{MR}$	69	(67-70)	80	(72-85)	<0.01
	WT_{MR}	1.5	(1.3-1.6)	1.9	(1.3-2.2)	0.01
	Skewness	0.84	(0.69-1.00)	1.17	(0.80-1.27)	0.02
	Mean	208	(185-247)	200	(162-230)	0.57
	Median	191	(164-228)	178	(156-210)	0.41
CT						
	WA_{CT}	22.3	(18.1-26.2)	27.1	(18.7-29.3)	0.16
	LA_{CT}	9.1	(7.3-10.1)	5.8	(4.2-8.7)	0.03
	$WA\%_{CT}$	69	(67-73)	78	(72-82)	<0.01
	WT_{CT}	1.4	(1.3-1.5)	1.7	(1.3-2.1)	0.04

Data are median with (95% confidence interval)

Abbreviations: WA=bronchial wall area in mm^2; LA=lumen area in mm^2; WA% =ratio WA/WA+LA*100; WT=wall thickness in mm.

Table E6. Comparison of patients' baseline characteristics between chronic obstructive and intermittent obstructive asthma

		intermittent obstructive		chronic obstructive		p-value
		21		9		
Age	Years	60	(39-63)	52	(34-60)	0.40
Sex ratio	Men/Women	1/	20	1/	8	1.00
BMI	$kg.m^{-2}$	24	(21-29)	26	(21-33)	0.80
Tobacco	Never smoker	15		8		0.39
	Former smoker	6		1		

Data are median with (95% confidence interval) for continuous variables and absolute number for categorical variables.

Abbreviations: BMI=body mass index

Table E7. Correlations of bronchial measurements with pulmonary function tests

		Whole population (n=30)						
		FEV_1 (% pred)	**FVC (%pred)**	**FEV_1/FVC**	**FEF_{25-75} (%pred)**	**PF (l/min)**	**FeNO (ppb)**	**Blood Eos (cells/µl)**
MRI								
	WA_{MR}	-0.47	-0.41	-0.52	-0.55	-0.32	-0.10	-0.12
		(0.01)	(0.02)	(0.003)	(0.01)	(0.07)	(0.60)	(0.51)
	LA_{MR}	0.25	0.28	0.16	0.17	0.26	-0.22	-0.28
		(0.16)	(0.12)	(0.58)	(0.34)	(0.15)	(0.25)	(0.12)
	$WA\%_{MR}$	-0.58	-0.59	-0.44	-0.56	-0.48	0.01	-0.13
		(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.92)	(0.47)
	WT_{MR}	-0.53	-0.52	-0.51	-0.56	-0.33	-0.07	-0.01
		(0.01)	(0.01)	(0.003)	(0.01)	(0.07)	(0.70)	(0.94)
	Skewness	-0.41	-0.15	-0.41	-0.47	-0.35	0.09	-0.15
		(0.02)	(0.40)	(0.02)	(0.007)	(0.055)	(0.64)	(0.41)
CT								
	WA_{CT}	-0.34	-0.27	-0.42	-0.44	-0.28	-0.18	-0.09
		(0.05)	(0.14)	(0.02)	(0.01)	(0.13)	(0.36)	(0.60)
	LA_{CT}	0.26	0.31	0.11	0.10	0.05	-0.40	-0.36
		(0.15)	(0.09)	(0.55)	(0.59)	(0.78)	(0.06)	(0.05)
	$WA\%_{CT}$	-0.59	-0.54	-0.43	-0.46	-0.23	0.22	0.25
		(0.01)	(0.01)	(0.01)	(0.01)	(0.21)	(0.26)	(0.17)

	WT_{CT}	-0.50 (0.01)	-0.43 (0.01)	-0.51 (0.003)	-0.54 (0.01)	-0.30 (0.09)	-0.05 (0.77)	-0.02 (0.90)

Non-severe asthma (n=15)

		FEV_1 (% pred)	**FVC (%pred)**	**FEV_1/FVC**	**FEF_{25-75} (%pred)**	**PF (l/min)**	**FeNO (ppb)**	**Blood Eos (cells/µl)**
MRI								
	WA_{MR}	0.04 (0.87)	-0.03 (0.90)	-0.28 (0.30)	-0.34 (0.21)	-0.14 (0.61)	-0.45 (0.09)	-0.41 (0.12)
	LA_{MR}	0.48 (0.06)	0.34 (0.21)	0.18 (0.49)	0.28 (0.29)	0.36 (0.18)	-0.18 (0.52)	0.07 (0.77)
	$WA\%_{MR}$	-0.56 (0.03)	-0.44 (0.09)	-0.45 (0.09)	-0.67 (0.01)	-0.55 (0.03)	-0.24 (0.39)	-0.44 (0.10)
	WT_{MR}	0.20 (0.45)	0.26 (0.33)	-0.35 (0.19)	-0.50 (0.05)	-0.17 (0.53)	-0.31 (0.24)	-0.31 (0.24)
	Skewness	-0.54 (0.03)	-0.39 (0.14)	-0.40 (0.13)	-0.54 (0.03)	-0.43 (0.11)	-0.05 (0.86)	-0.35 (0.19)
CT								
	WA_{CT}	0.22 (0.41)	-0.14 (0.60)	-0.43 (0.10)	-0.55 (0.03)	-0.39 (0.15)	-0.47 (0.08)	-0.34 (0.21)
	LA_{CT}	0.09 (0.75)	0.30 (0.26)	-0.30 (0.26)	-0.44 (0.10)	-0.44 (0.09)	-0.42 (0.06)	-0.28 (0.30)
	$WA\%_{CT}$	-0.50	-0.47	-0.14	-0.10	0.18	0.16	0.17

		(0.05)	(0.07)	(0.64)	(0.72)	(0.51)	(0.56)	(0.52)
	WT_{CT}	0.27	-0.25	-0.39	-0.45	-0.14	-0.49	-0.23
		(0.32)	(0.35)	(0.14)	(0.09)	(0.60)	(0.07)	(0.39)

Severe asthma (n=15)

		FEV_1 (% pred)	**FVC (%pred)**	**FEV_1/FVC**	**FEF_{25-75} (%pred)**	**PF (l/min)**	**FeNO (ppb)**	**Blood Eos (cells/µl)**
MRI								
	WA_{MR}	-0.76	-0.72	-0.51	-0.61	0.36	0.38	0.07
		(0.01)	(0.01)	(0.05)	(0.01)	(0.18)	(0.21)	(0.78)
	LA_{MR}	0.03	0.09	-0.09	-0.16	0.08	-0.38	-0.25
		(0.91)	(0.73)	(0.73)	(0.54)	(0.75)	(0.15)	(0.42)
	$WA\%_{MR}$	-0.55	-0.59	-0.32	-0.37	0.30	0.43	0.41
		(0.03)	(0.02)	(0.24)	(0.16)	(0.27)	(0.10)	(0.18)
	WT_{MR}	-0.62	-0.65	-0.39	-0.46	-0.24	0.19	0.35
		(0.01)	(0.01)	(0.14)	(0.08)	(0.36)	(0.48)	(0.26)
	Skewness	0.03	0.22	-0.22	-0.25	-0.09	-0.22	0.36
		(0.90)	(0.42)	(0.41)	(0.38)	(0.73)	(0.24)	(0.24)
CT								
	WA_{CT}	-0.26	-0.30	-0.07	-0.07	-0.04	0.09	0.01
		(0.34)	(0.27)	(0.78)	(0.79)	(0.29)	(0.76)	(0.96)
	LA_{CT}	0.23	0.24	0.21	0.03	0.26	-0.49	-0.41
		(0.40)	(0.37)	(0.43)	(0.48)	(0.34)	(0.06)	(0.12)
	$WA\%_{CT}$	-0.60	-0.54	-0.44	0.19	-0.29	0.46	0.26
		(0.02)	(0.03)	(0.09)	(0.07)	(0.28)	(0.13)	(0.34
	WT_{CT}	-0.60	-0.50	-0.45	-0.47	-0.27	0.39	0.15
		(0.02)	(0.05)	(0.08)	(0.06)	(0.32)	(0.20)	(0.59)

Data are Spearman correlation coefficients with p-value in parentheses.

Abbreviations: WA=bronchial wall area in mm^2; LA=lumen area in mm^2; WA%=ratio WA/WA+LA*100; WT=wall thickness in mm; FEV1=forced expiratory volume in 1 second; FVC=forced volume capacity; FEF25-75=forced expiratory flow at 25%-75% of FVC; %pred=percentage of predicted value; PF=peak flow; FeNO=fractional exhaled nitric oxide; Eos=eosinophils count.

Supplemental Figure

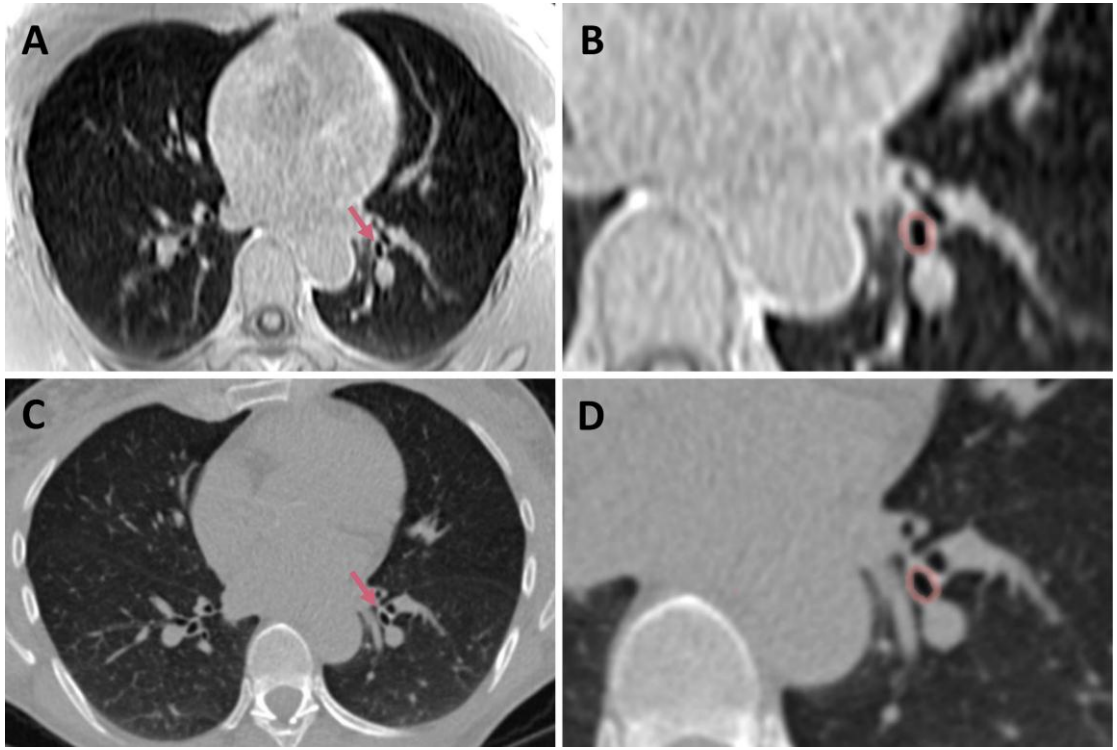

Figure E1: Representative lung images of a 56-year old non-severe asthmatic patient

Visualization of wall area measurements of LB-10 (red arrow) using magnetic resonance imaging with ultrashort echo time pulse sequence (A, B, C) or computed tomography (D, E, F).