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Lumen areas and homothety factor influence airway resistance in COPD

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ABSTRACT

The remodelling process of COPD may affect both airway calibre and the homothety factor, which is a constant parameter describing the reduction of airway lumen (h_d: diameter of child/parent bronchus) that might be critical because its reduction would induce a frank increase in airway resistance. Airway dimensions were obtained from CT scan images of smokers with ($n = 22$) and without COPD ($n = 9$), and airway resistance from plethysmography. Inspiratory airway resistance correlated to lumen area of the sixth bronchial generation of right lung, while peak expiratory flow correlated to the area of the third right generation ($p = 0.0009$, $R = 0.57$). A significant relationship was observed between h_d and resistance ($p = 0.036$; $R^2 = 0.14$). A modelling approach of central airways (5 generations) further described the latter relationship. In conclusion, a constant homothety factor can be described by CT scan analysis, which partially explains inspiratory resistance, as predicted by theoretical arguments. Airway resistance is related to lumen areas of less proximal airways than commonly admitted.

1. Introduction

The ability to measure airway dimensions is important for clinicians, interventional bronchoscopists and researchers in order to accurately quantify structural abnormalities and track their changes over time or in response to treatment, and emerging techniques have been developed for those goals (Williamson et al., 2009). The structure/function relationships between emerging techniques and conventional tests deserve to be determined (de Jong et al., 2005; Williamson et al., 2009). Accordingly, several studies already have assessed the relationships between forced expiratory flows (especially FEV_1) and airway dimensions obtained from multidetector computed tomography (MDCT) in chronic obstructive pulmonary disease (COPD) patients (de Jong et al., 2005; Nakano et al., 2005; Orlandi et al., 2005; Hasegawa et al., 2006; Achenbach et al., 2008; Matsuoka et al., 2008; Fain et al., 2009; Williamson et al., 2009). From a physiological point of view, forced expiratory flows would not be the best lung function tests to correlate with airway dimensions because flow limiting sections move down along bronchial tree during the forced expiration and the decrease in FEV_1 in COPD patients has further been related to loss of lung recoil and dynamic airway compression due to forced expiration. By contrast, airway resistance (Raw) and calibre are physically related, but the recent ATS/ERS task force on standardisation of lung function testing stated that airflow resistance is more sensitive for detecting narrowing of extrathoracic or large central intrathoracic airways than of more peripheral intrathoracic airways (Pellegrino et al., 2005), based on theoretical arguments. However, we recently found that Raw better correlated to $FEF_{50\%}$ than to FEV_1, suggesting that Raw explores less proximal airways than previously believed (Mahut et al., 2009).

The progression of COPD has been associated with an increase in the volume of tissue in the wall of the small airways (Hogg et al., 2004), the remodelling process, which reduces lumen areas of these airways, increasing the wall area ratio. Nevertheless, the finite airway calibre depends on both magnitude of remodelling and initial size of bronchi. Physiologically, in healthy lung, the progressive reduction of airway lumen after each division can be described by a

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quantitative parameter called the homothety factor that is the ratio of the diameter of one child bronchus related to the diameter of the parent bronchus (h_d). Based on a purely mathematical argument, it has been demonstrated that the successive airway segments of an ideal tree are homothetic with a constant size ratio equal to ~0.79 (Mauroy et al., 2004). If h_d decreases then Raw increases. Mauroy et al. (2004) have shown that this physical optimisation is critical in the sense that small variations in the geometry can induce very large variations in Raw. One may hypothesize that the remodelling process could increase the wall area ratio and result in a mild modification of the homothety factor leading to a significant functional consequence. If the homothety concept is relevant, one may expect a low intra-individual variation of h_d among the airway tree, a relationship between h_d and Raw and perhaps, a link between wall area ratio and h_d. To the best of our knowledge the correlation of homothety and Raw has not been tested.

Consequently, the first aim of our study was to assess the relationships between airway geometry and pulmonary function indices (resistance and forced expiratory flows), and the second aim was to determine h_d, and to establish its relationships with Raw and wall area ratio (proof-of-concept study). For these two objectives, we used MDCT scan images acquired in smokers with and without COPD together with a physical model to further reinforce our main results.

2. Materials and methods

2.1. Study design

In order to assess the relationships between Raw and both lumen areas and homothety factor, a wide range of Raw was necessary. Consequently we chose to include smokers without or with COPD, based on GOLD criteria (Anonymous, 2008). We further compared patients without and with increased Raw (>120% predicted). The absence of healthy subjects is not a limitation for evaluation of correlations.

Clinical, functional (pulmonary function tests) and morphological (CT scan images) data from 31 de-identified smokers (>15 pack-year) without major comorbidities were retrospectively selected from our hospital databases (Fig. 1 of the Appendix). Due to the retrospective character of the study, the ethical committee waived the need for informed consent according to French Law of Bioethics (Lemaire, 2006; Neff, 2008).

2.2. Pulmonary function tests

Body plethysmography and spirometry (MasterScreen PFT, Jaeger, CareFusion) were performed according to international guidelines (Miller et al., 2005), and reference equations were those of ECCS (Quanjer et al., 1993). Thoracic gas volume and specific resistance of airways (sRaw) were obtained during quiet breathing by body plethysmography allowing the calculation of Raw (Raw_{insp} and Raw_{exp} were determined using the slope of the sRaw during inspiratory and expiratory phase, respectively) (Dubois et al., 1956; Jaeger and Bouhuys, 1969). During a forced expiration dynamic airway compression increases airway resistance. Consequently, inspiratory resistance was selected rather than Raw, which was further justified by the results of the modelling approach (see Appendix A).

2.3. CT scan study

2.3.1. Lung data acquisition

Volumetric acquisitions (with the following parameters: 120-kV tube voltage, 53-mA s tube current, 0.625-mm collimation and 0.625–1.25-mm reconstruction section thickness) of the whole thorax that have been obtained using a 64-slice MDCT scanner (VCT, General Electric Medical Systems Milwaukee, USA) at full inspiration. Images were then transferred on a workstation (ADW 4.4, General Electric Medical Systems Milwaukee, USA) and analysed using a dedicated software.

2.3.2. Description of the software

The images were analysed with Thoracic application using a preliminary version of "Airways Analysis" software (General Electric Healthcare, Buc, France). Preliminary experiments (phantom study) have been made by General Electric Healthcare (MMN: initials of one of the contributing authors). The analysis consists in several steps: an automatic segmentation of the bronchial tree is launched starting by an automatic detection of tracheal lumen and then the centreline of the whole bronchial tree is automatically detected to allow measurements of the lumen area, wall thickness and wall area on planes orthogonal to this centreline, as previously done (Hasegawa et al., 2006; Fain et al., 2009). The measures are computed on each orthogonal plane to the centreline, using the full width at half max principle (FWHM).

2.3.3. CT scan parameters

The software automatically determined the middle position between two successive divisions of the tracheal–bronchial tree (in the middle portion of a bronchial segment, see Fig. 1) and calculated lumen area (LA, mm^2) and wall area ratio (WAR that is (total area − LA)/total area). These two parameters were selected for the generations showed in Fig. 2 (dashed line). The bronchial pathways from the trachea to the posterior basal bronchi (RS10, LS10, Fig. 2) were automatically displayed after the operator has selected one distal point in each posterior basal bronchus. Bifurcating segments in the lower lobes were selected to calculate the h_d as D_n/D_{n-1}, each diameter being calculated based on LA. This automatic detection of the middle position allowed a very good reproducibility of the analyses between both intra- and inter-observers (coefficients of variation < 5%; data not shown), which was evaluated by the analysis of the first five CT scan by four investigators (PB, PAB, BM, and CD_2). CD_2 performed all subsequent CT scan analyses, under supervision of an experienced senior radiologist (MPR).

2.4. Modelling study

The methods, results and discussion of this modelling study are provided in an Appendix A section.

2.5. Statistical analyses

All analyses were performed using the Statview 4 package (SAS Institute, Grenoble, France). Results were expressed as median [25th–75th percentile]. Quantitative variables of smokers with and without COPD were compared using Mann–Whitney *U*-test, while qualitative variables were compared using chi-test (Fisher's correction). Paired variables were compared using Wilcoxon test. Correlations between CT scan and pulmonary function test parameters were evaluated using linear, power or exponential laws, as stated in the text. One potential confounding factor is that both airway sizes and PFT parameters are related to anthropometric parameters (Fain et al., 2009). Since lumen areas and Raw_{insp}/peak expiratory flows also linearly correlated to height of the subjects, a stepwise regression was performed to determine which CT scan parameters were independently associated with inspiratory resistance/peak expiratory flows. Statistical significance was defined by a P value ≤ 0.05.

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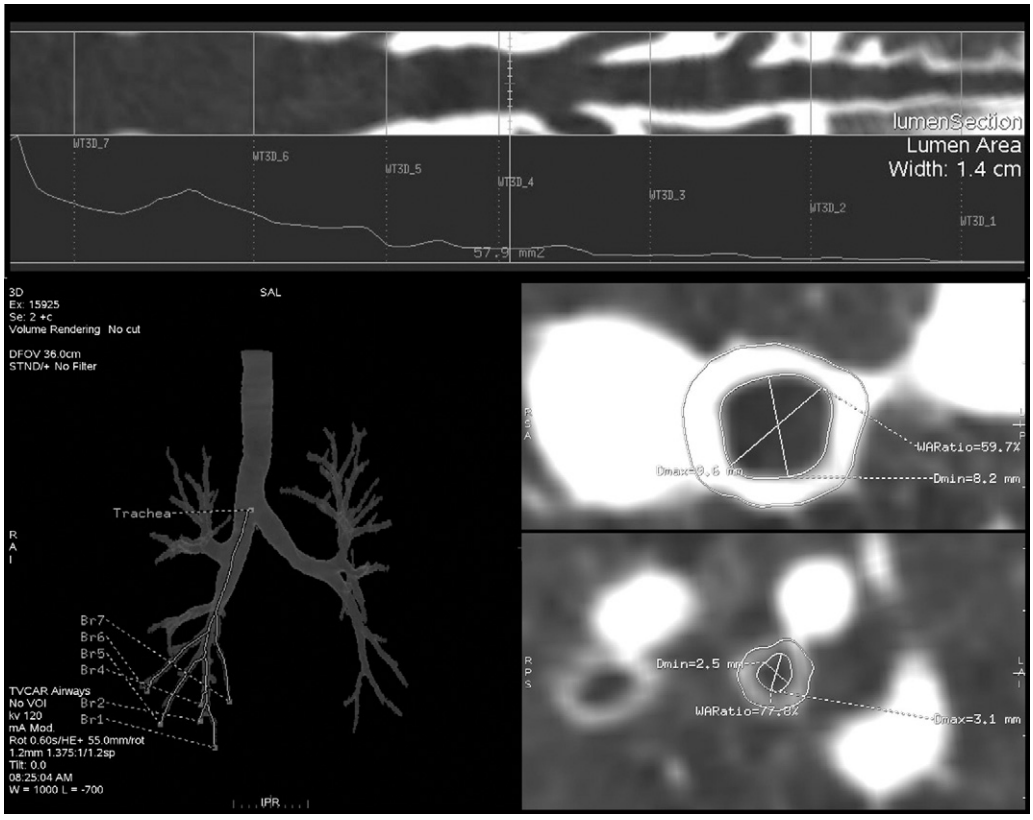

Fig. 1. A representative example of data obtained with Thoracic application. Lower left panel: the bronchial pathway from trachea to posterior basal bronchi (RS10, Br 1 in the figure) was manually selected, and then bronchial divisions from this bronchial pathway were selected in the lower lobe (dashed lines). A graph shows all the selected bronchi in Fig. 2. The dedicated software automatically determined the middle position between two successive divisions of the tracheal-bronchial tree (in the middle portion of a bronchial segment) and calculated lumen area (LA, mm^2) and wall area ratio (WAR that is (total area − LA)/total area, expressed as percentage). Then, in the lower lobes, bifurcating segments were selected to calculate the h_d factor as D_n/D_{n-1}, each diameter being calculated based on LA. The upper panel shows the bronchial pathway that has been selected and below a graph (X axis: length, Y axis: lumen area) with automatic detection of the middle positions of the bronchial segments (vertical lines). A cursor (central bold vertical line) is then manually positioned on the vertical lines, and automatic computation of LA and WAR at the chosen bronchial section is made. The middle and lower panels on the right show automatic detection of lumen and wall areas at two different levels of bronchial tree, and WAR calculation.

3. Results

The clinical and functional characteristics of the patients are described in Table 1.

3.1. Relationships between PFT test parameters and CT scan parameters

3.1.1. Lumen areas

Despite airway obstruction, the lumen areas of airways correlated (exponential) to the height of the subjects for the right lung up to the 6th bronchial generation while the correlation was significant only for the first and second generations of the left lung (data not shown). Tracheal area also correlated to the height of the subjects (tracheal area = $5.7 \times e^{(0.023 \times \text{height})}$, $p = 0.0004$). Since we also observed a linear relationship between the height of the subject and both Raw_{insp} and peak expiratory flow (data not shown), we further evaluated whether lumen areas were independent predictors of results of pulmonary function tests.

Table 2 describes the correlations observed between LA and Raw_{insp}. This latter index (for Raw, see Table 2 legend) independently correlated to areas of intralobar segmentations, mainly of the sixth generation of the right lung (see Table 2 legend and Fig. 3).

Peak expiratory flow (raw value) exponentially correlated to LA of third generation of the right lung ($p = 0.0009$, $R = 0.57$). The correlation remained significant when subject's height was taken into account. This independent association was further confirmed by the significance of the correlation between this LA and peak expiratory flow expressed as percentage of predicted value ($p = 0.006$, $R = 0.48$). The other forced expiratory flows (FEV_1, $FEF_{25-75\%}$, and $FEF_{50\%}$, raw values and % predicted) did not correlate to any LA, even when the latter were corrected by subject's height.

3.1.2. WAR

Raw_{insp} linearly correlated to WAR of generations 5L-6R and 6L-7R ($p = 0.002$, $R = 0.54$ and $p = 0.015$, $R = 0.45$; respectively) (see legends of Figs. 2 and 5 for explanations of generation numbering).

There was no significant difference for WAR between smokers with and without COPD, but patients with increased Raw (>120% predicted, $n = 19$) had higher WAR over several generations as compared to smokers with normal Raw (≤120% predicted, $n = 12$): WAR_{G4L-5R}, 74% [69–79] versus 71% [68-72], $p = 0.067$; WAR_{G5L-6R}, 77% [72–79] versus 71% [69–74], $p = 0.006$; WAR_{G6L-7R}, 79% [75–80] versus 75% [72–78], $p = 0.012$.

3.2. Relationship between Raw and homothety factor

3.2.1. A constant h_d factor can be described in the intralobar segmentations

The h_d factor obtained in left and right lung are shown in Fig. 4 confirming that bronchial divisions are asymmetric in lower lobes, where each parent bronchus gives a major and a minor child bronchus. In the proximal generations, i.e. from 1 to 3 corresponding to extralobar segmentations, the major h_d factor (corresponding to the ratio of the diameter of a major daughter bronchus to the diameter of the parent bronchus) was highly variable, while it was

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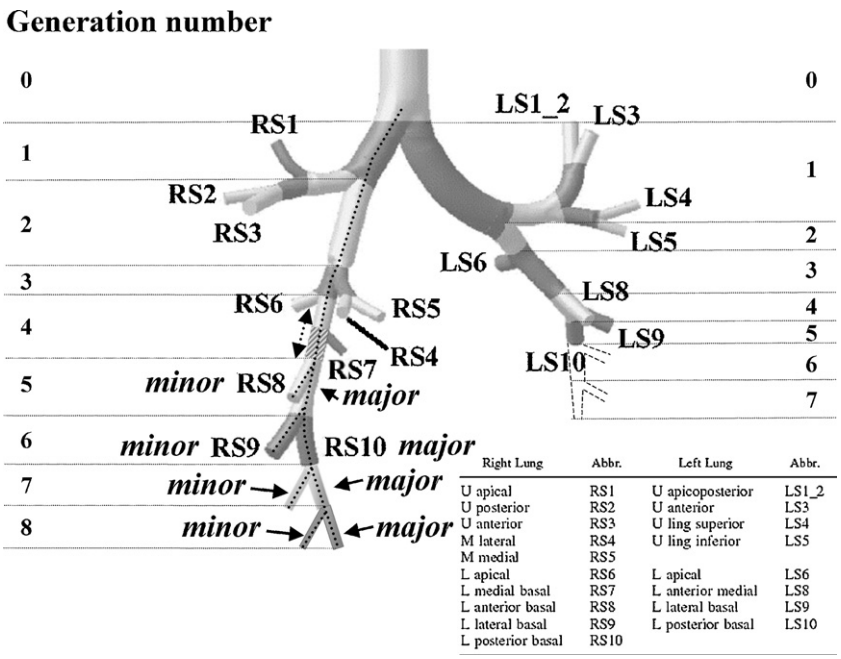

Right Lung	Abbr.	Left Lung	Abbr.
U apical	RS1	U apicoposterior	LS1_2
U posterior	RS2	U anterior	LS3
U anterior	RS3	U ling superior	LS4
M lateral	RS4	U ling inferior	LS5
M medial	RS5		
L apical	RS6	L apical	LS6
L medial basal	RS7	L anterior medial	LS8
L anterior basal	RS8	L lateral basal	LS9
L lateral basal	RS9	L posterior basal	LS10
L posterior basal	RS10		

Fig. 2. Schematic representation of the bronchial segments that were analysed using the Thoracic application. Automatic segmentation of the bronchial tree is launched, and then the centreline of the whole bronchial tree is automatically detected. The longest bronchial pathway was manually selected in each lower lobe (posterior basal segments, RS10 and SL10). In the lower lobes, bifurcating segments were selected to determine whether asymmetric branching can be evidenced (the dashed line shows the centreline of all bronchial segments that were manually selected in order to calculate major and minor h_d factors). Medial basal bronchus of right lung was not selected since this division induced almost no modification of parent airway calibre. This figure is adapter from reference (van Ertbruggen et al., 2005). A representative example of a patient is shown in Fig. 1. This figure also shows the numbering of bronchial generations. Due to the presence of three lobes in right lung versus two lobes in left lung, a bronchial segment at the same level in the lower lobe is differently numbered (also see legends of Figs. 5 and 6).

nearly constant in the four subsequent divisions (generations 4–7 [right lung] and 3–6 [left lung], in the last generation that can be analysed, h_d decreased). None of these morphological factors depicted any significant difference between smokers with or without COPD.

3.2.2. The h_d factor observed in intralobar segmentations contributes to resistance to flow

Fig. 5 shows the relationship between h_d factor and $Raw_{insp-exp}$. It has to be noted that h_d factor weakly contributed to Raw_{insp} variance (14%), while there was no significant relationship between h_d factor and Raw_{exp}.

3.2.3. Relationships between h_d and WAR

In the lower lobes, major and minor h_d factors linearly correlated to WAR of their respective generations (Fig. 6).

4. Discussion

The main results of this study are the following: (1) the best correlation between lumen areas and Raw (independent of sub-

Table 1
Clinical and functional characteristics of the patients.

Characteristic	Smokers without COPD $n=9$	Smokers with COPD $n=22$	P value
Sex ratio, female/male	3/6	4/18	0.56
Current smokers, n	3	9	0.69
GOLD class, 1/2/3/4		2/7/10/3	
Age, years	56 [46–57]	63 [56–70]	0.011
BMI, kg m^{-2}	25.7 [24.3–26.8]	22.4 [20.0–25.1]	0.098
Tobacco, pack-year	45 [34–52]	40 [30–50]	0.79
MRC scale	1.00 [1.00–1.25]	2.00 [2.00–4.00]	0.004
FEV_1/FVC, %	78 [76–83]	49 [43–62]	<0.001
FEV_1, % predicted	104 [101–110]	41 [33–52]	<0.001
FVC, % predicted	112 [105–113]	70 [61–85]	<0.001
Slow VC, % predicted	108 [100–111]	77 [62–85]	<0.001
$FEF_{25-75\%}$, % predicted	75 [63–107]	15 [11–25]	<0.001
$FEF_{50\%}$, % predicted	86 [66–113]	14 [10–24]	<0.001
Raw, % predicted	87 [65–109]	222 [149–287]	<0.001
Raw_{insp}, $cmH_2O\,s\,L^{-1}$	0.22 [0.19–0.25]	0.45 [0.37–0.58]	<0.001
Raw_{exp}, $cmH_2O\,s\,L^{-1}$	0.34 [0.21–0.47]	0.99 [0.62–1.28]	<0.001
sRaw, % predicted	81 [76–137]	339 [195–528]	<0.001
TLC, % predicted	104 [101–118]	119 [103–128]	0.016
FRC, % predicted	116 [105–130]	163 [148–194]	<0.001
RV, % predicted	119 [106–135]	188 [166–220]	<0.001

COPD denotes chronic obstructive pulmonary disease.
GOLD stage according to international 2006 classification (Anonymous, 2008).
BMI denotes body mass index.
MRC denotes Medical Research Council dyspnea scale (1–5).

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Table 2
Power law relationships between lumen areas and inspiratory airway resistance.

Lumen areas (LA)	Raw_{insp} (kPa L^{-1} s^{-1})	
	Power value	*P* value
$Trachea_{G0}$		0.19
Right lung		
LA_{G1}		0.17
LA_{G2}		0.20
LA_{G3}	−0.52	0.019
LA_{G4}	−0.41	0.052
$LA_{G5,major}$	−0.45	0.035
$LA_{G5,minor}$	−0.50	0.005
$LA_{G6,major}$ [a]	−0.49	0.004
$LA_{G6,minor}$	−0.50	0.060
$LA_{G7,major}$	−0.34	0.032
$LA_{G7,minor}$	−0.39	0.10
$LA_{G8,major}$		0.15
$LA_{G8,minor}$		0.82
Left lung		
LA_{G1}		0.35
LA_{G2}		0.36
LA_{G3}		0.23
$LA_{G4,major}$		0.27
$LA_{G5,major}$		0.16
$LA_{G6,major}$		0.22
$LA_{G7,major}$		0.99

G: bronchial generation; major and minor are related to major and minor bronchi after asymmetric division.
Raw also correlated with lumen areas (LA) of right lung (only small trends were evidenced for left lung). Multivariate analyses showed that Raw_{insp} was independently (from subject's height) related to lumen areas of right lung for $LA_{G5,minor}$, $LA_{G6,major}$ and $LA_{G6,minor}$.
[a] See Fig. 3.

ject's height) is observed for the 6th bronchial generation of the right lung, which emphasizes that Raw is sensitive for detecting narrowing of less proximal intrathoracic airways than previously stated (based on the classical theoretical relationship between total bronchial area and resistance it has been stated in international recommendations that "airflow resistance is more sensitive for detecting narrowing of extrathoracic or large central intrathoracic

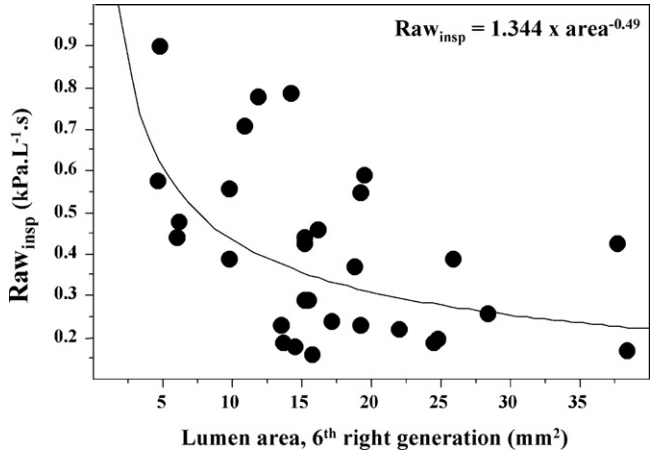

Fig. 3. Relationship between lumen area of the sixth right generation and inspiratory airway resistance (Raw_{insp}) in the 31 smokers. Lumen area was automatically measured at the middle position of the 6th generation of the right lung (see Fig. 1) using CT scan and Raw_{insp} was measured using body plethysmography (the normal value of Raw in adults is 0.30 kPa/(L/s)). We found a power law to be the best fit of this correlation. The value of the power was −0.49, which can be explained by the nature of the correlation between the inspiratory resistance and the h_d obtained by computational simulation ($y = 2.507(x^{-5.543})$, see Fig. 3 of the Appendix). The lumen areas of the 6th generation bronchi scale like h_d on the power 12. Hence, inspiratory resistance is proportional to the area of the sixth generation elevated at power −5.543/12 = −0.462, which is close to the observed value.

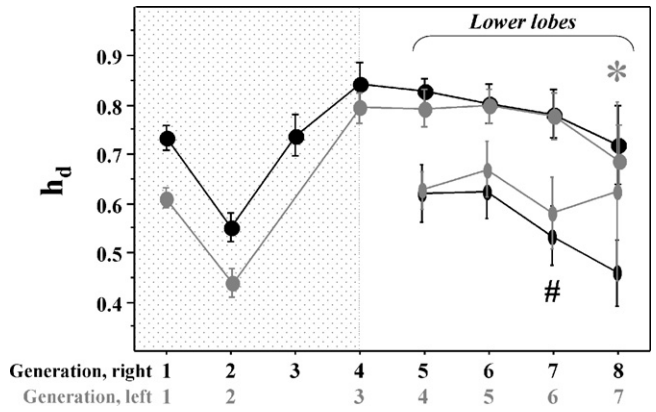

Fig. 4. Homothety ratios (h_d) calculated in the 31 smokers using CT scan according to bronchial generations. The h_d factors obtained in left (grey colour) and right (black colour) lung are shown confirming that bronchial divisions are asymmetric in lower lobes, giving a major and a minor child bronchus (error bars are 95% CI). The dashed background delimits extralobar divisions. In the lower lobes, both major (circles) and minor (ovals) h_d factors are showed. *: comparison (paired test, $p < 0.05$) versus preceding major h_d factor for left lung. #: comparison (paired test, $p < 0.05$) versus preceding minor h_d factor for right lung.

airways"); (2) using MDCT scan, h_d factors of both major and minor bronchial intralobar divisions can be described with a constant h_d factor over several generations; (3) this h_d factor influences Raw, a result that has never been shown from human data; and (4) the remodelling process that would increase WAR may affect this h_d factor.

4.1. Correlations between lumen areas and pulmonary function tests

We found an exponential relationship between patients' height and lumen areas in spite of airflow limitation, suggesting that the height of the patient is a major determinant of airway lumen areas. A similar exponential relationship has been demonstrated in children (de Jong et al., 2006), and recently, Sheel and colleagues used CT scan to show that when male and female subjects were pooled there were significant associations between lung size and airway size (Sheel et al., 2009). The description of the relationships between forced expiratory flows and lumen areas is a complex

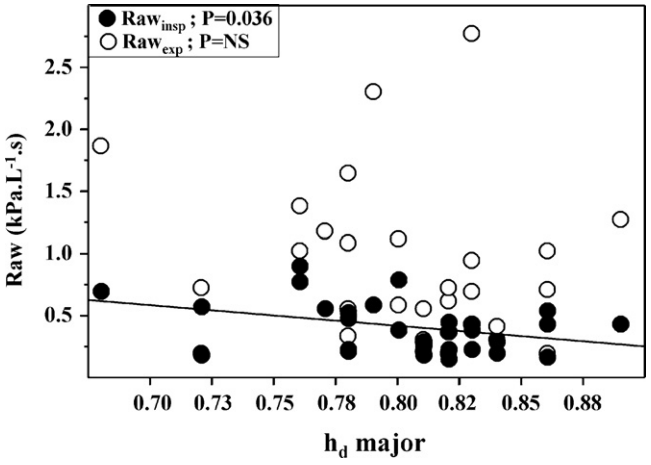

Fig. 5. Relationships between major homothety (h_d) factor and Raw. Major h_d factor is the mean value of major h_d factors calculated for left and right lungs from generations 3 (left: L)–4 (right: R) to generations 6L-7R (where h_d factor is constant, see Fig. 4). Inspiratory (Raw_{insp}: closed circles) and expiratory (Raw_{exp}: open circles) Raw were measured using body plethysmography. The degree of significance of the linear correlations is provided in the upper left corner of the figure.

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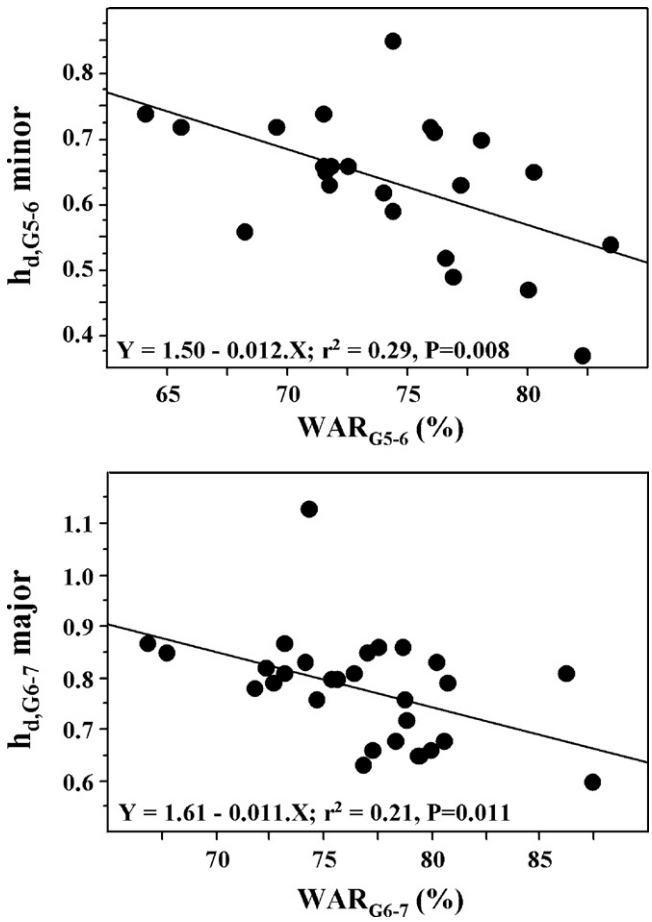

Fig. 6. Relationships between wall/area ratio (WAR, expressed as %) and homothety (h_d) factors. In the lower lobes, mean major h_d factor, minor h_d factor, and WAR were calculated for a given level of generations (mean of right and left lungs, see Fig. 4). The upper panel shows the relationship between WAR of generation 5 (left lung) and 6 (right lung) and the corresponding minor h_d factor (obtained in the same generations), whereas the lower panel shows the relationship between WAR of generation 6 (left lung) and 7 (right lung) and the corresponding major h_d factor.

issue. Raw values (L/s) of instantaneous forced expiratory flows (like PEF or $FEF_{50\%}$) and of Raw would logically depend on lumen areas, and the latter depend on subject's height. It is well known that the values of these expiratory flows depend on subject's height.

Previous investigators evaluated the relationships between lumen areas mainly in the right lung (raw values or raw values/subject's body surface area or height) and percentage of predicted values of FEV_1 (de Jong et al., 2005; Nakano et al., 2005; Orlandi et al., 2005; Hasegawa et al., 2006; Achenbach et al., 2008; Matsuoka et al., 2008; Fain et al., 2009; Williamson et al., 2009). Some previous correlations (for instance linearity between lumen area and % predicted FEV_1 (Hasegawa et al., 2006)) are unrealistic from a physiological point of view. Dividing lumen area by body surface area or height could seem a logical approach. It implies that a relationship between indexes obtained from CT scan and those anthropometrical parameters has first been established, according to recent findings of Fain and colleagues (Fain et al., 2009). Nevertheless, we did not find significant relationships between lumen areas corrected for height and FEV_1% predicted in our COPD patients, which may have several explanations. Firstly, FEV_1 is a volume that is sensitive to both airflow limitation and airway closure (Sorkness et al., 2008), and a reduction of vital capacity is frequent in COPD patients. Secondly, the flow limiting segment that impacts FEV_1 is deemed to move distally during the forced expiration (from proximal to more distal segments with decreasing vital capacity). Thirdly, besides airway obstruction, the decrease in FEV_1 in COPD patients is also related to loss of lung recoil and dynamic airway compression due to forced expiration. Accordingly to this latter explanation, Matsuoka et al. (2008) recently demonstrated that forced expiratory flows better correlated to lumen areas measured from expiratory CT scan than to areas measured from inspiratory CT scan. Overall, relationships between structure and function have been assessed in both asthma and COPD. Conflicting results have been obtained concerning the correlations between lumen areas and expiratory flows (Nakano et al., 2002; de Jong et al., 2005). It remains to emphasise that we observed a relationship between peak expiratory flow and a proximal area (third generation that corresponds to the minimal total section of airways). Due to limitation for forced expiratory flows, we deliberately chose to assess the relationships between airway geometry and resistance during quiet breathing. Inspiratory Raw was chosen because the effects of dynamic expiratory compression are eliminated. The significant relationships were observed for the right lung, and more importantly the shape of the relationships (power law) is consistent with the physical properties of bronchial tree, namely can be explained by the correlation between inspiratory resistance and h_d obtained by computational simulation (see Fig. 3 legend). When subject's height was taken into account, Raw mainly correlated to the area of the lumen of the sixth bronchial generation of right lung, and also correlated to WAR at the same bronchial level, which emphasizes that Raw is sensitive for detecting narrowing of less central intrathoracic airways than previously stated (Pellegrino et al., 2005), but in agreement with our recent study in asthma (Mahut et al., 2009). Interestingly, the bronchial generations (3rd and 6th) that correlated with either PEF or Raw are consistent with the calculations obtained using Poiseuille flow or Pedley and colleagues formula (Pedley et al., 1970), respectively. Obviously, the site of airway obstruction in COPD is in small airways that are not evaluated by CT scan, but Nakano et al. (2005) demonstrated that the dimensions of relatively large airways assessed using CT reflect small airway dimensions measured histologically. The absence of significant correlations for the left lung may be related to measurement artefacts due to cardiac motion, and related to the lowest h_d factors of the first bronchial generations (1st and 2nd, see Fig. 2 and Appendix A section: resistance mainly depends on major h_d).

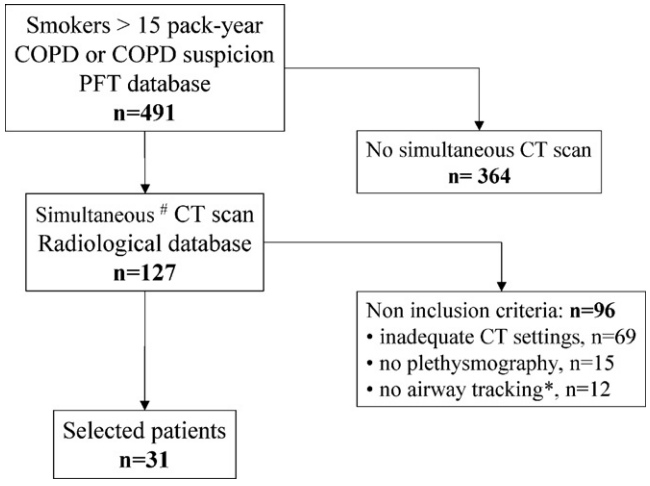

Fig. A.1. Flow-chart describing the selection of the patients. The selection process was made by an independent investigator of our hospital, Department of Medical Information (CD_1). PFT: pulmonary function test. #: a 1-week delay was tolerated between PFT and CT scan (both done under regular respiratory treatment). *: no airway tracking means that the software was unable to perform automatic lung segmentation (mainly due to respiratory movements during acquisition).

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4.2. Description and functional consequences of the homothetic factor of lumen diameters

Based on a purely mathematical argument, it has been suggested that the best tree is fractal; in such an ideal tree, the successive airway segments are homothetic (Mauroy et al., 2004). This ideal factor represents the best compromise between Raw to flow and airway dead space. This h_d factor would be constant over bronchial generations and would dictate the diameters of all bronchial divisions based on initial tracheal area. We show that lungs of smokers cannot be described by this "simple" ratio. Firstly, h_d factor of the first three generations exhibits frank variations, and subsequently depicted a plateau in subsequent distal generations. Secondly, bronchial divisions are asymmetric, as previous shown (Weibel, 1963; Schlesinger and McFadden, 1981; Tawhai et al., 2004), and two h_d factors can be described, for major and minor child bronchus. Our results are in close agreement with those of previous investigators obtained in human lung casts (major h_d factor ($\pm$SD) = 0.88 ± 0.10, minor h_d factor = 0.69 ± 0.12 (Weibel, 1963; Schlesinger and McFadden, 1981; Majumdar et al., 2005)). To our best knowledge, only two studies have measured h_d factor by CT scan. In one study, two ratios were described for a single human lung (h_d major ($\pm$SD) = 0.79 ± 0.12; h_d minor = 0.66 ± 0.12) (Tawhai et al., 2004). In another study involving 10 healthy subjects, the authors did not try to describe these two ratios, only a mean factor was reported (from 0.75 for the first generation to 0.97 for the 8th generation) (Montaudon et al., 2007b). Recently, Hasegawa et al. (2009) evaluated the bronchodilator effect of tiotropium bromide in 15 COPD patients using CT scan. Homothety ratios can be calculated from their results (see there Table 2), which are 0.83, 0.81 and 0.81 within the right lower lobe (posterior basal). Incidentally, we show that the h_d factors may explain the few number of bronchi that is visualized by CT scan (see Appendix A).

Despite all these confounding factors, a mean h_d major measured over the four bronchial segments where it is constant seems to affect inspiratory Raw. The functional consequence of this relationship is modest since only 14% of resistance variance is explained, which further justify the absence of difference of h_d between patients with and without COPD. But due to the several previous limitations of a "constant" h_d concept, this significant relationship was quite unexpected. Interestingly, the remodelling process of airways may affect the homothety factor if this process explains the increase in WAR. This result was not obvious, a constant percentage of increase in airway wall would not affect h_d factor. By contrast, a constant increase in airway thickness (for instance, adding a constant layer of smooth muscle cells) will reduce h_d factor in the distal generations.

4.3. Implications of the asymmetry of bronchial divisions

One could ask whether there are any physiological benefits of this asymmetry. Asymmetry probably plays a role in the resistance and volume of the bronchial tree. Recently, Mauroy and Bokov developed a model that predicted, even if the population is adapted at best, that there always exist individuals whose bronchial trees are associated with larger costs of breathing comparatively to the average and who ought to be more sensitive to geometrical remodelling (Mauroy and Bokov, 2010). Consequently, the ability to describe this individual variability of asymmetry using CT scan is an important development.

4.4. Limitations of the study

The retrospective selection of patients from two databases may constitute a bias, but the investigators were blinded for the results of PFT and CT scan. CT scan and functional (Raw) measurements were obtained at different lung histories (near TLC versus FRC, respectively), which influence airway calibre. Nevertheless, inspiratory measurements were obtained (Raw at FRC and CT scan images at TLC), which could be a better approach than comparison of a forced expiratory volume (FEV_1) and airway calibres at TLC, as usually done. We deliberately did not evaluate the degree of emphysema that was probably mild to moderate in our patients (see the degree of hyperinflation in Table 1), which affects forced expiratory flows to a great extent but weakly inspiratory Raw. As pointed out by a recent study of Yamashiro et al. (2009), even in patients with alpha (1)-antitrypsin deficiency in which emphysema of the lower lung is the predominant component, airway disease also had a significant impact on airflow limitation. Similarly, Kim et al. (2009) also showed significant associations between either wall thickness or square root of wall area and densitometric measures of emphysema with the postbronchodilator FEV1% predicted. The FWHM method has been widely used to investigate airway changes in obstructive lung diseases (Nakano et al., 2002; de Jong et al., 2005; Fain et al., 2009; Williamson et al., 2009). However, this method systematically overestimates wall area and underestimates lumen area (de Jong et al., 2003; Achenbach et al., 2008; Williamson et al., 2009). This underestimation of lumen area would induce a progressive reduction of h_d that was indeed observed for the more distal generations (7th for left lung and 8th for right lung for major bronchi). The h_d description was restricted to lower lobes that is another limitation. If this ratio varied from division to division, it would have implied that a fractal tree with homothetic segments cannot describe human lung. Overall, our results show that human lung is not so far from optimality but not so closed too, which may explain the weak relationship between h_d major and inspiratory resistance. The ability to describe a homothety factor was the first step to evaluate whether underlying geometry (congenitally acquired) may constitute a risk factor for subsequent respiratory diseases such as asthma and COPD.

The modelling approach has limitations, only the first five bronchial generations were modelled since it has been stated that Raw would be affected by central airway areas. A symmetric model with constant rotating and branching angles was used despite our demonstration of asymmetrical bronchial divisions. Overall, this modelling approach was used to strengthen our main results (selection of inspiratory resistance, explanation for the shape of the relationship between inspiratory resistance and airway lumen, correlation between h_d and inspiratory resistance and explanation for the few number of bronchi visualised by CT scan).

In conclusion, CT scan allows the description of several morphological parameters of bronchial tree, which were related to bronchial obstruction (increased Raw). Airway resistance is sensitive to the reduction of lumen area of the sixth bronchial generation of right lung (intralobar division). Two constant homothetic factors (major and minor) for the diameters of several intralobar generations are described, which are consistent with previous results obtained in a limited number of casts. Finally, the major homothetic factor affects to some extent Raw that is consistent with theoretical approaches (proof-of-concept).

Competing interests

PB, BM_1, CP, CD_1, BM_2 and CD_2 declare no competing interest. MPR has received a free software from General Electric Medical Systems. PAB and MMN are employed by General Electric Medical Systems. The decision to submit the paper for publication was taken by the authors who conceived the study (see below).

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Authors' contributions

PB, BM2 (Mahut) and CD2 (Delclaux) conceived the study. PB and BM performed the modelling study. PAB, MMN and MPR performed the preliminary experiments on CT scan and conceived the CT scan analysis that was performed by PAB and CD2. CD1 made the selection process of the patients and helped for the study design. BM2 and CP performed the statistical analyses. All the authors helped to draft the manuscript, read and approved the final manuscript.

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Appendix A.

A.1. Modelling study

The modelling approach was done to evaluate whether central airways anatomy (homothety factor) may affect airway inspiratory/expiratory resistance in an inertial laminar flow, as encountered physiologically, since Mauroy et al. (2004) previously established that relationship in distal lung under laminar flow.

A.1.1. A five generations model of the central bronchial tree

A model of 5 generations of central bronchial tree was developed to explain the influence of geometry on airway inspiratory and expiratory resistances (Appendix Fig. A.2). We supposed that the outflow profile after the fifth generation is described by a fully developed laminar flow (Poiseuille flow). We used a 5-generation symmetrical tree, which consisted of a three-dimensional cascade of bifurcating cylinders. Each bifurcation is coplanar as found approximately in real lung; each generation is rotated by 90° compared with the previous generation.

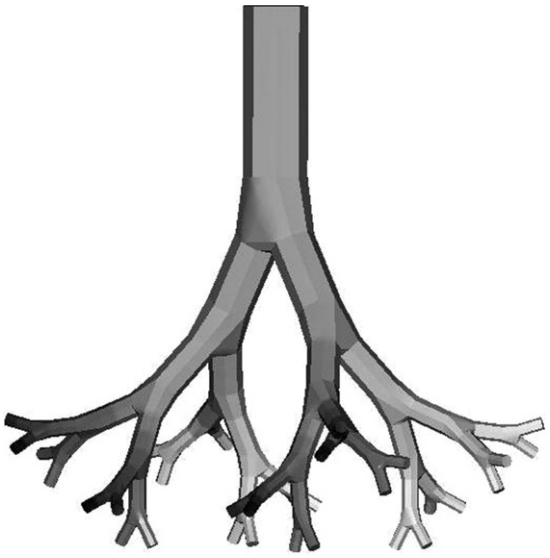

Fig. A.2. Model of the first five bronchial generations. A 5-generation symmetrical tree, which consisted of a three-dimensional cascade of bifurcating cylinders was used. Each bifurcation is coplanar as found approximately in real lung; each generation is rotated by 90° compared with the previous generation.

Homothety factor (h_d) defines the transformation of the diameters from generation $n-1$ to generation n, as follows $h_d = Dn/Dn-1$, where Dn and $Dn-1$ are respectively the diameters of the bronchi of generation n and $n-1$.

The mathematical description for the detailed fluid mechanics in the branched structure is based on the steady-state form of the continuity and Navier–Stokes equations.

$$\nabla \cdot u = 0, \tag{1}$$

$$\rho u \cdot \nabla p + \eta \nabla^2 u \tag{2}$$

where μ and p are the local velocity and pressure fields, respectively. The diameter (D) of the first tube is equal to 2 cm, corresponding to the diameter of the human trachea, the length (L) is 6 cm; the ratio L/D of the bronchi is considered constant in the tree, independent of the generation and equal to 3, which is close to the physiological situation (Weibel, 1963). The fluid can move along the tree in both directions (inspiration/expiration). In order to refer easily to the different open surfaces of the geometry, we will call entrance the surface mimicking the trachea orifice and exits the surfaces corresponding to the extremities of the fifth generation branches.

The fluid is air with viscosity $\eta = 1.9 \times 10^{-5}$ kg m^{-1} s^{-1} and density $\rho = 1.25$ kg m^{-3} and the flow is considered to be incompressible. Nonslip boundary conditions are imposed on the tube walls (Dirichlet condition $\mu = 0$). The pressure at the entrance and at the exits of the model is maintained constant. Eqs. (1) and (2) are solved using finite elements [COMSOL Multiphysics] and the relative error of convergence is always smaller than 10^{-3} for all the computations.

Information about the importance of inertia in the tree is given by the Reynolds number, $\mathrm{Re} \equiv \rho DV/\eta$, where V is the mean velocity and D is the hydraulic diameter of the pipe.

Parameter-dependant stationary CFD (Computer Fluid Dynamics) simulations were performed using the software COMSOL Multiphysics. The parameter governed the value of the pressure at the entrance while the pressure at the exit was maintained constant. The parameter was changed slowly step by step and a fully converged steady-state solution was calculated for each step. During inspiration, the maximal pressure drop simulated was 10 Pa, during expiration this pressure drop was −10 Pa. This low level of pressure drop was chosen to ensure a Reynolds number between 2000 and 5000 at inspiration in trachea, accordingly to previous authors (Weibel, 1963; Pedley et al., 1970) and to the Reynolds numbers at trachea calculated during Raw measurement in our patients (mean ± SD, 2966 ± 951 at inspiration using the mean inspiratory flow). Calculations of the flow were performed by integration of the velocity on a surface of interest (generally at the middle of an airway segment). Using this pressure drop, the flow in the first generation reached ∼1 L/s during inspiration and ∼0.5 L/s during expiration.

A.1.2. Relationship between h_d and Raw

The model predicted that Raw_{exp} is higher than Raw_{insp}, and that Raw_{insp} is more influenced by h_d than Raw_{exp} (Appendix Fig. A.3), which is in accordance with our observed results (see Fig. 5) despite the absence of dynamic compression of airways in the model.

For a fully developed laminar flow ($\mathrm{Re} \ll 1$), velocities profiles and pressure distribution are the same during inspiration and expiration, so it is impossible to make any distinction between the inspiration and the expiration. On the other hand, when the laminar flow is no longer developed ($\mathrm{Re} > 1$) the previsions of the Poiseuille's model are no longer true. One finding of our model is that Raw_{exp} is higher than Raw_{insp}, which is something known by clinicians. Several factors have been described to explain why expiratory resistance is higher than the inspiratory one (Jaeger and Bouhuys, 1969). However we show here that it can be explained

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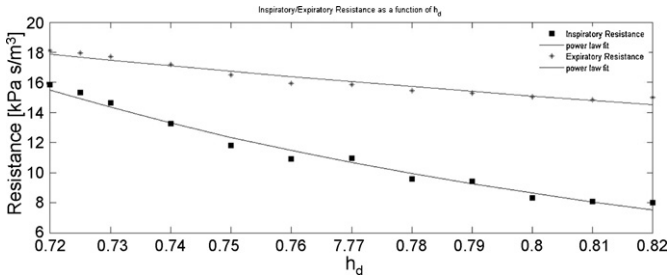

Fig. A.3. Inspiratory and expiratory resistance as a function of homothety factor (h_d). The relationship between homothety factor and resistance was evaluated by a modelling study (a 5-generation symmetric bronchial tree, see Appendix for the detailed model). The equations of the fits are $y = 2.507(x^{-5.543})$ for inspiratory resistance and $y = 10.534(x^{-1.611})$ for expiratory resistance. A power law fit was found to be a better fit than an exponential law.

by the only particularity of the expiratory flow distribution within a section of the trachea. During expiration the velocity profile in the trachea has a peak-like distribution, which means that there is a region of high velocity in the center of the trachea and a large region of low velocity around the wall of the trachea. Since only the radial component of the velocity gradient creates energy dissipation and hence resistance, this situation is similar to a flow into an airway section of the size of the central area of high velocity. This functional reduction of the area results in a higher resistance.

A.1.3. Calculated versus observed resistances

The calculated resistances were substantially lower that those measured in patients, which may be explained by the limitations of our model. Since we fixed the level of pressure drop of our model to obtain physiological Reynolds numbers in trachea (calculated during Raw measurement), the only explanation is geometrical differences between the model and human lung, which is obvious (see Fig. A.2 of the Appendix). Nevertheless, the resistance was calculated for only the first five generations, which may further emphasize that Raw is less proximal than previously stated.

A.1.4. Symmetric versus asymmetric tree

We chose to model the bronchial tree as a symmetric assembly of segments, which means that at each division a bronchial segment (called the parent segment) divides into two identical segments (called daughters segments), as previously (Mauroy et al., 2004). However, we confirm in this work that the human bronchial tree is not symmetric but asymmetric. Hence, one can question the validity of the assumptions of symmetry we made for the modelling of the bronchial tree and what implications this could have for the calculation of the Raw.

Nevertheless in an asymmetric tree, the Raw can be described by a symmetric tree with a factor of homothety (h_{deq}) simply calculated by the following relationship (found to be exact in a Poiseuille flow (Mauroy et al., 2004)).

$$2h_{deq}^3 = h_{dmaj}^3 + h_{dmin}^3 \quad (3)$$

We found that such a tree ($h_{deq} = 0.725$) underestimates the true resistance of an asymmetrical tree (h_{dmaj}; h_{dmin}) = (0.80; 0.63) by 8% at inspiration and 4% at expiration for a pressure gradient of 10 Pa. Thus, this difference is relatively small and do not change the qualitative conclusions of the study.

Finally, it is interesting to note that h_{dmaj} should play a more important role in determining the total resistance than h_{dmin} because the resistance is a function of $1/(h_{dmaj}^3 + h_{d\,min}^3)$, which is close, in order of magnitude, to $1/h_{dmaj}^3$. This latter result may explains that the observed relationship between h_{dmaj} and resistance (see Fig. 5).

A.1.5. Homothety factors explain the low percentage of bronchi visualized by CT scan

Previous investigators showed that a decreasing percentage of bronchi toward distal generations were visualized by CT scan (Montaudon et al., 2007a,b). Since it is obvious that few bronchi were visualized (see for instance Fig. 1), we then evaluated whether this selection bias could be explained by major and minor h_d. It emphasizes that homothety factors may induce a systematic selection bias, explaining why similar bronchial pathways are visualized whatever the subject.

A.1.6. Calculation of the expected number of bronchial segments to be seen on a CT of the thorax

We chose the following values: $h_{dmaj} = 0.80$ the major homothetic factor and $h_{dmin} = 0.63$ the minor homothetic factor. When considering a bronchial segment of the generation n, its diameter is obtained by multiplying the diameter of the trachea D_0 by h_{dmaj} as many times as there are major bifurcations in the pathway leading to the bronchial segment of consideration starting from the trachea: k_{maj}. It is clear that the remaining divisions, $n - k_{maj}$, correspond to minor divisions. Hence, one can write the following relationship that gives the diameter D_n of the bronchial segment considered:

$$D_n = D_0 h_{dmaj}^{k_{maj}} h_{dmin}^{n-k_{maj}} \quad (4)$$

Table A.1
Estimation of the number of visible bronchial segments compared to the number of segments actually observed after numerical treatment of a CT pulmonary scan.

Generation (Weibel)	Theoretical number of bronchi	Predicted bronchi[a] (% of total)	Observed bronchi (% of total) present study[b]	Observed bronchi (% of total) [26]
0	1	100	100	100
1	2	100	100	100
2	4	100	100	100
3	8	100	100	115
4	16	100	99 [95–100]	119
5	32	97	90 [83–98]	114
6	64	89	77 [63–84]	84
7	128	50	42 [29–58]	39
8	256	14	ND	14
9	512	2	ND	4

ND: not determined [range].
The results obtained by Montondon and colleagues are shown for comparison, demonstrating that our computation accurately predicted the number of bronchi that can be evidenced using CT scan by other investigators.
[a] Number of predicted bronchi according to our calculation (see results) based on two h_d factors.
[b] As a preliminary experiment, one of the authors (PAB) counted (visual inspection) the number of bronchi visualized by CT scan in a representative patient.

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Therefore, bronchial segments of the generation n that will still be visualized verify the condition, $D_n \geq D_c$, where D_c is the cut off bronchial diameter. We hypothesized that bronchi with diameters inferior to D_c (2 mm) will not be seen on CT scans. This condition gives a minor bound $K_{maj,n}$ on k_{maj}. Thus, the number of visualized of the generation n (V_n) are those belonging to a bronchial segment having at least $K_{maj,n}$ major divisions, thus.

$$V_n = \sum_{k=K_{maj,n}}^{n} C_n^k \quad (5)$$

where $C_n^k = n!(k!(n-k)!)$. Appendix Table A.1 shows the different values of V_n calculated with this method.

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