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Homothety ratio of airway diameters and site of airway resistance in healthy and COPD subjects

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ABSTRACT

Our objective was to evaluate whether a decrease in the homothety ratio (*h*: diameter of child/parent bronchus, constant over generations) explains the shift in airway resistance toward periphery in chronic obstructive pulmonary disease (COPD). Using a validated computational model of fluid motion, we determined that reduced values of *h* (<0.76) were associated with a shift in resistance toward periphery. The calculated luminal diameters of terminal bronchioles using normal *h* (0.80–0.85) or reduced *h* (0.70–0.75) fitted well with measured micro-CT values obtained by McDonough et al. (N. Engl. J. Med., 2011; 365:1567–75) in control and COPD patients, respectively. A semi-analytic formula of resistance using tracheal dimensions and *h* was developed, and using experimental data (tracheal area and *h* from patients [Bokov et al., Respir. Physiol. Neurobiol., 2010; 173:1–10]), we verified the agreement between measured and calculated resistance ($r = 0.42$). In conclusion, the remodeling process of COPD may reduce *h* and explain the shift in resistance toward lung periphery.

1. Introduction

For some time, the measurement of airway resistance (Raw) has been considered the "gold standard" by physiologists for assessing airway obstruction due to its physiological background (Dubois et al., 1956). However, Raw measurement has recently become less popular in pulmonary function test laboratories because it requires complex equipment (body plethysmograph) and, more importantly, because the site of obstruction (i.e., the bronchial generations that are the most resistive) that is assessed is deemed to be very proximal. Along this line, the American Thoracic Society and European Respiratory Society have stated in their recommendations for pulmonary function tests 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). Nevertheless, direct measurement of the distribution of resistance in the lower respiratory tract has long established that small airways (i.e., <2 mm in internal diameter) become the major sites of obstruction in patients with chronic obstructive pulmonary disease (COPD) (Hogg et al., 1968). Resistance to flow through tubes is inversely related to the reduction in the radius raised to the fourth power for fully developed laminar flow. Since loss of half of such airways will only double the total peripheral resistance because of their parallel arrangement, an increase in peripheral airway resistance by a factor of 4–40, as has been reported in patients with COPD (Hogg et al., 1968), has recently been explained by both generalized narrowing and loss of airways (McDonough et al., 2011).

On theoretical grounds, sections of the entire airway tree can be described by only two parameters, the tracheal diameter and the homothety ratio, which is a constant parameter describing the subsequent reduction in the airway lumen (*h*: diameter of the child/parent bronchus) at each bronchial generation. Considering the lower part of the bronchial tree (generations 6–16) and assuming that air flow in this duct system obeys Poiseuille's law (a good approximation below the sixth generation at rest), a "best" structure can be deduced by minimizing the total viscous dissipation in a finite tree volume. A purely mathematical argument, the Hess–Murray law, suggests that the best tree is fractal with a fractal dimension equal to 3. In such an ideal tree, the successive airway

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segments are homothetic with a size ratio equal to 0.79. Mauroy et al. have suggested that the morphology of the human bronchial tree is close to providing maximal efficiency in assuring air distribution with minimal viscous dissipation (with an average homothety ratio of 0.85) (Mauroy et al., 2004). This homothety ratio has been measured in a limited number of human casts and, more recently, using lung CT scans in a larger number of subjects (Bokov et al., 2010; Montaudon et al., 2007; Tawhai et al., 2004). Using CT scans of COPD patients, we have suggested that the remodeling process could decrease this ratio in intralobar airways, thereby increasing airway resistance (Bokov et al., 2010). We now hypothesize that this decrease in the homothety ratio, leading to a generalized narrowing of the airways, may explain the shift of airway resistance toward the lung periphery in COPD patients, as demonstrated experimentally by Hogg et al. (1968).

The objectives of our study were to provide a formula linking airway resistance, tracheal characteristics (length, section) and the homothety ratio while taking into account inertia related to non-fully developed laminar flow in the bronchial tree, and to assess the consequences of homothety ratio changes on the site of airway resistance on both theoretical and experimental (data from COPD patients) grounds.

2. Methods

2.1. Design

2.1.1. The model and its results compared to literature data

A computational model of fluid motion in an airway tree was developed and was fitted with the results determined by three formulas taken from the literature obtained using experimental data from human casts (Collins et al., 1993; Pedley et al., 1970a,b; Reynolds, 1982).

2.1.2. Determination of the site of hydrodynamic resistance and a semi-analytic formula for resistance

After this validation process, we first checked whether the measured values of the homothety ratio obtained in a previous study in smokers with and without COPD (Bokov et al., 2010) would give diameters of the terminal bronchioles consistent with those measured by McDonough et al. in healthy and COPD patients (McDonough et al., 2011). Then, a semi-analytic formula of airway resistance using tracheal dimensions and the homothety ratio was determined, and the agreement between Raw calculated by our semi-analytic formula and measured airway resistance in our previous study was assessed.

2.2. Airway model

A direct 3D numerical solution of the Navier–Stokes equations was used and the simplified tree model consisted of a three-dimensional cascade of cylinders branching through five bifurcations, as previously described (figure provided in the Appendix section of (Bokov et al., 2010)). The bronchi aspect ratio (L/D = length over diameter) is considered constant and equal to 3 for each generation which is close to the mean value actually found in studies of human airway geometry by CT scan (Bokov et al., 2010). The homothetic factor h was defined as the ratio of the diameter between the $p+1$th generation and the pth generation, assuming that bifurcating branches are symmetric. Obviously, the human bronchial tree is not symmetric but rather asymmetric (each parent bronchus gives a major and a minor child bronchus), but we previously demonstrated that $h_{d,major}$ should play a more important role in determining the total resistance than $h_{d,minor}$ (Bokov et al., 2010).

Navier–Stokes equations were solved using finite elements commercial software (COMSOL Multiphysics). These equations characterize mass and momentum conservation in the fluid:

$$\nabla . u = 0$$

$$\rho u . \nabla u = -\nabla p + \eta \nabla^2 u$$

where u and p are the local velocity and pressure fields, respectively. The diameter of the first generation tube is equal to 2 cm, corresponding approximately to the diameter of the human trachea. The fluid viscosity $\eta = 1.9 \times 10^{-5}$ Pa s and density $\rho = 1.25$ kg m^{-3} are those of air in normal conditions. We imposed nonslip boundary conditions at the tube walls (Dirichlet condition $u = 0$) and the velocity at the entrance of the trachea is considered uniform. A pressure condition is applied at the outlets, implying a Neumann like condition for the velocity field $\partial u/\partial n = 0$.

Each model is composed of approximately 10^5 tetrahedral mesh elements and consequently of 5×10^5 degrees of freedom. We used a direct solver (PARDISO) and set the relative tolerance at 10^{-6}, which means that the iterations stop when the relative error of the solution is less than 10^{-7}. A model with 2×10^5 elements ($h = 0.87$ and an expiratory flow of 100 L/min) gave an expiratory resistance with 8% deviation. The interpolation Lagrangian polynomials were of degree 2 for the velocity field and 1 for the pressure field.

Even though our model tree was only of six generations, we were able to give results concerning generations as deep as the 20th generation by stacking four trees and transferring the computed velocity profile at the exit of a tree to the entrance of the downward tree. The exit conditions were always fixed pressure conditions. The expiration regimes studied always led to almost identical flow properties at the exit of the six-generation tree (symmetric flow distribution, defined by a relative deviation of less than 1% in flow distribution between the different exit branches), thus making it possible to use only one tree for each range of generations (vertical stacking).

2.2.1. Fitting with a formula obtained from experimental data

Pedley et al. experimentally derived a formula to evaluate the viscous resistance in a lung bronchus (R) (Pedley et al., 1970a,b): $R = R_P(C/4\sqrt{2})(Re(D/L))^{1/2}$, where C is a constant depending solely on geometry.

This formula permits calculating the total viscous resistance of the bronchial tree by simple estimation of Poiseuille's resistances and Reynolds numbers (Re) at each generation. Reynolds performed experiments at expiration on a bronchial cast, which covered a wide range of scales, beginning with a lobular bronchus and ending with 2 mm diameter bronchi (Reynolds, 1982). He found that the total expiratory pressure drop could be scaled as: $\Delta P = (76.0 + 0.0607Re_0)\Delta P_P$, where ΔP_P is the pressure drop predicted by Poiseuille's formula ($R_P = 128\eta L/\pi D^4$) and Re_0 is the Reynolds number ($Re = \rho UD/\eta$, where U is the velocity of the fluid, D is the diameter of the tube, ρ is the air density and η is the air viscosity) in the first bronchus.

Reynolds predicted that the pressure drop in each generation scales as (for a generation indexed by n):

$$\Delta P_n = \Delta P_{Pn}(a + bRe_n) \quad (1)$$

He determined that $a = 1.5$ and $b = 0.0035$ permit fitting the total pressure drop measured experimentally. He also found that, at each generation, the pressure drop was greater than the pressure drop predicted by Poiseuille even at low Reynolds numbers, as was expected by the entrance theory of fluid flows. The values of a and b were established over a large range of variation in the Reynolds number (up to 50,000) in the cast of a pulmonary bronchial tree of five to six generations.

More recently, Collins et al. proposed another formula for the resistance at expiration based on experiments using a three-generation model starting from the right intermediate bronchus (Collins et al., 1993). They found that the pressure drop due to viscous dissipation (P_V) for one bronchial generation was scaled as: $\Delta P_V = \Delta P_P(0.556 + 0.060Re^{1/2})$. The total pressure drop, which was found by taking into account the kinetic energy loss from one generation to the other scaled as: $\Delta P_{2-1} = \Delta P_V - [(\rho U_0^2/2)(1.09 + 6.54/\sqrt{Re})]_1^2$. U_0 is the air velocity averaged over a cross-section and the subscripts 1 and 2 represent two locations, at the exit and the entrance of the bifurcation, respectively.

3. Results

3.1. Fitting of the model with three experimental formulas

Fig. 1 describes the airway pressure drop along the airway generations, according to our model and the three formulas of the literature. Since the best fit (using minimization of the quadratic error) was observed with the Reynolds formula, in subsequent experiments, the coefficients a and b of this formula were compared with those obtained from our computational model to further validate our model.

3.2. Expiratory pressure distribution for $h = 0.85$ and $h = 0.74$

We present the numerical results for expiratory flow of 10 L/min and 100 L/min, which correspond to Reynolds numbers at the trachea of approximately 750 and 7500, respectively, which correspond to flow rates observed at rest and on exercise, respectively. We show in Fig. 2 the pressure increase and the corresponding fit by the Reynolds formula (1) with $h = 0.85$ for those two flow rates.

For $\dot{V} = 10$ L/min, $Re = 758$ at the trachea (Fig. 2, upper panel), the best fit was obtained with the Reynolds formula for $a = 1.04$ and $b = 0.00640$, giving a total deviation from the computed values of 2.5% for the whole pressure increase. When the flow was increased to 100 L/min ($Re = 7580$), the expiratory pressure drop was fitted by a similar formula than the one previously found, i.e. $a = 1.261$; $b = 0.00637$ (Fig. 2, lower panel). Hence, the value of b seems to be independent on the Reynolds number, a result that was verified over the other values of h tested (data not shown).

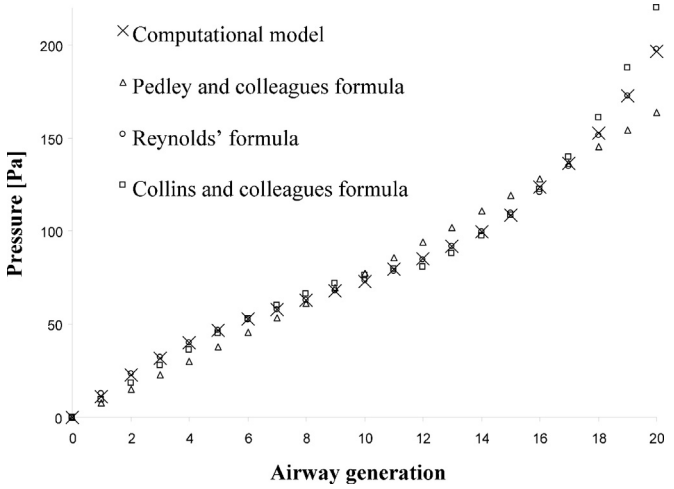

Fig. 1. Relationship between airway generations and airway pressure drop. This relationship is described for the three formulas of the literature and for our computational model.

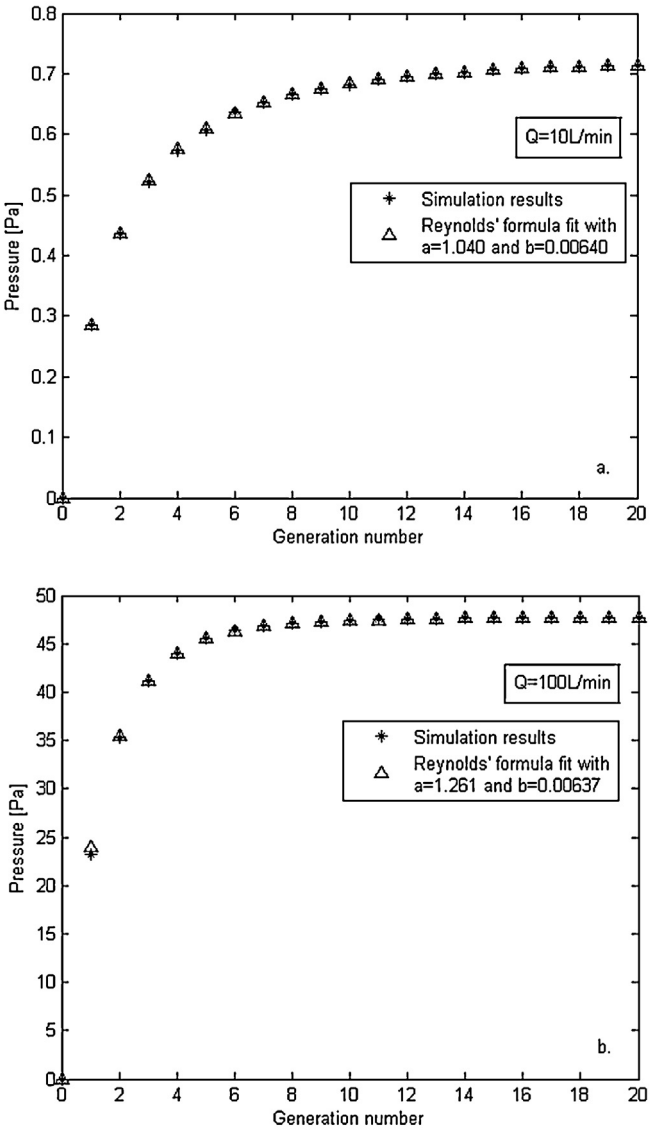

Fig. 2. Plot of expiratory pressure distribution as a function of generation for $h = 0.85$, at two different expiratory flows; (upper panel) $Q\,(=\dot{V}) = 10$ L/min and (lower panel) $Q\,(=\dot{V}) = 100$ L/min. Excellent fits were obtained with the Reynolds' formula. The parameter a (proportional to the Poiseuille's component of the pressure variation) varied between the two simulations but the variation was not significant. The parameter b, which is associated to the pressure variation due to inertia was identical for the two flows.

3.3. Site of hydrodynamic resistance using our computational model: healthy conditions and COPD

3.3.1. Healthy condition

From Fig. 3, one can see that the main part of the airway resistance is in the proximal bronchi (0–5), even for low flow (Fig. 3, upper panel), provided that h is greater than 0.80. From this value of h, the relative weight of the proximal airways is more than 60%. Only for values of h less than 0.76 is the relative weight of the distal airways more important. The situation is skewed toward the proximal airways when the flow is increased and more than 60% of the hydrodynamic resistance remains in the proximal airways provided that $h \geq 0.77$ (Fig. 3, lower panel).

3.3.2. COPD

We schematized the effect of the distal remodeling process of COPD by considering that h decreased from 0.85 to 0.77 (9%

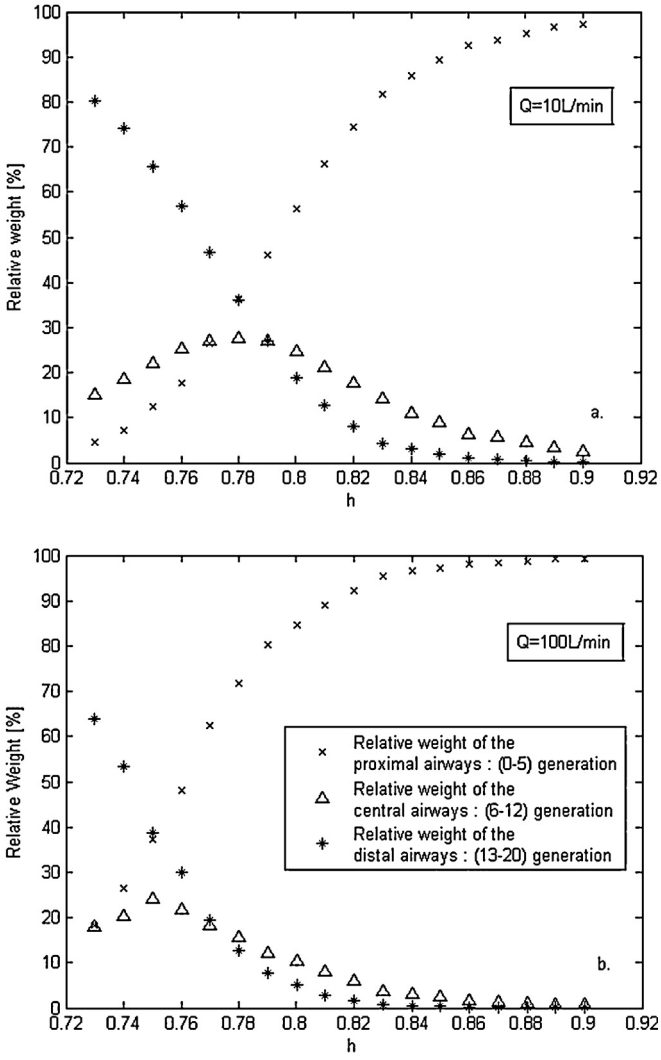

Fig. 3. Plots of the relative weight of hydrodynamic resistance of each part of the bronchial tree. Proximal airway (0–5) generations, central airway (6–12) generations and distal airway (13–20) generations. Upper panel: plots for expiratory flow of 10 L/min; lower panel: plots for expiratory flow of 100 L/min. *X* axes are homothety ratios, *h*; *Y* axes are relative weights expressing the percentages of the resistance of proximal, central and distal generation related to the whole airway resistance.

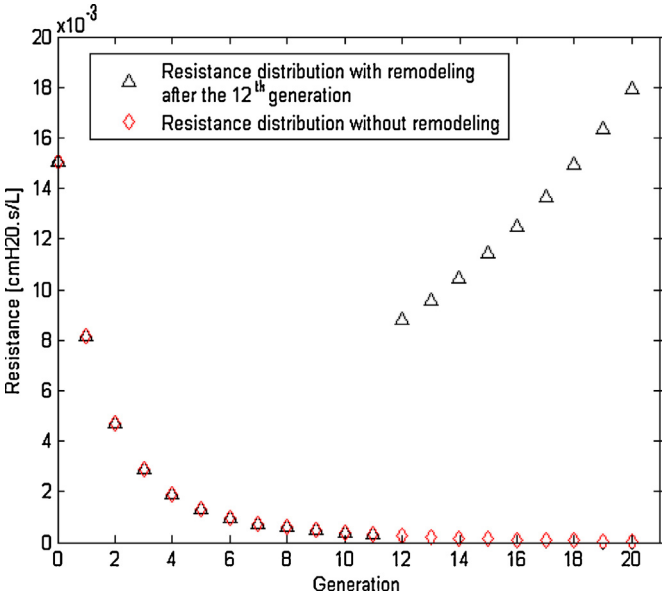

Fig. 4. Plots of the resistance distribution as a function of the generation. (Δ) Resistance distribution considering a bronchial tree model with bronchial thickening after the 12th generation, reflecting the remodeling activity of a diseased lung. Consequently, the homothetic factor varies from 0.85 to 0.77. This variation is responsible for a net increase of the resistance. (◊) Resistance distribution in a bronchial tree model with $h = 0.85$.

variation) abruptly after the 12th generation. The Fig. 4 shows the consequences of this decrease in *h*. The total resistance increased from 0.04 (normal lung) to 0.15 cm H_2O s/L in the diseased lung. The ratio of peripheral airways resistance over total resistance varied from 3% to 75%.

3.4. Can a reduction in h explain the measured values of the terminal bronchioles?

In order to assess whether the values of *h* that we measured are consistent with the diffuse reduction in airway caliber in COPD, we compared the calculated values of the terminal airways with those effectively measured by McDonough et al. (2011). These results are depicted in Table 1.

3.5. Semi-analytic formula for hydrodynamic resistance

3.5.1. Our semi-analytic formula

The Reynolds formula (Eq. (1)) gives us the opportunity to express the airway resistance of the entire bronchial tree. It is possible to include the relationship found between *b* and *h*, and to obtain a general formula the resistance that would include the inertial effects and would depend only on *h* and *Re*. Using the fit for $b(h)$, one finds:

$$R = \frac{128\eta L_0}{\pi D_0^4} \sum_{n=0}^{19} \left(\frac{1 + (h^{3.8}/90)(Re_0/(2h)^n)}{(2h^3)^n} \right) \quad (4)$$

Eq. (4) gives the resistance of the entire (20 generations) bifurcating tree, expressed solely by Poiseuille's hydrodynamic resistance of the trachea, where L_0 and D_0 are its length and diameter, respectively (corresponding to generation 0), and Re_0 is the Reynolds number at the entrance of the trachea. The factor $(2h)^n$ by which Re_0 is divided corresponds to the Reynolds number at the entrance of the *n*th generation bronchi, and is obtained by flow conservation.

Table 1
Calculated versus measured diameters of terminal bronchioles.

Condition	Patients studied (*n*)	Luminal diameter of terminal bronchioles 17th generation (μm)
Without COPD		
MicroCT calculated	4	424 ± 48
$h = 0.85$	9	673
$h = 0.80$	9	288
With COPD		
MicroCT[a] calculated	4/8	52 ± 30/210 ± 48
$h = 0.75$	22	117
$h = 0.70$	22	44

For the calculation we used the mean tracheal diameter (20.26 mm) observed in our 31 patients (9 smokers without COPD and 22 smokers with COPD). The first three ratios of diameters are not homothetic, the mean values (major divisions from right and left lungs) of our patients were used for the calculation (0.66, 0.59 and 0.83, respectively); subsequently a constant *h* (see table: from 0.70 to 0.85 for major ratio) was used for subsequent bronchial generations. In our previous study the median value of h_{major} was 0.79 (range: 0.67–0.86).

[a] In the study of McDonough et al. (2011), 16 isolated lungs were studied using microCT (4 patients with centrilobular emphysema, 8 patients with panlobular emphysema and 4 controls).

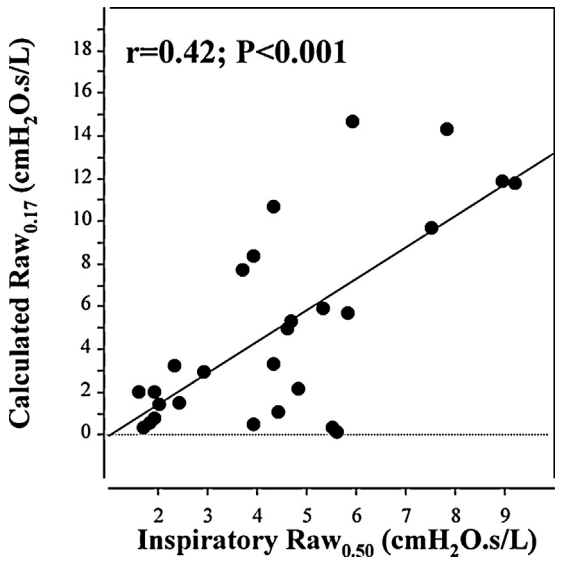

Fig. 5. Relationship between measured and calculated resistance. Airway resistance (inspiratory $R_{aw0.5}$: see Section 2) was measured using body plethysmography in smokers with and without COPD, while airway resistance was calculated using the measured values of tracheal diameter and *h* obtained in the same patients, and our semi-analytic formula.

3.5.2. Practical applications using our semi-analytic formula

The results comparing analytical Eq. (4) and simulations demonstrated a very good agreement between simulations and the analytical calculation of resistance. Indeed, the mean relative error over *h* for the estimation of the resistance was 7.6% for both $\dot{V} =$ 100 L/min and $\dot{V} = 10$ L/min. On the other hand, the estimation using Poiseuille's formula was poor. Unsurprisingly, Poiseuille's formula underestimates the hydrodynamic resistance and the mean relative error over *h* was 75% and 43% for $\dot{V} = 100$ L/min and $\dot{V} = 10$ L/min, respectively.

We then applied our method of calculation of bronchial resistance using the morphometric data of Weibel (1979), established from an excised normal human lung cast. We found that the resistance was 0.28 cm H_2O s/L for an expiratory flow of 10 L/min and 1.26 cm H_2O s/L for $Q\dot{V} = 100$ L/min using our formula.

We further calculated the airway resistances using the measured values of the tracheal diameter and *h* obtained in our previous study, with our semi-analytic formula. 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: $2h^3_{deq} = h^3_{d,major} + h^3_{d,minor}$ (Bokov et al., 2010). In the healthy lung, the h_{deq} value is 0.72 (Bokov et al., 2010). Using this *h* value, the calculated resistance over our "mean" bronchial tree using our semi-analytic formula would be 2.48 cm H_2O s/L, a value that is in the normal range of healthy subjects (<3 cm H_2O s/L). Consequently, using our semi-analytic formula and h_{deq} values determined in our previous series of smokers (Bokov et al., 2010), we calculated their Raw compared to inspiratory $Raw_{0.5}$ (Raw at 0.5 L s^{-1}) measured in these patients. A significant but modest correlation was observed (Fig. 5).

4. Discussion

Our objectives were to provide a formula linking airway resistance, tracheal characteristics (length, section) and the homothety ratio and to assess, using this formula, whether COPD could be characterized by a reduction in the homothety ratio.

4.1. A computational model to manipulate the homothety ratio

We used a computational model that was previously developed in which the homothety ratio can be manipulated. The results (pressure drops) observed with the computational model were compared to those obtained experimentally by three groups of investigators who gave analytic formula of their results. The best fit was observed with the formula of Reynolds, and the values of *a* and *b* were very close to the values given by Reynolds in his study (Reynolds, 1982). Then, we further assessed the site of hydrodynamic resistance and the potential consequences of reduction of the homothety ratio (in the lung periphery only, or in the whole lung) using our "validated" computational model.

Our results indicated that inertial effects have an important influence on the total resistance of the tree and give quantitative information on pressure drops. Inertia increases pressure drops, mostly because of bifurcations, where the flow must alter its direction to follow the shape of the geometry; the velocity profiles become more skewed and squashed toward the walls, thereby increasing viscous dissipation and, consequently, the pressure drop.

In inflammatory bronchial diseases (such as COPD), the bronchial wall is the site of thickening and remodeling, which may be more marked in the peripheral bronchi (Hogg et al., 2004). We showed a linear negative relationship between wall area ratio (an index of bronchial remodeling) and the homothetic factor, from which it can be calculated that a 5% increase in thickening is responsible for a 5–10% decrease in the homothetic factor in the peripheral bronchi (Bokov et al., 2010). We thus evaluated the effect of such a decrease in the homothety ratio on the resistance distribution (see Fig. 4). A localized, distal reduction in homothety ratio (9% variation) was modeled because the 12th generation has a diameter of approximately 3 mm, generally considered as the boundary between the central and peripheral airways (Silvers et al., 1974). The almost four-fold increase in total resistance in the diseased lung is in agreement with that experimentally measured in emphysematous subjects by Hogg et al. (1968).

In fact, the remodeling process in COPD is diffuse, and it has been shown that the dimensions of relatively large airways assessed using computed tomography reflect small airway dimensions measured histologically (Nakano et al., 2005). Consequently, we assessed whether homothety ratio values consistent with those observed in our previous study (Bokov et al., 2010) would give diameters of terminal airways similar to those effectively measured by McDonough et al. (2011). This additional experiment further suggested that our measured values of homothety ratio are realistic.

4.2. A semi-analytic formula to assess the concept of a reduction of the homothety ratio in COPD

Based on the formula of Reynolds, a general semi-analytic formula of the resistance including the inertial effects and depending on the homothety ratio was developed. The calculated airway resistance using our formula and the morphometric data of Weibel (1979) was clearly underestimated. The fact that we failed to obtain an accurate estimate of airway resistance even using Weibel's lung model may have several explanations. The measures of peripheral airways could have been overestimated. Firstly, when injecting silicone oil in a post-mortem lung sample, the pressure applied induces overinflation of the bronchi and thus an overestimation of the bronchial diameter. This phenomenon is present at each level of the bronchi, but could be more pronounced in some lung regions (with greater compliance of the airways (Williamson et al., 2011)). Secondly, the measured diameters are those at full inflation (total lung capacity), and are overestimated compared to ventilation at a physiological level, i.e. at functional respiratory capacity.

Thirdly, physiological bronchoconstrictor tone is relieved when post-mortem measurements are made, which may also affect the homothety ratio since this cholinergic tone predominates in central airways (Ingram et al., 1977).

The semi-analytic formula allowed us to calculate airway resistance based on morphological data obtained in patients (Bokov et al., 2010) and to compare this calculated resistance with that measured by body plethysmography in the same patients. A fairly good agreement was observed (see Fig. 5), suggesting the validity of the concept, namely a reduction in the homothety ratio in COPD.

4.3. Limitations of the study

One important issue is the applicability of the laminar flow conditions for Reynolds numbers as high as 8000, and the effect of turbulence on bronchial pressure drop. In pipes, the distance x after which a laminar boundary layer becomes instable (and hence turbulent) is:

$$\frac{x}{d} \approx \frac{80\,000}{Re} \tag{5}$$

It follows that, in the lung, the boundary layers do remain laminar throughout the bronchi because even at a flow rate of 250 L/min when the Re in the first generation bronchus is approximately 15,000, the instability distance x given by Eq. (5) is greater than the length of the bronchus ($L/D = 3$). Another limitation was the numerical requirements of the model, especially for high h ($h > 0.79$), in which cases we did not achieve very good accuracy of the solution (10% relative deviation between a normal model and a model with twice as many mesh elements). Finally, we assumed that the bronchial tree can be obtained by vertical stacking of the first six generations, which has some limitations since bifurcation angles vary along airway tree. Nevertheless, these geometrical variations will have limited impact on resistance in a fully developed laminar flow.

4.4. Clinical perspectives

The lung architecture may constitute an important risk factor for airway diseases such as COPD or asthma. Disease-related lung deficits can be due to both acquired deficits in the growth of lung function in childhood and a steeper decline in lung function in adult life (Martinez, 2009). These trajectories of lung function are likely to differ across subgroups of individuals with respiratory diseases, suggesting that different windows of opportunity may exist to modify the natural course of disease before irreversible deficits are established. Our study was designed to establish whether two basic parameters are enough to describe the entire respiratory tree: tracheal diameter and the homothety factor. Our results suggest that the concept of the homothety factor is valid in both healthy and COPD lungs. It has to be stated that, in our previous study, we were unable to show a decrease in h in COPD patients as compared to smokers without COPD (Bokov et al., 2010), but this study was not powered for such a demonstration. Obviously, in this latter study the relationship between h and bronchial wall area ratio obtained from CT scans in smokers with and without COPD was obtained in central airways and may not be representative of more distal processes. We hypothesize that lower values of h in asthma (congenitally acquired) would be a more relevant concept. Whether the determination of two "easy-to-measure" parameters (tracheal area and h) may help to predict the occurrence of respiratory disease remains to be established using a prospective study design.

In summary, the present paper assessed inertial flow in branching dichotomous structures. A simple formula for hydrodynamic expiratory resistance based on computer simulations was proposed, which emphasizes the critical role of tracheal geometry and the homothety factor. We further show that the contribution of peripheral resistance to total resistance can become critical in COPD due to remodeling of the peripheral airways and a generalized decrease in caliber related to a reduction in the homothety factor.

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Competing interests

The authors declare no competing interest.

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