

Departures from the physical optimality in the bronchial tree of rats (*Rattus norvegicus*)

MAURICIO CANALS M¹, CRISTIAN ATALA¹, RICARDO OLIVARES², FRANCISCO F NOVOA¹, MARIO ROSENMANN¹.

¹ Departamento de Ciencias Ecológicas, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile, e-mail: mcanals@abello.dic.uchile.cl

² Departamento de Ciencias Biológicas, Facultad de Ciencias Veterinarias, Universidad de Chile, Casilla 2, Correo 15, La Granja, Santiago, Chile.

ABSTRACT

We studied the departure from the physical optimality of the bronchial tree of rats using both i) the minimum volume and power and ii) the minimum surface and drag criteria, considering the bronchial junction as the unit study based on Zamir's model for vascular trees. Our results show deviations of the junctions of the bronchial tree from the expected optimums in the proximal airway that can be explained by both, the turbulent or transitional flow regime, and the airway's necessity to distribute its terminal branches in the alveolar surface filling the thoracic volume. The departures of the observed values at the optimum for the minimum volume and power were significantly different than the obtained departure values for the minimum surface and drag criteria. The departure from the optimum was directly related to the diameter of the smallest branch. The slopes of the regressions for the two criteria were different. The regression lines intercept at a bronchial diameter $d_2 = 0.129$ mm. This result agreed with the idea that the tube diameter is limited at small values by the increasing flow resistance with decreasing tube diameter while at large values is limited by the increasing tube volume and dead space with increasing tube diameter.

Key terms: Lung, Junction optimality, Optimization, Broncography

INTRODUCTION

Most distribution systems of living organisms can be described by a branching network in which the tubes sizes, such as in the vertebrate circulatory and respiratory systems, decrease regularly (West et al., 1997). The hypothesis that the characteristics of the bronchial tree design assume values basically equivalent to the minimization of the total hydrodynamic resistance of the system, is sustained by several reports (Horstfield, 1990; Weibel et al., 1998). Among the different forms of this principle, it has been reported that the bronchial tree design is determined by an optimum air flow to the alveoli (Rhorer, 1915; Murray, 1926) with a minimum metabolism or entropy production in the respiratory musculature (Wilson, 1967) and

by the minimum materials and energy cost (Weibel et al., 1991; Weibel et al., 1998).

The bronchial tree design is also influenced by the adjustment of its parts in order for the system's function (Weibel et al., 1998) and by the geometrical constraints that can act as limiting factors. These are especially evident in the respiratory system in which a small three-dimensional volume of air must be distributed on a large two-dimensional alveolar surface, determining a branching volume-filling airway with fractal-like geometry (West et al., 1986; Mandelbrot, 1982; McNamee, 1991). Using bronchographs, Canals et al (1998) showed this fractal-like geometry of the airway of *Rattus norvegicus*. Preliminary estimations of the fractal dimension of the bronchial tree of this species were similar to that of *Oryctolagus cuniculus* and that of humans.

Corresponding Author: M Canals, Laboratorio de Ecofisiología, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile. Fax: (56-2) 272-7363. e-mail: mcanals@abello.dic.uchile.cl

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A slight ontogenetic variation in the fractal dimension of *R. norvegicus* was also reported (Canals et al., 2000). The physical and geometrical constraints that regulate the design of the airway, do not necessarily lead to the same optimum values.

In a series of papers, Zamir studied the optimality principles underlying the arterial branching, based on the physical principles shared by all distribution systems (Zamir, 1978; 1986; Zamir and Bigelow, 1984). He proposed the arterial junction as the study unit, considering four hypotheses: an arterial junction is in an optimum state i) when the total lumen surface of the arteries is minimum, ii) when the total lumen volume of the arteries involved is minimum, iii) when the power required for pumping blood through that junction is minimum, and iv) when the total drag force acting on the lumen walls is minimum. The Zamir's model yields the optimum angles associated to a particular ratio between the diameters of the branches of an artery (bifurcation index $\alpha = d_2/d_1$ with d_2 the diameter of the thinnest branch) needed to satisfy these four hypotheses. Zamir also demonstrated that, considering the relation between flow (q) and radius (r), $q = c r^{1/3}$ (c , a constant), the optimum angles for minimum power became the same as those for minimum volume, and the optimum angle for minimum drag became the same as those for minimum lumen surface (Zamir, 1978):

$$\cos \theta_{10} = ((1 + \alpha^3)^{4/3} + 1 - \alpha^4) / (2(1 + \alpha^3)^{2/3})$$

$\cos \theta_{20} = ((1 + \alpha^3)^{4/3} + \alpha^4 - 1) / (2\alpha^2(1 + \alpha^3)^{2/3})$
for minimum lumen volume and pumping power, and

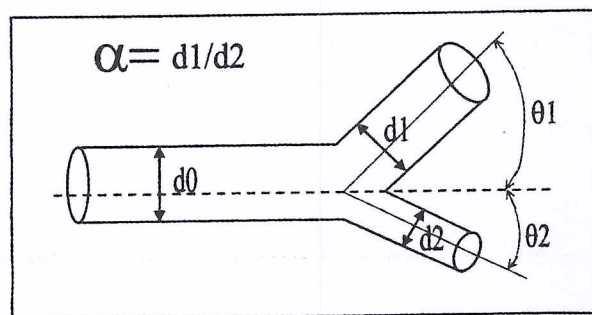


Figure 1. The basic structural unit of the bronchial tree: the junction. At a bifurcation site a parental bronchi of diameter d_0 splits into two branches of diameters d_1 and d_2 (the smallest) with branching angles θ_1 and θ_2 .

$$\cos \theta_{10} = ((1 + \alpha^3)^{2/3} + 1 - \alpha^2) / (2(1 + \alpha^3)^{1/3})$$

$$\cos \theta_{20} = ((1 + \alpha^3)^{2/3} + \alpha^2 - 1) / (2\alpha(1 + \alpha^3)^{1/3})$$

for minimum lumen surface and endothelial drag, where α the bifurcation index and θ_{10} the optimum angles θ_1 and θ_2 (figure 1). Zamir and Bigelow (1984) developed a method for representing the optimum in a rectangular box called the "junction box". In this box, the optimum is represented by the position of the junction point (x_0, y_0) determined by the angles θ_i (figure 2). An observed junction point will then be represented by a point (x, y) in the junction box at a non-dimensional distance $\delta = \sqrt{(y - y_0)^2 + (x - x_0)^2} = \sqrt{(\Delta x)^2 + (\Delta y)^2}$ from the optimum.

Despite the differences between liquid and gas transport systems, the bronchial tree, as with all branched conduction systems, satisfies the principles used by Zamir in the study of the optimality of arterial branches. Furthermore, the predictions advanced in his model agree with other exclusively respiratory models (see Kitaota et al. 1999).

In this study we examine the departure from the physical optimality of the bronchial tree of rats using Zamir's methodology as well as his four criteria.

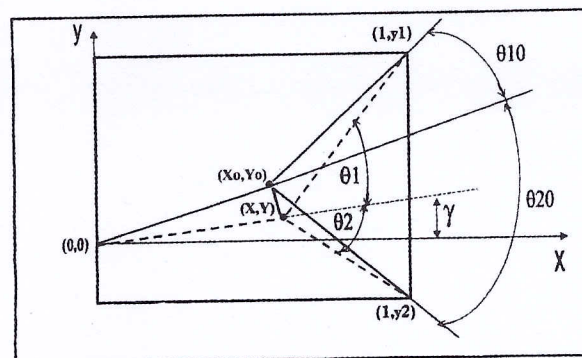


Figure 2. The junction box. The optimum bifurcation (solid lines) is enclosed in a box such that the three bronchi have equal lengths. An observed bifurcation (dashed lines) having the same bifurcation index is then fitted in the same box as shown. The distance between the observed nonoptimum junction point (x, y) and the optimum (x_0, y_0) represents the departure from optimality.

MATERIAL AND METHODS

We dealt with 23 adult rats, 12 males and 11 females ($W_b = 338.2 \pm 97.8$ g). All animals were sacrificed, and a bronchograph of each individual was performed using a 18g plastic catheter introduced into the trachea. First, 1.5 ml of diluted barium sulfate and then air, to displace the contrast medium filling the smoother airway, were introduced into the airway. The airway was contrasted in such a way that it permitted the recognition of the rotation of the branching planes, by transparency. The entire procedure was performed under radiosopic visualization in the X-Ray service of a public Hospital in Chile (Hospital Del Salvador). Radiographs were taken at a distance of 1 m, with 100 mA, 0.04 s and between 24 and 40 kV. The bronchographs were digitalized in a standard format of 120 pixels from the clavicle plane to the distal bronchi. The images were studied using the Scion Image software. The bronchographs were examined assigning the order of bronchi by both the Horsfield and the Strahler systems (Strahler, 1957; Schreiner et al., 1976; Horstfield, 1990; Ramchandani et al., 2001). We assigned relative Horstfield and Strahler orders to the observed bronchi, considering that the distal bronchi has the lowest order. A bronchograph was considered as sufficient whenever more than 12 Horsfield or 3 Strahler relative orders were recognized in the bronchial tree. After this selection, a total of 11 bronchographs were analyzed. Each bifurcation was classified following the Strahler order of the branch with the smallest diameter. Whenever it was possible, three junction points of each order were selected and analyzed measuring d_i and θ_i . The junctions selected from a particular level were those that had the largest θ_i in order to avoid underestimation of the angles as a consequence of the projection of the radiograph. With this restrictive criteria, a total number of 68 junction points were studied. We preferred to sacrifice a little of the sample number to favor the quality of the data. General measurements of the bronchial tree were

analyzed with ANOVA. Linear and exponential regressions between bronchial diameter and order were performed.

We studied the optimality of the junctions by analyzing the deviations of the pair (Δx , Δy) from the point (0,0) with a Hotelling T^2 test. We also studied the effect of the order on this pair with a one way MANOVA (multivariate ANOVA) for each criteria.

We compared the distances yielded with each, minimum drag and surface vs. minimum volume and power criteria, with an ANCOVA, using the diameter of the smallest branch of the junction (d_2) as a covariable. Regression analyses between δ and d_2 were performed, analyzing the homogeneity of the slopes. The effect of the order of the junction (understood as the order of the minor bronchi) over δ was tested with a two-way ANOVA, considering δ to be the response variable, the order of the junction as a source of variation, and the criteria as blocks. One-way ANOVA and Tukey multiple comparisons were also performed individually for each criteria.

RESULTS

The bronchial tree of the rats showed a marked asymmetry with a Horstfield delta, the difference in order between two daughter branches meeting at a bifurcation,

$\Delta = 3.07 \pm 2.31$ (mean $\pm$ 1Sd) in junctions with Horstfield orders higher than 5. The bifurcation index was $\alpha = 0.515 \pm 0.172$ (mean $\pm$ 1Sd). It did not vary from 0 to 3 Strahler orders: 0.606, 0.476, 0.510 and 0.588 respectively ($F_{3,66} = 0.787$, $p > 0.05$). The average bifurcation angle was $\theta = \theta_1 + \theta_2 = 64.78 \pm 25.16$ (mean $\pm$ 1Sd), changing between 78.12, 72.61, 48.37 and 28.00 from 0 to 3 Strahler orders, increasing from proximal to distal zones ($F_{3,66} = 8.84$, $p < 0.001$). As we expected, the diameter increases with the order of the bronchi (Table I). The increase in diameter was nearly linear ($F_{1,66} = 105.4$, $p < 0.001$, $R^2 = 91.33$ for Strahler and $F_{1,66} = 362.2$ $p < 0.001$, $R^2 = 97.31$ for Horstfield order).

Exponential models for the increase in diameter also had an adequate goodness of fit ($F_{1,66} = 38.54$, $p < 0.001$, $R^2 = 79.4$ for

TABLE I

Airway diameters (mean $\pm$ Sd) in rats as function of relative Strahler and Horstfield orders .

Strahler order	Horstfield order	Diameter (mm)	Sd
3	12	3.26	0.38
3	11	3.00	0.31
3	10	2.93	0.39
2	9	2.30	0.19
2	8	2.20	0.20
2	7	2.17	0.30
2	6	1.95	0.42
1	5	1.65	0.43
1	4	1.45	0.38
1	3	0.94	0.42
1	2	0.56	0.15
0	1	0.29	0.08

Strahler and $F_{1,66} = 47.22$, $p < 0.001$, $R^2 = 82.52$ for Horstfield order).

The observed junctions were near to the optimum (Figures 3 and 4), but the analysis of the departure pair (Δx , Δy) showed that this is different to (0,0) (Hotelling- $T^2 = 38.4$, $F_{2,66} = 18.9$ and Hotelling- $T^2 = 56.7$, $F_{2,66} = 27.9$; $p < 0.01$). The pair is affected by the junction order, being progressively near to (0,0) in the junctions of lower orders

(Wilk's- $\lambda = 0.657$, Rao's $R_{6,126} = 4.91$ and Wilk's- $\lambda = 0.712$,

Rao's $R_{6,126} = 3.87$, $p < 0.01$ for the minimum volume and power and minimum surface and drag criteria respectively) in the one way MANOVA (Table II).

The distances from the optimum for both criteria were significantly different:

i) for minimum volume and power: $d_{vp} = 0.343 \pm 0.043$ (mean $\pm$ 1Se) and ii) for

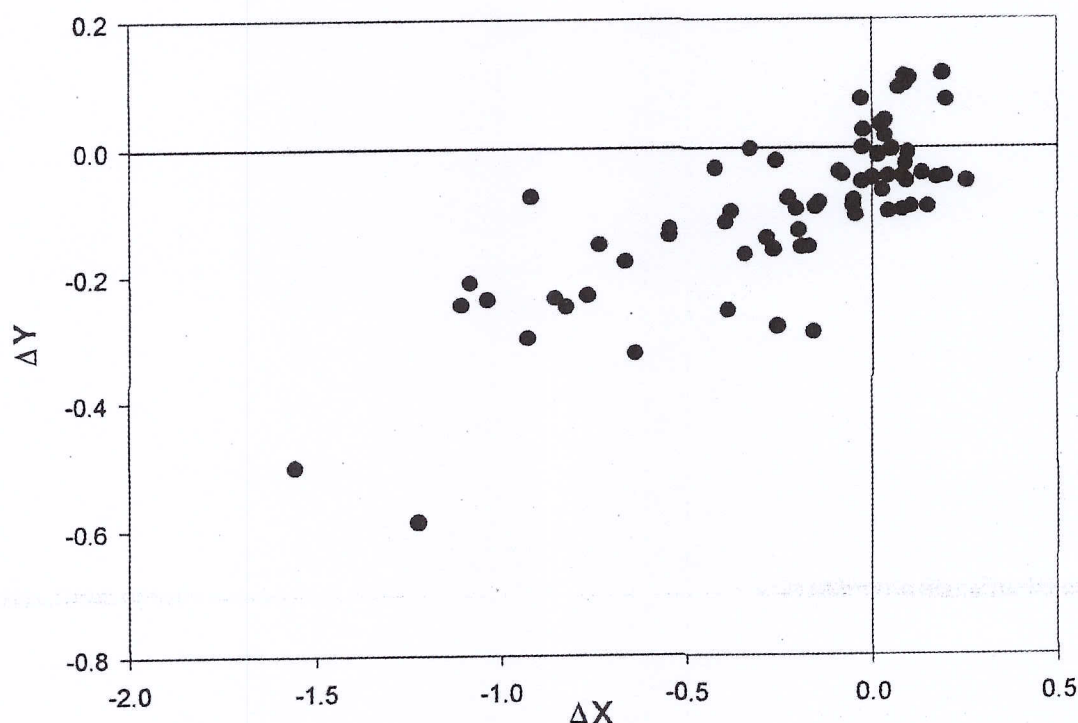


Figure 3. Departures of Bronchi branching data from the optimum of eleven rats, plotted for interpretation of their degree of optimality with respect to minimum pumping power and lumen volume.

TABLE II

Departures (Δx , Δy) from the optimum of the bronchial bifurcations (mean $\pm$ 1Sd) as function of the junction order for both optimality criteria: minimum volume and pumping power and minimum surface and drag.

Strahler order	Horstfield order	Minimum Volume Δx	And Power Δy	Minimum Surface Δx	And Drag Δy
3	10-12	-0.928 $\pm$ 0.381	-0.300 $\pm$ 0.262	-1.458 $\pm$ 0.560	-0.384 $\pm$ 0.236
2	6-9	-0.505 $\pm$ 0.449	-0.152 $\pm$ 0.157	-0.845 $\pm$ 0.646	-0.290 $\pm$ 0.354
1	2-5	-0.116 $\pm$ 0.317	-0.065 $\pm$ 0.092	-0.346 $\pm$ 0.431	-0.995 $\pm$ 0.127
0	1	-0.002 $\pm$ 0.147	-0.060 $\pm$ 0.115	-0.214 $\pm$ 0.184	-0.704 $\pm$ 0.124

minimum surface and drag: $d_{sd} = 0.558 \pm 0.067$. d_{vp} were lower than d_{sd} ($F_{1.133} = 9.4$, $p < 0.01$) (Table III). The departure from the optimum (δ) was directly related to the diameter of the smallest branch: i) $\delta_{vp} = 0.336d_2 - 0.027$ ($F_{1.66} = 64.2$, $R^2 = 49.62$, $p < 0.001$), ii) and $\delta_{sd} = 0.561d_2 - 0.051$ ($F_{1.66} = 89.6$, $R^2 = 57.0$, $p < 0.001$), d_2 in mm. The slopes were different ($F_{1.132} = 9.57$, $p = 0.002$). The regression lines intercept at $d_2 = 0.129$ mm (figure 5).

There was an effect of the generation of the junction on δ in the two-way ANOVA

($F_{3.128} = 16.8$; $p < 0.01$) (see Table III). This is also true for each criteria (minimum volume and power and minimum surface and drag) in a one-way ANOVA ($F_{3.63} = 8.12$ and $F_{3.64} = 9.13$, $p < 0.01$ respectively). A posteriori Tukey multiple comparisons showed that the two junctions of the greatest order have higher δ than those of lower order.

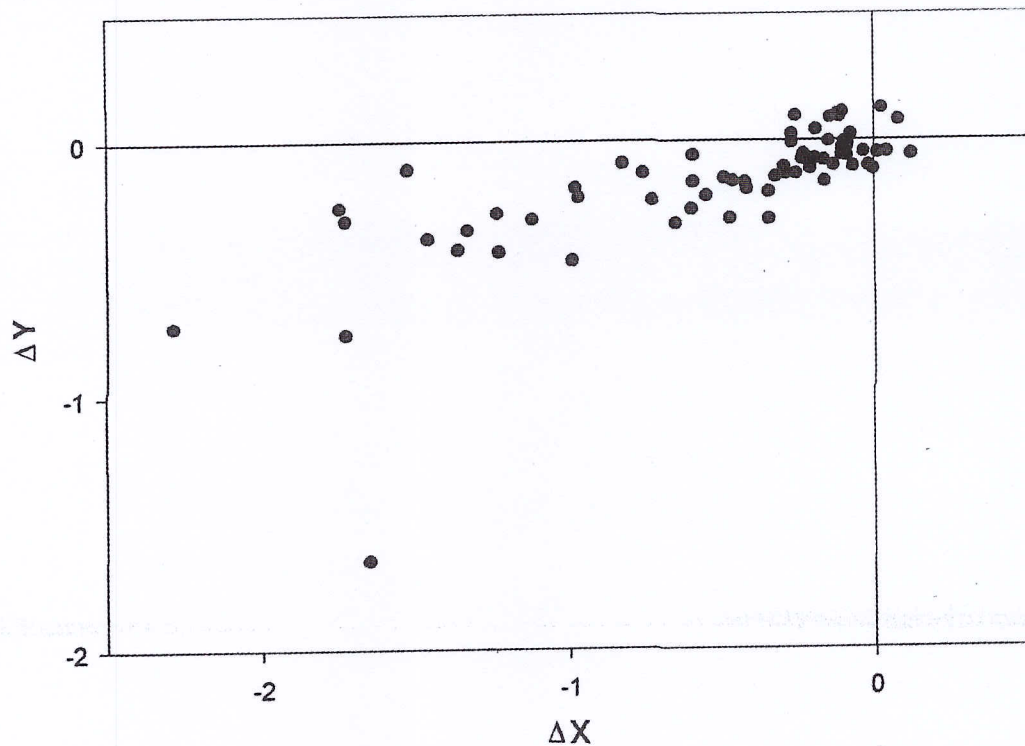


Figure 4. Departures of Bronchi branching data from the optimum of eleven rats, plotted for interpretation of their degree of optimality with respect to minimum drag and surface.

TABLE III

Average distance to the optimum as function of the order of the junction for both optimality criteria: minimum volume and power pumping (δ_{vp}) and minimum surface and drag (δ_{sd}).

Strahler Order	Horstfield Order	δ_{vp}	Se	δ_{sd}	Se
3	10-12	0.976	0.135	1.509	0.183
2	6-9	0.561	0.088	0.914	0.042
1	2-5	0.237	0.052	0.386	0.083
0	1	0.161	0.025	0.263	0.028

DISCUSSION

The bronchial tree of the rats studied showed to be asymmetric, with a delta coefficient $\Delta = 3.07$ in the proximal zone, similar to that of human (Horstfield, 1990) and rabbit airways (Canals et al., 2002). In the distal zone, this coefficient progressively approaches 0, as expected, because in the Horstfield system the numeration is from distal to proximal branches, so terminal bronchi have similar orders and Δ approach 0 (see Horstfield, 1990; Rachmandani. 2001). The diameter of

the bronchi increases with their Horstfield or Strahler order, decreasing from proximal to distal airway. The increase in diameter was nearly linear, but exponential models for the increase were also an adequate goodness of fit. This fact agrees with previous results obtained in the airway of rabbits (Canals et al., 2002) showing the difficulties in studying the degree of optimality of an asymmetrical airway from the perspective of the exponential increase of the diameter along the order (Horstfield et al., 1976) or the decrease along the generation (Weibel and

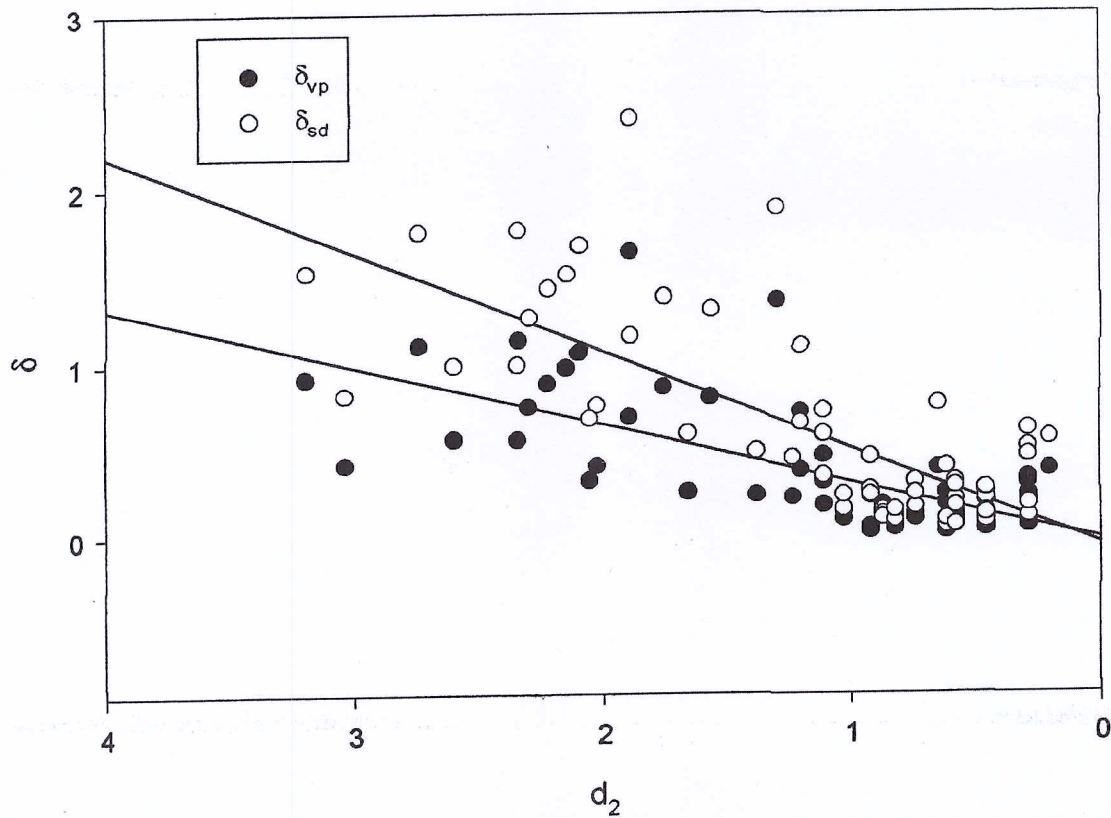


Figure 5. Variation of the distance from the optimum (δ) as function of the diameter of the thinnest bronchi of a junction for both criteria: minimum volume and power and minimum drag and surface .

Gomez, 1962; Horstfield et al., 1976; Horstfield., 1977).

Our results show departures from the physical optimality based on Zamir's model. The analysis of the departures (Δ s) showed differences with the expected (0,0) values. The average Δ s are in the negative range as a consequence of the bifurcation angles, lower than expected optimum angles for the observed bifurcation index. This can be explained by one hand by the airway's need to distribute its terminal branches in the alveolar surface filling the thoracic volume (geometrical optimality). Recently, angles around $\theta = 60^\circ$ have been mentioned as optimum angles for a bronchial tree, based on the following assumptions: i) dichotomic fractal tree, ii) minimum embedding volume and iii) maximum dispersion of the terminal branches (Canals, 2001). In contrast, from the Zamir physical perspective for $\alpha = 1$, angles $\theta = 75^\circ$ for minimum volume and power and $\theta = 102^\circ$ for minimum surface and drag are expected. Similarly, an optimum physical value $\theta = 74.93$ can be obtained in a symmetric bronchial tree with $\alpha = 1$, from the relation derived by Kamiya et al. (1974):

$$\cos \theta_1 = [1 + r^{4/n} - (1-r)^{4/n}]/2r^{2/n}$$

$\cos \theta_2 = [1 + (1-r)^{4/n} - r^{4/n}]/2(1-r)^{2/n}$, where r is the ratio of flow in the daughter branch that receives the minor flow and the parent bronchial flow, and n an exponent suggested to be three for laminar flow on the basis of a minimum energy loss principle (Kitaota et al., 1999).

Another explanation is that the air flow in the proximal airway can be turbulent or transitional, implying a smaller n in the Kamiya et al. (1974) relations (<2.7) (Kitaota et al., 1999). As a consequence, the optimum angle can be lower, for example $\theta = 66.7^\circ$ for $n = 2.7$ and $\theta = 50.1^\circ$ for $n = 2.33$. This is particularly possible because the breathing rate in rats is very high, implying higher Reynolds's number.

In the observed region of the airway the distance from the optimum for the minimum power pumping and lumen volume criteria were lower than that of the minimum drag and surface criteria. A similar result was obtained by Zamir (1986) for the arterial

branching. The distances from the optimum decreased in junctions of smaller bronchi or smaller relative Strahler and Horstfield orders (distal airway). Furthermore, the slopes of reduction of the distance from the optimum are different. Thus, the regression lines intersect when the diameter of the smallest bronchi of the junction is about 0.129 mm (Figure 5). Below this diameter the regression lines forecast minor distances to the optimum for the minimum surface and drag criteria. In our data this intersection point corresponds to generations distal to the 12th. These results can be explained by the change in the dominant physical principles that account for gas transport. Weibel and Gomez (1962) found that the average diameter of the airway (d) followed a $d = d_0 \cdot 2^{-z/3}$ relationship where d_0 is the initial diameter and z the "generation" of the bronchi. Later, Wilson (1967) and Weibel et al. (1998) associated this result to accommodate minimum volume in the lumen, minimum entropy production in the respiratory mechanics, and minimum costs in mass and energy, respectively. However, Weibel and Gomez (1962) showed that diameters for generations 19 to 23 do not lie on the expected straight line in a semi-log graph. In the Weibel and Gomez plot, the curve changes its slope at about the 10th to 12th generation. This is in agreement with the intersection of our regressions. The first 10th to 12th generations have been associated with the mass movement of air (Weibel and Gomez, 1962; McNamee, 1991), which explains the dominant minimum volume and pumping power criteria (lower distances to the optimum) found in our data. In even higher generations (smaller orders and bronchial diameters) a transition occurs, where the primary driving force is the diffusive transport. Our results suggest that in this zone the distance to the optimum is very small for both criteria, but the minimum surface and drag criteria could be dominant.

West et al. (1986) proposed that the deviations from the exponential model were not explained by the transition zone. They proposed an alternative model (renormalization) in which the airway's

size followed a more general power law relationship $d_n = A_n \cdot n^{-u}$, where d_n is the diameter of a bronchi of the generation n , u is a scaling power that is 0.8 in humans, and A_n is a periodic function that introduces harmonic deviations in scaling. In this sense, it could be more than one scale factor that may determine the size reduction of airways from one generation to the next. This relationship predicts the airway's diameter through the first 20 generations of branching and it agrees with the measurements obtained by Raabe et al (1976) as well as with the airways of dogs, rats and hamsters (Nelson et al., 1990). However, Horstfield (1990) showed by means of simulated bronchial trees that the West et al. (1986) model is a consequence of the asymmetry of the bronchial tree and of the exponential relationship of the diameter with the order (rather than the generation) of the bronchi. The same result was evident in one empirical study in rats and rabbits (Canals et al., 2002). This exponential relationship is found in many different types of trees, including airways (Horstfield et al., 1971; 1976; Horstfield and Thurlbeck 1981, Ramchandani et al., 2001; Maina and van Gils, 2001), veins (Horstfield and Gordon, 1981; Yen et al., 1983; Maina and van Gils, 2001) and pulmonary arteries (Singhal et al., 1973; Yen et al., 1984; Maina and van Gils, 2001). Our results suggest a change, or at least a convergence, in the dominant optimum criteria for diameters below 0.129 mm, independent of the order or generation. In this sense, our results agree more with the Weibel and Gomez (1962) hypothesis of a transition zone than with the proposition of a new mechanism called "renormalization," replacing the convection and diffusion to explain the structure of the conducting airway in mammalian lungs (West et al., 1986; McNamee, 1991). The latter hypothesis suggests that the process of renormalization could offer some degree of protection against errors during lung development by preventing distal propagation of random fluctuations in airway's diameter.

The change in the dominant criteria below 0.129 mm of bronchial diameter in the

conductive zone of the bronchial tree could be explained by a gradual increase of the area/volume relationship in smaller bronchi, with the superficial drag as the main force opposing the air flow. In this sense, in larger bronchi an air flow that impells a minimal pumping power would be necessary, and on the other hand, with minimum drag in smaller bronchi. This result agrees with Wilson's theoretical analysis (1967) in which the entropy production $S = H \cdot V_{O_2} / T$ (H is the energy released per ml of oxygen burned in the respiratory muscles; V_{O_2} the oxygen consumption, and T the temperature) is minimized ($dS/dd = 0$), yielding a quantitative expression of the idea that the tube diameter is limited at small values by the increasing flow resistance with decreasing tube diameter and is limited at large values by the increasing tube volume and dead space with increasing tube diameter: $dS/dd = (H/T) \cdot [\delta V_{O_2} / \delta V \cdot \delta V / \delta d + \delta V_{O_2} / \delta \Delta p \cdot \delta \Delta p / \delta d]$, where V is the total ventilation (related to the volume and dead space) and Δp is the pressure drop across a generation (related to the viscosity and the fourth power of the diameter).

Moreover, our results suggest a gradual approach to the physical optimum following the decreasing diameter, the decreasing order and the increasing generation of the bronchi. These results can be explained by a transition from a central distributive zone to a physical domain in the generation of the airway. The proximal branching process could be dominated by higher flow velocities with a turbulent or transitional flow and the necessity to increase the branches to fill a space. In the distal zone, the system brings down the velocity of the air flow to a sufficiently low level that permits gas exchange. The dominant principles gradually change from a volume and pumping power problem in the conductive zone, to a drag and surface problem in the respiratory zone where convection and diffusion are relevant.

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REFERENCES

- CANALS M (2001) Un modelo de optimización geométrica del árbol bronquial. *Biol Res* 34: R115-193
- CANALS M, OLIVARES R, LABRA F, CAPUTO L, RIVERA A, NOVOA FF (1998) Caracterización de la geometría fractal del árbol bronquial en mamíferos. *Rev Chil Anat* 16: 237-244
- CANALS M, OLIVARES R, LABRA F, NOVOA FF (2000) Ontogenetic Changes in the fractal geometry of the bronchial tree in *Rattus norvegicus*. *Biol Res* 33: 31-35
- CANALS M, ATALA C, OLIVARES R, NOVOA FF, ROSENMAN M (2002) La asimetría y el grado de optimización del árbol bronquial en *Rattus norvegicus* y *Oryctolagus cuniculus*. *Rev Chil Hist Nat* 75: 271-282
- HORSTFIELD K (1977) Morphology of branching trees related to entropy. *Respir Physiol* 29: 179-184
- HORSTFIELD K (1990) Diameters, generations and orders of branches in the bronchial tree. *J Appl Physiol* 68: 457-461
- HORSTFIELD K, GORDON I (1981) Morphometry of the pulmonary veins in man. *Lung* 159: 211-218
- HORSTFIELD K, DART G, OLSON DE, FILLEY GF, CUMMING G (1971) Models of the human bronchial tree. *J Appl Physiol* 31: 201-217
- HORSTFIELD K, RELEA FG, CUMMING G (1976) Diameter, length and branching ratios in the bronchial tree. *Respir Physiol* 26: 351-356.
- HORSTFIELD K, THURLBECK A (1981) Relation between diameter and flow in branches of the bronchial tree. *Bull Math Biol* 43: 681-691
- KAMIYA A, TOGAWA T, YAMAMOTO A (1974) Theoretical relationship between the optimal models of the vascular tree. *Bull Math Biol* 36: 311-323
- KITAOTA H, TAKAKI R, SUKI B, (1999) A three-dimensional model of the human airway tree. *J Appl Physiol* 87: 2207-2217
- MAINA JN, VAN GILS P (2001) Morphometric characterization of the airway and vascular systems of the lung of the domestic pig, *Sus scrofa*: comparison of the airway, arterial and venous systems. *Comp Biochem Physiol (A)* 130: 781-798
- MANDELBROT BB (1982) The fractal geometry of the nature. New York: WH Freeman and Company
- MCNAMEE JE (1991) Fractal perspectives in pulmonary physiology. *J Appl Physiol* 71: 1-8
- MURRAY CD (1926) The Physiological principle of minimum work. *Proc Natl Acad Sci USA* 12: 207-214
- NELSON TR, WEST BJ, GOLDBERGER AL (1990) The fractal lung: universal and species-related scaling patterns. *Experientia* 46: 251-254
- RAABE OG, YEH HC, SCHUM GM, PHALEN RF (1976) Tracheobronchial Geometry: Human, Dog, Rat, Hamster. Albuquerque, NM: Lovelace Foundation Medical Education Research
- RAMCHANDANI R, BATES JHT, SHEN X, SUKI B, TEPPER RS (2001) Airway branching morphology of mature and immature rabbit lungs. *J Appl Physiol* 90: 1584-1592
- RHORDER F (1915) Flow resistance in human air passages and the effect of irregular branching of the bronchial system on the respiratory process in various regions of the lungs. *Pfluegers Archives* 162: 255-299
- SCHREINER W, NEUMANN F, NEUMANN M, END A, MULLER MR (1976) Structural quantification and bifurcation symmetry in arterial tree models generated by constrained constructive optimization. *J Theor Biol* 180: 161-174
- SINGHAL S, HENDERSON R, HORSTFIELD K, HARDING K, CUMMING G (1973) Morphometry of the human pulmonary arterial tree. *Circ Res* 33: 190-197
- STRAHLER AN (1957) Quantitative analysis of watershed geomorphology. *Trans Am Geophys Union* 38: 913-920
- WEIBEL ER, GOMEZ DM (1962) Architecture of the human lung. *Sci* 137: 577-585
- WEIBEL ER, TAYLOR R, HOPPELER H (1991) The concept of symmorphosis: a testable hypothesis of structure function relationship. *Proc Nat Acad Sci* 88: 10357-10361
- WEIBEL ER, TAYLOR R, HOPPELER H (1991) Variation in function and design: testing symmorphosis in the respiratory system. *Respir Physiol* 60: 325-348
- WEIBEL ER, TAYLOR R, BOLIS L (1998) Principles of Animal design. Cambridge: Cambridge University Press
- WEST BJ, BHARGAWA V, GOLDBERGER AL (1986) Beyond the principle of similitude: renormalization in the bronchial tree. *J Appl Physiol* 60: 1089-1097
- WEST GB, BROWN JH, ENQUIST BJ (1997) A general model for the origin of allometric scaling laws in biology. *Sci* 276: 122-126
- WILSON T (1967) Design of the bronchial tree. *Nature* 668-669
- YEN RT, ZHUANG FY, FUNG YC, HO HH, TREMAR H, SOBIN SS (1983) Morphometry of cat pulmonary venous tree. *J Appl Physiol* 55: 236-242
- YEN RT, ZHUANG FY, FUNG YC, HO HH, TREMAR H, SOBIN SS (1984) Morphometry of cat's pulmonary arterial tree. *J Biomech Eng* 106: 131-136
- ZAMIR M (1978) Nonsymmetrical bifurcation in arterial branching. *J Gen Physiol* 72: 837-845
- ZAMIR M (1986) Cost analysis of arterial branching in the cardiovascular system of man and animals. *J Theor Biol* 120: 111-123
- ZAMIR M, BIGELOW DC (1984) Cost of departure from optimality in arterial branching. *J Theor Biol* 109: 401-409