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Morphological hysteresis of the small airways

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Summary. The resistance to airflow that develops in most obstructive processes takes place in the small airways. The aim of the present paper is to describe bronchial hysteresis morphometrically in a respiratory cycle model. As a working hypothesis, it is proposed that the changes that take place in the respiratory tract during the respiratory cycle are related to the bronchial size.

Specimen rat lungs were organized into five groups: In the first group, the lungs were filled with a liquid fixative to 25 cm of H_2O transpulmonary pressure. The following four groups were inflated with air and fixed through the pulmonary artery. Groups 2 and 3 were fixed at 10 and 20 cm transpulmonary pressure in inflation. The last two groups were fixed in deflation and, for this purpose, the transpulmonary pressure was increased to 27 cm and decreased to 20 and 10 cm, respectively. The lungs were processed for morphometrical study and the following variables were quantified: pulmonary volume, internal area, internal perimeter, wall area, internal area radius and bronchial wall radius. The diameter of the airways studied varied between 84.06 μm and 526.4 μm. The results were classified into three subgroups consisting of small, medium-sized and large bronchi.

With a single exception - the internal area in the medium-sized bronchi inflated to 20 cm - all the results obtained in deflation were higher than those obtained in inflation. The internal area increased or decreased significantly upon raising or lowering the transpulmonary pressure respectively, in the small and medium-sized bronchi. The wall area in the large bronchi showed significant differences between inflation and deflation at 10 and 20 cm transpulmonary pressure. The wall area was modified significantly in the lungs fixed at 20 cm in the small bronchi and at 10 cm in medium-sized bronchi. The bronchial wall radius was significantly greater in the large bronchi and smaller in the small bronchi.

The lumen of the medium-sized and small bronchi increases in inspiration and decreases in expiration. The wall thickness displayed differences between inflation and deflation. The most marked hysteresis was presented by the bronchial wall in the large bronchi. Our results suggest that the behavior of the bronchi varies according to their size

Key words: Bronchus, Hysteresis, Rat, Morphometry

Introduction

The possibility of the airway narrowing has been studied by administering substances that reduce the bronchial lumen, either by stimulating the smooth muscle (James et al., 1988a; Sasaki et al., 1996; Mitchell et al., 1997; Adamicza et al., 1999; Mitchell and Gray, 1999) or by producing an edema in the bronchial wall (Matheson et al., 1998; Mitchell et al., 1999). It has been described how different parts of the bronchus may be modified, such as the bronchial lumen (James et al., 1988a; Mitchell et al., 1997), the wall area (Mitchell and Gray, 1999; Rubio et al., 2000) and the adventitia (Sasaki et al., 1996; Matheson et al., 1998).

Many of the proposals concerning the behavior of the airway have been developed in experiments performed on bronchi dissected from lung parenchyma (Mitchell et al., 1997, 1999; Mitchell and Gray, 1999; Tiddens et al., 1999). Nevertheless, it has been proposed that the behavior of the bronchus is related to that of the parenchyma (Adamicza et al., 1999).

Pulmonary hysteresis refers to the differences that exist between inspiration and expiration at a single transpulmonary pressure (TPP) (Brusasco and Pellegrino 1995). Graphically (Fig. 1), it corresponds to the surface that exists between the ascending and descending parts of the pressure-volume curve (p-v) (Brusasco and Pellegrino, 1995). Pulmonary hysteresis is the sum of parenchymatous hysteresis and bronchial hysteresis (Ahmad et al., 1995; Brusasco and Pellegrino, 1995; Pellegrino et al., 1998) and bronchial hysteresis has been demonstrated radiologically in dog lungs (Hughes et al., 1970). Among the different factors that may influence bronchial hysteresis, the bronchial smooth muscle, non-

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distensible bronchial tissue elements and parenchymatous hysteresis have been pointed out (Pellegrino et al., 1998; King et al., 1999; Tiddens et al., 1999).

Functional studies propose that distal airway hysteresis is different from proximal airway hysteresis (Cheng et al., 1999). This is of great interest because the distal airway narrows more than the proximal airway in obstructive processes (Pellegrino et al., 1996).

The aim of this study is to objectify the airway modifications taking place in healthy lungs during the respiratory cycle. Considering that bronchial hysteresis is an accepted fact, it is proposed as a hypothesis that bronchial hysteresis is related to airway size. The model of the respiratory cycle will entail a deep inhalation.

Materials and methods

Animal preparation

Seventy five-month-old healthy Fischer 344 rats were used (Pinkerton et al., 1982), with 50% male and 50% female in all groups. The animals were supplied by Iffa Credo®. The sacrifice protocol has been described in a previous study (Escolar et al., 2002). The animals were divided into five groups of 14 animals each and were anesthetized with pentothal (0.1 mg/Kg body weight intraperitoneally). The lungs were removed from the thorax by means of a thoracotomy and were fixed in 10% formalin. In the first group, the lungs were fixed by instillation through the trachea to a pressure of 25 cm of H_2O (25-cm group). The remaining groups were fixed through the pulmonary artery, to 20 cm of H_2O TPP, maintaining the lungs full of air. In the second group the lungs were inflated via the trachea to 10 cm of H_2O TPP (10-cmI group); the third group was inflated to 20 cm of H_2O (20 cmI); the fourth group was inflated up to 27 cm and was deflated to 20 cm TPP (20 cmD); the fifth group was also inflated up to 27 cm of H_2O pressure and was deflated to 10 cm TPP (10 cmD). The air pressure was generated with a Safam® REM+.

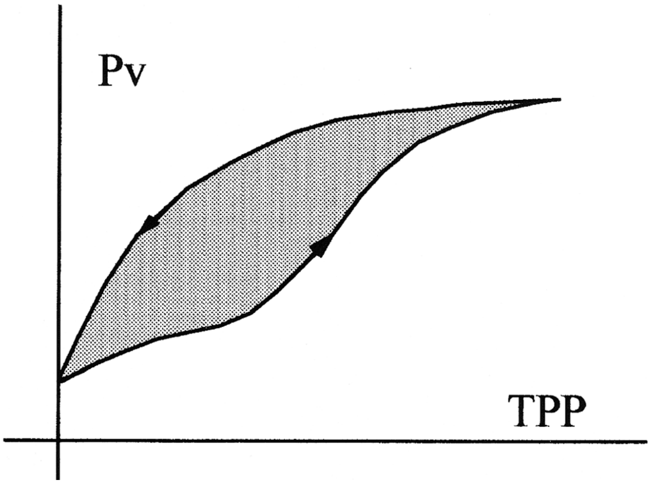

Fig. 1. Pulmonary P-V curve. Ascending portion (lower) and descending portion, (higher). The hysteresis area (lined) is included in the ascending and descending portions. Pv: pulmonary volume; TPP: transpulmonary pressure.

Tissue handling

The fixation lasted forty-eight hours. Post-fixation was performed by immersion of the lung in the same fixing liquid for 15 days. When the post-fixation period had elapsed, the lungs were cut transversally into 0.5 cm-thick sections. Three sections per lung were selected using systematic uniform random sampling and were dehydrated and embedded in paraffin. 7-μm cuts were made and were stained with hematoxylin-eosin.

Histological study

Initially, all the bronchi were studied visually in order to describe the different structures of the bronchial wall, the epithelium, the lamina propria, the smooth muscle and adventitia (Bai et al., 1994). The morphometric study was then carried out according to the measurement protocol below.

The following devices were used in the morphometric study: an Olympus® BX50 microscope, a Sony® XC-57CE video camera, a Data Translation® DT 3155-PM digitizing card, a Power Macintosh® 7200/90 computer, a Grabber® capture program and an NIH Image® processing and quantification program. The protocol was systematized into three phases: capture, processing and quantification (Escolar et al., 1994).

Capture

The images were captured in 256 gray tones at a size of 551/400 pixels, at x40, x100 and x200 magnifications (Fig. 2). All the bronchi found to be smaller than or equal to the size of the histological field were captured.

Processing

The captured images were processed according to a previously described procedure (James et al., 1988a; Sasaki et al., 1996; Mitchell et al., 1997; Rubio et al., 2000). The images were transformed with the threshold option into two-colored, black and white images (fig. 3A). In order to eliminate background noise, an erode filter (Fig. 3B) and a dilate filter (Fig. 3C), were applied on the black color. The alveolar attachment was eliminated by the scissors tool option (Fig. 3D). With the aim of studying only the bronchi cut perpendicularly to their longitudinal axis, all the bronchi whose greatest diameter was at least twice as large as the least diameter were discarded.

Quantification

The following variables were quantified:
The pulmonary volume (Pv) was measured by liquid displacement, by submerging the lungs in liquid with the trachea clamped. This is expressed in cm^3

Greatest and least diameters: These were quantified directly by the computer on the processed image (Fig. 3D)

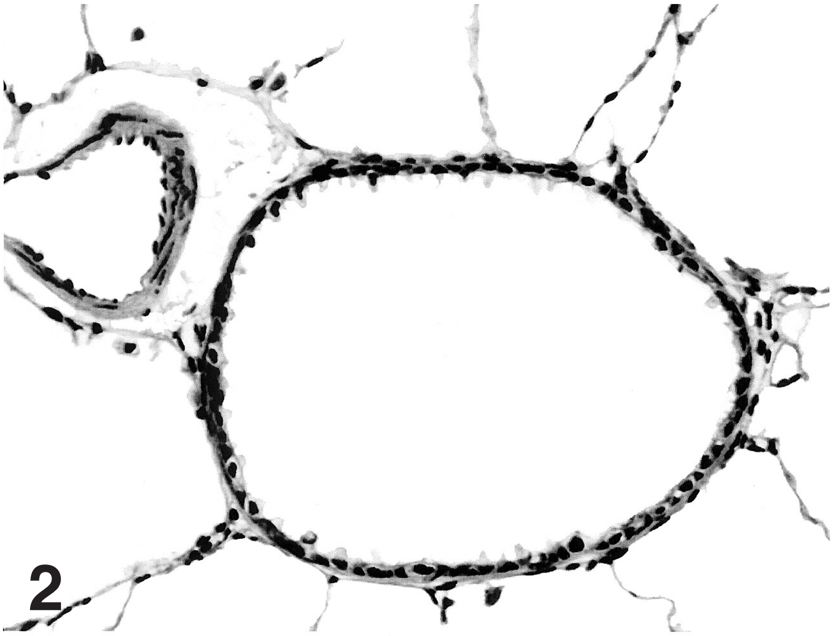

Fig. 2. Bronchus with a histological cut captured in 256 shades of gray. Stained with hematoxylin-eosin. x 200

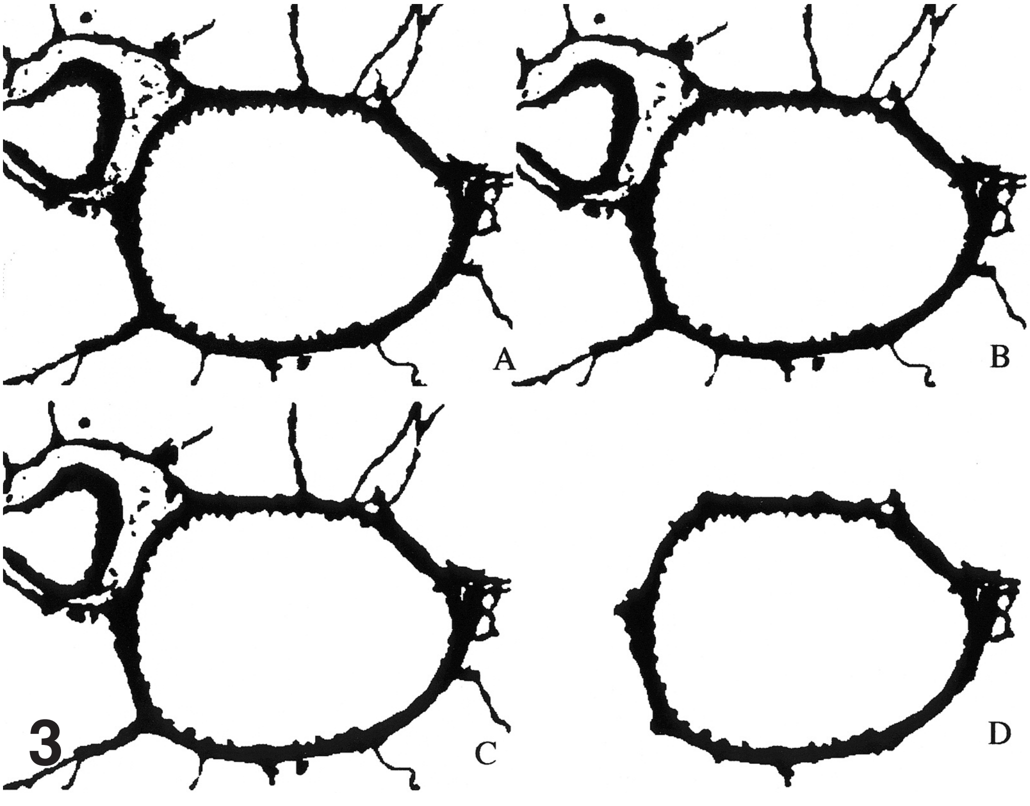

Fig 3. A) Image of figure 2, which has been transformed into two colors. **B)** Figure A after applying one erode filter. **C)** Figure B after applying one dilate filter. **D)** Figure C after deleting alveolar attachment. Wall area in black and internal area inside in white, surrounded by the internal perimeter. The cross-sectional area is the sum of the wall and internal areas.

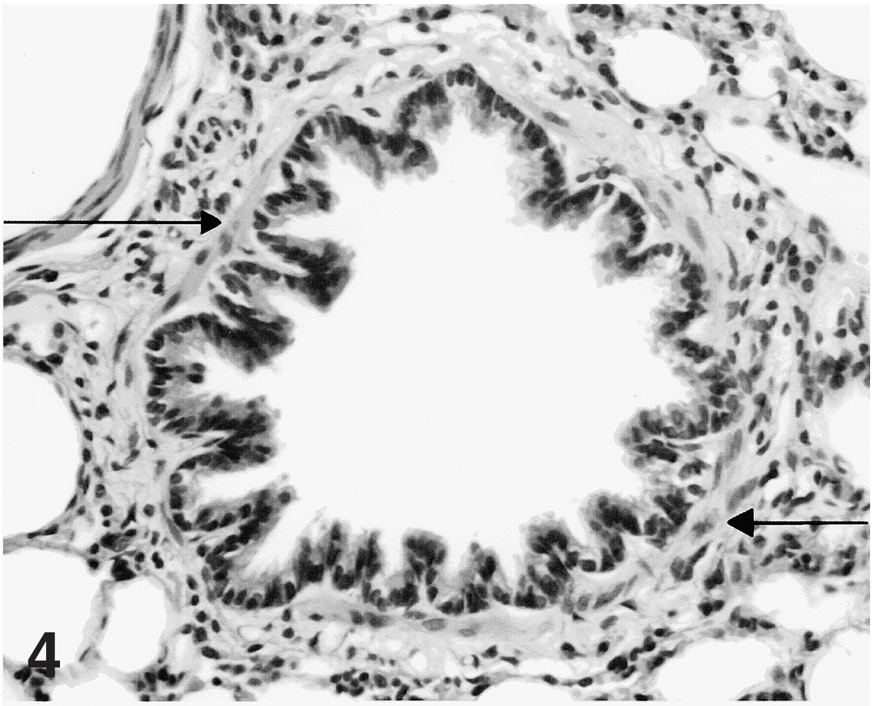

Fig. 4. Histological cut of the airway captured in 256 shades of gray. The epithelium can be observed to be folded; the smooth muscle fibers (arrows) can also be observed. The tissue between the internal area and the smooth muscle corresponds to the lamina propria and the tissue between the smooth muscle and the outside to the adventitia. Stained with hematoxylin-eosin. x 200

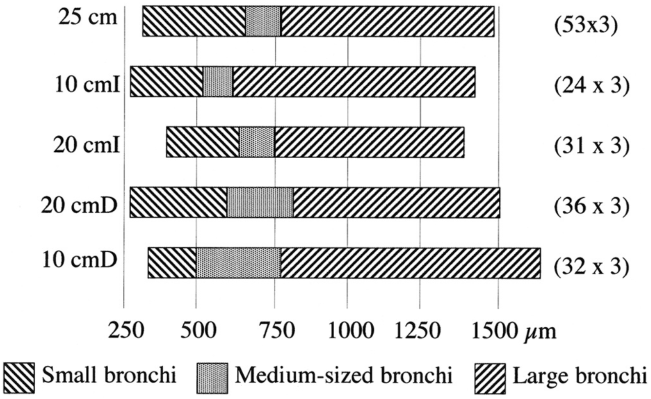

Fig. 5. Graphic representation of the result of the variable internal perimeter, ordered according to size. The number of elements in each subgroup is indicated on the right.

Internal area (A_i): This applies to the bronchial lumen surface (Bai et al., 1994). The computer measured the internal area (Fig. 3D).

Internal perimeter (P_i): On the previously selected image (Fig. 3D) (Bai et al., 1994), the computer measured the perimeter of the bronchial lumen. It is expressed in μm.

Total area (At): This is the entire bronchial area (Fig. 3D) (Bai et al., 1994). It is calculated with the purpose of finding other variables.

Wall area (WA): This is the area of the bronchial wall (Bai et al., 1994). It was calculated by subtracting A_i from At (Fig. 6 D). It is expressed in μm^2.

Radius of internal area: The internal area was considered as a circle and the relevant was applied. It is expressed in μm.

Total bronchial radius: Calculated from the total area. This was calculated in order to find the radius of the bronchial wall. It is expressed in μm

Radius of the bronchial wall: The internal area radius was subtracted from the total area radius. It is expressed in μm.

Statistical study

The bronchi were classified according to size into small, medium-sized and large groups. For this purpose, each group was organized according to the size of the Pi and was divided into three subgroups with an equal number of components (Fig. 5). P_i was selected due to its having been used as a reference in other works (James et al., 1988a; Rubio et al., 2000) because it is considered the part of the bronchus that is modified least (James et al., 1988a; Sasaki et al., 1996; Chun et al., 2000).

The mean values are presented as ± one standard deviation. When the distribution of the results was close to normal (Kurtosis and Skewness indexes), they were compared using the ANOVA test. When the results did

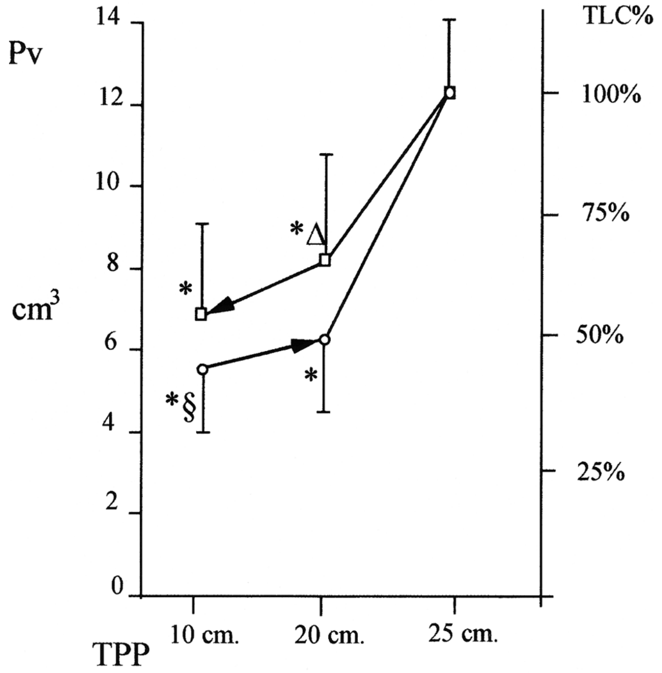

Fig. 6. Graphic representation of the pulmonary volume after applying the different TPP's. The mean and one standard deviation are given. Circular values were obtained in inflation and square values were obtained in deflation. They are presented in cm^3 on the left and the percentage value of the total lung capacity (TLC)volume is presented on the right. 100% TLC was considered to be the mean volume reached in the lungs of the 25 cm group. *: $p<0.05$ with respect to the group fixed at 25 cm. Δ: $p<0.05$ with respect to the group fixed at 20 cmI. §: $p<0.05$ with respect to the group fixed at 20 cmD.

not coincide with normal distribution, non-parametric tests were used, first that of Kruskal-Wallis, followed by Mann-Whitney's U-test. Values were considered significant when $p<0.05$. A correlation test was performed and the rates were considered valid where r> 0.6. The statistical program StatView® 5.0 was used.

Results

We would draw attention to three aspects of the visual description of the bronchi. Firstly, smooth muscle fiber was appreciable in very few bronchi and in very small quantity (Fig. 3). The absence of smooth muscle fiber prevented the lamina propria of the adventitia from being differentiated, making it impossible to quantify any of these layers. Secondly, the bronchi studied were morphologically similar: none of the groups of bronchi displayed singular morphological characteristics. Thirdly, in only one of the 528 bronchi studied was the wall observed to have thickened and the epithelium folded as a result of the possible contraction of its muscle layer; this is shown in Fig. 7.

The results of the morphometric study are shown in Figs. 6-9.

The Pv rose when the TPP was increased, as shown in Fig. 6, attaining the highest value in the bronchi fixed at 25 cm, which was significant compared to the rest. The pulmonary volume decreased when the TPP was lowered. We would point out that significant differences only arose between bronchi fixed at the same 20-cm pressure. The air-inflated lungs displayed a range of pulmonary volume of between 45% and 66% of the

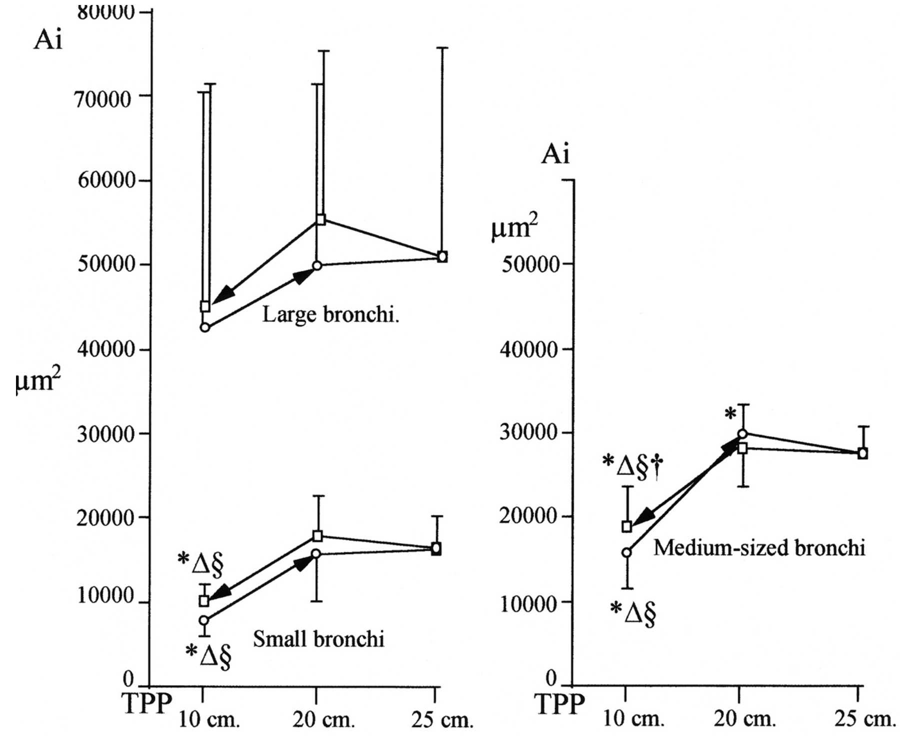

Fig. 7. Graphic representation of the result of the internal area (A_i) obtained in the three bronchial subgroups. The mean and one standard deviation are given. Circular values were obtained in inflation and squared values in deflation. *: $p<0.05$ with respect to the group fixed at 25 cm. Δ: $p<0.05$ with respect to the group fixed at 20 cmI. §: $p<0.05$ with respect to the group fixed at 20 cmD. †: $P<0.05$ with respect to the group fixed at 10 cmI.

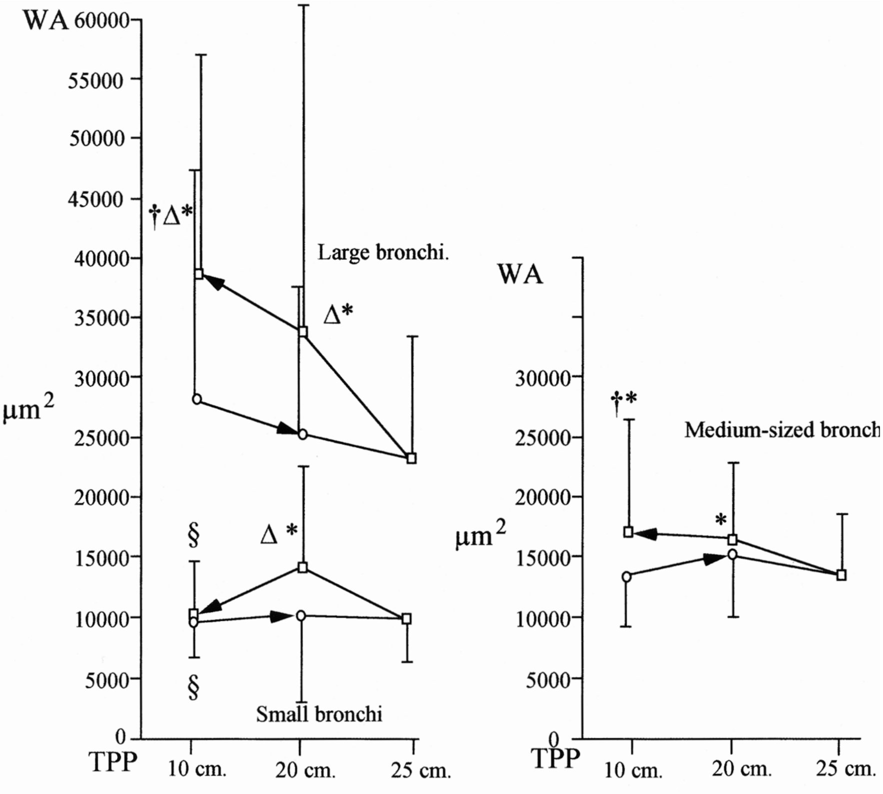

Fig. 8. Graphic representation of the results of the wall area (WA) obtained in the three bronchial subgroups. The mean and one standard deviation are given. Circular values were obtained in inflation and squared values in deflation. *: p<0.05 with respect to the group fixed at 25 cm. Δ: p<0.05 with respect to the group fixed at 20 cml. §: p<0.05 with respect to the group fixed at 20 cmD.

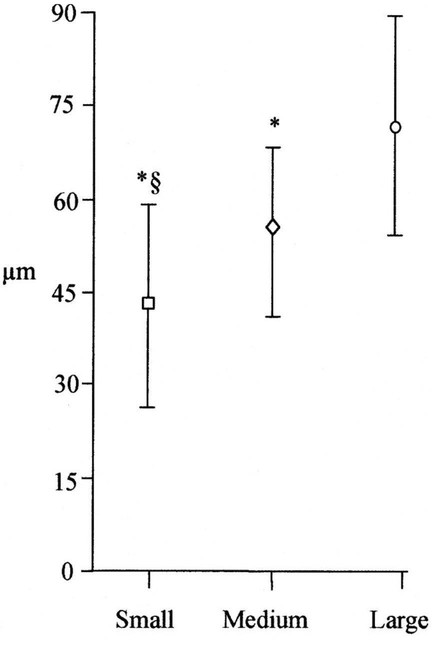

Fig. 9. Graphic representation of the results of the wall thickness radius obtained according to the size of the bronchus. The mean and one standard deviation are given. *: p< 0.05 with respect to the large bronchi. Δ: p< 0.05 with respect to the small and medium-sized bronchi.

Table 1. Correlation rates obtained after having related internal area with wall area, in the different bronchial sizes.

Small bronchi	0.277
Medium-sized	0.07
Large bronchi	0.407

volume obtained in the lungs instilled with fixer at 25 cm TPP.

For the study of the various components of the bronchus, 528 bronchi, whose diameters oscillated between 84.06 mμ and 526.4 mμ were measured, the mean value being 211.774 mμ. The diameter of the small bronchi ranged between 84.65 and 204.64 μm; that of the medium-sized bronchi between 153 and 243.42 μm, and that of the large bronchi between 199.46 and 526.4 μm (Fig. 5).

In the large bronchi no significant differences between any of the groups were found for Ai (Fig. 7). The small and medium-sized bronchi showed significant variations with the changes in TPP. In the medium-sized bronchi Ai increased significantly in the airways fixed at 10 cm in deflation when compared with those fixed at the same pressure in inflation.

Varying behaviors were reflected for WA (Fig. 8). It increased significantly in the small bronchi fixed at 20 cm in deflation, when compared with the other groups. In the medium-sized bronchi the only modification was a significant increase in the bronchi fixed at 10 cm in deflation with respect to those fixed at the same pressure in inflation. In the large bronchi, significant differences were found for WA between the bronchi fixed in inflation and deflation at the same pressure.

Significant differences were found between the radius of the bronchial wall (Fig. 9); the large bronchi displayed the greatest diameter and the small ones the least diameter.

Correlation rates were found when A_i was related to WA (Table 1).

Discussion

We found that the behavior of the small and medium-sized bronchi differed from that of the large bronchi when the transpulmonary pressure was modified. In fact, the internal area of the small and medium-sized bronchi was altered with changes in this pressure. However, the internal area of the large bronchi did not vary significantly. Together with this, the wall of the large bronchi increased to a greater extent in deflation than that of the small and middle-sized bronchi.

It should be pointed out that, in accordance with the methodology used, the deflation phase began after simulation of a deep inhalation; that is, after raising the transpulmonary pressure to 27 cm and lowering it to 20 cm and 10 cm. A respiratory cycle model falling within the tidal volumes could have been used, but the proposal of deep inhalation is based on the ability of the airway to distend in such conditions (Pellegrino et al., 1998). Lungs filled with liquid fixer have been used as a reference of total lung capacity (Escolar et al., 2000). In this way, we succeeded in establishing the total lung capacity fraction reached in the air-filled fixed lungs (Fig. 6). The bronchial size is another factor to be taken into account because the diameter of the smallest bronchi used in previous studies was 300 μm (Chun et al., 2000; Rubio et al., 2000), while we used bronchi with a diameter of 80 μm. Lastly, the system used for classifying the bronchi (Fig. 5) involved the maximum size of the small bronchi (25 cm) also being included in the large bronchi (10 cmI). Consequently, all the bronchi classified as medium-sized are found within the categories of small and large bronchi. Another way of classifying bronchi is by organizing the results of all the bronchi according to size and marking the limits of each class (Rubio et al., 2000). Proceeding thus, the 10 cmI group would have been represented within the large bronchi group by twelve units instead of forty-four.

These findings are interesting because the bronchial wall hysteresis was clearer than that of the internal area. This leads us to propose that the internal area behavior model is different from that of the bronchial wall. The low correlation rate between the bronchial wall (Table 1) and the bronchial area supports this proposal.

Previous studies, performed on dogs, have shown that the internal area increases when transpulmonary pressure is increased (Hughes et al., 1972), which coincides with our results. The bronchial wall has only been measured in deflation (James et al., 1988a); a non-significant increase of the wall took place when the lung was deflated from 100% to 20% of the total lung capacity. All the anatomical systematizations of the bronchial wall refer to the smooth muscle fiber layer (Yeh et al., 1979), as do bronchial pathology studies (James et al., 1988a; Tiddens et al., 1999; Opazo Saez et al., 2000). However, some authors have studied disease-free bronchi and have concluded that the muscle fibers rarely fully surround the bronchus (James et al., 1988b). Together with this, one must bear in mind the size of the bronchi; we have not found any reference in which bronchi with a diameter of under 300 μm are described.

The concept of bronchial hysteresis is usually associated with the modifications taking place in the internal area during a respiratory cycle (Hughes et al 1972; Pellegrino et al., 1998). This may contradict the proposal that the size of the airway depends on bronchial and parenchymatous hysteresis (Pellegrino et al., 1998). We propose that when the transpulmonary pressure is raised, the lung expands and the lung parenchyma exerts centrifugal traction on the bronchial attachments. This force may be transferred by parenchymal tethering (Balasy et al., 1995) towards the internal bronchial wall. The bronchial wall lies between the pulmonary parenchyma and the internal area; it is an imperfect elastic structure, which is why hysteresis takes place. (Pellegrino et al., 1998). Indeed, the bronchial wall was greater in deflation than in inflation. Bronchial hysteresis depends on non-contractile components (Pelegrino et al., 1998) and the smooth muscle (Froeb and Mead 1968; King et al 1999). The participation of the smooth muscle in bronchial hysteresis is quite considerable in lungs with obstructive airway diseases, since a large amount of smooth muscle is found in their bronchial walls (James et al., 1988a; Tiddens et al., 1999; Opazo Saez et al., 2000). However, in our case, very few smooth muscle fibers were present, leading us to consider their participation in bronchial hysteresis of little importance. Hysteresis should be clearer where there is more tissue. Thus, it was more marked in the wall of the large bronchi, the wall radius of which is greater.

We conclude, firstly, that bronchial hysteresis takes place fundamentally in the airway wall and is more evident in bronchi with greater wall radius; that is, in the largest bronchi. Secondly, we consider that the hypothesis has been demonstrated because the behavior of the large bronchi differed from that of the medium-sized and small bronchi. Finally, we consider that a similar model of the respiratory cycle should be developed in bronchi with obstructive pathology because the small airway offers greatest resistance to airflow in obstructive crises.

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