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Density dependence of pulmonary resistance: correlation with small airway pathology

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Density dependence of pulmonary resistance: correlation with small airway pathology. S. Guillemi, J.L. Wright, J.C. Hogg, B.R. Wiggs, P.T. Macklem, P.D. Paré. ©ERS Journals Ltd 1995.

ABSTRACT: The density dependence of maximal expiratory flow is not an effective test of the site of airway narrowing in obstructive lung disease. We hypothesized that the density dependence of pulmonary resistance (DD,RL) would be more closely related to the degree of airway narrowing and peripheral airway pathology in smokers.

We measured maximal expiratory flow at 50% vital capacity (V'_{max50}) and lung resistance (R_L) breathing air and 80% helium-20% oxygen, and calculated density dependence of V'_{max50} and R_L in 40 patients who had moderate airflow obstruction and in 10 normal subjects. We compared the density dependence of R_L and V'_{max50} with the degree of airway obstruction and bronchiolar pathology scores in 27 patients with resected lung specimens.

There were no differences in DD of V'_{max50} or R_L between normal subjects and patients, and no relationship between the degree of obstruction or the bronchiolar pathology score and the DD of these measurements. There were significant relationships between V'_{max50}, R_L and the bronchiolar pathology scores.

In conclusion, lung resistance and maximal expiratory flow are related to the severity of peripheral airway pathology, but there is no relationship between the severity of obstruction or the severity of peripheral airway pathology and the density dependence of maximal expiratory flow or lung resistance.

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Intraparenchymal pulmonary airways less than 2–3 mm diameter contribute a relatively small percentage to pulmonary airflow resistance in normal subjects, but are the major site of increased resistance in chronic obstructive pulmonary disease (COPD) [1–4]. The normally low resistance in small airways means that considerable narrowing must develop before conventional measures of airway calibre (maximal flows and total airway or pulmonary resistance) become abnormal, and this led to the development of a number of tests designed to detect early small airway dysfunction before an irreversible stage [5–8].

One of these tests, the density dependence of maximal expiratory flow, has proved less effective than was anticipated. It was hypothesized that as peripheral airway obstruction increased, the sites of flow limitation (choke points) would move from central toward peripheral airways. Since Reynolds' numbers are lower in peripheral airways, viscous pressure losses would predominate with the result that density dependence would decrease. However, we [9] and others [10] have demonstrated that many patients with established airflow obstruction have well-preserved density dependence of maximal expiratory flow (V'_{max}).

DESPAS *et al.* [11] and LISBOA *et al.* [12] showed that the density dependence of pulmonary resistance (R_L) did not correlate with the density dependence of V'_{max} in asthmatic subjects. They suggested that the density dependence of resistance might be a better measure of the central and peripheral contributions to total pulmonary resistance, since the dynamics associated with flow limitation do not normally occur during measurement of R_L.

The purpose of this study was to measure the density dependence of V'_{max} and inspiratory and expiratory resistance in 40 patients who had mild to moderate airflow obstruction, and compare the physiological data to semiquantitative estimates of peripheral airway pathology. We hypothesized that there would be decreased density dependence of resistance with increasing airway obstruction and peripheral airway pathology.

Methods

The patients were part of an ongoing study of lung structure and function in our institution. Any patient who had radiographic evidence of obstructive pneumonitis or bronchoscopic or pathological evidence of obstruction

of a segmental or larger airway was excluded. The 40 patients who were included (32 males and 8 females) were admitted to hospital for investigation and possible resection of peripheral lung nodules. The mean age of the 40 patients was 61±10 yrs; they had smoked an average of 67±37 pack-years, and values for TLC, FVC and FEV1 were 107±15, 100±15 and 83±19 % predicted. Within the week before surgery, the patients completed a questionnaire regarding smoking and respiratory symptoms, and had measurements of lung mechanics in a volume displacement body plethysmograph [13]. Functional residual capacity (FRC) was measured using Boyle's law, and three maximal expiratory flow-volume curves were obtained, breathing air and after equilibration with 80% helium and 20% oxygen$_2$ (He-O_2) (until end-tidal N_2 was less than 5%). A Fleisch No. 3 pneumotachometer separately calibrated for air and He-O_2 was used. A Validyne 45 MP±100 cm H_2O (Validyne Engineering Corp., Northridge, CA, USA) differential pressure transducer was used to measure transpulmonary pressure using a standard oesophageal balloon technique [14], and for measurement of R_L the pressure-flow curve was closed using the electrical subtraction technique of MEAD and WHITTENBERGER [15]. During the measurement of R_L, patients breathed at FRC at a rate of 30 breaths·min^{-1}, and a fixed tidal volume (0.6–1.0 L) which was displayed to the patient using an oscilloscope. Once the pressure-flow curve was closed on the oscilloscope, the pressure and flow data were directed to an Apple IIE computer, where a custom designed program sampled flow and pressure at a frequency of 100 Hz. Each pressure-flow curve was derived from a minimum of 10 breaths collected whilst viewing the cumulative averaged pressure-flow curves, and curves that were technically inadequate were discarded. Pressure-flow curves were repeated after equilibration with He-O_2. Three air and three He-O_2 curves were performed in each patient, and at least two adequate curves breathing each gas mixture were obtained. Pulmonary resistance at 1 L·s^{-1} on inspiration and expiration were calculated from the digitized data as the change in pressure from zero flow divided by flow (P/V'). The reciprocal of R_L pulmonary conductance, (G_L) was also calculated for inspiration ($G_{L,I}$) and expiration ($G_{L,E}$).

Three air and three He-O_2 flow-volume curves were recorded on each subject. The forced expiratory manoeuvre with the largest sum of forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) was selected for analysis. An additional criterion was that the air and He-O_2 FVC were within 8% of each other (mean difference 2.8±2.4%). Density dependence of maximal expiratory flow was calculated by comparing flow at 50% of FVC on the air and the He-O_2 forced expiratory manoeuvre. Air and He-O_2 curves were matched by splitting any difference between residual volume (RV) and total lung capacity (TLC), and density dependence (DD) was calculated as maximal expiratory flow at 50% vital capacity (V'_{max50}) on He-O_2 divided by V'_{max50} on air ($DD_{,V'max50}$). The values of inspiratory resistance ($R_{L,I}$) and expiratory resistance ($R_{L,E}$) at 1 L·s^{-1} from the air and He-O_2 curves were measured and the density dependence of R_L was calculated as R_L on air divided by R_L on He-O_2 ($DD_{,RL}$).

Because normal values for density dependence of R_L are not available, we also studied 10 normal subjects (7 males and 3 females). For the normal subjects we determined within day and between days reproducibility of resistance and density dependence of resistance. The mean age of the subjects was 32 (SD±9) yrs and all were nonsmokers or ex-smokers. R_L was measured, as described above, at the same time of day on four separate days one week apart. On each study day, three satisfactory averaged pressure-flow curves were obtained breathing air and after equilibration with He-O_2. Density dependence was measured at a flow of 1.0 L·s^{-1}. The coefficient of variation of $R_{L,I}$, $R_{L,E}$ and the density dependence of $R_{L,I}$ and $R_{L,E}$ were calculated within day and between days as the SD/mean×100. For the calculation of between day coefficient of variation the mean within day values of resistance were used. Measurements of $R_{L,I}$ and $R_{L,E}$ were also compared to measurements of maximal expiratory flow (FEV1 and V'_{max50}) in these normal subjects.

Twenty seven of the 40 patients eventually had a lung or lobar resection, and in these subjects peripheral airway pathology was measured. Immediately following surgery, the resected lung or lobe was inflated with 10% formalin or 2% buffered glutaraldehyde using a distending pressure of 25 cmH_2O; 24 h later, the inflated lobe or lung was sectioned in the sagittal plane and multiple stratified random blocks were obtained for histological examination. The mid-sagittal sections were graded for emphysema, using a modification of the method of THURLBECK [16]. The processed histological sections were graded semiquantitatively for abnormalities in membranous and respiratory bronchioles [17]. Membranous bronchioles (0.8–3.0 mm internal diameter) were individually graded for inflammation, fibrosis, squamous cell metaplasia, goblet cell metaplasia, muscle hypertrophy, and pigment deposition. Respiratory bronchioles were similarly graded for fibrosis, inflammation, smooth muscle cell hypertrophy, pigment deposition, and intralumenal macrophages. The pathological variables were calculated individually as a percentage of the maximal possible score for each case, and total scores for membranous and respiratory bronchioles were calculated by summing the scores for all variables.

Data analysis

Measurements of airflow obstruction (V'_{max50}, $R_{L,I}$ and $R_{L,E}$) were compared to each other and to the density dependence measurements $DD_{,V'max50}$ and $DD_{,RL}$ using least squares regression analysis. In addition, V'_{max50}, $R_{L,I}$ and $R_{L,E}$, and the density dependence of V'_{max50}, $R_{L,I}$ and $R_{L,E}$ were compared with the semiquantitative estimates of abnormalities in membranous and respiratory bronchioles and to emphysema score by least squares linear regression analysis. P-values were corrected for multiple comparisons using a Bonferoni method [18].

Values for FEV1, FVC and V'_{max50} were expressed as

Table 1. – Resistance, maximal flow and density dependence in normal subjects and patients

	Patients (n=40)	Normal subjects (n=10)		
			CoV,wd	CoV,bd
$R_{L,I}$ $cmH_2O \cdot L^{-1} \cdot s$	2.03±1.06	1.33±0.38	16±11.8	15±7.3
$R_{L,E}$ $cmH_2O \cdot L^{-1} \cdot s$	2.85±1.46	1.79±0.56	13±8.1	14±6.8
V'_{max50} $L \cdot s^{-1}$	59±28*	4.93±0.8	3.6±1.4	8±7.1
$DD_{,RL,I}$	1.41±0.47	1.29±0.16	19±14	20±10.3
$DD_{,RL,E}$	1.26±0.34	1.19±0.09	14±10.4	17±6.5
$DD_{,V'max50}$	1.32±0.16	1.41±0.16	7±3.3	6±5.5

Data are presented as mean±SD. $R_{L,I}$: inspiratory resistance; $R_{L,E}$: expiratory resistance; V'_{max50}: maximal expiratory flow at 50% of vital capacity; DD: density dependence; CoV,wd: coefficient of variation within day; CoV,bd: coefficient of variation between days. *: V'_{max50} in patients is expressed as percentage predicted.

percentage predicted, using the prediction equations of KNUDSON *et al.* [19]. Values for TLC % predicted were derived from the prediction equations of GOLDMAN and BECKLAKE [20].

Results

Mean values of R_L, V'_{max50} and the density dependence of R_L and V'_{max50} in the 10 normal subjects, as well as the mean within day and between day coefficients of variation for these variables, are shown in table 1. R_L breathing He-O_2 was less than R_L breathing air on inspiration and expiration ($p<0.01$). The density dependence of $R_{L,I}$ was 1.29±0.16 and of $R_{L,E}$ was 1.19±09.

The mean values for R_L, V'_{max50} and the density dependence of R_L and V'_{max50} for patients are shown in table 1. The patients had a moderate degree of airflow obstruction, shown by a mean V'_{max50} of 59 % pred, although there was a large range of values. Values of $R_{L,I}$ and $R_{L,E}$ were significantly greater than those in the normal subjects ($p<0.05$). There were no differences in the density dependence of V'_{max50}, $R_{L,I}$ and $R_{L,E}$ between normal subjects and patients.

Figures 1 and 2 show $G_{L,I}$ and $G_{L,E}$ at 1 $L \cdot s^{-1}$ plotted against V'_{max50} ($G_{L,I}$ *vs* V'_{max50}, $R^2=0.41$, $y= 0.295+0.109x$; $p<0.01$; $G_{L,E}$ *vs* V'_{max50}, R^2 0.35, $y=0.205+0.082x$, $p<0.01$). These correlations show that there were significant relationships between the degree of airflow obstruction as measured by V'_{max50} and conductance on inspiration and expiration. A similar relationship was seen between $G_{L,I}$, $G_{L,E}$ and V'_{max50} in the normal subjects ($G_{L,I}$ *vs* V'_{max50}, $R^2=0.31$, $y=0.192x+0.117$, $p<0.005$, ($G_{L,E}$ *vs* V'_{max50} $R^2=0.52$, $y=0.116x+0.147$, $p<0.025$). There was no significant difference between the slopes and the intercepts relating R_L and V'_{max50} in the normal subjects and patients.

The correlation between $R_{L,I}$ and $R_{L,E}$ in patients ($R^2=0.79$, $y=0.65x+0.19$. $p<0.001$) is shown in figure 3. $R_{L,E}$ was always equal to or greater than $R_{L,I}$. This pattern was also observed in the normal subjects ($R_{L,I}$ *vs* $R_{L,E}$, $R^2=0.81$, $y=0.61x+0.23$, $p<0.005$). There was no difference in the relationship of $R_{L,I}$ and $R_{L,E}$ in normal subjects and patients (slopes and intercepts).

There was no relationship between $R_{L,I}$ and $DD_{,RL,I}$ ($R^2=0.01$) and there was also no relationship between $R_{L,E}$ and $DD_{,RL,E}$ ($R^2=0.11$) or between V'_{max50} and $DD_{,Vmax50}$ ($R^2=0.07$) or V'_{max50} % pred and $DD_{,V'max50}$ ($R^2=0.08$).

The correlation coefficients for the relationships between the pathological scores for membranous and respiratory bronchioles and V'_{max50}, $R_{L,I}$, $R_{L,E}$ and the density

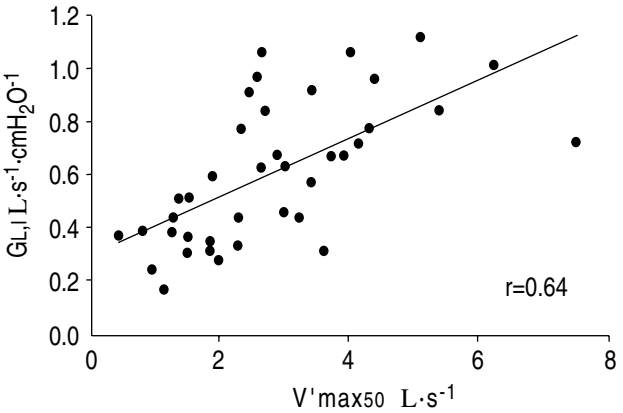

Fig. 1. – A scatter plot of inspiratory conductance($G_{L,I}$) *versus* maximal flow at 50% of vital capacity (V'_{max50}) breathing air for the 40 patients.

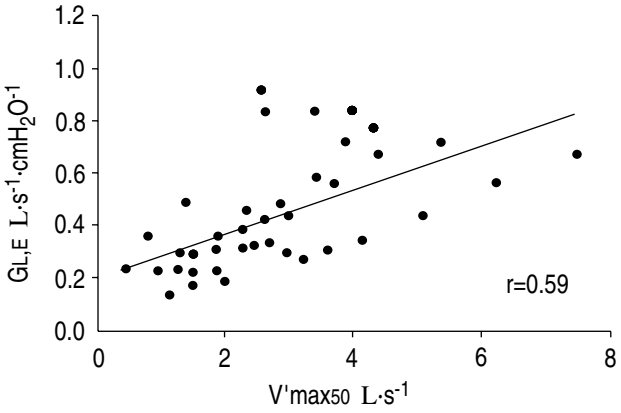

Fig. 2. – A scatter plot of expiratory conductance ($G_{L,E}$) *versus* maximal expiratory flow at 50% vital capacity (V'_{max50}) breathing air for the 40 patients.

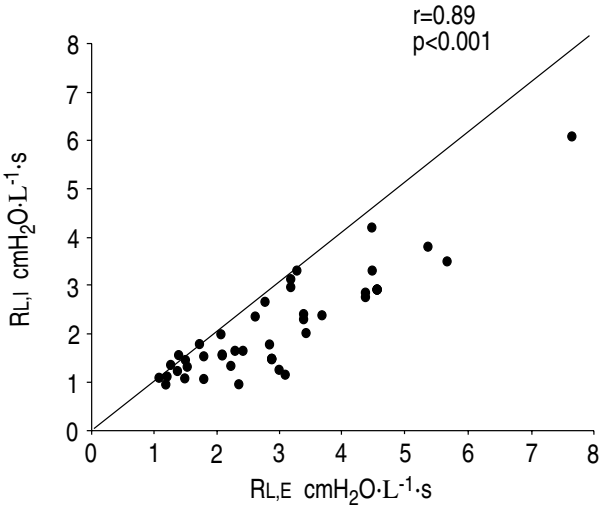

Fig. 3. – Inspiratory ($R_{L,E}$) *versus* expiratory resistance for the 40 patients. The solid line represents the line of identity.

dependence of these variables ($DD_{,V'max50}$, $DD_{,RL,I}$, $DD_{,RL,E}$) are shown in table 2. There was a significant relationship between V'_{max50}, $R_{L,E}$, $R_{L,I}$ and the total respiratory bronchiolar pathology score. The components of the respiratory bronchiolar pathology score which were significantly related to measurements of airway calibre were fibrosis and intralumenal macrophages (fibrosis *vs* V'_{max50}, R^2=0.16, p<0.05; fibrosis *vs* $R_{L,I}$ R^2=0.26, p<0.025; fibrosis *vs* $R_{L,E}$ R^2=0.22, p<0.025; intralumenal macrophages *vs* $R_{L,I}$ R^2=0.16, p<0.05; intralumenal macrophages *vs* $R_{L,E}$ R^2=0.18, p<0.05).

Although the total membranous bronchiolar pathology score was not significantly related to measurements of airway calibre, there was a trend for more severe pathology in those with higher R_L, and the fibrosis component of the membranous bronchiolar score was significantly related to $R_{L,I}$ (R^2=0.40, p<0.001) and $R_{L,E}$ (R^2=0.30, p<0.025). No relationship was found between emphysema score (ES) and R_L ($R_{L,I}$ *vs* ES, R^2=0.02, $R_{L,E}$ *vs* ES, R^2=0.02), or between ES and V'_{max50} (R^2=0.06).

Table 2. – Relationships of airway function and pathology scores in 27 patients with lung or lobar resection

	Total membranous bronchiolar score	Total respiratory bronchiolar score
V'_{max50} L·s^{-1}	-0.18	-0.50*
$R_{L,I}$ cmH$_2$O·L^{-1}·s	0.33	0.40*
$R_{L,E}$ cmH$_2$O·L^{-1}·s	0.31	0.47*
$DD_{,V50}$	-0.01	-0.07
$DD_{,RL,I}$	-0.28	0.06
$DD_{,RL,E}$	0.12	0.34

Correlation coefficients (r) of maximal expiratory flow at 50% vital capacity (V'_{max50}), inspiratory resistance ($R_{L,I}$), expiratory resistance ($R_{L,E}$) and density dependence of V'_{max50}, $R_{L,I}$, $R_{L,E}$ with total membranous and respiratory bronchiolar scores. DD_{V50}: $DD_{,RL,I}$ and $DD_{,RL,E}$ are the density dependence of V'_{max50}, inspiratory resistance and expiratory resistance respectively. *: p<0.025.

In the 27 patients with lung or lobar resection there was no relationship between the density dependence of V'_{max50}, $R_{L,I}$, $R_{L,E}$ and the total bronchiolar pathology scores for membranous or respiratory bronchioles or for emphysema score. However, density dependence of $R_{L,E}$ was significantly related to the degree of fibrosis in both respiratory (R^2=0.27, p<0.005) and membranous bronchioles (R^2=0.17, p<0.025). The relationship is the opposite of that which we predicted, that is the patients with more fibrotic small airways had a greater density dependence of R_L, rather than decreased density dependence. There was no similar relationship between $DD_{,RL,I}$ and fibrosis in the small airways ($DD_{,RL,I}$ *vs* fibrosis in membranous bronchioles, R^2=-0.001, $DD_{,RL,I}$ *vs* respiratory bronchiolar fibrosis, R^2=0.001).

Discussion

In this study, pulmonary resistance and the density dependence of pulmonary resistance were measured in 40 patients with peripheral lung tumours before they had resectional surgery. Thirty eight of the 40 patients were long-term smokers, and although the mean value for FEV_1 as percentage predicted was within the normal range, there was a wide variability in the degree of airway obstruction. In addition, the mean inspiratory and expiratory resistance were significantly greater than normal values in our laboratory, and there was a wide range of values for pulmonary resistance (1–6 cmH$_2$O·L·s^{-1}). We found a close correlation between V'_{max50} % pred and $G_{L,I}$ and $G_{L,E}$, suggesting that the pathological processes which decrease maximal expiratory flow are also responsible for increased pulmonary resistance.

The major purpose of this study was to explore whether the density dependence of pulmonary resistance was decreased in patients with mild expiratory airflow obstruction, and whether this decrease in density dependence was correlated with pathological abnormalities in peripheral airways. There is agreement that the peripheral airways are the major site of increased resistance in COPD [1–4]. Since Reynolds' numbers are low in these airways, an increase in their resistance would cause a greater percentage of the pressure drop during flow to be related to viscous losses, and, therefore, would decrease the influence of the less dense but more viscous He-O_2 [25]. This was the rationale for suggesting that the density dependence of maximal expiratory flow could be used as a test to detect the major site of airway narrowing [8]. However, more recent studies in patients with COPD [9, 10] have shown that in the presence of mild or advanced airflow obstruction, density dependence of maximal expiratory flow can be preserved and there was no correlation between peripheral airway pathology and the density dependence of maximal expiratory flow [9]. Since the dynamics of maximal expiratory flow are complex and the density dependence of maximal flow may not accurately reflect the major site of increased resistance, we measured the density dependence of pulmonary resistance during quiet respiration when dynamic airway compression should not occur. Our results do not show a

relationship between the severity of airflow obstruction, the severity of peripheral airway pathology and the density dependence of resistance.

One contributing factor to our failure to find a relationship between R_L and $DD_{,RL}$ could be the large variability of the measurement. The coefficients of variation for within and between day measurements Of $DD_{,RL}$ exceed those for the measurements of R_L and V'_{max} even in normal subjects, and it is likely that the variation would be even greater in the patients. In theory, the DD of R_L can vary between 0.92 in a purely laminar flow situation (because the viscosity of He-O_2 (2.05×10^{-4} $g\cdot cm^{-1}\cdot s^{-1}$) is greater than air ($1.88\times10^{-4}$ $g\cdot cm^{-1}\cdot s^{-1}$)) and 2.51 in a maximally density-dependent flow situation (density of air=1.13×10^{-3} $g\cdot L^{-1}$, density of He-O_2=0.45×10^{-3} $g\cdot L^{-1}$). One of our values for $DD_{,RL}$ fell below the theoretical lower limit (0.87), and two subjects had values for $DD_{,RL}$ that were above this theoretical maximum (2.56 and 2.75). It is likely that these values represent "noise". Another possible contributing factor to our failure to find a decrease in $DD_{,RL}$ in the obstructed patients is the relatively low mean values for $DD_{,RL}$ in the normal subjects, leaving little "room" for a significant decrease in the obstructed patients. We were surprised by the relatively low value of $DD_{,RL}$ in the normal subjects at flows of 1.0 $L\cdot s^{-1}$. The low values could be due to the contribution of tissue resistance to pulmonary resistance. The greater the contribution of tissue resistance (which is not density-dependent) the lower will be the density dependence of R_L. We also calculated resistance and density dependence of resistance at flows of 1.5 $L\cdot s^{-1}$ in the normal subjects, and both the values for resistance ($R_{L,I}$=1.46±42) and density dependence ($DD_{,RL,I}$=1.37±21) were greater at this higher flow rate. However, not all of the patients achieved these flow rates during the measurements, so that a similar analysis could not be performed on the patients. Despite these considerations, the fact that the mean DD of $R_{L,I}$ and $R_{L,E}$ tended to be greater in the obstructed patients, suggests to us that technical difficulties are not the reason we did not detect a lower DD in obstructed patients or a relationship between R_L and DD.

The possible physiological explanations for the negative results are: 1) central airways do contribute to the increased resistance observed in COPD, or, alternatively; 2) with the development of disease and narrowing, density-dependent flow situations develop in peripheral airways. The site of increased central resistance could be at the level of the larynx or the large cartilaginous airways. Although pathological abnormalities of mucous glands and airway epithelium in large airways have been described in patients with COPD, these pathological processes would not be expected to produce much narrowing. There is evidence that extrathoracic upper airway resistance increases disproportionately in patients with COPD [22–24]. CAMPBELL *et al.* [22] found an increase in upper airway resistance in 11 patients with chronic obstructive lung disease as compared to normal subjects. HIGENBOTTAM and PAYNE [23] measured the separation of the vocal cords during inspiration and expiration in 34 patients with varying degrees of airway obstruction. They observed narrowing of the vocal cords both during inspiration and expiration, and the degree of narrowing was greater in patients with more severe airflow obstruction. More recently, similar results have been observed in patients with asthma [24]. If the upper airway narrowing both on inspiration and expiration was proportional to the increase in peripheral resistance, one might expect that the ratio of peripheral to central resistance would be maintained despite the development of peripheral airway disease. If this were the case, density dependence of resistance would remain constant despite the increase in peripheral airway resistance.

The second possibility is that, with the development of disease and narrowing in peripheral airways, density-dependent flow conditions develop at these sites. To test this possibility, we have performed calculations of total airway resistance breathing air and helium oxygen using the computational model of lung resistance described by PEDLEY *et al.* [25]. This model gives values for total pulmonary resistance of 1.2 $cmH_2O\cdot L^{-1}\cdot s$ breathing air at 1 $L\cdot s^{-1}$. We increased the total resistance of the model in two ways. Firstly, we subtracted sufficient airways less than 2.5 mm in diameter (generation 8 and distally) to result in an increase of total resistance to 5 $cmH_2O\cdot L\cdot s^{-1}$. Secondly, we increased the resistance to a similar extent by diffusely narrowing the same small airways. Density dependence of R_L for the model with normal airway geometry was 1.47, and this value decreased to 1.32 with peripheral airway narrowing but actually increased slightly to 1.50 when the resistance was increased by subtracting peripheral airways. Therefore, it is possible that peripheral airway pathology, especially if it results in loss of airways, could lead to preserved density dependence.

In conclusion, the results of this study do not support the hypothesis that the density dependence of pulmonary resistance is an accurate measure of small airway pathology in mildly obstructed smokers.

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