

Lung structure and function in cigarette smokers

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Abstract

Background – Cigarette smoking produces an inflammatory response in the airways of everyone but only 15–20% of smokers develop airways obstruction. The present study concerns the relative importance of peripheral airways inflammation and the emphysematous destruction of the parenchymal support of the airways in the pathogenesis of this obstruction.

Methods – A total of 407 patients with a diagnosis of lung tumour performed pulmonary function tests a day or two before a lung or lobar resection. The specimens were fixed in inflation and analysed at the gross and microscopic level to determine the extent and severity of the emphysematous process, the number of alveoli supporting the outer walls of the airways, and the average distance between alveolar walls. The severity of the inflammatory process in the respiratory and non-respiratory bronchioles was also assessed using a previously established grading system.

Results – The lung function test showed that a decline in FEV₁ was associated with an increase in residual volume and a decrease in the diffusing capacity for carbon monoxide and a reduction in the lung maximum elastic recoil pressure. The prevalence of grossly visible emphysema increased as FEV₁ declined, but the extent and severity of these lesions and the number of alveoli supporting the outer walls of the peripheral airways was similar at all levels of FEV₁. The system used to grade inflammatory response in the peripheral airways failed to identify a specific defect responsible for the physiological abnormalities.

Conclusion – The reduction in FEV₁ associated with chronic cigarette smoking can be partially explained by loss of lung elastic recoil pressure which reduces the force driving air out of the lung. This loss of elastic recoil pressure is attributed to microscopic enlargement of the air spaces rather than to grossly visible emphysema. The exact nature of the lesions responsible for the peripheral airways obstruction remains to be identified.

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Chronic obstructive pulmonary disease (COPD) is characterised by decreased expiratory flow rates, increased pulmonary resist-

ance, and hyperinflation.¹ A current working hypothesis is that these functional abnormalities are caused by an inflammatory process in the peripheral lung, but the exact nature of the structural defect responsible for the functional abnormalities has been difficult to define. Some authors favour the concept that emphysematous destruction of the lung is responsible for adversely affecting expiratory flow by either interfering with the parenchymal support of the peripheral airways,^{2–4} or by decreasing the elastic recoil force responsible for driving air out of the lung.⁵ Others have argued that the major cause of the reduction in forced expiratory flow is an inflammatory process in the small conducting airways that causes them to narrow and close prematurely.^{6–11}

A study was undertaken to re-examine this problem using information collected from patients requiring lung resection for peripheral tumours. The data were collected prospectively over a 10 year period and the analysis was designed to determine the relative importance of parenchymal destruction and peripheral airways inflammation to the functional abnormalities in COPD.

Methods

PATIENT POPULATION

The study was based on 407 patients from whom a lung or lobe was resected for a peripheral lung tumour over the 10 year period from 1979 to 1989. Data summarising the age, sex distribution, and smoking habits of the 407 patients included in the study are presented in table 1. The protocol described below was approved by the Human Experimentation Committee of both the University of British Columbia and St Paul's Hospital.

PHYSIOLOGICAL STUDIES

Pulmonary function tests were performed in the immediate preoperative period. Spirometric measurements were made with either a nine litre Steadwell or a Collins computerised spirometer (Warren B. Collins, Braintree, Massachusetts, USA). The percentage predicted forced expiratory volume in one second (FEV₁) was calculated according to the formula of Crapo and coworkers.¹³ The subdivisions of lung volume were determined by helium dilution and reported using the predicted values of Goldman and Becklake.¹⁴ The transfer factor for carbon monoxide (TLCO) was measured either by the steady state method of Bates and coworkers¹⁵ or by the single breath method of Ogilvie and associates¹⁶ on a P K Morgan automated diffusing capacity analyser using the appropriate pre-

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Table 1 Mean (SD) patient data in relation to FEV₁ category

	FEV ₁ (% predicted) categories							
	<50 (n=22)	50-59 (n=32)	60-69 (n=65)	70-79 (n=71)	80-89 (n=88)	90-99 (n=75)	100-110 (n=30)	>110 (n=24)
M/F	16/6	24/8	50/15	54/17	57/31	56/19	14/16	11/13
Age	66 (9)	61 (8)	63 (9)	63 (9)	60 (12)	63 (10)	60 (8)	58 (13)
Pack yrs	52 (32)	56 (33)	71 (41)	55 (33)	48 (34)	49 (33)	47 (33)	30 (30)
TLC (% pred)	107 (19)	102 (19)	102 (17)	103 (17)	103 (14)	107 (15)	112 (14)	112 (15)
FRC (% pred)	141 (36)	127 (33)	122 (28)	120 (26)	115 (30)	118 (25)	119 (22)	121 (21)
RV (% pred)	175 (50)	151 (42)	143 (39)	132 (35)	125 (41)	124 (33)	122 (34)	113 (26)
TLco (% pred)	78 (19)	72 (18)	80 (15)	80 (19)	83 (26)	102 (34)	81 (18)	106 (53)
PLmax (cm H ₂ O)	17.3 (6.2)	18 (5.8)	23.1 (14)	22.4 (8.3)	25.3 (8.5)	24.1 (9.3)	23.7 (8)	26.9 (7.8)
	(n=7)	(n=24)	(n=46)	(n=48)	(n=61)	(n=57)	(n=21)	(n=16)
PL(FRC) (cm H ₂ O)	1.1 (0.8)	1.4 (1.1)	1.2 (0.8)	1.3 (0.8)	1.3 (0.7)	1.3 (0.9)	1.2 (0.6)	1.4 (0.8)
	(n=6)	(n=24)	(n=44)	(n=46)	(n=60)	(n=56)	(n=20)	(n=16)
ΔN ₂ /l (% pred)	801 (518)	491 (175)	349 (166)	315 (119)	257 (194)	214 (118)	180 (103)	161 (132)
	(n=9)	(n=22)	(n=51)	(n=54)	(n=70)	(n=62)	(n=24)	(n=18)
FEF ₂₅₋₇₅ (% pred)	19 (8)	29 (15)	37 (17)	45 (20)	59 (23)	66 (24)	80 (33)	102 (34)
	(n=21)	(n=27)	(n=61)	(n=67)	(n=81)	(n=64)	(n=30)	(n=7)

FEV₁ = forced expiratory volume in one second; TLC = total lung capacity; FRC = functional residual capacity; RV = residual volume; TLco = carbon monoxide transfer factor; PLmax = pleural pressure at maximal inflation; PL(FRC) = pleural pressure at FRC; ΔN₂/l = single breath nitrogen washout curve; FEF₂₅₋₇₅ = forced expiratory flow between 25% and 75% of vital capacity.

dicted values to report the results.^{15,17} In as many patients as possible (table 1) lung volume was also measured in a variable volume body plethysmograph and pleural pressure was estimated with an oesophageal balloon. In these cases pressure-volume curves of the lung were constructed according to the method of Mead *et al*¹⁸ and pleural pressure at maximal inflation (PLmax) was recorded by the method of Colebatch and colleagues.¹⁹ Flow-volume curves were obtained breathing both air and helium as part of the plethysmographic studies and the volume of isoflow, the difference in flow between air and helium at 25% and 50% of the vital capacity, and the forced expiratory flow between 25% and 75% (FEF₂₅₋₇₅) of the vital capacity were determined. Nitrogen washout curves were also obtained by the method of Buist and Ross,²⁰ and the slope of phase 3 of the washout was reported as a percentage predicted using their equations.

PATHOLOGICAL STUDIES

All of the resected lung specimens were taken directly from the operating theatre and inflated with buffered fixative overnight at 25 cm H₂O. They were then cut into 2 cm thick sagittal slices and the mid sagittal slice was stored. Two pathologists (JCH and JLW) graded the gross emphysematous lesions present in the lung using a modification²¹ of the method described by Thurlbeck and colleagues.²² Three to six stratified random blocks of tissue were cut from the medial and lateral slices of the lung using a template that allowed for correction for tissue shrinkage during processing. These were processed into paraffin in

the standard fashion and 5 μm sections were cut onto glass slides and stained with haematoxylin and eosin, Masson trichrome, and periodic acid Schiff (PAS) stains.

The extent and severity of the disease in the non-respiratory bronchioles – that is, airways of < 2 mm internal diameter without cartilage in their walls – and respiratory bronchioles were evaluated by a single pathologist (JLW) using a previously described system which allowed the epithelial changes, cellular infiltration, and connective tissue deposition associated with the inflammatory process to be graded against a standard set of photomicrographs.²³ Both gross and microscopic examinations of the lungs were performed by the pathologists without knowledge of the patients' clinical histories or functional data.

In the subset of patients indicated in table 2 the internal perimeter, external perimeter, and number of alveolar attachments to the external perimeter of non-respiratory bronchioles cut in cross section were measured using previously described methods.^{4,24} These data were used to compare the number of alveolar attachments/mm of external airways perimeter at all levels of FEV₁. In a separate subset of patients, also indicated in table 2, the histological sections were used to measure the mean linear intercept (LM) which estimates the average distance between alveolar walls.

DATA ANALYSIS

The data obtained concerning age, smoking history, lung function, and the grades assigned to parenchymal destruction (emphysema score), membranous and respiratory bron-

Table 2 Mean (SD) morphological data in relation to FEV₁ category

	FEV ₁ (% predicted) categories							
	<50	50-59	60-69	70-79	80-89	90-99	100-110	>110
Pneumonectomy (% of group)	4.5	15.6	21.5	15.5	15.9	14.6	0.0	12.5
Emphysema prevalence	11/22 (50%)	17/32 (55%)	32/65 (50%)	37/71 (55%)	29/88 (33%)	25/75 (33%)	8/30 (27%)	2/24 (9%)
Emphysema score	32 (15)	29 (17)	24 (14)	23 (15)	25 (14)	22 (9)	23 (13)	24 (19)
Attachments (mean no./airway)								
Total	16 (4)	16 (5)	16 (3)	17 (3)	18 (6)	16 (3)	16 (2)	18 (3)
Intact	11 (3)	11 (3)	14 (3)	14 (2)	13 (3)	13 (3)	13 (3)	13 (4)
Damaged	5 (2)	6 (2)	3 (2)	4 (2)	4 (3)	3 (1)	3 (2)	5 (3)
n	5	5	13	11	14	8	5	5
LM (μm) (n=5)	175 (55)*	148 (43)	138 (19)	125 (33)	137 (19)	155 (21)	145 (17)	143 (32)

LM = distance between alveolar walls.

* Significantly different (p < 0.05) from all categories.

chioles (airway pathology scores) were stored in a microcomputer database. The patients were divided into groups based on their percentage predicted FEV₁ (table 1) using SPSS Data Entry II (SPSS Inc). Analysis of pathological variables, age, smoking history, and lung function was made using a one way analysis of variance. Differences between FEV₁ categories following a statistically significant ANOVA ($p < 0.05$) were detected using multiple contrasts.²⁵ Differences between the current study and previously published work were tested with multiple *t* tests using a Bonferroni correction for multiple comparisons.²⁶ All possible subsets regression was used to relate pathological correlates to lung function values.²⁷ This allowed the data to be sorted by FEV₁ percentage predicted, reported in tables, and analysed for relation with reduction in FEV₁.

Results

LUNG FUNCTION

Table 1 shows the number of patients, their sex, and the mean (SD) values for age, smoking history, subdivision of lung volume, and TLC₀% for FEV₁ groups ranging from > 110% to < 50% of the predicted values. The FEV₁ was normally distributed around a mean value of 80 (18)% with 22 of 407 (5%) having an FEV₁ < 50% and 24 of 407 (6%) and FEV₁ > 110% of the predicted value. No statistically significant trend for either age or smoking history was identified as FEV₁ declined from the highest to the lowest values. The total lung capacity (TLC) and functional residual capacity (FRC) were similar at all levels of FEV₁ but residual volume increased ($p < 0.005$) and the TLC₀ decreased ($p < 0.05$) as FEV₁ declined.

Static elastic recoil pressures, single breath nitrogen washout, and flow-volume curves were obtained from a subset of the total population indicated in table 1. These data showed that there was a decline ($p < 0.05$) in elastic recoil pressure measured at TLC ranging from 27 (8) cm H₂O in patients whose FEV₁ was > 110% predicted to 17 (6) in patients whose FEV₁ was < 50% predicted. This difference was not apparent at FRC where the elastic recoil pressure varied between 1.4 (0.8) and 1.1 (0.8) cm H₂O over the full range of FEV₁ observed. The FEF₂₅₋₇₅ ranged from 102 (34)% predicted in the patients with the best lung function to 19 (8)% predicted in patients where FEV₁ was < 50% of the predicted values. However, measurements of the difference in flow between air and helium and the volume of isoflow (data not shown) did not change in any of the FEV₁ groups. The data also showed an increase ($p < 0.05$) in the slope of the single breath nitrogen washout curve ($\Delta N_2/l$) from 161 (132) to 801 (518) over the same range of FEV₁.

PATHOLOGY

The 407 resected lung specimens consisted of 251 from the right lung and 156 from the left

lung. The right lung specimens included 22 pneumonectomies, 112 upper, 17 middle, and 52 lower lobectomies, with the remaining 48 specimens consisting of combinations of more than one lobe. The left lung specimens included 37 pneumonectomies, 74 upper and 43 lower lobectomies, with the remaining two specimens consisting of combinations of one lobe and segments of the other. Combining results showed that the average right lung weighed 505 (97) g and the average left lung 451 (98) g. The volume of fixative in each lung obtained by subtracting the fresh from the fixed weight was 1279 (488) ml on the right and 1072 (603) ml on the left. Comparison of these values with TLC measured preoperatively suggests that the pathological studies were performed on lungs that were inflated to approximately 43% of TLC. The total number of pneumonectomies present in the series (59 of 407) accounted for 14.5% of the specimens. This percentage ranged from 12% to 21% for the FEV₁ groups that were between 50% and 100% predicted. Only two of the FEV₁ groups (those < 50% and 100–110% predicted FEV₁) had fewer pneumonectomies. As similar results were obtained when patients who provided pneumonectomy specimens were analysed separately from those undergoing lobectomy only, the data in table 2 represent the analysis of the combined groups.

The estimate of emphysema present in the lungs (table 2) shows that the prevalence of macroscopic lesions increased from two of 24 (9%) of the cases with an FEV₁ of > 110% to 11 of 22 (50%) where the FEV₁ was < 50% of the predicted value. However, the extent and severity of these lesions estimated by the emphysema score was similar (24 (19) to 32 (15)) over the entire range of FEV₁. There was no significant difference in the number of normal or abnormal alveolar attachments/mm of airway external perimeter at any level of FEV₁ but the average distance between alveolar walls (LM), which reflects airspace size, was increased ($p < 0.05$) in cases where FEV₁ was < 50% predicted.

The pathological information obtained for the non-respiratory and respiratory bronchioles provides separate assessments of the epithelial changes, cellular infiltrate, connective tissue, and carbon pigment deposition associated with the cigarette smoke induced inflammatory process. The total airway score which includes the score for all of the parameters assessed by the grading system ranged from 118 (47) to 155 (60) in the non-respiratory bronchioles, and 83 (37) to 102 (43) in the respiratory bronchioles as FEV₁ declined from > 110 to < 50% of the predicted values (table 3). Analysis of both these total scores and the values obtained for the individual components which make them up (data not shown) failed to establish any trend relating these estimates of airways disease to a decline in FEV₁.

Discussion

The results of this study are based on patients who had lung cancer. Although all were heavy

Table 3 Mean (SD) airway pathology scores in relation to FEV₁ category

	FEV ₁ (% predicted) categories							
	< 50 (n = 22)	50–59 (n = 32)	60–69 (n = 65)	70–79 (n = 71)	80–89 (n = 88)	90–99 (n = 75)	100–110 (n = 30)	> 110 (n = 24)
Airway score (MB)	155 (60)	160 (61)	144 (50)	148 (51)	146 (55)	132 (51)	124 (52)	118 (47)
Airway score (RB)	102 (43)	119 (55)	108 (49)	109 (43)	104 (47)	92 (46)	90 (44)	83 (37)

MB = membranous bronchioles; RB = respiratory bronchioles.

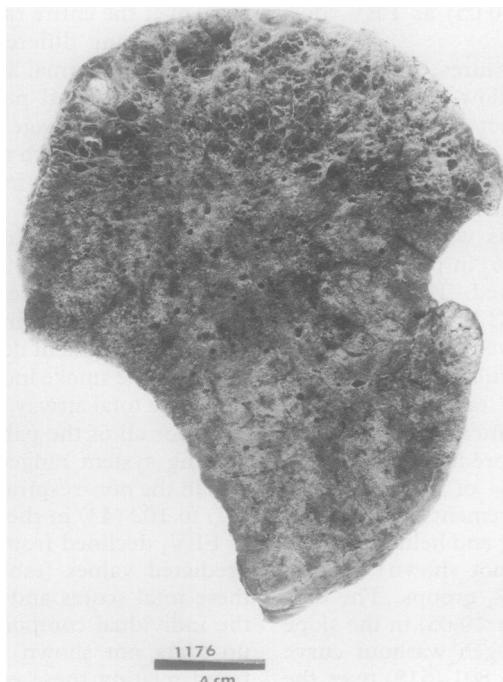
smokers, only 5% (22 of 407) had an FEV₁ < 50% of the predicted values; approximately 50% (216 of 407) had an FEV₁ that was > 80% of the predicted value and therefore within the normal range. These findings are consistent with those from more extensive epidemiological studies which have established that only a minority of heavy smokers develop forced expiratory airflow limitation.^{28–30} Taken together, these findings strongly suggest that host and environmental factors other than smoking make a major contribution to this form of airways disease.

The gross pathological features of emphysema³¹ were readily visible on the cut surface of the fixed inflated lung (figure). However, the hypothesis that visible emphysematous lung destruction contributes to the pathophysiology of the airways obstruction was not supported by our results. Table 2 shows that the relation between the decline in FEV₁ and the presence of emphysema is the result of an increase in prevalence rather than to a greater extent and severity of these macroscopic lesions. This result is consistent with a recent report by Gelb *et al*³² who used computed tomographic scans of patients with advanced COPD to show that the presence of respiratory failure

was independent of the severity of the gross emphysema visible on the scan.

Analysis of the pressure-volume curve data from our patients showed that the decline in FEV₁ correlated with a reduction in PL_{max} whereas PL measured at FRC did not change at any level of FEV₁. Previous direct measurements of the pressure-volume characteristics of the centrilobular emphysematous space³³ have shown that these structures undergo large changes in pressure with little change in volume near TLC, and large changes in volume with little change in pressure at lower lung volumes. The observed decline in PL_{max} as FEV₁ falls is therefore probably not related to the pressure-volume characteristics of the centrilobular emphysematous lesions because they would be fully expanded before the lung containing them reached TLC. Data reported by Osborne *et al*³⁴ have shown that a loss of lung elastic recoil correlates better with microscopic measurement of alveolar size (LM) than with the presence of the macroscopic lesions of emphysema. We therefore suggest that the decline in PL_{max} observed in our study is the result of microscopic changes in the lung parenchyma which only became apparent in this study when FEV₁ had declined to < 50% of the predicted value. The values for LM reported here are smaller than those reported in other studies of human lungs. This is because LM was measured at a higher magnification in our study where there is a tendency to obtain measurements in areas containing more alveoli than alveolar ducts. As the same yardstick was used for all lungs, however, the increase in LM observed in the patients with the worst lung function supports the concept that the decline in function is associated with microscopic evidence of enlarged alveolar size.

Butler *et al*² were the first to suggest that loss of elastic recoil properties of emphysematous lungs contributed to the narrowing of the airways by decreasing the support on the outer airway walls. Direct measurements of peripheral airways resistance in lungs from patients with COPD showed that peripheral airways resistance was increased in COPD.⁶ However, as this increased resistance could not be lowered by raising transpulmonary pressure to increase the parenchymal support, and was the same on both the inspiratory and expiratory portion of each respiratory cycle, it was argued that the loss of parenchymal support was not the cause of the airways obstruction.⁶ This observation might have been explained if the alveolar attachments around the airways were destroyed to prevent the force associated with lung inflation from being adequately transmitted to the outer walls of the airways.⁴ The present study shows, however,



The cut surface of the mid saggital slice of resected upper lobe with extensive emphysema from a patient with normal lung function (FEV₁ 99%, TLC 113%, FRC 110%, RV 95%, TLCO 89%, and PL_{max} 132% predicted). Data in table 2 show that 10 of 54 patients with FEV₁ > 100% predicted had emphysema of similar severity.

Table 4 Mean (SD) pathology scores in comparison with those of Cosio *et al*⁷

Group	No. of cases		Pathology		Age (years)		Smoking history*		FEV ₁ /FVC	
	Cosio <i>et al</i> ⁷	Present study	Cosio <i>et al</i> ⁷	Present study	Cosio <i>et al</i> ⁷	Present study	Cosio <i>et al</i> ⁷	Present study	Cosio <i>et al</i> ⁷	Present study
1	6	202	99 (38)	100 (27)	44 (8)	61 (10)	322 (20)	1037 (694)	81 (2)	70 (10)
2	10	112	165 (12)	158 (11)	52 (15)	62 (10)	770 (294)	1094 (977)	71 (4)	70 (9)
3	9	48	195 (11)	194 (9)	63 (3)	63 (10)	854 (143)	1146 (681)	64 (4)	63 (11)
4	11	42	238 (72)	244 (31)	63 (2)	63 (11)	824 (100)	932 (558)	56 (4)	69 (8)

Note that subjects in group 1 of the study by Cosio *et al*⁷ were younger ($p < 0.001$) and had smoked less ($p < 0.01$) than those in the current study.

* Numbers for smoking are in cigarette years and can be converted to American pack years by dividing by 20.

that the number of supporting alveoli/mm of outer airway perimeter, and the number of these alveolar attachments judged to be damaged,^{35,36} did not change over the entire range of FEV₁. The results reported here therefore support the conclusion reached 25 years ago⁶ that the decline in FEV₁ cannot be attributed to a reduction in parenchymal support to the outer wall of the peripheral airways.

An alternative hypothesis for linking the decline in elastic recoil pressure with the fall in FEV₁ was suggested by Mead *et al*.⁵ Their analysis was based on the fact that both pleural pressure and alveolar pressure rise during forced expiration whereas airway pressure falls from the alveolus to the mouth. This defines points in the airway where the pressure outside the airway (pleural pressure) must be equal to that inside the airway, and showed that the elastic recoil pressure of the lung was the force driving air from the alveoli to these equal pressure points. The present study supports this concept by showing a good correlation between the reduced elastic recoil pressure (P_{Lmax}) and decline in FEV₁. However, since Corbin *et al*³⁷ have shown that there can be a considerable loss in elastic recoil without change in FEV₁ it is reasonable to assume that the resistance of the airways upstream from the equal pressure point is an important cause of the reduced forced expiratory flow in COPD.

The fact that residual volume increased as FEV₁ declined in this study strongly suggests that the airways narrow and/or close where their total cross sectional area is small enough to affect forced expiration. Our previous studies^{7,10} suggested that the abnormalities in structure responsible for the reduced FEV₁ could be roughly quantitated using a grading system to assess the disease in the peripheral airways, but the present results fail to confirm those reports. Table 4 shows that the pathology scores assigned to the non-respiratory bronchioles from the 407 cases presented here are closely similar to those from the 36 cases originally reported by Cosio *et al*.⁷ It also shows that the group with the lowest patho-

logy score in that study was younger (44 (8) *v* 61 (10)), had smoked less (16 (0.1) *v* 51.8 (3.5) pack years) and had a better FEV₁/FVC ratio (81 (2) *v* 70 (10)) than the group with comparable pathology in the present study. This means that when age and smoking history were better matched in the much larger group of patients in this study, an increased pathology score was not associated with a decline in lung function. A similar comparison of the present study with the earlier report of Wright *et al*¹⁰ also shows that when smoking levels are better matched with a larger number of cases in each FEV₁ group the pathological grades for the respiratory bronchioles also failed to change over the range of FEV₁ observed (table 5).

The fact that the abnormalities identified by this pathological grading system of the airways did not correlate with a decline in FEV₁ in the large group of patients reported here means that the narrowing and/or closure of the airways responsible for the increased residual volume and decline in FEV₁ were determined by parameters which the pathological grading system does not measure. Several possibilities could explain this result. Some years ago Macklem *et al*³⁸ showed that surfactant was present in the peripheral airways and that increasing the normal low surface tension in these airways caused them to become unstable and to close. It is entirely possible that an inflammatory process in the peripheral airways could deposit an exudate of plasma on the surface of the lumen and increase the surface tension from very low values (3 dynes/cm) to that of plasma (50 dynes/cm). This would increase the transmural pressure required to keep the airway open and lead to instability and closure of the peripheral airways in a way that could not be detected by the morphological techniques employed. Recent studies of the airways from asthmatic patients have shown that there is a definite inflammatory thickening of the walls of the peripheral airways.³⁹ This finding contrasts sharply with the changes in the same airways in patients with COPD which were only slightly thicker than

Table 5 Mean (SD) results in comparison with those of Wright *et al*¹⁰

FEV ₁	No. of cases		Pathology		Age (years)		Smoking history*	
	Wright <i>et al</i> ¹⁰	Present study	Wright <i>et al</i> ¹⁰	Present study	Wright <i>et al</i> ¹⁰	Present study	Wright <i>et al</i> ¹⁰	Present study
> 100	10	90	77 (12)	85 (42)	62 (6)	62 (11)	309 (142)	875 (662)†
90-99	17	67	128 (7)	98 (45)	57 (3)	62 (11)	658 (129)	962 (662)
80-89	21	77	129 (8)	99 (46)	59 (2)	62 (11)	959 (183)	1079 (934)
70-79	16	58	115 (7)	118 (46)	61 (2)	61 (8)	1187 (142)	1206 (627)
60-69	12	41	118 (7)	112 (43)	61 (4)	61 (11)	1118 (216)	1196 (696)
< 60	20	59	129 (12)	120 (52)	65 (2)	64 (8)	978 (118)	1205 (714)

Note that the patients in the best FEV₁ group had smoked less in the study by Wright *et al*.

* Numbers for smoking are in cigarette years and can be converted to American pack years by dividing by 20.

† Present study > study by Wright *et al* $p < 0.01$.

those from appropriate controls matched for age and smoking history.³⁸ Lambert⁴⁰ has recently suggested that subtle changes in the basement membrane and in the lamina reticularis just beneath the basement membranes are a major determinant of airway closure. These changes in the structure of the airway wall would not be detected by the grading systems used in our study. In addition, Macklem and Permutt⁴¹ have argued that the lesions responsible for abnormal function in COPD may be heterogeneously distributed along different parallel pathways in a manner that would be difficult to detect using the anatomical techniques applied here.

In summary, the results obtained in the group of heavy smokers requiring lung resection for cancer are consistent with previous reports²⁸⁻³⁰ showing that only a relatively small proportion of heavy smokers develop airways obstruction. They also show that the decline in FEV₁ can be partially explained by a loss in lung elastic recoil which decreases the force driving air out of the lung during forced expiration. Also, this loss of recoil is better explained by a microscopic increase in airspace size than by the gross emphysematous lung destruction that is visible in the resected specimens. Although our results confirm that an inflammatory process is present in the peripheral airways of heavy cigarette smokers, they fail to identify the structural lesions responsible for the rise in residual volume and decline in FEV₁ that characterise the airways obstruction that develops in these subjects.

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