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Relation between small airways disease and parenchymal destruction in surgical lung specimens

Luuk NA Willems, Johannes A Kramps, Theo Stijnen, Peter J Sterk, Jan J Weening, Joop H Dijkman

Abstract

The relation between small airways disease and parenchymal destruction was investigated in lungs and lobes removed at surgery from 27 patients aged 15–70 years. Eight of the 27 patients were lifelong non-smokers. The degree of small airways disease was assessed by semiquantitative grading (SAD score) and by measuring diameter and wall thickness of membranous bronchioles. Parenchymal destruction was measured in three ways. Firstly, the number of alveolar attachments on membranous bronchioles per millimetre of circumference (AA/mm) was counted; the number of broken attachments was subtracted from the total AA/mm to give the numbers of intact attachments (normal AA/mm). Secondly, a point counting technique was used to give a destructive index (DI). Thirdly, the mean linear intercept (Lm) was determined. Total and normal AA/mm correlated negatively with the SAD score of membranous bronchioles (r_s = −0·48 and −0·51) and with wall thickness (r_s = −0·37 and −0·45) and DI correlated with wall thickness (r_s = 0·5) and with the SAD score of respiratory bronchioles (r_s = 0·53). Lm did not correlate with indices of small airway disease and total and normal AA/mm did not correlate with diameter. Multiple regression analyses showed that the correlation of total AA/mm with the SAD score of membranous and respiratory bronchioles and with wall thickness were not confounded by age or smoking. It is concluded that small airways disease is related to destruction of peribronchiolar alveoli, and it is postulated that small airways disease has a direct role in the causation of centrilobular emphysema.

Department of Pulmonology, University Hospital, Leiden
LNA Willems
JA Kramps
PJ Sterk
JH Dijkman

Department of Medical Statistics, University of Leiden
T Stijnen

Laboratory of Pathology, University of Groningen, The Netherlands
JJ Weening

Address for reprint requests: Dr L N A Willems, Department of Pulmonology, University Hosital Leiden, 2333 AA Leiden, The Netherlands.

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Small airways disease and pulmonary emphysema are two diseases that occur in the distal parts of the human lung and are linked aetiologically to cigarette smoking. Small airways disease, recognised by Hogg *et al* as a collection of histological features of chronic inflammation in airways with an internal diameter of less than 2 mm, was considered to be responsible for airflow obstruction in cigarette smokers.[1] Since then several studies have confirmed the susceptibility of smokers to develop morphological bronchiolar lesions leading to lung function abnormalities.[2–4] Pulmonary emphysema is characterised by abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by destruction of their walls and without obvious fibrosis.[5] It is beyond doubt that cigarette smoking is important in the pathogenesis of this condition as well.[6]

As features of small airways disease and emphysema are often present in the same lung, possibly both diseases not only have a common aetiologic factor but are causally linked. The possibility that small airway inflammation may lead to emphysema was put forward 30 years ago by Leopold and Gough[7] and later by Anderson and Foraker.[8] The inflammatory process in the airways could lead to a weakening of surrounding alveolar walls, or it could be responsible for an imbalance between proteinases and their inhibitors, which it is thought will induce emphysema.[9] Recent studies on destructive lesions of alveolar attachments on bronchioles suggest that indeed this might happen.[10 11] The events may also develop in the reverse order: loss of alveolar walls around bronchioles might lead to abnormal bronchiolar morphology.[11 12] In either case parenchymal and bronchiolar disease might be expected to share the same distribution pattern within the lung. Some investigators have tried to prove such a topographic association by comparing upper and lower lobes, but have obtained contradictory results.[3 13 14] If small airways disease does lead to the development of emphysema, it would be expected to occur at an earlier stage than emphysema. Recently, however, Petty *et al*[15] found minimal differences in small airway disease and no differences in FEV_1 or closing capacity between normal and mild emphysematous lungs. The precise relation between small airways disease and the development of emphysema remains to be determined.[16]

The purpose of our study was to look for evidence for a causal relation between small airways disease and emphysema by performing microscopic measurements for these two pathological conditions in surgical lung specimens.

Methods

PATIENTS

Lungs and lobes were obtained from 19 male

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and 8 female patients who were treated by surgery for a solitary lesion in the lung. Eight were lifelong non-smokers. The subjects were not deficient for α_1 proteinase inhibitor (PiZZ or PiSZ), determined by phenotyping using isoelectric focusing, and did not have any disease known to influence lung structure other than chronic bronchitis or emphysema. Pulmonary function tests were performed preoperatively according to standardised methods.[17] Six subjects had an FEV_1 below 80% predicted.[17] The mean FEV_1 of the subjects was 86% predicted (range 44·9–114%), vital capacity 94·1% predicted (range 80·0–111·6%), and residual volume 117·6% predicted (range 67·0–166·5%). Surgical specimens unsuitable for inflation were excluded.

TISSUE PROCESSING

Within one hour of surgical removal the lung specimens were inflated via the airway with Bouin's fixative by balloon tipped catheters to a distending pressure of 25 cm fixative for four hours. The specimens were then sliced and tissue blocks were sampled from each slice randomly; processed to paraplast; cut into 4 μm sections; and stained with haematoxylin-eosin, van Gieson, Verhoeff-van Gieson, and periodic acid-Schiff after treatment with amylase.

MORPHOMETRY

Small airways disease

Small airways disease was graded semi-quantitatively according to the method of Cosio *et al*[18] on the basis of reference pictures. Respiratory bronchioles were graded for mural chronic cellular infiltrate, pigment deposition, muscle hypertrophy, fibrosis, and goblet cell metaplasia. Membranous bronchioles were graded for the same features and for squamous cell metaplasia in addition. For each bronchiole the scores for all the features were summed and expressed as a percentage of the maximum possible small airway disease (SAD) score, all features thus being given the same weight in each bronchiole.

In membranous bronchioles the external adventitial and internal basal laminar diameters were measured by dividing the perimeter, as measured on a digitising tablet, by π. Wall thickness was calculated by subtracting the internal from the external diameter, and dividing the difference by 2. Tangentially or obliquely sectioned bronchioles were eliminated.

Parenchymal destruction

The number of alveolar attachments on membranous bronchioles per mm of perimeter was counted (AA/mm). Disrupted or broken attachments were subtracted from the total number per bronchiole (total AA/mm) to give the number of intact attachments (normal AA/mm), a method similar to that of Saetta *et al* being used.[10] Bronchioles with a quarter or more of their perimeter bordered by non-parenchymal structures were excluded.

A microscopic point counting technique was used in six sections of each lobectomy specimen and in four sections of both upper and lower lobes of the pneumectomy specimens to obtain the percentage of airspaces that were destroyed—that is, the destructive index or DI.[19] This was done using a $\times 10$ objective and a $\times 8$ eyepiece containing a counting grid. Each airspace, coinciding with a crossing point of the grid, was assessed, and defined as being destroyed when it met one of the following criteria: (1) Two or more breaks in the alveolar wall; (2) two or more parenchymal rags in the lumen of alveolar ducts; (3) clearly abnormal morphology; (4) classic emphysematous change.[19] About 500 points were evaluated in each tissue section.

The mean linear intercept (Lm) was measured in tissue sections according to the method of Dunnill.[20] Dimensions were corrected for tissue shrinkage after fixation;[21] the linear shrinkage factor was found to be 0·81. All measurements were performed by the same observer. Intraobserver agreement, expressed as the correlation between two readings of tissue sections, ranged from 0·78 to 0·99 for bronchiolar measurements and from 0·62 to 0·88 for parenchymal measurements.

STATISTICAL ANALYSIS

Data on bronchioles and parenchyma in all the tissue sections were averaged. The mean data for each subject were computed from the average tissue section data. The association between two variables was evaluated by use of the Spearman rank correlation coefficient (r_s).

Differences between upper and lower lobes regarding bronchiolar and parenchymal variables were evaluated by a two sample t test. Data from the lower lobes from the six pneumonectomy cases were added to those from the eight lower lobectomy cases. These 14 lower lobes were compared with the specimens from the 12 upper lobectomy cases.

Multiple regression analyses on the basis of all 27 cases were performed to assess whether correlations between bronchiolar and parenchymal variables would still be significant when age and smoking history were included in the calculations.

Results

The age of the subjects, the resected areas, and the morphometric data are presented in table 1.

The correlations between bronchiolar and parenchymal variables of the 27 lung specimens are shown in table 2. There was a significant negative correlation between total and normal AA/mm and the SAD scores of membranous bronchioles, and between normal AA/mm and wall thickness (see figs 1 and 2). The destructive index was positively correlated with goblet cell metaplasia and wall thickness of membranous bronchioles and with SAD score, goblet cell metaplasia, and fibrosis of respiratory bronchioles. There was no significant correlation of Lm with any of the bronchiolar variables.

Data on the upper and lower lobes are compared in table 3. Total and normal AA/mm values were significantly lower in the upper

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Table 1 Age of the subjects and morphological characteristics of the 27 lung specimens

Subject No	Age (y)	Pack years	Resected area	Membranous bronchioles: SAD score (%)	Membranous bronchioles: Wall thickness (mm)	Respiratory bronchioles: SAD score (%)	Parenchymal variables: DI (%)	Lm (mm)	Total AA/mm	Normal AA/mm
NON-SMOKERS										
1	63	0	LLU*	30·16	0·08	25·79	17	0·310	7·01	5·09
2	59	0	LUL	26·97	0·06	24·31	8	0·252	7·50	7·10
3	68	0	LUL	27·78	0·06	17·92	20	0·351	7·09	6·50
4	15	0	LLL	13·11	0·05	9·59	3	0·246	7·93	7·63
5	69	0	RLL	21·47	0·05	16·60	23	0·383	8·09	7·66
6	49	0	RLL	26·39	0·08	21·63	14	0·339	7·37	7·11
7	59	0	LLL	22·83	0·07	16·12	32	0·389	8·41	7·75
8	22	0	RLL	13·56	0·05	9·17	2	0·214	9·17	8·83
Mean	50·5			22·78	0·06	17·64	15	0·311	7·82	7·21
SD	(20·8)			(6·44)	(0·01)	(6·17)	(10)	(0·66)	(0·73)	(1·09)
SMOKERS AND EX-SMOKERS										
9	66	59	RUL	27·00	0·11	26·15	43	0·343	7·88	5·15
10	43	27	LLL	20·08	0·06	18·78	9	0·252	8·88	8·33
11	65	45	LLU	21·74	0·05	22·53	27	0·390	8·11	7·70
12	61	32	RUL	33·51	0·09	34·01	46	0·450	6·81	6·34
13	32	24	RUL	19·77	0·07	20·40	26	0·355	7·15	5·95
14	59	24	RUL	21·30	0·08	29·68	26	0·391	8·38	8·05
15	47	78	LUL	20·03	0·08	27·79	15	0·388	8·52	8·29
16	66	16	RLU	23·67	0·06	27·36	40	—	8·06	7·96
17	64	95	RUL	26·56	0·07	30·99	30	0·309	7·47	6·78
18	58	55	LUL	29·22	0·08	34·79	43	0·308	7·35	6·86
19	56	34	RUL	20·44	0·08	25·38	48	0·354	6·80	5·79
20	63	36	LLL	22·21	0·06	19·50	35	0·306	7·93	6·63
21	52	24	LUL	34·01	0·13	36·67	34	0·299	4·82	4·49
22	65	†	LLU	17·12	0·07	20·83	41	0·323	8·37	7·89
23	70	†	RLU	23·97	0·07	27·77	48	0·348	6·45	5·71
24	67	13	RLU	21·11	0·07	25·04	49	0·380	7·61	7·01
25	60	63	RLL	29·78	0·07	40·89	45	0·352	7·99	7·36
26	67	52	RLU	26·85	0·07	30·17	26	0·292	6·98	6·45
27	62	9	RUL	15·89	0·05	13·72	19	0·335	6·94	6·45
Mean	59·1			23·91	0·07	26·97	34·2	0·343	7·50	6·80
SD	(9·6)			(5·13)	(0·02)	(6·83)	(11·7)	(0·045)	(0·91)	(1·06)

*Only two segments available for morphometric studies.
†Pack years cannot be calculated accurately because of changing smoking habit with use of cigars and pipe.
LLU, LUL, LLL—left lung, upper lobe, lower lobe; RLU, RUL, RLL—right lung, upper lobe, lower lobe; SAD score—pathological score for small airways disease; DI—destructive index; Lm—mean linear intercept; AA/mm—number of alveolar attachments/mm of circumference of membranous bronchioles.

lobes and there was a tendency to higher SAD scores in membranous and respiratory bronchioles in the upper lobes. There were no significant differences between upper and lower lobes with regard to DI and Lm.

Table 4 shows the results of multiple regression analyses, parenchymal data being dependent variables and bronchiolar data, age, and cigarette pack years being independent variables. Total AA/mm was correlated inversely with the SAD score for membranous and respiratory bronchioles and with wall thickness of membranous bronchioles, but not with age or pack years of smoking. The destructive index correlated with SAD score of respiratory bronchioles, wall thickness of membranous bronchioles and age, but not with SAD score of membranous bronchioles or with pack years of smoking. Mean linear intercept (Lm) correlated only with age.

Discussion

This study addressed the question of whether the presence and severity of small airways disease and parenchymal destruction are related, using several types of measurement. A close association between both disease processes would suggest a causal relation. Our data have shown significant inverse relations between the SAD score for membranous bronchioles and total and normal AA/mm, indicating a positive relation between small airways disease and destruction, or loss, of alveolar attachments. Wall thickness, which will reflect small airway inflammation, was also inversely correlated with AA/mm. In addition, the SAD score of respiratory bronchioles and wall thickness show significant positive correlations with the destructive index. Thus the lung specimens with small airways worst affected by pathological features showed the greatest parenchymal destruction.

If small airways disease and alveolar wall destruction are causally related, the two pathological conditions would be expected to share the same topographic distribution within the lung. In the present study this was investigated

Table 2 Spearman rank correlation coefficients with p values for correlation between bronchiolar and parenchymal variables

	Total AA/mm		Normal AA/mm		DI		Lm	
	r_s	p	r_s	p	r_s	p	r_s	p
Membranous bronchioles								
SAD score	−0·48	0·01	−0·51	0·01	0·33	0·09	0·06	0·78
Goblet cell metaplasia	−0·34	0·08	−0·36	0·06	0·48	0·01	0·08	0·08
Fibrosis	−0·21	0·28	−0·29	0·14	0·36	0·07	0·19	0·34
Wall thickness	−0·37	0·06	−0·45	0·02	0·50	0·01	0·23	0·25
Respiratory bronchioles								
SAD score	−0·35	0·07	−0·32	0·10	0·53	0·004	0·18	0·39
Goblet cell metaplasia	−0·12	0·55	−0·16	0·42	0·49	0·01	0·27	0·18
Fibrosis	−0·31	0·12	−0·28	0·16	0·69	<0·001	0·26	0·19

For abbreviations see table 1.

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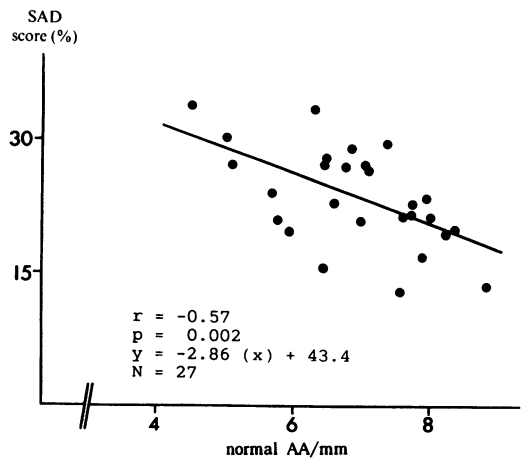

Figure 1 Number of normal alveolar attachments on membranous bronchioles/mm of circumference (normal AA/mm) plotted against the degree of small airways disease (SAD score) of membranous bronchioles. The Pearson correlation coefficient and the regression line are shown.

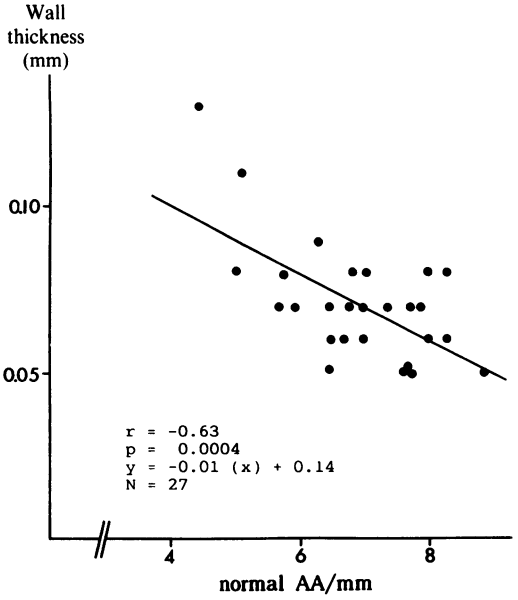

Figure 2 Number of normal alveolar attachments on membranous bronchioles/mm of circumference (normal AA/mm) plotted against wall thickness of membranous bronchioles. The Pearson correlation coefficient and the regression line are shown.

by comparing the data of the upper and lower lobes. There were significantly fewer alveolar attachments as well as a tendency to a greater degree of small airways disease in the upper lobe than in the lower lobe. This suggests that the same regions of the lung are vulnerable to small airway inflammation and disruption of peribronchiolar alveolar walls. To some extent this supports a causal association.

Age and cigarette smoking may affect these relationships, as both are linked with small airway and parenchymal disease.[3 6] When smoking pack years and age were included as independent variables in a multiple regression analysis the SAD score of membranous and respiratory bronchioles and wall thickness were still correlated inversely with total AA/mm (table 4). Thus the association between small airway inflammation and peribronchiolar destruction of parenchyma is most probably not just an epiphenomenon as the two main factors in this respect, age and smoking, did not confound the association. In our view this provides even stronger support for a causal association between small airways disease and centrilobular emphysema.

As smoking is an important aetiological agent in the pathogenesis of small airways disease and emphysema, it is remarkable that lung tissue from non-smokers had SAD scores and destructive indices of up to 30%. Two points, however, should be made. Firstly, the pathological features of inflammation in airways and airspaces, as assessed by our morphometric techniques, are not specific for sequelae of cigarette smoking and may be induced by any noxious airborne irritation, such as industrial and traffic pollutants, allergens, respiratory infections, and—last but probably not least—passive smoking. Secondly, the morphometric techniques we used are not specific or diagnostic: they are a tool to quantify a pathological process in a way that is as unbiased and objective as possible for comparative and statistical purposes. Certainly these techniques have their limitations, and will measure abnormality in lung tissue that appears healthy to the experienced pathologist.

So far, three studies have compared the severity of small airways disease in the upper and lower lobes, obtaining three different results.[3 13 14] Perhaps there is indeed a topographical association between small airways disease and emphysema but in lungs with severe emphysema this association is disturbed: the most diseased bronchioles in the most emphysematous areas may have become fibrotic without other pathological features and may therefore have a low pathological score. Alternatively, these bronchioles may have disappeared in the emphysematous lesion. The resected lung specimens in our study came from individuals who were able to undergo thoracic surgery, and they are likely therefore to have had relatively mild disease. Loss of alveolar attachments may represent an early stage of emphysema, and accordingly we may have been able to find more destruction of these structures as well as a tendency to more severe small airways disease in the upper lobe, while upper and lower lobes were still similar in regard to the destructive index and linear intercept. Differences in the range of disease severity between the relatively small groups of patients in the different studies may at least partly explain the differences in the results.

Table 3 Data for the upper and lower lobes: mean (SD) values with p values for the two sample t test

	Upper lobes (n = 12)	*Lower lobes (n = 14)*	*p*
Membranous bronchioles			
SAD score (%)	25·2 (5·7)	22·1 (5·5)	0·18
Wall thickness (mm)	0·079 (0·002)	0·065 (0·010)	0·06
Respiratory bronchioles			
SAD score (%)	26·8 (7·0)	21·2 (8·1)	0·07
Parenchyma			
DI (%)	29·7 (0·051)	28·6 (16·5)	0·85
Lm (mm)	0·347 (0·051)	0·323 (0·059)	0·32
Total AA/min	7·25 (0·95)	8·11 (0·74)	0·02
Normal AA/min	6·41 (1·12)	7·57 (0·86)	0·008

For abbreviations see table 1.

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*Table 4 Parameter estimates (B) and p values for multiple regression analyses**

	Independent variables					
	Bronchiolar index		*Age*		*Pack years*	
Dependent variable	B_1	*p*	B_2	*p*	B_3	*p*
	SAD score of membranous bronchioles					
DI	0·18	0·38	0·42	0·05	0·27	0·13
Lm	−0·06	0·18	0·53	0·03	0·06	0·78
Total AA/mm	−0·68	0·004	0·11	0·59	0·16	0·39
	SAD score of respiratory bronchioles					
DI	0·44	0·05	0·36	0·05	0·06	0·77
Lm	0·12	0·64	0·46	0·04	−0·02	0·94
Total AA/mm	−0·68	0·02	−0·02	0·94	0·43	0·08
	Wall thickness					
DI	0·39	0·02	0·47	0·006	0·17	0·31
Lm	0·08	0·72	0·49	0·02	0·03	0·90
Total AA/mm	−0·68	0·0008	−0·17	0·31	0·29	0·12

*In each analysis a parenchymal index is the dependent variable, and one bronchiolar index, age, and pack years (PY) are the independent variables, according to the formula:
Parenchymal index = B_1 × (bronchiolar index) + B_2 × (age) + B_3 × (PY) + constant.
For abbreviations see table 1.

Two previous studies analysed the relation between the number of alveolar attachments and the degree of small airways disease. Saetta *et al*[10] reported significant correlations between small airways disease of membranous bronchioles and three indices of loss of alveolar attachments. This is confirmed by our results. Petty *et al*[11] found a significant inverse correlation between the mean number of attachments and the small airway fibrosis score only. They determined the mean number of attachments per cross sectioned bronchiole, through which bias may be introduced by bronchiolar dimension, larger bronchioles having a greater number of alveolar attachments. This may explain why the association between small airways disease and number of alveolar attachments in their study was not strong.

We have shown that features of small airways disease in membranous and respiratory bronchioles are related to loss of alveolar attachments; the association with destructive index was weaker and with linear intercept there was no association. These findings are in line with those of a study of Cosio and coworkers[22] in smokers' lungs using scanning electron microscopy. These investigators found the greatest destructive changes of alveoli to be present in areas close to terminal airways. Perhaps loss of alveolar attachments may be regarded as reflecting the greater tendency to peribronchiolar wall disruption in centrilobular emphysema, and the destructive index and linear intercept as measuring the more diffuse disease pattern of panlobular emphysema or severe centrilobular emphysema. This is consistent with our observation that total and normal AA/mm values were reduced to a greater extent in the upper lobe, corresponding to the topographic distribution of centrilobular emphysema,[23] whereas we found no differences between upper and lower lobes in terms of destructive index and linear intercept.

Features of small airways disease have been shown to start earlier in life than emphysema.[18] The first centrilobular emphysematous lesions have been reported to develop around areas of intense bronchiolar inflammation with peribronchiolar macrophage accumulation.[2 18 24] All these observations support the view that small airways disease is directly and causally concerned in the development of centrilobular emphysema. According to this view, bronchiolar inflammation leads to destruction of the surrounding alveoli. Several mechanisms may be implicated. As proposed earlier by Saetta *et al*,[10] byproducts of the inflammatory interactions in bronchioles possibly weaken surrounding alveolar walls and make them vulnerable to destruction. Rupture would then take place at the site where mechanical stress is probably the strongest, at the junction of the alveolar wall with the bronchiolar wall.[25] Alternatively or additionally, the elastase-antielastase balance is disturbed by elastase released by inflammatory cells in the bronchiolar wall or by the macrophages, accumulating in adjacent alveoli, and the elastase then attacks elastic fibres in peribronchiolar alveoli directly. Elastase has been found on elastic fibres of the lung parenchyma, especially in emphysema,[26] though a more recent study has not been able to confirm this localisation of elastase.[27] Of interest are some recent studies in which we found that the elastase inhibitor antileucoprotease was localised in association with elastic fibres in the walls of airways and alveoli.[28 29] Features of small airways disease and loss of alveolar attachments were associated with an increased amount of antileucoprotease in distal airways.[30] Perhaps antileucoprotease is produced in increased amounts in response to both small airway inflammation and peribronchiolar parenchymal destruction, and these two conditions are causally related features of the same process.

In conclusion, in 27 surgically removed lungs and lobes we have shown a relation between loss of alveolar attachments and inflammatory changes in membranous and respiratory bronchioles that is not dependent on age or smoking habit. In our view these findings suggest that small airways disease is directly concerned in the causation of centrilobular emphysema.

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