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Regional Impairment of Mucociliary Clearance in Chronic Obstructive Pulmonary Disease*

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Asthmatic subjects with tidal expiratory flow limitation have mucociliary clearance (MC) impairment in central airways. Because tidal flow limitation develops in COPD, it is possible that regional MC in these patients also may be affected. We tested this hypothesis by measuring MC in the presence or absence of flow limitations. Patients with COPD and chronic flow limitation were compared with non-flow-limited normal volunteers. Deposition was normalized for regional lung volume and expressed as the specific central to peripheral (sC/P) ratio. In COPD subjects, clearance from the whole lung and central airways was significantly different from that of normal subjects after 20 min of observation. In the peripheral airways, there were no significant differences between COPD and normal subjects. An alternative analysis of regional MC indicated patients retained particles in central airways while normal subjects, with intact MC, emptied central airways. Thus, COPD subjects with tidal expiratory flow limitation have impaired MC in their central airways.

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C/P ratio = central and peripheral lung count ratio; FLS = flow-limiting segments; MC = mucociliary clearance; sC/P ratio = specific C/P ratio

In asthma, some patients have markedly impaired mucociliary clearance (MC) of inhaled radioactively labeled particles from their central airways.[1,2] Most of these patients have evidence of tidal expiratory flow limitation. In contrast, asthmatic subjects without evidence of tidal flow limitation do not appear to have regional clearance abnormalities and some may have faster than normal rates of MC. The regional nature of the MC impairment in subjects with flow limitation suggests that local mechanical factors may be contributing to the MC abnormality. The presence of tidal flow limitation may be such a factor. Animal and human data suggest that the induction of flow limitation can cause similar changes in MC.[3,4] If flow limitation is contributing to regional MC changes in asthmatic subjects with flow limitation, we would expect a similar pattern of MC abnormality in subjects who have tidal flow limitation but do not have asthma. While such a demonstration would not constitute proof of a cause-and-effect relationship between flow limitation and regional impairment of MC, it would be a basis for further study.

Tidal expiratory flow limitation means that during tidal breathing, flow-limiting segments (FLS) form at discrete points in the airways, so that incremental increases in pleural pressure are no longer associated with increases in expiratory flow. The FLS are not fixed anatomical strictures. The FLS formation is a functional, transient but repetitive process involving 1- to 2-cm sections of the lobar and segmental bronchi.[5] The presence of tidal flow limitation can be discerned by observing the relationship between the tidal flow-volume loop and the maximal expiratory flow-volume (MEFV) curve.[6,7] If a subject's expiratory tidal loop is noted to overlap the MEFV curve and if the expiratory part of the tidal loop is similar in shape to the forced loop, it can be concluded that during quiet breathing, FLS are forming in the airways. In normal subjects, FLS form during coughing and during performance of a MEFV maneuver. The tidal loop in normal subjects will not overlap the MEFV curve and will have a different configuration.

We therefore decided to study MC in subjects with COPD whose flow volume curves indicated that they form expiratory FLS during tidal respiration.[6,7] We chose COPD subjects because, by definition,[8] their degree of airway obstruction does not vary significantly over time, and hence, they tend to have constant rather than intermittent FLS formation. For comparison, we chose to use nonsmoking normal volunteers in preference to subjects with non-flow-limited chronic bronchitis because the latter groups can have intermittent flow limitation from coughing, and their data could be difficult to interpret.

In order to compare MC studies between two groups of subjects, the deposition patterns of the radioactively labeled aerosol should be similar. To accomplish this in two groups with different airway caliber, it is often necessary for both groups to use different breathing patterns or different size particles. The type of radio-

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actively labeled aerosol and the breathing pattern during deposition have been recently shown to potentially influence MC.[9,10] Therefore, the use of two types of aerosol and two different breathing patterns within both groups of subjects enables us to demonstrate that any potential relationship, between flow limitation and regional MC, was independent of these two factors.

Methods

Selection of Subjects

We selected nine patients who satisfied the American Thoracic Society definition of COPD[8] and who had evidence of expiratory flow volume limitation on tidal respiration.[6] In addition, ten volunteers with no history of lung disease and normal flow volume curves were recruited by advertisement. The presence of chronic flow-limitation can be assessed by observing the relationship between the tidal flow-volume loop and the MEFV curve. The individual flow volume curves of all subjects are shown in Figure 1. The tidal loops of the COPD subjects overlap their MEFV curves. In addition, the expiratory portions of their tidal loops are similar in shape to their MEFV curves. The subjects and their pulmonary function tests are listed in Table 1. Normal subjects were adults with no history of smoking or lung disease and without evidence of tidal flow limitation on their flow-volume loops.

Aerosol Deposition

The subject sat with his or her back to a gamma camera (Picker Dynacamera, Northford, Conn, low energy parallel hole collimator) initially peaked for xenon 133. The camera was interfaced with a computer (Data General Nova 3, Anaheim, Cal) which controlled data acquisition and processing. While quietly breathing at functional residual capacity (FRC), an equilibrium xenon scan was obtained to position the subject's lungs over the camera and determine regional lung volumes. Then the camera was adjusted for technetium 99m, and the subject inhaled radioactive monodisperse aerosol. In the normal subjects, central deposition was obtained using inspiratory impaction. That is, relatively large particles were inhaled rapidly with impaction in central airways. In the patient group, central deposition was attained in two ways: first, using inspiratory impaction in the same manner as the normal subjects, and second, using the FLS itself to deposit particles during the expiratory phase of quiet tidal breathing.[11,12] Further, two aerosols were used, iron oxide and condensed sebacate vapor. This variation in deposition techniques and the use of different aerosols tested the independence of our results in patients, from breathing pattern, and in all subjects, from labeling technique.

The iron oxide aerosol, labeled with technetium 99m, was generated by spinning disk.[13] The mass median aerodynamic diameter was 5.3 μm with a geometric SD of 1.1. The subject inhaled aerosol via a mouthpiece, with a nose clip in place, from FRC using tidal breaths of approximately 1 L and an inspiratory flow of 1 to 2 L/s. Breathing pattern was recorded using a hot wire anemometer (Thermo-Systems, St. Paul, Minn) to measure flow and tidal volume (integrated flow). Using this technique, deposition in central airways was attained in both normal and flow-limited subjects.

The sebacate aerosol (mass median aerodynamic diameter, 2.5 μm; geometric SD, 1.1) was generated by condensation of bis-(2-ethyl-hexyl) sebacate vapor on nuclei of technetium-99m-labeled human serum albumin.[14] These particles were inhaled at 3 L/s from FRC in all normal subjects. In the FL patients who inhaled sebacate, central deposition occurred during quiet tidal breathing. The presence of FLS during tidal ventilation resulted in deposition of the 2.5 μm aerosol in the same airways as in the normal subjects breathing the same aerosol with rapid inhalation.[11,12] Flow and tidal volume (integrated flow) were monitored with a Fleisch No. 1 pneumotachograph.

Deposition was continuously monitored with the gamma camera, and when counts were sufficient (approximately 5,000 counts/min), the inhalation was stopped (total time of deposition, approximately 5 to 10 min). The subject washed his oropharynx and esophagus by drinking a glass of water; next, whole lung clearance was obtained by measuring serial lung scans at 1-min intervals and storing the images in the computer. Serial images were obtained for 2 h.

Analysis

With the computer, regions of interest were drawn over the xenon equilibrium scan; these represented a region over the entirety of both lungs called the whole lung zone and another region centered over the large central airways comprising 30 percent of the lung area which we called the central zone. The area remaining after the central zone was deducted from the whole lung zone was called the peripheral zone.

Using the xenon regions of interest, the ratio between the central and peripheral lung counts (C/P) was calculated in a manner which was normalized for differences in relative lung thickness by dividing

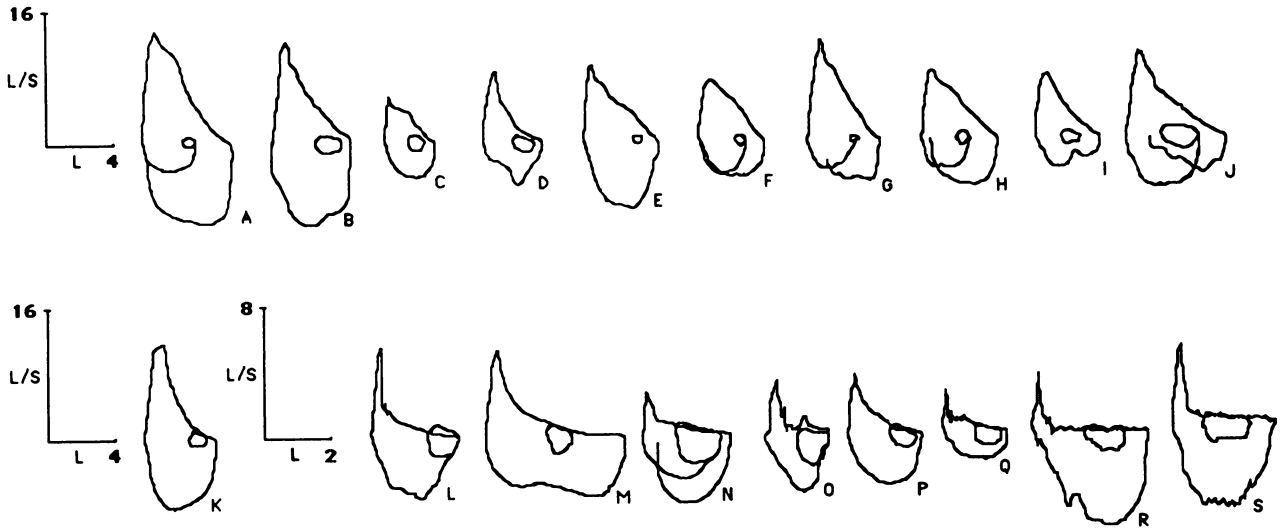

Figure 1. Maximal flow volume curves and tidal loops for all subjects.

the C/P ratio technetium 99m counts of the initial aerosol scan by the C/P ratio xenon 133 counts. This ratio defined the specific C/P ratio (sC/P).[1] Using the resulting sC/P values, a ratio of 1.0 reflects particle deposition in a pattern similar to the xenon ventilation scan. Because the central region outlines both central airways and the lung parenchyma surrounding them, an sC/P ratio of unity reflects predominantly alveolar deposition. Increasing sC/P ratios greater than unity reflect increasing deposition in the proximal airways. The determination of the sC/P ratio allowed quantification of the initial deposition patterns and comparison between patients.

Classic lung retention curves were generated by computer using regions of interest similar in size to the actual central and peripheral lung outlines described previously and relating the counts on the serial images (corrected for decay) to time. We previously have demonstrated that these regions of interest can be used to detect regional MC abnormalities.[1,2] The regions are based on measurements of lung volume from xenon 133 equilibrium images. In addition to classic lung retention curves, serial sC/P ratios also were employed to assess regional changes in MC.[1,2] Our definition of central and peripheral airways is not synonymous with the frequently cited definition by Hogg et al[15] who used a diameter of 2 to 3 mm, measured by retrograde catheter, to demarcate central from peripheral airways.

Statistical group comparisons of clearance curves were made using 95 percent confidence intervals (*ie*, ±1.96 SEM)[16] and unpaired *t* tests. Paired *t* tests were used to compare the sC/P ratios at the beginning and end of the study. Unpaired *t* tests were used to compare spirometry, age, and initial deposition patterns between groups.

Results

Clinical and spirometric data for all subjects are shown in Table 1. The subjects are classified as normal or those with COPD as discussed before. Further, they are subdivided into iron oxide and sebacate deposition groups. There were ten normal subjects (four with iron oxide and six with sebacate deposition). There were nine COPD subjects (four with iron oxide and five with sebacate deposition). The normal group was younger than the COPD group (mean age ± SD = 35 ± 16 years and 56 ± 9 years, respectively; $p<0.002$). However, the normal and COPD iron oxide subgroups were of similar age (mean of 50 and 57 years, respectively). The mean FEV_1 (percent forced vital capacity) of the COPD patients was lower than normal (mean ± SD, 48 ± 18 and 81 ± 6, respectively;

Table 1—*Pulmonary Function and Regional Deposition for Normal Subjects Without Flow Limitation and COPD Patients With Flow-Limitation*

Subject	Age, yr	Vital Capacity (% Predicted)	FEV_1 (% Forced Vital Capacity)	FRC (% Predicted)	Regional Aerosol Deposition sC/P Ratio
Normal, iron oxide deposition					
A*	34	5.13 (107)	4.70 (85)	3.56 (95)	2.67
B†	43	5.18 (107)	3.85 (78)	2.41 (60)	2.47
C	59	3.01 (105)	2.35 (76)	. . .	4.50
D	65	3.81 (117)	2.75 (74)	3.24 (100)	2.51
Normal, sebacate deposition					
E	23	4.41 (99)	3.82 (87)	2.71 (78)	2.21
F*	21	3.98 (123)	3.46 (87)	1.90 (84)	2.08
F*					2.52
G	29	4.35 (93)	3.85 (87)	2.78 (87)	2.70
A*		. . .	. . .	. . .	2.10
H	26	4.64 (110)	3.82 (82)	3.45 (104)	1.95
I	24	3.94 (99)	3.11 (79)	. . .	1.94
J	24	6.04 (118)	4.20 (70)	3.21 (94)	2.17
All normal subjects					
Mean	35	108	81	88	2.49
±SD	16	9	6	14	0.69
COPD, iron oxide deposition					
K†	40	4.75 (109)	3.41 (74)	2.76 (79)	2.22
L	55	4.17 (95)	2.55 (63)	3.72 (93)	2.91
M	65	4.64 (123)	1.95 (45)	4.55 (122)	2.67
N	68	3.16 (83)	1.08 (41)	3.62 (97)	5.47
COPD, sebacate deposition					
O	63	2.30 (61)	0.69 (63)	5.07 (146)	1.87
P	57	2.33 (75)	1.13 (57)	3.25 (109)	2.64
Q	54	3.58 (82)	1.23 (34)	6.18 (165)	2.24
R	47	3.91 (78)	0.60 (31)	7.56 (178)	2.10
S	61	3.41 (70)	0.69 (21)	. . .	3.03
All COPD patients					
Mean	56	73	41	150	2.79
±SD	6	8	18	30	0.46
p value (normal vs COPD)	0.002	0.007	<0.001	0.02	NS

*Subjects were studied twice.
†Subjects were obese.

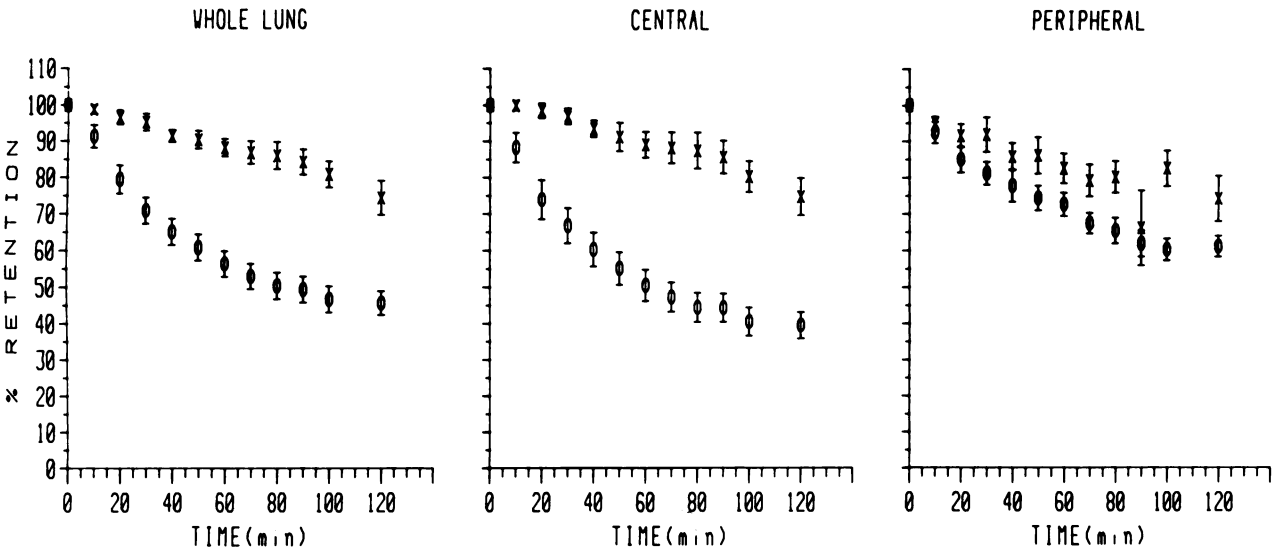

FIGURE 2. Average pulmonary retention curves of inhaled radioisotope for chronically flow-limited COPD patients (X) and normal, non flow-limited subjects (O). Each set of curves represents regions of interest placed over the whole lung, central, and peripheral airways. The error bars represent standard errors of the mean.

$p<0.0001$). The mean vital capacity of the COPD group was significantly lower ($p=0.006$) and the FRC of the COPD group was increased ($p=0.035$).

The patterns of aerosol deposition of all subjects are also listed in Table 1, expressed as the sC/P ratio. Initial patterns were matched between the normal and COPD groups (mean ± SD 2.49 ± 0.69 vs 2.38 ± 1.07, respectively, p = NS).

The average retention curves for the whole lung, central region, and peripheral region of both groups are shown in Figure 2. Decay-corrected activity retained in the lung as a percentage of the initial lung deposition is plotted on the ordinate with time in minutes on the abscissa. For the whole lung and central regions, mean retention of activity in the COPD patients was significantly higher over 2 h than in the normal subjects as assessed by separation of 95 percent confidence intervals (±1.96 SEM).[16] In addition, using unpaired *t* tests, whole lung and central regional percent retention in the COPD patients were significantly greater than in the normal subjects from 20 min ($p \leq 0.01$). While mean percent retention for the COPD patients in the peripheral region was also higher, there was overlap of individual percent retention values and the confidence intervals between the two groups, indicating that peripheral differences were not significant. Similarly, using unpaired tests, differences in percent retention in the lung periphery were not significant over the first 60 min and then only at 70 and 100 min.

In Figure 3, serial sC/P ratios (the ratio of actual counts normalized for regional volume in the central and peripheral regions) are plotted against time. In the normal subjects, the sC/P ratio decreases from the start of the study. After 60 min, the mean sC/P ratio for the normal subjects fell from the initial value of 2.49 ± 0.20 SE to the significantly lower ratio of 2.00 ± 0.18 ($p=0.03$; paired *t* test) and continued to fall to 1.64 ± 0.20 at 120 min after deposition. In contrast, the COPD patients did not experience a change in sC/P ratios with time. After 120 min, their mean sC/P ratio was 2.86 ± 0.65, no different than the initial value of 2.79 ± 0.36. In some patients, the sC/P ratio actually increased at 60 min, but the mean increase in sC/P above their initial value seen in the COPD patients at 60 min was not significant for the group (using 95 percent confidence intervals).

The effects of breathing pattern and particle type are shown in Figure 4. For a characteristic time (100

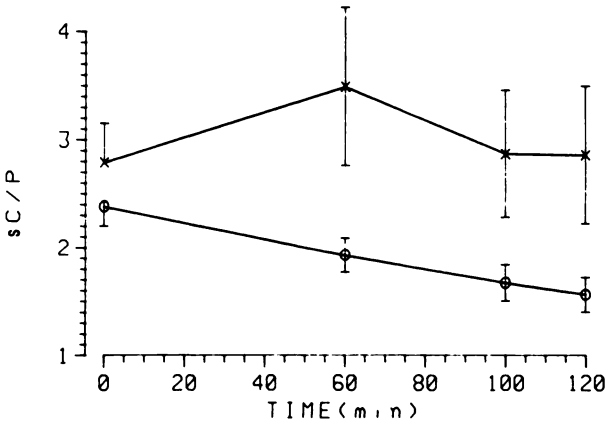

FIGURE 3. Average sC/P ratios plotted against time for the flow-limited COPD patients (X) and the non-flow-limited normal subjects (O). The error bars represent standard errors. In the normal subjects, relatively more activity clears from central airways and the sC/P ratio decreases. In the patients, sC/P ratios do not change significantly with time.

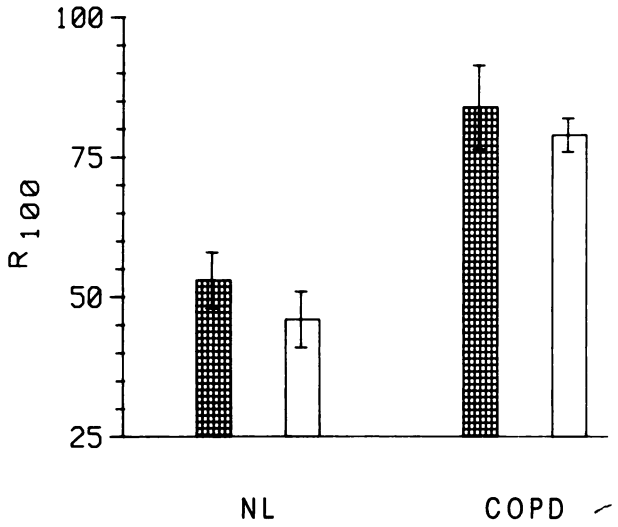

FIGURE 4. Lung retention as a percentage of the initial deposition at 100 min (R100) illustrated for the normal subjects and the patients separated by type of aerosol. The error bars are standard errors. The iron oxide and normal sebacate depositions were performed by rapid inhalation. The COPD sebacate depositions were performed during tidal breathing. Differences were not significant.

min), the percent retention is shown for the COPD and normal individuals separated by aerosol type (iron oxide and sebacate). The difference in retention between normal and COPD subjects is significant irrespective of the choice of aerosol, assessed by unpaired tests and by separation of 95 percent confidence intervals of the normal and COPD subjects.

Discussion

This study demonstrates that patients with COPD and chronic flow limitation on tidal breathing have delayed MC that disproportionately affects airways in the central region of the lung. Evidence for the regional impairment is provided by serial sC/P analysis and by classic retention curves. Since MC is thought to be faster in central airways than in peripheral airways in normal subjects,[17,18] the sC/P ratio would be expected to decrease as inhaled particles are cleared from the central airways. Such is the pattern seen in our normal subjects (Fig 3). Similar patterns of serial sC/P ratio changes have been demonstrated in normal subjects and patients with asthma who do not have tidal flow limitations.[1,2] For the sC/P ratio to remain unchanged or to increase with time indicates that particles are moving into the central airways from the periphery at equal or faster rates than the central airways are clearing material into the trachea. In this study, we have shown that subjects who have tidal flow limitation develop a pattern of aerosol retention in the lung that is the opposite of the normal situation; central airways, which normally clear the most rapidly, become rate-limiting. In the COPD patients, failure of serial sC/P ratios to decrease, while peripheral clearance was occurring at a near normal rate, is strongly suggestive that distal airways have equal MC to central airways in this group. In a few subjects, the sC/P ratio increased, indicating the peripheral rates actually exceeded central clearance. In parallel to this analysis, the classic retention curves (Fig 2) support the presence of regional abnormalities as demonstrated by the wide differences between the central regional retention curves of the COPD and normal groups in contrast to the peripheral retention curves, where the differences are less obvious.

Asthmatic subjects with tidal flow limitation also demonstrate regional impairment of MC in their central airways.[1,2] The regional nature of the impairment and the demonstration of such in two distinct patient populations (COPD and asthmatic subjects), suggest that the MC abnormality may be mediated partly by local factors, such as turbulence at sites of flow limitation. The FLS formation in humans is believed to occur predominantly in the central airways. It has been demonstrated, using mobile catheters, that FLS formation occurs in lobar and segmental bronchi in human subjects at FRC.[5,19,20] In patients with airway obstruction, the site of FLS formation may move distal to the segmental bronchi[19,20] at lung volumes below FRC, but this should not occur in the subjects in this study who breathed tidally. Further evidence for the occurrence of FLS formation in central airways comes from radioactively labeled aerosol deposition studies. Patients with emphysema with well preserved inspiratory flow rates but expiratory flow limitation exhibited similar aerosol deposition patterns to normal subjects who inhaled particles tidally but exhaled using a FLS-generating maneuver.[11,12]

The suggestion that FLS are involved in slowing MC is supported by animal and human data. Smaldone et al[3] induced FLS formation in the dog trachea *in vivo* by repetitive coughing and demonstrated residual, post-cough changes in the clearance pattern at the site of FLS. In those experiments, the movement of saline droplets was markedly reduced near the location of FLS, while clearance, "upstream" and "downstream," in the trachea was preserved. Similar observations were made by Foster et al[4] in three human subjects, but confirmation by a larger study is needed.

While previous studies have shown reduced whole lung clearance in COPD,[21,22] this is the first study to demonstrate, using regional analysis, that MC is disproportionately reduced in the central airways. In COPD, which diffusely affects lung parenchyma and airways, there is no reason to suspect *a priori* that the major clearance defect would be in central airways, although the preponderance of lung cancers in the central airways have led to speculation that clearance of carcinogens may be abnormal in this region.[17]

Attempts to relate FLS formation to regional MC abnormalities in COPD patients are facilitated by the stability of their spirometric parameters. By contrast, subjects with simple chronic bronchitis may be flow-limited intermittently due to coughing. Hence, we elected to compare our COPD flow-limited subjects with normal control subjects rather than patients with non-flow-limited obstructive airways disease.

A potential disadvantage of using COPD subjects to study tidal flow limitation is that they tend to have significant smoking histories, and smoking is another potential cause of MC impairment. However, review of the literature indicates that there is uncertainty as to whether the abnormalities of MC in COPD described by previous investigators are due to smoking or to other factors. Acute exposure to cigarette smoke reduces ciliary activity *in vitro*,[17] but *in vivo* studies have been contradictory including different studies suggesting that smoking increased, had no effect, or decreased MC.[17] The long-term effects also are unclear. A study by Lourenço et al[23] in smokers with normal spirometry suggests that relative to normal volunteers MC in central airways of smokers appears to be impaired. In contrast, Foster et al[24] suggest that in young smokers central airways clearance is normal, but peripheral airways have impaired MC. Goodman et al[25] found decreased mucous velocities in the trachea of smokers while Yeates et al[26] found no differences in tracheal mucous velocities in smokers and nonsmokers. The inconsistencies just outlined in the studies obtained on smokers with normal spirometry may be due to the effect of smoker's cough which was not quantified and which may have impaired MC in the central airways of some of the subjects by FLS formation. This may have been the case, for example, in the study by Lourenço et al.[23] In the present study, all of the COPD subjects had a history of heavy smoking except for subject K who was a nonsmoker but obese. While we cannot exclude that the central airways MC impairment is due to smoking, the literature does not at present indicate that the regional MC dysfunction in this study could be due to a regional toxic effect of cigarette smoke.

Since the COPD patients are older than the normal subjects, the effect of age on MC has to be considered. The effect of age on particle clearance is controversial. In normal subjects, Puchelle et al[27] demonstrated that there is a loose but statistically significant correlation between decreasing MC with increasing age ($r = 0.472$, $p < 0.05$) but regional analysis was not performed and the magnitude of the differences between their group of young volunteers and their elderly subjects was much less than the magnitude of the differences between the normal and COPD subjects in this study. Furthermore, Agnew et al[28] demonstrated no significant differences in regional MC between younger and older asthmatic subjects. Finally, in our study, the iron oxide groups are of similar age, and yet, Figure 4 demonstrates that the difference in MC between COPD and normal subjects remains obvious, indicating that it is unlikely that age accounts for the regional impairment noted in this study.

Our observations were independent of the type of aerosol and breathing pattern used to label the airways. Bennett et al[10] have suggested that increased inspiratory flow rates can potentially stimulate MC. In our study, the normal subjects had to inhale more rapidly than the COPD subjects in order to achieve matching initial deposition patterns. However, the differences in particle sizes also meant that the normal iron oxide subjects had to inhale less rapidly than the normal sebacate subjects. The fact that the differences in MC rates between the COPD and normal subjects remain obvious when both the iron oxide and sebacate deposition groups are analyzed separately (Fig 4) means that the findings of this study cannot be ascribed to the differences in breathing pattern between the COPD and normal subjects. In addition, the demonstration of similar degrees of MC impairment in the COPD subjects with both aerosols (Fig 4) suggests that the differences between the COPD group and the normal group are not dependent on the use of different aerosols.

This study does not imply that clearance abnormalities in COPD are confined to central airways. We found significant evidence of peripheral impairment at some observation points after 60 min. However, the peripheral changes are small compared with the marked reduction seen centrally where the effects of flow limitation may be superimposed on a generalized decrease in MC due to bronchitis, smoking, age, or other factors.

In conclusion, we have found that abnormalities in MC in COPD with tidal expiratory flow limitation are most marked in the central airways. Similar findings have been noted in asthmatic subjects with flow limitation. While prior animal and human data suggest that regional impairment can be induced by the formation of local FLS, further studies are needed to see if such a causative relationship exists.

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