

Pulmonary Abnormalities in Intermediate Alpha-1-Antitrypsin Deficiency

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ABSTRACT Pulmonary function studies were carried out in a group of asymptomatic nonsmoking adults with intermediate alpha-1-antitrypsin deficiency who were attending an early disease detection unit in Rochester, N. Y. All subjects were identified by specific protease inhibitor (Pi) typing. Fifteen MZ and 14 MS subjects who had never smoked cigarettes were matched by sex and age to MM controls. Spirometry, static lung volumes, and single breath-diffusing capacity were identical in all Pi type groups with no statistically significant differences noted. Maximal expiratory flow volume curves were obtained in all subjects. MZ subjects demonstrated statistically significant impaired maximal flow rates at 75%, 50%, and 25% of vital capacity compared to their MM controls. Total pulmonary resistance by the oscillometric method was measured at 3, 5, 7, and 9 cycle/s in the same subjects. Increased frequency dependence of resistance (defined as the difference between total pulmonary resistance at 3 cycle/s and 9 cycle/s) was observed in MZ subjects compared to MM controls. No differences were noted by this method in MS-MM pairs. The data suggest that detectable mechanical abnormalities are present in subjects with the MZ phenotype, even in the absence of established risk factors such as cigarette smoking and high air pollution.

INTRODUCTION

Laurell and Eriksson first described in 1963 an association between alpha-1-antitrypsin (AAT)¹ deficiency and pulmonary emphysema (1). It is now known that serum AAT is inherited in a multiallelic, autosomal, codominant pattern. So far, 23 codominant protease inhibitor (Pi) alleles that determine the amount of circulating serum AAT have been described (2). Approximately 90% of human subjects have Pi type MM with levels of alpha-1-antitrypsin of approximately 225 mg/100 ml. In contrast, subjects with the rare Pi type ZZ have serum AAT levels in the order of only 25 mg/100 ml. This ZZ state has been unequivocally associated with pulmonary emphysema characterized by onset in early adulthood (3).

The clinical significance of intermediate levels of AAT is currently under intensive investigation. In particular, attention has been focused on individuals with Pi type MZ, who characteristically have only 55–60% of normal AAT-concentration, and Pi type MS, with 80–85% of normal values (4). The MZ heterozygote state has been estimated to occur in about 2–5% and the MS in 6–8% of various normal populations (5). Studies to date have not conclusively established that intermediate deficiency of AAT is an important risk factor in the pathogenesis of chronic obstructive pulmonary disease (COPD). Several factors that may have contributed to varying results have been identified. For example, in many studies, specific Pi typing has not been utilized, and only quantitative determinations of AAT have been used (6–8). It is now known that these simpler tests

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¹Abbreviations used in this paper: AAT, alpha-1-antitrypsin; COPD, chronic obstructive pulmonary disease; Pi, protease inhibitor; R_s, R₉, R_R, total pulmonary resistance by oscillometric technique at 3 and 9 cycle/s and at resonant frequency; V_{max}, maximal expiratory flow rate.

cannot in all cases accurately discriminate Pi types MZ and MS from MM individuals (9). Additionally, the individuals examined in some studies have been relatives of patients with Pi type ZZ, (10), and therefore a familial predisposition to COPD other than AAT deficiency may have introduced an unintentional bias (11, 12). Several studies of patients with COPD have demonstrated a higher proportion of MZ subjects than in the general population (13). However, it has not been possible to quantitate this risk factor independently from other well-recognized factors, especially cigarette smoking.

To circumvent some of these inherent difficulties, some studies have focused on asymptomatic individuals. Utilizing specialized physiologic techniques, these studies suggest that there are detectable abnormalities of pulmonary function, even in healthy MZ subjects (10, 14). However, the samples in these studies have generally included relatives of a ZZ propositus, or have studied predominantly smokers, and therefore may not have adequately

isolated AAT deficiency as the sole or predominant risk factor.

This study compares lung function in subjects with MZ and MS Pi types with the findings observed in MM subjects matched for age, sex, and smoking history. To avoid the criticism directed at earlier studies, all subjects were lifelong nonsmokers. They were randomly selected from a population in which the prevalence of intermediate AAT deficiency had been determined. Pi typing was used to identify the heterozygote, and all subjects were studied with pulmonary function tests designed to detect subtle abnormalities in lung mechanics. The data indicate that in the group of asymptomatic nonsmoking subjects the MZ Pi type, but not the MS, have demonstrable mechanical abnormalities of pulmonary function.

METHODS

Populations. 1,000 consecutive patients attending an early disease detection unit (15) were initially studied. From a venous blood sample two tests were performed:

TABLE I
Mean \pm SE Population Characteristics, AAT Determinations, and Pulmonary Function Studies in MM Controls Compared to the Matched MZ and MS Heterozygote Subjects

Parameters	Groups							
	MZ		MM		MS		MM	
Pi type								
Age, yr	47	(4)	47	(4)	48	(4)	46	(4)
Height, cm	168	(2)	163	(3)	168	(3)	167	(3)
AAT determination, mg/100 ml	125	(5)	205	(19)	178	(7)	195	(12)
Males/females	8/7		8/7		9/5		9/5	
Pulmonary function data								
FEV ₁ , % pred.	110	(3)	107	(3)	105	(3)	107	(3)
FEV ₁ /FVC, %	75	(1)	74	(2)	76	(1)	77	(1)
MMEFR, % pred.	104	(5)	99	(8)	102	(6)	99	(7)
S _{gaw} , s ⁻¹ cm H ₂ O ⁻¹	0.311	(0.03)	0.310	(0.03)	0.291	(0.04)	0.268	(0.02)
TLC, % pred.	105	(6)	101	(7)	102	(5)	101	(5)
RV, % pred.	108	(7)	94	(5)	107	(6)	94	(4)
RV/TLC	0.32	(2)	0.33	(3)	0.32	(2)	0.30	(1)
D _L , % pred.	137	(6)	131	(5)	128	(7)	111	(3)
\dot{V}_{75} , s ⁻¹	1.08	(0.05)†	1.43	(0.05)	1.38	(0.05)*	1.47	(0.05)
\dot{V}_{50} , s ⁻¹	0.60	(0.03)†	0.82	(0.04)	0.85	(0.04)	0.85	(0.04)
\dot{V}_{25} , s ⁻¹	0.28	(0.02)†	0.56	(0.03)	0.50	(0.05)	0.53	(0.06)
R ₃ , cm H ₂ O/liter/s	2.41	(0.12)	2.37	(0.13)	2.73	(0.18)	2.72	(0.21)
R _R , cm H ₂ O/liter/s	2.18	(0.11)	2.24	(0.12)	2.64	(0.17)	2.56	(0.21)
R ₉ , cm H ₂ O/liter/s	1.90	(0.12)	2.13	(0.12)	2.44	(0.16)	2.42	(0.20)
R ₃ -R ₉ (FDI), cm H ₂ O/liter/s	0.511	(0.045)†	0.239	(0.036)	0.266	(0.039)	0.293	(0.025)
R ₉ /R ₃	0.783	(0.022)	0.898	(0.015)	0.893	(0.015)	0.886	(0.01)

Abbreviations: EID, electroimmunodiffusion; % pred., percent of normal values drawn from published data (see text); FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEFR, maximal mid-expiratory flow rate; S_{gaw}, specific airway conductance; TLC, total lung capacity; RV, residual volume; D_L, single breath diffusing capacity; \dot{V}_{75} , \dot{V}_{50} , \dot{V}_{25} , maximal expiratory flow rate in percent of lung volume seen at 75, 50, and 25% of vital capacity.

* $P < 0.05$ for MZ-MM pairs.

† $P < 0.01$ for MZ-MM pairs.

(a) Pi typing with acid starch gel and antigen-antibody crossed electrophoresis according to the method of Fagerhol and Laurell (16, 17); and (b) quantitative levels of AAT by a modification of the original immunologic procedure of Laurell (17). Details of these methods have been described elsewhere (15). In the present study, 36 MZ subjects and 60 MS subjects were identified. Of these MZ subjects 15 had never smoked cigarettes, cigars, or pipes. For this study, these individuals were matched with consecutive nonsmoking MM controls for sex and age. Of the MS subjects, 24 had never smoked. To construct a study group numerically compatible to the MZ group, 14 consecutively identified nonsmoking MS subjects were matched with appropriate MM controls. Pairs were age-matched according to decades. These individuals were asked to return for detailed pulmonary function testing. All of these subjects initially contacted agreed to participate.

Pulmonary function testing. Forced expiratory flow rates were obtained in the standing position with a 13.5-liter Stead-Wells spirometer and calculated by methods described by Kory et al. (18). Values were expressed as percent of predicted normal values published by Morris et al. (19). Functional residual capacity and airway resistance were measured in a body plethmograph (20, 21). Single breath carbon monoxide-diffusing capacity was determined by the methods of Ogilvie, et al. (22). Values were expressed as a percentage of normal values published by Bates et al. (23). Maximal expiratory flow volume curves were obtained in all subjects with a Med-Science model 70 spirometer (Med-Science Electronics, Inc., St. Louis, Mo.) whose output was displayed on a cathode ray storage oscilloscope and photographed (24). Maximal flow rates (\dot{V}_{max}) at 75%, 50%, and 25% of the forced vital capacity maneuver were calculated and the maximal expiratory flow volume curve was plotted from these three points. To correct for differences in the size of subjects, all flow rates were expressed as flow divided by the instantaneous lung volume present at that flow rate (25). Total pulmonary resistance (R_T) was measured in all subjects with a modification of the forced oscillometric technique as described by Interiano et al. (26). R_T was measured at 3 (R_3), 5 (R_5), 7 (R_7), and 9 (R_9) cycle/s. R_T at resonant frequency of the subjects (R_R) was between 5 and 7 cycle/s. Theoretical aspects of this procedure have been described elsewhere (27, 28).

Statistical methods. Various flow rates, resistance measurements, and some composites of the resistance measurements, such as R_3-R_9 and R_9/R_3 , discussed later, were analyzed by various parametric and nonparametric statistical methods. Several two-sided univariate parametric and nonparametric tests, such as the *t*-test, the Wilcoxon signed rank test, and the sign test (29) were performed on each of the variables. The significance probabilities (*P* values) from some of these tests provide measures of the statistical significance of the observed differences between the pulmonary functions of the matched pairs. A number of parametric and nonparametric multivariate tests, such as Hotelling's T^2 -test (30) and multivariate signed rank tests (31) were also performed on the data and yielded essentially the same conclusions.

RESULTS

Table I lists the pertinent characteristics of the study population and mean values for pulmonary function measurements. As previously documented, the overall sample from which these subjects were derived closely

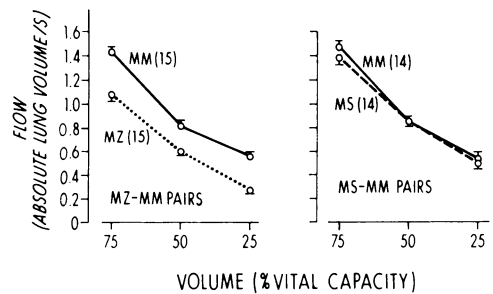


FIGURE 1 Mean \pm SE maximal expiratory flow rates in MZ and MS heterozygotes compared to MM control subjects. Flow is expressed as a function of absolute lung volume to correct for differences in lung size. Differences in flow rates at 75%, 50%, and 25% of vital capacity are statistically significant ($P < 0.01$) between MZ and MM pairs. No significant differences were present between MS and MM pairs.

reflected the age and sex distribution of metropolitan Rochester, N. Y. (15). None of these individuals participating in the health screen had identifiable respiratory complaints for which they were seeking medical attention. Specifically, respiratory symptoms elicited by the British Medical Research Council Questionnaire were minimal and comparable in each of the phenotype groupings. As might be expected in this group of life-long nonsmokers, none complained of chronic cough or sputum production. Quantitative levels of AAT concentration demonstrated the expected lower mean values for MS and MZ groupings compared to the MM control group.

Residual volume determinations were elevated in both MS and MZ subjects compared to MM controls. Single breath diffusing capacity demonstrated slightly higher values for MZ and MS subjects than MM controls. None of these differences was statistically significant.

Mean maximal expiratory flow volume curves for both pair groupings are displayed in Fig. 1, and are listed in Table I. In addition, complete individual data for each MZ-MM pair are presented in Table II. MS subjects demonstrated lower flow rates at \dot{V}_{max} 75%, statistically significant compared to MM controls. However, flow rates at 50% and 25% of vital capacity were identical in MS and MM pairs. Highly significant differences (Table I) in flow rates at all lung volumes were observed in MZ-MM pairs. MZ subjects demonstrated impaired maximal flow rates at each of the calculated points (Fig. 1).

Total pulmonary resistance by the oscillometric method was measured at 3, 5, 7, and 9 cycle/s. No significant differences in airway resistance at any of the frequencies measured were observed between either MS-MM or MZ-MM pairs (Table III). The relationship between oscillatory frequency and resist-

TABLE II
Maximal Expiratory Flow Rates (\dot{V}_{\max}) Expressed as Percentage of Absolute Lung Volume at 75%, 50%, and 25% of the Vital Capacity in Nonsmoking MZ Subjects Compared to MM Controls Matched for Age, Sex, and Smoking History

	\dot{V}_{\max} (% absolute lung volume)					
	75%		50%		25%	
	MZ	MM	MZ	MM	MZ	MM
	s^{-1}					
1	1.18	1.50	0.60	0.91	0.31	0.65
2	1.20	1.50	0.60	0.80	0.31	0.67
3	1.14	1.42	0.60	0.80	0.22	0.40
4	1.12	1.38	0.60	0.75	0.25	0.60
5	1.16	1.43	0.56	0.77	0.31	0.59
6	0.95	1.32	0.60	0.72	0.24	0.40
7	0.75	1.32	0.45	0.80	0.18	0.55
8	1.06	1.41	0.57	0.74	0.31	0.50
9	0.93	1.47	0.65	0.85	0.25	0.62
10	1.06	1.34	0.62	0.90	0.28	0.76
11	1.50	1.55	0.93	0.90	0.45	0.53
12	0.80	1.12	0.48	0.52	0.25	0.29
13	0.89	1.44	0.55	0.89	0.23	0.58
14	1.15	1.98	0.48	1.20	0.16	0.75
15	1.23	1.33	0.74	0.75	0.51	0.50
Mean	1.08*	1.43	0.60*	0.82	0.28*	0.56

* $P < 0.01$ for MZ-MM pairs.

ance in a representative MZ-MM matched pair is demonstrated in Fig. 2. Note that at R_9 , values are nearly equal for both subjects, but R_3 is higher in the MZ subject. The slope of the resultant curve is therefore steeper for the MZ subject compared to his MM control. A simple expression of this slope was

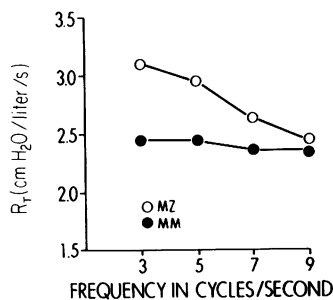


FIGURE 2 Relationship of total pulmonary resistance (R_T) by oscillometrics to frequency of superimposed oscillations measured at 3, 5, 7, and 9 cycle/s. Shown are the resultant curves for an MZ (○) subject and matched MM control (●). Frequency dependence index (FDI) was calculated from the difference between R_T at 3 cycle/s and R_T at 9 cycle/s ($R_3 - R_9$). FDI for the MM subject was 2.47 - 2.38 or 0.09 cm H_2O /liter/s; for the MZ subject: 3.08 - 2.46 or 0.62 cm H_2O /liter/s.

derived by subtracting R_9 from R_3 . In interpreting this "frequency dependence index" (FDI), the higher the resultant numerical value, the greater the degree of frequency dependence of total pulmonary resistance. In addition, the relationship of oscillatory frequency and resistance was analyzed by simply dividing R_9 by R_3 . In this instance, a steeper slope will produce a lower numerical value. Mean $R_3 - R_9$ values and R_9/R_3 values for MZ subjects were significantly elevated over MM controls, but MS subjects were indistinguishable from MM controls (Table I, Fig. 3).

Fig. 4 demonstrates the relationship between $R_3 - R_9$ and \dot{V}_{\max} at 25% of vital capacity. A high degree of correlation was obtained. Similar results were observed comparing individual values of $R_3 - R_9$ with \dot{V}_{\max} at 50% of vital capacity.

DISCUSSION

The relationship of intermediate AAT deficiency state to an enhanced risk of pulmonary disease remains controversial. Some studies of AAT phenotype frequencies in groups of patients with COPD have demonstrated an increased incidence of MZ subjects in such populations (13, 32, 33), but others have not been able to document this correlation (9, 34). Another approach has been the study of relatively asymptomatic heterozygote populations as in the present study. Some studies have utilized offspring and siblings of severely deficient subjects with documented lung disease (10, 14). This approach is open to the criticism that an observed higher prevalence of pulmonary function abnormalities in these samples could reflect genetic factors other than AAT deficiency (11, 12). To avoid this source of bias, the subjects in this study were randomly selected from an

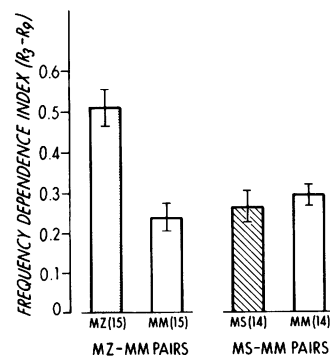


FIGURE 3 Frequency dependence index (FDI) for MZ-MM and MS-MM matched pairs. Bar graphs depict mean FDI and 1 SE for each group. Number of subjects in each group is specified in parentheses. Differences in FDI values between MZ-MM pairs are statistically significant. No significant differences are present between MS and MZ pairs.

TABLE III
Pulmonary Resistances and Resultant Frequency Dependence Index (FDI) in Nonsmoking MZ Subjects Compared to MM Controls Matched for Age and Sex

Pi type pair grouping	MZ				MM			
	R _s	R _R	R _p	FDI	R _s	R _R	R _p	FDI
	<i>cm H₂O/liter/s</i>				<i>cm H₂O/liter/s</i>			
1	2.76	2.66	2.26	0.50	3.08	2.90	2.86	0.22
2	2.08	1.86	1.68	0.40	2.31	2.25	2.20	0.11
3	2.60	2.31	2.05	0.55	2.20	2.00	1.86	0.34
4	2.96	2.56	2.30	0.66	3.08	2.76	2.66	0.42
5	3.20	2.84	2.64	0.56	2.96	2.76	2.66	0.30
6	2.08	1.60	1.15	0.93	2.97	2.60	2.55	0.42
7	3.08	2.85	2.46	0.62	2.47	2.47	2.38	0.09
8	2.56	2.38	2.08	0.48	2.40	2.38	2.32	0.08
9	1.40	1.40	1.00	0.40	1.68	1.60	1.54	0.14
10	2.48	2.21	2.01	0.47	2.46	2.38	2.30	0.16
11	2.00	1.80	1.67	0.33	1.35	1.29	1.14	0.21
12	2.56	2.38	2.10	0.46	2.22	2.00	1.68	0.54
13	2.07	1.86	1.45	0.62	2.00	1.86	1.80	0.20
14	2.22	2.00	1.68	0.54	2.23	2.20	2.10	0.13
15	2.07	2.00	1.93	0.14	2.15	2.07	1.93	0.22
Mean	2.41	2.18	1.90	0.51*	2.37	2.24	2.13	0.24

* $P < 0.01$ for MZ-MM pairs.

early disease detection unit. This unit differs in at least one important respect from a pure random population, in that some stimulus must have brought these subjects to the detection unit for evaluation. Several indices were monitored to see if this stimulus caused bias. First, it was determined that the population in the detection unit reflected closely the distribution of age, sex, and race of persons living in the metropolitan Rochester, N. Y., area (15). Second, the prevalence of phenotypes was compared to a completely random census tract study of the greater Rochester population (15). Prevalence rates did not differ significantly. For example, in the census tract study 2.3% of the 930 subjects were the MZ Pi type, and 3.3% of the 1,018 subjects studied in the early disease detection unit were Pi type MZ. These were not statistically significant differences. These data suggest that the subjects in this study accurately reflected the community at large.

In our present study, and in the previously reported survey from which this sample was derived, measurement of conventional spirometry failed to distinguish intermediate subjects from normals. Similarly, Morse, et al. (8) found in a large population study that intermediate levels of AAT were not associated with any diminution in expiratory flow rates. Determinations of static lung volumes and diffusing capacity demonstrated no clear-cut difference between pair groupings.

It is well recognized that asymptomatic individuals showing normal conventional tests of pulmonary function may have significant degrees of mechanical dysfunction. Our study utilized two rapid, simple methods currently believed capable of detecting early airway obstruction in asymptomatic populations. First, according to some investigators, maximal expiratory flow-volume curves (\dot{V}_{max}), especially if they are corrected for lung volume, can detect early airway obstruction associated with cigarette smoking (25).

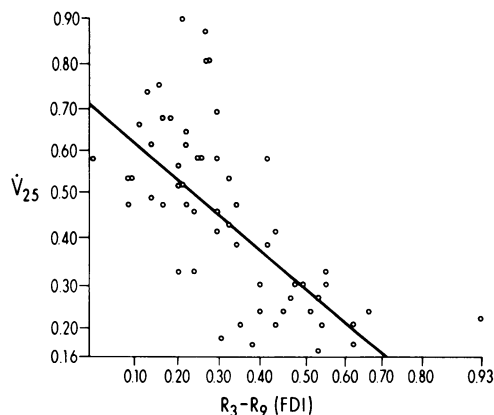


FIGURE 4 Relationship between \dot{V}_{max} at 25% vital capacity (\dot{V}_{25}) and $R_3 - R_p$ (FDI) (see text) for all subjects regardless of AAT Pi type. Heavy line indicates calculated regression line. A correlation coefficient of -0.6769 was observed.

TABLE IV
Effect of Changes in Compliance of One Lung on Total Pulmonary Resistance at 3 cycles/s (R_3), 9 cycles/s (R_9), and R_3-R_9 (FDI)

Dimension of "diseased" compartment			Resultant values of resistance for both lungs		
C_L	R_A	TC	R_3	R_9	FDI
<i>liter/cm</i>	<i>cm/liter/s</i>	<i>s</i>	<i>cm/liter/s</i>	<i>cm/liter/s</i>	<i>cm/liter/s</i>
0.005	4	0.02	3.08	2.29	0.79
0.01	4	0.04	2.46	2.07	0.39
0.05	4	0.2	2.01	2.00	0.01
0.10	4	0.4	2.00	2.00	0.00
0.20	4	0.8	2.00	2.00	0.00
0.5	4	2.0	2.01	2.00	0.01
1.0	4	4.0	2.01	2.00	0.01
2.0	4	8.0	2.01	2.00	0.01
5.0	4	20.0	2.01	2.00	0.01

Abbreviations: C_L , lung compliance; R_A , airway resistance; TC, time constant; FDI = frequency dependence index. Note: The other lung of the two compartments has the dimensions of $C_L = 0.1$ liter/cm, $R_A = 4$ cm/liter per s and TC = 0.4 s. Note that only very low compliances cause significant frequency dependence of resistance.

We noted statistically significant diminutions in expiratory flow in MZ subjects. Other investigators, studying nonsmoking MZ relatives of ZZ individuals, have noted similar findings (10).

Second, the development of uneven airway time constants was determined by the technique of measuring total pulmonary resistance at varying frequencies. According to the theoretical work of Otis et al. (35), both the observed airway resistance and lung compliance will fall as the frequency of airflow increases in the presence of asynchronous time constants in the lung. Recent work from our laboratory indicates that frequency dependence of total pulmonary resistance is closely correlated with frequency dependence of dynamic compliance in young adult smokers (36). Several previous studies (14, 37) have noted frequency dependence of dynamic compliance in patients with intermediate levels of AAT.

Pathogenesis of mechanical abnormalities in MZ heterozygotes

The present data, along with previously published studies, permit some speculation regarding the pathophysiology of intermediate AAT deficiency. In particular the limitation in expiratory flow rates in MZ subjects was highly correlated with the presence of asynchronous time constants as measured by frequency dependence of resistance, suggesting that

these two mechanical abnormalities are related to a common pathophysiological mechanism (Fig. 4). Several alternative methods may be proposed.

Regional alterations in lung compliance. The frequency dependence of pulmonary resistance in this study and the frequency dependence of dynamic compliance described by others (14) in MZ subjects are presumably the sequelae of asynchronous time constants explainable by regional alterations in lung compliance. A predilection for basilar involvement has been described in severely deficient homozygous subjects by lung scanning and autopsy examination (38, 39). If the same process were present in intermediate deficient subjects, the disease process might exaggerate the gravity-dependent regional differences in time constants present in normal lungs, thus creating true regional asynchronous time constants. Several factors reason against this hypothesis. While Fallat et al. (40) have described delayed clearance of ^{133}Xe from the base of the lungs in intermediate deficient subjects, this finding may be related to smoking, since these regional differences were not observed in nonsmoking intermediate subjects. Moreover, theoretical considerations do not seem to fit this model. Based on the equations of Otis and co-workers (35), the frequency-dependent characteristics of such a two-compartment lung with asynchronous time constants can be analyzed. Compliance of a two-compartment lung must differ by more than 10-fold to produce the observed changes in resistance from 3 to 9 cycle/s noted in our MZ subjects (Table IV). In addition, an alteration in regional compliance of this order of magnitude would likely be associated with other physiologic abnormalities. For example, in pathological studies of homozygotes (Pi type ZZ) there is marked pulmonary capillary as well as parenchymal destruction in involved areas of lung (37). Thus, the patients with intermediate deficiency would be expected to have some diminution in diffusing capacity if the disease process has a predilection for the base of the lungs. Such marked regional increases in lung compliance would also be expected to increase residual volume, impair distribution of ventilation, and increase closing volumes. Since these types of abnormalities have only been seen in a small proportion of MZ subjects drawn from a smoking population (10), regional loss of elastic recoil is not a satisfactory explanation for the mild abnormalities found in our nonsmoking MZ subjects.

Generalized loss of lung function. Our data support an alternate pathophysiological mechanism. Subjects with intermediate AAT deficiency may have generalized rather than regional abnormalities of the structural elements of the lung, causing frequency dependence of resistance and diminished flow rates.

Mead (41) first pointed out that frequency-dependent behavior of the lungs can be present in the absence of peripheral parenchymal time-constant discrepancies, as described in the classic Otis et al. model (35). He showed that if the lung is divided into two compartments, one containing the central conducting airways with low compliance, and the other containing the more compliant peripheral airways, a rise in peripheral resistance will cause the pattern of frequency dependence of resistance and compliance seen in human disease states. Fig. 5A shows how this model of uneven time constants between conducting airways and lung parenchyma results in frequency dependence of resistance when peripheral airway resistance increases. It also shows that if loss of elastic recoil results in a rise in compliance of the peripheral airways without a rise in peripheral resistance, the resultant increase in airway time constants would not produce frequency dependence of resistance. Alternatively, a rise in compliance of the more central conducting airways will result in frequency dependence of resistance and compliance (Fig. 5B).

These ingenious explanations for frequency dependence of resistance and compliance imply that two basic physiological alterations may cause the frequency dependence of resistance seen in the MZ subjects (41, 42). First, there may be a rise in peripheral resistance but not of peripheral compliance. Second, there could be an increase in compliance of the conducting airways such as might result from loss of elastic support or an alteration in the intrinsic properties of these airways. Either mechanism would result in limitation of maximal expiratory flow rates. Currently available data in MZ subjects do not permit a distinction between these two mechanisms.

The hypothesis that mechanical abnormalities in MZ subjects reflect generalized rather than regional abnormalities in lung structure and function is consistent with biochemical data regarding the relationship of AAT and pulmonary emphysema. While there is no direct biochemical evidence linking deficiency of protease inhibitors and human emphysema (43), enzymatic alteration of connective tissue of the lung, particularly elastin, remains a possibility. For example, AAT inhibits human granulocytic proteases, including both an elastase and a collagenase (44). Deficiency of AAT might lead to increased levels of enzymes and destruction of lung tissue.

The clinical significance of these physiologic abnormalities described remains unclear. Prospective studies would be needed to determine if these subjects will eventually develop symptomatic lung disease. Others have recently pointed out that cigarette smoking may be the significant determinant of the development of COPD in MZ heterozygotes (45, 46).

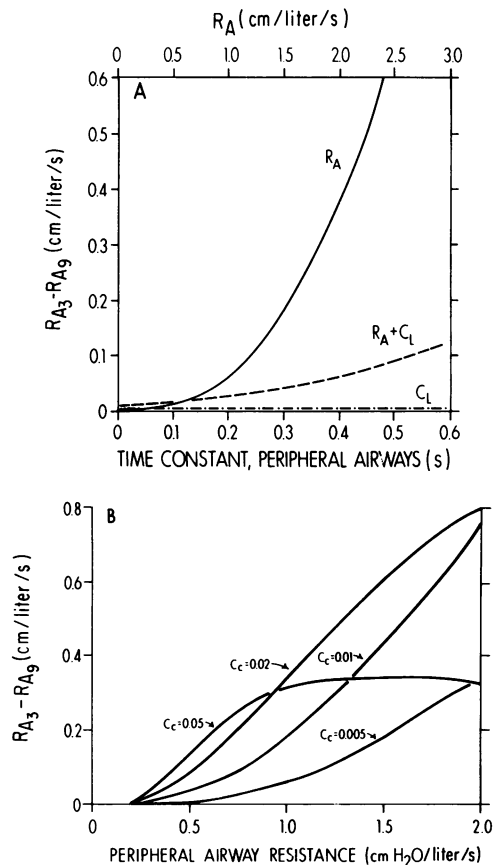


FIGURE 5 A. Theoretical effect of varying the time constant of the peripheral airways on frequency dependence of airway resistance (R_A), recorded as the difference between R_A measured at 3 cycles/s (R_{A3}) and at 9 cycles/s (R_{A9}) ($R_{A3} - R_{A9}$). We assumed, with Mead (41), that the lung had a dead space compartment with $C_L = 0.005$ liter/cm and $R_A = 0$, and a normal peripheral airway time constant of 0.1 s due to C_L of 0.2 liter/cm and R_A of 0.5 cm/liter per s. The solid curve labeled R_A gives the values for $R_{A3} - R_{A9}$ if the increase in time constants of the peripheral airways were due only to variations in R_A and the dotted line if the changes were due only to varying peripheral airway compliance (C_L). Resistance values across the top of the figure only pertain to the solid curve labeled R_A . The dashed curve gives the values for $R_{A3} - R_{A9}$ if R_A and C_L equally contributed to alterations in the time constant. Note that only rises in resistance contribute to the development of frequency dependence of resistance. Loss of elastic recoil, causing a rise in compliance without a rise in resistance, would not cause frequency dependence of resistance or compliance. B. Effect of rise in compliance of the conducting airways (C_c) on frequency dependence of airway resistance. Curve for $C_c = 0.005$ liter/cm H₂O is the same curve labeled "R_A" in Figure 5A. Note that if the compliance of the conducting airways (C_c) doubles from 0.005 liter/s to 0.01 liter/cm H₂O, frequency dependence of resistance, recorded as R_{A3}/R_{A9} , approximately doubles. However, if C_c increased to 0.02 liter/cm H₂O, the change is less pronounced at higher values of resistance. Further increases in C_c to values as high as 0.05 liter/cm H₂O may result in a decrease in $R_{A3} - R_{A9}$ at high resistance values.

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