Assessment of alpha-1-antitrypsin deficiency heterozygosity as a risk factor in the etiology of emphysema. Physiological comparison of adult normal and heterozygous protease inhibitor phenotype subjects from a random population.

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Research Article

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Assessment of Alpha-1-Antitrypsin Deficiency Heterozygosity as a Risk Factor in the Etiology of Emphysema

PHYSIOLOGICAL COMPARISON OF ADULT NORMAL AND HETEROZYGOUS PROTEASE INHIBITOR PHENOTYPE SUBJECTS FROM A RANDOM POPULATION

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ABSTRACT For plethysmographic studies of lung mechanics and measurement of pulmonary diffusing capacity, 62 subjects were drawn from a randomly selected population sample. Data obtained from the 24 subjects of heterozygous phenotype for alpha-1-antitrypsin deficiency (PiMZ) were compared by age group with data from 38 normal (PiM) subjects matched for sex, age, and smoking history. Comparison of mean values by age group for lung volumes, diffusing capacity, lung elastic recoil, maximum expiratory flow, and the occurrence of frequency dependence of dynamic compliance revealed no differences between phenotype groups. There was no evidence of an accelerated effect of aging among PiMZ subjects when compared with normal counterparts nor was there evidence of an increased effect of smoking. From these data it appears that the PiMZ phenotype per se is not a risk factor in the development of emphysema.

INTRODUCTION

The etiology of emphysema is still unknown, though many factors, genetic and environmental, acting singly or in concert, have been implicated. The suggestion by Laurell and Eriksson (1) in 1963, soon confirmed by Eriksson (2, 3), that a genetically determined deficiency of alpha-1-antitrypsin was associated with clinical emphysema provided the first identification of a long-sought hereditary factor. Subsequent reports have substantiated the increased risk of individuals homozygous for, and with a severe degree of, alpha-1-antitrypsin deficiency (PiZ)[1] (4–8). Although the absolute risk of PiZ individuals for developing emphysema is uncertain, Black and Kueppers (9) recently suggested that the clinical course may be quite variable, and that, in the absence of respiratory irritants, the prognosis may not be as ominous as previously indicated.

Even if the PiZ phenotype constitutes an inherited risk factor, it occurs in only a small proportion (0.1–0.3%) of the population and can account for a proportionately small proportion of the total number of cases of pulmonary emphysema. A larger proportion of the general population (≅3%) is of the protease inhibitor phenotype heterozygous for alpha-1-antitrypsin de-

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[1] *Abbreviations used in this paper*: Cdyn, dynamic compliance; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; FRC, functional residual capacity; FVC, forced vital capacity; MEFV, maximal expiratory flow volume; P-V, pressure-volume; Pi, protease inhibitor; PiM, protease inhibitor phenotype of normal individuals; PiMZ, protease inhibitor phenotype of individuals heterozygous for alpha-1-antitrypsin deficiency; PiZ, protease inhibitor phenotype of individuals homozygous for, and with a severe degree of, alpha-1-antitrypsin deficiency; Pst(L), transpulmonary pressure; RV, residual volume; STIC, serum trypsin inhibitory capacity; $\dot{V}_{max}$, maximum flow; VC, vital capacity.

ficiency (PiMZ). The relative risk of emphysema occurring in PiMZ individuals has also been studied, but the results have been quite conflicting. Early studies addressing this question were limited by the serum trypsin inhibitory capacity as the only available measurement to identify heterozygous individuals. Because alpha-1-antitrypsin is an acute phase reactant, the serum level can vary widely depending on such factors as the presence of inflammation or the influence of estrogens, and this can result in PiMZ individuals being mistaken for normal (PiM) individuals (10). The recent use of starch-gel electrophoresis followed by crossed immunoelectrophoresis (11) and electrofocusing (12) have allowed for exact phenotyping, and have thus circumvented the problem of inadequate identification.

Some of the conflicting data in the PiMZ studies have resulted from the use of physiologic tests too insensitive to detect early or subtle pathophysiologic changes. Indeed, Gelb et al. (13), in a study correlating the anatomic and physiologic findings in subclinical emphysema, emphasized the insensitivity of lung volume measurements, vital capacity, timed vital capacity, and airway resistance in unveiling the diagnosis. These authors concluded that, short of the direct measurement of lung elastic recoil, the maximum expiratory flow-volume curve and the measurement of the diffusing capacity were the most sensitive parameters to be obtained.

Another factor adding to the confusion about the relative risk of PiMZ phenotypes and emphysema has been the populations under study. In those studies involving patients with chronic obstructive pulmonary disease (COPD) (14–16), the relatives of such patients or other obligate heterozygotes (17–19), and nonrandomly selected PiMZ individuals (20), the results have generally suggested that PiMZ individuals are at significant risk for developing emphysema. In contrast, those reports involving random populations (21–26), epidemiologic health surveys (27), and individuals within an age strata of a general population (28) have generally demonstrated either no risk or a minimal risk for emphysema.

To address the question of the risk of PiMZ phenotypes for premature emphysema, we undertook the study of subjects with accurately defined protease inhibitor phenotypes from a randomly selected population utilizing detailed physiologic testing. The remainder of this paper constitutes the results of our endeavor.

METHODS

A random, stratified, cluster sample of the white, non-Mexican Americans of Tucson, Ariz. had been identified as the population for a prospective longitudinal study of the natural history of chronic obstructive lung disease (29). Of this population, 92.4% of subjects over the age of 5 yr had blood samples drawn for alpha-1-antitrypsin screening. Satisfactory protease inhibitor (Pi) phenotype was determined on 2,944 subjects (21) together with serum trypsin inhibitory capacity (STIC) (23). The STIC was determined by a modification of the method of Laurell and Eriksson (1), and the Pi phenotypes were determined by discontinuous acid starch-gel electrophoresis followed by crossed immunoelectrophoresis (11). Mean STIC for the total population was 1.45 mg/ml. 3% of those tested, or 88 subjects, were PiMZ phenotype. The mean STIC of these PiMZ subjects was 68±15.3% of the mean for the total population.

Because physiological changes that occur during growth and development introduce additional variables and depend on the rate of maturation, for this study we excluded subjects under 25 yr of age. There were 47 adult PiMZ subjects above this age considered eligible for study. To obtain an adequate number of control subjects, 80 people were identified from the 2,637 persons of PiM phenotype, matched with the PiMZ subjects for sex, age, and smoking history.

Not all the potential candidates thus identified participated in full. Of the 47 PiMZ subjects, 1 had died, and 2 had moved out of the city since first enrolled. 5 refused all testing, and 10 were excluded because of confounding variables of severe cardiovascular disease, malignancy, mental retardation, physical disability precluding body plethysmography, or advanced age (over 75 yr). Because of technical difficulties or poor subject compliance, only partial data were obtained on five subjects. Complete studies were performed on 24, or 51%, of the original 47 PiMZ subjects. Of the 80 matched PiM control subjects identified, 1 had died, 4 relocated, 13 refused, and 7 were excluded because of confounding variables and advanced age. Partial data were obtained on 17 subjects because of poor compliance, technical difficulties, and, in two subjects, because of pulmonary impairment. Thus, complete studies were performed on 38, or 48%, of the original 80 PiM subjects. For purposes of data analysis, subjects were divided into three age groups. The characteristics of these groups are listed in Table I. The mean STIC was 1.45 mg/ml (±0.34) for the 38 PiM subjects and 1.09 mg/ml (±0.31) for the 24 PiMZ subjects who participated in this study.

All subjects signed informed consent, and all were given detailed instructions before each of the physiologic tests. It was required that each subject had been free of any symptoms of an upper respiratory tract infection for at least 4 wk before testing.

Initial tests consisted of at least three satisfactory forced vital capacity maneuvers. Data were recorded as flow through a pneumotachograph field device (30), digitized, and analyzed using computer techniques previously described (31). The best forced vital capacity (FVC) and the best forced expiratory volume in the first second (FEV_1) were selected and the FEV_1/FVC ratio derived. Lung diffusing capacity for carbon monoxide was measured in duplicate with a Collins Modular Lung Analyzer (Warren E. Collins, Inc., Braintree, Mass.) the single-breath method of Ogilvie et al. (32), and the best of the measurements was recorded as diffusing capacity per unit lung volume.

The remainder of the physiologic studies were performed with subjects seated in a pressure-compensated, integrated-flow, volume displacement body plethysmograph (J. H. Emerson Co., Cambridge, Mass.). Air conditioning was controlled for thermal stability and a final volume calibration adjustment was made. Flow at the mouth was measured by a Fleisch pneumotachograph connected to a differential pressure transducer (Sanborn 270). The dead space of the apparatus was reduced to that of the mouthpiece alone by a bias flow from the environment through the pneumotachograph toward the mouth at a flow of 0.5 liters/s. The bias flow

TABLE I
Study Group Characteristics

	No. of subjects		Age (mean)		Sex (male/female)		Smokers	
	PiM	PiMZ	PiM	PiMZ	PiM	PiMZ	PiM	PiMZ
			yr					
Young (25–41 yr)	10	6	34.7	33.5	3/7	1/5	8	4
Middle-aged (42–59 yr)	16	9	50.4	50.8	9/7	4/5	12	6
Elderly (60 plus yr)	12	9	65.7	66.4	5/7	5/4	7	6
All subjects	38	24	50.2	50.2	17/21	10/14	27 (71%)	16 (67%)

was offset electrically. Transpulmonary pressure [Pst(L)] was measured by a differential pressure transducer (Hewlett-Packard 268B, Hewlett-Packard Co., Palo Alto, Calif.) as the difference between the mouth pressure and the esophageal pressure. All data were recorded on a multichannel oscillograph (Hewlett-Packard model 7788A).

Esophageal pressures were measured by the method of Milic-Emili et al. (33). A 10-cm balloon (0.06-mm thickness, 3.5-cm perimeter) mounted on a 110-cm long polyethylene tube (PE 200), was passed transnasally into the esophagus to the point of the maximum negative pressure with the least cardiac artifact. For each balloon used, the optimum volume had been previously determined by the water immersion technique of Lemen and co-workers (34), and this volume was checked periodically throughout the study.

Thoracic gas volume at functional residual capacity (FRC) was determined by the method of DuBois et al. (35), after which the subject inspired maximally to total lung capacity (TLC) and then expired maximally to residual volume (RV). Maximal expiratory flow-volume (MEFV) curves were measured as mouth flow vs. plethysmographic volume and were recorded on a cathode ray storage oscilloscope (Tektronix 564B, Tektronix, Inc., Beaverton, Oreg.) from which they were transcribed onto graph paper by use of a beam splitter. The best of three endeavors or two reproducible curves constituted the MEFV envelope. Maximum flow ($\dot{V}_{max}$) was then tabulated at increments of the vital capacity and TLC.

After a volume history of three maximal inspirations from FRC, a static deflation pressure-volume curve (P-V) was obtained. The final P-V curve was the best fit by eye to the values derived from at least three static deflation maneuvers, and the static compliance was calculated as the 0.5-liter vol change above FRC on this curve divided by the corresponding pressure change. The subjects then breathed in time to a metronome at rates of 20, 40, 60, 80, and 100 breaths/min, and dynamic compliance (Cdyn) was calculated at these frequences. Results were corrected mathematically for inertance (36), and expressed as the ratio of the lowest Cdyn value divided by the Cdyn value at the lowest respiratory frequency.

Resistance upstream from the equal pressure point (37) was calculated as the Pst(L) divided by the $\dot{V}_{max}$ at increments of the vital capacity and the TLC.

The data were analyzed by standard statistical methods using the Statistical Package for the Social Sciences on the CYBER 175 Computer (Control Data Corporation) of the University of Arizona Computer Center.

RESULTS

The anthropometric data, smoking status, lung volumes, static recoil pressures, maximum expiratory flows, and lung diffusion are listed by Pi phenotype for each subject by age group in Table II. Table III lists the means, SE, and SD for these same physiologic parameters by Pi phenotype, with the subjects categorized into young (25–41 yr), middle-aged (42–59 yr), and elderly (60+ yr) age groups. The Pst(L) and $\dot{V}_{max}$ data are given at percent increments of the TLC only to 40% of TLC because measurement of Pst(L) is considered to be unreliable at lower lung volumes using the esophageal balloon technique (33).

The static lung volumes and vital capacity changed as anticipated with increasing age, but these trends were not significant. The RV/TLC ratio increased significantly and by the same order of magnitude in both groups, a finding consistent with previous reports (38). When the PiM and PiMZ subjects were compared by age groups, no significant difference was found in any lung volume or in RV/TLC ratios.

The flow data were size-compensated by dividing these values by the TLC, and the mean flows were then plotted at percent increments of the expired vital capacity (VC) for each age group within a phenotype. The resulting MEFV curves are shown in Fig. 1. Maximum lung deflation or RV is represented by 100% expired VC on the abscissa. With advancing age, both the PiM and PiMZ subjects showed a decrease in $\dot{V}_{max}$ that was statistically significant only after 70% of the VC had been expired. This age-related decrease in terminal flows is consistent with the data of Knudson et al. (39), although the study populations are not similar. Although the age-related decrease in flows appears greatest in the middle-aged PiMZ subjects, this was not statistically significant. Analysis of variance in all age groups revealed no significant difference between PiM and PiMZ subjects in any measured flows.

The static deflation P-V curves for each age group within a phenotype are depicted in Fig. 2. The mean Pst(L) values in centimeters H_2O for each age group are plotted at increments of the TLC to standardize for lung size. Within each phenotype, there was a loss of lung elastic recoil with increasing age, with the greatest loss occurring at high lung volumes. When the PiM and

TABLE II

Individual Data on all Subjects (Grouped by Pi Phenotype and Age Group)

Subject	Ht	Age	Sex	Smoking status*	TLC	VC	FRC	$FEV_1/FVC \times 100$
	cm	*yr*			*liters*	*liters*	*liters*	
PiM subjects								
MM1	183	32	M	X	6.27	4.10	3.65	81.2
MM2	183	35	M	X	7.16	5.86	2.88	75.4
MM3	183	35	M	X	6.39	5.70	2.64	80.8
MM4	168	28	F	S	4.58	3.70	2.20	79.5
MM5	163	29	F	S	4.60	3.25	2.70	94.4
MM6	163	34	F	S	4.43	3.55	2.38	76.0
MM7	165	37	F	S	5.21	3.85	2.22	80.9
MM8	168	38	F	S	5.46	4.40	2.93	81.1
MM9	157	38	F	N	4.79	3.75	2.69	89.8
MM10	168	41	F	N	5.06	3.81	1.93	81.4
MM11	175	42	M	S	5.00	3.85	2.72	85.9
MM12	165	44	M	S	5.71	4.46	2.62	71.6
MM13	173	48	M	N	5.57	4.70	1.88	87.6
MM14	188	48	M	S	8.10	6.20	4.59	62.5
MM15	183	49	M	X	5.38	3.45	2.72	70.8
MM16	183	49	M	N	7.33	6.20	3.26	72.0
MM17	191	50	M	S	9.69	5.90	5.29	62.2
MM18	157	53	M	X	3.30	2.45	1.59	84.7
MM19	170	55	M	S	6.21	3.80	3.26	74.3
MM20	145	45	F	N	4.15	2.90	1.78	76.3
MM21	163	49	F	S	5.28	3.90	2.48	73.4
MM22	163	50	F	N	5.14	3.49	3.06	76.8
MM23	152	54	F	S	4.25	3.20	2.08	80.3
MM24	163	56	F	S	4.26	3.58	2.55	73.1
MM25	160	57	F	S	4.64	3.30	3.06	77.0
MM26	168	57	F	X	4.30	2.80	2.48	72.4
MM27	170	60	M	N	5.37	3.76	2.50	77.6
MM28	178	63	M	X	6.20	3.60	3.83	52.9
MM29	173	64	M	N	4.07	3.35	2.02	79.0
MM30	165	69	M	X	5.11	3.15	2.64	68.9
MM31	168	74	M	S	4.85	2.90	2.77	67.1
MM32	168	62	F	N	5.02	3.35	2.59	80.8
MM33	163	64	F	X	4.88	3.80	2.59	71.0
MM34	179	64	F	X	3.87	2.28	2.81	71.5
MM35	157	66	F	X	4.01	2.36	2.57	69.8
MM36	169	67	F	X	4.46	3.00	2.77	76.2
MM37	160	67	F	N	5.14	2.55	2.98	72.0
MM38	157	68	F	N	4.19	2.65	2.35	74.2
PiMZ subjects								
MZ1	178	36	M	S	6.36	5.55	2.60	79.1
MZ2	168	25	F	S	4.96	4.10	1.85	81.0
MZ3	173	29	F	S	5.29	3.90	2.98	91.5
MZ4	165	34	F	S	4.83	3.80	2.62	76.5
MZ5	173	36	F	N	5.98	4.80	3.11	94.3
MZ6	178	41	F	N	4.53	3.20	3.20	88.1
MZ7	175	44	M	S	7.02	5.50	3.34	77.7
MZ8	178	49	M	N	7.16	5.30	3.06	84.5
MZ9	175	50	M	S	6.15	5.20	2.23	74.2
MZ10	183	55	M	S	8.68	6.80	4.00	74.0
MZ11	165	46	F	N	5.38	3.45	2.75	66.9
MZ12	163	49	F	S	4.44	2.90	2.59	72.3

Pst(L) at % TLC							Vmax at % TLC						
100	90	80	70	60	50	40	90	80	70	60	50	40	D_L/V_A‡
			cm H_2O						*liters/s*				
22.0	15.4	13.0	10.8	8.8	—	—	8.6	5.6	4.2	3.0	2.0	1.2	5.64
46.0	21.6	15.5	11.3	8.4	6.3	4.7	8.5	7.4	5.9	4.3	3.0	1.6	—
32.0	17.3	12.8	10.1	7.8	6.0	4.4	9.1	9.2	8.5	7.2	4.6	3.0	6.88
28.0	17.0	13.3	10.3	8.0	5.7	3.5	5.7	6.3	5.4	3.8	2.5	1.5	6.02
39.0	17.8	13.1	10.2	7.9	5.9	4.0	5.1	6.2	6.0	4.4	3.7	2.2	6.16
36.0	18.5	14.5	12.1	9.9	8.2	6.6	5.6	5.4	4.4	2.9	1.8	0.7	5.54
32.0	13.8	10.8	13.4	6.3	4.5	2.7	6.4	5.8	4.6	3.1	1.7	0.7	3.69
46.0	16.3	12.2	9.0	6.4	4.4	2.7	6.9	4.6	3.4	2.3	1.2	0.6	6.05
30.0	15.7	12.5	10.0	7.8	6.2	3.8	6.8	7.0	5.9	4.7	3.1	1.6	6.70
29.0	18.5	15.0	12.0	9.3	7.0	4.8	6.9	6.9	5.7	4.2	2.6	1.1	7.08
46.0	17.4	12.5	9.3	6.7	4.6	2.6	6.7	8.5	7.8	5.1	2.7	1.1	5.42
—	16.7	13.7	11.0	8.9	7.0	6.0	8.9	7.6	5.2	3.6	1.8	0.8	5.06
28.5	17.4	14.0	11.7	9.8	8.2	6.7	9.9	9.8	9.5	7.4	5.2	3.2	6.57
18.0	11.0	8.8	7.4	6.4	5.7	5.2	7.5	6.3	4.9	3.7	2.2	1.0	3.60
31.0	14.2	11.4	9.2	7.4	6.0	4.7	9.0	5.2	3.6	2.0	1.0	0.2	4.34
38.0	22.2	18.5	15.8	13.0	10.4	8.0	10.3	10.2	6.6	4.6	2.2	0.8	6.10
33.0	14.6	10.7	7.9	6.0	4.1	0.3	9.5	6.0	3.3	1.2	0.3	—	5.13
16.0	10.5	8.2	6.2	4.5	3.0	1.6	5.4	5.9	4.2	2.6	1.4	0.5	5.33
17.5	11.6	8.2	6.5	4.8	3.4	—	7.1	4.9	3.0	1.6	0.7	—	3.81
37.0	15.4	11.5	8.7	6.3	4.3	—	5.1	5.0	3.6	2.3	0.7	0.2	8.78
25.0	14.7	11.1	8.3	6.1	4.1	2.5	5.3	5.6	4.6	3.5	1.8	0.7	5.23
28.8	19.2	16.6	14.2	11.8	9.5	6.6	6.4	5.9	4.4	2.4	1.2	0.4	5.23
22.0	13.2	9.5	7.0	5.0	3.7	2.5	6.3	5.8	5.1	3.1	1.9	0.5	5.76
24.0	15.1	12.2	10.2	8.6	7.3	6.2	6.4	5.6	4.9	2.9	1.5	0.7	5.05
41.0	15.7	10.7	8.6	7.7	5.3	—	5.5	4.5	2.7	1.1	0.2	—	3.85
20.8	13.7	9.3	6.5	4.6	2.8	1.5	4.3	3.5	2.2	1.2	0.5	0.1	—
32.0	14.8	11.6	9.4	7.4	5.6	3.5	7.1	5.7	4.1	3.1	1.4	0.4	5.97
17.0	12.2	9.0	6.8	4.7	—	—	6.8	3.5	1.9	0.6	0.1	—	5.16
17.0	11.3	9.2	7.4	5.8	4.5	3.2	7.9	7.4	6.4	5.2	3.9	1.1	5.20
23.0	14.5	11.5	9.5	7.6	6.0	—	4.4	6.1	3.8	2.2	0.9	0.3	4.39
17.0	13.0	10.8	9.0	—	—	—	6.4	4.4	1.9	0.7	0.2	—	2.97
—	12.7	9.3	6.9	5.2	4.1	3.4	5.4	5.2	3.9	2.7	1.0	0.2	5.78
23.5	14.5	11.5	9.6	8.2	6.7	5.6	4.8	4.0	3.7	3.0	1.9	0.7	4.80
17.0	12.5	9.6	7.4	5.4	—	—	4.0	3.0	1.5	0.5	0.1	—	5.81
27.0	14.5	11.5	9.0	7.0	4.8	—	5.2	4.9	2.6	1.2	0.4	—	8.58
15.5	12.1	9.0	6.4	4.1	2.1	—	6.6	4.9	3.3	2.1	1.1	0.4	6.37
19.5	12.2	9.7	8.5	7.4	—	—	5.5	2.9	1.5	0.4	—	—	5.29
—	15.0	10.7	8.0	5.9	4.2	2.8	3.8	3.5	3.1	1.3	0.4	0.1	6.79
25.0	13.7	11.4	9.7	8.3	6.8	5.3	9.2	8.5	6.8	5.8	4.4	2.8	4.67
40.0	19.0	15.8	13.6	12.0	10.2	8.5	6.0	5.6	4.8	3.8	2.8	1.8	5.82
32.5	17.2	12.5	9.6	7.5	5.8	4.3	5.5	5.3	4.7	4.0	2.7	1.8	6.53
34.0	21.3	16.2	13.0	10.2	7.8	5.7	6.9	7.7	6.2	4.2	2.6	1.4	5.71
27.0	16.0	12.6	10.0	8.0	6.1	4.7	7.4	6.4	5.9	5.0	4.1	2.6	6.27
27.0	15.3	12.0	9.0	6.8	4.7	—	6.4	6.0	4.4	3.3	2.4	1.7	4.83
22.5	15.5	13.0	11.2	9.7	8.2	6.7	10.3	8.9	6.8	5.7	3.4	1.4	4.59
27.0	14.6	11.8	9.4	7.2	5.1	3.1	10.8	10.0	7.5	4.7	2.3	0.3	5.56
30.0	15.8	12.3	9.9	8.0	6.5	5.2	9.6	8.1	6.6	4.6	2.9	1.5	3.93
20.0	10.5	8.5	7.5	6.3	6.1	4.9	9.6	9.0	5.1	3.3	1.5	0.4	—
37.0	19.0	15.5	12.3	9.5	6.7	—	4.0	2.6	1.7	1.0	0.4	0.1	7.29
33.0	17.7	14.0	11.0	9.1	7.9	—	7.1	5.8	3.8	2.4	1.0	0.4	5.18

TABLE II (*Continued*)

Subject	Ht	Age	Sex	Smoking status*	TLC	VC	FRC	$FEV_1/FVC \times 100$
	cm	*yr*			*liters*	*liters*	*liters*	
MZ13	170	53	F	S	4.75	3.00	2.75	68.9
MZ14	165	55	F	S	5.72	3.20	3.36	88.0
MZ15	155	56	F	N	5.47	3.40	2.89	66.0
MZ16	177	62	M	N	6.60	4.65	3.59	81.0
MZ17	175	63	M	S	5.98	4.68	2.90	76.6
MZ18	183	64	M	X	7.93	4.80	4.61	73.3
MZ19	173	72	M	X	5.53	3.30	2.96	96.0
MZ20	180	74	M	S	6.60	4.73	4.34	66.3
MZ21	163	62	F	N	3.90	3.03	1.84	88.6
MZ22	157	64	F	N	4.73	3.23	2.05	83.3
MZ23	157	64	F	X	4.16	2.70	2.26	70.6
MZ24	170	73	F	X	3.63	2.45	1.68	66.7

* Smoking status: X, ex-smoker; S, present smoker; N, never smoked.
‡ Diffusing capacity per unit lung volume.

PiMZ subjects were compared by age groups, no statistical difference was found, and the curves were similar enough to be superimposable. Similar differences between phenotype groups in static compliance, calculated as the slope of the P-V curve over the 0.5-liter vol above FRC, were not statistically significant in any of the age groups.

To assess the rate of loss of lung elastic recoil, age

TABLE III
Mean Values by Phenotype and Age

	PiM									PiMZ								
	Young (n = 10)			Middle-aged (n = 16)			Elderly (n = 12)			Young (n = 6)			Middle-aged (n = 9)			Elderly (n = 9)		
	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE
Age, *yr*	34.7	4.1	1.30	50.4	4.6	1.15	65.7	3.7	1.07	33.5	5.7	2.33	50.8	4.2	1.40	66.4	5.0	1.67
Ht, *cm*	170	9.5	3.00	169	12.9	3.23	166	8.2	2.37	173	5.2	2.12	170	8.7	2.90	171	9.6	3.20
TLC, *liters*	5.40	0.92	0.29	5.52	1.64	0.41	4.76	0.68	0.20	5.33	0.71	0.29	6.09	1.34	0.45	5.46	1.46	0.49
VC, *liters*	4.20	0.89	0.28	4.01	1.18	0.30	3.06	0.53	0.15	4.22	0.81	0.33	4.31	1.41	0.47	3.73	0.97	0.32
FRC, *liters*	2.62	0.48	0.15	2.84	0.97	0.24	2.70	0.43	0.12	2.73	0.50	0.20	3.00	0.52	0.17	2.91	1.07	0.36
RV/TLC, %	22.4	6.62	2.09	27.0	7.80	1.95	35.5	9.03	2.61	21.3	5.80	2.37	30.4	9.54	3.18	31.3	6.58	2.19
FEV_1/FVC, %	82.0	5.82	1.84	75.1	7.21	1.80	71.8	7.29	2.10	85.1	7.23	2.95	74.7	7.57	2.52	78.0	10.10	3.37
Pst(L) at % TLC, *cm* H_2O																		
100%	34.0	7.78	2.46	28.4	9.15	2.36	20.9	5.41	1.71	30.9	5.66	2.31	27.3	6.74	2.25	24.4	4.31	1.44
90%	17.2	2.13	0.68	15.2	3.03	0.76	13.3	1.29	0.37	17.1	2.73	1.11	15.0	3.16	1.05	13.5	2.99	0.99
80%	13.3	1.40	0.44	11.7	2.90	0.73	10.3	1.08	0.31	13.4	2.05	0.84	11.9	2.81	0.94	10.5	2.51	0.84
70%	10.9	1.29	0.41	9.3	2.75	0.69	8.2	1.15	0.33	10.8	1.96	0.80	9.6	2.32	0.77	8.4	2.22	0.74
60%	8.1	1.14	0.36	7.4	2.52	0.63	6.2	1.34	0.40	8.8	1.94	0.79	7.7	1.98	0.66	6.8	2.12	0.71
50%	6.0	1.17	0.39	5.6	2.31	0.58	4.8	1.41	0.50	6.9	1.92	0.78	6.5	1.24	0.47	5.5	2.00	0.67
40%	4.1	1.20	0.40	4.5	2.26	0.65	3.7	1.10	0.49	5.7	1.66	0.74	5.0	1.48	0.74	4.0	1.20	0.54
$\dot{V}_{max}$ at % TLC, *liters/s*																		
90%	7.0	1.37	0.43	7.1	1.88	0.47	5.7	1.30	0.38	6.9	1.31	0.53	7.2	3.05	1.02	6.3	2.05	0.68
80%	6.4	1.28	0.40	6.3	1.85	0.46	4.6	1.35	0.39	6.6	1.26	0.51	6.2	2.94	0.98	5.7	1.87	0.62
70%	5.4	1.40	0.44	4.7	1.91	0.48	3.1	1.40	0.41	5.5	0.97	0.39	4.2	2.30	0.77	4.3	1.56	0.52
60%	4.0	1.37	0.43	2.8	1.21	0.30	1.9	1.43	0.41	4.4	0.90	0.37	2.8	1.88	0.63	2.3	0.80	0.27
50%	2.6	1.02	0.32	1.6	1.21	0.30	1.0	1.11	0.34	3.2	0.85	0.35	1.4	1.22	0.41	0.9	0.37	0.12
40%	1.4	0.75	0.24	0.8	0.79	0.22	0.5	0.34	0.13	2.0	0.55	0.23	0.6	0.59	0.22	0.2	0.11	0.04
D_L/V_A*	6.0	1.01	0.34	5.3	1.29	0.33	5.6	1.36	0.39	5.64	0.75	0.31	5.21	1.03	0.37	4.43	0.74	0.26

* Diffusing capacity per unit lung volume.

Pst(L) at % TLC							Vmax at % TLC						
100	90	80	70	60	50	40	90	80	70	60	50	40	D_L/V_A‡
			cm H_2O						*liters/s*				
21.2	10.5	7.5	5.4	3.8	—	—	2.1	2.1	1.9	1.1	0.5	0.1	4.46
35.0	18.3	14.8	11.8	9.2	—	—	5.9	4.8	2.6	1.0	0.2	—	4.87
19.8	13.0	9.6	7.5	6.1	5.0	—	5.7	4.2	2.2	1.0	0.2	—	5.77
17.5	10.6	8.1	6.4	5.0	3.9	—	4.8	4.5	2.6	1.4	0.5	0.1	3.53
22.0	12.1	9.5	7.7	6.5	5.6	4.8	9.1	8.9	6.5	3.4	1.4	0.4	3.56
27.0	15.5	13.0	11.2	10.0	9.1	—	7.8	6.0	4.2	2.2	0.5	—	4.75
20.5	11.7	8.9	6.7	4.8	3.3	—	6.3	5.2	3.6	2.2	0.7	—	4.66
29.0	19.1	15.1	11.8	9.5	7.5	—	9.1	8.2	6.4	3.3	1.2	0.2	—
26.0	11.6	8.4	6.0	4.3	3.2	2.1	4.6	6.4	5.2	2.9	1.2	0.2	5.80
27.0	13.4	10.1	8.1	6.6	5.2	4.1	5.9	5.1	4.5	2.4	1.0	0.2	4.53
21.0	10.7	8.8	7.2	5.9	4.8	3.7	5.8	3.8	2.1	1.0	0.4	0.1	4.63
30.0	16.8	13.0	10.7	8.8	6.8	5.2	3.1	3.4	3.2	2.1	1.1	0.3	3.97

regressions were developed from the P-V data for all subjects collectively, and separately for each phenotypic group. In Table IV, these age regressions are shown for the Pst(L) at decile increments from 100 to 50% of the TLC. For comparison, the data of Knudson and associates (39) have been included, although the latter were obtained from a highly select group of normal subjects of the PiM phenotype. A plot of the rate of loss of recoil per year of age is shown in Fig. 3. From this figure it is apparent that our subjects, viewed either collectively or by phenotype, lose elastic recoil at a greater rate than those subjects studied by Knudson and co-workers. Despite the greater loss of elastic recoil in our subjects vs. those of Knudson et al., there is no evidence of an accelerated effect of age on the PiMZ subjects when compared with the PiM subjects.

The upstream resistance was calculated from the Pst(L) at percent increments of the VC divided by the size-compensated $\dot{V}_{max}$ at the same percent VC. Analysis of variance of this parameter revealed no significant differences between subjects of PiM vs. PiMZ phenotypes by age groups. This lack of statistical significance also held true for analysis of the lung diffusing capacity for carbon monoxide and for occurrence of frequency dependence of Cdyn when phenotypic age groups were compared.

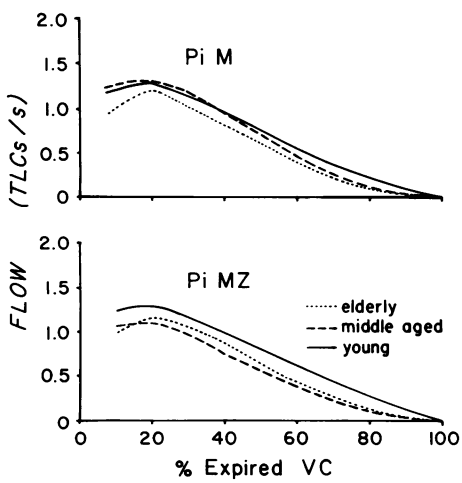

FIGURE 1 Mean MEFV curves by age group for PiM subjects (top) and PiMZ subjects (bottom). To compensate for differences in size, flow is expressed as TLCs/s and volume as percent expired VC. Only effort-independent portions of the curves are shown.

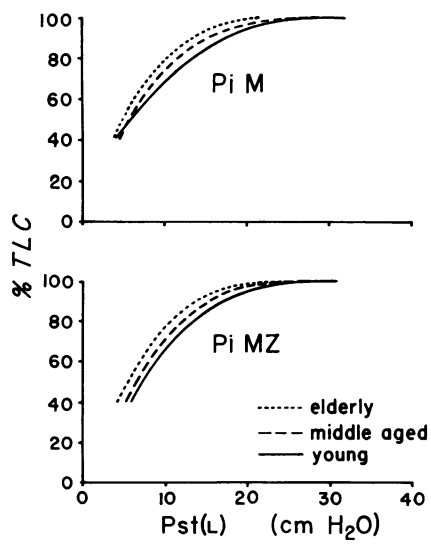

FIGURE 2 Mean static deflation P-V curves by age group for PiM subjects (top) and PiMZ subjects (bottom). Volume is expressed as percent of TLC to compensate for differences in size.

TABLE IV

Age Regressions of Elastic Recoil Pressure [Pst(L)] with Age in Years

Volume TLC	Select normal* (n = 51)			PiMZ (n = 24)			PiM (n = 38)			PiMz + PiM (n = 62)		
	A	B	P	A	B	P	A	B	P	A	B	P
%												
100	40.44	−0.1872	0.002	37.80	−0.2040	0.019	49.95	−0.4376	<0.001	44.59	−0.3324	<0.001
90	21.00	−0.0953	0.000	20.08	−0.0979	0.038	21.56	−0.1264	<0.001	20.93	−0.1141	<0.001
80	15.82	−0.0670	0.000	16.04	−0.0817	0.039	16.68	−0.0983	0.001	16.38	−0.0908	<0.001
70	12.44	−0.0502	0.001	13.19	−0.0715	0.036	13.79	−0.0867	0.002	13.51	−0.0798	<0.001
60	9.77	−0.0358	0.013	10.89	−0.0623	0.044	10.39	−0.0630	0.019	10.51	−0.0612	0.002
50	7.56	−0.0250	0.072	8.73	−0.0487	0.070	7.87	−0.0476	0.094	8.07	−0.0452	0.020

A, regression constant; B, slope; P, significance; Pst(L), A + (B × age).

* Data from Knudson et al. (39).

To examine the contribution of smoking as an additive factor disposing PiMZ subjects to premature emphysema as has been reported (8, 17, 20), we separated the subjects in both phenotypes into smokers and nonsmokers. Smokers included those who were currently or had previously smoked cigarettes on a regular basis, and nonsmokers included those who had never smoked or those who had smoked cigarettes only occasionally. As shown in Table II, approximately two-thirds of the subjects would be considered smokers. When analyzed as described, no significant difference was found between PiM and PiMZ smokers in lung volumes, size-compensated flows, P-V data, upstream resistance, or diffusing capacity. Because the limited number of smokers prohibited extensive analysis of the dose effect of smoking, subtle changes were sought by studying age regressions in only those PiM and PiMZ subjects who smoked more than one pack of cigarettes per day. This included 16 PiM and 13 PiMZ subjects. Age regressions were developed to examine both the loss of size-compensated flow and lung elastic recoil, and both of these regressions failed to demonstrate an accelerated loss in either parameter in the PiMZ smokers with increasing age.

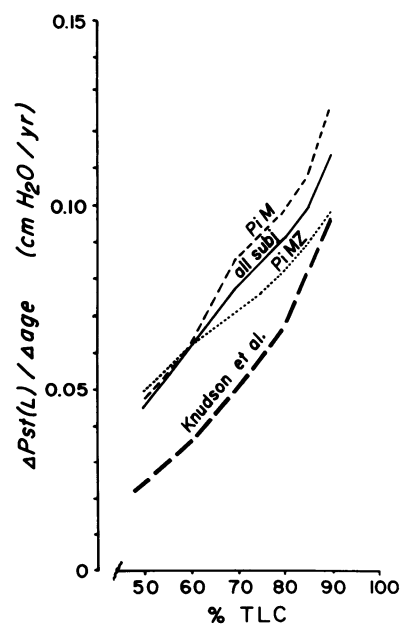

FIGURE 3 Changes in lung recoil with age at different lung volumes. This compares data from our subjects with those of Knudson and co-workers (39). Age regressions are shown on Table IV.

DISCUSSION

It is clear that only a fraction of those people exposed to the same environmental or microenvironmental factors, such as cigarette smoke, develop clinical emphysema. It is tempting to postulate that other factors must also be present to render certain individuals susceptible to developing the disease and that such factors may be constitutional or hereditary. Although both Osler (40) and Flint (41) suggested that emphysema may be a hereditary affliction, this has long been a matter of some controversy. In 1831–1833, James Jackson, Jr., (1810–1834), while working with P-C-A. Louis (42), a pioneer in the collection, enumeration, and critical analysis of medical observations, first called attention to a familial predisposition to develop emphysema. Very soon, in 1845, the concept of emphysema as a hereditary disease was brought into question by Watson (43) with the words "I am not convinced . . ." As data continue to accumulate, it indeed appears that heredity does play a role but the specific genetic factors contributing to the development of emphysema remain largely unknown. McKusick et al. (44) speculated that these genetic factors are of a complex nature, with many genes operating under the influence of the environmental stresses to which an individual is subjected. In an attempt to control for the effect of environmental stresses, Larson et al. (45) studied the timed VC and mid-expiratory flows of first degree relatives of COPD patients and compared the results with

those of their spouses. Although the first degree relatives had seven times more abnormalities in these tests than their spouses cohabitating the same environment, alpha-1-antitrypsin could be associated with only a few abnormal studies. The authors concluded that other genetic factors must exist to account for the observed abnormalities of pulmonary function. Cohen and associates (46) also observed a familial aggregation of pulmonary impairment which exists independent of phenotype or smoking history.

The association of a genetically determined deficiency of alpha-1-antitrypsin and clinical emphysema provided the first concrete scientific evidence for a hereditary factor involved in the etiology of emphysema. A homozygous deficiency of alpha-1-antitrypsin has frequently been associated with the development of premature clinical emphysema, but the relationship of a heterozygous deficiency, with intermediate serum levels of alpha-1-antitrypsin, and emphysema has remained a controversial issue.

The pivotal point of the heterozygote controversy is whether or not individuals with the PiMZ phenotype are at increased risk for premature clinical emphysema. An abundance of evidence exists supporting either contention. The differing populations from which the alpha-1-antitrypsin-deficient subjects were selected, the laboratory techniques used to identify these subjects, and the design of the individual studies, make it extremely difficult, if not impossible, to reconcile the opposing conclusions. Those studies in which the PiMZ subjects were drawn from a large, general population have tended to conclude that PiMZ subjects are not predisposed to premature clinical emphysema (21, 23–27). Conversely, a great many of the studies involving PiMZ subjects drawn from highly select populations of COPD patients and their relatives have concluded that the PiMZ phenotype does predispose individuals to premature clinical emphysema (14–16, 20). It is possible, however, that the reports of an increased incidence of premature emphysema in highly select populations are a consequence of the inclusion of other genetic factors in the population selection process. These other genetic factors may operate as modifying genes (47) with the PiMZ phenotype in the development of premature emphysema.

In a study of nonsmokers, Hall and co-workers (48), drawing from subjects attending a disease detection unit, found that 15 PiMZ subjects had significantly lower maximum expiratory flows than a comparable group of PiM subjects. These results differ from those reported from our randomly selected general population (21, 22).

Although our data did not demonstrate a difference between our PiMZ and PiM smokers, other studies have found PiMZ smokers to be at greater risk for emphysema (8, 17, 20, 26). Very few studies of the effect of other environmental factors on the PiMZ phenotype are available. Szczeklik et al. (49) reported on coal power plant workers and found a greater decrease in the VC and more right ventricular electrocardiographic abnormalities in the PiMZ subjects than seen in the PiM co-workers, but no differences were seen in PiMZ and PiM sawmill workers in British Columbia (25). Further investigation of these and other environmental factors, and their influence on the Pi phenotypes is currently under investigation (46).

The available data on the lung elastic recoil, the accepted hallmark of emphysema, of PiMZ subjects also differs depending upon the nature of the population from which the PiMZ subjects were selected. Ostrow and Cherniack (18), Stevens et al. (19), Patterson et al. (50), and Cooper et al. (17) studied alpha-1-antitrypsin heterozygotes from select populations of obligate heterozygotes (i.e., offspring of PiZ parents) or close relatives of patients with liver disease or emphysema. All of these studies reported an accelerated loss of lung elastic recoil in the heterozygote subjects as compared with the control groups. PiMZ subjects selected from general populations were studied by Gelb et al. (51) and Larsson et al. (28), and no accelerated loss of elastic recoil was found in the PiMZ nonsmokers compared with the PiM nonsmokers. Larsson et al. did find a greater loss of elastic recoil in the PiMZ smokers.

Lung elastic recoil decreases with increasing age, and this loss of recoil may be accelerated in alpha-1-antitrypsin heterozygotes. Many physiologic tests such as spirometric or flow-volume measurements and the single-breath nitrogen test, may be too insensitive to detect subtle changes in lung elastic recoil. Therefore, we studied the mechanical properties of the lung in PiMZ subjects and compared these results with a group of PiM subjects matched by age, sex, and smoking history. All subjects were selected from the same random population sample.

Our data, derived from measurements of lung volumes, maximum expiratory flows, static deflation P-V curves, upstream segment resistance, Cdyn, and lung diffusing capacity, show no differences between the PiMZ and PiM subjects when compared by age groups for any of the parameters studied. Lung elastic recoil decreased with advancing age in all subjects in this cross-sectional study, but comparison of the PiMZ subjects with the PiM subjects revealed no evidence of an accelerated loss of lung elastic recoil in the PiMZ subjects. We also compared our PiMZ data with the data on the aging of the normal lung reported by Knudson et al. (39). To isolate the effects of aging, Knudson et al. examined the mechanical properties of the lung in a highly select group of subjects who were asymptomatic nonsmokers of the PiM phenotype with no evidence of cardiopulmonary abnormalities by physical examination and chest roentgenogram, with an FEV_1/FVC ratio of 75% or greater, and a normal vectorcardiogram. A

comparison of the age regressions of elastic recoil pressures between PiMZ and PiM subjects revealed no accelerated loss of recoil with age in the PiMZ subjects, but both the PiMZ and PiM subjects demonstrated a greater loss of elastic recoil with time than the normal subjects of Knudson et al. To assess the magnitude of this loss, the mean P-V curves for the PiMZ age groups were compared with the range of normal mean P-V data described by Knudson and co-workers, and this is shown in Fig. 4. It is apparent that the P-V data of our PiMZ subjects lie within the range of normal derived from the P-V data of this highly select group of normal subjects. The greater loss of lung elastic recoil seen in the age regressions of our subjects compared with these normal subjects can be accounted for by the fact that the same rigorous selection criteria regarding smoking, roentgenographic and vectorcardiogram abnormalities, FEV_1/FVC ratios, and cardiopulmonary signs and symptoms were not applied to our subjects.

Our data, utilizing detailed physiologic measurements, are an extension of the results previously reported from studies of the same general population from which our PiMZ and PiM subjects were selected. Morse et al. (21) determined the Pi variants in the population and found no significant differences in the prevalence of respiratory symptoms and the prevalence of physician-confirmed respiratory disease between the PiMZ and PiM subjects. In addition, no significant differences were found in the FEV_1, FVC, FEV_1/FVC ratio, and $\dot{V}_{max}$ at 25, 50, and 75% of the expired VC between the Pi phenotypes. Lebowitz et al. (22) compared the PiMZ subjects with the PiM subjects as a group, and as matched pairs stratified by age, sex, and smoking history, and found no difference in the results of the single-breath nitrogen test and the MEFV curves. Both Morse et al. and Lebowitz et al. examined the effects of smoking in their respective studies and found that PiMZ smokers did not differ from PiM smokers in the parameters studied. Our data extend these observations by demonstrating no difference in lung volumes, maximum expiratory flows, lung elastic recoil, upstream segment resistance, or lung diffusing capacity between PiMZ and PiM subjects when analyzed by age groups and by smoking status. On the basis of these cumulative observations, we conclude that PiMZ subjects do not differ symptomatically or physiologically from PiM subjects in a randomly selected population. The data suggest that the PiMZ phenotype per se does not predispose individuals to premature clinical emphysema and the data provide no evidence that PiMZ smokers are at greater risk for developing emphysema than PiM smokers.

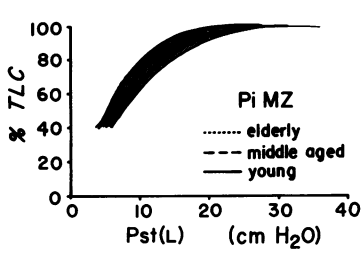

FIGURE 4 Mean static deflation P-V curves by age group for PiMZ subjects. The stippled area depicts the range of the mean curves from Knudson and co-workers (39) using as limits the mean curve for their young men and their elderly women. The mean curves for PiMZ subjects fall within these limits.

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