Smoking and intermediate α_1 -antitrypsin deficiency and lung function in middle-aged men

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Summary

Lung function was evaluated in a representative population sample of 50-year-old men living in one Swedish city. Twenty-four smoking and 15 non-smoking men heterozygous for α_1 -antitrypsin deficiency—that is, with the protease-inhibitor (Pi) phenotype MZ—were carefully matched for weight and smoking habit with Pi M controls. The pulmonary function of non-smoking Pi MZ subjects did not differ from that of non-smoking Pi M controls. In contrast, smoking heterozygotes showed a significant loss of elastic recoil, enlarged residual volumes, and increased closing capacity but no signs of obstructive ventilatory impairment. Most smoking Pi MZ individuals reported mild exertional dyspnoea.

The findings support the concept that smoking and intermediate α_1 -antitrypsin levels in Pi MZ heterozygotes interact additively in the development of emphysema. Nevertheless, up to the age of 50 this may be of only minor clinical importance.

Introduction

In 1963 Laurell and Eriksson¹ noted the relation between serum α_1 -antitrypsin deficiency and chronic obstructive lung disease. In 1965 Eriksson² documented this association in a large group of patients and described a familial type of early-onset emphysema. It is now known that many co-dominant alleles determine the structure and concentration of serum α_1 -antitrypsin. So far, over 20 genetic variants, or protease-inhibitor (Pi) types, have been identified.³ Homozygosity of the Z-allele (Pi Z) leads to a severe α_1 -antitrypsin deficiency with plasma concentrations of about 15% of normal. Even patients with the Pi SZ phenotype, who have concentrations about 40% of normal, have an increased risk of developing emphysema.⁴ The heterozygous phenotype Pi MZ is present in about 4-5% of a Scandinavian population^{2,5} and is the most common of several phenotypes associated with intermediate serum concentrations of α_1 -antitrypsin.

There is still considerable controversy about the clinical importance of the Pi MZ phenotype. Several surveys of patients attending chest clinics with chronic obstructive pulmonary disease have shown an increased incidence of heterozygotes, whereas other investigators have not found such an increase,^{6,7} and various lung function studies have produced conflicting findings.⁸⁻¹⁴ This divergence may be due to inexact Pi typing, selection of study populations, age factors, and use of non-specific pulmonary function tests. Also of interest is the relevance of

Pi MZ heterozygosity to exogenous risk factors for emphysema. Lieberman first suggested that lung disease evolves selectively in smoking heterozygotes,¹⁵ and others have confirmed this.^{8,9}

To clarify these points we studied lung function in 39 men with the Pi MZ phenotype who were identified in a non-selected population sample of 50-year-old Swedish men and compared with carefully matched Pi M subjects taken from the same population.

Population study and methods

All 50-year-old men living in the city of Malmö, Sweden (260 000 inhabitants) were invited to the division of preventive medicine, General Hospital, for screening. Blood pressure and several biochemical values (blood lipids, glucose tolerance, γ -glutamyltranspeptidase, etc) were measured. Seventy-six per cent of the invited men attended the examination. Blood samples were drawn from 1126 consecutive subjects. Serum protein electrophoresis including α_1 -antitrypsin measurement was performed at the department of clinical chemistry according to the methods of Johansson¹⁶ and Laurell¹⁷ on fresh blood samples. Pi typing was performed on samples kept frozen at -70°C for less than one month according to the method of Jeppsson *et al*¹⁸ using electrofocusing.

Of 190 subjects with serum α_1 -antitrypsin levels of 70% of normal or less, 43 (3.8% of the studied population sample) had MZ phenotypes. Of the remaining 147 subjects with subnormal α_1 -antitrypsin levels, 122 had phenotype Pi M, 4 phenotype Pi SZ, 2 phenotype Pi FZ, 18 phenotype Pi MS, and 1 phenotype Pi Z. Four subjects with the MZ phenotype were excluded from the study because of other disease. Of the remaining 39 MZ heterozygotes, who all consented to lung function studies, 24 were smokers and 15 had never smoked. Each MZ individual was carefully matched with a control with Pi M phenotype, who was identified by a systematic search in the birth date files for men with α_1 -antitrypsin concentrations of 80% of normal or more and Pi M phenotypes on electrofocusing. Each MZ individual was thus paired with an M individual of the same sex and closest possible birth date. They were also matched for body weight (weight in proportion to height) to within 10 kg and for number of cigarettes smoked to within 10 a day. The α_1 -antitrypsin concentrations, body weights, and cigarette consumption of the 39 MZ heterozygotes and their 39 controls are shown in table I.

At their first visit to the division of preventive medicine, before the results of biochemical and other tests were known, all the men had answered a standardised questionnaire, which gave detailed information on smoking habits, cough, wheezing, sputum production, and shortness of breath. None of the men had been exposed to heavy occupational air pollution.

TABLE I— α_1 -Antitrypsin level, body weight, and cigarette consumption in Pi MZ and M subjects. Values are means $\pm$ SD

	Pi MZ		Pi M	
	Smokers	Non-smokers	Smokers	Non-smokers
α_1 -Antitrypsin (% of normal) ..	63 $\pm$ 6	56 $\pm$ 9	103 $\pm$ 10	97 $\pm$ 13
Body weight (kg) ..	73 $\pm$ 9	75 $\pm$ 7	74 $\pm$ 7	74 $\pm$ 7
Daily cigarette consumption .. ($\cdot$ 10 years)	16 $\pm$ 11		14 $\pm$ 8	

LUNG FUNCTION STUDIES

Routine spirometry was performed in the sitting position with a Bernstein-type spirometer and included measurements of vital capacity (VC), forced expiratory volume in one second (FEV₁),

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FEV₁ as a percentage of VC (FEV₁/VC %), and maximal voluntary ventilation. Functional residual capacity was measured with a multiple-breath N₂ washout technique.¹⁹ The results were expressed as a percentage of the predicted values obtained from the reference material of this laboratory.

The washout volume—that is, the expired volume required to reach 2% N₂ in the expiratory gas when breathing pure O₂—was used as an index of intrapulmonary gas distribution.²⁰ The closing volume (CV), CV as a percentage of VC (CV %), closing capacity (CC %: CV plus residual volume (RV) as percentage of total lung capacity (TLC)), and slope of phase III (ΔN₂ %/l) were measured by the N₂ method.²¹ The normal values were taken from the same published material.

Lung mechanics were also studied in the sitting position using a latex rubber oesophageal balloon with a length of 10 cm, perimeter of 2.4 cm, and wall thickness of 0.05 mm. It was filled with 0.5 ml of air. The pressure difference between the mouth and the oesophageal balloon, positioned just below the mid-oesophagus, was measured at maximal inspiration (PMI) and divided by TLC to determine the coefficient of retraction. After repeated full inflations to TLC, dynamic compliance was measured during normal tidal breathing as the ratio of tidal volume to the change of pleural pressure at instants of zero flow at the mouth.

Conventional electrodes (Instrumentation Laboratories Inc, Boston, Mass, USA) were used to determine arterial O₂ and CO₂ tensions.

Standard statistical tests for significance were used (Student's *t* and χ^2 tests). *P* values less than 0.05 were considered significant.

Results

Table II summarises the influence of Pi type on lung function in 24 smoking and 15 non-smoking Pi MZ-Pi M pairs. In the smoking MZ subjects all values studied tended towards abnormality and PMI was significantly decreased at the 1% level. The individual PMI values scattered widely (see figure), and one Pi M control showed a pronounced increase of elastic recoil (PMI 44.8 cm H₂O). Exclusion of this man, who probably had lung fibrosis, did not, however, affect the statistical differences indicated in table II. RV/TLC % and CC %

were both increased in smoking heterozygotes but reached significance only at the 5% level. N₂-washout volume, CV %, and slope of phase III all tended to be increased in smoking heterozygotes, but the differences were insignificant.

Dynamic compliance and blood gas tensions showed no differences. There was no evidence of obstructive ventilatory impairment (FEV₁/VC %) in smoking MZ individuals. A similar comparison of values in 15 non-smoking Pi MZ-Pi M pairs showed no tendency towards more abnormal lung function in the heterozygotes.

Table II also shows the specific influence of smoking in heterozygotes and controls. In the controls there were no differences or even tendencies between smokers and non-smokers, except for the slope index, which was increased in the smokers (0.05 > *P* > 0.01). More important differences emerged from a comparison of smoking and non-smoking MZ individuals. Again the smokers showed no sign of obstructive ventilatory impairment (FEV₁/VC %), but they did, however, show significantly increased residual volumes (RV/TLC %), washout volumes, and CC % values and decreased PMI values, the last being significant only at the 5% level. The increase of slope index persisted in the MZ group.

Respiratory symptoms elicited by the detailed questionnaire are summarised in table III. Ten of the 24 smokers in both the Pi MZ and Pi M groups reported cough or sputum production, or both, but only one man in each group fulfilled the diagnostic criteria for chronic bronchitis according to the World Health Organisation definition.²²

TABLE III—Relation between Pi type and respiratory symptoms in smokers and non-smokers

	Smokers		Non-smokers	
	Pi MZ (n = 24)	Pi M (n = 24)	Pi MZ (n = 15)	Pi M (n = 15)
Cough and or expectorate	10	10	2	0
Exercise dyspnoea	14	5	2	2

χ^2 test: *P* < 0.01.

Fourteen smoking Pi MZ subjects, however, reported dyspnoea on climbing stairs or slopes compared with only five smoking Pi M controls (*P* < 0.01). None of the men who made these complaints, however, had had an earlier diagnosis of chronic obstructive lung disease or had considered the symptoms severe enough to seek medical advice for them.

Respiratory symptoms among non-smoking Pi MZ and Pi M subjects were minimal and comparable in the two groups.

Discussion

Homozygous (Pi Z) α_1 -antitrypsin deficiency is associated with a greatly increased risk of developing pulmonary emphysema,²⁻⁶ but attempts to elucidate the relative risk for heterozygotes (Pi MZ) with an intermediate plasma level have produced conflicting results.⁸⁻¹⁴ Morse *et al*¹⁴ have recently reviewed and analysed the possible approaches to the problem,

Distribution of PMI in smoking heterozygotes and controls.

TABLE II—Lung function data according to smoking habit and Pi type. Values are means $\pm$ SD

	Smokers (24 pairs)			Non-smokers (15 pairs)			Heterozygotes Pi MZ (39)			Controls Pi M (39)		
	Pi MZ	Pi M	Sig-nificance	Pi MZ	Pi M	Sig-nificance	Smokers (24)	Non-smokers (15)	Sig-nificance	Smokers (24)	Non-smokers (15)	Sig-nificance
FEV ₁ /VC % (% of predicted)	97 $\pm$ 11	101 $\pm$ 7	NS	102 $\pm$ 7	102 $\pm$ 7	NS	97 $\pm$ 11	102 $\pm$ 7	NS	101 $\pm$ 7	102 $\pm$ 7	NS
RV/TLC % (% of predicted)	123 $\pm$ 19	110 $\pm$ 18	< 0.05	104 $\pm$ 12	106 $\pm$ 17	NS	123 $\pm$ 19	104 $\pm$ 12	< 0.01	110 $\pm$ 18	106 $\pm$ 17	NS
Washout volume (% of predicted)	129 $\pm$ 30	117 $\pm$ 22	NS	101 $\pm$ 24	109 $\pm$ 17	NS	129 $\pm$ 30	101 $\pm$ 24	< 0.01	117 $\pm$ 22	109 $\pm$ 17	NS
CV % (% of predicted)	145 $\pm$ 41	132 $\pm$ 22	NS	132 $\pm$ 22	128 $\pm$ 24	NS	145 $\pm$ 41	132 $\pm$ 22	NS	132 $\pm$ 22	128 $\pm$ 24	NS
CC % (% of predicted)	121 $\pm$ 16	111 $\pm$ 12	< 0.05	106 $\pm$ 9	107 $\pm$ 8	NS	121 $\pm$ 16	106 $\pm$ 9	< 0.01	111 $\pm$ 12	107 $\pm$ 8	NS
ΔN ₂ %/l	2.40 $\pm$ 1.93	1.80 $\pm$ 1.05	NS	1.11 $\pm$ 0.50	1.05 $\pm$ 0.42	NS	2.40 $\pm$ 1.93	1.11 $\pm$ 0.50	< 0.05	1.80 $\pm$ 1.05	1.05 $\pm$ 0.42	< 0.05
PMI (cm H ₂ O)	17.5 $\pm$ 5.5	22.7 $\pm$ 7.1	< 0.01	21.5 $\pm$ 5.8	21.9 $\pm$ 4.8	NS	17.5 $\pm$ 5.5	21.5 $\pm$ 5.8	< 0.05	22.7 $\pm$ 7.1	21.9 $\pm$ 4.8	NS

NS = Not significant.

which is important because of the high prevalence of heterozygotes in the population.

Ideally studies should be based on large unselected populations allowing both lung function and clinical symptoms to be compared in subjects with Pi MZ and Pi M phenotypes. Lung function studies should include values that are easily interpreted in relation to symptoms—for example, forced expiratory volumes—and also values that give the most information on the pathophysiological events that occur early in the development of emphysema. Study populations should be chosen so that extrapolation of age-dependent changes in lung function can be avoided. Although the actual level of plasma α_1 -antitrypsin and not the phenotype should be the major determinant of vulnerability of lung tissue, exact genetic typing should be performed. We cannot at present exclude the possibility that different phenotypes with roughly equal plasma levels have different metabolic behaviour or that plasma levels of different phenotypes may respond differently to similar stimuli. Heterozygotes cannot be identified by quantitative estimation of α_1 -antitrypsin without the aid of phenotyping.

Against this background we decided to study one group of 50-year-old men, living in one community, who were invited to the unit of preventive medicine for a screening procedure primarily intended to detect various risk factors for cardiovascular disease. Heterozygotes were identified among men with plasma α_1 -antitrypsin levels 70% of normal or below. The MZ phenotype was confirmed by electrofocusing,¹⁸ a simple and reliable method for phenotyping. Pi M controls were chosen in a similar way among individuals with plasma levels 80% of normal or over. Heterozygotes and controls were then carefully matched with respect to birth date, smoking habits, and weight. Although only 76% of the men invited attended the examination, we think that this procedure produced a representative subsample of the population. The prevalence of heterozygotes was 3.8%—a figure close to that expected.²⁻⁵ Although the final series, 39 MZ-M pairs, was not large, it should have been free from the factors that produce bias in clinic populations or relatives with severe deficiency. By choosing one age group for study questionable age variations were avoided. By the age of 50 the men should have been exposed to both exogenous (smoking) and endogenous (subnormal α_1 -antitrypsin levels) factors for long enough to give detectable effects with the methods used. We used both simple measurements of forced expiratory and residual volumes and more sophisticated methods aimed at detecting early disturbances in lung mechanics. The choice of methods was based on earlier studies of presymptomatic individuals with SZ and Z deficiency,⁴ disclosing early changes in elastic recoil, nitrogen washout, and closing volume.

Clearly lung function in non-smoking Pi MZ individuals is no different from that in non-smoking controls. This finding agrees well with the results of several other workers.¹¹⁻¹³ It is also evident that smoking itself does not result in impaired lung function in 50-year-old Pi M subjects. The only abnormality noted in this group was an increased slope of phase III, considered to be the most sensitive index of lung dysfunction in smokers.²³ Smokers with the Pi MZ phenotype, on the other hand, had significant changes in several values, which suggests that smoking and moderately reduced α_1 -antitrypsin levels have an additive effect. It is important to note that no sign of obstructive ventilatory impairment (FEV/VC %) was discernable in this group, indicating that these patients were not actually suffering from advanced emphysema with associated collapse of large airways during forced expiration. Our data, however, support the concept that the lung function abnormalities in smoking heterozygotes can basically be explained by impaired elastic properties of the lungs. The abnormal PMI reflects reduction of elastic recoil²⁴⁻²⁵ and was accompanied by enlarged residual volumes. CV % tended to be increased but not significantly. High CC % was considered to be an effect of enlarged residual volumes, and uneven ventilation (enlarged N₂—washout volume) was considered to be a secondary phenomenon.

Although the abnormalities we found are consistent with early emphysema, their clinical importance is doubtful. A significant number of smoking heterozygotes (14 out of 24) gave unbiased reports of mild exertional dyspnoea before we knew their α_1 -antitrypsin concentrations or lung function values. Morse *et al*¹⁴ noted moderate exertional dyspnoea in 30% of their MZ subjects and 19% of Pi M controls. The mean age of their subjects was only 42 years, so that data are not strictly comparable. Mild exertional dyspnoea might be related to a selective reduction of elastic recoil, but it is certainly not related to advanced emphysema. Only long-term follow-up studies of these men can show whether serious disease will evolve. Smoking heterozygotes at the age of 50 undoubtedly had signs of early emphysema, but these may be considered to be unimportant as none of the subjects had sought medical advice for pulmonary symptoms.

Other investigators²⁶⁻²⁷ have reported a more complex and heterogeneous pattern of lung disease in MZ heterozygotes than is usually seen in patients with severe deficiency. In our 50-year-old smoking heterozygotes the pattern was very clearcut and basically similar to that seen in homozygotes, loss of recoil being the common denominator. This was also found by Ostrow and Cherniack,²⁸ who studied 10 offspring or siblings of homozygotes. Repeated studies in this group will probably show a more complex pattern. The effects of smoking, usually detectable at the age of 50-54,²⁹ as well as those of aging will probably blur this lung function pattern considerably.

A key function of α_1 -antitrypsin in the lungs is to inhibit proteases released from intact and destroyed leucocytes, sequestered in the pulmonary capillary bed.³⁰ Complex formation has been shown with granulocyte elastase and collagenase.³¹⁻³² Excessive uninhibited elastolytic activity in subjects with severe α_1 -antitrypsin deficiency (Pi Z) may damage elastic fibres in the lung tissue.³³ In the non-smoking heterozygous MZ individuals with plasma α_1 -antitrypsin concentrations of 60% of normal sufficient extracellular amounts seem to exist effectively to protect lung tissue against free proteases.

Smoking has been reported to increase both the number of alveolar macrophages³⁴ and their elastolytic activity.³⁵ In spite of one report³⁶ stating that macrophage elastase is not inhibited by α_1 -antitrypsin, it is tempting to assume that smoking, because of its pronounced qualitative and quantitative effects on alveolar macrophages, precipitates impaired pulmonary function in individuals with severe or intermediate α_1 -antitrypsin deficiency via these cells.

Our results underline the importance of smoking on the development of pulmonary dysfunction in Pi MZ heterozygotes and suggest an additive interaction. At the age of 50 this dysfunction, which is characterised by loss of recoil but without obstruction, is not a serious clinical problem, but we cannot preclude the possibility that additional environment or genetic factors may precipitate severe disease in several of these individuals. Nevertheless, we consider that the abnormalities at the age of 50 are so slight that an overall shortening of life expectancy seems improbable. This view agrees well with an earlier necropsy study at this hospital which showed an increased prevalence of emphysema in MZ heterozygotes but a normal life expectancy.³⁷

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Changes in distribution of gestational age and birth weight among firstborn infants of Cardiff residents

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Summary

We studied data on firstborn singleton infants born to primiparous Cardiff residents during the decade 1965-1974. Both mean birth weight and gestational age at delivery fell appreciably during 1965-74. Changes in maternal age, height, smoking habits, or history of abortion did not explain these findings.

The increased proportion of infants weighing <2500 g may be explained by the overall reduction in gestational age at delivery, which, in turn, may have resulted from increased use of elective delivery during the second quinquennium.

Introduction

A study¹ of neonatal practice and outcome among infants born to Cardiff residents during the decade 1965-1974 showed a significant shift in the distribution of birth weight and gestational age at delivery. During the second quinquennium relatively more infants were born weighing <2500 g and before completion of 36 weeks' gestation. Both these observed shifts persisted after further analysis within parity groups. Because low birth weight and preterm delivery are such important indicators of neonatal mortality and morbidity, we investigated these changes in greater detail.

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Materials and methods

We used the Cardiff Births Survey^{2,3} to study liveborn singleton infants of primiparous Cardiff residents delivered during the quinquennia 1965-69 and 1970-74. Cases were included if the date of the last menstrual period was certain and the birthweight, maternal age, height, smoking habits, and history of abortion (spontaneous or induced) were known. There were 12 357 such cases, almost equally divided between the two quinquennia. Restriction of the study population to primiparae removes the effect of the declining birth rate (which has resulted from a decrease in completed family size), and eliminates artefactual biases caused by reproductive compensation.⁴

We analysed birth weight and gestational age in terms of mean and standard deviation because of the virtually parallel shift in cumulative frequency distributions (figure). We compared characteristics of the parturient populations in the two quinquennia by using the χ^2 test at one degree of freedom with Yates's correction (table I). To analyse further the decrease in mean birth weight and gestational age adjustment was made for each of the "explanatory" variables individually, and a summary variable taking 16 values representing all possible combinations of the dichotomies indicated in table I was used; t tests were performed using pooled variances from within quinquennia. Thus, for example, the fall in gestational age was calculated separately in non-smokers and smokers (by quantity smoked); a weighted mean was then formed, appropriate for a $2 \times n$ analysis of variance.⁵

Results

Table I shows how some characteristics of the primiparous population changed. The increased prevalence of a history of abortion may reflect a real change or a greater readiness to volunteer information on previous termination of pregnancy. There were relatively more teenage primiparae in the second quinquennium. The proportion of women who had never smoked increased slightly; among those who smoked, the mean number of cigarettes consumed daily increased, but this was partly offset by changes in cigarette size and composition.⁶

Both mean birth weight and mean gestational age at delivery fell appreciably (table II and figure). This cannot be explained by changes