Airways obstruction and two year survival in patients

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Airways obstruction and two year survival in patients with severe alpha$_1$-antitrypsin deficiency. N. Seersholm, A. Dirksen, A. Kok-Jensen. ©ERS Journals Ltd 1994.
ABSTRACT: Because of the limited number of donor organs available, the selection of patients for lung transplantation is crucial. One important issue in setting priorities is the life expectancy without transplantation. The purpose of this study was to estimate survival, based on lung function, in alpha$_1$-antitrypsin deficient patients.

Data from the Danish alpha$_1$-antitrypsin deficiency registry were analysed. The basic element of the analysis was two year intervals, characterized by date of spirometry and known mortality status 2 yrs later.

We found a simple exponential relationship between lung function (forced expiratory volume one second (FEV$_1$)) and two year survival on conservative treatment. The formula implies an almost 100% two year survival until FEV$_1$ falls below one third of predicted normal; at this level two year mortality increases and will reach 50% at a FEV$_1$ of 15% predicted.

In conclusion, the two year mortality of emphysema patients due to alpha$_1$-antitrypsin deficiency increases exponentially with decreasing FEV$_1$, and the results imply that only a few patients who underwent lung transplantation would have had a better two year prognosis without this procedure.
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With the introduction of heart-lung transplantation (HLT) in 1981 at Stanford (USA), a valuable treatment for pulmonary cardiovascular disease and end-stage lung disease became available. A few years later, single (SLT) and double (DLT) lung transplantation were introduced, and at present (1992) over 2,000 HLT, SLT, and DLT have been performed [1].

Between 1981 and 1985, most transplant patients had advanced pulmonary hypertension related to Eisenmenger's syndrome or primary pulmonary hypertension. More recently, an increasing number of patients with end-stage lung disease (such as cystic fibrosis, emphysema with or without alpha$_1$-antitrypsin deficiency (α_1ATD), lung fibrosis, *etc*.) have been successfully treated by transplantation [2].

Apart from medical and technical problems, the lack of donors is a major obstacle, necessitating well-defined indications for transplantation [3]. The outcome should be an improvement in survival and/or quality of life. Consequently, the patients referred for transplantation should have an expected survival below that which can be achieved by transplantation. The most recent and comprehensive report describes a one and two year survival rate of 59 and 52% for HLT, 62 and 51% for DLT, and 69 and 62.5% for SLT respectively [1].

The purpose of the present paper is to describe the two year mortality as a function of FEV$_1$ in patients with severe α_1ATD.

Patients and Methods

Patients were selected from The Danish α_1ATD registry. Since 1979, patients have been notified to the registry by pulmonologists and paediatricians from all over Denmark. Once a patient is registered, a family record is obtained and family members at risk are offered examination of α_1ATD. In this way, more than 2,500 family members of the probands have been tested, and as a result the registry consists of 312 families, with 513 persons deficient of alpha$_1$-antitrypsin Pi type SZ and ZZ. On January 1st 1992, 361 were still alive as verified by the Danish Central Population Registry (CPR).

Determination of alpha$_1$-antitrypsin Pi type was verified by the Department of Clinical Chemistry at Bispebjerg Hospital by isoelectric focusing, as described by FAGERHOL and COX [4]. Lung function measurements of the patients in the registry were either reported by the referring physician or performed (spirometry) at the chest clinic in Copenhagen. Measurements were performed in accordance with the recommendations by the Danish Pulmonary Society [5]. Predicted values of FEV$_1$ were calculated according to Danish reference tables [6].

The smoking history was recorded [7]. A smoker was defined as a person who had smoked at least 20 packs of cigarettes or at least 1 cigarette·day^{-1} for at least one year in a lifetime. A current smoker was a person who was a regular smoker up to a month previously.

The basic element of the statistical analysis was two year intervals, characterized by date of spirometry and known mortality status 2 yrs later at the end of the interval. Two year intervals were chosen because few of the deceased patients had had spirometry performed within one year of their death. Patients with long periods of observation after enrolment in the registry supplied several two year intervals per patient to the analysis, but each interval from the same patient were independent.

For each patient, the intervals were defined as follows: 1) the first recorded spirometry of the patient defined the start of the first interval; 2) the next two year interval started as soon as possible after the observation period of the previous interval had ended, *i.e.* at the next spirometry at least 2 yrs after the spirometry of the previous interval; 3) the process continued in this way until the patient died or the period of observation after the next spirometry was less than 2 yrs.

Eligible for the present study were patients with a Pi-type of ZZ, with reported date and result of spirometry, and with known mortality status (*i.e.* dead or alive) 2 yrs after the spirometry. Furthermore, if dead, the immediate cause of death should have been coded as respiratory failure in the central death registry of the National Board of Health.

Mortality as a function of FEV_1 was calculated in a linear regression analysis. Odds ratios were calculated by logistic regression analysis.

Results

Of the 513 patients registered, 67 were Pi type SZ and 164 had not had spirometry performed, or the spirometry was not within 2 yrs of their death, leaving 282 eligible patients with 96 deaths, and a total of 537 two year intervals. Twelve intervals were either lost to follow-up (1) or interrupted by lung transplantation (11), leaving a total of 525 intervals available for analysis.

Basic characteristics of the two year intervals are shown in table 1. Mean age and proportion of males and females in the six lung function categories did not differ, but there was a marked difference in smoking habits, with an increasing percentage of ex-smokers and lifetime nonsmokers with increasing FEV_1. One exception was the 12% lifetime nonsmokers in the group with the poorest lung function, which resulted from seven intervals with two patients having very poor lung function
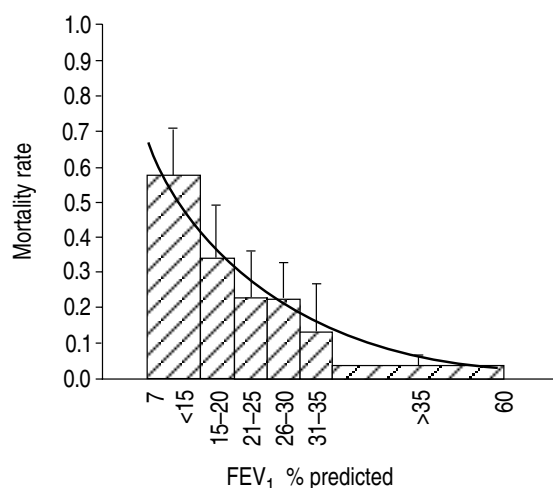

Fig. 1. – Two year mortality rate according to forced expiratory volume in one second (FEV_1) % predicted in patients with alpha$_1$-antitrypsin deficiency. The error bars denote 95% confidence intervals. The line represents the exponential model fitted to the data.

over a number of years before their death. These two patients died at the ages 61 and 89 yrs. Figure 1 shows the proportion of deaths within 2 yrs for 5% intervals of FEV_1 % predicted (% pred). A minor proportion of deaths within 2 yrs was found in patients with a FEV_1 % pred above 35%, and the approximate level of FEV_1 at which 50% died within 2 yrs was around 15% pred.

Mortality as a function of FEV_1 in various mathematical models was implemented in a linear regression analysis, using FEV_1 in the middle of the intervals; and for FEV_1 above 35%, 60% was used. An exponential (exp) model fitted our data almost perfectly (r^2=99.5%) giving the formula:

$$\text{Two year mortality} = \exp(-0.058 \times FEV_1 \text{ \% pred})$$

To control for age, gender and smoking habits, we applied a logistic regression model to the data, with FEV_1 % pred grouped in the same intervals as above, and four variables indicating age, gender, current smokers and ex-smokers. The age variable indicates whether the patient is under or over 40 yrs. Thus, the baseline is held by female lifetime nonsmokers under 40 yrs of age with FEV_1 % pred above 35%. In table 2, the resulting odds ratios with 95% confidence intervals are shown. Males and patients under 40 yrs of age had a significantly better two year survival, but smoking habits did

Table 1. – Basic characteristics of 525 two year intervals of 282 patients with alpha$_1$-antitrypsin deficiency, grouped according to FEV_1 % predicted

FEV_1 % pred	Intervals n	Persons* n	Deaths n	Mean age yrs	Sex % M	Smoking history		
						Current %	Ex- %	Never %
<15	59	40	34	45	58	46	42	12
15–20	50	40	17	50	52	44	54	2
21–25	57	48	13	50	54	31	63	6
26–30	81	61	18	50	51	28	64	8
31–35	46	43	6	52	57	18	71	11
>35	232	153	8	46	44	23	51	26

*: the sum is larger than the number of patients in the study, because some of the patients appear in more than one group of FEV_1 % pred. FEV_1: forced expiratory volume in one second; % pred: percentage of predicted value; M: males.

Table 2. – Result of logistic regression analysis; the variables are coded one or zero

Factor	OR	95% CI
FEV_1 <15%	41	16–106
15% ≤ FEV_1 <20%	12.8	4.7–35
20% ≤ FEV_1 <25%	9.8	3.6–27
25% ≤ FEV_1 <30%	7.9	3.1–20
30% ≤ FEV_1 <35%	3.3	0.92–12
Current smokers	0.92	0.36–2.4
Ex-smokers	0.47	0.20–1.13
Males	0.52	0.29–0.92
Age >40 yrs	3.1	1.72–7.4

FEV_1: forced expiratory volume in one second; OR: odds ratio; CI: 95% confidence interval.

not have a significant influence on two year survival. The exponential relationship of FEV_1 % pred and two year survival was maintained in this model, with very high odds ratios for low values of FEV_1 % pred.

Discussion

We found a simple exponential relationship between FEV_1 and two year survival on conservative treatment. The formula implies an almost 100% two year survival until FEV_1 falls below one third of the predicted normal; at this level two year mortality increases exponentially and will reach 50% at an FEV_1 of 15% predicted.

The data of the Danish α_1ATD deficiency registry have been collected over 12 yrs, during which conservative treatment has had little impact on the life expectancy of these patients. They develop severe emphysema at a young age where other causes of death are rare, hence it seems reasonable to expect a close relationship between lung function and mortality in this group of patients.

It is well-known that cigarette smoking is a major risk factor in the development of emphysema in α_1ATD patients, but among probands with impaired lung function previous studies have not shown any significant difference in slopes of decline in FEV_1 between current smokers and ex-smokers [8, 9]. In the logistic regression model, we did not find any significant influence in two year survival of current smokers, ex-smokers and lifetime nonsmokers. Males had a better survival than females and, although we have controlled for smoking habits, it is possible that the lifetime tobacco consumption was different between males and females. Our data are not sufficient to control for pack-years.

Another explanation to consider is that the results of the logistic regression analysis may be biased, especially the confidence intervals, due to the use of measurements performed in the same individuals.

Airways obstruction is one aspect only of the deterioration in emphysema, and the prediction of mortality might have been more precise, had data on additional parameters been available, such as: right heart failure, the diffusing capacity, or the arterial blood gas status. However, in emphysema, FEV_1 and these factors are usually correlated.

The present data indicate an exponential relationship between lung function and death, and although the biological mechanisms behind this formula are elusive, an exponential function is well-known from other aspects of life, as for instance the relationship between age and mortality in the entire adult population.

It is possible that the formula derived from these α_1ATD patients is applicable to all patients with emphysema, but not to patients with other lung diseases, such as cystic fibrosis, where KEREM et al. [10] found that the approximate level of FEV_1 at which 50% of the patients died within 2 yrs was around 30% of the predicted value. This level is higher than our findings of 15%, but in cystic fibrosis chronic infection is a major cause of death.

According to the latest report from the Registry of the International Society for Heart and Lung Transplantation [1], the two year survival rate after lung transplantation ranges 50–63%, and pretransplantation FEV_1 in chronic obstructive pulmonary disease (COPD), emphysema, and cystic fibrosis was reported to be 15–20% of predicted, with no difference among the three groups [2, 11]. Our formula implies that only few of the highly selected emphysema patients would have had a better two year prognosis without lung transplantation. Quality of life with a FEV_1 of 15–20% of predicted is very poor, and usually improves markedly after transplantation.

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