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Long-term oxygen therapy in parenchymal lung diseases: an analysis of survival

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Long-term oxygen therapy in parenchymal lung disease: an analysis of survival. K. Ström, G. Boman, The Swedish Society of Chest Medicine. ©ERS Journals Ltd.

ABSTRACT: We have analysed the predictors of survival in patients starting long-term domiciliary oxygen therapy (LTO) for chronic hypoxia caused by parenchymal lung disease.

In 240 patients (136 males) LTO was started at a mean age of 70 yrs. Survivors have been followed up for a minimum of 28 months (range 28–57 months). Interstitial fibrosis was the sole cause of hypoxia in 51 patients, and late sequelae of pulmonary tuberculosis in 48 patients. More than one (mixed) disease caused hypoxia in 124 patients. Patients with tuberculosis (TB) started LTO with significantly higher values of arterial carbon dioxide tension ($Paco_2$) and markedly lower spirometry volumes than patients with interstitial fibrosis.

In the total patient group survival was correlated in the univariate analysis to cause(s) of hypoxia, performance status and $Paco_2$ when breathing air. TB had a relatively good prognosis, whilst interstitial fibrosis implied a poor long-term survival. A $Paco_2$ of below 5.5 kPa and a poor performance class was associated with increased mortality rates. In TB patients, survival was better when thoracic deformity contributed to hypoxia. In patients with interstitial fibrosis, a forced vital capacity of below 2.1 *l* was associated with increased mortality. Concomitant chronic obstructive pulmonary disease was associated with better survival than interstitial fibrosis alone. In the multivariate analysis, survival was found correlated to performance status, presence or absence of thoracic deformity and forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). A high FEV_1 and a low FVC were associated with increased mortality rates. After consideration of spirometry values, cause(s) of hypoxia, apart from thoracic deformity, was not significantly associated with survival.

The reason for the increased mortality rate in patients developing chronic hypoxia at high FEV_1 levels could be more advanced diffusion impairment or ventilation-perfusion mismatch in patients developing chronic hypoxia at less advanced stages of obstruction.
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Long-term domiciliary oxygen therapy (LTO) improves survival and quality of life when administered to patients with chronic hypoxia caused by chronic obstructive pulmonary disease (COPD) [1–3]. In these patients, the forced expiratory volume in one second (FEV_1) and World Health Organization (WHO) performance status [4] have been identified as two of the best prognostic factors of survival [5–8]. No controlled trials have been published on the impact of LTO on chronic hypoxia caused by pulmonary diseases other than COPD. The outcome of patient groups with hypoxia from various causes when treated with LTO has been reported from some countries [9, 10]. There are no data in the literature on the prognostic factors of survival in patients starting LTO for chronic hypoxia caused by diseases other than COPD.

We have analysed the outcome and predictors of survival in 240 patients with chronic hypoxia caused by parenchymal lung diseases, registered in The Swedish Oxygen Register when starting LTO between January 1st 1987 and June 30th 1989. The Swedish Oxygen Register is a national register covering 85–90% of the patients receiving LTO in Sweden, which has a population of 8.5 million [11].

Methods

Details of the organization of the Swedish Oxygen Register have been published, and it will therefore only be described briefly [11]. All the departments of Lung Medicine, two departments of Infectious Diseases and one department of Internal Medicine participate in the registration. Prescribing guidelines for LTO, with a cut-off point for hypoxia of around 7.5 kPa, were issued in 1985 [11]. A three week period assessing the stability of hypoxia during optimum medical treatment is recommended. The oxygen

dose is adjusted in hospital, and an arterial oxygen tension (Pa_{O_2}) when breathing oxygen of above 8 kPa is preferred. Oxygen is prescribed for a minimum of 16 h·day^{-1}, preferably longer.

Clinical data, including the cause of hypoxia (more than one cause could be registered), haematocrit, arterial blood gas tensions when breathing air and oxygen, each for a minimum of 20 min, FEV_1, FEV_1 percentage predicted (% FEV_1), forced vital capacity (FVC), FVC percentage predicted (% FVC) and WHO performance status [4] are registered at the start of LTO. The predicted normal values of FEV_1 and FVC were obtained from BERGLUND *et al.* [12]. The record forms did not permit the ranking of the different diagnoses noted as causes of hypoxia. COPD was defined as chronic bronchitis, emphysema, alpha$_1$-antitrypsin deficiency or asthma, or any combination of these diagnostic subgroups contributing to chronic hypoxia. The WHO performance status scale is a clinical classification, comprising five classes ranging from 0 meaning capable of normal activity to 4 meaning bedridden (table 1) [4]. The follow-up of the patients is reported every 6 months.

Oxygen is administered from concentrators or high-pressure compressed gas cylinders. Small cylinders were available for patients who were prescribed oxygen during ambulation. Compliance with oxygen therapy was controlled with concentrator meter readings, pharmacy reports on oxygen cylinder deliveries and fall in haematocrit during the first 18 months of LTO [13]. During follow-up, 13 patients with late sequelae of pulmonary tuberculosis received artificial ventilation at home, in addition to LTO, during part or all of the entire observation period.

All the patients gave their informed consent. The register was approved by the Swedish Board of Health and Welfare, the Data Inspection Board and all of the regional Ethics Committees.

Statistical methods

The data processing was performed with the aid of the Quest data-base programme [14]. Comparisons between two groups were made using Student's t-tests or the Mann-Whitney rank test, if the data distribution was skewed indicating abnormal distribution. Comparisons between groups with different types of lung disease were performed using one-way analysis of variance (ANOVA) and Spearman's rank correlation. The influence of age, sex, clinical history, smoking history, haematocrit, arterial blood gas tension when breathing air and oxygen, spirometry values and performance status on survival was analysed. Univariate analysis of survival was performed using the Kaplan-Meier method and a log-rank Chi-squared test was used for comparison of survival between groups [15]. Patients receiving home ventilator treatment have been excluded from the analyses of survival, unless otherwise specified. Patients who were withdrawn from LTO due to improvement of hypoxia or lack of co-operation were withdrawn from the analyses of survival on the day of withdrawal from LTO.

Survival was analysed in the following patient groups, with exclusion of ventilator patients: all patients, patients with late sequelae of pulmonary tuberculosis constituting the sole parenchymal cause of hypoxia ("TB"), patients with TB being the sole cause of hypoxia ("TB-sole"), patients with interstitial fibrosis constituting the sole parenchymal cause of hypoxia ("IF"), patients with IF being the sole cause of hypoxia ("IF-sole"). Survival was also analysed in patients with TB as the sole parenchymal disease causing hypoxia, including the ventilator patients. Confidence limits for the relative risks were calculated as test-based confidence intervals according to MIETTINEN [16]. Cox's proportional hazards model was used for multivariate analysis of the relationship between the following baseline variables and survival: age,

Table 1. – Characteristics of patients with parenchymal lung diseases at the start of long-term oxygen therapy by disease (n=223)

Characteristic	Cause of hypoxia			p value
	TB	Fibrosis	Mixed	
Patients n	48	51	124	
Males %	46	63	58	NS
Lifetime nonsmokers %	56	39	36	<0.05
Age yrs	70±7	72±11	70±7	NS
Haematocrit	45±6	44±6	45±6	NS
Pa_{O_2} (air) kPa	6.4±0.9	6.3±1.0	6.5±0.9	NS
Pa_{CO_2} (air) kPa	7.0±1.3	5.5±1.3	6.2±1.2	<0.001
FEV_1 *l*	0.8±0.4	1.6±0.6	1.0±0.6	<0.001
FEV_1 % pred	35±18	61±26	38±20	<0.001
FVC *l*	1.3±0.5	2.2±0.8	1.8±0.9	<0.001
FVC % pred	36±15	56±19	48±18	<0.001
Performance class	1.4	1.5	1.5	NS

Data are presented as mean±SD. Performance class (WHO): 0=normal activity; 1=restricted in activity, but ambulatory; 2=confined to bed part of waking hours, up and about for more than 50% of waking hours; 3=confined to bed for more than 50% of waking hours; 4=totally confined to bed. TB: tuberculosis; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; NS: nonsignificant; WHO: World Health Organization.

cause of hypoxia, smoking history, performance status, arterial blood gas tensions while breathing air, FEV_1 and FVC. Multivariate analysis was performed in all patients together, and separately for patients with TB, TB-sole, IF and IF-sole excluding patients receiving ventilator treatment. It was also performed in patients with TB and TB-sole including ventilator patients.

A two-sided p-value of <0.05 was accepted as significant. For plotting the survival graphs the actuarial method was used.

Results

Patients

During the period January 1st 1987 to June 30th 1989, 240 patients (136 men) were included as they started LTO for chronic hypoxia caused by parenchymal lung disease, as classified by the treating physicians. The patients have been followed for a mean of 21 months (range 1 day to 57 months). The surviving patients have been followed up for a minimum of 28 months. More than one disease process (mixed disease), whether more than one parenchymal disease or other disease contributing to hypoxia, such as COPD, led to respiratory failure in 124 patients. In patients with mixed disease, COPD was present in 96 patients (77%). Interstitial fibrosis was the cause of hypoxia in 77 patients, and the sole cause of hypoxia in 51 patients (IF-sole). Tuberculosis was the cause of hypoxia in 118 patients, and the sole cause of hypoxia in 48 patients (TB-sole). In the remaining 17 patients, chronic hypoxia was caused by sarcoidosis in 9, pneumoconiosis in 4, exogenous allergic alveolitis in 2, and a collagen disorder in 2 patients.

The clinical characteristics of patients with hypoxia caused by the single disease processes TB-sole and IF-sole and patients with mixed disease at the start of LTO are presented in table 1. One hundred patients were noted as lifetime nonsmokers, 137 as ex-smokers and two as current smokers. In women, 64% were lifetime nonsmokers, while 24% of men were lifetime nonsmokers (p<0.001). COPD was present in 7 lifetime nonsmokers and 14 ex-smokers with IF. In patients with TB, COPD was noted in 14 lifetime nonsmokers and 40 ex-smokers. A past smoking history was more common in women with IF than in women with chronic hypoxia caused by TB (p<0.05). LTO was started at a mean age of 70 yrs (range 24–87 yrs). In women, exsmokers were younger at the start of LTO than lifetime nonsmokers. This smoking-correlated difference in age at the start of LTO was seen in women with IF-sole (67±8 yrs when compared with 78±6 yrs, p<0.01), but not in women with TB or mixed disease. In men, there was no significant difference in the mean age at the start of LTO due to smoking history.

Long-term oxygen therapy

Oxygen was prescribed for a mean of 18 $h \cdot day^{-1}$ in the whole patient group. The oxygen concentration varied from 39–100%. In patients with TB-sole, oxygen was prescribed for a mean of 17 $hours \cdot day^{-1}$, which was significantly lower than the mean daily hours of oxygen prescribed for patients with IF-sole (19 h) and mixed disease (18 h) (p<0.05). LTO was withdrawn in 11 patients (5%) due to the improvement of hypoxia, and in one patient due to the lack of co-operation. Concentrator meter readings and pharmacy reports of cylinder use were sometimes unreliable, due to concentrator breakdown and insufficient cylinder filling or emptying. The calculations showed that compliance might have been deficient in some 30% of the patients. The fall in haematocrit during the first 18 months of LTO was 2.0%. The fall in haematocrit from baseline during the first 18 months of LTO was significantly higher in patients with IF and IF-sole than in patients with TB and TB-sole (p<0.05).

Arterial blood gas tensions

With oxygen treatment, the mean Pao_2 rose from 6.5±0.9 to 9.0±1.4 kPa. At the first follow-up recording, the mean Pao_2 (air) had risen in patients with TB-sole (p=0.001) and in patients with mixed disease (p=0.001), but not in patients with IF-sole. The arterial carbon dioxide tension ($Paco_2$) (air) at the start of LTO was significantly lower in patients with IF-sole than in patients with TB-sole and mixed disease (table 1) (p<0.001). The $Paco_2$ (air) decreased from the start of LTO to the first follow-up in patients with TB-sole (p<0.05) and mixed disease (p<0.05), but not in patients with IF-sole.

Lifetime nonsmokers started LTO at significantly higher values of $Paco_2$ than ex-smokers and current smokers in all patients and patients with IF (p<0.05). A similar tendency was seen also in patients with IF-sole (p=0.06).

Spirometry

Patients with IF-sole and, to a lesser extent, patients with mixed disease started LTO at significantly higher dynamic lung volumes than patients with TB-sole (table 1) (p<0.001).

Patients with TB and with concomitant thoracic deformity started LTO with significantly lower values of FEV_1 (p<0.05), FVC (p<0.01) and % FVC (p<0.01) than patients without thoracic deformity. % FEV_1 and arterial blood gas tensions did not differ significantly between these two patient groups. Patients with concomitant COPD had significantly lower values of FEV_1 and % FEV_1 in all patients (p<0.01) and patients with TB (p=0.01).

There were significant negative correlations between FEV_1 (p=0.000, r=-0.6331), FVC (p=0.000, r=-0.5591) and $Paco_2$ (air). There were no significant correlations between performance status class and $Paco_2$ (air) in any patient group (p>0.5).

Thirteen patients with TB, 12 of whom also had a thoracic deformity caused by tuberculosis, received home ventilator therapy during some part of the follow-up period. Patients receiving home ventilator treatment had higher values of $Paco_2$ (air) (7.5±1.0 kPa in ventilator patients *versus* 6.6±1.2 kPa in patients without ventilator) and $Paco_2$ (oxygen) than patients not receiving ventilator treatment (p<0.05). The arterial oxygen tensions and spirometry values did not differ significantly between patients receiving

and not receiving ventilator treatment, but there was a tendency to lower % FVC values in patients with ventilator treatment (p=0.06).

Cause and place of death

One hundred and forty four patients (60%) died during follow-up. No patient was lost to follow-up. Respiratory disease was the only or a contributory cause of death in 87%, and cardiovascular disease in 7% of the patients who died. One hundred and twenty five patients (87%) died in hospital, one died during transport to hospital, and 18 patients (12%) died in their homes. Death was sudden in seven of the patients, who died at home.

Predictors of survival

The median survival in the whole patient group was 23 months. In the univariate analysis, survival correlated with the following characteristics registered at baseline: cause of hypoxia ($p<0.01$), performance status ($p<0.01$), $Paco_2$ (air) ($p<0.01$), FEV_1 ($p<0.01$) and FVC ($p<0.01$). Univariate analysis of survival showed that survival was better in patients with TB-sole than in patients with IF-sole and mixed disease (fig. 1) (table 2). Patients with a poor performance status had an increased mortality rate (table 2). Patients with a $Paco_2$ (air) of above 5.5 kPa had a better survival rate than patients with lower values of $Paco_2$ (air). Survival was better in patients with low values of FEV_1 and FVC. Survival was not correlated with smoking history.

In the multivariate analysis, performance status, presence or absence of thoracic deformity, FEV_1 and FVC were found to be independently associated with survival (table 3). Patients with a poor performance status and patients without thoracic deformity had increased mortality rates. Patients with high FEV_1 values had an increased mortality rate, and patients with high FVC values had a decreased mortality rate. $Paco_2$ and other diagnoses contributing to chronic hypoxia than thoracic deformity did not significantly influence mortality in the multivariate analysis.

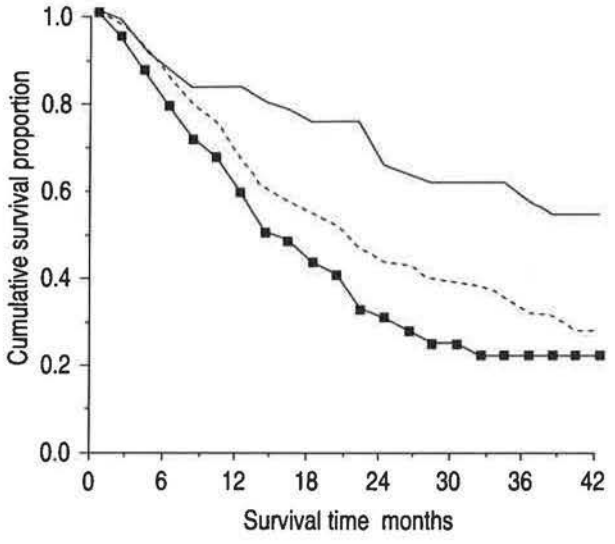

Fig. 1. – Survival in patients with parenchymal lung disease treated with long-term oxygen therapy according to cause(s) of chronic hypoxia. ---- : mixed=more than one cause of hypoxia (n=210); ——: TB-sole=sequalae of tuberculosis sole cause of hypoxia; —■—: IF-sole=interstitial fibrosis sole cause of hypoxia

Table 2. – Relative risks of mortality (RR) with 95% confidence intervals (CI) in patients with parenchymal lung diseases receiving long-term oxygen therapy, by univariate analysis

Characteristic	RR	CI
All patients (n=227)		
Cause of hypoxia		
Sequelae of tuberculosis	1	-
Interstitial fibrosis	2.48	1.44–4.27
Mixed	1.84	1.18–2.68
WHO Performance status		
0, 1	1	-
2	1.80	1.32–2.45
3, 4	2.11	1.42–2.13
$Paco_2$		
<5.5 kPa	1.64	1.18–2.28
>5.5 kPa	1	-
Tuberculosis patients (n=105)		
WHO performance status		
0, 1	1	-
2	3.8	1.84–7.40
3, 4	9.1	3.09–27.03
Thoracic deformity		
Present	1	-
Absent	1.78	1.05–1.70
Interstitial fibrosis patients (n=77)		
FVC		
<2.1 *l*	1.89	1.01–5.53
>2.1 *l*	1	-
COPD		
Present	1	-
Absent	2.60	1.25–5.43

COPD: chronic obstructive pulmonary disease. For further abbreviations and details of performance status see legend to table 1.

Tuberculosis

In TB patients, performance status ($p<0.01$) and the presence or absence of thoracic deformity were correlated with subsequent survival in the univariate analysis (fig. 2) (table 2). Patients with a co-existing thoracic deformity had a better survival rate ($p<0.05$). Patients with concomitant COPD displayed a tendency towards increased mortality ($p=0.05$). In patients with TB-sole, survival was correlated with performance status ($p<0.01$) alone.

In the multivariate analysis, presence or absence of thoracic deformity was the only significant predictor of survival in TB patients (table 3). In patients with TB-sole, presence or absence of thoracic deformity and performance status were significant predictors of survival.

When the survival analysis was performed including the ventilator patients, survival was correlated with performance status ($p<0.01$), presence or absence or thoracic deformity ($p<0.01$) and FVC ($p<0.05$) in the univariate analysis. Patients with a good performance status and patients with concomitant thoracic deformity had better survival rates.

Table 3. – Relative risks of mortality (RR) with 95% confidence intervals (CI) in patients with parenchymal lung diseases receiving long-term oxygen therapy, by multivariate analysis

Characteristic	RR	CI
All patients (n=227)		
WHO performance status		
Class 0, 1	1	-
Class 2	1.70	1.24–2.34
Class 3, 4	2.89	1.53–5.46
Thoracic deformity		
Present	1	-
Absent	2.16	1.22–3.82
FEV_1		
Reference	1	-
Reference + 1 *l*	1.92	1.14–3.22
FVC		
Reference	1	-
Reference + 1 *l*	0.52	0.34–0.82
Tuberculosis patients (n=105)		
Thoracic deformity		
Present	1	-
Absent	2.27	1.07–3.34
Interstitial fibrosis patients (n=77)		
FEV_1		
Reference	1	-
Reference + 1 *l*	3.77	1.26–11.25
FVC		
Reference	1	-
Reference + 1 *l*	0.29	0.11–0.74

For definitions of abbreviations and details of performance status see legend to table 1.

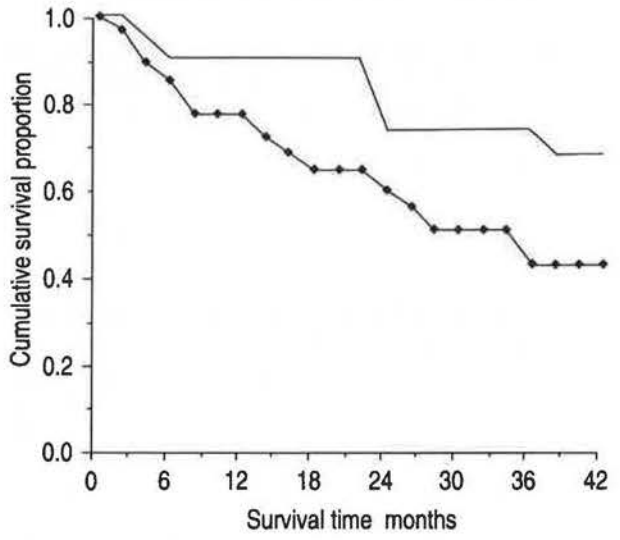

Fig. 2. – Survival in patients with late sequalae of pulmonary tuberculosis treated with long-term oxygen therapy according to the presence or absence of thoracic deformity (n=105). ——: deformity; —◆— : no deformity.

Patients with a FVC of below median value of 1.3 *l* had a better survival than patients with higher values of FVC. In the multivariate analysis including ventilator patients, presence or absence of thoracic deformity and performance status, but not FVC, were significantly associated with survival in TB and TB-sole patients.

Interstitial fibrosis

In all patients with IF, a FVC value of above the median value of 2.1 *l* predicted a better survival rate in the univariate analysis ($p<0.05$) (fig. 3) and (table 2). In this patient group, the presence of COPD was associated with a better survival rate ($p<0.05$). In patients with IF as the sole cause of hypoxia, no predictor of survival was found.

In the multivariate analysis, survival was predicted by FEV_1 and FVC in patients with IF (table 3). Presence or absence of COPD did not significantly influence survival after consideration of the spirometry values. Survival was better in patients with low values of FEV_1 and in patients with high values of FVC. No significant predictor of survival was found in patients with IF-sole in the multivariate analysis.

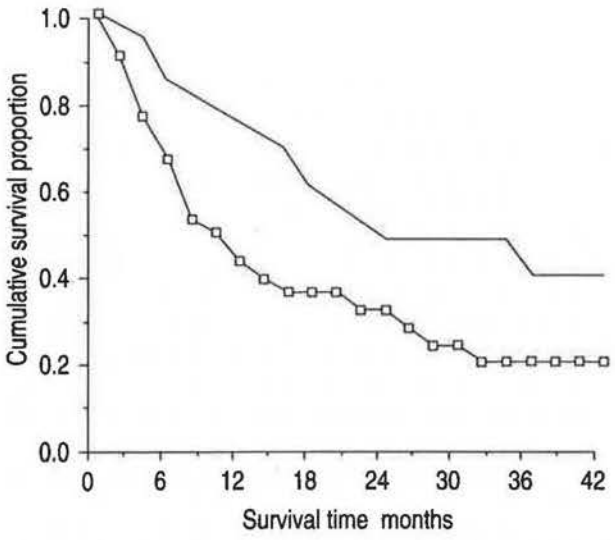

Fig. 3. – Survival in patients with interstitial fibrosis treated with long-term oxygen therapy according to forced vital capacity (n=77). —❑—: FVC <2.1 *l*; ——: FVC >2.1 *l*.

Discussion

The main purposes of LTO is to improve survival and quality of life. Controlled trials have shown that these goals can be achieved in COPD, although to a limited extent [1–3]. Preventing and postponing the onset of respiratory failure and need for LTO are, therefore, of utmost importance. Considering the proven effect of LTO in COPD, a control group was considered unethical in our investigation, and any conclusions concerning the benefit of LTO must be drawn by comparing with historical controls or other patient groups [17]. When compared with our patients with COPD, patients with hypoxia caused by TB had a better survival rate [8, 13]. It therefore seems likely that oxygen supplementation was beneficial.

Patients with symptomatic hypoventilation caused by thoracic deformity are best treated with artificial ventilation at home (AVH) [18–20]. We have previously shown that some of these patients may achieve long-term survival with LTO, but that AVH is needed in a growing proportion of patients, as hypoventilation worsens with time [21]. The patients with hypoxia caused by thoracic deformity registered

in the Swedish Oxygen Register had a better survival rate when treated with LTO than patients with COPD [13]. These patients are checked regularly as out-patients at chest clinics, and LTO is substituted or complemented with AVH when needed. The fact that patients with high $Paco_2$ values had a better survival rate indicated that chronic hypoxia caused by hypoventilation carries a better prognosis than hypoxia caused by parenchymal lung disease [13]. A similar observation was made in the patients in this investigation: patients with chronic hypoxia caused by thoracic deformity in addition to lung parenchymal disease had a better survival rate than patients without thoracic deformity. In fact, the patients with TB and without thoracic deformity had a survival rate that was virtually identical to that of patients with COPD registered in The Swedish Oxygen Register at the same time [13, 22].

Chronic hypoxaemia developed at different levels of ventilation, measured as $Paco_2$ and different ventilatory capacity, measured with spirometry, when caused by TB and in IF. The reason is evidently the different impact of these diseases on the respiratory function. In TB, the disease had destroyed large parts of the lungs and the unaffected lung parenchyma was presumably relatively normal. Normal blood gases could, therefore, usually be preserved until only a small ventilatory capacity remained. In IF, the alveolitis and fibrosis affected most or all of lung parenchyma, resulting in impaired diffusion capacity and ventilation-perfusion mismatch, thus explaining why chronic hypoxaemia develops at relatively high ventilatory capacity and spirometry volumes. In the multivariate analysis of survival, spirometry volumes predicted survival better than the cause of hypoxaemia. The paradoxical situation was found, that patients with low values of FEV_1 had a better survival than patients with high values of FEV_1. When patients with TB and IF were analysed together in the univariate survival analysis, survival was found to be better in patients with low FEV_1 and FVC values, presumably due to the fact that survival was better in TB than in IF, and TB patients started LTO at markedly lower lung volumes than IF patients (table 1). In the multivariate analysis, however, survival was better in patients with low FEV_1 values, both when all patients were analysed together and in IF patients. As expected, survival was better in all patients and in IF patients with high FVC values, in the multivariate analysis. The reason why a low FEV_1 value should be associated with a better survival in IF patients is not immediately clear. It was not caused by lower values of FEV_1 in patients with COPD and IF than in patients with IF without COPD. It is reasonable to assume that in IF, patients who develop chronic hypoxaemia at higher FEV_1 values have more advanced diffusion impairment or ventilation-perfusion mismatch contributing to chronic hypoxaemia and, hence, a poorer prognosis.

The reason for the increased mortality in patients with a $Paco_2$ of below 5.5 kPa found in the univariate analysis was not merely the fact that patients with TB and a better survival rate had a higher mean $Paco_2$ value than patients with IF. There was also a tendency towards increased mortality both in patients with TB and patients with IF with less than median $Paco_2$ values ($0.05<p<0.1$). With respect to patients with IF, the reason might again be that patients with higher degrees of minute ventilation, and therefore a lower $Paco_2$ at virtually identical degrees of hypoxia, have more advanced diffusion disturbances or a more advanced ventilation-perfusion mismatch and a poorer prognosis.

There is conflicting evidence in the literature on the impact of respiratory symptoms and smoking on prognosis in interstitial fibrosis. Smoking has been shown to influence lung function in idiopathic pulmonary fibrosis (IPF) and has been suggested as an explanation for at least part of the wide variability in lung function in IPF [23]. Chronic mucus hypersecretion was found, irrespective of current smoking habits, in patients with IPF, by HIWATARI *et al.* [24], and they concluded that it probably represented a part of the lung parenchymal disease. They found that in patients with IPF who survived for longer than one year from the onset of symptoms, survival was better in patients without symptoms of chronic mucus hypersecretion [24]. In contrast, TURNER-WARWICK *et al.* [25] found no correlation between sputum production and survival in patients with IF at different stages of the disease. In our material ex-smoking women, but not ex-smoking men, with IF started their LTO at an earlier age than lifetime nonsmokers. The difference in age that we observed in women according to past smoking habits cannot be ascribed with any certainty to COPD, since it was observed in women without the diagnosis of COPD. A possible explanation could be that the diagnosis of COPD was overlooked in the presence of IF. Considering the fact that associated COPD implied a better survival rate in our study, and that one-third of our patients with IF and COPD were lifetime nonsmokers, it appears more likely that smoking had enhanced the fibrosing alveolitis responsible for the loss of lung function in IF. This explanation would also account for the lower levels of $Paco_2$ at the start of LTO associated with smoking but not with COPD. Our results support the findings of HIWATARI *et al.* [24] that airways symptoms in interstitial fibrosis might be part of the disease process, but not their finding that airways symptoms imply a poorer prognosis.

The fact that patients with IF showed a greater decrease in haematocrit than patients with TB indicates that they complied better with the daily hours of oxygen. The reason might be a greater palliative effect of oxygen in patients with IF.

Our results show that chronic hypoxia usually occurs relatively late in life. In women with IF, a smoking history was associated with starting LTO at a younger age, raising the question of whether smoking had enhanced the loss of lung function leading to respiratory failure. Survival with LTO is mainly determined by the disease process in the lung parenchyma causing hypoxia. Thoracic deformity, whether in conjunction with late sequelae of pulmonary tuberculosis or not, is associated with a better survival rate than COPD. Patients with IF have a particularly poor survival rate. There is a need for controlled trials to assess the effects of LTO in terms of survival and quality of life in interstitial lung fibrosis.

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