Nutritional Status as a Predictor of Mortality in Severe Chronic Obstructive Pulmonary Disease

A thesis submitted to the faculty of Graduate Studies and Research in partial fufillment of the requirements for the degree of Master of Science

July 1990

Laurie Gibbons
Department of Epidemiology and Biostatistics
McGill University
Montreal, Quebec, Canada

ABSTRACT

In order to determine the role of nutritional status as a predictor of mortality in patients with chronic obstructive pulmonary disease (COPD), 348 patients with severe airway obstruction were followed for 1 to 3 years. Baseline measurements were done on patients recruited for a clinical trial of negative pressure ventilation in severe COPD. A subgroup of 184 patients, randomized to two treatment arms, had more extensive baseline assessment. Subjects were telephoned every three months; vital status was determined on those lost to follow-up by the retrieval of their death certificate. Separate survival analyses using Cox's multivariate regression model were performed in the recruited group and in the subgroup of randomized patients. When adjusted for the severity of disease, as assessed by the forced expiratory volume in one second (FEV_1) and the use of oxygen therapy, body mass index (BMI) was a significant predictor of mortality in the recruited group. The relative risk (RR) for BMI comparing the 25^{th} to the 75^{th} percentile was 1.86 (1.76,1.97). Both BMI and triceps skinfold thickness (TSF) were the nutritional parameters which significantly predicted mortality in the subgroup of randomized patients when adjusted for the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and use of oxygen therapy. The RR's comparing the 25^{th} to the 75^{th} percentile for BMI and TSF respectively, were 2.09 (1.92, 2.27) and 1.80 (1.66, 1.96).

RÉSUMÉ

Le rôle du statut nutritionel en tant que prédicteur de mortalité chez les patients atteints de maladie pulmonaire obstructive chronique (MPOC) fut évalué à partir d'un suivi de 1 à 3 ans effectué sur 348 patients. Des mesures de base ont été prises lors du recrutement des patients pour un essai clinique sur la ventilation par pression négative dans les MPOC graves. Une évaluation de base détaillée de ces mesures fut effectuée dans le sous-groupe de 184 patients répartis aléatoirement entre les traitements de l'essai. Les patients furent contactés par téléphone à intervalles de 3 mois; l'état vital, établi a partir de certificats de décès, fut déterminé pour les patients perdus au suivi. Des analyses de survie furent effectuées séparément pour le groupe de recrutement ainsi que pour le sous-groupe de patients selon le modèle de régression multivariée de Cox. L'indice de masse corporelle (IMC) prédit de façon significative la mortalité dans le groupe de recrutement après avoir ajusté pour la gravité de la maladie telle que déterminée par le volume expiratoire forcé 1 (VEF1) et l'utilisation du traitement par oxygène. Le risque relatif (RR) pour l'IMC en comparant les $25^{ième}$ et $75^{ième}$ centiles était de 1.86 (1.76, 1.97). Parmi les paramètres associés avec le statut nutritionel, seuls l'IMC et le pli cutané tricipital (PCT) furent des prédicteurs significatifs de mortalité après avoir ajusté pour le $PaCO_2$ et l'utilisation de traitement par oxygène. Les RRs en comparant les $25^{ième}$ et $75^{ième}$ centiles étaient de 2.09 (1.92, 2.27) et de 1.80 (1.66, 1.96) pour la IMC et le PCT, respectivement.

ACKNOWLEDGEMENTS

My advisor, Katherine Gray-Donald, provided valuable guidance throughout my work on this project. Her constant support has been invaluable. Stan Shapiro was very helpful with statistical matters and Jim Martin lent his considerable research and clinical expertise. I also wish to thank Diane Laforte and Patricia Furci for all their help in telephoning the patients, and Marielle Olivier for her help with the computing. This project was funded by the National Health Research and Development Program.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an important cause of mortality in Canada today. While cigarette smoking is the most important cause of COPD, the considerable variation in response to this exposure indicates that other factors affect the course of the disease. It has long been recognized that weight loss and malnutrition are common phenomena in patients with COPD and are associated with a poorer prognosis. At present, however, it is not clear whether the relationship between malnutrition in COPD patients and subsequent mortality is causal or whether malnutrition is a manifestation of more severely impaired lung function. If it can be shown that nutritional status influences the course and prognosis of COPD independently of lung function, there are important clinical implications concerning the treatment of patients. The focus of this thesis is on the impact of nutritional status on the mortality of patients with severe COPD. Cox's proportional hazards regression model will be used to control for those confounding variables reflecting the level of lung function impairment. The result of this analysis will be an estimate of the effect of various measures of nutritional status on mortality.

BACKGROUND

DEFINITION

Chronic obstructive pulmonary disease (COPD) refers to a condition in patients presenting with chronic cough and expectoration, with various degrees of exertional dyspnea accompanied by a significant and progressive reduction in expiratory airflow as measured by the maximum forced expiratory volume in one second (FEV_1) (1). This condition is differentiated from asthma by its lack of major reversibility. Only recently has COPD been used as somewhat of a catch-all term to describe the endstage condition resulting from the inflammatory processes to airways and alveoli in older patients who exhibit signs of either chronic bronchitis, emphysema, or, most often, both (1).

PREVALENCE

Prevalence studies report that COPD is a common disorder. Population studies of Tecumseh, Michigan report that 9% of males and 6% of females aged 16 and over exhibited significant airways obstruction as measured by their FEV_1 (2). The population of Glenwood Springs, Colorado aged 20-69 was sampled and the prevalence of significant airways obstruction was reported to be 13% in the males and 2% in the females (3). There is probably a significant asthmatic component to the levels of airway obstruction

in these populations, especially in the younger ages. Major risk factors for COPD include age, cigarette smoking, family history of COPD, and male gender (4).

In 1985, Canadian figures showed COPD to be the fifth leading cause of death among men and the seventh leading cause of death among women (5). These figures are based on the age standardized mortality rates for the ages 25 to 74 and include mortality from asthma. Canadian data reveal increasing mortality from COPD since 1950 in both males and females, particularly at ages over 55 years. Since 1975 the mortality rates among men have levelled off somewhat, but mortality among older women continues to rise from this condition. Smoking related obstructive pulmonary disease (SROPD) is a definition based on the ninth revision ICDA codes 491, 492, and 496 thus excluding asthma (7). SROPD caused a total of 6245 deaths in Canada and a total of 1836 deaths in Quebec during 1987. Morbidity from this condition is considerable. In 1985 there were 36,025 hospital admissions requiring 695,356 hospital days in Canada and 7,380 hospital admissions representing 164,121 hospital days in Quebec due to SROPD alone.

PROGNOSIS

The time course of COPD is approximately thirty years or more (1), but the disease may remain asymptomatic for many years before it is detected by the presence of an established symptom complex

and by conventional physiological testing such as spirometry. COPD is thus usually diagnosed well into the advanced stages of the disease at which point the symptoms of dyspnea, cough and expectoration as well as FEV_1 become progressively worse. Various treatment regimens serve to alleviate some of the symptoms, but do little to stop the progressive deterioration of lung function. Respiratory failure is a common cause of death in these patients. Time to death varies considerably with respect to a number of individual characteristics, very few of which are potentially modifiable.

MORTALITY

Currently in Canada, annual mortality from all causes is approximately 0.7% for all ages (8). Mortality increases with age. Annual mortality for those 35 years and older is 1.3% while amongst the population 60 years and over, mortality jumps to 3.8% per year (8).

A number of prospective studies of study subjects with COPD have reported the overall mortality rates of their cohorts (9-22). Those studies describing three year mortality experiences report rates ranging from 23% to 44% (9-15). The entry criteria for study subjects was often based on the ratio of the maximum forced expiratory volume in one second to the maximum forced expiratory volume (FEV_1/FVC), an index of airway obstruction. The entry

criteria as well as the reporting of physiological variables that indicate the clinical status, or severity of disease of the study population, varied from study to study. Table 1 lists the pertinent characteristics of these studies. Large-scale prospective studies with stringent spirometric entry criteria creating relatively homogenous study populations report mortality rates that vary. Three such studies selected subjects with an FEV_1 less than 60% of its predicted value (9-11). Two hundred subjects selected by this criteria with a mean FEV_1 of 1.0 L had a three year mortality of 34% (9). Damsgaard and colleagues (10) used this criteria to select 187 patients with COPD, followed them for three years and reported a mortality rate of 29%. The largest (N=985) and most recent of these studies selected only non-hypoxemic patients (PaO_2 greater than 55 mm Hg), who nonetheless exhibited severe airway obstruction (mean FEV_1=36.1% predicted), and reported a three year mortality of 23% (11).

The initial severity of disease of the study subjects clearly has an impact on survival. This can be seen in studies which report the clinical status of their cohorts. A large prospective study of 487 subjects with a clinical diagnosis of COPD, 79% of whom had moderate to severe airway obstruction (FEV_1 less than 1.49 L), reported a three year mortality of 44% (14). Weitzenblum and associates (15) studied a group of 175 patients with a similar level of disease severity, (mean FEV_1= 1.2 L, mean PaO_2= 63.2 mm Hg, mean $PaCO_2$= 39.7 mm Hg, and mean age= 59.8 years) and reported

a three year mortality of 26%.

A smaller prospective study of 85 subjects with more severe manifestations of COPD (mean FEV_1= 0.74 L, mean PaO_2= 43.6 mm Hg, and mean $PaCO_2$= 53.3 mm Hg), reported a four year mortality of 41% (16). A similar 4 year mortality of 43.5% (17) was reported in a study of 115 subjects with comparable clinical characteristics, (mean FEV_1= 0.79 L, mean PaO_2= 53.2 mm Hg, and mean $PaCO_2$= 48.5 mm Hg).

PREDICTORS OF MORTALITY

FEV_1

Several of these studies have examined the association of various characteristics of COPD patients to their subsequent survival. The methods of statistical analysis and length of follow-up vary tremendously from study to study, yet a consistent finding is that the degree of airway obstruction, usually measured by FEV_1, is strongly predictive of subsequent mortality among subjects with COPD (9,11,18-21). The direction of the effect is always the same; patients with a greater degree of airway obstruction as manifested by lower initial values of FEV_1 are at a greater risk of dying.

FEV_1, measured in litres, is usually expressed in terms of its

percent of the predicted value for each subject, controlling for age, gender, and height. FEV_1 is also conventionally measured before and after the administration of a bronchodilator in order to determine the extent of the asthmatic component, or airway reactivity, in the individual's disease.

Burrows and Earle (9) followed 200 men with severe COPD (mean FEV_1= 33.5% predicted) for 4-8 years; using multiple linear regression analysis with survival days at both three and five years as the dependent variable, FEV_1 percent predicted emerged as the most important predictor of mortality. After controlling for the effect of percent predicted FEV_1, the change in FEV_1 with a bronchodilator became a significant predictor of mortality. That is, the subjects with a greater reversible component to their disease were at a lower risk for death during the follow-up period.

The same group of subjects was re-analyzed at fifteen years using the log-rank method (19). Subjects were divided into three groups based on each measured variable; observed deaths in each group were compared to the expected deaths, which were based on the survival experience of the entire sample, and chi-square values were used to test for statistically significant differences between groups. This method can be used to control for the effect of specified variables while examining the independent effect of the variable under study. Mortality at fifteen years was 88%. Initial analyses found the percent predicted FEV_1 to be significantly

associated with mortality; after controlling for FEV_1, the change in FEV_1 with a bronchodilator was also significantly associated with mortality. The percent predicted FEV_1 measured post-bronchodilator alone was also a significant predictor of mortality.

Burrows and colleagues (23) selected members of the general population and followed 207 subjects whose FEV_1 was less than 65 percent of the predicted value. They found that for the same age and FEV_1, subjects with clinical features suggestive of asthma demonstrated a slower rate of decline of their FEV_1 over time as well as a lower mortality rate than those subjects with a more emphysematous type of chronic airways obstructive disease.

A previously described study conducted by Anthonisen and colleagues (11) used Cox's proportional hazards regression model to predict survival and noted the same phenomenon. Both pre-bronchodilator FEV_1 and the percent increase of FEV_1 with bronchodilator were significantly related to survival, but post-bronchodilator FEV_1 in the regression equation expressed the effect of both the bronchodilator response and FEV_1 in the regression model.

Postma and associates (20) enrolled 129 subjects with an FEV_1 less then one litre and clinical symptoms of chronic airflow limitation and followed them annually for five years. Analysis by multiple regression of 72 baseline variables found that mortality

was significantly higher in those subjects with the largest annual rates of decrease in the FEV_1. Change in FEV_1 with the administration of the bronchodilator thiazinanium was also significantly predictive of mortality, with subjects exhibiting the greatest bronchodilator response at the lowest risk for dying. Initial FEV_1 measurements were not of any prognostic significance and were not correlated with the pattern of decrease in FEV_1 per year. At eighteen years the data were re-analyzed by the log-rank method and the strongest predictors were found to be the initial FEV_1 percent predicted post-bronchodilator and the change in FEV_1 post-bronchodilator expressed as a ratio of the maximum attainable increase, i.e., to the predicted FEV_1 (18).

Other physiological features of subjects with COPD have been found to be significantly predictive of mortality, but none are as consistent a predictor as the severity of airway obstruction (FEV_1).

AGE

Age has been found by some investigators to be a significant predictor of mortality (11,19). Traver, Cline, and Burrows' analysis of 200 COPD subjects at fifteen years by the log-rank test found that age along with post-bronchodilator FEV_1 were the most important predictors of mortality (19). When these same subjects had been analyzed at three and five years by multiple regression

methods, age did not enter the model as an important predictor (9). Anthonisen and associates, using Cox's proportional hazards model, also found that age and post-bronchodilator FEV_1 were the two important predictors of mortality (11).

$PaCO_2$

The degree of carbon dioxide retention, measured by the partial pressure of carbon dioxide in the arterial blood ($PaCO_2$), has been found by several groups to be significantly associated with mortality (12,14,17), but others have not found such a relationship (11,16,18,21). Boushy and Coates (12) conducted a mixed retrospective/prospective study of 81 subjects selected on the basis of a history of progressive exertional dyspnea associated with clinical findings of diffuse airway obstruction. They divided the study subjects into three groups representing mild, moderate, and severe impairment for each measured parameter of pulmonary function. A chi-square test identified significantly higher mortality rates at six years in the severely hypercapneic group ($PaCO_2$ greater than 45 mm Hg). The degree of airway obstruction, as measured by FEV in three seconds, was not found to be associated with mortality.

Renzetti and colleagues (14) followed 487 subjects with

clinical findings of COPD for 4 years; 65.8% of the study population had an FEV_1 between 0.5 and 1.49 L. Within this range of FEV_1 the authors noted a difference in mortality between the hypercapneic group ($PaCO_2$ greater than 48 mm Hg) and normocapneic group, but did not test for statistical significance. Within the same range of FEV_1 it was also noted that there was a difference in mortality rates between the subjects with a high resting oxygen content in their blood (oxygen saturation greater than 92%) and the group with oxygen saturation values less than 92%. Again the difference was not formally tested for statistical significance.

PaO_2

Other investigators have found that the amount of oxygen in the blood, also measured by the oxygen tension in arterial blood (PaO_2), is a significant predictor of survival (12,17). Boushy and Coates' previously described study (12) reported significantly different mortality rates at six years in three groups of subjects divided on the basis of their oxygen saturation values. Highest mortality rates were found in the severely hypoxemic group (oxygen saturation less than 80%).

France and associates (17) followed 115 patients with a clinical diagnosis of COPD and a FEV_1/FVC ratio of less than 70% for a mean of 2.5 years. The study subjects had a mean FEV_1 of 0.79 L but the range of values was quite wide (0.2 to 3.7 L), as

were the range of values for $PaCO_2$ (31.6-78.2) and PaO_2 (32.3-90.2 mm Hg). Using Cox's proportional hazards model, PaO_2 was found to be the only significant predictor of mortality; when it was controlled no other variables entered the model, although $PaCO_2$ approached statistical significance (p=0.06). Interestingly, this study found no effect of FEV_1 on mortality.

COR PULMONALE

Right heart failure, or cor pulmonale, is a common clinical finding in patients with severe COPD and is caused by pulmonary hypertension. Several investigators have found the presence of cor pulmonale to be significantly related to mortality (9,14,19). Renzetti and colleagues (14) noted different mortality rates at 4 years in patients with and without evidence of cor pulmonale, but there was no control for the confounding effect of severity of disease, nor any formal statistical testing of these differences.

Burrows and Earle's analysis by multiple linear regression found cor pulmonale to be significantly predictive of mortality at three and five years after controlling for the effect of the percent predicted FEV_1 (9). At fifteen years of follow-up the authors controlled for the effects of both age and post-bronchodilator FEV_1 with the log-rank test and found the presence of cor pulmonale to be a significant predictor of mortality, but only in subjects less than 65 years of age (19).

DIFFUSING CAPACITY

The single-breath diffusing capacity (DLCO) is a measure of pulmonary function which describes the ability of the lung to perform gas exchange; i.e., to permit diffusion of oxygen and carbon-dioxide across the capillary bed. Boushy and associates (21) followed 163 male subjects with a clinical diagnosis of COPD for five years, A stepwise multiple linear regression method with survival time as the dependent variable identified DLCO to be the only important predictor after controlling for the effect of FEV_1. Burrows and Earle (9) also found DLCO to be an important predictor of survival at three and five years while controlling for FEV_1 in a stepwise regression. At fifteen years of follow-up there was no significant association between DLCO and mortality (19). Other investigators have examined the relationship between DLCO and mortality in COPD and have found no significant effect (11,19).

SMOKING

Few studies have investigated the possible role of smoking and mortality in this population. Of those investigators that measured the frequency of current smokers entering their studies (11,14,18,20) only Postma and colleagues (18) found that continuing to smoke significantly influenced mortality; in fact, it was the only significant predictor of mortality at eighteen years after

controlling the effects of percent predicted FEV_1 post-bronchodilator and the increase in FEV_1 with bronchodilator. This population, 64% of whom were current smokers at baseline, had been analyzed at five years when current smoking was not a significant predictor of mortality (20). The frequency of current smoking in the other two study populations where no association with three-year mortality was found, ranged from 39.9% (11) to 71.1% (14). Current smoking may not be the best measure of smoking status as a predictor of mortality; COPD patients with more severe symptoms may be more likely to quit smoking than the "healthier", or less symptomatic patients, who in turn are less likely to die.

NUTRITIONAL STATUS

Nutritional status has long been associated with both mortality (12-13,22,24,27) and morbidity (27-29) in subjects with COPD. An early study conducted by Boushy and Coates (12) in 1964 divided 81 subjects with a history of progressive exertional dyspnea into three groups classified by clinical type. One group of ten subjects was created on the basis of a weight loss of greater than 10 pounds with the onset of dyspnea. A significantly higher mortality rate after six years was found in this "cachectic" group when compared by the chi-square test against the primarily dyspneic group (n=21) and the bronchitic group (n=44).

An essentially descriptive study conducted in 1965 in which

44 patients with a clinical diagnosis of COPD were followed for three years, reported that 37% of the cohort had lost at least 10% of their initial weight at the end of the follow-up period (13). This group experienced double the mortality (32% vs. 16%) of the subjects who had not lost weight and showed evidence of a greater degree of airway obstruction as manifested by a reduction of maximum mid-expiratory flow rates and increased airway resistance.

Vandenbergh and colleagues (22), in 1966, conducted a five-year follow-up of 100 patients with a clinical diagnosis of COPD and a $PaCO_2$ greater than 45 mm Hg. A 10% loss of initial body weight which persisted to the end of the follow-up period was described in 71% of the study population. At both three and five years there was a mortality rate approximately twice that in the group that lost weight as compared to the control group, but these differences were not formally tested for statistical significance. Of importance as well, none of the above mentioned studies made an attempt to control for the severity of disease so no conclusions may be drawn concerning the independent association of weight loss and mortality in these subjects.

More recently, Wilson and associates (24) examined a subset of 779 non-hypoxemic men drawn from the Intermittent Positive Pressure Breathing (IPPB) trial (11). These investigators set out to ascertain the independent influence of nutritional status on mortality using Cox's proportional hazards model. Each subject's

body weight was expressed as a percentage of the ideal standard (%IBW) and used in a stepwise multiple regression equation. When adjusted for age, % predicted FEV_1, % predicted total lung capacity (TLC), exercise capacity, and resting heart rate, the % IBW was a borderline significant predictor of mortality ($p=0.05$). Adjustment for exercise capacity, known to be associated with weight loss (24,25), may in fact overadjust since decrease in muscle mass may be caused by weight loss.

A one year follow-up of 39 patients with severe COPD (mean FEV1=972 ml) examined both mortality and morbidity endpoints (27). Thirty one percent of the patients required hospitalization during the subsequent year, of these 5 died. There was no difference in the frequency of 5% weight loss during the previous year in the hospitalized and non-hospitalized groups, nor were there any differences in age or measured pulmonary function parameters. Mean triceps skinfold thickness (TSF) values, expressed as a percentage of standard, were significantly lower in the hospitalized group, implying that body fat stores were significantly lower in this group. Given that there is known to be a decline in nutritional status during hospitalization, it was important that all measures in the hospitalized group were made on admission.

Hoch and colleagues (28) sought to examine the relationship between nutritional status and morbidity in 189 patients identified as having chronic airflow limitation by virtue of an FEV_1/FVC ratio

of less than 60%. Seventy patients (37%) were identified as having at least one nutritional risk factor: %IBW less than 90%, arm muscle circumference (AMC) less than 90% standard, or weight loss of greater than 15 pounds. These subjects had significantly more overall and pulmonary-related hospital admissions than the controls. The authors did not attempt to control for the severity of airway obstruction in their analysis.

Driver and associates (29) compared 18 stable COPD men with an FEV_1 less than 60% predicted to 9 men with COPD suffering from acute respiratory failure requiring mechanical ventilatory assistance. Significantly lower values of TSF, AMC, and IBW, all measured immediately upon admission to hospital, were reported in the 9 patients with acute respiratory failure.

Measurements of nutritional status have been associated with various parameters of pulmonary function in patients with COPD (30-32) and as such will be important to consider as potential confounding variables. Openbrier and colleagues (30) described the relationship between lung function and nutritional status in 14 patients defined as having emphysema; they were differentiated from subjects with chronic bronchitis on the basis of a diffusing capacity less than 60% predicted and all had an FEV_1/FVC ratio less than 70% predicted. Initial measures identified 43% of the subjects with an ideal body weight of less than 90%. Significant correlations were reported between %IBW and both FEV_1 ($r=0.70$) and

DLCO (r=0.61). In an even smaller study the authors described a 22 month follow-up of eight well-nourished (greater than 90% IBW) and 6 poorly-nourished (less than 90% IBW) patients with the same criteria for emphysema (31). Those patients with low initial ideal body weights had a more rapid decline in FEV_1 than those with higher body weights. Univariate analyses performed at the beginning and end of follow-up found that percent IBW correlated significantly with FEV_1, FEV_1/FVC, DLCO, and maximum inspiratory mouth pressure (PI_{max}). A similar cross-sectional study of 60 outpatients with COPD (FEV_1 less than 80% predicted) reported that percent IBW was directly correlated with percent predicted FEV_1 and percent predicted DLCO, and was inversely related to $PaCO_2$ and oxygen consumption at rest (32). In neither of these two studies were the correlation coefficients reported.

Several small clinical trials have looked at the effect of nutritional supplementation on some of the clinical indicators of COPD (33-35). A small, but well-designed, study conducted by Efthimiou and colleagues (33) demonstrated that three months of supplemental oral nutrition improved the nutritional status of malnourished COPD patients as well as their respiratory muscle and handgrip strength. General well-being, breathlessness scores, and six-minute walking distances also improved significantly with improved nutritional status.

The other two studies (34,35), where the nutritional

supplementation was only delivered for eight weeks found no effect of supplementation on either the respiratory muscle strength or endurance of malnourished COPD patients. Neither of these studies were successful in improving the nutritional status of their patient population by such parameters as TSF, AMC, serum albumin, or the lymphocyte count, although one study reported a significant increase in mean body weight (34).

Malnutrition is clearly known to be a significant clinical feature of COPD, yet apart from percent ideal body weight, weight loss and anthropometric measurements (TSF and AMC), there is little information on other indicators of nutritional status in this patient population. To date, no large scale epidemiologic survey has investigated the extent of malnutrition among COPD patients and very few studies have examined the independent role that malnutrition plays with respect to mortality in patients with COPD. The need to control for confounders in order to establish whether malnutrition is an independent predictor of mortality is obvious. Without such control it will not be clear whether weight loss is a marker of disease severity, i.e., a natural consequence of disease, or whether weight loss independently has a negative impact on the clinical course of patients with COPD.

MATERIALS AND METHODS

PATIENT POPULATION

The study population consists of all patients recruited into the National Institutes of Health (NIH) trial of the effectiveness of negative pressure ventilation (NPV) in severe chronic obstructive pulmonary disease (COPD). The sampling frame for the study is composed of patients from all major hospital centres in Montreal as well as self-referrals. Patients attending respiratory clinics at the following hospitals were routinely screened to identify potential study subjects: Montreal Chest Hospital, Montreal General Hospital, Royal Victoria Hospital, Hopital Notre-Dame, Hopital St. Luc, Hopital Sacre-Coeur, Hopital Maisonneuve-Rosemont, and Hopital Hotel-Dieu. In addition, personal letters were sent to every practising respiratory physician in the Montreal area, and newspaper, television and radio coverage was arranged to solicit volunteers.

ELIGIBILITY

All patients with symptomatic COPD were potentially eligible if they were between the ages of 30-75, had a pre-bronchodilator FEV_1 of less than 50% predicted, a pre-bronchodilator FEV_1/FVC ratio of less than 0.6, were able to speak English or French, and lived

in the greater Montreal area. In addition they must have reported a grade 4 or 5 dyspnea score on the American Thoracic Society (ATS) questionnaire (36); that is, they became breathless upon walking 100 yards or upon dressing or undressing.

Patients were excluded if, in response to two inhalations of salbutamol (100 mcg each), their FEV_1 increased to greater than 60% predicted, or if their FEV_1 increased by 25% or more. Patients with a risk of acute medical emergencies such as severe or unstable angina pectoris, previous episodes of acute pulmonary edema, previous GI hemorrhage, or brittle insulin-dependent diabetes were excluded, as were patients unable to participate in the trial of NPV owing to morbid obesity, endstage metastatic malignancy, significant neurological abnormality, or pregnancy.

A total of 1231 subjects were identified, of these 348 met the initial eligibility requirements and agreed to participate in the study. Reasons for not including the 883 other patients are listed in Figure 1. The most frequent reasons were lack of sufficient dyspnea, patient refusal, and medical contraindications.

The 348 recruited patients participated in a four-week stabilization period during which time they were visited at home by a nurse who assessed the candidates' suitability in terms of living arrangements and social support. At this time blood samples were drawn for biochemistry and haematology work-ups. A number of

patients, 51 (15%), did not receive a home visit, so do not have these variables recorded. These patients were excluded from the trial at this point.

A total of 164 subjects were excluded from the NPV trial during the stabilization period. Figure 1 lists the reasons for exclusion. Of these, 73 declined further participation, 40 had new or previously unreported medical contraindications, 20 had psychological or social problems precluding participation, 19 had unstable lung function or unstable sensation of dyspnea, 8 patients died during this period, and 4 patients could not be treated owing to the distance from home to hospital. Of the 40 medical contraindications, 10 were physical problems such that the subjects would have been unable to complete a cycle ergometry test, an additional 8 were various mental problems, chiefly depression, and 7 were cardiac problems. Only one patient was excluded at this point because of a possible neoplasm. A total of 184 patients entered the Montreal Chest Hospital Centre for extensive testing and training with the respirator, and were subsequently randomized into the NPV trial.

BASELINE DATA

All 348 patients recruited for the NPV trial had the following baseline data obtained on an initial hospital visit.

Demographic Information

The age, sex, place of residence, current living arrangements, and smoking status were collected by interview.

Physiological Variables

Spirometric data, which included the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC), were collected on a Vitalograph spirometer. Volumes were corrected to the barometric pressure and temperature standard (BTPS). The best FEV_1 and FVC were selected from two reproducible volume-time curves as recommended by the ATS (37). Spirometry was obtained pre- and post-administration of two inhalations of 100 mcg each of salbutamol.

Anthropometric Measures

Height and weight were measured wearing indoor clothing but no shoes. The body mass index (BMI) was used in order to quantify weight adjusted for height. This index is derived by dividing body weight in kilograms by height in meters squared. Body composition differences between men and women are such that slightly different cutoffs must be used when defining weight categories for each sex. Men with BMI's less than 20 were categorized as underweight, whereas the cutoff for underweight women was 18.8. The cutoff BMI

value for overweight was 27 for both men and women. These cutoff values are based on the 5th and 95th percentiles, respectively, of US white men and women aged 65-90 years (38).

HOME VISIT DATA

As stated above, blood samples were drawn on a total of 297 patients who received a home visit. The biochemistry work-up included values for serum albumin, calcium, and phosphorus. The haematology assessment included values for hemoglobin, haematocrit, red blood cell volume, as well as the leucocyte count and differential.

NPV TRIAL DATA

Anthropometric measures including height, weight, triceps skinfold thickness (TSF), and mid-arm circumference (MAC) were obtained by a single technician. The site for the measurement of the TSF and MAC was located at the midpoint between the olecranon and acromion processes. Three measurements were taken and the mean of the two closest readings were used (39). The arm muscle circumference (AMC) was derived from the MAC minus the TSF multiplied by 0.314 (39).

In addition to spirometry data collected as previously described, lung volumes were measured on 184 patients who entered

the hospital for testing, training, and randomization into the trial of NPV. Lung volume measurements were performed with the patient seated in a volume displacement body plethysmograph. The thoracic gas volume was measured by the Boyle's Law technique (40).

Single breath diffusing capacity for carbon monoxide (DLCO) was measured using a Morgan gas transfer system (P.K. Morgan Ltd. Chatham, Kent, England). The average of the two highest values was selected if these were within 10%, or, if not achieved in five trials, the highest DLCO measured was used. DLCO was corrected to a standard hemoglobin concentration of 14.6 g/dL (41).

Maximal respiratory mouth pressures were measured using a Vacuumed 1002 mouthpiece attached to a Validyne pressure transducer (± 200 cm H_2O). Maximal inspiratory pressure was measured at functional residual capacity (FRC) with a small air leak provided by a 14 gauge needle through the mouthpiece. Maximal expiratory pressure was measured at total lung capacity (TLC). The best of three trials was reported for each maximal inspiratory and expiratory pressure.

Arterial blood gases were collected with the patient sitting and at rest. Arterial oxygen and carbon dioxide tensions (PaO_2 and $PaCO_2$) were measured using a Fischer Scientific blood gas analyzer (Lenepton, MA).

FOLLOW-UP INFORMATION

Patients meeting the eligibility criteria described previously were asked to provide written consent to be followed after the completion of the NPV trial, which lasted three months. Ethical approval for this study was obtained from the ethics committee of the Department of Epidemiology and Biostatistics, McGill University. Those patients providing written consent were contacted by a research assistant every three months by telephone to obtain data on any hospitalizations and their duration, data on weight change and vital status. Patients who were not entered into the NPV trial were first contacted three months after their recruitment clinic visit.

Patients who were unable to be reached were traced through the home-care program at Maisonneuve-Rosemont Hospital and through the hospital or personal physician providing the patient's regular care. The vital status of all patients lost to follow-up was traced through the Direction Generale de l'administration et des systèmes d'informations in Quebec City and a copy of the death certificate was obtained for each death. This request was approved by the commission de l'acces a l'information de Québec.

OUTCOME DATA

Mortality

The event, date, and cause of death as recorded on a death certificate was requested for all patients known to have died during the follow-up period.

Weight

At each telephone interview the respondent was asked to report current weight, which was recorded in kilograms. A pattern of weight change over the follow-up period was thus obtained for each patient. Weight change will be expressed as a percentage change from baseline, i.e., weight recorded at recruitment. Percent weight change over the entire follow-up period will be divided by the total survival time in years in order to get a mean percent weight change per year for each subject.

DATA ANALYSIS

Descriptive analysis consisted of reporting the mean values and standard deviations of those continuous variables as well as the percentages of those categorical variables which describe the physiological and demographic characteristics of the entire study population (n=348) and the population randomized into the NPV trial (n=184). These analyses were performed using the SAS statistical

program for personal computers (42).

The survival experiences of the study population grouped by categories of each of the possible predictors of survival were examined and those of possible interest will be presented. The product-limit (Kaplan-Meir) estimate was used to determine the cumulative survival distributions (43). The Mantel Cox (44) statistic was used to test for the equality of the survival curves.

Multivariate survival analysis was performed in order to examine the relationship between survival and a set of explanatory variables. This analysis is based on the Cox proportional hazards regression model (45). All analyses performed with respect to survival were done using the BMDP statistical program (46). The proportional hazards model is given by

$$hi(t) = ho(t)\ \exp(\underline{B})$$

or

$$\ln[hi(t)/ho(t)] = \underline{B}$$

where hi(t) is the hazard rate for an individual, $\underline{B}$ is a vector of unknown regression coefficients and ho(t) is an unknown hazard function for an individual. The model contains two assumptions. The first assumption is that of proportionality, i.e. the multiplicative relationship between the underlying hazard function and the log-linear function of the covariates. Thus the ratio of the hazard functions for two individuals with different sets of covariates does not depend upon time. The second assumption of the

model is the log-linear effect of the covariates upon the hazard function.

The regression coefficient indicates the relationship between the covariate and the hazard function. The estimated set of regression coefficients arising from this process relates the effect of each covariate to the survival function and permits identification of those variables significantly associated with survival. A positive coefficient increases the value of the hazard function, i.e., negatively effects survival. A negative coefficient has the reverse interpretation.

The relative risk is given by hi(t)/ho(t), the ratio of the risk of death per unit time for a subject with a given set of covariates, to the death rate for a subject whose covariates are at "baseline" level.

The regression model was fitted using a stepwise approach; at each step a variable is entered or removed from the regression equation on the basis of a significance probability computed by the maximum partial likelihood ratio (MPLR) test. This method estimates chi-square statistics and their corresponding p-values for each variable. The variable with the largest p-value is removed from the full model if it is larger than the remove limit of 0.15. If no variable has a p-value larger than the remove limit, the term with the smallest p-value is entered if it is less than the enter

limit of 0.10. The change in -2 log likelihood, a chi-square statistic, was used to test the significance of the association with mortality of a subset of variables after adjusting for other independent variables.

Determination of the predictors of mortality by the Cox regression model was performed on two sets of data. The first data set consisted of the 384 study subjects who were initially recruited into the NPV trial. The variables available for this analysis included the baseline variables: age, gender, current smoking status, spirometry values, blood chemistry and hematology values, home oxygen status, and body mass index; weight change over the follow-up period was also examined as a predictor of mortality.

The second data set consisted of the 184 patients who entered the hospital for extensive testing and randomization into the NPV trial. Variables that were examined in addition to those above include: complete lung function values, the arterial oxygen and carbon dioxide tensions as well as the anthropometric measures of triceps skinfold thickness (TSF) and arm muscle circumference (AMC).

RESULTS

The results presented are of a one to three year follow-up of 384 patients with severe COPD. The baseline characteristics of the population are described, as well as the survival experiences of various subgroups. Significant predictors of mortality are described in terms of a regression equation using Cox's proportional hazards model.

RECRUITED PATIENT POPULATION

Baseline Characteristics

The characteristics of the entire study population, i.e. all 348 subjects recruited into the trial, are summarized in Table 2. The mean age of the sample was 63 years, the youngest subject being 31 years old and the oldest being 75 years old. Half of the study subjects were between the ages of 60 and 70 and 15% were older than 70 years. The data set consisted of 133 (68.1%) men. A small percentage of the study subjects (21.3%) were still smoking cigarettes at the time of recruitment; virtually all subjects had smoked in the past. The spirometric values are consistent with those described for patients with severe airway obstruction. The mean FEV_1 was 27.7% predicted, the median value was 27% predicted and 38% of the subjects had an FEV1 less than 30% predicted. The mean body mass index (BMI) was 24, and the median value was also

24, with a range of 13 to 41.

There were 56 subjects (16.2%) recruited while receiving home oxygen for their disease. Table 3 summarizes the comparison of groups receiving home oxygen and those not in terms of disease severity. As would be expected, those receiving home oxygen are more severely affected by COPD; this is reflected in lower percent predicted FEV_1 values for this group. The mean age differs between groups as well, with younger subjects more likely to receive home oxygen. There was only one subject who continued to smoke while on home oxygen as this is clearly contraindicated.

A comparison of the characteristics of the study population by gender is presented in Table 4. As expected, mean heights and weights were significantly greater amongst the male subjects. Plasma hemoglobin values were also significantly higher among the men. There were no other significant differences by gender.

As described in the methods chapter, BMI values were used to define underweight, normal weight, and overweight categories. A total of 62 subjects (18%) were categorized as underweight; 45 were men and 17 were women. There were 171 subjects (50%) defined has having a normal weight for height, 111 men and 60 women. Overweight subjects numbered 109 (32%) and 76 of them were men and 33 were women.

The range of mean percent weight change from baseline per year ranged from a gain of 21% to a loss of 20% and the mean change in weight was a loss of 1.5%. Just over one-quarter of the sample (26.1%) gained weight, 20.3% reported no weight change, and 53.6% reported some weight loss over the follow-up period. Nearly one-fifth of the subjects (19.1%) reported a loss of greater than 5% of their recruitment weight per year and 6.4% reported a mean weight loss per year of greater than 10%.

Those subjects who reported weight losses of greater than 5% baseline tended to be normal or even overweight at recruitment. Only 14.5 % of the subjects who were underweight at recruitment reported a loss of 5% or more of their initial weight per year; in fact, 43.6% of the underweight subjects reported some weight gain over the follow-up period. The accuracy of these self-reported weights is however, open to question and it is important to note for the interpretation of survival analyses, that the last reported weight is not always that directly preceding death.

A comparison of the population characteristics by weight category is presented in Table 5. Analysis of variance procedures revealed statistically significant differences between the mean percent weight loss, percent predicted FEV_1, and the plasma hemoglobin concentrations in the three weight categories. A trend was noted in all three variables; their values increased with increasing BMI. Correlation coefficients revealed the same

pattern; BMI expressed as a continuous variable was directly correlated with hemoglobin concentration, percent predicted FEV_1, and mean percent weight loss per year.

Follow-up

Subjects who contributed no follow-up time (n=29) were excluded from further analysis. Table 6 summarizes the comparison of the baseline characteristics of those not followed, 8.3% of the sample, and the remaining 91.2% of the sample on whom follow-up information was obtained. The only difference between the two groups of subjects was their percent predicted FEV_1; those subjects not followed had significantly higher percent predicted values (31.6%) than those who were followed (27.4%). Only partial follow-up was obtained on an additional 57 subjects, the majority of whom (n=46) were lost at various stages of the follow-up because they had moved or changed their phone number; these subjects were included in all stages of the analysis.

Mean survival time of the 319 subjects who contributed some follow-up time was 20.3 months; the median survival time was 20.2 months. The minimum follow-up time was 36 days, this patient was identified as someone who refused to participate in the follow-up one month after recruitment; the shortest time to death was 47 days. The maximum follow-up time was 1155 days, or 38 months.

At the end of the follow-up period 65 subjects (18.7%) had died and provincial death certificates had been obtained for 52 of those cases. The underlying cause of death for 41 (79%) of these patients was respiratory failure due to COPD. Various malignant neoplasms caused the death of a further 5 (10%) and the 6 (12%) remaining subjects died from a variety of other causes.

Survival Experience

In order to identify variables associated with survival in this population, the cumulative survival distribution using the product-limit (Kaplan-Meir) estimate was determined for the study subjects grouped by categories of suspected predictors of mortality. The continuous variables were grouped into three categories according to their frequency distribution; the bottom 25^{th} percentile, the 26^{th} to 74^{th} percentile, and the top 25^{th} percentile of each variable were grouped together to form three categories. The only exception was the grouping of BMI which was done according to the standards described above in which 18% were categorized as underweight, 50% were normal weight, and 32% were overweight. Sex, home oxygen status, and smoking were already naturally categorized into two groups. The Mantel-Cox statistic was used to test the equality of the survival curves.

Figures 2-6 contain the cumulative survival functions of each of the independent variables examined with the product-limit

estimate and tested by the Mantel-Cox statistic. Survival curves grouped by body mass index (Fig 2) were strongly significantly different ($p < 0.005$) and exhibited a direct relationship with survival. The crude mortality rate for the underweight group was 34%, while mortality was 21% in the normal weight group and 12% in the overweight group. This direct relationship was evident throughout the greater part of the follow-up period.

The three survival curves of percent original weight change per year (Fig 3) were also highly significantly different. However, it was the subjects with the middle percentile values for weight loss (between 0.38% weight gain and 3.71% weight loss) who had the poorest survival experience. These subjects had an overall mortality of 30%; those who reported annual losses of 4% or more of their original weight had a mortality of 15% and those subjects who reported some weight gain during the follow-up period had a mortality rate of 7.5%. The most recent weight recorded for subjects is within the three months preceding death, but these data were not available for 17 subjects.

The survival curves for the three groupings of percent predicted FEV_1 (Fig 4) were significantly different. Subjects with low values for percent predicted FEV_1 demonstrated a higher overall mortality (38%) than the other two groups whose mortality rates were both 14%. The difference in mortality experiences became very pronounced after approximately one year of follow-up.

The survival experience for those subjects receiving home oxygen was far worse than those not receiving this treatment (Fig 5). Mortality among the subjects receiving home oxygen was 50% compared to a mortality rate of 15% in the group not receiving home oxygen. The difference in mortality rates was highly significant ($p < 0.0001$).

There was no statistical difference between the survival curves of those patients who continued to smoke and those who had stopped before recruitment. There were only 4 deaths in the group of current smokers (n=59) and these occurred early in the follow-up period, whereas the much larger group of non-smokers (n=215) had 39 deaths which occurred later in the follow-up period.

The three survival curves for each of the blood values, hemoglobin, serum albumin, and lymphocytes were not statistically different, however, subjects with low values of hemoglobin (Fig 6) appear to fare worse throughout the entire follow-up period than those with the middle and high values.

Male and female survival curves did not produce evidence of a significant gender effect. Overall mortality for males was 22%; mortality for females was 16%. There was no difference by age group.

Multivariate Survival Analysis

Cox's proportional hazards regression model was used to determine the significant predictors of mortality in this population. In order to identify the significant predictors of mortality in our study population our first model employed a purely forward approach; i.e., only those variables with p-values computed by the MPLR method less than 0.10 were entered into the regression equation. The results from this approach are summarized in Table 7. The significant predictors of mortality and their corresponding relative risks (RR) and 95% confidence intervals (CI) comparing the 25^{th} to the 75^{th} percentile were as follows: percent predicted FEV_1, RR=1.54, 95% CI (1.49, 1.59); BMI, RR=1.86, 95% CI (1.76, 1.97). The relative risk for receiving home oxygen therapy compared to not receiving oxygen was 3.17, 95% CI (1.85, 5.45).

In order to determine the extent, if any, of the influence of percent weight change on the survival of these patients a new regression model was estimated with percent weight change forced in separately. The coefficients and standard errors of percent predicted FEV_1, body mass index, and home oxygen changed very slightly when annual percent weight loss was included in the regression equation. The relative risk for every percentage point change of annual weight loss was 1.02, 95% CI (0.97, 1.06).

The forward stepwise approach was used to identify the

significant predictors of survival in the 263 subjects who did not receive home oxygen. In this analysis the number of deaths was reduced from 65 to 39. When subjects on home oxygen were eliminated from the analysis, the only significant predictor of mortality was the percent predicted FEV_1. The relative risk for every percent predicted decrease in FEV_1 was 1.09, 95% CI(1.02, 1.15); the p-value for BMI in this regression equation was 0.31.

SUB-GROUP OF RANDOMIZED PATIENTS

A separate analysis was conducted on the subset of 184 study subjects who had been randomized into the NPV trial. These subjects had more extensive baseline testing than those subjects who were recruited but not randomized. As a consequence this analysis has the advantage of examining a greater variety of risk factors and potential confounders.

Baseline Characteristics

Table 8 summarizes the baseline characteristics of the randomized study subjects. There were no notable differences between the recruited and randomized study subjects (Tables 2 and 8, respectively). There were slightly more men and less smokers in the randomized group, but these differences were not statistically significant. The demographic and physiological variables measured in both groups were similar.

There were a total of 27 subjects (15%) randomized into the NPV trial while receiving home oxygen. Table 9 summarizes the comparison of the groups receiving and not receiving home oxygen. Again, a significantly lower mean percent predicted FEV_1 was found in the group receiving home oxygen; the mean percent predicted diffusing capacity (DLCO) and mean vital capacity (VC) were also significantly lower in this group. The arterial carbon dioxide concentration ($PaCO_2$) was considerably higher in the group receiving home oxygen and there were no smokers in this group.

A comparison of the characteristics of the population by sex is found in Table 10. As with the recruited population, there were significantly higher mean heights, weights, and plasma hemoglobins among the men. Females had significantly lower body mass indexes, as well as lower arm muscle circumferences (AMC). Higher triceps skinfold thicknesses (TSF) were found in the women, as expected.

Subjects were categorized into three body mass index groups according to the criteria described previously. Of the 34 subjects (18.5%) defined as underweight, 23 were men and 11 were women. There were 93 subjects (50.5%) defined as having a normal weight for height; 66 were men and 27 were women. Overweight subjects numbered 57 (31%), of these 44 were men and 13 were women.

The study subjects lost an average of 1.7% of their initial

body weight per year over the follow-up period. Yearly weight change ranged from a gain of 21% of initial recruitment weight to a loss of 20% of initial weight. Just under 1/3 (30%) of the subjects reported a yearly weight gain, 10% reported no weight change, and 60% reported some weight loss in one year. Of those who lost weight, 20% lost greater than 5% of their recruitment weight and 8% lost over 10% of their initial weight per year.

As in the larger study population, those subjects who lost a larger percent of initial weight tended to have larger body mass indices. Only 14.7 % of the subjects who were classified as underweight at recruitment reported weight loss of 5% or more of their initial weight in one year, as opposed to 25% of the overweight who lost the same percentage of initial weight. Just over 1/3 (35.3%) of the underweight subjects reported some weight gain.

Table 11 summarizes the comparison of the study population by weight category as defined by body mass index. As in the population of all recruited subjects, values for hemoglobin were significantly different by BMI category. Again these values exhibited a direct relationship with body mass index.

Several variables measured in the randomized group of patients but not in the recruited group were found to be significantly different by BMI category. Diffusing capacity, expressed as the

percent predicted value, expiratory mouth pressure and the FEV_1/FVC ratio were significantly different by weight group; the values for each variable were higher in each increasing weight category. As might be expected, both triceps skinfold thickness and arm muscle circumference were related to increasing weight.

Follow-up

Only four subjects (2%) refused to be followed after randomization into the trial. These subjects contributed no survival time in the follow-up period, so were excluded from further analysis. Table 12 summarizes the comparison of the baseline characteristics of those subjects followed and those not. The only difference between the two groups was in pack years of cigarettes smoked; those subjects not followed had accumulated significantly more pack years of cigarettes (127.3) than those who were followed (64.4). Of the 180 subjects with some follow-up, 40 subjects (22%) contributed only partial follow-up. The majority of these subjects (n=34) were lost to follow-up because they moved or changed their phone number. The other 6 subjects refused further participation.

The median survival time to date for these 180 subjects was 20.1 months; mean survival time was 20.5 months. Minimum length of follow-up was 82 days; this was a patient who refused to participate any further in the follow-up. The shortest time to

death after recruitment was 88 days, while the longest follow-up was 1155 days, or 38 months.

At the end of the follow-up period 30 (16.3%) of these subjects had died. Death certificates received for 23 of these subjects revealed that 20 (87%) died from respiratory failure due to COPD. A malignant neoplasm caused the death of 1 subject; the other 2 deaths were due to complications from ulcers.

Survival Experience

The cumulative survival distributions determined by the product-limit estimate as above, were produced for the subjects grouped according to the frequency distributions of various independent variables. Body mass index was grouped according to previously described standards and arterial carbon dioxide concentration ($PaCO_2$) was dichotomized into hypercapneic (PaCO2 > 45 mm Hg) and normocapneic groups. All other continuous variables were grouped by frequency as described above. Figures 7-11 present the survival curves of those independent variables showing significant effects.

Again the survival experience for those subjects receiving home oxygen was significantly different from those not receiving home oxygen (Fig 7). There was considerably higher mortality among those subjects receiving home oxygen than those not receiving home

oxygen in this subset. Of the 26 subjects receiving home oxygen, 14 (54%) died by the end of the follow-up period. Of the 152 subjects not receiving home oxygen, only 16 (11%) had died by the same time.

The survival curves of subjects grouped by BMI category were not significantly different in this population. Mortality for the underweight group was 21%, the medium weight group had an overall mortality of 19%, and the overweight group had a mortality of 11%. There was no difference between the three survival curves of subjects grouped by mean annual weight change distribution. There were 7 subjects on whom weight status 3 months before death was not available.

There was no significant difference between the survival curves for those subjects grouped by values of percent predicted FEV_1. The survival curves for subjects grouped by the percentile values for hemoglobin, serum albumin, or lymphocytes were not different.

There was no difference between the survival curves of men and women in this population; the men appeared to do worse in the first year of follow-up, but the curves were not statistically different. Overall mortality among men was 19%, among women mortality was 10%.

There was no difference in the survival experiences between the group of subjects who continued to smoke and the group who had stopped sometime previous to recruitment. There were only two deaths in the small group of smokers (n=30). Neither was there a difference in survival between subjects grouped on the percentile values of their cumulative pack years of cigarettes.

Subjects defined as hypercapneic ($PaCO_2$ > 45 mm Hg), had a significantly higher mortality throughout the follow-up period (Fig 8). The mortality rate in the hypercapneic group was 36% compared to a mortality of 8% in the normocapneic group. Subjects grouped on percentile values for PaO_2 did not have different survival experiences.

The survival curves for subjects grouped by frequency of percent predicted diffusing capacity were significantly different (Fig 9). There was evidence of a direct relationship with survival; subjects with low diffusing capacities had an overall mortality rate of 28%, those with middle values had a mortality rate of 18%, and those with high percent predicted values of diffusing capacity had a mortality of 3%.

Survival experiences for subjects grouped by their FEV_1/FVC ratio were also significantly different (Fig 10). There was a direct relationship between the percentile values of FEV_1/FVC and mortality; those with low FEV_1/FVC ratios had the highest mortality

(29%) and subjects with high values had the lowest mortality (9%). Subjects with mid-range values of their FEV_1/FVC ratio had an overall mortality of 14%.

Subjects grouped by their values for triceps skinfold thickness (TSF) showed no statistical difference in mortality over the follow-up (Fig 11). Those with low TSF values however, had a higher overall mortality (25%) than those with medium (14%) and high values (13%) for this variable. There was no difference in mortality experience between the subject grouped by their values of arm muscle circumference (AMC).

There were no different survival experiences noted in the study subjects grouped by the percentile values of any of the lung volume measurements (TLC, FRC, or VC). Neither were there different survival curves for those subjects grouped by the percentile values of their inspiratory or expiratory mouth pressures (PI_{max} or PE_{max}).

Multivariate Survival Analysis

Cox's proportional hazards model was used to create a regression equation containing the predictors of mortality in this population. A forward stepwise approach identified a model which included the significant predictors of mortality. They were home oxygen and arterial carbon dioxide concentration. When these two

variables were included in a regression model with each of the nutritional variables separately, both body mass index, and triceps skinfold thickness expressed as continuous variables significantly predicted survival. The results of this regression modelling are summarized in Table 13. The inclusion of DLCO in the regression model caused multicollinearity because of its strong correlation with both FEV_1 and $PaCO_2$. As a result, it was not included in the forward stepwise model and did not have the opportunity to be identified as a significant predictor.

Comparing the 25^{th} to the 75^{th} percentile, the relative risk (RR) for BMI was 2.09, 95% CI (1.92, 2.27) and the RR for TSF was 1.80, 95% CI (1.66, 1.96). When BMI and TSF were included in the regression model along with use of home oxygen and $PaCO_2$, only home oxygen use and $PaCO_2$ were significant predictors. The relative risk for receiving home oxygen compared to not receiving home oxygen was 3.03, 95% CI (1.16, 7.92). The relative risk for $PaCO_2$ comparing the 25^{th} to the 75^{th} percentile was 0.93, 95% CI (0.87, 0.98). Risk of mortality increased with the rise in values of PaCO2. The inclusion of annual weight change and arm muscle circumference did not change the parameters for home oxygen or $PaCO_2$, nor were they significant predictors of survival.

When the forward stepwise approach was employed on the population of randomized subjects who received no home oxygen (n=152), none of the measured variables were able to significantly

predict survival. Only 10 deaths occurred among this group, so the power of this analysis was severely limited.

In summary, two survival models are apparent for the different study populations, those recruited and those randomized. In the larger sample where few baseline variables were measured, the significant predictors of mortality were, receiving home oxygen, the percent predicted FEV_1, and body mass index. In the subset that had more variables describing the physiological characteristics, receiving home oxygen, arterial carbon dioxide concentration, and either body mass index or triceps skinfold thickness were the significant predictors of mortality.

DISCUSSION

This chapter includes a discussion of the study results in relation to other studies of a similar nature. The representativeness of the study population with respect to previously studied COPD patient populations in terms of the severity of disease manifested as well as the prevalence of malnutrition will be discussed. The mortality experience and the predictors of mortality in COPD populations will be examined as well as the methodology used to derive those estimates. The impact of malnutrition in COPD will be discussed as well as the implications for clinical practice and treatment of COPD. Finally, the important limitations of this study will be identified with suggestions for possible directions for the future.

STUDY POPULATION

The study population was, by definition, severely affected with COPD. Study subjects were selected on the basis of both the degree of airway obstruction, (FEV_1 < 50% predicted) and severe dyspnea. The patients meeting these criteria had a mean FEV_1 of 28% of the predicted value. One-third of the study subjects were hypercapneic ($PaCO_2$ >= 45 mm Hg).

Body mass index (BMI) estimates total body mass and is highly correlated with the amount of body fat (47). According to

published standards of BMI in the elderly population (38), 16% of the men and 22% of the women in our study fell below the 5th percentile of the distribution and the study population had an overall prevalence of malnutrition of 18%. This compares to 27% of the subjects defined as underweight when classified according to an ideal body weight (IBW) of less than 90% of that predicted by height and weight tables (48).

Triceps skinfold thickness, another measure of nutritional status, is highly correlated with total body fat among the elderly (38). According to published standards (39), TSF values for men and women of 7.5 mm and 9.9 mm, respectively, represent 60% of the standard and are found in less than 5% of the general population. These levels represents significant loss of adipose tissue (39). Nearly one-quarter (24%) of the men in our study and 12% of the women had TSF measurements of less than 60% of the standard.

The measure of arm muscle circumference (AMC) is traditionally used to determine the body's protein stores (39). It reflects muscle wastage, so correlates well with manifestations of protein-calorie malnutrition (39). According to published standards (39), AMC values for men and women of 15.2 and 13.9 mm respectively are less than 60% of standard and reflect severe protein-calorie malnutrition. Only two of the men and none of the women in our study had AMC values reflecting this level of severe malnutrition. In fact, except for those 2 men, all AMC values were above the

standard.

The reported prevalence of malnutrition in patients with COPD varies from study to study. Reports range from as high as 63% (32) and 50% (49) among hospitalized patients to 24% (24) in out-patients when 90% IBW is defined as malnutrition. Braun and colleagues (32) studied a COPD population similar to ours and found that 33% of the subjects had TSF measurements of less than 60% of standard. While reporting a prevalence of malnutrition of 63%, they found no patients with AMC values less than 60% standard.

MORTALITY

The recruitment time for the NPV trial covered a period of approximately two years. The study subjects were entered into follow-up throughout this entire period, so not all were followed for the same period of time. In order to derive an average mortality rate, person years can be used, assuming a constant mortality rate over time. The total number of deaths in our population of 348 was 65 and the total number of person-years they were followed was 542, so the average three-year mortality in this study population was 36%, assuming a constant rate of 12% per year.

Mortality studies of populations with COPD are difficult to compare given the wide range of entry criteria. France and colleagues (17) however studied a population with values of FEV_1

similar to those in our population and reported a four year mortality of 44%. Another study of a population with comparable values of FEV_1 conducted by Middleton and associates (16) reported a four year mortality of 41%.

Amongst the studies that recorded arterial blood gases (12,14,16,18,22), overall mortality seems to be associated with the proportion of the study population who were hypercapneic. Three year mortality rates of 38% and 44% respectively, were reported in two studies where approximately 2/3 of the study subjects had a $PaCO_2$ greater than 45 mm Hg (12,14). Only one published study, by Postma and colleagues (18), recorded values for $PaCO_2$ similar to those in this population; with hypercapnia in approximately 1/3 of the study subjects, the five year mortality was 31%.

METHODOLOGY

In order to derive a valid estimate of the effect of nutritional status on mortality in this population, potential confounding variables must be identified. Such variables would be associated with mortality in this population as well as be associated with nutritional status independently, i.e., outside the causal pathway, of mortality. The temporal precedence of potential causal factors is also an important issue. If certain factors are intermediate in the causal pathway between nutritional status and

death, then it is important to identify them so they will not be treated as confounders. In order to establish that malnutrition is independently associated with mortality, and to derive an unbiased estimate of effect, we must adequately control any characteristic that might cause malnutrition in COPD patients and also predispose them to a higher risk of dying. A variable that is caused by malnutrition and also predisposes towards death must not be controlled, or any estimate of effect will be biased.

The methods commonly used to control for confounding in the data analysis stage include stratification, restriction, and multiple regression. Adjustment for more than one confounder is most conveniently done when using a multivariate regression model such as Cox's proportional hazards model. Cox's model is the model of choice when the outcome of interest is mortality (or survival). Not only does it allow for more than one predictor to be related to death, but it uses the follow-up information from all patients including those who are not followed until death. Individuals with only partial follow-up provide information on the risk of death in some of the time periods studied, even though their own death has not been observed (45). This form of data "censoring" is very common in studies of survival because data are often analyzed before the death of all individuals in the study, or because some individuals are lost to follow-up or withdrawn from the study before death.

PREDICTORS OF MORTALITY

Confounding variables that are known to be associated with mortality in patients with COPD are those which best describe the severity of lung function impairment as this has often shown to be related to weight loss as well. The severity of disease in our patient population was best described by the prescribed use of home oxygen. Oxygen therapy is indicated for low partial pressure of oxygen in the arterial blood (PaO_2 < 55 mm Hg). Those patients receiving home oxygen were clearly at the end stages of their disease process; tneir lung function was such that they were unable to sufficiently oxygenate their blood in order to maintain life. Although we can attach a relative risk of dying to patients receiving home oxygen, such a measure is merely the indication for the prescription of home oxygen; the treatment itself does not place the subjects at greater risk.

When the prescription of home oxygen is controlled in Cox's multivariate regression model, $PaCO_2$ also predicts mortality. The partial pressure of carbon dioxide in arterial blood describes the severity of disease in this population independently of the indication for home oxygen treatment.

In the study population of subjects recruited for the NPV trial (n=348), PaCO2 was not measured and FEV_1 predicted mortality in this population. In the subset of patients who entered hospital

for NPV training and had many more physiological variables measured, $PaCO_2$ was significantly associated with mortality, whereas FEV_1 was not. $PaCO_2$ was a more powerful predictor of mortality than FEV_1; given the fact that the total population and its subset were similar in all recorded variables, it is safe to say that had $PaCO_2$ been measured in the larger study population, it would have replaced FEV_1 as a predictor of mortality.

The entry criteria of most studies of mortality in COPD use the degree of airway obstruction as measured by the FEV_1 and/or the FEV_1/FVC ratio to define the patient population in terms of disease severity. Using different methods of analysis and populations with varying degrees of disease severity a number of studies have found that FEV_1 is strongly associated with mortality in populations with COPD (9,11,18-21). Most of these studies perform some sort of multivariate analyses which allow for control for more than one confounder, (9,11,20,21) but only one study used Cox's proportional hazard's regression model (11).

The follow-up studies conducted by Burrows and colleagues (9,19) which found initial values of percent predicted FEV_1 to be significantly associated with mortality, did not measure arterial blood gases. Anthonisen's group (11) did measure $PaCO_2$ and PaO_2 but excluded hypoxemic patients; it is not surprising that $PaCO_2$ did not predict mortality given that the group of patients most likely to retain carbon dioxide were excluded from the study. The

five and eighteen year follow-up studies conducted by Postma's group (18,20) did not find $PaCO_2$ to be associated with mortality over such a long follow-up. The initial measurement of FEV_1 was also not a predictor, but the annual rate of decrease in FEV_1 was significantly associated with mortality at both follow-up analyses.

Studies including relatively healthy populations, where the range of FEV_1 values is much wider than in the COPD populations previously described, have found that FEV_1 is an important predictor of mortality (50-52). The entry criteria of our study was such that only severely obstructed patients were eligible, so the range of FEV_1 values in our study subjects was relatively small; the range of the 25^{th} to the 75^{th} percentile was 20-34% predicted in the large sample and 21-37% predicted in the small sample. It may be that in our study population the range of FEV_1 values was too restricted to show any effect of FEV_1 over and above that of $PaCO_2$.

BMI, measured both as a categorical (underweight, normal weight, and overweight) and as a continuous variable, was a significant predictor of mortality in the recruited subjects. TSF was not measured in this group. Neither BMI nor TSF, when grouped into the three categories mentioned above, had a significant association with survival on a univariate level in the subset of randomized patients; yet as continuous variables each was a significant predictor of mortality in a multiple regression

equation that included home oxygen status, $PaCO_2$ and FEV_1. The continuous treatment of this variable is more appropriate given that the very low values of BMI would be expected to have a higher risk of mortality than those at borderline levels. The statistical power of the continuous treatment of the variable is greater as well.

Nutritional status as measured by BMI and TSF significantly predicted survival in this population whereas weight loss and AMC did not. The range of values for AMC did not reflect any sort of malnutrition so it is not surprising that AMC had no effect. It is thought that weight loss is often masked in COPD; edema fluid can replace lean body mass, so patients may have stable or increased weight (27).

The group in our study population which experienced the highest mortality were those who had lost less than 4% of their initial weight in ore year, but the greatest weight losses observed were in the heavier weight groups. Those patients with high BMI's tended to lose weight, very few (15%) of the patients with low BMI's went on to lose more than 5% of their initial body weight. It is known that being overweight carries a higher risk of mortality, so perhaps those patients were losing weight voluntarily and were indeed becoming somewhat healthier.

Involuntary weight loss among the less healthy study subjects

may be closely linked with severe impairment of lung function. Since disease severity was controlled, only the baseline measures of nutritional status were predictive of mortality. Analysis using a multivariate regression model has shown that patients with low initial BMI's or low initial TSF's were rendered more susceptible to the disease process than those patients with higher BMI or TSF and the same initial level of disease severity.

Restricting the analysis to the subset of patients not receiving home oxygen is another method of controlling for the severity of disease in this population. When analyzing the subgroup of patients not receiving home oxygen for predictors of mortality only FEV_1 was significant in the larger recruited population and no measured variables were significant in the subset of randomized subjects. Only 39 patients not receiving home oxygen died in the recruited group while only 10 died in the randomized group. With this small number of deaths it seems that the analysis lacked sufficient statistical power to accurately detect the effect of any variable on mortality on these patients. A longer follow-up time in order to accumulate more deaths is needed to properly perform this analysis.

Previous studies have found that loss of 10% initial body weight is associated with mortality (13,22), but neither of these studies controlled for the confounding effect of disease severity. Wilson and colleagues (24) whose study used Cox's proportional

hazards regression model to control for disease severity, found that weight adjusted for height as measured by % ideal body weight (IBW) significantly predicted mortality. Weight change over time was not measured.

EXCESS MORTALITY RELATED TO MALNUTRITION

The reported causes of death in this study population were primarily of a respiratory nature. The immediate cause of death as recorded on the death certificates was due to the underlying processes of COPD in 79% of the recruited subjects and 87% of the subset of randomized patients. Underlying causes of death due primarily to cardiac causes were reported in 12% of the recruited group; it is possible that respiratory processes played a role in these deaths as right heart failure (cor pulmonale) is a common feature of COPD. Malignant neoplasm was the underlying cause of death in 10% (n=5) of the recruited subjects but only in one patient from the randomized group. Although weight loss and malnutrition are common features in patients with malignant neoplasms this infrequent cause of death cannot explain the association between nutritional status and survival in our study population.

Multivariate regression analysis has shown that nutritional status measured by either BMI or TSF is not merely a marker for disease severity but affects the course of COPD. There are various

theories as to how nutritional status may affect the course of COPD. Malnutrition impairs the local pulmonary as well as the systemic immunological defense mechanisms. Nutritional deficiencies have been shown to be associated with impairments of T-lymphocytes, B-lymphocyte function, and antibody production, as well as alveolar macrophage, or local lung immune cell, activity (51). It is thought that these abnormalities of the immune system may contribute to the incidence and severity of pulmonary infections in malnourished patients (54).

It is also postulated that malnutrition affects the respiratory system such that the capacity of patients to sustain adequate levels of ventilation is reduced (54). Doekel and colleagues (55) found that healthy subjects restricted to 550 Kcal per day for 10 days decreased their ventilatory response to hypoxia.

Respiratory muscle strength and endurance can also affect the ability to sustain ventilation. Studies have shown that malnourished patients without pulmonary disease exhibit decreased respiratory muscle strength and endurance (56-57). Malnourished patients with COPD have reduced diaphragmatic muscle weight as compared to normal weight patients with COPD (58). COPD patients already have reduced respiratory muscle strength as a clinical feature of their disease; any further reduction of respiratory muscle function caused by malnutrition will serve to impair the

capacity of patients to handle an increased ventilatory load and make them more prone to develop acute respiratory failure (54).

IMPLICATIONS

Studies which identify predictors of mortality in specific populations can be useful clinically if those predictors represent modifiable characteristics which are prevalent in the patient population. Our study as well as others (13,22,24) have identified nutritional status as a significant predictor of mortality in patients with severe COPD.

There is evidence to support the concept that malnourished COPD patients will improve clinically with supplemental oral nutrition, though not all studies agree (33-35). It is obvious that the studies should have adequate numbers of study subjects and appropriate control groups, but it is also important to ensure that the nutritional intervention under study is successful in improving nutritional status before assessing its efficacy in improving clinical performance. Goldstein and colleagues (59) discuss the importance of the duration of the nutritional support in terms of improving respiratory and skeletal muscle function. Achieving a significant increase in caloric consumption is clearly an important issue that has been largely overlooked. If the duration and intensity of the refeeding techniques are not adequate to achieve an important increase in the caloric intake then nutritional status

will not improve.

More studies are needed to examine the mechanisms by which COPD patients loose weight. Determination of the physiological processes that bring about weight loss in these patients will enable preventive strategies to be implemented. Controlled clinical trials examining the improvements resulting from nutritional support are important to assess the benefits of preventing or reversing malnutrition in COPD.

LIMITATIONS

There are several possible sources of bias in this study. The loss of patients during follow-up is a problem that plagues all longitudinal studies and is possibly the most serious source of bias in our study. If the loss to follow-up is differential with respect to the risk of death and the independent variables of interest, then our estimates of relative risk are biased. Based on the measured baseline characteristics, the subjects we were able to follow are similar to those not followed, but there is always the possibility that those patients who refused to be followed or those we lost along the way are different in some unmeasured way that would affect their risk of dying. By tracing the vital status of all patients lost to follow-up we should detect deaths as they occur and thus decrease this bias.

Our method of obtaining weight status by a verbal question may lack the sensitivity required to notice any effect of weight loss on mortality. Unfortunately it was not feasible to bring each patient in every three months to be weighed on the same scale from where their baseline weight was determined. An average value of weight change per year over the one to three year follow-up was used in the analysis which may have lacked the sensitivity required to note any effects of weight changes at specific points in time.

Adequate control for confounding is performed only when all potential confounders are validly measured. There is always the possibility that confounding is occurring by some unmeasured variable(s) or that the measured confounders were invalidly assessed. Care was taken in the randomized study group to record all possible measures of disease severity and to record them accurately and reliably. Despite this, there always remains the possibility that some unknown variable is confounding the relationship between nutritional status and mortality.

In populations with (18,20) and without COPD (50-52), changes in FEV_1 over time have been found it to strongly predict mortality. We did not measure FEV_1 over the follow-up. It is possible that the rate of decrease of FEV_1 over time would have more accurately reflected the severity of the disease process in our population however given the very weak association of baseline FEV_1 and malnutrition in our data, one might expect little association with

change in FEV_1 as well. The FEV_1 measured at randomization represents a value that is known to have been stable over a one month period. It would be difficult to get such accurate FEV_1 measures on a follow-up basis in this population.

The follow-up of subjects is continuing and a re-analysis at five years will undoubtably yield interesting results. Deaths occurring later in the follow-up might be due to different risk factors. Analyses of different subgroups of patients will be possible with a longer follow-up period as will analyses of respiratory versus non-respiratory deaths. The accumulation of more deaths over time and the results of aggressive tracing of the patients lost to follow-up will increase the power of the study to accurately estimate the effects of the various predictors of mortality in this population.

CONCLUSIONS

We have established that nutritional status independently affects the course of COPD. The variables which best describe the nutritional status of our sample of COPD patients are BMI and TSF. Either BMI or TSF significantly predict survival when lung function, as measured by prescription of home oxygen and $PaCO_2$, is controlled for in a multivariate regression equation. Patients with lower lean body mass (BMI) and/or lower stores of body fat (TSF) are at a greater risk of dying from COPD than patients with a greater BMI and/or larger TSF and a comparable level of lung function. There is a high prevalence of malnutrition due to weight loss in patients with COPD; the physiological process by which weight loss occurs in this disease is still unknown, as is the process by which poor nutritional status increases the risk of mortality in these patients. Clearly, what is of greatest importance is the ability to decrease the malnourished COPD patient's risk of dying by some appropriate program of nutritional repletion. While preliminary results have been promising, this area of clinical research is still in its infancy and needs further study.

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TABLE 1

OVERALL MORTALITY

AUTHORS	YEAR	N	ENTRY CRITERIA	MORTALITY (3 YEAR)
Boushy (12)	1964	81	FEV_3 < 85% FVC	38.3%
Sukulmachantra (13)	1965	44	Clinical diagnosis	23%
Vandenbergh (22)	1966	100	Clinical diagnosis	43% *
Renzetti (14)	1966	487	RV/TLC > 35% TLC > 80% pred	44%
Burrows (9)	1969	200	FEV_1 < 60% pred	34%
Damsgaard (10)	1974	187	FEV_1 < 60% pred	29%
Middleton (16)	1979	85	Clinical diagnosis	41% **
Weitzenblum (15)	1981	175	Mean FEV_1=1.2 L	26%
Postma (18)	1985	129	FEV_1 < 1 L	31% *
Anthonisen (11)	1986	985	FEV_1 < 60% pred	23%
France (17)	1988	115	FEV_1/FVC < 70%	43.5% **

* 5-year mortality

** 4-year mortality

TABLE 2

CHARACTERISTICS OF RECRUITED SUBJECTS (N=348)

VARIABLE	MEAN	SD	RANGE
AGE (YEARS)	63.4	7.70	31-75
SEX (%MALE)	68.1		
SMOKERS (%CURRENT)	21.3		
FEV_1 (L)	0.71	0.25	0.26-1.81
FVC (L)	1.81	0.62	0.61-4.22
FEV_1 (%PREDICTED)	27.7	9.28	9.0-51.0
HOME OXYGEN (%PRESCRIBED)	16.2		
BMI (Kg/M^2)	24.0	4.77	13-41
SERUM ALBUMIN (g/dl)	4.07	0.30	2.9-4.9
HEMOGLOBIN (g/dl)	15.5	1.57	10.3-20.9
LYMPHOCYTES ($10^9/L$)	1503.4	1167.5	5.5-9860

TABLE 3

CHARACTERISTICS OF RECRUITED SUBJECTS BY HOME OXYGEN

VARIABLE	HOME OXYGEN (N=56)	NO HOME OXYGEN (N=292)	
AGE (YEARS)	61.3 ± 8.27	63.9 ± 4.57	*
SEX (%MALE)	62.5	69.6	
SMOKERS (%CURRENT)	1.85	24.0	*
FEV_1 (%PREDICTED)	22.2 ± 8.28	28.9 ± 9.07	**
BMI (K/M^2)	23.3 ± 5.56	24.1 ± 4.57	
WEIGHT LOSS/YEAR (% BASELINE)	1.31 ± 6.89	1.78 ± 5.39	
SERUM ALBUMIN (g/dl)	4.07 ± 0.30	4.07 ± 0.30	
HEMOGLOBIN (g/dl)	15.4 ± 1.92	15.6 ± 1.45	
LYMPHOCYTES ($10^9/L$)	1320.5 ± 876.9	1546.2 ± 1225.6	

* $p < 0.05$

** $p < 0.0001$

TABLE 4

CHARACTERISTICS OF RECRUITED SUBJECTS BY GENDER

	MALES (N=237) MEAN ± SD	FEMALES (N=111) MEAN ± SD
HEIGHT (cm)	167.9 ± 6.70	155.6 ± 5.7 *
WEIGHT (kg)	68.6 ± 14.7	56.9 ± 12.0 *
BMI (K/M^2)	24.2 ± 4.70	23.5 ± 4.89
%UNDERWEIGHT(BMI < 20)	19.4	15.5
%OVERWEIGHT(BMI > 27)	32.8	30.0
WEIGHT LOSS/YEAR (% BASELINE)	1.84 ± 4.99	1.45 ± 6.86
FEV_1 (% PREDICTED)	27.5 ± 9.5	28.3 ± 8.8
HOME OXYGEN (%PRESCRIBED)	14.8	19.0
SERUM ALBUMIN (g/dl)	4.08 ± 0.28	4.07 ± 0.33
HEMOGLOBIN (g/dl)	15.8 ± 1.67	15.0 ± 1.21 *
LYMPHOCYTES ($10^9/L$)	1458.9 ± 1240.9	1601.5 ± 986.5
SMOKERS (% CURRENT)	21.2	21.5

* $p < 0.0001$

TABLE 5

CHARACTERISTICS OF RECRUITED SUBJECTS BY WEIGHT CATEGORY

	UNDERWEIGHT (N=62)	NORMAL WEIGHT (N=171)	OVERWEIGHT (N=109)	
FEV_1 (%PREDICTED)	25.1 ± 9.82	27.7 ± 8.83	29.4 ± 9.41	*
HOME OXYGEN (%PRESCRIBED)	22.6	15.2	15.0	
AGE (YEARS)	61.6 ± 9.02	63.6 ± 7.67	64.1 ± 6.65	
WEIGHT LOSS/YEAR (% BASELINE)	0.0 ± 4.72	1.64 ± 5.05	2.12 ± 4.96	*
SERUM ALBUMIN(g/dl)	4.03 ± 0.31	4.09 ± 0.32	4.08 ± 0.25	
HEMOGLOBIN(g/dl)	15.0 ± 1.64	15.5 ± 1.52	15.8 ± 1.57	*
SEX (%MALE)	72.6	64.9	69.7	
SMOKERS (%CURRENT)	18.8	20.3	23.2	

* $p < 0.05$

TABLE 6

COMPARISON OF BASELINE CHARACTERISTICS OF ALL RECRUITED SUBJECTS BY FOLLOW-UP STATUS

VARIABLE	NO FOLLOW-UP (n=29)	SOME FOLLOW-UP (N=319)
AGE (YEARS)	64.7 ± 7.51	63.3 ± 7.72
SEX (%MALE)	62.1	68.7
SMOKERS (%CURRENT)	18.2	21.5
FEV_1 (%PREDICTED)	31.6 ± 8.69	27.4 ± 9.26 *
HOME OXYGEN (%PRESCRIBED)	10.3	16.7
BMI (K/M^2)	23.9 ± 4.72	24.0 ± 4.78
SERUM ALBUMIN (g/dl)	4.05 ± 0.24	4.08 ± 0.30
HEMOGLOBIN (g/dl)	15.2 ± 1.49	15.6 ± 1.58
LYMPHOCYTES ($10^9/L$)	1426.3 ± 887.1	1510.7 ± 1191.8

* $p < 0.05$

TABLE 7

RESULTS OF SURVIVAL ANALYSIS BY COX REGRESSION ON N=319 SUBJECTS

VARIABLE	COEFFICENT	STANDARD ERROR	RR (low/high)	95% CI
FEV_1 (%PRED)	-0.0308	0.0162	1.03	1.00, 1.07
BMI (K/M^2)	-0.0888	0.0290	1.09	1.03, 1.16
HOME OXYGEN	-1.1547	0.2761	3.17*	1.85, 5.45

* RR for receiving home O_2 compared to those not receiving home O_2

TABLE 8

CHARACTERISTICS OF RANDOMIZED SUBJECTS (N=184)

VARIABLE	MEAN	SD	RANGE
AGE (YEARS)	63.1	7.65	32-75
SEX (%MALE)	72.3		
SMOKERS (%CURRENT)	16.9		
CIGARETTES(PK YEARS)	65.8	40.9	0-236.3
FEV_1 (L)	0.78	0.30	0.24-2.02
FVC (L)	2.43	0.77	0.78-4.34
FEV_1 (%PREDICTED)	29.6	10.30	11-58
HOME OXYGEN (%PRESCRIBED)	14.8		
BMI (K/M^2)	23.9	4.61	14-35
TSF (mm)	12.6	6.75	2.8-39.9
AMC (mm)	25.4	4.19	8-34
$PaCO_2$ (mm Hg)	44.1	6.97	26-73
PaO_2 (mm Hg)**	71.2	9.14	52-114
DLCO (%PREDICTED)	76.4	36.3	15-229
TLC (L)	7.13	1.09	4.48-9.74
FRC (L)	5.68	1.05	1.36-8.63
PI_{MAX} (cm H_2O)	43.0	15.2	15-87.5
PE_{MAX} (cm H_20)	83.2	36.7	4.5-218
SERUM ALBUMIN (g/dl)	4.1	0.27	3.2-4.9
HEMOGLOBIN (g/dl)	15.7	1.5	10.4-20.9
LYMPHOCYTES (10^9/L)	1467.8	1189.4	5.5-9860

** PaO_2 values exclude those on home oxygen

TABLE 9

CHARACTERISTICS OF RANDOMIZED SUBJECTS BY HOME OXYGEN

VARIABLE	HOME OXYGEN (N=27)	NO HOME OXYGEN (N=155)	
AGE (YEARS)	61.8 ± 7.79	63.4 ± 7.64	
SEX (%MALE)	74.1	72.3	
SMOKERS (%CURRENT)	0.0	19.2	*
CIGARETTES (PK YRS)	58.8 ± 27.0	67.2 ± 43.0	
FEV_1 (%PREDICTED)	24.2 ± 9.46	30.6 ± 10.2	*
FEV_1/FVC (%)	29.9 ± 7.0	32.7 ± 7.86	
BMI (K/M^2)	23.8 ± 4.95	24.0 ± 4.52	
WEIGHT LOSS/YEAR (% BASELINE)	1.64 ± 7.28	1.79 ± 5.63	
TSF (mm)	15.2 ± 9.21	12.2 ± 6.18	
AMC (mm)	24.3 ± 3.50	5.6 ± 4.27	
$PaCO_2$ (mm Hg)	54.5 ± 8.33	42.3 ± 4.86	**
PaO_2 (mm Hg)	70.0 ± 17.3	71.2 ± 9.14	
DLCO (%PREDICTED)	61.5 ± 22.4	79.3 ± 38.0	*
PI_{MAX} (cm H_2O)	41.9 ± 14.0	43.4 ± 15.5	
PE_{MAX} (cm H_2O)	90.3 ± 39.7	81.7 ± 34.9	
SERUM ALBUMIN (g/dl)	4.08 ± 0.31	4.12 ± 0.26	
HEMOGLOBIN (g/dl)	15.4 ± 1.74	15.7 ± 1.39	
LYMPHOCYTES ($10^9/L$)	1379.4 ± 1051.1	1491.2 ± 1224.7	
TLC (L)	7.15 ± 0.96	7.12 ± 1.12	
FRC (L)	6.07 ± 0.89	5.62 ± 1.07	
VC (L)	2.05 ± 0.51	2.45 ± 0.75	*

* $p < 0.05$
** $p < 0.0001$

TABLE 10

CHARACTERISTICS OF RANDOMIZED SUBJECTS BY SEX

	MALES (N=133) MEAN ± SD	FEMALES (N=51) MEAN ± SD
HEIGHT (cm)	168.4 ± 6.52	156.3 ± 4.26 *
WEIGHT (kg)	68.8 ± 14.2	55.4 ± 11.70 *
BMI (K/M^2)	24.4 ± 4.39	22.7 ± 4.97 **
%UNDERWEIGHT (BMI < 20)	17.3	21.6
%OVERWEIGHT (BMI > 27)	33.1	25.5
WEIGHT LOSS/YEAR (% BASELINE)	2.09 ± 5.04	0.93 ± 7.55
TSF (mm)	10.5 ± 4.37	18.2 ± 8.69 *
AMC (mm)	26.6 ± 4.0	22.0 ± 2.70 *
FEV_1 (%PREDICTED)	29.7 ± 10.7	29.2 ± 1.32
HOME OXYGEN (%PRESCRIBED)	15.2	14.0
SERUM ALBUMIN (g/dl)	4.10 ± 0.26	4.13 ± 0.30
HEMOGLOBIN (g/dl)	16.0 ± 1.51	14.9 ± 1.17 *
LYMPHOCYTE ($10^9/L$)	1453.1 ± 1237.5	1505.4 ± 1067.8
SMOKERS (%CURRENT)	16.4	18.0
CIGARETTES (PK YRS)	71.5 ± 39.1	50.7 ± 42.0 **
$PaCO_2$ (mm Hg)	43.7 ± 6.65	44.9 ± 7.76
PaO_2 (mm Hg)***	71.1 ± 8.39	71.4 ± 11.0

* $p < 0.0001$

** $p < 0.05$

*** PaO_2 values exclude those on home oxygen

TABLE 11

CHARACTERISTICS OF RANDOMIZED SUBJECTS BY WEIGHT CATEGORY

VARIABLE	UNDERWEIGHT (N=34)	NORMAL WEIGHT (N=93)	OVERWEIGHT (N=57)
AGE (YEARS)	61.5 ± 8.71	63.7 ± 7.99	63.3 ± 6.32
SEX (%MALE)	67.7	71.0	77.2
SMOKERS (%CURRENT)	26.7	36.7	36.7
CIGARETTES (PK YRS)	59.0 ± 40.2	64.3 ± 42.1	72.2 ± 38.9
FEV_1 (%PREDICTED)	26.7 ± 9.34	29.9 ± 10.6	30.7 ± 10.3
FEV_1/FVC (%)	30.1 ± 6.69	31.8 ± 7.02	34.0 ± 9.11*
HOME OXYGEN (%PRESCRIBED)	12.1	17.2	12.5
SERUM ALBUMIN (g/dl)	4.04 ± 0.23	4.12 ± 0.29	4.14 ± 0.24
HEMOGLOBIN (g/dl)	14.8 ± 1.16	15.8 ± 1.59	16.1 ± 1.33*
PaO_2 (mm Hg)**	75.5 ± 14.4	70.7 ± 9.51	69.1 ± 9.09*
$PaCO_2$ (mm Hg)	43.3 ± 5.71	43.6 ± 7.21	45.3 ± 7.20
TSF (mm)	7.62 ± 3.40	12.0 ± 5.05	16.4 ± 8.38*
AMC (mm)	21.9 ± 2.64	24.8 ± 3.38	28.4 ± 4.14*
WEIGHT LOSS/YEAR (% BASELINE)	0.64 ± 4.31	1.64 ± 5.68	2.40 ± 4.96
PI_{MAX} (cm H_2O)	40.5 ± 18.3	41.5 ± 13.9	46.9 ± 15.0
PE_{MAX} (cm H_2O)	68.8 ± 27.8	80.5 ± 37.0	95.7 ± 37.3*
TLC (L)	7.06 ± 0.96	7.26 ± 1.04	6.95 ± 1.23
FRC (L)	5.71 ± 1.21	5.81 ± 0.94	5.45 ± 1.12
VC (L)	2.14 ± 0.76	2.46 ± 0.70	2.47 ± 0.74
DLCO (%PREDICTED)	69.2 ± 23.4	70.7 ± 36.4	88.8 ± 38.8*

* $p < 0.05$ ** PaO_2 values exclude those on home oxygen

TABLE 12

COMPARISON OF BASELINE CHARACTERISTICS OF ALL RANDOMIZED SUBJECTS BY FOLLOW-UP STATUS

VARIABLE	NO FOLLOW-UP (n=4)	SOME FOLLOW-UP (n=180)
AGE (YEARS)	62 ± 5.83	63.2 ± 7.70
SEX (%MALES)	75.0	72.2
SMOKERS (%CURRENT)	0.0	17.2
CIGARETTES (PK YRS)	127.3 ± 59.7	64.4 ± 2.97
FEV_1 (%PREDICTED)	34.3 ± 8.81	29.5 ± 10.3
HOME OXYGEN (%PRESCRIBED)	25.0	14.4
BMI (K/M^2)	25.0 ± 3.74	23.9 ± 4.63
TSF (mm)	16.6 ± 11.4	12.5 ± 6.63
AMC (mm)	27.3 ± 3.59	25.3 ± 4.20
$PaCO_2$ (mm Hg)	42.0 ± 2.45	44.1 ± 7.04
PaO_2 (mm Hg)	76.0 ± 7.96	71.0 ± 10.7
DLCO (%PREDICTED)	75.0 ± 19.0	76.4 ± 36.6
TLC (L)	6.55 ± 0.23	7.14 ± 1.10
FRC (L)	5.09 ± 0.44	5.69 ± 1.06
VC (L)	2.68 ± 0.71	2.40 ± 0.74
PI_{MAX} (cm H_2O)	46.9 ± 12.3	42.9 ± 15.3
PE_{MAX} (cm H_2O)	104.4 ± 39.6	82.8 ± 36.6
SERUM ALBUMIN (g/dl)	4.0 ± 0.40	4.11 ± 0.27
HEMOGLOBIN (g/dl)	14.4 ± 0.71	15.7 ± 1.50
LYMPHOCYTES (10^9/L)	1737.8 ± 1511.7	1462.8 ± 1187.9

TABLE 13

RESULTS OF SURVIVAL ANALYSIS BY COX'S REGRESSION ON N=180 SUBJECTS

MODEL1

VARIABLE	COEFFICENT	STANDARD ERROR	RR (low/high)	95% CI
HOME OXYGEN	-1.120	0.4970	3.06*	1.16, 8.12
$PaCO_2$ (mm Hg)	0.0581	0.0280	0.94	0.98, 1.00
BMI (K/M^2)	-0.1052	0.0424	1.11	1.02, 1.21

MODEL 2

VARIABLE	COEFFICENT	STANDARD ERROR	RR (low/high)	95% CI
HOME OXYGEN	-1.1575	0.4756	3.18*	1.25, 8.08
$PaCO_2$ (mm Hg)	0.0758	0.0289	0.93	0.88, 0.98
TSF (mm)	-0.0934	0.0421	1.10	1.01, 1.19

MODEL 3

VARIABLE	COEFFICENT	STANDARD ERROR	RR (low/high)	95% CI
HOME OXYGEN	-1.1092	0.4900	3.03*	1.16, 7.92
$PaCO_2$ (mm Hg)	0.0799	0.0294	0.93	0.87, 0.98
BMI (K/M^2)	-0.0394	0.0506	1.04	0.94, 1.15
TSF (mm)	-0.0762	0.0459	1.08	0.99, 1.18

* RR for receiving home 02 compared to not receiving home 02

FIGURE 1

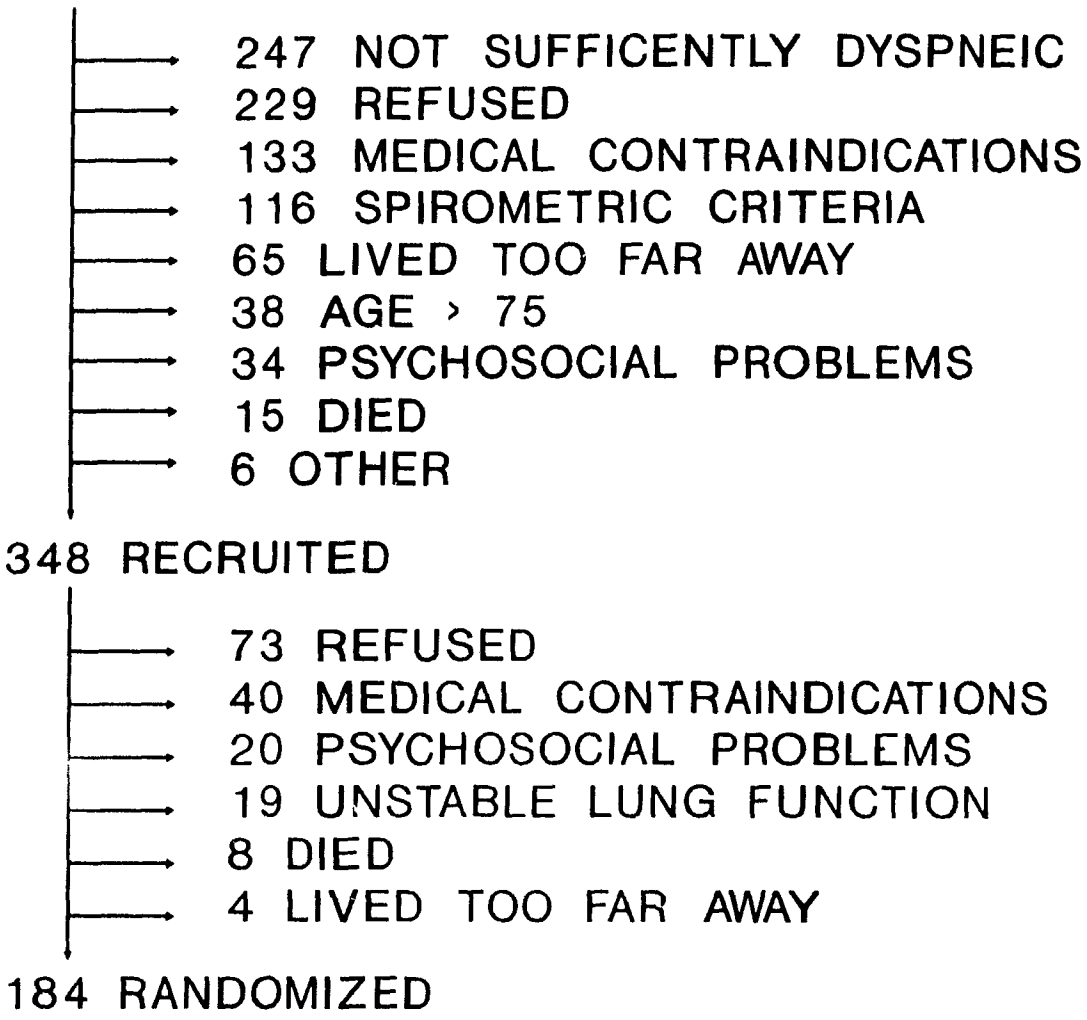
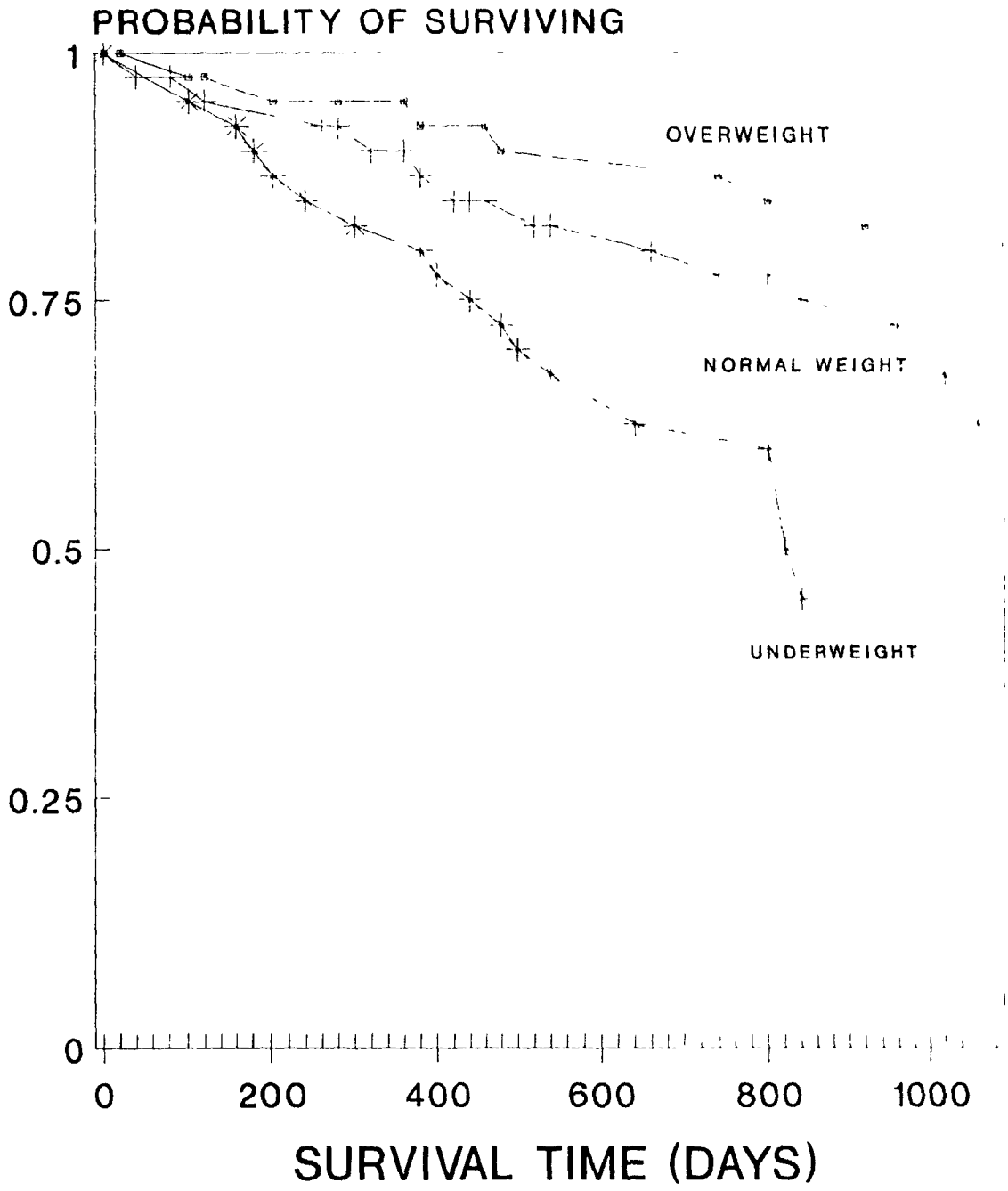
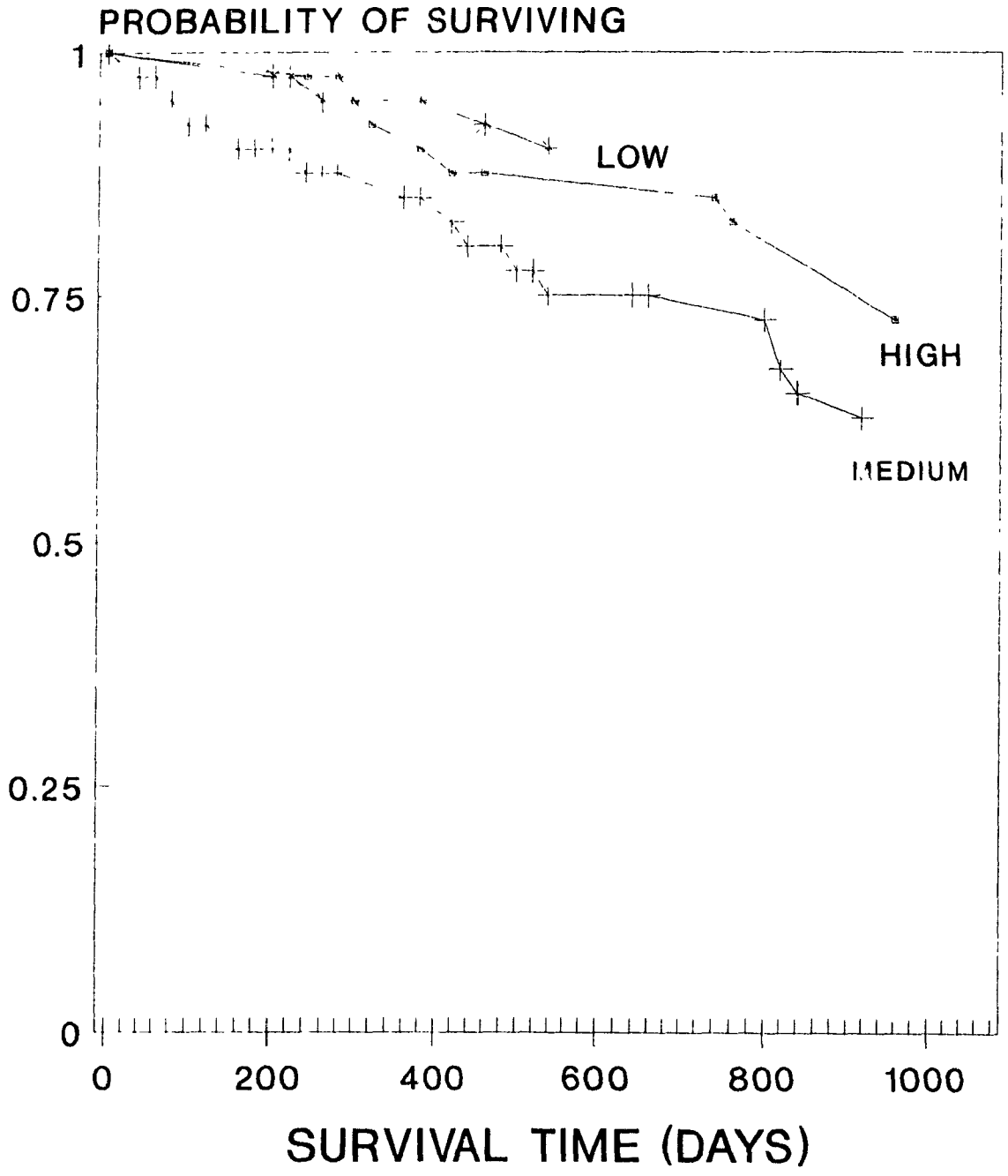

1231 SUBJECTS IDENTIFIED
247 NOT SUFFICENTLY DYSPNEIC
229 REFUSED
133 MEDICAL CONTRAINDICATIONS
116 SPIROMETRIC CRITERIA
65 LIVED TOO FAR AWAY
38 AGE > 75
34 PSYCHOSOCIAL PROBLEMS
15 DIED
6 OTHER
348 RECRUITED
73 REFUSED
40 MEDICAL CONTRAINDICATIONS
20 PSYCHOSOCIAL PROBLEMS
19 UNSTABLE LUNG FUNCTION
8 DIED
4 LIVED TOO FAR AWAY
184 RANDOMIZED

FIGURE 2
SURVIVAL CURVES-BODY MASS INDEX



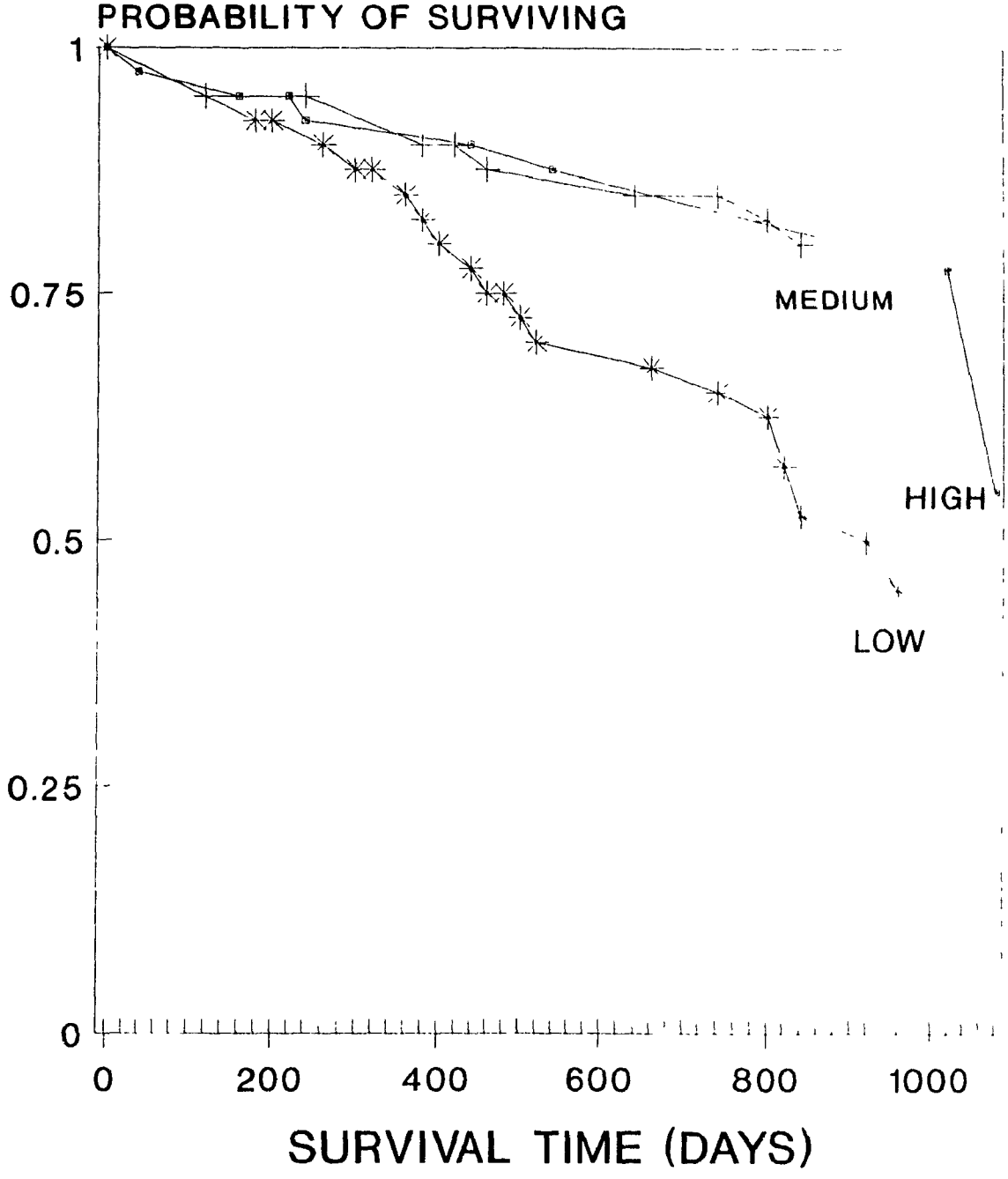
N=319

FIGURE 3
SURVIVAL CURVES-WEIGHT CHANGE



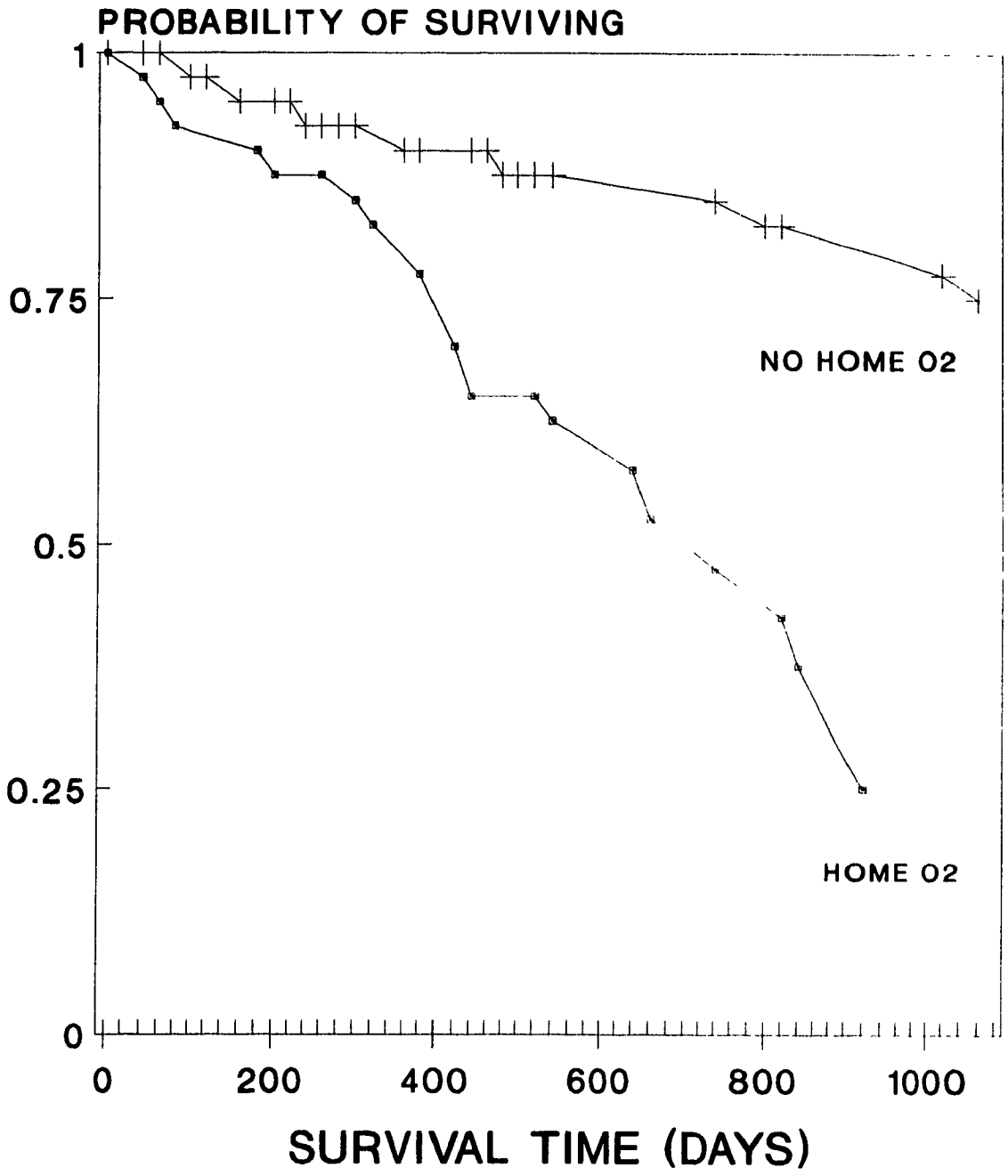
N=319

FIGURE 4
SURVIVAL CURVES-% PREDICTED FEV1



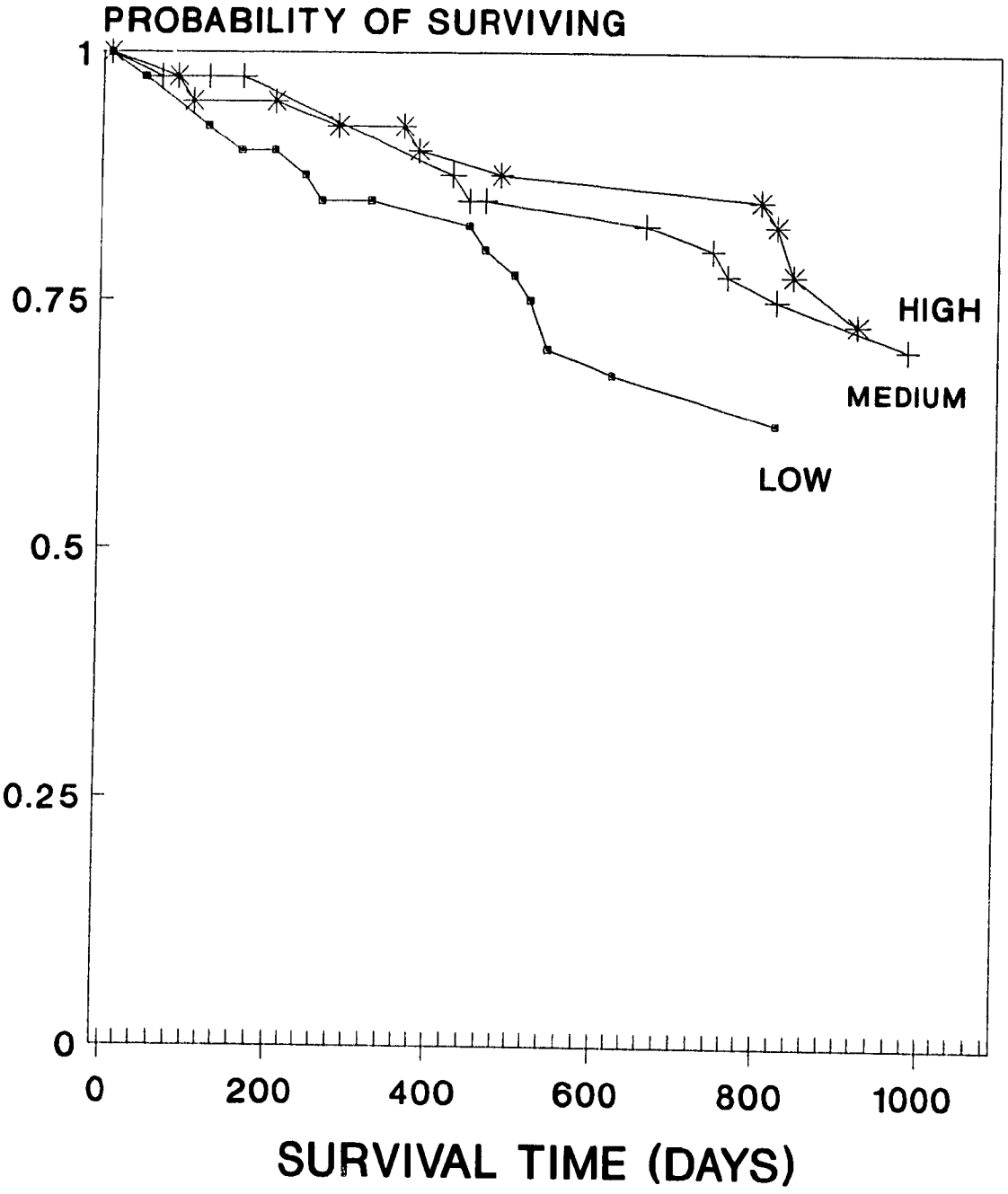
N=319

FIGURE 5
SURVIVAL CURVES-HOME OXYGEN



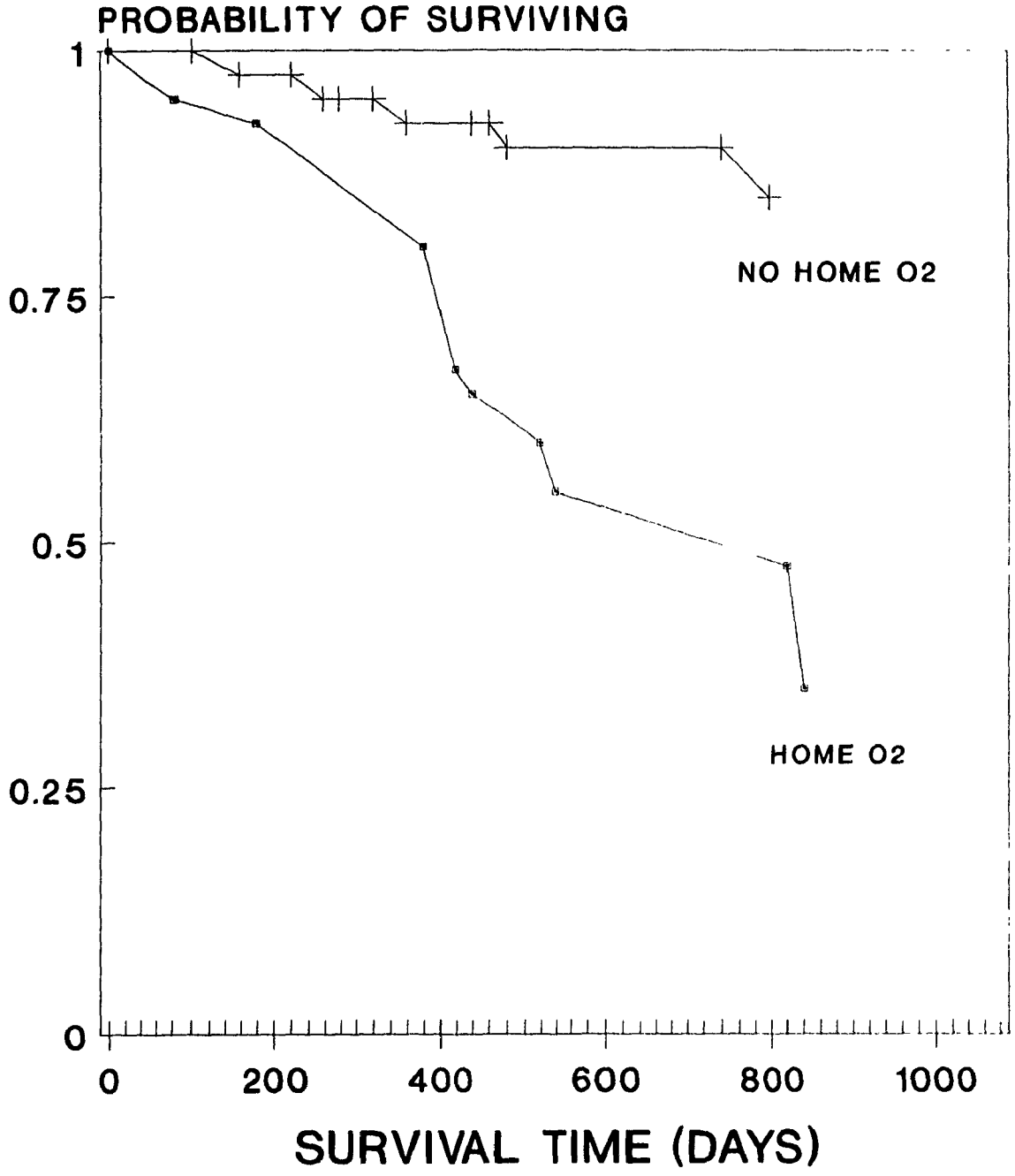
N=319

FIGURE 6
SURVIVAL CURVES-HEMOGLOBIN



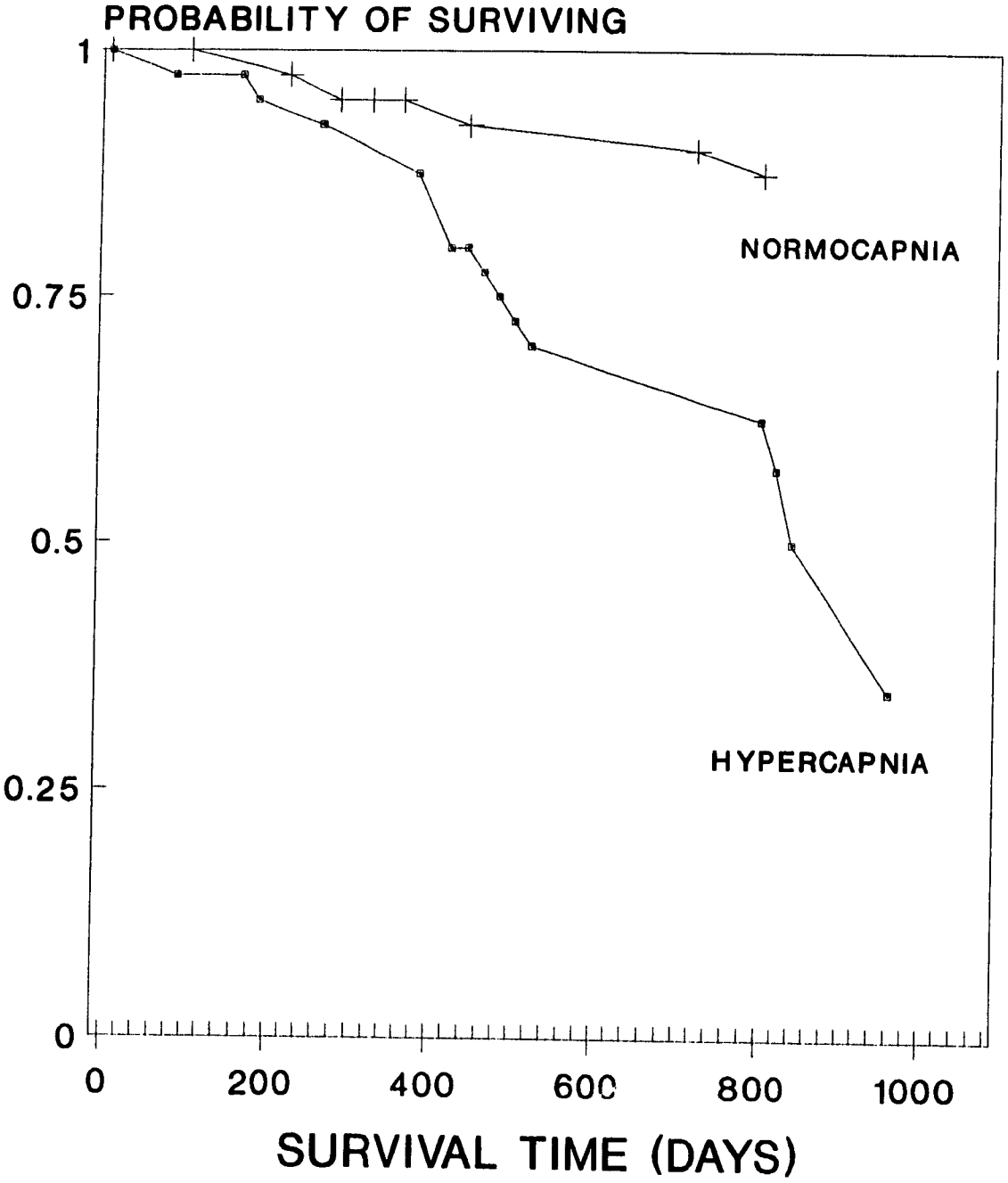
N=319

FIGURE 7
SURVIVAL CURVES-HOME OXYGEN



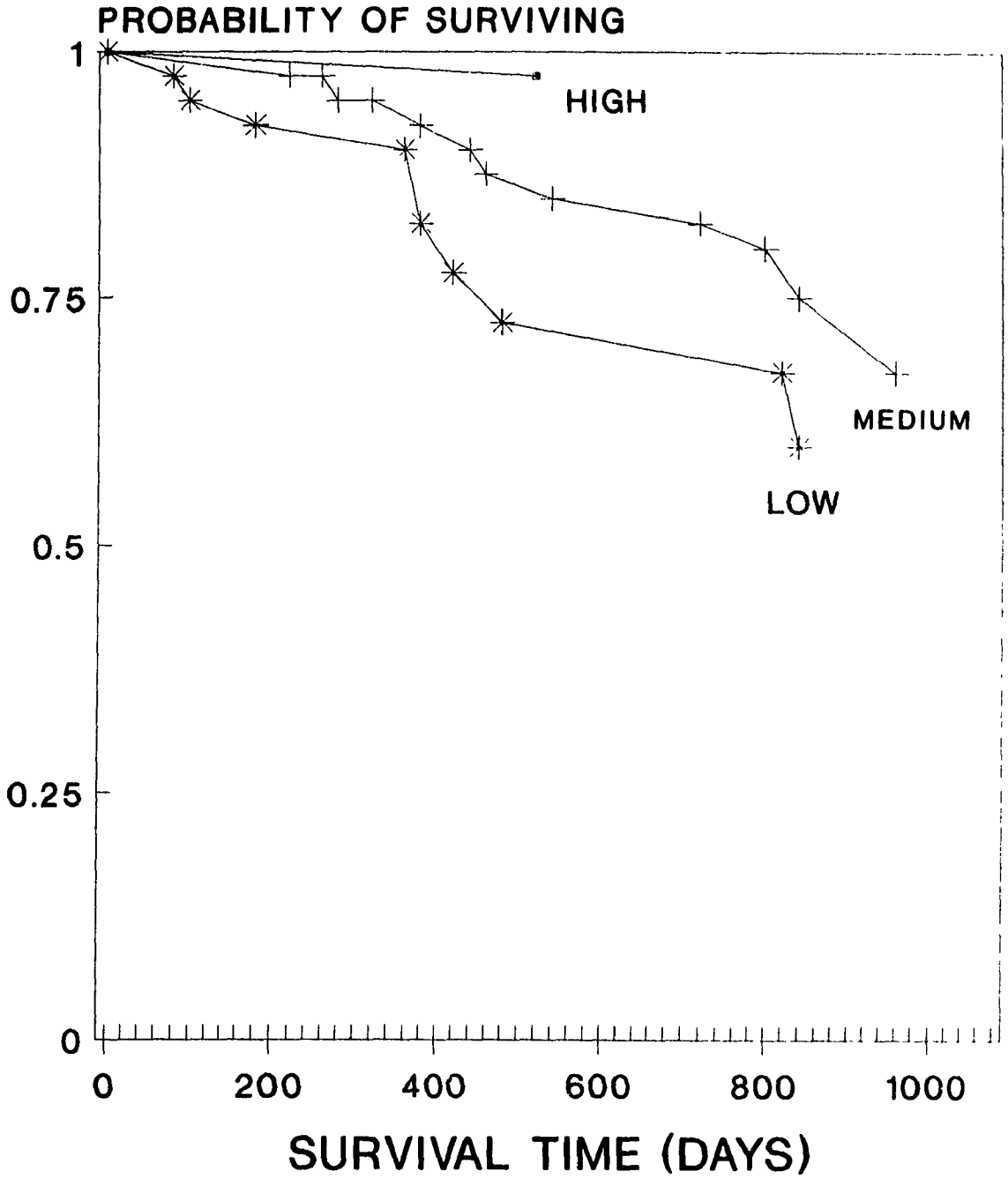
N=180

FIGURE 8
SURVIVAL CURVES-PACO2



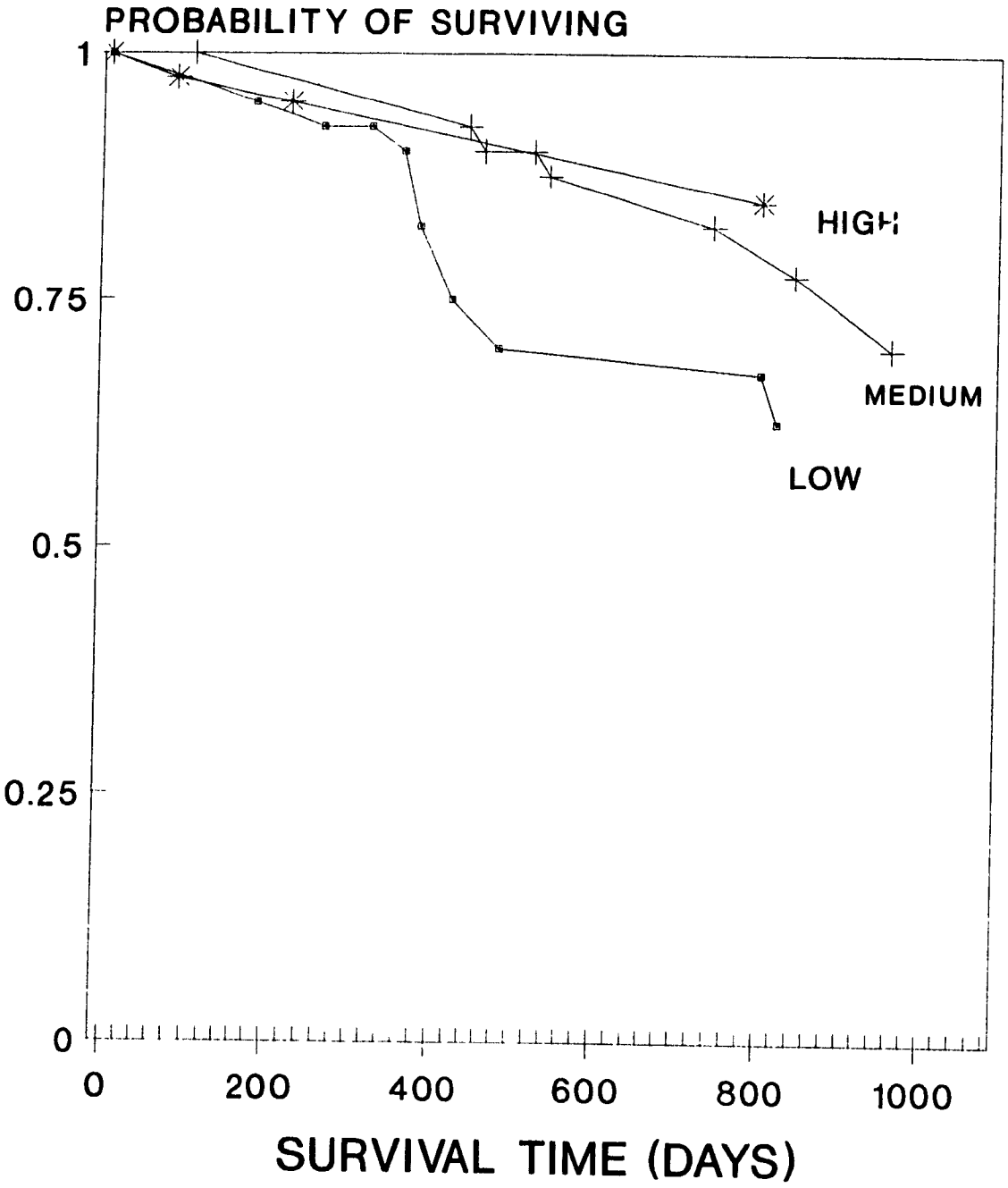
N=180

FIGURE 9
SURVIVAL CURVES-DIFFUSING CAPACITY



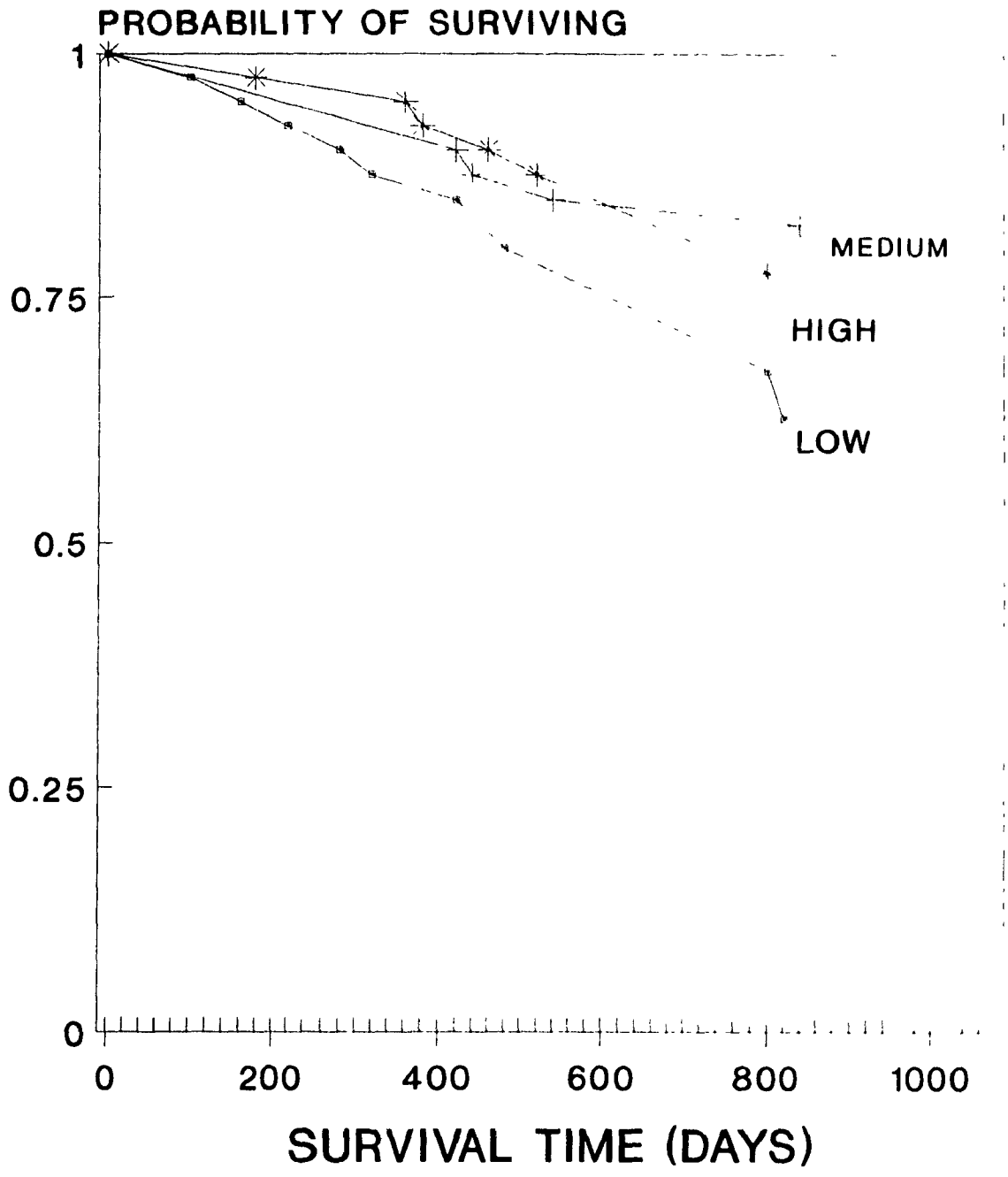
N=180

FIGURE 10
SURVIVAL CURVES-FEV1/FVC RATIO



N=180

FIGURE 11
SURVIVAL CURVES-TSF THICKNESS



N=180

APPENDIX A

Votre participation à l'étude du repos des muscles inspiratoires pour les maladies pulmonaires obstructives chroniques est grandement appréciée.

Afin de mieux évaluer les effets à long terme de ce traitement et de documenter les changements de l'état de santé sur une periode de temps prolongée, nous aimerions continuer de vous suivre par le biais d'une série de courtes entrevues téléphoniques (d'une dureé d'environ 5 minutes) à tous les trois mois pendant une ou deux années. Nous vous poserons des questions concernant votre état de santé et nous noterons chaque hospitalisation qui pourrait être survenue dans l'intervalle.

Je, __ _____, consens à participer au contrôle continu de l'étude du repos des muscles inspiratoires chez les malades pulmonaires obstructifs chroniques. Je comprends que ma participation à cette étude est entièrement volontaire, et que je suis libre de me retirer à tout moment, et ceci sans aucun préjudice à mes présents soins. Je comprends également que toute l'information recueillie sera strictement confidentielle. Les résultats de cette étude seront publiés dans la litérature scientifique, mais les patients ne seront pas identifiés de façon individuelle.

_____ _____

Signature de participant Date

APPENDIX B

ENTREVUE DE CONTROL (4 MOIS POST-RECRUTEMENT)

NO D'ETUDE: __ __ __ __

DATE: __ __ __ __ __ __

CONTROLE: __ __

SI LE PATIENT N'A PAS ETE CONTACTE, CODEZ LA RAISON __

J'aimerais vous posez quelques questions afine de voir comment vous vous etes senti durant les quatre derniers mois, soit depuis notre premiere rencontre concernant l'etude.

1. **Avez-vous ete hospitalise depuis _____? (SPECIFIEZ LE MOIS DU DERNIER CONTACT)**
   1. oui 2. non 3. incertain __

2. **A quel hopital etiez-vous? _____**

3. **Nombre de jours d'hospitalisation _____ jours** __ __ __

4. **Pour quelle(s) raison(s) avez-vous ete hospitalise?**
   1._____ __ __
   2._____ __ __
   3._____ __ __

5. **Avez-vous eu des visites non planifiees chez le medicin?**
   1. oui 2. non 3. incertain __
   Si oui, combien? __
   Si oui, pour quelle raison? __ __

6. **Quel est votre poids le plus recent?** kg __ __ __
   lbs __ __ __
   Quand cette mesure a-t-elle ete prise?_____

SI LE PATIENT EST DECEDE, DEMANDEZ LA CAUSE DE DECES SI CECI EST APPROPRIE ET OFFREZ VOS SYMPATHIES.
PATIENT DECEDE 1. OUI, AUTREMENT CODEZ 8 ET TERMINEZ __
SI OUI, CAUSE DU DECES 1._____ __ __
2._____ __ __

HOPITAL OU LE PATIENT EST DECEDE_____ __ __