Carbon Monoxide Diffusing Capacity As Predictor of Outcome in Systemic Sclerosis

MARC PETERS-GOLDEN, M.D.
ROBERT A. WISE, M.D.
MARC C. HOCHBERG, M.D.
MARY BETTY STEVENS, M.D.
FREDRICK M. WIGLEY, M.D.
Baltimore, Maryland

In order to determine the predictive value of lung function studies for subsequent prognosis in systemic sclerosis, 71 patients with systemic sclerosis were followed up for a mean of five years after pulmonary function testing. A carbon monoxide diffusing capacity less than or equal to 40 percent of the predicted reference value was associated with only a 9 percent five-year cumulative survival rate compared with a 75 percent cumulative five-year survival in patients with a carbon monoxide diffusing capacity greater than 40 percent of predicted. An obstructive ventilatory defect was also associated with increased mortality, and all six patients with obstruction and a diffusing capacity less than 70 percent of the predicted died during the study period. Male gender, independent of abnormalities of pulmonary function, was also associated with a poor prognosis. Although it is not clear whether a severely impaired diffusing capacity is indicative of interstitial pulmonary fibrosis or pulmonary vasculopathy or is a marker of generalized vascular disease, a severely depressed carbon monoxide diffusing capacity is an important predictor of mortality in patients with systemic sclerosis.

Pulmonary function impairment occurs in approximately 70 percent of patients with systemic sclerosis [1]. Common pathologic abnormalities include both interstitial fibrosis and pulmonary vascular changes [1]. Several studies have shown that pulmonary involvement defined by clinical and radiographic criteria is associated with decreased survival rates [2–4]. Abnormal pulmonary function has been shown to be an excellent predictor of mortality in patients with obstructive and interstitial lung disease, as well as in the general population [5–7]. In order to determine whether specific patterns or degrees of impairment of pulmonary function predict mortality in systemic sclerosis, we determined the outcome of 71 patients with systemic sclerosis followed up for a mean of five years after pulmonary function testing.

PATIENTS AND METHODS

Patient Population. Between January 1, 1972, and June 30, 1979, 76 patients with a diagnosis of systemic sclerosis satisfying ARA criteria [8] were seen by the rheumatology or pulmonary services at Good Samaritan Hospital. Pulmonary function studies were performed in all patients. The vital status of each patient was sought in 1982 and 1983. Follow-up information was obtained from review of medical records, contact with private physicians or family, and the Social Security Administration. In five patients in whom the precise date of death was not known, the midpoint of the interval in which the patient was known to have died was used to calculate

From the Department of Medicine, Johns Hopkins Medical Institutions, Good Samaritan and Baltimore City Hospitals, Baltimore, Maryland. This work was supported in part by Grants HL-00914 and AM-20558 from the National Institutes of Health, Bethesda, Maryland. Requests for reprints should be addressed to Dr. Robert A. Wise, Division of Pulmonary Medicine, Baltimore City Hospitals, 4940 Eastern Avenue, Baltimore, Maryland 21224. Manuscript accepted June 14, 1984.

TABLE I Demographic Features and Pulmonary Function of Survivors and Nonsurvivors*

	Number of Patients	Age	Percent White	Percent Female	Forced Vital Capacity (percent predicted)	FEV_1/FVC (percent)	Carbon Monoxide Diffusing Capacity (percent predicted)
Total	71	48.8 ± 1.42	77	83	77.6 ± 2.46 (67)	80.9 ± 1.25 (67)	68.7 ± 2.94 (71)
Survivors	46	46.9 ± 1.86	74	93	80.0 ± 2.98 (44)	82.6 ± 1.21 (44)	76.3 ± 2.97 (46)
Nonsurvivors	25	52.4 ± 2.00	84	64	73.1 ± 4.27 (23)	77.6 ± 2.70 (23)	54.7 ± 5.36 (25)
p (survivors versus nonsurvivors)		NS	NS	<0.005	NS	NS	<0.0001

* Mean ± SEM; numbers in parentheses indicate number of patients studied.
FEV_1/FVC = ratio of one-second forced expiratory volume to forced vital capacity expressed as a percentage.

survivorship. In five patients, vital status could not be determined, and they were excluded from the analysis. The 71 patients in whom follow-up information was available constitute the study group. Entry into the study was defined as the date of initial pulmonary function testing. Duration of disease was defined as the time since the first definite diagnosis of systemic sclerosis.

Pulmonary Function Testing. All patients underwent pulmonary function testing without selection for known pulmonary involvement. Of the 71 patients, 67 underwent complete studies at entry, including forced expiratory spirometric measurements, lung volume determination, and measurement of single-breath diffusing capacity for carbon monoxide. In four patients, only carbon monoxide diffusing capacity was measured. We defined a normal forced vital capacity [9], total lung capacity [9], and carbon monoxide diffusing capacity [10] to be greater than 80 percent of predicted according to published standards, and a normal ratio of one-second forced expiratory volume to forced vital capacity to be greater than 75 percent. Pulmonary function tests were conducted in accordance with standard protocols, with the exception that the carbon monoxide diffusing capacity was calculated without correction for carbon dioxide absorption [11].

The 67 patients who underwent complete pulmonary function testing were grouped according to four patterns: a *normal pattern*, an *isolated gas transfer defect*, a *restrictive ventilatory defect*, and an *obstructive ventilatory defect*. Those patients classified as showing a normal pattern had normal lung volumes, carbon monoxide diffusing capacity, and forced expiratory spirometric results. An isolated gas transfer defect was defined as an isolated reduction in carbon monoxide diffusing capacity. A restrictive ventilatory defect was defined as a reduction in total lung capacity or vital capacity with a normal ratio of one-second forced expiratory volume to forced vital capacity. An obstructive ventilatory defect was defined as a reduction in the ratio of one-second forced expiratory volume to forced vital capacity, irrespective of other values.

Data Analysis. Mean values of pulmonary function measures and demographic characteristics were compared between those patients who survived and those who died during the follow-up period, using the chi-square test for discontinuous variables or the Student t test for continuous variables [12]. The relative importance of demographic features and pulmonary function measures as predictors of mortality was determined by stepwise multiple linear regression analysis [13]. The case-fatality rate (number of deaths/number of patients at entry) was tabulated for the entire study group and for patient subgroups, with differences compared by the chi-square test. Life tables were constructed using the actuarial life table method to determine the survivorship function for the entire study group, as well as for various subgroups [14]. Differences in the survivorship function between the various subgroups were evaluated by the Mantel-Haentzel test [14], and five-year cumulative survival was compared by the chi-square test [12]. Data are expressed as mean ± standard error. Statistical significance was inferred for p values of <0.05.

RESULTS

The overall patient population was 77 percent white and 83 percent female, with a mean age of 48.8 ± 1.4 years old (range 23 to 73 years). The mean duration of disease prior to entry into the study was 32.0 ± 6.0 months. The mean interval from entry to follow-up, if alive, or death, was 60.0 ± 4.1 months. For those who died, the mean interval from entry until death was 24.8 ± 4.7 months. The population as a whole demonstrated a mild reduction in forced vital capacity and carbon monoxide diffusing capacity with a normal ratio of one-second forced expiratory volume to forced vital capacity, consistent with a mild restrictive ventilatory defect (**Table I**).

During the study period, 25 patients died, giving a case-fatality rate of 35.2 percent. The cumulative survival rates at one, three, and five years after entry were 84, 77, and 66 percent, respectively (**Figure 1**). Sixteen of 21 patients in whom the month of death was known died during the fall and winter months, October through March.

The 25 patients who died tended to be older than the 46 survivors, but this difference was not significant (Table I). There was no difference in racial composition

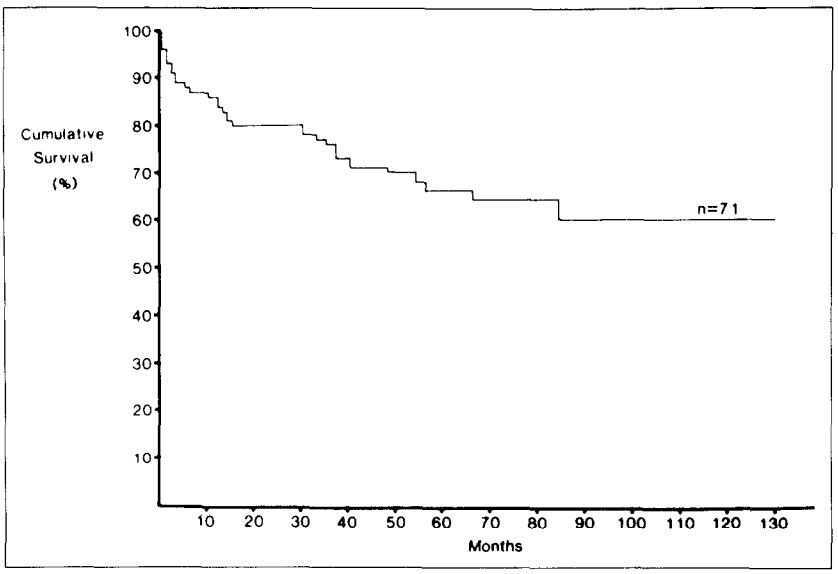

Figure 1. *Cumulative survival of the entire cohort of patients with systemic sclerosis following entry into the study.*

between those who survived and those who died. Females constituted 93 percent of survivors, but only 64 percent of nonsurvivors, indicating excess mortality in males ($p < 0.005$). The case-fatality rate for males was 75 percent compared with 27 percent for females ($p < 0.001$).

There was no significant difference in forced vital capacity or ratio of one-second forced expiratory volume to forced vital capacity between patients who survived and patients who died during the study period. However, a highly significant ($p < 0.001$) reduction in carbon monoxide diffusing capacity was seen in nonsurvivors as compared with survivors. Stepwise multiple regression analysis of demographic features and pulmonary function measures showed that the carbon monoxide diffusing capacity was the most important ($p < 0.001$), and male gender the second most important ($p < 0.01$) predictor of death. The ratio of one-second forced expiratory volume to forced vital capacity was of borderline predictive value ($p < 0.05$). After the carbon monoxide diffusing capacity, sex, and ratio of one-second forced expiratory volume to forced vital capacity were accounted for, predictive value was not enhanced by including vital capacity in the analysis. Carbon monoxide diffusing capacity and male gender were independent risk factors, with the carbon monoxide diffusing capacity for the 12 males (62.5 ± 8.5 percent of predicted) not being different from the carbon monoxide diffusing capacity of the 59 females (69.9 ±3.1 percent of predicted).

Case-fatality rate was inversely related to carbon monoxide diffusing capacity expressed as percent of predicted (**Figure 2**). In the patients with a carbon monoxide diffusing capacity above 60 percent of predicted, the case-fatality rate was 23 percent; in those with a carbon monoxide diffusing capacity between 40 and 60 percent of predicted, it was 33 percent; and in those with a carbon monoxide diffusing capacity of 40 percent of predicted or less, it was 91 percent. The relationship between initial carbon monoxide diffusing capacity and survival is also apparent in the cumulative survival curves (**Figure 3**). The survival in the patients whose initial carbon monoxide diffusing capacity was 40 percent of predicted or less declined significantly faster than that in the group with an initial carbon monoxide diffusing capacity above 40 percent of pre-

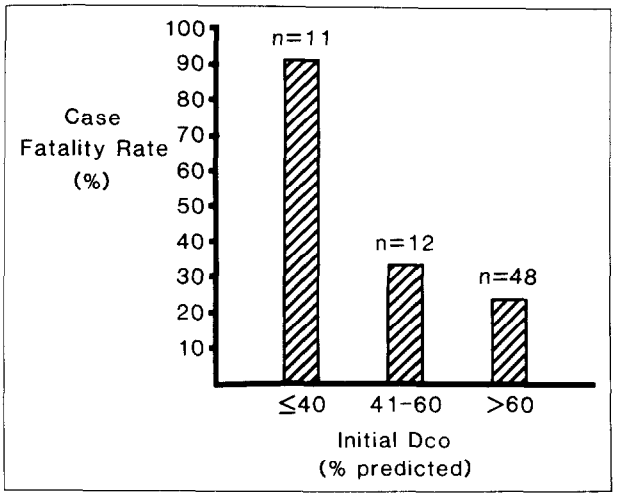

Figure 2. *Case-fatality rate in patients with systemic sclerosis during the study for various levels of initial carbon monoxide diffusing capacity (Dco) expressed as a percent of predicted normal reference value.*

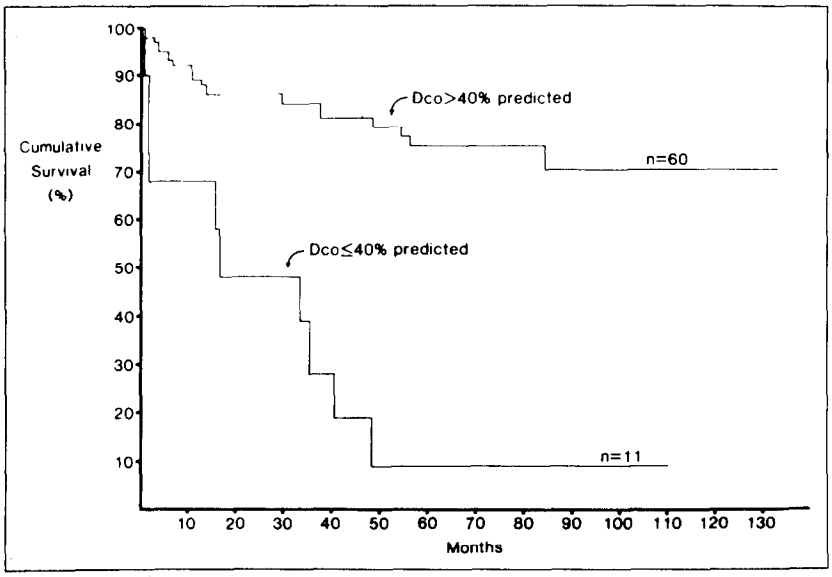

Figure 3. *Cumulative survival function in patients with systemic sclerosis who had carbon monoxide diffusing capacities (Dco) above and below 40 percent of the predicted normal reference value. Patients with a carbon monoxide diffusing capacity of 40 percent of predicted or less had significantly lower survivorship ($p < 0.01$).*

dicted ($p < 0.01$). The five-year survivorship for patients with a carbon monoxide diffusing capacity of 40 percent of predicted or less was only 9 percent, compared with a 75 percent survivorship in those patients with a carbon monoxide diffusing capacity above 40 percent of predicted ($p < 0.001$). Moreover, the fall in survivorship in this high-risk subgroup was rapid, with all deaths occurring within four years.

As expected, a restrictive defect was the most common pattern, occurring in 45 percent of the patients (**Table II**). Twenty-two percent of the patients had an obstructive defect, with a mean ratio of one-second forced expiratory volume to forced vital capacity of 66.5 ± 2.1 percent. A normal pattern and isolated gas transfer defect each occurred in 16 percent of patients. In the group with an isolated gas transfer defect, the carbon monoxide diffusing capacity was only moderately reduced (66.9 ± 3.7 percent of predicted). The pulmonary function pattern had an important influence on cumulative survival and case-fatality rate (**Figure 4**). Patients with normal pulmonary function exhibited a high survival rate, and those with an isolated gas transfer defect showed a rate similar to that in patients with normal lung function. The survivorship at five years tended to be reduced in patients with restriction but did not achieve statistical significance. Patients with obstruction had significantly reduced five-year survivorship when compared with patients with either normal function ($p < 0.05$) or isolated gas transfer defects ($p < 0.01$).

TABLE II **Pulmonary Function Classification (n = 67)**

	Frequency (percent)	Case-Fatality Rate (percent)
Normal	16	18
Isolated gas transfer defect	16	9
Restrictive ventilatory defect	45	40
Obstructive ventilatory defect	22	60

In patients with restriction, there was no difference in the degree of lung volume restriction between survivors (forced vital capacity: 65.4 ± 3.6 percent of predicted, total lung capacity: 69.3 ± 3.7 percent of predicted) and nonsurvivors (forced vital capacity: 62.8 ± 4.2 percent of predicted, total lung capacity: 63.5 ± 3.0 percent of predicted). The nonsurvivors, however, had a significantly lower initial carbon monoxide diffusing capacity (47.0 ± 7.6 percent of predicted) than did survivors (68.6 ± 5.1 percent of predicted) (**Figure 5**).

Similarly, in patients with obstruction, survivors (ratio of one-second forced expiratory volume to forced vital capacity 69.2 ± 1.9 percent) and nonsurvivors (ratio of one-second forced expiratory volume to forced vital capacity 64.6 ± 3.2 percent) did not differ in the severity of airways obstruction. However, the nonsurvivors had a significantly lower mean initial carbon monoxide diffusing capacity (55.8 ± 9.57 percent of predicted) than did survivors (85.3 ± 5.03 percent of predicted) (**Figure 6**). The patients with obstruction and a carbon monoxide diffusing capacity less than 70 percent of predicted were at significantly higher risk for death than those patients with obstruction and a higher carbon monoxide diffusing capacity ($p < 0.05$). In fact, all six patients who

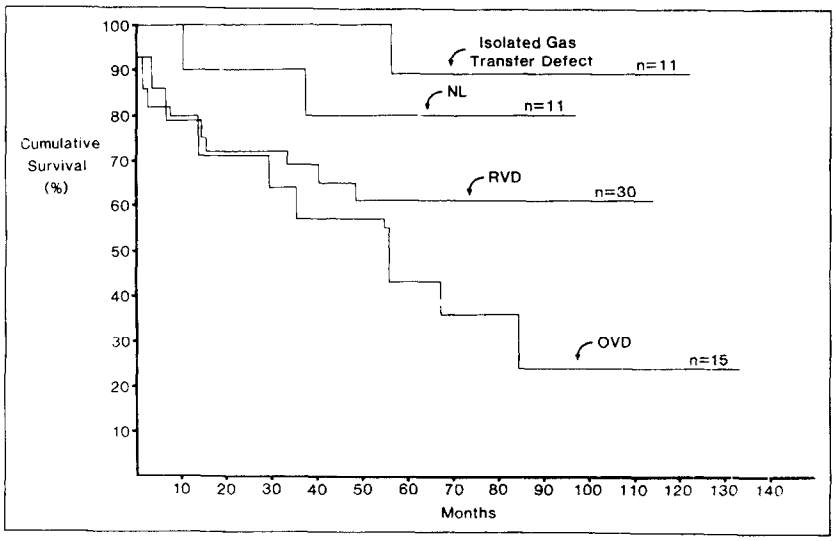

Figure 4. *Cumulative survival function in patients with systemic sclerosis grouped by classification of pulmonary function pattern. Patients with an obstructive ventilatory defect (OVD) had significantly reduced five-year survival compared with normal subjects (NL) ($p < 0.05$) and subjects with an isolated gas transfer defect ($p < 0.01$). Patients with a restrictive ventilatory defect (RVD) did not have significantly reduced survival compared with normal.*

had an obstructive pattern and a carbon monoxide diffusing capacity less than 70 percent died during the follow-up period.

We were able to ascertain a definite cause or major contributing factor toward death in nine of the 25 (36 percent) patients who died. In five of these nine, death could be attributed to organ involvement by systemic sclerosis: three patients died of respiratory failure, one of renal failure, and one of complications resulting from severe lower gastrointestinal tract involvement. Of the remaining four patients, one patient died from a myocardial infarction, one died from a cerebrovascular accident, and two patients died from bronchogenic carcinoma (one adenocarcinoma and one large cell undifferentiated carcinoma). In the 25 patients who died, the clinically apparent visceral involvement at last evaluation before death was as follows: pulmonary in 12, cardiac in eight, renal in five, and lower gastrointestinal in five patients.

COMMENTS

This report describes the relationship between the specific pattern and degree of pulmonary function impairment and the probability of death in patients with systemic sclerosis. In previous studies, Medsger et al [2] and Eason et al [4] identified renal, cardiac, and pulmonary involvement, in declining order of importance, as significant risk factors for death in systemic sclerosis. Bennet et al [3] also found that interstitial fibrosis was associated with an increased mortality rate, but Farmer et al [15] found no relationship between lung involvement and prognosis. All of these studies defined lung involvement primarily by either clinical or radiographic features.

Our present study determined that pulmonary function abnormalities, in particular the carbon monoxide diffusing capacity, are important predictors of death. There was a highly significant reduction in carbon monoxide diffusing capacity in patients who died, present in both males ($p < 0.05$) and females ($p < 0.005$). Discriminant analysis identified a subgroup of 11 patients with a carbon monoxide diffusing capacity of 40 percent of

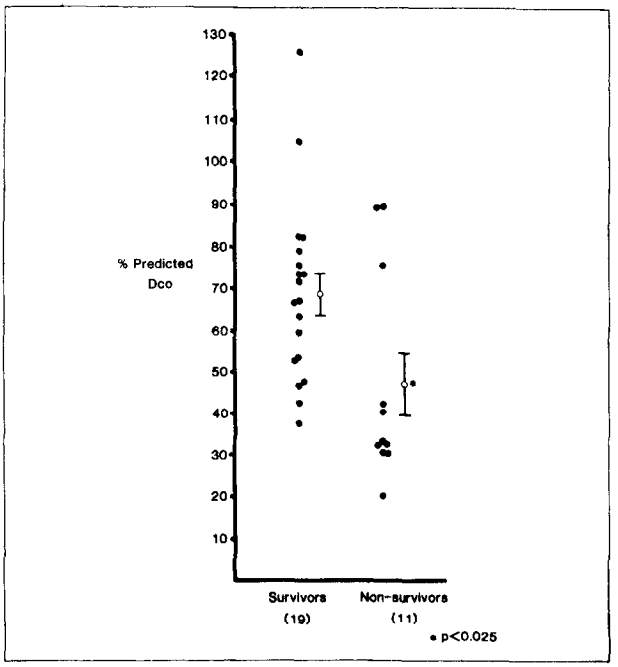

Figure 5. *Among patients with restriction, the carbon monoxide diffusing capacity (Dco) was significantly reduced in those who died during the course of the study ($p < 0.025$). Six of seven patients with a carbon monoxide diffusing capacity of 40 percent of predicted or less did not survive.*

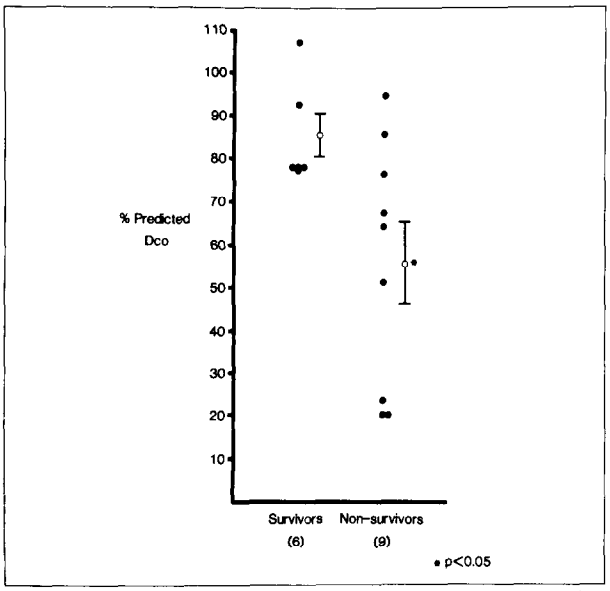

Figure 6. *Among patients with obstruction, those who died had a significantly reduced carbon monoxide diffusing capacity (Dco) ($p < 0.05$). All six patients with a carbon monoxide diffusing capacity less than 70 percent of predicted died during the study period.*

predicted or less who had an extraordinary risk. These patients had a case-fatality rate of 91 percent. The subpopulation with a low carbon monoxide diffusing capacity did not have a longer duration of disease prior to entry (25.9 ± 12.7 months) than subjects with a carbon monoxide diffusing capacity greater than 40 percent of predicted (32.1 ± 6.7 months). Thus, the high mortality rate did not merely reflect the late course of a progressive disease.

The low carbon monoxide diffusing capacity in systemic sclerosis could be due to destruction of the alveolar-capillary bed by interstitial fibrosis or primary pulmonary vascular disease. Whatever the mechanism, we think it likely that most of the patients with very low diffusing capacities had pulmonary hypertension. This is based on the finding of Ungerer et al [16] who noted that a carbon monoxide diffusing capacity less than 43 percent of predicted had an 88 percent specificity in detecting pulmonary hypertension with a 67 percent positive predictive value. Although we did not measure pulmonary artery pressures in our patients, it is reasonable to speculate that the high mortality rate in patients with a markedly low carbon monoxide diffusing capacity is attributable either directly or indirectly to pulmonary hypertension.

A reduction in carbon monoxide diffusing capacity has been suggested to be the earliest detectable pulmonary functional abnormality in systemic sclerosis [17,18]. A dissociation between reduction in vital capacity and carbon monoxide diffusing capacity has been noted previously in systemic sclerosis [1] and in interstitial fibrosis in general [6]. In the present study, an isolated reduction in diffusing capacity was a common finding, but did not indicate a poor prognosis. When a decreased diffusing capacity was the sole abnormality, it tended to be only moderately abnormal and frequently reverted toward the normal range on repeated testing. These results indicate that an isolated abnormality of carbon monoxide diffusing capacity is relatively common, but it may reflect variability of the test itself and has no bearing on survivorship.

The low cumulative survival rate associated with airways obstruction was an unexpected finding. There appears to be an interaction between the presence of obstruction and reduced carbon monoxide diffusing capacity based on the observation that all patients with obstruction and a carbon monoxide diffusing capacity less than 70 percent of predicted died. Although possible, we do not believe that the combination of airways obstruction and low carbon monoxide diffusing capacity in these patients is indicative of emphysema, since these patients did not demonstrate a significant increase in total lung capacity over survivors. It may be that airway disease and increased mortality are related to a common pathogenetic mechanism such as cigarette smoking. A reduction in the ratio of one-second forced expiratory volume to forced vital capacity is associated with decreased survival from all causes in a general population [7].

In the present study, male gender was a significant independent risk factor for mortality. Medsger et al [2] and Barnett [19] also found decreased survival in men, but Eason et al [4], Farmer et al [15] and Bennet et al [3] failed to identify a difference in survival between men and women. Although the cause for this is not clear, it is of interest that male gender is associated with increased pulmonary and bronchial smooth muscle reactivity [20,21]. Since pulmonary vascular abnormalities are a prominent feature of this disease, men may be more susceptible to the underlying disease process or exogenous aggravating factors.

Our patient population is similar to other reported series in age, race, sex and five-year cumulative survival [3,15,19,22–26]. The mean values of pulmonary function were also similar to those reported in other series [17,22,24,25,27–32] and indicate a mild restrictive ventilatory defect with a mild gas transfer defect. When subjects were classified according to pulmonary function pattern, a restrictive defect was most common, as reported by others [24,27,30,33]. A relatively high incidence (22 percent) of airways obstruction was present in this population, although it tended to be mild in degree. A similar incidence of obstruction has been found by some authors

[27,30,31,34] but not by others [28]. The proportion of our patients with normal pulmonary function exceeds that reported in several other series [17,24,27,28,30] and may reflect the fact that our patient population was not biased toward the presence of lung involvement.

A marked seasonal variation in mortality was evident, with 76 percent of the deaths occurring in the fall and winter. This is consistent with the finding of Cannon et al [35] who reported that two thirds of deaths in an autopsy series occurred in the fall and winter months. By contrast, only 52 percent of the annual mortality of the general United States population occurs from October through March [36]. This raises the possibility that patients with systemic sclerosis are adversely affected by cold weather. Possible explanations include cold-induced visceral vasospasm [35,37,38] or other environmental factors such as increased infectious complications. A seasonal change in climate may be more important than the degree of cold weather, since there is no difference in mortality in this disease between the northern and southern United States [39–41].

In summary, we have found that a low carbon monoxide diffusing capacity—40 percent of predicted or less—is associated with a striking increase in mortality rates in patients with systemic sclerosis. The presence of an obstructive ventilatory defect also indicates a poor prognosis when the carbon monoxide diffusing capacity is less than 70 percent of predicted. An isolated defect in diffusing capacity in the absence of other abnormalities of pulmonary function does not, however, imply a poor prognosis. Although it is not clear whether the low diffusing capacity is due to interstitial fibrosis or a primary pulmonary vasculopathy, it is likely that this high mortality rate is associated with the presence of pulmonary hypertension. We conclude that pulmonary function testing is an important prognostic tool in the management of patients with systemic sclerosis.

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