Peak Expiratory Flow Rate: Relationship to Risk Variables and Mortality

The Wisconsin Epidemiologic Study of Diabetic Retinopathy

BARBARA E.K. KLEIN, MD[1]
SCOT E. MOSS, MA[1]
RONALD KLEIN, MD[1]
KAREN J. CRUICKSHANKS, PHD[1,2]

OBJECTIVE — To examine correlates of peak expiratory flow rate in people with type 1 diabetes and to evaluate the relationship of peak expiratory flow rate to mortality.

RESEARCH DESIGN AND METHODS — A cohort study that was originally designed to determine the prevalence, incidence, and severity of diabetic retinopathy also provided the opportunity to measure peak expiratory flow rate. This was first measured at a 10-year follow-up and was evaluated in regard to risk factors for microvascular complications of diabetes. Mortality during 6 years of follow-up after the measurement was also ascertained.

RESULTS — In multivariable analysis, peak expiratory flow rate was associated with sex, age, height, BMI, history of cardiovascular disease, pulse rate, duration of diabetes, glycosylated hemoglobin, and end-stage renal disease. Peak expiratory flow rate was significantly associated with survival in categorical analyses. Even after considering age, sex, renal disease, history of cardiovascular disease, respiratory symptoms, duration of diabetes, cigarette smoking, and hypertension, peak expiratory flow rate was still significantly related to survival (hazard ratio 0.61 [95% CI 0.46–0.82]).

CONCLUSIONS — These data indicate that peak expiratory flow rate is associated with risk factors for other complications of diabetes. In addition, peak expiratory flow rate is a significant predictor of survival over even a relatively short period of time (6 years) in patients with younger-onset diabetes.

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Those patients with type 1 (1–6) and type 2 (7) diabetes have been found to have pulmonary function abnormalities in addition to other better-known complications of diabetes, such as retinopathy, nephropathy, sores and ulcers on the feet and ankles, and amputations. Many of the latter complications have been found to be associated with the level of glycemia. In a small clinical study, Ramirez et al. (3) found that those insulin-dependent subjects whose glycemia was controlled by an insulin pump had better pulmonary function than those who received standard care and had higher levels of glycemia. However, Buckingham et al. (4) did not find an effect of glycemia in the 375 patients they studied. We had an opportunity to investigate whether certain characteristics known to be associated with the risk of other complications in type 1 diabetes were also associated with peak expiratory flow rate in the well-characterized cohort participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). Measurements were taken at the third examination (1990–1992).

From the [1]Department of Ophthalmology and Visual Sciences, University of Wisconsin Medical School, Madison; and the [2]Department of Preventive Medicine, University of Wisconsin Medical School, Madison, Wisconsin.

Address correspondence to Barbara E.K. Klein, MD, MPH, Department of Ophthalmology and Visual Sciences, University of Wisconsin-Madison, 610 North Walnut St., 460 WARF, Madison, WI 53705-2397. E-mail: klein@epi.ophth.wisc.edu.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

— A description of the sampling procedures and population attributes have appeared in previous reports (8–10). In summary, all patients receiving care for diabetes in an 11-county area of south central Wisconsin were identified in 1979–1980 (n = 10,135). All patients who had been diagnosed with diabetes before 30 years of age and who were taking insulin (n = 1,210) were invited to participate in a study of diabetic retinopathy; of these, 996 participated in the baseline examination. They were seen for study evaluations 4, 10, and 14 years after the baseline evaluation, and peak expiratory flow rate measurement was added to the standard examination at the 10- and 14-year examinations. Examination procedures and measurements were standardized, and those that were repeated at all examinations were done with the same protocols used at baseline. The sections of the evaluation regarding pulmonary function included questions from the Respiratory Symptom Questionnaire recommended by the American Thoracic Society (11). We dichotomized symptom scores into categories of none or mild versus present (more severe than mild), because those with mild symptoms did not differ from those with no symptoms. Categorization of responses has been used in analyses by other investigators (12). Measurements of peak expiratory flow rate were made with the subject in a standing position using the mini-Wright Peak Flow Meter (Clement Clarke, Columbus, OH). The procedure was adopted from that used in a study in East Boston conducted as part of the evaluation of the established populations for the Epidemiologic Studies of the Elderly (13).

Measures of height, weight, blood pressure, urinary protein, pulse rate, and glycosylated hemoglobin were performed using standard protocols with quality control procedures (9,10,14). A standardized history was taken that included questions about age, age at onset of dia-

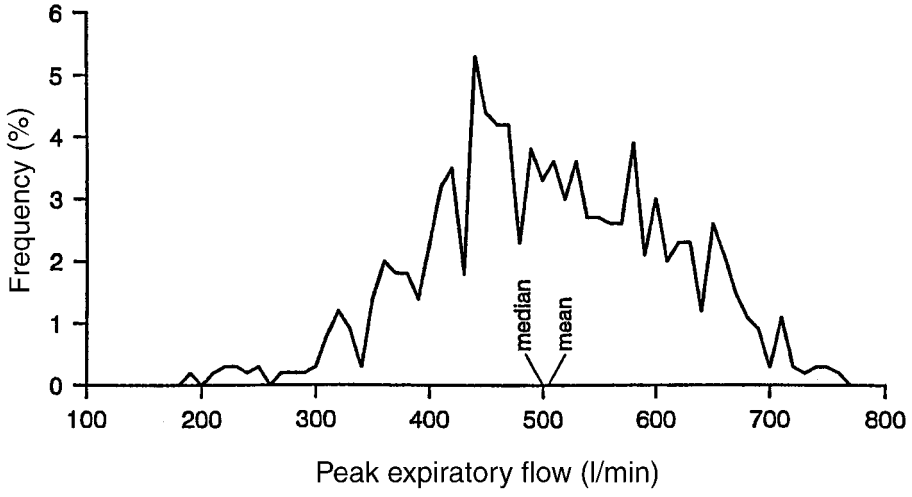

Figure 1—*Distribution of peak expiratory flow rate in subjects with younger-onset diabetes at the 10-year examination. From the Wisconsin Epidemiologic Study of Diabetic Retinopathy.*

betes, cardiovascular disease, smoking, and physical activity. For categorical analyses, conventional cut points, where available, were applied. Otherwise, distributions were divided into quartiles of the distributions as they occurred in our population. Multivariate linear regression was used to evaluate the relationships of several variables for their independent effects on peak expiratory flow rate.

Definitions

The current age was the person's age when examined in 1990–1992. Age at diagnosis was that at which diabetes was first recorded on the patient's chart or hospital record by a physician. The duration of diabetes was the period between the age at diagnosis and the age when examined for this study. The mean systolic blood pressure was the average of two systolic pressure determinations, and the mean diastolic blood pressure was the average of two diastolic pressures. Hypertension was defined as a mean systolic pressure of ≥140 mmHg, a mean diastolic pressure of ≥90 mmHg, or a history of hypertension with use of antihypertensive medication. A history of diuretic or antihypertensive medication use, including the specific medications used, was obtained from the participants. If there was any question regarding the medication, its use was verified by a physician's report.

Cardiovascular disease history status was determined as follows: a person was classified as having a history of cardiovascular disease if he or she had a physician-verified report of angina, a heart attack, or a stroke. Subjects were classified as having never smoked if they had smoked ≤100 cigarettes in their lifetime and as being ex-smokers if they had smoked more than that amount and had stopped smoking before the examination. They were classified as currently smoking if they had not stopped smoking before the examination. For purposes of analysis, we compared the ex-smokers with those who had never smoked and the current smokers with those who had never smoked. Proteinuria was defined as urine protein concentrations ≥0.30 g/l as measured by a dipstick.

One of the original aims of the WESDR was to examine mortality in the population. Thus, all subjects have been contacted annually by telephone to determine vital status; designated individuals, relatives, and physicians are contacted; and newspaper obituaries are reviewed daily. In all cases an attempt is made to obtain an exact or approximate date of death. Periodically, a request is made to the Wisconsin Center for Health Statistics, Section of Vital Statistics, for death certificate information for these individuals. Names of participants who are not known to be dead, but have been unavailable for follow-up, are submitted for matching against the death records. Finally, information on those who have moved out of Wisconsin and are suspected of being dead and those who are unavailable for follow-up are submitted to the National Death Index for matching against national death data.

The survival interval begins on the date of the 1990–1992 examination. Median follow-up to date has been 6 years. Only deaths that have been confirmed by a death certificate were included in the analysis. Those subjects for whom a death certificate has not been located were considered to be alive as of the last contact date on which they were known to be alive.

Multivariate analyses were performed by Cox proportional hazards regression (15). This permits the evaluation of the effect of peak expiratory flow rate on survival while controlling for other risk factors. Age and sex were included in the model because these are generally regarded as important factors for mortality. Additional risk factors were selected in stepwise fashion, remaining in the final model if significant at the 0.05 level. Finally, peak expiratory flow rate was added to the model to determine its independent effect on mortality. Hazard ratios for mortality were computed as $exp(\beta)$, where β is the coefficient of a variable in the model and *exp* is the exponential function. The 95% CIs for the hazard ratio were computed as $exp(\beta \pm [1.96 \times SE\beta])$, where $SE\beta$ is the standard error of the coefficient.

RESULTS — Of the 996 subjects who had participated at the baseline examination, 784 participated at the 10-year follow-up examination. Most of those who were not included at follow-up had died. Participants at the 10-year examination had been younger, had shorter duration of diabetes, and were more likely to be women, less likely to be hypertensive, and less likely to be smokers than the entire cohort.

Figure 1 describes the distribution of peak expiratory flow rate in the population. The mean flow rate (± SD) was 504 (±104) l/min and the median was 500 l/min. Characteristics that were individually significantly associated with peak expiratory flow rate were sex (men greater than women), age (inverse association), duration of diabetes (inverse association), body weight (direct association), height (direct association), history of cardiovascular disease (lower when present), pulse rate (inverse association), physical activity (direct association), lifestyle (active greater than sedentary), and respiratory symptoms (none or mild greater than presence of more severe symptoms) (Table 1).

To determine the independent contri-

butions of the characteristics of these subjects to peak expiratory flow rate while accounting for correlations among them, we performed multivariable analyses (Table 2). Whereas the leading contributions to this model were those related to body size (sex, height, age, and BMI), characteristics related to diabetes and its complications added significant information to describing peak expiratory flow rate. Smoking did not contribute significantly to the model, but respiratory symptoms did. The squared terms for age and BMI indicate the decreasing strength of the relationship of these variables to peak expiratory flow rate as their values increase. The total R^2 for this model was 62%. We have had the opportunity to evaluate a group of nondiabetic volunteers who were of similar age to our diabetic study participants. We developed a linear regression model including data from these subjects and using the same set of variables we had used for those with diabetes, but this time we included diabetes status as another variable. Parameter estimates were little changed from those in Table 3. However, diabetes status was significantly associated (inversely) with peak expiratory flow rate.

The survival experience of the cohort by quartile of peak expiratory flow rate at examination is seen in Fig. 2. Those with the highest rates had better survival. The mean age of this population at the time of measurement of peak expiratory flow rate was 37.2 years.

To account for the influence of other characteristics on survival, we performed proportional hazards regression analyses (Table 3). After including characteristics found to be important in predicting survival in other analyses, peak expiratory flow rate still added significantly to the model. Respiratory symptoms did not change the association of peak expiratory flow rate to survival.

CONCLUSIONS — We have found that factors associated with other complications of diabetes are related to peak expiratory flow rate. Primhak et al. (16) and Lange et al. (17) report decreased lung function in diabetes, whereas Schernthaner et al. (1) found no abnormalities. We note that Primhak et al. (16) did not find associations of diminished function with either duration of diabetes or glycosylated hemoglobin whereas Lange et al. (17) did find an association with level of

Table 1—*Associations of peak expiratory flow rate at the third examination with other subject characteristics*

Characteristic	*n*	Peak expiratory flow rate (1/min)	*P*
Sex			
Female	324	436 ± 66	<0.001
Male	339	570 ± 90	
Age (years)			
13–24	85	508 ± 83	<0.001
25–29	116	535 ± 110	
30–34	118	511 ± 92	
35–39	104	505 ± 95	
40–44	101	521 ± 104	
45–49	50	480 ± 111	
50+	89	447 ± 111	
Duration (years)			
11–14	125	533 ± 89	<0.001
15–19	195	529 ± 101	
20–24	126	504 ± 99	
25–29	82	504 ± 100	
30–34	53	471 ± 90	
35+	82	425 ± 104	
Glycosylated hemoglobin (%)			
5.3–8.7	155	504 ± 102	0.20
8.8–9.8	177	513 ± 106	
9.9–11.0	163	509 ± 105	
11.1–17.4	160	490 ± 102	
BMI			
16.0–23.1	152	479 ± 99	0.40
23.2–25.2	157	524 ± 106	
25.3–27.7	161	526 ± 105	
27.8–47.4	159	496 ± 91	
Weight (kg)			
40.5–63.7	142	438 ± 81	<0.001
63.8–72.0	156	488 ± 93	
72.1–81.3	165	536 ± 98	
81.4–137.8	168	551 ± 97	
Height (cm)			
140.0–162.0	149	430 ± 63	<0.001
162.1–168.0	161	457 ± 84	
168.1–174.8	151	529 ± 88	
174.9–197.4	171	599 ± 73	
Urine protein			
Absent	442	508 ± 102	0.27
Present	166	498 ± 108	
Dialysis/transplant	43	486 ± 102	
Cardiovascular disease history			
Absent	599	512 ± 102	<0.001
Present	61	437 ± 93	
Smoking status			
Nonsmoker	367	501 ± 103	0.67
Ex-smoker	152	510 ± 110	
Current smoker	144	507 ± 100	
Pulse (per 30 s)			
23–36	180	532 ± 102	<0.001
37–41	166	487 ± 109	
42–45	145	516 ± 104	
46–74	166	479 ± 91	
Physical activity (h per week)			
0	359	494 ± 105	0.01
1	36	516 ± 102	
2	65	520 ± 95	
3	77	522 ± 99	
4	51	517 ± 114	
5	39	517 ± 99	
6+	36	502 ± 105	
Lifestyle			
Active	203	516 ± 104	0.05
Sedentary	460	499 ± 104	
Respiratory symptoms			
None or mild	558	509 ± 104	<0.01
Present	102	480 ± 100	

Data are means ± SD unless otherwise indicated.

Table 2—*Multiple linear regression model describing association with peak expiratory flow rate at the 10-year examination

Characteristic	*P*	Parameter estimate†
Sex (male)	<0.001	83.9
Age (years)	0.002	3.79
Age (years) squared		−0.053
Height (cm)	<0.001	4.02
BMI (kg/m^2)	<0.001	17.1
BMI squared		−0.271
Cardiovascular disease history (present)	0.003	−29.9
Respiratory symptoms (severe)	0.007	−9.51
Duration (years)	0.008	−1.32
Pulse rate, per 30 s	0.007	−1.07
Dialysis/renal transplant (present)	0.02	−26.3
Glycosylated hemoglobin, 1%	0.02	−3.66

The dependent variable was the peak expiratory flow rate. *Total $R^2 = 0.62$; †parameter estimate indicates change in peak flow rate per unit change in the independent variable.

plasma glucose. The population studied by Primhak et al. (16) was composed of children whose mean age was 11.8 ± 2.7 years and whose duration of diabetes was 4.6 ± 3.8 years. It is possible that the range of these variables and the range of lung function were not great enough to demonstrate important relationships. Some authors have suggested that diminished pulmonary function in diabetes may reflect diminished elastic recoil (2,16), possibly caused by changes in collagen in patients with diabetes (18–20) and in animal models (21). However, whereas the collagen changes may be similar to those found in aging individuals (22,23), the functional pulmonary changes in diabetes and aging are not all the same (24).

There appeared to be paradoxical relationships between glycosylated hemoglobin and peak expiratory flow rate, such that there was no significant effect on univariable analysis, but there was one in the multivariable model. This is likely the result of negative confounding so that once adjustment is made for sex and BMI, a consistent inverse relationship between HbA_{1c} and peak expiratory flow rate is revealed (data not shown).

The peak expiratory flow rate in our group of subjects with relatively long duration of diabetes was strongly associated with age. When we evaluated correlates of peak expiratory flow rate in the combined group of subjects, including both the cohort with diabetes and the nondiabetic comparison group, the effect of age was still apparent, although the parameter estimate was slightly decreased. It is possible that this may reflect a slightly lower effect of age on peak expiratory flow rate in those without diabetes.

We note that smoking did not add significant information to either of our multivariable models (Tables 2 and 3). It may be that the information included in the smoking status variable was "included" in the other variables in the model, especially respiratory symptoms.

Our cross-sectional data indicate a significant relationship between peak expiratory flow rate and glycemia. Long-term longitudinal studies will better inform us about changes in levels of glycemia with respect to changes in this measure of lung function. In addition to finding that peak expiratory flow rate was associated with renal disease and cardiovascular disease cross-sectionally, we also found that there were demonstrable differences in survival over a 6-year follow-up by peak expiratory flow rate. Age and sex were important confounders of the relationship of peak expiratory flow rate to survival in participants in a study in East Boston in the Massachusetts Established Populations for Epidemiologic Studies of the Elderly. However, even after including significant complications of diabetes, such as renal disease and history of cardiovascular disease, peak expiratory flow rate was still a significant predictor of mortality.

Limitations of our study may derive from the fact that measurements of peak expiratory flow rate were taken in a cohort that was defined 10 years before our measurement. Thus, we are studying individuals with type 1 diabetes of long duration. This implies that our subjects are long-term survivors and that their experience with respect to risk factors for death is better than had been true for the original cohort. They had more favorable distributions of risk factors, such as duration of diabetes, blood pressure, smoking, and possibly of lung function at the baseline examination. One might then wonder whether our estimate of the relationship between peak expiratory flow rate and survival underestimates the relationship

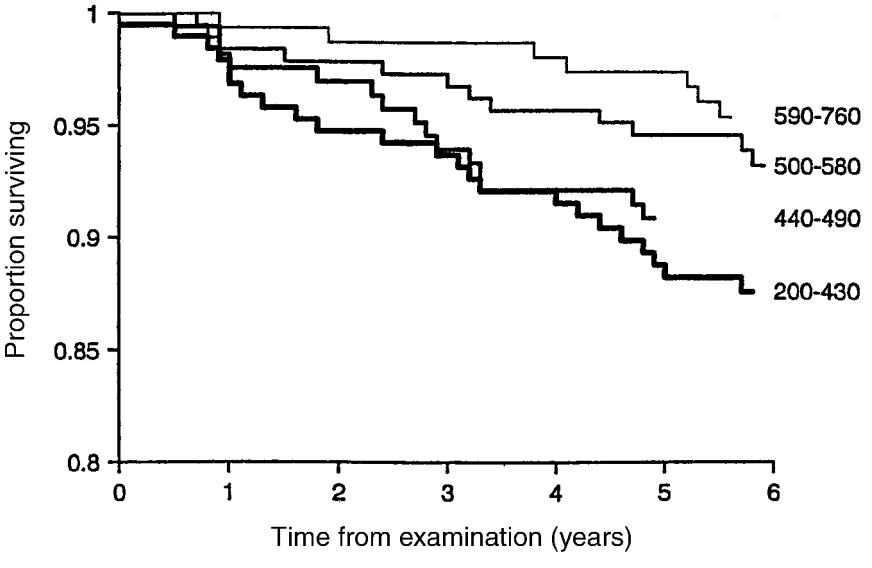

Figure 2—*Survival after the 10-year examination (exam 3) by quartile of peak expiratory flow rate for younger-onset cohort. From the Wisconsin Epidemiologic Study of Diabetic Retinopathy.*

Table 3—*Association of participant characteristics* to mortality†*

Characteristic	Increment	Hazard ratio	95% CI	*P*
Age	10 years	1.65	1.31–2.08	<0.001
Sex	Male	2.65	1.38–5.10	0.004
Renal disease	Urine protein	2.64	1.40–4.98	<0.001
	Dialysis/transplant	4.95	2.36–10.39	
Cardiovascular disease history	Present	2.14	1.15–3.96	0.02
Respiratory symptoms	Severe	1.93	1.07–3.49	0.03
Peak expiratory flow rate	100/min	0.61	0.46–0.82	0.001

*Duration of diabetes, cigarette smoking status, and hypertension did not contribute significantly to the model; †based on proportional hazards regression analyses.

should these models be applied to a different cohort or our full cohort from baseline. The potential importance of our findings to all individuals with type 1 diabetes might be best addressed by a study specifically designed to evaluate the hazard ratio associated with peak expiratory flow rate in subjects comparable for all relevant confounders and differing only by diabetes status.

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