Chlamydial infection is an important source of gynaecological morbidity, being commonly associated with acute and chronic pelvic inflammatory disease and therefore infertility.¹³ Both problems have a large impact on the provision of gynaecological services in a given area. Screening and treatment for chlamydial infection before transcervical instrumentation that breaches the internal cervical os may prevent iatrogenic pelvic inflammatory disease,¹⁴ especially when retained products of conception within the uterine cavity provide an ideal medium for bacterial growth. We think that in cases of termination of pregnancy our results justify prior screening for chlamydia in the west of Scotland and in other areas with similar prevalence rates. If screening facilities are lacking, prophylaxis may be justified. Screening has been endorsed by workers elsewhere in the United Kingdom.³

The high percentage of women with asymptomatic genital chlamydial infection makes the use of effective antibiotics—for example, a tetracycline or erythromycin—important in cases of pelvic inflammatory disease and suspected postpartum and postabortion endometritis. Treatment of the partners of patients with genital chlamydial infection is recommended in order to prevent reinfection and reduce the pool of genital chlamydial strains within the general population. For the gynaecologist this may entail shared management with the genitourinary physicians. In our study the prevalence of other sexually transmitted diseases was very low, which may reflect regional differences. This low prevalence, however, should not be regarded as unimportant.

We have detected a high incidence of chlamydial infection in both general practice and colposcopy clinics in Glasgow. General practitioners and gynaecologists should be more aware of the importance of investigating and treating chlamydial infection in both asymptomatic women and their partners.

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Ventilatory function as a predictor of fatal stroke

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Abstract

Objective—To investigate the relation between ventilatory function and subsequent mortality due to cerebrovascular disease.

Design—Prospective longitudinal study.

Subjects—A total of 18403 male civil servants aged 40-64 years at entry examination for the Whitehall study.

Main outcome measure—Mortality from cerebrovascular disease (ICD8 430-438) after 18 years of follow up.

Results—In all, 262 men with sinus rhythm at entry died due to stroke during the 18 years of follow up. Compared with men with a forced expiratory volume in one second of ≥ 3.5 litres those with a value of < 3.0 litres were almost twice as likely to die of cerebrovascular disease (rate ratio adjusted for age and systolic blood pressure=1.88, 95% confidence interval 1.32 to 2.69). This increased risk occurred within each tertile of systolic blood pressure. Nested case-control analyses were used to control precisely for confounding effects of age, height, and smoking (by matching) and employment grade and physiological risk factors (by modelling). The effect of forced expiratory volume in one second was independent of age, height, smoking habits, employment grade, blood pressure, weight, cholesterol concentration, glucose tolerance, electrocardiographic abnormalities, history of chest pain, and history of intermittent claudication.

Conclusions—Measurements of ventilatory function may assist clinical decisions about whether to treat mild hypertension. Impaired ventilatory function and stroke may share common causes.

Introduction

Reduced ventilatory function is a predictor of mortality due to cardiovascular causes and non-fatal coronary heart disease.¹⁻⁸ Four studies have reported specifically the relation of ventilatory function to subsequent fatal⁶ or non-fatal^{2,5,9} cerebrovascular disease. An inverse association between spirometric indices and stroke was found in each case, although in none did it reach conventional levels of significance when adjusted for other risk factors.

This paper explores the relation between ventilatory function and mortality due to cerebrovascular disease among a cohort of middle aged civil servants who were followed up for 18 years. It also updates earlier findings from this cohort that related cardiovascular risk factors to fatal stroke.¹⁰

Methods

STUDY POPULATION

For the Whitehall study death certificates were obtained for 19018 male civil servants who were examined during 1967-9.¹¹ This analysis was limited to the 18403 men aged 40-64 years at examination and to deaths

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occurring on or before 31 January 1987. The underlying cause of death was coded throughout according to the eighth revision of the International Classification of Diseases (ICD8).

The examination at entry¹¹ included measurement of height, weight, and blood pressure (with the London School of Hygiene's sphygmomanometer with the subject seated). A six limb lead electrocardiogram was recorded and classified by the Minnesota code.¹² Three forced expiratory manoeuvres were recorded with a Vitalograph spirometer and the mean values of the highest two measurements of forced expiratory volume in one second (FEV₁) and the corresponding measurements of forced vital capacity were entered into a computer for analysis. Subjects attended after an overnight fast, and capillary blood samples were collected two hours after a 50 g oral glucose load for measurement of blood glucose and cholesterol concentrations. The subjects were requested to complete a questionnaire, which included questions on lifetime smoking habits, employment grade, and history of cardiorespiratory symptoms.¹³

My analysis follows the conventions of previous reports¹⁰ for classifying electrocardiographic abnormalities and blood glucose concentrations (details of these classifications are given as footnotes to table III).

STATISTICAL ANALYSIS

The statistical analysis system (SAS)¹⁴ was used for data processing, and statistical modelling was performed with the epidemiological graphics, estimation, and testing package (EGRET).¹⁵ Mortality among the whole cohort was analysed by log linear Poisson regression models and adjusted for age by fitting separate variables for each single year of age at examination.

More complex analyses including continuous variables were conducted by a "nested" (within the cohort) case-control approach. Cases were defined as men who died of cerebrovascular disease (ICD8 430-438) during the 18 years of follow up. Matched controls were selected for each case from among the men who survived longer than the subjects who died from the date of examination. The matching criteria were age at examination (single years), height (measured to the nearest half inch (1.3 cm)), and smoking habit (never, former, or current smoker). All eligible controls were included, resulting in variable numbers of controls for each case.

The matched case-control sets were analysed by conditional logistic regression. Case-control state was the outcome variable, and measurements of ventilatory function and other cardiovascular risk factors were entered as explanatory variables. Coefficients from such regression models are equivalent to those obtained by proportional hazards regression¹⁶ and estimate the logarithm of the rate ratio per unit increase in an

explanatory variable. In this instance these rate ratios are mortality ratios and are all adjusted for the matching variables (age, height, and smoking habit), in addition to other explanatory variables in the model.

Results

MORTALITY DUE TO STROKE IN COHORT

Of 18 403 men aged 40-64 at examination, 272 died of cerebrovascular disease during an average of 16.6 years of follow up. Table I shows the distribution of deaths due to stroke by age at death and certified underlying cause of death.

Six out of 69 men with atrial fibrillation at entry died compared with the figure of 1.3 expected deaths according to the age specific rates in the remainder of the cohort (rate ratio 4.6; 95% confidence interval 2.1 to 10.5). Inclusion of men with atrial fibrillation in subsequent case-control analyses resulted in failure to attain convergence in some of the models fitted. These six men and one other man whose electrocardiogram was not recorded at entry were therefore excluded from the remainder of the analyses.

Tobacco smoking at entry was associated with fatal stroke among men with sinus rhythm. The age adjusted rate ratios for current smokers compared with lifelong non-smokers were 1.38 (95% confidence interval 0.96 to 2.00) for all deaths due to stroke, 2.21 (1.28 to 3.84) for fatal strokes occurring before age 70, and 0.89 (0.38 to 2.08) for fatal strokes occurring after age 70. The corresponding rate ratios for former smokers compared with lifelong non-smokers were 1.02 (0.68 to 1.48), 1.59 (0.89 to 2.82), and 0.64 (0.37 to 1.10).

CASE-CONTROL ANALYSES

The case-control study was based on 261 patients and 3247 controls matched for age, height, and smoking habit. The number of controls ranged from one to 34 per case. In all, 111 (43%) cases had fewer than 10 matched controls, but only 51 (20%) had fewer than five matched controls. No controls could be matched to one man (height 152 cm) who died of subarachnoid haemorrhage. Table I gives the other patients who were excluded because of missing data or atrial fibrillation at entry.

In single factor conditional logistic regression models fatal stroke was significantly more common among those with a low FEV₁. The rate ratio per litre decrease in FEV₁ (controlling for age, height, and smoking habit by matching) was 1.46 (95% confidence interval 1.16 to 1.84, $\chi^2=10.3$, df=1). Inclusion of a quadratic term for FEV₁ did not significantly improve the fit of the model ($\chi^2=1.56$, df=1). The relation of forced vital capacity to death caused by stroke was of a similar strength (rate ratio=1.42/litre decrease, confidence interval 1.13 to 1.80) but was less significant ($\chi^2=8.68$, df=1). There was a weak association between fatal stroke and the ratio of FEV₁ to forced vital capacity (rate ratio=1.09 per 10% decrease, 0.95 to 1.25, $\chi^2=1.42$, df=1).

As expected, raised blood pressure was strongly related to mortality due to stroke. Taken individually, systolic blood pressure was a more powerful predictor of fatal stroke, as judged by the likelihood ratio statistic ($\chi^2=113.7$, df=1) than was phase IV diastolic pressure ($\chi^2=92.3$, df=1). When modelled jointly, however, the effect of diastolic pressure was significant ($\chi^2=7.58$, df=1) after adjustment for systolic pressure. Quadratic terms for systolic ($\chi^2=3.38$, df=1) or diastolic pressure ($\chi^2=2.59$, df=1) did not significantly improve the model, but terms describing their interaction with age at death (above or below 70 years) were jointly significant ($\chi^2=7.13$, df=2). Four terms were therefore used in subsequent analyses to adjust for the effects of blood pressure on mortality due to stroke: linear terms

TABLE 1—Number of deaths due to cerebrovascular disease in a cohort of 18 403 men during an average of 16.6 years of follow up by age at death and certified cause of death

ICD8 code	Cause of death	Age at death (years)					Total included in case-control study
		47-59	60-64	65-69	70-74	75-82	
430	Subarachnoid haemorrhage	10*	7	9†‡	2	1	26
431	Cerebral haemorrhage	12§	14	10	10		44
432	Occlusion of precerebral arteries	1	1		1		3
433	Cerebral thrombosis	1§	2	6	12	6	26
434	Cerebral embolism			1			1
436	Acute ill defined cerebrovascular disease	8*	17§	42¶	41	36	140
437	Generalised ischaemic cerebrovascular disease	1	1	4	8§	3	16
438	Other and ill defined cerebrovascular disease		1	1	2	1	5
Total included in case-control study		29	42	69	74	47	261

The figures in the body of the table include the following subjects excluded from the case-control study: *one man with unknown smoking habit and FEV₁; †one man with unknown blood pressure; ‡one man with no matching controls; §one man with atrial fibrillation; ||one man with no electrocardiogram; ¶two men with atrial fibrillation.

for systolic and diastolic pressure, each for deaths among men above and below 70 years of age.

When FEV₁ was added to this model its effect was similar to that obtained before adjustment for blood pressure. The rate ratio/litre decrease in FEV₁ was 1.41 (95% confidence interval 1.12 to 1.79), which remained highly significant ($\chi^2=8.11$, df=1). Table II gives the rate ratios for blood pressure and FEV₁ by age at death due to stroke. Although a low FEV₁ was more strongly associated with fatal stroke occurring in men before age 70 than with deaths due to cerebrovascular causes in older men, the interaction between FEV₁ and age at death was not significant ($\chi^2=2.88$, df=1). There was no significant difference in the degree of association of reduced FEV₁ with subarachnoid haemorrhage, cerebral haemorrhage, and other types of stroke (χ^2 for interaction=3.27, df=2). The effect of reduced FEV₁ was similar among current smokers, former smokers, and lifelong non-smokers (χ^2 for interaction=2.66, df=2). Further modelling therefore included only one

term to describe the effect of FEV₁ on mortality due to stroke.

The effect of other cardiovascular risk factors on the risk of fatal stroke and the association between low FEV₁ and mortality due to stroke was investigated by adding them, in turn, to a "core model" consisting of the four blood pressure terms (shown in table II) plus FEV₁. Table III shows the adjusted rate ratio estimates for each risk factor with associated 95% confidence intervals and likelihood ratio χ^2 statistics. None of the risk factors were significantly associated with fatal stroke at the 5% level, although the rate ratio for history of intermittent claudication was of borderline significance (p=0.06). The changes in the rate ratio for FEV₁ when each cardiovascular risk factor was included in the model were small, indicating minimal confounding by these variables of the association between FEV₁ and stroke (table III).

CLINICAL PREDICTION OF FATAL STROKE

The value of measurements of blood pressure and ventilatory function in clinically predicting fatal stroke was investigated among all men with sinus rhythm at entry. Table IV gives the mortality ratios (relative to 100 for all men) by tertiles of systolic blood pressure and tertiles of FEV₁ (as measured), adjusting for age alone and for age, smoking habit, and employment grade.

In each third of the distribution of systolic blood pressure men in the lowest third of the distribution of FEV₁ had higher age adjusted mortality due to stroke. The interaction between systolic blood pressure and FEV₁ was not significant ($\chi^2=3.56$, df=4, adjusting for age alone). Comparing men with FEV₁ <3 litres with those whose FEV₁ was ≥ 3.5 litres, the rate ratio adjusted for age (single years) and tertile of systolic blood pressure was 1.88 (95% confidence interval 1.32 to 2.69). After further adjustment for smoking habit and employment grade the corresponding rate ratio was 1.70 (1.18 to 2.46).

A non-significant excess of deaths due to stroke remained among the current cigarette smokers, independent of age, employment grade, tertile of systolic blood pressure, and tertile of FEV₁ (rate ratio=1.32 compared with lifelong non-smokers, 95% confidence interval 0.91 to 1.92). The rate ratio for men in "low" employment grades compared with those in "high" grades, adjusted for age, smoking, tertile of systolic blood pressure, and tertile of FEV₁, was 1.20 (0.92 to 1.58).

Discussion

Recent reviews do not mention impaired ventilatory function as a possible risk factor for cerebrovascular disease.^{17,18} The results presented here, considered alongside the findings of previous studies,^{2,5,6,9} suggest that this may be an important omission. The association between spirometric indices and stroke can be con-

TABLE II—Rate ratio estimates* (95% confidence intervals) for fatal stroke associated with increase in blood pressure and decrease in FEV₁ by age at death due to cerebrovascular disease

	Age at death	
	<70 years	≥ 70 years
Systolic blood pressure (per 10 mm Hg increase)	1.31 (1.17 to 1.47)	1.19 (1.06 to 1.34)
Diastolic blood pressure (per 10 mm Hg increase)	1.23 (1.05 to 1.46)	1.10 (0.92 to 1.33)
FEV ₁ (per litre decrease)	1.71 (1.24 to 2.34)	1.13 (0.79 to 1.61)
Number of cases/controls†	140/2193	121/1054

*Mutually adjusted by conditional logistic regression.

†Matched for age, height, and smoking habit.

TABLE III—Rate ratio estimates* (95% confidence intervals) for fatal stroke associated with various cardiovascular risk factors and rate ratio/litre decrease in FEV₁ before and after adjustment for each risk factor

Risk factor	Independent* effect of risk factor	χ^2 (df=1)	Rate ratio/litre decrease in FEV ₁	
			Before adjustment†	After adjustment
Cigarette consumption (per 10 pack years)	1.01 (0.94 to 1.09)	0.10	1.40	1.39
Employment grade‡ ("low" v "high")	1.19 (0.88 to 1.59)	1.26	1.43	1.40
Body weight (per 10 kg increase)	0.98 (0.95 to 1.01)	1.19	1.41	1.41
Plasma cholesterol (per mmol/l increase)	0.98 (0.84 to 1.15)	0.04	1.38	1.38
Blood glucose§ (per mmol/l increase)	0.95 (0.83 to 1.08)	0.72	1.42	1.43
Glucose intolerance§ (v normal tolerance)	0.97 (0.53 to 1.79)	0.12	1.45	1.45
Diabetes§ (v normal glucose tolerance)	1.18 (0.44 to 3.15)	(df=2)	1.43	1.42
History of angina (yes v no)	1.11 (0.64 to 1.94)	0.71	1.43	1.42
History of possible myocardial infarction	1.07 (0.63 to 1.82)	0.07	1.43	1.42
History of intermittent claudication	2.19 (1.00 to 4.74)	3.45	1.42	1.40
Abnormal electrocardiogram	1.35 (0.88 to 2.07)	0.18	1.42	1.41

*Adjusted for age, height, and smoking habit by matching, and systolic blood pressure, diastolic blood pressure, and FEV₁ by conditional logistic regression modelling.

†Rate ratios before adjustment differ because of missing data for certain variables. Number of cases and controls varied from 261/3247 for body weight to 252/3129 for plasma cholesterol.

‡"Low" grades—clerical and messenger grades; "high" grades—administrative, professional, and executive. Civil servants in the British Council and Diplomatic Service are excluded from these classifications.

§Blood glucose measured two hours after 50 g glucose load. Glucose tolerance categories defined as "normal"—below 95% centile point (5.4 mmol/l); "intolerant"—5.4–11.0 mmol/l; "diabetic"— ≥ 11.1 mmol/l. Previously diagnosed diabetic subjects are included in the "diabetic" group.

||Minnesota codes for Q/QS waves (1.1–1.3), ST depression (4.1–4.4), T wave inversion or flattening (5.1–5.3), or left bundle branch block (7.1).

TABLE IV—Standardised mortality ratios* for cerebrovascular disease (adjusted for age alone and age, smoking habit, and employment grade) in men with sinus rhythm by tertiles of distribution of systolic blood pressure and FEV₁

Tertile of FEV ₁	Tertile of systolic blood pressure								
	Low (<126 mm Hg)			Middle (126–142 mm Hg)			High (≥ 143 mm Hg)		
	Age alone	Age, smoking habit, employment grade	(Deaths)	Age alone	Age, smoking habit, employment grade	(Deaths)	Age alone	Age, smoking habit, employment grade	(Deaths)
High (≥ 3.5 l)	21	22	(5)	52	55	(13)	127	135	(26)
Middle (3.0–3.5 l)	26	26	(6)	55	57	(15)	151	155	(41)
Low (<3.0 l)	63	60	(20)	115	109	(41)	201	194	(95)†

*Relative to standardised mortality ratio for all men=100. Adjusted by Poisson regression for: age at examination (single years), and age, smoking habit (never, former, current), and employment grade ("low," "high," unknown).

†Includes one unmatched patient, who was excluded from the case-control analysis.

firmed only by longitudinal studies as hemiparesis results in abnormalities of ventilatory function,¹⁹ which would invalidate a case-control comparison. Even a prospective design may, however, be susceptible to bias if subclinical cardiovascular disease results in poorer lung function. In the Framingham study reduced vital capacity seemed to be a sign of early congestive cardiac failure, but FEV₁ did not show a similar association.²⁰

This analysis was limited to deaths and therefore cannot distinguish between the effects of risk factors on incidence of disease and on case fatality. Short term survival after stroke is primarily determined by the severity of the stroke and the degree of comorbidity.²¹ Premorbid level of ventilatory function may influence case fatality, particularly among comatose patients. Reduced lung function may be a marker of physiological abnormalities which in turn predispose to stroke, such as polycythaemia²² or sleep apnoea.²³ Alternatively, reduced FEV₁ and fatal stroke may have environmental causes in common. Such causes may include heavy alcohol consumption,^{24,25} vitamin C deficiency,^{26,27} or even air pollution.²⁸ Early influences on the development of the lung may be implicated in the proposed link between the intrauterine environment and subsequent mortality due to stroke.²⁹

The effects of current (but not former) cigarette smoking and the stronger influence of systolic than of diastolic blood pressure were both consistent with previous reports,^{30,31} although no dose-response relation was found among the smokers. The association of stroke with smoking was, however, largely independent of the reduced levels of ventilatory function among current smokers. The lack of association with plasma cholesterol concentration is consistent with previous studies,¹⁷ but this may conceal opposing trends for haemorrhagic and ischaemic strokes.³² There was no substantial increase in risk of stroke among diabetic patients when the effects of blood pressure were controlled in some detail. Other studies, however, have found an independent effect,^{33,34} and the confidence interval around the estimated rate ratio for diabetes is too wide to draw firm conclusions.

Identification and control of raised blood pressure is currently the main strategy for prevention of stroke.³⁵ Under the common (but rarely tested) assumption that the relative benefits of treatment are the same for different patient groups greater absolute benefits may be expected for patients at higher underlying risk of disease. The balance of risks and benefits, and hence the choice of cut off at which to recommend pharmacological treatment, may therefore depend on levels of other risk factors for stroke.³⁶ In this context measurements of ventilatory function may be more useful than many conventional cardiovascular risk factors for guiding clinical decisions about the management of patients with mild hypertension.

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