



# Forced vital capacity, airway obstruction and survival in a general population sample from the USA

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## ABSTRACT

**Background** Many studies show a link between forced expiratory volume in 1 s (FEV<sub>1</sub>) and survival in the general population and this has been interpreted as a link between airway obstruction and survival. However, the observation that vital capacity is also associated with survival weakens this interpretation.

**Methods** Data on spirometry and survival were taken from the Atherosclerosis Risk in Communities (ARIC) limited access dataset. Survival among 7489 participants with usable spirometry and complete data was regressed against measures of ventilatory function after controlling for many other factors likely to be associated with survival.

**Results** Survival was strongly associated with forced vital capacity (FVC) after adjustment for FEV<sub>1</sub>, but not the other way round. The fully adjusted hazard ratio (HR) associated with high FVC was 0.90 in men (95% CI 0.80 to 1.00;  $p=0.049$ ) and 0.82 in women (95% CI 0.70 to 0.95;  $p=0.01$ ). This compares with 0.98 for FEV<sub>1</sub> in men (95% CI 0.90 to 1.07;  $p=0.72$ ) and 1.01 in women (95% CI 0.89 to 1.15;  $p=0.84$ ). There was no association between survival and airway obstruction as measured by the FEV<sub>1</sub>/FVC ratio.

**Conclusions** FVC but not airway obstruction predicts survival in asymptomatic adults without chronic respiratory diagnoses or persistent respiratory symptoms. The association is not explained by age, anthropometry, smoking, income occupation or blood pressure. As FVC later in life, cardiovascular risk, type II diabetes mellitus and low-grade systemic inflammation are all associated with poor fetal growth, these other conditions may be partly responsible for the poor survival in those with low FVC.

## INTRODUCTION

Over the last 40 years many studies have demonstrated a relation between survival and forced expiratory volume in 1 s (FEV<sub>1</sub>) in general population samples,<sup>1,2</sup> and have shown that low FEV<sub>1</sub> is associated with high mortality from cardiovascular causes.<sup>3,4</sup> This has been interpreted as evidence for an association between chronic obstructive lung disease (COPD) and atherosclerosis.<sup>5</sup> FEV<sub>1</sub>, however, does not define COPD and an association has also been identified between mortality and vital capacity.<sup>3</sup> Very few studies have specifically investigated which component of ventilatory function best predicts survival, and the few studies that have looked at the prognosis associated with a lower ratio of FEV<sub>1</sub> to forced vital capacity (FVC) have given inconclusive answers. Anderson showed an association between the FEV<sub>1</sub>/FVC ratio and survival in New Guinea,<sup>6</sup> but neither Friedman<sup>3</sup> in his original study nor Lange in the Copenhagen

Heart Study<sup>4</sup> showed a convincing association with cardiovascular end points.

In this analysis we have used data from the Atherosclerosis Risk in Communities (ARIC) limited access dataset to separate out the effects of different spirometric indices on survival.

## METHODS

Participants in the ARIC study were drawn from the general population of four American communities: Forsyth County, North Carolina; Jackson, Mississippi; the north-western suburbs of Minneapolis, Minnesota; and Washington County, Maryland. In Jackson, only black subjects were included in the sample. Four thousand participants aged 45–64 years were to be selected from each centre.<sup>7</sup>

The protocol was ambitious and mainly aimed at identifying potential risk factors for cardiovascular disease. Importantly for this analysis, FEV<sub>1</sub> and FVC were also measured using a volume displacement water-sealed spirometer.<sup>7</sup> From a minimum of five forced expiratory manoeuvres, at least three acceptable blows were required and the best of these selected according to the contemporary ATS guidance.<sup>8,9</sup> Quality control was managed from a central monitoring service at Johns Hopkins University.<sup>7</sup> Subjects were followed up over the following years and, in particular, any deaths were noted.

The limited access dataset includes those participants in the ARIC cohort who gave informed consent for their data to be used in this way, and in some instances has small subgroups recoded to preserve anonymity. We analysed only individuals who were asymptomatic at baseline—that is, excluding those reporting persistent cough or phlegm, wheeze, breathlessness or doctor-diagnosed asthma, chronic bronchitis or emphysema. Except where otherwise indicated, we analysed only those with usable spirometry (at least two reproducible manoeuvres out of at least three judged to be acceptable).

In those with complete data, we modelled the effects on overall mortality of baseline characteristics observed at entry to the study. These included age, height, body mass index (BMI), waist-hip ratio, sitting height, income category, current working status, most recent occupation, ever smoked, current smoking, pack-years of smoking, education level and systolic blood pressure. Participants for whom the most recent occupation was missing were not distinguished from those with 'other' occupations in the limited access dataset, and the relatively high proportion of people with unreported income were analysed as a separate

category. We analysed those participants with complete data on the remaining predictors and outcome. We compared characteristics of asymptomatic individuals with and without complete data using a Mann–Whitney test (age) and  $\chi^2$  tests (sex and smoking status).

Mortality was analysed using Cox regression, looking at men and women separately. We looked at main effects of age, height, BMI, waist-hip ratio, sitting height, income category, current working status, most recent occupation, ever smoked, current smoking, pack-years of smoking, education category, systolic blood pressure and ethnic group (divided into black and non-black subjects in the limited access dataset). We also looked at what happened if we included quadratic effects of the continuous variables age, height, BMI, waist-hip ratio, sitting height, pack-years and systolic blood pressure. We concluded that linear effects were reasonable for all the continuously-scaled variables except for systolic blood pressure, which we divided into quintiles (calculated separately for men and women).

Having obtained in this way a model for the effects of confounding variables on mortality, we considered the additional effects of  $\log(\text{FEV}_1)$ ,  $\log(\text{FVC})$  and  $\log(\text{FEV}_1/\text{FVC}$  ratio). Taking logarithms of lung function measurements made conceptual sense because the three log values are linearly related, and also produced better-fitting models.

We also conducted a sensitivity analysis using all asymptomatic subjects with a recorded assessment of lung function regardless of quality.

All analyses were done with Stata 11.

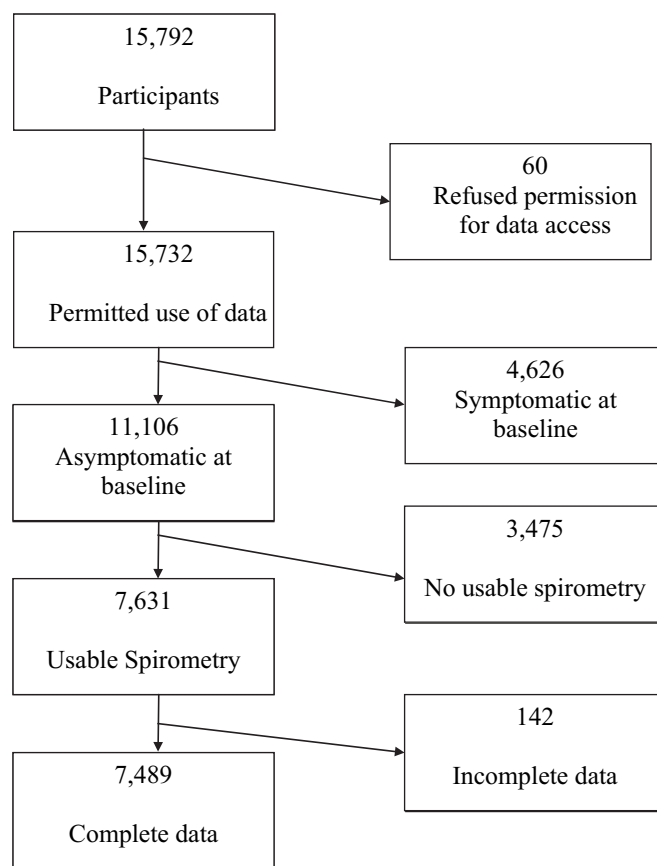
## RESULTS

The study began in 1986 and recruited 15 792 participants, 15 732 of whom gave permission for their data to be included in the ARIC limited access dataset; 11 106 were asymptomatic, 7631 had usable spirometry and 7489 had complete data. There were 792 deaths recorded over 102 576 person-years of follow-up (figure 1).

There were small but statistically significant differences in the characteristics of asymptomatic individuals with and without complete data. Of those with complete data, 3982 (53%) were women compared with 2045 (57%) of those without complete data ( $p=0.001$ ). The median interquartile range (IQR) age of those with complete data was 53 (49–58) compared with 54 (49–59) for those without complete data ( $p<0.001$ ). Of those with complete data, 1478 (20%) were current smokers and 2635 (35%) were ex-smokers, compared with 826 (23%) and 1080 (30%) of those without complete data ( $p<0.001$ ).

The characteristics of asymptomatic individuals with usable spirometry and complete data are shown in table 1. The association of these factors (excluding lung function) with mortality is given in table 2. Table 3 shows that both  $\text{FEV}_1$  and FVC were strongly associated with mortality (expressed as a hazard ratio (HR)) even after adjusting for the identified confounders, although there was no association between the  $\text{FEV}_1/\text{FVC}$  ratio and survival for either sex. When further mutual adjustment was made for  $\text{FEV}_1$  and FVC, only FVC remained as an important predictor of mortality in the model, a higher FVC being associated with a lower HR: 0.90 for men (95% CI 0.81 to 1.00;  $p=0.049$ ) and 0.82 for women (95% CI 0.70 to 0.95;  $p=0.01$ ).  $\text{FEV}_1$  had no association with survival independent of its association with FVC.

Among 2988 asymptomatic black people, 1418 (47%) had usable spirometry while, among 8118 asymptomatic non-black people, 6213 (77%) had usable spirometry ( $p<0.001$ ). However, when we repeated the analyses in table 3 using all individuals with spirometry data regardless of quality, the results were qualitatively the same.



**Figure 1** Inclusion and exclusion of participants from the analyses.

## DISCUSSION

In this general population cohort from the USA, excluding participants with chronic respiratory diagnoses or persistent respiratory symptoms, survival was associated with FVC in both men and women. Neither the  $\text{FEV}_1$  nor the  $\text{FEV}_1/\text{FVC}$  ratio had any independent effect on survival. This result is at variance with the general assumption that the association of  $\text{FEV}_1$  with mortality—and more specifically with cardiovascular mortality—represents an association with airways obstruction.

Supporting our findings, there have been several other studies showing an association between FVC and both survival<sup>6 10 11</sup> and more specific cardiovascular outcomes,<sup>3 4 12</sup> and this alone makes interpretation of  $\text{FEV}_1$  as a marker of obstruction less convincing. Although it is true that some studies have failed to find an association with  $\text{FEV}_1$ ,<sup>13</sup> this has been uncommon. In addition, where it has been studied, there is very little evidence of the  $\text{FEV}_1/\text{FVC}$  ratio being of prognostic significance.<sup>3 4</sup>

It is extremely unlikely that the restriction observed in this analysis is due to the restrictive lung diseases as they are usually defined. These are rare conditions. Some restriction may be seen where there is a physical constriction of the lungs due either to abdominal obesity or where rib or diaphragm movement is limited.<sup>14</sup> We were unable to specifically exclude the latter, but the findings here are adjusted for BMI and waist-hip ratio. Some restriction may also be seen in early obstructive airway disease due to gas trapping.<sup>15 16</sup> We have no measurement of residual volume in this study, but it seems extremely unlikely that a subtle measure of early obstruction would have a strong association with mortality but that the  $\text{FEV}_1/\text{FVC}$  ratio would not.

The association between mortality and low ventilatory function has been ascribed to comorbidities—specifically

**Table 1** Baseline characteristics of asymptomatic individuals with usable spirometry and complete data

	Men		Women	
	Black (n = 578)	Non-black (n = 2929)	Black (n = 786)	Non-black (n = 3196)
Age (years)	53.2 (5.9)	54.3 (5.7)	52.7 (5.5)	53.7 (5.6)
Height (cm)	176.1 (6.6)	176.4 (6.4)	163.5 (5.8)	162.2 (5.9)
BMI (kg/m <sup>2</sup> )	27.9 (4.6)	27.4 (3.7)	30.1 (5.8)	26.2 (5.1)
Waist-hip ratio	0.94 (0.05)	0.96 (0.05)	0.89 (0.08)	0.88 (0.08)
Sitting height (cm)	89.9 (3.3)	92.9 (3.3)	84.6 (3.2)	86.5 (3.2)
Income (%)				
<\$5000	6.7	0.3	11.7	0.9
\$5000–7999	5.0	0.7	7.9	1.3
\$8000–11999	7.4	1.6	12.1	4.2
\$12000–15999	10.7	3.7	10.3	5.4
\$16000–24999	19.2	10.2	18.2	14.1
\$25000–34999	15.4	17.4	13.7	19.0
\$35000–50000	11.2	24.3	9.8	21.0
\$50000+	13.8	38.5	5.9	29.2
Not reported	10.4	3.2	10.4	5.1
Working status (%)				
Homemaker*	—	—	12.2	23.7
Employed	80.1	79.1	77.1	64.7
Unemployed	3.6	1.3	2.3	2.0
Retired	16.3	19.6	8.4	9.7
Most recent occupation (%)				
Managerial/professional specialty or retired	41.0	53.1	45.3	54.3
Technical/sales/admin support	9.2	18.6	16.2	30.2
Service occupations	9.2	2.8	26.5	8.4
Precision production/craft/repair	15.6	14.5	0.0	1.5
Operators/fabricators/labourers	22.7	9.6	9.9	5.3
Missing/other	2.4	1.3	2.2	0.3
Ever smoked (%)	67.5	67.8	41.7	44.1
Current smoker (%)	33.6	17.5	23.9	18.3
Pack-years of smoking (if ever smoked)	22.6 (18.9)	29.2 (21.8)	15.7 (13.5)	19.7 (16.5)
Education (%)				
Grade school	18.0	4.7	10.3	2.9
High school, did not graduate	17.5	9.1	18.8	9.6
High school graduate	21.1	28.3	23.0	43.1
Vocational school	6.4	10.0	8.4	8.4
College	20.1	33.3	21.4	29.4
Graduate/professional school	17.0	14.6	18.1	6.7
Systolic blood pressure (mm Hg)	129.3 (20.3)	119.4 (15.7)	126.6 (20.5)	116.3 (17.2)
FEV <sub>1</sub> (l)	3.10 (0.56)	3.56 (0.65)	2.34 (0.41)	2.60 (0.44)
FVC (l)	4.09 (0.67)	4.82 (0.77)	3.00 (0.51)	3.45 (0.53)
FEV <sub>1</sub> /FVC (%)	76.0 (6.8)	73.9 (6.9)	78.0 (6.1)	75.5 (5.7)

Values are mean (SD) or percentage.

\*In the dataset, male subjects who reported they were homemakers were given a missing value for current working status to help preserve anonymity. Since these participants could not be identified they were not included in the analysis.

BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity.

cardiovascular disease—and the link with cardiovascular disease is often ascribed to common risk factors such as smoking. The assumption behind many of these speculations, however, has been that the relevant pathology was airway obstruction.<sup>5</sup> The same factors may, however, affect FVC. In the ARIC study, FVC was more closely associated with traffic exposure than was the FEV<sub>1</sub>/FVC ratio,<sup>17</sup> and incident coronary heart disease was linked to both FVC and FEV<sub>1</sub>.<sup>18</sup> Interestingly, the link with FVC was particularly noted in non-smokers and after adjusting for many other cardiovascular risk factors.

A link between diabetes (another comorbidity that could explain an excess mortality) and low FVC has been reported from many studies including ARIC,<sup>19</sup> and has more often been ascribed to an adverse effect of diabetic pathology on ventilatory function,<sup>20</sup> a view that is supported by the more rapid decline of lung function in those with diabetes.<sup>21</sup>

A further possibility is that the low FVC associated with increased mortality is associated with poor intrauterine lung growth. Barker's early study of adult ventilatory function and birth weight reported an association between lower birth weights and lower FEV<sub>1</sub> in adulthood but did not report an association with a reduction in FVC.<sup>22</sup> Since then, however, in spite of a few studies reporting no association between birth weight and subsequent ventilatory function,<sup>23–25</sup> most studies have shown that the deficit in adult lung function associated with low birth weight is a deficit in FVC as well as FEV<sub>1</sub><sup>26,27</sup> and not in the FEV<sub>1</sub>/FVC ratio.<sup>28–33</sup>

As cardiovascular disease is also closely associated with birth weight,<sup>34</sup> this may also explain the association between lung function and cardiovascular mortality. The metabolic syndrome has similarly been associated with low birth weight,<sup>35</sup> and this could also explain the particularly strong association of low lung

**Table 2** Association of potential confounders with mortality

	Men			Women		
	HR	95% CI	p Value	HR	95% CI	p Value
Age (per year)	1.09	1.06 to 1.11	<0.001	1.08	1.05 to 1.10	<0.001
Height (per cm)	1.01	0.99 to 1.03	0.33	1.04	1.00 to 1.07	0.023
Black versus non-black	1.45	1.07 to 1.95	0.015	1.20	0.84 to 1.72	0.31
BMI (per kg/m <sup>2</sup> )	1.03	1.00 to 1.06	0.035	1.02	1.00 to 1.05	0.10
Waist-hip ratio (per unit)	32.7	3.4 to 311.4	0.002	3.7	0.6 to 21.4	0.15
Sitting height (per cm)	0.97	0.93 to 1.02	0.25	0.96	0.91 to 1.02	0.17
Income (per category)*	0.92	0.86 to 0.98	0.011	0.91	0.85 to 0.97	0.006
Unreported income	0.71	0.43 to 1.15	0.16	0.75	0.45 to 1.23	0.25
Working status			0.023			0.29
Homemaker†	—	—		1.33	0.88 to 2.01	
Employed	1.00	—		1.00	—	
Unemployed	1.60	0.91 to 2.79		0.95	0.44 to 2.05	
Retired	1.46	1.07 to 1.98		0.97	0.60 to 1.55	
Most recent occupation			0.042			0.17
Managerial/professional specialty or retired	1.00	—		1.00	—	
Technical/sales/admin support	1.49	1.09 to 2.03		0.96	0.64 to 1.45	
Service occupations	1.05	0.63 to 1.76		0.79	0.48 to 1.31	
Precision production/craft/repair	0.93	0.65 to 1.33		0.47	0.11 to 2.01	
Operators/fabricators/labourers	1.14	0.79 to 1.65		1.12	0.63 to 2.01	
Missing/other	0.61	0.24 to 1.53		2.39	0.98 to 5.84	
Ever smoked	1.08	0.82 to 1.42	0.57	1.04	0.76 to 1.44	0.80
Current smoker	1.65	1.32 to 2.06	<0.001	1.96	1.42 to 2.69	<0.001
Pack-years of smoking (per 10 pack-years)	1.10	1.05 to 1.15	<0.001	1.15	1.07 to 1.23	<0.001
Education (per category)	0.93	0.87 to 1.00	0.052	0.96	0.87 to 1.06	0.45
Systolic blood pressure (quintiles)			0.52			0.010
1	1.00	—		1.00	—	
2	0.79	0.57 to 1.09		1.71	1.08 to 2.71	
3	0.93	0.69 to 1.26		1.76	1.13 to 2.73	
4	0.99	0.74 to 1.34		1.88	1.21 to 2.92	
5	1.01	0.75 to 1.35		2.23	0.84 to 1.72	

\*Unreported income in same category as lowest income for estimating effect per category, but also estimated as a separate effect.

†In the dataset, male subjects who reported they were homemakers were given a missing value for current working status to help preserve anonymity. Since these participants could not be identified they were not included in the analysis.

BMI, body mass index; HR, hazard ratio.

function with metabolic syndrome<sup>36</sup> and the increased mortality from COPD in those with metabolic syndrome.<sup>37</sup>

Another common feature of both cardiovascular disease and poor ventilatory function is low-grade systemic inflammation,<sup>38</sup> and this has been used to explain at least part of the association between the two conditions.<sup>39–40</sup> Low-grade inflammation is, however, also associated with poor intrauterine growth, as shown in both the MIDSPAN study<sup>41</sup> and the North Finnish birth cohort,<sup>42–44</sup> and this association may also reflect a common origin.

The observation that low FVC, type II diabetes, cardiovascular disease and low-grade systemic inflammation are all

associated with each other and with low birth weight does not demonstrate that these conditions have a common cause, nor that low birth weight itself is the cause of the different conditions. Low birth weight is itself a combination of premature birth and poor fetal growth, and its causes are poorly understood. There is no guarantee that increasing birth weights within the normal range would reduce any of the associated conditions. Nor should it be assumed that, because the origins of the conditions are in early life, later efforts to mitigate the consequences would be ineffective. Nevertheless, the observation provides a potentially fruitful hypothesis to explain a very common condition.

**Table 3** Association of spirometric values with mortality

	Unadjusted*			Adjusted†			Mutually adjusted‡		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Men									
FEV <sub>1</sub>	0.82	0.79 to 0.86	<0.001	0.92	0.88 to 0.97	0.001	0.98	0.90 to 1.07	0.72
FVC	0.78	0.74 to 0.83	<0.001	0.89	0.83 to 0.94	<0.001	0.90	0.81 to 1.00	0.049
FEV <sub>1</sub> /FVC	0.91	0.84 to 0.99	0.024	0.99	0.91 to 1.08	0.77			
Women									
FEV <sub>1</sub>	0.80	0.76 to 0.84	<0.001	0.88	0.83 to 0.93	<0.001	1.01	0.89 to 1.15	0.84
FVC	0.75	0.70 to 0.80	<0.001	0.83	0.77 to 0.89	<0.001	0.82	0.70 to 0.95	0.010
FEV <sub>1</sub> /FVC	0.90	0.79 to 1.02	0.11	0.99	0.87 to 1.14	0.93			

\*Adjusted for age and height only.

†Adjusted for the variables in table 2.

‡Adjusted for the variables in table 2 and also mutually adjusted for FEV<sub>1</sub> and FVC.

FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, hazard ratio.



The ARIC study is a large prospective study of good quality. Although the conclusions of a multiple regression analysis may be influenced by the relative quality of the information on different variables so that the better measured variables will tend to dominate the analyses, this does not seem to be a likely problem in this instance. If the results in table 3 were simply an artefact related to data quality, it would be expected that the more easily measured variable (in this case FEV<sub>1</sub>) would dominate the analysis. In the end it is the FVC that dominates the regression. There is no reason to suppose that the results from this large American study would be different in another population.

The results reported here apply to asymptomatic people. We looked at this group because we were interested in the association between mortality and spirometric values in the general population independent of overt obstructive disease. This group nevertheless has a substantial number of people with airway obstruction. Our results should not, however, be extrapolated to symptomatic populations. When we re-ran the analyses on this group, the results were different (see table E1 in the online supplement). Here all three spirometric measures (FEV<sub>1</sub>, FVC and the FEV<sub>1</sub>/FVC ratio) were associated with mortality and, when FEV<sub>1</sub> and FVC were mutually adjusted for, each provided an estimated HR of 0.92 for both men and women. Only the HR for FEV<sub>1</sub> in men was significantly different from 1, which may partly reflect the relatively small sample size of this group.

These findings may provide a partial explanation for why investigators have found that FEV<sub>1</sub> rather than a measure of air flow obstruction predicts the prognosis of airway obstruction.<sup>45–47</sup> The more obvious staging by the extent of the reduction in FEV<sub>1</sub>/FVC ratio would clearly not be as effective at estimating prognosis in this group at least. Although FVC might theoretically be more appropriate, the strong correlation with FEV<sub>1</sub> makes the latter an adequate marker.

Survival in asymptomatic adults without chronic respiratory diagnoses or persistent respiratory symptoms is associated with FVC and not with airway obstruction as measured by the FEV<sub>1</sub>/FVC ratio. The relation of FEV<sub>1</sub> to survival is indeed strong, but secondary to the association of FEV<sub>1</sub> to FVC. The association with survival is not explained by age, anthropometry, smoking, income, occupation or blood pressure. As FVC later in life, cardiovascular risk, type II diabetes mellitus and low-grade systemic inflammation are all associated with poor fetal growth, these other conditions may be partly responsible for the poor survival in those with low FVC.

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**Competing interests** None.

**Ethics approval** The ARIC study was approved by local institutional review boards in the USA and the analysis was approved by the Imperial College research ethics committee.

**Contributors** PB had the original idea and wrote the first draft of the introduction and discussion. RH undertook the analysis and wrote the first draft of the methods and results.

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## Pulmonary puzzle

### An unusual case of refractory asthma

#### CLINICAL PRESENTATION

A 34-year-old woman with atopic asthma since the age of 16 years presented with increasing exertional dyspnoea and wheeze over a period of 12 months. She had no symptomatic benefit from escalation of bronchodilator therapy and her peak expiratory flow (PEF) remained reduced despite multiple courses of oral corticosteroid. Lung function at rest showed mild air flow obstruction with forced expiratory volume in 1 s (FEV<sub>1</sub>) of 2.27 l (75% predicted), forced vital capacity (FVC) of 3.13 l (89% predicted) and a FEV<sub>1</sub>/FVC ratio of 73%. Both inspiratory and expiratory limbs of the flow-volume loop (FVL) had a flattened appearance. She was also noted to have a right-sided aortic knuckle on chest x-ray.

To determine the mechanisms of exercise limitation, she underwent an incremental cardiopulmonary exercise test on a cycle ergometer with maximal FVL measured during exercise. Her exercise performance was limited by breathlessness, achieving a peak work rate of 77 Watts (55% predicted) and a peak oxygen uptake of 1.17 l/min (61% predicted). End-exercise minute ventilation was 49.1 l/min (62% of predicted maximal voluntary ventilation), indicating a normal breathing

reserve. However, the ventilatory pattern was abnormal with over-reliance on respiratory frequency (52 breaths/min at peak exercise) and restriction in tidal volume (0.83 l at peak exercise). In addition, the maximal FVL changed during exercise (figure 1).

#### QUESTION

What is the diagnosis?

*See page 74 for answer*

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**Figure 1** Maximal flow-volume loops performed during incremental cardiopulmonary exercise test showed that, during exercise, peak inspiratory flow (PIF) fell from 5.1 l/s at rest to 3.2 l/s and peak expiratory flow (PEF) from 3.36 l/s at rest to 2.35 l/s. This inspiratory and expiratory flow limitation led to a 20% reduction in both forced expiratory volume in 1 s and inspiratory capacity during exercise. PIF and PEF returned to resting values at recovery.

