

Infants with Flow Limitation at 4 Weeks Outcome at 6 and 11 Years

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Within a longitudinal study of lung function in 243 infants, we identified a group of 23 individuals with flow limitation in tidal expiration. In infancy, flow-limited children have reduced lung function and increased airway responsiveness (AR), and at 2 years of age they are diagnosed with asthma more frequently. We hypothesized that these observations would persist throughout childhood. Data from ages 3 to 11 years were analyzed. Only at 4 years of age did the flow-limited group have increased wheeze compared with other cohort members (odds ratio, 4.25; 95% confidence interval [CI], 1.11 to 16.2; $p = 0.04$; $n = 114$). At 6 years of age, 117 cohort members were seen. The flow-limited group ($n = 14$) had greater AR ($p = 0.009$) and reduced mean FEV₁ (131 ml; 95% CI, 16 to 246; $p = 0.03$) and FEF₂₅₋₇₅ (0.28 L/second; 95% CI, 0.05 to 0.52; $p = 0.02$). At 11 years of age, 183 children were seen and the flow-limited group ($n = 18$) had greater AR ($p = 0.02$) and a trend toward reduced mean FEF₂₅₋₇₅ (0.24 L/second; 95% CI, -0.02 to 0.49; $p = 0.08$). Atopy and parental asthma were not increased in the flow-limited group. We suggest that the physiologic abnormality that causes flow limitation in early infancy may identify an at-risk group, different from asthma, who have reduced lung function and increased airway responsiveness in later life.

Keywords: bronchial hyperreactivity; child; longitudinal studies; respiratory function tests

Prospective longitudinal studies have the potential to associate pulmonary function in early life with respiratory symptoms and outcome later in life. A study of individuals from the age of 7 years found that frequent wheezing and reduced pulmonary function persisted in two-thirds of individuals 21 years later (1), and one-third of 28-year-olds with recent-onset wheeze had previously reported wheezing illness as young children. This finding and those from other studies (2-4) provide evidence that reduced pulmonary function and respiratory symptoms in childhood persist into adult life, but it is not clear whether reduced pulmonary function is acquired after birth or is a congenital phenomenon. This question can be answered only by longitudinal studies from early infancy.

A few studies have demonstrated that parameters of pulmonary function measured shortly after birth are predictive of respiratory outcome in early childhood. One study has described an association between reduced maximal flow at functional residual capacity ($\dot{V}_{max_{FRC}}$) at 2 months of age and wheezing illness up to 3 years of age (5). A second group has reported increased wheezing lower respiratory tract infection

in the first year of life in boys with reduced $\dot{V}_{max_{FRC}}$ and in girls with increased airway responsiveness (AR) at 1 month of age (6). In our cohort of healthy term infants, pulmonary function and AR were measured at 1 month of age in 243 individuals (7). Those who wheezed only in the first year had reduced $\dot{V}_{max_{FRC}}$ at 4 weeks of age, whereas those who wheezed in the second year or in the first 2 years had reduced $\dot{V}_{max_{FRC}}$ at 1, 6, and 12 months of age (7). At 6 years of age, increased AR at 4 weeks of age correlated positively with wheeze, cough, and physician-diagnosed asthma and negatively with FEV₁ and FVC (8).

A group of infants from our cohort was found to be flow-limited in tidal expiration at 4 weeks of age (9). Flow limitation occurs when expiratory flow in tidal breathing cannot be increased by increasing expiratory effort and is associated with severely reduced pulmonary function in infants with bronchopulmonary dysplasia (10), bronchiolitis (11), and cystic fibrosis (12). The flow-limited group in our cohort had reduced lung function at 4 weeks and 6 months of age and increased AR at 12 months of age (9). These infants made up 10% of this randomly selected cohort and were asymptomatic at 4 weeks of age, but by 2 years of age they had a 7-fold higher incidence of physician-diagnosed asthma. The aim of this study was to test the hypothesis that the flow-limited group would continue to experience reduced pulmonary function, increased AR, and increased respiratory symptoms through childhood.

METHODS

Subjects

Healthy term infants were recruited as previously described (13). The method for infant pulmonary function testing at 4 weeks of age, including airway responsiveness, has been previously described (9). The terms "flow-limited" and "not flow-limited" at 6 and 11 years of age refer to the flow limitation at 4 weeks of age. The Medical Ethics Committee of Princess Margaret Hospital (Perth, Australia) approved this study.

Questionnaire Data

Close to the child's third to fifth birthday, an abbreviated American Thoracic Society questionnaire (14) was mailed to the parents. For studies at 6 and 11 years of age, a researcher completed a modified American Thoracic Society questionnaire in the presence of the child and parent. Questions were related to respiratory illnesses and symptoms, exposure to tobacco smoke and aeroallergens, and development of physician-diagnosed asthma.

Childhood Pulmonary Function and Airway Responsiveness

Pulmonary function at 6 and 11 years of age was assessed with a portable spirometer (Pneumocheck spirometer 6100; Welch-Allyn, Skaneateles Falls, NY) according to published guidelines (15). At 11 years of age, five children (one flow-limited) were no longer resident in this state and pulmonary function was measured in a local accredited pediatric respiratory laboratory. The Yan rapid technique was used to determine AR (16), and a histamine dose-response slope (DRS) was calculated as described by O'Connor and coworkers (17); see online data supplement for details (1). A bronchodilator response was not measured.

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TABLE 1. DETAILS OF FLOW-LIMITED GROUP AT 4 WEEKS COMPARED WITH REMAINDER OF COHORT*

	Flow-Limited (n = 23)	Not Flow-Limited (n = 220)
Male	15 (65%)	121 (55%)
Maternal asthma ever, reported at enrollment	2 (9%)	40 (18%)
Paternal asthma ever, [†] reported at enrollment	6 (26%)	28 (13%)
Maternal smoking in pregnancy	5 (23%)	62 (28%)
Paternal smoking in pregnancy [†]	8 (36%)	81 (39%)
Birth weight, kg (± SD)	3.54 (0.51)	3.40 (0.48)

* No differences between groups.

[†] Data not available from 12 fathers.

Skin Prick Tests and Eosinophil Count

Skin reactivity was assessed using the method described by Pepys (18). Allergens used were as follows: cow's milk, egg white, rye grass, mixed grass (no. 7), *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat dander, dog dander, *Alternaria alternans*, and *Aspergillus fumigatus* (Hollister-Stier, Elkhart, IN). The positive control (histamine sulfate, 10 mg/ml) was read after 10 minutes; all other tests (including the negative control, 0.9% saline) were read after 15 minutes. A positive skin test was defined as a wheal at least 3 mm in length. Atopy was defined as at least one positive skin test. Eosinophils were counted in peripheral blood samples and expressed as the absolute cell count ($\times 10^9/L$).

Statistics

Chi square analysis was used for comparison of dichotomous variables, Student *t* test was used for normally distributed continuous variables, and the Mann-Whitney U test was used for those not normally distributed. The DRS values at 6 and 11 years of age were skewed to the right and were \log_e transformed after a constant of 1 was added to allow DRS values of 0 or less to be included in analyses. The flow-limited group was compared with the remainder of the cohort by the following analyses: χ^2 analysis was used to compare questionnaire data obtained at 3, 4, and 5 years of age; differences in pulmonary function and DRS were determined by multilinear regression, adjusting for age, sex, height, current smoke exposure, and *in utero* smoke exposure; in addition atopy was used in analyses of DRS. For graphic demonstration of pulmonary function data, percent predicted (%pred) FEV₁ and FEF₂₅₋₇₅ values were derived from linear regression coefficients and compared

by the Student *t* test. Analyses were performed with a standard statistical software package (SPSS release 9.0.1; SPSS, Chicago, IL).

RESULTS

Subjects

Of the 253 infants recruited, 243 attended at 4 weeks of age for an assessment including pulmonary function and histamine challenge. A description of the 23 flow-limited infants at 4 weeks of age compared with other cohort members is given in Table 1. At 6 years of age, 117 (48%) subjects were seen (14 flow-limited; mean age, 6.2 years [range, 4.2–8.7 years]). At 11 years of age, 183 (75%) of the subjects who were seen at 4 weeks of age were seen again (18 flow-limited individuals; mean age, 11.0 years [range, 8.3–13.1 years]). Six (5%) children seen at 6 years of age were not seen at 11 years of age, including three flow-limited cases. Table 2 compares details of those seen at 6 and 11 years of age with those seen at 4 weeks of age. Tables 3 and 4 compare the flow-limited group with the rest of the cohort at 6 and 11 years, respectively.

Questionnaire Data

Of the infants seen at 4 weeks of age, questionnaire data were available for 113 (47%) at 3 years of age, 126 (52%) at 4 years of age, and 106 (44%) at 5 years of age. Questionnaire data were available for all children at 6 years of age and in all but one case at 11 years of age (in this case the parent refused to provide any information). For eight subjects who participated in the 11-year study, questionnaire data were available, but not data concerning pulmonary function, airway responsiveness, or markers of atopy. There was increased wheeze in the absence of upper respiratory tract infection among the flow-limited group only at 4 years of age (4 of 12 compared with 12 of 114; odds ratio, 4.25; 95% confidence interval [CI], 1.11 to 16.2; *p* = 0.04). Between 3 and 11 years of age, there was no increase in physician-diagnosed asthma in the flow-limited group.

Childhood Pulmonary Function and Airway Responsiveness

Reliable pulmonary function data were obtained from 105 (90%) children at 6 years of age, of whom 13 were in the flow-limited group, and reliable AR data were obtained from 98 children (84%, 10 flow-limited). Corresponding figures for the 11-year study were 171 (93%, 17 flow-limited) and 166 (91%,

TABLE 2. COMPARISON OF CASE DATA AT 4 WEEKS, 6 YEARS, AND 11 YEARS

	Seen at 4 Weeks (n = 243)	Seen at 6 Years (n = 117)	Seen at 11 Years (n = 183)
Male	56% (136/243)	53% (62/117)	56% (102/183)
$\dot{V}_{max_{FRC}}$ at 4 weeks of age, ml (SD)	98.9 (49.6)	98.0 (48.5)	98.2 (49.8)
PC ₄₀ at 4 weeks of age, g/L histamine*	1.00 (0.83, 1.20)	1.07 (0.83, 1.38)	0.95 (0.78, 1.15)
Maternal asthma ever, reported at enrollment	21% (50/243)	19% (22/117)	20% (36/183)
Paternal asthma ever, reported at enrollment	15% (34/232)	14% (16/114)	16% (28/179)
Maternal smoking during pregnancy	28% (67/242)	20% [†] (23/117)	24% [†] (44/182)
Paternal smoking during pregnancy	39% (89/230)	35% (40/114)	34% [†] (61/178)

Definition of abbreviations: PC₄₀ = provocative concentration of histamine causing a 40% reduction in $\dot{V}_{max_{FRC}}$ (mg/ml); $\dot{V}_{max_{FRC}}$ = maximal flow at functional residual capacity.

* Geometric mean and 95% CI (± 1.96 [SEM]).

[†] *p* < 0.05 compared with group seen at 4 weeks.

TABLE 3. COMPARING FLOW-LIMITED AND NOT FLOW-LIMITED GROUPS AT 6 YEARS

	Flow-Limited (n = 14)	Not Flow-Limited (n = 103)
Male, n (%)	7 (50%)	55 (53%)
Height, m (SD)	1.17 (0.07)	1.17 (0.06)
Age, years (SD)	6.04 (0.60)	6.23 (0.57)
Wheeze in last 12 months, %	3 (21%)	22 (21%)
Current physician-diagnosed asthma	4 (29%)	24 (23%)
Mean FEV ₁ , L (SD)	1.21 (0.25)	1.33 (0.23)*
Mean FVC, L (SD)	1.45 (0.25)	1.53 (0.26)
Mean FEF ₂₅₋₇₅ , L/minute (SD)	1.21 (0.38)	1.48 (0.43)*
DRS, † (geometric mean ± 1.96 SEM)	5.78 (2.11, 15.84)	1.62 (1.25, 2.09)‡
Eosinophil count, × 10 ⁹ (SD)	0.54 (0.37)	0.50 (0.49)
Atopic, n (%)	6/13 (46%)	32/94 (34%)

Definition of abbreviation: DRS = dose-response slope.

Note that numbers of subjects differ somewhat from the group total for spirometry, airway responsiveness, eosinophil count, and atopic status and that this information is given in text.

* p = 0.02 compared with flow-limited group, adjusting for height and sex.

† Dose-response slope, percent reduction in FEV₁ per milligram of inhaled histamine.

‡ p = 0.009 compared with flow-limited group, adjusting for atopy.

16 flow-limited). At 6 years of age, FEV₁ was reduced in the flow-limited group by a mean of 130 ml (95% CI, 20 to 250; p = 0.03) and FEF₂₅₋₇₅ was reduced by a mean of 0.28 L/second (95% CI, 0.05 to 0.52; p = 0.02) (see Figures 1 and 2). At 11 years of age, mean FEF₂₅₋₇₅ was also reduced in the flow-limited group, but not significantly (0.24 L/second; 95% CI, -0.02 to 0.049; p = 0.08) (see Figure 2). There were no differences in FVC or peak expiratory flow between groups at 6 or 11 years of age. The flow-limited group had increased AR at 6 and 11 years of age, DRS steeper by a 2.15% drop in FEV₁ per microgram of histamine (95% CI, 0.35 to 6.39; p = 0.009), and a 0.73% drop in FEV₁ per microgram of histamine (95% CI, 0.08 to 1.77; p = 0.02). Lung function and DRS at 6 and 11 years of age were not influenced by current maternal or paternal smoking or by smoking during pregnancy.

Skin Prick Tests and Eosinophil Count

Skin prick testing was performed in 107 subjects (91%, 13 flow-limited) at 6 years of age and in 172 subjects (94%, 17 flow-limited) at 11 years of age. Eosinophil counts were performed in 100 subjects (85%, 13 flow-limited) at 6 years of age and in 152 subjects (83%, 12 flow-limited) at 11 years of age.

TABLE 4. COMPARING FLOW-LIMITED AND NOT FLOW-LIMITED GROUPS AT 11 YEARS

	Flow-Limited (n = 18)	Not Flow-Limited (n = 165)
Male, n (%)	10 (56%)	92 (56%)
Height, m (SD)	1.45 (0.08)	1.45 (0.09)
Age, years (SD)	11.0 (0.8)	11.0 (1.0)
Wheeze in last 12 months, %	3 (17%)	26 (16%)
Current physician-diagnosed asthma	3 (17%)	27 (16%)
Mean FEV ₁ , L (SD)	2.28 (0.41)	2.29 (0.43)
Mean FVC, L (SD)	2.59 (0.54)	2.49 (0.47)
Mean FEF ₂₅₋₇₅ , L/minute (SD)	2.43 (0.56)	2.63 (0.63)*
DRS, † (geometric mean ± 1.96 SEM)	1.68 (1.02, 2.77)	1.04 (0.90, 1.22)‡
Eosinophil count, × 10 ⁹ (SD)	0.47 (0.38)	0.37 (0.27)
Atopic, n (%)	7 (41%)	82 (53%)

Definition of abbreviation: DRS = dose-response slope.

Note that numbers of subjects differ somewhat from the group total for spirometry, airway responsiveness, eosinophil count, and atopic status and that this information is given in text.

* p = 0.08 compared with flow-limited group when adjusted for height and sex.

† Dose-response slope, percent reduction in FEV₁ per milligram of inhaled histamine.

‡ p = 0.02, adjusting for atopy.

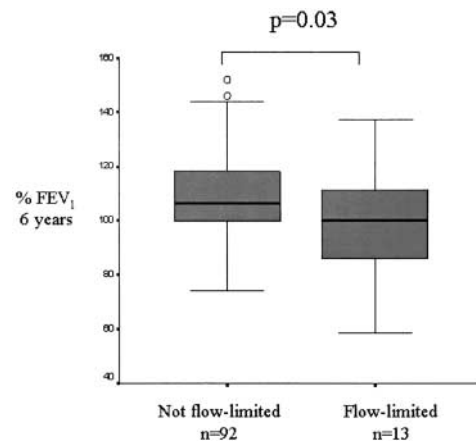


Figure 1. Box-and-whisker plot showing percentage of predicted FEV₁ at 6 years of age in flow-limited and not flow-limited groups. There were no differences between groups at 11 years of age.

There were no differences between the flow-limited group and the remainder of the cohort at 6 or 11 years of age with respect to atopy or eosinophil count.

DISCUSSION

We have followed a group of individuals with flow limitation of tidal expiration in infancy and found increased AR and reduced pulmonary function in childhood. This is the first study to follow up infants with flow limitation and the first to associate reduced infant lung function with increased childhood AR. Extrapolating the results from other studies (1, 19) to our cohort, individuals in the flow-limited group may be expected to retain their increased AR and trend in reduced pulmonary function into adult life.

Our results are consistent with those of Martinez and co-workers (20), who have described the presence of abnormal but asymptomatic pulmonary function in a group of six-year-old children with reduced V_{max}FRC in early infancy and who wheezed transiently, that is, only in the first 3 years. Our study has described the group outcome at a much later age with larger numbers and has included an assessment of airway responsiveness. We are able to report that among subjects with reduced V_{max}FRC at 4 weeks of age, reduced FEV₁ at 6 years of age resolves fully, and reduced FEF₂₅₋₇₅ at 6 years of age has mostly resolved by 11 years of age. The presence of increased AR at 11 years of age suggests an ongoing airway abnormality in the flow-limited group, the clinical significance of which is not apparent. Regression to the mean of reduced infant lung function and increased AR may be occurring and perhaps the subclinical findings of the flow-limited group may disappear in time. Increased AR has persisted in the flow-limited group throughout childhood but significant differences in pulmonary function at 6 years of age have resolved by 11 years of age, although the trend in FEF₂₅₋₇₅ persists. Recurrence of wheeze in young adults with trivial wheeze during early childhood but not adolescence has been previously reported (1); we hypothesize that the flow-limited group will regain their symptoms in adult life.

The association between increased AR and reduced lung function has been reported in cross-sectional (21, 22) and longitudinal studies (22-25). Longitudinal studies have shown increased AR to be a risk factor for reduced growth in FEV₁ in late childhood (23) and accelerated decline in FEV₁ in middle age (24, 25). No such associations were found between in-

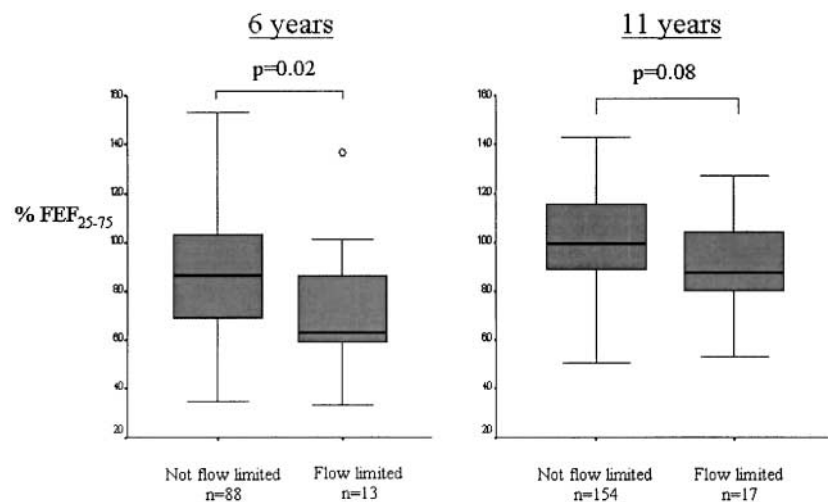


Figure 2. Box-and-whisker plot showing percentage of predicted FEF_{25-75} at 6 and 11 years of age in flow-limited and non-flow-limited groups.

creased AR and reduced FVC, suggesting that increased AR is associated with reduced airway caliber and not reduced lung size. What is not clear is whether the relationship between increased AR and reduced pulmonary function is the result of one upon the other or whether both are influenced by a third factor. O'Connor and coworkers (25) suggest three hypotheses to account for the association: (1) exogenous stimulants such as tobacco smoke causes airway inflammation, which results in both increased AR and reduced lung function; (2) an intrinsic epithelial abnormality causes both phenomena; and (3) reduced lung function causes obstructed, distended airways and this physical stress induces increased AR. The same group adds in a later article the suggestion that neuroregulatory alterations to the airways and lung parenchyma could account for both increased AR and reduced lung function (26).

Reduced airway caliber, reduced airway compliance, or both of these properties at birth could link flow limitation, wheezing illness in early childhood, and subsequent reduction in pulmonary function and increase in AR. At 1 and 6 months of age, the flow-limited group had reduced total respiratory compliance and reduced \dot{V}_{maxFRC} (an index of airway caliber) (9). Among infants, other groups have reported increased wheezing illness in association with altered airway compliance (27), reduced \dot{V}_{maxFRC} (6, 20, 28), and reduced total respiratory resistance (5). There are at least two mechanisms that could explain the increased AR associated with flow limitation. First, the reduced airway caliber and compliance could be a consequence of increased airway smooth muscle mass or tone, so that when the smooth muscle is stimulated by inhaled histamine, a greater degree of bronchoconstriction is reached more readily. Second, the obstructed airways of the flow-limited group could limit the distribution of inhaled histamine, resulting in a much higher histamine concentration in more proximal airways, causing them to undergo more intense bronchoconstriction.

The follow-up of our cohort was less than 50% at 6 years of age and improved to more than 75% at 11 years of age. In pooling the data from the 6- and 11-year studies, 21 members (88%) of the flow-limited group were seen in childhood along with 167 members (76%) of the remainder of the cohort. We have made exhaustive efforts to contact subjects, and in the process we have located five in other states and are aware of at least another six that have moved overseas. Significantly, more children whose parents were nonsmokers at enrollment were available for follow-up compared with those who had smoking parents. This may have affected the analysis, al-

though among those followed up successfully, neither maternal nor paternal smoking was a significant factor in outcome measures. The consistency in increased AR and trend in reduced FEF_{25-75} seen among subjects at 6 to 11 years of age indicate that the observations are likely to be valid and not influenced by incomplete follow-up.

We believe that the flow-limited group forms one end of a continuous spectrum rather than a group discrete from the general population. Their anthropomorphic measurement from birth, current markers of atopy, and respiratory symptoms are not different from the remainder of the cohort, suggesting that the underlying cause for the group differences is not *in utero* nutrition or growth failure or atopy in childhood. We find that the association between increased AR and reduced lung function is present in infancy and persists into childhood. This strongly suggests that the association is due to an underlying factor present in very early life that may include *in utero* tobacco exposure or genetic factors.

In summary, we have observed increased AR and reduced pulmonary function in the flow-limited group during childhood. We suggest that the mechanism(s) responsible for flow limitation in infancy accounts for the association between reduced pulmonary function and increased AR seen in our population and others. We will monitor this cohort to establish whether over time the flow-limited group experiences an accelerated decline in lung function and again becomes symptomatic.

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