Occult Pulmonary Abnormalities in Asymptomatic Asthmatic Children*

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The pulmonary status of 178 asymptomatic asthmatic children with normal time-volume spiromgrams was further evaluated using flow-volume loops, body plethysmographic studies, and blood gas tensions in arterialized capillary blood. Residual volume (RV) was abnormal in 26 percent, total lung capacity (TLC) in 33 percent, RV/TLC% in 41 percent, and arterial oxygen pressure in 23 percent of them. All values for expiratory flow measured relative to observed vital capacity (VC), i.e., the forced expiratory volume in one second [FEV$_1$], the mean forced expiratory flow during the middle half of the forced vital capacity [FEF25-75%; FVC], the FEV$_1$/VC, and the instantaneous forced expiratory flow after 75 percent and after 50 percent of the FVC has been exhaled) were normal, and VC was subnormal in only five instances, but flow rates measured relative to TLC were abnormal in 26 percent of the patients. Some abnormality of pulmonary function was present in all but 13 percent of these asymptomatic children. Reliance upon conventional evaluation of pulmonary function by forced expiratory spiromgrams and freedom from wheezing may frequently give the clinician a false impression of the true condition of the lungs of the asthmatic child.

Bronchial asthma is one of the most important chronic diseases in childhood and accounts for more lost school days than any other chronic disease. The natural history of the disease is incompletely understood, but certainly the number of children who are overtly symptomatic declines markedly towards the end of the first decade of life. Several investigators have demonstrated abnormalities of pulmonary function in asymptomatic asthmatic children. Weng and Levison studied a group of asthmatic children from acute attack to symptom-free status and noted that abnormalities of static lung volumes, of mean forced expiratory flow during the middle half of the forced vital capacity (FEF25-75%), and of arterial oxygen tension (PaO$_2$) were common in the interval phase. The FEF25-75% was found to be a highly sensitive test in that and in a subsequent study. This work has been extended by investigating a number of asthmatic children who were not only asymptomatic but had normal values for FEF25-75% and other dynamic indices of airway obstruction from the time-volume spirogram.

Materials and Methods

Tests of pulmonary function were performed in 178 asthmatic children when they came for regular outpatient visits. Sixty-two were girls, and 116 were boys, and their ages ranged from 5 to 17 years, with a modal age of eight years (Fig 1).

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Table 1—Mean Observed Data of Asthmatic Children Compared with Mean Predicted Normal Data Used in This Study*11

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Observed*</th>
<th>Predicted**</th>
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<tbody>
<tr>
<td>TLC, percent of predicted normal</td>
<td>117.2 ± 18.7</td>
<td>100 ± 6.4</td>
</tr>
<tr>
<td>RV, percent of predicted normal</td>
<td>168.0 ± 53.3</td>
<td>100 ± 11.2</td>
</tr>
<tr>
<td>TGV, percent of predicted normal</td>
<td>139.3 ± 30.0</td>
<td>100 ± 9.4</td>
</tr>
<tr>
<td>VC, percent of predicted normal</td>
<td>105.7 ± 15.0</td>
<td>100 ± 6.2</td>
</tr>
<tr>
<td>RV/TLC%</td>
<td>28.7 ± 9.9</td>
<td>21 ± 3.5</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>81.5 ± 5.9</td>
<td>88.7 ± 3.1</td>
</tr>
<tr>
<td>Vmax50%, TLC/sec</td>
<td>0.93 ± 0.25</td>
<td>1.29 ± 0.25</td>
</tr>
<tr>
<td>Vmax70%, TLC/sec</td>
<td>0.72 ± 0.24</td>
<td>1.10 ± 0.28</td>
</tr>
<tr>
<td>Vmax60%, TLC/sec</td>
<td>0.54 ± 0.26</td>
<td>0.86 ± 0.25</td>
</tr>
</tbody>
</table>

*Number of patients observed was 178, except that only 51 patients were observed for Vmax60%, Vmax70%, and Vmax80%.
**Number of subjects observed was 139, except that only 105 subjects were observed for PaO2, Vmax60%, Vmax70%, and Vmax80%.

All of the children were free from dyspnea and expiratory wheezing when tested and had been so for at least one month. All of the patients fell into either type C (76 percent) or type D (24 percent) of the classification of Hill and associates, and several were inpatients of a chronic care hospital at the time of study. Regularly prescribed medications were not withheld for testing. The FEF25-75% in all children fell within or above the 95-percent confidence limits of previously established normal values from this laboratory. These children represent 19 percent of all asthmatic children studied in this laboratory during the 15-month sampling period.

Subjects performed at least three expirations for forced vital capacity (FVC) into a 9-L valveless water-sealed spirometer (Collins), and the breath with the largest vital capacity (VC) was analyzed for VC, FEF25-75%, and forced expiratory volume in one second (FEV1). During a similar series of breaths, maximal expiratory flow-volume curves were obtained in 51 of the patients, measuring flow and volume at the mouth using a wedge spirometer (Med Sciences model 370). Instantaneous forced expiratory flow was measured after 50 percent and after 75 percent of the FVC was exhaled (FEF50% and FEF75%, respectively) and also at 60, 70, and 80 percent of observed total lung capacity (Vmax60%, Vmax70%, and Vmax80%, respectively); the latter were standardized by dividing by observed total lung capacity (TLC).

The TLC and its subdivisions were measured using conventional techniques in a variable-volume body plethysmograph. The PaO2 was measured in duplicate samples of arterialized capillary blood ten minutes after the application of a vasodilator cream. Normal standards used were previously established in this laboratory using the equipment that was used to test the patients in this study. For all tests a result was judged as abnormal if it lay beyond the 95-percent confidence limits of the mean normal value.

RESULTS

An overall pattern of residual abnormalities of pulmonary function was observed repeatedly, hypoxemia with increased residual volume (RV) and TLC and with a normally sized VC. Mean values for tests are given in Table 1.

Lung Volumes

Residual volume and TLC were abnormally increased in 26 percent and 33 percent of the patients, respectively, and in no instance was an abnormally

![Figure 2. Data on RV/TLC% of patients as function of age. Mean (middle line) and 95-percent confidence interval (outer lines) of normal range are shown.]

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low value detected. The ratio, RV/TLC\%, was abnormal, with 41 percent of the observed values falling above the upper extreme of the normal range (Fig 2). The VC was normal in all but five patients, in whom the recorded value fell below the lower limit of the normal range.

**Dynamic Lung Volumes and Flow Rates**

A criterion of the study was that all values of FEV\textsubscript{1}, FEV\textsubscript{1}/VC, and FEF25-75\% fell within the normal range. The FEF75\% was abnormally low in only one patient, and none had an abnormal value for FEF50\%. When flow rates from the maximal expiratory flow-volume curve were analyzed relative to TLC, rather than VC (ie, V\textsubscript{max60\%}, V\textsubscript{max70\%}, and V\textsubscript{max80\%}), 26 percent of the patients had subnormal values (Fig 3). Hypoxemia was common, with 23 percent of the observed values of PaO\textsubscript{2} falling below the normal range (Fig 4). No child had an elevated value for carbon dioxide tension (PaCO\textsubscript{2}) in arterialized capillary blood.

No significant associations were observed between any of the physiologic variables measured, with the exception of that noted between RV and TLC (RV = 1.81 TLC - 43.5 [± 41.4]; r = 0.63). Only 13 percent of the patients had both a normal thoracic gas volume and a normal PaO\textsubscript{2}, and the data on RV were similar in all respects.

**Discussion**

The results of this study clearly show the limitations of the routine spirogram in detecting residual abnormalities of pulmonary function in the asymptomatic asthmatic child. The FEF25-75\% has been previously noted to be a highly sensitive indicator of compromised expiratory flow in asthmatic children\textsuperscript{3,7}, that these children all had normal values for FEF25-75\% implies that they were truly in remission when studied.

The incidence of abnormalities in static lung volume was higher than one may have expected in the face of normal time-volume spiromgrams, although abnormalities, particularly of RV, have been reported in asymptomatic children by previous observers\textsuperscript{3,6}. It should be noted that many of the previous studies have employed dilution of inert gas, rather than plethysmographic techniques to measure static lung volumes and, hence, may have missed a significant number of abnormalities. The nature of the pathologic changes of bronchial asthma is such that nonventilating or slowly ventilating regions
exist much of the time, and when they do, techniques using gas dilution will underestimate lung volumes to an extent dependent upon the size of these regions.

The pattern of observed static lung volumes is of interest, since flow indices measured from both the time-volume spirogram and the flow-volume curve relative to VC were normal, as were the values for VC, except in five instances. Flow indices from both sources are almost invariably reduced in symptomatic patients. Presumably, the presence of an appropriately sized VC within an abnormally large TLC preserves flow rates by allowing the patient to breathe at higher than normal absolute lung volumes. This would tend to compensate for residual airway obstruction by two mechanisms: (1) by increasing airway conductance, since airway conductance increases linearly with increasing lung volume, and (2) by increasing elastic recoil over the range of VC, for recoil, like conductance, increases with absolute lung volume. Analyzing flow rates relative to TLC allows measurement of expiratory flow at a more or less constant distending pressure (elastic recoil), regardless of the prevailing relationships between RV and TLC. This technique unmasked low flow rates in 26 percent of the patients in whom the flow rates relative to height or VC were normal.

Subnormal values for PaO2 occurred in 23 percent of the patients and were commonly, but not invariably, associated with increased values for RV and thoracic gas volume. Subnormal values for PaO2 have been previously recorded in wheeze-free asthmatic children, most of whom had obvious spiographic evidence of airway obstruction (abnormalities in FEF25-75%) and gas trapping, as evidenced by increased values for RV. Of those patients with values for PaO2 within the normal range, 43 percent had high values for RV, and 42 percent had high values for thoracic gas volume; this difference was not significant. Only 13 percent and 15 percent of the patients, respectively, had normal values for thoracic gas volume and RV in the presence of normal values for PaO2.

The presence and extent of the physiologic abnormalities raise the question of the true reversibility of bronchial asthma. Although several authors have noted increased values for RV in a number of children, only Kraepelien found that increased values for RV tended to revert to normal over a period of several years. Kraepelien measured lung volumes using a technique of inert gas dilution, and it is almost certain that the use of body plethysmographic data would have increased both the incidence and degree of detected abnormalities in static lung volumes.

The possible reversibility of these residual abnormalities with pharmacologic agents has been examined in two previous studies, in which marked physiologic changes in asthmatic patients were reversed in most, but not all, instances by comparatively short regimens of intensive treatment. The long-term behavior of these changes in response to various types of therapy remains unstudied or unreported, and likewise, the true natural history of the untreated increased RV remains unreported.

In summary, the following observations can be made of the pulmonary function of a group of asymptomatic asthmatic children; abnormalities of static lung volumes or arterial hypoxemia were observed in all but 13 percent of 178 children who had normal forced expiratory spiograms. Examination of flow rates relative to TLC, rather than VC, revealed subnormal flow rates in 26 percent of the children. This technique is both rapid and simple but requires the use of a body plethysmograph to obtain maximal expiratory flow-volume curves at known levels of pulmonary inflation or to generate data on lung volume to standardize such curves obtained elsewhere. It appears that even the most sensitive indices of obstruction of air flow derived from the FVC maneuver are inadequate to assess recovery from childhood asthma unless allowance is made for the degree of pulmonary inflation present when these tests are performed.

References


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von Recklinghausen’s Disease

My experience with patients with advanced forms of this disease remains an unforgettable revelation. Credit for the histo-etiolic identification of this condition and for naming it neurofibromatosis belongs to Friedrich von Recklinghausen (1833-1910) who was professor of pathologic anatomy at Königsberg, Germany, and subsequently at Wurzburg and Strassburg (Multiple Fibromas of the Skin and their Relation to Multiple Neuromas, Berlin, A Hirschwald, 1882). The disease is familial and is thought to be transmitted as an autosomal dominant trait with incomplete penetrance. Its estimated incidence is 1 in 3,000 births. Pathologic manifestations, also called neurofibromatosis, appear in the motor and sensory nerves, usually peripherally, or in the autonomic nervous system; too, it is asserted that they may originate from proliferation of fibrous tissue. Characteristic changes are multiple neurofibromas, also called fibroma molluscum, of smooth surface and soft consistency, in the skin or subcutaneously along peripheral nerves or without direct relation to nerves, most frequently in the axilla and at the waist but often over the entire body surface, including the scalp, face, nose, ear lobes and the neck. The overlying skin may be of violaceous color. The tumors vary in configuration and from pea-size to enormous masses. They may be sessile or pedunculated and increase in size and number after puberty. Sheklakov, N (Vestnik Veneorial Dermatol 3: 51, 1950) observed a case of RD with 9,242 tumors. Other sites of involvement are: cranial nerves, spinal roots, cauda equina, sympathetic ganglia, digestive tract and genito-urinary tract. According to Halpern, M et al (New Engl J Med 273:248, 1963) vascular lesions in RD may cause hypertension. Radiologically demonstrable bone and joint changes were noted in more than 50 percent of patients with RD and listed by Hunt, JC et al (Radiology 76:1, 1961): severe angular scoliosis with vertebral dysplasia; defect of the posterior superior wall of the orbit; congenital bowing and pseudoarthrosis of the lower leg; erosive defects of bone from contiguous neurogenic tumors, most common in the ribs; ribs resembling twisted ribbons; sinuous elongation of bones of the lower extremities; possible deformity of occipital and facial bones. These changes may be associated with elephantoid overgrowth of soft tissues, thus adding to the grotesque, sometimes pathetic appearance of the subject. Another manifestation of RD is widespread presence of cafe au lait spots of tan, yellow-brown or chocolate-brown color; their shape is irregular; their longest diameter may be 15 cm. In the mediastinum, solitary or multiple tumors of RD are usually found posteriorly; involvement of the thoracic segment of the vagus nerve has been reported; in the patient of Rees (Chest 60:414, 1971), with RD, the recurrent laryngeal nerve was involved by neurofibroma at the level of the aortic arch; the patient remained well after resection of the tumor. In some patients with RD, x-ray may reveal many, widely-scattered, sharply-demarcated, circular, homogeneous densities throughout both lungs, simulating metastatic neoplasms. Solitary neurofibroma, bullous changes in one of the upper lobes, and cystic lung disease of the honeycomb variety were also recorded. Israel-Asselain, R et al (Thorax 20:150, 1965) first reported the occurrence of interstitial pulmonary fibrosis in subjects with RD. The disease may involve the soft tissues and/or the bones of the chest wall. A composite review of pertinent data indicates that malignant transformation of neurofibromas may occur in from 2 to 16 percent of patients with RD.

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