LUNG HYPOPLASIA IN CONGENITAL PVS/De Troyer, Yernault, Englert

Lung Hypoplasia in Congenital Pulmonary Valve Stenosis

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SUMMARY The pulmonary function of ten adult patients with congenital pulmonary valvular stenosis was investigated. The patients clearly showed smaller lungs than healthy control subjects of equivalent age and height; lung elastic recoil pressure was normal at any given percentage of measured total lung capacity, indicating that postnatal parenchymal damage is not the cause of the small lungs. The lung diffusing capacity for carbon monoxide was reduced, reflecting the anatomical alterations of the pulmonary vascular bed. Finally, the maximal flow-static recoil curves showed a fixed (not dynamic) reduction of airway dimensions: the critical transmural pressure in the collapsible flow-limiting segment (Ptm') was normal, but the conductance of the S segment was lowered. These abnormalities most likely reflect inadequate development of the lung and suggest that pulmonary blood pressure may be an important determinant of lung growth in the postnatal period.

THE POSTNATAL DEVELOPMENT OF THE LUNG has been the subject of extensive research in the last 20 years. Investigators generally agree that most of the alveoli appear in the postnatal period, but the age at which alveolar multiplication ceases is still debated. Earlier data supported the view that alveolar multiplication stopped at the age of eight years, or even by the end of the first year of life. In contrast, recent morphometric investigations seem to indicate that alveolar multiplication goes on throughout childhood, and does not cease completely before somatic growth stops. This latter view is supported by recent studies of lung mechanics during growth.

Moreover, the factors affecting lung growth in the postnatal period are not well understood, as discussed by Thrulbeck in a recent and extensive review. Until now, the amount of blood flow through the lung has not been considered an important determinant of parenchymal development. This conclusion was based only on morphologic findings made in a few cases of congenital lobar over-inflation. Human lung growth in conditions of abnormal pulmonary blood flow and pressure has not been studied. The present work reports the investigation of lung mechanics in ten patients with congenital pulmonary valvular stenosis in order to elucidate the role of pulmonary hemodynamics in lung growth during the postnatal period.

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Material and Methods

Lung mechanics were measured in ten adult nonsmoking patients with congenital pulmonary valvular stenosis, four men and six women whose ages ranged from 16 to 34 years (mean ± SEM: 22 ± 2 years). The results were compared with those obtained in ten healthy young subjects of equivalent age and height, who had no clinical, radiographic or functional evidence of respiratory disease. All patients had a well-documented congenital pulmonary valvular stenosis; the valvular stenosis was mild in one subject, moderate in three and severe in six, based on the criteria used by Johnson and coworkers. None of the patients had a history of lung disease; all patients but one had a normal cardiothoracic index on chest X-ray. In three patients, the pulmonary valvular stenosis was associated with a small right-to-left shunt, due to a ventricular septal defect in one case, and to a patent foramen ovale in two cases.

The techniques used for pulmonary function studies have been described in detail elsewhere. All pulmonary function tests were carried out with the patient in the sitting position. Vital capacity (VC), total lung capacity (TLC), and forced expiratory volume in 1 sec (FEV 1) were recorded by spirometry, in conjunction with measurement of functional residual capacity (FRC) and of residual volume (RV) by the helium dilution technique. Lung diffusing capacity for carbon monoxide (DLco) and Krogh's constant (Kco) were measured by the single-breath method.

Airway resistance (Raw) and plethysmographic FRC were measured in a constant volume body plethysmograph. Plethysmographic TLC was calculated by adding the plethysmographic FRC to the inspiratory capacity obtained.
during direct XY recording of the quasistatic expiratory pressure-volume (PV) curve. 8, 13, 14 Individual PV curves were constructed as the mean of two to four correctly recorded curves. The pressure variation between FRC and FRC + 0.5 liter was used to calculate the expiratory compliance (C_{E}), and specific compliance, defined here as compliance-TLC ratio (C_{L}/TLC).

Maximal expiratory flow-volume (MEFV) curves were obtained by measuring airflow at the mouth, with a Lilly type pneumotachograph (the response of which was linear up to 10 L/sec), and the volume by electric integration of the flow signal. Maximal flow-static recoil (MFSR) curves were constructed by plotting maximal expiratory flow (V_{E max}) expressed in TLC/sec against static transpulmonary pressure at the same lung volume using MEFV and PV curves. From the MFSR curves we calculated the slope of the curve between 80% and 50% TLC, which is the conductance of the S segment (Gs) according to the model described by Pride and associates. 15 We also calculated the intercept on the pressure axis by extrapolating the MFSR curve to zero V_{E max}, using the slope between 80 and 50% TLC; this intercept represents the critical transmural pressure (Ptm') of the collapsible flow-limiting segment. 16

Results

The anthropometric data and pulmonary function measurements of patients and control subjects are presented in table 1. For all the parameters of lung function, no difference appeared between the patients without and those with right-to-left shunts. The VC, TLC, FEV_{1}, C_{L} and C_{L}/TLC were significantly lowered in the patients as compared to controls. There was no significant difference in RV, FRC, FEV_{1}/VC, or Raw. In addition, the patients showed a significant reduction in diffusing capacity; this reduction was not due to the reduction in lung volume alone, since Kco was significantly lowered also.

In figure 1, the mean PV curve obtained in the patients is compared to that obtained in the control subjects. The graph demonstrates clearly that the PV curve of the patients was reduced on its volume axis: for any given transpulmonary pressure there was a decrease in absolute lung volume. However, when volume was expressed as a fraction of measured TLC (fig. 2), the curve was identical to the normal one.

### Table 1. Anthropometric and Pulmonary Function Data (mean ± SEM) in Ten Patients with Congenital Pulmonary Valve Stenosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24 ± 2</td>
<td>22 ± 2</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>6 : 4</td>
<td>6 : 4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169 ± 3</td>
<td>168 ± 3</td>
</tr>
<tr>
<td>VC (liter)</td>
<td>4.74 ± 0.37</td>
<td>3.46 ± 0.24†</td>
</tr>
<tr>
<td>FRC (liter)</td>
<td>3.28 ± 0.31</td>
<td>2.70 ± 0.15</td>
</tr>
<tr>
<td>RV (liter)</td>
<td>1.42 ± 0.17</td>
<td>1.42 ± 0.14</td>
</tr>
</tbody>
</table>
| TLC (liter) | 6.16 ± 0.51 | 4.88 ± 0.30*
| FEV_{1} (liter) | 3.79 ± 0.20 | 2.73 ± 0.19† |
| FEV_{1}/VC (%) | 79 ± 3 | 79 ± 2 |
| DLco (ml·min^{-1}·mm Hg^{-1}) | 28.0 ± 1.5 | 21.5 ± 1.8† |
| Kco (min^{-1}) | 4.81 ± 0.09 | 3.94 ± 0.27† |
| Raw (cm H_{2}O·1·sec^{-1}) | 1.9 ± 0.2 | 1.8 ± 0.2 |
| C_{L} (liter·cm H_{2}O^{-1}) | 0.234 ± 0.028 | 0.140 ± 0.015† |
| C_{L}/TLC (cm H_{2}O^{-1}) | 0.038 ± 0.003 | 0.028 ± 0.002† |

*Significantly different from predicted values (P <0.05).
†P <0.01.

Abbreviations: VC = vital capacity; FRC = functional residual capacity; RV = residual volume; TLC = total lung capacity; FEV_{1} = forced expiratory volume in one second; DLco = diffusing capacity for carbon monoxide; Kco = Krogh's constant; Raw = airway resistance; C_{L} = lung compliance; C_{L}/TLC = specific compliance.
The relationship between \( V_E \) max and lung volume is presented in figure 3. At any given volume between 80 and 50% TLC, \( V_E \) max was clearly decreased (\( P < 0.005 \)); as shown in figure 4, this reduction in airflow could not be accounted for by the loss of lung volume alone.

The relationship between \( V_E \) max and lung static recoil is presented in figure 5. In order to correct for differences in lung size between patients and control group, \( V_E \) max was divided by TLC (\( V_E \) max, TLC/s). The mean plots between 80 and 50% TLC are remarkably linear, both in patients and in controls. The graph demonstrates that at any given driving pressure, flow rates in the patients were lower than normal (\( P < 0.02 \) or less), and moreover, the slope was steeper in the control subjects than in the patients. The \( G_s \) (mean ± SEM) in the control group was 0.079 ± 0.004 TLC per sec per cm \( H_2O \); it was below the normal range in seven of the patients (mean ± SEM: 0.061 ± 0.009 TLC per sec per cm \( H_2O \)), and the difference between the groups was significant (\( P < 0.05 \)). In contrast, \( P_{tm} \) was within normal limits in all patients, and the mean value of the intercept on the pressure axis was similar to that obtained in normal subjects (−3.03 cm \( H_2O \)).

Discussion

Lung function in patients with pulmonary valvular stenosis has not been studied extensively. Only isolated cases have been reported, and the data are poor and conflicting\(^{18-19}\). Dynamic compliance has been reported to be normal\(^{16, 17}\) or low\(^{18}\), but other lung mechanical properties have not been investigated.

The decrease in diffusing capacity found in our group of patients is not surprising: a reduction both in number and in caliber of preacinar and intraacinar arterioles has been described in pulmonary valvular stenosis,\(^{19}\) and in adult patients thrombi are frequently found in pulmonary arteries.\(^{30, 31}\) A reduction of available capillary bed, and thereby a decreased lung diffusing capacity, could thus be expected.

In contrast, the alterations observed in mechanical lung properties were unexpected since anatomical studies reported the lung parenchyma to be normal in patients with

![Figure 3. Relationship of maximal expiratory flow (\( V_E \) max) to lung volume in patients with congenital pulmonary valvular stenosis, and in normal subjects. Each bar represents ± 1 SEM.](http://circ.ahajournals.org/)

![Figure 4. Relationship of maximal expiratory flow (\( V_E \) max) to lung volume expressed in percent of predicted total lung capacity (TLC) in patients with congenital pulmonary valvular stenosis, and in normal subjects. Each bar represents ± 1 SEM.](http://circ.ahajournals.org/)

![Figure 5. Relationship of volume-corrected maximal expiratory flow (\( V_E \) max) to lung static recoil (\( P_{st(1)} \)) in patients with congenital pulmonary valvular stenosis, and in normal subjects. Each bar represents ± 1 SEM.](http://circ.ahajournals.org/)
congenital pulmonary valve stenosis. The current data clearly demonstrate, however, that those patients have smaller lungs than normal subjects of similar height and age.

Analysis of the PV curves indicates that postnatal parenchymal damage is not the cause of the small lungs. Indeed, there is an essential difference between subjects with small lungs due to parenchymal injury (for instance, in diffuse pulmonary fibrosis) and those with the same small lungs but without parenchymal damage. In the former case, the subject has a chest wall which is appropriate for a larger lung and the effect on the PV curve will be the same as a true increase in muscle strength: then, because of the greater mechanical advantage of the inspiratory muscles, a super-normal maximum distending pressure can be applied to the lungs so that Pst (1) max is abnormally high, and in addition, when the PV curve is plotted as percent of the actual TLC, the curve lies to the right of the predicted one, at least at high lung volumes. In contrast, subjects with small but normal lungs have a chest wall appropriate for the small lungs; Pst (1) max is then normal and the PV curve, when plotted as percent of the actual TLC, is normal. This is the pattern observed in our patients (fig. 2), and is consistent with anatomical studies that failed to demonstrate any abnormality in the alveolar wall of patients with congenital pulmonary valvular stenosis. It seems, thus, very likely that the small lungs of these patients result from a growth failure of the lung parenchyma. Whether this is due to a decrease in number or in size of functional units cannot be definitely assessed, since no morphometric data are available. Nevertheless, the low values obtained for specific compliance would mean that the ratio of lung tissue to air per unit lung volume is increased, i.e., that the number of alveoli per unit volume is higher than normal. On theoretic grounds, it thus may be speculated that the alveoli are decreased more in size than in number.

In addition to alveoli, the small airways of patients with congenital pulmonary valvular stenosis also appear to be affected by growth failure. Indeed, the volume-corrected MFSR curve shows that, at any given driving pressure, the airflow is lower than normal. There is, thus, a greater than normal upstream resistance (absolute value of Rg max divided by the value of Pst (1)) during forced expiration. Since Raw is normal, obstruction to airflow must be located in the small peripheral bronchioles. Further analysis of MFSR curves in terms of ΔVe max/ΔPst (1) slope and of the intercept of this slope on the static recoil axis (Ptm') supports the presence of a fixed (not dynamic) reduction of airway dimensions in our patients. It is to be noted here that the values obtained both for Gs and for Ptm' in our normal subjects are very close to those previously reported. The Ptm' of the patients is similar to those of normal subjects, which implies that the compliance of the bronchial wall (collapsible flow-limiting segment) is normal. In contrast, the lowered Gs means that the cross-sectional area of airways at the equal pressure points is smaller than normal. All of the patients being nonsmokers, it seems reasonable to assume that this reduction in airway dimensions is also a consequence of underdevelopment of the lung. We are unable to determine whether this is due to a reduction in the number or in the caliber of parallel airways.

The commonly accepted assumption that pulmonary hemodynamics are not important determinants of human postnatal lung growth is not supported by the results of the current study. Indeed, from our data, it appears that an inflow obstruction, resulting in low intravascular pressure, prevents the normal development of lung parenchyma and peripheral bronchial system. The hypothesis that the valvular heart disease and lung hypoplasia are independent malformations, without cause-and-effect relationship, is possible but seems very unlikely.

**Acknowledgment**

We gratefully acknowledge the excellent technical assistance of Mrs. H. Malrait, J. Bourbigon, and C. Van de Zande; and the secretarial work of Mrs. B. Noell.

**Appendix**

**Definitions and Abbreviations of Terms of Pulmonary Mechanics**

Lung elastic recoil pressure (Pst (1)): the difference between the alveolar and the pleural pressures at a specified lung volume measured under static conditions. Pst (1) max is the elastic recoil pressure of the lung at total lung capacity.

Lung compliance (Cve): the change in lung volume produced by a unit change in lung elastic recoil pressure.

Specific compliance: compliance per unit of lung volume.

Flow-limiting segment: that segment of the bronchial tree which collapse during forced expiration when its transmural pressure reaches a critical value (Ptm'), so that expiratory flow is limited despite further increase in driving pressure.

Conductance of the S segment (Gs): conductance of the airway segment which extends from the alveoli to the flow-limiting segment.

**References**

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SUMMARY In preparation for the measurement of blood pressure in children of a total geographic community, several preliminary studies of the validity and reliability of various methods and instruments for indirect blood pressure measurements were performed. These studies included Graeco-Latin Square designs, examination of children in a field setting, and assessments of the replicability of reading automatically recorded blood pressures.

THE IMPORTANT ROLE OF MASS SURVEYS in detecting individuals with hypertension has stimulated an interest in improving techniques and instruments for measuring indirect blood pressure. As new technology is applied, new insights are gained into the pathophysiology of blood pressure control, furthering the need for improved methods that will obtain valid and reliable indirect measurements. Although automatic instruments could reduce such factors as examiner fatigue and observer bias in measuring blood pressure, a recent report suggests that the available instruments are not adequate for use in epidemiologic studies. Our studies do not support this conclusion.

In preparing for an extensive survey of cardiovascular risk factors in children, we investigated the currently available automatic blood pressure instruments for measurement reliability. The mercury sphygmomanometer was considered the general reference instrument since it is so widely used by physicians; however, several questions were posed: 1) Are there differences among commonly used instruments that are comparable to the standard mercury sphygmomanometer? 2) Do examiners using the same instruments on the same subjects obtain different measurements? 3) Which instruments would be most satisfactory for studying children, especially in a large survey? 4) In a complete field setting, will the measurements be similar to those obtained under a rigidly controlled statistical design? 5) Can the graphic recordings of automatic measuring devices be interpreted without reader bias? 6) Can differences among equally trained readers be explained?

Materials and Methods

In these studies a number of instruments were used in several experimental designs (table 1). We used as many automatic instruments as became available. A recent catalogue of all available automatic instruments has been published, which gives particulars concerning the instruments.

Arteriosonde 1216. The Arteriosonde registers phonosound Korotkoff signals detected by an ultrasonically produced Doppler principle. Systolic and diastolic pressures are registered directly on vertical mercury columns when the falling mercury automatically stops at these levels.6,8

Bonn [Sela Electronics Co.]. This instrument converts Korotkoff sounds into visual or sonic signals but does not produce a permanent record. The transducer is a phonosound microphone.

Kass-Zinner (Boston) Automatic Recorder. Korotkoff sounds, detected by phonosound microphone, are recorded on electrocardiographic paper moving at a constant speed. As in the Narco Physiograph, these sounds are superimposed on the cuff pressure curve, which is calibrated by reference standard square waves.9

Mercury Sphygmomanometer (Baumanometer). We used

A Study of Instruments in Preparation for a Blood Pressure Survey of Children

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For automatic instruments, the Physiometrics recorder, was selected and used in conducting epidemiologic studies where it complements the measurements by the mercury sphygmomanometer.
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