Early detection of lung function abnormalities in infants with cystic fibrosis

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Introduction

Consideration of the first critical events in the airways of infants with cystic fibrosis (CF) remains a necessary preliminary to an understanding of the disease process. Their detection and treatment, however, are crucial since early diagnosis of CF depends on clinical and laboratory facilities to recognize the onset of symptoms and organ involvement in these infants. Cystic fibrosis is characterized by a wide variability in the onset, expression and severity of symptoms. Several years ago, our group looked first on cumulative survival rates within different symptom groups. The data obtained in these studies showed marked differences in survival, depending on the clinical signs, which are primarily present at the time of diagnosis[1]. There was a particularly bad 12-year-survival for the group presenting pulmonary symptoms at the time of diagnosis, and it has been demonstrated that pulmonary involvement appears to be much more important for the prognosis than any other feature of the disease. In a subsequent study it has been demonstrated that height-corrected relative underweight as a clinical parameter is of considerable prognostic value[2]. Relative underweight correlates closely with survival. Moreover, relative underweight was greatest in the group presenting initially with pulmonary symptoms which had the poorest survival[2]. It has been assumed that not only gastrointestinal involvement plays a role in determining growth and weight gain, but that there must be a common factor in the more pronounced underweight and poor survival between lung involvement and weight gain. In the meantime, this parameter was introduced in many follow-up studies as a factor of progression and recent studies carried out in our department have shown that relative underweight improves during hospitalization for intensive antibiotic treatment in CF-patients admitted due to pulmonary exacerbation[3,4].

The micro-osmometer sweat-test, a technique developed by our group[5] is used to detect CF in early infancy. The questions, therefore, were whether lung function abnormalities could be detected in infants who have been diagnosed as having CF, and whether functional abnormalities can be treated with systemically given adrenoreceptor agonists.

Patients and methods

Twenty-four infants aged 0.3 to 7.6 months (mean 2.8 months) newly diagnosed as having CF were

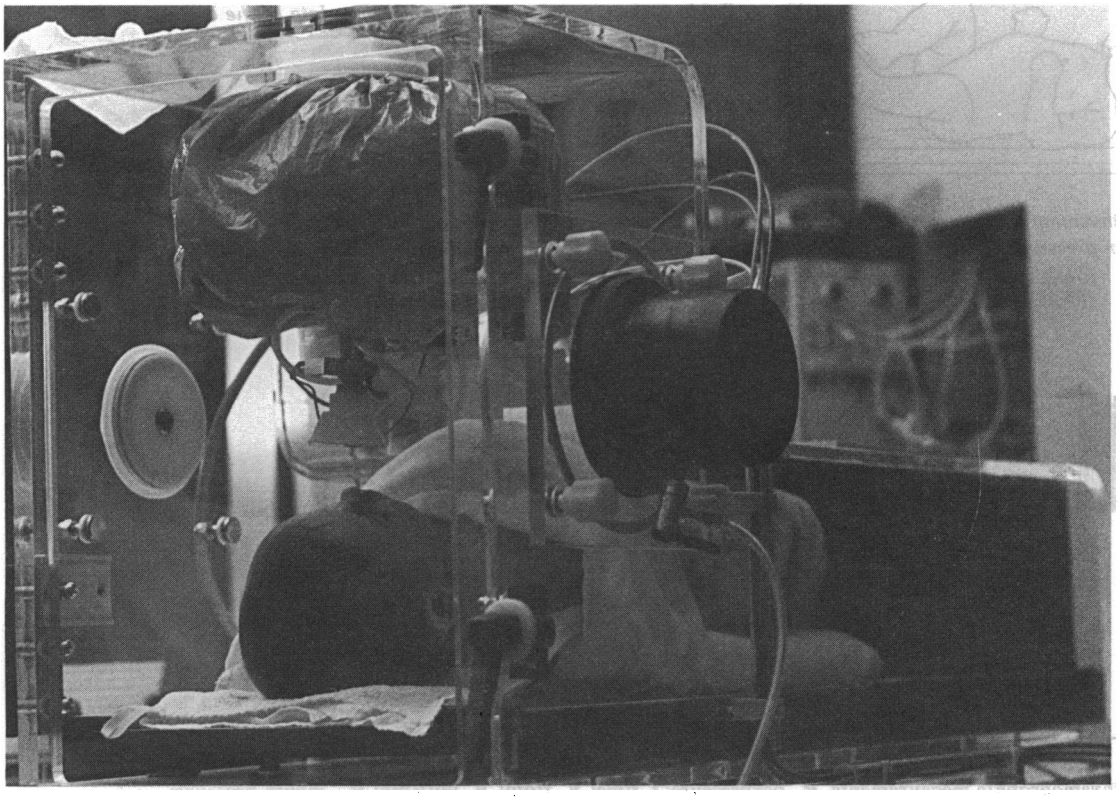

Figure 1. Infant whole-body plethysmograph

investigated. In view of the still limited number of infants, no classification into clinical groups was performed. Lung function was assessed by whole-body infant plethysmography.

Whole-body infant plethysmography measures thoracic gas volume (TGV) to show the degree of pulmonary hyperinflation and airway resistance (Raw), which in turn, indicates the degree of bronchial obstruction. The test procedure is an adaptation of the plethysmographic technique routinely applied in adults[6]. Figure 1 shows the commercially available infant plethysmograph (Jaeger, Wuerzburg, GFR) used in this study. Fifteen to twenty minutes postprandially, the infant, lightly sedated with chloral hydrate (80-100 mg/kg), was placed in the supine position inside the body box. During the plethysmographic measurements heart rate and blood oxygen saturation were monitored by a pulse-oximeter (Biox III, Omeda, Bolder USA). Figure 2 shows a scheme of the infant body-box from which the four signals, the body box pressure (P_b), the flow ($\dot{V}$), its integral, the volume (V) and the mouth pressure (P_M), can be collected. After closing the box, the infant breathed air from the box through a triple-valve-system until a thermal equilibrium has been reached between the infant and the box. A differential pressure transducer was used to detect changes in box pressure relative to a compensating chamber of similar volume (P_b). By an airtight-fitting mask the infant was then switched to the body temperature pressure saturated (BTPS) bag from which air at 36.5°C and 100% humidity is rebreathed. The phase relationship between flow ($\dot{V}$), measured by a small pneumotachograph, and box pressure (P_b) was checked by displaying both signals on an oscilloscope. Figure 3 shows the traces which were plotted on a XY-recorder. From the traces of $\dot{V}$ and P_b, the uncorrected specific airway resistance (sRaw) and its reciprocal, the specific airway conductance (sGaw), can be calculated. Changes in mouth pressure (ΔP_M) were obtained after the shutter has been closed to occlude the airway while the infant made 2 or 3 respiratory efforts. TGV is measured from the angle β of the box-pressure/mouth-pressure ($\Delta P_b/\Delta P_M$)-plot (Figure 3) and Raw is calculated from the angle α of the box-pressure/flow ($\Delta P_b/\Delta \dot{V}$)-plot. To compare infants at different stages of growth, lung function data were expressed as a percentage of the valves given by Stocks and Godfrey[7] (predicted valves).

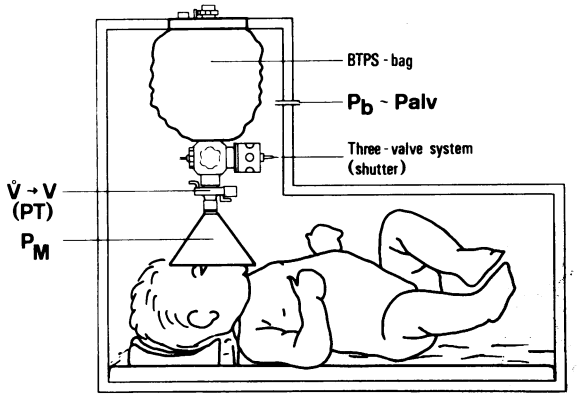

Figure 2. Scheme of plethysmographic measurements. P_b, boxpressure; P_{alv}, alveolar pressure; $\dot{V}$, flow; V, volume; P_M, mouth pressure

Results

Lung function data

These are presented in Table 1. From the values of the TGV it can be seen that considerable pulmonary hyperinflation was already present at this early stage of disease. In addition, due to the increased values of Raw and sGaw, bronchial obstruction has to be considered. As in previous publications[8,9], the infants were stratified into four functional groups. Infants presenting TGV and Raw within the range of the mean±2 standard deviations were considered to be *functionally normal.* Infants with a TGV greater than 130% of the predicted value and Raw less than 130% of the predicted value were defined as predominantly *hyperinflated.* Infants with hyperinflation and bronchial obstruction (TGV greater than 130% predicted, Raw greater than 130% predicted) are collected in a functional *mixed group.* Finally, infants showing a normal TGV but Raw greater than 130% predicted are defined as having *bronchial obstruction*

Table 1. Age, weight and lung function data of the cystic fibrosis infants investigated (n=24)

Age	(months)	2.8±2.1
Weight	(kg)	6.5±2.8
TGV	(% predicted)	156± 57
Raw	(% predicted)	165±114
sRaw	(% predicted)	241±143
sGaw	(% predicted)	55± 29

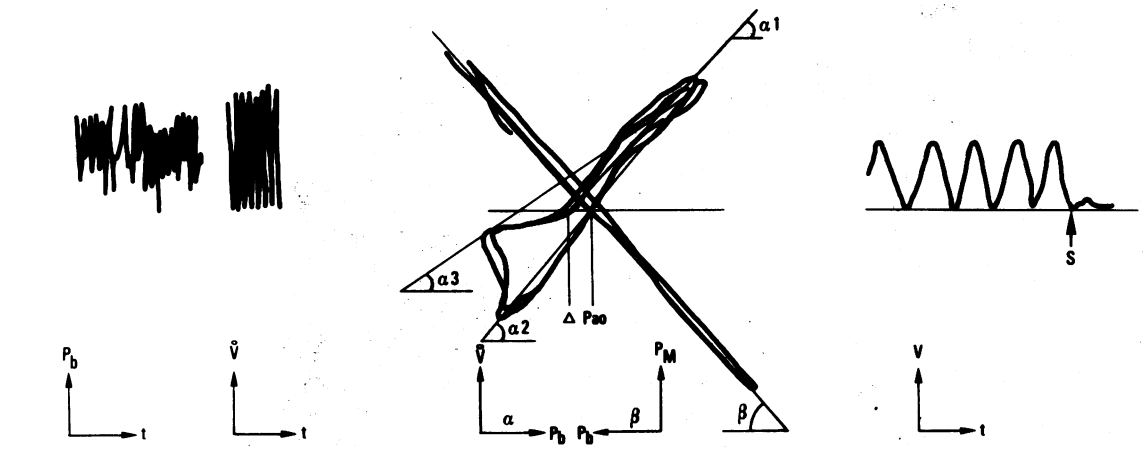

Figure 3. Tracings of plethysmographic measurements, P_b, boxpressure; t, time; $\dot{V}$, flow; V, volume; P_M, mouth pressure; S, shutter closing

Table 2. Stratification into functional groups according to the values of thoracic gas volume (TGV) and airway resistance (Raw) (sGaw, specific conductance)

	TGV (% predicted)	*Raw*	*sGaw*
CF (normal): TGV, Raw within mean±2SD (n=5)	110±8	86±16	89±11
CF (hyperinflated): TGV>130% predicted (n=6)	213±57	71±25	71±29
CF (mixed): TGV and Raw >130% predicted (n=9)	173±29	233±123	29±7
CF (obstructed): Raw >130% predicted (n=4)	88±5	253±70	50±14

without hyperinflation. As it can be seen from Table 2, of the 24 infants studied 5 were within the normal range for lung function, 6 had pulmonary hyperinflation, 9 showed a mixed type of derangement, and 4 had bronchial obstruction without hyperinflation.

Response to systemic adrenoreceptor agonists

There is considerable controversy concerning the role of bronchodilators in infants under the age of 18 months[10-21], although this has not been studied intensively in infants with cystic fibrosis. For wheezy infants, several studies have reported no benefit[10-15] or even a paradoxical deterioration[16,17] after administration of beta agonists. In other reports some infants with broncho-pulmonary disease have responded favourably[18-21] and clinical observations appear to support these findings. Several technical factors could be responsible for the failure to demonstrate a response in infants to beta agonists. In most studies, the beta agonists were inhaled from conventional jet-type nebulizers and a first question is whether the drug reached its site of action. This is especially important in CF, since mucus plugging may substantially impede penetration of aerosols into the lower respiratory tract. A second question relates to the lung function techniques used to evaluate the response. Most studies showing no bronchodilator response to nebulized sympathicomimetics[12-17] were performed using the forced oscillation technique or inductive jacket-plethysmography. Le Souef *et al.*[22] showed that the external compression used to generate partial expiratory flow-volume curves (PEFV) has to be standardized with respect to both the degree of flow limitation and lung volume. In addition, estimation of thoracic gas volume (TGV) during airway occlusion by the jacket method has been questioned[23,24]. Finally, Ding *et al.* recently demonstrated that change in lung volume is a major determinant of the bronchoconstrictor response to methacholine challenge in healthy adults[25], where a change in lung volume alters the forces of interdependence between airways and parenchyma that oppose airway smooth muscle contraction. Change in airway function has, therefore, to be evaluated in close relation to change in static lung volume, particularly since beta-2-agonists have been shown to affect the pressure-volume characteristics in asthmatic children[26].

There are only limited data on the dose-response characteristics and time-course of the bronchodilator responses in infants. In a previous study looking at the efficacy of beta agonists in such infants (survivors after hyaline membrane disease, wheezy bronchitis, CF) we demonstrated that at least by systemic application of salbutamol, an efficacy could be determined when patients were stratified into functional groups, and changes in the degree of bronchial obstruction were estimated with respect to concomitant changes in end-expiratory levels (decrease of pulmonary hyperinflation)[9].

We therefore applied the same protocol in infants with CF. After having obtained a reproducible set of at least two baseline measurements, salbutamol 0.225 mg/kg was administered orally (3 doses 0.075 mg/kg every 10 min) by a nasogastric tube. Measurements were repeated every 5 min and data registered 30 min after drug administration were compared with the baseline values.

The response to salbutamol, expressed as changes in TGV, Raw and sGaw within the three functionally abnormal groups, is presented in Table 3. Pulmonary hyperinflation decreased by a mean of 39% and 26% for CF infants in the hyperinflation and mixed groups, respectively. Bronchial obstruction improved by 53% and 73% for CF infants in the mixed and obstructed groups, respectively. As in previous studies[8,9], the infants have been stratified according to the type of reaction into 5 response groups (Table 4). In the hyperinflated group there was one *non-responder*, whereas pulmonary hyperinflation was decreased in 5 of the 6 infants (*volume-responder*). In the mixed-type group 3 of the 9 infants improved airway resistance (*flow-responder*) and 4 infants improved both pulmonary hyperinflation and airway resistance (*mixed-responder*). One infant showed a *paradoxical reaction*, as pulmonary hyperinflation was worse after medication. In the functional group with bronchial obstruction all of the 4 infants improved airway resistance (*flow-responder*).

Table 3. Changes in thoracic gas volume (TGV), airway resistance (Raw) and specific conductance (sGaw) 30 min after systemical administration of salbutamol (3 time 0.075 mg/kg body weight each 10 min)

	ΔTGV (% predicted)	*ΔRaw*	*ΔsGaw*
CF hyperinflated (n=6)	−39±19	2±11	9±15
CF mixed (n=9)	−26±23	−53±91	11±9
CF obstructed (n=4)	9±7	−73±53	12±19

Table 4. Stratification into different response groups of infants with cystic fibrosis, treated systemically with salbutamol (0.225 mg/kg body weight)

	Non-responders	*Volume-responders*	*Flow-responders*	*Mixed-responders*	*Paradox-responders*
CF hyperinflated	1/6	5/6			
CF mixed		1/9	3/9	4/9	1/9
CF obstructed			4/4		
Total	1/19	6/19	7/19	4/19	1/19

Discussion

The resistance of an airway bears an inverse fourth-power relationship to its diameter[27]. As an airway narrows, a progressively greater change in resistance is expected for a given change in smooth muscle length (and hence inspiratory level of lung volume). This implies that the bronchodilator response to beta agonists must be measured in infants by methods which evaluate changes in airway function in relation to changes in thoracic gas volume. We have already demonstrated in older asthmatic children that changes in airway function need to be closely monitored with respect to changes in static lung volumes[28].

Infant whole-body plethysmography allows the influence of a drug on both static lung volume and airway resistance to be measured. A response to the systemic beta agonist was demonstrated in 18 of the 19 infants with CF. Of the responders 6 were volume-responders, 7 were flow-responders and 4 were mixed responders. Only one infant with CF increased TGV after administration of beta agonists and was considered as a paradox responder. This may be due to the momentarily blocking of some peripheral airways by mobilization of mucus, a situation which is reversible when the infant coughs.

Pulmonary hyperinflation

In a previous paper we have shown that the younger the infant, the more pronounced and frequent the pulmonary hyperinflation may be[8]. The absolute dimensions of the airways from the trachea to the respiratory bronchioles are smaller[29] and the less rigid chest wall of young infants provides little passive support to the lungs, so that end-expiratory resting volume increases more readily[29]. The mechanism (Figure 4) which leads to hyperinflation may be similar to that originally described in adults[30]. The effect of bronchial obstruction is greater in expiration so the normal tidal volume may not be expelled in the time available for expiration, whereas for the lesser inspiratory resistance, adequate time is available for a normal tidal volume to be inspired. The end-expiratory resting level (functional residual capacity; thoracic gas volume) will rise accordingly until a new point of equilibrium is reached. This will provide a greater elastic recoil of the lungs and chest wall to aid expiration and an increased elastic traction on the airways, increasing their intrinsic calibre. Consistent with findings in adults, we have shown that the elastic recoil decreases following beta-2-medication, especially in asthmatic children with a large lung volume[26]. This may be due to a dilatation of terminal lung units relaxing smooth muscle in the alveolar ducts.

In summary, the findings of the present work show that CF-infants with abnormal lung function respond to systemically given bronchodilators. However, efficacy can only be demonstrated if both changes in TGV and airway function are evaluated. The improvement in lung function may be due to bronchodilatation increasing flow with a consequent decrease in end-expiratory resting level. A decrease in lung volume will narrow the airways and airway resistance may not fall unless the diameter of the airway has changed substantially.

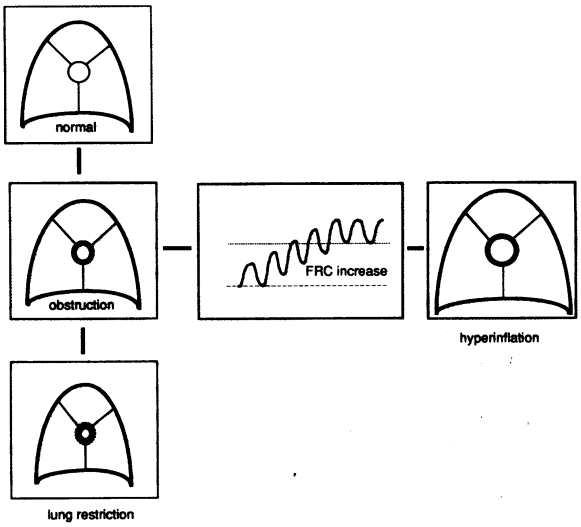

Figure 4. Scheme concerning interrelationship between state of pulmonary inflation and airway calibre and the different alterations in lung disease (bronchial obstruction, pulmonary hyperinflation, pulmonary restriction)

Mucus mobilization and improved mucus clearing must be studied using different protocol measuring lung function on two separate days after administration of an adrenoreceptor agonist like the new oral sustained release preparation of salbutamol.

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