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# Improved detection of abnormal respiratory function using forced expiration from raised lung volume in infants with cystic fibrosis

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*Improved detection of abnormal respiratory function using forced expiration from raised lung volume in infants with cystic fibrosis. D.J. Turner, C.J. Lanteri, P.N. LeSouef, P.D. Sly. ©ERS Journals Ltd 1994.*

**ABSTRACT: The raised volume rapid thoracic compression (RVRTC) technique is a recently developed method of measuring lung function in infants. The measurements of forced expiratory volume-time ($FEV_t$) parameters from raised lung volumes have been shown to be less variable than maximal flow at functional residual capacity ($\dot{V}$maxFRC), obtained from the conventional rapid thoracic compression (RTC) technique. Measurements of $\dot{V}$maxFRC are highly variable, and may not be sensitive enough to detect a difference between normal infants and infants with cystic fibrosis (CF). The aim of this study was to determine whether the raised volume rapid thoracic compression technique could detect abnormal lung function in a group of CF infants with no current respiratory symptoms.**

**Twelve CF infants were studied (median age 10.5 months, range 3–18 months), and compared to normative data collected previously on 26 healthy infants (median age 14 months, range 3–23 months).**

**We found that $\dot{V}$maxFRC failed to detect any difference between the two groups. CF infants had significantly smaller $FEV_{0.5}$ and $FEV_{0.75}$ measurements at a lung volume set by 17.5 $cmH_2O$ predetermined inflation pressure (PP) both as raw values and when expressed as percentage predicted.**

**We conclude that the raised volume rapid thoracic compression technique is a sensitive tool, able to detect abnormal lung function in infants with cystic fibrosis. This abnormality was not demonstrated by measurements derived from the conventional rapid thoracic compression technique in the tidal volume range.**

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To date, studies of respiratory mechanics in infants with cystic fibrosis (CF) have not been conclusive. Several investigators have shown infants with CF to have relatively normal respiratory function early in life, both in larger [1, 2] and small airways [3–6]. Others have found reduced respiratory mechanics in the presence of respiratory symptoms [2, 3, 5].

Maximal flow at functional residual capacity ($\dot{V}$maxFRC) is obtained using the rapid thoracic compression (RTC) technique, and is used as an indicator of small airway function in infants [7]. $\dot{V}$maxFRC is a highly variable parameter, much of this variability being attributable to the instability of functional residual capacity (FRC) as its volume reference point [8, 9]. Determining abnormal lung function with this parameter may, therefore, be difficult.

We have recently developed a new technique, which raises lung volume in the infant prior to generation of forced expiratory flow-volume (FEFV) curves [10]. The raised volume rapid thoracic compression (RVRTC) technique allows measurements of forced expiratory volume-time ($FEV_t$) parameters similar to those produced by spirometry in adults and older children. $FEV_t$ parameters from raised lung volumes are far less variable than flow parameters in the conventional tidal volume range [10]. Recent work has shown that $FEV_t$ parameters can readily detect reduced lung function associated with disease state in recurrently wheezy infants [11], and with histamine-induced bronchoconstriction [12].

The aim of the present study was to determine whether $FEV_t$ parameters, derived from the RVRTC technique, would detect abnormal respiratory function in CF infants with no respiratory symptoms.

## Materials and methods

### *Subjects*

Twelve infants with cystic fibrosis were studied, 9 males and 3 females. They were recruited from the respiratory clinic at Princess Margaret Hospital for Children and had no respiratory symptoms at the time of testing. Of the 12 infants, seven had normal chest X-rays and

eight had at least one episode of respiratory symptoms prior to enrolment in this study. At the time of diagnosis, four infants presented with respiratory symptoms, four with meconium ileus, one with gastrointestinal symptoms. The remaining three were diagnosed antenatally. Written informed consent was obtained from the parents and the study was approved by the hospital Medical Ethics Committee. Table 1 details the anthropometric data for these infants and compares them to 26 normal infants studied previously using the same equipment [10].

*Equipment*

The equipment has already been described in detail [10, 13]. Briefly, a small air cushion rim face–mask (Vital Signs Inc, Totowa, NJ, USA) was held over the mouth and nose forming a leak–free seal. Connected to the mask was an apparatus consisting of several electrically operated solenoid–valves, a pneumotachograph (Fleisch No 1, PK Morgan Ltd, Chatham, UK), a modified nebulizer pump (Vital Air, Allersearch, Sydney, Australia) and a variable underwater blow-off valve. Lung volume was raised in the infant by activating the pump; air was pulled through the pneumotachograph and into the infant until a predetermined inflation pressure (PP) was reached. Once the desired PP was obtained, the blow-off valve was activated and no more air was pulled through the pneumotachograph. FEFV curves were then generated by inflating the squeeze jacket wrapped around the infant's chest and abdomen. The arms remained outside the jacket in order to avoid possible splitting of the chest wall [14]. Timing of the jacket inflation, in the tidal volume range, was determined in conjunction with observing flow-volume loops on a Tektronix 5223 digitizing storage oscilloscope (Tektronix, Beaverton, Oregon, USA). FEFV curves were generated from raised lung volume once the blow-off valve was activated. The pressure used to inflate the jacket (Pj) was measured using a Gould Statham P23 pressure transducer (Gould Inc, Dayton, Ohio, USA). Airway opening pressure (Pao) was measured by a second Gould Statham P23 transducer from a port adjacent to the face-mask.

Oxygen saturation was continuously monitored throughout the study using a Nellcor N-200 E pulse oximeter (Nellcor Inc., Hayward, Ca, USA). All signals were collected and analysed on computer using LABDAT-ANADAT 5.1 data acquisition and analysis package (RHT-INFODAT, Montreal, Canada).

*Protocol/variables measured*

Infants were studied in the respiratory function laboratory after sedation with chloral hydrate (80 $mg \cdot kg^{-1}$). FEFV curves were obtained in each infant from end-tidal inspiration and from lung volumes set by a range of PP (10–20 $cmH_2O$). $\dot{V}$maxFRC was measured from tidal FEFV curves, while forced expiratory volume at 0.5, 0.75 and 1.0 s were determined from raised FEFV curves.

Table 1. – Anthropometric data for 12 infants with cystic fibrosis (CF) and 26 normal controls (N)

| | CF | N |
|---|---|---|
| Age months | 10 (3–18) | 14 (3–23) |
| Weight kg | 9 (5–13) | 11 (5–14) |
| Height cm | 72 (57–81) | 77 (57–87) |

Data are presented as median, and range in parenthesis.

Pj was determined for each infant from a run of flow-volume curves in the tidal range. The Pj that produced the highest $\dot{V}$maxFRC without evidence of negative effort dependence was then used to generate FEFV curves from raised lung volumes [10, 13, 15].

*Statistical analysis*

In order to standardize for lung volume, the relationship of $FEV_t$ to Pao was examined in each individual using linear regression. Regression equations were then established for $FEV_t$ *versus* height, at a standardized Pao of 17.5 $cmH_2O$, and compared to predictive values established previously in normal infants, see below [10]. A Pao of 17.5 $cmH_2O$ was chosen, as this was the mid-point of the range of data previously collected in normal infants (15–20 $cmH_2O$).

Regression equations for $FEV_t$ measurements and height (ht) were generated from data collected in 26 normal infants, they are standardized to a Pao of 17.5 $cmH_2O$. Regression coefficients (r) and significance values (p) are shown:

$FEV_{0.5}$ (ml): y = -148+4.35ht, r=0.677, p<0.0001;

$FEV_{0.75}$ (ml): y = -174+5.09ht, r=0.647, p<0.005;

$FEV_{1.0}$ (ml): y = -81+4.0ht, r=0.544, p<0.05.

The mean value of $\dot{V}$maxFRC was determined from five manoeuvres. $\dot{V}$maxFRC and $FEV_t$ measurements were compared between CF and normal infants using Student's unpaired t-tests.

## Results

All 12 infants were able to produce $FEV_{0.5}$ and $FEV_{0.75}$ measurements, whilst only seven generated $FEV_1$ measurements. There was no difference in the number of $FEV_{0.5,\ 0.75,\ 1.0}$ measurements generated by CF infants to that of normal infants (26, 25 and 19, respectively).

Figure 1 illustrates the $FEV_t$ data obtained from one representative CF infant over a range of Pao. Figure 2 shows the relationship of $FEV_{0.5}$ and $FEV_{0.75}$ data (calculated at a Pao of 17.5 $cmH_2O$) and height for the 12 CF infants. Note that eight of the 12 CF infants had $FEV_{0.5}$ measurements that fell below the regression line of the normative data. In figure 2b, 10 of the 12 infants had $FEV_{0.75}$ measurements that fell below the regression line of the normative data; however, three of these infants have data that are below the height range of the normal data. Care must be taken in extrapolating

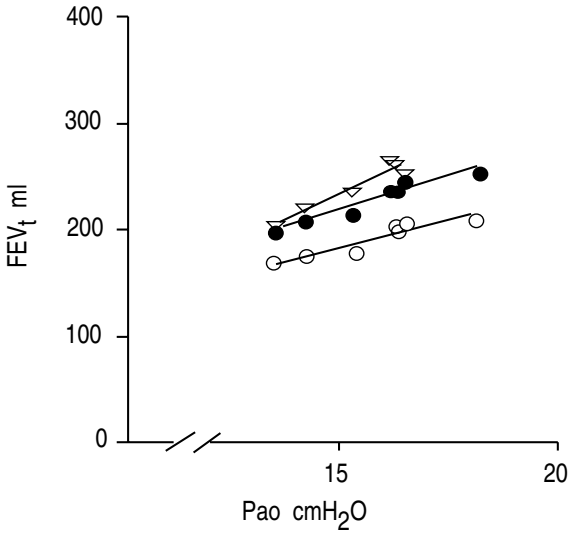


Fig. 1. – FEV$_t$ data collected from one representative cystic fibrosis (CF) infant. ○: FEV$_{0.5}$; ●: FEV$_{0.75}$; Δ: FEV$_1$. Linear regression lines are shown. FEV$_t$: forced expiratory volume in time (t); FEV$_{0.5}$, FEV$_{0.75}$ and FEV$_1$: forced expiratory volume in seconds; Pao: airway opening pressure.

Table 2. – Flow and volume data for infants with cystic fibrosis (CF) and normal controls (N)

| | CF | N |
|---|---|---|
| $\dot{V}$maxFRC ml·s$^{-1}$ | 117.2 (12) | 133.4 (9.8) |
| FEV$_{0.5}$ ml | 138.8 (14.1)* | 174.8 (7.1) |
| FEV$_{0.5}$ % pred | 84.9 (5.6)* | |
| FEV$_{0.75}$ ml | 152.2 (16.2)** | 204.5 (9.2) |
| FEV$_{0.75}$ % pred | 79.8 (5.3)*** | |
| FEV$_1$ ml | 166.7 (24.9) | 217.9 (10.3 |
| FEV$_1$ % pred | 79.5 (8.8) | |

The data are presented as group mean (SEM), at a standardized lung volume (Pao=17.5 cmH$_2$O). The FEV$_t$ data of the CF infants are also presented as mean percentage predicted, using regression equations obtained previously from 26 normal infants [10]. Results are compared between diagnostic groups using unpaired Student's t-test. $\dot{V}$maxFRC: maximal flow at functional residual capacity; FEV$_{0.5}$, FEV$_{0.75}$ and FEV$_1$: forced expiratory volume at 0.5, 0.75 and 1 s, respectively; % pred: percentage of predicted normal value; Pao: pressure at airway opening. *,**,***: p<0.05, 0.01, 0.005 compared to normals.

the normal data to fit these infants. If we consider only the infants who fall within the height range of the normal data, 7 out of 9 have FEV$_{0.75}$ measurements that fall on or below the lower 95% confidence interval of the mean.

Table 2 details the group mean (SEM) $\dot{V}$maxFRC and FEV$_t$ data (at a Pao of 17.5 cmH$_2$O) for the CF and normal infants. For the CF infants, FEV$_t$ data are shown both as raw values and as percentage predicted values. FEV$_{0.5}$ and FEV$_{0.75}$ measurements were significantly reduced in the CF group compared to those of the normal infants (p<0.05 and p<0.01 respectively). FEV$_1$ measurements failed to showed a significant difference between the diagnostic groups, as did $\dot{V}$maxFRC.

When expressed as percentage predicted, FEV$_t$ parameters were approximately 80% of that predicted from the normal data (table 2). These differences were significant for FEV$_{0.5}$ and FEV$_{0.75}$ (p<0.05 and p<0.005, respectively), however FEV$_1$ failed to reach significance (p=0.06). We were unable to express $\dot{V}$maxFRC in terms of % predicted, as the regression of $\dot{V}$maxFRC to height was not significant in the previous study of 26 normal infants.

Clinical scores, in terms of X-ray status, past evidence of respiratory symptoms and mode of presentation did not appear to correlate with lung function data (table 3).

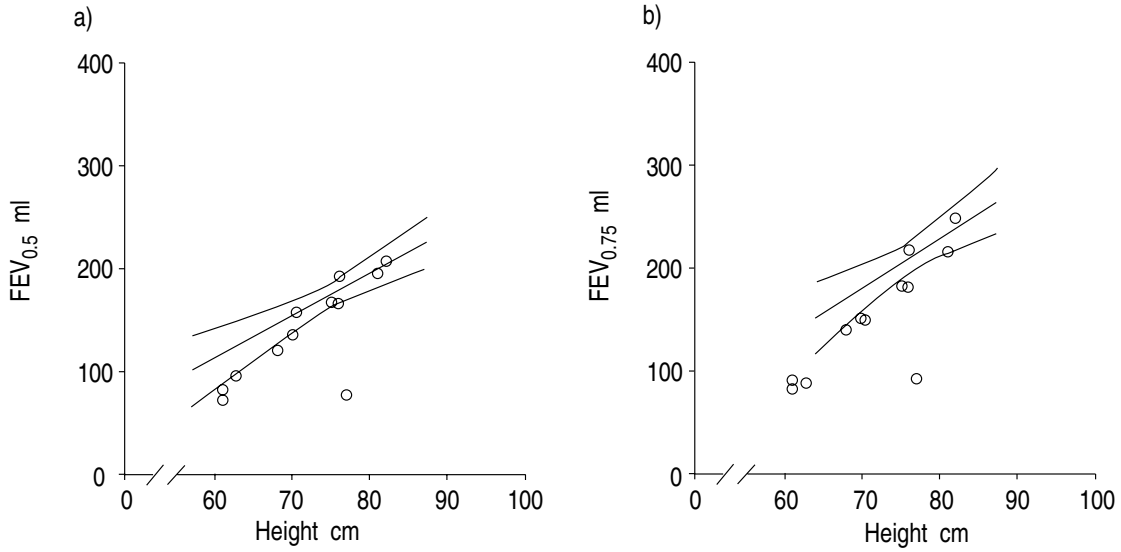


Fig. 2. – The relationship of: a) FEV$_{0.5}$; and b) FEV$_{0.75}$ to height in 12 cystic fibrosis (CF) infants. Each data point represents the FEV$_t$ value of a CF infant calculated at a Pao of 17.5 cmH$_2$O. These values are derived from individual regression equations of FEV$_t$ and Pao, as illustrated in figure 1. The solid lines represent the regression line and its 95% confidence interval from 26 (FEV$_{0.5}$) and 25 (FEV$_{0.75}$) normal infants studied previously. Note that the majority of CF data falls below the regression line of the normative data. For abbreviations see legend to figure 1.

Table 3. – Clinical and lung function data for 12 infants with cystic fibrosis

| Study | Age | Sex | CXR | MOP | Symptoms | $FEV_{0.75}$ | | $\dot{V}maxFRC$ |
|---|---|---|---|---|---|---|---|---|
| | months | | | | | ml | % pred | $ml \cdot s^{-1}$ |
| 1 | 3.5 | M | N | R | Yes | 148 | 82 | 71 |
| 2 | 3.5 | M | N | R | Yes | 185 | 90 | 75 |
| 3 | 5.5 | M | N | A | No | 181 | 87 | 76 |
| 4 | 6.0 | M | N | G | Yes | 214 | 93 | 81 |
| 5 | 8.0 | F | Ab | MI | Yes | 150 | 85 | 70 |
| 6 | 10.0 | M | Ab | R | Yes | 140 | 82 | 68 |
| 7 | 10.0 | M | Ab | R | Yes | 213 | 103 | 76 |
| 8 | 13.0 | M | Ab | A | Yes | 246 | 104 | 82 |
| 9 | 14.0 | M | Ab | MI | Yes | 91 | 67 | 61 |
| 10 | 16.5 | M | N | A | No | 92 | 43 | 77 |
| 11 | 17.0 | F | N | MI | No | 88 | 61 | 63 |
| 12 | 17.0 | F | N | MI | No | 82 | 60 | 61 |

Chest X-ray (CXR) results, modes of presentation (MOP), previous respiratory symptoms (Symptoms), $FEV_{0.75}$ at a Pao of 17.5 $cmH_2O$ expressed both as raw data (ml) and as % predicted using normative data obtained previously (% pred), and $\dot{V}maxFRC$ data ($ml \cdot s^{-1}$) are shown. M: male; F: female; N: normal; Ab: abnormal; R: respiratory; A: antenatal; G: gastrointestinal; MI: meconium ileus. For further abbreviations see legend to table 2.

## Discussion

The raised volume rapid thoracic compression (RVRTC) technique detected reduced respiratory function in CF infants free of respiratory symptoms when compared with healthy controls. The conventional measure of $\dot{V}maxFRC$ in the tidal volume range failed to detect a difference between these groups. These data suggest that the new RVRTC technique is more sensitive than the tidal volume RTC technique in detecting respiratory disease.

The extent of respiratory damage occurring in infancy due to cystic fibrosis remains unclear. Studies assessing the larger airways suggest that lung function is essentially normal early in life. PHELAN *et al*. [1] used measurements of thoracic gas volume (TGV), dynamic compliance (Crs) and resistance of the respiratory system (Rrs) to determine lung function in CF infants. Only three out of the nine CF infants studied had increased TGV, whilst four had increased Rrs. A similar study by GODFREY *et al*. [2] compared the lung function of eight infants with CF to that of 24 normal infants, and reassessed them at 5 years of age. In infancy, only those with severe symptoms had reduced lung function while at 5 yrs of age they all showed abnormalities. They concluded from this study that CF infants had essentially normal lungs at birth and early in life, with damage occurring later even in the absence of respiratory symptoms.

Two more recent studies have used $\dot{V}maxFRC$, an indicator of small airway function, to determine respiratory function in CF infants. BEARDSMORE *et al.* [3] divided a group of 28 infants with CF into two groups according to their level of specific airway conductance (sGaw). They found that CF infants with normal sGaw had a low clinical score and normal $\dot{V}maxFRC$ and TGV values whilst those with low sGaw had a higher clinical score, decreased $\dot{V}maxFRC$ and raised TGV. TEPPER *et al*. [5] studied 25 infants with CF within 2 weeks of diagnosis. They found that CF infants with respiratory symptoms had reduced $\dot{V}maxFRC$, reduced mixing index and increased FRC compared to normal infants. CF infants without respiratory symptoms showed no differences from normal infants. All 12 infants within this current study were free of respiratory symptoms at the time of testing. We were unable to detect differences in lung mechanics within the 12 CF infants based on chest X-ray status, past history of respiratory symptoms, or mode of presentation when diagnosed. However, this may be attributable to the relatively small number of infants studied.

The data from this present study, in agreement with the findings of BEARDSMORE *et al*. [3] and TEPPER *et al*. [5], show that CF infants without current symptoms have values of $\dot{V}maxFRC$ within the normal range. However, using a more sensitive index of lung function we are able to demonstrate respiratory abnormalities in our asymptomatic group of CF infants. Both $FEV_{0.5}$ and $FEV_{0.75}$ were able to differentiate CF lung function from normal mechanics. $FEV_1$ measurements were unable to differentiate the two diagnostic groups, probably due to the small number of infants able to generate this parameter. GODFREY *et al*. [2] determined that abnormalities not detected in infancy were present at 5 yrs, even in the absence of respiratory symptoms. The data from this study suggest that those abnormalities may be present much earlier in life.

Standardization of the data was necessary as the age range of 3–18 months provided considerable variability in size between infants. We utilized our own predictive values taken from an earlier study of 26 normal infants [10]. Although the data set is relatively small, it covers the appropriate age range and the correlation coefficients of $FEV_1$ to height are very tight.

We conclude from this study that the RVRTC technique is a sensitive methodology able to detect abnormalities in CF lung function early in life. These abnormalities remain undetected using $\dot{V}maxFRC$ measurements from the conventional RTC technique.

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