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Research Article

Tracheomegalia in CF: Alarms in Spirometry Performance

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Abstract

Introduction: Cystic Fibrosis (CF) patients may develop tracheomegalia (TM). Forced expiration during spirometry may cause TM collapse, while reducing FEV1. Large difference in FEV1 values, initiated by maximal and sub-maximal expiratory effort, (dFEV1 %max, within technical acceptable criteria) may affect lung function interpretation.

Methods: Data from CT-imaging and spirometry tests, performed within the same year, were gathered from the medical files of 49 CF patients (age-range 12 - 44 yrs). A pediatric-radiologist measured the tracheal diameter from CT-images, by obtaining sagittal and coronal diameter, calculating surface area 2 cm above the carina. An area of 1.64 z-scores above normal was defined as TM. We defined a submaximal spirometry effort by an acceptable rise-time to peak expiratory flow (PEF) up to 13% below the maximal PEF effort.

Results: A difference in FEV1 (dFEV1 %max) above 6% suggests TM. 35/49 (71%) patients showed TM by CT and 22/35 had significantly improved their dFEV1 at submaximal expiratory effort ($p = 0.0121$). 17 of those 22 patients improved FEV1 between 120-350ml. 10/35 patients with FEV1 below 30% predicted, enhanced their FEV1 at submaximal effort up to 36%predicted values. High dFEV1 was linked with increased number of hospitalization days/year ($r2 = 0.168$; $p = 0.0034$).

Conclusion: Large differences between maximal and submaximal effort during forced spirometry may suggest TM in CF patients. The finding that both TM and dFEV1 correlate with increased days of hospitalization, insinuates a probable under-estimated FEV1 in some patients. The finding may have clinical significance. Due to the importance of FEV1 in the management of CF patients, it may be valuable to follow dFEV1 to improve surveillance and treatment. More studies are needed to establish an adequate approach.

Keywords: *Cystic Fibrosis; Tracheomegalia; Spirometry; Pulmonary function tests; Chest CT*

Introduction

Cystic fibrosis (CF) is a life-shortening autosomal recessive disorder, caused by mutations in the gene encoding the CF "trans-membrane conductance regulator protein" (CFTR). The extensive airways and lung damage is related to the abnormal CFTR, which participates in electrolyte homeostasis and fluid movement across mucosal surfaces within the airways [1,2]. This may lead to recurrent infections,

inflammation and persistent cough, resulting in tracheal structural abnormalities, which include cartilaginous weakening or development of tracheomegalia (TM) [3-6] and even trachea diverticula [7]. TM is also associated with lower FEV1 and Pseudomonas acquisition in children with CF [8].

TM may be present in CF patients in any period of life, ranging from 15% in infancy and childhood [8,9] to 69% of adult CF patients [10]. The common way to discover TM is via diagnostic imaging [10].

The forced vital capacity maneuver is a well-established procedure that measures airflow limitation [11,12]. During maximal expiratory effort, a flaccid trachea and/or central bronchi may collapse leading to early airway closure [13,14]. In return, the collapsibility may reduce the expiratory flow stream, bringing the forced expiratory volume at 1st second of expiration (FEV1) values downward, to artificially lower levels [15,16]. Lebecque., *et al*. [17] had formerly suggested a connection between larger than normal trachea, measured by radiology, and obstructed FEV1 in CF patients, but their study did not explore the use of submaximal FEV1 as an indicator of TM.

We hypothesize that differences above the one standard deviation between maximal and submaximal expiratory efforts as measured by FEV1 may indicate the collapsibility of the trachea and central airways due to TM in CF individuals

Aim of the Study

The study aimed to explore if CF individuals having TM proven by radiology will also show larger than expected differences between FEV1 performed at maximal and submaximal expiratory effort.

Subjects and Methods

We retrospectively obtained data from the medical files of 49 CF patients who routinely visited the national CF Center at the Edmond and Lily Safra Children's Hospital of Sheba Medical Center, Israel. The data included:

a) Spirometry maneuvers containing maximal and sub-maximal efforts performed during 2011 - 2015. We excluded spirometry data obtained during exacerbations.

b) Thoracic computerized tomography (CT) of the same patients that were performed within a year prior to or following the spirometry. We also collected clinical information on the patients' status, specifically the number of hospitalizations days per year.

The retrospective study was approved by the ethics committee of the Sheba Medical Center (Approval no. 9446-12-SMC).

Spirometry data: All maximal spirometry maneuvers were performed according to ATS/ERS recommendations [11,12] using a KoKo PDS spirometer (nSpire Health, Inc. CO, USA). According to global standardizations [11,12], we defended maximal effort as a time rise to PEF below 120ms. A sub-maximal target effort as a peak expiratory flow (PEF) of at most 13% below the maximal effort, providing it was technically acceptable within the rise time to PEF (within the limited rise time of 120 ms).

For each patient we calculated a dFEV1 as the difference between the maximal and the sub maximal efforts. dFEV1 values exceeding more than 150 ml (6% above baseline FEV1) of the maximal effort were considered significant. Similarly, we defined a significant difference in FVC as a 200ml (6%) enlargement between efforts.

Predicted spirometry values were obtained from the GLI reference values [18] and predicted peak-flow values were from the ECSC reference [19].

Chest CT measurements: Chest CTs were performed by standard techniques at the Imaging Institute of Sheba Medical Center, Israel. All dimension measurements were calculated using a Care-stream PACS software notebook™ by a specialist in pediatric radiologist (J.J.).

The tracheal diameter, calculated from the length and width, was measured at identical anatomical locations, two centimeters above the carina.

Figure 1 demonstrates the calculation method. The illustrations show that the enlarged trachea is neither rectangular nor elliptic. The trachea surface area (Tsa) was then calculated using two-methods:

a) Rectangle (R-Tsa) where Tsa = (length × width).

b) Ellipse (E-Tsa) where Tsa = π × (width/2 × length/2).

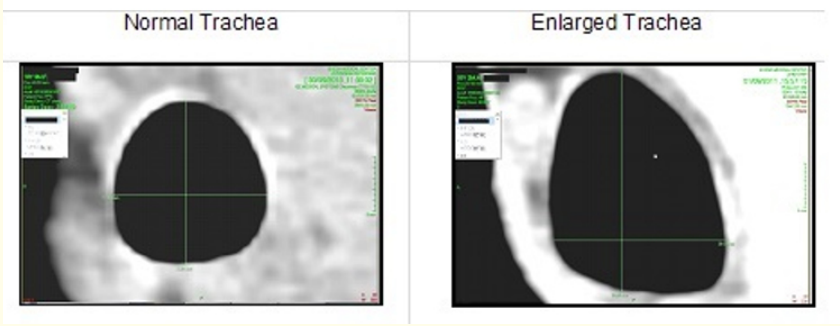

Figure 1: *Demonstrates the calculation method. The illustrations show that the enlarged trachea is neither rectangular nor elliptic. The trachea surface area (Tsa) was then calculated using two-methods.*

Tracheal measurements were compared to those of Lebecque., *et al.* [17] who measured the Tsa in healthy subjects. A tracheal area of more than 1.64 zScores above the healthy population was defined as enlargement of the trachea (Confidence levels 2 sides of 90%). Accordingly, our patient data were divided into three subgroups: Normal tracheal diameter if values were below 1.64 z-scores. We defined Mild TM if z-score was above 1.64 using the elliptic-Tsa method and Severe TM if z-scores were above 1.64 in both calculated methods.

Statistical analysis

Data was analyzed using SPSS package version 19. The statistical analysis was performed at the statistical division of the Sackler Medical School at Tel-Aviv University, Israel. The differences between FEV1 at maximal force vs. sub-maximal expiratory effort of the same individual were tested using paired t-tests. To analyze the differences between subgroups we used either unpaired t-test or Chi-square tests. To establish the effect of TM presence and clinical parameters we used ANOVA tests. Linear correlations were sought between dFEV1, TM and yearly hospitalization days, Data is presented in mean values ± standard deviation (± SD) when distribution was normal and as median and 95%CI range when distribution was abnormal. Differences were considered significant if p values were < 0.05.

Results

Spirometry data, including maximal and submaximal efforts, and thoracic CT were eligible from 49 (m/f = 27/22) CF patients. The average age of our patients was 26 ± 8 years, and average BMI was 19.3 ± 2.4 (kg/cm^2).

Trachea measurements revealed that 14 patients (29%) had normal tracheal area and 35 patients (71%) showed tracheal enlargement. 14 of the 35 patients had mild tracheal enlargement according to Elliptic-Tsa only, and other 21 of 49 patients had severe tracheal enlargement, according to both Elliptic and rectangular-Tsa calculations.

The anthropometric data of the patients and their basic lung function tests at maximal effort are presented in table 1, according to the presence of either normal tracheal size (n = 14) or TM (n = 35). There were no significant differences between the groups.

	Normal trachea	Tracheomegalia	p value
N	14	35	
Age (years)	24 ± 8	28 ± 8	0·1192
BMI	19 ± 2	19 ± 3	0·2021
Spirometry maximal effort (%predicted)			
FVC	61 ± 16	56 ± 18	0·2750
FEV1	47 ± 16	43 ± 17	0·2248
FEF25-75	27 ± 16	29 ± 19	0·7805
PEF	69 ± 23	61 ± 21	0·3507

Table 1: *Baseline anthropometric data and maximal effort spirometry values.*

Spirometry (maximal (max) vs. sub-maximal (s-max): The median (95%CI range) rise-time to peak flow increased from 63ms (58 - 70ms) at max effort to 109ms (95 - 118ms) at s-max effort. These values were within the restrictions of technically accepted spirometry [11]. The differences in spirometry parameters caused by the maximal and submaximal expiratory effort are presented in table 2. The table shows that submaximal effort generated improvements in lung function: 17 of 35 patients with TM increased their FEV1 between 120 - 350 ml and 20/35 increased their FVC between 120 - 450 ml. there was no significant change in these parameters in the normal trachea group. Ten of 35 patients increased of both dFVC and dFEV1. The individual dFEV1 values in relation to trachea size are showed in figure 2, presents the TM size in relation to FEV1. We did not find any correlation between percent predicted FEV1 at maximal effort and the degree of tracheal enlargement.

Figure 3 showed the dFEV1 in relation to TM according to the groups. The dFEV1 increased > 6% in: three of 14 (21%) individuals having normal trachea size, in seven of 14 (50%) individuals with mild TM and in 8/21 (38%) individuals with severe TM.

Twelve of the 49 examined patients were listed for lung transplantation and their initial FEV1max was equal to or below 30%predicted values at maximal effort. Two of these 12 patients showed normal tracheal size by CT. The other 10 patients, with TM, enhanced their FEV1 up to 36% predicted values by performing submaximal effort with technical restrictions.

Eleven of 14 patients having normal tracheal size and normal dFEV1 were hospitalized 7.6 ± 6.3 days/year while 24 of 35 patients with a high dFEV1 and TM were hospitalized 13.9 ± 7.6 day/year (p = 0.0187). A trend correlation was found between dFEV1 and the number of hospitalizations/days/year (p = 0.0523).

	Maximal Effort	Sub-Max. Effort	Difference (%max)	p-value
Normal trachea (n = 14)				
FVC (L)	2.30 ± 0.71	2.43 ± 0.74	2.7 ± 1.1	0.0002
FEV1 (L)	1.48 ± 0·52	1.55 ± 0·57	4.6 ± 1·8	0.0001
Tracheomegalia (n = 35)				
FVC (L)	2.57 ± 1.08	2.72 ± 1·07	7.7 ± 4·8	0.0002
FEV1 (L)	1.66 ± 0.77	1.77 ± 0·80	6.9 ± 4·9	0.0001

Table 2: *Maximal and submaximal expiratory effort differences.*

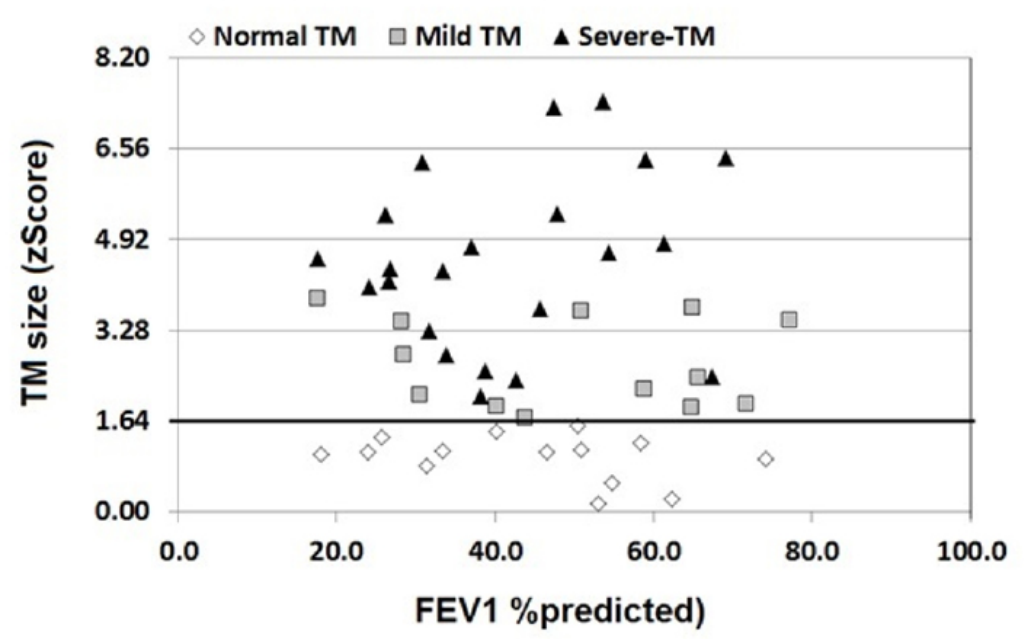

Figure 2: *The TM size in relation to FEV1. The figure shows that enlarged TM can appear at any FEV1 level.*

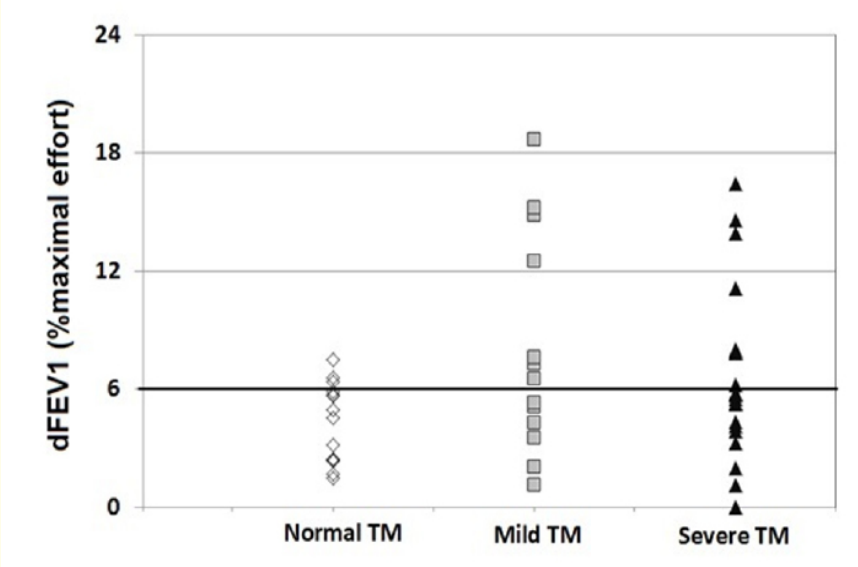

Figure 3: *Showed the dFEV1 in relation to TM according to the groups.*

Discussion

In the present study we examined a possible connection between tracheal enlargement and large differences in FEV1 values (or FVC), measured at maximal and submaximal expiratory efforts performed within global recommendations [11]. We found that the majority of our tested group had TM of various severities. This finding is compatible with previous studies [9,10]. Fisher., *et al*. [8] showed a correlation between TM and low FEV1 in 15% of their examined children with CF. Our study indicates that TM, may lead to a significant additional decrease when using maximal expiratory effort not only in FEV1 but also in FVC values regardless of % predicted rates. Our findings therefore imply a presence of TM if a submaximal expiratory effort leads to a significant increase in FEV1 and/or FVC over values found during maximal effort (dFEV1). If true, our study outcomes may directly raise uncertainty as to the accuracy of both the vital capacity and the FEV1 measurements at maximal effort in patients with CF. Moreover, our findings raise the question if the spirometry should be modified for CF patients to contain both maximal and submaximal efforts, within the technically acceptable flow volume maneuvers.

Can FEV1 variation between submaximal effort and maximal effort suggest a component of TM that may influence clinical care? The answer could have a potential impact in CF care.

TM is a condition in which the tracheal cartilage is weak and is then also unable to prevent airway collapse from increased intrathoracic pressure during forced exhalation. It was previously shown that increased thoracic pressure will alter FVC maneuver [13,14]. Therefore, forced expiration may decrease flow in the presence of TM. Our findings strengthen a connection between a simple change in peak flow performance, indicated by dFEV1max above 150 ml (> 6%), and the presence of TM as seen in a large proportion of CF patients. Furthermore, the technical guidelines for correct performance of the FVC maneuver may actually worsen true FEV1. The finding that a relatively small change in the spirometry performance may indicate TM in CF patients is intriguing and may be of clinical significance. For example, following the discovery of TM in a patient, different medical approaches can be used to improve the symptoms such as the use of continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP) ventilation modalities to prevent collapse of airways during quiet breathing [20].

One of the many benchmarks leading to referral for lung transplantation is FEV1 below 30% predicted value [21-23]. We found that in the presence of TM, a patient may have a maximal effort FEV1 below 30% predicted while a submaximal effort may portray FEV1of 36%predicted. This finding immediately raises the question of premature referral to lung transplantation. Conversely, we question if in the presence of TM, a patient may need to be moved up on the transplant list before TM worsens, as the trachea is not replaced during lung transplantation and a correlation was found between TM and shortened survival after lung transplantation in CF patients [7].

In our present study we found a trend showing that patients with TM were hospitalized more days per year than others. This finding may be linked to the flaccidity of the trachea impairing cough efficiency [24] and may indicate the need for a cough assist device.

We acknowledge some limitations of our study. The study was retrospectively made from review of previously performed chest CTs in Israel. Yet, this may also be an advantage, as patients were tested by the same technicians in one pulmonary function laboratory, while the analysis of trachea size was performed independently in a different department by their own specialists.

Tracheal sizes were compared to those in healthy adults obtained by Lebecque [17]. Indeed, as for today there are more sophisticated measurements to study trachea size, such as acoustic reflection method [25] but these are not available in our center. Further the respiratory cycle point may affect caliber of the trachea size on CT imaging. Still, we find our results reasonable reproducible.

Conclusion

We conclude that exploring the presence of large differences between FEV1 (or FVC) measured at maximal and submaximal expiratory efforts may reflect the presence of tracheal enlargement as seen on CT in CF patients. The presence of a large dFEV1 as seen in patients with TM is associated with increased hospitalization days. Measurements of dFEV1 in CF patients may also give a more reliable picture

of the patient's maximal respiratory flows, which in turn may affect respiratory physiotherapy methods, clinical interventions, and the decision to transplant to enable more appropriate treatment. A prospective study with a standardize CT procedure and perhaps evidence of dynamic airway collapse radiographically could be more supportive of the proposed hypothesis.

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