ORIGINAL ARTICLE

Infant Pulmonary Function Tests in Children with Airway Anomalies and Correlation with Bronchoscopy Findings

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ABSTRACT

Objectives: To evaluate the role infant pulmonary function tests (Tidal Breathing Flow Volume Loops, TBFVL) in children with airway anomalies and to correlate the TBFVL so obtained with bronchoscopy findings.

Methods: In this prospective cohort study, we enrolled children aged 0-2 years with airway anomalies and performed TBFVL and bronchoscopy. The primary outcome measure was graphic pattern of TBFVL in laryngomalacia. Secondary outcome measures were types of TBFVL results in various airway anomalies and controls.

Results: Out of 53 children enrolled, 28 (52.3%) had laryngomalacia. Pattern 3 (fluttering of inspiratory limb) was commonest TBFVL pattern in laryngomalacia. Among TBFVL parameters, the ratio of inspiratory time to expiratory time (Ti/Te) and tPTEF/tE was significantly high in children with isolated laryngomalacia compared to controls. At six months of follow-up, TBFVL pattern 1 (normal) became the commonest pattern.

Conclusion: A particular type of airway anomaly may have a characteristic graphic pattern in TBFVL and TBFVL pattern may indicate improvement in airway anomalies in follow-up.

Keywords: *Fluttering pattern, Laryngomalacia, Tracheomalacia, Tidal Breathing Flow Volume Loop*

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INTRODUCTION

Airway anomalies are not uncommon in children below two years of age and usually present with noisy breathing (stridor and/or wheezing). The exact incidence is unknown; however, studies have revealed an estimated 1 in 2,100 children. For the diagnosis of airway anomalies, bronchoscopy is the gold standard [1]. Infant pulmonary function tests (IPFT) are being explored for their clinical utility, specifically in diagnosing airway abnormalities. A review by Godfrey et al concluded that IPFT has potential clinical use in diagnosing and monitoring airway malacias [2].

A study by Majid et al evaluated the role of tidal breathing flow volume loop (TBFVL) in patients with tracheomalacia [3]. However, there is a need to generate more data as not many studies determine the clinical role of IPFT in airway anomalies. We conducted this study to assess the IPFT in children with suspected airway anomalies and to correlate the TBFVL so obtained with bronchoscopy findings.

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METHODS

We performed a prospective cohort study in the Department of Pediatrics of a tertiary care institute in Delhi, India, from July 2018 to April 2020 in children aged upto 2 years with physician suspected airway anomalies. The study was approved by Institutional Ethics Committee. Written informed consent was taken from the parents/guardians.

We suspected airway anomalies in infants with either persistent (more than two weeks) inspiratory or biphasic (both inspiratory and expiratory) stridor or in those with persistent (more than two weeks) barking or brassy cough, unexplained wheezing that was not responding to inhaled steroids for 4-8 weeks despite proper compliance and technique, or, in those with choking while feeding without significant developmental delay. We excluded children with hypoxia (SpO2 < 92%), hemodynamic instability, nasofacial deformities, tracheostomy and pulmonary bleed. We recorded a detailed history, physical examination and baseline data of all enrolled children. All enrolled infants underwent IPFT and bronchoscopy. The two investigations were done within a week of each other.

The person performing the IPFT was not aware of bronchoscopy findings, if bronchoscopy was done earlier. IPFT was performed during sleep or light sedation using triclofos single oral dose (50 mg/kg). TBFVL was performed in the pulmonary function test laboratory with EXHALYZER-D equipment (Eco Medics, Duernten, Switzerland) having Spiroware-1 software. IPFT included TBFVL. IPFT parameters evaluated were tidal volume (TV), inspiratory time (Ti), expiratory time (Te), Ti/Te, respiratory rate, peak tidal inspiratory flow (PTIF), peak tidal expiratory flow (PTEF), PTEF/PTIF, time to PTIF, time to PTEF, time to peak tidal expiratory flow/total time to expiration (tPTEF/tE), and the ratio of mid-tidal expiratory flow to mid-tidal inspiratory flow (MTEF/MTIF). We used normative data for a similar number of age (±1 month), gender and birth weight-matched healthy infants from the birth cohort study database from our department for reference [4]. We categorized the IPFT curve into five patterns as shown in **Fig. 1**, modified from the study by Filippone et al [5].

IPFT were reported by three observers blindly, and in case of discrepancy, the final diagnosis was made by discussion. Bronchoscopy was performed as per unit protocol under conscious sedation. Three observers independently reported abnormalities and severity after seeing the saved bronchoscopy video. Patterns and parameters of IPFT were compared with findings of bronchoscopy.

Enrolled children were followed-up for upto six months and a repeat IPFT was conducted. Bronchoscopy was not repeated at six months follow-up. The primary outcome measure was a graphic pattern of TBFVL in children with laryngomalacia. Secondary outcome measures were bronchoscopic diagnosis of various airway anomalies, graphic patterns in children with airway anomalies other than laryngomalacia, measurement of TBFVL parameters and measurement of change in TBFVL graphic patterns and parameters at six months follow up. We did not perform any intervention other than supportive care in the study.

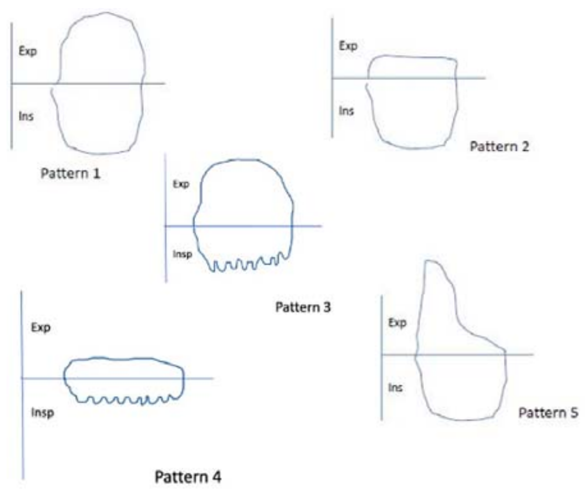

Fig. 1 Patterns of Infant Pulmonary Function Tests

The sample size was not calculated as ours was an exploratory study. We included all consecutive eligible children below 2 years of age during the study period.

Statistical analysis: The data was recorded in an Excel sheet, and statistical analyses were done using STATA software version 12. The pattern of IPFT loops and type of airway anomalies observed were presented using descriptive statistics. TBFVL parameters were compared among historical controls and those infants with various bronchoscopy airway anomalies using Student t test if data were normally distributed or Mann Whitney test if data had non-normal distribution. ANOVA test was used to compare differences between two or more means. Changes in TBFVL graphic patterns and parameters were analyzed after six months by paired t test.

RESULTS

A total of 88 children with suspected airway anomalies were screened. We included 53 infants for whom both bronchoscopy and IPFT were performed. The flow of patients is given in **Fig. 2**. The demographic and clinical characteristics of included participants are shown in **Table I**.

The median age of children was six months, ranging from 3 weeks to 20 months. Most were boys, and 92% were born at term gestation. The commonest symptom was noisy breathing in 44 (83%) children. The median age of appearance of noisy breathing was one month. Stridor was present in 24 (45%) children commonly noticed at the end of the 2nd week of life. Bronchoscopy was performed in 53 children; 28 (52.8%) had isolated laryngomalacia. The details of bronchoscopy findings are shown in **Table II**. The graphic patterns of TBFVL are shown in **Table III**. Pattern 3 (normal expiratory limb and fluttered inspiratory limb) was the most common pattern in children with isolated laryngomalacia. In 21 out of 28 isolated laryngomalacia cases, the graphic pattern was consistent with a fluttered inspiratory limb (pattern 3 plus pattern 4).

Forty per cent of children with bronchomalacia had an early expiratory peak with the concave expiratory limb. Tracheomalacia was present in 13 children (in seven associated with laryngomalacia and in six associated with laryngomalacia and bronchomalacia), and six out of these had flattened expiratory limb (three had pattern 2; three had pattern 4). One child with pharyngomalacia had a

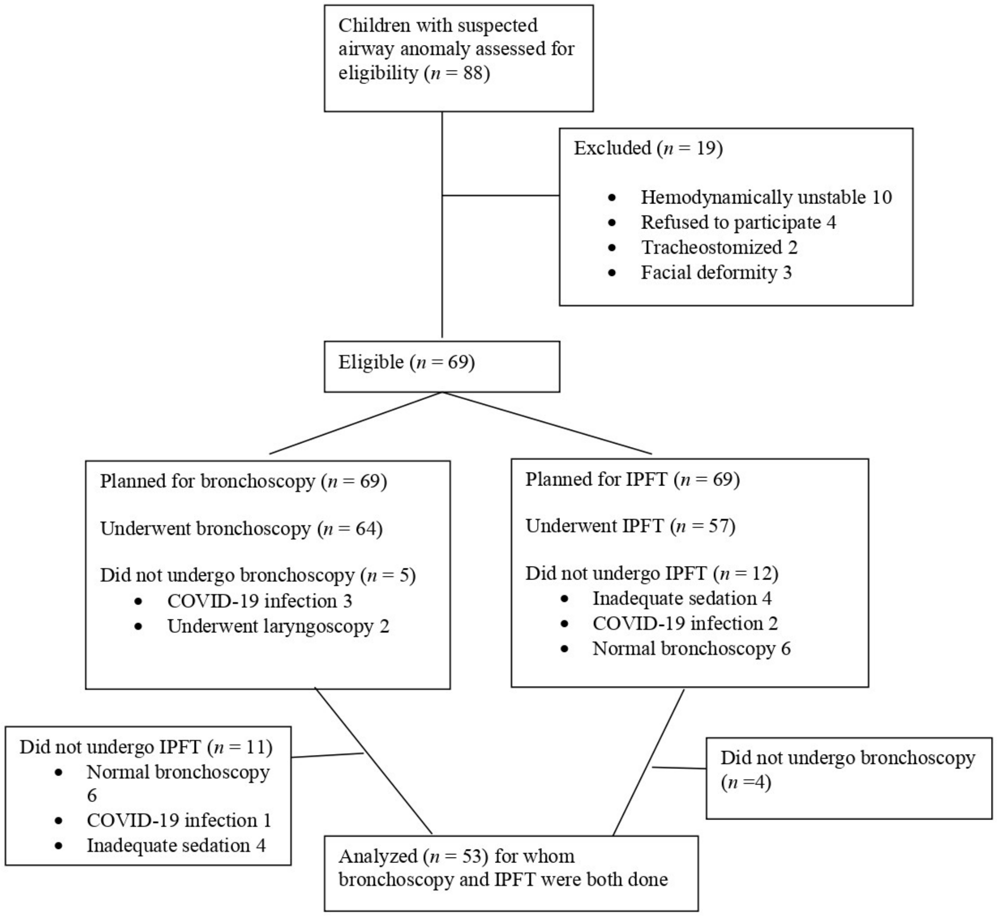

Fig.1 Flow of participants in the study

normal IPFT pattern (pattern 1). Out of four children with subglottic stenosis, three had a flattened expiratory limb. The representative patterns are shown in **Web Fig. 1**.

The TBFVL parameters in children with laryngomalacia and other airway anomalies compared to controls are shown in **Table IV.** There was a significantly high ratio of inspiration to expiration time in children with isolated laryngomalacia. The remaining TBFVL parameters were similar in children with isolated laryngomalacia and controls.

We could follow 14 children six months after diagnosis. The TBFVL Patterns 1, 2, 3, 4 and 5 were present in 3 (21.4%), 2 (14.3%), 4 (28.6%), 2 (14.3%), and 3 (21.4%) respectively at baseline. At six months follow up, TBFVL patterns 1, 2, 3, 4, and 5 were seen in 4 (28.6%), 2 (14.3%), 3 (21.4 %), 3 (21.4.3%), and 2 (14.3%) respectively. At baseline, pattern 3 was most common, followed by pattern 4. At six months of follow-up, pattern 1 (normal) was most common, followed by patterns 3 and 4. Out of these 14 patients, 4 had the same TBFVL pattern in follow up and TBFVL pattern had become normal in 2 patients and they also improved clinically.

Web Table I shows TBFVL parameters at baseline and after six months. There was no difference in TBFVL parameters except expiratory time, which significantly increased in follow-up.

DISCUSSION

In this study, we evaluated the IPFTs in 53 children with airway anomalies and corelated with bronchoscopy findings. Isolated laryngomalacia (n = 28) was the most common airway anomaly, followed by laryngo-tracheomalacia (n = 7), laryngotracheobronchomalacia (n = 6), and laryngomalacia with subglottic stenosis (n = 4). Among patients with isolated laryngomalacia, pattern 3 was most commonly observed followed by pattern 4.

In our study, isolated laryngomalacia was found in 28 (52.8%), and laryngomalacia was associated with other airway anomalies in 24 (45.3%) children, which is

Table I Demographic and Clinical Characteristics of the Study Population (*n* = 53)

Patient characteristics	*Value*
Age (mo)[a]	6 (3, 9)
Male Gender[b]	38 (71.7)
Delivered at term gestation[b]	49 (92.4)
Birth weight (kg)[a]	2.6 (1.7, 3.5)
Weight for age *z*-score at enrolment[a]	-2.82 (-3, -1.95)
Length for age *z*-score at enrolment[a]	-2.32 (-3.24, -1.46)
Clinical features at presentation[b]	
Noisy breathing	44 (83)
Stridor	24 (45.3)
Wheeze	7 (13.2)
Cough	21 (39.6)
Barking cough	8 (15.1)
Breathlessness	4 (7.55)
Feeding difficulty	22 (41.5)
Occasional choking while feeding	16 (30.2)
Recurrent lower respiratory tract infection	19 (35.8)
Examination at presentation[b]	
Inspiratory stridor at rest	9 (16.9)
Retrognathia	3 (5.6)
Pallor	3 (5.6)
Down facies	2 (3.8)
Pectus excavatum	1 (1.8)
High arch palate	1 (1.8)
Hemangioma face	1 (1.8)
Club foot	1 (1.8)
Respiratory system examination[b]	
Tachypnea	11 (20.7)
Chest retraction	7 (13.2)
Audible wheeze	2 (3.8)
Chest Auscultation	
Normal	36 (67.9)
Generalized rhonchi	9 (16.9)
Crepitations	3 (5.6)
Biphasic rhonchi	5 (9.4)

Values presented as [a]median (IQR), [b]n (%)

comparable with other studies [6,7]. Filippone et al studied TBFVL patterns in 113 children and reported that pattern 3 was always associated with laryngomalacia (100% sensitive) [5]. In our study, 21 children with isolated laryngomalacia had fluttered inspiratory limb; 13 had an only inspiratory flutter (pattern 3), and eight had associated expiratory flattening (pattern 4). Out of 24 cases of laryngomalacia 24 were associated with other

Table II Airway Anomalies Diagnosed by Bronchoscopy (*n* = 53)

Type of anomaly	*n (%)*
Isolated laryngomalacia	28 (52.8)
Laryngotracheomalcia	7 (13.2)
Laryngotracheobronchomalacia	6 (11.32)
Laryngomalacia and subglottic stenosis	4 (7.55)
Laryngomalacia and Bronchomalacia	3 (5.66)
Laryngomalacia and grade 1 laryngeal cleft	1 (1.89)
Pharyngomalacia	1 (1.89)
Laryngomalacia and pharyngomalacia	1 (1.89)
Laryngomalacia and vallecular cyst	1 (1.89)
Laryngomalacia and tracheal diverticulum/ blind pit	1 (1.89)

airway anomalies; 12 (50%) had inspiratory fluttering, 5 of these had only inspiratory fluttering (pattern 3), and the remaining 7 had inspiratory fluttering with expiratory flattening (pattern 4). The slight discrepancy in pattern 3 (fluttered inspiratory limb) for isolated laryngomalacia in our study may be explained by that we performed TBFVL in a few children after bronchoscopy on the same day. In our study, 18 children had obstruction between glottis and bifurcation of the trachea (7 had laryngotracheomalacia, 6 had laryngotracheobronchomalacia, 4 had laryngomalacia with subglottic stenosis, and 1 had laryngomalacia with tracheal diverticulum). Of these 18 children, nine (50%) had expiratory flattening (4 had isolated expiratory flattening, and 5 had expiratory flattening and inspiratory fluttering). In our study, the Ti/Te ratio was significantly higher in children with isolated laryngomalacia compared to controls. The possible explanation for these findings may be prolonged inspiratory time in cases of isolated laryngomalacia. We found significantly high PTEF/tE in laryngomalacia plus subglottic stenosis compared to controls that was different from a study by Filippone et al [5]. The possible explanation for this difference may be that study by Filippone et al [5] had a variety of diagnosis in pattern 2, and only four cases out of 46 had associated laryngomalacia, whereas in our study, all four patients in this category had laryngomalacia plus subglottic stenosis.

Filippone et al [5] performed follow-up TBFVL in 12 cases of airway obstruction between glottis and carina after surgical or medical intervention (five had subglottic hemangioma, one had postintubation tracheal stenosis, five had secondary tracheomalacia) and found improvement in the expiratory limb from pattern 2 (flattened expiratory limb) to pattern 1 (normal pattern) and increase in expiratory flow rates [8]. We followed up 14 children (mostly laryngomalacia) without any specific intervention. We found a significant improvement in the pattern of

Table III Tidal Breath Flow-Volume Loop Graphic Patterns in Children With Different Airway abnormalities Detected on Bronchoscopy

Bronchoscopy diagnosis	*Pattern 1*	*Pattern 2*	*Pattern 3*	*Pattern 4*	*Pattern 5*
Isolated laryngomalacia (*n* = 28)	3 (10.7)	3 (10.7)	13 (46.4)	8 (28.6)	1 (3.6)
Pharyngomalacia (*n* = 1)	1 (100)	-	-	-	-
Laryngomalacia and pharyngomalacia (*n* = 1)	-	-	1 (100)	-	-
Laryngotracheomalcia (*n* = 7)	-	1 (14.2)	2 (28.6)	2 (28.6)	2 (28.6)
Laryngotracheobronchomalacia (*n* = 6)	1 (16.6)	2 (33.3)	0	1 (16.6)	2 (33.3)
Laryngomalacia and subglottic stenosis (*n* = 4)	0	1 (25)	1 (25)	2 (50)	0
Laryngomalacia and Bronchomalacia (*n*= 3)	0	1 (33.3)	0	0	2 (66.7)
Laryngomalacia and others (*n* = 3)	-	-	1 (33.3)	2 (66.7)	0

Pattern1 Normal TBFVL graphic curve, Pattern 2 Normal inspiratory limb and flattened expiratory limb of TBFVL curve, Pattern 3 Normal expiratory limb and fluttered inspiratory limb of TBFVL curve, Pattern 4 Inspiratory limb fluttered and expiratory limb flattened, Pattern 5 Early expiratory peak with the concave expiratory limb

TBFVL towards normal pattern, though we could not find a difference in TBFVL parameters, likely due to a small number of follow up cases. Moore et al evaluated 21 children at a median (range) age of 9.4 (7.6 - 14.3) mo who were diagnosed with tracheobronchomalacia during infancy and reported persistence of symptoms and abnormal pulmonary functions [8].

Based on our study and reviewing the literature, it may be said that graphic patterns in TBFVL may be suggestive of airway obstruction at a particular site (larynx or below the larynx). Using TBFVL as initial screening test for airway anomalies may obviate the need for invasive bronchoscopy procedures in many infants with airway anomalies. Although, TBFVL pattern will usually suggest a site of obstruction, not a specific diagnosis. Airway anomalies frequently occur in combination, and TBFVL patterns may be combined. As seen in our study, these may be challenging to interpret, where about 50% of cases had combined airway anomalies. Although Pattern 3 on TBFVL may be almost diagnostic of laryngomalacia, other patterns may warrant the need for bronchoscopy as well. Thus, findings of TBFVL must be interpreted in context and history and physical examination findings.

Table IV Tidal Breathing Flow Volume Loop Parameters in Various Types of Airway Anomalies

TBFVL parameter	*LM (n=28)*	*LM + TM (n = 7)*	*LM + TM + BM (n = 6)*	*LM + SS (n = 4)*	*LM + Others[a] (n = 4)*	*Miscella-neous[b] (n = 4)*	*Controls (n = 53)*	*P value*
Tidal volume(mL)	43.7 (20.5)	35.8 (18.8)	38.2 (12.4)	34.7 (13.8)	53.0 (28.2)	62.2 (36.8)	33.7 (22.5)	0.700
Tidal volume (mL/kg)	8.0 (2.7)	7.10 (0.96)	8.48 (4.04)	8.33 (1.3)	7.18 (1.17)	8.13 (2.82)	7.65 (2.81)	0.440
Insp time (sec)	0.69 (0.21)	0.54 0.18)	0.53 (0.18)	0.52 (0.13)	0.75 (0.14)	0.66 (0.11)	0.60(0.14)	0.214
Exp time (sec)	0.77 (0.28)	0.6 (0.25)	0.59 (0.19)	0.78 (0.41)	1.09 (0.28)	0.97 (0.31)	0.76 (0.26)	0.723
Ti/Te	96.9 (31)	92.9 (31)	94.3 (13.7)	77.8 (17.8)	59.5 (43.9)	76.8 (30.5)	76.3 (21.2)	0.064[c]
Resp rate/min	44.7(14.6)	46.3(14.6)	57.9(16.3)	52.5(14.4)	33.2(5.3)	39.3(12.2)	50.2(10.4)	0.076
PTIF	0.10 (0.04)	0.09 (0.04)	0.12 (0.06)	0.11 (0.04)	0.18 (0.16)	0.15 (0.06)	0.08 (0.05)	0.089
PTEF	0.09 (0.03)	0.07 (0.04)	0.13 (0.03)	0.09 (0.05)	0.08 (0.03)	0.13 (0.06)	0.07 (0.04)	0.179
Time to PTIF	0.30 (0.13)	0.34(0.13)	0.25 (0.13)	0.34 (0.14)	0.35 (0.18)	0.36 (0.15)	0.30 (0.09)	0.794
Time to PTEF	0.19 (0.10)	0.16 (0.05)	0.19 (0.10)	0.32 (0.22)	0.15 (0.03)	0.17 (0.09)	0.21 (0.11)	0.941
tPTEF/t E	30.0 (14.3)	23.6 (14.3)	34.6 (14.8)	41.9 (15.5)	14.8 (6.1)	18.8 (8.3)	30.6 (13.3)	0.024
MTEF/MTIF	103.2 (42.6)	80.2 (42.6)	106.7 (38.8)	74.7 (22)	68.6 (22.7)	85.4 (42)	95.1 (16)	0.112

Values expressed as mean (SD). LM Laryngomalacia; TM Tracheomalacia; BM Bronchomalacia; SS Subglottic stenosis; MTEF Mid tidal expiratory flow; MTIF Mid tidal inspiratory flow; PTIF Peak tidal inspiratory flow; PTEF Peak tidal expiratory flow; tPTEF/tE Time to peak tidal expiratory flow/total time to expiration; TBFVL Tidal Breathing Flow Volume Loop. [a]Others (Vallecular cyst 1, Laryngeal cleft 1, Tracheal diverticulum 2), [b]Miscellaneous (Pharyngomalacia 1, Pharyngomalacia + LM 1, LM + bronchomalacia 1). [c]P value for comparison of Ti/Te for laryngomalacia versus controls is 0.005.

WHAT THIS STUDY ADDS?

- Where-ever available, IPFT based on TBFVL can be used as a screening tool to detect airway anomalies in infants.
- TBFVL pattern and parameters may suggest airway obstruction at a particular site (larynx or below the larynx).

Our study is one of the few studies that evaluated IPFT in children with airway anomalies with a reasonable number of participants. It is also possibly one of the few studies wherein children with airway anomalies were followed up with repeat IPFT. IPFT parameters were compared with a similar number of controls, matched with birth weight, sex and age. The IPFT was performed successfully in most children with mild sedation or during sleep. Reporting of IPFT patterns and bronchoscopy findings was done by three persons independently to decrease observer bias. Also, the reporting IPFT and bronchoscopy were done without knowing the results of other procedures.

Unfortunately, follow up of all participants could not be completed due to the COVID pandemic. Also, a uniform sequence of first doing IPFT and then doing bronchoscopy could not be done in all patients as there are fixed days for bronchoscopy in our institute. Controls were taken from a birth cohort, and we did not perform bronchoscopy on them (gold standard to diagnose airway anomaly). We could not do IPFT of children who had normal bronchoscopy.

We concluded that graphic patterns in TBFVL may suggest the site of airway obstruction. Where-ever the facility of TBFVL is available, it may be used as a screening test for airway anomalies, and invasive bronchoscopy procedures may be avoided for screening. Abnormal patterns observed in TBFVL may be confirmed with bronchoscopy as per the clinician’s judgement.

Contributors: AP: Conception of work, acquisition, analysis and interpretation of data, and drafting of the work. KRJ, RL, SKK, JS: Conception of work, interpretation of data, and revising of the work. All authors have approved the final version and are accountable for the accuracy of the work. KRJ will act as guarantor of the manuscript.

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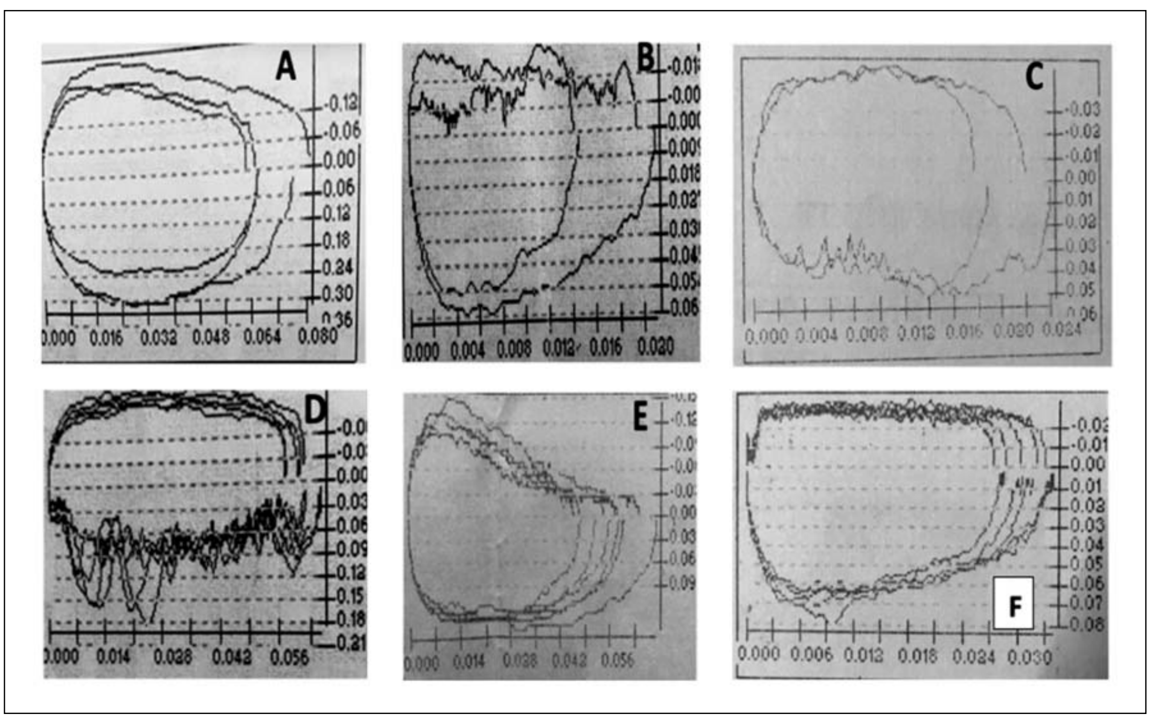
Web Table I Tidal Breathing Flow Volume Loop Parameters in Children With Airway Anomalies at Baseline and Follow up (*n* = 14)

TBFVL parameter	*Baseline*	*At six months of follow up*	*P value*
Tidal volume (mL)[a]	45 (30, 59.4)	55.5 (34,72)	0.187
Inspiratory time (s)[b]	0.62 (0.20)	0.68 (0.19)	0.236
Expiratory time (s)[b]	0.70 (0.24)	0.83 (0.29)	0.026
Ti/Te[b]	93.3 (21.1)	88.51 (20.57)	0.525
Respiratory rate (breath/min)[b]	45.6 (13.60)	44.6 (13.90)	0.688
PTIF (L/min)[a]	0.11 (0.061, 0.15)	0.13 (0.09, 0.17)	0.533
PTEF (L/min)[b]	0.11 (0.04)	0.12 (0.04)	0.135
Time to PTIF[b]	0.31 (0.11)	0.34 (0.11)	0.485
Time to PTEF[a]	0.16 (0.12, 0.19)	0.16 (0.14, 0.27)	0.593
tPTEF /tE[b]	26.2 (6.90)	27.2 (9.10)	0.734
MTEF/MTIF[b]	99.6 (30.40)	92.0 (22.30)	0.495

Values expressed as [a]median (IQR) or [b]mean (SD). MTEF Mid tidal expiratory flow, MTIF Mid tidal inspiratory flow, PTIF Peak tidal inspiratory flow, PTEF Peak tidal expiratory flow, TBFVL Tidal Breathing Flow Volume Loop, Te Expiratory time, tE total time to expiration, Ti Inspiratory time, tPTEF Time to peak tidal expiratory flow



Web Fig. 1 Representative images of each type of IPFT pattern and subglottic stenosis, A Pattern 1 Normal, B Pattern 2 Normal inspiratory limb and flattened expiratory limb; C Pattern 3 Normal expiratory limb and fluttered inspiratory limb, D Pattern 4 Inspiratory limb fluttered and expiratory limb flattened, E Pattern 5 Early expiratory peak with the concave expiratory limb, F Subglottic stenosis