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

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July 27, 2022

Abstract

Introduction: For the diagnosis of airway anomalies, bronchoscopy is the gold standard. Infant pulmonary function testing is an emerging modality to assess airways and its utility in diagnosis and monitoring is unexplored in clinical studies. **Objectives**: To evaluate infant Pulmonary Function Test [Tidal Breathing Flow Volume Loop (TBFVL)] in children with airway anomalies and to correlate with bronchoscopy findings. **Methods**: We performed a prospective cohort study from July 2018 to April 2020 in children from 0-2 years with physician suspected airway anomalies. We performed TBFVL (graphic pattern and parameters) and bronchoscopy in these children and correlated the results. The primary outcome measure was a graphic pattern of TBFVL in children with laryngomalacia. Secondary outcome measures were bronchoscopy diagnosis of various airway anomalies, graphic pattern 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 compared TBFVL parameters with controls without airway anomalies. **Results**: We enrolled 53 children with both Infant Pulmonary Function Tests and bronchoscopy data. Isolated laryngomalacia (28, 52.8%) was the most common airway anomaly, followed by laryngo-tracheomalacia (7, 13.2%), laryngo-tracheo-bronchomalacia (6, 11.3%), and laryngomalacia with subglottic stenosis (4, 7.5%). Among isolated laryngomalacia, pattern 3 (fluttering of inspiratory limb) was most common in TBFVL, followed by pattern 4 (fluttering of inspiratory limb and flattening of expiratory limb) in 13 (46.4) and 8 (28.6%) cases, respectively. There was no strikingly predominant pattern in other groups of bronchoscopy diagnoses. Among TBFVL parameters, the ratio of Ti/Te was significantly high in children with isolated laryngomalacia compared to controls. Compared to controls, the tPTEF/tE was significantly higher in laryngomalacia plus sub-glottic stenosis. At six months of follow-up, clinical symptoms improved significantly, TBFVL pattern 1 (normal) became the most common pattern, and expiratory time increased significantly among TBFVL parameters. **Conclusion**: A particular type of airway anomaly may have a characteristic graphic pattern in TBFVL. Further, the TBFVL pattern may indicate improvement in the follow-up either spontaneously or after an intervention.

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 (1). For the diagnosis of airway anomalies, bronchoscopy is the gold standard (2). 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. However, there is a need to generate more data as not many studies determine the clinical role of IPFT in airway anomalies (3). Very few studies have evaluated the role of TBFVL in patients with tracheomalacia (4). We did this study to assess infant Pulmonary Function Tests (TBFVL- Tidal Breathing Flow Volume Loop) in children with suspected airway anomalies and to correlate it with bronchoscopy findings.

Methods

We performed a prospective cohort study from July 2018 to April 2020 in children from 0-2 years with physician suspected airway anomalies. We suspected airway anomalies in the presence of either persistent (more than two weeks) inspiratory or biphasic (both inspiratory and expiratory) stridor or children with persistent (more than two weeks) barking or brassy cough or children with unexplained wheezing that is not responding to inhaled steroids for 4-8 weeks with proper compliance and technique or choking while feeding without significant developmental delay. We excluded children with hypoxia (SpO2 <92%), hemodynamic instability, naso-facial deformities, tracheostomy and pulmonary bleed. We recorded detailed history, physical examination and baseline data of all enrolled children. Then these children underwent IPFT and bronchoscopy. The two investigations were done within a week of each other. The person doing the IPFT was not aware of bronchoscopy findings if bronchoscopy was done earlier.

The IPFTs (TBFVL) were done during sleep or light sedation by trichlophos single dose of 50 mg/kg. TBFVL was performed in the pulmonary function test lab with EXHALYZER-D equipment (ECO MEDICS, Duernten, Switzerland) having Spiroware-1 software. Bronchoscopy was performed as per unit protocol under conscious sedation. Three observers (SKK, KRJ, AP) independently reported abnormalities and severity after seeing the saved bronchoscopy video. IPFT were also reported by three observers blindly, and in case of discrepancy, the final diagnosis was made by discussion.

Patterns and parameters of IPFT were compared with findings of bronchoscopy. We categorized the IPFT curve into the following five patterns, as shown and explained in Figure 1, modified from the study by Filippone et al. (5).

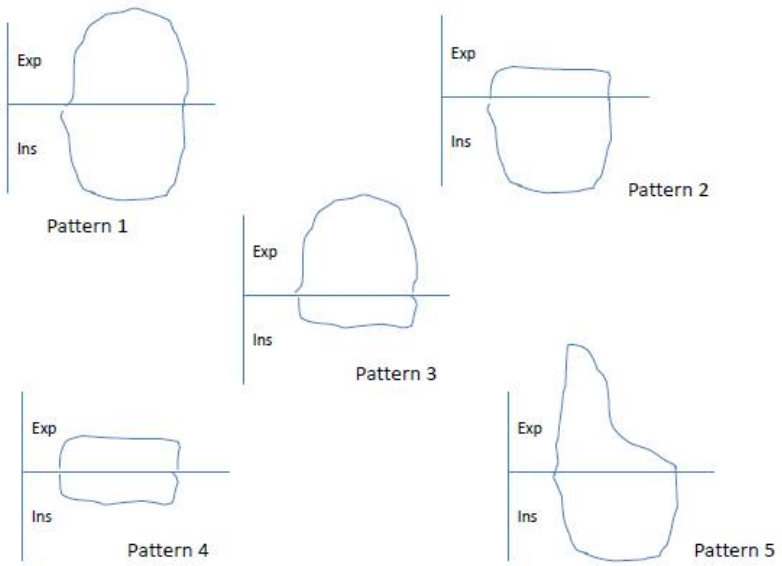

Figure1: Five Patterns of IPFT curve. Pattern1- Normal TBFVL graphic curve; Pattern 2- Normal inspiratory limb and FLATTENED expiratory limb of TBFVL curve; Pattern 3- Normal expiratory limb and FLUTTERED inspiratory limb of TBFVL curve; Pattern 4- Inspiratory limb FLUTTERED and expiratory limb FLATTENED; Pattern 5- Early expiratory peak with the concave expiratory limb.

IPFT parameters evaluated were: tidal volume, inspiratory time (Ti), expiratory time (Te), Ti/Te, respiratory rate, peak tidal inspiratory flow (PTIF), peak tidal expiratory flow (PTEF), the ratio of PTEF/PTIF, time to PTIF, time to PTEF, time to peak tidal expiratory flow/total time to expiration (t_PTEF /t_ E),

and the ratio of mid-tidal expiratory flow to mid-tidal inspiratory flow (MTEF/MTIF). For controls for this study, we extracted data for a similar number of age (±1 month), gender and birth weight-matched healthy controls from the birth cohort study database from another project of our department. (6)

Enrolled children were followed six months after enrolment. Clinical details were recorded, and a repeat IPFT was conducted. Bronchoscopy was not repeated at six months follow-up. For follow-up controls, IPFT of the same children matched earlier were taken after six months. The primary outcome measure was a graphic pattern of TBFVL in children with laryngomalacia. Secondary outcome measures were bronchoscopy diagnosis of various airway anomalies, graphic pattern 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.

The pattern of IPFT loops and type of airway anomalies were analyzed by simple frequency as a percentage. TBFVL parameters were compared among historical controls and various bronchoscopy airway anomalies. If data were symmetrically distributed, we applied a t-test. When there was asymmetrical distribution, we used the Mann-Whitney test. ANOVA 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. The data was recorded in an excel sheet, and statistical analyses were done using STATA software version 12. Ethical clearance was taken from the institutional ethical committee.

Result

A total of 88 children with suspected airway anomalies were screened. We included 53 for the final analysis who had both bronchoscopy and IPFT. The flow of patients is given in Figure 2.

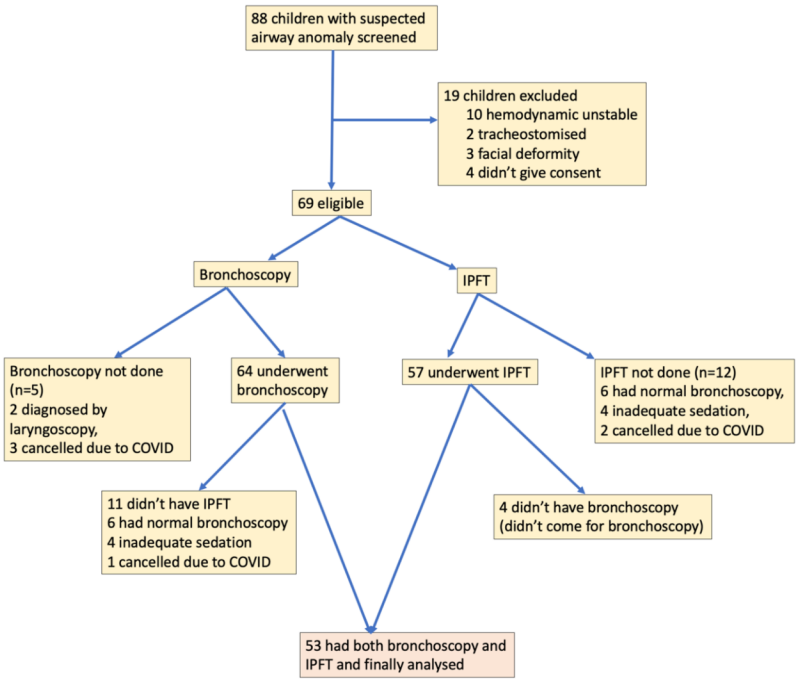

Figure 2: Flow of patients

The demographic and clinical characteristics of included children are shown in Table1.

The median age of children was six months, ranging from 3 weeks to 20 months. Most were boys, and 92% were term children. The commonest symptom was noisy breathing in 44 (83%) children. The median age of appearance of noisy breathing was within 1st month. Stridor was present in 24 (45%) children commonly noticed at the end of the 2nd week of life.

Table 1- Demographic and clinical characteristics of the study population (N=53)

S.no	Patient characteristics	Value
1	Age (months), median, (IQR)	6 (3, 9)
2	Gender, Male/Female	38/15
3	Term/ Preterm	49/4
4	Birth weight, kg, median, (IQR)	2.6 (1.7, 3.5)
5	Weight for age, Z-score at enrolment, median, (IQR)	-2.82 (-3, -1.95)
6	Length for age Z-score at enrolment, median, (IQR)	-2.32 (-3.24, -1.46)
7	**Clinical features at presentation**	**Number (% of total)**
	Symptoms Noisy breathing Stridor Wheeze Cough Barking cough Breathlessness Feeding difficulty Occasional choking while feeding Recurrent lower respiratory tract infection	44 (83) 24 (45.3) 7 (13.2) 21 (39.6) 8 (15.1) 4 (7.55) 22 (41.5) 16 (30.2) 19 (35.8)
8	**Examination General** Inspiratory stridor at rest Retrognathia Pallor Down facies Others (Pectus excavatum, high arch palate, hemangioma face, club foot,)	9 (16.9) 3 (5.6) 3 (5.6) 2 (3.8) 1 (1.8) each
	Respiratory Tachypnea Chest retraction Audible wheeze	11 (20.7) 7 (13.2) 2 (3.8)
	Chest Auscultation Normal Generalized rhonchi Crepitations Biphasic rhonchi	36 (67.9) 9 (16.9) 3 (5.6) 5 (9.4)

Bronchoscopic findings : Out of 53 children, 28 (52.8%) had isolated laryngomalacia. The details of bronchoscopy findings are shown in Table 2.

Table 2: Type of airway anomaly as diagnosed by bronchoscopy (N=53)

Sl. No.	Type of anomaly	Number (% of total)
	Isolated Laryngomalacia	28 (52.8)
	Laryngo-tracheomalcia	7 (13.2)
	Laryngo-tracheo-bronchomalacia	6 (11.32)
	Laryngomalacia + subglottic stenosis	4 (7.55)
	Laryngomalacia + Bronchomalacia	3 (5.66)
	Laryngomalacia + grade 1 laryngeal cleft	1 (1.89)

Sl. No.	Type of anomaly	Number (% of total)
	Pharyngomalacia	1 (1.89)
	Laryngomalacia and pharyngomalacia	1 (1.89)
	Laryngomalacia + vallecular cyst	1 (1.89)
	Laryngomalacia + tracheal diverticulum/ blind pit	1 (1.89)

The graphic patterns of TBFVL in cases of laryngomalacia are shown in Table 3. Pattern 3 (normal expiratory limb and fluttered inspiratory limb) was the most common (present in 46.4%) pattern in children with isolated laryngomalacia. In 21 (pattern three plus pattern 4) out of 28 isolated laryngomalacia cases, the graphic pattern was consistent with a fluttered inspiratory limb.

Table 3: Graphic patterns of TBFVL in children with laryngomalacia (N=28)

Type of pattern
Pattern 1
Pattern 2
Pattern 3
Pattern 4
Pattern 5
Pattern1- Normal TBFVL graphic curve; Pattern 2- Normal inspiratory limb and FLATTENED expiratory limb of TBFVL

The IPFT (TBFVL) patterns in bronchoscopy diagnosis other than laryngomalacia are shown in Table 4.

Table 4: TBFVL graphic pattern in children with bronchoscopy diagnosis other than laryngomalacia alone

Bronchoscopy diagnosis (number)
Pharyngomalacia (N= 1)
Laryngomalacia and pharyngomalacia (N= 1)
Laryngo-tracheomalcia (N= 7)
Laryngo-tracheo-bronchomalacia (N= 6)
Laryngomalacia + subglottic stenosis (N= 4)
Laryngomalacia + Bronchomalacia (N= 3)
Laryngomalacia + others (N= 3)
Total (25)
Pattern1- Normal TBFVL graphic curve; Pattern 2- Normal inspiratory limb and FLATTENED expiratory limb of TBFVL

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 (in three only flattened expiratory limb, the pattern two and in three associated with fluttered inspiratory limb, the pattern 4). One child with pharyngomalacia had a normal IPFT pattern (pattern 1). Children with subglottic stenosis had a flat expiratory limb in 3 out of 4. The representative patterns are shown in Figure 3.

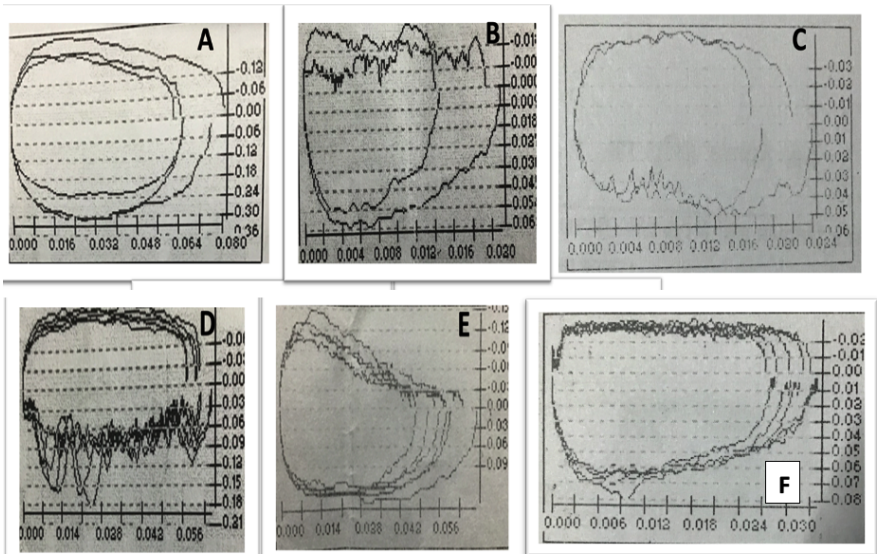

Figure 3: Representative images of each type of IPFT pattern and subglottic stenosis; A-Pattern1, Normal TBFVL graphic curve; B-Pattern 2, Normal inspiratory limb and FLATTENED expiratory limb of TBFVL curve; C-Pattern 3, Normal expiratory limb and FLUTTERED inspiratory limb of TBFVL curve; D-Pattern 4, Inspiratory limb FLUTTERED and expiratory limb FLATTENED; E-Pattern 5, Early expiratory peak with the concave expiratory limb; F. Representative TBFVL image of subglottic stenosis

TBFVL parameters in different bronchoscopy diagnoses-The TBFVL parameters in children with laryngomalacia compared to controls are shown in Supplementary Table S1. 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. The TBFVL parameters in various types of airway anomaly (other than laryngomalacia) and controls are shown in Supplementary Table S2.

Supplementary Table S1: TBFVL parameters in children with laryngomalacia compared to controls

TBFVL parameter (mean±SD)	**Isolated Laryngomalacia (N=28)**	**Controls (N=28)**	**P value**
Tidal volume (mL)	43.7±20.5	33.7±22.5	0.086
Tidal volume/kg (mL)	8.38±2.44	7.65±2.81	0.315
Insp time, Ti (sec)	0.691±0.210	0.603±0.146	0.077
Exp time, Ti (sec)	0.772±0.281	0.762±0.264	0.912
Ti/Te	96.9±31.0	76.3±21.2	**0.005**
Resp rate/ min	44.7±14.6	50.2±10.4	0.112
PTIF	0.103±0.042	0.081±0.052	0.087
PTEF	0.094±0.031	0.078±0.047	0.138
Time to PTIF	0.302±0.133	0.303±0.096	0.974
Time to PTEF	0.195±0.102	0.218±0.110	0.420
tPTEF /tE	30.0±14.3	30.6±13.3	0.869
MTEF/MTIF	103.2±42.6	95.1±16.0	0.350

TBFVL parameter (mean±SD)	**Isolated Laryngomalacia (N=28)**	**Controls (N=28)**	**P value**
PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E- Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF- Ratio of mid tidal expiratory flow to mid tidal inspiratory flow.	PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E- Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF- Ratio of mid tidal expiratory flow to mid tidal inspiratory flow.	PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E- Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF- Ratio of mid tidal expiratory flow to mid tidal inspiratory flow.	PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E- Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF- Ratio of mid tidal expiratory flow to mid tidal inspiratory flow.

Supplementary Table S2: TBFVL parameters in various types of airway anomaly and controls

TBFVL parameter (mean±SD)	LM (n=28)	LM+TM (n=7)	LM+TM+BM (n=6)	LM+SS (n=4)	LM+ others* (n=4)	Miscellaneous** (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	0.702
Tidal volume/kg (ml)	8.0±2.7	7.1 ± 0.96	8.48 ± 4.04	8.33 ± 1.3	7.18 ± 1.17	8.13 ± 2.82	7.65 ± 2.81	0.44
Insp time (sec)	0.691±0.210	0.541±0.184	0.537±0.189	0.520±0.130	0.753±0.149	0.662±0.112	0.603±0.146	0.214
Exp time (sec)	0.772±0.281	0.628±0.253	0.599±0.192	0.782±0.419	1.09±0.289	0.970±0.311	0.762±0.264	0.723
Ti/Te	96.9±31.0	92.9±31.0	94.3±13.7	77.8±17.8	59.5±43.9	76.8±30.5	76.3±21.2	0.064
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	0.103±0.042	0.093±0.042	0.129±0.062	0.111±0.040	0.182±0.165	0.149±0.060	0.081±0.052	0.089
PTEF	0.094±0.031	0.077±0.040	0.133±0.032	0.093±0.051	0.084±0.030	0.136±0.064	0.078±0.047	0.179
Time to PTIF	0.302±0.133	0.344±0.135	0.258±0.136	0.341±0.143	0.355±0.186	0.369±0.151	0.303±0.096	0.794
Time to PTEF	0.195±0.102	0.169±0.055	0.194±0.105	0.328±0.226	0.156±0.031	0.173±0.098	0.218±0.110	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	**0.0247**
MTEF/MTIF	103.2±42.6	80.2±42.6	106.7±38.8	74.7±22.0	68.6±22.7	85.4±42.0	95.1±16.0	0.112

TBFVL parameter (mean±SD)	LM (n=28)	LM+TM (n=7)	LM+TM+BM (n=6)	LM+SS (n=4)	LM+ others* (n=4)	Miscellaneous** (n=4)	Controls (n=53)	P value
LM-Laryngomalacia, TM-tracheomalacia, BM-bronchomalacia, SS-Subglottic stenosis, *others-vallecular cyst (1), laryngeal cleft (1), tracheal diverticulum (2), **Miscellaneous-pharyngomalacia (1), pharyngomalacia+LM (1), LM+bronchomalacia(1) PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E-Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF-Ratio of mid tidal expiratory flow to mid tidal	LM-Laryngomalacia, TM-tracheomalacia, BM-bronchomalacia, SS-Subglottic stenosis, *others-vallecular cyst (1), laryngeal cleft (1), tracheal diverticulum (2), **Miscellaneous-pharyngomalacia (1), pharyngomalacia+LM (1), LM+bronchomalacia(1) PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E-Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF-Ratio of mid tidal expiratory flow to mid tidal	LM-Laryngomalacia, TM-tracheomalacia, BM-bronchomalacia, SS-Subglottic stenosis, *others-vallecular cyst (1), laryngeal cleft (1), tracheal diverticulum (2), **Miscellaneous-pharyngomalacia (1), pharyngomalacia+LM (1), LM+bronchomalacia(1) PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E-Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF-Ratio of mid tidal expiratory flow to mid tidal	LM-Laryngomalacia, TM-tracheomalacia, BM-bronchomalacia, SS-Subglottic stenosis, *others-vallecular cyst (1), laryngeal cleft (1), tracheal diverticulum (2), **Miscellaneous-pharyngomalacia (1), pharyngomalacia+LM (1), LM+bronchomalacia(1) PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E-Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF-Ratio of mid tidal expiratory flow to mid tidal	LM-Laryngomalacia, TM-tracheomalacia, BM-bronchomalacia, SS-Subglottic stenosis, *others-vallecular cyst (1), laryngeal cleft (1), tracheal diverticulum (2), **Miscellaneous-pharyngomalacia (1), pharyngomalacia+LM (1), LM+bronchomalacia(1) PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E-Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF-Ratio of mid tidal expiratory flow to mid tidal	LM-Laryngomalacia, TM-tracheomalacia, BM-bronchomalacia, SS-Subglottic stenosis, *others-vallecular cyst (1), laryngeal cleft (1), tracheal diverticulum (2), **Miscellaneous-pharyngomalacia (1), pharyngomalacia+LM (1), LM+bronchomalacia(1) PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E-Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF-Ratio of mid tidal expiratory flow to mid tidal	LM-Laryngomalacia, TM-tracheomalacia, BM-bronchomalacia, SS-Subglottic stenosis, *others-vallecular cyst (1), laryngeal cleft (1), tracheal diverticulum (2), **Miscellaneous-pharyngomalacia (1), pharyngomalacia+LM (1), LM+bronchomalacia(1) PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E-Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF-Ratio of mid tidal expiratory flow to mid tidal	LM-Laryngomalacia, TM-tracheomalacia, BM-bronchomalacia, SS-Subglottic stenosis, *others-vallecular cyst (1), laryngeal cleft (1), tracheal diverticulum (2), **Miscellaneous-pharyngomalacia (1), pharyngomalacia+LM (1), LM+bronchomalacia(1) PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E-Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF-Ratio of mid tidal expiratory flow to mid tidal	LM-Laryngomalacia, TM-tracheomalacia, BM-bronchomalacia, SS-Subglottic stenosis, *others-vallecular cyst (1), laryngeal cleft (1), tracheal diverticulum (2), **Miscellaneous-pharyngomalacia (1), pharyngomalacia+LM (1), LM+bronchomalacia(1) PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E-Time to peak tidal expiratory flow/total time to expiration, MTEF/MTIF-Ratio of mid tidal expiratory flow to mid tidal

TBFVL parameter (mean±SD)	LM (n=28)	LM+TM (n=7)	LM+TM+BM (n=6)	LM+SS (n=4)	LM+ others* (n=4)	Miscellaneous** (n=4)	Controls (n=53)	P value

Change in TBFVL patterns at six months follow-up: We could follow 14 children six months after diagnosis as IPFT services were closed due to the COVID pandemic. The TBFVL patterns after six months in these 14 children are shown in Table 5. 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. However, there was no significant difference in the pattern of IPFT in follow-up overall; it may be because of a small number of children.

Table 5: IPFT graphic parameters in TBFVL in children with Airway anomalies at baseline and after six months of follow-up (N=14)

TBFVL parameter	**Baseline N (%)**	**At six months of follow up N (%)**	**P-value**
Graphic pattern, n (%) Pattern 1 Pattern 2 Pattern 3 Pattern 4 Pattern 5	3 (21.4) 2 (14.3) 4 (28.6) 2 (14.3) 3 (21.4)	4 (28.57) 2 (14.29) 3 (21.43) 3 (21.43) 2 (14.29)	0.378
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	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	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	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

Change in TBFVL parameters at six months follow-up: Supplementary Table S3 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.

Supplementary Table S3: TBFVL parameters in children with Airway anomalies at baseline and after six months of follow-up (N=14)

TBFVL parameter

TBFVL parameter
Tidal volume, mLmedian (IQR)
Inspiratory time (Ti), sec, mean (SD)
Expiratory time (Te), sec, mean (SD)
Ti/Te, mean (SD)
Respiratory rate, /min, mean (SD)
PTIF, L/min, median (IQR)
PTEF, L/min, mean (SD)
Time to PTIF, mean (SD)
Time to PTEF, median (IQR)
tPTEF /t E, mean (SD)
MTEF/MTIF, mean (SD)
PTIF-Peak tidal inspiratory flow, PTEF-Peak tidal expiratory flow, tPTEF /t E- Time to peak tidal expiratory flow/total t

Discussion

In this study, we evaluated the Infant Pulmonary Function Tests in 53 children with airway anomalies and co-related with bronchoscopy findings. The isolated laryngomalacia (28, 52.8%) was the most common airway anomaly, followed by laryngo-tracheomalacia (7, 13.2%), laryngo-tracheo-bronchomalacia (6, 11.3%), and laryngomalacia with subglottic stenosis (4, 7.5%). Among isolated laryngomalacia, pattern 3 (fluttering of inspiratory limb) was most common in TBFVL, followed by pattern 4 (fluttering of inspiratory limb and flattening of expiratory limb) in 13 (46.4) and 8 (28.6%) cases, respectively.

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 comparable with other studies (7)(8). Filippone et al. used TBFVL as the first test to evaluate 113 children to predict the possible airway anomaly based on TBFVL patterns (5). They reported that pattern 3 (fluttering of inspiratory limb) was always associated with laryngomalacia (100% sensitive). In our study, 21 (75%) children with isolated laryngomalacia had pattern 3; the fluttered inspiratory limb (13 had an only inspiratory flutter, and eight had associated expiratory flattening). Out of 24 cases of laryngomalacia had associated with other airway anomalies, 12 (50%) had inspiratory fluttering, 5 had only inspiratory fluttering (pattern 3), and 7 had inspiratory fluttering with expiratory flattening. The slight discrepancy in pattern 3 (fluttered inspiratory limb) for isolated laryngomalacia in our study may be explained by the 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 laryngo-tracheo-bronchomalacia, 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. In contrast, in a study by Filippone et al., we found significantly high PTEF/tE in laryngomalacia plus sub-glottic stenosis compared to controls. The possible explanation may be that they had a variety of diagnoses in pattern 2, and only four cases had associated laryngomalacia out of 46. In contrast, all four patients in this category had laryngomalacia plus subglottic stenosis.

Filippone et al. performed follow-up TBFVL in 12 cases of airway obstruction between glottis and carina after surgical or medical intervention (five had sub-glottic 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 (9). We had 14 children (mostly laryngomalacia) follow-up without any specific intervention. We found significant

improvement in the pattern of 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) who were diagnosed with tracheobronchomalacia during infancy. They found that symptoms and abnormal function tests persisted for a long time, and there was no evidence of reactive airway disease (10).

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) and may also suggest an associated component of reactive airway disease. Similarly, this non-invasive TBFVL pattern may indicate improvement in the follow-up spontaneously and after an intervention. Therefore, if the facility of TBFVL is available, it may be used as a screening test for airway anomalies, and invasive bronchoscopy procedures may be avoided in many infants with airway anomalies. But, it should be remembered that the TBFVL pattern will usually suggest a site of obstruction, not a specific diagnosis. For example, pattern 2 (flattening of expiratory limb) suggests an obstruction between glottis and carina. The specific lesion may be sub-glottic stenosis (a haemangioma or post-extubation) or primary/secondary tracheomalacia. Similarly, pattern 3 (fluttering of inspiratory limb) may suggest obstruction at the glottic level like laryngomalacia or laryngeal papilloma. Finally, the airway anomaly frequently occurs in combination, and TBFVL patterns may be combined. As seen in our study, they may be challenging to interpret, where about 50 % of cases had combined airway anomalies. Thus, findings of TBFVL must be interpreted in context and history and physical examination findings. If TBFVL had pattern 3 (fluttering of inspiratory limb) and history and examination are compatible with laryngomalacia, the bronchoscopy can be avoided. Suppose TBFVL had pattern 2 (flattening of expiratory limb). In that case, bronchoscopy should be considered as it suggests an obstruction between glottis and carina, and various airway anomalies may cause this pattern, as mentioned above. Further, TBFVL may help to identify airway anomalies in children with recurrent wheezing who respond poorly to asthma therapy.

Strengths

It is one of the few studies that evaluated IPFT in children with airway anomalies with a reasonable number of participants. It is possibly the first study in which follow-up IPFT was done in airway anomalies patients. 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, spontaneous sleep or when the child is quietly watching videos on a mobile. Reporting of IPFT patterns and bronchoscopy findings was done by three persons independently.

Limitations

Follow-up of all participants could not be completed due to the COVID pandemic. 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 to avoid discomfort to the patient (additional hospital visit). However, the reporting IPFT and bronchoscopy were done without knowing the results of other procedures. Controls were taken from a birth cohort, and we didn't perform bronchoscopy on them (gold standard to diagnose airway anomaly). We could not do IPFT of children who had normal bronchoscopy.

Conclusion

Graphic patterns in TBFVL may suggest airway obstruction at a particular site (larynx or below the larynx and may also suggest an associated component of reactive airway disease). TBFVL pattern may also indicate improvement in the follow-up either spontaneously or after an intervention. Therefore, if the facility of TBFVL is available, it may be used as a screening test for airway anomalies, and invasive bronchoscopy procedures may be avoided in many infants with airway anomalies. However, the TBFVL pattern usually suggests a site of obstruction but not a specific diagnosis.

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