Clinical Investigations

Respiration

Respiration 2021;100:11–18
DOI: 10.1159/000511694

Received: June 20, 2020
Accepted: September 18, 2020
Published online: January 7, 2021

Peak In- and Expiratory Flow Revisited: Reliability and Reference Values in Adults

Shane Hanon Eef Vanderhelst Walter Vincken Daniel Schuermans Sylvia Verbanck

Respiratory Division, University Hospital UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium

Keywords
Peak expiratory flow · Peak inspiratory flow · Reference equations

Abstract
Background: While peak in- and expiratory flow rates offer valuable information for diagnosis and monitoring in respiratory disease, these indices are usually considered too variable to be routinely used for quantification in clinical practice. ***Objectives:*** The aim of the study was to obtain reproducible measurements of maximal inspiratory flow rates and to construct reference equations for peak in- and expiratory flows (PIF and PEF). ***Method:*** With coaching for maximal effort, 187 healthy Caucasian subjects (20–80 years) performed at least 3 combined forced inspiratory and expiratory manoeuvres, until at least 2 peak inspiratory flow measurements were within 10% of each other. The effect on PIF preceded by a slow expiration instead of a forced expiration and PIF repeatability over 3 different days was also investigated in subgroups. Reference values and limits of normal for PIF, mid-inspiratory flow, and PEF were obtained according to the Lambda-Mu-Sigma statistical method. ***Results:*** A valid PIF could be obtained within 3.3 ± 0.6(SD) attempts, resulting in an overall within-test PIF variability of 4.6 ± 3.2(SD)%. A slow instead of a forced expiration prior to forced inspiration resulted in a significant ($p < 0.001$) but small PIF increase (2.5% on average). Intraclass correlation coefficient for between-day PIF was 0.981 (95% CI: 0.960–0.992). Over the entire age range, inter-subject PIF variability was smaller than in previous reports, and PIF could be predicted based on its determinants gender, age, and height ($r^2 = 0.53$). ***Conclusions:*** When adhering to similar criteria for the measurement of effort-dependent portions of inspiratory and expiratory flow-volume curves, performed according to current ATS/ERS standards, it is possible to obtain reproducible PIF and PEF values for use in routine clinical practice.

Introduction

The maximal flow-volume loop, consisting of a forced expiration followed by a forced inspiration, is a widely used lung function test, yielding several informative spirometric indices for which global reference equations exist [1]. The forced expiration is the mainstay for diagnosing chronic obstructive lung disease [2, 3] and quality standards for its measurement have been well established and updated, including a very recent standardization

karger@karger.com
www.karger.com/res

Shane Hanon
University Hospital UZ Brussel, Respiratory Division
Laarbeeklaan 101
BE–1090 Brussels (Belgium)
shane.hanon@uzbrussel.be

document [4–6]. Besides the most commonly used spirometric indices, peak expiratory flow (PEF) provides additional clinical information about intrathoracic airway obstruction or expiratory muscle strength. PEF is also being used as an outcome measure in asthma trials, as a home monitoring tool for severe asthma patients, and PEF variability has been suggested as a predictor of asthma worsening [7–9]. PEF has also been used to detect and discriminate intra- from extrathoracic upper airway obstruction [10–12]. Finally, PEF is recognized as a tool for nonspecific assessment of respiratory muscle weakness in neuromuscular disease [13].

The latest ATS/ERS spirometry update also emphasizes the role of the forced inspiration as an integral part of the spirometric manoeuvre [6]. In the past, the clinical use of the inspiratory flow-volume curve consisted mostly of a visual inspection of its flattening, to suggest upper airway obstruction [10, 14, 15]. Attempts towards automated indices based on peak or mid-inspiratory flow (PIF and FIF_{50}) resulted in poor sensitivity for detection of upper airway obstruction [12]. PIF has been used as an indicator of upper airway calibre changes after therapeutic interventions in the ear-nose-throat or neck regions [16, 17]. A low PIF or FIF_{50} can also signal inspiratory muscle weakness [18], prompting an additional measurement of maximal static inspiratory pressures at the mouth. If it were possible to obtain a good quality PIF or FIF_{50} during a screening spirometry, values below the LLN would provide an easily available first clue towards respiratory muscle weakness of various origins [19]. Finally, PIF is increasingly being recognised as a crucial determinant of effective inhaled drug delivery using dry powder inhaler devices [20, 21]. In elderly healthy subjects and COPD patients, spirometric PIF has even been identified as an independent predictor for the inspiratory flow that can be achieved over a resistance [22].

Despite the potential range of clinical applications for PEF and PIF, it is common perception that these flow rates are poorly reproducible and highly variable because of their effort-dependency, and hence are not included in common reference values such as Global Lung Function Initiative (GLI) [1]. We hypothesized that if we would apply the quality/acceptability criteria of the PEF measurement to the forced inspiratory manoeuvre, reliable PIF (and FIF_{50}) values can be obtained, which are also reproducible. We also assessed whether a slow instead of a forced expiratory manoeuvre preceding forced inspiration significantly affects PIF, and we provide reference equations for PEF, PIF, and FIF_{50} in Caucasian adults.

Table 1. Characteristics of the study population

	Male n = 95		Female n = 92	
	mean	SD	mean	SD
Age, years	49	18	51	17
Height, cm	178	7	165	6
BMI, kg/m^2	25	3	24	4
FVC				
L	5.2	0.9	3.7	0.7
%pred*	105	12	106	13
z-score*	0.3	0.9	0.4	0.9
FEV_1				
L	4.1	0.8	3.0	0.6
%pred*	105	12	105	12
z-score*	0.3	0.9	0.4	0.9
FEV_1/FVC	0.79	0.05	0.80	0.05
z-score*	0.0	0.8	−0.2	0.6
PIF, L/s	7.4	1.5	5.1	1.0
PEF, L/s	9.9	1.6	7.0	1.2
FIF_{50}, L/s	7.0	1.6	4.8	1.1

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PIF, peak inspiratory flow; FIF_{50}, forced inspiratory flow at 50% vital capacity; PEF, peak expiratory flow. * According to GLI, 2012 [1].

Materials and Methods

Subjects

Between January 2018 and July 2019, healthy non-smoking subjects between 20 and 80 years of age were recruited until at least 15 subjects per decade and sex were included in the study; this number was based on the recommended number of subjects per decade over the age range 2.5–95 years [23]. The local UZ Brussel Ethics Committee granted approval for this study (B.U.N. 143201525127), and written informed consent was obtained from all participants. Subjects were required to have a BMI <35 kg·m^2 and were defined as healthy through clinical screening, with no medical history of respiratory disease. Subjects with a medical history of major cardiovascular or neurological disease were excluded, as were patients having undergone neck or thoracic surgery.

Spirometry

All flow-volume loops were performed (MasterScreen PFT, SentrySuite 2.19, Mettawa, IL, USA) in accordance with the ERS/ATS quality standards for spirometry [4, 5]. Each forced expiration was followed by a forced inspiration. The equipment was set to automatically check whether the trials were acceptable according to the ATS/ERS 2005 criteria in regards to the expiratory flow-volume limb [5]. Acceptability of individual trials was based on the following criteria: (a) expiration must be at least 6 s, (b) an end-expiratory plateau must be present, that is, the measured volume must not exceed 25 mL during the last second, (c) back-extrapolated volume <5% of forced vital capacity (FVC) or 150 mL. In ad-

Table 2. Coefficients for L, M, and S to obtain predicted, ULN, and LLN values for PIF, FIF_{50}, and PEF, respectively

	r^2	*M* coefficients		Age	Age²	Intercept	*S* coefficients		Age²	Intercept	L coefficient
		sex	height				height	age			intercept
PIF, L/s	0.53	−1.560	0.0509	−0.0079	−0.000083	−1.07	−0.00013	−0.0055	0.000090	−1.63	0.809
FIF_{50}, L/s	0.49	−1.435	0.0554	−0.0138	−0.000014	−2.09	−0.00410	0.0010	0.000028	−0.98	1.184
PEF, L/s	0.62	−2.118	0.0648	0.0463	−0.000632	−2.14	−0.00433	−0.0101	0.000075	−0.85	1.012

PIF, peak inspiratory flow; FIF_{50}, forced inspiratory flow at 50% vital capacity; PEF, peak expiratory flow.

dition, we verified that all flow-volume loops fulfilled the criterion that forced inspiratory vital capacity and forced expiratory vital capacity differ by less than 5% FVC; in the meantime, this is part of the acceptability and usability criteria for FEV_1 and FVC in the ATS/ERS 2019 guidelines, as an indicator of a duly completed spirometric manoeuvre even when only expiratory spirometric indices are considered [6]. Finally, the test sequence was only stopped after obtaining at least 3 complete, acceptable flow-volume loops and provided the second highest peak inspiratory flow was within 10% of the highest peak inspiratory flow, or when a maximum of 8 consecutive manoeuvres had been performed.

In order to assess between-day reproducibility of PIF the testing procedure was repeated on 3 different days in a relatively young subgroup, thereby avoiding cumbersome transfers to the hospital for the older age groups. Another subgroup of subjects (aiming for 3 out of 4 subjects evenly distributed across age groups and sex) were asked to also perform the inspiratory flow-volume curve after a slow expiration instead of a forced expiration.

Selection of Lung Function Parameters and Reference Equations

For each subject, the reported PEF was defined as the highest peak expiratory flow from all acceptable forced expirations according to the ERS/ATS2005 criteria. The reported PIF was also defined as the highest peak inspiratory flow of all acceptable forced inspirations, and the reported FIF_{50} was selected from the same inspiration as the reported PIF. In case of a slow expiration preceding forced inspiration, the resulting the highest peak inspiratory flow was reported as PIF_{slow}. For the regression equations, we used the procedure previously described in Verbanck et al. [24]. Briefly, the GAMLSS package (version 4.3–4) in R (version 2.15.2; R Foundation, Vienna, Austria) was used to obtain an Lambda-Mu-Sigma model fit that allows the median and spread of the distribution to vary with sex, height and age or age squared, guided by the Schwarz Bayesian Criterion. The obtained coefficient for M is the predicted value, whereas S and L serve to compute LLN and ULN (5th and 95th percentile) as $M \times (1–1.645 \times L \times S)(1/L)$ and $M \times (1 + 1.645 \times L \times S)(1/L)$. As in our previous study of reference values for standard lung function and ventilation distribution indices [24], no splines were included, facilitating computation based on the coefficients provided here. A practical worked out example can be found in the online supplement (for all online suppl. material, see www.karger.com/doi/10.1159/000511694).

Between-days reproducibility was assessed using repeated measures ANOVA and Intraclass correlation (Medcalc 17.9.7, Mariakerke, Belgium). PIF measured after a slow expiration (PIF_{slow}) as compared to PIF measured after a forced expiration was assessed with the paired t test. The normal distribution of residuals was tested using the χ^2 test. In all the above analyses, statistical significance was accepted at $p < 0.05$.

Results

Recruitment of 15 subjects per decade and per sex resulted in 187 subjects who completed a valid set of measurements for PIF selection; their characteristics are shown in Table 1, including also z-scores for FEV_1, FVC, and FEV_1/FVC according to GLI [1]. An average number of 3.3 trials per subject (3.3 ± 0.6 [SD]) was necessary to obtain a valid set of measurements for PIF selection; only 1 subject (67 years) required 6 trials, and 7 subjects (ranging 50–75 years) needed 5 trials. For the group as a whole, the actual difference (in absolute value) between the highest peak inspiratory flow (i.e., reported PIF) and the second best 1 was 0.29 ± 0.23(SD)L/s on average, which corresponded to 4.6 ± 3.2(SD)% of PIF. When using those same spirometric manoeuvres to select the 2 highest peak expiratory flow values, the difference between the highest peak expiratory flow (i.e., reported PEF) and the second best 1 was on average 0.39 ± 0.41(SD)L/s, corresponding to 4.6 ± 4.7(SD)% of PEF.

Reference equations were calculated for PIF, FIF_{50}, and PEF, resulting in coefficients for sex, height, age and age^2, which can be readily used to obtain L, M, and S, respectively (Table 2). A worked out example to obtain predicted values and z-scores for PIF is shown in the Online Supplement. Scatterplots of individual PIF and PEF values (Fig. 1) and FIF_{50} (Fig. 2) for female and male subjects and the predicted value and limits of normal for a male and female of average height are also shown. As per definition, FIF_{50} is lower than PIF, but Figure 2 shows that the differences are small and FIF_{50} has a slightly greater variability at any given age. We compared our reference equations for PIF or PEF to those that were previously pub-

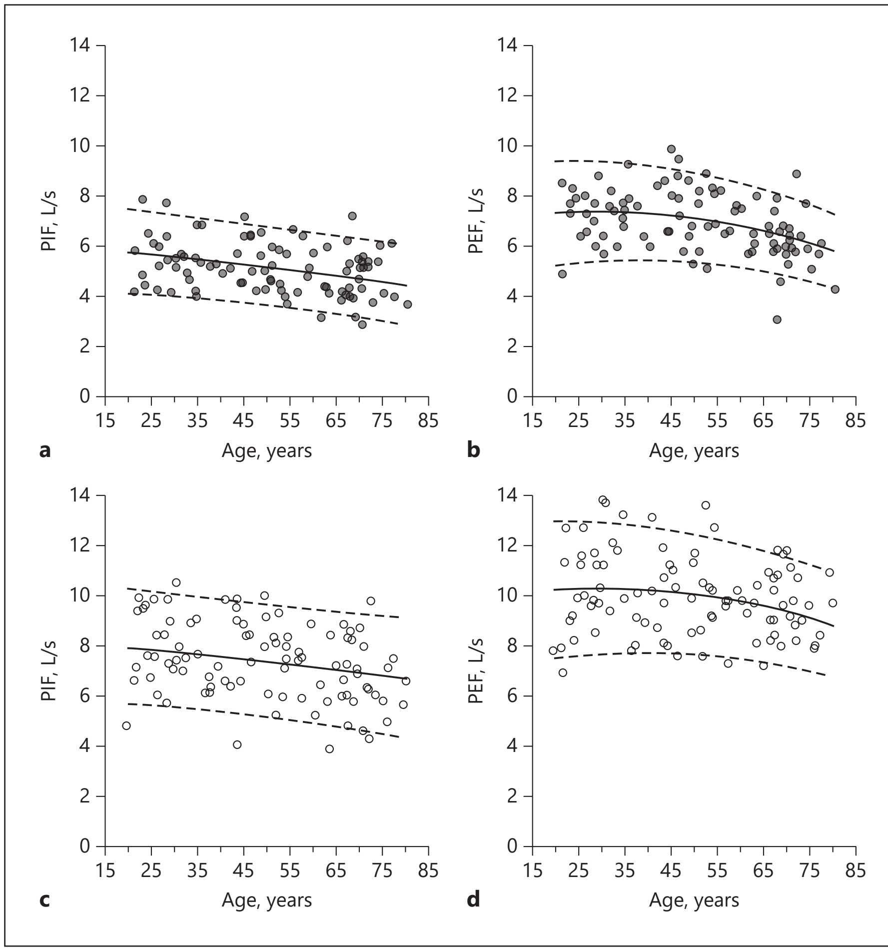

Fig. 1. Scatterplot of individual PIF and PEF values for female (**a**, **b**) and male (**c**, **d**) subjects; all drawn to the same scale. Also shown are predicted median (solid lines) and limits of normal (dashed lines) for an average male or female height at each given age. PIF, peak inspiratory flow; PEF, peak expiratory flow.

lished in a graphic and colour-coded representation of predicted and lower limits of normal in the Online Supplement (online suppl. Fig. 1, 2). Finally, for PEF, we also verified agreement with data previously obtained on 252 normal subjects with a different device (Vyaire Medical, Mettawa, IL, USA) [24]. Using the coefficients from Table 2, on this older PEF dataset, we obtained a z-score of −0.2 ± 1.1(SD).

Table 3 shows reproducibility of peak inspiratory flow and its dependence on whether the prior expiratory manoeuvre was slow (PIF_{slow}) or not (PIF). For PIF assessments on 3 different days, with standard-deviation on time-of-day across the 3 visits averaging 1.7 h, there was no significant PIF difference between days (repeated measures ANOVA; $p > 0.1$). Also, the number of trials to obtain PIF on any given visit was similar between visits ($p > 0.1$). Expressing PIF repeatability as an intraclass correlation coefficient, this was 0.981 (95% CI: 0.960–0.992); a Bland-Altman type representation is in online suppl. Figure 3. The impact on PIF of a slow expiration (PIF_{slow}) was significant ($p < 0.001$), but the average PIF increase due to the slow manoeuvre was only 2.5%; a Bland-Altman type representation is in online suppl. Figure 4. Finally, the average number of trials to obtain a valid set of spirometric measurements for PIF selection was comparable for PIF and PIF_{slow}.

Discussion

We have shown here that reliable PIF (and FIF_{50}) values can be obtained that are also reproducible. In particular, the criterion that the second highest peak flow should be within 10% of the highest one could be readily applied to the inspiratory flow-volume curves, to obtain reliable PIF data within 3–4 trials. Moreover, this number of trials for acceptable PIF was sufficient to also obtain acceptable PEF. This implies that, provided the inspiratory curve is

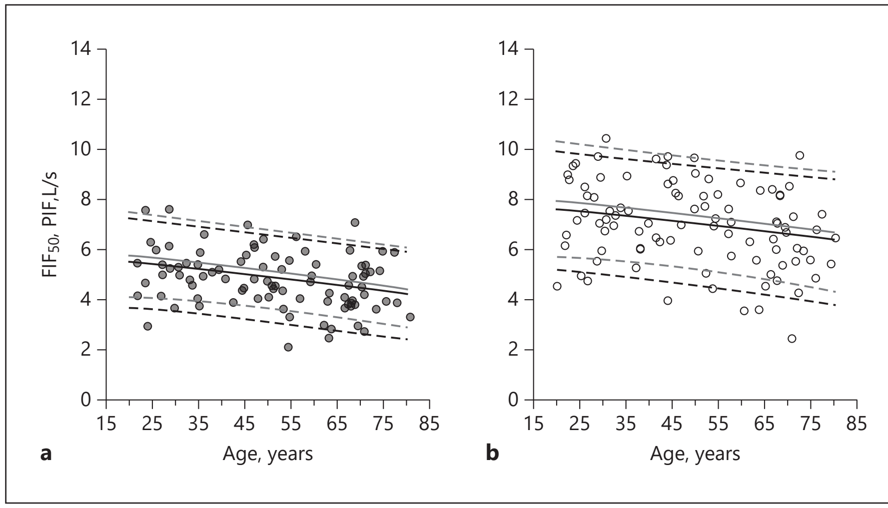

Fig. 2. Scatterplot of individual FIF_{50} values for female (**a**) and male (**b**) subjects; drawn to the same scale as peak flows in Figure 1. Black lines: predicted median (solid) and limits of normal (dashed) for an average male or female height at each given age. Grey lines: superimposed PIF predicted median and lower limit of normal from Figure 1. FIF_{50}, mid-inspiratory flow; PIF, peak inspiratory flow.

Table 3. PIF reproducibility and dependence on expiratory VC manoeuvre

Reproducibility (3 visits)	Age mean (±SD) [range]		PIF visit 1	PIF visit 2	PIF visit 3	*p* value
n = 20 (50% male)	28 (±4) [23–38]	Mean	7.15	7.23	7.42	>0.1[1]
		SD	2.01	2.08	2.11	
			Number of trials			
		Mean	3.1	3.2	3.2	
		SD	0.2	0.4	0.5	
Slow expiration prior to PIF (same visit)				PIF	PIFslow	*p* value
n = 142 (56% male)	50 (±18) [20–81]	Mean		6.34	6.50	<0.001[2]
		SD		1.69	1.66	
				Number of trials		
		Mean		3.3	3.1	
		SD		0.6	0.3	

PIF_{slow}, peak inspiratory flow after slow manoeuvre. [1] Significance of repeated-measures ANOVA. [2] Significance of paired *t* test.

equally well coached as the expiratory one, as per recent ATS/ERS 2019 technical document [6], the resulting number of flow-volume loops are sufficient to obtain a set of peak inspiratory flows and a set of peak expiratory flows from which acceptable PIF and PEF values can be derived.

We did observe a significant increase of PIF (by 2.5% on average) when the forced inspiration was preceded by a slow expiration instead of a forced expiration. However, we contend that this gain in PIF value is not of sufficient magnitude to justify the patient burden of performing an additional set of flow-volume loops. The measurement of PIF on 3 different days did not show significant differences across visit days, and the average number of trials to achieve a valid PIF remained close to 3 trials on each of the 3 visits. Since these consecutive measurement visits showed no learning effect, a quantitative assessment of PIF can be done at the first lung function testing. Predicted values have been proposed for PIF before, sometimes including lower limits of normal, but in any case with a fixed variability about the mean [25, 26]. While GLI did include age and height in both predicted value and limits of normal, the resulting normal reference values for spirometry did not include peak flows [1].

The 2019 ATS/ERS Standardization of Spirometry Update emphasizes that the manoeuvre to obtain forced expiratory indices should include the forced inspiration following the forced expiration [6]. Recommendations thus include vigorous coaching for the inspiratory and expiratory manoeuvres and a limit on the difference between forced inspiratory vital capacity and FVC to serve as a quality criterion for spirometry. We have demonstrated here that it is also feasible to extract valid PIF and PEF values from 3 to 4 such spirometric manoeuvres, by applying the criterion that the 2 highest peak inspiratory flows should be within 10% of each other. We used the criterion that for 2 out of 3 acceptable forced inspirations, peak flows needed to be within 10% of each other rather than all 3 of them being within 10% of each other. The latter condition would have undoubtedly resulted in a larger number of trials than the 3–4 trials we observed here. However, we believed that with respect to feasibility in a clinical context, the potential disadvantage of missing the true maximum peak flow would be outweighed by potential tiring of the patient. Older studies had suggested that effort-dependent expiratory flow rates do not differ significantly from effort-independent flow rates in terms of variability, with a coefficient of variation of 5.6% for PEF in healthy subjects [27]. We have confirmed this here for PEF and for PIF, and the obtained level of within-test variability across ages 20–80 years, makes the construction of reference equations meaningful.

While the 2019 ATS/ERS document states that GLI reference equations should be used by default, these lack reference values for peak inspiratory and expiratory flow rates, in which case other reports can be consulted for PEF [24, 25, 28–30] or PIF [25, 26]. The inter-subject variability reflected in our PEF reference equations (i.e., difference between predicted value and limits of normal) was similar to that in previous reports (online suppl. Fig. 2). By contrast, our PIF variability was generally lower than that previously obtained in a Finnish population by Viljanen et al. [25] and Kainu et al. [26] (online suppl. Fig. 1). As was expected from the typical semi-circular shape of the inspiratory flow-volume curve, the difference between PIF and FIF_{50} was small. Because FIF_{50} also showed a slightly higher variability than PIF, the latter is probably the preferable parameter for use in clinical practice.

Depending on the clinical application, peak flows are relevant in absolute value or in terms of z-score, but in both cases this requires a low measurement variability. For the diagnosis of upper airway obstruction, our z-scores for the various peak flows (Table 2), which take into account the patient's age and height, should present a considerable advantage over the use of fixed cut-offs [11, 12]. This also pertains to therapeutic interventions for upper airway obstruction, where in addition to the relative changes in peak flow, the z-scores can signal a restoration to normal upper airway calibre. For the diagnosis of respiratory muscle weakness, peak flow z-scores may be useful at diagnosis [18, 19], but for monitoring purposes, relative changes probably suffice. Finally, absolute PIF values from good quality spirometry can provide guidance for proper use of DPIs, particularly in COPD or asthma patients [31, 32].

In the routine lung function clinic, the pragmatic use of global reference values wherever possible does not preclude the usefulness of measuring a limited sample of a local population representative of a particular clinic patient base [1]. In doing so for PIF or PEF, exact values of coefficients may vary depending on whether age and age^2 [28, 29] are considered instead of age^2 alone [24], and whether ln(height) [29] or $height^2$ [28] or height [24] is included in the statistical model, and how sex-dependence of the equations are dealt with. Attesting to the compatibility of the present PEF equations with those previously obtained in the same laboratory with other equipment and on a different normal population sample, the application of the present equations to previous PEF data showed average z-scores for PEF less than 0.5 in absolute value, signalling satisfactory alignment between devices and reference equations for PEF [33].

Study Limitations

Representative of our patient population, we only included normal Caucasian adults for PIF and PEF measurement. The inclusion of data from subjects younger than 20 would probably have defined the relationship between age and PIF more accurately in young adulthood where a local maximum in PIF and PEF occurs. This is a limitation of any adult study by us or others, where reference values are obtained from subjects above the age of 18, 20, or 25 years, depending on local preferences. On the other hand, a study in adults does not suffer from potential equipment and coaching differences that may exist between adult and paediatric lung function settings, when compiling all-aged data. The average BMI of the subjects might seem relatively high (24 and 25 kg/m^2 for females and males, respectively), but is actually lower than the 2016 WHO estimate for BMI in Europe averaging 27 kg/m^2 for adults [34]. Finally, we acknowledge that patients may not always be able to obtain acceptable trials according to ATS/ERS2005 criteria in the first place, mainly owing to a failure to exhale for at least 6 s [35], a problem that we have not encountered here. It remains to be determined to what extent it is possible to obtain peak flows under such circumstances.

In conclusion, we contend that with rigorous coaching of expiratory and inspiratory limbs of the spirometric manoeuvre, and adherence to similar acceptability criteria for the respective peak flows, reliable PIF measurements can be obtained, typically requiring only 3–4 full flow-volume loops. The peak inspiratory flows were reproducible on different days, and a slow expiratory manoeuvre prior to forced inspiration only led to a minor increment. Hence, one set of flow-volume loops can serve to obtain both inspiratory and expiratory peak flows, for which we provide adult reference values.

Statement of Ethics

Subjects have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

Conflict of Interest Statement

S.H. has no conflicts of interest; E.V. has no conflicts of interest; W.V. has no conflicts of interest; D.S. has no conflicts of interest and S.V. has no conflicts of interest.

Funding Sources

This project was supported by the Fund for Scientific Research-Flanders (FWO-Vlaanderen, Belgium).

Author Contributions

S.H. is the guarantor of the content of the manuscript, including the data and analysis. S.H., E.V., W.V., and S.V. conceived of the study. D.S. performed the experiments. S.H. and S.V. analysed the data and co-wrote the manuscript. All authors provided a scientific critique of the data and edited the manuscript.

References

1 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40:1324–43.
2 Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD). 2020 report. Available from: https://goldcopd.org/gold-reports.
3 Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948–68.
4 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl. 1993;16(Suppl 16):5–40.
5 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–38.
6 Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70–88.
7 Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009:18059–99.
8 Global Initiative for Asthma. 2020 GINA main report. Available from: https://ginasthma.org/gina-reports.
9 Frey U, Brodbeck T, Majumdar A, Taylor DR, Town GI, Silverman M, et al. Risk of severe asthma episodes predicted from fluctuation analysis of airway function. Nature. 2005;438(7068):667–70.
10 Empey DW. Assessment of upper airways obstruction. Br Med J. 1972;3(5825):503–5.
11 Rotman HH, Liss HP, Weg JG. Diagnosis of upper airway obstruction by pulmonary function testing. Chest. 1975;68(6):796–9.
12 Modrykamien AM, Gudavalli R, McCarthy K, Liu X, Stoller JK. Detection of upper airway obstruction with spirometry results and the flow-volume loop: a comparison of quantitative and visual inspection criteria. Respir Care. 2009;54(4):474–9.
13 Pfeffer G, Povitz M. Respiratory management of patients with neuromuscular disease: current perspectives. Degener Neurol Neuromuscul Dis. 2016;6:111–8.
14 Miller RD, Hyatt RE. Evaluation of obstructing lesions of the trachea and larynx by flow-volume loops. Am Rev Respir Dis. 1973;108(3):475–81.
15 Kryger M, Bode F, Antic R, Anthonisen N. Diagnosis of obstruction of the upper and central airways. Am J Med. 1976;61(1):85–93.
16 Franco RA Jr, Husain I, Reder L, Paddle P. Awake serial intralesional steroid injections without surgery as a novel targeted treatment for idiopathic subglottic stenosis. Laryngoscope. 2018;128(3):610–7.
17 Szakács L, Sztanó B, Matievics V, Bere Z, Castellanos PF, Rovó L. Glottic configuration changes and outcomes of endoscopic arytenoid abduction lateropexy. Eur Arch Otorhinolaryngol. 2019;276(1):167–73.
18 Vincken WG, Elleker MG, Cosio MG. Flow-volume loop changes reflecting respiratory muscle weakness in chronic neuromuscular disorders. Am J Med. 1987;83(4):673–80.
19 American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518–624.
20 Tiddens HA, Geller DE, Challoner P, Speirs RJ, Kesser KC, Overbeek SE, et al. Effect of dry powder inhaler resistance on the inspiratory flow rates and volumes of cystic fibrosis patients of six years and older. J Aerosol Med. 2006;19(4):456–65.
21 Ghosh S, Ohar JA, Drummond MB. Peak inspiratory flow rate in chronic obstructive pulmonary disease: implications for dry powder inhalers. J Aerosol Med Pulm Drug Deliv. 2017;30:381–7.
22 Janssens W, VandenBrande P, Hardeman E, De Langhe E, Philps T, Troosters T, et al. Inspiratory flow rates at different levels of resistance in elderly COPD patients. Eur Respir J. 2008;31(1):78–83.
23 Quanjer PH, Stocks J, Cole TJ, Hall GL, Stanojevic S. Global Lungs Initiative. Influence of secular trends and sample size on reference equations for lung function tests. Eur Respir J. 2011;37:658–64.

24 Verbanck S, Van Muylem A, Schuermans D, Bautmans I, Thompson B, Vincken W. Transfer factor, lung volumes, resistance and ventilation distribution in healthy adults. Eur Respir J. 2016;47(1):166–76.
25 Viljanen AA, Halttunen PK, Kreus KE, Viljanen BC. Spirometric studies in non-smoking, healthy adults. Scand J Clin Lab Invest Suppl. 1982;159:5–20.
26 Kainu A, Timonen KL, Vanninen E, Sovijärvi AR. Reference values of inspiratory spirometry for Finnish adults. Scand J Clin Lab Invest. 2018;78(4):245–52.
27 Stanescu D, Veriter C, Van Leemputten R, Brasseur L. Constancy of effort and variability of maximal expiratory flow rates. Chest. 1979;76(1):59–63.
28 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999;159:179–87.
29 Kuster SP, Kuster D, Schindler C, Rochat MK, Braun J, Held L, et al. Reference equations for lung function screening of healthy never-smoking adults aged 18–80 years. Eur Respir J. 2008;31(4):860–8.
30 Kainu A, Timonen KL, Toikka J, Qaiser B, Pitkäniemi J, Kotaniemi JT, et al. Reference values of spirometry for Finnish adults. Clin Physiol Funct Imaging. 2016;36(5):346–58.
31 Sulaiman I, Cushen B, Greene G, Seheult J, Seow D, Rawat F, et al. Objective assessment of adherence to inhalers by patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2017;195(10):1333–43.
32 Sulaiman I, Greene G, MacHale E, Seheult J, Mokoka M, D'Arcy S, et al. A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. Eur Respir J. 2018;51(1):1701126.
33 Verbanck S, Schuermans D, Thompson BR, Vanderhelst E. Aligning lung function equipment and reference values in adults. Respiration. 2019;98(3):246–52.
34 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. 2017;390:2627–42.
35 Giner J, Plaza V, Rigau J, Solà J, Bolíbar I, Sanchis J. Spirometric standards and patient characteristics: an exploratory study of factors affecting fulfillment in routine clinical practice. Respir Care. 2014;59(12):1832–7.