PEAK IN- AND EXPIRATORY FLOW REVISITED:

RELIABILITY AND REFERENCE VALUES IN ADULTS.

Shane Hanon MD*, Eef Vanderhelst MD PhD, Walter Vincken MD PhD,
Daniel Schuermans RN and Sylvia Verbanck PhD.

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

Short title: Utility and feasibility of peak flow measurement.

* Corresponding author: Shane Hanon
Respiratory Division, University Hospital UZ Brussel
Laarbeeklaan 101
1090 Brussels, Belgium
Email: shane.hanon@uzbrussel.be

Number of Tables: 3
Number of Figures: 2

Word count text: 2945
Word count abstract: 258

Key words: 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
To obtain reproducible measurements of maximal inspiratory flow rates, and to construct reference equations for peak in- and expiratory flows (PIF, 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 were also investigated in subgroups. Reference values and limits of normal for PIF, FIF 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). Intra-class 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 (r²=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 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 intrathoracic from extrathoracic upper airway obstruction [10-12]. Finally, PEF is recognised as a tool for non-specific assessment of respiratory muscle weakness in neuromuscular disease [13].

The latest ATS/ERS spirometry update also emphasises 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, 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 (DPI) 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 hypothesised 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, that 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.

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 body mass index <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 seconds, (b) an end-expiratory plateau must be present, i.e. the measured volume must not exceed 25 mL during the last second, (c) back-extrapolated volume < 5% of FVC or 150 mL. In addition, we verified that all flow-volume loops fulfilled the criterion that forced inspiratory vital capacity (FIVC) and forced expiratory vital capacity (FVC) 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 maneuver 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*(1-1.645*L*S)(1/L) and M*(1+1.645*L*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.

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 Chi-squared 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 one subject (67 years) required 6 trials, and seven 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 one 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 two highest peak expiratory flow values, the difference between the highest peak expiratory flow (i.e., reported PEF) and the second best one 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$^2$, that can be readily used to obtain L, M and S (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 published in a graphic and color-coded representation of predicted and lower limits of normal in the Online Supplement (e-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$_{\text{slow}}$) or not (PIF). For PIF assessments on 3 different days, with standard-deviation on time-of-day across the 3 visits averaging 1.7 hours, 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 intra-class correlation coefficient, this was 0.981 (95%CI: 0.960-0.992); a Bland-Altman type representation is in e-Figure 3 of the Online Supplement. The impact on PIF of a slow expiration (PIF$_{\text{slow}}$) 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 e-Figure 4 of the Online Supplement. Finally, the average number of trials to obtain a valid set of spirometric measurements for PIF selection, was comparable for PIF and PIF$_{\text{slow}}$.

**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 to 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 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 emphasises 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 FIVC 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 two 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 three 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 [25]. We have confirmed this here for PEF and for PIF, and the obtained level of within-test variability across ages 20 to 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, 29, 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 (e-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] (e-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 \( \ln(\text{height}) \) [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 body mass index (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 6s [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.
ACKNOWLEDGEMENT

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

SH has no conflicts of interest; EV has no conflicts of interest; WV has no conflicts of interest; DS has no conflicts of interest and SV 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


**FIGURE LEGENDS**

**Fig. 1.** Scatterplot of individual peak inspiratory and expiratory flow (PIF, 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.

**Fig. 2.** Scatterplot of individual mid-inspiratory flow ($F_{IF_{50}}$) 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.
Table 1: Characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>age (years)</td>
<td>49 ± 18</td>
<td>51 ± 17</td>
</tr>
<tr>
<td>height (cm)</td>
<td>178 ± 7</td>
<td>165 ± 6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 ± 3</td>
<td>24 ± 4</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>5.2 ± 0.9</td>
<td>3.7 ± 0.7</td>
</tr>
<tr>
<td>(%pred)*</td>
<td>105 ± 12</td>
<td>106 ± 13</td>
</tr>
<tr>
<td>z-score*</td>
<td>0.3 ± 0.9</td>
<td>0.4 ± 0.9</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>4.1 ± 0.8</td>
<td>3.0 ± 0.6</td>
</tr>
<tr>
<td>(%pred)*</td>
<td>105 ± 12</td>
<td>105 ± 12</td>
</tr>
<tr>
<td>z-score*</td>
<td>0.3 ± 0.9</td>
<td>0.4 ± 0.9</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.79 ± 0.05</td>
<td>0.80 ± 0.05</td>
</tr>
<tr>
<td>z-score*</td>
<td>0.0 ± 0.8</td>
<td>-0.2 ± 0.6</td>
</tr>
<tr>
<td>PIF (L/s)</td>
<td>7.4 ± 1.5</td>
<td>5.1 ± 1.0</td>
</tr>
<tr>
<td>PEF (L/s)</td>
<td>9.9 ± 1.6</td>
<td>7.0 ± 1.2</td>
</tr>
<tr>
<td>FIF₅₀ (L/s)</td>
<td>7.0 ± 1.6</td>
<td>4.8 ± 1.1</td>
</tr>
</tbody>
</table>

FEV₁: forced expiratory volume in 1s; FVC: forced vital capacity; PIF: peak inspiratory flow; FIF₅₀: forced inspiratory flow at 50% vital capacity; PEF: peak expiratory flow.

* according to GLI 2012 [1]
Table 2: Coefficients for L, M, and S to obtain predicted, ULN and LLN values for PIF, FIF$_{50}$, and PEF.

<table>
<thead>
<tr>
<th></th>
<th>M coefficients</th>
<th></th>
<th>S coefficients</th>
<th></th>
<th>L coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r^2$</td>
<td>sex</td>
<td>height</td>
<td>age</td>
<td>age$^2$</td>
</tr>
<tr>
<td>PIF (L/s)</td>
<td>0.53</td>
<td>[-1.560, 0.0509]</td>
<td>[-0.0079, -0.000083]</td>
<td>[-1.07]</td>
<td>[-0.00013, -0.0055]</td>
</tr>
<tr>
<td>FIF$_{50}$ (L/s)</td>
<td>0.49</td>
<td>[-1.435, 0.0554]</td>
<td>[-0.0138, -0.000014]</td>
<td>[-2.09]</td>
<td>[-0.00410, 0.0010]</td>
</tr>
<tr>
<td>PEF (L/s)</td>
<td>0.62</td>
<td>[-2.118, 0.0648]</td>
<td>[0.0463, -0.000632]</td>
<td>[-2.14]</td>
<td>[-0.00433, -0.0101]</td>
</tr>
</tbody>
</table>

PIF: peak inspiratory flow; FIF$_{50}$: forced inspiratory flow at 50% vital capacity; PEF: peak expiratory flow.
Table 3: PIF reproducibility and dependence on expiratory VC manoeuvre.

<table>
<thead>
<tr>
<th>age</th>
<th>mean (±SD)</th>
<th>PIF</th>
<th>PIF</th>
<th>PIF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[range]</td>
<td>visit 1</td>
<td>visit 2</td>
<td>visit 3</td>
<td></td>
</tr>
<tr>
<td>Reproducibility (3 visits)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=20 (50% male)</td>
<td>28 (±4)</td>
<td>mean</td>
<td>7.15</td>
<td>7.23</td>
<td>7.42</td>
</tr>
<tr>
<td></td>
<td>[23 - 38]</td>
<td>SD</td>
<td>2.01</td>
<td>2.08</td>
<td>2.11</td>
</tr>
<tr>
<td>number of trials</td>
<td></td>
<td>mean</td>
<td>3.1</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>0.2</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Slow Expiration prior to PIF (same visit)</td>
<td></td>
<td>PIF</td>
<td>PIF&lt;sub&gt;slow&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=142 (56% male)</td>
<td>50 (±18)</td>
<td>mean</td>
<td>6.34</td>
<td>6.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>[20 - 81]</td>
<td>SD</td>
<td>1.69</td>
<td>1.66</td>
<td></td>
</tr>
<tr>
<td>number of trials</td>
<td></td>
<td>mean</td>
<td>3.3</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>0.6</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>

PIF<sub>slow</sub> : peak inspiratory flow after slow manoeuvre

(1): significance of repeated measures ANOVA

(2): significance of paired t-test
PEAK IN-AND EXPIRATORY FLOW RATES REVISITED:

RELIABILITY AND REFERENCE VALUES IN ADULTS.

Shane Hanon MD*, Eef Vanderhelst MD PhD, Walter Vincken MD PhD,
Daniel Schuermans RN and Sylvia Verbanck PhD.

Supplemental material
1. Example computation of predicted value and upper limits of normal (ULN) and lower limits of normal (LLN) for peak inspiratory flow (PIF) in a female subject

Based on the M, L, and S coefficients provided in Table 2, the obtained coefficients for M are to be used in a linear expression to obtain the predicted value, whereas the obtained coefficients for S are to be used in an exponential expression to obtain the spread; L is a constant coefficient.

For a 65 year-old female subject of 163 cm standing height, M was computed as follows:

\[
M = -2.12 \times \text{sex} + 0.0648 \times \text{height} + 0.0463 \times \text{age} - 0.000632 \times (\text{age} \times \text{age}) - 2.14
\]

where sex is 1 for a female subject, height is in cm, and age in years.

Thus,

\[
M = -2.12 \times (1) + 0.0648 \times (163) + 0.0463 \times (65) - 0.000632 \times (65 \times 65) - 2.14
\]

\[
= 6.64 \text{ L/s}
\]

This corresponds to predicted PIF value for this person.

Then, S is computed as:

\[
S = \exp \left\{ -0.00433 \times \text{height} - 0.0101 \times \text{age} + 0.0000746 \times (\text{age} \times \text{age}) - 0.85 \right\}
\]

\[
= \exp \left\{ -0.00433 \times (163) - 0.0101 \times (65) + 0.0000746 \times (65 \times 65) - 0.85 \right\}
\]

\[
= 0.150
\]

Finally, L is 1.012.

Hence, LLN and ULN can be computed as:
LLN = M*(1-1.645*L*S)^{(1/L)}
= 6.64*(1-1.645*1.012*0.150)^{(1/1.012)}
= 5.00 L/s

ULN = M*(1+1.645*L*S)^{(1/L)}
= 6.64*(1+1.645*1.012*0.150)^{(1/1.012)}
= 8.28 L/s

These predicted, LLN and ULN values can also be appreciated from the solid and dashed lines in the right panel of Figure 1C, since 163cm more or less corresponds to the average height at 65 years for a female population.

2. Figures of predicted PIF and PEF compared to previous reference values from the literature

The plots of ULN and LLN values of PIF (e-Fig. 1) and PEF (e-Fig. 2) based on coefficients in Table 2, compared to that from previous reports, where both PIF and PEF measurements and regression methods originated from the same laboratory (recruiting from the same local populations). To optimize comparison between present and previous curves for an average person, height dependence on age was used from that observed in our study population.
e-Fig. 1. Predicted median (solid lines) and lower limit of normal (dashed lines) for peak inspiratory flow (PIF) values, obtained here (green), and based on reference equations obtained from measurement in 368 Finnish adults aged 19-83 by Kainu et al. [1] (purple) and in 553 Finish adults aged 18-65 by Viljanen et al. [2] (blue); drawn to the same scale as Figure 1.

3. Data corresponding to Table 3 represented as Bland-Altman plots.
e-Fig. 3. Bland-Altman representation of 2\textsuperscript{nd} and 3\textsuperscript{rd} visit PIF measurement, using 1\textsuperscript{st} visit PIF as a reference. Data corresponding to Table 3.

e-Fig. 4. Bland-Altman representation of the slow PIF measurement (PIF\textsubscript{slow}), using PIF as a reference. Data corresponding to Table 3.
