REFERENCE VALUES FOR FORCED EXPIRATION PARAMETERS IN BULGARIAN CHILDREN AND ADOLESCENTS AGED 7 TO 18 YEARS

Stoilka K. Mandadzhieva, Blagoi I. Marinov, Stefan S. Kostianev
Department of Pathophysiology, Medical University, Plovdiv, Bulgaria

ABSTRACT

INTRODUCTION: A diagnosis of lung function impairment in childhood is highly dependent on the respective reference values. Population differences in the pulmonary function of children have been frequently reported.

The aim of this study was to derive normal spirometric reference values for Bulgarian children and adolescents and to compare these results with other data set including our own reference equations developed 20 years ago.

MATERIAL AND METHODS: Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), and parameters of maximum expiratory flow-volume curves were measured in 671 healthy Bulgarian school children (339 males and 332 females) aged 7-18 years. Multiple linear regression analysis was performed for each spirometric parameter against age, height, weight, chest circumferences and fat free mass in both sexes.

RESULTS: Excluding ratios, all measured spirometric parameters increased nonlinearly with age and height, and were significantly higher in boys than girls in adolescence.

Height (H) explained the maximum variance for spirometric parameters and the best-fit regression equation relating functional parameters and body height was a power function (Y = a.Hᵇ). FVC and FEV₁ showed close correlations with height (r² between 0.85 and 0.92), whereas the coefficients of determination for the flows were less close (r² from 0.85 for PEF to 0.67 for MEF₂₅%; always higher in boys).

CONCLUSIONS: The developed prediction equations can be used in clinical practice. In comparison with reference equations based on European or USA populations, regional reference values are biologically more suitable for the interpretation of spirometric data.

Key words: reference values, spirometric parameters, children and adolescents

INTRODUCTION

Spirometry is one of the most important measurements in respiratory medicine in clinical practice and for research purposes. This is the basic way to obtain information about the lung volumes, vital capacity (VC), forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) of the lungs.

Pulmonary function tests (PFT) are a useful and important tool to assess children and adolescents with pulmonary disorders. They are a sensitive and objective way of detecting and measuring the severity of lung dysfunction, of monitoring the progress of disease, and of assessing treatment results.¹

The interpretation of these tests is usually based on comparison of measurement results with reference or predicted values, obtained from studies of “normal” or “healthy” subjects with matching anthropometric (gender, height, age, weight and ethnicity) or other characteristics.

The diagnosis of lung function impairment in childhood is highly dependent on the reference values used. The ideal situation is when spirometric reference values were derived from a population similar to the individual person using the same kind of instrument and testing procedure.

The choice of appropriate reference values and the interpretation of the data are all as important as the accuracy and precision of the original
measurement.²

Currently there are not any specific set of reference equations recommended for use in Europe. A new Europe-wide study to derive updated reference equations for lung function is needed.

International guidelines on standardization of lung function measurements and interpretation recommend the development of population-specific lung function prediction equations.³

AIM

The aim of this study was to derive normal spirometric reference values for Bulgarian children and adolescents in the age span 7 – 18 years and to compare these results with other data sets including our own reference equations developed 20 years ago.

MATERIAL AND METHODS

A cross-sectional study was performed in eight hundred and nine healthy Bulgarian school children (389 males and 420 females) in the age span 7 – 18 years. All of the subjects were residents of several cities in the region of South Bulgaria with average altitude of 150 m.

Parents or guardians were sent a questionnaire concerning questions about respiratory symptoms and diseases, medical history or any drug intake, smoking habits of the parents etc. Children aged 12 years and older were asked directly about smoking habits and were considered smokers if they smoked more than one cigarette per week.

Before the test procedure written informed consent was obtained from a parent or guardian for each participant.

A total of 809 children performed spirometry and those who met exclusion criteria were excluded from the analysis. The exclusion criteria were: current or past history of asthma or other chronic respiratory disease; recent respiratory tract infection (within the past month); personal history of smoking; unacceptable spirometric measurements; forced expiratory time under 1 s.

All the participants were subjected to complete anthropometric measurements. Standing height and body weight were measured in all subjects without wearing shoes. Height was measured with a stadiometer using standard techniques (child standing erect with the head in the Frankfort horizontal plane) to nearest cm. Weight was measured to nearest kg.

Skinfold thickness was measured over the triceps and subscapular regions. The measurements were performed on the right side of the body with a caliper (Harpenden, British Indicators, UK). The values of the skinfolds were added together and the sum was used to calculate percent body fat (and the respective fat free mass – FFM) utilizing Slaughter equations.⁴

Body surface area (BSA) was calculated using the equation of Gehan & Georges:² BSA (m²) = 0.02350 x H⁰.⁴²²⁴⁶ x W⁰.⁵¹⁴⁵⁶ where H is height in cm and W is weight in kg.

Dimensions of the thorax were assessed through the measurements of chest circumference at full inspiration (CCI) corresponding to total lung capacity (TLC), as well as the measurements of chest circumference at full expiration (CCE), corresponding to residual volume (RV).

All the participants underwent comprehensive pulmonary function assessment – spirometric tests, maximal respiratory pressures, and determination of diffusion capacity by Single Breath method (MasterScreen Diffusion®, Jaeger, Wuerzburg, Germany) in a certified laboratory applying the ATS and ERS criteria to ensure quality.

Regular calibration was done with a 3 liter calibration syringe. The equipment was suited for pediatric measurements and the whole setting was accommodated to fit children’s proportions.

Pulmonary function testing was carried out in a seated position with a nose clip in the following order:
1. Slow spirometry;
2. Diffusion measurement;
3. Forced expiration;
4. Maximal inspiratory and expiratory pressures.

To obtain measurements of forced expiration children were instructed on the technique of the spirometry maneuver in small groups and the instruction was repeated to each child individually before the test start. After exhaling as deeply as possible each child was asked to breathe in to total lung capacity (TLC), subsequently blow out as hard and as fast as possible to residual volume (RV) and than similarly to breathe in back to TLC. Forced expiratory maneuvers complied with the general acceptability criteria. At least three technically acceptable attempts of maximal forced expiratory flow-volume curves were recorded. Reproducibility of forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁) was considered acceptable when the highest FVC and FEV₁ value did not exceed the second highest value by more than 5%. The largest FEV₁ and the largest FVC are selected from 3 technically acceptable maneuvers.

Some healthy children < 8 yrs of age have very
short expiration time, and they can perform FVC in less than 1 second, even making it impossible to obtain FEV₁. We excluded these children from analysis and analyzed only children whose forced expiratory time exceeded 1 second.

For analysis children were subdivided into 10-cm groups according to their height. Stepwise regression analysis was performed for each spirometric parameter as dependent variable against age, height, weight, BSA, chest circumferences and FFM as independent variables. The most appropriate regression model was chosen on the basis of the following considerations: the highest explained variation of the dependent variable, the coefficient of determination (R²) and a constant residual standard deviation (RSD) over the whole age range.

The statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, USA).

RESULTS
A cross-sectional study was performed in 809 healthy Bulgarian school children (389 males and 420 females) in the 7 – 18 age span. Of the 809 that completed tests 138 children were excluded on the basis of the exclusion criteria and a total of 671 (339 males) non-smoking clinically healthy children were included in the present analysis.

The smaller number of the children in the 7 – 9-year age groups was because of the higher exclusion rate. In the age groups 13 – 17-year old there were more girls per classroom and some boys were excluded because of smoking so the number of girls in the respective age groups was higher.

The mean ages were 12.7 years for boys and 12.9 for girls; the mean standing heights were 157.0 cm for boys and 153.7 cm for girls.

The measurements of chest circumference at full inspiration (CCI) corresponding to total lung capacity (TLC), as well as the measurements of chest circumference at full expiration (CCE), corresponding to residual volume (RV) increased with age, always higher in boys – especially after age of 14 years.

It is evident by the results that excluding FEV₁/FVC% ratio, all other measured spirometric parameters increased nonlinearly with age and height. In adolescence these parameters were significantly higher in boys than in girls.

All measured pulmonary function parameters were strongly correlated with age, height, weight, BSA and fat free mass (FFM), with the strongest correlation being with height in both genders. The increase in these parameters was similar in boys and girls up to height of 146 cm, whereas in the range 146 – 156 cm girls had always higher values than boys especially for peak expiratory flow (PEF) and FEV₁. After 160 cm boys showed significant higher values. The pattern of increase of these parameters with age was similar, but boys always had significantly greater values than girls, rapidly increased after age of 13 years.

The distribution of FEV₁, FVC and PEF vs. standing height in boys and girls is presented in Fig. 1.
The estimated parameters and regression equations for both sexes are presented in Table 1.

FEV$_1$/FVC% was not included in the regression because it was relatively independent of age and height. The mean values were 89.5 ± 4.9 for girls and 86.8 ± 5.3 for boys, always higher in girls in the whole age range.

With respect to FVC and FEV$_1$ there were close correlations with height ($r^2$ between 0.85 and 0.92), whereas the coefficients of determination for the flows were less close ($r^2$ from 0.78 for PEF to 0.44 for mid expiratory flow$_{25\%}$ (MEF$_{25\%}$); always higher in boys).

Comparison with other population data was made, using three sets of reference equations: the first one previously developed by Kostianev et al.\textsuperscript{6,7}, Quanjer et al.\textsuperscript{8}, and Stanojevic et al.\textsuperscript{9}

Table 2 present the reference equation sets used to compare predicted values of FEV$_1$ in both genders.

The power function with the most important determinant – stature was derived and applied as reference equation by Kostianev et al. in Bulgarian children aged 7 to 14 years. Although during adolescence stature and spirometric indices increased at different rates, this equation was suitable for our population.

The reference equation of Quanjer et al, is most widely used and this model describes the lung function throughout adolescence and reflects the changes in body dimensions and growth. When combined with height as an age x height interaction (A x St) that model greatly improves the description of spirometric indices in European adolescents of Caucasian origin.

The models used by Stanojevic were based on large white population aged 4 to 80 years and were constructed with LMS method, widely used to build growth reference charts. The methods used do not produce equations per se but comprehensive look-up tables.\textsuperscript{9}

The present study included children in the age span 7–18 years and derived equation that attempt to explain the shift between increase in height and lung function indices especially during the adolescence growth spurt.

Figs 2 and 3 show the mean values of FEV$_1$ calculated by the above mentioned set of equations against height groups in boys and in girls. Reference values were quite close but always lower in boys than those reported by Kostianev et al., and

### Table 1. Reference equations for lung function parameters in 7-18-year-old children

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (L)</td>
<td>$0.1563 \times 1.0193^{\text{HI}}$</td>
<td>$0.1732 \times 1.0190^{\text{HI}}$</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>$0.1480 \times 1.0195^{\text{HI}}$</td>
<td>$0.1541 \times 1.0195^{\text{HI}}$</td>
</tr>
<tr>
<td>FEV$_1$ (L)</td>
<td>$0.1513 \times 1.0188^{\text{HI}}$</td>
<td>$0.1495 \times 1.0190^{\text{HI}}$</td>
</tr>
<tr>
<td>FEV$_1$/FVC (%)</td>
<td>$89.6 \pm 4.9$</td>
<td>$86.8 \pm 5.3$</td>
</tr>
<tr>
<td>PEF (L.s$^{-1}$)</td>
<td>$0.4597 \times 1.0162^{\text{HI}}$</td>
<td>$0.3629 \times 1.0178^{\text{HI}}$</td>
</tr>
<tr>
<td>MEF$_{50%}$ (L.s$^{-1}$)</td>
<td>$0.3576 \times 1.0149^{\text{HI}}$</td>
<td>$0.2339 \times 1.0173^{\text{HI}}$</td>
</tr>
<tr>
<td>MEF$_{25%}$ (L.s$^{-1}$)</td>
<td>$0.0896 \times 1.0193^{\text{HI}}$</td>
<td>$0.0665 \times 1.0204^{\text{HI}}$</td>
</tr>
</tbody>
</table>

### Table 2. Reference equation sets, used to compare predicted values of FEV$_1$ in both sexes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kostianev et al.</td>
<td>$FEV_1 = 0.1589 \times 1.0188^{\text{HI}}$</td>
<td>$FEV_1 = 0.1180 \times 1.0205^{\text{HI}}$</td>
</tr>
<tr>
<td>Quanjer et al.</td>
<td>$FEV_1 = \exp((1.2669 + 0.0174 \times \text{Age}) \times \text{Height/cm}/100.0 - 1.2933)$</td>
<td>$FEV_1 = \exp((1.5016 + 0.0119 \times \text{Age}) \times \text{Height/cm}/100.0 - 1.5974)$</td>
</tr>
<tr>
<td>Stanojevic et al.</td>
<td>No specification of reference equations – look-up table</td>
<td>No specification of reference equations – look-up table</td>
</tr>
<tr>
<td>Resent</td>
<td>$FEV_1 = 0.1495 \times 1.0190^{\text{HI}}$</td>
<td>$FEV_1 = 0.1513 \times 1.0188^{\text{HI}}$</td>
</tr>
</tbody>
</table>
Figure 2. Regression curves for 4 different reference equations (from Kostianev et al., Quanjer et al., Stanojevic et al. and the current study) of mean FEV₁ against height groups in boys.

Figure 3. Regression curves for 4 different reference equations (from Kostianev et al., Quanjer et al., Stanojevic et al. and the current study) of mean FEV₁ against height groups in girls.
Quanjer et al. Our results for girls were similar to that reported by Quanjer et al. only up to a height of 150 cm. Values obtained for taller girls (over 150 cm) were usually lower than those reported by Kostianev et al. and Quanjer et al.

Comparison was performed also with spirometric equations for Greek children and adolescents 6 to 18 years old.8 We found that both equations were similar and generally comparable, and as Alexandraki et al.8 stated they might be used in neighboring Balkan countries.

**DISCUSSION**

Our study developed normal spirometric reference values for Bulgarian children and adolescents in the age span 7 – 18 years.

Similar to previous reports mean spirometric parameters increased with age, height and weight with the best correlation being with height.10-12 Standing height explained the highest proportion of the variation in lung function parameters as in our study, as in European, Asian and American children.7,10,14-16

For the same age boys have greater spirometric parameters than girls. It was only at height 146 to 156 cm that higher PEF and FEV1 values in girls than in boys were found; similar findings were established by Gonzalez Barcala et al.17 Probably this is due to the earlier onset of puberty in girls, but we do not examine the pubertal stage in our study.

Although height, BSA, weight, age and FFM correlated very closely with the mean spirometric parameters, the contribution of age and weight was negligible, so we used height as single independent variable in the final derivation of the prediction equation. These predictors are common and easy to obtain in clinical practice, but in our data the inclusion of age does not significantly contribute to improving the goodness of fit. It is well known that lung function prediction equations based only on height can result in erroneous under- or overestimation of the lung function parameters especially at early ages or in late pubertal adolescents18, but we used the best fit model to our own population.

Weight and especially fat free mass (FFM) might contribute to the predictive power of the spirometric equations because they are associated with body composition and can influence the lung function. FFM in our population increased with age and with height and our findings demonstrate that higher values in boys rapidly increased after age of 13 years until 18 years. Girls showed higher values only at age between 12 and 13 years and height of 149 – 159 cm, probably because weight and height growth spurts occurred earlier and at different ages compared to boys. This predictor even significant is difficult to obtain and calculate, so we excluded FFM from our final equations.

In similar studies to ours, conducted in almost the same age span (7 to 19 years and 6 to 18 years) in China and Singapore neither age nor weight were seen to have significant effect on goodness of fit.14,19 Significantly higher FVC and FEV1 were noted in boys and some authors20 stated that the height influences the prediction equation in males to a great extent, whereas age and weight had greater influence in girls.

Our findings agree with those of previous studies in children in which FEV1/FVC% ratio was not related to age and anthropometric measurements and female values were higher than male ones.7,10,19

For the same height Caucasians have greater spirometric parameters than African-American or Indian children.15,20 Hankinson et al. analyzed 3 ethnic groups aged 8 to 80 years and found that height and age but not weight improved the predictive power of the derived regression equations. Compared with European values for most spirometric parameters children from other ethnicity show smaller lung volumes and lower forced expiratory flows.19,15 We examined previously the anthropometric and spirometric parameters in Bulgarian and Romany children and found that Bulgarians were significantly taller and heavier than Romany children.21 There was a significant difference in percent body fat (20.5 ± 8.1% vs. 17.8 ± 7.6% in Romanies) between the two ethnic groups. It was established also that Bulgarian children had higher mean absolute values of VC, FEV1 and TLC – respectively, 7.8%, 7.3% and 10.2% lower for Romany than for Bulgarian children.

The best fit of the data was obtained by Tomalak et al.22, with the power model (Y = A.Hb) and the coefficients of correlation between flows and height ranged from 0.66-0.77, and were slightly greater for boys – our correlation for the flows were similar for PEF – 0.79.

Comparison was made with another data set derived by the same authors (Kostianev et al.) but 20 years ago, Quanjer et al.8 and Stanoevic et al.9 Reference values were close but always lower in boys than those reported by Kostianev et al. and higher than Quanjer et al. and Stanoevic et al. Our results for girls were similar to those by Quanjer et al. and Stanoevic et al. but over the height of
150 cm. Girls (up to 150 cm) had usually higher values than those reported by Kostianev et al., Quanjer et al., and Stanojevic et al.

If we used the equations derived by other studies to predict the lung function in our recent population even similar results, they would have been overestimated.

The differences between our predictions and other studies might be due to differences in the study samples – children up to age 14 (Kostianev et al.) compared with our group up to 18 years. Probably, many of the children and adolescents were in earlier stage of puberty than those in our study, and it is well known that pubertal growth influences lung function and extrapolation to other age groups can affect the precision of the predictions.

On the other hand R. Pellegrino et al. considered that updating reference equations on a regular basis e.g. every 10 years will take into account the applicability of the newer reference equations and also the changes of the characteristics of the population of “normal” or “healthy” subjects. So our reference values study was performed with instruments and procedures that meet international standards for accuracy and precision in the same laboratory as 20 years ago (Kostianev et al.) and demonstrated the necessity of population specific prediction equations for assessment of spirometric parameters.

Some of the limitations of our study were: the study was cross-sectional and included pre- and post pubertal individuals, where the onset and duration of puberty varies from one gender to the other and also from one person to other. The level of sexual development was not assessed precisely and we do not measure some specific anthropometric variables as sitting height and all thoracic dimensions, and we cannot comment on different body proportions like trunk/leg length ratio and the prediction power of these parameters in comparison to standing height.

CONCLUSIONS

The developed prediction equations for lung function parameters in Bulgarian 7-to-18-year-old children can be used in clinical practice. In comparison with reference equations based on European or USA populations, population-specific reference values are biologically more suitable and this reduces the risk of errors by the interpretation of test results.

REFERENCES


РЕФЕРЕНТНЫЕ СТОИМОСТИ ФОРСИРОВАННЫХ ЭКСПИРИАТОРНЫХ ПОКАЗАТЕЛЕЙ У БОЛГАРСКИХ ДЕТЕЙ И ЮНОШЕЙ В ВОЗРАСТЕ ОТ 7 ДО 18 ЛЕТ

Ст. Мандаджиева, Бл. Маринов, Ст. Костянев

ВВЕДЕНИЕ: Диагностика поражений легочных функций в детском возрасте во многом зависит от применяемых референтных уравнений. Часто наблюдаются различия в легочных функциях у детей различных популяций.

ЦЕЛЬ: Вывести нормальные спирометрические референтные стоимости для болгарских детей и юношей и сравнить эти результаты с другими данными, включительно и с референтными уравнениями авторов, выведенными 20 лет назад.

МАТЕРИАЛ И МЕТОДЫ: Форсированная жизненная емкость (ФЖЕ), форсированный экспираторный объем (ФЭО) и показатели максимальных экспираторных дебит-объемных кривых измерены у здоровых болгарских школьников – 671 (339 мальчиков и 332 девочки) в возрасте от 7 до 18 лет. Множественный регрессионный анализ использован для каждого спирометрического показателя в зависимости от возраста, роста, массы тела, окружности груди и от активной массы тела и при обоих полах.

РЕЗУЛЬТАТЫ: За исключением соотношений для всех остальных измеренных спирометрических показателей устанавливается нелинейное нарастание с возрастом и ростом, при чем в юношестве они сдвигаются более высокие у мальчиков.

Рост лучше всего отражает вариабельность спирометрических показателей. Самое подходящее регрессионное уравнение имеет вид power функция (Y=a.Rⁿ). ФЖЕ и ФЭО показывают сильнейшую корреляцию с ростом (r² между 0.85 и 0.92), в то время как коэффициенты, определяющие дебиты, показывают более слабую корреляцию (r² от 0.85 для пикового экспираторного дебита до 0.67 для минутного экспираторного дебита); они всегда более высокие у мальчиков.

ЗАКЛЮЧЕНИЕ: Предложенные референтные уравнения подходящи для применения в клинической практике. Сравнение с референтными уравнениями для других популяций показывает, что эти, полученные на основании местных референтных стоимостей, более подходящи в целях интерпретации спирометрических данных.